Univerzita Tomáše Bati ve Zlíně
Fakulta technologická

Disertační práce

Syntézy nových sloučenin vycházející ze 4-hydroxychinolin-2(1*H*)-onů potenciálně využitelných k úpravě vlastností nebo k ochraně materiálů

Syntheses of Novel Compounds Based on 4-Hydroxyquinolin-2(1*H*)-ones Potentially Applicable for Properties Modification or Protection of Materials

ÚSTAV CHEMIE

Autor:	**Ing. Karel Proisl**	
Studijní program:	Chemie a technologie materiálů	P2808
Studijní obor:	Chemie a technologie materiálů	2808V009
Školitel:	Doc. Ing. Stanislav Kafka, CSc.	
Oponenti:	prof. RNDr. Jan Hlaváč, Ph.D. prof. RNDr. Milan Potáček, CSc. Mgr. Robert Vícha, Ph.D.	

Zlín, říjen 2017

Klíčová slova: *4-hydroxychinolin-2-on, chinolin-2,4-dion, anthranilová kyselina, organická synthesa, biologická aktivita*

Key words: *4-hydroxyquinolin-2-one, quinoline-2,4-dione, anthranilic acid, organic synthesis, biological activity*

Abstrakt

Předložená disertační práce se zabývá syntézou a reaktivitou 4-hydroxychinolin-2(1*H*)-onů, chinolin-2,4(1*H*,3*H*)-dionů a sloučenin z těchto látek dostupných, především derivátů kyseliny anthranilové.

V literární části je kromě reaktivity přiblížena také biologická aktivita, přírodní výskyt a potenciální využití těchto sloučenin k úpravě vlastností nebo k ochraně materiálů. V druhé části práce jsou komentovány výsledky výzkumné činnosti autora publikované v odborné literatuře.

Abstract

Presented dissertation thesis is focused on a synthesis and reactivity of 4-hydroxyquinolin-2(1*H*)-ones, quinoline-2,4(1*H*,3*H*)-diones and the substances available therefrom, especially anthranilic acid derivatives.

In the literary part, biological activity, natural occurrence, and potential application of these compounds at modifying properties and/or protecting materials are discussed in addition to reactivity. The second part of the thesis deals with the results of the research activities of the author published in the literature.

Děkuji svému školiteli, Doc. Ing. Stanislavovi Kafkovi, CSc., za množství rad, trpělivost a pomoc během mého doktorského studia i při přípravě této práce.

Tato práce by nemohla ve své podobě vzniknout, nebýt spolupráce s kolegy, kteří zajišťovali měření nutná pro strukturní analýzu izolovaných produktů. Díky patří kolegům z Univerzity v Lublani – panu profesorovi Janezu Košmrljovi, Martinu Gazvodovi a Damianě Urankar, kteří zajišťovali měření NMR a HRMS. Dále chci poděkovat Ing. Michalovi Rouchalovi, PhD., který v některých případech realizoval měření ESI-MS a Ing. Lence Trhlíkové, která v mnoha případech prováděla elementární analýzy a hmotnostní spektrometrii (EIMS).

Rád bych poděkoval také celému kolektivu Ústavu chemie za mnohaletou podporu a obohacující pracovní prostředí. Děkuji paní Haně Geržové a Ing. Ondřejovi Rudolfovi, PhD. Chci také poděkoval diplomantům a stážistům se kterými jsem spolupracoval a kteří se ve svých pracích podíleli na výzkumu titulních sloučenin. Za pomoc v laboratoři i inspiraci při řešení teoretických problémů děkuji Darji Višenkové, Aleně Ščerbové, Filipu Křemenovi, Anně Srholcové a Sylvii Jurečkové.

Za podporu děkuji také mé rodině a přátelům.

OBSAH

1. ÚVOD

Sloučeniny, které obsahují ve své struktuře 4-hydroxychinolin-2-onový systém a z nich odvozené chinolin-2,4-diony patří mezi velmi početnou a zajímavou skupinu chemických látek, které jsou dlouhodobě zkoumány také na Ústavu chemie FT UTB ve Zlíně. Proto není zvláštní, že na tomto pracovišti bylo v minulosti publikováno mnoho diplomových a také několik disertačních[1,2] prací s podobnou tematikou. Toto pojednání ke Státní závěrečné zkoušce jsem se rozhodl pojmout z pohledu, který se snaží mapovat nejen syntézu titulních sloučenin, ale také jejich praktický význam, výskyt v přírodě a nastínit další výzkumný potenciál těchto zajímavých chemických individuí. Do této skupiny patří i několik používaných (laquinimod) či potenciálních (chinoxikain, L-701324) farmak a řada sloučenin vykazujících slibnou biologickou aktivitu, což jen zdůrazňuje význam výzkumu v oblasti hydroxychinolonů.

Rešeršní část disertační práce se zaměřuje na 4-hydroxychinolony a chinolin-2,4-diony, které byly izolovány z přírody a na syntetické sloučeniny, které vykazují zajímavou biologickou aktivitu. V druhé části jsou popsány některé syntézy těchto sloučenin s důrazem na recentní literaturu. Pevně doufám, že pro čtenáře bude tento text zajímavým a inspirativním zdrojem informací. Toto pojednání se také stalo předlohou pro přehledný článek publikovaný v časopise *Current Organic Chemistry*, který je součástí této disertační práce.

2. ZNÁMÉ 4-HYDROXYCHINOLIN-2-ONY A CHINOLIN-2,4-DIONY

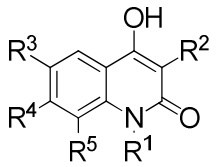
Databázovým nástrojem Reaxys bylo nalezeno bezmála 10 000 derivátů 4-hydroxychinolin-2-onu, z nichž u menší poloviny byly zkoumány některé biologické účinky. Chinolin-2,4-dionů je známo *cca* 2000. Zástupci obou skupin byly izolovány z některých hub, bakterií či rostlin a řada látek obsahujících strukturu 4-hydroxychinolonu či chinolin-2,4-dionu vykazuje *in vivo* nebo alespoň *in vitro* zajímavé biologické účinky.

V této sekci rešeršní části disertační práce budou popsány přírodní 4-hydroxychinolin-2-ony a chinolin-2,4-diony a také významné syntetické deriváty.

2.1 4-Hydroxychinolin-2-ony izolované z přírody

Některé jednoduché 4-hydroxychinolin-2-ony se vyskytují v přírodě. Nejjednodušší derivát této skupiny, sloučenina **1**, byla izolována z plísně

Penicillium citrinum[3] a také z asijského keře *Haplophyllum bucharicum*[4]. Z plísně *P. citrinum* byl izolován[5] také *N*-methylderivát **2**, který vykazuje[6] schopnost vychytávání volných radikálů a v biologických testech vykazoval také jistou cytotoxickou aktivitu[7]. Z routovité rostliny *Micromelum falcatum* byl izolován[8] 3-methoxyderivát **3**, jehož analog s dvěma methoxylovými skupinami, swietenidin **4**, byl izolován[9] z pryskoně zelenodřevé (*Chloroxylon swietenia*), což je indický strom.

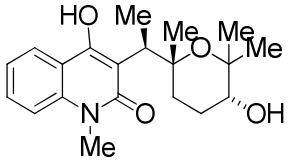


1-7

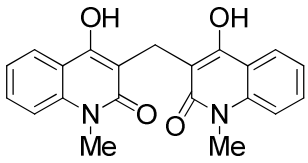
1-7	R^1	R^2	R^3	R^4	R^5
1	H	H	H	H	H
2	Me	H	H	H	H
3	Me	MeO	H	H	H
4	Me	MeO	H	H	MeO
5	H	H	Br	H	H
6	H	H	Br	Br	H
7	H	H	MeO	H	MeO

*Tabulka 1. Substituenty sloučenin **1**-7.*

Za zajímavou skutečnost lze považovat existenci přírodních bromchinolonů **5** a **6**, které byly izolovány[10] z mořského houbovce *Hyrtios erecta*. Sloučenina **5** částečně inhibuje krysí neuronální synthasu oxidu dusného. Ze dřeva stromu *Halfordia scleroxyla* byl izolován[11] dimethoxychinolon **7**. Zajímavý přírodní hydroxychinolon bucharidin byl izolován[12] z keře *Haplophyllum bucharicum* a v experimentech na myších[13] vykazoval estrogenní účinky.

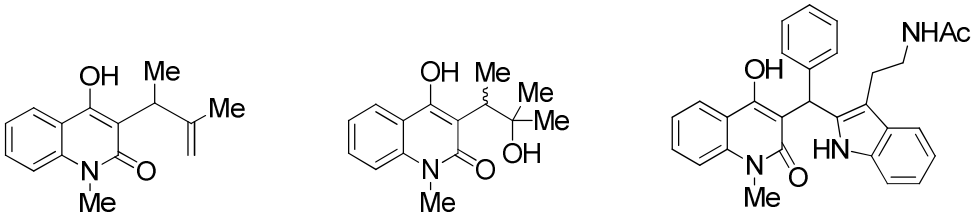


bucharidin



8

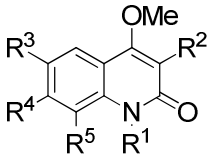
Sloučenina **8** se dvěma chinolonovými jednotkami byla získána[14] ze dřeva žlutodřevu *Zanthoxylum mutans*.



ravenolin **paraensin** **SF2809-V**

Čeleď routovitých zahrnuje řadu rostlin, které obsahují chinolonové deriváty. Z citrusu *Ravenia spectabilis* byl izolován 4-hydroxychinolin-2-on ravenolin, strukturně příbuzný paraensin byl izolován[15] z amarella (*Euxylophora paraensis*). Z kultivačního média bakterií rodu *Dactylosporangium* je možno izolovat[16] indolový derivát SF2809-V.

Řada derivátů 4-hydroxychinolin-2-onu se v přírodě vyskytuje ve formě etherů, tedy jako 4-alkoxychinolin-2-ony.



9-15

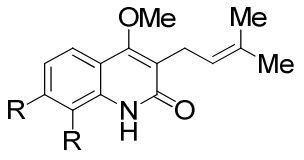
9-15	R^1	R^2	R^3	R^4	R^5
9	H	H	H	H	H
10	Me	H	H	H	H
11	MeO	H	H	H	H
12	H	H	H	H	MeO
13	H	H	MeO	H	MeO
14	H	CHO	H	MeO	MeO
15	H	Et	H	OH	MeO

*Tabulka 2. Substituenty methoxychinolonů **9** – **15**.*

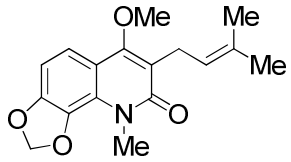
Nejjednodušší zástupce této skupiny, methoxychinolon **9**, byl izolován z řady rostlin čeledi routovitých – ze dřeva exotického ovocného stromu *Clausena lansium*[17], z listů a dřeva tropické rostliny *Peltostigma guatemalense*[18], ze dřeva *Myrtopsis sellingi*[19] a také ze dřeva a listů *Haplophyllum bungei* a *H. bucharicum*[20]. V laboratorních testech *in vitro* vykazovala[18] tato sloučenina mírný antiplasmodický účinek. Ještě hojněji je v přírodě zastoupen methylderivát **10**. Ten byl izolován z hortií *Hortia superba*[21], *H. brasiliana* a *H. oreadica*, z feronie *Feronia limonia*[22], ze žlutodřevů *Zanthoxyllum wuthayenze*[23] a *Z. monophyllum*[24], z routovité rostliny *Raputia praetermissa*[25], z asijského keře *Toddalia asiatica*[26] a podobně jako sloučenina **9** také ze dřeva *Clausena lansium*[13]. Sloučenina **10** byla izolována[27] také ze středozemské routy halebské (*Ruta chalepensis*). U této

sloučeniny byly zjištěny antifungální a antialgiální účinky[28]. Haplotusin (**11**) byl izolován[29] z *Haplophyllum obtusifolium*. Edulitin (**12**) byl získán z hortie *H. superba*[30], z plodů jarvy *Cnidium monnieri*[31] a z kořene tlustoslupky latnaté[32] (*Murraya paniculata*). Ze vzdušných částí těhozevu *Agathosma bisulca* byl izolován[33] trimethoxychinolon halfordamin (**13**). Glykocitridin (**14**) je přírodní aldehyd vyskytující se[34] v melikopě *Melicopa semecarpifolia* a v citrusu *Glycosmis citrifolia*[35]. Haplosin (**15**) byl nalezen[36] v *Haplophyllum perforatum* a obsahuje ve své struktuře ethylové uskupení v poloze 3 chinolinového kruhu, což je pro přírodní chinolony netypické.

Poměrně rozšířený v rostlinné říši je atanin, který byl izolován ze stonků a z listů *Clausena lansium*[37], ze dřeva žluotedřevu *Zanthoxylum wutaiense*[38], z nezralých plodů ampáku *Evodia rutaecarpa*[39], z tropického citrusu *Afraegle paniculata*[40] a z *Ravenia spectabilis*[41]. Jeho dimethoxyderivát preskimmianin byl izolován z boronie *Boronia pinnata*[42], z šedoku (*Citrus grandis*)[43] a z třemdavy bílé (*Dictamnus albus*)[44].

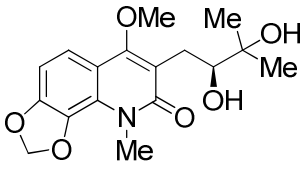


atanin (R = H)
preskimmianin (R = OMe)

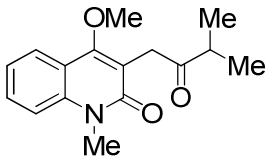


pteleprenin

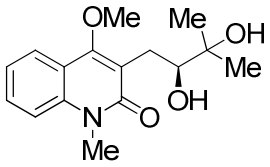
Ze vzdušných částí orixy japonské (*Orixa japonica*) byl izolován[45] chinolon pteleprenin. Z orixy japonské byl izolován také noroxirin[46] a orixiarin[47]. Edulinin byl izolován z listů a plodů routovité rostliny *Teclea nobilis*[48], z listů a plodů *Citrus macroptera*[49], z natě routy vonné (*Ruta graveolens*)[50] a dále z čilského keře *Fagara mayu*[51] a *Pelea barbigera*[52]. Lunacridin byl izolován[53] z *Lunasia amara*.



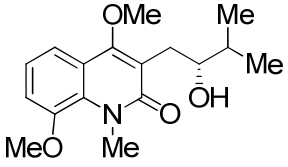
nororixin



orixiarin



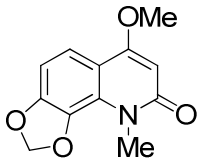
edulinin



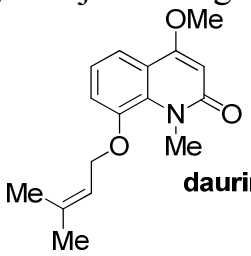
lunacridin

Ze semen zapoty bílé (*Cassimiroa edulis*) byl získán cassimiroin, který ve své struktuře obsahuje dioxolanový motiv. Daurin byl izolován[54] z *Haplophyllum*

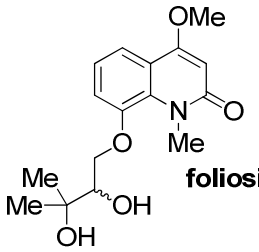
dauricum. Chemicky příbuzný vicinální diol foliosidin byl izolován[55] z *Haplophyllum foliosum* a vykazuje[13] estrogenní aktivitu.



cassimiroin

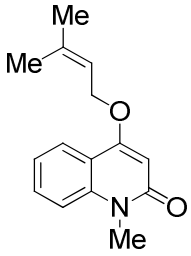


daurin

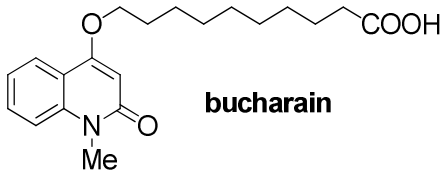


foliosidin

Naprostá většina těchto přírodních etherů obsahuje v poloze 4 chinolinového kruhu methoxylové uskupení. Příkladem sloučenin, u kterých je vázán jiný alkoholový zbytek je ravenin a karboxylová kyselina bucharain. Ravenin byl izolován[41] z *Ravenia spectabilis*, bucharain se vyskytuje[56] v *Haplophyllum bucharicum*.



ravenin

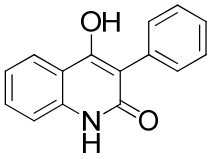


bucharain

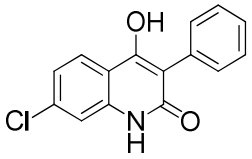
Pestrá škála chinolinových alkaloidů obsahuje ve své struktuře podjednotku 4-hydroxychinolin-2-onu, kdy dochází k vytvoření dalšího heterocyklického kruhu zapojením kyslíku z hydroxylového uskupení v poloze 4 chinolinového kruhu. Zajímavá diskuse takových přírodních sloučenin by však přesahovala rámec tohoto pojednání.

2.2 Biologicky aktivní syntetické 4-hydroxychinolin-2-ony

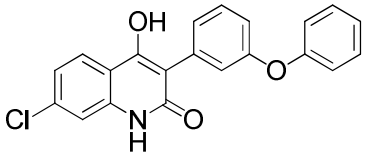
Jednoduchý fenylchinolon označovaný jako NSC 16582 je antagonistou NMDA receptoru na vazebné straně pro glycin[57,58,59]. Jeho chlorderivát MDL 104653 je ještě účinějším antagonistou[59] NMDA receptorů a vykazuje[60] antikonvulzivní účinky. Na základě výzkumu těchto sloučenin byl syntetizován selektivní antagonista NMDA receptorů L-701324.



NSC 16582



MDL 104653

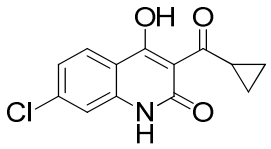


L-701324

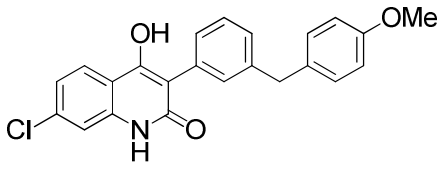
Sloučenina L-701324 působí jako velmi účinný antagonista[61] NMDA receptorů na glycinové straně a $NMDA_{1A/2B}$ receptorů[61]. V experimentech na myších

způsobovala orálně podaná sloučenina především hypolokomoci[62], na myších byly také prokázány její antikonvulzivní účinky[63,58]. Sedativní účinky sloučeniny L-701324 jsou srovnatelné[64] s účinky diazepamu. Sloučenina působí také jako hypotensivum[65]. Využití sloučeniny L-701324 k léčbě různorodých neurologických a psychiatrických obtíží včetně škály neurodegenerativních chorob bylo[66] patentováno.

Schopnost inhibovat receptor NMDA a související sedativní, neuroprotektivní a antikovulzivní účinky byla prokázána i u dalších chinolonů, jako je např. sloučenina L-701252[58] (**16**) či L-703717[67] (**17**).

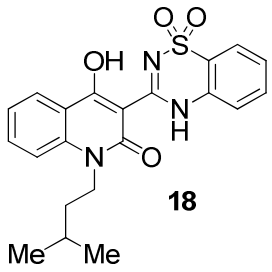


16

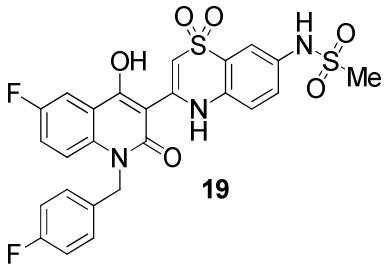


17

Mezi deriváty 4-hxdroxychinolin-2-onu patří i některé sloučeniny s významným antivirotickým účinkem[68]. Sloučeniny **18** a **19** jsou reprezentativními[69,70] vysoce účinnými inhibitory replikace viru infekční žloutenky C. Mechanismem účinku sloučenin typu **18** a **19** je inhibice virové RNA polymerasy[71,72].

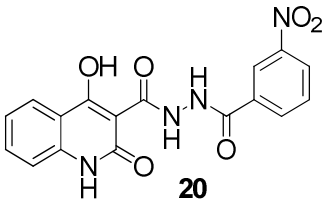


18



19

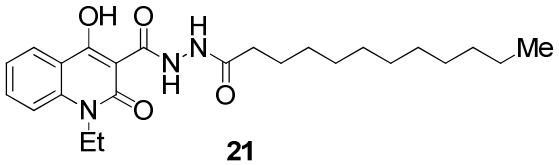
Jiné deriváty 4-hydroxychinolin-2-onu inhibují[73,74,75] HIV-1 integrasu. Byla syntetizována široká série hydrazidů 4-hydroxychinolin-2-on-3-karboxylové kyseliny, které vykazovaly různou schopnost inhibovat HIV-1 integrasu, zdaleka nejúčinnější sloučeninou tohoto typu je hydrazid **20**.



20

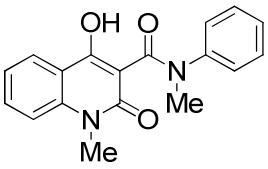
Zajímavé je, že podobné hydrazidy působí[76,77,78] jako alosterické modulátory enzymu glykogen synthasa kinasa GSK-3. Příkladem účinného modulátoru tohoto receptoru je sloučenina VP0.7 (**21**). Výzkum v oblasti

modulátorů GSK-3 může přinést nové poznatky v léčbě některých autoimunitních nemocí[76].

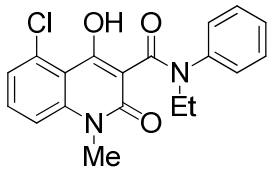


21

Některé 4-hydroxychinolin-2-ony jsou významnými imunomodulátory, výzkum v této oblasti vedl až k vývoji linomidu a laqunimodu. Linomid představuje starší sloučeninu, farmakum vyvíjené společností Active Biotech. Linomid je imunomodulátor[79,80,81] zvyšuje aktivitu NK lymfocytů a cytotoxicitu makrofágů. Je to inhibitor angiogeneze[82] a zvyšuje sekreci TNF-α. Sloučenina byla zkoumána jako lék pro léčbu některých druhů rakoviny a autoimunitních onemocnění. Výzkum linomidu však byl ukončen z důvodu kardiovaskulární toxicity. Linomid vykazuje vasodilatační účinky[83].



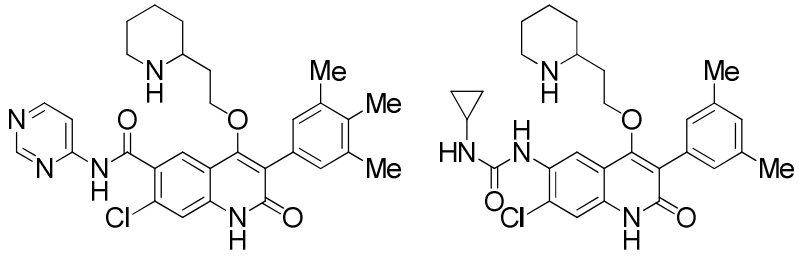
linomid
(roquinimex)



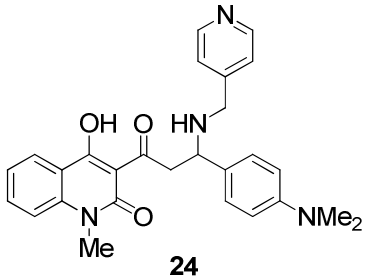
laquinimod

Novějším preparátem je laquinimod, který je jako farmakum vyvíjen společnostmi Active Biotech a Teva. Sloučenina působí jako imunomodulátor[84,85,86,87] a je zkoumána jako farmakum pro léčbu roztroušené sklerózy. V Rusku byl laquinimod povolen jako farmakum pro léčbu roztroušené sklerózy a je k dostání[88] pod komerčním názvem Nerventra.

Některé piperidinem substituované chinolony jsou[89] antagonisté gonadotropin uvolňujícího hormonu (GnRH). Příkladem účinné sloučeniny[90,91] je substance Q89 (**22**), jejíž potenciální využití při léčbě hypogonadismu bylo patentováno[92]. Za stejným účelem byla patentována[93] také podobně účinná[94] sloučenina Q76 (**23**).



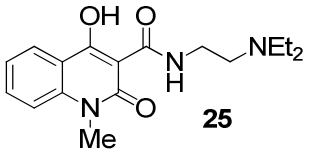
22 **23**



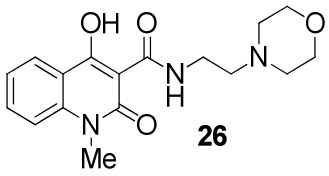
24

Sloučenina LT 232244 (**24**) byla patentována jako inhibitor glyceraldehyd-3-fosfát dehydrogenasy S (GAPDH-S), což je enzym produkovaný výhradně v mužských gametách. Inhibitory GAPDH-S by se dle uvedeného patentu mohly stát mužskými kontraceptivy. Bylo patentováno využití této sloučeniny ke reverzibilnímu snížení motility mužských spermií a k modulaci reprodukčních funkcí[95].

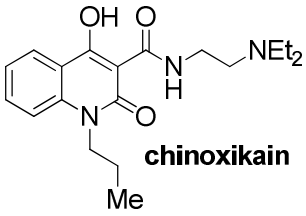
Skupina ukrajinských autorů, dlouhodobě se zabývající biologickými účinky chinolonů připravila[96] sérii amidů 4-hydroxychinolin-2-on-3-karboxylové kyseliny jako látek s potenciálním lokálně anestetickým účinkem. Identifikovaly nejúčinnější sloučeniny **25** a **26**, které vykazovaly srovnatelnou (**25**) či dokonce vyšší (**26**) účinnost jako lidokain přičemž jsou podstatně méně toxické než toto používané lokální anestetikum.



25



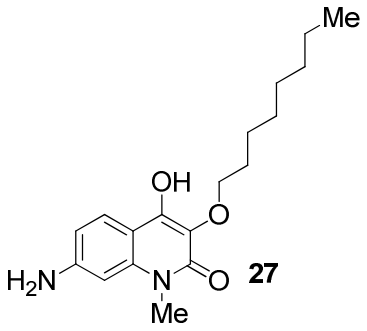
26



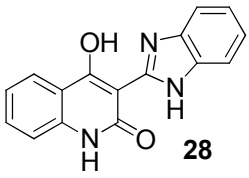
chinoxikain

Výzkum nového typu lokálních anestetik vyvrcholil syntézou chinoxikainu[97], který byl patentován[98] pro využití jako injekční lokální anestetikum.

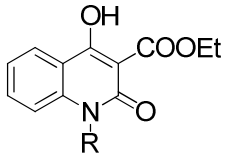
Poměrně nedávno bylo také patentováno[99,100,101] využití některých 3-alkoxy-4-hydroxychinolin-2-onů jako protialergických léčiv. Příkladem účinného antialergika, které bylo testováno na morčatech je sloučenina **27**.



27



28



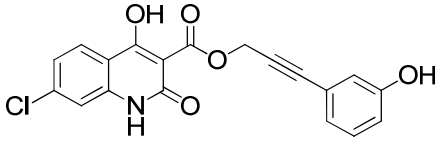
29-34

29 (R = H)
30 (R = Me)
31 (R = Et)
32 (R = Pr)
33 (R = Bu)
34 (R = hexyl)

Celá řada substituovaných 4-hydroxychinolin-2-onů vykazuje rozmanité biologické účinky, na rozdíl od výše uvedených účinných sloučenin však nebyly dostatečně prozkoumány a v budoucnu může jejich výzkum přinést nové biologicky účinné chinolony či na nich založená farmaka. Sloučenina **28** inhibuje některé tyrosin kinasy u myší (VEGFR-2 a PDFGR-β tyrosin kinasy[102]) a serin/threonin kinasy[103]. Právě na principu inhibice tyrosin kinas tato sloučenina inhibuje[104] fosforylaci některých peptidových substrátů a vykazuje[104] *in vitro* antiproliferativní účinky. Sloučenina **28** a některé podobné deriváty vykazují[105] také schopnost inhibovat činnost štítné žlázy.

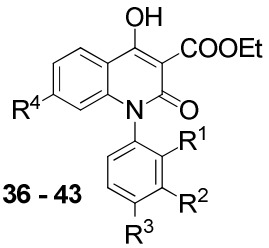
Ethylester **29** vykazuje antagonismus receptorů NMDA na glycinové straně, v experimentech na králicích a krysách bylo zjištěno, že sloučenina vykazuje[106] analgetické a protizánětlivé účinky stejně jako účinky protisrážlivé, diuretické a nootropické. Její jednoduché *N*-alkylderiváty (**30-34**) vykazují[107] pouze účinky analgetické a protizánětlivé. Nejsilnější analgetické účinky byly pozorovány u *N*-butylderivátu **33**.

Byla připravena a prozkoumána také řada esterů typu **29**, které byly substituovány na aromatickém jádře nebo nesly jiný alkoholový zbytek na karboxylové funkci. Také tyto sloučeniny působily antagonisticky na receptor NMDA a některé z nich také vykazovaly antiepileptické vlastnosti na modelu audiogenních křečí u myší. Nebyly však tak účinné jako výše zmíněné 3-arylchinolony. Za zmínku stojí sloučenina L-701273 (**35**), která účinně inhibovala receptor NMDA ale zcela selhala při testování antiepileptických účinků.



35

Výrazné protizánětlivé účinky pak byly pozorovány[107] u *N*-arylderivátů **36** – **43**. Tyto sloučeniny tlumily exsudativní reakci u myšího modelu akutního zánětu vyvolaného karagenanem.

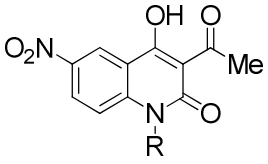


36 - 43

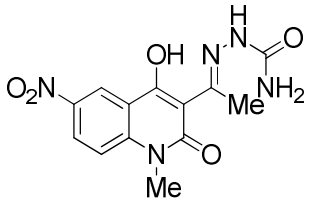
36-43	R^1	R^2	R^3	R^4
36	H	H	H	H
37	H	Me	Me	Cl
38	H	H	Me	H
39	H	H	MeO	H
40	H	MeO	H	H
41	Me	Me	H	H
42	H	H	Me	Cl
43	H	H	MeO	Cl

*Tabulka 3. Substituenty na aromatických jádrech sloučenin **36** – **43**.*

Egyptští autoři připravili sérii jednoduchých 6-nitrochinolonů, které zkoumali[108] jako látky s potenciálním antibakteriálním a antifungálním účinkem. Sloučeniny **44-46** vykazovaly antimikrobiální aktivitu, velmi účinně inhibovaly růst *Bacillus cereus*, sloučeniny **44** a **45** inhibovaly také růst *Escherichia coli*. Sloučeniny **44** – **46** inhibovaly růst plísní *Aspergillus flavus* a *A. niger*.

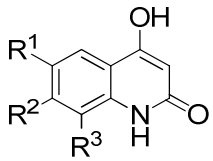


44 (R = Me)
45 (R = Et)



46

Skupina indických autorů[109] připravila sérii fluorovaných chinolonů **47** – **52**, které v biologických testech vykazovaly mírnou fotocytotoxickou aktivitu a schopnost inhibovat růst *Mycobacterium tuberculosis*. Nejvyšší fotocytotoxická aktivita byla pozorována u sloučeniny **51**, Tato sloučenina také nejvíce inhibovala růst *M. tuberculosis*. Zcela inaktivní v provedených testech byl nesubstituovaný 4-hydroxychinolin-2-on.

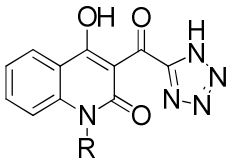


47 - 52

47 – 52	R^1	R^2	R^3
47	F	H	H
48	H	F	H
49	H	H	F
50	CF_3	H	H
51	H	CF_3	H
52	H	H	CF_3

*Tabulka 4. Substituenty chinolonů **47** – **52**.*

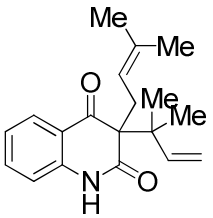
Tetrazolové deriváty **53** a **54** byly patentovány[110,111] jako antidota proti benzoylisoxazolovým herbicidům, která snižují jejich fototoxicitu a chrání zasažené rostliny.



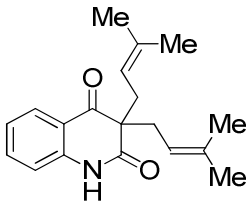
53 (R = Me)
54 (R = Et)

2.3 Chinolin-2,4-diony izolované z přírody

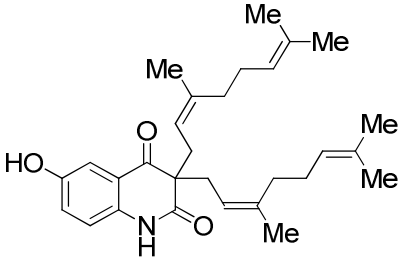
Buchapsin byl izolován ze vzdušných částí *Haplophyllum bucharicum*[112] a *H. tuberculatum*[113,112]. Buchapsin inhibuje[114] replikace viru HIV a vykazuje určitou cytotoxicitu. Podobný derivát **55** byl izolován ze dřeva *Esenbeckia flava*[115] a *E. almawillia*[116].



buchapsin



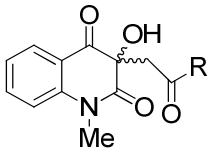
55



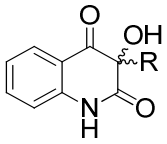
severibuxin

Posledním chinolindionem s obdobnou strukturou je severibuxin, izolovaný[8] z ozdobné citrusové rostliny *Severinia buxifolia*. Tato sloučenina vykazuje cytotoxickou aktivitu.

Z Micromelum falcatum byly izolovány[117] dva 3-hydroxychinolin-2,4-diony **56** a **57**. Podle autorů článku, kde byla izolace těchto sloučenin popsána vykazují obě sloučeniny jistou toxicitu vůči larvám žábronožek, což naznačuje, že další výzkum těchto sloučenin by mohl prokázat určitou biologickou aktivitu. Z pseudomonády *P. aeruginosa* byly izolovány[118] dva 3-hydroxychinolindiony, heptylderivát **58** a nonylderivát **59**.



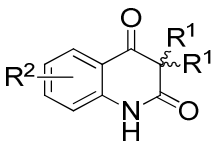
56 (R = Me)
57 (R = MeO)



58 (R = nonyl)
59 (R = heptyl)

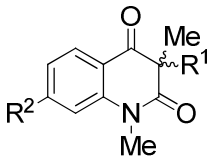
2.4 Biologicky aktivní syntetické chinolin-2,4-diony

Jak již bylo zmíněno v předešlé kapitole, u některých přírodních 3,3-dialkylchinolin-2,4-dionů byla zjištěna schopnost inhibovat replikaci viru HIV a také cytotoxická aktivita. Na základě struktury buchapsinu byla připravena[114] série podobných derivátů **60** (12 sloučenin) u kterých byla zjišťována schopnost chránit lymfoblasty před infekcí virem HIV a zároveň cytotoxicita vůči těmto lymfoblastům[119].



60

R^1=
-CH2CH=CH2,
-CH2CH=C(CH3)2,
-CH2CH2CH=C(CH3)2,
Pr, Bu
R^2= H, 7-Cl, 6-F, 8-F

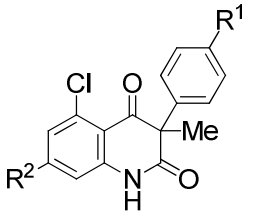


61 (R^1 = Me, R^2 = H)
62 (R^1 = Me, R^2 = Cl)
63 (R^1 = Me, R^2 = MeO)
64 (R^1 = Et, R^2 = H)

Bylo zjištěno, že tyto sloučeniny představují nadějnou skupinu inhibitorů replikace HIV a také zajímavý fakt, že jakákoliv substituce na aromatickém kruhu vyústila v úplnou ztrátu biologické aktivity sloučenin.

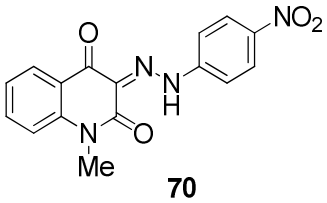
V publikaci z roku 1974 je zmíněna[120] příprava čtyř chinolin-2,4-dionů **61** – **64**, s kterými byly prováděny experimenty na myších. Vyhodnocovala se toxicita, schopnost sloučenin tlumit elektrogenní křeče a prodlužovat dobu spánku. Sloučeniny vykazovaly nízkou toxicitu (LD_{50} v rozmezí 300 – 472 mg/kg) a jen mírné antikonvulzivní účinky. Výraznější antikonvulzivní účinky vykazovala sloučenina **61**. Sloučeniny **61** – **63** prodlužovaly délku spánku u myší, z tohoto hlediska byla nejúčinnější sloučenina **62**.

3-Aryl-3-methylchinolin-2,4-diony vykazují[121,122,123] vysokou afinitu k serotoninovým receptorům $5HT_6$. Je patentováno[124] 120 sloučenin typu **65** – **68**, které jsou vysoce účinnými a selektivními inhibitory 5-HT_6 receptorů a jsou patentovány k léčbě různých psychiatrických chorob. Všechny sloučeniny vykazovaly vysokou schopnost inhibovat zmíněné receptory (IC_{50} = 0,015 – 2,471 μmol), přičemž působily pouze nepatrně na ostatní subtypy receptorů 5-HT_1, 5-HT_2 a 5-HT_7 a na dopaminové receptory D_1 – D_4. Nejúčinnějšími inhibitory serotoninových receptorů jsou látky **65** – **68**, jejichž inhibiční koncentrace IC_{50} se pohybovala v rozmezí 0,015 (**67**) – 0,073 (**68**) μmol.

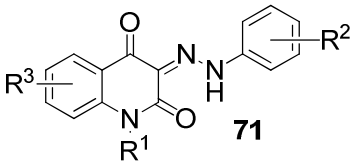


65 (R^1 = OH, R^2 = Cl)
67 (R^1 = NHEt, R^2 = Cl)
68 (R^1 = NEt2, R^2 = Cl)
69 (R^1 = Br, R^2 = MeO)

Biologická aktivita byla zkoumána u pestré palety derivátů chinisatinu, především u příslušných oximů a hydrazonů. U barviva C.I. disperzní žluť 79 (**70**) byla zjištěna schopnost inhibovat růst *Mycobacterium tuberculosis*. Byla syntetizována[125] široká série sloučenin (celkem 79 derivátů) vycházejících ze struktury fenylhydrazonu chinisatinu. Tyto sloučeniny (**71**) účinně inhibují[126,125] růst *M. tuberculosis* a jejich další výzkum může přinést nová antituberkulotika.

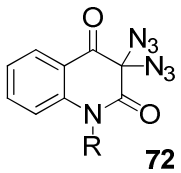


70



71

R^1 = H, Me
R^2 = NO_2, Cl, F, Me, Ph
R^3 = NO_2, Cl, Me



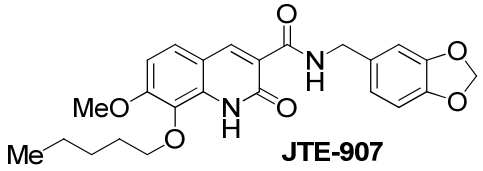
72 (R = H)
73 (R = Bu)

Některé deriváty chinisatinu vykazují schopnost inhibovat NMDA receptor na vazebném místě pro glycin. Byla patentována řada chinisatinových derivátů, které působí jako NMDA antagonisté a jsou patentovány pro léčbu některých obtíží souvisejících s poškozením mozku a neurodegenerativními chorobami.

Kolektiv rakouských autorů připravil sérii substituovaných 3-azidochinolin-2,4-dionů u kterých byla zkoumána[127] schopnost inhibovat

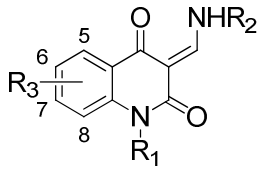
agregaci lidských krevních destiček. Ze série sloučenin byly nejúčinnější 3,3-diazidochinolindiony **72** a **73**.

Recentně bylo objeveno[128], že některé chinolin-2,4-diony jsou vysoce selektivními agonisty kanabinoidních receptorů CB_2. U sloučenin obsahujících ve své struktuře chinolonovou jednotku bylo již dříve prokázáno, že vykazují afinitu ke kanabinoidních receptorů[129] (např. antagonista CB_2 receptorů JTE-907).



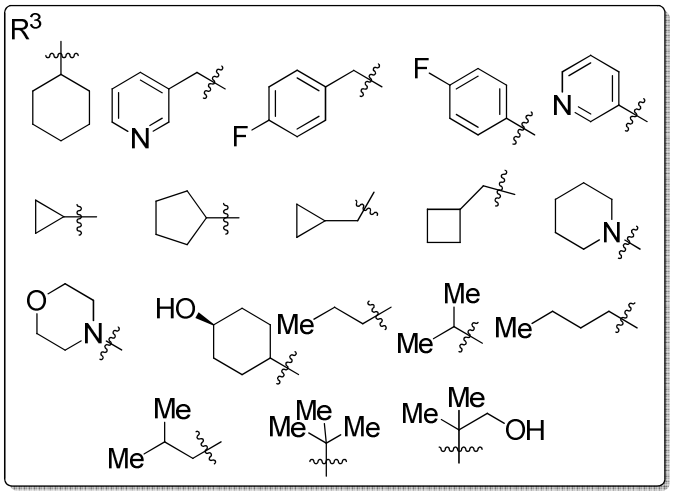
JTE-907

V publikaci[128] z roku 2015 byla popsána syntéza široké série sloučenin **74** u kterých byla posuzována schopnost vázat se na kanabinoidní receptory CB_1 a CB_2. Sloučeniny nevykazovaly afinitu k receptorům CB_1, ale řada jich se účinně vázala na receptory CB_2. Tento receptor je důležitý z medicinálního hlediska, protože pravděpodobně zodpovídá za léčebné účinky kanabinoidů (protizánětlivé, imunomodulační, analgetické) přičemž CB_2-agonismus nesouvisí s psychotropními účinky kanabinoidů. Zajímavou skutečností je, že sloučeniny, které byly na aromatickém kruhu substituovány v poloze 8, vykazovaly schopnost agonistů CB_2 receptorů a sloučeniny, které byly substituovány v polohách 6 nebo 7 na aromatickém kruhu vykazovaly účinky CB_2 antagonistů.



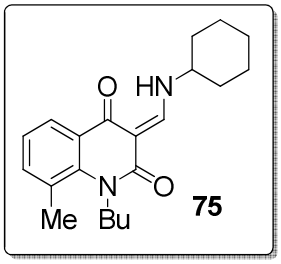
74

R^1 = Et, Pr, Bu, pentyl, hexyl
R^3 = H, Me, MeO, Cl, Br, CF_3, *t*Bu



Nejúčinnější sloučeninou z této série byla[128] látka **75**, se kterou byly také úspěšně utlumeny symptomy experimentální autoimunitní encefalomyelitidy u

myší. Sloučenina úspěšně chránila centrální nervový systém před imunitním poškozením.



3. Syntéza 4-hydroxychinolin-2-onů a derivátů chinolin-2,4-dionu

Vzhledem ke značnému zájmu odborné veřejnosti o titulní sloučeniny, bylo popsáno mnoho postupů jejich přípravy. Většina z nich využívá klasické metody organické syntézy, některé postupy však vzešly z pečlivého studia reaktivity chemických sloučenin a o to jsou zajímavější (reakce využívající deriváty ethynu, str. 24). Řada preparací však vycházela z potřeby získat konkrétní deriváty pro jejich další výzkum.

3.1 Syntéza substituovaných 4-hydroxychinolin-2-onů

Nejstarší a nejpoužívanější metodou syntézy 4-hydroxychinolonů je tepelná kondenzace substituovaných anilinů se substituovanými deriváty kyseliny malonové. Metoda se postupně vyvíjela, nejdříve se používaly velké přebytky substituovaných diethyl-malonátů, později se objevily další postupy využívající např. aktivované bis(aryl)malonáty. Na Ústavu chemie FT UTB se nejlépe osvědčil postup, využívající substituované diethyl-malonáty v mírném nadbytku vůči použitému anilinu. Touto metodou je dostupná pestrá škála substituovaných chinolonů **76**, jak si lze povšimnout ve schématu níže (*Schéma 1*). Reakce probíhá přes ketenový meziprodukt a je známo, že při ni mohou vznikat vedlejší produkty (např. dianilidy malonových kyselin).

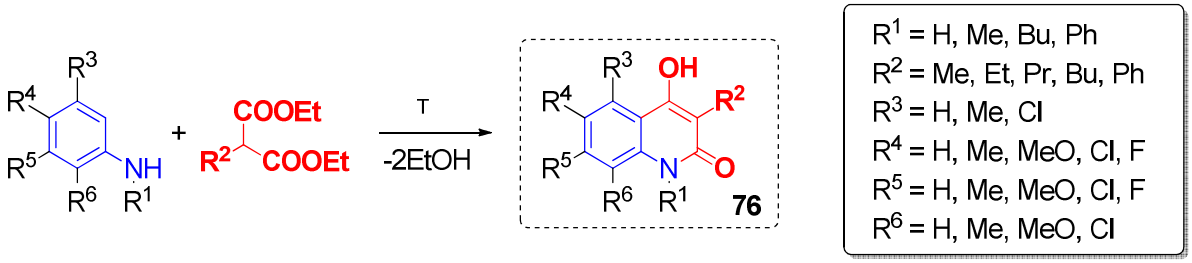


Schéma 1. Příprava 4-hydroxychinolin-2-onů klasickou metodou tepelné kondenzace anilinů s diethyl-malonáty.

Některé chinolony je však možné touto metodou připravit jen s malými výtěžky, proto byly hledány i nové cesty k titulním sloučeninám. Recentně se

v literatuře objevují zmínky o přípravě chinolonů za podmínek mikrovlnného ohřevu.

Příkladem může příprava chinolonu **77**, uvedená ve *Schématu 2*. Tato pohodlná mikrovlnná syntéza s využitím aktivovaných malonátů[130] nalézá využití především při syntéze těch derivátů, které jsou staršími způsoby hůře dostupné.

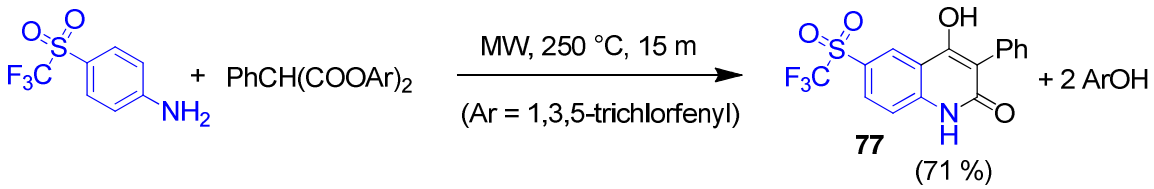


Schéma 2. Mikrovlnná synthesa fenylchinolonu 77.

Klasická metoda tepelné kondenzace anilinů se substituovaným malonáty selhává zejména v případě přípravy 3-nesubstituovaných 4-hydroxychinolin-2-onů. Za podmínek, kdy vzniká chinolonový cyklus dochází zároveň ke vzniku pyranového cyklu za účasti další molekuly malonátu. Níže uvedená reakce naznačuje princip vzniku[131,132,133] pyranochinolindionů **78** (*Schéma 3*).

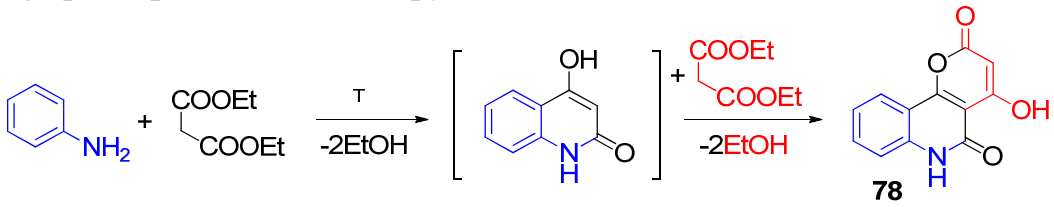


Schéma 3. Princip vzniku pyranochinolindionů při reakcích anilinů s diethyl-malonátem.

3-Nesubstituované chinolony se tedy většinou získávaly zmiňovanou reakcí, kdy byl následně pyranový kruh hydrolyticky odstraněn. Takový postup může být ilustrován poměrně recentní syntézou níže (*Schéma 4*).

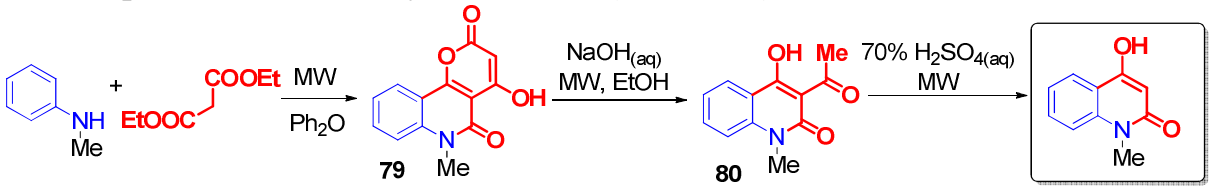


Schéma 4. Příprava 4-hydroxy-1-methylchinolinonu přes pyranochinolindion.

Tento postup může být využit také jako cesta k 3-acetylchinolonům **80**, které vznikají jako meziprodukt při štěpení pyranového kruhu sloučenin **79**.

Mikrovlnná syntéza vycházející ze substituovaných anilinů a volné kyseliny malonové byla na sérii 4-hydroxychinolonů ověřena[109] jako jedna z cest k přípravě 3-nesubstituovaných sloučenin s dobrými výtěžky (*Schéma 5*).

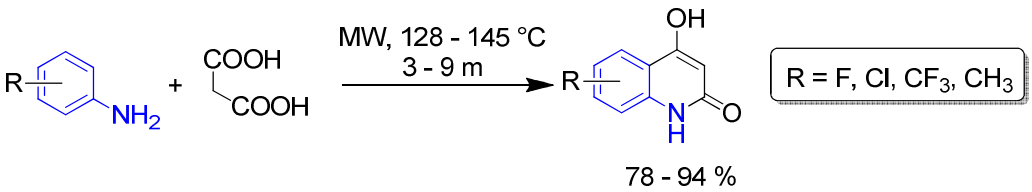


Schéma 5. Příklad syntézy 3-nesubstituovaných chinolonů z volné kyseliny malonové.

Další možností přípravy 3-nesubstituovaných sloučenin je například cyklizace anilidu kyseliny malonové **81** působením kyseliny polyfosforečné[134] (*Schéma 6*). Skutečnost, že dianilidy kyseliny malonové mohou za vysokých teplot poskytovat keten, který následně cyklizuje za vzniku 4-hydroxychinolonu, je dobře známá.

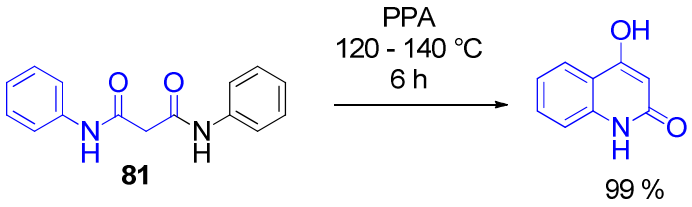


Schéma 6. Transformace dianilidu kyseliny malonové na příslušný chinolonový derivát.

Poměrně nedávno byla publikována[135] také elegantní dvoukroková syntéza 3-nesubstituovaného 4-hydroxychinolinu vycházející z anilinu a reaktivního substituovaného dioxandionu (Meldrumova kyselina). Intermediární malonanilid **82** byl následně dehydratován působením Eatonova činidla (*Schéma 7*).

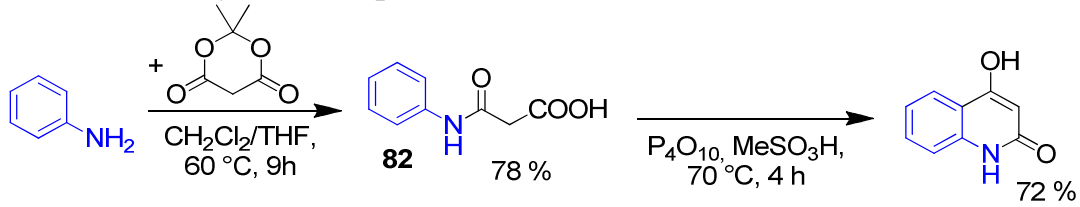


Schéma 7. Příklad aplikace Meldrumovy kyseliny při dvoukrokové syntéze 4-hydroxychinolin-2-onu.

V některých případech může být dokonce přínosné zvolit k syntéze 3-substituovaných chinolonů postup, vycházející z nesubstituovaných sloučenin. Taková metoda byla recentně popsána[114] a vychází z chinolonů připravených mikrovlnou syntézou ze substituovaných anilinů a diethyl-malonátu za přítomnosti katalytického množství DMF. Takto získané výchozí sloučeniny mohou být snadno alkylovány použitím příslušných alkyljodidů a hydroxidu lithného jako base (*Schéma 8*).

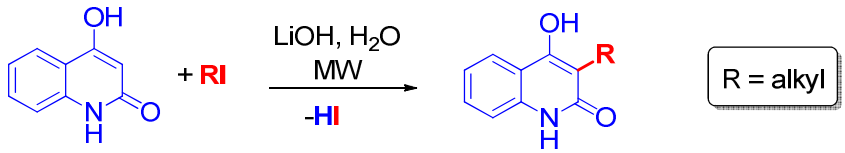


Schéma 8. Příprava chinolonových derivátů alkylací jednoduchého 4-hydroxychinolin-2-onu.

Alternativní metodou přípravu chinolonů je Claisenova kondenzace příslušných *N*-acylanthranilátů[106]. Příklad syntézy 3-fenyl-4-hydroxychinolonů touto metodou ze sloučenin **83** je uveden ve *Schéma 9*. Tato metoda je dle odborné literatury také hojně používána, především u sloučenin, které při klasické tepelné kondenzaci vznikají v malém výtěžku (3-allyl či 3-methyl deriváty).

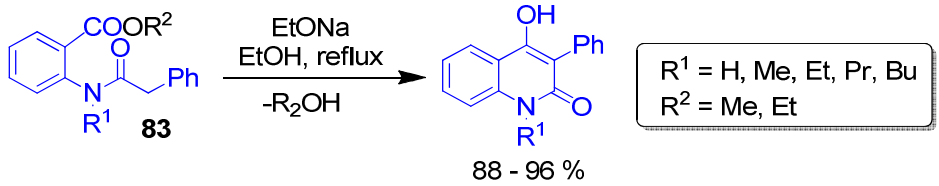


Schéma 9. Příklad využití Claisenovy kondenzace pro přípravu 3-fenylchinolonů.

Příprava některých substituovaných chinolonů byla také realizována metodou využívající cyklizaci Claisenova typu, kdy se na snadno dostupné *N*-acylanthraniláty **84** působí basickým katalyzátorem v methanolu a vznikající chinolon je následně uvolněn trifluoroctovou kyselinou (*Schéma 10*).

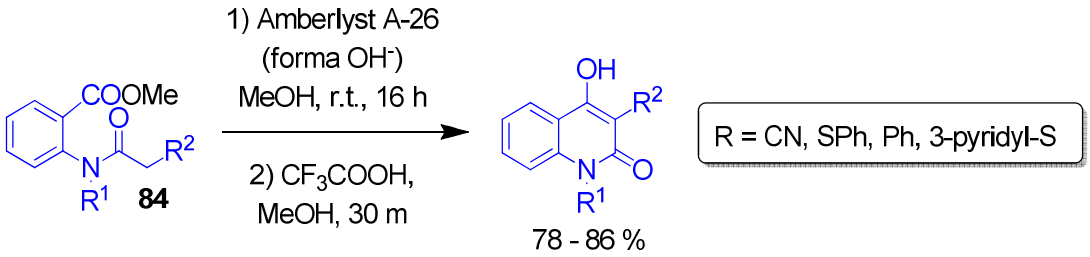


Schéma 10. Modifikovaná Claisenova reakce navržená pro přípravu některých 4-hydroxychinolin-2-onů.

Velmi zajímavá reakce, vedoucí k chinolonům, byla popsána[136] kolektivem japonských autorů (*Schéma 11*). Tato reakce vychází ze substituovaných ethynů **85**, které reagují s oxidem uhličitým za přítomnosti katalytického množství stříbrné soli a silné nenukleofilní base (DBU).

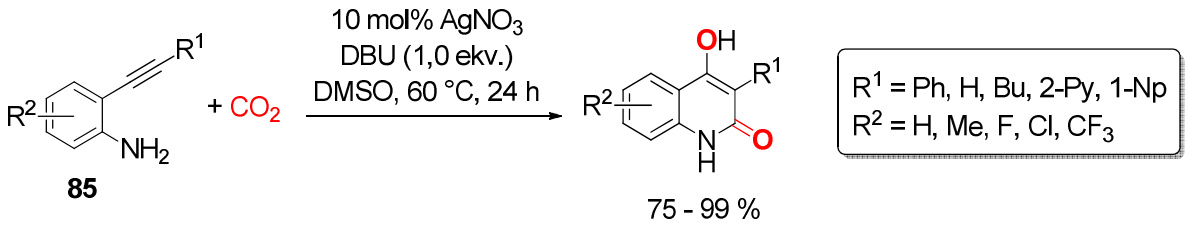


Schéma 11. Neobvyklá reakce substituovaných ethynů s oxidem uhličitým, vedoucí k chinolonovým derivátům.

Tato reakce není zajímavá pouze z hlediska inovativního přístupu k substituovaným 4-hydroxychinolin-2-onům, ale také z pohledu reakčního mechanismu. Reakce, při kterých je do molekuly začleněn oxid uhličitý jsou stále ještě málo prozkoumané. Navržený reakční mechanismus této neobvyklé transformace je uveden ve schématu níže (*Schéma 12*).

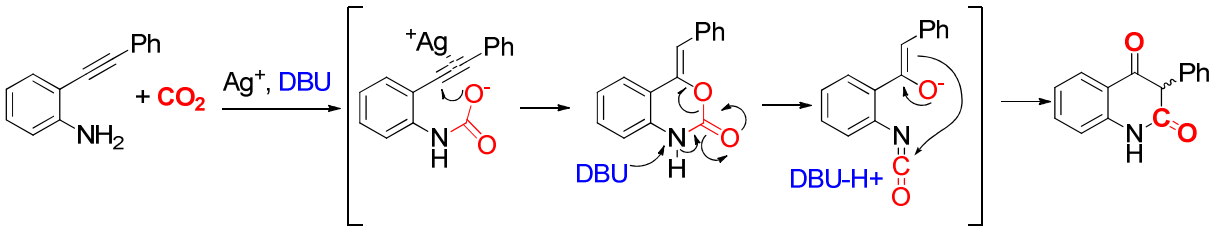


*Schéma 12. Navržený mechanismus vzniku 4-hydroxychinolin-2-onů reakcí vycházející z látek **85**.*

3.2 Syntéza chinolin-2,4-dionů

3-Halogenderiváty chinolin-2,4-dionů lze snadno připravit adiční reakcí halogenu na 4-hydroxychinolin-2-ony. Takových příprav bylo v literatuře popsáno velké množství a byly vypracovány spolehlivé postupy přípravy 3-halogenchinolin-2,4-dionů, řada z nich je používána i na Ústavu chemie FT UTB ve Zlíně.

Chlorace 4-hydroxychinolinonů jsou obvykle[137,138,139] prováděny v dioxanu za tepla a s použitím sulfuryl chloridu jako donoru chloru. Příkladem může příprava[140] chlorderivátu **86** ve schématu níže (*Schéma 13*).

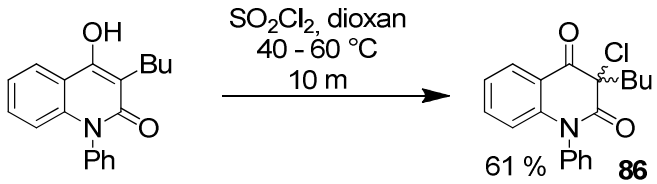


Schéma 13. Příklad přípravy 3-chlorchinolindionů z příslušného chinolonu.

Příprava 3,3-dichlorchinolindionů vychází obvykle z nesubstituovaných 4-hydroxychinolin-2-onů a sulfurylchloridu[141] v horkém dioxanu jako donoru

chloru. Popsány jsou však také chlorace ve vodném prostředí, kde je zdrojem chloru směs chlorečnanu, chloridu a kyseliny sírové[142]. Byl popsán i postup, kdy je nejprve příslušný 4-hydroxychinolon nitrován a získaný 3-nitroderivát **87** konvertován na 3,3-dichlorderivát **88** působením thionylchloridu[143] (*Schéma 14*).

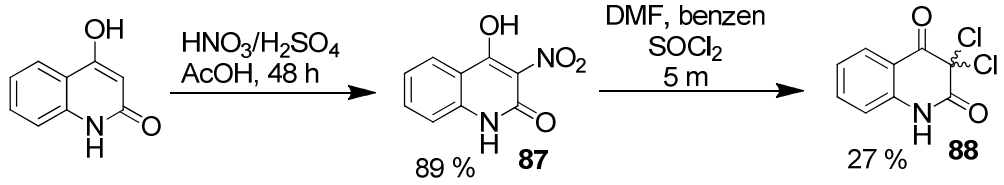


*Schéma 14. Dvoukroková příprava dichlorchinolindionu **88** přes příslušný 3-nitroderivát.*

3,3-Dibromderiváty lze připravit obdobně[144] z příslušných chinolonů působením bromu v horkém dioxanu. Používaným postupem je[140,145,146,147] bromace v kyselině octové, která byla také prakticky ověřena k syntéze celé škály bromderivátů. Příkladem je bromace fenylchinolonu uvedená[137] v publikaci S. Kafky (*Schéma 15*).

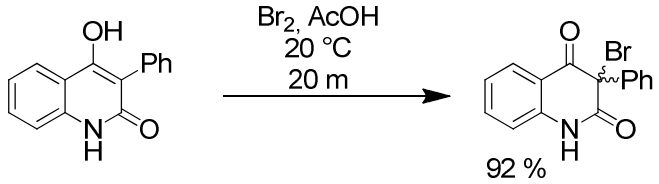


Schéma 15. Bromace 3-fenyl-4-hydroxychinolin-2-onu bromem v kyselině octové.

Působením směsi jodidu draselného a jodu na 4-hydroxychinolony ve vodném roztoku uhličitanu draselného je možno[148] připravit také některé 3-jodchinolindiony, tato tematika však ještě není dostatečně prozkoumána.

3-Halogenderiváty chinolindionů pak otevírají cestu k syntéze pestré palety substituovaných chinolindionů. Substitučními reakcemi je možné je hladce převést na nitrily, aminy[137,149] azidy[140,145] a další sloučeniny.

Oxidací 4-hydroxychinolin-2-onů jsou snadno dostupné 3-hydroxychinolin-2,4-diony. V odborné literatuře je popsáno více metod vedoucích ke zmíněným 3-hydroxychinolindionům. Působením různých oxidačních činidel na chinolonový systém dochází k jeho transformaci na 3-hydroxychinolin-2,4-diony. Z popsaných oxidačních činidel byl použit např. peroxid vodíku[150], kyselina peroxooctová[152] či kyselina 3-chlorperoxobenzoová[151]. Jeden z možných postup[152] zahrnuje také nitraci hydroxychinolonů, při které dochází k současné hydrolýze a vzniku 3-hydroxyderivátů. Reakce využívající kyselinu peroxyoctovou byla ověřena a je úspěšně používána na Ústavu chemie FT UTB. Příkladem tak může být jednoduchá oxidace 3-ethylchinolonu, popsána[153] v recentní publikaci S. Kafky (*Schéma 16*).

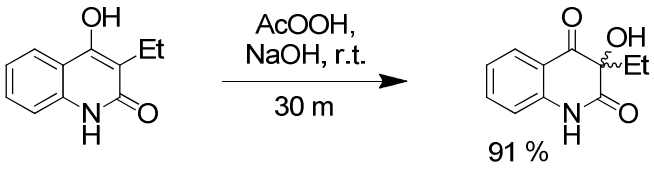


Schéma 16. Příklad elegantní oxidace chinolonového systému kyselinou peroxyoctovou.

Je známo, že deriváty chinisatinu mohou být připraveny hydrolysou 3,3-dibromchinolindionů[154], redukcí a oxidací 3-nitrosoderivátů[155] či z 3-chlor-3-nitrochinolin-2,4-dionů[156]. Jednoduchá syntéza derivátů chinisatinu z chinolin-2,3,4-triolu oxidací jodistanem draselným v kyselině sírové (*Schéma 17*) byla patentována[157].

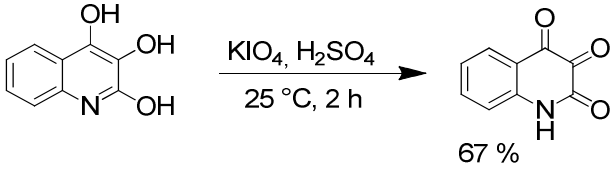


Schéma 17. Příprava chinisatinu oxidací chinolin-2,3,4-triolu.

Alkylací 4-hydroxychinolin-2-onů přebytkem alkylačního činidla jsou dostupné[158] 3,3-dialkylchinolindiony. Příkladem může být metoda, ilustrovaná ve *Schéma 18*, která využívá alkylbromidy jako alkylační činidla a hydroxid lithný ve vodném prostředí. Reakce poskytovala dobré výtěžky očekávaných produktů.

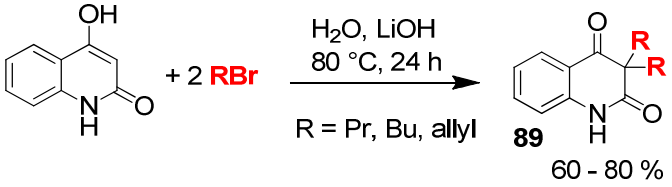


Schéma 18. Příprava 3,3-dialkylchinolindionů přebytkem alkylačního činidla.

Komplikací těchto alkylací však můžou být vedlejší reakce[159], které vedou ke vzniku nežádoucích produktů. Dobrým příkladem tohoto jevu je reakce uvedená ve *Schéma 19*, kdy vedlo použití propargylbromidu v horkém toluenu, vodného hydroxidu sodného a jodidu draselného za podmínek katalýzy fázového přenosu k izolaci 4 produktů.

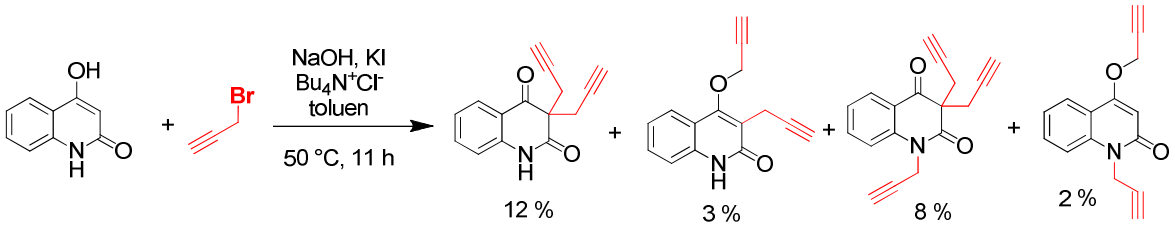


Schéma 19. Alkylace hydroxychinolonu propargylbromidem, poskytující čtyři různé produkty.

U přípravy významných 3-aryl-3-methylchinolonů je sice popsána[160] příprava vycházející z fenylchinolonu, ale detaily nelze vyhledat, nebyly nalezeny recentní zmínky o využití tohoto postupu:

Podle zmínek v literatuře, je možné alkylací 3-substituovaných 4-hydroxychinolonů získat příslušné 3,3-disubstituované chinolindiony, detaily této reakce však nebylo možné vyhledat a recentně nebyly nalezeny žádné zmínky o praktickém využití této reakce, což je překvapivé, vzhledem k recentnímu zájmu o 3-aryl-3-methylchinolindiony (str. 17). Příklad takové přípravy chinolindionu **90** je uveden ve *Schéma 20*.

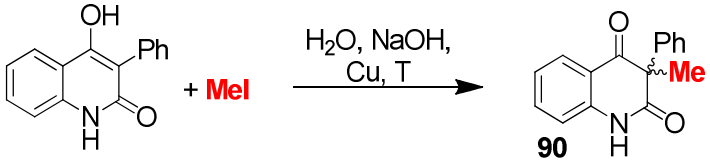


*Schéma 20. V literatuře nalezená zmínka o přípravě chinolindionu **90** methylací.*

Pro přípravu biologicky aktivních 3-aryl-3-methylchinolindionů je dle odborné literatury používána výhradně Claisenova kondenzace substituovaných anthranilátů[161]. Příkladem metody využívající tuto reakci je příprava 3-fenyl-3-methylchinolindionu z příslušného *N*-acylanthranilátu **91** působením bis(trimethylsilyl)amidu lithného jako base ve směsi hexanu a THF (*Schéma 21*).

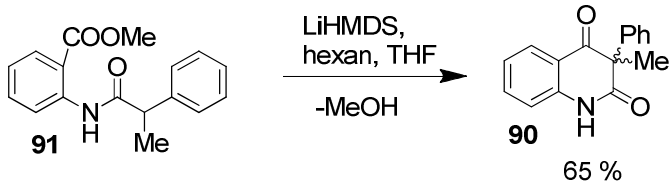


*Schéma 21. Příklad recentně používané Claisenovy kondenzace, která umožňuje přípravu sloučenin typu **90**.*

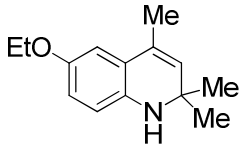
4. Potenciální využití 4 hydroxychinolin-2-onů a sloučenin z nich vycházejících k úpravě vlastností nebo k ochraně materiálů

Jak bylo probráno v předešlých kapitolách, řada 4-hydroxychinolin-2-onů a substituovaných chinolin-2,4-dionů či chinolin-2,3,4-trionů vykazují zajímavé účinky na živé organismy. Mnoho těchto sloučenin se také přirozeně v živých systémech vyskytuje. Tyto sloučeniny jsou zajímavé i z hlediska chemické struktury, reaktivity a případných chemických a fyzikálních vlastností. Idea jejich využití pro úpravu vlastností přírodních i syntetických materiálů je tedy poměrně logická. V následující kapitole budou stručně nastíněny možnosti využití těchto chemických individuí pro zmíněné účely.

4.1 Potenciální využití jako antioxidanty a antidegradanty

Některé jednoduché přírodní chinolony, jako je např. 4-hydroxy-1-methylchinolon (**2**, str. 6) vykazuje schopnost vychytávat[6] volné radikály. Podobný 4-methoxy-1-methylchinolon (**10**, str. 7) vykazuje[8] navíc antifungální a antialgiální účinky (str. 8). Je známo[96,107,105,147], že také řada jednoduchých syntetických 4-hydroxychinolin-2-onů vykazuje antioxidační vlastnosti a schopnost vychytávat volné radikály. Tyto sloučeniny by tedy bylo možno potenciálně využít jako antidegradanty, které chrání materiál, do kterého jsou přidány proti oxidačnímu poškození.

Je vhodné zmínit, že za chemicky podobnou sloučeninu lze považovat i etoxychin[162], který je průmyslově využíván jako antioxidant a stabilizátor tuků pro potraviny (označován jako E324). Toto potravinové aditivum je povoleno v USA, v Evropské unii je jeho využití pro potraviny zakázáno.



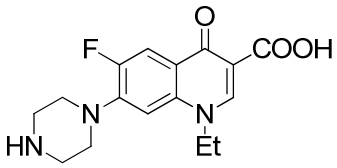
Etoxychin

4.2 Potenciální využití jako biocidních aditiv

Chinolony vykazují antibakteriální a antifungální účinky. U 6-nitrochinolonů (**44**-**46**, str. 14) byly prokázány výrazné antibakteriální a antifungální účinky, sloučeniny účinně inhibovaly[108] i růst plísní *Aspergillus niger* a *A. flavus*, které často napadají různé materiály. Jednoduché fluorované 4-hydroxychinolony (**47** – **52**, str. 14) inhibují[109] růst *Mycobacterium tuberculosis*, stejně jako chinisatinové barvivo C. I. disperzní žluť 79 a řada podobných derivátů chinolin-2,3,4-trionu (str. 17). Některé podobné sloučeniny vykazují[8] i algicidní účinky. Je

tedy reálné, že některé podobné sloučeniny by bylo možné využít k ochraně různorodých materiálů před škodlivými organismy. Takové sloučeniny by bylo možné aplikovat buď ve formě vhodného postřiku či impregnace nebo přímo jako přísady, která by byla součástí směsi pro přípravu materiálu. Zajímavou otázkou je, zda by bylo možné připravit polymerní materiály, které by byly přímo modifikovány takovými sloučeninami, případně kopolymery, kde by byla vhodná chinolonová sloučenina jedním z monomerů.

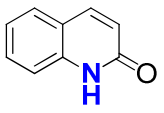
Podobné antibakteriálně funkcionalizované polymery byly již dříve připraveny na bázi polymethakrylátu či polyurethanu[163], byly však modifikovány známými antibiotickými chinolin-4-ony. Byl také připraven[164] polymer na bázi norfloxacinu, do jehož molekuly byl zaveden akrylový zbytek a následnou polymerací byl získán materiál vykazující mimořádnou antibakteriální účinnost. Tento polymer byl následně úspěšně přidáván do směsí s polyethylenem, polypropylenem či polykaprolaktonem[164].



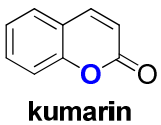
norfloxacin

4.3 Využití chinolonových derivátů jako fluorescenčních sloučenin

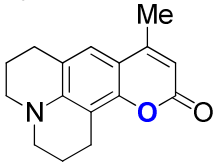
Je na místě připomenout, že kyslíkaté analogy chinolin-2-onů – substituované kumariny představují významné fluorescenční sloučeniny, široce využívané v průmyslu[166]. Příkladem může být kumarin 102, významné laserové barvivo.



chinolin-2(1*H*)-on

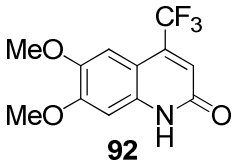


kumarin

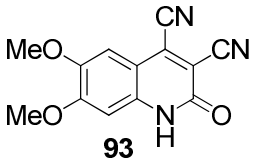


kumarin 102

Některé deriváty chinolin-2-onu, dostupné ze 4-hydroxychinolin-2-onů, vykazují velmi nadějné fluorescenční vlastnosti; takovými sloučeninami jsou[165,166] také 4-trifluormethyl-, 4-kyano- a 3,4-dikyanchinolony. Příkladem mohou být dimethoxychinolony **92** a **93**.



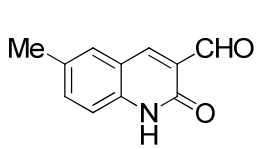
92



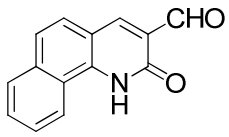
93

Řada chinolonů substituovaných pyrazolovým, isoxazolovým či pyridinovým uskupením byla zkoumána[167] jako potenciální luminofory. Je známa celá řada chinolinových derivátů, které vykazují fluorescenci a mohou nalézt uplatnění např. jako fluorescenční sondy pro detekci bakterií[168], nádorových buněk[169] či cysteinu uvnitř živých buněk[170].

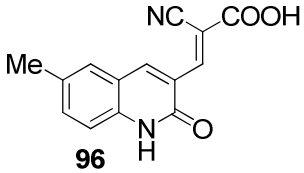
Recentně byla popsána[171] nová fluorescenční barviva[172] na bázi chinolin-2-onů. Takovými fluorescenčními barvivy jsou například aldehydy **94** a **95** a kyselina **96**, získaná chemickými přeměnami[172] aldehydu **94**.



94



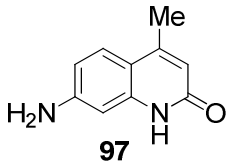
95



96

Jiné deriváty chinolin-2-onu mohou nalézt uplatnění jako fluorescenční sondy pro detekci kovových iontů, některé chinolinové a chinolonové deriváty byly také navrženy k šetrnému fluorescenčnímu značení pestré škály biomolekul[173]. Takové sloučeniny by mohly nalézt uplatnění jako luminofory, optické zjasňovače či absorbery UV-záření pro úpravu vlastností polymerních či jiných materiálů.

Některé polymerní materiály, které byly modifikovány tak, že ve své struktuře obsahují chinolin-2-onové jednotky jsou již známy[174]. Materiál založený na modifikovaném PVP vykazoval[175] intenzivní fluorescenci v přítomnosti terbitých iontů. Později byl připraven[176] obdobný materiál na bázi modifikovaného polystyrenu.
Za zmínku stojí, že tento výzkum byl realizován odborníky z AVČR. K modifikaci polymerů byla použita sloučenina **97**.

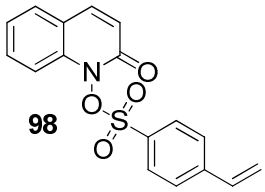


97

4.4 Další možná využití chinolonových derivátů pro úpravu materiálů

Velmi zajímavé vlastnosti byly pozorovány u některých 1-hydroxychinolin-2-onů. U těchto sloučenin dochází působením světla k rozštěpení labilní vazby N–O. Byly připraveny kopolymery chinolonu **98** a methyl-methakrylátu či akrylátu. Takto byly získány nové fotoresponzivní

materiály u kterých byla prokázáno, že lze cíleně měnit smáčivost jejich povrchů pomocí světla[177].



4.5 Využití derivátů kyseliny 2-aminobenzoové a benzoxazin-4-onů

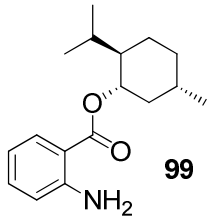
Oxidačním štěpením 3-hydroxychinolin-2,4-dionů je možno[153] připravit širokou paletu derivátů kyseliny 2-aminobenzoové, které by rovněž mohly nalézt uplatnění pro modifikaci některých materiálů.

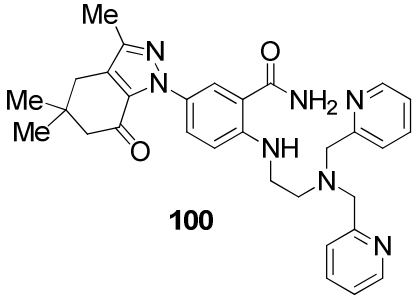
Řada derivátů kyseliny anthranilové vykazuje[178] zajímavé fluorescenční vlastnosti a nachází uplatnění ve fluorescenční spektroskopii[179]. Označování některých biologických substrátů jednotkami 2-aminobenzamidu je běžnou součástí některých chromatografických metod[180,181,182].

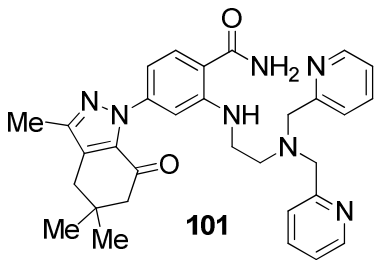
Nedávno bylo zjištěno, že některé deriváty 2-aminobenzamidu jsou zajímavými dipolovými elektrety[183], které mohou otevřít cestu k vývoji materiálů se zajímavými vlastnostmi a mohou nalézt uplatnění ve fotovoltaice či fotokatalýze.

Některé deriváty kyseliny anthranilové lze využít jako UV-absorbery, příkladem může být menthyl-anthranilát[184] (**99**).

Na bázi substituovaných 2-aminobenzamidů bylo v nedávné době připraveno [185,186] několik zajímavých fluorescenčních sond selektivně citlivých vůči některým kovovým iontům. Sloučenina **100** označovaná jako ZnABA je selektivní fluorescenční sondou pro zinečnaté ionty, CdABA (**101**) je selektivní pro ionty kademnaté.



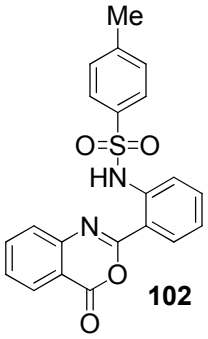




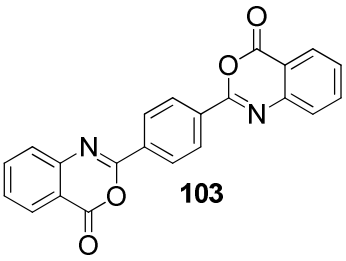
Vaječná papírová blána, na které byla imobilizována kyselina anthranilová se osvědčila jako fluorescenční biosenzor[187] pro detekci tetracyklinu. Kopolymery

polyanthranilové kyseliny byly recentně zkoumány[188] v rámci výzkumu nových systémů distribuce léčiv. Přídavek komplexů kyseliny anthranilové do polyethylenu byl také zkoumán[189].

Deriváty kyseliny anthranilové, včetně těch dostupných oxidací chinolindionů, lze využít k syntéze substituovaných benzoxazinonů, u kterých byly v literatuře popsány zajímavé fluorescenční vlastnosti. Nedávno bylo připraveno[190] několik elektroluminiscenčních zařízení OLED založených na benzoxazinonu **102**. Řada benzoxazinonů již nalezla uplatnění jako UV absorbery pro stabilizaci polymerů. Příkladem může být sloučenina **103**, komerčně dostupná[191] jako OMNISTAB UV 3638.



102



103

4.6 Možná omezení

Je nutno připomenout, že u některých přírodních 4-hydroxychinolonů bylo zjištěno, že vykazují estrogenní aktivitu. Takovými sloučeninami jsou např. foliosidin[13] (str. 9) či bucharidin[13] (str. 6). Takové vlastnosti by představovaly komplikaci při praktickém využití těchto sloučenin, jelikož řada aditiv do polymerních materiálů byla z důvodů estrogenní aktivity výrazně omezena (ftaláty, bisfenol A). Některé syntetické 4-alkoxychinolin-2-ony ovlivňují metabolismus gonadotropin uvolňujícího hormonu[89-91,94] a 4-hydroxychinolon **24** (str. 11) je patentován[95] ke snížení motility mužských spermií. Některé chinolony, obsahující v poloze 3 chinolonového kruhu imidazolové uskupení inhibují[105] činnost štítné žlázy (str. 12). Také tyto vlastnosti by mohly představovat problém při aplikaci některých 4-hydroxychinolonů pro úpravu materiálů.

Historické zkušenosti s podobnými průmyslovými aditivy, které zasahují do systému hormonální regulace či reprodukčních funkcí by měly nabádat k důkladnému prozkoumání 4-hydroxychinolonů a jejich derivátů před případnou praktickou aplikací. Na druhou stranu by mohly chinolony představovat poměrně bezpečné látky z hlediska toxicity. Dosud testované chinolin-2,4-diony[120] (str. 16) a 4-hydroxychinolony[79-83,96,99-101] (str. 17) vykazují nízkou toxicitu.

5. CÍLE DISERTAČNÍ PRÁCE

Cíle disertační práce byly logickým pokračováním mnohaletého výzkumu reaktivity 4-hydroxychinolin-2-onů, který dlouhodobě probíhá na Ústavu chemie a také částečně navazovaly na tematiku, kterou se autor disertační práce zabýval během bakalářského a magisterského studia.

Hlavním cílem bylo připravit substituované 4-hydroxychinolony a z nich příslušné chinolin-2,4-diony, které by byly podrobený dalším reakcím za účelem výzkumu reaktivity chinolindionového systému. Výzkum reaktivity byl zaměřen především na 3-hydroxychinolin-2,4-diony a 3-aminochinolin-2,4-diony. Hlavním cílem disertační práce pak bylo připravit sérii 4-hydroxychinolin-2-onů, převést je na 3-hydroxychinolin-2,4-diony a z těch následně oxidačním štěpením získat příslušné *N*-*α*-ketoacylanthranilové kyseliny. Z těch je možné připravit Fischerovou indolovou reakcí příslušné indolové deriváty.

Kromě výzkumu reaktivity studovaných sloučenin bylo cílem připravit také konkrétní deriváty, které by mohly být dále studovány z hlediska možných aplikací (biologická aktivita, využití při úpravě vlastností materiálů).

Během řešení problematiky také vyplynuly některé zajímavé skutečnosti, které byly dále zkoumány.

6. PŘEHLED PUBLIKOVANÝCH VÝSLEDKŮ A ŘEŠENÍ OKRUHŮ ZADÁNÍ

Okruh zadání: Syntéza a oxidační štěpení 3-hydroxychinolin-2,4-dionů.

Kafka, S.; Proisl, K.; Kašpárková, V.; Urankar, D.; Kimmel, R.; Košmrlj, J.: Oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones into *N*-(α-ketoacyl)anthranilic acids. *Tetrahedron*, **2013**, *69*, 10826–10835.

DOI: 10.1016/j.tet.2013.10.092

Komentář k PUBLIKACI I

Prvním důležitým tématem mé práce bylo studium oxidačního štěpení 3-hydroxychinolindionů kyselinou jodistou (popř. jodistanem sodným) a související příprava *N*-(*α*-ketoacyl)anthranilových kyselin. Tato reakce byla

studována již během autorovy diplomové práce a následně byla její aplikace rozšířena na celou řadu substituovaných sloučenin. Reakční podmínky byly také optimalizovány pro preparativní účely.

Nejprve byly připraveny jednotlivé 4-hydroxychinolony tepelnou kondenzací substituovaných malonátů se substituovanými aniliny. Tyto látky byly následně působením kyseliny peroxyoctové převedeny na 3-hydroxychinolindiony. Tyto reakce probíhaly snadno a ve většině případů bylo dosaženo vysokých výtěžků. Samotné štěpení 3-hydroxychinolindionů bylo realizováno v prostředí vodného ethanolu působením kyseliny pentahydrogenjodisté nebo jodistanu sodného. Obě činidla se ukázala jako účinná, pro jednotlivé substituce však byly pozorovány individuální rozdíly. Publikace popisuje přípravu 16 substituovaných *N*-(*α*-ketoacyl)anthranilových kyselin, které se tímto způsobem podařilo získat ve vysokých výtěžcích.

Při optimalizaci reakčních podmínek se ukázalo, že v některých případech dochází k rozkladu výchozích sloučenin za vzniku řady neidentifikovaných, často barevných produktů. K tomuto jevu docházelo především pokud byly reakce vedeny při vyšší teplotě nebo byla-li reakční doba dlouhá (několik dní). Významný vliv na případný vznik vedlejších produktů však mají pravděpodobně také nečistoty přítomné ve výchozí sloučenině nebo v použitém rozpouštědle.

Během práce na publikaci se autor potýkal s problémy při pokusu o oxidaci 3-benzyl-3-hydroxychinolin-2,4-dionu, kdy docházelo k rozkladu výchozí látky za vzniku složité směsi, benzaldehydu a barevných produktů. Jedním z prokázaných produktů reakce byl kromě benzaldehydu také isatin. Příčinou byla pravděpodobně vyšší citlivost benzylového substituentu vůči silně oxidujícímu prostředí. Tento problém byl vyřešen a úspěšná syntéza byla zveřejněna až v publikaci II. Vedením reakce v dvoufázovém prostředí (voda – ethyl-acetát) za přítomnosti katalyzátoru fázového přenosu byla úspěšně provedena oxidace i u benzylového derivátu. Dalším omezením byla také vyšší cena použitých jodistanových činidel, postupem času se však ukázalo, že k provedení reakce ve vysokém výtěžku stačí i jen malé přebytky oxidačního činidla.

Jako spoluautor jsem se významně podílel na jednotlivých syntézách včetně příprav jednotlivých výchozích sloučenin. Po domluvě se školitelem jsem se snažil optimalizovat reakční podmínky tak, aby bylo dosaženo vysokých výtěžků. Také jsem se podílel na sestavování rukopisu, především při sepisování experimentálních dat.

Okruh zadání: Fischerova indolová reakce u *N*-(*α*-ketoacyl)anthranilových kyselin.

Proisl, K.; Kafka, S.; Urankar, D.; Gazvoda, M.; Kimmel, R.; Košmrlj, J.: Fischer indolisation of *N*-(*α*-ketoacyl)anthranilic acids into 2-(indol-2-carboxamido)benzoic acids and 2-indolyl-3,1-benzoxazin-4-ones and their NMR study. *Organic & Biomolecular Chemistry*, **2014**, *12*, 9650–9664.

DOI: 10.1039/C4OB01714E

Komentář k PUBLIKACI II

Další odborná publikace shrnuje možnosti konverze *N*-(*α*-ketoacyl)anthranilových kyselin na příslušné indolové deriváty s využitím Fischerovy indolové reakce. Příprava těchto sloučenin byla hlavní snahou mé disertační práce. Možnost přípravy těchto sloučenin jsem nastínil již v mé diplomové práci. Protože tyto sloučeniny jsou zajímavé jak z hlediska možné biologické aktivity, tak i z hlediska možných aplikací při úpravě vlastností materiálu, byly hledány cesty, jak je elegantně z výchozích anthranilových kyselin připravit.

Byla připravena široká série substituovaných anthranilových kyselin, které byly následně podrobeny reakcím s fenylhydrazinem za podmínek Fischerovy indolové reakce. Původní myšlenka přípravy příslušných fenylhydrazonů s následným tepelným přesmykem se neosvědčila – při těchto pokusech docházelo k rozkladu sloučenin což mělo dramatický vliv na výtěžky produktů. Nejlépe se osvědčily reakce ve vroucí kyselině octové – za těchto podmínek sice vznikaly dva (v některých případech i tři) typy reakčních produktů (příslušné anthranilové kyseliny nesoucí indolové uskupení a také produkty jejich dehydratace – substituované benzoxazinony), produkty se však daly snadno oddělit krystalizací. Změnou reakčních podmínek (doba reakce, záměna kyseliny octové za výše vroucí kyselinu propionovou) bylo v některých případech možné ovlivnit poměr jednotlivých produktů.

V publikaci je také částečně diskutována reaktivita vznikajících benzoxazinonů, které se ukázaly jako poměrně reaktivní nukleofily s možným využitím v syntéze dalších sloučenin (např. amidů kyseliny anthranilové nesoucích indolový kruh). U získaných benzoxazinonů byly následně zkoumány také jejich fluorescenční vlastnosti, výsledky tohoto výzkumu však dosud nebyly publikovány.

Jako autor jsem provedl většinu syntéz a také jsem za konzultace se školitelem navrhoval jednotlivé syntetické postupy. Připravil jsem návrh rukopisu, který byl následně dokončen mým školitelem (ve spolupráci s ostatními spoluautory).

Okruh zadání: Příprava 1,4-benzodiazepin-2,5-dionů z 3-aminochinolin-2,4-dionů.

Křemen, F.; Gazvoda, M.; Kafka, S.; Proisl, K.; Srholcová, A.; Klásek A.; Urankar, D.; Košmrlj, J.: Synthesis of 1,4-Benzodiazepine-2,5-diones by Base Promoted Ring Expansion of 3−Aminoquinoline-2,4-diones. *Journal of Organic Chemistry*, **2016**, *82*, 715–722.

DOI: 10.1021/acs.joc.6b01497

Komentář k PUBLIKACI III

Další publikovaná práce byla zaměřena na reaktivitu 3-aminochinolindionů, které za vhodných podmínek v bazickém prostředí podléhají přesmyku, jehož produktem jsou substituované benzodiazepin-2,4-diony. Tyto sloučeniny pro mne byly zajímavé, protože obsahují strukturní podjednotku kyseliny anthranilové.

Během studia této reakce byla vyzkoušena celá řada různých podmínek a vhodných činidel. Nejlépe se osvědčilo použití benzyltrimethylamonium hydroxidu, tetramethylguanidinu a ethoxidu sodného v ethanolu.

Hledáním vhodných podmínek se zabývalo také několik studentů během svých diplomových prací, především Ing. Filip Křemen, u jehož práce jsem byl konzultantem a který také provedl řadu syntéz. K největším problémům docházelo při pokusu o přesmyky 1-fenylderivátů, důvod tohoto chování nebyl objasněn. V těchto případech se nejlépe osvědčilo použití tritonu B jako báze.

Zajímavou skutečností také je, že připravené sloučeniny existují ve formě dvou konformerů – pseudo-axiálního a pseudo-ekvatoriálního. Tato skutečnost byla zjištěna a studována NMR experimenty.

Jako spoluautor jsem se podílel především při hledání vhodných podmínek reakce, při syntézách jednotlivých produktů a také při přípravě výchozích látek. Také jsem se teoreticky zabýval výskytem substituovaných benzodiazepindionů v přírodě a jejich možnými aplikacemi.

Okruh zadání: Potenciální aplikace připravovaných sloučenin.

Proisl, K.; Kafka, S.; Košmrlj, J.: Chemistry and Applications of 4-Hydroxyquinolin-2-one and Quinoline-2,4-dione based Compounds. *Current Organic Chemistry*, **2017**, *21*, 1949–1975.

DOI: 10.2174/1385272821666170711155631

Komentář k PUBLIKACI IV

Poslední předložená publikace je rešeršní prací a shrnuje poznatky o 4-hydroxychinolin-2-onech a chinolin-2,4-dionech, které jsem shromáždil během mého doktorského studia. Překvapilo mne, že na toto zajímavé téma v odborné literatuře ještě nevzniklo větší množství přehledných prací.

Tento článek vznikl jako společné dílo spolu s mým školitelem panem docentem Kafkou a panem profesorem Košmrljem. Podkladem pro článek bylo mé pojednání ke státní zkoušce a v něm obsažené poznatky, i když během přípravy článku došlo ještě k doplnění řady informací a dalším důležitým úpravám.

Vzhledem k povaze článku a k tomu, že řada informací je uvedena v literární části považuji další komentování článku za nadbytečné.

7. PŘÍNOS PRO VĚDU A PRAXI

Přínos mé disertační práce spočívá v několika rovinách. Během studia jsem získal řadu poznatků o reaktivitě zkoumaných sloučenin, které budou dále využity při výzkumu chinolonových derivátů na Ústavu chemie FT UTB ve Zlíně a řada z nich byla také již publikována v odborné literatuře. Byly získány také nové poznatky o aplikacích Fischerovy indolové syntézy, o reaktivitě některých benzoxazinonů, substituovaných anthranilových kyselin a benzodiazepindionů. Během mé práce bylo pozorováno několik zajímavých reakcí a přesmyků, které jsou námětem pro další odbornou práci.

Dále byla připravena řada nových sloučenin, které by mohly nalézt uplatnění jako biologicky aktivní látky nebo při ovlivňování vlastností materiálů. V některých případech byly připravené látky již zkoumány nebo testovány na případnou biologickou aktivitu, výsledky však dosud nebyly publikovány.

PŘÍLOHY

Tetrahedron 69 (2013) 10826–10835

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones into *N*-(α-ketoacyl)anthranilic acids

Stanislav Kafka [a,*], Karel Proisl [a], Věra Kašpárková [a], Damijana Urankar [b], Roman Kimmel [a], Janez Košmrlj [b,*]

[a] Department of Chemistry, Faculty of Technology, Tomas Bata University in Zlin, 762 72 Zlin, Czech Republic
[b] Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 8 August 2013
Received in revised form 14 October 2013
Accepted 28 October 2013
Available online 1 November 2013

Dedicated to Professor Slovenko Polanc on his 65th birthday

Keywords:
N-(α-Ketoacyl)anthranilic acid
Quinolinones
Quinolinediones
Paraperiodic acid
Periodate

ABSTRACT

N-(α-Ketoacyl)anthranilic acids were prepared by oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones by using paraperiodic acid (H_5IO_6) or sodium periodate ($NaIO_4$). The optimisation of the reaction conditions is described as well as the utilisation of *N*-(α-ketoacyl)anthranilic acids in the preparation of anthranilic acid hydrochlorides.

1. Introduction

N-(α-Ketoacyl)anthranilic acids, exemplified by *N*-pyruvoylanthranilic acid A in Fig. 1, can serve as valuable precursors for the construction of heterocycles, such as 4*H*-benzo[*d*][1,3]oxazin-4-ones (**B**)[1] and 1*H*-benzo[*e*][1,4]oxazepin-2,5-diones (**C** and **D**).[2] In coordination chemistry, *N*-(α-ketoacyl)anthranilic acid derivatives can serve as multidentate ligands for transition metal ions.[3] *N*-Pyruvoylanthranilic acid (**A**) has been proposed to be an intermediate in the biosynthesis of anthranilic acid.[4]

Despite potential biological and synthetic relevance the synthesis of *N*-(α-ketoacyl)anthranilic acids has remained largely unexplored. Although several methods exist for the preparation of α-ketoamides,[5] to our knowledge, the synthetic procedures to the title compounds are largely limited to amidation of α-ketoacyl chlorides with anthranilic acid.[2,6–9] An exception is the work of Podesva and co-workers[8] who reported in 1968 that oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones with paraperiodic acid (H_5IO_6)[10,11] leads to *N*-(α-ketoacyl)anthranilic acids. Unfortunately, this reaction was only demonstrated on two substrates and was not investigated further. Induced by our research interest in the chemistry of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones[12–24] and due to a need for preparing *N*-(α-ketoacyl)anthranilic acids we were prompted to explore the scope of the title reaction. Herein we report the optimisation of the reaction conditions and comparison between paraperiodic acid and sodium periodate ($NaIO_4$) to finally afford the target compounds in good to excellent yields.

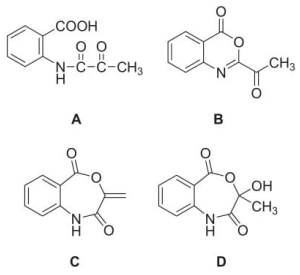


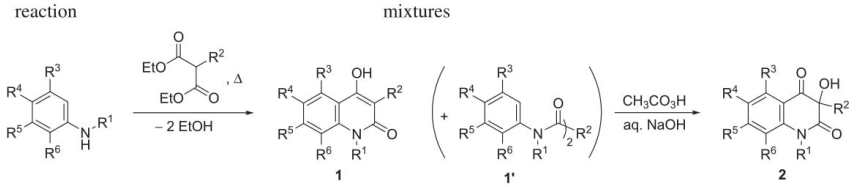
Fig. 1. The structure of *N*-pyruvoylanthranilic acid **A** and its heterocyclic products **B**–**D**.

* Corresponding authors. Fax: +420 57 72 10 172 (S.K.); fax: +386 1 241 9220 (J.K.); e-mail addresses: kafka@ft.utb.cz (S. Kafka), janez.kosmrlj@fkkt.uni-lj.si (J. Košmrlj).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.10.092

2. Results and discussion

The starting compounds for this study were prepared by known thermal condensation of the appropriate anilines with substituted malonates to give 4-hydroxyquinolin-2(1*H*)-ones **1**.[12,25,26] In few cases very small amounts of propanediamide side products **1′** were formed, which were easily removed from the reaction mixtures by filtration. Subsequent oxidation of 4-hydroxyquinolin-2(1*H*)-ones **1** into 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** was accomplished with peroxyacetic acid in aqueous alkali following the literature reported methods.[12,16,27] Employing several anilines and 2-substituted diethyl malonates afforded sixteen 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2**. The key of substituents is given in Scheme 1 and Table 1.

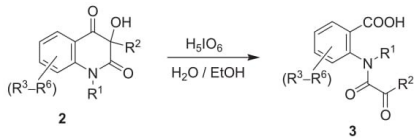


Scheme 1. The preparation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2**. For key of substituents, see Table 1.

Table 1
Key of substituents R^1–R^6

2	R^1	R^2	R^3	R^4	R^5	R^6
a	H	Me	H	H	H	H
b	H	Et	H	H	H	H
c	H	Et	H	OMe	H	H
d	H	Et	H	H	OMe	H
e	H	Et	H	H	H	OMe
f	H	Et	H	Me	H	H
g	H	Et	H	H	H	Me
h	H	Et	Cl	H	H	Me
i	H	Bu	H	H	H	H
j	H	Bu	H	Me	H	Me
k	H	Bu	H	OMe	H	OMe
l	H	Bu	H	H	–(CH)$_4$–	
m	H	Ph	H	H	H	H
n	Me	Et	H	H	H	H
o	Me	Bu	H	H	H	H
p	Me	Ph	H	H	H	H

Having in hand the library of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2a**–**p** we focused our attention on the oxidative ring opening as shown in Scheme 2. Initially, the transformation was attempted with 3-ethyl-3-hydroxyquinoline-2,4(1*H*,3*H*)-dione (**2b**). By employing an equimolar amount of paraperiodic acid (H_5IO_6) in wet ethanol at room temperature, the reaction was conducted for 24 h with 2-[(2-oxobutanoyl)amino]benzoic acid (**3b**) isolated in good yield (Table 2, Entry 1). These reaction conditions as well as the outcome were comparable to those reported by Podesva and co-workers[8] for H_5IO_6 oxidation of 6-chloro-3-hydroxy-3-phenylquinoline-2,4(1*H*,3*H*)-dione and its *N*-methyl derivative. Unfortunately, as it is evident by comparing entries 1, 5, 7, 10, 17, 22, 26 and 27 (Table 2) the generalization of this reaction protocol to other analogues **2** turned out to be rather limited requiring prolonged reaction times of as much of several days and affording products **3** in moderate yields. These unacceptably slow conversions of compounds **2** could be attributed to their sparing solubility in water-rich reaction media. Attempts to accelerate the reactions by heating were counterproductive, resulting in complex mixtures of products and consequently low yield of **3** (compare entries 27 with 28). Also unsatisfactory were the results of oxidations conducted in other solvents, such as acetic acid and *N*,*N*-dimethylformamide (compare entry 17 with 19 and 20, and entry 26 with 31).



Scheme 2. Oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** with paraperiodic acid (H_5IO_6) into *N*-(α-ketoacyl)anthranilic acids **3**.

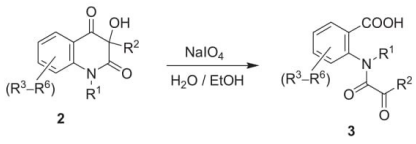
Table 2
Screening for the optimal reaction conditions for the oxidation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** with paraperiodic acid (H_5IO_6) into *N*-(α-ketoacyl)anthranilic acids **3** shown in Scheme 2 [a]

Entry	2	Equiv of H_5IO_6	Solvent (mL/mmol of **2**)	Temperature	Reaction time	**3**, yield[b]
1	**2b**	1.0	30% EtOH (11)	rt	24 h[c]	**3b**, 92,[d] 47
2	**2b**	3.0	60% EtOH (4.8)	rt	9 h	**3b**, 88
3	**2b**	4.0	EtOH (7.7)	rt	24 h	**3b**, 84
4	**2b**	7.9	EtOH (32.5)	rt	24 h	**3b**, 85
5	**2c**	1.3	EtOH (15)	rt	5 days	**3c**, 63
6	**2c**	8.0	EtOH (15)	rt	21 h	**3c**, 73
7	**2d**	1.3	60% EtOH (8.6)	rt	7 days	**3d**, 89,[d] 59
8	**2d**	6.0	EtOH (10)	rt	30 h	**3d**, 81,[e] 70
9	**2d**	8.0	EtOH (10)	rt	7 h	**3d**, 51
10	**2e**	1.3	EtOH (5.9)	rt	3 days	**3e**, 88
11	**2e**	6.0	EtOH (5.0)	rt	24 h	**3e**, 81
12	**2e**	8.0	EtOH (5.5)	rt	22 h	**3e**, 79,[d] 63
13	**2f**	4.0	EtOH (5.4)	rt	27 h	**3f**, 88
14	**2h**	6.5	EtOH (6.5)	rt	24 h	**3h**, 71
15	**2j**	4.0	EtOH (4.9)	rt	11	**3j**, 73
16	**2k**	3.0	EtOH (2.5)	rt	23 h	**3k**, 97,[e] 87
17	**2m**	1.5	EtOH (15)	rt	9 days[c]	**3m**, 46
18	**2m**	8.0	EtOH (40)	rt	5.5 h	**3m**, 95,[e] 84
19	**2m**	1.1	AcOH (20)	rt	5 days	**3m**, 59
20	**2m**	1.1	DMF (3.3)	rt	4 days	**3m**, 38
21	**2n**	6.0	EtOH (15)	rt	2 h	**3n**, 62
22	**2o**	1.5	EtOH (13)	rt	5 days[c]	**3o**, 50[f]
23	**2o**	2.0	EtOH (8.3)	rt	6 h	**3o**, 64
24	**2o**	4.1	EtOH (4.4)	rt	4.5 h	**3o**, 63
25	**2o**	8.0	EtOH (4.8)	rt	4.5 h	**3o**, 65
26	**2p**	1.1	EtOH (11)	rt	3 days	**3p**, 59
27	**2p**	1.3	EtOH (16)	rt	2 days	**3p**, 58
28	**2p**	1.3	EtOH (5.3)	reflux	5.5 h	**3p**, 25[f]
29	**2p**	8.0	EtOH (25)	rt	5 h	**3p**, 92
30	**2p**	8.0	EtOH (12.5)	rt	6 h	**3p**, 75,[e] 63
31	**2p**	2.0	DMF (3.3)	rt	3 days	**3p**, 39[f]

[a] *Reaction conditions*: 1 mmol of **2** in solvent, equiv of H_5IO_6 (aqueous solution, 1.25 mL of water/mmol of H_5IO_6), temperature.
[b] Refers to percent yield of pure product obtained after purification by recrystallization, unless otherwise noted.
[c] The reaction was stopped despite the fact that some starting material remained unconsumed (TLC).
[d] Crude product, isolated by filtration from the reaction mixture, contaminated by small amounts of impurities by TLC.
[e] Crude product, isolated by filtration from the reaction mixture, pure according to TLC and IR analysis.
[f] Isolated by column chromatography.

Finally, we found out that using paraperiodic acid in 3–8 M excess to 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** significantly reduced the reaction times giving products **3** in good to excellent yields (entries 2–4, 6, 8, 9, 11–16, 18, 21, 24, 25, 29, 30). It is also evident from Table 2 that for the optimal performance the amount of paraperiodic acid should not be exceeded as this can cause a serious loss of products **3**, presumably by overoxidation (compare entries 8 with 9 and 11 with 12, for example). Thus, fine tuning of the reaction conditions for optimal results is suggested for each specific substrate **2**.

Periodic acid is known to equilibrate in solution with different species including periodate.[10] Since considerably different reactivity towards organic compounds have been reported for these two species we were prompted to test the oxidation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** also with sodium periodate ($NaIO_4$) (Scheme 3). As demonstrated in Table 3, this oxidizing agent proved to be equally or in some instances slightly less reactive than H_5IO_6 providing the same products, *N*-(α-ketoacyl) anthranilic acids **3**, in up to 91% yield.



Scheme 3. Oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** with sodium periodate ($NaIO_4$) into *N*-(α-ketoacyl)anthranilic acids **3**.

Table 3
Oxidation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** with sodium periodate ($NaIO_4$) into *N*-(α-ketoacyl)anthranilic acids **3** shown in Scheme 3 [a]

Entry	**2**	Equiv of $NaIO_4$	Solvent (mL/mmol of **2**)	Reaction time	**3**, yield[b]
1	**2a**	3.0	EtOH (4.0)	2 days	**3a**, 90
2	**2b**	8.0	EtOH (7.5)	24 h	**3b**, 79,[c] 44
3	**2c**	8.0	EtOH (25)	3 days[d]	**3c**, 67
4	**2d**	8.0	EtOH (27)	3 days[d]	**3d**, 26
5	**2e**	8.0	EtOH (3.8)	10 h	**3e**, 70
6	**2g**	8.0	EtOH (2.5)	20 h	**3g**, 44
7	**2i**	3.1	EtOH (3.3)	22 h	**3i**, 95,[e] 83
8	**2i**	3.7	EtOH (1.0)	8 h	**3i**, 86,[e] 71
9	**2l**	3.1	EtOH (6.9)	28 h	**3l**, 65
10	**2m**	8.0	EtOH (41)	24 h	**3m**, 91[e]
11	**2o**	8.0	EtOH (25)	4 h	**3o**, 60
12	**2p**	8.0	EtOH (25)	21 h	**3p**, 56,[c] 49

[a] *Reaction conditions*: 1 mmol of **2** in solvent, equiv of $NaIO_4$ (aqueous solution, 1.25 mL/mmol of $NaIO_4$), room temperature.
[b] Refers to percent yield of pure product obtained after purification by recrystallization, unless otherwise noted.
[c] Crude product, isolated by filtration from the reaction mixture, contaminated by small amounts of impurities by TLC.
[d] The reaction was stopped after 3 days despite the fact that some starting material remained unconsumed (TLC).
[e] Crude product, isolated by filtration from the reaction mixture, pure according to TLC and IR analysis.

The fact that sodium periodate ($NaIO_4$) and paraperiodic acid equilibrate in solution and comparable results from Tables 2 and 3 suggests that the same species is operating in the oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2**.

All compounds under this investigation were fully characterized by standard analytical and spectroscopic techniques. Some compounds were previously described in the literature with limited or no NMR spectroscopic data, which we decided to provide herein. For compounds **2h**, **j** and **3a**, **h**, **i**, **j**, **l**, **p** proton and carbon peak assignments were made on the basis of 2D NMR spectra: $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC, $^1H-^{13}C$ HMBC and $^1H-^{15}N$ HMBC. Characteristic in ^{13}C NMR spectra of *N*-(α-ketoacyl)anthranilic acids **3a**–**m** (R^1=H, R^2=alkyl) are resonances for the carboxyl, amide (NCO) and α-ketoacyl (NC(O)CO) carbon atoms, resonating at 166–169 ppm, 158–161 ppm and 196–201 ppm, respectively. The presence of a methyl group at the amide nitrogen atom (**3n**, **o**) results in downfield shift of amide (NCO) and α-ketoacyl (NC(O)CO) carbon resonances to 166 ppm and 200–201 ppm, respectively. The phenyl group in compounds **3m**, **p** shows a considerable effect to α-ketoacyl (NC(O)CO) carbon atom, shifting its resonance upfield to 187–192 ppm (Fig. 2). In a few instances (**2j** and **3a**, **h**, **i**, **j**), ^{15}N NMR chemical shifts were extracted from 2D $^1H-^{15}N$ HMBC spectra. In comparison to **2j** (δ_N=129 ppm), the nitrogen atom in **3j** is shielded and resonates at 118 ppm. Single crystal analysis confirmed the structures of compounds **1e**,[38] **1p**[28] and **2e**,[29] as reported previously.

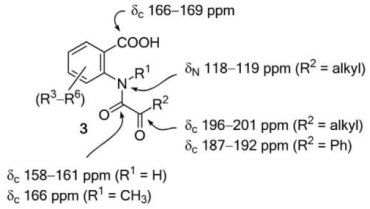
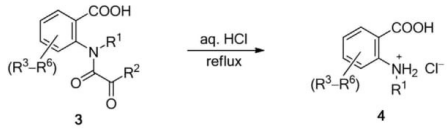


Fig. 2. Selected ^{13}C and ^{15}N chemical shifts for compounds **3**.

An easy access to *N*-(α-ketoacyl)anthranilic acids **3** renders these compounds as attractive precursors for the preparation of various benzo-fused heterocyclic compounds. Additionally, through a simple hydrolytic workup compounds **3** can be converted into the corresponding anthranilic acid derivatives. In this context it is noteworthy that the chemistry reported herein provides a facile entry to highly functionalized anthranilic acids that are inaccessible through other routes. To demonstrate this, selected *N*-(α-ketoacyl)anthranilic acids **3b**–**e**, **n** were hydrolysed with hot aqueous HCl, affording anthranilic acid hydrochlorides **4b**–**e**, **n** in good to excellent yields as shown in Scheme 4 and Table 4.



Scheme 4. Hydrolysis of *N*-(α-ketoacyl)anthranilic acids **3** into anthranilic acid hydrochlorides **4**.

Table 4
Hydrolysis of **3** into anthranilic acid hydrochlorides **4**

Entry	**3**	Reaction time (h)	**4**, yield (%)
1	**3b**	4	**4b**, 85
2	**3c**	6	**4c**, 91
3	**3d**	7	**4d**, 64
4	**3e**	1	**4e**, 68
5	**3n**	2	**4n**, 73

3. Conclusions

We report an easy approach to *N*-(α-ketoacyl)anthranilic acids by paraperiodic acid or sodium periodate mediated ring opening of

3-hydroxyquinoline-2,4(1*H*,3*H*)-diones. The scope of the reaction was investigated and under optimized reaction conditions *N*-(α-ketoacyl)anthranilic acids were obtained in good to excellent isolated yield. These compounds can serve as valuable precursors for the preparation of highly functionalized anthranilic acid derivatives that are inaccessible through other routes.

4. Experimental section

4.1. General

The column chromatography was carried out on Fluka Silica gel 60 (particle size 0.063–0.2 mm. activity acc. Brockmann and Schodder 2–3). Melting points were determined on the microscope hot stage, Kofler, PolyTherm, manufacturer Helmut Hund GmbH, Wetzlar. TLC was carried out on pre-coated TLC sheets ALUGRAM® SIL G/UV$_{254}$ for TLC, MACHEREY-NAGEL. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C), and Bruker Avance III 500 MHz NMR instrument operating at 500 MHz (^{1}H), 126 MHz (^{13}C) and 51 MHz (^{15}N). Proton spectra were referenced to TMS as internal standard. Carbon chemical shifts were determined relative to the ^{13}C signal of DMSO-d_6 (39.5 ppm). ^{15}N chemical shifts were extracted from ^{1}H–^{15}N HMBC spectra determined with respect to external nitromethane and are corrected to external ammonia by addition of 380.5 ppm. Chemical shifts are given on the δ scale (parts per million). Coupling constants (J) are given in Hertz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened). Infrared spectra were recorded on Mattson 3000 FTIR Spectrometer or Thermo Scientific Nicolet iS10 FT-IR Spectrometer using samples in potassium bromide disks and only the strongest/structurally most important peaks are listed; absorption bands intensities are indicated as follows: s (strong), m (medium), w (weak) or b (broad). MS (EI) spectra were recorded on a Shimadzu QP-2010 instrument at 70 eV. HRMS spectra were recorded with Agilent 6224 Accurate Mass TOF LC/MS system. Elemental analyses (C, H, N) were performed with FlashEA1112 Automatic Elemental Analyzer (Thermo Fisher Scientific Inc.).

4.2. General procedure for the preparation of 4-hydroxyquinolin-2(1*H*)-ones (1)

A mixture of the appropriate aniline (100 mmol) and substituted diethyl malonate (102 mmol) was heated in a flask equipped with distillation head on a metal bath at 220–230 °C for 1 h and then at 260–270 °C until the distillation of ethanol stopped (3–6 h). With the exception of preparation of **1f**, **l**, **m**, the hot liquid reaction mixture was carefully poured into stirred toluene (50 mL), cooled down to room temperature and the precipitate was collected by filtration. In the case of **1f**, **l**, **m**, the hot reaction mixture solidified and it was cooled down to room temperature. The above precipitate or solidified material was mixed with aqueous sodium hydroxide solution (0.5 M, 250 mL) and toluene (50 mL). The substance that remained undissolved (in the preparation of **1c** and **1m**) was removed by filtration, purified by recrystallization and identified as propanediamide derivatives (**1c′** and **1m′**, respectively). The layers of the filtrate were separated and the aqueous layer was washed with toluene (2×40 mL). The water layer was treated with decolorizing charcoal, filtered and then acidified with 10% HCl to Congo red. The precipitated hydroxyquinolone **1** was collected by filtration, washed with water, and if necessary, purified by recrystallization.

*4.2.1. 4-Hydroxy-3-methylquinolin-2(1H)-one (**1a**).*[30,31] White powder, yield 13.5 g (77%), mp 274–275 °C (ethanol), mp[30] 268 °C, mp[31] 265–268 °C (butanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02 (s, 3H), 7.15 (ddd, 1H, J=7.7, 7.7, 1.0 Hz), 7.27 (d, 1H, J=7.7 Hz), 7.44 (ddd, 1H, J=7.7, 7.7, 1.0 Hz), 7.89 (dd, 1H, J=8.1, 1.0 Hz), 10.13 (br s, 1H), 11.36 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.4, 106.8, 114.8, 115.4, 121.0, 122.4, 129.6, 137.2, 157.1, 163.8; IR (cm^{-1}): ν 2600–3400 br, 1643 s, 1607 s, 1501 m, 1478 m, 1401 s, 1342 m, 1284 m, 1274 s, 1225 m, 1160 m, 752 m. HRMS (ESI+): m/z calcd for $C_{10}H_{10}NO_2^+$ $[M+H]^+$ 176.0706, found 176.0707.

*4.2.2. 3-Ethyl-4-hydroxyquinolin-2(1H)-one (**1b**).*[32–34] Colourless solid, yield 13.1 g (69%), mp 265–267 °C (ethanol), mp[33] 260–261 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.4 Hz). 2.59 (q, 2H, J=7.4 Hz). 7.14 (ddd, 1H, J=7.6, 7.6, 1.0 Hz). 7.26 (d, 1H, J=7.6 Hz), 7.44 (ddd, 1H, J=7.6, 7.6, 1.0 Hz), 7.88 (dd, 1H, J=7.6, 1.0 Hz), 10.06 (br s, 1H), 11.31 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.2, 16.4, 113.0, 114.8, 115.4, 120.9, 122.5, 129.6, 137.3, 156.6, 163.4; IR (cm^{-1}): ν 2600–3400 br, 1638 s, 1605 s, 1590 s, 1553 m, 1500 m, 1428 m, 1401 m, 1269 m, 1207 s, 1151 m, 754 m. IR:[34] 1641 cm^{-1}. HRMS (ESI+): m/z calcd for $C_{11}H_{12}NO_2^+$ $[M+H]^+$ 190.0863, found 190.0866.

*4.2.3. 3-Ethyl-4-hydroxy-6-methoxyquinolin-2(1H)-one (**1c**).*[32,35] Yellowish solid, yield 14.0 g (64%), mp 220–224 °C (ethanol), mp[35] 172 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (t, 3H, J=7.3 Hz), 2.60 (q, 2H, J=7.3 Hz), 3.80 (s, 3H), 7.10 (dd, 1H, J=8.9, 2.5 Hz), 7.22 (d, 1H, J=8.9 Hz), 7.39 (d, 1H, J=2.5 Hz), 9.98 (br s, 1H), 11.20 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.2, 16.4, 55.4, 104.3, 113.5, 115.8, 116.2, 118.6, 131.8, 153.8, 156.2, 162.9; IR (cm^{-1}): ν 2700–3500b, 1648 s, 1623 s, 1556 m, 1511 s, 1466 m, 1446 m, 1422 m, 1380 m, 1330 m, 1288 m, 1271 m, 1243 m, 1222 s, 1179 m, 1147 m, 1118 m; MS (EI) m/z (%): 220 ($[M+1]^+$, 13), 219 ($[M]^+$, 95), 218 (35), 204 (100), 106 (23), 55 (26): Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39%. Found: C, 65.50; H, 5.93; N, 6.41%.

*4.2.4. 3-Ethyl-4-hydroxy-7-methoxyquinolin-2(1H)-one (**1d**).*[32,36] White solid, yield 14.9 g (68%), mp 262–266 °C (ethanol), mp[36] 260–261 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.4 Hz), 2.56 (q, 2H, J=7.4 Hz), 3.80 (s, 3H), 6.77 (d, 1H, J=8.5 Hz), 6.79 (s, 1H), 7.80 (d, 1H, J=8.5 Hz), 9.92 (br s, 1H), 11.15 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.3, 16.2, 55.2, 97.7, 109.4, 109.5, 110.5, 124.0, 139.0, 156.9, 160.5, 163.8; IR (cm^{-1}): ν 2700–3300, 2971 m, 1624 s, 1595 s, 1556 s, 1437 s, 1425 s, 1272s, 1222 s, 1153 m, 1112 m, 1031 m, 882, 856 m, 833 m; MS (EI) m/z (%):220 ($[M+1]^+$, 7), 219 ($[M]^+$, 50), 204 (100), 191 (22); Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39%. Found: C, 65.69; H, 6.22; N, 6.22%.

*4.2.5. 3-Ethyl-4-hydroxy-8-methoxyquinolin-2(1H)-one (**1e**).*[32,34,37] White solid, yield 13.6 g (62%), mp 225–227 °C (ethanol), mp[34] 226–227 °C, mp[37] 225–226 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (t, 3H, J=7.3 Hz). 2.58 (q, 2H, J=7.3 Hz). 3.89 (s, 3H). 7.08–7.13 (m, 2H), 7.48 (dd, 1H, J=4.6, 4.6 Hz), 10.04 (br s, 1H), 10.11 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.1, 16.4, 56.0, 110.3, 113.4, 114.3, 115.9, 120.8, 127.3, 145.4, 156.7, 162.7; IR (cm^{-1}): ν 2700–3400 br, 1635 s, 1604 s, 1571 s, 1492 m, 1393 m, 1333 m, 1302 m, 1267 m, 1254 m, 1223 m, 1155 m, 1089 s, 771 m,724 m; IR:[34] 1640 cm^{-1}. MS (EI) m/z (%): 220 ($[M+1]^+$, 5), 219 ($[M]^+$, 34), 218 (23), 204 (31), 149 (28), 71 (27), 69 (28), 57 (100), 55 (35), 43 (30), 41 (34). X-ray structure is reported.[38]

*4.2.6. 3-Ethyl-4-hydroxy-6-methylquinolin-2(1H)-one (**1f**).* White solid, yield 12.0 g (59%), mp 261–264 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (t, J=7.4 Hz, 3H), 2.35 (s, 3H), 2.58 (q, 2H, J=7.4 Hz), 7.16 (d, 1H, J=8.2 Hz), 7.26 (dd, 1H, J=8.2, 1.6 Hz), 7.68 (s, 1H), 9.96 (br s, 1H), 11.22 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.2, 16.3, 20.6, 112.9, 114.6, 115.2, 122.0, 129.6, 130.7, 135.2, 156.3, 163.2; IR (cm^{-1}):

ν 3131 m, 2976 m, 1640 s, 1622 s, 1558 s, 1513 m, 1433 m, 1416 m, 1332 m, 1233 m, 1207 m, 1149 m, 1116 m, 855 w, 814 w; HRMS (ESI+): *m/z* calcd for $C_{12}H_{14}NO_2^+$ ([M+H]$^+$): 204.1019, found 204.1022. Anal. Calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89%. Found: C, 70.75; H, 6.43; N, 6.79%.

4.2.7. 3-Ethyl-4-hydroxy-8-methylquinolin-2(1H)-one (***1g***).[39] Yellow solid, yield 12.2 g (60%), mp 228–229 °C (acetic acid), mp[39] 217.5–220 °C (acetic acid). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.04 (t, 3H, *J*=7.4 Hz), 2.41 (s, 3H), 2.61 (q, 2H, *J*=7.4 Hz), 7.06 (dd, 1H, *J*=7.7, 7.7 Hz), 7.30 (d, 1H, *J*=7.7 Hz), 7.77 (d, 1H, *J*=7.7 Hz), 10.04 (br s, 1H), 10.47 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.2, 16.4, 17.4, 112.7, 115.5, 120.5, 120.6, 122.9, 130.9, 135.7, 157.0, 163.7; IR (cm^{-1}): ν 3395 m, 2966 m, 2934 m, 1636 s, 1601 s, 1565 s, 1488 m, 1396 m, 1334 m, 1292 m, 1238 s, 1210 s, 1151 s, 766 m; HRMS (ESI+): *m/z* calcd for $C_{12}H_{14}NO_2^+$ [M+H]$^+$ 204.1019, found 204.1024.

4.2.8. 5-Chloro-3-ethyl-4-hydroxy-8-methylquinolin-2(1H)-one (***1h***). White solid, yield 11.6 g (49%), mp 235–238 °C (ethanol). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.02 (t, 3H, *J*=7.3 Hz), 2.38 (s, 3H), 2.60 (q, 2H, *J*=7.3 Hz), 7.10 (d, 1H, *J*=8.0 Hz), 7.23 (d, 1H, *J*=8.0 Hz), 9.98 (br s, 1H), 10.41 (br s, 1H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 12.8, 16.2, 17.4, 112.4, 114.3, 122.5, 124.2, 127.0, 130.7, 137.8, 157.2, 162.4; IR (cm^{-1}): ν 3471 m, 3166 w, 2959 w, 2870 w, 1647 s, 1459 w, 1338 w, 1324 w, 1210 w, 1147 m, 822 w, 628 w; HRMS (ESI+): *m/z* calcd for $C_{12}H_{13}ClNO_2^+$ [M+H]$^+$ 238.0629, found 238.0630. Anal. Calcd for $C_{12}H_{12}ClNO_2$ (237.68): C, 60.64; H, 5.09; N, 5.89%. Found: C, 60.53; H, 5.05; N, 5.92%.

4.2.9. 3-Butyl-4-hydroxyquinolin-2(1H)-one (***1i***).[20] White solid (microscopic crystals). yield 14.1 g (65%). mp 195–201. 54%. mp 201–204 °C (ethanol), mp[20] 199–200 °C (ethanol). For ^{1}H and ^{13}C NMR spectra see Ref. 20. IR (cm^{-1}): ν 2700–3400 br, 2954 m, 1639 s, 1604 s, 1590 s, 1557 m, 1503 m, 1480 m, 1469 m, 1426 m, 1404 m, 1273 m, 1197 s, 1154 s, 761 s; Anal. Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45%. Found: C, 71.67; H, 6.04; N, 6.39%.

4.2.10. 3-Butyl-4-hydroxy-6,8-dimethylquinolin-2(1H)-one (***1j***). Colourless shiny crystals, yield 14.7 g (60%), mp 225–228 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.90 (t, 3H, *J*=7.3 Hz), 1.30–1.45 (m, 4H), 2.31 (s, 3H), 2.37 (s, 3H), 2.56–2.60 (m, 2H), 7.12 (s, 1H), 7.56 (s, 1H), 9.88 (br s, 1H), 10.40 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.1, 17.2, 20.6, 22.3, 22.8, 30.5, 111.4, 115.4, 120.0, 122.8, 129.4, 132.2, 133.7, 157.1, 163.7; IR (cm^{-1}): ν 3382 s, 2931 m, 2849 m, 1645 s, 1618 s, 1381 m, 1329 m, 1257 m, 1238 s, 1168 s, 1134 s, 1103 m, 1069 m, 871 m, 493 m; HRMS (ESI−): *m/z* calcd for $C_{15}H_{18}NO_2^-$ [M−H]$^-$ 244.1343, found 244.1338; calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71%. Found: C, 73.51; H, 6.52; N, 5.11%.

4.2.11. 3-Butyl-4-hydroxy-6,8-dimethoxyquinolin-2(1H)-one (***1k***). Colourless crystals, yield 15.3 g (55%), mp 240–244 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.90 (t, 3H, *J*=7.3 Hz), 1.29–1.46 (m, 4H), 2.54–2.59 (m, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 6.74 (d, 1H, *J*=2.4 Hz), 6.98 (d, 1H, *J*=2.4 Hz), 9.96 (br s, 1H), 10.12 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.1, 22.3, 23.0, 30.4, 55.4, 56.1, 95.2, 100.8, 112.8, 115.7, 122.2, 146.6, 154.0, 156.7, 162.5; IR (cm^{-1}): ν 3374 s, 2954 m, 2929 m, 1661 m, 1613 s, 1583 m, 1504 s, 1327 m, 1257 s, 1228 m, 1206 s, 1162 s, 1093 s, 1056 m; HRMS (ESI+): *m/z* calcd for $C_{15}H_{20}NO_4^+$ [M+H]$^+$ 278.1387, found 278.1386. Anal. Calcd for $C_{15}H_{19}NO_4$ (277.32): C, 64.97; H, 6.91; N, 5.05%. Found: C, 65.02; H, 6.94; N, 5.04%.

4.2.12. 3-Butyl-4-hydroxybenzo[h]quinolin-2(1H)-one (***1l***). General procedure was followed for the preparation of this compound with one exception; the temperature of the metal bath was kept at 180 °C throughout the condensation. White crystals, yield 24.9 g (93%), mp 309–313 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.93 (t, 3H, *J*=7.2 Hz), 1.35–1.44 (m, 2H), 1.46–1.53 (m, 2H), 2.65–2.70 (m, 2H), 7.58–7.67 (m, 3H), 7.96 (d, 1H, *J*=7.4 Hz), 7.99 (d, 1H, *J*=8.9 Hz), 8.90 (d, 1H, *J*=8.0 Hz), 10.19 (br s, 1H), 11.82 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.1, 22.3, 22.9, 30.4, 111.2, 111.8, 120.0, 121.3, 121.4, 122.3, 126.2, 127.4, 128.3, 133.5, 134.0, 157.9, 164.0; IR (cm^{-1}): ν 1763 s, 1618 m, 1601 m, 1196 s, 1067 m, 779 m; MS (EI) *m/z* (%): 268 ([M+1]$^+$, 5), 267 (M$^+$, 24), 238 (17), 226 (16), 225 (100), 224 (33), 115 (16), 55 (18); HRMS (ESI−): *m/z* calcd for $C_{17}H_{16}NO_2^-$ [M−H]$^-$ 266.1187, found 266.1187. Anal. Calcd for $C_{17}H_{17}NO_2$ (267.32): C. 76.38; H. 6.41; N. 5.24%. Found: C. 76.29; H. 6.49; N, 5.07%.

4.2.13. 4-Hydroxy-3-phenylquinolin-2(1H)-one (***1m***).[32,40] White solid, yield 20.9 g (88%), mp 334–338 °C (acetic acid), mp[40] 325–327 °C (DMF). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.16–7.21 (m, 1H), 7.28–7.33 (m, 2H), 7.37–7.43 (m, 4H), 7.49–7.53 (m, 1H), 7.96 (dd, 1H, *J*=8.1, 1.0 Hz), 10.10 (br s, 1H), 11.49 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 112.6, 114.9, 115.4, 121.1, 123.1, 126.9, 127.7, 130.6, 131.2, 133.4, 138.0, 157.3, 162.7; IR (cm^{-1}): ν 2700–3330 br, 1645 s, 1610 s, 1588 s, 1499 m, 1408 m, 1365 m, 1289 m, 1244 m, 1226 m, 757 m, 696 m, 557 m; HRMS (ESI+): *m/z* calcd for $C_{15}H_{12}NO_2^+$ [M+H]$^+$ 238.0863, found 238.0866.

4.2.14. 3-Ethyl-4-hydroxy-1-methylquinolin-2(1H)-one (***1n***).[41] White solid, yield 18.1 g (89%), mp 188–191 °C, mp[41] 184–185 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.03 (t, 3H, *J*=7.4 Hz), 2.63 (q, 2H, *J*=7.4 Hz), 3.59 (s, 3H), 7.22–7.27 (m, 1H), 7.46 (br d, 1H, *J*=8.3 Hz), 7.55–7.60 (m, 1H), 7.99 (dd, 1H, *J*=8.0, 1.4 Hz), 10.09 (br s, 1H): ^{13}C NMR (126 MHz. DMSO-d_6) δ 13.2, 17.2, 29.1. 112.6, 114.2, 116.3, 121.2, 123.0, 130.1, 138.2, 155.4, 162.6; IR (cm^{-1}): ν 2700–3400 br, 2964 w, 1641 s, 1607 s, 1584 s, 1571 s, 1392 m, 1219 s, 1205 s, 1165 s, 1126 m, 750 s; HRMS (ESI+): *m/z* calcd for $C_{12}H_{14}NO_2^+$ [M+H]$^+$ 204.1019, found 204.1020.

4.2.15. 3-Butyl-4-hydroxy-1-methylquinolin-2(1H)-one (***1o***). Colourless crystals, yield 16.4 g (71%), mp 145–149 °C (ethanol), mp[42] 141 °C. For NMR data, see Ref. 20. IR (cm^{-1}): ν 2800–3400 br, 2954 w, 1632 m, 1604 s, 1582 s, 1466 w, 1342 w, 1192 s, 1165 m, 1157 m, 1083 w, 747 m, 471 w.

4.2.16. 4-Hydroxy-1-methyl-3-phenylquinolin-2(1H)-one (***1p***).[43] White solid, yield 23.4 g (93%), mp 227–230 °C, mp[43] 226 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.61 (s, 3H), 7.27–7.31 (m, 1H), 7.30–7.37 (m, 3H), 7.39–7.43 (m, 2H), 7.52 (br d, 1H, *J*=8.3 Hz), 7.63–7.67 (m, 1H), 8.05 (dd, 1H, *J*=8.0, 1.4 Hz), 10.07 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 29.5, 112.3, 114.4, 116.3, 121.4, 123.6, 127.0, 127.8, 131.0, 131.2, 133.7, 139.0, 156.2, 162.0; IR (cm^{-1}): ν 2750–3250 br, 3060 w. 2953 w. 1629 s. 1612 s. 1594 s. 1581 s, 1572 s, 1328 m, 1251 m, 755 m, 693 m, 511 w; MS (EI) *m/z* (%): 252 ([M+1]$^+$, 16), 251 ([M]$^+$, 96), 250 (100), 134 (45), 125 (11), 116 (12), 91 (10), 77 (27). HRMS (ESI+): *m/z* calcd for $C_{16}H_{14}NO_2^+$ [M+H]$^+$ 252.1019, found 252.1022. X-ray structure is reported.[28]

4.2.17. 2-Ethyl-N,N′-bis(4-methoxyphenyl)propanediamide (***1c′***). White solid, yield 1.37 g (4%), mp 237–241 °C (ethanol–benzene). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J*=7.4 Hz) 1.91 (dq, 2H, *J*=7.4, 7.4 Hz), 3.33 (t, 1H, *J*=7.4 Hz), 3.72 (s, 6H), 6.86–6.91 (m, 4H), 7.50–7.54 (m, 4H), 9.80 (br s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.0, 23.1, 55.2, 56.2, 113.8, 120.9, 132.0, 155.3, 167.5; IR (cm^{-1}): ν 3279 m, 2968 w, 2836 w, 1673 s, 1601 m, 1539 m, 1512 s, 1412 m, 1249 m, 1236 m, 1166 m, 1029 m, 824 m; MS (EI) *m/z* (%): 343 ([M+1]$^+$, 10), 342 (M$^+$, 47), 193 (38), 178 (63), 149 (20), 124 (13), 123 (100), 122 (42), 108 (40), 55 (10);

HRMS (ESI+): *m/z* calcd for $C_{19}H_{23}N_2O_4^+$ $[M+H]^+$ 343.1652, found 343.1650.

*4.2.18. N,N′,2-Triphenylpropanediamide (**1m′**).*[44] White solid, yield 1.65 g (5%), mp 198–202 °C (ethanol), mp[44] 201–202 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.88 (s, 1H), 7.04–7.08 (m, 2H), 7.28–7.34 (m, 5H), 7.36–7.40 (m, 2H), 7.44–7.48 (m, 2H), 7.59–7.63 (m, 4H), 10.25 (br s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 59.9, 119.3, 123.6, 127.4, 128.2, 128.8, 129.0, 135.5, 138.9, 166.6; IR (cm^{-1}): ν 3313 m, 1672 s, 1647 m, 1618 m, 1605 s, 1551 s, 1497 s, 1443 s, 1334 m, 763 m, 749 m, 718 m, 697 m; HRMS (ESI+): *m/z* calcd for $C_{21}H_{19}N_2O_2^+$ $[M+H]^+$ 331.1441, found 331.1441.

4.3. General procedure for the preparation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones (2)

To a solution of the appropriate 4-hydroxyquinolin-2(1*H*)-one (**1**, 20 mmol) in aqueous sodium hydroxide solution (0.5 M, 20 mL), peroxyacetic acid (32–36 wt. % in dilute acetic acid, 20 mL, 100 mmol) was added dropwise under stirring during 30 min. The precipitate was collected by filtration and washed with small portions of 5% aqueous potassium carbonate solution until the filter cake is free of potentially unreacted starting material **1** (until the filtrate is not clear solution upon acidification with conc. hydrochloric acid). Then the solid was washed with water (3×30 mL), air dried and recrystallized from the appropriate solvent. Analytical and spectral data of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones **2** are given below.

*4.3.1. 3-Hydroxy-3-methylquinoline-2,4(1H,3H)-dione (**2a**).*[45] White solid, yield 2.94 g (77%), mp 212–216 °C (ethanol), mp[45] 201 °C (ethanol–water). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (s, 3H), 5.81 (s, 1H), 7.09 (d, 1H, *J*=8.0 Hz), 7.10–7.14 (m, 1H), 7.60 (ddd, 1H, *J*=7.7, 7.7, 1.5 Hz), 7.75 (dd, 1H, *J*=7.7, 1.3 Hz), 10.76 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 26.2, 78.0, 116.2, 118.4, 122.5, 127.0, 136.0, 141.5, 173.3, 196.2; IR (cm^{-1}): ν 1709 s, 1671 s, 1614 s, 1598 m, 1487 m, 1455 m, 1441 m, 1405 m, 1243 m, 1190 m, 753 m; HRMS (ESI+): *m/z* calcd for $C_{10}H_{10}NO_3^+$ $[M+H]^+$ 192.0655, found 192.0658.

*4.3.2. 3-Ethyl-3-hydroxyquinoline-2,4(1H,3H)-dione (**2b**).*[27] White solid, yield 3.73 g (91%), mp 174–176 °C (benzene–ethanol), mp[27] 170–172 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.78 (t, 3H, *J*=7.4 Hz), 1.66–1.82 (m, 2H), 5.65 (s, 1H), 7.07 (d, 1H, *J*=8.0 Hz), 7.09–7.13 (m, 1H), 7.59 (ddd, 1H, *J*=7.7, 7.7, 1.5 Hz), 7.72 (dd, 1H, *J*=7.7, 1.4 Hz), 10.76 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.4, 32.8, 82.0, 116.2, 119.1, 122.5, 126.7, 135.9, 141.4, 172.9, 196.0; IR (cm^{-1}): ν 3457 m, 1709 s, 1667 s, 1617 m, 1487 m, 1365 m, 1185 m, 774 m, 753 m; MS (EI) *m/z* (%): 97(22), 83(25), 74(26), 72(73), 71(22), 69(32), 59(100), 55(48); HRMS (ESI+): *m/z* calcd for $C_{11}H_{12}NO_3^+$ $[M+H]^+$ 206.0812. found 206.0816. Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.23; H, 5.40; N, 6.83%. Found: C, 64.08; H, 5.37; N, 6.65%.

*4.3.3. 3-Ethyl-3-hydroxy-6-methoxyquinoline-2,4(1H,3H)-dione (**2c**).*[35] Yellow solid, yield 4.29 (89%), mp 186–193 °C (ethanol), mp[35] 198 °C (water–DMF). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.78 (t, 3H, *J*=7.5 Hz), 1.65–1.82 (m, 2H), 3.78 (s, 3H), 5.62 (br s, 1H), 7.02 (d, 1H, *J*=8.8 Hz), 7.18 (d, 1H, *J*=3.0 Hz), 7.22 (dd, 1H, *J*=8.8 Hz, 3.0 Hz), 10.58 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.4, 32.9, 55.5, 81.8, 108.4, 117.8, 119.6, 123.8, 135.4, 154.6, 172.5, 196.1; IR (cm^{-1}): ν 3414 m, 3200–2800 br, 3072 m, 1709 s, 1669 s, 1625 m, 1502 s, 1431 m, 1282 s, 1212 m, 1182 m, 1160 m, 848 m; MS (EI) *m/z* (%): 236 ($[M+1]^+$, 9), 235 (M^+, 63), 220 (20), 123 (20), 122 (47), 109 (29), 106 (28), 79 (26), 57 (21), 52 (26); HRMS (ESI+): *m/z* calcd for $C_{12}H_{14}NO_4^+$ $[M+H]^+$ 236.0917, found 236.0916; Anal. Calcd for $C_{12}H_{13}NO_4 \cdot {}^1/_3\ H_2O$ (241.24): C, 59.76; H, 5.71; N, 5.81%. Found: C, 59.82; H, 5.78; N, 5.52%.

*4.3.4. 3-Ethyl-3-hydroxy-7-methoxyquinoline-2,4(1H,3H)-dione (**2d**).* White solid, yield 83%, mp 162–164 °C (benzene). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (t, 3H, *J*=7.4 Hz), 1.63–1.84 (m, 2H), 3.83 (s, 3H), 5.57 (s, 1H), 6.58 (d, 1H, *J*=2.3 Hz), 6.70 (dd, 1H, *J*=8.7, 2.3 Hz), 7.70 (d, 1H, *J*=8.7 Hz), 10.67 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 33.2, 55.7, 81.2, 100.0, 109.7, 112.6, 129.0, 143.6, 165.1, 173.1, 194.2; IR (cm^{-1}): ν 3258 s, 3067 m, 1713 s, 1668 s, 1612 s, 1589 s, 1482 m, 1461 m, 1409 m, 1349 m, 1274 s, 1207 s, 1173 s, 1119 s, 1108 m; Anal. Calcd for $C_{12}H_{13}NO_4 \cdot 1/6C_6H_6$: C, 62.90; H, 5.68; N, 5.64%. Found: C, 63.01; H, 5.73; N, 5.60%. The presence and quantity of residual benzene in the sample is confirmed by ^{1}H and ^{13}C NMR resonances at δ 7.37 ppm and 128.3 ppm, respectively.

*4.3.5. 3-Ethyl-3-hydroxy-8-methoxyquinoline-2,4(1H,3H)-dione (**2e**).*[29] Yellow crystals, yield 83%, mp 70–72 °C (benzene). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (t, 3H, *J*=7.4 Hz), 1.61–1.86 (m, 2H), 3.87 (s, 3H), 5.63 (s, 1H), 7.09 (dd, 1H, *J*=7.9, 7.9 Hz), 7.29 (d, 1H, *J*=7.9 Hz), 7.31 (d, 1H, *J*=7.9 Hz), 9.85 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.3, 32.9, 56.2, 82.2, 117.1, 117.7, 119.5, 122.6, 131.0, 146.3, 172.4, 196.0; IR (cm^{-1}): ν 3579 m, 3486 m, 1710 s, 1667 s, 1615 m, 1591 m, 1508 m, 1384 m, 1266 s, 1203 m, 1187 m, 1018 m, 1004 m. Anal. Calcd for $C_{12}H_{13}NO_4 \cdot H_2O$: C, 56.91; H, 5.97; N, 5.53%. Found: C, 56.90; H, 5.88; N, 5.57%. The presence of H_2O in a 1:1 ratio relative to **2e** was confirmed by single crystal structure analysis.[29]

*4.3.6. 3-Ethyl-3-hydroxy-6-methylquinoline-2,4(1H,3H)-dione (**2f**).* White solid, yield 91%, mp 198–205 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.78 (t, 3H, *J*=7.4 Hz), 1.65–1.81 (m, 1H), 2.25 (s, 3H), 5.62 (s, 1H), 6.98 (d, 1H, *J*=8.2 Hz), 7.41 (dd, 1H, *J*=8.2, 1.7 Hz), 7.52 (d, 1H, *J*=1.7 Hz), 10.67 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.3, 20.0, 32.9, 81.9, 116.1, 118.9, 126.3, 131.7, 136.7, 139.1, 172.7, 196.1; IR (cm^{-1}): ν 3588 w, 3449 w, 3191 w, 2914 w, 1712 s, 1670 s, 1618 m, 1504 m, 1421 w, 1200 w, 1159 w, 849 w, 540 w; HRMS (ESI−): *m/z* calcd for $C_{12}H_{12}NO_3^-$ ($[M-H]^-$) 218.0823, found 218.0827.

*4.3.7. 3-Ethyl-3-hydroxy-8-methylquinoline-2,4(1H,3H)-dione (**2g**).* Yellow solid, yield 66%, mp 164 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.78 (t, 3H, *J*=7.2 Hz), 1.64–1.81 (m, 1H), 2.31 (s, 3H), 5.66 (br s, 1H), 7.04 (dd, 1H, *J*=7.6, 7.6 Hz), 7.45 (d, 1H, *J*=7.6 Hz), 7.58 (d, 1H, *J*=7.6 Hz), 9.94 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.3, 17.2, 32.8, 82.0, 119.5, 122.3, 124.4, 124.6, 137.0, 139.3, 173.1, 196.2; IR (cm^{-1}): ν 3585 m, 3472 m, 3294 m, 1706 s, 1668 s, 1598 m, 1469 m, 1374 m, 1194 m; HRMS (ESI+): *m/z* calcd for $C_{12}H_{14}NO_3^+$ $[M+H]^+$ 220.0968, found 220.0974.

*4.3.8. 5-Chloro-3-ethyl-3-hydroxy-8-methylquinoline-2,4(1H,3H)-dione (**2h**).* Colourless solid. yield 4.16 g (82%). mp 158–166 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.80 (t, 3H, *J*=7.2 Hz, CH_3CH_2), 1.76 (q, 2H, *J*=7.2 Hz, CH_2), 2.28 (s, 3H, CH_3–C8), 5.76 (br s, 1H, OH), 7.11 (d, 1H, *J*=8.1 Hz, H6), 7.38 (d, 1H, *J*=8.1 Hz, H7), 9.99 (br s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) 7.8 (CH_3CH_2), 17.3 (CH_3–C8), 32.2 (CH_2), 83.2 (C3), 117.8 (C4a), 124.2 (C8), 124.7 (C6), 129.5 (C5), 136.2 (C7), 140.3 (C8a), 172.0 (C2), 194.9 (C4); IR (cm^{-1}): ν 3438 m, 3294 m, 1717 s, 1682 s, 1587 s, 1499 m, 1458 m, 1389 m, 1375 m, 1272 m, 1250 m, 1187 s, 1064 m, 1053 m, 813 m; HRMS (ESI+): *m/z* calcd for $C_{12}H_{13}ClNO_3^+$ $[M+H]^+$ 254.0578, found 254.0578.

*4.3.9. 3-Butyl-3-hydroxyquinoline-2,4(1H,3H)-dione (**2i**).* Yield[24] 3.73 g (80%), mp[24] 146–149 °C (benzene). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.77 (t, 3H, *J*=7.0 Hz), 1.12–1.28 (m, 4H), 1.62–1.78 (m, 4H), 5.67 (br s, 1H), 7.08 (d, 1H, *J*=8.0 Hz), 7.09–7.13 (m, 1H), 7.59

(ddd, 1H, *J*=7.6, 7.6, 1.8 Hz), 7.72 (dd, 1H, *J*=7.6, 1.8 Hz), 10.79 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8, 22.0, 24.7, 39.3, 81.7, 116.2, 119.0, 122.5, 126.7, 135.9, 141.4, 172.9, 196.1; IR (cm^{-1}): ν 3476 m, 3192 w, 2950 m, 2866 m, 1705 s, 1666 s, 1617 m, 1595 m, 1486 m, 1382 m, 1091 m, 755 m; HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{16}NO_3^+$ $[M+H]^+$ 234.1125, found 234.1126.

*4.3.10. 3-Butyl-3-hydroxy-6,8-dimethylquinoline-2,4(1H,3H)-dione (**2j**).* Colourless microcrystals, yield 4.93 g (87%), mp 175–184 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.76 (t, 3H, *J*=7.5 Hz, CH_3CH_2), 1.10–1.29 (m, 4H, $CH_2CH_2CH_3$), 1.61–1.75 (m, 2H, CH_2–C3), 2.25 (s, 3H, CH_3–C6), 2.27 (s, 3H, CH_3–C8), 5.63 (s, 1H, OH). 7.27 (s. 1H. H7). 7.38 (s. 1H. H5). 9.86 (br s. 1H. NH): ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.7 (CH_3CH_2), 17.1 (CH_3–C8), 19.8 (CH_3–C6), 21.9 (CH_2CH_3), 24.6 (CH_2CH_2–C3), 39.3 (CH_2–C3), 81.7 (C3), 119.3, 124.1 (C5), 124.5, 131.4, 137.0, 137.9 (C7), 173.1 (C2), 196.3 (C4); ^{15}N NMR (DMSO-d_6, 51 MHz): 129; IR (cm^{-1}): ν 3455 m, 3231 m, 2954 m, 2932 m, 1704 s, 1662 s, 1615 m, 1491 s, 1378 s, 1283 m, 1236 m, 1220 m, 1158 m, 1068 m, 791 w; HRMS (ESI+): *m*/*z* Calcd for $C_{15}H_{20}NO_3^+$ $[M+H]^+$ 262.1438, found 262.1437; Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32): C, 72.07; H, 6.05; N, 4.94%. Found: C, 72.16; H, 6.13; N, 5.11%.

*4.3.11. 3-Butyl-3-hydroxy-6,8-dimethoxyquinoline-2,4(1H,3H)-dione (**2k**).* Pale yellow crystals, yield 3.34 g (57%), mp 119–121 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.77 (t, 3H, *J*=7.0 Hz), 1.11–1.28 (m, 4H), 1.60–1.75 (m, 2H), 3.78 (s, 3H), 3.85 (s, 3H), 5.64 (br s, 1H), 6.77 (d, 1H, *J*=2.6 Hz), 6.89 (d, 1H, *J*=2.6 Hz), 9.76 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) 13.8, 22.0, 24.7, 55.5, 56.3, 82.0, 98.8, 106.3, 119.4, 125.5, 147.6, 155.0, 172.3, 196.1 (one resonance not observed); IR (cm^{-1}): ν 3486 m, 3213 m, 2960 m, 2934 m, 1709 s, 1668 s. 1618 m. 1505 s. 1455 m. 1370 m. 1205 m. 1155 m. 841 w; HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{20}NO_5^+$ $[M+H]^+$ 294.1336, found 278.1338.

*4.3.12. 3-Butyl-3-hydroxybenzo[h]quinoline-2,4(1H,3H)-dione (**2l**).* Pale yellow solid, yield 4.59 (81%), mp 117–121 °C (benzene). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.76 (t, 3H, *J*=7.2 Hz), 1.11–1.36 (m, 4H), 1.71–1.86 (m, 2H), 5.79 (s, 1H), 7.62–7.68 (m, 2H), 7.71–7.79 (m, 2H), 7.99 (d, 1H, *J*=8.3 Hz), 8.65 (d, 1H, *J*=8.3 Hz), 11.00 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8, 22.0, 24.8, 81.9, 114.4, 121.6, 121.9, 122.7, 123.6, 126.8, 128.6, 129.6, 136.8, 139.7, 174.5, 196.2 (one signal not observed); IR (cm^{-1}): 3489 w, 3294 w, 2955 w, 2928 w, 1705 s, 1666 s, 1626 m, 1578 m, 1389 m, 820 w, 797 w, 765 w; MS (EI) *m*/*z* (%): 284 ([M+1]$^+$, 8), 283 (M$^+$, 41), 240 (38), 199 (100), 198 (50), 170 (13), 142 (14), 140 (17), 115 (45), 114 (16), 57 (22), 41 (19). HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{18}NO_3^+$ $[M+H]^+$ 284.1281, found 284.1279. Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32): C, 72.07; H, 6.05; N, 4.94%. Found: C, 71.96; H, 6.06; N, 4.81%.

*4.3.13. 3-Hydroxy-3-phenylquinoline-2,4(1H,3H)-dione (**2m**).*[46,24] White solid, yield 3.80 g (75%), mp 245–250 °C (ethanol), mp[46] 224–226 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.41 (br s, 1H), 7.08–7.15 (m, 2H), 7.27–7.35 (m, 3H), 7.36–7.39 (m, 2H), 7.61 (ddd, 1H, *J*=7.8, 7.8, 1.3 Hz), 7.68 (dd, 1H, *J*=7.8, 1.3 Hz), 11.11 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 82.5, 116.4, 119.0, 122.9, 125.4, 127.2, 128.6, 128.7, 136.4, 138.4, 141.4, 171.6, 194.2; IR (cm^{-1}): ν 3441 s, 3250 m, 1732 s, 1708 s, 1675 s, 1613 m, 1482 m, 1368 m, 1169 m, 760 m, 739 m, 696 m; HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{12}NO_3^+$ $[M+H]^+$ 254.0812, found 254.0813.

*4.3.14. 3-Ethyl-3-hydroxy-1-methylquinoline-2,4(1H,3H)-dione (**2n**).*[45] White solid, yield 3.16 g (72%), mp 121–126 °C (ethyl acetate), mp[45] 146 °C (xylene–cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.75 (t, 3H, *J*=7.4 Hz), 1.64–1.80 (m, 2H), 3.38 (s, 3H), 5.73 (br s, 1H), 7.20–7.24 (m, 1H), 7.36 (d, 1H, *J*=8.4 Hz), 7.69–7.74 (m, 1H), 7.80 (dd, 1H, *J*=7.7, 1.6 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.5, 29.8, 33.2, 82.4, 115.6, 120.4, 123.0, 126.8, 136.0, 142.6, 172.4, 195.3; IR (cm^{-1}): ν 3379 m, 2990 w, 2940 w, 1711 s, 1680 s, 1605 s, 1473 s, 1359 m, 1102 m, 707 w, 755 w, 666 w, 530 w; HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{14}NO_3^+$ $[M+H]^+$ 220.0968, found 220.0969.

*4.3.15. 3-Butyl-3-hydroxy-1-methylquinoline-2,4(1H,3H)-dione (**2o**).*[24] White solid, yield 4.20 g (85%), mp 104–108 °C (cyclohexane), mp[24] 104–108 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.74 (t, 3H, *J*=7.0 Hz), 1.08–1.28 (m, 4H), 1.61–1.75 (m, 2H), 3.37 (s, 3H), 5.73 (br s, 1H), 7.22 (dd, 1H, *J*=7.4, 7.4 Hz), 7.35 (d, 1H, *J*=8.4 Hz), 7.72 (ddd, 1H, *J*=8.2, 8.2, 1.7 Hz), 7.80 (dd, 1H, *J*=7.7, 1.6 Hz): ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.7, 21.9, 24.8, 29.8, 39.6, 82.1, 115.6, 120.4, 123.0, 126.9, 136.0, 142.5, 172.4, 195.4; IR (cm^{-1}): ν 3471 m, 2944 m, 1702 s, 1661 s, 1603 s, 1475 s, 1346 m, 1324 m, 1296 m, 1189 m, 1106 m, 1081 s, 1028 m, 1020 m, 769 m.

*4.3.16. 3-Hydroxy-1-methyl-3-phenylquinoline-2,4(1H,3H)-dione (**2p**).*[24,27] White solid, yield 4.81 g (90%), mp 159–162 °C (ethanol), mp[27] 160–162 °C (ethanol–water). For yield,[24] mp[24] and IR spectrum[27] see literature. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.49 (s, 3H), 6.49 (br s, 1H), 7.18 (dd, 1H, *J*=7.3, 7.3 Hz), 7.25–7.31 (m, 5H), 7.40 (d, 1H, *J*=7.3 Hz), 7.68–7.50 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 30.0, 83.0, 116.0, 120.5, 123.3, 125.6, 127.3, 128.7, 136.3, 138.5, 142.4, 171.0, 193.4 (one signal not observed); IR (cm^{-1}): ν 3615 w, 3422 w, 1709 s, 1668 s, 1602 m, 1474 s, 1359 s, 1297 m, 1099 m, 1015 m, 759 m, 744 m, 700 m; MS (EI) *m*/*z* (%): 268 ([M+1]$^+$, 5), 267 ([M]$^+$, 26), 162 (65), 146 (11), 105 (100), 91 (12), 77 (43), 51 (12). Anal. Calcd for $C_{16}H_{13}NO_3$ (267.28): C, 71.90; H, 4.90; N, 5.24%. Found: C, 71.71; H, 4.86; N, 5.00%.

4.4. Oxidation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones 2 with paraperiodic acid into *N*-(α-ketoacyl)anthranilic acids 3

An aqueous solution of H_5IO_6 (1.25 mL of water per 1 mmol of H_5IO_6, Table 2) was added to the stirred solution of 3-hydroxyquinoline-2,4(1*H*,3*H*)-dione **2** (1 mmol) in Solvent (Table 2) at room temperature. The reaction mixture was stirred at the temperature and for the time indicated in Table 2. Then it was left overnight at 5–10 °C. The resulting precipitate was collected by filtration and repeatedly washed with small portions of water (totally 15–50 mL) to afford the first crop of product **3**. The filtrate was evaporated to dryness suspended in water and filtered. The filtrate was washed with water as described above to give the second crop of the product. Re-crystallisation of the combined crops from the solvent indicated below gave pure **3**.

4.5. Oxidation of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones 2 with sodium periodate into *N*-(α-ketoacyl)anthranilic acids 3

An aqueous solution of $NaIO_4$ (1.25 mL of water per 1 mmol of $NaIO_4$, Table 3) was added to the stirred solution of 3-hydroxyquinoline-2,4(1*H*,3*H*)-dione **2** (1 mmol) in ethanol (Table 3) at room temperature within 5 min. The stirring was continued for the time indicated in Table 3. The reaction mixture was left at 5–10 °C overnight. The precipitate was collected by filtration and washed repeatedly with small portions of water (totally 100–200 mL) to give the first crop of product **3**. The above water filtrates were combined, solvents were evaporated in vacuo and the residue was suspended in water (40 mL). The precipitate was collected by filtration and washed with water (3×5 mL) to give the second crop of product **3**. Re-crystallisation of the combined crops from the solvent indicated below gave pure **3**.

*4.5.1. 2-[(2-Oxopropanoyl)amino]benzoic acid (**3a**).* For UV, IR and ^{1}H NMR (60 MHz) data, see Ref. 2 White solid, mp 207–210 °C

(ethyl acetate), mp[2] 194–196 °C (benzene). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.45 (s, 3H, CH_3), 7.24 (dd, 1H, J=7.5, 7.5 Hz, H5), 7.67 (ddd, 1H, J=7.5, 7.5, 1.0 Hz, H4), 8.05 (dd, 1H, J=7.5, 1.0 Hz, H6), 8.67 (d, 1H, J=7.5 Hz, H3), 12.31 (br s, 1H, NH), 13.81 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.1 (CH_3), 117.1 (C1), 119.4 (C3), 123.7 (C5), 131.5 (C6), 134.3 (C4), 139.5 (C2), 158.8 (NCO), 169.2 (COOH), 196.2 ($COCH_3$); ^{15}N NMR (51 MHz, DMSO-d_6) δ 118; IR (cm^{-1}): ν 3260 m, 1725 s, 1700 s, 1673 s, 1585 m, 1520 s, 1451 m, 1419 s, 1281 s, 1253 s, 1138 s, 760 s; MS (EI) m/z (%): 208 ([M+1]$^+$, 1), 207 (M$^+$, 8), 164 (31), 146 (100), 119 (18), 90 (33), 65 (10), 43 (38). HRMS (ESI+): m/z calcd for $C_{10}H_{10}NO_4^+$ [M+H]$^+$ 208.0604, found 208.0610.

*4.5.2. 2-[(2-Oxobutanoyl)amino]benzoic acid (**3b**).* Off-white crystals, mp 179–182 °C (benzene); colourless needles, mp 194–196 °C (ethyl acetate); R_f=0.13 (5% ethanol in chloroform); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (t, 3H, J=7.0 Hz), 2.96 (q, 2H, J=7.0 Hz), 7.24 (dd, 1H, J=7.6, 7.6 Hz), 7.67 (dd, 1H, J=7.6, 7.6 Hz), 8.05 (d, 1H, J=7.6 Hz), 8.67 (d, 1H, J=7.6 Hz), 12.31 (br s, 1H), 13.77 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.0, 29.3, 117.0, 119.5, 123.6, 131.4, 134.2, 139.4, 158.6, 169.1, 198.6; IR (cm^{-1}): ν 2700–3300 br, 3266 w, 2983 w, 1721 m, 1693 s, 1672 s, 1602 m, 1584 m, 1519 s, 1416 m, 1277 s, 761 m, 662 w; MS (EI) m/z (%):222 ([M+1]$^+$, 1), 221 (M$^+$, 8), 164 (35), 146 (100), 119 (16), 90 (19), 57 (30). Anal. Calcd for $C_{11}H_{11}NO_4$ (221.21): C, 59.73; H, 5.01; N, 6.33%. Found: 59.72; H 5.03; N, 6.30%.

*4.5.3. 5-Methoxy-2-[(2-oxobutanoyl)amino]benzoic acid (**3c**).* Colourless shiny crystals, mp 205–207° C (ethyl acetate); R_f=0.11 (5% ethanol in chloroform); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.1 Hz), 2.94 (q, 2H, J=7.1 Hz), 3.80 (s, 3H), 7.27 (dd, 1H, J=9.2, 3.1 Hz), 7.52 (d, 1H, J=3.1 Hz), 8.60 (d, 1H, J=9.2 Hz), 12.05 (br s, 1H), 13.87 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 7.0, 29.4, 55.4. 115.4. 118.4. 120.1. 121.1. 132.7. 154.8. 158.2. 168.7. 198.9: IR (cm^{-1}): ν 2500–3300 br, 3270 w, 2978 w, 1722 m, 1697 s, 1689 s, 1673 s, 1525 s, 1439 s, 1299 s, 1287 s, 1251 s, 1216 s, 1045 m, 829 m; MS (EI) m/z (%): 251 (M$^+$, 4), 207 (15), 194 (17), 176 (51), 167 (46), 150 (28), 149 (70), 122(47), 107(15), 52(16), 45(24), 44(90); Anal. Calcd for $C_{12}H_{13}NO_5$ (251.24): C, 57.37; H, 5.22; N, 5.58%. Found: C, 57.53; H, 5.42; N, 5.58%.

*4.5.4. 4-Methoxy-2-[(2-oxobutanoyl)amino]benzoic acid (**3d**).* Off-white crystals, mp 201–203 °C (benzene–ethyl acetate), R_f=0.08 (5% ethanol in chloroform). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.1 Hz), 2.94 (q, 2H, J=7.1 Hz), 3.23 (s, 3H), 6.80 (dd, 1H, J=8.9, 2.5 Hz), 7.99 (d, 1H, J=8.9 Hz), 8.30 (d, 1H, J=2.5 Hz), 12.46 (br s, 1H), 13.40 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 7.0, 29.3, 55.5, 104.6, 109.3, 109.4, 133.3, 141.4, 158.8, 163.5, 168.9, 198.4; IR (cm^{-1}): ν 2800–3400 br, 3180 w, 2972 w, 1698 s, 1688 s, 1661 s, 1608 s, 1583 s, 1530s, 1248 s, 1211 s, 1140 m, 1027 m, 830 m, 624 w; MS (EI) m/z (%): 252 ([M+1]$^+$, 2), 251 (M$^+$, 6), 176 (55), 97 (43), 85 (49), 83 (45), 71 (79), 69 (43), 57 (100), 43 (77). Anal. Calcd for $C_{12}H_{13}NO_5$ (251.24): C, 57.37: H. 5.22: N. 5.58%. Found: C. 57.28: H 5.43: N. 5.41%.

*4.5.5. 3-Methoxy-2-[(2-oxobutanoyl)amino]benzoic acid (**3e**).* Off-white crystals, mp 142–146 °C (benzene–cyclohexane), R_f=0.13 (5% ethanol in chloroform). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.2 Hz), 2.87 (q, 2H, J=7.2 Hz), 3.81 (s, 3H), 7.27–7.41 (m, 3H), 9.83 (br s, 1H), 12.89 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 7.1, 30.2, 56.1, 115.3, 121.5, 124.3, 127.0, 128.8, 154.1, 159.5, 167.3, 199.2; IR (cm^{-1}): ν 2800–3400 br, 3330 m, 2974 w, 2943 w, 1716 s, 1679 s, 1537 m, 1479 m, 1287 m, 1203 m, 1054 m, 760 w, 760 w, 720 w, 647 w; Anal. Calcd for $C_{12}H_{13}NO_5 \cdot 0.25H_2O$ (255.74): C, 56.36; H, 5.32; N, 5.48%. Found: C, 56.31; H 5.25; N, 5.48%.

*4.5.6. 5-Methyl-2-(2-oxobutanamido)benzoic acid (**3f**).* Colourless shiny crystals, mp 199–205 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.2 Hz), 2.32 (s, 3H), 2.95 (q, 2H, J=7.2 Hz), 7.47 (dd, 1H, J=7.5, 2.0 Hz), 7.86 (d, 1H, J=2.0 Hz), 8.57 (d, 1H, J=7.5 Hz), 12.23 (br s, 1H), 13.76 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): 7.1, 20.3, 29.4, 116.9, 119.5, 131.6, 132.9, 134.8, 137.1, 158.5, 169.2, 198.7; IR (cm^{-1}): ν 3480 w, 3275 m, 1693 s, 1673 s, 1595 m, 1524 s, 1419 m, 1292 m, 1270 s, 1223 s, 916 m, 893 m, 794 m, 754 m, 665 m; HRMS (ESI+): m/z calcd for $C_{12}H_{14}NO_4^+$ [M+H]$^+$ 236.0917, found 236.0914.

*4.5.7. 3-Methyl-2-[(2-oxobutanoyl)amino]benzoic acid (**3g**).* Yellowish solid, mp 130–136 °C (benzene). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.03 (t, 3H, J=7.2 Hz), 2.20 (s, 3H), 2.90 (q, 2H, J=7.2 Hz), 7.29 (dd, 1H, J=7.7, 7.7 Hz), 7.48 (d, 1H, J=7.7 Hz), 7.69 (d, 1H, J=7.7 Hz), 10.29 (br s, 1H), 12.97 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.0. 18.2. 30.1. 126.2. 127.8. 127.9. 134.0. 134.5. 135.7. 159.4, 167.5, 199.0; IR (cm^{-1}): ν 2600–3400 br, 3343 w, 2985 w, 1724 s, 1697 s, 1678 s, 1597 m, 1515 s, 1468 m, 1431 m, 1405 m, 1291 s, 1193 m, 1113 m, 756 s; HRMS (ESI+): m/z calcd for $C_{12}H_{14}NO_4^+$ [M+H]$^+$ 236.0917; found 236.0922.

*4.5.8. 6-Chloro-3-methyl-2-[(2-oxobutanoyl)amino]benzoic acid (**3h**).* Colourless crystals, mp 189–191 °C (benzene). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (t, 3H, J=7.2 Hz, CH_3CH_2), 2.12 (s, 3H, CH_3–C_3), 2.87 (q, 2H, J=7.2 Hz, CH_2), 7.37 (d, J=8.3 Hz, 1H, H4), 7.41 (d, 1H, J=8.3 Hz, H5), 10.22 (br s, 1H, NH), 13.01 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.0 (CH_3CH_2), 17.2 (CH_3–C3), 30.4 (CH_2), 126.6 (C6), 128.1 (C5), 131.8 (C4), 133.2 (C2), 133.4 (C1), 135.6 (C3), 160.4 (NHCO), 165.9 (COOH), 199.0 ($COCH_2$); ^{15}N NMR (51 MHz, DMSO-d_6) δ 118; IR (cm^{-1}): ν 2700–3500 br, 3219 w, 2983 w, 2936 w, 1716 s, 1668 s, 1530 m, 1210 s, 1171 s, 1107 m, 694 m; HRMS (ESI–): m/z calcd for $C_{12}H_{11}ClNO_4^-$ [M–H]$^-$ 268.0382, found 268.0393.

*4.5.9. 2-[(2-Oxohexanoyl)amino]benzoic acid (**3i**).* Colourless shiny crystals. mp 147–151 °C (ethyl acetate): ^{1}H NMR (500 MHz. DMSO-d_6) δ 0.90 (t, 3H, J=2.4 Hz, CH_3), 1.29–1.37 (m, 2H, CH_2CH_3), 1.50–1.57 (m, 2H, $CH_2CH_2CH_3$), 2.93 (t, 2H, J=7.3 Hz, $COCH_2$), 7.24 (ddd, 1H, J=7.7, 7.7, 1.0 Hz, H5), 7.67 (ddd, 1H, J=7.7, 7.7, 1.6 Hz, H4), 8.05 (dd, 1H, J=7.7, 1.6 Hz, H6), 8.67 (dd, 1H, J=7.7, 1.0 Hz, H3), 12.33 (br s, 1H, NH), 13.81 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8 (CH_3), 21.6 (CH_2CH_3), 24.8 ($CH_2CH_2CH_3$), 35.4 (CH_2CO), 117.0 (C1), 119.5 (C3), 123.6 (C5), 131.5 (C6), 134.3 (C4), 139.4 (C2), 158.6 (NCO), 169.1 (COOH), 198.1 ($COCH_2$); ^{15}N NMR (51 MHz, DMSO-d_6) δ 119; IR (cm^{-1}): ν 2300–3300 br, 3252 w, 2957 w, 2871 w, 1723 m, 1695 s, 1668 s, 1603 m, 1586 s, 1521 s, 1412 m, 1283 s, 1265 s, 762 s, 662 m; MS (EI): m/z, (%) 249 (M$^+$, 6), 164 (43), 146 (100), 90 (19), 57 (32); HRMS (ESI+): m/z Calcd for $C_{13}H_{16}NO_4^+$ [M+H]$^+$ 250.1074; found 250.1075. Anal. Calcd for $C_{13}H_{15}NO_4$ (249.26): C, 62.64; H, 6.07; N, 5.62%. Found: C, 62.93; H 6.14; N, 5.70%.

*4.5.10. 3,5-Dimethyl-2-[(2-oxohexanoyl)amino]benzoic acid (**3j**).* Colourless crystals, mp 109–110 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, 3H, J=7.4 Hz, CH_3CH_2), 1.28–1.36 (m, 2H. CH_2CH_3). 1.50–1.57 (m. 2H. $CH_2CH_2CH_3$). 2.15 (s. 3H. CH_3–C3). 2.31 (s, 3H, CH_3–C5), 2.86 (q, 2H, J=7.3 Hz, $COCH_2$), 7.29 (d, 1H, J=1.3 Hz, H4), 7.50 (d, 1H, J=1.3 Hz, H6), 10.17 (br s, 1H, NH), 12.89 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.7 (CH_2CH_3), 18.0 (CH_3–C3), 20.2 (CH_3–C5), 21.5 (CH_2CH_3), 24.8 ($CH_2CH_2CH_3$), 36.2 ($COCH_2$), 127.6 (C1), 128.3 (C6), 132.0 (C2), 134.5 (C4), 135.5 (C3), 135.6 (C1), 159.6 (NHCO), 167.6 (COOH), 198.8 ($COCH_2$); ^{15}N NMR (51 MHz, DMSO-d_6) δ 118; IR (cm^{-1}): ν 3332 w, 2500–3300 br, 2963 w, 2930 w, 1726 m, 1690 s, 1671 s, 1511 s, 1431 m, 1313 m, 1242 m, 1150 w, 727 w; HRMS (ESI–): m/z Calcd for $C_{15}H_{18}NO_4^-$ [M–H]$^-$ 276.1241, found 276.1248.

*4.5.11. 3,5-Dimethoxy-2-[(2-oxohexanoyl)amino]benzoic acid (**3k**).* Pale yellow microcrystals, mp 101–105 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, 3H, J=7.4 Hz), 1.28–1.35 (m, 2H), 1.50–1.55 (m, 2H), 2.83 (t, 2H, J=7.2 Hz), 3.78 (s, 3H), 3.81 (s, 3H),

6.84 (d, 1H, *J*=2.7 Hz), 6.89 (d, *J*=2.7 Hz), 9.66 (br s, 1H), 12.93 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8, 21.7, 25.0, 36.4, 55.6, 56.2, 102.5, 105.4, 117.5, 129.9, 155.5, 158.2, 159.9, 167.1, 199.2; IR (cm^{-1}): ν 3384 m, 2500–3200 br, 2964 w, 2875 w, 1698 s, 1601 m, 1510 s, 1465 m, 1355 m, 1299 m, 1211 s, 1154 s, 1070 m, 1048 m; HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{20}NO_6^+$ $[M+H]^+$ 310.1285, found 310.1284; Anal. Calcd for $C_{15}H_{19}NO_6$ (309.31): C, 58.25; H, 6.19; N, 4.53%. Found: C, 58.07; H, 6.20; N, 5.02%.

*4.5.12. 1-[(2-Oxohexanoyl)amino]naphthalene-2-carboxylic acid (**3l**).* White powder, mp 98–105 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J*=7.4 Hz, CH_3CH_2), 1.32–1.40 (m, 2H, CH_2CH_3). 1.56–1.62 (m. 2H. $CH_2CH_2CH_3$). 2.92 (t, 3H. *J*=7.3 Hz. $COCH_2$), 7.60 (ddd, 1H, *J*=7.6, 7.6, 1.0 Hz, H7), 7.66 (ddd, 1H, *J*=7.6, 7.6, 1.0 Hz, H6), 7.91 (d, 1H, *J*=8.6 Hz, H3), 7.96 (d, 1H, *J*=8.6 Hz, H4), 8.00 (br d, 1H, *J*=7.6 Hz, H8), 8.01 (d, 1H, *J*=8.1 Hz, H5), 10.76 (br s, 1H, NH), 13.17 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8 (CH_2CH_3), 21.7 (CH_2CH_3), 25.0 ($CH_2CH_2CH_3$), 36.3 ($COCH_2$), 124.9 (C2), 125.4 (C2), 126.0 (C3), 126.7 (C7), 126.8 (C4), 127.8 (C5), 128.1 (C6), 129.3 (C8a), 134.1 (C1), 135.0 (C4a), 160.8 (NCO), 167.6 (COOH), 198.6 ($COCH_2$); IR (cm^{-1}): ν 2800–3300 br, 3294 w, 2961 w, 2877 w, 1694 s, 1675 s, 1571 m, 1501, 1409 m, 1284 m, 1258 m, 764 m; MS (EI, 70 eV) *m*/*z* (%): 300 ($[M+1]^+$, 2), 299 (M^+, 11), 214 (50), 197 (14), 196 (100), 187 (27), 169 (44), 141 (19), 140 (49), 115 (33), 114 (16), 85 (17), 57 (58), 43 (11), 41 (50). HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{18}NO_4^+$ $[M+H]^+$ 300.1230, found 300.1229. Anal. Calcd for $C_{17}H_{17}NO_4$ (173.60): C, 68.21; H, 5.72; N, 4.68%. Found: C, 68.45; H 5.91; N, 5.71%.

*4.5.13. 2-{[Oxo(phenyl)acetyl]amino}benzoic acid (**3m**).*[9] For IR and ^{1}H NMR (60 MHz) data, see Ref. 9 Colourless crystals, mp 199–200 °C (ethanol). mp[9] 200 °C. R_f=0.18 (5% EtOH in $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29 (dd, 1H, *J*=7.5, 7.5 Hz), 7.60 (dd, 2H, *J*=7.5, 7.5 Hz), 7.68–7.78 (m, 2H), 8.08 (d, 1H, *J*=7.5 Hz), 8.24 (d, 2H, *J*=7.5 Hz), 8.67 (d, 1H, *J*=7.5 Hz), 12.43 (br s, 1H), 13.80 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 117.7, 120.1, 124.0, 128.6, 130.8, 131.4, 133.0, 134.1, 134.4, 139.3, 160.2, 169.1, 187.4; IR (cm^{-1}): ν 2600–3300 br, 3236 w, 3070 w, 1696 s, 1682 s, 1672 s, 1585 s, 1524 s, 1409 m, 1265 s, 758 m, 689 w, 660 w.

*4.5.14. 2-[Methyl(2-oxobutanoyl)amino]benzoic acid (**3n**).* Colourless crystals, mp 113–115 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.75 (t, 3H, *J*=7.3 Hz), 2.50–2.71 (m, 2H), 3.17 (s, 3H), 7.44–7.50 (m, 2H), 7.64 (ddd, 1H, *J*=7.7, 7.7, 1.6 Hz), 7.90 (dd, 1H, *J*=7.7, 1.6 Hz), 13.29 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 6.8, 31.9, 36.6, 128.4, 128.5, 130.0, 131.3, 133.4, 141.5, 165.6, 166.4, 200.6; IR (cm^{-1}): ν 2800–3200, 2985 w, 1732 m, 1709 s, 1632 s, 1598 m, 1237 s, 861 w, 644 w; MS (EI) *m*/*z* (%): 179 (11), 178 (100), 134 (61), 105 (35), 104 (20), 77 (32), 57 (43); HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{14}NO_4^+$ $[M+H]^+$ 236.0917, found 236.0912.

*4.5.15. 2-[Methyl(2-oxohexanoyl)amino]benzoic acid (**3o**).* Colourless crystals, mp 101–105 °C (benzene), *Rf*=0.18 (5% ethanol in chloroform). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.74 (t, 3H, *J*=7.2 Hz), 0.98–1.11 (m, 2H, CH_2CH_3), 1.19–1.31 (m, 2H, $CH_2CH_2CH_2$), 2.43–2.70 (m, 2H, $COCH_2$), 3.17 (s, 3H), 7.42–7.52 (m, 2H), 7.64 (ddd, 1H, *J*=7.7, 7.7, 1.3 Hz), 7.91 (dd, 1H, *J*=7.7, 1.3 Hz), 13.25 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.5, 21.2, 24.3, 36.5, 38.1, 128.5, 128.6, 130.2, 131.3, 133.3, 141.3, 165.7, 166.3, 200.1; IR (cm^{-1}): ν 2600–3300 br, 2959 w, 2623 w, 1714 s, 1620 s, 1595 m, 1396 m, 1247 m, 1140 w, 1083 w, 1067 w, 784 w, 710 w; Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32%. Found: C, 63.70; H 6.47; N, 5.26%.

*4.5.16. 2-(N-Methyl-2-oxo-2-phenylacetamido)benzoic acid (**3p**).* Colourless crystals, mp 145–146 °C (benzene-cyklohexane), R_f=0.21 (5% ethanol in chloroform), 0.05 (20% ethyl acetate in benzene); ^{1}H NMR (500 MHz, CD_3CN) δ 3.37 (s, 3H, CH_3), 7.34 (dd, 1H, *J*=7.8, 1.2 Hz, H3), 7.39 (ddd, *J*=7.8, 7.8, 1.2 Hz, H5), 7.44–7.50 (m, 3H, H4, H3′, H5′), 7.61–7.65 (m, 1H, H4′), 7.79–7.82 (m, 2H, H2′, H6′), 7.89 (dd, 1H, *J*=7.8, 1.2 Hz, H6), resonances for exchangeable protons in the baseline; ^{13}C NMR (126 MHz, CD_3CN) δ 36.9 (CH_3), 129.9 (C3′, C5′), 130.1 (C5), 130.2 (C1), 130.4 (C2′, C6′), 132.0 (C3), 132.9 (C6), 134.1 (C1′), 134.6 (C4), 135.6 (C4′), 141.9 (C2), 166.2 (COOH), 166.8 (NCO), 192.0 (COPh); IR (cm^{-1}): ν 2500–3300 br, 1719 s, 1680 s, 1616 s, 1593 s, 1576 m, 1249 s, 1236 s, 1220 s, 1081 s, 779 s, 715 s, 668 m; MS (EI) *m*/*z* (%): 105 (69), 77 (58), 57 (26), 45 (28), 44 (100), 43 (92), 42 (27), 41 (36); HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{14}NO_4^+$ $[M+H]^+$ 284.0917. found 284.0918: Anal. Calcd for $C_{16}H_{13}NO_4$ (283.28): C, 67.84; H, 4.63; N, 4.94%. Found: C, 67.81; H 4.60; N, 4.90%.

4.6. Hydrolysis of *N*-(α-ketoacyl)anthranilic acids 3

To a stirred suspension of *N*-(α-ketoacyl)anthranilic acids **3** (3 mmol) in water (10 mL) aqueous hydrochloric acid (37%, 15 mL) was added portion-wise at room temperature. The reaction mixture was refluxed, until the starting compound **3** was present according to TLC analysis (1–7 h). The reaction mixture was cooled down to room temperature and the precipitate (if formed) was removed by filtration. The filtrate was evaporated to dryness using rotary evaporator and the residue was recrystallized to give anthranilic acid hydrochloride (**4**·**HCl**).

*4.6.1. 2-Aminobenzoic acid hydrochloride (**4b**·**HCl**).* *N*-(α-Ketoacyl) anthranilic acids **3b**; Reaction time: 4 h. White crystalline solid, yield 443 mg (85%), mp 167–172 °C (ethanol–ethyl acetate), mp[47] 193–194 °C: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.93 (dd. 1H. *J*=7.6. 7.6 Hz), 7.13 (d, 1H, *J*=7.6 Hz), 7.43 (dd, 1H, *J*=7.6, 7.6, 1.5 Hz), 7.8 (br s, 4H), 7.84 (dd, 1H, *J*=7.6, 1.5 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 115.5, 119.9, 120.2, 131.3, 133.9, 144.1, 168.4; IR (cm^{-1}): ν 2400–3300 br, 2980 w, 2681 w, 2569 w, 1693 s, 1561 m, 1494 m, 1460 m, 1393 m, 1219 s, 1100 m, 758 m, 752 m, 650 m; HRMS (ESI+): *m*/*z* calcd for $C_7H_8NO_2^+$ $[M+H]^+$ 138.0550, found 138.0548.

*4.6.2. 2-Amino-5-methoxybenzoic acid hydrochloride (**4c**·**HCl**).* *N*-(α-Ketoacyl)anthranilic acids **3c**; Reaction time: 6 h. Yellowish solid, yield 556 mg (91%), mp 211–214 °C (ethanol–ethyl acetate), mp[48] 213–214 °C (ethanol–diethyl ether); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.80 (s, 3H), 7.25 (dd, 1H, *J*=8.8, 3.0 Hz), 7.45 (d, 1H, *J*=3.0 Hz), 7.50 (d, 1H, *J*=8.8 Hz), 9.8 (br s, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.7, 115.5, 119.9, 122.8, 124.9, 128.8, 156.8, 166.8; IR (cm^{-1}): ν 2500–3300 br, 2845 w, 2617 w, 1698 s, 1614 s, 1509 s, 1404 m, 1273 s, 1234 s, 1025 m, 845 m, 741 m; HRMS (ESI+): *m*/*z* calcd for $C_8H_{10}NO_3^+$ $[M+H]^+$ 168.0655, found 168.0652.

*4.6.3. 2-Amino-4-methoxybenzoic acid hydrochloride (**4d**·**HCl**).* *N*-(α-Ketoacyl)anthranilic acids **3d**; Reaction time: 7 h. Colourless crystals, yield 391 mg (64%), mp 176–179 °C (ethanol–diethyl ether), mp[48] 178–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.72 (s, 3H), 6.11 (dd, 1H, *J*=8.9, 2.5 Hz), 6.25 (d, 1H, *J*=2.5 Hz), 7.61 (d, 1H, *J*=8.9 Hz), resonances for exchangeable protons in the baseline; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 54.9, 98.6, 103.16, 103.21, 132.9, 153.5, 163.6, 169.2; IR (cm^{-1}): ν 2600–3300 br, 2577 w, 1687 s, 1631 m, 1596 m; 1403 m, 1338 m, 1246 s, 1113 m, 1021 m; HRMS (ESI+): *m*/*z* calcd for $C_8H_{10}NO_3^+$ $[M+H]^+$ 168.0655, found 168.0653. Anal. Calcd for $C_8H_{10}ClNO_3$ (203.62): C, 47.19; H, 4.95; N, 6.88. Found: C, 47.38; H 5.10; N, 6.82.

*4.6.4. 2-Amino-3-methoxybenzoic acid hydrochloride (**4e**·**HCl**).* *N*-(α-Ketoacyl)anthranilic acids **3e**; Reaction time: 1 h. White solid, yield 415 mg (68%) (crude, analytically pure product), mp

178–188 °C, mp[49] 205–206 °C (hydrochloric acid); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.82 (s, 3H), 6.61 (dd, 1H, J=8.0, 8.0 Hz), 7.02 (dd, 1H, J=8.0, 1.0 Hz), 7.36 (dd, 1H, J=8.0, 1.0 Hz), resonances for exchangeable protons in the baseline; ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.8, 111.1, 113.7, 115.4, 122.5, 139.6, 147.3, 169.4; IR (cm^{-1}): ν 3485 m, 3418 m, 2500–3400 br, 3064 w, 2616 w, 1699 s, 1651 s, 1589 m, 1478 s, 1362 s, 1286 s, 1213 s, 1049 s, 755 m; HRMS (ESI+): m/z calcd for $C_8H_{10}NO_3^+$ $[M+H]^+$ 168.0655, found 168.0653. Anal. Calcd for $C_8H_{10}ClNO_3$ (203.62): C, 47.19; H, 4.95; N, 6.88%. Found: C, 47.32; H 5.11; N, 6.85%.

*4.6.5. 2-(Methylamino)benzoic acid hydrochloride (**4n**·**HCl**).* *N*-(α-Ketoacyl)anthranilic acids **3n**: Reaction time: 2 h. Colourless needles, yield 411 mg (73%), mp 136–140 °C (ethanol–benzene), mp[50] 141 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.85 (s, 3H), 6.65 (dd, 1H, J=7.7, 7.7 Hz), 6.78 (d, 1H, J=7.7 Hz), 7.42 (ddd, 1H, J=7.7, 7.7, 1.6 Hz), 7.81 (dd, 1H, J=7.7, 1.6 Hz), resonances for exchangeable protons in the baseline; ^{13}C NMR (126 MHz, DMSO-d_6) δ 29.8, 111.0, 111.8, 115.2, 131.6, 134.5, 150.6, 169.7; IR (cm^{-1}): ν 3386 m, 2898 m, 2730 m, 2650 m, 1694 m, 1662 s, 1304 s, 1271 s, 1122 m, 772 m, 750 s, 699 m; HRMS (ESI−): m/z Calcd for $C_8H_8NO_2^-$ $[M-H]^-$ 150.0561, found 150.0558. Anal. Calcd for $C_8H_{10}ClNO_2$ (187.62): C, 51.21; H, 5.37; N, 7.47%. Found: C, 51.32; H 5.24; N, 7.71%.

Acknowledgements

This study was supported by the internal grant of the TBU in Zlin (No. IGA/FT/2013/003) funded from the resources of specific university research and the Ministry of Higher Education, Science and Technology of the Republic of Slovenia and the Slovenian Research Agency (Grant P1-0230-0103). This work was also partly supported through the infrastructure of the EN-FIST Centre of Excellence, Ljubljana.

References and notes

1. Andreichikov, Y. S.; Krylova, I. V. *Zh. Org. Khim.* **1988**, *24*, 2212–2216.
2. Lingens, F.; Sproessler, B. *Justus Liebigs Ann. Chem.* **1967**, *702*, 169–179.
3. Akbas, E.; Sonmez, M.; Celebi, M.; Aslanoglu, F. *J. Chem. Res.* **2008**, 256–259.
4. Wegfahrt, P. F.; Rapoport, H. *J. Org. Chem.* **1969**, *34*, 3035–3039.
5. Zhang, C.; Zong, X.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 3280–3283.
6. Shibuya, M.; Sakurai, H.; Maeda, T.; Nishiwaki, E.; Saito, M. *Tetrahedron Lett.* **1986**, *27*, 1351–1354.
7. Filippo Rossi, P.; Massimino, A. *Gazz. Chim. Ital.* **1962**, *92*, 1478–1480.
8. Podesva, C.; Solomon, C.; Vagi, K. *Can. J. Chem.* **1968**, *46*, 435–439.
9. Rabilloud, G.; Sillion, B. *Bull. Soc. Chim. Fr.* **1975**, 2682–2686.
10. Fatiadi, A. J. *Synthesis* **1974**, 229–272.
11. Ermolinsky, B. S.; Mikhailov, S. N. *Russ. J. Bioorg. Chem.* **2000**, *26*, 429–504.
12. Klásek, A.; Kafka, S.; Kappe, T. *Collect. Czech. Chem. Commun.* **1995**, *60*, 2137–2146.
13. Klásek, A.; Kafka, S. *J. Heterocycl. Chem.* **1998**, *35*, 307–311.
14. Klásek, A.; Koristek, K.; Polis, J.; Košmrlj, J. *Heterocycles* **1998**, *48*, 2309–2326.
15. Klásek, A.; Koristek, K.; Polis, J.; Košmrlj, J. *Tetrahedron* **2000**, *56*, 1551–1560.
16. Kafka, S.; Klásek, A.; Košmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394–6399.
17. Klásek, A.; Polis, J.; Mrkvička, V.; Košmrlj, J. *J. Heterocycl. Chem.* **2002**, *39*, 1315–1320.
18. Kafka, S.; Klásek, A.; Polis, J.; Košmrlj, J. *Heterocycles* **2002**, *57*, 1659–1682.
19. Klásek, A.; Koristek, K.; Kafka, S.; Košmrlj, J. *Heterocycles* **2003**, *60*, 1811–1820.
20. Klásek, A.; Mrkvička, V.; Pevec, A.; Košmrlj, J. *J. Org. Chem.* **2004**, *69*, 5646–5651.
21. Košmrlj, J.; Kafka, S.; Leban, I.; Grad, M. *Magn. Reson. Chem.* **2007**, *45*, 700–704.
22. Pomeisl, K.; Kvíčala, J.; Paleta, O.; Klásek, A.; Kafka, S.; Kubelka, V.; Havlíček, J.; Čejka, J. *Tetrahedron* **2007**, *63*, 10549–10561.
23. Kafka, S.; Klásek, A.; Polis, J.; Rosenbrejerová, V.; Palík, C.; Mrkvička, V.; Košmrlj, J. *Tetrahedron* **2008**, *64*, 4387–4402.
24. Kafka, S.; Kovář, M.; Klásek, A.; Kappe, T. *J. Heterocycl. Chem.* **1996**, *33*, 1977–1982.
25. Baumgarten, P.; Kärgel, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 832–842.
26. Bowman, R. E.; Campbell, A.; Tanner, E. M. *J. Chem. Soc.* **1959**, 444–447.
27. Stadlbauer, W.; Lutschounig, H.; Schindler, G.; Witoszynskyj, T.; Kappe, T. *J. Heterocycl. Chem.* **1992**, *29*, 1535–1540.
28. Kafka, S.; Pevec, A.; Proisl, K.; Kimmel, R.; Košmrlj, J. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2013**, *E69*, o231.
29. Kafka, S.; Pevec, A.; Proisl, K.; Kimmel, R.; Košmrlj, J. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, *E68*, o3199–o3200.
30. Ficini, J.; Krief, A. *Tetrahedron Lett.* **1968**, 947–951.
31. Curd, F. H. S.; Raison, C. G.; Rose, F. L. *J. Chem. Soc.* **1947**, 899–909.
32. Kimmel, R.; Kafka, S.; Košmrlj, J. *Carbohydr. Res.* **2010**, *345*, 768–779.
33. Ukrainets, I. V.; Taran, S. G.; Evtifeeva, O. A.; Gorokhova, O. V.; Bezuglyi, P. A.; Turov, A. V.; Voronina, L. N.; Filimonova, N. I. *Khim. Geterotsikl. Soedin.* **1994**, 673–678.
34. McCorkindale, N. J. *Tetrahedron* **1961**, *14*, 223–229.
35. Stadlbauer, W.; Kappe, T. *Monatsh. Chem.* **1985**, *116*, 1005–1015.
36. Cooke, R. G.; Haynes, H. F. *Aust. J. Chem.* **1959**, *7*, 273–276.
37. Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc.* **1959**, *81*, 3738–3743.
38. Kafka, S.; Pevec, A.; Proisl, K.; Kimmel, R.; Košmrlj, J. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, *E68*, o3198.
39. Rügheimer, L.; Schramm, C. G. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 299–307.
40. Bezuglyi, P. A.; Ukrainets, I. V.; Treskach, V. I.; Turov, A. V. *Khim. Geterotsikl. Soedin.* **1992**, *4*, 522–524.
41. I. G. Farbenindustrie AG, Patent DE 490274, 1926.
42. Stadlbauer, W.; Laschober, R.; Lutschounig, H.; Schindler, G.; Kappe, T. *Monatsh. Chem.* **1992**, *123*, 617–636.
43. Stadlbauer, W.; Schmut, O.; Kappe, T. *Monatsh. Chem.* **1980**, *111*, 1005–1013.
44. Braeuniger, H.; Stens, B. *Pharmazie* **1963**, *18*, 585–600.
45. Stadlbauer, W.; Kappe, T. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, *37*, 1196–1200.
46. Nishimura, H.; Nagai, Y.; Suzuki, T.; Sawayama, T. *Yakugaku Zasshi* **1970**, *90*, 818–828 *Chem. Abstr.* **1970**, *73*, 77020.
47. Fischer, E. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 2062–2064.
48. Karimov, A.; Telezhenetskaya, M. V.; Yunusov, S. *Khim. Prir. Soedin.* **1982**, *18*, 498–504.
49. Nyc, J. F.; Mitchell, H. K. *J. Am. Chem. Soc.* **1948**, *70*, 1847–1848.
50. Schultz, G.; Flachslaender, J. *Z. Farben- Text.-Chem.* **1902**, *1*, 353–354.

Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 9650

Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids into 2-(indol-2-carboxamido)benzoic acids and 2-indolyl-3,1-benzoxazin-4-ones and their NMR study†‡

Karel Proisl,[a] Stanislav Kafka,*[a] Damijana Urankar,[b] Martin Gazvoda,[b] Roman Kimmel[a] and Janez Košmrlj*[b]

Received 11th August 2014,
Accepted 1st October 2014

DOI: 10.1039/c4ob01714e

www.rsc.org/obc

N-(α-ketoacyl)anthranilic acids reacted with phenylhydrazinium chloride in boiling acetic acid to afford 2-(indol-2-carboxamido)benzoic acids in good to excellent yields and 2-indolyl-3,1-benzoxazin-4-ones as by-products. The formation of the latter products could easily be suppressed by a hydrolytic workup. Alternatively, by increasing the reaction temperature and/or time, 2-indolyl-3,1-benzoxazin-4-ones can be obtained exclusively. Optimisations of the reaction conditions as well as the scope and the course of the transformations were investigated. The products were characterized by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The corresponding resonances were assigned on the basis of the standard 1D and gradient selected 2D NMR experiments (^{1}H–^{1}H *gs*-COSY, ^{1}H–^{13}C *gs*-HSQC, ^{1}H–^{13}C *gs*-HMBC) with ^{1}H–^{15}N *gs*-HMBC as a practical tool to determine ^{15}N NMR chemical shifts at the natural abundance level of ^{15}N isotope.

Introduction

Molecules containing indole[1] and anthranilic acid[2] scaffolds are ubiquitous in many natural products with diverse biological activities. Thus, it is not surprising that the compounds featuring both the indole and the anthranilic acid fragments are encountered in nature. Alkaloids cephalandole C and cephalinone B, isolated from the native orchid plant *Cephalanceropsis gracilis*,[3] and the alkaloids secofascaplysins, isolated from the sponge *Fascaplysinopsis reticulate*,[4] consist of the 2-(indol-2-carboxamido)benzoic acid **1** substructures, for example (Fig. 1). Derivatives of 2-(indol-2-carboxamido)benzoic acid **1** are receiving attention because of their antibacterial activities.[5] In materials sciences, the 2-(indol-2-carboxamido)-benzoic acid derivatives are used as UV absorbers.[6] Compounds with indol-2-carboxamide scaffold are potent inhibitors of HIV-1 replication (Delavirdine, *Rescriptor*®)[7] and the androgen receptor binding function 3 (BF3),[8] and were identified as hydrogen-bonding organocatalysts for the ring-opening polymerization of cyclic esters.[9]

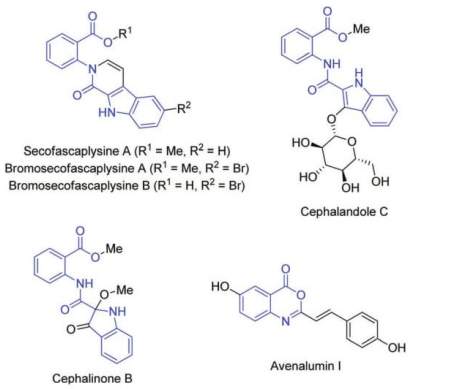
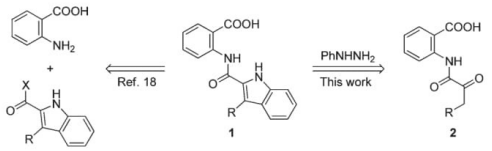


Fig. 1 Naturally occurring compounds containing 2-(indol-2-carboxamido)benzoic acid and 3,1-benzoxazin-4-one substructures (blue).

3,1-Benzoxazin-4-ones serve as valuable precursors for the preparation of fused heterocycles including an important pharmacophore, quinazolin-4-one.[10] It is also noteworthy that 3,1-benzoxazin-4-ones are potent inhibitors of the human leukocyte elastase,[11] human chymase,[12] chymotrypsin[13] and

[a]*Department of Chemistry, Faculty of Technology, Tomas Bata University in Zlin, 762 72 Zlin, Czech Republic. E-mail: kafka@ft.utb.cz*
[b]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia. E-mail: janez.kosmrlj@fkkt.uni-lj.si*
† Dedicated to Professor Marijan Kočevar on his 65th birthday.
‡ Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c4ob01714e



Scheme 1 Two retrosynthetic approaches to 2-(indol-2-carboxamido) benzoic acids **1**.

proteases of herpes simplex type 1,[14] human cathepsin G[15] and serine,[16] for example. Avenalumin I, phytoalexin of the 3,1-benzoxazin-4-one structure that is inhibitory to the growth of rust fungi, was isolated from oat leaves (Fig. 1).[17]

Surprisingly, despite the biological relevance and synthetic potential of 2-(indol-2-carboxamido)benzoic acids **1**, to our knowledge, the only published approach to access these compounds makes use of N-acylation of anthranilic acids with 1*H*-indol-2-carboxylic acid derivatives.[18] As an alternative to this, herein we report the protocol that is based on the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids **2** (Scheme 1). Optimization of the reaction conditions and the scope as well as multinuclear NMR spectral analysis of the products is reported.

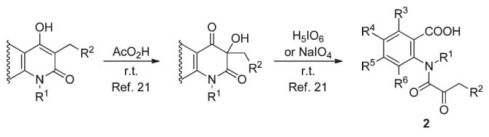
Results and discussion

Synthesis

Out of the available methods to access indoles, the Fischer indole synthesis remains one of the most important and versatile methods.[19] It is generally conducted by reacting an aryl hydrazine with a carbonyl compound.[19,20] Thus, for the construction of 2-(indol-2-carboxamido)benzoic acid **1** through this pathway *N*-(α-ketoacyl)anthranilic acid **2** appears to be the most suitable carbonyl substrate. Based on our recent report,[21] the latter is easily accessible through the consecutive oxidation protocol from 4-hydroxyquinolin-2-one as shown in Scheme 2.

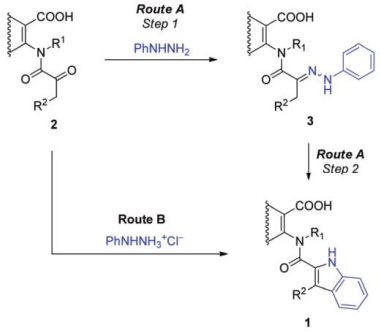
The Fischer indolisation is known to proceed through an intermediately formed hydrazone, which then undergoes several consecutive transformations. It isomerises to an enamine, which after protonation rearranges to an imine and then a cyclic aminal. Acid catalysed elimination of ammonia from the latter finally gives rise to the indole ring. The above mentioned hydrazone can in principle be pre-assembled by condensation of aryl hydrazine with an appropriate carbonyl compound. Herein, we decided to compare the stepwise protocol that proceeds through the isolated phenylhydrazone **3** (*Route A*, Scheme 3) with the direct-one in which *N*-(α-ketoacyl) anthranilic acids **2** are treated with phenylhydrazine directly into the 2-(indol-2-carboxamido)benzoic acid **1** (*Route B*).

To examine the stepwise protocol, *Route A*, phenylhydrazones **3a,c–e** were initially prepared by the condensation of *N*-(α-ketoacyl)anthranilic acids **2a,c–e** with phenylhydrazine. The isolated phenylhydrazones were in the subsequent step subjected to the thermally induced rearrangement into



2	R^1	R^2	R^3	R^4	R^5	R^6
a	H	Me	H	H	H	H
b	H	Me	H	OMe	H	H
c	H	Me	H	H	OMe	H
d	H	Me	H	H	H	OMe
e	Me	Me	H	H	H	H
f	H	*n*-Pr	H	H	H	H
g	H	Me	H	H	H	Me
h	H	Me	H	Me	H	H
i	H	Me	Me	H	H	Cl
j	H	*n*-Pr	H	Me	H	Me
k	H	*n*-Pr	H	OMe	H	OMe
l	H	Ph	H	H	H	H
m	H	*n*-Pr	H	H	–(CH)4–	

Scheme 2 The preparation of the starting *N*-(α-ketoacyl)anthranilic acids **2** and the key of substituents R^1–R^6.



Scheme 3 The stepwise (*Route A*) and direct (*Route B*) routes to the 2-(indol-2-carboxamido)benzoic acids **1** by the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids **2**.

Table 1 Results of the stepwise protocol to indoles 1 (Scheme 3, Route A)

Step 1		Step 2	
Reaction conditions	**3**, yield[a]	Reaction conditions	**1**, yield[a]
AcOH, 60 °C, 2 h	**3a**, 88	235 °C, 20 min	**1a**, 27
AcOH, 60 °C, 3 h	**3c**, 80	180 °C, 10 min	**1c**, 17
AcOH, 60 °C, 3 h	**3d**, 79	245 °C, 15 min	**1d**, 28
AcOH, 60 °C, 1.25 h	**3e**, 78	180 °C, 15 min	**1e**, 33

[a] Percent yields of isolated pure products are given.

2-(indol-2-carboxamido)benzoic acids **1a,c–e**. The results are collected in Table 1. Although the preparation of the phenylhydrazones **3a,c–e** proceeded in high 78–88% yields, the sub-

Table 2 Solvent and catalyst screening for the Fischer indolisation of **2** into **1** following the Route B (Scheme 3)

Entry	2	Solvent[a]	Additive, reaction time in h	1	Yield[b]
1	**2a**	AcOH	None, 9	**1a**	78
2	**2a**	MeOH	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 8	**1a**	26
3	**2a**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 5	**1a**	65
4	**2a**	MeCN	10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 12	**1a**	55
5	**2a**	MeCN	20 mol% $ZnCl_2$, 28	**1a**	49
6	**2a**	H_2O	130 mol% HCl, 3	**1a**	7[c]
7	**2a**	H_2O	120 mol% H_2SO_4, 2	**1a**	8[c]
8	**2a**	MeCN	2000 mol% AcOH, 22	**1a**	70
9	**2b**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 12	**1b**	53
10	**2b**	MeCN	10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 19	**1b**	52
11	**2c**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 16	**1c**	71
12	**2d**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 11	**1d**	75
13	**2e**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 11	**1e**	69

[a] All reactions were conducted under reflux. [b] Percent yields of isolated pure products are given. [c] Anthranilic acid was isolated as the main product in 35% (entry 6) and 26% (entry 7) yield (Experimental).

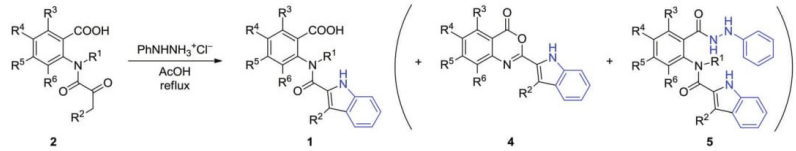
sequent indolisation step into the target 2-(indol-2-carboxamido)benzoic acids **1a,c–e** returned low 17–33% yields.

The disappointing overall results of the stepwise procedure prompted us to test the direct approach, outlined as *Route B* in Scheme 3. In screening for the optimal reaction conditions, a mixture of selected *N*-(α-ketoacyl)anthranilic acid **2** and phenylhydrazinium chloride was heated under reflux in different solvents including acetonitrile, acetic acid, methanol and water. Since Lewis[22] and Brønsted acids[23] are well known to promote the Fischer indolisation, we selected to test hydrochloric acid, sulphuric acid, acetic acid, zinc(II) chloride and bismuth(III) nitrate pentahydrate ($Bi(NO_3)_3{\cdot}5H_2O$)[24] as acid catalysts (Table 2). Good results in terms of the reaction time and the product yields were obtained for the reactions in boiling acetonitrile either in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ (entries 3, 4, 9–13) or acetic acid (entry 8). However, the highest yields of the products **1** were seen by conducting the reaction in boiling acetic acid in the absence of the additives (entry 1). As expected, the heating of *N*-(α-ketoacyl)anthranilic acid **2a** in aqueous hydrochloric or sulphuric acid resulted in an amide bond hydrolysis to produce anthranilic acid (entries 6 and 7).

Having identified the optimal reaction conditions we turned to examine the scope of the reaction. Several *N*-(α-ketoacyl)anthranilic acids (**2a–l**) were allowed to react with phenylhydrazinium chloride in boiling acetic acid, which afforded the target 2-(indol-2-carboxamido)benzoic acids (**1a–l**) in good to excellent yields of the isolated products (Table 3). In few instances, the reactions were accompanied by the formation of small amounts of by-products, which were isolated and identified as 3,1-benzoxazin-4-ones **4** and phenylhydrazides **5**. The only exception to this was compound **2m**, which afforded naphthoxazinone **4m** as the sole product, with the anthranilic acid **1m** being undetected in the reaction mixture (entry 13).

In principle, the formation of 2-indolyl-3,1-benzoxazin-4-ones **4** could be realised by two different pathways as shown in Scheme 4. An initial formation of 2-acyl-3,1-benzoxazin-4-one **4′** through the *Path a* could be followed by the Fischer indolisation with phenylhydrazinium chloride. This pathway was, however, ruled out on the basis of the 3,1-benzoxazin-4-ones reactivity considerations. In the presence of nucleophiles these compounds are prone to undergo rapid ring opening into the anthranilic acid derivatives (*vide infra*) suggesting that somehow higher amounts of the phenylhydrazides **5** should

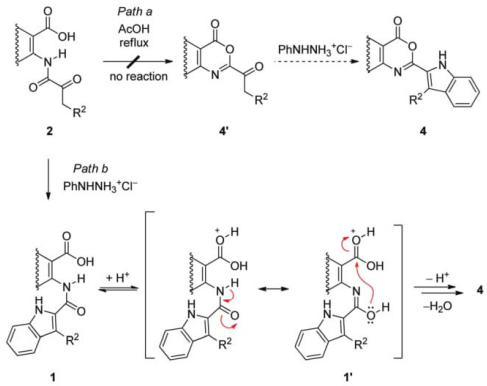
Table 3 The Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids 2 in boiling acetic acid



2 **1** **4** **5**

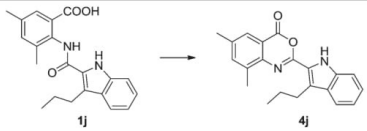
		Substituents							Product, yield[a]		
Entry	2	R^1	R^2	R^3	R^4	R^5	R^6	Reaction time (h)	**1**	**4**	**5**
1	**a**	H	Me	H	H	H	H	9	78		
2	**b**	H	Me	H	OMe	H	H	14	83	5	2
3	**c**	H	Me	H	H	OMe	H	15	89		
4	**d**	H	Me	H	H	H	OMe	9	81	5	
5	**e**	Me	Me	H	H	H	H	8	91		
6	**f**	H	*n*-Pr	H	H	H	H	10	91	2	1
7	**g**	H	Me	H	H	H	Me	14	55	14	
8	**h**	H	Me	H	Me	H	H	14	76		
9	**i**	H	Me	Cl	H	H	Me	17	78	4	
10	**j**	H	*n*-Pr	H	Me	H	Me	12	51	12	
11	**k**	H	*n*-Pr	H	OMe	H	OMe	13	56	10	
12	**l**	H	Ph	H	H	H	H	19	62		
13	**m**	H	*n*-Pr	H	H	–$(CH)_4$–		9	0	87	

[a] Percent yields of isolated pure products are given.



Scheme 4 The proposed formation of 3,1-benzoxazin-4-ones 4.

Table 4 The influence of the reaction time and temperature on transformation of 2-(indol-2-carboxamido)benzoic acid **1j** into 3,1-benzoxazin-4-one **4j**



Entry	Reaction conditions	Reaction time (h)	Yield of **4j**[a]
1	AcOH, reflux	12	12[b]
2	AcOH, reflux	40	65
3	CH_3CH_2COOH, reflux	17	72

[a] Percent yields of isolated pure products are given. [b] For comparison reasons the result is taken from Table 3, entry 10.

have been formed in the reactions shown in Table 3. The *Path a* was also ruled out experimentally by heating compound **2a** in neat acetic acid under the reflux conditions in the absence of phenylhydrazinium chloride, which resulted in no detectable formation of 2-acyl-3,1-benzoxazin-4-one **4′**. This left the *Path b*, *i.e.* the initial Fischer indolisation of the *N*-(α-ketoacyl)-anthranilic acid **2** with phenylhydrazinium chloride into 2-(indol-2-carboxamido)benzoic acid **1** and subsequent cyclodehydration into 2-indolyl-3,1-benzoxazin-4-one **4**, as the most plausible.

Generally, the 3,1-benzoxazin-4-one skeleton is formed by the reaction of anthranilic acids with an appropriate acid anhydride at the elevated temperatures.[25] Mechanistically, the amino group of the anthranilic acid is *N*-acylated and the carboxylic group is transformed into a mixed anhydride intermediate. This intermediate then undergoes an intramolecular nucleophilic displacement of the carboxylate ion from the anhydride moiety by the amide in its iminol form.[26] In turn, heating the 2-(indol-2-carboxamido)benzoic acid **1** in acetic acid is unlikely to produce mixed anhydride. Since an intramolecular nucleophilic attack of the carboxylic group to the amide is also unlikely because of the low electrophilicity of the amide, the formation of 3,1-benzoxazin-4-ones **4** could best be rationalized through the intramolecular nucleophilic attack of the iminol **1′** to the protonated carboxylic group as shown in Scheme 4. The formation of naphthoxazinone **4m** as the sole product from **2m** (Table 3, entry 13) could be accounted for by an enhanced resonance stabilisation of iminol **1m′**, the result of an extended conjugation through the naphthalene ring.

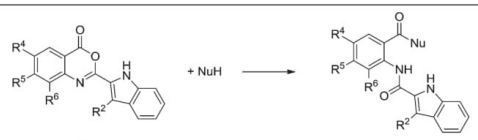
If the mechanism shown in Scheme 4 is operating, it can be expected that a prolonged reaction time and/or an elevated reaction temperature would work beneficially to the formation of 3,1-benzoxazin-4-one **4**. Indeed, by prolonging the heating of compound **1j** with phenylhydrazinium chloride in acetic acid (bp_{AcOH} = 118 °C) from 12 h to 40 h increased the yield of the expected product **4j** from 15% to 65% (compare entries 1 and 2 in Table 4). The use of the higher boiling propanoic acid (bp = 141 °C) in place of acetic acid afforded the 3,1-benzoxazin-4-one **4j** in 72% yield already within 17 h (entry 3). It is noteworthy that these reaction conditions can potentially be utilized as a convenient one-pot protocol for the preparation of 3,1-benzoxazin-4-ones **4** from *N*-(α-ketoacyl)anthranilic acids **2** and aryl hydrazines. The synthetic methodologies toward 3,1-benzoxazin-4-ones, other than those utilizing anthranilic acids, have been reviewed.[27]

Minute amounts of the hydrazides **5** also accompanied the formation of 2-(indol-2-carboxamido)benzoic acids **1** (Table 3). As it is less likely that under the applied reaction conditions phenylhydrazinium chloride reacts with the carboxyl group of either the starting *N*-(α-ketoacyl)anthranilic acids **2** or the product 2-(indol-2-carboxamido)benzoic acids **1**, it is reasonable to assume that the formation of hydrazides **5** proceeds through the ring-opening at the 3,1-benzoxazin-4-ones **4**. Smooth reactivity of the 3,1-benzoxazin-4-ones towards different nucleophiles is well documented.[26,28] In our case the reactivity of compound **4f** towards phenylhydrazine to form **5f** was independently confirmed in boiling toluene as the reaction solvent (Table 5). Analogously, treatment with *n*-butylamine gave the appropriate amide **6f**.

Aqueous sodium hydroxide in DMSO mediated complete hydrolysis of 3,1-benzoxazin-4-ones **4f,j,m** to the corresponding 2-(indol-2-carboxamido)benzoic acids **1f,j,m** (Table 5). High tendency of related 3,1-benzoxazin-4-ones for hydrolysis into the corresponding anthranilic acids has been documented.[29,30] With these results in mind it can be assumed that higher quantities of the 3,1-benzoxazin-4-one products **4** are actually formed during the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids **2** shown in Table 3 as they were actually isolated. During the isolation workup the latter most probably partly hydrolyse back into the 2-(indol-2-carboxamido)benzoic acids **1**.

The elemental composition of all the compounds under investigation was confirmed by combustion analysis and high-resolution mass spectrometry with electrospray ionization. In addition, low resolution mass spectra with electron impact

Table 5 Reaction of 3,1-benzoxazin-4-ones **4** with some nucleophiles



Entry	4	NuH	Reaction conditions, reaction time in h	Product, yield[a]
1	**4f**	$PhNHNH_2$	Toluene, reflux, 2	**5f**, 86
2	**4f**	*n*-$BuNH_2$	Toluene, reflux, 2	**6f**, 84%
3	**4f**	H_2O	DMSO, H_2O, NaOH, rt, 1	**1f**, 91%
4	**4f**	H_2O	dioxane, 0.1 M H_2SO_4, rt, 2	**1f**, 70%
5	**4j**	H_2O	DMSO, H_2O, NaOH, rt, 3	**1j**, 98%
6	**4m**	H_2O	DMSO, H_2O, NaOH, rt, 12	**1m**, 95%

[a] Percent yields of isolated pure products are given.

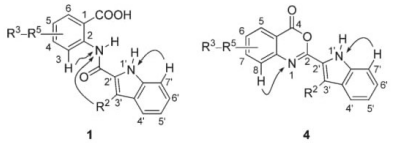


Fig. 2 Atom numbering scheme for compounds **1** and **4**. Curved arrows denote long-range $^1H-^{15}N$ *gs*-HMBC connectivities.

ionization and the infrared spectra were provided. In the latter, the characteristic absorption bands belonging to the indole N–H, C=O and C=N bonds were identified, where appropriate.

NMR study

The compounds **1**, **3–6** were fully characterized by ^1H, ^{13}C and ^{15}N NMR spectroscopy. The corresponding resonances were assigned on the basis of gradient-selected 2D NMR experiments including $^1H-^1H$ *gs*-COSY, $^1H-^{13}C$ *gs*-HSQC, $^1H-^{13}C$ *gs*-HMBC and $^1H-^{15}N$ *gs*-HMBC. The spectra of compounds **1**, **3**, **5** and **6** were recorded in DMSO-d_6. For 3,1-benzoxazin-4-ones **4**, which proved to rapidly hydrolyse in DMSO-d_6 into the 2-(indol-2-carboxamido)benzoic acids **1**, less polar $CDCl_3$ was identified as a suitable solvent. Acetone-d_6 was used as an alternative for dissolving compound **4k** due to its sparing solubility in $CDCl_3$. Some characteristic spectral features are discussed below. For the atom numbering scheme, see Fig. 2.

There is a wealth of ^1H and ^{13}C data[31] as well as ^{15}N NMR data[32] on indoles reported in the literature. The relatively unsubstituted indole ring in the compounds **1** and **4** enabled us to unequivocally assign all proton, carbon and nitrogen resonances *via* long-range $^1H-^{13}C$ and $^1H-^{15}N$ heteronuclear coupling pathways, which we found in agreement to those discussed in the literature.[33] For the indole ring in 2-(indol-2-carboxamido)benzoic acids **1** the order of shielding in the ^{13}C NMR spectra is C7′ > C3′ > C5′ > C4′ > C6′ > C2′ ≅ C3a′ > C7a′ (Table 6). By changing the indole C-2′ substituent from the carbamoyl group in compounds **1** into the 3,1-benzoxazin-4-one ring in **4**, the most dramatic changes in the chemical shift are seen for the carbon atoms of the fused 5-membered ring. In comparison with compounds **1**, the C2′ atoms of the indole ring in **4** are shielded by *ca.* 4 ppm, whereas the C3′ and C3a′ atoms are deshielded by *ca.* 6 ppm and *ca.* 1 ppm, respectively. By changing the R^2 = Me to the R^2 = *n*-Pr in either **1** or **4**, the carbon atom C3′ becomes more shielded for *ca.* 5–6 ppm (Tables 6 and 7).

The three-bond long-range couplings were observed in the $^1H-^{15}N$ *gs*-HMBC spectra from H7′ to the indole N1′ resonance in both **1** and **4** (Fig. 2). In addition, a one-bond direct NH doublet response corroborated the assignment of N1′ (Fig. 3). The chemical shifts of the N1′ atoms in indoles **1** appear at δ 130.2–136.9 ppm and are in good agreement with the literature values reported for Delavirdine.[34] In compounds **4**, the indole nitrogen atoms N1′ resonate in the narrow range of δ 120.3–121.4 ppm (Tables 6 and 7).

Systematic NMR investigations of 3,1-benzoxazin-4-ones are more scarce.[29,35] As pointed out by Osborne and Goolamali some early NMR data should be taken with care because these compounds often show high tendency for hydrolysis into the corresponding anthranilic acids, especially when measured in polar solvents such as DMSO-d_6.[29] High susceptibility towards hydrolysis has been illustrated by 2-methyl-3,1-benzoxazin-4-one that reacts with water into 2-acetylaminobenzoic acid already in the solid state.[30] Osborne and Goolamali reported an unequivocal differentiation between anthranilic acids and 3,1-benzoxazin-4-ones that was achieved through determination of characteristic J_{CH} coupling interactions in the carbonyl region of the proton coupled ^{13}C NMR spectra.[29]

Herein, the proton, carbon and nitrogen resonances belonging to the anthranilic moiety in **1** and the 3,1-benzoxazin-4-one group in **4** were rapidly assigned using the gradient-selected 2D NMR experiments. The results are collected in Tables 6 and 7. Characteristic for the downfield regions of the ^{13}C NMR spectra of the acylanthranilic acids **1** were two signals appearing at δ 160.2–161.6 ppm and δ 166.5–169.7 ppm for the amide carbonyl and for the carboxylic group, respectively. In 3,1-benzoxazin-4-one **4**, the downfield region of the spectra were occupied with three signals for C8a (δ 133.1–147.8 ppm), C2 (δ 151.0–154.3 ppm) and C4 (δ 156.2–159.7 ppm). Our results are in agreement with the literature data.[29]

Chemical shifts for the 3,1-benzoxazin-4-one nitrogen atoms in compounds **4** were in the range of δ 212.0–222.8 ppm (Table 7). Due to the lack of the ^{15}N NMR data no comparison with the literature could be done. In C8-unsubstituted 3,1-benzoxazin-4-ones **4b,c,f,h** (R^6 = H), three-bond long-range couplings were observed in the $^1H-^{15}N$ *gs*-HMBC spectra from H8 to the N1 resonance as illustrated in Fig. 2. The strongly electron donating C8-methoxy substituent in derivatives **4d,k**

Table 6 ^{13}C and ^{15}N NMR chemical shifts for 2-(indol-2-carboxamido)benzoic acids **1** in ppm[a]

Atom[b]	1a	1b	1c	1d	1f	1g	1h	1i	1j	1k	1l[c]	1m[d]
C1	116.5	118.0	108.6	—[e]	116.4	126.8	116.4	—[e]	—[e]	—[e]	116.4	
C2	141.0	134.3	143.0	—[e]	140.8	136.3	138.6	—[e]	133.7	118.8	140.4	
C3	120.6	122.4	105.3	153.7	120.5	135.8	120.6	—[e]	—[e]	155.1	120.4	
C4	134.2	120.3	163.6	115.0	134.1	134.4	134.7	131.6	134.8	102.4	134.0	
C5	122.8	154.3	108.6	126.1	122.8	125.7	132.0	—[e]	—[e]	157.5	122.9	
C6	131.3	114.8	133.2	121.5	131.2	128.1	131.3	—[e]	128.3	105.1	131.1	
C3(CH_3)						18.7		17.5	18.4			
C5(CH_3)							20.2		20.2			
C3(OCH_3)				56.1						56.2		
C4(OCH_3)			55.5									
C5(OCH_3)		55.4								55.6		
C2′	128.2	128.2	128.1	127.2	127.7	127.3	128.1	126.8	126.8	—[e]	128.0	—[e]
C3′	113.3	112.9	113.4	115.2	119.3	114.6	113.1	114.6	120.2	120.6	118.5	121.2
C3a′	128.0	128.1	128.1	128.0	127.5	128.1	128.1	127.8	127.6	127.7	126.7	127.7
C4′	120.1	120.0	120.2	119.9	120.1	120.0	120.1	119.8	119.9	120.0	120.2	120.2
C5′	119.4	119.3	119.4	119.2	119.4	119.3	119.4	119.1	119.2	119.2	120.6	119.4
C6′	124.4	124.2	124.4	124.2	124.2	124.2	124.3	124.0	124.0	124.0	124.5	124.3
C7′	112.2	112.2	112.2	112.0	112.2	112.1	112.2	111.9	112.0	112.0	112.6	112.2
C7a′	136.0	135.9	136.1	135.6	136.0	135.7	136.0	135.4	135.5	135.5	136.0	135.7
C3′CH_2					25.7				26.0	26.1		
C3′CH_2CH_2					24.0				23.9	23.9		
C3′$(CH_2)_2CH_3$					13.9				14.0	14.1		
C3′CH_3	9.7	9.7	9.7	9.8		9.8	9.7	9.6				
*C*ONH	160.5	160.2	160.7	160.2	160.5	160.4	160.4	160.8	160.2	160.2	160.2	161.6
COOH	169.7	169.3	169.6	167.9	169.6	168.4	169.7	166.5	168.3	167.7	168.7	168.3
N1′	132.7	132.7	132.7	130.3	132.2	131.3	132.7	130.9	130.8	130.2	136.9	130.5
CO*N*H	126.9	125.1	127.7	116.1	126.6	122.8	126.3	120.7	121.4	113.9	129.5	—[f]

[a] In DMSO-d_6. [b] For atom numbering scheme, see Fig. 2. [c] Resonances for the C3′ phenyl ring: 132.9 ppm (C1″), 130.2 ppm (C2″, C6″), 128.7 ppm (C3″, C5″), 127.2 ppm (C4″). [d] For the complete set of resonances, see the Experimental section. [e] Could not be assigned unequivocally; for the complete list of resonances, see the Experimental section. [f] Not observed.

Table 7 ^{13}C and ^{15}N NMR chemical shifts for 3,1-benzoxazin-4-ones **4** in ppm[a]

Atom[b]	4b	4c	4d	4f	4g	4i	4j	4k[c]
C2	151.8	154.3	153.1	153.3	152.1	152.6	151.0	151.4
C4	159.3	158.7	158.9	159.0	159.6	156.2	159.7	159.6
C4a	117.1	—[d]	117.4	116.6	116.4	113.8	116.1	—[d]
C5	108.7	—[d]	120.0	128.7	126.3	133.1	125.9	100.6
C6	158.9	130.4	127.8	127.6	127.1	129.3	137.4	160.6
C7	126.1	166.3	117.1	136.6	137.4	136.8	138.7	108.0
C8	128.1	—[d]	153.8	126.6	135.5	134.5	135.3	156.7
C8a	141.4	—[d]	137.4	147.3	145.6	147.8	143.6	133.1
C6(CH_3)							17.2	
C8(CH_3)					17.3	17.7	21.2	
C6(OCH_3)	56.0							56.4
C7(OCH_3)		56.0						
C8(OCH_3)			56.4					57.0
C2′	123.4	123.3	123.5	123.0	123.4	122.9	123.2	—[d]
C3′	119.4	120.5	120.3	125.6	120.3	121.2	125.0	124.2
C3a′	129.3	129.2	129.2	128.9	129.2	129.2	128.9	129.6
C4′	120.5	120.6	120.6	120.8	120.5	120.6	120.6	121.0
C5′	120.1	120.2	120.1	120.1	120.2	120.3	120.1	120.6
C6′	125.6	125.9	125.9	125.8	125.8	126.1	125.5	125.7
C7′	111.3	111.4	111.5	111.5	111.5	111.6	111.5	113.0
C7a′	136.5	136.6	136.8	136.7	136.5	136.6	136.4	138.0
C3′CH_2				26.9			27.0	27.6
C3′CH_2CH_2				24.2			23.8	25.0
C3′$(CH_2)_2CH_3$				14.2			14.3	14.7
C3′CH_3	10.4	10.5	10.5		10.6	10.7		
N1	222.4	222.6	212.0	222.8		—[e]	—[e]	216.4
N1′	120.5	120.9	121.4	121.1	120.5	120.3	120.9	—[e]

[a] In $CDCl_3$, unless otherwise stated. [b] For atom numbering scheme, see Fig. 2. [c] In acetone-d_6. [d] Could not be unequivocally assigned. [e] Not observed.

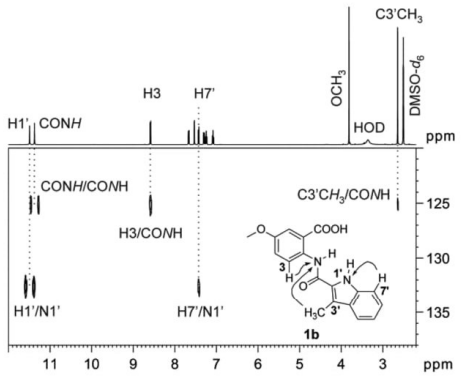


Fig. 3 $^{1}H–^{15}N$ *gs*-HMBC spectrum of 2-(indol-2-carboxamido)benzoic acid **1b** recorded in DMSO-d_6, optimized for 5 Hz long-range coupling. Direct responses for the N1′ and CO*N*H resonances were observed as doublets at 132.7 ppm and 125.1 ppm, respectively. The spectrum also features three-bond long-range response to N1′ and CO*N*H from H7′ and H3, respectively. Five-bond long-range correlation to CO*N*H from C3′CH_3 is also observed.

(R^6 = OMe) enabled a four-bond long-range couplings from H7 to the N1 whereas no such correlation could be observed in the C8-methyl substituent analogues **4g,i,j** (R^6 = Me).

The amide nitrogen atoms (CO*N*H) in acylanthranilic acids **1** resonate in the range of δ 113.9–129.5 ppm (Table 6). In analogy with the above, the cross-peaks between H3 and CO*N*H resonance were observed in $^{1}H–^{15}N$ *gs*-HMBC spectra of **1a–c,h,l**. In the 4-methoxy substituted acylanthranilic acid **1c** there was also a four-bond long-range coupling from H6 to the CO*N*H. With the exception of **1l** and **1m**, the $^{1}H–^{15}N$ *gs*-HMBC spectra also featured the one-bond direct NH doublet response. Interestingly, in 3-methylindoles **1a,b,g,h**, five-bond long-range couplings were observed in the $^{1}H–^{15}N$ *gs*-HMBC spectra from the C3′CH_3 to the amide nitrogen (CO*N*H) resonance. With the 2-(indol-2-carboxamido)benzoic acid **1b** as a representative example, the above mentioned $^{1}H–^{15}N$ *gs*-HMBC spectral features are illustrated in Fig. 3.

Conclusions

We have demonstrated that Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids can serve as a mild and highly efficient alternative for the preparation of 2-(indol-2-carboxamido) benzoic acids. By simple changes in the reaction conditions, this protocol offers a potential to access 2-indolyl-3,1-benzoxazin-4-ones. The anthranilic acid, indol-2-carboxamide and 3,1-benzoxazin-4-one structural motifs discussed herein were fully characterized by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The data presented will help in unequivocal identification of these classes of compounds.

Experimental section

General

The reagents and solvents were used as obtained from commercial sources. Compounds **2a–k,m** were prepared according to the literature procedure.[21] Column chromatography was carried out on Fluka Silica gel 60 (particle size 0.063–0.2 mm, activity acc. Brockmann and Schodder 2–3). Melting points were determined on the microscope hot stage, Kofler, PolyTherm, manufacturer Helmut Hund GmbH, Wetzlar and are uncorrected. TLC was carried out on pre-coated TLC sheets ALUGRAM® SIL G/UV_{254} for TLC, MACHEREY-NAGEL. NMR spectra were recorded with a Bruker Avance III 500 MHz NMR instrument operating at 500 MHz (^{1}H), 126 MHz (^{13}C) and 51 MHz (^{15}N). Proton spectra were referenced to TMS as an internal standard. Carbon chemical shifts were determined relative to the ^{13}C signal of DMSO-d_6 (39.5 ppm), $CDCl_3$ (77.0 ppm) or acetone-d_6 (high-field at 20.8 ppm). ^{15}N chemical shifts were extracted from $^{1}H–^{15}N$ *gs*-HMBC spectra (with 20 Hz digital resolution in the indirect dimension and the parameters adjusted for a long-range $^{1}H–^{15}N$ coupling constant of 5 Hz) determined with respect to external nitromethane and are corrected to external ammonia by addition of 380.5 ppm. Nitrogen chemical shifts are reported to one decimal place as measured from the spectrum; however, the data should not be considered to be more accurate than ±0.5 ppm because of the digital resolution limits of the experiment. Chemical shifts are given on the δ scale (ppm). Coupling constants (J) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broadened). Infrared spectra were recorded on a Mattson 3000 FTIR Spectrometer or a Thermo Scientific Nicolet iS10 FT-IR Spectrometer using samples in potassium bromide disks and only the strongest/structurally most important peaks are listed; absorption band intensities are indicated as follows: s (strong), m (medium), w (weak) or b (broad). Electron impact mass spectra (EI) were recorded on a Shimadzu QP–2010 instrument at 70 eV. HRMS spectra were recorded with the Agilent 6224 Accurate Mass TOF LC/MS system with electrospray ionization (ESI). Elemental analyses (C, H, N) were performed with the FlashEA1112 Automatic Elemental Analyzer (Thermo Fisher Scientific Inc.).

2-(2-Oxo-3-phenylpropanamido)benzoic acid (2l)

To a solution of 3-benzyl-3-hydroxyquinoline-2,4(1*H*,3*H*)-dione (669.4 mg, 2.50 mmol) in ethyl acetate (120 mL), a solution of sodium periodate (1.62 g, 7.55 mmol) in water (60 mL) was added. The two-phase reaction mixture was vigorously stirred for 7 hours at room temperature. The organic layer was separated, and extracted with 5% aqueous sodium thiosulphate (2 × 20 mL), 5% aqueous hydrochloric acid (2 × 20 mL) and finally with 5% aqueous potassium carbonate (7 × 10 mL). The potassium carbonate extract was washed with benzene (30 mL) and neutralised by addition of 10% aqueous hydrochloric acid. The resulting solution was extracted with ethyl acetate. The organic layer was separated, dried over sodium sulphate and

concentrated *in vacuo*. The crude product was recrystallized from cyclohexane (85 mL) to give compound **2l** (424.3 mg, 60%) as colourless microcrystals, mp 179–181 °C, R_f = 0.49 (10% ethanol in chloroform), ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.32 (s, 2H), 7.23–7.37 (m, 6H), 7.67–7.72 (m, 1H), 8.07 (dd, 1H, J = 8.0, 1.6 Hz), 8.72 (d, 1H, J = 8.5 Hz), 12.39 (br s, 1H), 13.84 (br s, 1H); due to decomposition, no ^{13}C NMR spectrum could be recorded. IR (cm^{-1}): ν 3221 w, 3063 w, 3031 w, 1697 s, 1672 s, 1603 m, 1583 s, 1531 s, 1451 m, 1420 s, 1270 s, 1055 m, 755 m, 695 m; MS (EI) m/z (%): 284 (3), 283 (17, [M$^+$]), 164 (20), 146 (100), 137 (25), 118 (14), 92 (15), 91 (54), 90 (25), 65 (16); HRMS (ESI$^+$): m/z calcd for $C_{16}H_{14}NO_4^+$ [M + H]$^+$ 284.0917, found 284.0917; HRMS (ESI$^-$): m/z calcd for $C_{16}H_{12}NO_4^-$ [M − H]$^-$ 282.0772, found 282.0773. Found: C, 67.9; H, 4.6; N, 4.9. Calc. for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6; N, 4.9%.

The synthesis of phenylhydrazones (3a,c–e) (Table 1)

To a solution of an appropriate *N*-(α-ketoacyl)anthranilic acid **2** (3.0 mmol) in acetic acid (25 mL), phenylhydrazine (0.49 g, 4.5 mmol) was slowly added and the resulting solution was stirred at 60 °C until TLC analysis revealed complete consumption of the starting compound (Table 1). The reaction mixture was cooled and poured into crushed ice (200 g). For phenylhydrazones **3a,d,e**, the precipitated solid was collected by filtration and washed with water (3 × 20 mL) and cyclohexane (2 × 10 mL). For phenylhydrazone **3c** the filter cake was dried at 50 °C and recrystallized from ethyl acetate to yield **3c**·AcOH. The yields of compounds **3a,c–e** are collected in Table 1.

2-(2-(2-Phenylhydrazono)butanamido)benzoic acid (3a). Pale yellow solid, yield 822 mg (88%), mp 208–210 °C (benzene), R_f = 0.42 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.07 (t, 3H, J = 7.2 Hz, CH_3), 2.68–2.78 (m, 2H, CH_2), 6.91 (dd, 1H, J = 7.1, 7.1 Hz, H4 of phenyl), 7.14 (dd, 1H, J = 7.5, 7.5 Hz, H5), 7.30 (dd, 2H, J = 7.6, 7.6 Hz, H3 and H5 of phenyl), 7.55 (dd, 2H, J = 7.6, 7.6 Hz, H2 and H6 of phenyl), 7.59–7.64 (m, 1H, H4), 8.06 (dd, 1H, J = 1.5, 7.7 Hz, H6), 8.80 (d, 1H, J = 8.4 Hz, H3), 9.98 (s, 1H, NNH), 12.40 (s, 1H, CONH), 13.54 (br s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.2 (CH_3), 16.2 (CH_2), 113.7 (C2, C6 of phenyl), 115.9 (C1), 119.3 (C3), 120.7 (C4 of phenyl), 121.9 (C5), 129.0 (C3, C5 of phenyl), 131.4 (C6), 134.2 (C4), 139.5 (C=N), 141.2 (C2), 144.4 (C1 of phenyl), 163.2 (CONH), 169.4 (COOH); ^{15}N NMR (51 MHz, DMSO-d_6) δ 116.4 (CONH), 144.1 (NHPh), 327.6 (C=N); IR (cm^{-1}): ν 3287 m, 2970 w, 1665 s, 1650 s, 1604 m, 1586 m, 1577 m, 1518 s, 1496 s, 1449 m, 1241 s, 1225 s, 748 m, 694 m; MS (EI) m/z (%): 312 (8), 311 (40, [M$^+$]), 147 (11), 146 (91), 145 (16), 93 (19), 92 (55), 91 (100), 90 (18), 65 (46). Found: C, 65.6; H, 5.5; N, 13.25. Calc. for $C_{17}H_{17}N_3O_3$: C, 65.6; H, 5.5; N, 13.5%.

4-Methoxy-2-(2-(2-phenylhydrazono)butanamido)benzoic acid, acetic acid salt (3c·AcOH). Pale yellow microcrystals, yield 795 mg (66%), mp 223–226 °C (ethyl acetate), R_f = 0.66 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06 (t, 3H, J = 7.5 Hz), 1.92 (s, 3H, CH_3CO$_2$H), 2.72 (q, 2H, J = 7.5 Hz), 3.84 (s, 3H), 6.70 (dd, 1H, J = 8.9, 2.6 Hz), 6.90 (dd, 1H, J = 7.3, 7.3 Hz), 7.28 (dd, 2H, J = 7.9, 7.9 Hz), 7.56 (d, 2H, J = 7.7 Hz), 7.99 (d, 1H, J = 8.9 Hz), 8.47 (d, 1H, J = 2.6 Hz), 9.99 (s, 1H), 12.54 (br s, 1H), 12.57 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.2, 16.2, 21.1 (CH_3CO_2H), 55.4, 103.9, 108.1, 108.4, 113.8, 120.7, 129.0, 133.2, 139.5, 143.2, 144.4, 163.4, 163.6, 169.3, 172.0 (CH_3CO_2H); IR (cm^{-1}): ν 2971 w, 2937 w, 1694 m, 1603 s, 1585 s, 1494 s, 1462 m, 1231 s, 1059 m, 751 m, 751 m, 692 w. Found: C, 59.6; H 5.7; N, 10.8. Calc. for $C_{20}H_{23}N_3O_6$: C, 59.8; H, 5.8; N, 10.5%.

3-Methoxy-2-(2-(2-phenylhydrazono)butanamido)benzoic acid (3d). Colourless crystals, yield 809 mg (79%), mp 210–212 °C (ethyl acetate), R_f = 0.52 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (t, 3H, J = 7.5 Hz), 2.65 (q, 2H, J = 7.5 Hz), 3.85 (s, 3H), 6.86–6.91 (m, 1H), 7.22–7.40 (m, 7H), 9.69 (br s, 1H), 9.97 (br s, 1H), 12.82 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.2, 16.4, 56.2, 113.5, 114.8, 120.5, 121.3, 125.0, 126.1, 127.3, 129.1, 139.3, 144.5, 153.0, 162.0, 168.2; IR (cm^{-1}): ν 3334 w, 3303 m, 3249 m, 2967 m, 1695 s, 1650 s, 1603 s, 1583 s, 1493 s, 1461 s, 1277 s, 1261 s, 1232 s, 1056 s, 748 m, 691 m; MS (EI) m/z (%): 341 (1, [M]$^+$), 167 (78), 134 (54), 121 (73), 119 (59), 106 (59), 93 (76), 92 (64), 91 (100), 77 (73), 43 (74); HRMS (ESI$^+$): m/z calcd for $C_{18}H_{20}N_3O_4^+$ [M + H]$^+$ 342.1448, found 342.1450; HRMS (ESI$^-$): m/z calcd for $C_{18}H_{18}N_3O_4^-$ [M − H]$^-$ 340.1303, found 340.1303. Found: C, 63.15; H, 5.6; N, 12.15. Calc. for $C_{18}H_{19}N_3O_4$: C, 63.3; H, 5.6; N, 12.3%.

2-(*N*-Methyl-2-(2-phenylhydrazono)butanamido)benzoic acid (3e). Pale yellow microneedles, yield 761 mg (78%), mp 173–178 °C (ethyl acetate–benzene), R_f = 0.73 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (t, 3H, J = 5 Hz), 2.37–2.52 (m, 2H, CH_2), 3.23 (s, 3H), 6.49 (d, 2H, J = 10 Hz), 6.67 (dd, 1H, J = 7.5, 7.5 Hz), 7.01 (dd, 2H, J = 7.5, 7.5 Hz), 7.28 (dd, 1H, J = 7.5, 7.5 Hz), 7.45 (d, 1H, J = 7.5 Hz), 7.63 (ddd, 1H, J = 7.7, 7.7, 1.6 Hz), 7.76 (d, 1H, J = 10 Hz), 9.15 (br s, 1H), 12.94 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 18.8, 38.4, 112.9, 119.5, 126.3, 127.8, 128.4, 129.3, 131.0, 132.8, 139.9, 144.5, 146.0, 166.5, 166.8; IR (cm^{-1}): ν 3326 m, 1707 s, 1619 s, 1598 s, 1577 s, 1454 m, 1392 m, 1256 s, 1203 m, 760 m, 747 m, 694 m; MS (EI) m/z (%): 325 (1, [M]$^+$), 174 (100), 151 (24), 146 (24), 145 (34), 105 (28), 104 (26), 91 (34), 77 (37), 43 (25). Found: C, 66.2; H, 5.9; N, 12.7. Calc. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.9; N, 12.9%.

General procedure for the Fischer indolisation of phenylhydrazones 3a,c–e into 2-(indol-2-carboxamido)benzoic acids 1a,c–e (Table 1)

Phenylhydrazones **3a,d,e** or **3c**· AcOH (2.0 mmol) were heated under a nitrogen atmosphere on a metal bath at the temperature and for the time given in Table 1. The course of reaction was monitored by a moistened pH test strip (alkaline reaction of released ammonia gas). After cooling the reaction mixture, the corresponding product was isolated as follows.

Compound **1a** was obtained from the solidified reaction mixture by two subsequent recrystallizations from ethanol and isopropyl alcohol.

Compound **1c** was obtained from the oily reaction mixture by trituration with toluene (10 mL). The precipitate that formed was collected by filtration, recrystallized from isopropyl alcohol and additionally purified by column chromatography on silica gel using successive mixtures of ethyl acetate and ethanol as eluents.

Compound **1d** was obtained by triturating the solidified reaction mixture with toluene for 1 hour at ambient temperature followed by filtration. Pure **1d** was obtained after recrystallization of the filter cake from isopropyl alcohol.

Compound **1e** was obtained by washing the solidified reaction mixture with toluene (10 mL) and cyclohexane (10 mL). The solid was subjected to column chromatography on silica gel using successive mixtures of ethyl acetate and ethanol as eluents. Recrystallisation from the benzene–ethyl acetate mixture afforded pure **1e**.

Solvent and catalyst screening for the Fischer indolisation of 2 into 1 (Table 2)

A stirred mixture of *N*-(α-ketoacyl)anthranilic acid **2** (2.00 mmol), phenylhydrazinium chloride (310 mg, 2.15 mmol) and the catalyst in the solvent (entry 1: 7.5 mL; entries 2–13: 13 mL) was heated under reflux until TLC analysis indicated complete consumption of the starting material. The progress of the reaction was accompanied by the colour change of the reaction mixture from pale yellow to green and finally to dark red. The products were isolated as follows.

Entries 1 and 5: the cooled reaction mixture was poured into ice water (35–60 mL). The solid was collected by filtration, washed with water (20–60 mL) and recrystallized from ethanol affording pure compound **1a**.

Entries 2–4, 9–13: the cooled reaction mixture was poured into ice water (35 mL). If an oily organic phase was formed (entry 13), the resulting mixture was stirred overnight. The resulting solid was collected by filtration, washed with 10% HCl (16 mL) and water (25 mL), and recrystallized from ethanol affording the appropriate pure compound **1**.

Entries 6 and 7: the cooled reaction mixture was filtered. The filter cake was washed with water (10 mL) and recrystallized from ethanol affording a pure compound **1a**. The filtrate was evaporated to dryness and the residue was dissolved in a minimal amount of water (*ca.* 25 mL). The solution was made alkaline with 0.5 M NaOH, washed with benzene (3 × 5 mL) and carefully neutralised with 5% HCl. The precipitated anthranilic acid was filtered off as colourless crystals.

Entry 8: the reaction mixture was concentrated *in vacuo* and the oily residue was triturated with water (10 mL) to give white precipitate of pure **1a**, which was collected by filtration and washed with water (2 × 3 mL).

General procedure for the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids 2 into 2-(indol-2-carboxamido)-benzoic acids 1 (Table 3)

A mixture of *N*-(α-ketoacyl)anthranilic acid **2** (2.00 mmol) and phenylhydrazinium chloride (310 mg, 2.15 mmol) in acetic acid (7.5 mL) was heated under reflux until TLC indicated complete consumption of the starting material **2**. In the case of **2m** (entry 13), at the onset of the reaction the formation of solid prevented an efficient stirring of the reaction mixture. Thus an additional amount of acetic acid (5 mL) was added. The reaction mixture was cooled and diluted with ice water (60 mL). After stirring the resulting mixture for several hours, the *Precipitate A* was collected by filtration and washed with water (20 mL). The filtrates were combined into the *Filtrate A*. The *Precipitate A* and the *Filtrate A* were treated as follows.

Entries 1–6, 8, 10–12: recrystallization of the *Precipitate A* from ethanol gave pure products **1a–f,h,j–l**.

Entries 2, 4, 6, 11: the *Filtrate A* was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel using 30% ethyl acetate in chloroform as an eluent to isolate benzoxazinones **4d,f,k** and phenylhydrazides **5b,f** as indicated in Table 3.

Entry 7: recrystallisation of the *Precipitate A* from ethanol afforded the appropriate benzoxazinones **4g**. The mother liquor was concentrated *in vacuo*. From the residue the second crop of **1g** crystallized, which was collected by filtration and washed with a small amount of benzene and recrystallized from ethanol. The yield of the combined crops of **1g** is given in Table 3, entry 7.

Entry 13: recrystallisation of the *Precipitate A* from ethanol afforded benzoxazinone **4m**.

Entry 9: the *Precipitate A* was washed with boiling benzene (15 mL) and recrystallized from ethanol affording a pure compound **1i**. The benzene extract was concentrated to the oily residue and subjected to column chromatography on silica gel using 10% ethyl acetate in chloroform as an eluent, to give benzoxazinone **4i**.

Entry 10: the *Filtrate A* was evaporated to dryness and subjected to column chromatography on silica gel with chloroform as an eluent, affording benzoxazinone **4j**.

2-{[(3-Methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1a). Colourless solid, mp 276–284 °C (ethanol), R_f = 0.48 (20% methanol in ethyl acetate), R_f = 0.18 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.66 (s, 3H, CH_3), 7.09 (dd, 1H, J = 7.5, 7.4 Hz, H5′), 7.22 (dd, 1H, J = 7.6, 7.6 Hz, H5), 7.26 (dd, 1H, J = 7.6, 7.6 Hz, H6′), 7.44 (d, 1H, J = 8.2 Hz, H7′), 7.66–7.71 (m, 2H, H4 and H4′), 8.07 (dd, 1H, J = 7.9, 1.1 Hz, H6), 8.69 (d, 1H, J = 8.4 Hz, H3), 11.53 (s, 1H, H1′), 11.69 (s, 1H, CONH), 13.82 (br s, 1H, COOH); IR (cm^{-1}): ν 3328 s, 3061 w, 1682 s, 1664 s, 1581 w, 1524 s, 1450 m, 1412 m, 1338 m, 1261 s, 727 m, 662 w; MS (EI) *m*/*z* (%): 295 (12), 294 (63, [M]$^+$), 158 (95), 157 (100), 130 (56), 129 (48), 128 (26), 120 (78), 103 (36), 77 (36) *m*/*z* (%). Found: C, 69.1; H 4.8; N, 9.7. Calc. for $C_{17}H_{14}N_2O_3$: C, 69.4; H, 4.8; N, 9.5%.

5-Methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1b). Yellowish solid, mp 265–269 °C (ethanol), R_f = 0.41 (20% methanol in ethyl acetate), R_f = 0.16 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.64 (s, 3H, C3′ CH_3), 3.81 (s, 3H, OCH_3), 7.09 (dd, 1H, J = 7.3, 7.3 Hz, H5′), 7.25 (ddd, 1H, J = 7.6, 7.6, 0.8 Hz, H6′), 7.30 (dd, 1H, J = 9.2, 3.1 Hz, H4), 7.43 (d, 1H, J = 8.2 Hz, H7′), 7.53 (d, 1H, J = 3.2 Hz, H6), 7.67 (d, 1H, J = 8.0 Hz, H4′), 8.59 (d, 1H, J =

9.2 Hz, H3), 11.37 (s, 1H, CONH), 11.49 (s, 1H, H1′), 13.88 (br s, 1H, COOH); IR (cm^{-1}): ν 3321 s, 1638 s, 1521 s, 1337 m, 1289 m, 1245 s, 1218 m, 1036 w, 744 s; MS (EI) *m*/*z* (%): 325 (19), 324 (90, $[M]^+$), 307 (16), 306 (71), 158 (97), 157 (40), 150 (57), 130 (65), 129 (41), 77 (41); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{17}N_2O_4^+$ $[M + H]^+$ 325.1183, found 325.1184. Found: C, 66.5; H, 5.0; N, 8.6. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6%.

4-Methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1c). Colourless solid, mp 264–267 °C (iPrOH), R_f = 0.61 (20% methanol in ethyl acetate), R_f = 0.23 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.65 (s, 3H, C3′CH_3), 3.87 (s, 3H, OCH_3), 6.79 (dd, 1H, *J* = 8.9, 2.6 Hz, H5), 7.09 (ddd, 1H, *J* = 7.2, 7.2, 0.6 Hz, H5′), 7.26 (ddd, 1H, *J* = 7.6, 7.6, 0.8 Hz, H6′), 7.43 (d, 1H, *J* = 8.3 Hz, H7′), 7.68 (d, 1H, *J* = 8.0 Hz, H4′), 8.02 (d, 1H, *J* = 8.9 Hz, H6), 8.38 (d, 1H, *J* = 2.6 Hz, H3), 11.53 (s, 1H, H1′), 11.91 (s, 1H, CONH), 13.47 (br s, 1H, COOH); IR (cm^{-1}): ν 3320 m, 3054 w, 2975 w, 1671 s, 1640 m, 1613 s, 1577 m, 1524 m, 1407 m, 1337 m, 1269 s, 1243 s, 1235 s, 1151 m, 740 m; MS (EI) *m*/*z* (%): 325 (2), 324 (8, $[M]^+$), 306 (42), 158 (35), 157 (26), 150 (28), 130 (33), 129 (23), 45 (30), 44 (100); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{17}N_2O_4^+$ $[M + H]^+$ 325.1183, found 325.1187. Found: C, 66.6; H, 5.0; N, 8.45. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6%.

3-Methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1d). Colourless solid, mp 265–267 °C (ethyl acetate), R_f = 0.39 (20% methanol in ethyl acetate), R_f = 0.24 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.58 (s, 3H, C3′CH_3), 3.85 (s, 3H, OCH_3), 7.08 (dd, 1H, *J* = 7.4, 7.4 Hz, H5′), 7.25 (ddd, 1H, *J* = 7.6, 7.6, 0.7 Hz, H6′), 7.30–7.34 (m, 2H, H4 and H5), 7.39–7.46 (m, 2H, H6 and H7′), 7.65 (d, 1H, *J* = 8.1 Hz, H4′), 9.31 (br s, 1H, CONH), 11.47 (br s, 1H, H1′), 12.91 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 9.8, 56.1, 112.0, 115.0, 115.2, 119.2, 119.9, 121.4, 124.2, 125.7, 126.1, 127.2, 128.0, 128.5, 135.6, 153.7, 160.2, 167.9; IR (cm^{-1}): ν 3387 w, 3292 s, 2837 m, 1690 s, 1619 s, 1538 m, 1506 s, 1478 s, 1459 m, 1280 s, 1257 s, 1056 m, 747 m, 510 w; MS (EI) *m*/*z* (%): 324 (3, $[M]^+$), 323 (26), 322 (100), 250 (13), 149 (48), 111 (6), 97 (8), 85 (8), 71 (10), 57 (24), 43 (8), 41 (13); HRMS (ESI^-): *m*/*z* calcd for $C_{18}H_{15}N_2O_4^-$ $[M - H]^-$ 323.1037, found 323.1039. Found: C, 66.5; H, 5.0; N, 8.5. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6%.

2-{Methyl[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1e). White solid, mp 216–219 °C (EtOAc–benzene), R_f = 0.54 (20% methanol in EtOAc), R_f = 0.36 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 1.95 (br s, 3H), 3.35 (s, 3H), 6.88–7.72 (m, 8H), 10.56 (br s, 1H), 13.07 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.0, 38.0, 111.3, 111.6, 118.6, 119.2, 122.7, 127.1, 127.3, 128.3, 129.7, 130.9, 132.7, 135.5, 143.5, 164.3, 166.5; IR (cm^{-1}): ν 3233 s, 2913 m, 1704 s, 1614 s, 1590 s, 1545 m, 1445 m, 1421 m, 1395 m, 1349 m, 1287 m, 1256 s, 759 m, 752 m, 741 m; MS (EI): *m*/*z* (%) 309 (14), 308 (67, $[M]^+$), 290 (100), 250 (89), 234 (37), 233 (80), 232 (63), 204 (52), 158 (48), 102 (37), 77 (42), 44 (53); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{17}N_2O_3^+$ $[M + H]^+$ 309.1234, found 309.1237.

2-{[(3-Propyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1f). Colourless solid, mp 239–246 °C (ethanol), R_f = 0.23 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 0.94 (t, 3H, *J* = 7.3 Hz, C3′$(CH_2)_2CH_3$), 1.67–1.74 (m, 2H, C3′CH_2CH_2), 3.08–3.14 (m, 2H, C3′CH_2), 7.08 (dd, 1H, *J* = 7.7, 7.7 Hz, H5′), 7.22 (dd, 1H, *J* = 8.0, 8.0 Hz, H5), 7.26 (dd, 1H, *J* = 7.8, 7.8 Hz, H6′), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.65–7.70 (m, 2H, H4, H4′), 8.07 (dd, 1H, *J* = 1.4, 8.0 Hz, H6′), 8.66 (d, 1H, *J* = 8.4 Hz, H3), 11.52 (br s, 1H, H1′), 11.64 (br s, 1H, CONH), 13.79 (br s, 1H, COOH); IR (cm^{-1}): ν 3311 s, 2956 m, 2870 w, 1673 s, 1655 s, 1580 m, 1540 m, 1521 m, 1511 m, br, 1449 m, 1407 m, 1262 s, 1166 m, 752 m, 730 m; MS (EI) *m*/*z* (%): 324 (4), 323 (11), 322 (56, $[M]^+$), 304 (11), 275 (39), 186 (40), 185 (100), 170 (21), 168 (15), 156 (48), 130 (21), 129 (22), 128 (47), 120 (50), 77 (13); HRMS (ESI^+): *m*/*z* calcd for $C_{19}H_{19}N_2O_3^+$ $[M + H]^+$ 323.1390, found 323.1390. Found: C, 70.8; H, 5.75; N, 8.6. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.8; H, 5.6; N, 8.7%.

3-Methyl-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1g). Colourless solid, mp 234–241 °C (benzene), R_f = 0.26 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H, C3CH_3), 2.62 (s, 3H, C3′CH_3), 7.08 (dd, 1H, *J* = 7.4, 7.4 Hz, H5′), 7.25 (dd, 1H, *J* = 7.5, 7.5 Hz, H6), 7.30 (dd, 1H, *J* = 7.7, 7.7 Hz, H5), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.53 (d, 1H, *J* = 7.4 Hz, H4), 7.66 (d, 1H, *J* = 8.0 Hz, H4′), 7.77 (d, 1H, *J* = 7.1 Hz, H6), 9.83 (s, 1H, CONH), 11.45 (s, 1H, H1′), 13.14 (br s, 1H, COOH); IR (cm^{-1}): ν 3460 w, 3303 s, 3059 w, 2966 w, 1673 s, 1647 s, 1622 s, 1505 s, 1463 s, 1447 s, 1335 s, 1243 s, 744 s, 739 m; HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{17}N_2O_3^+$ $[M + H]^+$ 309.1234; found 309.1236.

5-Methyl-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1h). Pale yellow crystals, mp 268–274 °C (ethanol), R_f = 0.63 (20% methanol in ethyl acetate), R_f = 0.30 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.34 (s, 3H, C5CH_3), 2.65 (s, 3H, C3′CH_3), 7.09 (ddd, 1H, *J* = 7.5, 7.5, 0.7 Hz, H5′), 7.25 (ddd, 1H, *J* = 7.6, 7.6, 0.9 Hz, H6′), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.49 (dd, 1H, *J* = 8.6, 2.0 Hz, H4), 7.67 (d, 1H, *J* = 8.0 Hz, H4′), 7.88 (d, 1H, *J* = 1.8 Hz, H6), 8.58 (d, 1H, *J* = 8.5 Hz, H3), 11.51 (s, 1H, H1′), 11.58 (s, 1H, CONH), 13.76 (br s, 1H, COOH); IR (cm^{-1}): ν 3316 m, 2919 w, 2863 w, 1672 m, 1648 m, 1586 m, 1520 s, 1418 m, 1398 m, 1336 m, 1296 m, 1259 s, 1217 m, 736 m, 671 w; MS (EI) *m*/*z* (%): 310 (1), 309 (8), 308 (36, $[M]^+$), 290 (53), 158 (65), 157 (49), 134 (100), 130 (60), 129 (42), 103 (40), 77 (57); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{17}N_2O_3^+$ $[M + H]^+$ 309.1234, found 309.1234. Found: C, 70.2; H, 5.4; N, 9.1. Calc. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1%.

6-Chloro-3-methyl-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}-benzoic acid (1i). Colourless solid, mp 256–264 °C (ethanol), R_f = 0.38 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.23 (s, 3H, C3CH_3), 2.57 (s, 3H, C3′CH_3), 7.07 (ddd, 1H, *J* = 7.8, 7.2, 0.7 Hz, H5′), 7.24 (ddd, 1H, *J* = 8.1, 7.1, 0.9 Hz, H6′), 7.40–7.45 (m, 3H, H4, H5 and H7′), 7.64 (d, 1H, *J* = 8.0 Hz, H4′), 9.43 (br s, 1H, CONH), 11.35 (br s, 1H, H1′), 13.59 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.6, 17.5, 111.8, 114.6, 119.1, 119.8, 124.0, 126.3, 126.8, 127.75, 127.83, 131.6, 134.1, 134.2, 135.4, 136.3, 160.8, 166.5; IR

(cm^{-1}): ν 3820 m, 3057 w, 2927 m, 1734 s, 1686 s, 1624 s, 1617 s, 1583 s, 1556 s, 1509 s, 1335 s, 1296 s, 743 s; MS (EI) *m*/*z* (%): 327 (7), 326 (35), 325 (22), 324 (100, $[M - H_2O]^+$), 295 (48), 130 (76), 129 (56), 128 (50), 103 (40), 102 (57), 77 (60), 44 (70); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{16}ClN_2O_3^+$ $[M + H]^+$ 343.0844, found 343.0849. Found: C, 62.8; H, 4.5; N, 7.9. Calc. for $C_{18}H_{15}ClN_2O_3$: C, 63.1; H, 4.4; N, 8.2%.

3,5-Dimethyl-2-{[(3-propyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1j). Colourless solid, mp 240–244 °C (benzene), R_f = 0.51 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J* = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.67 (tq, 2H, *J* = 7.4, 7.4 Hz, C3′CH_2CH_2), 2.23 (s, 3H, C3CH_3), 2.34 (s, 3H, C5CH_3), 3.07 (t, 1H, *J* = 7.6 Hz, C3′CH_2), 7.07 (ddd, 1H, *J* = 7.9, 7.2, 0.7 Hz, H5′), 7.24 (ddd, 1H, *J* = 8.1, 7.1, 0.9 Hz, H6′), 7.34, (d, 1H, *J* = 1.3 Hz, H4), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.58 (d, 1H, *J* = 1.7 Hz, H6), 7.66 (d, 1H, *J* = 8.1 Hz, H4′), 9.71 (br s, 1H, CONH), 11.41 (br s, 1H, H1′), 13.06 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 14.0, 18.4, 20.2, 23.9, 26.0, 112.0, 119.2, 119.9, 120.2, 124.0, 126.4, 126.8, 127.6, 128.3, 133.7, 134.8, 134.9, 135.5, 160.2, 168.3; IR (cm^{-1}): ν 3368 w, 3301 m, 3263 m, 3052 m, 2956 m, 1663 s, 1618 w, 1603 w, 1547 m, 1527 w, 1477 w, 1444 m, 1405 m, 1336 w, 1300 m, 1231 m, 742 w; MS (EI) *m*/*z* (%): 351 (11), 350 (46, $[M]^+$), 332 (5, $[M - H_2O]^+$), 186 (44), 185 (70), 156 (33), 148 (100), 130 (30), 129 (25), 128 (39); HRMS (ESI^+): *m*/*z* calcd for $C_{21}H_{23}N_2O_3^+$ $[M + H]^+$ 351.1703, found, 351.1702. Found: C, 71.7; H, 6.3; N, 7.9. Calc. for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.3; N, 8.0%.

3,5-Dimethoxy-2-{[(3-propyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1k). Pale yellow solid, mp 227–230 °C (ethanol), R_f = 0.33 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J* = 7.3 Hz, C3′$(CH_2)_2CH_3$), 1.64 (tq, 2H, *J* = 7.4 Hz, C3′CH_2CH_2), 3.05 (t, 3H, *J* = 7.6 Hz, C3′CH_2), 3.82 (s, 3H, C3OCH_3), 3.83 (s, 3H, C5OCH_3), 6.88 (d, 1H, *J* = 2.7 Hz, H4), 6.92 (d, 1H, *J* = 2.7 Hz, H6), 7.06 (dd, 1H, *J* = 7.4 Hz, H5′), 7.23 (ddd, 1H, *J* = 7.9, 7.2, 0.7 Hz, H6′), 7.43 (d, 1H, *J* = 8.2 Hz, H7′), 7.64 (d, 1H, *J* = 8.0 Hz, H4′), 9.06 (br s, 1H, CONH), 11.40 (br s, 1H, H1′), 12.92 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.1, 23.9, 26.1, 55.6, 56.2, 102.4, 105.1, 112.0, 118.8, 119.2, 120.0, 121.0, 124.0, 126.8, 127.7, 129.6, 135.5, 155.1, 157.5, 160.2, 167.7; IR (cm^{-1}): ν 3409 w, 3288 m, 2957 m, 1694 s, 1657 s, 1597 m, 1502 s, 1471 m, 1454 m, 1334 s, 1309 m, 1215 m, 1067 m, 1043 m, 752 m; MS (EI) *m*/*z* (%): 382 (6, $[M]^+$), 365 (25), 364 (100), 335 (82), 221 (35), 179 (50), 156 (32), 129 (38), 128 (56), 73 (51); HRMS (ESI^+): *m*/*z* calcd for $C_{21}H_{23}N_2O_5^+$ $[M + H]^+$ 383.1601, found 383.1601. Found: C, 65.9; H, 5.8; N, 7.1. Calc. for $C_{21}H_{22}N_2O_5$: C, 66.0; H, 5.8; N, 7.3%.

2-{[(3-Phenyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1l). Colourless crystals, mp 237–246 °C (ethanol), R_f = 0.36 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 7.11–7.17 (m, 2H, H5, H5′), 7.29–7.36 (m, 2H, H6′, H4″), 7.44 (dd, 2H, *J* = 7.7, 7.7 Hz, H3″, H5″), 7.53–7.55 (m, 3H, H7′, H2″, H6″), 7.59 (d, 1H, *J* = 8.1 Hz, H4′), 7.64 (ddd, 1H, *J* = 8.6, 7.1, 1.6 Hz, H4), 7.91 (dd, 1H, *J* = 7.9, 1.5 Hz, H6), 8.60 (dd, 1H, *J* = 8.4, 0.6 Hz, H3), 11.28 (br s, 1H, CONH), 12.03 (br s, 1H, H1′), 13.36 (br s, 1H, COOH); IR (cm^{-1}): ν 3309 s, 3057 w, 1671 s, 1655 s, 1605 m, 1580 m, 1519 s, 1449 m, 1405 m, 1332 m, 1296 m, 1262 s, 1230 m, 754 m, 700 m; MS (EI) *m*/*z* (%): 357 (3), 356 (13, $[M]^+$), 339 (24), 338 (100), 337 (44), 293 (17), 220 (29), 219 (31), 207 (20), 191 (27), 190 (47), 165 (31), 164 (18), 90 (21), 44 (54); HRMS (ESI^+): *m*/*z* calcd for $C_{22}H_{17}N_2O_3^+$ $[M + H]^+$ 357.1234; found 357.1228. Found: C, 74.1; H, 4.6; N, 7.8. Calc. for $C_{22}H_{16}N_2O_3$: C, 74.2; H, 4.5; N, 7.9%.

6-Methoxy-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4b). Pale-yellow microcrystals, mp 220–225 °C, R_f = 0.44 (20% ethyl acetate in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 2.78 (s, 3H, C3′CH_3), 3.92 (s, 3H, OCH_3), 7.15 (ddd, 1H, *J* = 7.8, 7.0, 0.9 Hz, H5′), 7.32 (ddd, 1H, *J* = 7.5, 7.5, 0.9 Hz, H6′), 7.36–7.39 (m, 2H, H7 and H7′), 7.55 (d, 1H, *J* = 9.0 Hz, H8), 7.59 (d, 1H, *J* = 2.9 Hz, H5), 7.67 (d, 1H, *J* = 8.1 Hz, H4′), 8.94 (br s, 1H, H1′); IR (cm^{-1}): ν 3399 m, 3047 w, 2836 w, 1747 s, 1624 s, 1603 m, 1492 s, 1354 m, 1335 m, 1326 m, 1240 s, 1035 m, 838, 743 m; MS (EI) *m*/*z* (%): 307 (8), 306 (35, $[M]^+$), 181 (100), 158 (30), 157 (18), 130 (28), 129 (17), 103 (18), 77 (16); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1080.

7-Methoxy-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4c). Pale-yellow crystals, mp 234–236 °C (benzene), R_f = 0.52 (20% ethyl acetate in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 2.79 (s, 1H, C3′CH_3), 3.95 (s, 1H, OCH_3), 6.99–7.02 (m, 2H, H5 and H8), 7.16 (ddd, 1H, *J* = 7.8, 7.1, 0.8 Hz, H5′), 7.34 (ddd, 1H, *J* = 7.9, 7.2, 0.7 Hz, H6′), 7.39 (d, 1H, *J* = 8.2 Hz, H7′), 7.69 (d, 1H, *J* = 8.0 Hz, H4′), 8.11 (d, 1H, *J* = 9.0 Hz, H6), 8.98 (br s, 1H, H1′); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.5, 55.8, 108.4, 109.3, 111.4, 116.6, 120.2, 120.5, 120.6, 123.3, 125.9, 129.2, 130.4, 136.6, 149.7, 154.3, 158.7, 166.3; IR (cm^{-1}): ν 3376 m, 2946 w, 1736 s, 1622 s, 1599 s, 1565 s, 1548 s, 1493 m, 1444 m, 1439 m, 1287 m, 1203 m, 1043 m, 744 m; MS (EI) *m*/*z* (%): 308 (2), 307 (19), 306 (100, $[M]^+$), 277 (27), 249 (25), 157 (14), 150 (23), 130 (17), 129 (20), 128 (17), 120 (10), 103 (12), 102 (13), 77 (18); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1081; found: C, 70.2; H, 4.6; N, 9.0. Calc. for $C_{18}H_{14}N_2O_3$: C, 70.6; H, 4.6; N, 9.15%.

8-Methoxy-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4d). Yellow microcrystals, mp 238–240 °C (benzene), R_f = 0.54 (20% ethyl acetate in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 2.79 (s, 3H, C3′CH_3) 4.03 (s, 3H, OCH_3), 7.15 (ddd, 1H, *J* = 7.4, 7.0, 0.5 Hz, H5′), 7.27 (dd, 1H, *J* = 8.2, 0.7 Hz, H7), 7.32 (ddd, 1H, *J* = 7.5, 7.0, 0.6 Hz, H6′), 7.38 (d, 1H, *J* = 8.8 Hz, H7′), 7.40 (dd, 1H, *J* = 8.1, 8.1 Hz, H6), 7.68 (d, 1H, *J* = 8.1 Hz, H4′), 7.81 (dd, 1H, *J* = 7.9 Hz, 1.0 Hz, H5), 9.23 (br s, 1H, H1′); IR (cm^{-1}): ν 3379 m, 2838 w, 1755 s, 1612 s, 1597 s, 1574 s, 1488 m, 1445 m, 1335 s, 1274 s, 1046 m, 1023 m, 754 m, 738 m, 720 m; MS (EI) *m*/*z* (%): 308 (2), 307 (19), 306 (100, $[M]^+$), 305 (9, $[M - H]^+$], 260 (12), 130 (27), 129 (16), 128 (18), 103 (17), 102 (14), 77 (23); HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1075. Found: C, 70.5; H, 4.6; N, 9.2. Calc. for $C_{18}H_{14}N_2O_3$: C, 70.6; H, 4.6; N, 9.15%.

2-(3-Propyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4f). Pale-yellow microcrystals, mp 160–165 °C (cyclohexane), R_f =

0.60 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.81 (tq, 2H, J = 7.4, 7.4 Hz, C3′CH_2CH_2), 3.27 (t, 2H, J = 7.5 Hz, C3′CH_2), 7.15 (ddd, 1H, J = 7.8, 7.1, 0.8 Hz, H5′), 7.31 (ddd, 1H, J = 8.0, 7.1, 0.9 Hz, H6′), 7.39 (d, 1H, J = 8.2 Hz, H7′), 7.46 (ddd, 1H, J = 8.0, 7.1, 1.0 Hz, H6), 7.60 (d, 1H, J = 7.9 Hz, H8), 7.70 (d, 1H, J = 8.0 Hz, H4′), 7.79 (ddd, 1H, J = 8.4, 7.0, 1.5 Hz, H7), 8.21 (dd, 1H, J = 7.9, 1.2 Hz, H5), 9.01 (br s, 1H, H1′); IR (cm^{-1}): ν 3372 s, 2957 w, 1754 s, 1621 s, 1603 s, 1571 m, 1472 m, 1261 m, 1240 w, 1055 m, 766 w, 741 m, 684 w; MS (EI) m/z (%): 305 (14), 304 (66, $[M]^+$), 289 (10, $[M - CH_3]^+$), 276 (24), 275 (100, $[M - CH_2CH_3]^+$), 257 (12), 247 (19), 146 (15), 128 (26), 90 (14); HRMS (ESI^+): m/z calcd for $C_{19}H_{17}N_2O_2^+$ $[M + H]^+$ 305.1285, found 305.1283. Found: C, 75.25; H, 5.45; N, 9.3. Calc. for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.3; N, 9.2%.

8-Methyl-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4g). Yellow microcrystals, mp 251–254 °C (benzene), R_f = 0.62 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64 (s, 3H, C8CH_3), 2.80 (s, 3H, C3′CH_3), 7.15 (ddd, 1H, J = 7.9, 7.1, 0.8 Hz, H5′), 7.34 (ddd, 1H, J = 8.1, 8.1, 1.0 Hz, H6′), 7.35 (dd, 1H, J = 7.5, 7.5 Hz, H6), 7.41 (d, 1H, J = 8.2 Hz, H7′), 7.66 (d, 1H, J = 7.4 Hz, H7), 7.69 (d, 1H, J = 8.0 Hz, H4′), 8.06 (dd, 1H, J = 7.6, 0.6 Hz, H5), 8.93 (br s, 1H, H1′); IR (cm^{-1}): ν 3365 s, 2918 w, 1746 s, 1623 s, 1597 m, 1548 m, 1446 m, 1322 m, 1322(m), 1234 m, 1062 m, 1029 m, 764 m, 740 m; MS (EI) m/z (%): 291 (23), 290 (100, $[M]^+$), 289 (17), 261 (21), 233 (20), 165 (22), 158 (99), 157 (86), 145 (18), 130 (68), 129 (55), 128 (27), 104 (17), 103 (37), 102 (24), 77 (46); HRMS (ESI^+): m/z calcd for $C_{18}H_{15}N_2O_2^+$ $[M + H]^+$ 291.1128, found 291.1127. Found: C, 74.4; H, 4.9; N, 9.4. Calc. for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.9; N, 9.65%.

5-Chloro-8-Methyl-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]-oxazin-4-one (4i). Pale-yellow microcrystals, mp 251–256 °C (cyclohexane), R_f = 0.82 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H, C8CH_3), 2.79 (s, 3H, C3′CH_3), 7.17 (ddd, 1H, J = 7.9, 7.0, 0.9 Hz, H5′), 7.35 (ddd, 1H, J = 8.6, 7.7, 1.0 Hz, H6′), 7.36 (d, 1H, J = 8.1 Hz, H6), 7.42 (d, 1H, J = 8.3 Hz, H7′), 7.53 (dd, 1H, J = 8.1, 0.6 Hz, H7), 7.69 (dd, 1H, J = 7.5, 0.5 Hz, H4′), 8.92 (br s, 1H, H1′); IR (cm^{-1}): ν 3384 m, 3351 m, 3057 w, 2917 w, 1739 s, 1629 s, 1576 m, 1328 m, 1262 m, 1232 w, 1028 w, 914 m, 744 m, 730 m; MS (EI) m/z (%): 327 (7), 326 (34), 325 (22), 324 (100, $[M]^+$), 323 (4), 295 (49), 130 (53), 129 (46), 128 (44), 102 (50), 77 (51); HRMS (ESI^+): m/z calcd for $C_{18}H_{14}ClN_2O_2^+$ $[M + H]^+$ 325.0738, found 325.0740. Found: C, 66.4; H, 4.0; N, 8.8. Calc. for $C_{18}H_{13}ClN_2O_2$: C, 66.6; H, 4.0; N, 8.6%.

6,8-Dimethyl-2-(3-propyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4j). Pale-yellow microcrystals, mp 201–202 °C (benzene), R_f = 0.93 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.81 (tq, 2H, J = 7.4, 7.4 Hz, C3′CH_2CH_2), 2.41 (s, 3H, C6CH_3), 2.59 (s, 3H, C8CH_3), 3.27 (t, 2H, J = 7.6 Hz, C3′CH_2), 7.14 (ddd, 1H, J = 7.8, 7.2, 0.7 Hz, H5′), 7.32 (ddd, 1H, J = 8.0, 7.2, 0.8 Hz, H6′), 7.40 (d, 1H, J = 8.2 Hz, H7′), 7.46 (s, 1H, H7), 7.69 (d, 1H, J = 8.0 Hz, H4′), 7.84 (s, 1H, H5), 8.93 (br s, 1H, H1′); IR (cm^{-1}): ν 3363 s, 2953 w, 1740 s, 1623 s, 1603 s, 1477 m, 1249 m, 1054 m, 789 m, 729 m; MS (EI) m/z (%): 334 (3), 333 (18), 332 (77, $[M]^+$), 303 (100), 288 (33), 128 (37), 85 (31), 71 (36), 57 (65); HRMS (ESI^+): m/z calcd for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$ 333.1598, found 333.1597. Found: C, 75.9; H, 6.1; N, 8.35. Calc. for $C_{21}H_{20}N_2O_2$: C, 75.9; H, 6.1; N, 8.4%.

6,8-Dimethoxy-2-(3-propyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]-oxazin-4-one (4k). Yellow crystals, mp 202–204 °C (cyclohexane), R_f = 0.69 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 0.97 (t, 1H, J = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.71 (tq, 2H, J = 7.7, 7.4 Hz, C3′CH_2CH_2), 3.19 (t, 2H, J = 7.7 Hz, C3′CH_2), 3.85 (s, 3H, C6OCH_3), 3.93 (s, 3H, C8OCH_3), 6.93 (d, 1H, J = 2.6 Hz, H7), 7.01 (ddd, 1H, J = 7.9, 7.2, 0.7 Hz, H5′), 7.05 (d, 1H, J = 2.6 Hz, H5), 7.18 (ddd, 1H, J = 8.1, 7.1, 0.9 Hz, H6′), 7.46 (d, 1H, J = 8.2 Hz, H7′), 7.62 (d, 1H, J = 8.0 Hz, H4′), 10.80 (br s, 1H, H1′); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 14.6, 25.0, 27.6, 56.4, 57.0, 100.6, 108.0, 113.0, 118.9, 120.6, 121.0, 124.2, 125.7, 129.6, 133.1, 138.0, 151.4, 156.7, 159.6, 160.6; IR (cm^{-1}): ν 3368 m, 2963 w, 1736 s, 1619 s, 1491 m, 1437 m, 1373 s, 1325 m, 1300 m, 1219 m, 1036 m, 782 m, 739 m; MS (EI) m/z (%): 366 (4), 365 (24), 364 (100, $[M]^+$), 349 (18), 336 (22), 335 (82), 179 (48), 156 (24), 129 (29), 128 (44); HRMS (ESI^+): m/z calcd for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$ 365.1496, found 365.1494. Found: C, 69.1; H, 5.5; N, 7.6. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.5; N, 7.7%.

2-(3-Propyl-1*H*-indol-2-yl)-4*H*-naphtho[1,2-*d*][1,3]oxazin-4-one (4m). Bright yellow crystals, mp 273–274 °C (ethanol), R_f = 0.73 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.4 Hz), 1.92 (tq, 2H, J = 7.6, 7.4 Hz), 3.42 (t, 2H, J = 7.6 Hz), 7.19 (dd, 1H, J = 7.4, 7.4 Hz), 7.38 (dd, 1H, J = 7.2, 7.2 Hz), 7.46 (d, 1H, J = 8.2 Hz), 7.72–7.80 (m, 3H), 7.86 (d, 1H, J = 8.6 Hz), 7.94 (dd, 1H, J = 8.1, 1.6 Hz), 8.13 (d, 1H, J = 8.6 Hz), 8.98 (dd, 1H, J = 8.2, 1.6 Hz), 9.10 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.4, 24.0, 27.2, 111.6, 112.3, 120.3, 120.9, 122.7, 123.2, 125.3, 126.1, 126.4, 127.4, 127.7, 128.1, 128.9, 129.0, 130.2, 136.7, 137.3, 146.6, 159.4 (one resonance could not be determined due to low solubility of the compound and thus the low signal/noise ratio); IR (cm^{-1}): ν 3360 m, 3057 w, 2951 w, 1744 s, 1602 s, 1564 s, 1542 w, 1509 w, 1444 w, 1394 w, 1272 m, 780 w, 765 m, 736 m, 626 w; MS (EI) m/z (%): 355 (22), 354 (86), 326 (27), 325 (100), 297 (23), 283 (18), 269 (18), 170 (23), 169 (18), 156 (17), 140 (46), 129 (15), 128 (49), 115 (18), 101 (17), 77 (12); HRMS (ESI^+): m/z calcd for $C_{23}H_{19}N_2O_2^+$ $[M + H]^+$ 355.1441; found 355.1438. Found: C, 78.1; H, 5.1; N, 8.0. Calc. for $C_{23}H_{18}N_2O_2$: C, 78.0; H, 5.1; N, 7.9%.

***N*′-Phenyl-5-methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]-amino}benzohydrazide (5b).** White solid *mp* 243–253 °C (benzene), R_f = 0.47 (20% benzene in ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.52 (s, 3H, C3′CH_3), 3.87 (s, 3H, OCH_3), 6.72 (t, 1H, J = 7.3 Hz, H4″), 6.82 (d, 2H, J = 7.7 Hz, H2 and H6 of phenyl), 7.05 (ddd, 1H, J = 7.5, 7.5, 0.6 Hz, H5′), 7.14 (dd, 2H, J = 8.2, 7.6 Hz, H3 and H5 of phenyl), 7.20–7.25 (m, 2H, H4 and H6′), 7.40 (d, 1H, J = 8.2 Hz, H7′), 7.48 (d, 1H, J = 3.0 Hz, H6), 7.62 (d, 1H, J = 8.1 Hz, H4′), 8.00 (d, 1H, J = 1.0 Hz, N*H*Ph), 8.35 (d, 1H, J = 9.1 Hz, H3), 10.65 (d, 1H, J =

1.0 Hz, N*H*NHPh), 11.00 (br s, 1H, C2NH), 11.45 (br s, 1H, H1′); ^{13}C NMR (126 MHz, DMSO-d_6): δ 9.7 (C3′*C*H$_3$), 55.6 (O*C*H$_3$), 112.1 (C7′), 112.4 (C2 and C6 of phenyl), 112.8 (C6), 113.0 (C3′), 117.9 (C4), 118.9 (C4 of phenyl), 119.3 (C5′), 120.0 (C4′), 121.9 (C1), 123.6 (C3), 124.1 (C6′), 127.9 (C3a′), 128.1 (C2′), 128.8 (C3 and C5 of phenyl), 131.6 (C2), 135.9 (C7a′), 149.1 (C1 of phenyl), 154.7 (C5), 160.1 (C2′*C*O), 168.0 (COOH); ^{15}N NMR (51 MHz, DMSO-d_6) δ 89.0 (NPh), 123.2 (C2N); 132.3 (N1′), 137.6 (C1CON); IR (cm^{-1}): ν 3374 m, 3302 m, 3053 w, 1655 s, 1609 m, 1541 s, 1524 s, 1494 m, 1419 m, 1335 m, 1283 m, 1234 m, 1223 m, 740 m; MS (EI) *m*/*z* (%): 338 (43), 181 (100), 158 (38), 130 (32), 129 (25), 77 (25), 60 (23), 45 (35), 44 (39), 43 (40); HRMS (ESI$^+$): *m*/*z* calcd for $C_{24}H_{23}N_4O_3^+$ $[M + H]^+$ 415.1765; found 415.1760; Found: C, 69.6; H, 5.3; N, 13.35. Calc. for $C_{24}H_{22}N_4O_3$: C, 69.6; H, 5.35; N, 13.5%.

***N*′-Phenyl-2-{[(3-propyl-1*H*-indol-2-yl)carbonyl]amino}benzohydrazide (5f).** Colourless needles, mp 214–216 °C (benzene), R_f = 0.61 (20% methanol in ethyl acetate), R_f = 0.28 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.83 (t, 3H, *J* = 7.4, Hz, CH$_3$), 1.58 (tq, 2H, *J* = 7.4, 7.4 Hz, C*H*$_2$CH$_3$), 3.02 (t, 2H, *J* = 7.4 Hz, C3′CH$_2$), 6.72 (t, 1H, *J* = 7.3 Hz, H4 of phenyl), 6.82 (d, 2H, *J* = 7.8 Hz, H2 and H6 of phenyl), 7.05 (dd, 1H, *J* = 7.4, 7.4, Hz, H5′), 7.14 (dd, 2H, *J* = 7.8, 7.8 Hz, H3 and H5 of phenyl), 7.22 (dd, 1H, *J* = 7.5, 7.5 Hz, H6′), 7.27 (ddd, 1H, *J* = 7.6, 7.6, 0.7 Hz, H5), 7.41 (d, 1H, *J* = 8.2 Hz, H7′), 7.60–7.65 (m, 2H, H4 and H4′), 7.96 (dd, 1H, *J* = 7.9, 1.1 Hz, H6), 7.98 (br d, 1H, *J* = 2.3 Hz, CONHN*H*), 8.45 (d, 1H, *J* = 8.1 Hz, H3), 10.66 (br d, 1H, *J* = 2.3 Hz, CON*H*NH), 11.33 (br s, 1H, C2NH), 11.49 (br s, 1H, H1′); ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.7 (CH$_3$), 24.0 (*C*H$_2$CH$_3$), 25.6 (C3′*C*H$_2$), 112.1 (C7′), 112.2 (C2 and C6 of phenyl), 118.8 (C4 of phenyl), 119.26 (C3′), 119.29 (C5′), 120.0 (C4′), 120.3 (C1), 121.8 (C3), 123.1 (C5), 124.1 (C6′), 127.3 (C2′), 127.7 (C3a′), 128.0 (C6), 128.7 (C3 and C5 of phenyl), 132.2 (C4), 135.9 (C7a′), 138.5 (C2), 149.0 (C1 of phenyl), 160.3 (C2′*C*O), 168.2 (COOH); ^{15}N NMR (51 MHz, DMSO-d_6) δ 88.9 (NPh), 124.6 (C2N), 131.9 (N1′), 137.6 (C1CON); IR (cm^{-1}): ν 3319 s, 2953 w, 2869 w, 1655 s, 1631 s, 1593 s, 1540 m, 1515 s, 1493 m, 1446 m, 1281 m, 1244 m, 740 s; MS (EI) *m*/*z* (%): 413 (3), 412 (12, $[M]^+$), 306 (21), 305 (100), 186 (67), 146 (28), 130 (22), 128 (22), 120 (68), 108 (37), 77 (21); HRMS (ESI$^+$): *m*/*z* calcd for $C_{25}H_{25}N_4O_2^+$ $[M + H]^+$ 413.1972, found 413.1971. Found: C, 72.7; H, 5.9; N, 13.6. Calc. for $C_{25}H_{24}N_4O_2$: C, 72.8; H, 5.9; N, 13.6%.

Reaction of 4f with phenylhydrazine into hydrazide 5f (Table 5, entry 1)

A mixture of benzoxazinone **4f** (332 mg, 1.09 mmol) and phenylhydrazine (143 mg, 1.32 mmol) in toluene (15 mL) was heated under reflux for 2 hours. After cooling, the precipitated solid was filtered off with suction and crystallized from benzene to give hydrazide **5f** (382 mg, 86%). The spectral and analytical data were in agreement with those for the authentic sample, as prepared above.

Reaction of 4f with *n*-butylamine into amide 6f (Table 5, entry 2). A mixture of benzoxazinone **4f** (305 mg, 1.00 mmol) and *n*-butylamine (90 mg, 1.23 mmol) in toluene (15 mL) was stirred at room temperature for 2 hours. The precipitated solid was filtered off with suction and crystallized from benzene to give amide **6f** (316 mg, 84%) as a white crystalline solid, mp 187–188 °C (benzene), R_f = 0.41 (20% methanol in ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, 3H, *J* = 7.4 Hz, NH(CH$_2$)$_3$*C*H$_3$), 0.95 (t, 3H, *J* = 7.3 Hz, C3′(CH$_2$)$_2$C*H*$_3$), 1.29–1.38 (m, 2H, NH(CH$_2$)$_2$*C*H$_2$), 1.49–1.57 (m, 2H, NHCH$_2$*C*H$_2$), 1.62–1.72 (m, 2H, C3′CH$_2$*C*H$_2$), 3.08–3.14 (m, 2H, C3′*C*H$_2$), 3.26–3.32 (m, 2H, NH*C*H$_2$), 7.07 (ddd, 1H, *J* = 7.8, 7.2, 0.6 Hz, H5′), 7.21 (ddd, 1H, *J* = 8.4, 7.4, 1.0 Hz, H5), 7.24 (ddd, 1H, *J* = 7.9, 7.2, 0.8 Hz, H6′), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.56 (ddd, 1H, *J* = 7.4, 7.4, 1.3 Hz, H4), 7.67 (d, 1H, *J* = 8.0 Hz, H4′), 7.78 (dd, 1H, *J* = 7.8, 1.3 Hz, H6), 8.53 (dd, 1H, *J* = 8.3, 0.5 Hz, H3), 8.83 (br t, 1H, *J* = 5.4 Hz, C1′CONH), 11.48 (br s, 1H, H1′), 11.71 (br s, 1H, C2NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (NH(CH$_2$)$_3$*C*H$_3$), 13.8 (C3′(CH$_2$)$_2$*C*H$_3$), 19.6 (NHCH$_2$*C*H$_2$), 24.1 (C3′CH$_2$*C*H$_2$), 25.7 (C3′*C*H$_2$), 30.9 (NHCH$_2$*C*H$_2$), 38.8 (NHCH$_2$), 112.2 (C7′), 118.6 (C3′), 119.2 (C5′), 120.0 (C4′), 121.2 (C3), 121.5 (C1), 122.7 (C5), 124.0 (C6′), 127.6 (C2′), 127.7 (C3a′), 128.0 (C6), 131.6 (C4), 135.9 (C7a′), 138.6 (C2), 160.3 (C2′*C*O), 168.1 (C1*C*O); ^{15}N NMR (51 MHz, DMSO-d_6) δ 120.33 (Cα-NH), 125.0 (C2-NH), 132.6 (N1′); IR (cm^{-1}): ν 3320 s, 2956 m, 2932 w, 2869 w, 1653 s, 1626 s, 1595 s, 1538 m, 1518 s, 1465 w, 1446 m, 1432 w, 1338 w, 1325 w, 1281 s, 1241 m, 762 w, 736 s, 677 m; MS (EI) *m*/*z* (%): 378 (19), 377 (70), 305 (20), 304 (76), 276 (22), 275 (88), 247 (15), 219 (20), 186 (29), 185 (100), 170 (62), 168 (39), 167 (20), 159 (20), 158 (33), 157 (31), 156 (56), 146 (23), 130 (46), 129 (36), 128 (58), 120 (66), 119 (30), 77 (15); HRMS (ESI$^+$): *m*/*z* calcd for $C_{23}H_{28}N_3O_2^+$ $[M + H]^+$ 378.2176, found 378.2168. Found: C, 73.0; H, 7.3; N, 11.1. Calc. for $C_{23}H_{27}N_3O_2$: C, 73.2; H, 7.2; N, 11.1%.

General procedure for the hydrolysis of benzoxazinones 4f,j,m into 2-(indol-2-carboxamido)benzoic acids 1f,j,m (Table 5, entries 3–6)

A mixture of benzoxazinone **4** (343 mg, 0.968 mmol), dimethyl sulfoxide (10 mL) and aqueous sodium hydroxide (0.5 M, 1 mL) was stirred at room temperature for the time indicated in Table 5 (for the reaction in entry 4, dioxane (3 mL) and aqueous sulphuric acid (0.1 M, 2 mL) were used). The reaction mixture was diluted with water (50 mL) and acidified with 10% hydrochloric acid to Congo red (for the reaction from entry 4, no additional acid was added). After stirring for 1 h, the precipitate was filtered off, washed with water and dried to afford 2-(indol-2-carboxamido)benzoic acid **1**. Yields of the products are indicated in Table 5. The spectral and analytical data for **1f,j** were in agreement with those for the authentic samples, prepared above.

1m: Colourless solid, mp 227–230 °C (ethanol), R_f = 0.39 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.94 (t, 3H, *J* = 7.1 Hz, C3′(CH$_2$)$_2$C*H*$_3$), 1.69 (tq, 2H, *J* = 7.1, 7.1 Hz, C3′CH$_2$*C*H$_2$), 3.11 (t, 2H, *J* = 7.1 Hz, C3′CH$_2$), 7.10 (dd, 1H, *J* = 7.5, 7.5 Hz, H5′), 7.28 (dd, 1H, *J* = 7.5, 7.5 Hz, H6′), 7.50 (d, 1H, *J* = 8.2 Hz, H7′), 7.61 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 7.67 (dd, 1H, *J* = 7.5, 7.5 Hz, H6), 7.70 (d, 1H, *J* = 8.0 Hz, H4′), 7.95

(d, 1H, J = 8.7 Hz, H4), 7.98 (d, 1H, J = 8.6 Hz, H3), 8.03 (d, 1H, J = 8.1 Hz, H5), 8.09 (d, 1H, J = 8.4 Hz, H8), 10.27 (br s, 1H, CONH), 11.54 (br s, 1H, H1′), 13.30 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.2 (C3′(CH_2)$_2$$CH_3$), 24.1 (C3′$CH_2$$CH_2$), 26.2 (C3′$CH_2$), 112.2 (C7′), 119.4 (C5′), 120.2 (C4′), 121.2 (C3′), 123.8 (C2), 124.3 (C6′), 125.5 (C8), 126.0 (C3), 126.2 (C4), 126.6 (C7), 126.7 (C2′), 127.7 (C3a′), 128.0 (C5), 128.1 (C6), 129.5 (C8a), 135.2 (C4a), 135.7 (C7a′), 135.8 (C1), 161.6 (CONH), 168.3 (COOH); IR (cm^{-1}): ν 3311 s, 3051 w, 2957 m, 2927 m, 2865 w, 1675 s, 1641 s, 1604 w, 1571 m, 1530 w, 1482 m, 1465 w, 1451 w, 1416 m, 1335 m, 1285 m, 1259 m, 1238 s, 1224 w, 1204 w, 1178 w, 767 m, 749 s; MS (EI) m/z (%): 373 (2), 372 (7), 355 (23), 354 (87), 326 (28), 325 (100), 297 (23), 283 (19), 269 (19), 170 (46), 169 (26), 156 (27), 140 (48), 129 (20), 128 (58), 115 (25), 77 (16); HRMS (ESI$^+$): m/z calcd for $C_{23}H_{21}N_2O_3^+$ [M + H]$^+$ 373.1547, found 373.1544. Found: C, 74.4; H, 5.5; N, 7.7. Calc. for $C_{23}H_{20}N_2O_3$: C, 74.2; H, 5.4; N, 7.5%.

Acknowledgements

This study was supported by the internal grant of the TBU in Zlin (no. IGA/FT/2014/010) funded from the resources of specific university research and The Ministry of Education, Science and Sport, Republic of Slovenia, the Slovenian Research Agency (P1-0230 and Post-doctoral Grant to M. G. (430-168/2013/114). This work was also partly supported through the infrastructure of the EN-FIST Centre of Excellence, Ljubljana.

Notes and references

1 (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930; (*b*) R. J. Sundberg, in *Indoles*, Academic Press, San Diego, 1996; (*c*) G. W. Gribble, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Ress, E. F. V. Scriven and C. W. Bird, Pergamon Press, Oxford, 1996, vol. 2, p. 207.

2 P. Wiklund and J. Bergman, *Curr. Org. Synth.*, 2006, **3**, 379–402.

3 P.-L. Wu, Y.-L. Hsu and C.-W. Jao, *J. Nat. Prod.*, 2006, **69**, 1467–1470.

4 C. Jimènez, E. Quiñoa, M. Adamczeski, L. M. Hunter and P. Crews, *J. Org. Chem.*, 1991, **56**, 3403–3410.

5 (*a*) M. S. Shengelia, V. G. Avramenko, L. N. Kuleshova, N. N. Suvorov, V. A. Silin and E. N. Padeiskaya, *Khim.-Farm. Zh.*, 1985, **19**, 1075–1078; (*b*) A. Thorarensen, C. J. Ruble, J. F. Fisher, D. L. Romero, T. J. Beauchamp and J. M. Northuis, *PCT Int. Appl*, WO 2004018428 A1; *Chem. Abstr.*, 2004, **140**, 235498; (*c*) J. Li, B. D. Wakefield, J. C. Ruble, C. M. Stiff, D. L. Romero, K. R. Marotii, M. T. Sweeney, G. E. Zurenko, D. C. Rohrer and A. Thorarensen, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2347–2350; (*d*) C. Stiff, D. R. Graber, A. Thorarensen, B. D. Wakefield, K. R. Marotti, E. P. Melchior, M. T. Sweeney, F. Han, D. C. Rohrer, G. E. Zurenko and D. L. Romero, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6293–6297.

6 I. Amasaki and N. Hanaki, *U.S. Pat. Appl. Publ*, US 2009/0239982 A1; *Chem. Abstr.*, 2008, **149**, 567210.

7 (*a*) T. J. Dueweke, S. M. Poppe, D. L. Romero, S. M. Swaney, A. G. So, K. M. Downey, I. W. Althaus, F. Reusser, M. Busso, L. Resnick, D. L. Mayers, J. Lane, P. A. Aristoff, R. C. Thomas and W. G. Tarpley, *Antimicrob. Agents Chemother.*, 1993, **37**, 1127–1131; (*b*) M.-P. de Béthune, *Antiviral Res.*, 2010, **85**, 75–90.

8 F. Ban, E. Leblanc, H. Li, R. S. N. Munuganti, K. Frewin, P. S. Rennie and A. Cherkasov, *J. Med. Chem.*, 2014, **57**, 6867–6872.

9 S. Koeller, J. Kadota, F. Peruch, A. Deffieux, N. Pinaud, I. Pianet, S. Massip, J. M. Leger, J. P. Desvergne and B. Bibal, *Chem. – Eur. J.*, 2010, **16**, 4196–4205.

10 For recent examples, see: (*a*) A. M. Alanazi, A. A. M. Abdel-Aziz, I. A. Al-Suwaidan, S. G. Abdel-Hamide, T. Z. Shawer and A. S. El-Azab, *Eur. J. Med. Chem.*, 2014, **79**, 446–454; (*b*) M. A. El-Hashash and Y. A. El-Badry, *Helv. Chim. Acta*, 2011, **94**, 389–396.

11 (*a*) A. Krantz, R. W. Spencer, T. F. Tam, T. J. Liak, L. J. Copp, E. M. Thomas and S. P. Rafferty, *J. Med. Chem.*, 1990, **33**, 464–479; (*b*) A. Arcadi, C. Asti, L. Brandolini, G. Caselli, F. Marinelli and V. Ruggieri, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1291–1294.

12 U. Neumann, N. M. Schechter and M. Gütschow, *Bioorg. Med. Chem.*, 2001, **9**, 947–954.

13 L. Hedstrom, A. R. Moorman, J. Dobbs and R. H. Abeles, *Biochemistry*, 1984, **23**, 1753–1759.

14 R. L. Jarvest, M. J. Parratt, C. M. Debouck, J. G. Gorniak, J. L. Jennings, H. T. Serafinowska and J. E. Strickler, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2463–2466.

15 M. Gütschow and U. Neumann, *Bioorg. Med. Chem.*, 1997, **5**, 1935–1942.

16 (*a*) R. Krantz, E. W. Spencer, T. F. Tam, E. Thomas and L. J. Copp, *J. Med. Chem.*, 1987, **30**, 589–591; (*b*) J. L. Gilmore, S. J. Hays, B. W. Caprathe, C. Lee, M. R. Emmerling, W. Michael and J. C. Jaen, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 679–682; (*c*) S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpali, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang and J. C. Jaen, *J. Med. Chem.*, 1998, **41**, 1060–1067.

17 S. Mayama, T. Tani, T. Ueno, K. Hirabayashi, T. Nakashima, H. Fukami, Y. Mizuno and H. Irie, *Tetrahedron Lett.*, 1981, **22**, 2103–2106.

18 For example, see: (*a*) M. S. Shengelia, V. G. Avramenko, L. N. Kuleshova, N. N. Suvorov, V. A. Silin and E. N. Padeiskaya, *Khim.-Farm. Zh.*, 1985, **19**, 1075–1078; (*b*) S. P. Hiremath, A. C. Bajji and J. S. Biradar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1988, **27**, 756–757; (*c*) S. A. Samsoniya, M. V. Trapaidze, N. A. Kuprashvili, D. S. Zurabishvili and N. N. Suvorov, *Chem. Heterocycl. Compd.*, 1998, **34**, 816–821; (*d*) E. S. Lee,

J. K. Son, Y. H. Na and Y. Jahng, *Heterocycl. Commun.*, 2004, **10**, 325–330.
19 For reviews of the Fischer indole synthesis, see: (*a*) B. Robinson, *Chem. Rev.*, 1963, **63**, 373–401; (*b*) B. Robinson, *Chem. Rev.*, 1969, **69**, 227–250; (*c*) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075.
20 For seminal studies of the Fischer indole synthesis, see: (*a*) E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2241–2245; (*b*) E. Fischer and O. Hess, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 559–568.
21 S. Kafka, K. Proisl, V. Kašpárková, D. Urankar, R. Kimmel and J. Košmrlj, *Tetrahedron*, 2013, **69**, 10826–10835.
22 (*a*) M. Nakazaki and K. Yamamoto, *J. Org. Chem.*, 1976, **41**, 1877; (*b*) G. Baccolini and P. E. Todesco, *J. Chem. Soc., Chem. Commun.*, 1981, 563.
23 (*a*) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes and Y. Cai, *Org. Lett.*, 2006, **8**, 5769–5771; (*b*) S. Gore, S. Baskaran and B. König, *Org. Lett.*, 2012, **14**, 4568–4571.
24 A. Sudhakara, H. Jayadevappa, H. N. H. Kumar and K. M. Mahadevan, *Lett. Org. Chem.*, 2009, **6**, 159–164.
25 M. Shariat, M. W. Samsudin and Z. Zakaria, *Chem. Cent. J.*, 2013, **7**(58), 1–6.
26 G. M. Coppola, *J. Heterocycl.. Chem.*, 1999, **36**, 563–588.
27 (*a*) X. L. Lian, H. Lei, X. J. Quan, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Chem. Commun.*, 2013, **49**, 8196–8198; (*b*) Z. Y. Ge, Q. M. Xu, X. D. Fei, T. Tang, Y. M. Zhu and S. J. Ji, *J. Org. Chem.*, 2013, **78**, 4524–4529.
28 H. M. F. Madkour, *ARKIVOC*, 2004, **i**, 36–54.
29 A. G. Osborne and Z. Goolamali, *Spectrochim. Acta, Part A*, 2000, **56**, 1079–1100.
30 J. Vicens, M. C. Etter and L. A. Errede, *Tetrahedron Lett.*, 1983, **24**, 723–724.
31 (*a*) E. Wenkert, E. W. Hagaman, N. Kunesch, N. Y. Wang and B. Zsadon, *Helv. Chim. Acta*, 1976, **59**, 2711–2723; (*b*) M. S. Morales-Rios, J. Espiñeira and P. Joseph-Nathan, *Magn. Reson. Chem.*, 1987, **25**, 377–395; (*c*) M. S. Morales-Rios and P. Joseph-Nathan, *Magn. Reson. Chem.*, 1987, **25**, 911–918; (*d*) P. Joseph-Nathan, R. E. del Río and M. S. Morales-Ríos, *Heterocycles*, 1988, **27**, 377–383; (*e*) A. A. Panasenko, A. F. Caprosh, O. M. Radul and M. A. Rekhter, *Russ. Chem. Bull.*, 1994, **43**, 60–63.
32 (*a*) E. Rosenberg, K. L. Williamson and J. D. Roberts, *Org. Magn. Reson.*, 1976, **8**, 117–119; (*b*) R. M. Claramunt, D. Sanz, C. Lopez, J. Jimenez, M. L. Jimeno, J. Elguero and A. Fruchier, *Magn. Reson. Chem.*, 1997, **35**, 35–75; (*c*) M. d'Ischia, A. Napolitano and A. Pezzella, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 3.
33 D. C. G. A. Pinto, C. M. M. Santos and A. M. S. Silva, in *Recent Research Developments in Heterocyclic Chemistry 2007*, ed. T. M. V. D. Pinho e Melo, 2007, pp. 397–475.
34 K. A. Farley, G. S. Walker and G. E. Martin, *Magn. Reson. Chem.*, 1997, **35**, 671–679.
35 L. Lázár and F. Fülöp, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 8.

JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Synthesis of 1,4-Benzodiazepine-2,5-diones by Base Promoted Ring Expansion of 3-Aminoquinoline-2,4-diones

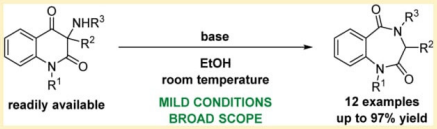
Filip Křemen,[†,#] Martin Gazvoda,[‡,#] Stanislav Kafka,[*,†] Karel Proisl,[†] Anna Srholcová,[†] Antonín Klásek,[†] Damijana Urankar,[‡] and Janez Košmrlj[*,‡]

[†]Department of Chemistry, Faculty of Technology, Tomas Bata University, Zlín 76272, Czech Republic

[‡]Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, Ljubljana SI 1000, Slovenia

Supporting Information

ABSTRACT: An unprecedented reactivity of 3-aminoquinoline-2,4-diones is reported. Under basic conditions, these compounds undergo molecular rearrangement to furnish 1,4-benzodiazepine-2,5-diones. The transformations take place under mild reaction conditions by using 1,1,3,3-tetramethylguanidine, NaOEt, or benzyltrimethylammonium hydroxide as a base. A proposed mechanism of the rearrangement and the conformational equilibrium of 1,4-benzodiazepine-2,5-dione rings are discussed.



The 1,4-benzodiazepine-2,5-dione scaffold, a subset of the 1,4-benzodiazepines, comprises a privileged structure, and numerous derivatives have been found to exhibit a diverse array of biological activities.[1−5] These activities include: histone deacetylase inhibition (Figure 1, structure I);[6] anticholinesterase activity (II, R = H, R′ = Br);[7] melanocortin agonist activity;[8] endothelin receptor antagonism (III);[9] glycoprotein IIb-IIIa antagonism (IV);[10,11] antagonism of the HDM2-p53 interaction (V);[12,13] anxiolytic activity;[14] antileishmanial activity;[15] and herbicidal activity.[16] The 1,4-benzodiazepine-2,5-dione motif appears in natural products including cyclopenin[17,18] (**II**; R = CH_3, R′ = H, Ar = C_6H_5), cyclopenol[17] (**II**; R = CH_3, R′ = H, Ar = 3-OH-C_6H_4), and cyclopeptin (**VI**).[19] They were predicted to be biosynthesized by the condensation of anthranilic acid and an amino acid.[20] In addition to diverse biological activities, 1,4-benzodiazepine-2,5-diones found widespread applications as intermediates in the preparation of products of medicinal interest.[21,22]

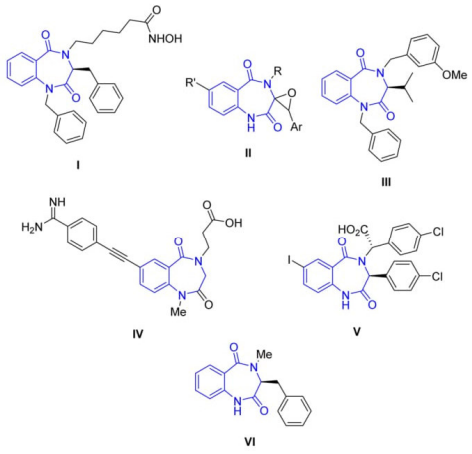


Figure 1. Selected 1,4-benzodiazepine-2,5-diones of biological relevance.

The synthesis of 1,4-benzodiazepine-2,5-dione has been reviewed.[1,23] There are two major strategies for their preparation. One relies on the condensation of an anthranilic acid or its derivative, e.g., isatoic anhydride, with α-amino acid (Figure 2a). Another versatile route takes advantage of Ugi reaction, a four component reaction of substituted *N*-Boc-protected anthranilic acid with an aldehyde, an amine, and an isonitrile to form bis-amide (Figure 2b).[24] Subsequent *N*-Boc-deprotection and condensation of the bis-amide Ugi product generate the 1,4-benzodiazepine-2,5-dione ring skeleton. With some exceptions,[25,26] this procedure has been largely executed to give N1 unsubstituted products (R^1 = H). After ring formation, late stage, selective alkylation (N1/N3) to form the desired product can sometimes be challenging.[27] High-throughput synthetic protocols have been realized by a combinatorial approach.[1,8,28−32]

Due to the remarkable synthetic and biological relevance of 1,4-benzodiazepine-2,5-diones and related compounds, there is an urge to discover new strategies for their preparation. As a part of our interest in the chemistry of quinoline-2,4(1*H*,3*H*)-diones,[33−42] herein we report a novel approach to this scaffold that is based on a rearrangement of 3-aminoquinoline-2,4(1*H*,3*H*)-diones (Figure 2c). In a simple four-step protocol, this method employs anilines as starting substrates. An

Received: June 22, 2016
Published: October 27, 2016

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715−722

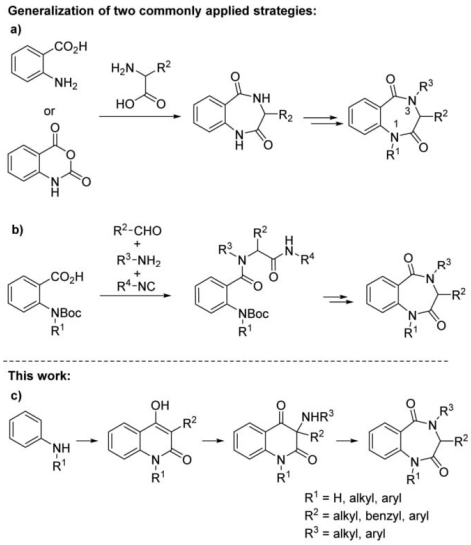
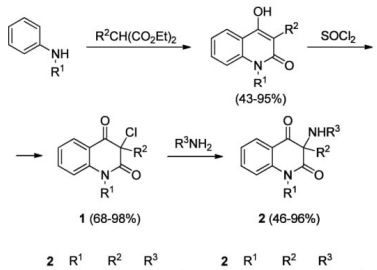


Figure 2. Approaches to 1,4-benzodiazepine-2,5-diones.

advantage of the method over those from Figure 2a–b is a broad availability of aniline derivatives in comparison to anthranilic acids and isatoic anhydrides, both, synthetically and commercially. It readily provides the 1,4-benzodiazepine-2,5-dione ring functionalized at N1 and N3 with an alkyl or aryl moiety. Optimization of the reaction conditions as well as the scope of the reaction are reported.

Differently functionalized starting compounds required for this study were prepared in three simple steps starting from commercially available anilines and diethyl malonates to initially afford 4-hydroxy-2(1*H*)-quinolones (Scheme 1). Chlorination of 4-hydroxy-2(1*H*)-quinolones with sulfuryl chloride gave 3-chloroquinolin-2,4(1*H*,3*H*)-diones **1**,[43,44] which subsequently readily underwent nucleophilic displacement of the chlorine atom with selected primary amines into 3-aminoquinoline-2,4(1*H*,3*H*)-diones **2**.[45]

Scheme 1. Preparation of Compounds 1 and 2



2	R^1	R^2	R^3
a	Me	Ph	*c*-Hex
b	Me	Ph	Me
c	Me	Ph	Ph
d	Me	Me	*c*-Hex
e	Me	Bn	Bu
f	Ph	Ph	*c*-Hex

2	R^1	R^2	R^3
g	Ph	Ph	Me
h	H	Ph	Me
i	H	Ph	Bu
j	H	Et	Bu
k	H	Bu	Bu
l	H	Bn	Me

Investigating the scope of the Wittig olefination at the C-4 carbonyl atom of 3-aminoquinoline-2,4(1*H*,3*H*)-diones, we have previously made a preliminary observation that these compounds are capable of ring expansion into 1,4-benzodiazepine-2,5-diones.[46] In one instance, the treatment of a selected 3-aminoquinoline-2,4(1*H*,3*H*)-dione with ethyl (triphenylphosphoranylidene)acetate ($Ph_3P{=}CHCO_2Et$) in xylene at elevated temperature unexpectedly resulted in its rearrangement into 1,4-benzodiazepine-2,5-dione instead of the anticipated olefination.

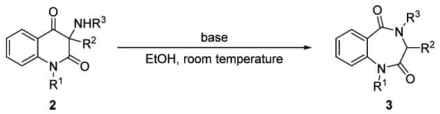
It is reasonable to assume that in the presence of $Ph_3P{=}CHCO_2Et$, the rearrangement was enabled by the assistance of a relatively basic Wittig reagent (pK_a[47] of the conjugated acid, $Ph_3P^+CH_2CO_2Et$, measured in DMSO = 8.50). To find out whether 3-aminoquinoline-2,4(1*H*,3*H*)-diones are in general susceptible to base-mediated transformations into 1,4-benzodiazepine-2,5-diones, we initially conducted some base screening experiments with compound **2a** as a model substrate. As the above-mentioned heating in xylene in the presence of a phophonium ylide would unlikely find practical applications, we decided to test amine bases including 4-dimethylaminopyridine (DMAP), triethylamine, piperidine, butylamine, and 1,1,3,3-tetramethylguanidine (TMG) in ethanol as the reaction solvent (Table 1). Whereas DMAP completely failed to react with **2a**, triethylamine resulted in a complex mixture of products, as judged by TLC analyses of the crude reaction mixtures. In contrast, piperidine, butylamine, and TMG afforded the desired (**3a**) in low to moderate yield. Out of these three bases, TMG was the most effective. It appeared that the efficiency of this rearrangement correlated with its basic character [pK_a data of conjugated acids in water for DMAP = 9.60;[48] triethylamine =10.68;[49] piperidine =11.12;[50] butylamine =10.6;[50] TMG (pK_a = 13.6,[51] 15.2[52])]. We next explored sodium ethoxide and Cs_2CO_3 as alternative nonamine bases and found out to perform similarly as TMG. Finally, benzyltrimethylammonium hydroxide (Triton B), a source of hydroxide ion that is soluble in organic solvents, turned out to be superior. Triton B, TMG, and NaOEt were thus selected for the subsequent substrate scope screening experiments. The results are shown in Table 1.

In the case of N1-substituted substrates **2a–2g** (R^1 = alkyl or phenyl), catalytic amounts of TMG, NaOEt, or Triton B could be employed for the rearrangement into **3**. However, the reactions with TMG and NaOEt were too slow and/or resulted in unacceptably low conversions for practical applications in preparative purposes. For the rearrangement of these substrates, Triton B was found to be superior. It is also noteworthy that the reactions with Triton B were extremely clean, as no side products could be detected by TLC or NMR analyses of the crude reaction mixtures. A simple extractive workup was only required to isolate pure products that needed no further chromatographic purification. In contrast, for N1 unsubstituted analogues **2h–2l** (R^1 = H), an excess of a base (NaOEt) had to be applied for an efficient rearrangement.

The proposed reaction mechanism that accounts for the rearrangement of **2** into **3** is shown in Scheme 2. The base-assisted intramolecular addition of the 3-amino nitrogen atom to the C-4 carbonyl group results in the formation of aziridine oxo-anion, which then undergoes cleavage of C-3/C-4 bond, followed by protonation. It is interesting to note that a reverse reaction, i.e., ring contraction of some 1,4-benzodiazepine-2,5-diones into the corresponding 3-aminoquinoline-2,4(1*H*,3*H*)-

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715–722

Table 1. Rearrangements of Compounds 2 into 3

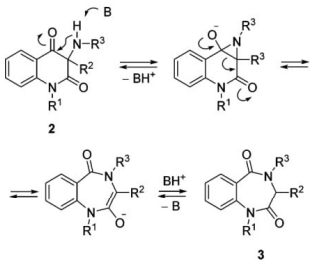


2 3

entry	2	R^1	R^2	R^3	base	equiv	t (h)	3	yield[a] (%)
1	**2a**	Me	Ph	c-Hex	DMAP	0.7	[b]	**3a**	0
2	**2a**	Me	Ph	c-Hex	Triethylamine	1.1	48	**3a**	[c]
3	**2a**	Me	Ph	c-Hex	Piperidine	1.0	[b]	**3a**	26
4	**2a**	Me	Ph	c-Hex	Butylamine	1.6	[b]	**3a**	41
5	**2a**	Me	Ph	c-Hex	TMG	1.0	72	**3a**	46
6	**2a**	Me	Ph	c-Hex	TMG	0.3	4[d]	**3a**	73
7	**2a**	Me	Ph	c-Hex	NaOEt	2.3	4	**3a**	68
8	**2a**	Me	Ph	c-Hex	NaOEt	0.2	1	**3a**	35[e]
9	**2a**	Me	Ph	c-Hex	Cs_2CO_3[f]	0.2	35[g]	**3a**	46
10	**2a**	Me	Ph	c-Hex	Triton B	0.2	1	**3a**	95
11	**2b**	Me	Ph	Me	TMG	2.2	23	**3b**	77
12	**2c**	Me	Ph	Ph	TMG	2.2	10	**3c**	76
13	**2d**	Me	Me	c-Hex	Triton B	0.2	1	**3d**	97
14	**2e**	Me	Bn	Bu	NaOEt	2.5	30	**3e**	68
15	**2e**	Me	Bn	Bu	Triton B	0.2	1	**3e**	94
16	**2f**	Ph	Ph	c-Hex	TMG	2.2	5[d]	**3f**	67
17	**2f**	Ph	Ph	c-Hex	Triton B	0.2	1	**3f**	34[e]
18	**2f**	Ph	Ph	c-Hex	Triton B	0.2	4	**3f**	65[e]
19	**2g**	Ph	Ph	Me	TMG	2.2	16	**3g**	97
20	**2g**	Ph	Ph	Me	Triton B	0.2	1	**3g**	90
21	**2h**	H	Ph	Me	TMG	2.2	32	**3h**	59
22	**2i**	H	Ph	Bu	NaOEt	2.3	12	**3i**	44
23	**2j**	H	Et	Bu	NaOEt	2.3	[h]	**3j**	58
24	**2k**	H	Bu	Bu	NaOEt	2.3	48	**3k**	71
25	**2k**	H	Bu	Bu	Triton B	2.5	24	**3k**	43[e]
26	**2k**	H	Bu	Bu	Triton B	2.5	72	**3k**	83[e]
27	**2k**	H	Bu	Bu	Triton B	0.2	24	**3k**	9[e]
28	**2l**	H	Bn	Me	NaOEt	2.3	51	**3l**	40

[a]Yield of isolated pure product is given. [b]24 h at rt and then heated at 50 °C for 30 h. [c]Complex mixture of products. [d]Reflux. [e]Conversion based on ^{1}H NMR integration. [f]DMF used as a solvent. [g]15 h at rt, then 14 h at 80 °C, then 6 h at 90 °C. [h]24 h at rt, then 4 h at 50 °C, then 4 h at 65 °C.

Scheme 2. Proposed Mechanism



diones, was recently reported by the groups of Dewynter[53] and Carlier.[54] The transformation was achieved by using LiHMDS or KHMDS at −78 °C.

The chemical compositions of all the compounds under investigation were confirmed by standard spectroscopic and analytical methods. Structure elucidation of compounds **3** as well as the assignments of proton and carbon resonances were performed by using 2D NMR experiments. ^{1}H NMR spectra of C3-alkyl and C3-benzyl derivatives **3d**, **3e**, **3j**−**3l**, recorded in DMSO-d_6 at 296 K, exhibited split signal patterns. This suggested the presence of two conformers that are slowly interconverting on the NMR time scale and was confirmed by variable-temperature (VT) ^{1}H NMR experiments. VT ^{1}H NMR spectra of compound **3l** in the temperature range of 293−353 K are shown in Figure 3. The spectrum at 293 K, in the slow exchange regime, is consistent with the presence of two isomers of the compound **3l**. At increase in the temperature, the broadening of the resonances occurs with the subsequent appearance of the average resonance above 323 K, where fast ring inversion takes place. The VT ^{1}H NMR spectra could be rationalized by the 1,4-benzodiazepine-2,5-dione seven-membered ring interconversion in which the C3 substituent has either pseudoequatorial or pseudoaxial orientation thus providing two pairs of enantiomers (*P*)-(*S*)-**3**/(*M*)-(*R*)-**3** and (*P*)-(*R*)-**3**/(*M*)-(*S*)-**3** in two diastereomeric forms (*P*)-(*R*)-**3**/(*M*)-(*S*)-**3** and (*M*)-(*R*)-**3**/(*P*)-(*S*)-**3**, respectively (Figure 4). The existence of two conformers in DMSO-d_6 at 296 K through the split signal patterns was also evident from ^{13}C NMR spectra and 2D NMR spectra. In contrast to the C3-benzyl and C3-alkyl derivatives **3d**, **3e**, **3j**−**3l**, the NMR spectra of the C3-phenyl-substituted products **3a**−**3c** and **3f**−**3i** indicated a single set of resonances. The conformational

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715−722

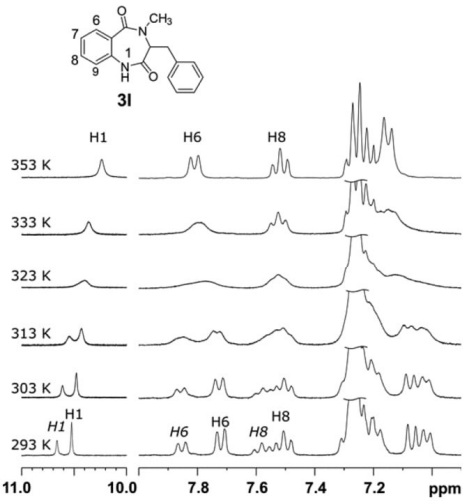


Figure 3. Selected parts of VT ^{1}H NMR spectra of **3l** in DMSO-d_6.

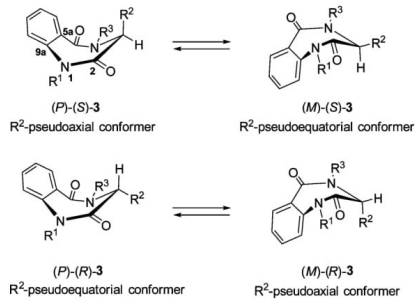


Figure 4. Conformational equilibrium in 1,4-benzodiazepine-2,5-dione ring at racemic compounds **3**. Conformational assignment (*M*/*P*) followed an earlier proposal to designate the sense of conformational chirality of the benzodiazepine ring and is based on the sign of the 2−1−9a−5a dihedral angle (*M* = minus, *P* = positive).[58,59]

behavior is consistent with that observed in related 1,4-benzodiazepine-2,5-diones.[6,11,53−57]

In conclusion, a novel approach to 1,4-benzodiazepine-2,5-dione scaffold is reported. It is based on a molecular rearrangement of easily available 3-aminoquinoline-2,4-(1*H*,3*H*)-diones in the presence of base, such as benzyltrimethylammonium hydroxide (Triton B), 1,1,3,3-tetramethylguanidine (TMG), or NaOEt. The transformations proceed under mild reaction conditions in environmentally friendly ethanol as a reaction solvent, at room temperature. In contrast to the known methods, this approach does not require N1/N3 post alkylation of the 1,4-benzodiazepine-2,5-dione parent ring.

■ EXPERIMENTAL SECTION

General Experimental Methods. The reagents and solvents were used as obtained from the commercial sources. Compounds **1a**,[43,45] **1d**,[60] **1e**,[61] **1f**,[61] **1h**,[45] **1j**,[43] **1k**,[43,61] and **1l**[43,45,61] were prepared as described in the literature. Column chromatography was carried out on Silica gel 60 (particle size 0.063−0.2 mm, activity acc. Brockmann and Schodder 2−3). Melting points were determined on the microscope hot stage and are uncorrected. TLC was carried out on TLC-cards with a fluorescent indicator, and visualization was accomplished with UV light (254 nm). NMR spectra were recorded with a 500 MHz NMR instrument operating at 500 MHz (^{1}H), 126 MHz (^{13}C), and 51 MHz (^{15}N) at 300 K. Proton spectra were referenced to TMS as internal standard, in some cases to the residual signal of DMSO-d_6 (at δ 2.50 ppm). Carbon chemical shifts were determined relative to the ^{13}C signal of DMSO-d_6 (39.5 ppm). ^{15}N chemical shifts were extracted from ^{1}H−^{15}N *gs*-HMBC spectra (with 20 Hz digital resolution in the indirect dimension and the parameters adjusted for a long-range ^{1}H−^{15}N coupling constant of 5 Hz), determined with respect to external nitromethane, and are corrected to external ammonia by addition of 380.5 ppm. Nitrogen chemical shifts are reported to one decimal place as measured of the spectrum, however, the data should not be considered to be more accurate than ±0.5 ppm because of the digital resolution limits of the experiment. Chemical shifts are given on the δ scale (ppm). Coupling constants (*J*) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened). The numbering used for the assignment of NMR signals is as follows: quinoline-2,4(1*H*,3*H*)-dione ring (**2**) and 1,4-benzodiazepine-2,5-dione (**3**), simple figures, R^1-substituent primed figures; R^2-substituent, double primed figures; and R^3-substituent, triple primed figures. NMR peak assignments are based on the analyses of ^{1}H−^{1}H *gs*-COSY, ^{1}H−^{13}C *gs*-HSQC, ^{1}H−^{13}C *gs*-HMBC, and ^{1}H−^{15}N *gs*-HMBC 2D NMR spectra. Infrared spectra were recorded on a FT-IR spectrometer using samples in potassium bromide disks, and only the strongest/structurally most important peaks are listed. Electron impact mass spectra (EI) were recorded at 70 eV. High-resolution mass spectra (HRMS) were obtained with a time-of-flight (TOF) mass spectrometer equipped with an electrospray source at atmospheric pressure ionization (ESI). Elemental analyses (C, H, N) were performed with a CHNS/O analyzer.

Synthesis of 3-Aminoquinoline-2,4(1*H*,3*H*)-diones 2. 3-Aminoquinoline-2,4(1*H*,3*H*)-diones **2** were prepared from 3-chloroquinolin-2,4(1*H*,3*H*)-diones **1** according to the procedures described in the literature.[45] Spectroscopic and analytical data for compounds **2a**,[45] **2b**,[45] **2c**,[45] **2e**,[42] **2h**,[45] **2g**,[45] **2i**,[45] **2k**,[45] and **2l**[45] were in agreement with the literature data. Spectroscopic and analytical data of new compounds **2d**, **2f**, **2g**, and **2j** are reported below.

*3-(Cyclohexylamino)-1,3-dimethylquinoline-2,4(1H,3H)-dione (**2d**).* Compound **2d** (1.67 g, 58.3 mmol, 58%) was prepared from **1d** (2.24 g, 10.0 mmol). Beige solid, mp 78−81 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88−1.09 (m, 5H), 1.32 (s, 3H), 1.40−1.60 (m, 5H), 2.34 (br s, 1H), 2.38−2.45 (m, 1H), 3.21 (s, 3H), 7.24 (dd, 1H, *J* = 7.4 Hz, 7.4 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.75 (ddd, 1H, *J* = 8.7, 7.0, 1,6 Hz), 7.91 (dd, 1H, *J* = 7.7, 1.6 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.7, 25.4, 26.6, 29.8, 34.0, 34.5, 52.8, 67.6, 115.8, 119.4, 122.9, 127.4, 136.4, 142.7, 173.1, 195.4; two ^{13}C resonances are overlapped; IR (cm^{-1}): ν 3326, 2924, 2854, 1693, 1658, 1597, 1491, 1468, 1363, 1345, 1298, 1101, 762, 579, 418; MS (EI) *m*/*z* (%): 286 (2, [M]$^+$), 243 (34), 214 (22), 191 (36), 189 (19), 160 (16), 98 (89), 83 (42), 71 (16); HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{23}N_2O_2^+$ [M + H]$^+$ 287.1754, found 287.1751. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30, H, 7.74, N, 9.78%. Found: C, 71.60, H, 7.99, N, 9.80.

*3-(Cyclohexylamino)-1,3-diphenylquinoline-2,4(1H,3H)-dione (**2f**).* Compound **2f** (3.91 g, 9.5 mmol, 96%) was prepared from **1f** (3.44 g, 9.9 mmol). Beige solid, mp 86−92 °C (benzene); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.98−1.15 (m, 5H), 1.45 (br s, 1H), 1.53−1.64 (m, 3H), 1.77 (d, 1H, *J* = 10.1 Hz), 2.60−2.67 (m, 1H, H1‴), 6.37 (d, 1H, *J* = 8.3 Hz, H8), 7.16 (dd, 1H, *J* = 7.3, 7.2 Hz, H6), 7.29−7.35 (m, 2H, H4′, H3′), 7.35−7.40 (m, 2H, H3″, H5″), 7.45−7.53 (m, 4H, H7, H2″, H6″, H3′), 7.58 (dd, 1H, *J* = 7.4, 7.4 Hz, H4′), 7.61−7.71 (m, 2H, H2′, H6′), 7.86 (dd, 1H, *J* = 7.8, 1.5 Hz, H5); NH proton not found, probably in fast exchange with HOD; ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.97, 25.00, 25.4, 34.5, 34.8, 53.0 (C1‴), 75.7 (C3), 116.7 (C8), 119.9 (C4a), 123.5 (C6), 126.7 (C2″, C6″),

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715−722

127.8 (C5), 128.6 (C4″), 128.7 (C3′ or C5′), 128.9 (C3″, C5″), 129.0 (C4′), 129.2 (C5′ or C3′), 130.3 (C2′ or C6′), 130.6 (C6′ or C2′), 136.1 (C7), 137.3 (C1′), 138.4 (C1″), 143.0 (C8a), 172.2 (C2), 192.7 (C4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 151.4 (N1); IR (cm^{-1}): ν 2924, 2850, 1705, 1672, 1599, 1491, 1461, 1332, 1301, 1240, 757, 717, 695; MS (EI) m/z (%): 411 (4, [M + 1]$^+$), 410 (12, [M]$^+$), 367 (14), 316 (11), 313 (26), 312 (25), 196 (14), 186 (16), 104 (100), 98 (82), 77 (12); HRMS (ESI+): m/z calcd for $C_{27}H_{27}N_2O_2^+$ [M + H]$^+$ 411.2067, found 411.2062 Anal. calcd for $C_{27}H_{26}N_2O_2$ (410.51): C 79.00, H 6.38, N 6.82; found: C 78.92, H 6.44, N 6.99.

*3-(Methylamino)-1,3-diphenylquinoline-2,4(1H,3H)-dione (**2g**).* Compound **2g** (1.58 g, 4.6 mmol, 90%) was prepared from **1f** (1.79 g, 5.1 mmol). White solid, mp 142−149 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.26 (s, 3H, H‴), 2.98 (br s, 1H, NH), 6.34 (d, 1H, J = 8.3 Hz, H8), 7.14 (dd, 1H, J = 7.5, 7.4 Hz, H6), 7.32 (dd, 1H, J = 7.2, 7.2 Hz, H4″), 7.39 (dd, 2H, J = 7.6, 7.6 Hz, H3″, H5″), 7.40−7.50 (m, 5H, H7, H3′, H5′, H2″, H6″), 7.57 (dd, 1H, J = 7.4, 7.4 Hz, H4′), 7.60−7.70 (m, 2H, H2′, H6′), 7.82 (dd, 1H, J = 7.8, 1.2 Hz, H5); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.7 (C‴), 78.0 (C3), 116.6 (C8), 120.6 (C4a), 123.3 (C6), 126,8 (C2″, C6″), 127.5 (C5), 128.7 (C4″), 128.9 (C3″, C5″), 129.0 (C4′), 129.1 (C3′, C5′), 130.4 (C2″, C6″), 135.9 (C7), 137.3 (C1″), 137.4 (C1′), 143.0 (C8a), 171.2 (C2), 192.7 (C4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 34.2 (NH), 152.1 (N1); IR (cm^{-1}): ν 3342, 3062, 2953, 2853, 2793, 1701, 1670, 1598, 1491, 1461, 1336, 1301, 1247, 763, 735, 690, 598, 537, 518; MS (EI) m/z (%):343 (6, [M + 1]$^+$), 342 (23, [M]$^+$), 313 (14), 312 (11), 119 (11), 118 (100), 104 (12), 77 (19); HRMS (ESI+): m/z calcd for $C_{22}H_{19}N_2O_2^+$ [M + H]$^+$ 343.1441, found 343.1440. Anal. calcd for $C_{22}H_{18}N_2O_2$ (342.39): C, 77.17, H, 5.30, N, 8.18; found: C, 76.89, H, 5.25, N, 8.07.

*3-(Butylamino)-3-ethylquinoline-2,4(1H,3H)-dione (**2j**).* Compound **2j** (597 mg, 2.3 mmol, 46%) was prepared from **1j** (1.12 g, 5.0 mmol). Yellowish solid, mp 86−89 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.71 (t, 3H, J = 7.4 Hz), 0.81 (t, 3H, J = 7.2 Hz), 1.20−1.29 (m, 2H), 1.29−1.36 (m, 2H), 1.68−1.82 (m, 2H), 2.17−2.33 (m, 3H), 7.09 (d, 1H, J = 8.0 Hz), 7.11 (dd, 1H, J = 7.6 Hz), 7.60 (dd, 1H, J = 7.6 Hz), 7.75 (d, 1H, J = 7.7 Hz), 10.94 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 7.8, 13.8, 19.8, 32.2, 32.8, 44.1, 73.5, 116.3, 119.3, 122.6, 126.6, 136.3, 141.7, 172.8, 196.5. IR (cm^{-1}): ν 3305, 2963, 2925, 2872, 1706, 1695, 1670, 1650, 1609, 1593, 1485, 1435, 1369, 757, 666. HRMS (ESI+): m/z calcd for $C_{15}H_{21}N_2O_2^+$ [M + H]$^+$ 261.1598, found 261.1596. Anal. calcd for $C_{15}H_{20}N_2O_2$ (260.33): C 69.20, H 7.74, N 10.76; found: C 68.98, H 7.88, N 10.53.

Rearrangement of 3-Aminoquinoline-2,4(1*H*,3*H*)-diones 2 into 1,4-Benzodiazepine-2,5-diones 3. *General Procedure for Rearrangement of **2** into **3**.* A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and a base in ethanol (9 mL) was stirred at room temperature for given time (see Table 1). Details of isolation are described below.

With Benzyltrimethylammonium Hydroxide (Triton B) as a Base. A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and Triton B (34 mg, 0.2 mmol; as 84 mg of 40 wt % solution in methanol) in ethanol (9 mL) was stirred for 1 h at room temperature. The reaction mixture was at room temperature concentrated under reduced pressure. The crude product was dissolved in ethyl acetate (30 mL), washed with water (2 × 15 mL) and brine (15 mL), dried over sodium sulfate, and evaporated to dryness to afford pure products **3** in excellent isolated yield (Table 1, entries 10, 13, 15, 20) or ratio of conversion (Table 1, entries 17, 18, 25−27), which was determined by ^{1}H NMR integration.

With TMG as Base. A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and TMG (230 mg, 2.0 mmol) in ethanol (9 mL) was stirred at room temperature until completion, as judged by TLC analysis (Table 1). The precipitated crude product was collected by filtration, washed with water (2 × 2 mL), and recrystallized from ethanol to afford pure 1,4-benzodiazepine-2,5-dione **3**.

With NaOEt as Base. A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and 0.5 M solution of NaOEt (4.5 mL, 2.25 mmol) was stirred at room temperature under exclusion of atmospheric moisture (the flask equipped with drying tube filled with potassium hydroxide) until completion as judged by TLC analysis (Table 1). The isolation of 1,4-benzodiazepine-2,5-diones **3** from the reaction mixture was done as follows:

From **2a** or **2e**: The reaction mixture was filtered. The filter cake was washed with water (2 mL) and dried at 50 °C to afford pure **3a** (212 mg, 68%) or **3e** (206 mg, 68%).

From **2i** and **2l**: The reaction mixture was acidified with 1 M HCl to Congo red and concentrated *in vacuo*. The oily residue was triturated with water (1 mL), and the resulting precipitate was collected by filtration. The filter cake was washed with water and dried at 50 °C to afford pure **3i** (121 mg, 44%) or **3l** (100 mg, 40%).

From **2j** or **2k**: The reaction mixture was acidified with 1 M HCl to Congo red and extracted with dichloromethane (3 × 9 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was subjected to column chromatography on silica gel using (i) benzene as an eluent to isolate product **3j**, which was additionally crystallized from a mixture of hexane and benzene to obtain pure **3j** (136 mg, 58%) or (ii) chloroform as an eluent to provide pure **3k** (185 mg, 71%).

*4-Cyclohexyl-1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,4]-diazepine-2,5-dione (**3a**).* Triton B: 298 mg, 95% yield; TMG: 232 mg, 74% yield; NaOEt: 212 mg, 68% yield. White solid, mp 192−193 °C (benzene/cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.11−1.22 (m, 1H, cyclohexyl), 1.32−1.89 (m, 9H, cyclohexyl), 3.37 (s, 3H, H1′), 4.73−4.81 (m, 1H, H1‴ of cyclohexyl), 5.59 (s, 1H, H3), 6.87 (d, 2H, J = 7.7 Hz, H2″, H6″), 6.95 (dd, 1H, J = 7.5, 7.5 Hz, H7), 6.99 (t, 1H, J = 6.8 Hz, H4″), 7.03 (d, 1H, J = 8.5 Hz, H9), 7.06 (dd, 2H, J = 7.5, 7.5 Hz, H3″, H5″), 7.21 (ddd, 1H, J = 8.5, 7.0, 1.6 Hz, H8), 7.38 (dd, 1H, J = 7.8, 1.5 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.6, 25.3, 25.4, 29.1, 30.4, 35.1 (C1′), 54.3 (C1‴), 61.1 (C3), 120.7 (C9), 124.0 (C2″, C6″), 124.6 (C7), 126.9 (C4″), 128.1 (C3″, C5″), 129.8 (C6), 129.9 (C5a), 131.4 (C8), 135.0 (C1″), 138.9 (C9a), 165.8 (C5), 170.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 124.3 (N1), 143.3 (N4); IR (cm^{-1}): ν 2936, 2856, 1664, 1629, 1601, 1493, 1475, 1457, 1432, 1366, 1246, 1145, 715; MS (EI) m/z (%):349 ([M + 1]$^+$, 12), 348 ([M]$^+$, 49), 291 (48), 266 (43), 251 (68), 161 (65), 132 (44), 105 (60), 104 (100), 55 (42); HRMS (ESI+): m/z calcd for $C_{22}H_{25}N_2O_2^+$ [M + H]$^+$ 349.1911, found 349.1907. Anal. calcd for $C_{22}H_{24}N_2O_2$ (348.74): C, 75.83; H, 6.94; N, 8.04%. Found: C, 75.62; H, 6.96; N, 8.07%.

*3,4-Dihydro-1,4-dimethyl-3-phenyl-1H-benzo[e][1,4]diazepine-2,5-dione (**3b**).* TMG: 194 mg, 77% yield. White solid, mp 183−186 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.38 (s, 3H, H1′), 3.41 (s, 3H, H1‴), 5.64 (s, 1H, H3), 6.83 (d, 2H, J = 7.8 Hz, H2″, H6″), 6.96 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.01 (t, 1H, J = 7.3 Hz, H4″), 7.08 (dd, 2H, J = 7.7, 7.7 Hz, H3″, H5″), 7.10 (d, 1H, J = 8.0 H, H9), 7.26 (ddd, 1H, J = 7.7, 7.7, 1.2 Hz, H8), 7.38 (dd, 1H, J = 7.8, 1.0 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.3 (C1′), 38.2 (C1‴), 68.0 (C3), 121.0 (C9), 123.9 (C2″, C6″), 124.8 (C7), 127.1 (C4″), 128.3 (C3″, C5″), 129.1 (C5a), 129.6 (C6), 131.6 (C8), 134.6 (C1″), 139.2 (C9a), 166.3 (C5), 169.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 119.2 (N4), 124.0 (N1); IR (cm^{-1}): ν 2933, 2852, 1702, 1670, 1602, 1473, 1443, 1356, 1307, 1124, 1098, 765, 704, 647; MS (EI) m/z (%):281 (8, [M + 1]$^+$, 280 (42, [M]$^+$), 175 (46), 161 (36), 133 (38), 120 (100), 118 (91), 105 (46), 104 (45), 78 (23), 77 (27); HRMS (ESI+): m/z calcd for $C_{17}H_{17}N_2O_2^+$ [M + H]$^+$ 281.1285, found 281.1283. Anal. Cald. for $C_{17}H_{16}N_2O_2$ (280.33): C 72.84, H 5.75, N 9.99, found C 72.76, H 5.77, N 10.04.

*3,4-Diphenyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3c**).* TMG: 234 mg, 76% yield. White solid, mp 202−204 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.48 (s, 3H, H1′), 5.78 (s, 1H, H3), 7.03 (dd, 1H, J = 7.6, 7.6 Hz, H7), 7.06 (d, 2H, J = 7.8 Hz, H2″, H3″), 7.07 (t, 1H, J = 7.8 Hz, H4″), 7.14 (dd, 2H, J = 7.5, 7.5 Hz, H3″, H5″), 7.16 (d, 1H, J = 8.3 Hz, H9), 7.32 (ddd, 1H, J = 8.5, 7.0, 1.4 Hz, H8), 7.36−7.41 (m, 1H, H4‴), 7.46 (dd, 1H, J = 7.8, 1.2 Hz, H6), 7.49−7.54 (m, 4H, H2‴, H3‴, H5‴, H6‴); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.4 (C1′), 69.9 (C3), 121.3 (C9), 124.0 (C2″, C6″), 125.0 (C7), 126.1 (C2‴, C6‴), 127.3 (C4‴), 127.4 (C4″), 128.5 (C3″, C5″), 129.4 (C5a, C3‴, C5‴), 129.9 (C6), 132.1 (C8), 134.2 (C1″), 139.2 (C9a), 143.8 (C1‴), 165.7 (C5), 169.1 (C2); ^{15}N NMR

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715−722

(51 MHz, DMSO-d_6) δ 124.1 (N1), 139.2 (N4); IR (cm^{-1}): ν 3064, 1667, 1654, 1600, 1494, 1473, 1458, 1417, 1369, 1243, 764, 712, 698, 614, 545, 524; HRMS (ESI+): m/z calcd for $C_{22}H_{19}N_2O_2^+$ $[M + H]^+$ 343.1441, found 343.1441. Anal. calcd for $C_{22}H_{18}N_2O_2$ (342.40) C, 77.17; H, 5.30; N, 8.18%. Found: C, 77.47; H, 5.35; N 8.22.

*4-Cyclohexyl-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]-diazepine-2,5-dione (**3d**).* Triton B: 250 mg, 97% yield; White solid, mp 120−124 °C (hexane). Major isomer:minor isomer = 88:12. Major isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (d, 3H, 7.5 Hz, 3-H″), 1.00−1.83 (m, 10H, H2‴, H3‴, H4‴, H5‴, H6‴), 3.30 (s, 3H, H1′), 4.41 (q, 1H, J = 7.5 Hz, H3), 4.53−4.60 (m, 1H, H1‴), 7.31 (dd, 1H, J = 7.4 Hz, H7), 7.38 (d, 1H, J = 8.2 Hz, H9), 7.60 (ddd, 1H, J = 7.8, 7.7, 1.3 Hz, H8), 7.68 (dd, 1H, J = 7.8, 1.3 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.0 (C1″), 24.7, 25.2, 25.3, 29.3, 29.8, 35.2 (C1′), 53.6 (C3), 54.2 (C1‴), 121.1 (C9), 125.1 (C7), 129.4 (C5a), 130.2 (C6), 132.0 (C8), 139.2 (C9a), 164.7 (C5), 170.9 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 123.0 (N1), 146.9 (N4). Minor isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.00−1.83 (m, 10H, H2‴, H3‴, H4‴, H5‴, H6‴), 1.36 (d, 3H, J = 6.8 Hz, H″), 3.26−3.31 (m, 1H, H1‴), 3.31 (s, 3H, H1′), 4.23 (q, 1H, J = 6.8 Hz, H3), 7.29 (dd, 1H, J = 7.4 Hz, H7), 7.38 (d, 1H, J = 8.2 Hz, H9), 7.57 (ddd, 1H, J = 7.8, 7.7, 1.3 Hz, H8), 7.68 (dd, 1H, J = 7.8, 1.3 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.5 (C1″), 25.0, 25.8, 28.5, 30.7, 34.1 (C1′), 51.0 (C3), 55.0 (C1‴), 121.0 (C9), 124.9 (C7), 129.7 (C5a), 130.1 (C6), 131.7 (C8), 140.4 (C9a), 167.4 (C5), 170.5 (C2), one resonance belonging to cyclohexane ring not visible; ^{15}N NMR (51 MHz, DMSO-d_6) δ 142.0 (N4); IR (cm^{-1}): ν 2931, 2918, 2850, 1678, 1636, 1601, 1454, 1423, 1377, 1368, 1318, 1248, 1138, 794, 766, 713; HRMS (ESI+): m/z calcd for $C_{17}H_{23}N_2O_2^+$ $[M + H]^+$ 287.1754, found 287.1753. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30, H, 7.74, N, 9.78%. Found: C, 71.10, H, 8.00, N, 9.69%.

*3-Benzyl-4-butyl-3,4-dihydro-1-methyl-1H-benzo[e][1,4]-diazepine-2,5-dione (**3e**).* Triton B: 286 mg, 94% yield; NaOEt: 206 mg, 68% yield. Pale yellow solid, mp 135−136 °C. Major isomer:minor isomer = 53:47. Major isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87 (t, 3H, J = 7.3 Hz, H4‴), 1.11−1.26 (m, 2H, H3‴), 1.39−1.49 (m, 1H, H2‴), 1.49−1.59 (m, 1H, H2‴), 3.13 (ddd, 1H, J = 13.9, 8.8, 4.5 Hz, H1‴), 3.22 (dd, 1H, J = 14.5, 7.3 Hz, PhCH$_2$), 3.32−3.38 (m, 1H, PhCH$_2$), 3.31 (s, 3H, H1′), 3.89 (ddd, 1H, J = 14.0, 8.2, 8.1 Hz, H1‴), 4.46 (t, 1H, J = 7.5 Hz, H3), 7.15−7.20 (m, 1H, H4″), 7.20−7.29 (m, 4H, H2″, H3″, H5″, H6″), 7.34 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.40 (d, 1H, J = 8.3 Hz, H9), 7.59 (ddd, 1H, J = 7.7, 7.7, 1.4 Hz, H8), 7.71 (dd, 1H, J = 7.7, 1.5 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (C4‴), 19.4 (C3‴), 29.9 (C2‴), 31.8 (PhCH$_2$), 34.4 (C1′), 41.3 (C1‴), 55.8 (C3), 121.4 (C9), 125.3 (C7), 126.5 (C4″), 128.4 (C3″, C5″), 128.9 (C2″, C6″), 129.1 (C5a), 129.7 (C6), 132.0 (C8), 137.2 (C1″), 140.4 (C9a), 167.2 (C5), 169.7 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 125.6 (N1), 132.0 (N4). Minor isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.82 (t, 3H, J = 7.3 Hz, H4‴), 1.11−1.26 (m, 2H, H3‴), 1.28−1.39 (m, 2H, H2‴), 2.44 (dd, 1H, J = 13.4, 9.3 Hz, PhCH$_2$), 2.49−2.55 (m, 1H, PhCH$_2$), 2.99 (ddd, 1H, J = 13.4, 8.1, 5.6 Hz, H1‴), 3.31 (s, 3H, H1′), 3.68 (ddd, 1H, J = 13.3, 7.8, 7.5 Hz, H1‴), 4.41 (t, 1H, J = 8.9 Hz, H3), 6.96 (d, 2H, J = 7.1 Hz, H2″), 7.20−7.29 (m, 3H, H3″, H4″, H5″), 7.41 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.50 (d, 1H, J = 8.2 Hz, H9), 7.70 (ddd, 1H, J = 7.4, 7.4, 1.4 Hz, H8), 7.79 (dd, 1H, J = 7.7, 1.3 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (C4‴), 19.2 (C3‴), 29.1 (C2‴), 34.3 (PhCH$_2$), 35.4 (C1′), 49.5 (C1‴), 66.0 (C3), 121.5 (C9), 125.4 (C7), 126.9 (C4″), 128.5 (C3″, C5″), 128.9 (C2″, C6″), 129.3 (C5a), 130.1 (C6), 132.4 (C8), 136.0 (C1″), 139.4 (C9a), 165.0 (C5), 169.2 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 124.4 (N1), 131.8 (N4); IR (cm^{-1}): ν 2951, 2866, 1676, 1640, 1629, 1602, 1459, 1408, 1384, 760, 707; HRMS (ESI+): m/z calcd for $C_{21}H_{25}N_2O_2^+$ $[M + H]^+$ 337.1911, found 337.1909. Anal. calcd for $C_{21}H_{24}N_2O_2$ (336.43): C, 74.97; H, 7.19; N, 8.33%. Found: C, 74.67; H, 7.43; N, 8.26%.

*4-Cyclohexyl-1,3-diphenyl-3,4-dihydro-1H-benzo[e][1,4]-diazepine-2,5-dione (**3f**).* TMG: 247 mg, 67% yield. Yellow solid, mp 224−227 °C (ethanol). ^{1}H NMR (DMSO-d_6, 500 MHz): 1.10−1.21 (m, 1H, cyclohexyl), 1.31−1.48 (m, 2H, cyclohexyl), 1.50−1.84 (m, 6H, cyclohexyl), 1.84−1.92 (m, 1H, cyclohexyl), 4.81−4.89 (m, 1H, H1‴), 5.72 (s, 1H, H3), 6.32 (d, 1H, J = 8.1 Hz, H9), 6.94 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.01−7.06 (m, 2H, H8, H4″), 7.08−7.15 (m, 4H, H2″, H3″, H5″, H6″), 7.31 (d, 2H, J = 7.4 Hz, H2′, H6′), 7.40 (t, 1H, J = 7.4 Hz, H4′), 7.47 (dd, 1H, J = 7.9, 1.5 Hz, H6), 7.50 (dd, 2H, J = 7.9, 7.6 Hz, H3′, H5′); ^{13}C NMR (DMSO-d_6, 126 MHz) 24.6, 25.3, 25.4, 29.0, 30.4, 54.6 (C1‴), 61.3 (C3), 123.2 (C9), 124.1 (C2″, C6″), 125.0 (C7), 127.1 (C4″), 127.8 (C4′), 128.3 (C3″, 5″), 128.5 (C2′, C6′), 129.5 (C3′, C5′), 130.1 (C6), 130.6 (C5a), 131.3 (C8), 134.8 (C1″), 138.5 (C9a), 140.7 (C1′), 165.6 (C5), 169.2 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 142.0 (N4), 145.3 (N1); IR (cm^{-1}): ν 2918, 2848, 1668, 1640, 1602, 1493, 1456, 1426, 1353, 1238, 1149, 765, 708, 693, 568; MS (EI) m/z (%): (411 5, $[M + 1]^+$), (410 (16, $[M]^+$), 328 (32), 327 (19), 313 (34), 305 (19), 291 (65), 223 (34), 196 (23), 195 (100), 167 (37), 132 (25), 77 (19); HRMS (ESI+): m/z calcd for $C_{27}H_{27}N_2O_2^+$ ($[M + H]^+$) 411.2067, found 411.2065. Anal. calcd for $C_{27}H_{26}N_2O_2$ (410.52): C 79.00, H 6.38, N 6.82, found: C 79.11, H 6.29, N 6.76.

*1,3-Diphenyl-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3g**).* Triton B: 276 mg, 90% yield; TMG: 298 mg, 97% yield. Yellow solid, mp 84−89 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.47 (s, 3H, H1‴), 5.77 (s, 1H, H3), 6.36 (d, 1H, J = 8.2 Hz, H9), 6.96 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.03−7.10 (m, 4H, H8, H2″, H4″, H6″), 7.15 (dd, 2H, J = 7.6, 7.6 Hz, H3″, H5″), 7.33 (d, 2H, J = 7.5 Hz, H2′, H6′), 7.40 (t, 1H, J = 7.5 Hz, H4′), 7.47 (dd, 1H, J = 7.9, 1.4 Hz, H6), 7.50 (dd, 2H, J = 7.5 Hz, H3′, H5′); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.2 (C1‴), 68.1 (C3), 123.4 (C9), 123.9 (C2″, C6″), 125.1 (C7), 127.3 (C4″), 127.8 (C4′), 128.5 (C3″, C5″), 128.6 (C2′, C6′), 129.5 (C3′, C5′), 129.8 (H6), 129.9 (C5a), 131.5 (C8), 134.4 (C1″), 138.8 (C9a), 140.8 (C1′), 166.2 (C5), 168.0 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 118.4 (N4), 145.8 (N1); IR (cm^{-1}): ν 3061, 2929, 1678, 1643, 1601, 1492, 1450, 1396, 1352, 1243, 1162, 758, 711, 695 595, 529; MS (EI) m/z (%): (8, $[M + 1]^+$), 342 (34, $[M]^+$), 237 (40), 223 (40), 196 (24), 195 (100), 167 (32), 118 (16), 77 (22); HRMS (ESI +): m/z calcd for $C_{22}H_{19}N_2O_2^+$ ($[M + H]^+$) 343.1441, found 343.1439.

*3,4-Dihydro-4-methyl-3-phenyl-1H-benzo[e][1,4]diazepine-2,5-dione (**3h**).* TMG: 142 mg, 59% yield. White solid, mp 249−252 °C; mp[62] 242−244 °C (DMF/water). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.46 (s, 3H, H1‴), 5.55 (s, 1H, H3), 6.93 (d, 1H, J = 8.1 Hz, H9), 6.98 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.00−7.08 (m, 2H, H2″, H6″), 7.14 (t, 1H, J = 7.2 Hz, H4″), 7.22 (dd, 2H, J = 7.6, 7.6 Hz, H3″, H5″), 7.28 (dd, 1H, J = 7.4, 7.4 Hz, H8), 7.54 (d, 1H, J = 7.7 Hz, H6), 10.80 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.6 (br, C1‴), 67.5 (br, C3), 119.9 (C9), 123.6 (C7), 124.3 (br, C2″, C6″), 126.7 (C5a), 127.4 (C4″), 128.4 (C3″, C5″), 130.3 (C6), 131.7 (C8), 134.3 (br, C1″), 135.2 (C9a), 166.4 (C5), 170.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 116.4 (N4), 135.7 (N1); IR (cm^{-1}): ν 3143, 2920, 1687, 1618, 1488, 1448, 1396, 1373, 1246, 1168, 795, 760, 728, 693, 495; MS (EI) m/z (%):267 (15, $[M + 1]^+$), 266 (81, $[M]^+$), 161 (100), 146 (13), 120 (60), 119 (43), 118 (44), 92 (32), 91 (14), 77 (12), 42 (21); HRMS (ESI+): m/z calcd for $C_{16}H_{15}N_2O_2^+$ $[M + H]^+$ 267.1128, found 267.1129. Anal. calcd for $C_{16}H_{14}N_2O_2$ (266.29): C 72.17, H 5.30, N 10.52%, found C 72.02, H 5.26, N 10.59.

*4-Butyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3i**).* NaOEt: 121 mg, 44% yield. Brownish solid, mp 166−170 °C (ethyl acetate); mp[40] 159−163 °C (benzene/hexane) ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, J = 7.3 Hz, H4‴), 1.34 (tq, 2H, J = 7.3, 7.3 Hz, H3‴), 1.58−1.71 (m, 2H, H2‴), 3.53 (ddd, 1H, J = 13.7, 7.7, 5.4 Hz, H1‴a), 4.07−4.17 (m, 1H, H1‴b), 5.47 (s, 1H, H3), 6.83 (d, 1H, J = 8.0 Hz, H9), 6.90 (dd, 1H, J = 7.5, 7.5 Hz, H7), 6.96 (br d, 2H, J = 6.9 Hz, H2″, H6″), 7.05 (t, 1H, J = 7.1, H4″), 7.14 (dd, 2H, J = 7.5, 7.5 Hz, H3″, H5″), 7.19 (dd, 1H, J = 7.5, 7.5 Hz, H8), 7.46 (d, 1H, J = 7.7 Hz, H6), 10.70 (s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6 δ 13.7 (C4‴), 19.4 (C3‴), 29.9 (C2‴), 49.7 (C1‴), 66.1 (C3), 119.9 (C9), 123.6 (C7), 124.2 (br, C2″, C6″), 127.3 (C4″, C5a), 128.4 (C3″, C5″), 130.3 (C6), 131.6 (C8), 134.5 (C1″), 135.1 (C9a), 166.1 (C5), 170.8 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 128.5 (N4), 135.5 (N1); IR (cm^{-1}): ν 3206, 3085, 2955, 2926, 2859, 1675, 1630, 1606, 1484, 1461, 1450, 1434, 1400, 765, 735; HRMS (ESI+): m/z calcd for $C_{19}H_{21}N_2O_2^+$ $[M + H]^+$ 309.1598, found

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715−722

309.1594. Anal. calcd for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; H, 6.54; N, 9.08%. Found: C, 73.70; H, 6.67; N, 9.01%.

*4-Butyl-3-ethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3j**).* NaOEt: 136 mg, 58% yield. Colorless solid, mp 98−104 °C (benzene/hexane). Major isomer:minor isomer = 59:41. Major isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.76 (t, 3H, J = 7.4 Hz, H2″), 0.89 (t, 3H, J = 7.3 Hz, H4‴), 1.23−1.31 (m, 2H, H3‴), 1.31−1.42 (m, 2H, H1″), 1.49−1.56 (m, 2H, H2‴), 3.19−3.27 (m, 1H, H1‴a), 3.90−4.01 (m, 2H, H3, H1‴b), 7.08 (d, 1H, J = 8.1 Hz, H9), 7.17 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.47 (dd, 1H, J = 7.7, 7.7 H, H8), 7.73 (d, 1H, J = 7.8 Hz, H6), 10.50 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.3 (C2″), 13.7 (C4‴), 19.3 (C3‴), 21.9 (C1″), 29.7 (C2‴), 49.8 (C1‴), 65.4 (C3), 119.9 (C9), 123.7 (C7), 126.6 (C5a), 130.7 (C6), 132.2 (C8), 135.5 (C9a), 164.9 (C5), 171.2 (C2). Minor isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, 3H, J = 7.1 Hz, H2″), 0.89 (t, 3H, J = 7.3 Hz, H4‴), 1.16−1.23 (m, 2H, H3‴), 1.41−1.49 (m, 2H, H2‴), 1.74−1.84 (m, 1H, H1″a), 1.92−2.03 (m, 1H, H1″b), 3.00−3.09 (m, 1H, H1‴a), 3.83 (t, 1H, J = 7.2 Hz, H3), 3.90−4.01 (m, 1H, H1‴b), 7.08 (d, 1H, J = 8.1 Hz, H9), 7.21 (dd, 1H, J = 7.6, 7.6 Hz, H7), 7.49 (dd, 1H, J = 7.8, 7.8 Hz, H8), 7.73 (d, 1H, J = 7.8 Hz, H6), 10.50 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.9 (C2″), 13.6 (C4‴), 19.1 (C1″), 19.5 (C3‴), 30.2 (C2‴), 41.0 (C1‴), 56.3 (C3), 120.5 (C9), 123.9 (C7), 127.3 (C5a), 130.7 (C6), 131.8 (C8), 136.7 (C9a), 167.4 (C5), 170.9 (C2); IR (cm^{-1}): ν 3223, 3169, 2956, 2930, 2871, 1709, 1616, 1604, 1482, 1414, 1391, 1220, 767, 757; HRMS (ESI+): m/z calcd for $C_{15}H_{21}N_2O_2^+$ $[M + H]^+$ 261.1598, found 261.1601. Anal. calcd for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20; H, 7.74; N, 10.76%. Found: C, 69.13; H, 7.73; N, 10.62%.

*3,4-Dibutyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3k**).* NaOEt: 185 mg, 71% yield, colorless oil. Major isomer:minor isomer = 61:39. Major isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.69 (t, 3H, J = 7.1 Hz, H4″), 0.89 (t, 3H, J = 7.4 Hz, H4‴), 1.05−1.57 (m, 10H, H3″, H2″, H1″, H3‴, H2‴), 3.16−3.26 (m, 1H, H1‴), 3.94 (dd, 1H, J = 7.6, 7.6 Hz, H1‴), 4.00 (dd, 1H, J = 8.5, 8.5 Hz, H3), 7.08 (d, 1H, J = 7.9 Hz, H9), 7.18 (ddd, 1H, J = 7.2, 7.2, 0.6 Hz, H7), 7.48 (ddd, 1H, J = 7.4, 7.4, 1.4 Hz, H8), 7.72 (d, 1H, J = 7.9 Hz, H6, H6), 10.49 (s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.5 (C4″), 13.7 (C4‴), 19.3 (C3‴), 21.5 (C3″), 27.6 (C2″), 28.2 (C1″), 29.7 (C2‴), 49.8 (C1‴), 64.2 (C3), 120.0 (C9), 123.8 (C7), 126.7 (C5a), 130.7 (C6), 132.2 (C8), 135.6 (C9a), 165.0 (C5), 171.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 129.2 (N4), 135.5 (N1). Minor isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.85 (t, 6H, J = 7.3 Hz, H4″, H4‴), 1.05−1.57 (m, 10H, H3″, H2″, H3‴, H2‴), 1.69−1.81 (m, 1H, H1″), 1.88−2.00 (m, 1H, H1″), 2.98−3.08 (m, 1H, H1‴), 3.88 (dd, 1H, J = 7.3, 7.3 Hz, H3), 3.97 (dd, 1H, J = 7.5, 7.5 Hz, H1‴), 7.07 (d, 1H, J = 8.0 Hz, H9), 7.21 (dd, 1H, J = 7.8, 7.8 Hz, H7), 7.49 (ddd, 1H, J = 7.4, 7.4, 1.3 Hz, H8), 10.49 (s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (C4‴), 13.8 (C4″), 19.5 (C3‴), 22.1 (C3″), 25.4 (C1″), 28.1 (C2″), 30.2 (C2‴), 41.1 (C1‴), 54.9 (C3), 120.5 (C9), 124.0 (C7), 127.3 (C5a), 130.7 (C6), 131.9 (C8), 136.7 (C9a), 167.5 (C5), 171.0 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 137.4 (N1); IR (cm^{-1}): ν 3221, 2958, 2930, 2871, 1689, 1636, 1620, 1484, 1437, 1380, 1164, 760, 703, 526; HRMS (ESI+): m/z calcd for $C_{17}H_{25}N_2O_2^+$ $[M + H]^+$ 289.1911, found 289.1909.

*3-Benzyl-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3l**).* NaOEt: 100 mg, 40% yield. Brownish solid, mp 121−124 °C; mp[63] 100.5−103 °C (acetone/hexane). Major isomer:minor isomer = 62:38. Major isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.95 (s, 3H, H1‴), 3.21 (dd, 1H, J = 14.4, 7.5 Hz, $PhCH_2$), 3.29 (dd, 1H, J = 14.4, 7.6 Hz, $PhCH_2$), 4.33 (t, 1H, J = 7.4 Hz, H3), 7.08 (d, 1H, J = 8.1 Hz, H9), 7.16−7.32 (m, 6H, H7, H2″, H3″, H4″, H5″, H6″), 7.50 (dd, 1H, J = 7.3, 7.3 Hz, H8), 7.73 (d, 1H, J = 7.6 Hz, H6), 10.51 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.7 (C1‴), 31.4 ($PhCH_2$), 56.0 ($PhCH_2$), 120.7 (C9), 124.1, 126.5, 127.0, 128.4, 129.0, 130.7 (C6), 132.0 (C8), 136.6 (C9a), 137.4, 167.6, 169.2 (C2). ^{15}N NMR (51 MHz, DMSO-d_6) δ 117.3 (N4), 136.9 (N1). Minor isomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.62 (dd, 1H, J = 13.2, 10.2 Hz, $PhCH_2$), 2.72 (dd, 1H, J = 13.3 H, 7.8 Hz, $PhCH_2$), 2.88 (s, 3H, H1‴), 4.32 (t, 1H, J = 7.8 Hz, H3), 7.02 (d, 2H, J = 7.2 Hz, H2″, H6″), 7.16−7.32 (m, 5H, H7, H9, H3″, H4″, H5″), 7.58 (dd, 1H, J = 7.4, 7.4 Hz, H8), 7.86 (d, 1H, J = 7.7 Hz, H6), 10.65 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 33.7 ($PhCH_2$), 38.7 (C1‴), 67.1 (C3), 120.2 (C9), 124.0, 126.4, 126.9, 128.5, 128.9, 131.0 (C6), 132.5 (C8), 135.6 (C9a), 136.0, 165.2, 169.8 (C2). ^{15}N NMR (51 MHz, DMSO-d_6) δ 115.5 (N4), 136.6 (N1); IR (cm^{-1}): ν 3602, 3084, 2904, 1691, 1613, 1607, 1482, 1454, 1436, 1396, 755, 700, 525, 499; HRMS (ESI+): m/z calcd for $C_{17}H_{17}N_2O_2^+$ $[M + H]^+$ 281.1285, found 281.1283. Anal. calcd for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H, 5.75; N, 9.99%. Found: C, 72.58; H, 5.98; N, 9.83%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01497.

Copies of ^{1}H and ^{13}C NMR spectra for new products **2** and **3** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kafka@ft.utb.cz.

*E-mail: janez.kosmrlj@fkkt.uni-lj.si.

Author Contributions

#These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financed by TBU in Zlín (internal grant no. IGA/FT/2016/004, funded from the resources of specific university research) and the Ministry of Education, Science, and Sport, Republic of Slovenia, the Slovenian Research Agency (grant: P1-0230). The authors are grateful to an anonymous reviewer for pointing out Triton B and Mrs. H. Geržová (Faculty of Technology, Tomas Bata University in Zlín) for technical assistance.

■ DEDICATION

Dedicated to Professor Milan Potáček on the occasion of his 72nd birthday.

■ REFERENCES

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(2) Gill, R. K.; Kaushik, S. O.; Chugh, J.; Bansal, S.; Shah, A.; Bariwal, J. *Mini-Rev. Med. Chem.* **2014**, *14*, 229−256.

(3) Smith, S. G.; Sanchez, R.; Zhou, M. M. *Chem. Biol.* **2014**, *21*, 573−583.

(4) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(5) Azzarito, V.; Long, K.; Murphy, N. S.; Wilson, A. J. *Nat. Chem.* **2013**, *5*, 161−173.

(6) Loudni, L.; Roche, J.; Potiron, V.; Clarhaut, J.; Bachmann, C.; Gesson, J.-P.; Tranoy-Opalinski, I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4819−4823.

(7) Mohamed, L. W.; El-yamany, M. F. *Arch. Pharmacol. Res.* **2012**, *35*, 1369−1377.

(8) Joseph, C. G.; Wilson, K. R.; Wood, M. S.; Sorenson, N. B.; Phan, D. V.; Xiang, Z.; Witek, R. M.; Haskell-Luevano, C. *J. Med. Chem.* **2008**, *51*, 1423−1431.

(9) Cheng, M.-F.; Yu, H.-M.; Ko, B.-W.; Chang, Y.; Chen, M.-Y.; Ho, T.-I.; Tsai, Y.-M.; Fang, J.-M. *Org. Biomol. Chem.* **2006**, *4*, 510−518.

(10) McDowell, R. S.; Blackburn, B. K.; Gadek, T. R.; McGee, L. R.; Rawson, T.; Reynolds, M. E.; Robarge, K. D.; Somers, T. C.; Thorsett,

E. D.; Tischler, M.; Webb, R. R., II; Venutil, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 5077−5083.
(11) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717−729.
(12) Parks, D. J.; LaFrance, L. V.; Calvo, R. R.; Milkiewicz, K. L.; Gupta, V.; Lattanze, J.; Ramachandren, K.; Carver, T. E.; Petrella, E. C.; Cummings, M. D.; Maguire, D.; Grasberger, B. L.; Lu, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 765−777.
(13) Grasberger, B. L.; Lu, T.; Schubert, C.; Parks, D. J.; Carver, T. E.; Koblish, H. K.; Cummings, M. D.; LaFrance, L. V.; Milkiewicz, K. L.; Calvo, R. R.; Maguire, D.; Lattanze, J.; Franks, C. F.; Zhao, S.; Ramachandren, K.; Bylebyl, G. R.; Zhang, M.; Manthey, C. L.; Petrella, E. C.; Pantoliano, M. W.; Deckman, I. C.; Spurlino, J. C.; Maroney, A. C.; Tomczuk, B. E.; Molloy, C. J.; Bone, R. F. *J. Med. Chem.* **2005**, *48*, 909−912.
(14) Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. *J. Med. Chem.* **1978**, *21*, 1087−1089.
(15) Clark, R. L.; Carter, K. C.; Mullen, A. B.; Coxon, G. D.; Owusu-Dapaah, G.; McFarlane, E.; Thi, M. D. D.; Grant, M. H.; Tettey, J. N. A.; Mackay, S. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 624−627.
(16) Karp, G. M. *J. Org. Chem.* **1995**, *60*, 5814−5819.
(17) Mohammed, Y. S.; Luckner, M. *Tetrahedron Lett.* **1963**, *4*, 1953−1958.
(18) Smith, H.; Wegfahrt, P.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 1668−1669.
(19) Afiyatullov, Sh. Sh.; Leshchenko, E. V.; Sobolevskaya, M. P.; Gerasimenko, A. V.; Khudyakova, Yu. V.; Kirichuk, N. N.; Mikhailov, V. V. *Chem. Nat. Compd.* **2015**, *51*, 111−115.
(20) Ishikawa, N.; Tanaka, H.; Koyama, F.; Noguchi, H.; Wang, C. C. C.; Hotta, K.; Watanabe, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 12880−12884.
(21) Kaur, N. *Int. J. Pharma Bio Sci.* **2013**, *4*, 485−513.
(22) Yin, W.-B.; Cheng, J.; Li, S.-M. *Org. Biomol. Chem.* **2009**, *7*, 2202−2207.
(23) Kaur, N.; Kishore, D. *Synth. Commun.* **2014**, *44*, 1375−1413.
(24) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8−20.
(25) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935−8939.
(26) Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021−8023.
(27) Blass, B. E.; Burt, T. M.; Liu, S.; Portlock, D. E.; Swing, E. M. *Tetrahedron Lett.* **2000**, *41*, 2063−2066.
(28) Boojamra, C. G.; Burrow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240−1256.
(29) Liu, A.; Zhou, H.; Su, G.; Zhang, W.; Yan, B. *J. Comb. Chem.* **2009**, *11*, 1083−1093.
(30) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132−143.
(31) Cheng, M.-F.; Fang, J.-M. *J. Comb. Chem.* **2004**, *6*, 99−104.
(32) Mayer, J. P.; Zhang, J.; Bjergarde, K.; Lenz, D. M.; Gaudino, J. J. *Tetrahedron Lett.* **1996**, *37*, 8081−8084.
(33) Proisl, K.; Kafka, S.; Urankar, D.; Gazvoda, M.; Kimmel, R.; Košmrlj, J. *Org. Biomol. Chem.* **2014**, *12*, 9650−9664.
(34) Kafka, S.; Proisl, K.; Kašpárková, V.; Urankar, D.; Kimmel, R.; Košmrlj, J. *Tetrahedron* **2013**, *69*, 10826−10835.
(35) Kafka, S.; Hauke, S.; Salcinovic, A.; Soidinsalo, O.; Urankar, D.; Košmrlj, J. *Molecules* **2011**, *16*, 4070−4081.
(36) Kafka, S.; Košmrlj, J.; Klásek, A.; Pevec, A. *Tetrahedron Lett.* **2008**, *49*, 90−93.
(37) Klásek, A.; Lyčka, A.; Mikšík, I.; Růžička, A. *Helv. Chim. Acta* **2009**, *92*, 689−708.
(38) Prucková, Z.; Klásek, A.; Lyčka, A.; Mikšík, I.; Růžička, A. *Tetrahedron* **2009**, *65*, 9103−9115.
(39) Klásek, A.; Mrkvička, V.; Lyčka, A.; Mikšík, I.; Růžička, A. *Tetrahedron* **2009**, *65*, 4908−4916.
(40) Klásek, A.; Lyčka, A.; Mikšík, I.; Růžička, A. *Tetrahedron* **2010**, *66*, 2015−2025.
(41) Mrkvička, V.; Lyčka, A.; Rudolf, O.; Klásek, A. *Tetrahedron* **2010**, *66*, 8441−8445.
(42) Mrkvička, V.; Rudolf, O.; Lyčka, A.; Klásek, A. *Tetrahedron* **2011**, *67*, 2407−2413.
(43) Stadlbauer, W.; Laschober, R.; Lutschounig, H.; Schindler, G.; Kappe, T. *Monatsh. Chem.* **1992**, *123*, 617−636.
(44) Klásek, A.; Kořistek, K.; Lyčka, A.; Holčapek, M. *Tetrahedron* **2003**, *59*, 5279−5288.
(45) Kafka, S.; Klásek, A.; Polis, J.; Košmrlj, J. *Heterocycles* **2002**, *57*, 1659−1682.
(46) Kafka, S.; Klásek, A.; Polis, J.; Rosenbreierová, V.; Palík, C.; Mrkvička, V.; Košmrlj, J. *Tetrahedron* **2008**, *64*, 4387−4402.
(47) Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968−972.
(48) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019−1028.
(49) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1865−1868.
(50) Gervasini, A.; Auroux, A. *J. Phys. Chem.* **1993**, *97*, 2628−2639.
(51) Angyal, S. J.; Warburton, W. K. *J. Chem. Soc.* **1951**, 2492−2494.
(52) Margetic, D. Physico-Chemical Properties of Organosuperbases. In *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; John Wiley & Sons: Chichester, 2009; p 25.
(53) Farran, D.; Archirel, P.; Toupet, L.; Martinez, J.; Dewynter, G. *Eur. J. Org. Chem.* **2011**, *2011*, 2043−2047.
(54) Antolak, S. A.; Yao, Z.-K.; Richoux, G. M.; Slebodnick, C.; Carlier, P. R. *Org. Lett.* **2014**, *16*, 5204−5207.
(55) Van den Bogaert, A. M.; Nelissen, J.; Ovaere, M.; Van Meervelt, L.; Compernolle, F.; De Borggraeve, W. M. *Eur. J. Org. Chem.* **2010**, *2010*, 5397−5401.
(56) Araújo, A. C.; Nicotra, F.; Airoldi, C.; Costa, B.; Giagnoni, G.; Fumagalli, P.; Cipolla, L. *Eur. J. Org. Chem.* **2008**, *2008*, 635−639.
(57) Carlier, P. R.; Zhao, H.; MacQuarrie-Hunter, S. L.; DeGuzman, J. C.; Hsu, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 15215−15220.
(58) Konowal, A.; Snatzke, G.; Alebić-Kolbah, T.; Kajfež, F.; Rendić, S.; Šunjić, V. *Biochem. Pharmacol.* **1979**, *28*, 3109−3113.
(59) Hsu, D. C.; Lam, P. C.-H.; Slebodnick, C.; Carlier, P. R. *J. Am. Chem. Soc.* **2009**, *131*, 18168−18176.
(60) Bowman, R. E.; Grey, T. F.; Huckle, D.; Lockhart, I. M.; Wright, M. *J. Chem. Soc.* **1964**, 3350−3353.
(61) Rudolf, O.; Mrkvička, V.; Lyčka, A.; Rouchal, M.; Klásek, A. *J. Heterocycl. Chem.* **2013**, *50* (S1), E100−E110.
(62) Mohrbacher, R. J.; Grous, P. P. 2-Aminobenzodiazepine-5-ones. U.S. Patent US4002610, January 11, 1977. *Chem. Abstr.* **1977**, *86*, 155710.
(63) Ishikura, M.; Mori, M.; Ikeda, T.; Terashima, M.; Ban, Y. *J. Org. Chem.* **1982**, *47*, 2456−2461.

DOI: 10.1021/acs.joc.6b01497
J. Org. Chem. 2017, 82, 715−722

Send Orders for Reprints to reprints@benthamscience.ae

Current Organic Chemistry, 2017, *21*, 1949-1975

REVIEW ARTICLE

Chemistry and Applications of 4-Hydroxyquinolin-2-one and Quinoline-2,4-dione-based Compounds

Karel Proisl[a], Stanislav Kafka[a,*] and Janez Košmrlj[b,*]

[a]*Faculty of Technology, Tomas Bata University, Vavrečkova 275, CZ-760 05 Zlin, Czech Republic;* [b]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia*

ARTICLE HISTORY

Received: March 19, 2017
Revised: June 18, 2017
Accepted: June 30, 2017

DOI:
10.2174/1385272821666170711155631

Abstract: ***Background*:** 4-Hydroxyquinolin-2-ones and quinoline-2,4-diones, a subset of the quinolone scaffold, have attracted attention due to their biological properties. These structures are present in many classes of natural products and pharmaceutical agents and show promise in antiviral and antibacterial treatment. They possess anticonvulsive effects, selective affinity to cannabinoid receptors, and other interesting biological activity. Some of these compounds have the potential for protection and properties modification of natural as well as synthetic materials as antioxidants, antidegradants, antifungal agents, UV absorbers, optical brighteners, luminophores, *etc*.

***Objective*:** The importance of these compounds stimulated the development of innovative conventional and modern catalytic methods for their preparation. The present review highlights recent progress in the above subjects.

Keywords: 4-hydroxyquinolin-2-one, quinoline-2,4-dione, organic synthesis, biological activity, applications, anticonvulsive effects.

1. INTRODUCTION

This review highlights 4-hydroxyquinolin-2-ones and quinoline-2,4-diones from several different aspects including natural occurrence, synthesis and applications. The type of compounds have been isolated from a broad range of living organisms, and exhibited diverse range of biological properties. The interest of many research laboratories worldwide, both from academia and industry, to study these molecules as potential therapeutic agents is thus not surprising. The requirements for novel derivatives thus prompted organic synthetic chemists to design new synthetic pathways.

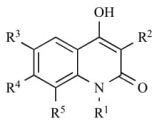
2. KNOWN 4-HYDROXYQUINOLIN-2-ONES AND QUINOLINE-2,4-DIONES

Till now almost 14,000 compounds with 4-hydroxyquinoline-2-one pattern have been reported in the literature with nearly half of them associated with investigations of bioactivity. Analogously, there are over 2,800 compounds with the quinoline-2,4-dione structure, with almost 800 records describing bioactivity studies. Representatives of both groups of compounds were isolated from fungi, bacteria or plants, and many of them proved to show interesting biological effects *in vivo* and *in vitro*.

2.1. 4-Hydroxyquinolin-2-ones Isolated from Natural Products

Some simple 4-hydroxyquinolin-2-ones are found in nature. The simplest representative, compound **1**, was isolated from the fungus *Penicillium citrinum* [1] as well as from the Asian bushes *Haplophyllum bucharicum* [2]. From the fungi *P. citrinum* was isolated *N*-methyl derivative **2** [3], possessing the ability of a free radical scavenger [4] and also some cytotoxic activity [5].

Table 1. Substituents of compounds 1-7.



1-7

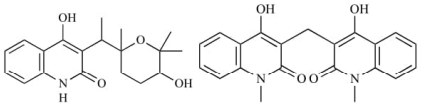
1-7	R^1	R^2	R^3	R^4	R^5
1	H	H	H	H	H
2	Me	H	H	H	H
3	Me	MeO	H	H	H
4	Me	MeO	H	H	MeO
5	H	H	Br	H	H
6	H	H	Br	Br	H
7	H	H	MeO	H	MeO

From the rutaceae plant *Micromelum falcatum*, 3-methoxy-derivative **3** was isolated [6], and its analogue having two methoxy groups, swietenidin **4**, was isolated from the bark of Indian tree *Chloroxylon Swietenia* [7]. Natural bromoquinolones **5** and **6** were isolated from marine sponge *Hyrtios erecta* [8]. Compound **5** was

*Address correspondence to these authors at the Faculty of Technology, Tomas Bata University, Vavrečkova 275, CZ-760 05 Zlin, Czech Republic; Tel: +420 57 603 1115; E-mail: kafka@ft.utb.cz
Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia; Tel: +386 1 4798558;
E-mail: janez.kosmrlj@fkkt.uni-lj.si

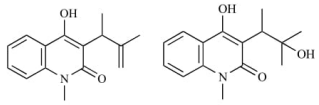
1875-5348/17 $58.00+.00

found to inhibit Wistar rat cerebellum neuronal nitric oxide synthase [8]. From the wood of tree *Halfordia scleroxyla* dimethoxyquinolone **7** was isolated (Table **1**) [9]. An interesting natural hydroxyquinolone bucharidine was obtained from the bush *Haplophyllum bucharicum* [10], which exhibited estrogenic activity in mice [11]. Compound **8**, named zanthobisquinolone, with two quinolin-2-one moieties, was obtained from the root wood of *Zanthoxylum mutans* [12].

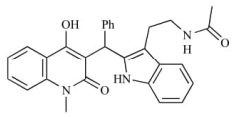


bucharidine **8**

Rutaceae (rue or citrus family) includes a variety of plants that contain quinolone derivatives. From the citrus *Ravenia spectabilis* ravenoline was isolated [13], whereas structurally related paraensine was obtained from woody plant yellowheart (*Euxylophora paraensis*) [14]. From the fermentation broth of bacteria *Dactylosporangium sp.* it is possible to isolate the indole derivative of SF 2809-V [15].



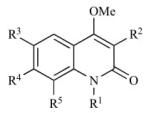
ravenoline **paraensine**



SF 2809V

A number of 4-hydroxyquinoline-2-one derivatives occur in nature in a form of ether, *i.e.* as 4-alkoxyquinolin-2-ones.

Table 2. Substituent of methoxyquinolones 9-16.

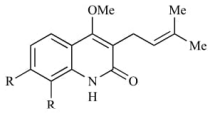


9-16

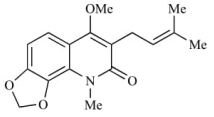
9-16	R^1	R^2	R^3	R^4	R^5
9	H	H	H	H	H
10	Me	H	H	H	H
11	OMe	H	H	H	H
12	H	H	H	H	OMe
13	H	H	OMe	H	OMe
14	H	CHO	H	MeO	OMe
15	H	Et	H	OH	OMe
16	H	MeO	H	H	OH

The simplest representative of this group, methoxyquinolone **9**, was isolated from plants of rue family - from stems and roots of citroid fruit trees or shrubs *Clausena lansium* [16], from leaves and wood of tropical plants *Peltostigma guatemalense* [17], from the wood of *Myrtopsis sellingi* [18], and also from the wood and leaves *Haplophyllum bungei* [19] and *H. bucharicum* [2, 19]. This compound showed a modest antiplasmodic effect in laboratory tests *in vitro* [17]. Methyl derivative **10** occurs in the nature even more abundantly. It was isolated from stem and branches of *Hortia superba* [20], from stems of *H. brasiliana* [20] and *H. oreadica* [20], from the roots of trees *Feronia limonia* [21], from the root wood of *Zanthoxyllum wuthayenze* [22], from leaves and bark of *Z. monophyllum* [23], from the stems of *Raputia praetermissa* [24], from the wood of the Formosan tree *Toddalia asiatica* [25], and similarly as compound **9**, also from stems and roots *Clausena lansium* [16]. Compound **10** was isolated from roots of *Ruta chalepensis* [26]. For this compound antifungal and antialgal activities were reported [27]. Haplotusin (**11**) was isolated [28] from *Haplophyllum obtusifolium*. Edulitin (**12**) was obtained from stem of *Hortia superba* [20], from fruit of *Cnidium monnieri* [29] and from *Murraya paniculata* [30]. Trimethoxyquinolone halfordamin (**13**) was isolated from the plants *Halfordia kendack* [31] and from the aerial parts of the plants *Agathosma bisulca* [32]. Glycocitridine (**14**) is a naturally occurring aldehyde in the leaves of the citrus *Glycosmis citrifolia* [33] and in the leaves of the plant *Melicopa semecarpifolia* [34]. Haplosin (**15**) was found in the seeds and roots of *Haplophyllum perforatum* [35]. It contains an ethyl group at position 3 of the quinoline ring, which is atypical for natural quinolones. The compound **16** was isolated from the dried body of centipede *Scolopendra subspinipes mutilans* L. KOCH (Scolopendridae), which has been utilized as a traditional Chinese and Korean medicine for a variety of diseases, such as spasm, childhood convulsions, seizures, poisonous nodules, diphtheria, and tetanus (Table **2**) [36].

Fairly widespread in the vegetable kingdom is atanine, which was isolated from the plant Fagara zanthoxyloides [37], from *Ravenia spectabilis* [13, 38], from tropical citrus *Afraegle paniculata* [39], from stem and root barks of *Almeidia guayinensis* [40], from unripe fruits of *Evodia rutaecarpa* [41], from the fruits of *Zanthoxylum integrifoliolum* [42], from root wood of *Zanthoxylum wutaiense* [43], and from stems and roots of *Clausena lansium* [16]. Its dimethoxy derivative preskimmianine was isolated from *Boronia pinnata* [44], from *Citrus grandis* [45] and from *Dictamnus albus* [31].



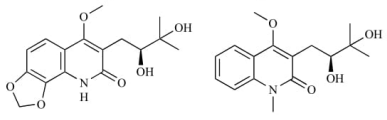
atanine (R = H)
preskimmianine (R = OMe)



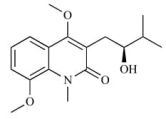
pteleprenine

Japan shrub *Orixa japonica* has been found to contain various quinoline alkaloids. Isolated were: pteleprenine from the stems [46], noroxirine from the root bark [47], *N*-demethyllunidonine, orixiarine (orijanone), isopteleflorine and 3'-*O*-methylorixine from the leaves and stems [48]. Edulinine was isolated from leaves of *Melicope semecarpifolia* (Rutaceae) [34], from cell cultures of *Ruta graveolens* [49], from the rutaceous Hawaiian shrub *Pelea barbigera* [50], from bark of *Citrus macroptera* [51], from leaves of shrubs *Fagara mayu* [52], from epigeal part of plant *Haplophyllum*

foliosum [53], from *Zanthoxylum williamsii* (Rutaceae) [54], from the leaves and fruits of African medicinal plant *Teclea nobilis* [55], from the leaves of *Teclea simplicifolia* [56], and from root wood of *Melicope semecarpifolia* [57]. Lunacridine was obtained from Indonesian medicinal plant *Lunasia amara* [58].

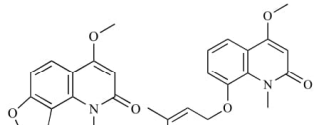


nororixine **edulinine**

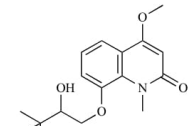


lunacridine

The so-called "zapota blanco", seeds and fruit of the citruses relative fruit tree *Casimiroa edulis*, native to Mexico and Central America, used to be an item of the Mexican Pharmacopoeia. From the mentioned seeds, casimiroine, which has dioxolane moiety in its structure, was isolated [59-62]. Daurine was isolated from the roots of *Haplophyllum dauricum* [63]. Chemically related vicinal diol foliosidine was isolated from *Haplophyllum foliosum* [64, 65], exhibiting estrogenic activity [11].

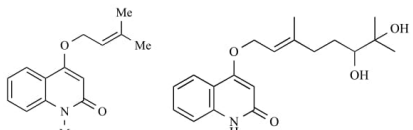


casimiroine **daurine**



pholiosidine

The vast majority of these natural ethers contain methoxy group at position 4 of the quinoline ring. Examples of compounds with other alkoxy group are ravenine and bucharaine. Ravenine was isolated from *Ravenia spectabilis* [13, 38], whereas bucharain occurs in *Haplophyllum bucharicum* [66-70]. In test of biological activity on mice or rats, bucharaine has shown a significant hypothermic effect [71] and had little or no effect on urinary excretion [72].

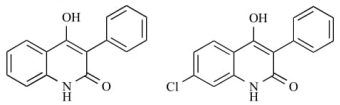


ravenine **bucharaine**

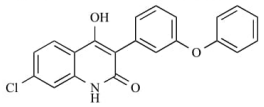
A variety of alkaloids contain 4-oxyquinoline-2-one pattern in the structure where the C4 oxygen atom is a part of an additional fused ring; however, this type of natural product is beyond the scope of this review.

2.2. Biologically Active Synthetic 4-hydroxyquinolin-2-ones

A simple phenylquinolone, NSC 16582, is an antagonist of the strychnine-insensitive glycine site on NMDA receptor ion channel complex [73-75]. Even more effective antagonist of NMDA receptor is its chloroderivative, MDL 104653 [75], exhibiting an anticonvulsant activity [76].

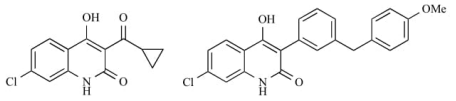


NSC 16582 **MDL 104653**



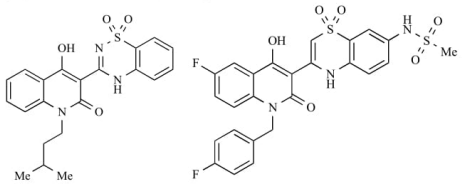
L-701324

The compound L-701324 acts as a very potent antagonist of NMDA receptors due to high affinity at the glycine site [77]. In experiments on mice, orally administered compound caused mainly hypolocomotion [78]. Anticonvulsant activity was also established on mice [74, 79]. Sedative effects of the compound L-701324 are comparable with those of diazepam [80]. This compound has also an inhibitory effect on both spreading depression initiation and propagation [81]. It has also been patented for the treatment of various neurological and psychiatric troubles, including a range of neurodegenerative diseases [82]. In addition to L-701324, the ability to inhibit NMDA receptor as well as related sedative, neuroprotective and anticonvulsant effects have also been documented for other quinolones, including compounds L-701252 (**17**) [74, 83] and L-703717 (**18**) [74, 84].



17 **18**

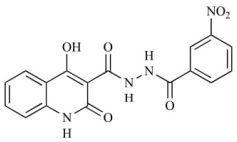
Some 4-hydroxyquinoline-2-one derivatives possess significant antiviral effect [85]. Compounds **19** and **20** are representatives of highly potent inhibitors of the replication of the hepatitis virus C [86, 87]. The effect of compounds **19** and **20** is due to a viral RNA polymerase inhibition [88, 89].



19 **20**

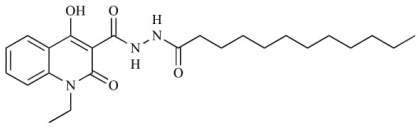
Other 4-hydroxyquinoline-2-one derivatives inhibit HIV-1 integrase [90-92]. 4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic

acid scaffold bearing a variety of substituents at position 1 (N1) and position 6 (C6) has also been designed and prepared as HIV-1 integrase inhibitors, potentially involved in a metal chelating mechanism [93]. A series of 4-hydroxyquinoline-2-one-3-carboxylic acids hydrazides were synthesized, which possess various high ability to inhibit HIV-1 integrase [92]. By far the most potent compound of this type is hydrazide **21** [92].



21

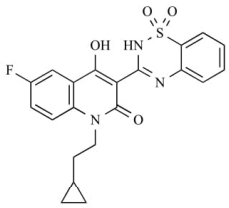
Interestingly, similar hydrazides act as allosteric modulators of the enzyme glycogen synthase kinase GSK-3 [94-96]. An example of an effective modulator of the receptor is the compound **VP-0.7** [94, 96-100]. Some human GSK-3 inhibitors could be applied as modulators of *Aspergillus fumigatus* growth and show promise in different applications to eradicate invasive aspergillosis [100].



VP-0.7

One compound with 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbohydrazide moiety in molecule was found to exhibit acetylcholinesterase inhibition activity [101].

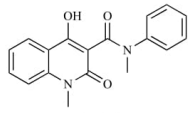
3-(1,1-Dioxo-2*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-ones, which have 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboximidamide pattern in their structure, potently inhibits Hepatitis C Virus (HCV) polymerase enzymatic activity and inhibits the ability of the subgenomic HCV replicon to replicate in Huh-7 cells. A structure-activity relationships investigation focused to substituents on the quinolinone ring culminated in the discovery of compound **22** [102].



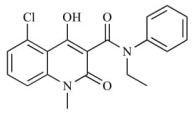
22

Some 4-hydroxyquinolin-2-ones are important immunomodulators. Currently available research in this area has led to the development of linomide and laquinimod. Linomide, developed by Active Biotech, is an immunomodulatory that increases the activity of NK lymphocytes and cytotoxicity of macrophages [103-105]. It is an inhibitor of angiogenesis and enhances the secretion of TNF-α [106].

The compound has been investigated as a drug for the treatment of certain cancers and autoimmune diseases. However, the research of linomide was cancelled because of its cardiovascular toxicity, showing vasodilating effects [107].



linomide (roquinimex)

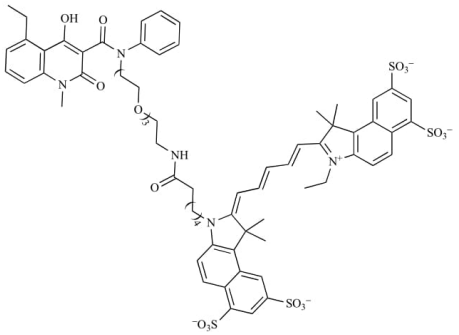


laquinimod

More recently, laquinimod, an alternative to linomide has been developed by Active Biotech and Teva. The compound acts as an immunomodulator and it is being explored for the treatment of multiple sclerosis [108-111]. In Russia, laquinimod has been approved as drug for the treatment of relapsing-remitting multiple sclerosis under the brand name Nerventra [112]. 4-Hydroxy-2-quinolone-3-carboxamides have been recently developed as a novel class of subnanomolar cannabinoid receptor 2 (CB2, CB2R) ligands with good water solubility [113, 114].

N-(3-Pyridylmethyl)-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamide has shown an analgesic activity [115]. Derivatives with noticeable increase in the analgesic activity have been derived by using bioisosteric replacement strategy in structural design [116]. Analgesic activity was also found for several other compounds having *N*-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide structure [117].

Ethyl-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamide is a part of recently developed specific molecular imaging probe such as Cy5.5-CES271 for optical imaging of local inflammatory activity *in vivo* [118].



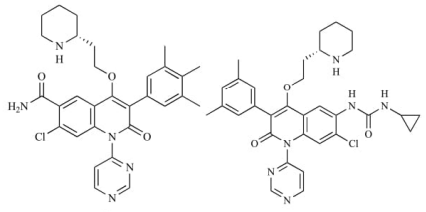
Cy5.5-CES271

Some 2-[(quinolin-3-yl)carbonyl]aminoacetic acid derivatives are inhibitors of prolyl hydroxylases, having potential in treating diseases benefiting from the inhibition of this enzyme including anemia [119].

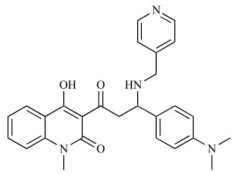
Derivatives of 4-(4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamido)benzoic acid are useful in the treatment of disorders related to a cell differentiation defect, especially of osteoblasts and osteoclasts [120]. In a program aimed at developing drugs against human African trypanosomiasis (HAT), a major tropical disease, sodium 3-(benzylcarbamoyl)-1-butyl-6-fluoro-7-morpholino-2-oxo-1,2-dihydroquinoline-4-olate was found to be active against *Trypanosoma brucei brucei* [121]. Recently, several *N*-substituted 4-hydroxy-

1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamides have been found to exhibit considerable anti-proliferative activity [122].

Some piperidine functionalized 4-hydroxyquinolin-2-ones derivatives are antagonists of gonadotropin releasing hormone (GnRH) [123-130]. An example is the compound Q89 (**23**) the potential use of which in the treatment of hypogonadism was patented [131]. Similar applies to Q76 (**24**) [131, 132].



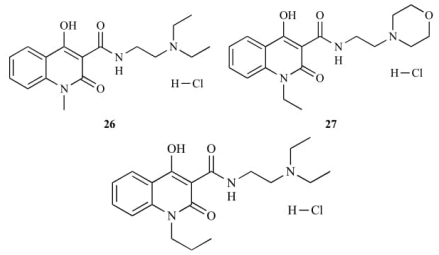
23 **24**



25

Compound **25** acts as an inhibitor of glyceraldehyde-3-phosphate dehydrogenase-s (GAPDHs), a glycolytic enzyme expressed only in male germ cells [133]. GAPDHs inhibitors could become a male contraceptive, therefore the use of the compound **25** was patented [133] to a reversible reduction in male sperm motility and for the modulation of reproductive function.

Ukrainian research group published the preparation of a series of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides with potential local anaesthetic effect [134, 135]. The most effective of the prepared compounds showed a comparable (compound **26**) or even higher (compound **27**) effect than lidocaine with a significantly lower toxicity [136].



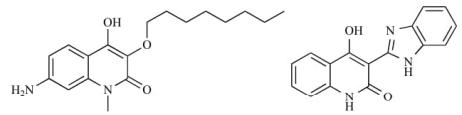
26 **27**

chinoxicaine

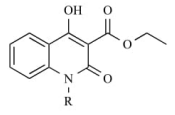
Research activities on a new type of local anesthetics led to the synthesis of chinoxicaine [136], which has been patented [137] for use as an injectable local anesthetic.

Among 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides derivatives were found exhibiting inhibition of cholinesterases [101, 138]. It has been suggested that these compounds are promising for the treatment of Alzheimer Disease [138].

Recently, the use of certain 3-alkoxy-4-hydroxyquinolin-2-ones as therapeutic agents for chronic obstructive pulmonary disease and as anti-allergic agents was patented [139, 140]. An example of substance with those effects, tested in guinea pigs, is the compound **28** [139, 140]. Although lacking solubility in the culture medium, selected 8-nitro-3-phenoxy-4-hydroxyquinolin-2-ones showed attractive *in vitro* antileishmanial activity [141].



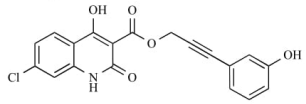
28 **29**



30 (R = H)
31 (R = Me)
32 (R = Et)
33 (R = Pr)
34 (R = Bu)
35 (R = hexyl)

30-35

Many substituted 4-hydroxyquinolin-2-ones exhibit multiple biological effects. Compound **29** inhibits several tyrosine kinases in mice (VEGFR-2 kinase and PDFGR-β tyrosine kinase) [142]), and serine/threonine kinases [143]. This compound inhibits phosphorylation of some peptide substrates and exhibits antiproliferative effects *in vitro* just due to the inhibition of tyrosine kinases [144]. Moreover, compound **29** and some similar derivatives inhibit the activity of the thyroid gland [145]. Ester **30** shows antagonism of NMDA receptors to glycine side. It was found in experiments with rabbits and rats that **30** has analgesic, anti-inflammatory, anticoagulant, diuretic and nootropic effects [146]. Its simple *N*-alkyl derivatives **31-35** exhibit only analgesic and anti-inflammatory effects [147], whereas the strongest analgesic effects were observed for the *N*-butyl derivative **34** [147]. A number of derivatives of structure **30** functionalized at the aromatic ring or having another alkoxycarbonyl group at position 3 have been prepared and investigated [74, 93, 147-169]. These compounds acted antagonistically on NMDA receptor and some of them showed antiepileptic properties on model of autogenic convulsions in mice. Worth mentioning is the compound L-701,273 (**36**) that effectively inhibited NMDA receptor, but failed completely when testing antiepileptic effects [74, 83, 157, 160, 170, 171].



36

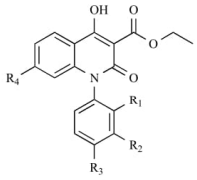
Apparent anti-inflammatory effects were observed in the *N*-aryl derivatives **37-44** (Table **3**), suppressing carrageenan-induced acute exudative inflammation in mice [147].

Egyptian researchers prepared and investigated a series of 4-hydroxy-6-nitro-1*H*-quinolin-2-ones as compounds with potential antibacterial and antifungal effects [172]. Compounds **45-47** showed antimicrobial activity, inhibiting the growth of bacteria *Bacillus cereus* and fungi *Aspergillus flavus* and *A. niger*. The compounds **45** and **46** also inhibited the growth of bacteria *Escherichia coli*.

A group of Indian researchers prepared a series of fluorinated quinolones **48-53** Table **4**, which showed moderate photocytotoxic

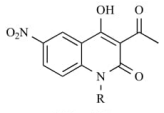
activity and ability to inhibit the growth of *Mycobacterium tuberculosis* [173]. The highest photocytotoxic activity as well as the most effective growth inhibition of *M. tuberculosis* was observed at compound **52**. Completely inactive turned out to be unsubstituted 4-hydroxyquinolin-2-one.

Table 3. Substituents on aromatic rings of compounds 37–44.

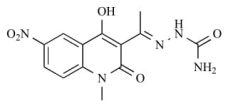


37 - 44

37-44	R^1	R^2	R^3	R^4
37	H	H	H	H
38	H	Me	Me	Cl
39	H	H	Me	H
40	H	H	MeO	H
41	H	MeO	H	H
42	Me	Me	H	H
43	H	H	Me	Cl
44	H	H	MeO	Cl

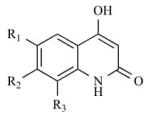


45 (R = Me)
46 (R = Et)



47

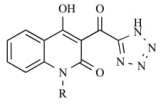
Table 4. Substituents of quinolones 48–53.



48 - 53

48 – 53	R^1	R^2	R^3
48	F	H	H
49	H	F	H
50	H	H	F
51	CF_3	H	H
52	H	CF_3	H
53	H	H	CF_3

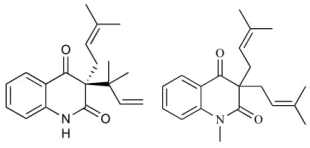
Tetrazole derivatives **54** and **55** were patented as antidotes against benzoylisoxazole herbicides that are reducing their phytotoxicity and protect the affected plants [174-178].



54 (R = Me)
55 (R = Et)

2.3. Quinoline-2,4-diones Isolated from Natural Sources

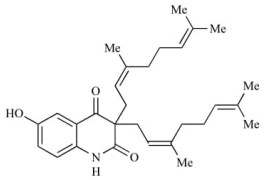
Buchapine was isolated from the epigeal part of *Haplophyllum bucharicum* [179] and *H. tuberculatum* [179, 180] as well as from *Euodia roxburghiana* [181]. Buchapine protects CEM-SS cells from the cytopathic effects of HIV-1 *in vitro* [181], inhibits the replication of HIV and shows some cytotoxicity [182-184]. A similar derivative **56** was isolated from the wood of *Esenbeckia flava* [185] and *E. almawillia* [186, 187].



buchapine **56**

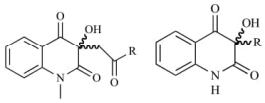
Another quinolinedione with a similar structure is severibuxine isolated from a citrus plant *Severinia buxifolia* [188]. This compound shows cytotoxic activity [188].

From the stem bark of *Micromelum falcatum* 3-hydroxyquinoline-2,4-diones **57** and **58** were isolated [6].



severibuxine

Both of them showed toxicity (LD_{50} values of 355 and 143 µg/mL) towards brine shrimp larvae [6]. Two 3-hydroxyquinoline-2,4-diones, heptyl derivative **59** and nonyl derivative **60**, were isolated from *Pseudomonas aeruginosa* [189].

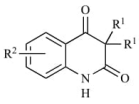


57 (R = Me)
58 (R = MeO)

59 (R = nonyl)
60 (R = heptyl)

2.4. Biologically Active Synthetic Quinoline-2,4-diones

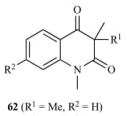
As mentioned in the previous chapter, some natural 3,3-dialkylquinoline-2,4-diones have been found to inhibit HIV replication. A series of 12 compounds structurally similar to buchapine **61** was prepared to investigate their ability to protect lymphoblasts against infection with HIV as well as their cytotoxicity [182, 190].



61

R^1=
-CH2CH=CH2,
-CH2CH=C(CH3)2,
-CH2CH2CH=C(CH3)2,
Pr, Bu

R^2= H, 7-Cl, 6-F, 8-F

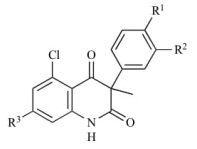


62 (R^1 = Me, R^2 = H)
63 (R^1 = Me, R^2 = Cl)
64 (R^1 = Me, R^2 = MeO)
65 (R^1 = Et, R^2 = H)

These compounds have been identified as promising inhibitors of HIV replication. Interestingly, the presence of any kind of substitution at the aromatic ring resulted in a complete loss of biological activity [182, 190].

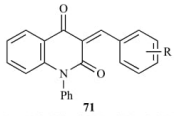
Tested on mice, compounds **62**-**65** were reported to show toxicity, anticonvulsant activity and sleeping time potentiation [191]. Low toxicity (LD_{50} in the range of 300 – 472 mg/kg) was reported with only moderate anticonvulsant activity. More significant anticonvulsant effects were shown by compound **62**. A sleeping time potentiation was shown by compounds **62**-**64**, the most effective from this point of view was the compound **63**.

3-Aryl-3-methylquinoline-2,4-diones show a high affinity to the serotonin receptors 5-HT_6 [192-194]. A series of 52 compounds, **66**-**70**, of this type is patented as highly potent and selective inhibitors of 5-HT_6 receptors, showing potential for the treatment of various psychiatric disorders [195]. All compounds exhibited a high ability (IC_{50} of 0.015–2.471 μmol/L) to inhibit aforementioned receptors, with only a marginal activity to other receptor subtypes including 5-HT_1, 5-HT_2 and 5-HT_7, and to dopamine receptors D_1-D_4. The most effective inhibitors of serotonin receptors are compounds **66**-**70**, whose inhibitory concentration IC_{50} ranged from 0.015 μmol/L (**68**) to 0.073 μmol/L (**70**).



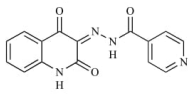
66 (R^1 = NEt_2, R^2 = H, R^3 = Cl)
67 (R^1 = OMe, R^2 = H, R^3 = Cl)
68 (R^1 = NHEt, R^2 = H, R^3 = Cl)
69 (R^1 = H, R^2 = OH, R^3 = Cl)
70 (R^1 = Br, R^2 = H, R^3 = OMe)

A series of 3-benzylidene-1-phenylquinoline-2,4(1*H*,3*H*)-diones **71** were found to exhibit antibacterial and antifungal activity [196].



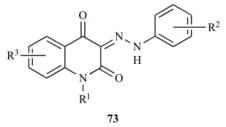
71
R = H, 3-NO_2, 4-NO_2, 3-Br, 2-OH, 4-F, 4-OH, 4-Cl, 4-OMe, 4-Br

Quinisatin hydrazone **72** is an isonicotinic acid hydrazide (isoniazid) derivative prepared in an effort to find compounds with a higher tuberculostatic activity than that of isoniazid itself [197]. Later, the QSAR antitubercular activity study was performed on a series of 79 quinisatin phenylhydrazones **73** [198]. These compounds effectively inhibited the growth of *M. tuberculosis* [198] and their further research may lead to new anti-tuberculars.

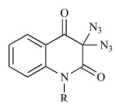


72

Austrian group of researchers prepared a series of substituted 3-azidoquinoline-2,4-diones, which were tested for their ability to inhibit human platelet aggregation [199]. The most effective compounds of the investigated series were 3,3-diazidoquinolinediones **74** and **75** [199].

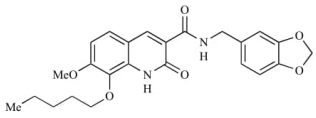


73
R^1 – H, Me
R^2 = NO_2, Cl, F, Me, Ph
R^3 = NO_2, Cl, Me



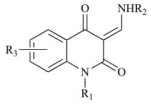
74 (R = H)
75 (R = Bu)

Some compounds containing the quinolone structural motif have previously been shown to possess affinity for cannabinoid receptors (*e.g.* antagonist of CB2 receptors JTE-907) [200]. Recently, it has been discovered that some quinoline-2,4-diones are highly selective agonists of cannabinoid CB2 receptors [201].



JTE-907

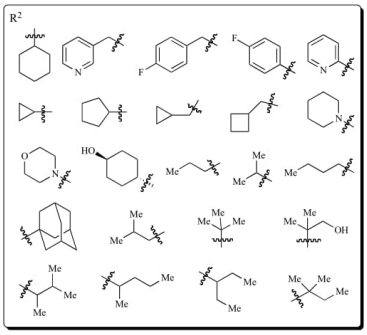
A large series of compounds **76** were designed, synthesized and evaluated for their potencies and binding properties toward the cannabinoid CB1 and CB2 receptor [201]. The compounds substituted at position 5 or 8 of the fused benzene ring demonstrated CB2 receptor agonist activity, whereas the analogues substituted at position 6 or 7 were antagonists of CB2 receptor [201]. These receptors are important from the medical point of view, probably because they are responsible for the therapeutic effects of cannabinoids (anti-inflammatory, immunomodulatory, analgesic), whereas CB2 agonism is not connected with the psychotropic effects of cannabinoids.



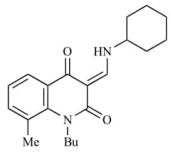
76

R^1 = Et, Pr, Bu, pentyl, hexyl, cyclopropylmethyl, but-3-en-1-yl

R^3 = H, 5/6/7/8-Me, 5/6/7/8-OMe, 8-Et, 6-tBu, 6-CF3, 6-OCF3, 6/7-Cl, 6-Br, 6-OMe-8-Me, 6-Cl-8-Me, 6,9-di-OMe



As the most effective compound of this series proved to be compound **77**, with which have been significantly reduced the clinical scores and ameliorate the disease severity of experimental autoimmune encephalomyelitis (EAE) by *in vivo* evaluation in mice with EAE [201].



77

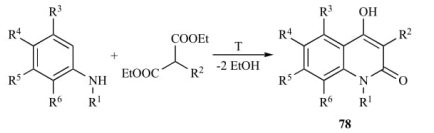
2-Oxo-1,2-dihydroquinoline-3-carboxylates are useful as anti-allergic agents [202].

3. SYNTHESIS OF 4-HYDROXYQUINOLIN-2-ONE AND QUINOLINE-2,4-DIONE DERIVATIVES

Due to a considerable interest in the title compounds, many methods for their preparation have been developed. Most of them employ conventional methods of organic synthesis. Some efforts have been motivated by the need to obtain target derivatives for further research.

3.1. Syntheses of Substituted 4-hydroxyquinolin-2-ones

A simple and widely used method for the preparation of 4-hydroxyquinolin-2-ones is thermal condensation of anilines with substituted malonic acid derivatives. The method has developed over the time. Initially, large excesses of substituted diethyl malonate were required, which was later improved by employing activated diaryl malonates. The most common protocol involves condensation of an aniline derivative with diethyl ester of substituted malonic acid in an equimolar ratio or with a slight excess of the malonate. By this method, a diverse range of substituted quinolones **78** is available (Scheme **1**) [73, 93, 111, 119, 120, 148, 203-257], including ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates (R^2 = COOEt). The later results from the use of triethyl methanetricarboxylate instead of malonate [93, 111, 113, 119, 120, 256]. The reaction proceeds *via* ketene intermediate. As by-products, corresponding malonyl dianilides were isolated in some cases [213, 217, 250, 258, 259].



78

R^1 = H, Me, Bu, Ph; R^2 = Me, Et, Pr, Bu, Ph, COOEt; R^3 = H, Me, Cl; R^4 = H, Me, MeO, Cl, F; R^5 = H, Me, MeO, Cl, F; R^6 = H, Me, MeO, Cl

Scheme 1. Preparation of 4-hydroxyquinolin-2-ones by thermal condensation of anilines with diethyl malonates.

Unfortunately, for some quinolones, this method is limited to low yields of the products, prompting to seek for alternative approaches. Recently, conducting these reactions under microwave heating conditions is reported in the literature as an alternative to the conventional heating [113, 260-265]. An example is the synthesis of quinolone **79** shown in Scheme **2** [261].

Generally, 3-unsubstituted 4-hydroxyquinolin-2-ones can not be obtained directly by the condensation of anilines with the malonic acid esters. This is due to the reaction of an intermediately formed hydroxyquinolone with the malonate forming the corresponding 4-hydroxy-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione **80** (Scheme **3**) [230, 266-277].

Alternatively, the 3-unsubstituted 4-hydroxyquinolin-2-ones can be prepared from the above pyranoquinolinediones by the degradation of pyran ring *via* 3-acetyl-4-hydroxyquinolin-2-ones [241, 271-274, 276]. A modern example of such a process is the synthesis of 4-hydroxy-1-methylquinolin-2-one shown in Scheme **4** [276].

Microwave assisted synthesis starting from anilines and malonic acid [171, 278] or diethyl malonate [179] was confirmed on several examples as one of the good yielding approaches to 3-unsubstituted 4-hydroxyquinolin-2-ones (Scheme **5**).

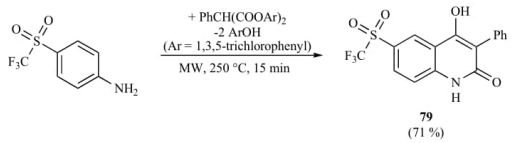
Another possibility for the synthesis of 3-unsubstituted 4-hydroxyquinolin-2-ones is cyclization of malonic acid dianilide **81** and its derivatives on the treatment with polyphosphoric acid (Scheme **6**) [279-290], methanesulfonic acid and phosphorus pentoxide [217, 291-294] or aluminium trichloride [295, 296]. At high temperatures, malonic acid dianilide forms ketene, which subsequently cyclizes to form 4-hydroxyquinolin-2-one.

Recently, an elegant two-step synthesis of unsubstituted 4-hydroxy-2-quinolone has been described, which started from aniline and a reactive substituted dioxanedione **82** (Meldrum's acid) [297]. Intermediary malonic acid monoanilide was dehydrated by means of Eaton's reagent (Scheme **7**).

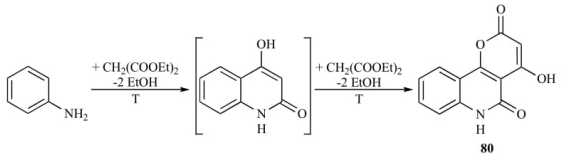
In addition to the above mentioned condensation of anilines with methanetricarboxylates, the general method of preparing of 2-oxo-1,2-dihydroquinoline-3-carboxylates is the condensation of isatoic anhydrides with unsubstituted malonates. These reactions have been carried out in dimethylacetamide [102, 202, 298-301] or dimethylformamide [101, 111, 113, 118, 121, 122, 138, 302-305] in the presence of bases such as sodium hydride [101, 102, 111, 118, 121, 122, 138, 202, 298-302, 305], sodium methoxide [304], or sodium *tert*-butoxide [113, 299, 303].

Modified Mukaiyama reaction of *N*-methylisatoic anhydride with ethyl trimethylsilyl methylketene acetal or ethyl trimethylsilyl phenylketene acetal catalyzed with titanium(IV) chloride afforded 4-hydroxy-1,3-dimethylquinolin-2-one (43 %) or 4-hydroxy-1-methyl-3-phenylquinolin-2-one (46 %), respectively (Scheme **8**) [306].

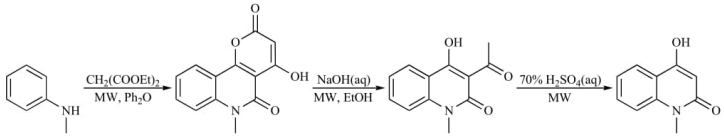
In some instances, 3-substituted 4-hydroxyquinolin-2-ones can be prepared by alkylation of the 3-unsubstituted analogues [182]. Alkylations were performed by alkyl iodides in aqueous lithium hydroxide (Scheme **9**) [182]. 3-Arylated 4-hydroxyquinolin-2-ones have been accessed by Suzuki–Miyaura cross-coupling at the corresponding iodinated quinolone. The method is limited by low-yielding 3-iodination of the parent 4-hydroxyquinolin-2-one scaffold [307]. An arylthio group can be introduced to position 3 of 4-hydroxyquinolin-2-one scaffold by the reaction of 3-unsubstituted precursors with arylsulfonylhydrazides in the presence of base, air oxygen and suitable catalyst [308]. A series of thirteen 3-arylthio-4-hydroxyquinolin-2-ones was obtained in 70-90 % yields performing this reaction in dioxane under reflux using 1,4-diazabicyclo [2.2.2]octane (DABCO) as a base and copper(I) bromide-dimethyl sulfide complex as a catalyst [308].



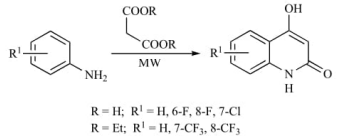
Scheme 2. An example of the microwave assisted cyclocondensation of substituted aniline with activated arylmalonate.



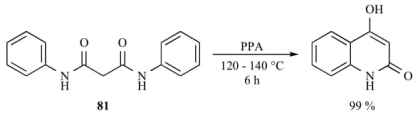
Scheme 3. Formation of 4-hydroxy-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-diones by reaction of anilines with diethyl malonate.



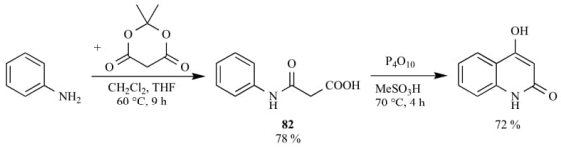
Scheme 4. Preparation of 4-hydroxy-1-methylquinolin-2-one *via* pyranoquinolinedione.



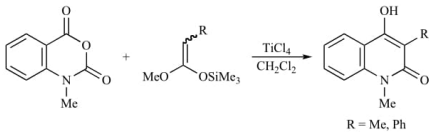
Scheme 5. Microwave synthesis of 3-unsubstituted 4-hydroxyquinolin-2-ones from anilines and malonic acid.



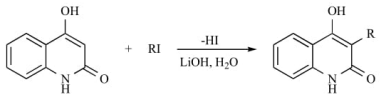
Scheme 6. Transformation of dianilide of malonic acid to the corresponding 4-hydroxyquinolin-2-one.



Scheme 7. Two-step synthesis of unsubstituted 4-hydroxyquinolin-2-one starting from aniline and Meldrum's acid.

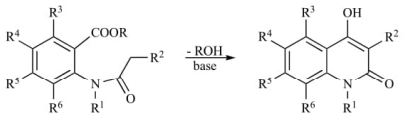


Scheme 8. Preparation of 3-substituted 4-hydroxy-1-methylquinolin-2-one from *N*-methylisatoic anhydride by modified Mukaiyama reaction.



R = alkyl

Scheme 9. Preparation of 3-alkyl-4-hydroxyquinolin-2-ones by alkylation of 4-hydroxyquinolin-2-one.



R = Me, Et

R^1 = H, Me, Et, *n*-alkyls C_3-C_{10}, *i*-C_5H_{11}, *n*-C_6H_{13}, $(CH_2)_2$-*c*-C_6H_{11}, $(CH_2)_2OEt$, $(CH_2)_4NHCOO$-*t*-Bu, allyl, CH_2Ph, $CH_2C_6H_4$-^{4}-OMe, 3,5-dimethoxy-^{4}-hydroxybenzyl, Ph, C_6H_4-^{4}-Me, 2,3-dimethylphenyl, 3,4-dimethylphenyl, C_6H_4-^{3}-OMe, C_6H_4-^{4}-OMe, COO-*t*-Bu, N=CHPh

R^2 = Me, Et, (1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)methyl, CH_2Ph, CH_2CF_3, CH_2COOMe, CH_2COOEt, COMe, COPr, COBu, CO-*i*-Bu, $CO(CH_2)_2Ph$, $CO(CH_2)_2OMe$, $COCH_2Ph$, 2-(thiophen-2-yl)acetyl, CO-*c*-C_3H_5, CO-*c*-C_6H_{11}, (1-phenylcyclopropyl)carbonyl, COPh, COOMe, COOEt, COO-*t*-Bu, $COOCH_2CN$, furan-^{2}-ylcarbonyl, thiophen-^{3}-ylcarbonyl, nicotinoyl, CONHCHMePh, CONH-C_6H_4-^{2}-COOMe, CO-NMePh, CO-NEtPh, methyl(thiophen-2-yl)carbamothioyl, methyl(phenyl)carbamothioyl, *tert*-butyl(phenyl)carbamothioyl, methyl(3-(trifluoromethyl)phenyl)carbamothioyl, methyl(4-methoxyphenyl)carbamothioyl, methyl(4-chlorophenyl)carbamothioyl, CN, $SO_2(NMe)(C_6H_4$-^{2}-COOMe)

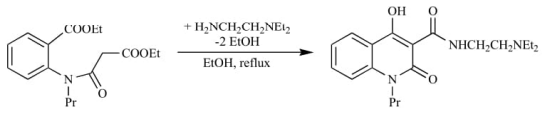
R^3 = H, Me, Cl, I, NO_2

R^4 = H, *n*-C_5H_{11}, C_6H_4-4-Cl, 2-naphthyl, 1-benzothiophen-2-yl, 1-benzothiophen-3-yl, pyrrol-1-yl, COPr, halogen, OMe, OTs, OCF_3, O-SO_2-C_6H_4-^{4}-I, O-$SiMe_2$-*t*-Bu, SMe, NO_2, NH_2

R^5 = H, Me, *c*-C_6H_{11}, 2-naphthyl, 1-benzothiophen-2-yl, CF_3, CN, F, Cl, OMe, NO_2, NH_2

R^6 = H, Me, C_6H_4-^{4}-OMe, 2-naphthyl, CF_3, F, OMe, NH_2

Scheme 10. Preparation of 4-hydroxyquinolin-2-ones by Dieckmann condensation of *N*-acylanthranilates.



83 **84**

Scheme 11. Preparation of some 4-hydroxyquinolin-2-ones by modified Dieckmann condensation.

An alternative method of preparation of 4-hydroxyquinolin-2-ones is Dieckmann condensation of *N*-acylanthranilates (Scheme **10**) using various basic reagents such as sodium in toluene or xylene [309-316], sodium alkoxides (in most cases sodium methoxide) [146, 317-339], potassium *tert*-butoxide in dimethylsulfoxide [339], sodium hydride [264, 338, 339, 340], lithium [341, 342], sodium [77, 125] or potassium [74, 84, 343-347] bis(trimethylsilyl) amide, lithium diisopropyl amide [348, 349], potassium carbonate in dimethylsulfoxide [350] or in dimethylformamide [351], triethylamine in methanol [339], and even potassium hydroxide in water [339].

Under Dieckmann condensation conditions methyl 2-(2-((2-(methoxycarbonyl)phenyl)(methyl)amino)-*N*-methyl-2-oxoethylsulfonamido)benzoate afforded 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-sulfonamide derivative in 88-94% yield. No formation of isomeric 4-hydroxy-1*H*-benzo[*c*][1,2]thiazine-3-carboxamide 2,2-dioxide could be observed [339].

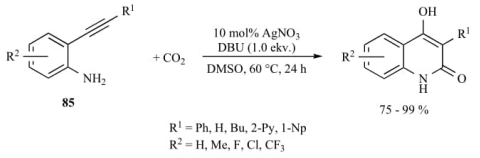
Diethyl 2,2'-[(1,3-dioxo-1,3-propanediyl)diimino]bis-benzoate undergoes Dieckmann condensation also thermally in boiling diphenyl ether [352]. The simultaneous intramolecular cyclization of ethyl 2-[(3-ethoxy-1,3-dioxopropyl)amino]benzoate and amidation with primary amines proved optimal for the preparation of the corresponding *N*-alkyl-4-hydroxy-2-quinolone-3-carboxamides [353]. There was patented the approach to *N*-[2-(diethylamino)ethyl]-1,2-dihydro-4-hydroxy-2-oxo-1-propylquinoline-3-carboxamide (**84**) by the procedure, in which ester **83** is subjected directly to condensation and amidation reaction simultaneously with N^1,N^1-diethylethane-1,2-diamine by boiling the reaction mixture in ethanol (Scheme **11**) [354].

An interesting reaction leading to 4-hydroxy-2-quinolones was described by a Japanese group of researchers [355] (Scheme **12**). The synthesis starts from substituted ethynes **85**, which react with carbon dioxide in the presence of a catalytic amount of a silver salt and strong non-nucleophilic base (DBU).

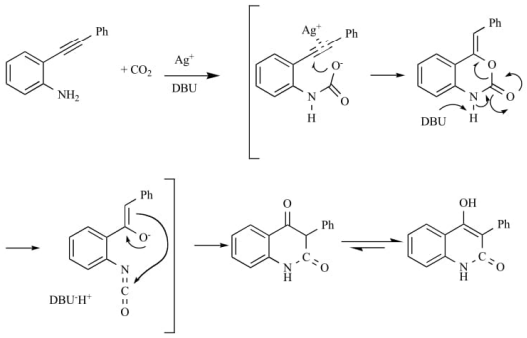
In addition to the innovative approach to the 4-hydroxy-2-quinolone skeleton, this reaction is interesting from a mechanistic point of view. The proposed reaction mechanism [355] is shown in Scheme **13**. It is noteworthy that reactions in which carbon dioxide become incorporated into a molecule of an organic compound, are still poorly explored.

3.2. Synthesis of 3,3-disubstituted Quinoline-2,4-diones

A large series of quinoline-2,4-diones with chlorine or bromine atom at position 3 can be prepared easily by chlorination or bromination of corresponding 4-hydroxyquinolin-2-ones. Chlorination of 4-hydroxyquinolin-2-ones substituted at position 3 with alkyl, cycloalkyl or aryl group is usually carried out with sulfuryl chloride in



Scheme 12. Reaction of substituted ethynes with carbon dioxide leading to 4-hydroxyquinolin-2-ones.

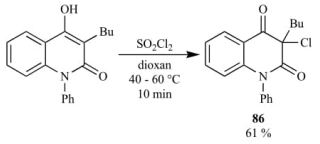


Scheme 13. Proposed reaction mechanism for the formation of 4-hydroxy-3-phenylquinolin-2-one by reaction of 2-(phenylethynyl)aniline with carbon dioxide.

dioxane at slightly elevated temperature [199, 223, 224, 244, 247, 254, 356-359]. An example is the preparation of chloroderivative **86** shown in Scheme **14** [254].

By analogy, 3,3-dichloroquinoline-2,4-diones are obtained from 3-unsubstituted 4-hydroxyquinolin-2-ones on treating with sulfuryl chloride [291, 295, 356, 360-376].

Alternatively, chlorination takes place with chlorine either from an external source [356] or generated *in situ* from hydrogen peroxide and hydrochloric acid [356, 364, 377-380], or chloride - chlorate mixture and diluted sulfuric acid [360, 381]. Dioxane or other solvents have been used in these procedures.

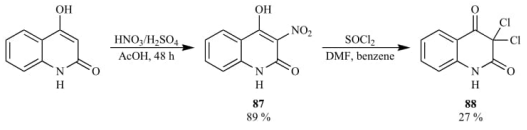


Scheme 14. An example of preparation of 3-chloroquinoline-2,4-dione from the corresponding 4-hydroxyquinolin-2-one.

An initial nitration of 4-hydroxyquinoline-2-one into 3-nitro derivative **87** and subsequent treatment with thionyl chloride afforded 3,3-dichloro derivative **88** (Scheme **15**) [382].

3-Bromo-3-substituted derivatives and 3,3-dibromoderivatives have been prepared from the appropriate 4-hydroxyquinolin-2-ones by the treatment with bromine, in most cases in acetic acid as a solvent [223, 224, 231, 244, 358, 383-390]. Bromination of the ring with bromine has also been accomplished in formic acid [391], aqueous sodium hydroxide [225], aqueous potassium bromide [392], aqueous dioxane [377], ethanol [377], tetrachloromethane [393], benzene [357], and there are protocols for bromination with pyridinium bromide perbromide in acetic acid [394], sodium hypobromite and potassium hydroxide in water and methanol [395, 396], *N*-bromosuccinimide and anhydrous magnesium perchlorate in acetonitrile [397-399], and *N*-bromosuccinimide in dichloromethane [400]. An example is bromination of 4-hydroxy-3-phenylquinoline-2-one shown in Scheme **16** [224, 244, 358].

3-Fluoro-3-alkyl/arylquinoline-2,4-diones as well as 3,3-difluoroquinolinediones can be prepared from the corresponding chloroderivatives by substitution of chlorine atom(s). These reactions have been carried out by treatment of the substrate with potasssium fluoride in presence of 18-crown-6 ether in acetonitrile [223, 224, 375]. Recently, fluorination of 6-nitro-1-propylquinoline-2,4-dione to its 3,3-difluoroderivative by the treatment with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), commercially called Selectfluor®, was patented [401].



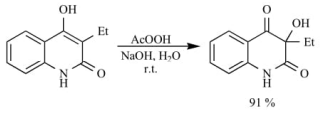
Scheme 15. Two-step preparation of 3,3-dichloroquinoline-2,4-dione **88** *via* the intermediacy of 3-nitroderivative **87**.

Scheme 16. Bromination of 4-hydroxy-3-phenylquinolin-2-one with bromine in acetic acid.

Treatment of 3-alkyl-4-hydroxyquinolin-2-ones in aqueous potassium carbonate solution with an aqueous solution of iodine and potassium iodide (Lugol solution) leads to introduction of iodine atom at the position 3 [402].

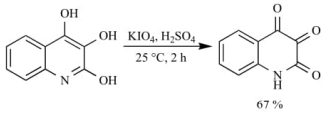
3-Halogenated quinolone-2,4-diones are valuable intermediates for the synthesis of a diverse range of substituted quinolone-2,4-diones. By substitution reactions these can be converted into other derivatives such as amines [247, 358, 359, 403-405], azidocompounds [199, 223, 224, 244, 358, 371, 375], *etc*.

4-Hydroxyquinolin-2-ones can be readily transformed into 3-hydroxyquinoline-2,4-diones by oxidation. A variety of oxidizing agents have been used including hydrogen peroxide [214, 223, 406], peroxyacetic acid (Scheme **17**) [225, 227, 229, 249, 250, 403, 407-409], 3-chloroperoxybenzoic acid [406, 223], and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) [410]. A two step procedure that involves nitration of 4-hydroxyquinolin-2-ones and subsequent hydrolysis of the intermediate also affords 3-hydroxyquinoline-2,4-diones [403].



Scheme 17. Example of the oxidation of 4-hydroxy-2-quinolone derivative with peroxyacetic acid.

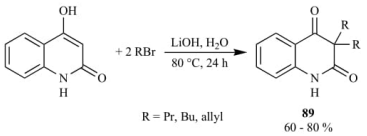
Quinisatin derivatives can be prepared from quinoline-2,4-diones, such as 3-chloro-3-nitroderivatives [360, 411], 3,3-dichloroderivatives [361] and 3,3-dibromoderivatives [412], or by the photochemical reaction of the corresponding 4-hydroxyquinolin-2(1*H*)-ones with singlet oxygen using methylene blue or rose bengal as the sensitizers [413]. An example of a simple method for the synthesis of quinisatin by oxidation of quinoline-2,3,4-triol with potassium periodate in sulfuric acid is shown in Scheme **18** [414].



Scheme 18. Preparation of quinisatin by oxidation of quinoline-2,3,4-triol.

Alkylation of 3-unsubstituted 4-hydroxyquinolin-2-ones with an excess of alkylating agent in the presence of base affords 3,3-dialkylquinoline-2,4-diones **89** [415]. An example is the reaction shown in Scheme **19**.

Alkylation of 4-hydroxyquinolin-2-ones is sometimes limited by side reactions [416]. An illustrative example is shown in Scheme **20** [415] where 4-hydroxyquinolin-2-one reacted with propargyl bromide into a complex mixture of products, from which four compounds were isolated.



Scheme 19. Preparation of 3,3-dialkylquinoline-2,4-diones.

3,3-Dialkyl- or 3-alkyl-3-arylquinoline-2,4-diones were also prepared by alkylation of 3-alkyl- or 3-aryl-4-hydroxyquinolin-2-ones with alkyl iodide or alkyl bromide in presence of sodium hydroxide in water or aqueous ethanol, catalysed with copper [417]. An example of such alkylation affording 3-methyl-3-phenylquinoline-2,4-dione is shown in Scheme **21** [416].

Recently, the transformation of 4-hydroxy-1,3-dimethyl-2-quinolone to 3-propargyl- and 3-[3-(4-chlorophenyl)-2-propynyl]-1,3-dimethylquinoline-2,4-dione have been described [418].

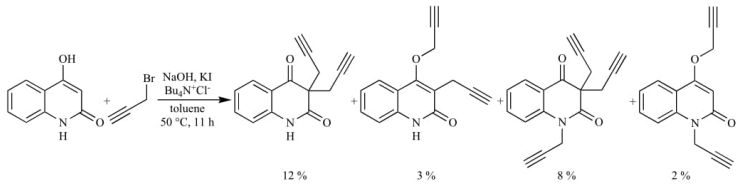
3,3-Dialkyl- and 3-alkyl-3-arylquinoline-2,4-diones have also been prepared by Dieckmann condensation of the appropriate substituted anthranilates [192]. An example is the preparation of 3-methyl-3-phenylquinoline-2,4-dione **91** from methyl *N*-(2-phenylpropanoyl)anthranilate **90** by treatment with lithium bis(trimethylsilyl)amide as base (Scheme **22**).

A multi-component synthesis of (*Z*)-3-benzylidene-1-phenylquinoline-2,4(1*H*,3*H*)-diones **71** has been reported to employ diphenylamine, diethyl malonate, and the appropriate substituted benzaldehyde as the starting materials (Scheme **23**), was published [196]. The reaction was carried out in aqueous ethanol in the presence of ZrO_2 nanoparticles as catalyst at 60-70 °C [196].

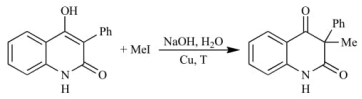
3,3-Dialkylquinoline-2,4-diones have been directly prepared also starting from isatoic anhydride or its derivatives. A series of four ethyl 3-alkyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylates were prepared by condensation of isatoic anhydride with the appropriate 2-alkyl-2-(diethoxyphosphoryl) acetates in benzene/ dimethylformamide mixture using sodium hydride as base (Scheme **24**) [419].

Modified Mukaiyama reaction of *N*-methylisatoic anhydride with methyl trimethylsilyl dimethylketene acetal (MTS) catalyzed with titanium(IV) chloride afforded 1,3,3-trimethylquinoline-2,4-dione. Small amounts of derivative substituted with 2-methoxycarbonylpropan-2-yl group in position 7 accompanied the reaction, a result of Friedel-Crafts alkylation of the target molecule (Scheme **25**) [420]. More recently, the application of this protocol to prepare other 3,3-disubstituted *N*-methylquinoline-2,4-diones was published [306], where ethyl trimethylsilyl acetals of various disubstituted ketenes were employed.

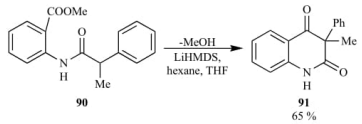
Recently, the syntheses of quinoline-2,4-diones through a radical addition/cyclization cascade reaction of *N*-(2-cyanophenyl)-*N*-methylmethacrylamide ($R^1 = R^2 = Me$) and other compounds having *o*-acrylamidobenzonitrile structure, were developed (Scheme **26**) [421-425]. Diphenylphosphineoxide [420], sodium trifluoromethanesulfinate (Langlois' reagent) [421] and other sulfinic acid sodium salts [421], α-ketoacids [422], aldehydes [422], arene/hetarene/ alkanesulfonohydrazides [423], and alcohols [424] were used as reactants. Wide substrate scope and good functional group tolerance have been reported, providing an efficient and practical access to a variety of quinoline-2,4(1*H*,3*H*)-diones. The reactions can be conducted in aqueous media, under ambient conditions, using readily available reactants and reagents. The products were obtained in moderate to excellent yields. However, the preparation of 1-unsubstituted and 1-acetylderivatives by these methods failed.



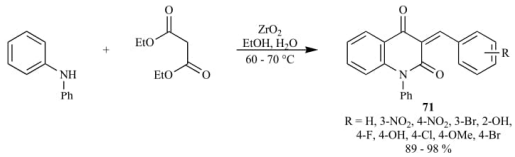
Scheme 20. Alkylation of 4-hydroxyquinolin-2-one with propargyl bromide providing four products.



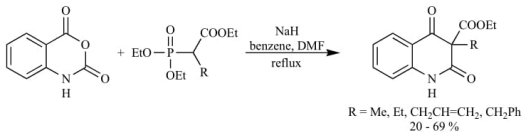
Scheme 21. Methylation of 4-hydroxy-3-phenyl-2-quinolone.



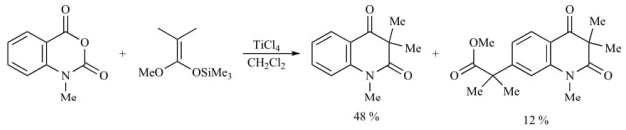
Scheme 22. Preparation of 3-methyl-3-phenylquinoline-2,4-dione (**91**) by Dieckmann condensation of methyl *N*-(2-phenylpropanoyl)anthranilate (**90**).



Scheme 23. Synthesis of (*Z*)-3-benzylidene-1-phenylquinoline-2,4(1*H*,3*H*)-diones.



Scheme 24. Condensation of isatoic anhydride with 2-alkyl-2-(diethoxyphosphoryl)acetates.



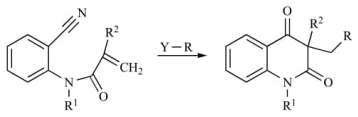
Scheme 25. Reaction of *N*-methylisatoic anhydride with MTS.

4. POTENTIAL APPLICATIONS OF 4-HYDROXY-QUINOLIN-2-ONES AND THEIR DERIVATIVES FOR PROPERTIES MODIFICATION OR PROTECTION OF MATERIALS

As discussed above, numerous 4-hydroxyquinolin-2-ones, quinoline-2,4-diones, and quinoline-2,3,4-triones show interesting effects on living organisms. Many of these compounds are also found in living systems. Thus, not only for their chemical structure and reactivity, these compounds can be interesting for their physical properties. This section will briefly outline the possibilities of using these chemical entities for the mentioned purposes.

4.1. Potential Applications as Antioxidants and Antidegradants

Some simple natural quinolones such as 4-hydroxy-1-methylquinolin-2-one (**2**) [4] and compound **16** [36] exhibit the ability to scavenge free radicals. It is known, that a number of



R^1 = Me, CH_2Ph, COMe
R^2 = Me, CH_2Ph, CH_2OCOMe, Ph, phthalimidomethyl
large-scale substitution on benzene ring of starting anthranilamide/resulting quinolinedione pattern
Y-R = H-P(O)R^3; R^3 = Ph, OEt; catalyst = $CuBr_2$ + $Mg(NO_3)_2$ · 6 H_2O when R^3 = Ph, $AgNO_3$ + $Mg(NO_3)_2$. 6 H_2O when R^3 = OEt
Y-R = NaO_2S-CF_3; catalyst = $Cu(ClO_4)_2$. 6 H_2O

· R = · S(O)$_2$—R^3 (from R^3SO_2Na); R^3 = Ph, C_6H_4-4-Me, C_6H_4-4-Cl, Me; catalyst = $Cu(ClO_4)_2$. 6 H_2O

Y-R = HOOC-C(O)R^3; R^3 = Ph, C_6H_4-2-Me, C_6H_4-2-OMe, C_6H_4-2-F, C_6H_4-2-Br, C_6H_4-3-F, C_6H_4-3-Cl, COC_6H_4-3-Br, COC_6H_4-4-Me, C_6H_4-4-OMe, C_6H_4-4-F, C_6H_4-4-Cl, C_6H_4-4-Br, C_6H_4-4-I, 3,4-methylenedioxyphenyl, 1-naphthyl, 2-naphthyl, acetyl; catalyst = $AgNO_3$ + $(NH_4)_2S_2O_8$
Y-R = H-C(O)R^3; R^3 = Ph, C_6H_4-2-Me, C_6H_4-3-Br, C_6H_4-4-OMe, C_6H_4-4-Br, Bu, CH_2Ph, *c*-C_3H_5; catalyst = PhCOOH + $K_2S_2O_8$

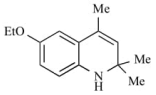
Y-R = H_2NHN—S(O)$_2$$R^3$; R^3 = Ph, C_6H_4-4-Me, C_6H_4-4-OMe, C_6H_4-4-Br, C_6H_4-4-NO_2, C_6H_4-2-Me, C_6H_4-3-OMe, 2-naphthyl, 2-thienyl, 3-pyridyl, Me, Bu, *c*-C_3H_5, (*E*)-styryl; catalyst/oxidant = CuI/$(NH_4)_2S_2O_8$

Y-R = H-C(O)R^3 generated *in situ* from RCH_2OH; R^3 = Ph, C_6H_4-2-Me, C_6H_4-2-Cl, C_6H_4-3-Me, C_6H_4-3-Br, C_6H_4-4-F, 2-thienyl; catalyst/oxidant = $FeCl_2$/*tert*-butyl peroxybenzoate

Scheme 26. Preparation of quinoline-2,4-diones by radical addition/cyclization cascade reaction from substituted *o*-acrylamidobenzonitriles.

simple synthetic 4-hydroxyquinolin-2-ones have antioxidant properties and the ability to scavenge free radicals [136, 145, 147, 383]. These compounds could therefore be potentially useful as antidegradants protecting materials against an oxidative damage.

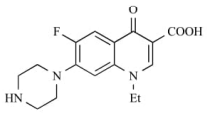
Noteworthy, structurally similar compound, ethoxyquin [426], is widely used in animal feed in order to protect it against lipid peroxidation for several decades and despite the search for new compounds that could be used as free radical scavengers, it is still the most effective antioxidant [427]. The negative health effects in domestic animals fed with ethoxyquin containing feed were observed some years ago, but the presence of its approved doses should not be hazardous [426].



ethoxyquin

4.2. Potential Use as Biocidal Additives

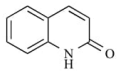
Quinolin-2-ones exhibit antibacterial and antifungal effects. For 6-nitro quinolones (**45**-**47**) significant antibacterial and antifungal effects have been proven. These compounds also effectively inhibited growth of the fungi *Aspergillus niger* and *A. flavus* [172], which often attack various materials. Simple fluorinated 4-hydroxyquinolin-2-ones **48**-**53**, as well as quinisatine phenylhydrazones **73**, inhibit the growth of *Mycobacterium tuberculosis*. Some of the discussed compounds also show fungicidal and algicidal effects [27]. Thus, some of these compounds could be used to protect various materials against harmful organisms. Such compounds could be applied either in the form of a suitable spraying or impregnation, or directly as additives, which would be components of the mixtures for the preparation of the materials. An interesting challenge is the preparation of materials based on polymers with bound compounds of these types. Polymers modified by quinolin-4-one moiety are already known. For example, a hydroxymethacrylate monomer containing a quinolin-4-one moiety (norfloxacin concretely) was synthesized and homopolymerized [428-430] as well as copolymerized with poly(ethylene glycol) methyl ether [428], while the monomer as well as the corresponding polymer exhibited an excellent antibacterial activity. The same applies to blends of poly(acrylated quinolone) with other ordinary synthetic polymers [427].



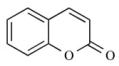
norfloxacin

4.3. The Use of Quinoline-2-one Derivatives as Fluorescent Substances

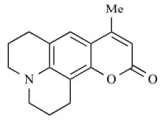
Oxygen analogues of quinolin-2-ones, chromen-2-ones, represent important fluorescent substances widely used in industry. An example is Coumarin 102, which represents a laser dye [431, 432].



quinolin-2(1*H*)-one

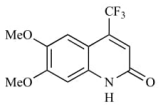


2*H*-chromen-2-one

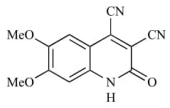


Coumarin 102

Some derivatives of quinolin-2-one available from 4-hydroxyquinolin-2-ones show very promising fluorescence properties. Such compounds include substituted 4-trifluoromethyl-, 4-cyano- and 3,4-dicyanoquinolones [433]. Examples are dimethoxyquinolones **92** [434-437] and **93** [374, 432, 438].



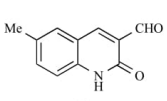
92



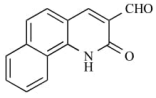
93

A comparative study of 6-methoxy-, 7-methoxy- and 6,7-dimethoxycarbostyrils revealed, that both, the 6- and the 7-methoxy group have different effects to the fluorescence properties of carbostyrils such as fluorescence wavelength, quantum yield and Stokes shift. A further important influence is visible from the electron acceptor properties of the substituent at position 4 [439].

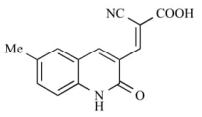
A number of 4-hydroxyquinolin-2-ones substituted by pyrazoline, isoxazole or pyridine groups at position 3 were examined as potential luminophores [440]. A series of quinoline derivatives is documented that exhibits fluorescence and may find use as fluorescent probes for detection of bacteria [441], tumour cells [442] or cysteine inside living cells [443]. Recently, novel fluorescent dyes based on quinolin-2-ones were described [444, 445]. Such fluorescent dyes include aldehydes **94** [443, 444] and **95** [444] as well as acid **96**, obtained by chemical transformations of the aldehyde **94** [444].



94

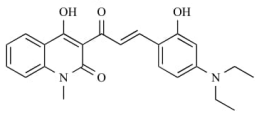


95

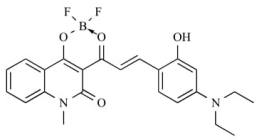


96

Other quinoline derivatives may find use as fluorescent probes for the detection of metal ions [446, 447]. Two 4-hydroxyquinolin-2-one dyes, compound **97** and its boron difluoride complex **98**, containing 4-diethylamino-2-hydroxyphenyl substituent, displayed high emission and bright fluorescence and thus offer promise for use in protein detection [448].



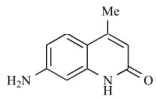
97



98

Some quinoline and quinolone derivatives have been designed as fluorescent markers of a diverse range of biomolecules [449]. Such compounds could find use as luminophores, colorants, optical brighteners and UV absorbers for modification of properties of polymeric or other materials.

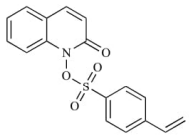
There are already known some polymeric materials, which have been modified so that quinolin-2-one groups are included in their structure [450]. Material based on maleic anhydride-styrene alternating copolymer containing quinolin-2-one fluorophore showed intense fluorescence in the presence of terbium(III) ions [451]. Later, a similar material based on quinolin-2-one modified polystyrene-block-poly(styrene-alt-maleic anhydride) copolymer was prepared and its luminescence was investigated [452]. For the modification of the mentioned polymers, 7-amino-4-methylquinolin-2-one (**99**) has been used.



99

4.4. Another Possible Use of Quinolone Derivatives for the Treatment of Materials

Interesting properties were observed for some 1-hydroxyquinolin-2-ones. In these compounds, light causes splitting of labile N-O bonds. Photoresponsive 1-(*p*-styrenesulfonyloxy)-2-quinolone - methyl methacrylate and 1-(*p*-styrenesulfonyloxy)-2-quinolone - lauryl acrylate copolymers were synthesized from photoacid generator monomer **100**. Surface wettability of these polymers can be specifically changed by light [453].



100

4.5. Possible Limitations

It should be noted that some natural 4-hydroxyquinolines have been found to exhibit estrogenic activity. Such compounds are *e.g.* foliosidin or bucharidin [11]. These properties would represent a complication in the practical exploitation of these compounds, inasmuch as a number of additives into polymeric materials has been for reasons of estrogenic activity significantly reduced (phthalates, bisphenol A). Some synthetic 4-alkoxyquinolin-2-ones affect the metabolism of gonadotropin-releasing hormone [123, 125, 129, 132] and 4-hydroxyquinolin-2-one **25** is patented to reduce the motility of male sperm [133]. Some quinolones, which contain imidazole group at position 3 of the quinolone ring, inhibit thyroid [145]. Also, these properties could pose a problem when applying some of 4-hydroxyquinolones for the treatment of materials. Historical experiences with industrial additives that interfere with the hormonal system or regulation of reproductive functions should encourage a thorough examination of the 4-hydroxyquinolones and its derivatives before eventual practical applications. On the other hand, quinolones could represent relatively safe substances for toxicity. Until now tested quinoline-2,4-diones [191] and 4-hydroxyquinolin-2-ones exhibit low toxicity [103-107, 136, 139, 140].

Another possible restriction on the use of quinolones and compounds accessible from them for the treatment of materials is their chemical reactivity. Quinolin-2-ones are relatively stable heterocyclic systems, however quinoline-2,4-dione group is relatively reactive and it is known that various unexpected chemical transforma-

tions and rearrangements can take place in these heterocycles. Some of those reactions have been investigated [227, 228, 232, 236, 243, 248, 359, 403, 404, 408, 409, 454-463]. Some chemical transformations of 1-hydroxyquinolin-2-ones [464] and quinoline-2,4-diones [465] have been reviewed.

CONCLUSION

The aim of this paper is to bring the reader insight into diverse group of derivatives of 4-hydroxyquinolin-2-ones and related quinoline-2,4-diones. It summarizes the information from the literature about the occurrence of these compounds in nature, their properties and potential applications. In the part devoted to the syntheses, some common methods of approach to these compounds are mentioned, and these methods are partially commented. The review ends with a brief outline of the potential use of these natural and synthetic compounds to modify the properties of materials or materials protection and possible restrictions on the applications of these compounds are there also discussed.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work was financed by TBU in Zlín (internal grant no. IGA/FT/2017/005, funded from the resources of specific university research) and the Slovenian Research Agency (research core funding No. P1-0230).

REFERENCES

[1] El-Neketi, M.; Ebrahim, W.; Lin, W.; Gedara, S.; Badria, F.; Saad, H.E.A.; Lai, D.; Proksch, P. Alkaloids and polyketides from *Penicillium citrinum*, an endophyte isolated from the Moroccan plant *Ceratonia siliqua*. *J. Nat. Prod.*, **2013**, *76*, 1099-1104.

[2] Bessonova, I.A. Components of *Haplophyllum bucharicum*. *Khim. Prir. Soedin.*, **2000**, 261-262; *Chem. Nat. Compd.*, **2000**, *36*, 323-324.

[3] Lai, D.; Broetz-Oesterhelt, H.; Mueller, W.E.G.; Wray, V.; Proksch, P. Bioactive polyketides and alkaloids from *Penicillium citrinum*, a fungal endophyte isolated from *Ocimum tenuiflorum*. *Fitoterapia*, **2013**, *91*, 100-106.

[4] Angeleska, S.; Kefalas, P.; Detsi, A. Crude peroxidase from onion solid waste as a tool for organic synthesis. Part III: Synthesis of tetracyclic heterocycles (coumestans and benzofuroquinolinones). *Tetrahedron Lett.*, **2013**, *54*, 2325-2328.

[5] Audisio, D.; Messaoudi, S.; Cojean, S.; Peyrat, J.F.; Brion, J.D.; Bories, C.; Huteau, F.; Loiseau, P.M.; Alami, M. Synthesis and antikinetoplastid activities of 3-substituted quinolinones derivatives. *Eur. J. Med. Chem.*, **2012**, *52*, 44-50.

[6] Luo, X.M.; Qi, S.H.; Yin, H.; Gao, C.H.; Zhang, S. Alkaloids from the stem bark of *Micromelum falcatum*. *Chem. Pharm. Bull.*, **2009**, *57*, 600-602.

[7] Bhide, K.S.; Mujumdar, R.B.; Rao, A.V.R. Phenolics from the bark of *Chloroxylon swietenia* DC. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **1977**, *15*, 440-443.

[8] Aoki, S.; Ye, Y.; Higuchi, K.; Takashima, A.; Tanaka, Y.; Kitagawa, I.; Kobayashi, M. Novel neuronal nitric oxide synthase (nNOS) selective inhibitors, aplysinopsin-type indole alkaloids, from marine sponge *Hyrtios erecta*. *Chem. Pharm. Bull.*, **2001**, *49*, 1372-1374.

[9] Crow, W.D.; Hodgkin, J.H. Alkaloids of the Australian Rutaceae: *Halfordia scleroxyla* and *Halfordia kendack*. IV. Co-occurrence of oxazole and quinoline alkaloids. *Aust. J. Chem.*, **1968**, *21*, 3075-3077.

[10] Faizutdinova, Z.S.; Bessonova, I.A.; Yunusov, S.Y. The structure of bucharidine. *Khim. Prir. Soedin.*, **1969**, 455-456; *Chem. Nat. Compd.*, **1969**, *5*, 380-381.

[11] Nazrullaev, S.S.; Bessonova, I.A.; Akhmedkhodzhaeva, K.S. Estrogenic activity as a function of chemical structure in Haplophyllum quinoline alkaloids. *Khim. Prir. Soedin.*, **2001**, 472-476; *Chem. Nat. Compd.*, **2001**, *37*, 551-555.

[12] Chen, I.S.; Wu, S.J.; Lin, Y.C.; Tsai, I.L.; Seki, H.; Ko, F.N.; Teng, C.M. Dimeric 2-quinolone alkaloid and antiplatelet aggregation constituents of Zanthoxylum simulans. *Phytochemistry*, **1994**, *36*, 237-239.

[13] Paul, B.D.; Bose, P.K. Quinolone alkaloids from *Ravenia spectabilis*. *Indian J. Chem.*, **1969**, *7*, 678-680.

[14] Jurd, L.; Benson, M.; Wong, R.Y. New quinolinone and bisquinolinone alkaloids from *Euxylophora paraensis*. *Aust. J. Chem.*, **1983**, *36*, 759-768.

[15] Yamamoto, Y.; Harimaya, K. Synthesis of SF2809-V, chymase inhibitor, and its analogs by three component reaction: Model study for high throughput synthesis of a chymase inhibitor library. *Chem. Lett.*, **2004**, *33*, 238-239.

[16] Song, W.W.; Zeng, G.Z.; Peng, W.W.; Chen, K.X.; Tan, N.H. Cytotoxic amides and quinolones from *Clausena lansium*. *Helv. Chim. Acta*, **2014**, *97*, 298-305.

[17] Cuca Suarez, L.E.; Pattarroyo, M.E.; Lozano, J.M.; Delle Monache, F. Biological activity of secondary metabolites from *Peltostigma guatemalense*. *Nat. Prod. Res.*, **2009**, *23*, 370-374.

[18] Hifnawy, M.S.; Vaquette, J.; Sevenet, T.; Pousset, J.L.; Cave, A. Plants of New Caledonia. 45. Neutral products and alkaloids from *Myrtopsis macrocarpa*, *M. myrtoidea*, *M. novae-caledoniae*, and *M. Sellingii*. *Phytochemistry*, **1977**, *16*, 1035-1038.

[19] Bessonova, I.A.; Yunusov, S.Y. Alkaloids of *Haplophyllum bungei*. *Khim. Prir. Soedin.*, **1989**, 23-25; *Chem. Nat. Compd.*, **1989**, *25*, 18-20.

[20] Severino, V.G.P.; de Freitas, S.D.L.; Braga, P.A.C.; Forim, M.R.; das G.F. da Silva, M.F.; Fernandes, J.B.; Vieira, P.C.; Venâncio, T. New limonoids from *Hortia oreadica* and unexpected coumarin from *H. superba* using chromatography over cleaning Sephadex with sodium hypochlorite. *Molecules*, **2014**, *19*, 12031-12047.

[21] Siridechakorn, I.; Laphookhieo, S. Chemical constituents from *Feronia limonia* roots. *Khim. Prir. Soedin.*, **2012**, 276-277; *Chem. Nat. Compd.*, **2012**, *48*, 308-309.

[22] Huang, H.Y.; Ishikawa, T.; Peng, C.F.; Chen, S.; Chen, I.S. Secondary Metabolites from the root wood of *Zanthoxylum wutaiense* and their antitubercular activity. *Chem. Biodiversity*, **2011**, *8*, 880-886.

[23] Rodriguez-Guzman, R.; Fulks, L.C.J.; Radwan, M.M.; Burandt, C.L.; Ross, S.A. Chemical constituents, antimicrobial and antimalarial activities of *Zanthoxylum monophyllum*. *Planta Med.*, **2011**, *77*, 1542-1544.

[24] Rosas, L.V.; Veiga, T.A.M.; Fernandes, J.B.; Vieira, P.C.; das G.F. da Silva, M.F. Prenylindole alkaloids from *Raputia praetermissa* (Rutaceae) and their chemosystematic significance. *J. Braz. Chem. Soc.*, **2011**, *22*, 1346-1353.

[25] Tsai, I.L.; Wun, M.F.; Teng, C.M.; Ishikawa, T.; Chen, I.S. Anti-platelet aggregation constituents from Formosan *Toddalia asiatica*. *Phytochemistry*, **1998**, *48*, 1377-1382.

[26] El Sayed, K.; Al-Said, M.S.; El-Feraly, F.S.; Ross, S.A. New Quinoline Alkaloids from *Ruta chalepensis*. *J. Nat. Prod.*, **2000**, *63*, 995-997.

[27] Cantrell, C.L.; Schrader, K.K.; Mamonov, L.K.; Sitpaeva, G.T.; Kustova, T.S.; Dunbar, C.; Wedge, D.E. Isolation and identification of antifungal and antialgal alkaloids from *Haplophyllum sieversii*. *J. Agric. Food Chem.*, **2005**, *53*, 7741-7748.

[28] Razakova, D.M.; Bessonova, I.A.; Yunusov, S.Y. Components of *Haplophyllum obtusifolium*. *Khim. Prir. Soedin.*, **1984**, 635-636; *Chem. Nat. Compd.*, **1984**, *20*, 599-600.

[29] Hitotsuyanagi, Y.; Kojima, H.; Ikuta, H.; Takeya, K.; Itokawa, H. Identification and structure-activity relationship studies of osthol, a cytotoxic principle from Cnidium monnieri. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1791-1794.

[30] Imai, F.; Itoh, K.; Kishibuchi, N.; Kinoshita, T.; Sankawa, U. Constituents of the root bark of Murraya paniculata collected in Indonesia. *Chem. Pharm. Bull.*, **1989**, *37*, 119-123.

[31] Storer, R.; Young, D.W. Synthesis of halfordamine, an alkaloid from Halfordia kendack. *Tetrahedron*, **1973**, *29*, 1215-1216.

[32] Campbell, W.E.; Finch, K.P.; Bean, P.A.; Finkelstein, N. Chemosystematic studies in the genera of the Diosmeae. Part 2. Alkaloids of the rutoideae: Tribe diosmeae. *Phytochemistry*, **1987**, *26*, 433-434.

[33] Wu, T.S.; Chang, F.C.; Wu, P.L. Flavonoids, amidosulfoxides and an alkaloid from the leaves of *Glycosmis citrifolia*. *Phytochemistry*, **1995**, *39*, 1453-1457.

[34] Chen, J.J.; Chang, Y.L.; Teng, C.M.; Su, C.C.; Chen, I.S. Quinoline alkaloids and anti-platelet aggregation constituents from the leaves of *Melicope semecarpifolia*. *Planta Med*., **2002**, *68*, 790-793.

[35] Rasulova, K.A.; Bessonova, I.A. Alkaloids of Haplophyllum perforatum. *Khim. Prir. Soedin*., **1992**, 249-251; *Chem. Nat. Compd*., **1992**, *28*, 214-216.

[36] Yoon, M.A.; Jeong, T.S.; Park, D.S.; Xu, M.Z.; Oh, H.W.; Song, K.B.; Lee, W.S.; Park, H.Y. Antioxidant effects of quinoline alkaloids and 2,4-di-*tert*-butylphenol isolated from *Scolopendra subspinipes*. *Biol. Pharm. Bull*., **2006**, *29*, 735-739.

[37] Eshiet, I.T.; Taylor, D.A.H. Extractives from *Fagara zanthoxyloides*. *Chem. Commun. (London)*, **1966**, 467-468.

[38] Paul, B.D.; Bose, P.K. New quinolone alkaloids from *Ravenia spectabilis*. *J. Indian Chem. Soc*., **1968**, *45*, 552-553.

[39] Reisch, J.; Mueller, M.; Mester, I. Studies in natural product chemistry. Part 83. Constituents from the rootbark and heartwood of *Afraegle paniculata*. *Planta medica*, **1981**, *43*, 285-289.

[40] Moulis, C.; Wirasutisna, K.R.; Gleye, J.; Loiseau, P.; Stanislas, E.; Moretti, C. A 2-quinolone alkaloid from *Almeidea guyanensis*. *Phytochemistry*, **1983**, *22*, 2095-2096.

[41] Perrett, S.; Whitfield, P.J. Atanine (3-dimethylallyl-4-methoxy-2-quinolone), an alkaloid with anthelmintic activity from the Chinese medicinal plant, *Evodia rutaecarpa*. *Planta Med*., **1995**, *61*, 276-278.

[42] Chen, I.S.; Chen, T.L.; Chang, Y.L.; Teng, C.M.; Lin, W.Y. Chemical constituents and biological activities of the fruit of *Zanthoxylum integrifoliolum*. *J. Nat. Prod*., **1999**, *62*, 833-837.

[43] Chen, I.S.; Chen, T.L.; Chang, Y.L.; Teng, C.M.; Lin, W.Y. Constituents of the root wood of *Zanthoxylum wutaiense* with antitubercular activity. *J. Nat. Prod*., **2008**, *71*, 1146-1151.

[44] Ito, C.; Itoigawa, M.; Otsuka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod*., **2000**, *63*, 1344-1348.

[45] Wu, T.S.; Kuoh, C.S.; Furukawa, H. Acridone alkaloids. Part VIII. Acridone alkaloids and a coumarin from Citrus grandis. *Phytochemistry*, **1983**, *22*, 1493-1498.

[46] Seya, K.; Miki, I.; Murata, K.; Junke, H.; Motomura, S.; Araki, T.; Itoyama, Y.; Oshima, Y. Pharmacological properties of pteleprenine, a quinoline alkaloid extracted from *Orixa japonica*, on Guinea-pig Ileum and Canine Left Atrium. *J. Pharm. Pharmacol*., **1998**, *50*, 803-807.

[47] Terasaka, M.; Narahashi, K.; Tomikawa, Y. Alkaloids of the root bark of *Orixa japonica*. X. Isolation of nororixine. *Chem. Pharm. Bull*., **1960**, *8*, 1142-1143.

[48] Noshita, T.; Tando, M.; Suzuki, K.; Murata, K.; Funayama, S. New quinoline alkaloids from the leaves and stems of *Orixa japonica*, orijanone, isopteleflorine and 3'-*O*-methylorixine. *Biosci. Biotechnol. Biochem*., **2001**, *65*, 710-713.

[49] Steck, W.; Bailey, B.K.; Shyluk, J.P.; Gamborg, O.L. Coumarins and alkaloids from cell cultures of *Ruta graveolens*. *Phytochemistry*, **1971**, *10*, 191-194.

[50] Higa, T.; Scheuer, P.J. Hawaiian plant studies. XV. Alkaloids from *Pelea barbigera*. *Phytochemistry*, **1974**, *13*, 1269-1272.

[51] Johns, S.R.; Lamberton, J.A.; Sioumis, A.A. Identification of a quinolone alkaloid from *Citrus macroptera*. *Aust. J. Chem*., **1976**, *23*, 419-420.

[52] Torres, R.; Cassels, B.K. Leaf alkaloids of *Fagara mayu*. *Phytochemistry*, **1978**, *17*, 838-839.

[53] Akhmedzhanova, V.I.; Bessonova, I.A.; Yunusov, S.Y. Alkaloids of *Haplophyllum foliosum*. *Khim. Prir. Soedin*., **1980**, 803-805; *Chem. Nat. Compd*., **1980**, *16*, 574-576.

[54] Stermitz, F.R.; Caolo, M.A.; Swinehart, J.A. Chemistry of Zanthoxylum. Part 5. Alkaloids and other constituents of *Zanthoxylum williamsii*, *Z. monophyllum*, and *Z. fagara*. *Phytochemistry*, **1980**, *19*, 1469-1472.

[55] Yenesew, A.; Dagne, E. Alkaloids of *Teclea nobilis*. *Phytochemistry*, **1988**, *27*, 651-653.

[56] Wondimu, A.; Dagne, E.; Waterman, P.G. Quinoline alkaloids from the leaves of *Teclea simplicifolia*. *Phytochemistry*, **1988**, *27*, 959-960.

[57] Chou, H.C.; Chen, J.J.; Duh, C.Y.; Huang, T.F.; Chen, I.S. Cytotoxic and anti-platelet aggregation constituents from the root wood of *Melicope semecarpifolia*. *Planta Med*., **2005**, *71*, 1078-1081.

[58] Takahashi, N.; Subehan; Kadota, S.; Tezuka, Y. Mechanism-based CYP2D6 inactivation by acridone alkaloids of Indonesian medicinal plant *Lunasia amara*. *Fitoterapia*, **2012**, *83*, 774-779.

[59] Power, F.B.; Callan, T. Constituents of the seeds of *Casimiroa edulis*. *J. Chem. Soc. Trans*., **1911**, *99*, 1993-2010.

[60] Kincl, F.A.; Romo, J.; Rosenkranz, G.; Sondheimer, F. The constituents of *Casimiroa edulis llave et lex*. *I. The seed*. *J. Chem. Soc*., **1956**, 4163-4169.

[61] Dreyer, D.L. Citrus bitter principles. IX. Extractives of *Casimiroa edulis*. Structure of zapoterin. *J. Org. Chem*., **1968**, *33*, 3577-3582.

[62] Ito, A.; Shamon, L.A.; Yu, B.; Mata-Greenwood, E.; Lee, S.K.; Van Breemen, R.B.; Mehta, R.G.; Farnsworth, N.R.; Fong, H.H.S.; Pezzuto, J.M.; Kinghorn, A.D. Antimutagenic constituents of *Casimiroa edulis* with potential cancer chemopreventive activity. *J. Agric. Food Chem*., **1998**, *46*, 3509-3516.

[63] Bessonova, I.A.; Batsuren, D.; Abdullaev, N.D.; Yunusov, S.Y. Daurine – a new alkaloid from *Haplophyllum dauricum*. *Khim. Prir. Soedin*., **1983**, 116; *Chem. Nat. Compd*., **1983**, *19*, 117-118.

[64] Eskairov, M.; Sidyakin, G.P.; Yunusov, S.Y. Alkaloids of *Haplophyllum foliosum*, foliosidine. *Dokl. Akad. Nauk UzSSR*, **1958**, (5), 23; *Chem. Abstr*., **1959**, *53*, 9574.

[65] Sidyakin, G.P.; Eskairov, M.; Yunusov, S.Y. Alkaloids of *Haplophyllum foliosum* Vved. Structure of dubinidine. *Zh. Obshch. Khim*., **1960**, *30*, 338-345.

[66] Sharafutdinova, S.M.; Yunusov, S.Y. The alkaloids of *Haplophyllum bucharicum*. *Khim. Prir. Soedin*., **1968**, *4*, 198; *Chem. Nat. Compd*., **1968**, *4*, 171.

[67] Jansen, O.; Akhmedjanova, V.; Angenot, L.; Balansard, G.; Chariot, A.; Ollivier, E.; Tits, M.; Frederich, M. Screening of 14 alkaloids isolated from Haplophyllum A. Juss. for their cytotoxic properties. *J. Ethnopharmacol*., **2006**, *105*, 241-245.

[68] Sharafutdinova, S.M.; Yunusov, S.Y. Structure of bucharaine. *Khim. Prir. Soedin*., **1969**, *5*(5), 394-397; *Chem. Nat. Compd*., **1969**, *5*(5), 327-329.

[69] Ubaidullaev, K.; Bessonova, I.A.; Yunusov, S.Y. Alkaloids of *Haplophyllum pedicellatum*, *Haplophyllum obtusifolium*, and *Haplophyllum bucharicum*. Structure of bucharamine. *Khim. Prir. Soedin*., **1972**, 343-346; *Chem. Nat. Compd*., **1972**, *8*, 337-339.

[70] Nesmelova, E.F.; Bessonova, I.A.; Yunusov, S.Y. Components of *Haplophyllum bucharicum*. *Khim. Prir. Soedin*., **1982**, 532; *Chem. Nat. Compd*., **1982**, *18*, 507-508.

[71] Polievtsev, N.P. Pharmacological properties of the alkaloid bucharaine. *Farmakol. Alkaloidov Serdechnykh Glikozidov*, **1971**, 164-167; *Chem. Abstr*., **1973**, *78*, 119188.

[72] Polievtsev, N.P.; Evdokimova, N.I.; Sultanov, M.B. Comparative effect of alkaloids of a Haplophyllum plant on animal diuresis. *Dokl. Akad. Nauk UzSSR*, **1970**, *27*(3), 31-32.

[73] McQuaid, L.A.; Smith, E.C.R.; Lodge, D.; Pralong, E.; Wikel, J.H.; Calligaro, D.O.; O'Malley, P.J. 3-Phenyl-4-hydroxyquinolin-2(1*H*)-ones: Potent and selective antagonists at the strychnine-insensitive glycine site on the *N*-methyl-D-aspartate receptor complex. *J. Med. Chem*., **1992**, *35*, 3423-3425.

[74] Rowley, M.; Kulagowski, J.J.; Watt, A.P.; Rathbone, D.; Stevenson, G.I.; Carling, R.W.; Baker, R.; Marshall, G.R.; Kemp, J.A.; Foster, A.C.; Grimwood, S.; Hargreaves, R.; Hurley, C.; Saywell, K.L.; Tricklebank, M.D.; Leeson, P.D. Effect of plasma protein binding on *in vivo* activity and brain penetration of glycine/NMDA receptor antagonists. *J. Med. Chem*., **1997**, *40*, 4053-4068.

[75] Buchstaller, H.P.; Siebert, C.D.; Steinmetz, R.; Frank, I.; Berger, M.L.; Gottschlich, R.; Leibrock, J.; Krug, M.; Steinhilber, D.; Noe, C.R. Synthesis of thieno[2,3-b]pyridinones acting as cytoprotectants and as inhibitors of [^{3}H]glycine binding to the *N*-methyl-D-aspartate (NMDA) receptor. *J. Med. Chem*., **2006**, *49*, 864-871.

[76] Carling, R.W.; Leeson, P.D.; Moore, K.W.; Moyes, C.R.; Duncton, M.; Hudson, M.L.; Baker, R.; Foster, A.C.; Grimwood, S.; Kemp, J.A.; Marshall, G.R.; Tricklebank, M.D.; Saywell, K.L. *J. Med. Chem*., **1997**, *40*, 754-765.

[77] Kreimeyer, A.; Laube, B.; Sturgess, M.; Goeldner, M.; Foucaud, B. Evaluation and biological properties of reactive ligands for the mapping of the glycine site on the *N*-methyl-D-aspartate (NMDA) receptor. *J. Med. Chem*., **1999**, *42*, 4394-4404.

[78] Wlaź, P.; Loscher, W. Weak anticonvulsant effects of two novel glycineB receptor antagonists in the amygdala-kindling model in rats. *Eur. J. Pharmacol*., **1998**, *342*, 39-46.

[79] Di Fabio, R.; Capelli, A.M.; Conti, N.; Cugola, A.; Donati, D.; Feriani, A.; Gastaldi, P.; Gavirighi, G.; Hewkin, C.T.; Micheli, F.; Missio, A.; Mugnaini, M.; Pecunioso, A.; Quaglia, A.M.; Ratti, E.; Rossi, L.; Tedesco, G.; Trist, D.G.; Reggiani, A. Substituted indole-2-carboxylates as *in vivo* potent antagonists acting as the strychnine-insensitive glycine binding site. *J. Med. Chem*., **1997**, *40*, 841-850.

[80] Hutson, P.H.; Barton, C.L. L-701,324, a glycine/NMDA receptor antagonist, blocks the increase of cortical dopamine metabolism by stress and DMCM. *Eur. J. Pharmacol*., **1997**, *326*, 127-132.

[81] Obrenovitch, T.P.; Zilkha, E. Inhibition of cortical spreading depression by L-701,324, a novel antagonist at the glycine site of the *N*-methyl-D-aspartate receptor complex. *Br. J. Pharmacol*., **1996**, *117*, 931-937.

[82] Haydon, P.G.; Halassa, M.M.; Fellin, T.; Ding, S.; Zhu, Y. Methods for treating neurological and psychiatric conditions, and test compound screening methods. *Chem. Abstr*., **2007**, *146*, 93591.

[83] Rowley, M.; Leeson, P.D.; Stevenson, G.I.; Moseley, A.M.; Stansfield, I.; Sanderson, I.; Robinson, L.; Baker, R.; Kemp, J.A.; Marshall, G.R.; Foster, A.C.; Grimwood, S.; Tricklebank, M.D.; Saywell, K.L. 3-Acyl-4-hydroxyquinolin-2(1*H*)-ones. Systemically active anticonvulsants acting by antagonism at the glycine site of the *N*-methyl-D-aspartate receptor complex. *J. Med. Chem.*, **1993**, *36*, 3386-3396.

[84] Kulagowski, J.J.; Baker, R.; Curtis, N.R.; Leeson, P.D.; Mawer, I.M.; Moseley, A.M.; Ridgill, M.P.; Rowley, M.; Stansfield, I.; Foster, A.C.; Grimwood, S.; Hill, R.G.; Kemp, J.A.; Marshall, G.R.; Saywell, K.L.; Tricklebank, M.D. 3'-(Arylmethyl)- and 3'-(aryloxy)-3-phenyl-4-hydroxyquinolin-2(1*H*)-ones: Orally active antagonists of the glycine site on the NMDA receptor. *J. Med. Chem*., **1994**, *17*, 1402-1405.

[85] Paeshuyse, J.; Vliegen, I.; Coelmont, L.; Leyssen, P.; Tabarrini, O.; Herdewijn, P.; Mittendorfer, H.; Easmon, J.; Cecchetti, V.; Bartenschlager, R.; Puerstinger, G.; Neyts, J. Comparative *in vitro* anti-hepatitis C virus activities of a selected series of polymerase, protease, and helicase inhibitors. *Antimicrob. Agents Chemother*., **2008**, *52*, 3433-3437.

[86] Barreca, M.L.; Manfroni, G.; Leyssen, P.; Winquist, J.; Kaushik-Basu, N.; Paeshuyse, J.; Krishnan, R.; Iraci, N.; Sabatini, S.; Tabarrini, O.; Basu, A.; Danielson, U.H.; Neyts, J.; Cecchetti, V. Structure-based discovery of pyrazolobenzothiazine derivatives as inhibitors of hepatitis C virus replication. *J. Med. Chem.*, **2013**, *56*, 2270-2282.

[87] de Vicente, J.; Hendricks, R.T.; Smith, D.B.; Fell, J.B.; Fischer, J.; Spencer, S.R.; Stengel, P.J.; Mohr, P.; Robinson, J.E.; Blake, J.F.; Hilgenkamp, R.K.; Yee, C.; Adjabeng, G.; Elworthy, T.R.; Tracy, J.; Chin, E.; Li, J.; Wang, B.; Bamberg, J.T.; Stephenson, R.; Oshiro, C.; Harris, S.F.; Ghate, M.; Leveque, V.; Najera, I.; Le Pogam, S.; Rajyaguru, S.; Ao-Ieong, G.; Alexandrova, L.; Larrabee, S.; Brandl, M.; Briggs, A.; Sukhtankar, S.; Farrell, R.; Xu, B. Non-nucleoside inhibitors of HCV polymerase NS5B. Part 2: Synthesis and structure–activity relationships of benzothiazine-substituted quinolinediones. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 3642-3646.

[88] Hendricks, R.T.; Fell, J.B.; Blake, J.F.; Fischer, J.P.; Robinson, J.E.; Spencer, S.R.; Stengel, P.J.; Bernacki, A.L.; Leveque, V.J.P.; Le Pogam, S.; Rajyaguru, S.; Najera, I.; Josey, J.A.; Harris, J.R.; Swallow, S. Non-nucleoside inhibitors of HCV NS5B polymerase. Part 1: Synthetic and computational exploration of the binding modes of benzothiadiazine and 1,4-benzothiazine HCV NS5b polymerase inhibitors. *Bioorg. Med. Chem. Lett*., **2009**, *19*, 3637-3641.

[89] Tedesco, R.; Chai, D.; Darcy, M.G.; Dhanak, D.; Fitch, D.M.; Gates, A.; Johnston, V.K.; Keenan, R.M.; Lin-Goerke, J.; Sarisky, R.T.; Shaw, A.N.; Valko, K.L.; Wiggall, K.J.; Zimmerman, M.N.; Duffy, K.J. Synthesis and biological activity of heteroaryl 3-(1,1-dioxo-2*H*-(1,2,4)-benzothiadizin-3-yl)-4-hydroxy-2(1*H*)-quinolinone derivatives as hepatitis C virus NS5B polymerase inhibitors. *Bioorg. Med. Chem. Lett*., **2009**, *19*, 4354-4358.

[90] Neamati, N.; Dayam, R.S. Compounds with HIV-1 integrase inhibitory activity and use thereof as anti-HIV/AIDS therapeutics. U.S. Pat. Appl. Publ. US 2009/0088420, Apr 2, 2009; *Chem. Abstr*., **2009**, *150*, 414208.

[91] Hurley, T.B.; Lee, K.; Peukert, S.; Wattanasin, S. Preparation of bicyclic heteroaryl amides as inhibitors of undecaprenyl pyrophosphate synthase. PCT Int. Appl. WO 2008/014307, Jan 31, 2008; *Chem. Abstr*., **2008**, *148*, 215033.

[92] Deng, J.; Sanchez, T.; Al-Mawsawi, L.Q.; Dayam, R.; Yunes, R.A.; Garofalo, A.; Bolger, M.B.; Neamati, N. Discovery of structurally diverse HIV-1 integrase inhibitors based on a chalcone pharmacophore. *Bioorg. Med. Chem*., **2007**, *15*, 4985-5002.

[93] Sechi, M.; Rizzi, G.; Bacchi, A.; Carcelli, M.; Rogolino, D.; Pala, N.; Sanchez, T.W.; Taheri, L.; Dayam, R.; Neamati, N. Design and synthesis of novel dihydroquinoline-3-carboxylic acids as HIV-1 integrase inhibitors. *Bioorg. Med. Chem*., **2009**, *17*, 2925-2935.

[94] Palomo, V.; Soteras, I.; Perez, D.I.; Perez, C.; Gil, C.; Campillo, N.E.; Martinez, A. Exploring the binding sites of glycogen synthase kinase 3. Identification and characterization of allosteric modulation cavities. *J. Med. Chem*., **2011**, *54*, 8461-8470.

[95] Martinez Gil, A.; Gil Ayuso-Gontan, C.; Palomo Ruiz, V.; Perez Martin, C.; Perez Fernandez, D.I.; Reyes Rodriguez, J.A. Preparation of heterocyclic derivatives, especially substituted quinolines, as glycogen synthase kinase 3 (GSK-3) allosteric modulators for treating neurodegenerative and inflammatory diseases, cancer, diabetes and for promoting regenerative processes. PCT Int. Appl. WO 2013/045736, Apr 4, 2013; *Chem. Abstr*., **2013**, *158*, 534730.

[96] Morales-Garcia, J.A.; Palomo, V.; Redondo, M.; Alonso-Gil, S.; Gil, C.; Martinez, A.; Perez-Castillo, A. Crosstalk between phosphodiesterase 7 and glycogen synthase kinase-3: Two relevant therapeutic targets for neurological disorders. *ACS Chem. Neurosci*., **2014**, *5*, 194-204.

[97] Martinez, G.A.; Gil Ayuso-Gontan, C.; Palomo Ruiz, V.; Perez Martin, C.; Perez Fernandez, D. I Heterocyclic GSK-3 allosteric modulators. Span. ES 2402503, May 13, 2013; *Chem. Abstr*., **2013**, *158*, 590108.

[98] Morales-Garcia, J.A.; Susin, C.; Alonso-Gil, S.; Perez, D.I.; Palomo, V.; Perez, C.; Conde, S.; Santos, A.; Gil, C.; Martinez, A.; Perez-Castillo, A. Glycogen synthase kinase-3 inhibitors as potent therapeutic agents for the treatment of parkinson disease. *ACS Chem. Neurosci*., **2013**, *4*, 350-360.

[99] Salado, I.G.; Redondo, M.; Bello, M.L.; Perez, C.; Liachko, N.F.; Kraemer, B.C.; Miguel, L.; Lecourtois, M.; Gil, C.; Martinez, A.; Perez, D.I. Protein kinase CK-1 inhibitors as new potential drugs for amyotrophic lateral sclerosis. *J. Med. Chem*., **2014**, *57*, 2755-2772.

[100] Sebastian, V.; Manoli, M.T.; Perez, D.I.; Gil, C.; Mellado, E.; Martinez, A.; Espeso, E.A.; Campillo, N.E. New applications for known drugs: Human glycogen synthase kinase 3 inhibitors as modulators of *Aspergillus fumigatus* growth. *Eur. J. Med. Chem*., **2016**, *116*, 281-289.

[101] Tomassoli, I.; Ismaili, L.; Pudlo, M.; de los Ríos, C.; Soriano, E.; Colmena, I.; Gandía, L.; Rivas, L.; Samadi, A.; Marco-Contelles, J.; Refouvelet, B. Synthesis, biological assessment and molecular modeling of new dihydroquinoline-3-carboxamides and dihydroquinoline-3-carbohydrazide derivatives as cholinesterase inhibitors, and Ca channel antagonists. *Eur. J. Med. Chem*., **2011**, *46*, 1-10.

[102] Tedesco, R.; Shaw, A.N.; Bambal, R.; Chai, D.; Concha, N.O.; Darcy, M.G.; Dhanak, D.; Fitch, D.M.; Gates, A.; Gerhardt, W.G.; Halegoua, D.L.; Han, C.; Hofmann, G.A.; Johnston, V.K.; Kaura, A.C.; Liu, N.; Keenan, R.M.; Lin-Goerke, J.; Sarisky, R.T.; Wiggall, K.J.; Zimmerman, M.N.; Duffy, K.J. 3-(1,1-Dioxo-2*H*-(1,2,4)-benzothiadiazin-3-yl)-4-hydroxy-2(1*H*)-quinolinones, potent inhibitors of hepatitis C virus RNA-dependent RNA polymerase. *J. Med. Chem*., **2006**, *49*, 971-983.

[103] Xiao, Z.Y.; Zhou, W.X.; Zhang, Y.X.; Cheng, J.P.; He, J.F.; Yang, R.F.; Yun, L.H. Roquinimex-mediated protection effect on the development of chronic graft-versus-host disease in mice is associated with induction of Th1 cytokine production and inhibition of proinflammatory cytokine production. *Life Sci*., **2007**, *81*, 1403-1410.

[104] Li, X.; Klintman, D.; Sato, T.; Hedlund, G.; Schramm, R.; Jeppsson, B.; Thorlacius, H. Interleukin-10 mediates the protective effect of linomide by reducing CXC chemokine production in endotoxin-induced liver injury. *Br. J. Pharmacol*., **2004**, *143*, 865-871.

[105] Bjork, A.; Jonsson, S.; Fex, T.; Hedlund, G. Quinoline derivatives. PCT Int. Appl. WO 2000/003991, Jan 27, 2000; *Chem. Abstr*., **2000**, *132*, 93219.

[106] Shi, J.; Xiao, Z.; Ihnat, M.A.; Kamat, C.; Pandit, B.; Hu, Z.; Li, P.K. Structure–activity relationships studies of the anti-angiogenic activities of linomide. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 1187-1189.

[107] Amerini, S.; Filippi, S.; Parenti, A.; Ledda, F.; Ziche, M. Vasorelaxant effects induced by the antiangiogenic drug linomide in aortic and saphenous vein preparations of the rabbit. *Br. J. Pharmacol*., **1997**, *122*, 1739-1745.

[108] Knappertz, V.; Kaye, J. Laquinimod combination therapy for treatment of multiple sclerosis. U.S. Pat. Appl. Publ. US 2015/0094332, Apr 2, 2015; *Chem. Abstr*., **2015**, *162*, 485042.

[109] Kaye, J; Tarcic, N. Treatment of multiple sclerosis with combination of laquinimod and fampridine. PCT Int. Appl. WO 2014/011827, Jan 16, 2014; *Chem. Abstr*., **2014**, *160*, 201497.

[110] Hallak, H.; Tarcic, N.; Flaxman Kaye, J. Treatment of multiple sclerosis with combination of laquinimod and fingolimod. PCT Int. Appl. WO 2013/055907, Apr 18, 2013; *Chem. Abstr*., **2013**, *158*, 553698.

[111] Joensson, S.; Andersson, G.; Fex, T.; Fristedt, T.; Hedlund, G.; Jansson, K.; Abramo, L.; Fritzson, I.; Pekarski, O.; Runstroem, A.; Sandin, H.; Thuvesson, I.; Bjoerk, A. Synthesis and biological evaluation of new 1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxamides for treatment of autoimmune disorders: Structure–activity relationship. *J. Med. Chem*., **2004**, *47*, 2075-2088.

[112] State Register of Medicinal Products. Registration certificate Nr ЛП-002125. [Online]; http://grls.rosminzdrav.ru/Grls_View_v2.aspx?idReg=64645&t= (accessed August 8, 2016).

[113] Pasquini, S.; De Rosa, M.; Pedani, V.; Mugnaini, C.; Guida, F.; Luongo, L.; De Chiaro, M.; Maione, S.; Dragoni, S.; Frosini, M.; Ligresti, A.; Di Marzo, V.; Corelli, F. Investigations on the 4-quinolone-3-carboxylic acid motif. 4. Identification of new potent and selective ligands for the cannabinoid type 2

receptor with diverse substitution patterns and antihyperalgesic effects in mice. *J. Med. Chem*., **2011**, *54*, 5444-5453.

[114] Mugnaini, C.; Brizzi, A.; Ligresti, A.; Allara, M.; Lamponi, S.; Vacondio, F.; Silva, C.; Mor, M.; Di Marzo, V.; Corelli, F. Investigations on the 4-quinolone-3-carboxylic acid motif. 7. Synthesis and pharmacological evaluation of 4-quinolone-3-carboxamides and 4-hydroxy-2-quinolone-3-carboxamides as high affinity cannabinoid receptor 2 (CB2R) ligands with improved aqueous solubility. *J. Med. Chem*., **2016**, *59*, 1052-1067.

[115] Ukrainets, I.V.; Mospanova, O.V.; Bereznyakova, N.L.; Davidenko, O.O. Polymorphism and the analgesic activity of *N*-(3-pyridylmethyl)-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamide. *Zh. Org. Farm. Khim*., **2015**, *13*, 41-46.

[116] Ukrainets, I.V.; Mospanova, E.V.; Davidenko, A.A. Using bioisosteric replacements to enhance the analgesic properties of 4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxamides. *Khim.-Farm. Zh*., **2016**, *50*(6), 15-18; *Pharm. Chem. J*., **2016**, *50*, 365-368.

[117] Ukrainets, I.V.; Taran, E.A.; Andreeva, K.V. Synthesis, hydrolysis, and analgesic activity of 3-[3-(1-arylethylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl]propanenitriles and their derivatives. *Khim.-Farm. Zh*., **2016**, *50*(7), 9-13; *Pharm. Chem. J*., **2016**, *50*, 431-435.

[118] Faust, A.; Voeller, T.; Busch, F.; Schaefers, M.; Roth, J.; Hermann, S.; Vogl, T. Development and evaluation of a non-peptidic ligand for the molecular imaging of inflammatory processes using S100A9 (MRP14) as a novel target. *Chem. Commun. (Cambridge, U. K.)*, **2015**, *51*, 15637-15640.

[119] Chai, D.; Colon, M.; Duffy, K.J.; Fitch, D.M.; Tedesco, R.; Zimmerman, M.N. Prolyl hydrolase antagonists. PCT Int. Appl. WO 2007/38571, Apr 05, 2007.

[120] Ruat, M.; Faure, H.; Gorojankina, T.; Mann, A.; Taddei, M.; Manetti, F.; Solinas, A. Quinolinone derivatives. Fr. Demande FR 2967353, May 18, 2012.

[121] Hiltensperger, G.; Hecht, N.; Kaiser, M.; Rybak, J.C.; Hoerst, A.; Dannenbauer, N.; Mueller-Buschbaum, K.; Bruhn, H.; Esch, H.; Lehmann, L.; Meinel, L.; Holzgrabe, U. Quinolone amides as antitrypanosomal lead compounds with *in vivo* activity. *Antimicrob. Agents Chemother*., **2016**, *60*, 4442-4452.

[122] Banu, S.; Bollu, R.; Bantu, R.; Nagarapu, L.; Polepalli, S.; Jain, N.; Vangala, R.; Manga, V. Design, synthesis and docking studies of novel 1,2-dihydro-4-hydroxy-2-oxoquinoline-3-carboxamide derivatives as a potential anti-proliferative agents. *Eur. J. Med. Chem*., **2017**, *125*, 400-410.

[123] Goulet, M.; Allen, E.E.; Jiang, J.; Smith, R.G.; Walsh, T.F.; Wyvratt, M.J.; Yang, Y.T.; Young, J.R.; Devita, R.J. Antagonists of gonadotropin releasing hormone. PCT Int. Appl. WO 97/44321, Nov 27, 1997; *Chem. Abstr*., **1998**, *128*, 48149.

[124] Goulet, M.; Allen, E.E.; Devita, R.J.; Jiang, J.; Walsh, T.F.; Young, J.R.; Wyvratt, M.J.; Toupence, R.B.; Ujjainwalla, F. Antagonists of gonadotropin releasing hormone. PCT Int. Appl. WO 97/44339, Nov 27, 1997; *Chem. Abstr*., **1997**, *128*, 48236.

[125] Young, J.R.; Huang, S.X.; Chen, I.; Walsh, T.F.; DeVita, R.J.; Wyvratt, M.J.; Goulet, M.T.; Ren, N.; Lo, J.; Yang, Y.T.; Yudkovitz, J.B.; Cheng, K.; Smith, R.G. Quinolones as gonadotropin releasing hormone (GnRH) antagonists: Simultaneous optimization of the C(3)-aryl and C(6)-substituents. *Bioorg. Med. Chem. Lett*., **2000**, *10*, 1723-1727.

[126] Jiang, J.; DeVita, R.J.; Goulet, M.T.; Wyvratt, M.J.; Lo, J.L.; Ren, N.; Yudkovitz, J.B.; Cui, J.; Yang, Y.T.; Cheng, K.; Rohrer, S.P. Syntheses and structure–activity relationship studies of piperidine-substituted quinolones as nonpeptide gonadotropin releasing hormone antagonists. *Bioorg. Med. Chem. Lett*., **2004**, *14*, 1795-1798.

[127] Janovick, J.A.; Goulet, M.; Bush, E.; Greer, J.; Wettlaufer, D.G.; Conn, P.M. Structure-activity relations of successful pharmacologic chaperones for rescue of naturally occurring and manufactured mutants of the gonadotropin-releasing hormone receptor. *J. Pharmacol. Exp. Ther*., **2003**, *305*, 608-614.

[128] Conn, P.M. Pharmacoperones for correcting disease states involving protein misfolding. U.S. Pat. Appl. Publ. US 2005/0203019, Sep 15, 2005; *Chem. Abstr*., **2005**, *143*, 299142.

[129] Heitman, L.H.; Ijzerman, A.P. G protein-coupled receptors of the hypothalamic-pituitary-gonadal axis: A case for gnrh, LH, FSH, and GPR54 receptor ligands. *Med. Res. Rev*., **2008**, *28*, 975-1011.

[130] Janovick, J.A.; Patny, A.; Mosley, R.; Goulet, M.T.; Altman, M.D.; Rush, T.S.; Cornea, A.; Conn, P.M. Molecular mechanism of action of pharmacoperone rescue of misrouted GPCR mutants: The GnRH receptor. *Mol. Endocrinol*., **2009**, *23*, 157-168.

[131] Conn, P.M. Restoring function to gonadotropin releasing hormone receptor mutants. PCT Int. Appl. WO 2004/069859, Aug 19, 2004; *Chem. Abstr*., **2004**, *141*, 185589.

[132] Janovick, J.A.; Brothers, S.P.; Cornea, A.; Bush, E.; Goulet, M.T.; Ashton, W.T.; Sauer, D.R.; Haviv, F.; Greer, J.; Conn, P.M. Refolding of misfolded mutant GPCR: Post-translational pharmacoperone action *in vitro*. *Mol. Cell. Endocrinol. Mol. Cell. Endocrinol*., **2007**, *272*, 77-85.

[133] O'Brien, D.A.; Eddy, E.M. Glyceraldehyde 3-phosphate dehydrogenase-S (GAPDHS), a glycolytic anzyme expressed only in male germ cells, is a target for male contraception. U.S. Pat. Appl. Publ. US 2005/0266515, Dec 1, 2005; *Chem. Abstr*., **2006**, *144*, 17596.

[134] Ukrainets, I.V.; Solobodzyan, S.V.; Krivobok, V.I.; Bezuglyi, P.A.; Triskach, V.I.; Turov, A.V.; Gladchenko, S.V.; Obolentseva, G.V. New local anesthetics derived from 2-oxo-4-hydroxyquinoline-3-carboxylic acid. *Farm. Zh. (Kiev, Ukr.)*, **1991**, (2), 78-80.

[135] Ukrainets, I.V.; Gorokhova, O.V.; Taran, S.G.; Bezugly, P.A.; Filimonova, N.I.; Turov, A.V. 4-Hydroxy-2-quinolones. 24. Improved synthesis and biological properties of hydrochlorides of β-dialkylaminoalkylamides of 1-alkyl-2-oxo-4-hydroxyquinoline-3-carboxylic acids. *Khim. Geterotsikl. Soedin*., **1994**, 1400-1405; *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, **1994**, *30*, 1214-1219.

[136] Ukrainets, I. Creation of New Local Anesthetics Based on Quinoline Derivatives and Related Heterocycles. In: *Pain Management - Current Issues and Opinions*; Racz, G.B.; Noe, C.E., Eds.; InTech: Rijeka, **2012**, pp. 63-81. http://www.intechopen.com/books/pain-management-current-issues-and-opinions/creation-of-new-local-anesthetics-based-on-quinoline-derivatives-and-related-heterocycles

[137] Ukrayinecz, I.V.; Bezuhliy, P.A. Injectable anesthetic containing chinoxicaine. U.S. Patent 6,340,692, Jan 22, 2002; *Chem. Abstr*., **2002**, *136*, 123651.

[138] Pudlo, M.; Luzet, V.; Ismaili, L.; Tomassoli, I.; Iutzeler, A.; Refouvelet, B. Quinolone-benzylpiperidine derivatives as novel acetylcholinesterase inhibitors and antioxidant hybrids for Alzheimer Disease. *Bioorg. Med. Chem*., **2014**, *22*, 2496-2507.

[139] Takagaki, H.; Aoki, Y.; Ishiwara, M.; Mizutani, N. Therapeutic agent for chronic obstructive pulmonary disease and method of treatment for chronic obstructive pulmonary disease with the same. PCT Int. Appl. WO 2005/012251, Feb 10 2005; *Chem. Abstr*., **2005**, *142*, 191276.

[140] Takagaki, H.; Abe, M.; Sakai, M.; Aoki, Y.; Nakanishi, S.; Kimura, N.; Koda, A. Quinolinone derivative and antiallergic agent with said quinolinone derivative as the active ingredient. Eur. Pat. Appl. EP 785190, Jul 23, 1997; *Chem. Abstr*., **1997**, *127*, 176353.

[141] Kieffer, C.; Cohen, A.; Verhaeghe, P.; Hutter, S.; Castera-Ducros, C.; Laget, M.; Remusat, V.; M'Rabet, M.K.; Rault, S.; Rathelot, P.; Azas, N.; Vanelle, P. Looking for new antileishmanial derivatives in 8-nitroquinolin-2(1*H*)-one series. *Eur. J. Med. Chem*., **2015**, *92*, 282-294.

[142] Frazier, K.; Jazan, E.; McBride, C.M.; Pecchi, S.; Renhowe, P.A.; Shafer, C.M.; Taylor, C.; Bussiere, D.; He, M.M.; Jansen, J.M.; Lapointe, G.; Ma, S.; Vora, J.; Wiesmann, M. Design and structure–activity relationship of heterocyclic analogs of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones as inhibitors of receptor tyrosine kinases. *Bioorg. Med. Chem. Lett*., **2006**, *16*, 2247-2251.

[143] Ni, Z.J.; Barsanti, P.; Brammeier, N.; Diebes, A.; Poon, D.J.; Ng, S.; Pecchi, S.; Pfister, K.; Renhowe, P.A.; Ramurthy, S.; Wagman, A.S.; Bussiere, D.E.; Le, V.; Zhou, Y.; Jansen, J.M.; Ma, S.; Gesner, T.G. 4-(Aminoalkylamino)-3-benzimidazole-quinolinones as potent CHK-1 inhibitors. *Bioorg. Med. Chem. Lett*., **2006**, *16*, 3121-3124.

[144] Renhowe, P.A.; Pecchi, S.; Shafer, C.M.; Machajewski, T.D.; Jazan, E.M.; Taylor, C.; Antonios-McCrea, W.; McBride, C.M.; Frazier, K.; Wiesmann, M.; Lapointe, G.R.; Feucht, P.H.; Warne, R.L.; Heise, C.C.; Menezes, D.; Aardalen, K.; Ye, H.; He, M.; Le, V.; Vora, J.; Jansen, J.M.; Wernette-Hammond, M.E.; Harris, A. Design, structure–activity relationships and *in vivo* characterization of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones: A novel class of receptor tyrosine kinase inhibitors. *J. Med. Chem*., **2009**, *52*, 278-292.

[145] Ukrainets, I.V.; Taran, S.G.; Gorokhova, O.V.; Marusenko, N.A.; Turov, A.V. 4-Hydroxy-2-quinolinones. 32. Synthesis and antithyroid activity of thio analogs of 3-benzimidazol-2-yl-4-hydroxy-2(1*H*)-quinolinone. *Khim. Geterotsikl. Soedin*., **1997**, 692-696; *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, **1997**, *33*, 600-604.

[146] Bezuglyi, P.A.; Ukrainets, I.V.; Treskach, V.I.; Turov, A.V.; Gladchenko, S.V.; Krylov, Yu.F.; Moryakov, N.P.; Aleksandrova, G.M. Biological properties of 2,4-dioxo-3*H*-quinoline-3-carboxylic acid and its ethyl ester. *Khim.-Farm. Zh*., **1992**, *26*(2), 33-35; *Pharm. Chem. J*., **1992**, *26*, 138-141.

[147] Ukrainets, I.V.; Gorokhova, O.V.; Taran, S.G.; Bezugly, P.A.; Turov, A.V.; Marusenko, N.A.; Evtifeeva, O.A. 4-Hydroxy-2-quinolinones. 22. Synthesis and biological properties of 1-alkyl(aryl)-2-oxo-3-carbethoxy-4-hydroxyquinolines and their derivatives. *Khim. Geterotsikl. Soedin*., **1994**, (7), 958-966; *Chem. Heterocycl. Compd*., **1994**, *30*, 829-836.

[148] Von Deyn, W.; Nuebling, C.; Kardorff, U.; Walter, H.; Westphalen, K.O.; Kappe, T.; Gerber, M. Chinolin-3-carbonsaeureamide, deren Herstellung und Verwendung. Ger. Offen. DE 41 38 820, May 5, 1993; *Chem. Abstr*., **1993**, *119*, 160140.

[149] Ferrini, P.G.; Haas, G.; Rossi, A. Quinoline-3-carboxylic acid derivs - with *e.g.* analgesic, antinociceptive, antiinflammatory and antiallergic props. Patentschrift (Switzerland) CH 578537, Aug 13, 1976; *Chem. Abstr*., **1977**, *86*, 29657.

[150] Ferrini, P.G.; Haas, G.; Rossi, A. Quinoline-3-carboxylic acid derivs - with *e.g.* analgesic, antinociceptive, antiinflammatory and antiallergic props. Patentschrift (Switzerland) CH 578536, Aug 13, 1976; *Chem. Abstr*., **1977**, *86*, 29659.

[151] Grimwood, S.; Gilbert, E.; Ragan, C.I.; Hutson, P.H. Modulation of 45Ca^{2+} influx into cells stably expressing recombinant human NMDA receptors by ligands acting at distinct recognition sites. *J. Neurochem*., **1996**, *66*, 2589-2595.

[152] Grimwood, S.; Le Bourdelles, B.; Atack, J.R.; Barton, C.; Cockett, W.; Cook, S.M.; Gilbert, E.; Hutson, P.H.; McKernan, R.M.; Myers, J.; Ragan, C.I.; Wingrove, P.B.; Whiting, P.J. Generation and characterization of stable cell lines expressing recombinant human *N*-methyl-D-aspartate receptor subtypes. *J. Neurochem*., **1996**, *66*, 2239-2247.

[153] Priestley, T.; Laughton, P.; Macaulay, A.J.; Hill, R.G.; Kemp, J.A. Electrophysiological characterization of the antagonist properties of two novel NMDA receptor glycine site antagonists, L-695,902 and L-701,324. *Neuropharmacology*, **1996**, *35*, 1573-1581.

[154] Molnar, P.; Erdo, S.L. Differential effects of five glycine site antagonists on NMDA receptor desensitization. *Eur. J. Pharmacol*., **1966**, *311*, 311-314.

[155] Wollenweber, H.W.; Maurer, K.H. Catalase inhibitors used to stabilise hydrogen peroxide - in industrial recycle waters, esp. in the paper industry. Ger. Offen. DE 19529444, Feb 13, 1997; *Chem. Abstr*., **1997**, *126*, 216409.

[156] Olesen, J.; Bendtsen, L.; Jensen, R.; Madsen, U. A method for treating tension-type headache. PCT Int. Appl. WO 98/19674, May 14, 1998; *Chem. Abstr*., **1998**, *129*, 23447.

[157] Hicks, C.A.; Ward, M.A.; Ragumoorthy, N.; Ambler, S.J.; Dell, C.P.; Dobson, D.; O'Neill, M.J. Evaluation of glycine site antagonists of the NMDA receptor in global cerebral ischemia. *Brain Res*., **1999**, *819*, 65-74.

[158] O'Neill, M.J. Method of treatment neurological disorders. PCT Int. Appl. WO 2000/061126, Oct 19, 2000; *Chem. Abstr*., **2000**, *133*, 305610.

[159] Angibaud, P.R.; Venet, M.G. Farnesyl transferase inhibiting 4-substituted quinoline and quinazoline derivatives. PCT Int. Appl. WO 02/051835, Jul 04, 2002; *Chem. Abstr*., **2002**, *137*, 78964.

[160] Patankar, S.J.; Jurs, P.C. Prediction of glycine/NMDA receptor antagonist inhibition from molecular structure. *J. Chem. Inf. Model*., **2002**, *42*, 1053-1068.

[161] Jung, J.C.; Oh, S.; Kim, W.K.; Park, W.K.; Kong, J.Y.; Park, O.S. Synthesis and biological properties of 4-substituted quinolin-2(1*H*)-one analogues. *J. Heterocycl. Chem*., **2003**, *40*, 617-623.

[162] Sapre, N.S.; Pancholi, N.; Gupta, S.; Sikarwar, A. 2-Dimensional quantitative structure-activity relationship modeling study of glycine/*N*-methyl-D-aspartate antagonist inhibition: Genetic function approximation vis-a-vis multiple linear regression methods. *Acta Chim. Slov*., **2007**, *54*, 797-804.

[163] Tachdjian, C.; Karanewsky, D.S.; Tang, X.Q.; Li, X.; Zhang, F.; Servant, G.; Chen, Q.; Darmohusodo, V.; Fine, R.; Fotsing, J.R.; Hammaker, J.R.; Kang, X.; Kimmich, R.D.A.; Klebansky, B.; Liu, H.; Petrovic, G.; Rinnova, M.; Adamski-Werner, S.; Yamamoto, J.; Zhang, H.; Zlotnik, A.; Zoller, M. Modulation of chemosensory receptors and ligands associated therewith. PCT Int. Appl. WO 2008/154221, Dec 18, 2008; *Chem. Abstr*., **2008**, *150*, 56216.

[164] Tschollar, W.; Lanser, M.E. Conjugates of glutamate and NMDA receptor channel blockers without excito-toxic effects. Eur. Pat. Appl. EP 1903028, Mar 26, 2008; *Chem. Abstr*., **2008**, *148*, 394414.

[165] Abeliovich, A. Methods for the treatment of neurodegenerative diseases using NMDA receptor glycine site antagonists. U.S. Pat. Appl. Publ. US 2009/0004112, Jan 01, 2009; *Chem. Abstr*., **2009**, *150*, 90561.

[166] Tachdjian, C.; Karanewsky, D.S.; Tang, X.Q.; Li, X.; Zhang, F.; Servant, G.; Chen, Q.; Darmohusodo, V.; Fine, R.; Fotsing, J.R.; Hammaker, J.R.; Kang, X.; Kimmich, R.D.A.; Klebansky, B.; Liu, H.; Petrovic, G.; Rinnova, M.; Adamski-Werner, S.; Yamamoto, J.; Zhang, H.; Zlotnik, A.; Zoller, M.; Zoller, K. Modulation of chemosensory receptors and ligands associated therewith. U.S. Pat. Appl. Publ. US 2011/0224155, Sep 15, 2011; *Chem. Abstr*., **2011**, *155*, 431895.

[167] Daugan, A.C.M.; Lamotte, Y.; Mirguet, O. Quinoline derivatives. PCT Int. Appl. WO 2012/119978, Sep 13, 2012; *Chem. Abstr*., **2012**, *157*, 465417.

[168] Sharma, M.; Gupta, V.B. Dual allosteric effect in glycine/NMDA receptor antagonism: A molecular docking simulation approach. *Int. J. Drug Des. Discovery*, **2012**, *3*, 718-730.

[169] Moskal, J.R. Combinations of NMDAR modulating compounds. PCT Int. Appl. WO 2015/171770, Nov 12, 2015; *Chem. Abstr*., **2015**, *163*, 681574.

[170] Carling, R.W.; Leeson, P.D.; Moore, K.W.; Smith, J.D.; Moyes, C.R.; Mawer, I.M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A.C.; Grimwood, S.; Kemp, J.A.; Marshall, G.R.; Tricklebank, M.D.; Saywell K.L. 3-Nitro-3,4-dihydro-2(1*H*)-quinolones. Excitatory amino acid antagonists acting at glycine-site NMDA and (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. *J. Med. Chem*., **1993**, *36*, 3397-3408.

[171] Joshi, K.A.; Patil, D.D.; Gejji, S.P. Electronic structure, charge distribution and vibrational characteristics of glycine/NMDA receptor antagonists. *J. Mol. Struct*., **2007**, *813*, 9-19.

[172] El-Agamey, A.G.A.; Abo Attaia, A.A. Synthesis and study of antimicrobial agents of newly 6-nitro-4-hydroxy-2-quinolone derivatives. *Arch. Appl. Sci. Res*., **2012**, *4*, 1339-1344.

[173] Arya, K.; Agarwal, M. Microwave prompted multigram synthesis, structural determination, and photo-antiproliferative activity of fluorinated 4-hydroxyquinolinones. *Bioorg. Med. Chem. Lett*., **2007**, *17*, 86-93.

[174] Giencke, W.; Bieringer, H.; Rosinger, C.; Kappe, T. 3-(5-Tetrazolylcarbonyl)-2-chinolone und diese enthaltende nutzpflanzenschützende Mittel. Ger. Offen. DE 19727410, Jan 07, 1999; *Chem. Abstr*., **1999**, *130*, 91667.

[175] Pallett, K.; Slater, A. New herbicidal compositions. PCT Int. Appl. WO 01/17350, Mar 15, 2001; *Chem. Abstr*., **2001**, *134*, 218316.

[176] Glock, J. Herbicidal compositions. PCT Int. Appl. WO 2001/017353, Mar 15, 2001; *Chem. Abstr*., **2001**, *134*, 218318.

[177] Haas, U. Herbicidal composition. Eur. Pat. Appl. EP 1 388 285, Feb 11, 2004; *Chem. Abstr*., **2004**, *140*, 159049.

[178] Koehn, A.; Van Almsick, A.; Ahrens, H.; Ziemer, F.; Doerner-Rieping, S.; Rosinger, C.H.; Hacker, E. Herbicide safener compositions. PCT Int. Appl. WO 2012/123420, Sep 20, 2012; *Chem. Abstr*., **2012**, *157*, 512455.

[179] Nesmelova, E.F.; Bessonova, I.A.; Yunusov, S.Y. Buchapine, a new alkaloid from *Haplophyllum bucharicum*. *Khim. Prir. Soedin*., **1982**, 532-533; *Chem. Nat. Compd*., **1982**, *18*, 508-509.

[180] Sheriha, G.M.; Abouamer, K.; Elshtaiwi, B.Z.; Ashour, A.S.; Abed, F.A.; Alhallaq, H.H. Quinoline alkaloids and cytotoxic lignans from *Haplophyllum tuberculatum*. *Phytochemistry*, **1987**, *26*, 3339-3341.

[181] McCormick, J.L.; McKee, T.C.; Cardellina, J.H.; Boyd, M.R. HIV-Inhibitory natural products. 26. Quinoline alkaloids from *Euodia roxburghiana*. *J. Nat. Prod*., **1996**, *59*, 469-471.

[182] Ahmed, N.; Brahmbhatt, K.G.; Sabde, S.; Mitra, D.; Singh, I.P.; Bhutani, K.K. Synthesis and anti-HIV activity of alkylated quinoline 2,4-diols. *Bioorg. Med. Chem*., **2010**, *18*, 2872-2879.

[183] Vishnu, K.; Sharma, U.; Mahatma, R. A review on: AIDS and herbal remedies. *Int. J. Res. Ayurveda Pharm*., **2011**, *2*, 1709-1713.

[184] Hadaruga, D.I. Natural and synthetic HIV-1 non-nucleoside reverse transcriptase inhibitors: A theoretical approach. *J. Agroaliment. Processes Technol*., **2011**, *17*, 360-370.

[185] Dreyer, David L. Chemotaxonomy of the Rutaceae. Part XIV. Alkaloids, limonoids, and furocoumarins from three Mexican *Esenbeckia* species. *Phytochemistry*, **1980**, *19*, 941-944.

[186] Barros-Filho, B.A.; Nunes, F.M.; de Oliveira, M.C.F.; Mafezoli, J.; Andrade-Neto, M.; Silveira, E.R.; Pirani, J.R. Volatile constituents from *Esenbeckia almawillia* (Rutaceae). *Biochem. Syst. Ecol*., **2004**, *32*, 817-821.

[187] Nunes, F.M.; Barros-Filho, B.A.; de Oliveira, M.C.F.; Mafezoli, J.; Andrade-Neto, M.; de Mattos, M.C.; Silveira, E.R.; Pirani, J.R. Total assignment of ^{1}H and ^{13}C NMR spectra of the alkaloid 3,3-diisopentenyl-*N*-methyl-2,4-quinoldione and novel reaction derivatives. *Magn. Reson. Chem*., **2005**, *43*, 180-183.

[188] Wu, T.S.; Leu, Y.L.; Chan, Y.Y.; Lin, F.W.; Li, C.Y.; Shi, L.S.; Kuo, S.C.; Chen, C.F.; Wu, Y.C. Severibuxine, a new quinoline-2,4-dione and other constituents from *Severinia buxifolia*. *Phytochemistry*, **1998**, *49*, 1467-1470.

[189] Neuenhaus, W.; Budzikiewicz, H.; Korth, H.; Pulverer, G. Bacterial constituents, III. 3-Alkyl-tetrahydroquinoline derivatives from *Pseudomonas*. *Z. Naturforsch., B: Anorg. Chem., Org. Chem*., **1979**, *34*, 313-315.

[190] Yang, S.S.; Cragg, G.M.; Newman, D.J.; Bader, J.P. Natural product-based anti-HIV drug discovery and development facilitated by the NCI developmental therapeutics program. *J. Nat. Prod.*, **2001**, *64*, 265-277.

[191] Daruwala, A.B.; Gearien, J.E.; Dunn, W.J., III; Benoit, P.S.; Bauer, L. β-Amino ketones. Synthesis and some biological activities in mice of 3,3-dialkyl-1,2,3,4-tetrahydro-4-quinolinones and related Mannich bases. *J. Med. Chem.*, **1974**, *17*, 819-824.

[192] Seong, C.M.; Park, W.K.; Park, C.M.; Kong, J.Y.; Park, N.S. Discovery of 3-aryl-3-methyl-1*H*-quinoline-2,4-diones as a new class of selective 5-HT6 receptor antagonists. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 738-743.

[193] Glennon, R.A.; Siripurapu, U.; Roth, B.L.; Kolanos, R.; Bondarev, M.L.; Sikazwe, D.; Lee, M.; Dukat, M. The medicinal chemistry of 5-HT6 receptor ligands with a focus on arylsulfonyltryptamine analogs. *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)*, **2010**, *10*, 579-595.

[194] Benhamu, B.; Martin-Fontecha, M.; Vazquez-Villa, H.; Pardo, L.; Lopez-Rodriguez, M.L. Serotonin 5-HT6 Receptor antagonists for the treatment of cognitive deficiency in Alzheimer's disease. *J. Med. Chem.*, **2014**, *57*, 7160-7181.

[195] Seong, C.; Park, N.; Jung, Y.; Choi, J.; Park, W.; Cho, H.; Kong, J.; Jung, D.; Kang, S.; Song, S.; Kwark, K. 3-Aryl-3-methylquinoline-2,4-diones, preparation method thereof, and pharmaceutical composition containing the same. U.S. Pat. Appl. Publ. US 2006/0084676, Apr 20, 2006; *Chem. Abstr.*, **2006**, *144*, 412383.

[196] Jadhav, S.A.; Sarkate, A.P.; Raut, A.V.; Shinde, D.B. ZrO2 nanoparticle catalyzed multi-component synthesis of 3-benzylidene-1-phenylquinoline-2,4(1*H*,3*H*)-diones and their antimicrobial activity. *Res. Chem. Intermed.*, **2017**, DOI: 10.1007/s11164-017-2894-7.

[197] Fedoryak, S.D.; Prisyazhnyuk, P.V.; Sidorchuk, I.I. Synthesis and biological activity of isonicotinoylhydrazones of certain di- and tricarbonyl compounds. *Khim.-Farm. Zh.*, **1982**, *16*(1), 48-50; *Pharm. Chem. J.*, **1982**, *16*, 37-40.

[198] Manvar, A.; Khedkar, V.; Patel, J.; Vora, V.; Dodia, N.; Patel, G.; Coutinho, E.; Shah, A. Synthesis and binary QSAR study of antitubercular quinolylhydrazides. *Bioorg. Med. Chem. Lett.*, **2013**, *23*, 4896-4902.

[199] Malle, E.; Stadlbauer, W.; Ostermann, G.; Hofmann, B.; Leis, H.J.; Kostner, G.M. Organic azides in heterocyclic synthesis. Part 10. Synthesis of new 2-, 3-, and 4-substituted azidoquinolines: Inhibitors of human blood platelet aggregation *in vitro*. *Eur. J. Med. Chem.*, **1990**, *25*, 137-142.

[200] Iwamura, H.; Suzuki, H.; Ueda, Y.; Kaya, T.; Inaba, T. *In vitro* and *in vivo* pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB2 receptor. *J. Pharmacol. Exp. Ther.*, **2001**, *296*, 420-425.

[201] Han, S.; Zhang, F.F.; Qian, H.Y.; Chen, L.L.; Pu, J.B.; Xie, X.; Chen, J.Z. Development of quinoline-2,4(1*H*,3*H*)-diones as potent and selective ligands of the cannabinoid type 2 receptor. *J. Med. Chem.*, **2015**, *58*, 5751-5769.

[202] Hardtmann, G.E. Pharmaceutical preparation and use of 4-hydroxy-2-quinolinone-3-carboxylic acid esters. U.S. Patent 4,190,659, Feb 26, 1980.

[203] Baumgarten, P.; Kärgel, W. A new synthesis of 2,4-dihydroxyquinolines. *Ber. Dtsch. Chem. Ges.*, **1927**, *60*, 832-842.

[204] Baker, R.H.; Lappin, G.R.; Riegel, B. Some 3-alkyl-2,4-quinolinediols. *J. Am. Chem. Soc.*, **1946**, *68*, 1284-1285.

[205] Curd, F.H.S.; Raison, C.G.; Rose, F.L. Synthetic antimalarials. XVII. Some (arylamino)(aminoalkylamino)quinoline derivatives. *J. Chem. Soc.*, **1947**, 899-909.

[206] Landquist, J.K. Synthetic antimalarials. XLVI. Some 4-[(dialkylaminoalkyl) amino]quinoline derivatives. *J. Chem. Soc.*, **1951**, 1038-1048.

[207] de Diesbach, H.; Gross, J.; Tschannen, W. Some derivatives of phenylhydroxyquinolines. *Helv. Chim. Acta*, **1951**, *34*, 1050-1060.

[208] Cooke, R.G.; Haynes, H.F. The alkaloids of Evodia littoralis. *Aust. J. Chem.*, **1954**, *7*, 273-276.

[209] Holmes, R.R.; Conrady, J.; Guthrie, J.; McKay, R. Heterocyclic quinones. I. The direct oxidation of 6-hydroxycarbostyrils to carbostyril-5,6-quinones. *J. Am. Chem. Soc.*, **1954**, *76*, 2400-2407.

[210] Gell, R.J.; Hughes, G.K.; Ritchie, E. Chemical constituents of Australian Flindersia species. VIII. The structure of maculine. *Aust. J. Chem.*, **1955**, *8*, 422-423.

[211] Gell, R.J.; Hughes, G.K.; Ritchie, E. Alkaloids of Evodia alata. *Aust. J. Chem.*, **1955**, *8*, 114-120.

[212] Rapoport, H.; Holden, K.G. Isolation of alkaloids from Balfourodendron riedelianum. The structure of balfourodine. *J. Am. Chem. Soc.*, **1959**, *81*, 3738-3743.

[213] Reisch, J. Chemistry of natural substances. VII. Furoquinoline derivatives by condensation of ethyl 2-propynyl malonate with aromatic amines. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **1967**, *300*, 532-539.

[214] Stadlbauer, W.; Schmut, O.; Kappe, T. Synthesis of benzofurans by cyclodehydrogenation of phenylmalonyl heterocyclics. *Monatsh. Chem.*, **1980**, *111*, 1005-1014.

[215] Yamaguchi, S.; Yoshimoto, Y.; Murai, R.; Masuda, F.; Yamada, M.; Kawase, Y. The synthesis of benzofuroquinolines. III. Two dihydroxybenzofuroquinolinones. *J. Heterocycl. Chem.*, **1984**, *21*, 737-739.

[216] Stadlbauer, W.; Kappe, T. Oxidative hydroxylation of heterocyclic β-dicarbonyl compounds. *Monatsh. Chem.*, **1985**, *116*, 1005-1015.

[217] Kappe, T.; Karem, A.S.; Stadlbauer, W. Synthesis of benzo-halogenated-4-hydroxy-2(1*H*)-quinolones. *J. Heterocycl. Chem.*, **1988**, *25*, 857-861.

[218] Nasr, M.; Drach, J.C.; Smith, S.H.; Shipman, C.; Burckhalter, J.H. 7-Aminoquinolines. A novel class of agents active against herpes viruses. *J. Med. Chem.*, **1988**, *31*, 1347-1351.

[219] Ohhira, Y.; Kawase, Y. The synthesis of benzofuroquinolines. IV. Some halobenzofuro[2,3-b]- and [3,2-c]quinoline derivatives. *J. Heterocycl. Chem.*, **1989**, *26*, 281-284.

[220] Mintas, M.; Mihaljevic, V.; Koller, H.; Schuster, D.; Mannschreck, A. Sterically hindered *N*-aryl-2(1*H*)-quinolones and *N*-aryl-6(5*H*)-phenanthridinones: Separation of enantiomers and barriers to racemization. *J. Chem. Soc., Perkin Trans. 2*, **1990**, 0, 619-624.

[221] Stadlbauer, W.; Laschober, R.; Kappe, T. Potential estrogens and antiestrogens. Part 3. Ylides of heterocycles. Part 11. Palladium-catalyzed ring closure reactions to benzofurans: A new and effective approach to azacoumestrols. *Liebigs Ann. Chem.*, **1990**, 531-539.

[222] Chauncey, M.A.; Grundon, M.F. Reactions of heterocyclic quinone methides: 1-Methyl-3-methylene-2,4(1*H*,3*H*)-quinolinedione. *Synthesis,* **1990**, *11*, 1005-1007.

[223] Laschober, R.; Stadlbauer, W. Synthesis of 3-heptyl- and 3-nonyl-2,4(1*H*,3*H*)-quinolinediones. *Liebigs Ann. Chem.*, **1990**, 1083-1086.

[224] Stadlbauer, W.; Laschober, R.; Lutschounig, H.; Schindler, G.; Kappe, T. Organic azides in heterocycle synthesis. Part 16. Halogenation reactions in position 3 of quinoline-2,4-dione systems by electrophilic substitution and halogen exchange. *Monatsh. Chem.*, **1992**, *123*, 617-636.

[225] Klásek, A.; Kafka, S.; Kappe, T. Synthesis and some reactions of 3-substituted 1,4-bis(4-hydroxy-2-oxo-1,2-dihydroquinolin-6-yloxy)butanes. *Collect. Czech. Chem. Commun.*, **1995**, *60*, 2137-2146.

[226] Fabian, W.M.F.; Niederreiter, K.S.; Uray, G. Stadlbauer Substituent effects on absorption and fluorescence spectra of carbostyrils. *J. Mol. Struct.*, **1999**, *477*, 209-220.

[227] Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. Synthesis of novel 3-acyloxy-1,3-dihydro-2*H*-indol-2-ones and isomeric 4-acyl-1,4-dihydro-3,1-benzoxazin-2-ones: Double rearrangement of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones. *Tetrahedron*, **2000**, *56*, 1551-1560.

[228] Xiao, Z.; Waters, N.C.; Woodard, C.L.; Li, Z.; Li, P.K. Design and synthesis of Pfmrk inhibitors as potential antimalarial agents. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 2875-2878.

[229] Kafka, S.; Klásek, A.; Košmrlj, J. Novel ring contraction of 3-hydroxy-2,4(1*H*,3*H*)-quinolinediones in aqueous alkali. The first convenient route to 2-hydroxyindoxyls. *J. Org. Chem.*, **2001**, *66*, 6394-6399.

[230] Chen, Y.L.; Chung, C.H.; Chen, I.L.; Chen, P.H.; Jeng, H.Y. Synthesis and cytotoxic activity evaluation of indolo-, pyrrolo-, and benzofuro-quinolin-2(1*H*)-ones and 6-anilinoindoloquinoline derivatives. *Bioorg. Med. Chem.*, **2002**, *10*, 2705-2712.

[231] Klásek, A.; Polis, J.; Mrkvička, V.; Košmrlj, J. Synthesis of 3-thiocyanato-1*H*,3*H*-quinoline-2,4-diones. *J. Heterocycl. Chem.*, **2002**, *39*, 1315-1320.

[232] Klásek, A.; Kořistek, K.; Sedmera, P.; Halada, P. A new synthesis of 4-alkyl/aryl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-diones and molecular rearrangement of their 3-bromo derivatives to 2-alkyl/aryl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-3-carboxylic acids. *Heterocycles*, **2003**, *60*, 799-815.

[233] Klásek, A.; Mrkvička, V. 1-Methyl-3-phenyl-3-thiocyanato-1*H*,3*H*-quinoline-2,4-dione: A novel thiocyanating agent. *J. Heterocycl. Chem.*, **2003**, *40*, 747-752.

[234] Hopkins, A.L.; Ren, J.; Milton, J.; Hazen, R.J.; Chan, J.H.; Stuart, D.I.; Stammers, D.K. Design of non-nucleoside inhibitors of HIV-1 reverse transcriptase with improved drug resistance properties. 1. *J. Med. Chem.*, **2004**, *47*, 5912-5922.

[235] Freeman, G.A.; Andrews, C.W.; Hopkins, A.L.; Lowell, G.S.; Schaller, L.T.; Cowan, J.R.; Gonzales, S.S.; Koszalka, G.W.; Hazen, R.J.; Boone, L.R.; Ferris, R.G.; Creech, K.L.; Roberts, G.B.; Short, S.A.; Weaver, K.; Reynolds, D.; Milton, J.; Ren, J.; Stuart, D.I.; Stammers, D.K.; Chan, J.H. Design of non-nucleoside inhibitors of HIV-1 reverse transcriptase with improved drug resistance properties. 2. *J. Med. Chem.*, **2004**, *47*, 5923-5936.

[236] Klásek, A.; Mrkvička, V.; Pevec, A.; Košmrlj, J. Novel tandem hydration/cyclodehydration of α-thiocyanatoketones to 2-oxo-3-thiazolines. Application to thiazolo[5,4-*c*]quinoline-2,4(3a*H*,5*H*)-dione synthesis. *J. Org. Chem*., **2004**, *69*, 5646-5651.

[237] Paleta, O.; Pomeisl, K.; Kafka, S.; Klásek, A.; Kubelka, V. New modification of the Perkow reaction: Halocarboxylate anions as leaving groups in 3-(acyloxy)quinoline-2,4(1*H*,3*H*)-diones. *Beilstein J. Org. Chem*., **2005**, *1*, No. 17.

[238] Hoekstra, W.J.; Patel, H.S.; Liang, X.; Blanc, J.B.E.; Heyer, D.O.; Willson, T.M.; Iannone, M.A.; Kadwell, S.H.; Miller, L.A.; Pearce, K.H.; Simmons, C.A.; Shearin, J. Discovery of novel quinoline-based estrogen receptor ligands using peptide interaction profiling. *J. Med. Chem*., **2005**, *48*, 2243-2247.

[239] Pomeisl, K.; Kvíčala, J.; Paleta, O.; Klásek, A.; Kafka, S.; Kubelka, V.; Havlíček, J.; Čejka, J. Limitations of the Wittig-Horner-type annulation of fluorobutenolide moiety to 3-hydroxyquinoline-2,4(2*H*,3*H*)-diones. Novel modifications of the Perkow reaction including fluorinated acyloxy leaving groups. *Tetrahedron*, **2007**, *63*, 10549-10561.

[240] Mrkvička, V.; Klásek, A.; Kimmel, R.; Pevee, A.; Košmrlj, J. Thermal reaction of 3a*H*,5*H*-thiazolo[5,4-*c*]quinoline-2,4-diones - an easy pathway to 4-amino-1*H*-quinoline-2-ones and novel 6*H*-thiazolo[3,4-*c*]quinazoline-3,5-diones. *ARKIVOC (Gainesville, FL, U. S.)*, **2008**, 289-302.

[241] Ahvale, A.B.; Prokopcová, H.; Šefčovičová, J.; Steinschifter, W.; Täubl, A.E.; Uray, G.; Stadlbauer, W. 4-Cyano-6,7-dimethoxycarbostyrils with solvent- and pH-independent high fluorescence quantum yields and emission maxima. *Eur. J. Org. Chem*., **2008**, 563-571.

[242] Kimmel, R.; Kafka, S.; Košmrlj, J. Selective formation of glycosidic linkages of *N*-unsubstituted 4-hydroxyquinolin-2-(1*H*)-ones. *Carbohydr. Res*., **2010**, *345*, 768-779.

[243] Mrkvička, V.; Lyčka, A.; Vícha, R.; Klásek, A. Reaction of 3-hydroxyquinoline-2,4-diones with isocyanates and thermally induced transformation of the reaction products. *Helv. Chim. Acta*, **2011**, *94*, 78-91.

[244] Kafka, S.; Hauke, S.; Salcinovic, A.; Soidinsalo, O.; Urankar, D.; Kosmrlj, J. Copper(I)-catalyzed [3+2] cycloaddition of 3-azidoquinoline-2,4(1*H*,3*H*)-diones with terminal alkynes. *Molecules*, **2011**, *16*, 4070-4081.

[245] Rudolf, O.; Mrkvička, V.; Lyčka, A.; Rouchal, M.; Klásek, A. Modified riemschneider reaction of 3-thiocyanatoquinolinediones. *Helv. Chim. Acta*, **2012**, *95*, 1352-1372.

[246] Enoua, G.C.; Uray, G.; Stadlbauer, W. 3-Aryl-6-methoxy-2-oxo-1,2-dihydroquinoline-4-carbonitriles as solvent and pH independent green fluorescent dyes. *J. Heterocycl. Chem*., **2012**, *49*, 1415-1421.

[247] Rudolf, O.; Mrkvička, V.; Lyčka, A.; Rouchal, M.; Klásek, A. Reaction of some 2-quinolone derivatives with phosphoryl chloride: Synthesis of novel phosphoric acid esters of 4-hydroxy-2-quinolone. *J. Heterocycl. Chem*., **2013**, 50(S1), E100-E110.

[248] Klásek, A.; Rudolf, O.; Rouchal, M.; Lyčka, A.; Růžička, A. Reaction of 4-hydroxy-2-quinolones with thionyl chloride - preparation of new spirobenzo[1,3]oxathioles and their transformations. *Tetrahedron*, **2013**, *69*, 492-499.

[249] Rudolf, O.; Rouchal, M.; Lyčka, A.; Klásek, A. Pinacol rearrangement of 3,4-dihydro-3,4-dihydroxyquinolin-2(1*H*)-ones: An alternative pathway to viridicatin alkaloids and their analogs. *Helv. Chim. Acta*, **2013**, *96*, 1905-1917.

[250] Kafka, S.; Proisl, K.; Kašpárková, V.; Urankar, D.; Kimmel, R.; Košmrlj, J. Oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones into *N*-(α-ketoacyl)anthranilic acids. *Tetrahedron*, **2013**, *69*, 10826-10835.

[251] Dooley, J.D.; Reddy Chidipudi, S.; Lam, H.W. Catalyst-controlled divergent C-H functionalization of unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compounds with alkynes and alkenes. *J. Am. Chem. Soc*., **2013**, *135*, 10829-10836.

[252] Klásek, A.; Lyčka, A.; Rouchal, M.; Rudolf, O.; Růžička, A. Reduction of 3-aminoquinoline-2,4(1*H*,3*H*)-diones and deamination of the reaction products. *Helv. Chim. Acta*, **2014**, *97*, 595-612.

[253] Patil, S.R.; Nandre, J.P.; Patil, P.A.; Bothra, S.; Sahoo, S.K.; Klásek, A.; Rodriguez-Lopez, J.; Mahulikar, P.P.; Patil, U.D. Quinolone based chemosensor for the naked-eye and spectrophotometric detection of Cu^{2+} in aqueous media. *Inorg. Chem. Commun*., **2014**, *49*, 59-62.

[254] Klásek, A.; Lyčka, A.; Křemen, F.; Rouchal, M. Stereochemistry of the reduction of α-chloroketones with sodium borohydride-application to 3-chloroquinoline-2,4-diones. *Tetrahedron*, **2016**, *72*, 4490-4497.

[255] Křemen, F.; Gazvoda, M.; Kafka, S.; Proisl, K.; Srholcová, A.; Klásek, A.; Urankar, D.; Košmrlj, J. Synthesis of 1,4-benzodiazepine-2,5-diones by base promoted ring expansion of 3-aminoquinoline-2,4-diones. *J. Org. Chem*., **2017**, *82*, 715-722.

[256] Corral, R.A.; Orazi, O.O.; Autino, J.C. Total synthesis of phenolic Balfourodendron alkaloids. *Tetrahedron Lett*., **1983**, *24*, 2359-2360.

[257] Ruat, M.; Faure, H.; Gorojankina, T. Use of quinolinone derivatives as a research tool. Fr. Demande FR 2967498, May 18, 2012,

[258] Lunney, E.A.; Hagen, S.E.; Domagala, J.M.; Humblet, C.; Kosinski, J.; Tait, B.D.; Warmus, J.S.; Wilson, M.; Ferguson, D.; Hupe, D.; Tummino, P.J.; Baldwin, E.T.; Bhat, T.N.; Liu, B.; Erickson, J.W. A novel nonpeptide HIV-1 protease inhibitor: Elucidation of the binding mode and its application in the design of related analogs. *J. Med. Chem*., **1994**, *37*, 2664-2677.

[259] Jaroszewski, J.W. Synthesis of some novel polyoxygenated quinolines. *J. Heterocycl. Chem*., **1990**, *27*, 1227-1232.

[260] Lange, J.H.M.; Verveer, P.C.; Osnabrug, S.J.M.; Visser, G.M. Rapid microwave-enhanced synthesis of 4-hydroxyquinolinones under solvent-free conditions. *Tetrahedron Lett*., **2001**, *42*, 1367-1369.

[261] Rivkin, A.; Adams, B. Solvent-free microwave synthesis of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones and variants using activated arylmalonates. *Tetrahedron Lett*., **2006**, *47*, 2395-2398.

[262] Rivkin, A.; Kim, Y.R.; Goulet, M.T.; Bays, N.; Hill, A.D.; Kariv, I.; Krauss, S.; Ginanni, N.; Strack, P.R.; Kohl, N.E.; Chung, C.C.; Varnerin, J.P.; Goudreau, P.N.; Chang, A.; Tota, M.R.; Munoz, B. 3-Aryl-4-hydroxyquinolin-2(1*H*)-one derivatives as type I fatty acid synthase inhibitors. *Bioorg. Med. Chem. Lett*., **2006**, *16*, 4620-4623.

[263] Goulet, M.T.; Munoz, B.; Rivkin, A.A. Preparation of 1,2-dihydroquinolin-2-one derivatives as inhibitors of fatty acid synthase for treatment of cancer. PCT Int. Appl. WO 2007/089634, Aug 9, 2007; *Chem. Abstr*., **2007**, *147*, 257661.

[264] Manetti, F.; Petricci, E.; Gabrielli, A.; Mann, A.; Faure, H.; Gorojankina, T.; Brasseur, L.; Hoch, L.; Ruat, M.; Taddei, M. Design, synthesis and biological characterization of a new class of osteogenic (1*H*)-quinolone derivatives. *Eur. J. Med. Chem*., **2016**, *121*, 747-757.

[265] Ranjith, P.K.; Mary, Y.S.; Panicker, C.Y.; Anto, P.L.; Armakovic, S.; Armakovic, S.J.; Musiol, R.; Jampilek, J.; Van Alsenoy, C. New quinolone derivative: Spectroscopic characterization and reactivity study by DFT and MD approaches. *J. Mol. Struct*., **2017**, *1135*, 1-14.

[266] Baumgarten, P.; Riedel, M. Reaction of carbazoles with malonic ester to form 1,9-malonylcarbazoles. *Ber. Dtsch. Chem. Ges*., **1942**, *75*, 984-986.

[267] Bowman, R.E.; Campbell, A.; Tanner, E.M. Reaction between diphenylamine and malonic esters. *J. Chem. Soc*., **1959**, 444-447.

[268] Ziegler, E.; Junek, H. Synthesis of heterocycles. XXII. Synthesis of 4-hydroxycarbostyril and its derivatives. *Monatsh. Chem*., **1959**, *90*, 762-767.

[269] Nair, M.D. Reaction of diethyl malonate with tetrahydroquinaldine. *Indian J. Chem*., **1971**, *9*, 107-109.

[270] Storer, R.; Young, D.W.; Taylor, D.R.; Warner, J.M.. Isolation and synthesis of *N*-methyl-4,7,8-trimethoxy-2-quinolinone from *Spathelia sorbifolia* L. *Tetrahedron*, **1973**, *29*, 1721-1723.

[271] Faber, K.; Kappe, T. Non-steroidal antiinflammatory agents. 2. Synthesis of 4-hydroxy-1-methyl-2-oxodihydroquinolin-3-yl acetic acid and related tetrazolyl derivatives. *J. Heterocycl. Chem*., **1984**, *21*, 1881-1883.

[272] Roschger, P.; Stadlbauer, W. Organic azides in heterocyclic synthesis. 11. Ring closure of 3-acetyl-4-azido-2-quinolones to isoxazolo[4,3-*c*]quinolones. *Liebigs Ann. Chem*., **1990**, 821-823.

[273] Roschger, P.; Fiala, W.; Stadlbauer, W. Nucleophilic substitution and ring closure reactions of 4-chloro-3-nitro-2-quinolones. *J. Heterocycl. Chem*., **1992**, *29*, 225-231.

[274] Kappe, T.; Aigner, R.; Hohengassner, P.; Stadlbauer, W. Syntheses of 3-acyl-4-hydroxy-2(1*H*)quinolones. *J. Prakt. Chem./Chem.-Ztg*., **1994**, *336*, 596-601.

[275] Sheibani, H.; Mosslemin, M.H.; Behzadi, S.; Islami, M.R.; Saidi, K. A convenient one-pot synthesis of pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione and 2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-dione derivatives. *Synthesis*, **2006**, 435-438.

[276] Razzaq, T.; Kappe, C.O. Rapid preparation of pyranoquinolines using microwave dielectric heating in combination with fractional product distillation. *Tetrahedron Lett*., **2007**, *48*, 2513-2517.

[277] Dong, Y.; Shi, Q.; Pai, H.C.; Peng, C.Y.; Pan, S.L.; Teng, C.M.; Nakagawa-Goto, K.; Yu, D.; Liu, Y.N.; Wu, P.C.; Bastow, K.F.; Morris-Natschke, S.L.; Brossi, A.; Lang, J.Y.; Hsu, J.L.; Hung, M.C.; Lee, E.Y.H.P.; Lee, K.H. Antitumor Agents. 272. Structure-activity relationships and *in vivo* selective anti-breast cancer activity of novel neo-tanshinlactone analogues. *J. Med. Chem*., **2010**, *53*, 2299-2308.

[278] Jampilek, J.; Musiol, R.; Pesko, M.; Kralova, K.; Vejsova, M.; Carroll, J.; Coffey, A.; Finster, J.; Tabak, D.; Niedbala, H.; Kozik, V.; Polanski, J.; Csollei, J.; Dohnal, J. Ring-substituted 4-hydroxy-1*H*-quinolin-2-ones: Preparation and biological activity. *Molecules*, **2009**, *14*, 1145-1159.

[279] Shobana, N.; Yeshoda, P.; Shanmugam, P. A convenient approach to the synthesis of prenyl-, furo- and pyrano-quinoline alkaloids of the Rutaceae. *Tetrahedron*, **1989**, *45*, 757-762.

[280] Balasubramanian, C.; Kumaraswami, K.; Dharmaraj, N.; Mohan, P.S. Quinone methide reactions: Synthesis of novel pyranodiquinolines. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **1993**, *32*, 460-462.

[281] Subramanian, M.; Mohan, P.S.; Shanmugam, P.; Prasad, K.J.R. Quinoline alkaloids. Synthesis of khaplofoline, ribalinine, and flindersine. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, **1992**, *47*, 1016-1020.

[282] Moradi-e-Rufchahi, E.O. Synthesis of 6-chloro and 6-fluoro-4-hydroxyl-2-quinolone and their azo disperse dyes. *Chin. Chem. Lett.*, **2010**, *21*, 542-560.

[283] Cheng, P.; Gu, Q.; Liu, W.; Zou, J.F.; Ou, Y.Y.; Luo, Z.Y.; Zeng, J.G. Synthesis of quinolin-2-one alkaloid derivatives and their inhibitory activities against HIV-1 reverse transcriptase. *Molecules*, **2011**, *16*, 7649-7661.

[284] Yahyazadeh, A.; Yousefi, H. Synthesis, spectral features and biological activity of some novel hetarylazo dyes derived from 8-chloro-4-hydroxyl-2-quinolone. *Spectrochim. Acta, Part A*, **2014**, *117*, 696-701.

[285] Ferretti, M.D.; Neto, A.T.; Morel, A.F.; Kaufman, T.S.; Larghi, E.L. Synthesis of symmetrically substituted 3,3-dibenzyl-4-hydroxy-3,4-dihydro-1*H*-quinolin-2-ones, as novel quinoline derivatives with antibacterial activity. *Eur. J. Med. Chem.*, **2014**, *81*, 253-266.

[286] Vankayalapati, H.; Yoshioka, M.; Strovel, J.W.; Padia, J.K. Methods and compositions for inhibition of bromodomain-containing proteins. PCT Int. Appl. WO 2014/159837, Oct 2, 2014; *Chem. Abstr.*, **2014**, *161*, 559305.

[287] Moradi Rufchahi, E.O.; Mohammadinia, M. 6-Butyl-4-hydroxyquinolin-2-(1*H*)-one as an enol type coupling component for the synthesis of some new azo disperse dyes. *J. Mol. Liq.*, **2017**, *199*, 393-400.

[288] Chatterjee, A.; Cutler, S.J.; Doerksen, R.J.; Khan, I.A.; Williamson, J.S. Discovery of thienoquinolone derivatives as selective and ATP non-competitive CDK5/p25 inhibitors by structure-based virtual screening. *Bioorg. Med. Chem.*, **2014**, *22*, 6409-6421.

[289] Rufchahi, E.O.M.; Gilani, A.G.; Taghvaei, V.; Karimi, R.; Ramezanzade, N. Synthesis, structural elucidation, solvatochromism and spectroscopic properties of some azo dyes derived from 6-chloro-4-hydroxyquinoline-2(1*H*)-one. *J. Mol. Struct.*, **2016**, *1108*, 623-630.

[290] Yoshioka, M.; Strovel, J.W.; Padia, J.K. Preparation of 4-amino-1,2-dihydroquinolin-2-one derivatives and methods and compositions for inhibition of bromodomain and extraterminal proteins. PCT Int. Appl. WO 2016/077656; *Chem. Abstr.*, **2016**, *164*, 614524.

[291] Fischer, M.; Laschober, R.; Preiss, A.; Kappe, T. 3,4,8-Trimethoxy-2-quinolone. Synthesis of a new alkaloid from *Eriostemon gardneri*. *Sci. Pharm.*, **1996**, *64*, 353-358.

[292] Glasnov, T.N.; Stadlbauer, W.; Kappe, C.O. Microwave-assisted multistep synthesis of functionalized 4-arylquinolin-2(1*H*)-ones using palladium-catalyzed cross-coupling chemistry. *J. Org. Chem.*, **2005**, *70*, 3864-3870.

[293] Moradi-e-Rufchahi, E.O.; Ghanadzadeh, A. A study of solvatochromism in diazonium coupling products of 6-fluoro-4-hydroxy-2-quinolone. *J. Mol. Liq.*, **2011**, *160*, 160-165.

[294] Moradi Rufchahi, E.O.; Pouramir, H.; Yazdanbakhsh, M.R.; Yousefi, H.; Bagheri, M.; Rassa, M. Novel azo dyes derived from 8-methyl-4-hydroxyl-2-quinolone: Synthesis, UV-vis studies and biological activity. *Chin. Chem. Lett.*, **2013**, *24*, 425-428.

[295] Meier, H.; Luettke, W. Theoretical and spectroscopic studies on indigo dyes. XXII. Syntheses of 5,5'- and 6,6'-dialkylated indigo dyes. *Liebigs Ann. Chem.*, **1981**, 1303-1333.

[296] Klug, M.G.; Mattei, P.; Mueller, W.; Neidhart, W.; Nettekoven, M.H.; Pflieger, P.; Plancher, J.M. Quinoline derivatives as neuropeptide Y antagonists. PCT Int. Appl. WO 2003/028726, Apr 10, 2003; *Chem. Abstr.*, **2003**, *138*, 287536.

[297] Im, I.; Lee, E.S.; Choi, S.J.; Lee, J.Y.; Kim, Y.C. Structure–activity relationships of heteroaromatic esters as human rhinovirus 3C protease inhibitors. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 3632-3636.

[298] Coppola, G.M.; Damon, R.E.; Hardtmann, G.E. 4-Hydroxy-2-quinolinone-3-carboxylic acids. *Synthesis*, **1981**, 391-392.

[299] Beutner, G.L.; Kuethe, J.T.; Yasuda, N. A practical method for preparation of 4-hydroxyquinolinone esters. *J. Org. Chem.*, **2007**, *72*, 7058-7061.

[300] Mahmoud, A.H.; Abou El Ella, D.A.; Ismail, M.A.H.; Abouzid, K.A.M. A highly selective structure-based virtual screening model of Palm I allosteric inhibitors of HCV Ns5b polymerase enzyme and its application in the discovery and optimization of new analogues. *Eur. J. Med. Chem.*, **2012**, *57*, 468-482.

[301] Tomassoli, I.; Herlem, G.; Picaud, F.; Benchekroun, M.; Bautista-Aguilera, O.M.; Luzet, V.; Jimeno, M.L.; Gharbi, T.; Refouvelet, B.; Ismaili, L. Synthesis, regioselectivity, and DFT analysis of new antioxidant pyrazolo[4,3-*c*]quinoline-3,4-diones. *Monatsh. Chem.*, **2016**, *147*, 1069-1079.

[302] Wentland, M.P.; Perni, R.B.; Dorff, P.H.; Brundage, R.P.; Castaldi, M.J.; Bailey, T.R.; Carabateas, P.M.; Bacon, E.R.; Young, D.C.; Woods, M.G.; Rosi, D.; Drozd, M.L.; Kullnig, R.K.; Dutko, F.J. 3-Quinolinecarboxamides. A series of novel orally-active antiherpetic agents. *J. Med. Chem.*, **1993**, *36*, 1580-1596.

[303] Zuo, Y.; Wang, X.; Zhang, Y.; Wen, L.; Wu, S.; Yuan, X. Quinolinone compound and application thereof in drugs. Faming Zhuanli Shenqing CN 105384687, Mar 9, 2016; *Chem. Abstr.*, **2016**, *164*, 406576.

[304] Tang, Q.; Zhai, X.; Tu, Y.; Wang, P.; Wang, L.; Wu, C.; Wang, W.; Xie, H.; Gong, P.; Zheng, P. Synthesis and antiproliferative activity of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing the 2-oxo-4-chloro-1,2-dihydroquinoline-3-carboxamide moiety. *Bioorg. Med. Chem. Lett.*, **2016**, *26*, 1794-1798.

[305] Huang, Y.; Feng, Y.; Gao, W.; Zhang, C.; Chen, L. An efficient method for the synthesis of laquinimod. *J. Heterocycl. Chem.*, **2016**, *53*, 437-440.

[306] Zikou, L.C.; Igglessi-Markopoulou, O. Modified Mukaiyama reaction for the synthesis of quinoline alkaloid analogues: total synthesis of 3,3-diisopentenyl-*N*-methylquinoline-2,4-dione. *Synthesis*, **2008**, 1861-1866.

[307] Lamblin, M.; Bares, H.; Dessolin, J.; Marty, C.; Bourgougnon, N.; Felpin, F.X. Practical Pd/C-catalysed Suzuki-Miyaura reactions for the preparation of 3-aryl-4-oxypyridin-2(1*H*)-ones, 3-aryl-2,4-oxypyridines and 3-aryl-2,4-oxyquinolines as useful intermediates for the synthesis of biologically active compounds. *Eur. J. Org. Chem.*, **2012**, 5525-5533.

[308] Paul, S.; Shrestha, R.; Edison, T.N.J.I.; Lee, Y.R.; Kim, S.H. Copper(I) bromide-dimethyl sulfide-catalyzed direct sulfanylation of 4-hydroxycoumarins and 4-hydroxyquinolinones with arylsulfonylhydrazides and selective fluorescence switch-on sensing of cadmium(II) ion in water. *Adv. Synth. Catal.*, **2016**, *358*, 3050-3056.

[309] Tomita, K. The antibacterial properties of compounds containing the tricarbonylmethane group. V. The syntheses of 3-acyl-2,4-dihydroxyquinolines and of the related compounds with respect to their antibacterial properties. *Yakugaku Zasshi*, **1951**, *71*, 1100-1112; *Chem. Abstr.*, **1952**, *46*, 5044.

[310] Ohta, T.; Mori, Y. Syntheses of py-benzyl-4-hydroxycarbostyrils. *Pharm. Bull.*, **1955**, *3*, 388-391.

[311] Ohta, T.; Mori, Y. Furoquinolines. VI. Establishment of the linear tri-cyclic structures for dictamnine and skimmianine *Ann. Rept. Tokyo Coll. Pharm.*, **1955**, *5*, 336-338; *Chem. Abstr.*, **1956**, *50*, 13055.

[312] Terasaka, M.; Narahashi, K.; Ohta, T. Alkaloids of the root-bark of *Orixa japonica*. VI. Kokuginine. *Yakugaku Zasshi*, **1955**, *75*, 1040-1042; *Chem. Abstr.*, **1956**, *50*, 7824.

[313] Ohta, T.; Mori, Y. Synthesis of 3-alkyl-4-hydroxycarbostyrils. *Yakugaku Zasshi*, **1955**, *75*, 1162-1164; *Chem. Abstr.*, **1956**, *50*, 7802.

[314] Cooke, R.G.; Haynes, H.F. The synthesis of furoquinoline alkaloids: dictamnine and evolitrine. *Aust. J. Chem.*, **1958**, *11*, 225-229.

[315] Geissman, T.A.; Cho, A.K. Rearrangement of methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate to 2,4-dihydroxyquinoline-3-acetic acid in acid and base. *J. Org. Chem.*, **1959**, *24*, 41-43.

[316] Gyul'budagyan, L.V.; Aleksanyan, I.L.; Avetisyan, A.A. New method for preparation of 2,4-dihydroxy-3-(3',3'-dichloroallyl)quinoline. *Khim. Zh. Arm.*, **2000**, *53*, 55-59.

[317] Lutz, R.E.; Ashburn, G.; Freek, J.A.; Jordan, R.H.; Leake, N.H.; Martin, T.A.; Rowlett, R.J.; Wilson, J.W. Antimalarials. The synthesis of 2,4,7-trichloroquinoline. *J. Am. Chem. Soc.*, **1946**, *68*, 1285-1288.

[318] Brown, R.F.C.; Hobbs, J.J.; Hughes, G.K.; Ritchie, E. The chemical constituents of Australian Flindersia species. VI. The structure and chemistry of flindersine. *Aust. J. Chem.*, **1954**, *7*, 348-377.

[319] Lacey, R.N. Derivatives of acetoacetic acid. VII. α-Acetyltetramic acids. *J. Chem. Soc.*, **1954**, 850-854.

[320] Brown, R.F.C. Chemical constituents of Australian Flindersia species. VII. Synthesis of derivatives of kokusaginine and skimmianinic acids. *Aust. J. Chem.*, **1955**, *8*, 121-124.

[321] Grundon, M.F.; McCorkindale, N.J.; Rodger, M.N. Synthesis of furano [3',2',3,4]quinolines and the structure of dictamnic acid. *J. Chem. Soc.*, **1955**, 4284-4290.

[322] Cai, S.X.; Drewe, J.A.; Shelton, E.J.; Litvak, J.; Sperandio, D.; Spencer, J.R. Substituted 1,4-thiazepines and analogs as activators of caspases and

inducers of apoptosis and the use thereof. PCT Int. Appl. WO 01/079187, Oct 25, 2001; *Chem. Abstr*., **2001**, *135*, 331449.

[323] Spears, G.W.; Tsuji, K.; Tojo, T.; Nishimura, H.; Ogino, T. An efficient synthesis of a class of novel *N*-alkyl-*N*-aryl-4-hydroxy-1-methyl-2-oxo-1,2-dihydro-3-quinolinecarbothioamides. *J. Heterocycl. Chem*., **2002**, *39*, 799-804.

[324] Folkes, A.; Wang, S.; Golec, J.; Vicker, N.; Prisbylla, M.P.; Mac, M.B.; Epshteyn, S.P.; Webb, R.R. 2-Oxo, 4-hydroxy pyrroles and quinolines. Brit. UK Pat. Appl. GB 2372986, Sep 11, 2002; *Chem. Abstr*., **2003**, *138*, 55881.

[325] Pratt, J.K.; Betebenner, D.A.; Donner, P.L.; Green, B.E.; Kempf, D.J.; Mcdaniel, K.F.; Maring, C.J.; Stoll, V.S.; Zhang, R. Anti-infective agents. U.S. Pat. Appl. Publ. US 2004/0162285, Aug 19, 2004; *Chem. Abstr*., **2004**, *141*, 207235.

[326] Boyle, R.G.; Imogai, H.J.; Cherry, M.; Humphries, A.J.; Navarro, E.F.; Owen, D.R.; Dales, N.A.; Lamarche, M.; Cullis, C.; Gould, A.E. Chk-1 inhibitors. PCT Int. Appl. WO 2005/028474, Mar 31, 2005; *Chem. Abstr*., **2005**, *142*, 355175.

[327] Boyle, R.G.; Imogai, H.J.; Cherry, M.; Humphries, A.J.; Navarro, E.F.; Owen, D.R.; Dales, N.A.; Lamarche, M.J.; Cullis, C.; Gould, A.E.; Greenspan, P.D. 2,5-Dihydro-pyrazolo[4,3-*c*]quinolin-4-ones as Chk-1 inhibitors. PCT Int. Appl. WO 2005/118583, Dec 15, 2005; *Chem. Abstr*., **2005**, *144*, 51573.

[328] Pratt, J.K.; Donner, P.; McDaniel, K.F.; Maring, C.J.; Kati, W.M.; Mo, H.; Middleton, T.; Liu, Y.; Ng, T.; Xie, Q.; Zhang, R.; Montgomery, D.; Molla, A.; Kempf, D.J.; Kohlbrenner, W. Inhibitors of HCV NS5B polymerase: Synthesis and structure-activity relationships of *N*-1-heteroalkyl-4-hydroxyquinolon-3-yl-benzothiadiazines. *Bioorg. Med. Chem. Lett*., **2005**, *15*, 1577-1582.

[329] Blackburn, C.; LaMarche, M.J.; Brown, J.; Che, J.L.; Cullis, C.A.; Lai, S.; Maguire, M.; Marsilje, T.; Geddes, B.; Govek, E.; Kadambi, V.; Doherty, C.; Dayton, B.; Brodjian, S.; Marsh, K.C.; Collins, C.A.; Kym, P.R. Identification and characterization of amino-piperidinequinolones and quinazolinones as MCHr1 antagonists. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 2621-2627.

[330] Allen, J.R.; Burli, R.; Bryan, M.C.; Cao, G.Q.; Neira, S.C.; Reed, A.B. Quinolones and azaquinolones that inhibit prolyl hydroxylase. PCT Int. Appl. WO 2008/130600, Oct 30, 2008; *Chem. Abstr*., **2008**; *149*, 513704.

[331] Wagner, R.; Donner, P.L.; Kempf, D.J.; Maring, C.J.; Stoll, V.S.; Ku, Y.Y.; Pu, Y.M. HCV inhibitors. PCT Int. Appl. (2008), WO 2008/011337, Jan 24, 2008; *Chem. Abstr*., **2008**, *148*, 168752.

[332] Lunniss, C.; Eldred, C.; Aston, N.; Craven, A.; Gohil, K.; Judkins, B.; Keeling, S.; Ranshaw, L.; Robinson, E.; Shipley, T.; Trivedi, N. Addressing species specific metabolism and solubility issues in a quinoline series of oral PDE4 inhibitors. *Bioorg. Med. Chem. Lett*., **2010**, *20*, 137-140.

[333] Gao, J.; Zhang, J.; Chen, L.; Wang, A.; Yang, X.; Zhou, W. Synthesis and fungicidal activity of 3-substituted-phenyl-4-acyloxy-2(1*H*)-quinolinones. *Nongyaoxue Xuebao*, **2011**, *13*, 459-463; *Chem. Abstr*., **2011**, *156*, 337140.

[334] Marom, E.; Mizhiritskii, M.; Rubnov, S. Intermediate compounds and processes for the preparation of quinoline derivatives such as laquinimod sodium. PCT Int. Appl. WO 2012/070051, May 31, 2012; *Chem. Abstr*., **2012**, *157*, 45028.

[335] Liu, Y.X.; Zhao, H.P.; Wang, Z.W.; Li, Y.H.; Song, H.B.; Riches, H.; Beattie, D.; Gu, Y.C.; Wang, Q.M. The discovery of 3-(1-aminoethylidene)quinoline-2,4(1*H*,3*H*)-dione derivatives as novel PSII electron transport inhibitors. *Mol. Diversity*, **2013**, *17*, 701-710.

[336] Wang, Q.; Liu, Y.; Zhao, H. 4-Hydroxy-2-quinolinone compounds containing imine structure, and preparation and application thereof. Faming Zhuanli Shenqing CN 103508950, Jan 15, 2014; *Chem. Abstr*., **2014**, *160*, 19116.

[337] Leonard, K.A.; Barbay, K.; Edwards, J.P.; Kreutter, K.D.; Kummer, D.A.; Maharoof, U.; Nishimura, R.; Urbanski, M.; Venkatesan, H.; Wang, A.; Wolin, R.L.; Woods, C.R.; Fourie, A.; Xue, X.; Cummings, M.D.; Mcclure, K.; Tanis, V. Quinolinyl modulators of RORγt. PCT Int. Appl. WO 2015/057626, Apr 23, 2015; *Chem. Abstr*., **2015**, *162*, 577038.

[338] Kumaraswami, K.; Shanmugam, P. Synthesis of 3,4-dihydro-4-methyl-2-(3-quinolyl)-2*H*-pyrano[3,2-*c*]quinolines. *Tetrahedron Lett*., **1988**, *29*, 2235-2238.

[339] Ukrainets, I.V.; Petrushova, L.A.; Davidenko, A.A.; Grinevich, L.A. 4-Hydroxyquinolones-2. 247. 4-Hydroxy-2-oxo-1,2-dihydroquinoline or 4-hydroxy-2,2-dioxo-1*H*-2λ6,1-benzothiazine? *Khim. Geterotsikl. Soedin*., **2014**, 1569-1575; *Chem. Heterocycl. Compd*., **2015**, *50*, 1444-1449.

[340] Walser, A.; Silverman, G.; Flynn, T.; Fryer, R.I. Nucleophilic displacement of aromatic fluorine. III. Indoloquinolines and benzofuranoquinolines. *J. Heterocycl. Chem*., **1975**, *12*, 351-358.

[341] DeVita, R.J.; Walsh, T.F.; Young, J.R.; Jiang, J.; Ujjainwalla, F.; Toupence, R.B.; Parikh, M.; Huang, S.X.; Fair, J.A.; Goulet, M.T.; Wyvratt, M.J.; Lo, J.L.; Ren, N.; Yudkovitz, J.B.; Yang, Y.T.; Cheng, K.; Cui, J.; Mount, G.; Rohrer, S.P.; Schaeffer, J.M.; Rhodes, L.; Drisko, J.E.; McGowan, E.; MacIntyre, D.E.; Vincent, S.; Carlin, J.R.; Cameron, J.; Smith, R.G. A potent, nonpeptidyl 1*H*-quinolone antagonist for the gonadotropin-releasing hormone receptor. *J. Med. Chem*., **2001**, *44*, 917-922.

[342] March, S.; Pelletier, S.M.C.; Plant, A. Expedient synthesis of substituted 4-hydroxy-quinolin-2(1*H*)-ones. *Tetrahedron Lett.*, **2015**, *56*, 5859-5863.

[343] Birnberg, N.C.; Liu, H.; Weng, Q.P.; Shang, H.; Yin, P.; Rajur, S.B.; Kim, H.O.; Salgaonkar, P.D.; Peet, N.P. AMPK modulators. PCT Int. Appl. WO 2009/100130; Aug 13, 2009; *Chem. Abstr*., **2009**, *151*, 260695.

[344] Leonard, K.A.; Barbay, K.; Edwards, J.P.; Kreutter, K.D.; Kummer, D.A.; Maharoof, U.; Nishimura, R.; Urbanski, M.; Venkatesan, H.; Wang, A.; Wolin, R.L.; Woods, C.R.; Pierce, J.; Goldberg, S.; Fourie, A.; Xue, X. Methylene linked quinolinyl modulators of RORγt. U.S. Pat. Appl. Publ. US 2014/0107094, Apr 17, 2014; *Chem. Abstr*., **2014**, *160*, 606702.

[345] Leonard, K.A.; Barbay, K.; Edwards, J.P.; Kreutter, K.D.; Kummer, D.A.; Maharoof, U.; Nishimura, R.; Urbanski, M.; Venkatesan, H.; Wang, A.; Wolin, R.L.; Woods, C.R.; Fourie, A.; Xue, X.; Cummings, M.D. Secondary alcohol quinolinyl modulators of RORγt. U.S. Pat. Appl. Publ. US 2015/0105372, Apr 16, 2015; *Chem. Abstr*., **2015**, *162*, 527176.

[346] Leonard, K.A.; Barbay, K.; Edwards, J.P.; Kreutter, K.D.; Kummer, D.A.; Maharoof, U.; Nishimura, R.; Urbanski, M.; Venkatesan, H.; Wang, A.; Wolin, R.L.; Woods, C.R.; Fourie, A.; Xue, X.; Cummings, M.D.; Jones, W.M.; Goldberg, S. Methylene linked quinolinyl modulators of RORγt. PCT Int. Appl. WO 2015/057205, Apr 23, 2015; *Chem. Abstr*., **2015**, *162*, 577164.

[347] Leonard, K.A.; Barbay, K.; Edwards, J.P.; Kreutter, K.D.; Kummer, D.A.; Maharoof, U.; Nishimura, R.; Urbanski, M.; Venkatesan, H.; Wang, A.; Wolin, R.L.; Woods, C.R.; Fourie, A.; Xue, X.; Cummings, M.D.; Jones, W.M.; Goldberg, S. Methylene linked quinolinyl modulators of RORγt. U.S. Pat. Appl. Publ. US 2015/0105366, Apr 16, 2015; *Chem. Abstr*., **2015**, *162*, 538954.

[348] Poon, C.Y.; Chiu, P. A synthesis of the tetracyclic carboskeleton of isaindigotidione. *Tetrahedron Lett*., **2004**, *45*, 2985-2988.

[349] Cuny, G.D.; Lee, K.; Choi, S. Utilization of a tandem Michael-Dieckmann reaction to synthesize orixalone A. *Lett. Org. Chem*., **2006**, *3*, 68-72.

[350] Fuchigami, T.; Haradahira, T.; Fujimoto, N.; Nojiri, Y.; Mukai, T.; Yamamoto, F.; Okauchi, T.; Maeda, J.; Suzuki, K.; Suhara, T.; Yamaguchi, H.; Ogawa, M.; Magata, Y.; Maeda, M. Development of [*N*-^{11}C]methyl-amino 4-hydroxy-2(1*H*)-quinolone derivatives as PET radioligands for the glycine-binding site of NMDA receptors. *Bioorg. Med. Chem*., **2009**, *17*, 5665-5675.

[351] Gaweco, A.; Walker, J.; Monahan, J.B.; Cubbage, J.W.; Carroll, J. MIF inhibitors and their uses. PCT Int. Appl. WO 2012/142498, Oct 18, 2012; *Chem. Abstr*., **2014**, *160*, 310905.

[352] Ukrainets, I.V.; Taran, S.G.; Bezugly, P.A.; Evtifeeva, O.A. 4-Hydroxy-2-quinolones. 17. Dieckmann condensation as a thermally activated process. *Khim. Geterotsikl. Soedin*., **1993**, 1219-1222; *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, **1993**, *29*, 1041-1043.

[353] Ukrainets, I.V.; Bezuglyi, P.A.; Treskach, V.I.; Turov, A.V. 4-Hydroxy-2-quinolones. 4. Selection of the optimum path for synthesis of *N*–R-substituted 4-hydroxy-2-quinolone-3-carboxylic acid amides. *Khim. Geterotsikl. Soedin*., **1992**, 640-642; *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, **1992**, *28*, 538-540.

[354] Romanov, I.V.; Ukrainets, I.V. Method for preparing 1-propyl-2-oxo-4-hydroxyquinoline-3-carboxylic acid diethylamino ethylamide hydrochloride (chinoxycaine). Russ. RU 2285692, May 25, 2005; *Chem. Abstr*., **2006**, *145*, 438540.

[355] Ishida, T.; Kikuchi, S.; Yamada, T. Efficient preparation of 4-hydroxyquinolin-2(1*H*)-one derivatives with silver-catalyzed carbon dioxide incorporation and intramolecular rearrangement. *Org. Lett.*, **2013**, *15*, 3710-3713.

[356] Ziegler, E.; Salvador, R.; Kappe, T. Syntheses of heterocyclics. XLI. Cyclic dichloromalonyl compounds. *Monatsh. Chem*., **1962**, *93*, 1376-1382.

[357] Bowman, R.E.; Grey, T.F.; Huckle, D.; Lockhart, I.M.; Wright, M. The synthesis of some dialkylamino-2-quinolones. *J. Chem. Soc*., **1964**, 3350-3353.

[358] Kafka, S.; Klásek, A.; Polis, J.; Košmrlj, J. Syntheses of 3-aminoquinoline-2,4(1*H*,3*H*)-diones. *Heterocycles*, **2002**, *57*, 1659-1682.

[359] Klásek, A.; Kořistek, K.; Lyčka, A.; Holčapek, M. Reaction of 1-alkyl/aryl-3-amino-1*H*,3*H*-quinoline-2,4-diones with urea. Synthetic route to novel 3-(3-acylureido)-2,3-dihydro-1*H*-indol-2-ones, 4-alkylidene-1'*H*-spiro[imidazolidine-5,3'-indole]-2,2'-diones, and 3,3a-dihydro-5*H*-imidazo[4,5-*c*]quinoline-2,4-diones. *Tetrahedron*, **2003**, *59*, 5279-5288.

[360] Wittmann, H. New reagents for the paper chromatographic detection of amino acids. II. *Monatsh. Chem*., **1965**, *96*, 523-526.

[361] Fournier, C.; Decombe, J. Chemistry of homophthalimide and 4-hydroxy-carbostyril. I. *Bull. Soc. Chim. Fr*., **1967**, 3367-3371.

[362] Ziegler, E.; Foraita, H.G.; Kappe, T. Syntheses of heterocycles. XCII. Synthesis of substituted derivatives of indigo. *Monatsh. Chem*., **1967**, *98*, 324-328.

[363] Ziegler, E.; Werner, L.F.; Kappe, T. Syntheses of heterocycles. CXXIX. Indolone question. *Monatsh. Chem*., **1969**, *100*, 610-615.

[364] Ziegler, E.; Kappe, T.; Foraita, H.G.; Werner, L.F. Syntheses of heterocycles. 146. Synthesis of polymeric indigos with potential semiconductor properties. *Monatsh. Chem*., **1970**, *101*, 923-931.

[365] Schindler, G.; Kappe, T. Mesoionic six-membered heterocyclics; IX. Pyridinium ylides from malonyl heterocyclics. *Synthesis*, **1977**, 243-245.

[366] Kappe, T.; Lube, W. Rearrangements of heterocycles. VIII. Mesoionic six-membered-ring heterocycles. XII. Ketenoid rearrangements of mesoionic pyrimidines. *Chem. Ber*., **1979**, *112*, 3424-3431.

[367] Kappe, T.; Ravai, Y.; Stadlbauer, W. Rearrangement reactions of heterocycles. IX. Mesoionic six-membered heterocycles. XV. Ketenoide rearrangements of mesoionic pyrimido[1,2-*a*]quinolines. *Monatsh. Chem*., **1983**, *114*, 227-241.

[368] Faber, K.; Steininger, H.; Kappe, T. Non-steroidal antiinflammatory agents. 3. Synthesis of 3-hydroxy-3-hydroxyphenyl-2,4-dioxo-1,2,3,4-tetrahydroquinolines. *J. Heterocycl. Chem*., **1985**, *22*, 1081-1085.

[369] Buettelmann, B.; Godel, T.; Gross, L.; Heitz Niedhart, M.P.; Riemer, C.; Wyler, R. Tricyclic dicarbonyl derivatives. PCT Int. Appl. WO 95/32205, Nov 30, 1995; *Chem. Abstr*., **1996**, *124*, 232481

[370] Langhals, H. Brightly shining nanoparticles: Lipophilic perylene bisimides in aqueous phase. *New J. Chem*., **2008**, *32*, 21-23.

[371] Kim, C.H.; Jung, Y.S. Novel compound having hearing protection effects. PCT Int. Appl. WO 2011/155803, Dec 15, 2011; *Chem. Abstr*., **2011**, *156*, 35004.

[372] Pagani, G.A.; Beverina, L.; Sassi, M.; Salamone, M.M.; Mari, C.M.; Ruffo, R. Organic electrochromic materials having high transparency and high contrast in the visible range. PCT Int. Appl. WO 2013/03824, Mar 21, 2013; *Chem. Abstr*., **2013**, *158*, 419290.

[373] Enoua, G.C.; Lahm, G.; Uray, G.; Stadlbauer, W. 6-Methoxy-2-oxo-1,2-dihydroquinoline-3,4-dicarbonitriles, a red compound class with solvent and pH independent green fluorescence maxima. *J. Heterocycl. Chem*., **2014**, *51*, 492-501.

[374] Enoua, G.C.; Lahm, G.; Uray, G.; Stadlbauer, W. Syntheses and Fluorescent Properties of 6-methoxy-2-oxoquinoline-3,4-dicarbonitriles and 6,7-dimethoxy-2-oxoquinoline-3,4-dicarbonitriles. *J. Heterocycl. Chem*., **2014**, *51*, E263-E275.

[375] Jung, Y.S.; Han, S.B.; Park, U.G.; Lee, J.H.; Lee, B.H.; Song, J.S. Novel heterocyclic dione derivative or pharmaceutically acceptable salt thereof, preparation method thereof and pharmaceutical composition for protection of brain neural cell containing the same as an active ingredient. Repub. Korean Kongkae Taeho Kongbo KR 20140139669, Dec 8, 2014; *Chem. Abstr*., **2014**, *162*, 92711.

[376] Freeze, B.S.; Gigstad, K.M.; Janowick, D.A.; Lee, H.M.; Shi, Z.; Soucy, F.; Vyskocil, S. Quinazoline and quinoline compounds and uses thereof. PCT Int. Appl. WO 2016/118565, Jul 28, 2016; *Chem. Abstr*., **2016**, *165*, 223999.

[377] Ziegler, E.; Salvador, R.; Kappe, T. Syntheses of heterocyclics. L. Dibromomalonyl compounds. *Monatsh. Chem*., **1963**, *94*, 941-949.

[378] George, T.; Tahilramani, R Synthesis of quinolino heterocycles. *Tetrahedron*, **1968**, *24*, 1007-1010.

[379] Lutz, R.E.; Sanders, J.M. Antimalarials. 11. 2-Vinylogs of substituted 2-aryl-4-quinoline amino alcohols. *J. Med. Chem*., **1976**, *19*, 407-410.

[380] Bhide, K.S.; Mujumdar, R.B. Synthesis of swietenidin - A methyl ether. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem*., **1983**, *22*, 1254-1256.

[381] Fournier, C.; Decombe, J. 4-Hydroxycarbostyrils. *C. R. Seances Acad. Sci., Ser. C*, **1967**, *265*, 1169-1171.

[382] Drozd, V.N.; Knyazev, V.N.; Nam, N.L.; Lezina, V.P.; Mozhaeva, T.Y.; Savel'ev, V.L. Spirocyclic Meisenheimer complexes. XXXV. Possibility of anionic spiro-σ-complexes in the 3-nitro-2(1*H*)-quinolinone system. *Zh. Org. Khim*., **1993**, *29*, 782-788; *Russ. J. Org. Chem*., **1993**, *29*, 653-658.

[383] Hardman, R.; Partridge, M.W. Cyclic amidines. III. 2-Acylamino-4-alkoxyquinolines. *J. Chem. Soc*., **1955**, 510-515.

[384] Hardman, R.; Partridge, M.W. Cyclic amidines. VI. 5- and 7-Substituted 2-amino-4-hydroxyquinolines. *J. Chem. Soc*., **1958**, 614-620.

[385] Mehta, C.M.; Patel, G.H. Bromination of 2,4-substituted quinoline derivatives. *Curr. Sci*., **1961**, *30*, 15.

[386] Ukrainets, I.V.; Taran, S.G.; Evtifeeva, O.A.; Gorokhova, O.V.; Filimonova, N.I.; Turov, A.V. 4-Hydroxy-2-quinolones. 26. Bromination of 3-substituted 4-hydroxy-2-quinolones. *Khim. Geterotsikl. Soedin*., **1995**, 204-207; *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, **1995**, *31*, 176-179.

[387] Ismaili, L.; Refouvelet, B.; Robert, J.F. Synthesis of new pyrazolo[4,3-*c*]quinolin-3-one derivatives and some oxazolo[4,5-*c*]quinoline-2,4-diones. *J. Heterocycl. Chem*., **1999**, *36*, 719-722.

[388] Nishimura, T.; Igarashi, J.; Sunagawa, M. Conformational analysis of tandospirone in aqueous solution: Lead evolution of potent dopamine D4 receptor ligands. *Bioorg. Med. Chem. Lett*., **2001**, *11*, 1141-1144.

[389] Audisio, D.; Messaoudi, S.; Cegielkowski, L.; Peyrat, J.F.; Brion, J.D.; Methy-Gonnot, D.; Radanyi, C.; Renoir, J.M.; Alami, M. Discovery and biological activity of 6BrCaQ as an inhibitor of the Hsp90 protein folding machinery. *ChemMedChem*, **2011**, *6*, 804-815.

[390] Hamama, W.S.; Hassanien, A.E.; El-Fedawy, M.G.; Zoorob, H.H. Synthesis and antimicrobial evaluation of novel polyfused heterocycles-based quinolone. *J. Heterocycl. Chem*., **2015**, *52*, 492-496.

[391] Gaston, J.L.; Greer, R.J.; Grundon, M.F. Quinoline alkaloids. Part 25. Synthesis of isopropenylfuroquinolines and a hydroxyisopropylfuroquinolinone from copper(I) acetylides. *J. Chem. Res., Miniprint*, **1985**, 1877-1892.

[392] Okuzumi, T.; Sagi, K.; Yoshimura, T.; Tanaka, Y.; Nakanishi, E.; Ono, M.; Murata, M. Novel phenylalanine derivative. PCT Int. Appl. WO 03/053926, Jul 3, 2003; *Chem. Abstr*., **2003**, *139*, 85646.

[393] Harfenist M.; Magnien, E. Tetracyclic phenothiazines and related compounds. IV. Oxo amides alkylated and aminoalkylated on oxygen, and alkylated and aminated on carbon. *J. Org. Chem*., **1963**, *28*, 538-543.

[394] Huffman, J.W. Furanoquinoline alkaloids: Synthesis and reactions of some related 4-hydroxy-2-quinolinones. *J. Org. Chem*., **1961**, *26*, 1470-1474.

[395] Okamoto, T.; Nagakura, M. Reactions of 3-nitroquinoline derivatives with sodium hypobromite. *Chem. Pharm. Bull*., **1971**, *19*, 1745-1746.

[396] Okamoto, T.; Nagakura, M. Reaction mechanism in aromatic heterocyclic compounds. XI. Reaction of nitroquinoline with sodium hypobromite solution. I. 3-Nitroquinoline. *Yakugaku Zasshi*, **1972**, *92*, 158-166; *Chem.Abstr*., **1972**, *76*, 140457.

[397] Wu, J.; Zhang, L.; Sun, X. Synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones *via* palladium-catalyzed regioselective cross-coupling reactions of 3-bromo-4-trifloxyquinolin-2(1*H*)-one with arylboronic acids. *Chem. Lett*., **2005**, *34*, 550-551.

[398] Wang, Z.; Wu, J. Synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-ones *via* Pd-catalyzed regioselective cross-coupling reaction and cyclization. *Tetrahedron*, **2008**, *64*, 1736-1742.

[399] Wang, Z.; Xue, L.; He, Y.; Weng, L.; Fang, L. Access to functionalized 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones and thieno[2,3-*c*]quinolin-4(5*H*)-ones *via* domino reaction of 4-alkynyl-3-bromoquinolin-2(1*H*)-ones. *J. Org. Chem*., **2014**, *79*, 9628-9638.

[400] Rudd, M.T.; McCauley, J.; Liverton, N.; Grise-Bard, C.; Brouchu, M.C.; Charron, S.; Aulakh, V.; Bachand, B.; Beaulieu, P.; Zaghdane, H.; Han, Y.; Ferrara, M.; Harper, S.; Summa, V.; Chackalamannil, S.; Venkatraman, S.; Shah, U.; Velazquez, F. HCV NS3 protease inhibitors. PCT Int. Appl. WO 2013/074386, May 23, 2013; *Chem. Abstr*., **2013**, *159*, 9353.

[401] Wendeborn, S.V.; Cutler, S.R. 6-Sulfonylamino quinoline compounds as plant growth regulators. PCT Int. Appl. WO 2016/022915, Feb 11, 2016; *Chem. Abstr*., **2016**, *164*, 276921.

[402] Kafka, S. Unpublished results.

[403] Stadlbauer, W.; Lutschounig, H.; Schindler, G.; Witoszynskyj, T.; Kappe, T. Synthesis of 3-nitro- and 3-aminoquinoline-2,4-diones. An unexpected route to 3-hydroxyquinoline-2,4-diones. *J. Heterocycl. Chem*., **1992**, *29*, 1535-1540.

[404] Klásek, A.; Mrkvička, V.; Lyčka, A.; Mikšík, I.; Růžička, A. Reaction of 1-substituted 3-aminoquinoline-2,4-diones with isothiocyanates. An easy pathway to generate novel 2-thioxo-1'*H*-spiro[imidazoline-5,3'-indole]-2,2'-diones. *Tetrahedron*, **2009**, *65*, 4908-4916.

[405] Klásek, A.; Lyčka, A.; Mikšík, I.; Růžička, A. Reaction of 3-phenyl-3-aminoquinoline-2,4-diones with isothiocyanates. Facile access to novel spiro-linked 2-thioxoimidazolidine-oxindoles and imidazoline-2-thiones. *Tetrahedron*, **2010**, *66*, 2015-2025.

[406] Stadlbauer, W.; Kappe, T. Syntheses of 3-hydroxytetrahydroquinoline-2,4-diones. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, **1982**, *37B*, 1196-1200.

[407] Kafka, S.; Kovář, M.; Klásek, A.; Kappe, T. Reaction of 3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones with ethyl(triphenylphosphoranylidene)acetate. *J. Heterocycl. Chem.*, **1996**, *33*, 1977-1982.

[408] Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. Unprecedented reactivity of 5-substituted 3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones with ethyl (triphenylphosphoranylidene)acetate. *Heterocycles*, **1998**, *48*, 2309-2326.

[409] Klásek, A.; Kořistek, K.; Kafka, S.; Košmrlj, J. Thermal rearrangement of 3-hydroxy-1*H*,3*H*-quinoline-2,4-diones to 3-acyloxy-2,3-dihydro-1*H*-indol-2-ones. *Heterocycles*, **2003**, *60*, 1811-1820.

[410] Jansson, K.; Fristedt, T.; Olsson, A.; Svensson, B.; Joensson, S. Synthesis and reactivity of laquinimod, a quinoline-3-carboxamide: Intramolecular transfer of the enol proton to a nitrogen atom as a plausible mechanism for ketene formation. *J. Org. Chem.*, **2006**, *71*, 1658-1667.

[411] Kappe, T.; Ziegler, E. Syntheses of heterocycles. LIII. Chemistry of chloronitromalonyl compounds. *Monatsh. Chem.*, **1964**, *95*, 415-421.

[412] Mahran, M.R.; Abdou, W.M.; Sidky, M.M.; Wamhoff, H. Singlet oxygen photolysis of dihaloketones. A facile and efficient approach to vicinal triketones and their monohydrates. *Synthesis*, **1987**, 506-508.

[413] Ye, J.H.; Qin, Z.; Zhou, B.; Zhang, W.; Tian, G.; Yuan, L.; Xu, J.H. Thermal and photochemical approaches to the synthesis of vic-tricarbonyl compounds from 4-hydroxyquinolin-2(1*H*)-ones. *Org. Prep. Proced. Int.*, **2009**, *41*, 83-87.

[414] Cai, S.X.; Keana, J.F.W.; Weber, E. Glycine receptor antagonist pharmacophore. PCT Int. Appl. WO 96/04288, Feb 15, 1996; *Chem. Abstr.*, **1996**, *125*, 58541.

[415] Ahmed, N.; Brahmbhatt, K.G.; Singh, I.P.; Bhutani, K.K. Efficient chemoselective alkylation of quinoline 2,4-diol derivatives in water. *J. Heterocycl. Chem.*, **2011**, *48*, 237-240.

[416] Reisch, J.; Bathe, A. Acetylenic chemistry. Part 5. Phase-transfer catalytic reaction of 4-hydroxyquinolin-2-one and indolin-2-one with 3-bromo-1-propyne. *Arch. Pharm.*, **1987**, *320*, 737-742.

[417] Nishimura, H.; Nagai, Y.; Suzuki, T.; Sawayama, T. Synthesis of 4-hydroxy-2(1*H*)-quinolone derivatives. *Yakugaku Zasshi*, **1970**, *90*, 818-828; *Chem. Abstr.*, **1970**, *73*, 77020.

[418] Partridge, B.M.; González, J.S.; Lam, H.W. Iridium-catalyzed arylative cyclization of alkynones by 1,4-iridium migration. *Angew. Chem., Int. Ed.*, **2014**, *53*, 6523-6527.

[419] Minami, T.; Ogata, M.; Hirao, I.; Tanaka, M.; Agawa, T. Synthesis of a 3,1-benzoxazin-4-one, 2,4(1*H*,3*H*)-quinolinediones, and 2,4(1*H*,3*H*)-quinazolinediones from the reaction of phosphoryl-stabilized anions containing no α-hydrogen atoms with isatoic anhydride. *Synthesis*, **1982**, 231-233.

[420] Zografos, A.L.; Mitsos, C.A.; Igglessi-Markopoulou, O. One-step synthesis for the preparation of quinoline alkaloid analogues. *Org. Lett.*, **1999**, *1*, 1953-1955.

[421] Li, Y.M.; Wang, S.S.; Yu, F.; Shen, Y.; Chang, K.J. Copper-catalyzed cascade addition/cyclization: Highly efficient access to phosphonylated quinoline-2,4(1*H*,3*H*)-diones. *Org. Biomol. Chem.*, **2015**, *13*, 5376-5380.

[422] Fu, H.; Wang, S.S.; Li, Y.M. Copper-mediated oxidative radical addition/cyclization cascade: Synthesis of trifluoromethylated and sulfonated quinoline-2,4(1*H*,3*H*)-diones. *Adv. Synth. Catal.*, **2016**, *358*, 3616-3626.

[423] Wang, S.S.; Fu, H.; Shen, Y.; Sun, M.; Li, Y.M. Oxidative radical addition/cyclization cascade for the construction of carbonyl-containing quinoline-2,4(1*H*,3*H*)-diones. *J. Org. Chem.*, **2016**, *81*, 2920-2929.

[424] Wang, S.; Huang, X.; Wang, Q.; Ge, Z.; Wang, X.; Li, R. An efficient synthesis of sulfonated quinoline diones by copper catalyzed sulfonylation of activated alkenes with sulfonylhydrazides. *RSC Adv.*, **2016**, *6*, 11754-11757.

[425] Wang, S.S.; Fu, H.; Wang, G.; Sun, M.; Li, Y.M. Iron-catalyzed addition/cyclization cascade of activated alkenes with alcohols: Access to carbonyl substituted quinoline-2,4-diones. *RSC Adv.*, **2016**, *6*, 52391-52394.

[426] Taimr, L.; Prusikova, M.; Pospisil, J. Antioxidants and stabilizers. CXIII. Oxidation products of the antidegradant ethoxyquin. *Angew. Makromol. Chem.*, **1991**, *190*, 53-65.

[427] Blaszczyk, A.; Augustyniak, A.; Skolimowski, J. Ethoxyquin: An antioxidant used in animal feed. *Int. J. Food Sci.*, **2013**, 585931/1-585931/12.

[428] Moon, W.S.; Kim, J.C.; Chung, K.H.; Park, E.S.; Kim, M.N.; Yoon, J.S. Antimicrobial activity of a monomer and its polymer based on quinolone. *J. Appl. Polym. Sci.*, **2003**, *90*, 1797-1801.

[429] Dizman, B.; Mathias, L.J. Synthesis of novel methacrylate polymers containing norfloxacin. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, **2005**, *46*, 818-819.

[430] Dizman, B.; Elasri, M.O.; Mathias, L.J. Synthesis, characterization, and antibacterial activities of novel methacrylate polymers containing norfloxacin. *Biomacromolecules*, **2005**, *6*, 514-520.

[431] Mandl, A.; Klimek, D.E.; Chou, H.P.; Litzenberger, L.; Wang, Y. Single-mode operation of a long-pulse flashlamp pumped dye laser. *IEEE J. Quantum Electron.*, **1995**, *31*, 346-51.

[432] Han, F.; Liu, W.; Zhu, L.; Wang, Y.; Fang, C. Initial hydrogen-bonding dynamics of photoexcited coumarin in solution with femtosecond stimulated Raman spectroscopy. *J. Mater. Chem. C*, **2016**, *4*, 2954-2963.

[433] Kelterer, A.M.; Uray, G.; Fabian, W.M.F. Rational design of long-wavelength absorbing and emitting carbostyrils aided by time-dependent density functional calculations. *Comput. Theor. Chem.*, **2015**, *1055*, 25-32.

[434] Badgujar, N.S.; Pazicky, M.; Traar, P.; Terec, A.; Uray, G.; Stadlbauer, W. *N*-Carboxymethylated 6,7-dimethoxy-4-trifluoromethylcarbostyrils as fluorescence markers for amino acids, peptides, amino carbohydrates and amino polysaccharides. *Eur. J. Org. Chem.*, **2006**, 2715-2722.

[435] Uray, G.; Badgujar, N.S.; Kováčková, S.; Stadlbauer, W. Fluorescent 6-hydroxy- and 6,7-dihydroxy-4-trifluoromethylcarbostyrils and formation of O-carboxymethylated derivatives *via O*-succinimide esters. *J. Heterocycl. Chem.*, **2008**, *45*, 165-172.

[436] Stadlbauer, W.; Avhale, A.B.; Badgujar, N.S.; Uray, G. Syntheses and fluorescent properties of 2-amino substituted 6,7-dimethoxy-4-(trifluoromethyl)quinolines. *J. Heterocycl. Chem.*, **2009**, *46*, 415-420.

[437] Kramer, R.A.; Flehr, R.; Lay, M.; Kumke, M.U.; Bannwarth, W. Comparative studies of different quinolinone derivatives as donors in fluorescence-resonance-energy transfer (FRET) - systems in combination with a (bathophenanthroline)ruthenium(II) complex as acceptor. *Helv. Chim. Acta*, **2009**, *92*, 1933-1943.

[438] Kelterer, A.M.; Uray, G.; Fabian, W.M.F. Long wavelength absorbing carbostyrils as test cases for different TDDFT procedures and solvent models. *J. Mol. Model.*, **2014**, *20*, 1-10.

[439] Stadlbauer, W.; Uray, G.; Enoua, G.C. Flourescence properties of 6-methoxy- and 6,7-dimethoxyquinoline-3,4-dicarbonitriles. In: *International Electronic Conference on Synthetic Organic Chemistry*, *14th*, *Nov. 1-30*, *2010* [Online]; Seijas, J.A., Vazquez Tato, M.P., Eds.; MDPI AG: Basel; pp enoua3/1-enoua3/4. http://sciforum.net/conference/ecsoc-14/paper/392 (accessed August 8, 2016).

[440] Toche, R.B.; Kazi, M.A.; Patil, S.P.; Kanawade, S.B.; Jachak, M.N. Synthesis of quinolone substituted pyrazoles, isoxazoles and pyridines as a potential blue luminophores. *J. Fluoresc.*, **2010**, *20*, 1129-1137.

[441] Dhanapal, R.; Perumal, P.T.; Damodiran, M.; Ramprasath, C.; Mathivanan, N. Synthesis of quinoline derivatives for fluorescent imaging certain bacteria. *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 6494-6497.

[442] Wu, Z.; Shao, P.; Zhang, S.; Ling, X.; Bai, M. Molecular imaging of human tumor cells that naturally overexpress type 2 cannabinoid receptors using a quinolone-based near-infrared fluorescent probe. *J. Biomed. Opt.*, **2014**, *19*, 036006/1-036006/9.

[443] Jung, H.S.; Han, J.H.; Pradhan, T.; Kim, S.; Lee, S.W.; Sessler, J.L.; Kim, T.W.; Kang, C.; Kim, J.S. A cysteine-selective fluorescent probe for the cellular detection of cysteine. *Biomaterials*, **2012**, *33*, 945-953.

[444] Kowalska, A.; Kolińska, J.; Podsiadły, R.; Sokołowska, J. Dyes derived from 3-formyl-2(1*H*)-quinolone - Synthesis, spectroscopic characterisation, and their behaviour in the presence of sulfhydryl and non-sulfhydryl amino acids. *Color. Technol.*, **2015**, *131*, 157-164.

[445] Paramaguru, G.; Solomon, R.V.; Jagadeeswari, S.; Venuvanalingam, P.; Renganathan, R. Tuning the photophysical properties of 2-quinolinone-based donor-acceptor molecules through *N*- versus *O*-alkylation: Insights from experimental and theoretical investigations. *Eur. J. Org. Chem.*, **2014**, 753-766.

[446] Guo, Z.; Yu, H.; Ren, W.; Wang, Q. Selective aqueous fluorescent probes for metal ions based on benzoylhydrazone derivatives. *Anal. Methods*, **2015**, *7*, 8129-8137.

[447] Lee, J.J.; Lee, S.A.; Kim, H.; Nguyen, L.T.; Noh, I.; Kim, C. A highly selective CHEF-type chemosensor for monitoring Zn^{2+} in aqueous solution and living cells. *RSC Adv.*, **2015**, *5*, 41905-41913.

[448] Kovalska, V.B.; Volkova, K.D.; Manaev, A.V.; Losytskyy, M.Y.; Okhrimenko, I.N.; Traven, V.F.; Yarmoluk, S.M. 2-Quinolone and coumarin polymethines for the detection of proteins using fluorescence. *Dyes and Pigm.*, **2010**, *84*, 159-164.

[449] Pillai, S.; Kozlov, M.; Marras, S.A.E.; Krasnoperov, L.N.; Mustaev, A. New cross-linking quinoline and quinolone derivatives for sensitive fluorescent labeling. *J. Fluoresc.*, **2012**, *22*, 1021-1032.

[450] Kukla, S.; Cimrová, V.; Výprachtický, D. Terbium binding in highly luminescent polymer complexes. *Collect. Czech. Chem. Commun*., **2006**, *71*, 1333-1349.

[451] Výprachtický, D.; Cimrová, V.; Kukla, S.; Pavlačková, P. Efficient donor for terbium luminescence based on polymer ligand containing quinolinone fluorophore. *Macromol. Chem. Phys*., **2006**, *207*, 318-326.

[452] Výprachtický, D.; Mikeš, F.; Lokaj, J.; Pokorná, V.; Cimrová, V. Resonance energy transfer from quinolinone modified polystyrene-block-poly(styrene-alt-maleic anhydride) copolymer to terbium(III) metal ions. *J. Lumin*., **2015**, *160*, 27-34.

[453] Ikbal, M.; Banerjee, R.; Atta, S.; Jana, A.; Dhara, D.; Anoop, A.; Singh, N.D.P. Development of 1-hydroxy-2(1*H*)-quinolone-based photoacid generators and photoresponsive polymer surfaces. *Chem. - Eur. J*., **2012**, *18*, 11968-11975.

[454] Klásek, A.; Kořistek, K.; Lyčka, A.; Holčapek, M. Unprecedented reactivity of 3-amino-1*H*,3*H*-quinoline-2,4-diones with urea: An efficient synthesis of 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones. *Tetrahedron*, **2003**, *59*, 1283-1288.

[455] Klásek, A.; Lyčka, A.; Holčapek, M.; Kovář, M.; Hoza, I. Molecular rearrangement of 1-substituted 3-aminoquinoline-2,4-diones in their reaction with urea and nitrourea. Synthesis and transformations of reaction intermediates. *J. Heterocycl. Chem*., **2006**, *43*, 1251-1260.

[456] Klásek, A.; Lyčka, A.; Holčapek, M. Molecular rearrangement of 1-substituted 9b-hydroxy-3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-diones - An unexpected pathway to new indole and imidazolinone derivatives. *Tetrahedron*, **2007**, *63*, 7059-7069.

[457] Košmrlj, J.; Kafka, S.; Leban, I.; Grad, M. Spectral assignments and reference data formation and structure elucidation of two novel spiro[2*H*-indol]-3(1*H*)-ones. *Magn. Reson. Chem*., **2007**, *45*, 700-704.

[458] Kafka, S.; Klásek, A.; Polis, J.; Rosenbreierová, V.; Palík, C.; Mrkvička, V.; Košmrlj, J. The first entry to pyrrolo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones. *Tetrahedron*, **2008**, *64*, 4387-4402.

[459] Prucková, Z.; Klásek, A.; Lyčka, A.; Mikšík, I.; Růžička, A. Synthesis of 2-thioxoimidazolines *via* reaction of 1-unsubstituted 3-aminoquinoline-2,4-diones with isothiocyanates. *Tetrahedron*, **2009**, *65*, 9103-9115.

[460] Mrkvička, V.; Lyčka, A.; Rudolf, O.; Klásek, A. Reaction of 3-aminoquinoline-2,4-diones with isothiocyanic acid - an easy pathway to thioxo derivatives of imidazo[1,5-*c*]quinazolin-5-ones and imidazo[4,5-*c*]quinolin-4-ones. *Tetrahedron*, **2010**, *66*, 8441-8445.

[461] Mrkvička, V.; Rudolf, O.; Lyčka, A.; Klásek, A. Reaction of 1-substituted 3-aminoquinolinediones with isocyanic and isothiocyanic acid. *Tetrahedron*, **2011**, *67*, 2407-2413.

[462] Klásek, A.; Rudolf, O.; Rouchal, M.; Lyčka, A. Reaction of 3-hydroxyquinoline-2,4-diones with inorganic thiocyanates in the presence of ammonium or alkylammonium ions: The unexpected replacement of a hydroxy group by an amino group. *Helv. Chim. Acta*, **2015**, *98*, 318-335.

[463] Klásek, A.; Lyčka, A.; Křemen, F.; Růžicka, A.; Rouchal, M. Reduction of *N*-nitrosaminoquinolinediones with $LiAlH_4$ - an easy path to new tricyclic benzoxadiazocines. *Helv. Chim. Acta*, **2016**, *99*, 50-62.

[464] Abdou, M.M. Chemistry of 4-hydroxy-2(1*H*)-quinolone. Part 1: Synthesis and reactions. *Arabian J. Chem*., **2014**, http://dx.doi.org/10.1016/j.arabjc.2014.01.012.

[465] Hamama, W.S.; Hassanien, A.E.D.E.; Zoorob, H.H. Studies on quinolinedione: synthesis, reactions, and applications. *Synth. Commun*., **2014**, *44*, 1833-1858.

SEZNAM ZKRATEK

5HT	5-Hydroxytryptofan (označení receptorů).
Ar	Aryl.
Bu	Butyl.
CB	Kanabinoid (označení receptorů).
D	Dopamin (označení receptorů).
DBU	1,8-Diazabicyklo[5.4.0]undec-7-en.
DMF	Dimethylformamid.
DMSO	Dimethylsulfoxid.
Et	Ethyl.
GAPDH	Glyceraldehyd-3-fosfát dehydrogenasa.
GnRH	Gonadotropin uvolňující hormon.
GSK	Glykogen synthasa kinasa.
IC_{50}	Koncentrace, při které dojde k 50% inhibici zkoušeného systému.
LD_{50}	Dávka, při které dojde k úhynu poloviny testovaných jedinců.
LiHMDS	Bis(trimethylsilyl)amid lithný.
Me	Methyl.
MW	Mikrovlny.
NMDA	*N*-Methyl-D-aspartát (označení receptorů).
Me	Methyl.

PDFGR	Receptor růstového faktoru odvozený z krevních destiček.
Ph	Fenyl.
PPA	Kyselina polyfosforečná.
Pr	Propyl.
Py	Pyridyl.
T	Zvýšená teplota (záhřev).
THF	Tetrahydrofuran.
TNF-α	Faktor nádorové nekrózy (kachektin).
VEGR	Endoteliální vaskulární růstový faktor.

ŽIVOTOPIS AUTORA

Jméno:	Karel
Příjmení:	Proisl
Datum narození:	25. 11. 1985
Bydliště:	Študlov 170, 756 12 Horní Lideč
Kontakt:	603 388 832
	kproisl@itczlin.cz

Zaměstnání

2016–dosud Institut pro testování a certifikaci, a. s. – technický inženýr.

Vzdělání

2011–dosud Doktorské studium (předpokládané ukončení 2017, SZZ úspěšně proběhla 3. 2. 2016). Univerzita Tomáše Bati ve Zlíně, Fakulta technologická, Ústav chemie. Chemie a technologie materiálů. Nyní kombinovaná forma studia.

2009–2011 Magisterské studium. Univerzita Tomáše Bati ve Zlíně, Fakulta technologická. Chemie potravin a bioaktivních látek. Získán titul Ing.

2006–2009 Bakalářské studium. Univerzita Tomáše Bati ve Zlíně, Fakulta technologická. Chemie a technologie potravin. Získán titul Bc.

1997–2006 Gymnasium ve Valašských Kloboukách (osmileté gymnasium).

Účelové publikace

2016 Proisl, K.: Pojednání ke státní doktorské zkoušce.

2011 Proisl, K.: Studium reaktivity *N*-(*α*-ketoacyl)anthranilových kyselin. Diplomová práce.

2009 Proisl, K.: Studie oxidace chinolin-2,4-dionů kyselinou jodistou a jodistanem sodným. Bakalářská práce.

Původní sdělení v časopisech

2017 Proisl, K.; Kafka, S.; Košmrlj, J.: Chemistry and Applications of 4-Hydroxyquinolin-2-one and Quinoline-2,4-dione based Compounds. *Current Organic Chemistry*, **2017**, *21*, 1949–1975.

2016 Křemen, F.; Gazvoda, M.; Kafka, S.; Proisl, K.; Srholcová, A.; Klásek A.; Urankar, D.; Košmrlj, J.: Synthesis of 1,4-Benzodiazepine-2,5-diones by Base

Promoted Ring Expansion of 3-Aminoquinoline-2,4-diones. *Journal of Organic Chemistry*, **2016**, *82*, 715–722.

2014 Proisl, K.; Kafka, S.; Urankar, D.; Gazvoda, M.; Kimmel, R.; Košmrlj, J.: Fischer indolisation of *N*-(*α*-ketoacyl)anthranilic acids into 2-(indol-2-carboxamido)benzoic acids and 2-indolyl-3,1-benzoxazin-4-ones and their NMR study. *Organic & Biomolecular Chemistry*, **2014**, *12*, 9650–9664.

2013 Kafka, S.; Proisl, K.; Kašpárková, V.; Urankar, D.; Kimmel, R.; Košmrlj, J.: Oxidative ring opening of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones into *N*-(*α*-ketoacyl)anthranilic acids. *Tetrahedron*, **2013**, *69*, 10826–10835.

Kafka, S., Pevec, A.; Proisl, K.; Kimmel, R.; Košmrlj, J.: 4-Hydroxy-1-methyl-3-phenylquinolin-2(1*H*)-one. *Acta Crystallogr., Sect. E.*, **2013**, *69*, 231.

2012 Kafka, S.; Pevec, A.; Proisl, K.; Kimmel, R.; Košmrlj, J.: 3-Ethyl-3-hydroxy-8-methoxyquinoline-2,4(1*H*,3*H*)-dione monohydrate. *Acta Crystallogr., Sect. E.*, **2012**, *68*, 3199-3200.

Kafka, S.; Pevec, A.; Proisl, K.; Kimmel, R.; Košmrlj, J.: 3-Ethyl-4-hydroxy-8-methoxyquinolin-2(1*H*)-one. *Acta Crystallogr., Sect. E*., **2012**, *68*, 3198.

Proisl, K.; Kafka, S.: Preparation and potential application of 2-(indol-2-yl)-3,1-benzoxazin-4-ones. *Plasty a kaučuk*, **2012**, *49*, 42-47.

Granty

2015 Interní grantová agentura UTB ve Zlíně; IGA/FT/2015/008 – spoluřešitel.

2014 Interní grantová agentura UTB ve Zlíně; IGA/FT/2014/010 – hlavní řešitel.

2013 Interní grantová agentura UTB ve Zlíně; IGA/FT/2013/003 – hlavní řešitel.

2012 Interní grantová agentura UTB ve Zlíně; IGA/FT/2012/043 – hlavní řešitel.

2010 Interní grantová agentura UTB ve Zlíně; IGA/18/FT/10/A – spoluřešitel.

Projekty

2015 Účast na projektu OPVK CZ.1.07/2.3.00/45.0015. Centrum pro podporu přírodovědných a technických věd: Technická a přírodovědná laboratoř pro děti a mládež Zlínského kraje.

Aktivní účast na mezinárodních konferencích

2013 Proisl, K.; Košmrlj, J.; Urankar, D.; Kafka, S.: Novel scaffolds based on anthranilic acid. *15th Blue Danube Symposium on Heterocyclic Chemistry*. Olomouc, leden

2013. Hlaváč J., Potáček M.: Book of Abstracts, s. PO 62. ISBN: 978-80-263-0502-6. *Ústní presentace.*

Proisl, K.; Urbánek, P.; Kuřitka, I.; Urankar, D.; Košmrlj, J.; Kafka, S.: Spectral properties of selected indolylbenzoxazinones. *15th Blue Danube Symposium on Heterocyclic Chemistry*. Olomouc, leden 2013. Hlaváč J., Potáček M.: Book of Abstracts, s. PO 62. ISBN: 978-80-263-0502-6. *Posterové sdělení.*

2012 Proisl, K.; Košmrlj, J.; Urankar, D.; Kafka, S.: A study of 2-substituted 3,1-benzoxazin-4-ones. *4th EuCheMS Chemistry Congress*. Praha, srpen 2012. Chem. Listy 106, 1340 (2012). ISSN 1803-2389. *Posterové sdělení.*

Proisl, K.; Košmrlj, J.; Urankar, D.; Kafka, S.: 2-(Indol-2-yl)-3,1-benzoxazin-4-ones. *13th Belgian Organic Synthesis Symposium*. Leuven (Belgie) červen 2012. *Posterové sdělení.*

2010 Kafka, S.; Proisl, K.; Slintáková, L.; Kimmel, R.; Urankar, D.; Košmrlj, J.: Study of reactivity and potential synthetic utilization of N-(α-ketoacyl)anthranilic acids. *14th European Colloquium on Heterocyclic Chemistry*. Vídeň, srpen 2010. Book of Abstracts.com, Gumpoldskirchen 2010, ISBN 978-3-9502992-0-5. *Posterové sdělení.*

2009 Kafka, S.; Kašpárková, V.; Proisl, K.; Košmrlj, J.: Oxidative pyridine ring opening at 3 hydroxyquinoline-2,4(1H,3H)-diones. *13th Blue Danube Symposium on Heterocyclic Chemistry*. Bled, září 2009.

Získané certifikáty a absolvované kurzy

2017 Kurz interpretace vibračních spekter (Spektroskopická společnost Jana Marka Marci).

LITERATURA

[1]. O. RUDOLF. Syntéza heterocyklů na bázi chinolin-2,4-dionů a studium jejich vlastností a následných přeměn. Zlín, 2014. Disertační práce. Univerzita Tomáše Bati ve Zlíně. Vedoucí práce Prof. Ing. Antonín Klásek, DrSc.

[2]. R. KIMMEL. Glukosylace 4-hydroxychinolin-2(1H)-onů - cesta k analogům některých biologicky aktivních derivátů chinolinu. Zlín, 2010. Disertační práce. Univerzita Tomáše Bati ve Zlíně. Vedoucí práce Doc. Ing. Stanislav Kafka, CSc.

[3]. M. EL-NEKETI, W. EBRAHIM, W. LIN, S. GEDARA, F. BADRIA, H. E. A. SAAD, D. LAI, P. PROKSCH. Alkaloids and Polyketides from *Penicillium citrinum*, an Endophyte Isolated from the Moroccan Plant *Ceratonia siliqua*. *Journal of natural products*. 2013, **76**(6): 1099-1104. DOI: 10.1021/np4001366.

[4]. I. A. BESSONOVA. Components of *Haplophyllum bucharicum*. *Chemistry of Natural Compounds* . 2000, **36**(3): 323-324. DOI: 10.1007/bf02238348.

[5]. D. LAI, H. BRÖTZ-OESTERHELT, W. E. G. MÜLLER, V. WRAY a P. PROKSCH. Bioactive Polyketides and Alkaloids from *Penicillium citrinum*, a Fungal Endophyte Isolated from *Ocimum tenuiflorum*. *Fitoterapia* . 2013, **91**: 100-106. DOI: 10.1016/j.fitote.2013.08.017.

[6]. S. ANGELESKA, P. KEFALAS a A. DETSI. Crude Peroxidase from Onion Solid Waste as a Tool for Organic Synthesis. Part III: Synthesis of Tetracyclic Heterocycles (Coumestans and Benzofuroquinolinones). *Tetrahedron Letters* . 2013, **54**(19): 2325-2328. DOI: 10.1016/j.tetlet.2013.02.081.

[7]. D. AUDISIO, S. MESSAOUDI, S. COJEAN, J. F. PEYRAT, J. D. BRION, C. BORIES, F. HUTEAU, P. M. LOISEAU a M. ALAMI. Synthesis and Antikinetoplastid Activities of 3-Substituted Quinolinones Derivatives. *European Journal of Medicinal Chemistry* . 2012, **52**: 44-50. DOI: 10.1016/j.ejmech.2012.03.003.

[8]. X. M. LUO, S. H. QI, H. YIN, C. H. GAO a S. ZHANG. Alkaloids from the Stem Bark of *Micromelum falcatum*. *Chemical & Pharmaceutical Bulletin*. 2009, **57**(6): 600-602. DOI: 10.1248/cpb.57.600.

[9]. B. H. BHIDE. *Indian Journal of Chemistry, Section B*. 1977, **15**: 440-443.

[10]. S. AOKI, Y. YE, K. HIGUCHI, A. TAKASHIMA, Y. TANAKA, I. KITAGAWA, M. KOBAYASHI. Novel Neuronal Nitric Oxide Synthase (nNOS) Selective Inhibitor, Aplysinopsin-Type Indole Alkaloid, from Marine Sponge *Hyrtios erecta*. *Chemical and Pharmaceutical Bulletin*. 2001, **49**(10): 1372-1374. DOI: org/10.1248/cpb.49.1372.

[11]. W. D. CROW, J. H. HODGKIN. Alkaloids of the Australian Rutaceae: *Halfordia scleroxyla* and *Halfordia kendack*. IV. Co-occurrence of Oxazole and Quinoline Alkaloids. *Australian Journal of Chemistry*. 1968, **21**: 3075-3077. DOI: 10.1071/ch9683075.

[12]. Z. S. FAIZUTDINOVA, I. A. BESSONOVA, S. Y. YUNUSOV. The Structure of Bucharidine. *Chemistry of Natural Compounds* . 1969, **5**(5): 380-381. DOI: 10.1007/bf00595108.

[13]. S. S. NAZRULLAEV, I. A. BESSONOVA, K. S. AKHMEDKHODZHAEVA. *Chemistry of Natural Compounds* . 2001, **37**(6): 551-555. DOI: 10.1023/a:1014873000974.

[14]. C. IH-SHENG, W. SHWU-JEN, L. YUH-CHWEN, T. LIH, H. SEKI, K. FENG-NIEN, T. CHE-MING. Dimeric 2-Quinolone Alkaloid and Antiplatelet Aggregation Constituents of *Zanthoxylum simulans*. *Phytochemistry* . 1994, **36**(1): 237-239. DOI: 10.1016/s0031-9422(00)97045-6.

[15]. L. JURD, M. BENSON, R. Y. WONG. New Quinolinone and Bis-quinolinone Alkaloids from *Euxylophora paraensis*. *Australian Journal of Chemistry*. 1983, **36**(4): 759-768. DOI: 10.1071/CH9830759.

[16]. Y. YAMAMOTO, K. HARIMAYA. Synthesis of SF2809-V, Chymase Inhibitor, and Its Analogs by Three Component Reaction: Model Study for High Throughput Synthesis of a Chymase Inhibitor Library. *Chemistry Letters*. 2004, **33**(3): 238-239. DOI: org/10.1246/cl.2004.238.

[17]. W. W. SONG, G. Z. ZENG, W. W. PENG, K. X. CHEN a N. H. TAN. Cytotoxic Amides and Quinolones from *Clausena lansium*. *Helvetica Chimica Acta*. 2014, **97**(2): 298-305. DOI: 10.1002/hlca.201300323.

[18]. L. E. C. SUAREZ, M. E. PATTARROYO, J. M. LOZANO a F. D. MONACHE. Biological Activity of Secondary Metabolites from *Peltostigma guatemalense*. *Natural Product Research*. 2009, **23**(4): 370-374. DOI: 10.1080/14786410802228439.

[19]. M. S. HIFNAWY. *Phytochemistry*. 1977, **16**: 1035-1038.

[20]. I. A. BESSONOVA, S. YUNUSOV. *Chemistry of Natural Products*. 1989, **25**: 18-20.

[21]. V. SEVERINO, S. D. FREITAS, P. BRAGA, M. FORIM, M. D. SILVA, J. FERNANDES, P. VIEIRA a T. VENÂNCIO. New Limonoids from *Hortia oreadica* and Unexpected Coumarin from *H. superba* Using Chromatography over Cleaning Sephadex with Sodium Hypochlorite. *Molecules*. 2014, **19**(8): 12031-12047. DOI: 10.3390/molecules190812031.

[22]. I. SIRIDECHAKORN, S. LAPHOOKHIEO. Chemical Constituents from *Feronia limonia* Roots. *Chemistry of Natural Compounds* . 2012, **48**(2): 308-309. DOI: 10.1007/s10600-012-0231-3.

[23]. H. Y. HUANG, T. ISHIKAWA, C. F. PENG, S.CHEN, I. S. CHEN. Secondary Metabolites from the Root Wood of *Zanthoxylum wutaiense* and Their Antitubercular Activity. *Chemistry & Biodiversity*. 2011, **8**(5): 880-886. DOI: 10.1002/cbdv.201000127.

[24]. R. RODRÍGUEZ-GUZMÁN, L. J. FULKS, M. RADWAN, C. BURANDT, S. ROSS. Chemical Constituents, Antimicrobial and Antimalarial Activities of *Zanthoxylum monophyllum*. *Planta Medica*. 2011, **77**(13): 1542-1544. DOI: 10.1055/s-0030-1270782.

[25]. L. V. ROSAS, T. A. M. VEIGA, J. B. FERNANDES, P. C. VIEIRA, M. F. G. F. SILVA. Prenylindole Alkaloids from *Raputia praetermissa* (*Rutaceae*) and their Chemosystematic Significance. *Journal of the Brazilian Chemical Society*. 2011, **22**(7): 1346-1353. DOI: 10.1590/s0103-50532011000700021.

[26]. T. IAN-LIH. *Phytochemistry*. 1998, **48**(5): 880-886.

[27]. K. E. SAYED, M. S. AL-SAID, F. S. EL-FERALY, S. A. ROSS. New Quinoline Alkaloids from *Ruta chalepensis*. *Journal of Natural Products* . 2000, **63**(7): 995-997. DOI: 10.1021/np000012y.

[28]. C. L. CANTRELL, K. K. SCHRADER, L. K. MAMONOV, G. T. SITPAEVA, T. S. KUSTOVA, C. DUNBAR, D. E. WEDGE. Isolation and Identification of Antifungal and Antialgal Alkaloids from *Haplophyllum sieversii*. *Journal of Agricultural and Food Chemistry* . 2005, **53**(20): 7741-7748. DOI: 10.1021/jf051478v.

[29]. D. M. RAZAKOVA, I. A. BESSONOVA, S. Y. YUNUSOV. Components of *Haplophyllum obtusifolium*. *Chemistry of Natural Compounds*. 1984, **20**(5): 599-600. DOI: 10.1007/bf00580074.

[30]. V. SEVERINO, S. D. FREITAS, P. BRAGA, M. FORIM, M. D. SILVA, J. FERNANDES, P. VIEIRA a T. VENÂNCIO. New Limonoids from *Hortia oreadica* and Unexpected Coumarin from *H. superba* Using Chromatography over Cleaning Sephadex with Sodium Hypochlorite. *Molecules*. 2014, **19**(8): 12031-12047. DOI: 10.3390/molecules190812031.

[31]. Y. HITOTSUYANAGI, H. KOJIMA, H. IKUTA, K. TAKEYA, H. ITOKAWA. Identification and Structure-Activity Relationship Studies of Osthol, a Cytotoxic Principle from *Cnidium monnieri*. *Bioorganic & Medicinal Chemistry Letters*. 1996, **6**(15): 1791-1794. DOI: 10.1016/0960-894x(96)00315-0.

[32]. F. IMAI, K. ITOH, N. KISHIBUCHI, T. KINOSHITA, U. SANKAWA. Constituents of the Root Bark of *Murraya paniculata* Collected in Indonesia. *Chemical and Pharmaceutical Bulletin*. 1989, **37**(1): 119-123. DOI: org/10.1248/cpb.37.119.

[33]. W. E. CAMPBELL, K. P. FINCH, P. A. BEAN, N. FINKELSTEIN. Alkaloids of the *Rutoideae*: Tribe *Diosmeae*. *Phytochemistry*. 1987, **26**(2): 433-434. DOI: 10.1016/s0031-9422(00)81426-0.

[34]. J. J. CHEN, Y. L. CHANG, C. M. TENG, C. C. SU, I. S. CHEN. Quinoline Alkaloids and Anti-Platelet Aggregation Constituents from the Leaves of *Melicope semecarpifolia*. *Planta*. 2002, **68**(9): 790-793. DOI: 10.1055/s-2002-34412.

[35]. T. S. WU, F. C. CHANG, P. L. WU. Flavonoids, Amidosulfoxides and an Alkaloid from the Leaves of *Glycosmis citrifolia*. *Phytochemistry*. 1995, **39**(6): 1453-1457. DOI: 10.1016/0031-9422(95)00171-3.

[36]. K. A. RASULOVA, I. A. BESSONOVA. Alkaloids of *Haplophyllum perforatum*. *Chemistry of Natural Compounds*. 1992, **28**(2): 214-216. DOI: 10.1007/bf00630180.

[37]. W. W. SONG, G. Z. ZENG, W. W. PENG, K. X. CHEN, N. H. TAN. Cytotoxic Amides and Quinolones from *Clausena lansium*. *Helvetica Chimica Acta*. 2014, **97**(2): 298-305. DOI: 10.1002/hlca.201300323.

[38]. H. Y. HUANG, T. ISHIKAWA, C. F. PENG, I. L. TSAI, I. S. CHEN. Constituents of the Root Wood of *Zanthoxylum wutaiense* with Antitubercular Activity. *Journal of Natural Products*. 2008, **71**(7): 1146-1151. DOI: 10.1021/np700719e.

[39]. S. PERRET, P. J. WHITFIELD. Atanine (3-Dimethylallyl-4-methoxy-2-quinolone), an Alkaloid with Anthelmintic Activity from the Chinese Medicinal Plant, *Evodia rutaecarpa*. *Planta medica*. 1995, **61**(3): 276-278. DOI: 10.1055/s-2006-958073.

[40]. W. FROMMER, B. JUNGE, L. MUELLER, D. SCHMIDT, E. TRUSCHEIT. Neue Enzyminhibitoren aus Mikroorganismen. *Planta medica*. 1979, **35**(3): 195-217. DOI: 10.1055/s-0028-1097207.

[41]. B. D. PAUL, P. K. BOSE. New Quinolone Alkaloids from *Ravenia spectabilis*. *Journal of Indian Chemical Society*. 1968, **45**(6): 552-553.

[42]. C. ITO, M. ITOIGAWA, T. OTSUKA, H. TOKUDA, H. NISHINO, H. FURUKAWA. Constituents of *Boronia pinnata*. *Journal of Natural Products*. 2000, **63**(10): 1344-1348. DOI: 10.1021/np0000318.

[43]. W. T. SHUNG, K. C. SHENG, H. FURUKAWA. Acridone Alkaloids and a Coumarin from *Citrus grandis*. *Phytochemistry*. 1983, **22**(6): 1493-1498. DOI: 10.1016/S0031-9422(00)84044-3.

[44]. R. STORER, D. W. YOUNG. Synthesis of Halfordamine, an Alkaloid from *Halfordia kendack*. *Tetrahedron*. 1973, 2015-11-12, **29**(9): 1215-1216. DOI: 10.1016/0040-4020(73)80104-8. ISSN 00404020.

[45]. S. KAZUHIKO, I. MIKI, K. MURATA, H. JUNKE, S. MOTOMURA, T. ARAKI, Y. ITOYAMA a Y. OSHIMA. Pharmacological Properties of Pteleprenine, a Quinoline Alkaloid Extracted from *Orixa japonica*, on Guinea-pig Ileum and Canine Left Atrium. *Journal of Pharmacy and Pharmacology*. 1998, 2015-11-12, **50**(7): 803-807. DOI: 10.1111/j.2042-7158.1998.tb07143.x. ISSN 00223573.

[46]. M. TERASAKA, K. NARAHASHI, Y. TOMIKAWA. Alkaloids of the Root-bark of *Orixa japonica* THUNB. X. Isolation of Nor-orixine. *Chemical and Pharmaceutical Bulletin*. 1960, **8**(12): 1142-1143. DOI: org/10.1248/cpb.8.1142.

[47]. N. TOSHIRO, M. TANDO, K. SUZUKI, K. MURATA, S. FUNAYAMA. New Quinoline Alkaloids from the Leaves and Stems of *Orixa japonica*, Orijanone, Isopteleflorine and 3'-O-Methylorixine. *Bioscience, Biotechnology and Biochemistry*. 2014, **65**(3), 710-713. DOI: 10.1271/bbb.65.710. ISSN 0916-8451.

[48]. A. YENESEW, E. DAGNE. Alkaloids of *Teclea nobilis*. *Phytochemistry*. 1988, **27**(2), 651-653. DOI: 10.1016/0031-9422(88)83170-4. ISSN 00319422.

[49]. S. R. JOHNS, R. I. WILLING. ^{13}C N.M.R Spectra of Quinoline and Methylquinolines. The Magnitude of the Vicinal Coupling Constants. *Australian Journal of Chemistry*. 1976, **29**(7): 1617-1622. DOI: 10.1071/CH9761617.

[50]. W. STECK, B. K. BAILEY, J. P. SHYLUK a O. L. GAMBORG. Coumarins and Alkaloids from Cell Cultures of *Ruta graveolens*. *Phytochemistry*. 1971, **10**(1): 191-194. DOI: 10.1016/S0031-9422(00)90269-3. ISSN 00319422.

[51]. R. TORRES, B. K. CASSELS. Leaf Alkaloids of *Fagara mayu*. *Phytochemistry*. 1978, **17**(4), 838-839. DOI: 10.1016/S0031-9422(00)94261-4. ISSN 00319422.

[52]. T. HIGA, P. J. SCHEUER. Alkaloids from *Pelea barbigera*. *Phytochemistry*. 1974, **13**(7): 1269-1272. DOI: 10.1016/0031-9422(74)80116-0. ISSN 00319422.

[53]. N. TAKAHASHI, N. SUBEHAN, S. KADOTA, Y. TEZUKA. Mechanism-based CYP2D6 Inactivation by Acridone Alkaloids of Indonesian Medicinal Plant *Lunasia amara*. *Fitoterapia*. 2012, **83**(4): 774-779. DOI: 10.1016/j.fitote.2012.03.011. ISSN 0367326x.

[54]. I. A. BESSONOVA, D. BATSUREN, N. D. ABDULLAEV, S. Y. YUNUSOV. Daurine. A New Alkaloid from *Haplophyllum dauricum*. *Chemistry of Natural Compounds*. 1983, **19**(1): 117-118. DOI: 10.1007/BF00579995. ISSN 0009-3130.

[55]. M. ESKAIROW. *Doklady akademii nauk USSR*. **11958**(5): 23.

[56]. S. M. SHARAFUTDINOVA, S. Y. YUNUSOV. The Alkaloids of *Haplophyllum bucharicum*. *Chemistry of Natural Compounds*. 1968, **4**(3): 171-171. DOI: 10.1007/BF00565764. ISSN 0009-3130.

[57]. L. A. MCQUAID, E. C. R. SMITH, D. LODGE, E. PRALONG, J. H. WIKEL, D. O. CALLIGARO a P. J. O'MALLEY. 3-Phenyl-4-hydroxyquinolin-2(1H)-ones: Potent and Selective Antagonists at the Strychnine-insensitive Glycine Site on the N-Methyl-D-aspartate Receptor Complex. *Journal of Medicinal Chemistry*. 1992, **35**(18): 3423-3425. DOI: 10.1021/jm00096a019. ISSN 0022-2623.

[58]. M. J. ROWLEY, J. KULAGOWSKI, A. P. WATT, D. RATHBONE, G. I. STEVENSON, R. W. CARLING, R. BAKER, G. R. MARSHALL, J. A. KEMP. Effect of Plasma Protein Binding on *in Vivo* Activity and Brain Penetration of Glycine/NMDA Receptor Antagonists. *Journal of Medicinal Chemistry*. 1997, **40**(25): 4053-4068. DOI: 10.1021/jm970417o. ISSN 0022-2623.

[59]. H. P. BUCHSTALLER, C. D. SIEBERT, R. STEINMETZ, I. FRANK, M. L. BERGER, R. GOTTSCHLICH, J. LEIBROCK, M. KRUG, D. STEINHILBER, C. NOE. Synthesis of Thieno[2,3-b]Pyridinones Acting as Cytoprotectants and as Inhibitors of [3H]Glycine Binding to the N-Methyl-d-aspartate (NMDA) Receptor. *Journal of Medicinal Chemistry*. 2006, **49**(3): 864 – 871 DOI: 10.1021/jm0503493.

[60]. R. W. CARLING, P. D. LEESON, K. W. MOORE, C. R. MOYES, M. DUNCTON, M. L. HUDSON, R. BAKER, A. C. FOSTER, S. GRIMWOOD, J. A. KEMP, G. MARSHALL, M. TRICKLEBANK, K. SAYWELL. 4-Substituted-3-phenylquinolin-2(1H)-ones: Acidic and Nonacidic Glycine Site N-Methyl-d-aspartate Antagonists with *in Vivo* Activity. *Journal of Medicinal Chemistry*. 1997, **40**(5): 754 – 765. DOI: 10.1021/jm9605492.

[61]. A. KREIMEYER, B. LAUBE, M. STURGESS, M. GOELDNER, B. FOUCAUD. Evaluation and Biological Properties of Reactive Ligands for the Mapping of the Glycine Site on the N-Methyl-d-aspartate (NMDA) Receptor. *Journal of Medicinal Chemistry*. 1999, **42**(21): 4394 – 4404. DOI: 10.1021/jm9910730.

[62]. P. WLAŹ, W. LÖSCHER. Weak Anticonvulsant Effects of Two Novel Glycine Receptor Antagonists in the Amygdala-kindling Model in Rats. *European Journal of Pharmacology*. 1998, **342**(1): 39-46. DOI: 10.1016/S0014-2999(97)01452-0. ISSN 00142999.

[63]. R. D. FABIO, A. M. CAPELLI, N. CONTI, A. CUGOLA, D. DONATI, A. FERIANI, P. GASTALDI, G. GAVIRAGHI, C. T. HEWKIN. Substituted Indole-2-carboxylates as *in Vivo* Potent Antagonists Acting as the Strychnine-Insensitive Glycine Binding Site. *Journal of Medicinal Chemistry*. 1997, **40**(6): 841-850. DOI: 10.1021/jm960644a. ISSN 0022-2623.

[64]. P. H. HUTSON, C. L. BARTON. L-701,324, a Glycine/NMDA Receptor Antagonist, Blocks the Increase of Cortical Dopamine Metabolism by Stress and DMCM. *European Journal of Pharmacology*. 1997, **326**(2-3): 127-132. DOI: 10.1016/S0014-2999(97)85406-4. ISSN 00142999.

[65]. T. P. OBRENOVITCH, E. ZILKHA. Inhibition of Cortical Spreading Depression by L-701,324, a Novel Antagonist at the Glycine Site of the N-Methyl-D-aspartate Receptor Complex. *British Journal of Pharmacology*. 1996, **117**(5): 931-937. DOI: 10.1111/j.1476-5381.1996.tb15283.x. ISSN 00071188.

[66]. THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA. Methods for Treating Neurological and Psychiatric Conditions. WO 2007/2285 A2, 2007.

[67]. T. FUCHIGAMI, T. HARADAHIRA, N. FUJIMOTO, Y. NOJIRI, T. MUKAI, F. YAMAMOTO, T. OKAUCHI, J. MAEDA, K. SUZUKI. Development of N-[%C]Methylamino 4-Hydroxy-2(1H)-quinolone Derivatives as PET Radioligands for the Glycine-Binding Site of NMDA Receptors. *Bioorganic & Medicinal Chemistry*. 2009, **17**(15): 5665-5675. DOI: 10.1016/j.bmc.2009.06.014. ISSN 09680896.

[68]. J. PAESHUYSE, I. VLIEGEN, L. COELMONT, P. LEYSSEN, O. TABARRINI, P. HERDEWIJN, H. MITTENDORFER, J. EASMON, V. CECCHETTI, R. BARTENSCHLAGER, G. PUERSTINGER, J. NEYTS. Comparative *In Vitro* Anti-Hepatitis C Virus Activities of a Selected Series of Polymerase, Protease, and Helicase Inhibitors.

Antimicrobial Agents and Chemotherapy. 2008, **52**(9): 3433 – 3437. DOI: 10.1128/AAC.01534-07.

[69]. M. L. BARRECA, G. MANFRONI, P. LEYSSEN, J. WINQUIST, N. KAUSHIK-BASU, J. PAESHUYSE, R. KRISHNAN, N. IRACI, S. SABATINI. Structure-Based Discovery of Pyrazolobenzothiazine Derivatives As Inhibitors of Hepatitis C Virus Replication. *Journal of Medicinal Chemistry*. 2013, **56**(6): 2270-2282. DOI: 10.1021/jm301643a. ISSN 0022-2623.

[70]. J. D. VICENTE, R. T. HENDRICKS, D. B. SMITH, J. B. FELL, J. FISCHER, S. R. SPENCER, P. J. STENGEL, P. MOHR, J. E. ROBINSON. Non-nucleoside Inhibitors of HCV Polymerase NS5B. Part 2: Synthesis and Structure–activity Relationships of Benzothiazine-substituted Quinolinediones. *Bioorganic & Medicinal Chemistry Letters*. 2009, **19**(13): 3642-3646. DOI: 10.1016/j.bmcl.2009.05.004. ISSN 0960894x.

[71]. R. T. HENDRICKS, J. B. FELL, J. F. BLAKE, J. P. FISCHER, J. E. ROBINSON, S. R. SPENCER, P. J. STENGEL, A. L. BERNACKI, V. J. P. LEVEQUE. Non-nucleoside Ihibitors of HCV NS5B Polymerase. Part 1: Synthetic and Computational Exploration of the Binding Modes of Benzothiadiazine and 1,4-Benzothiazine HCV NS5b Polymerase Inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 2009, **19**(13): 3637-3641. DOI: 10.1016/j.bmcl.2009.04.119. ISSN 0960894x.

[72]. R. TEDESCO, D. CHAI, M. G. DARCY, D. DHANAK, D. M. FITCH, A. GATES, V. K. JOHNSTON, R. M. KEENAN, J. LIN-GOERKE. Synthesis and Biological Activity of Heteroaryl 3-(1,1-dioxo-2H-(1,2,4)-benzothiadizin-3-yl)-4-hydroxy-2(1H)-quinolinone Derivatives as Hepatitis C Virus NS5B Polymerase Inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 2009, **19**(15): 4354-4358. DOI: 10.1016/j.bmcl.2009.05.080. ISSN 0960894x.

[73]. UNIVERSITY OF SOUTHERN CALIFORNIA. Compounds with HIV-1 Integrase Inhibitory Activity and Use thereof as Anti-HIV/AIDS Therapeutics. US2009/88420 A1, 2009.

[74]. NOVARTIS AG, NOVARTIS PHARMA GmbH. Inhibitors of Undecaprenyl Pyrophosphate Synthase. WO 2008/14307 A2, 2008.

[75]. J. DENG, T. SANCHEZ, L. Q. AL-MAWSAWI, R. DAYAM, R. A. YUNES, A. GAROFALO, M. B. BOLGER, N. NEAMATI. Discovery of Structurally Diverse HIV-1 Integrase Inhibitors Based on a Chalcone Pharmacophore. *Bioorganic & Medicinal Chemistry*. 2007, **15**(14): 4985-5002. DOI: 10.1016/j.bmc.2007.04.041. ISSN 09680896.

[76]. V. PALOMO, I. SOTERAS, D. I. PEREZ, C. PEREZ, C. GIL, N. E. CAMPILLO, A. MARTINEZ. Exploring the Binding Sites of Glycogen Synthase Kinase 3. Identification and Characterization of Allosteric Modulation Cavities. *Journal of Medicinal Chemistry*. 2011, **54**(24): 8461-8470. DOI: 10.1021/jm200996g. ISSN 0022-2623.

[77]. CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS (CSIC). Heterocyclic GSK-3 Allosteric Modulators. US 2015/57311 A1, 2015.

[78]. J. A. MORALES-GARCIA, V. PALOMO, M. REDONDO, S. ALONSO-GIL, C. GIL, A. MARTINEZ a A. PEREZ-CASTILLO. Crosstalk Between Phosphodiesterase 7 and

Glycogen Synthase Kinase-3: Two Relevant Therapeutic Targets for Neurological Disorders. *ACS Chemical Neuroscience*. 2014, **5**(3): 194-204. DOI: 10.1021/cn400166d. ISSN 1948-7193.

[79]. Z. Y. XIAO, W. X. ZHOU, Y. X. ZHANG, J. P. CHENG, J. F. HE, R. F. YANG, L. H. YUN. Roquinimex-mediated Protection Effect on the Development of Chronic Graft-versus-host Disease in Mice is Associated with Induction of Th1 Cytokine Production and Inhibition of Proinflammatory Cytokine Production. *Life Sciences*. 2007, **81**(19-20): 1403-1410. DOI: 10.1016/j.lfs.2007.08.044. ISSN 00243205.

[80]. L. XIANG, D. KLINTMAN, S. TOHRU, H. GUNNAR, S. RENE, J. BENGT, H. THORLACIUS. Interleukin-10 Mediates the Protective Effect of Linomide by Reducing CXC Chemokine Production in Endotoxin-Induced Liver Injury. *British Journal of Pharmacology*. 2004, **143**(7): 865 – 871. DOI: 10.1038/sj.bjp.0706015.

[81]. ACTIVE BIOTECH AB. Quinoline derivatives. EP 1095021 B1, 2003.

[82]. J. SHI, Z. XIAO, M. A. IHNAT, C. KAMAT, B. PANDIT, Z. HU, P. K. LI. Structure–activity Relationships Studies of the Anti-angiogenic Activities of Linomide. *Bioorganic & Medicinal Chemistry Letters*. 2003, **13**(6): 1187-1189. DOI: 10.1016/S0960-894X(03)00047-7. ISSN 0960894x.

[83]. S. AMERINI, S. FILIPPI, A. PARENTI, F. LEDDA, M. ZICHE.Vasorelaxant Effects Induced by the Antiangiogenic Drug Linomide in Aortic and Saphenous Vein Preparations of the Rabbit. *British Journal of Pharmacology.* 1997, **122**(8): 1739 – 1745. DOI: 10.1038/sj.bjp.0701565.

[84]. TEVA PHARMACEUTICAL INDUSTRIES, LTD. Laquinimod Combination Therapy For Treatment Of Multiple Sclerosis. US 2015/94332 A1, 2015.

[85]. TEVA PHARMACEUTICAL INDUSTRIES, LTD. Treatment of Multiple Sclerosis with Combination of Laquinimod and Fampridine. US 2014/17226 A1, 2014.

[86]. TEVA PHARMACEUTICAL INDUSTRIES, LTD. Treatment Of Multiple Sclerosis With Combination Of Laquinimod And Fingolimod. US 2013/96158 A1, 2013.

[87]. S. JÖNSSON, G. ANDERSSON, T. FEX, T. FRISTEDT, G. HEDLUND, K. JANSSON, L. ABRAMO, I. FRITZSON, O. PEKARSKI. Synthesis and Biological Evaluation of New 1,2-Dihydro-4-hydroxy-2-oxo-3-quinolinecarboxamides for Treatment of Autoimmune Disorders: Structure−Activity Relationship. *Journal of Medicinal Chemistry*. 2004, **47**(8): 2075-2088. DOI: 10.1021/jm031044w. ISSN 0022-2623.

[88]. Nerventra (laquinimod) Capsules 0,6 mg. Registration certificate. State Register of Medicines (in Russian). Dostupné z: http://grls.rosminzdrav.ru/Grls_View_v2.aspx?idReg=64645.

[89]. J. JIANG, R. J. DEVITA, M. T. GOULET, M. J. WYVRATT, J. L. LO, N. REN, J. B. YUDKOVITZ, J. CUI, Y. T. YANG. Syntheses and Structure–activity Relationship Studies of Piperidine-substituted Quinolones as Nonpeptide Gonadotropin Releasing Hormone

Antagonists. *Bioorganic & Medicinal Chemistry Letters*. 2004, **14**(7): 1795-1798. DOI: 10.1016/j.bmcl.2003.12.101. ISSN 0960894x.

[90]. J. R. YOUNG, S. X. HUANG, I. CHEN, T. F. WALSH, R. J. DEVITA, M. J. WYVRATT, M. T. GOULET, N. REN, J. LO. Quinolones as Gonadotropin Releasing Hormone (GnRH) Antagonists: Simultaneous Optimization of the C(3)-Aryl and C(6)-Substituents. *Bioorganic & Medicinal Chemistry Letters*. 2000, **10**(15): 1723-1727. DOI: 10.1016/S0960-894X(00)00318-8. ISSN 0960894x.

[91]. L. H. HEITMAN, P. A. IJZERMAN. G Protein-coupled Receptors of the Hypothalamic-pituitary-gonadal Axis: A Case for Gnrh, LH, FSH, and GPR54 Receptor Ligands. *Medicinal Research Reviews*. 2008, 2015-11-12, **28**(6): 975-1011. DOI: 10.1002/med.20129. ISSN 01986325.

[92]. OREGON HEALTH AND SCIENCE UNIVERSITY. Restoring function to gonadotropin releasing hormone receptor mutants. WO 2004/69859 A2, 2004.

[93]. MERCK AND CO., INC. Antagonists of Gonadotropin Releasing Hormone. US 6147088 A1, 2000.

[94]. J. A. JANOVICK. Structure-Activity Relations of Successful Pharmacologic Chaperones for Rescue of Naturally Occurring and Manufactured Mutants of the Gonadotropin-Releasing Hormone Receptor. *Journal of Pharmacology and Experimental Therapeutics*. **305**(2), 608-614. DOI: 10.1124/jpet.102.048454. ISSN 00223565.

[95]. THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL. THE GOV. OF THE U.S.A AS REPRESENTED BY THE SECRETARY OF THE DEPT. OF HEALTH AND HUMAN SERVICES. Glyceraldehyde 3-Phosphate Dehydrogenase-S (GAPDHS), a Glycolytic Enzyme Expressed only in Male Germ Cells, is a Target for Male Contraception. US 2005/266515 A1, 2005.

[96]. I. V. UKRAINETS, O. V. GOROKHOVA, S. G. TARAN, P. A. BEZUGLYI, N. I. FILIMONOVA, A. V. TUROV. 4-Hydroxy-2-quinolenes. Improved Synthesis and Biological Properties of Hydrochlorides of β-Dialkylaminoalkylamides of 1-Alkyl-2-oxo-4-hydroxyquinoline-3-carboxylic acids. *Chemistry of heterocyclic compounds*. 1994, **30**(10): 1214-1219. DOI: 10.1007/BF01184888.

[97]. G. RACZ, C. NOE, I. UKRAINETS. Pain management – Current Issues and Opinions. Janeza Trdine 9, 51000 Rijeka, Croatia: InTech, 2011, s. 63-81. ISBN 978-953-307-813-7.

[98]. I. V. UKRAINETS, P. A. BEZUGLIY. Injectable anesthetic. US 6340692 B1.

[99]. DAINIPPON INK AND CHEMICALS, INC. Therapeutic Agent for Chronic Obstructive Pulmonary Disease with the Same. EP 1650191 A1, 2006.

[100]. DAINIPPON INK AND CHEMICALS, INC. Therapeutic Agent for Chronic Obstructive Pulmonary Disease with the Same. WO 2005/12251 A1, 2005.

[101]. DAINIPPON INK AND CHEMICALS, INC. Quinolinone Derivative and Anti-allergic Agent with Said Quinolinone Derivative as the Active Ingredient. US 5942521 A1, 1999.

[102]. K. FRAZIER, E. JAZAN, C. M. MCBRIDE, S. PECCHI, P. A. RENHOWE, C. M. SHAFER, C. TAYLOR, D. BUSSIERE, M. M. HE. Design and Structure–activity Relationship of Heterocyclic Analogs of 4-Amino-3-benzimidazol-2-ylhydroquinolin-2-ones as Inhibitors of Receptor Tyrosine Kinases. *Bioorganic & Medicinal Chemistry Letters*. 2006, **16**(8): 2247-2251. DOI: 10.1016/j.bmcl.2006.01.020. ISSN 0960894x.

[103]. Z. J. NI, P. BARSANTI, N. BRAMMEIER, A. DIEBES, D. J. POON, S. PECCHI, K. PFISTER, P. A. RENHOWE. 4-(Aminoalkylamino)-3-benzimidazole-quinolinones as Potent CHK-1 Inhibitors. *Bioorganic & Medicinal Chemistry*. 2006, **16**(12): 3121-3124. DOI: 10.1016/j.bmcl.2006.03.059. ISSN 0960894x.

[104]. P. A. RENHOWE, S. PECCHI, C. M. SHAFER, T. D. MACHAJEWSKI, E. M. JAZAN, C. TAYLOR, W. ANTONIOS-MCCREA, C. M. MCBRIDE, K. FRAZIER. Design, Structure−Activity Relationships and *in Vivo* Characterization of 4-Amino-3-benzimidazol-2-ylhydroquinolin-2-ones: A Novel Class of Receptor Tyrosine Kinase Inhibitors. *Journal of Medicinal Chemistry*. 2009, **52**(2): 278-292. DOI: 10.1021/jm800790t. ISSN 0022-2623.

[105]. I. V. UKRAINETS, S. G. TARAN, O. V. GOROKHOVA, N. A. MARUSENKO, A. V. TUROV. 4-Hydroxy-2-quinolones. 32. Synthesis and Antithyroid Activity of Thio analogs of 1H-2-Oxo-3-(2-Benzimidazolyl)-4-hydroxyquinoline. *Chemistry of Heterocyclic Compounds* . 1997, 2015-11-12, **33**(5): 600-604. DOI: 10.1007/BF02291946. ISSN 0009-3122.

[106]. P. A. BEZUGLYI, I. V. UKRAINETS, V. I. TRESKACH, A. V. TUROV, S. V. GLADCHENKO. Biological Properties of 2,4-Dioxo-3H-quinoline-3-carboxylic Acid and its Ethyl Ester. *Pharmaceutical Chemistry Journal.* 1992, 26(2): 138 – 141. DOI: 10.1007/BF00766452.

[107]. I. V. UKRAINETS, O. V. GOROKHOVA, S. G. TARAN, P. A. BEZULYI, A. V. TUROV, N. A. MARUSENKO, O. A. EVTIFEEVA. 4-Hydroxy-2-quinolones. 22. Synthesis and Biological Properties of 1-Alkyl(aryl)-2-oxo-3-carbethoxy-4-hydroxyquinolines and their Derivatives. *Chemistry of Heterocyclic Compounds* . 1994, **30**(7): 829-836. DOI: 10.1007/BF01169641. ISSN 0009-3122.

[108]. A. G. A. EL-AGAMEY, A. A. ATTAIA. Synthesis and study of antimicrobial agents of newly 6-nitro-4-hydroxy-2-quinolone derivatives. *Archives of Applied Science Research*. 2012, **4**(3):1339-1343.

[109]. K. ARYA, M. AGARWAL. Microwave Prompted Multigram Synthesis, Structural Determination, and Photo-antiproliferative Activity of Fluorinated 4-Hydroxyquinolinones. *Bioorganic & Medicinal Chemistry Letters*. 2007, **17**(1): 86-93. DOI: 10.1016/j.bmcl.2006.09.082. ISSN 0960894x.

[110]. BAYER CROPSCIENCE LIMITED. New Herbicidal Compositions. EP 1213966 B1, 2006.

[111]. SYNGENTA PARTICIPATIONS AG. Herbicidal Compositions. EP 1388285 A2, 2004.

[112]. E. F. NESMELOVA, I. A. BESSONOVA, S. Y. YUNUSOV. Buchapine — A New Alkaloid from *Haplophyllum bucharicum*. *Chemistry of Natural Compounds*. 1982, **18**(4): 508-509. DOI: 10.1007/BF00579671. ISSN 0009-3130.

[113]. G. M. SHERIHA, K. ABOUAMER, B. Z. ELSHTAIWI, A. S. ASHOUR, F. A. ABED, H. H. ALHALLAQ. Quinoline Alkaloids and Cytotoxic Lignans from *Haplophyllum tuberculatum*. *Phytochemistry*. 1987, **26**(12): 3339 – 3342. DOI: 10.1016/S0031-9422(00)82500-5.

[114]. N. AHMED, K. G. BRAHMBHATT, S. SABDE, D. MITRA, I. P. SINGH, K. K. BHUTANI. Synthesis and Anti-HIV Activity of Alkylated Quinoline 2,4-diols. *Bioorganic & Medicinal Chemistry*. 2010, **18**(8): 2872-2879. DOI: 10.1016/j.bmc.2010.03.015. ISSN 09680896.

[115]. D. L. DREYER, Alkaloids, Limonoids and Furocoumarins from Three Mexican *Esenbeckia* Species. *Phytochemistry* . 1980, 2015-11-12, **19**(5): 941-944. DOI: 10.1016/0031-9422(80)85142-9. ISSN 00319422.

[116]. F. M. NUNES, B. A. BARROS-FILHO, M. C. F. DE OLIVEIRA, J. MAFEZOLI, M. ANDRADE-NETO, M. C. D. MATTOS, E. R. SILVEIRA, J. R. PIRANI. Total Assignment of ^{1}H and ^{13}C NMR Spectra of the Alkaloid 3,3-Diisopentenyl-N-methyl-2,4-quinoldione and Novel Reaction Derivatives. *Magnetic Resonance in Chemistry*. 2005, **43**(2): 180 – 183. DOI: 10.1002/mrc.1511.

[117]. L. X. MING, Q. S: HUA, Y. HAO, G. C. HAI, Z. SI. Alkaloids from the Stem Bark of *Micromelum falcatum. Chemical and Pharmaceutical Bulletin*. 2009, **57**(6): 600 – 602. DOI: org/10.1248/cpb.57.600.

[118]. W. NEUENHAUS, H. BUDZIKIEWICZ, H. KORTH, G. PULVERER. Bakterieninhaltsstoffe, III 3-Alkyl-tetrahydrochinolinderivate aus *Pseudomonas* / Bacterial Constituents, III 3-Alkyl-tetrahydroquinoline Derivatives from *Pseudomonas*. *Zeitschrift für Naturforschung B* . 1979-01-1, 2015-11-12, **34**(2). DOI: 10.1515/znb-1979-0234. ISSN 1865-7117.

[119]. S. S. YANG, G. M. CRAGG, D. J. NEWMAN, J. P. BADER. Natural Product-Based Anti-HIV Drug Discovery and Development Facilitated by the NCI Developmental Therapeutics Program. *Journal of Natural Products*. 2001, **64**(2): 265 – 277. DOI: 10.1021/np0003995.

[120]. A. B. DARUWALA, J. E. GEARIEN, W. J. DUNN, P. S. BENOIT, L. BAUER. Beta-Amino Ketones. Synthesis and Some Biological Activities in Mice of 3,3-Dialkyl-1,2,3,4-tetrahydro-4-quinolinones and Related Mannich Bases. *Journal of Medicinal Chemistry*. 1974, **17**(8): 819-824. DOI: 10.1021/jm00254a008. ISSN 0022-2623.

[121]. C. M. SEONG, W. K. PARK, C. M. PARK, J. Y. KONG, N. S. PARK. Discovery of 3-Aryl-3-methyl-1H-quinoline-2,4-diones as a New Class of Selective 5-HT6 Receptor Antagonists. *Bioorganic & Medicinal Chemistry Letters*. 2008, **18**(2): 738-743. DOI: 10.1016/j.bmcl.2007.11.045. ISSN 0960894x.

[122]. R. A. GLENNON, U. SIRIPURAPU, B. L. ROTH, R. KOLANOS, M. L. BONDAREV, D. SIKAZWE, M. LEE a M. DUKAT. The Medicinal Chemistry of 5-HT6 Receptor Ligands with a Focus on Arylsulfonyltryptamine Analogs. *Current Topics in Medicinal Chemistry*. 2010, **10**(5): 579-595. DOI: 10.2174/156802610791111542. ISSN 15680266.

[123]. B. BENHAMÚ, M. M. FONTECHA, H. V. VILLA, L. PARDO, M. L. LÓPEZ-RODRÍGUEZ. Serotonin 5-HT6 Receptor Antagonists for the Treatment of Cognitive Deficiency in Alzheimer's Disease. *Journal of Medicinal Chemistry*. 2014, **57**(17): 7160 – 7181. DOI: 10.1021/jm5003952.

[124]. S. C. PARK, N. J. YUNGSIK, C. J. PARK, W. C. HEEYUNG, K. JAEYANG, J. DAEYOUNG, K. SUNHEE, S. SUKJIN, K. KYUNGRAN. 3-Aryl-3-methyl-quinoline-2, 4-diones, Preparation Method thereof, and Pharmaceutical Composition Containing the Same. US 2006/84676 A1, 2006.

[125]. A. MANVAR, V. KHEDKAR, J. PATEL, V. VORA, N. DODIA, G. PATEL, E. COUTINHO a A. SHAH. Synthesis and Binary QSAR Study of Antitubercular Quinolylhydrazides. *Bioorganic & Medicinal Chemistry Letters*. 2013, 23(17), 4896-4902. DOI: 10.1016/j.bmcl.2013.06.076. ISSN 0960894x.

[126]. S. D. FEDORYAK, P. V. PRISYAZHNYUK, I. I. SIDORCHUK. Synthesis and Biological Activity of Isonicotinoylhydrazones of Certain Di- and Tricarbonyl Compounds. *Pharmaceutical Chemistry Journal*. 1982, 16(1), 37-40. DOI: 10.1007/BF00761608. ISSN 0091-150x.

[127]. E. MALLE. Etude de L'action Antiagrégante Plaquettaire de Dérivés Substitués en 2-, 3- et 4- D'azidoquinoléines Nouvelles. *European Journal of Medicinal Chemistry*. 1990, **25**(2): 137-142. DOI: 10.1016/0223-5234(90)90022-U. ISSN 02235234.

[128]. S. HAN, F. ZHANG, F. Y. QIAN, L. L. CHEN, J. B. PU, X. XIE, J. Z. CHEN. Development of Quinoline-2,4(1 H ,3 H)-diones as Potent and Selective Ligands of the Cannabinoid Type 2 Receptor. *Journal of Medicinal Chemistry* . 2015, **58**(15): 5751-5769. DOI: 10.1021/acs.jmedchem.5b00227. ISSN 0022-2623.

[129]. H. IWAMURA, H. SUZUKI, Y. UEDA, T. KAYA, T. INABA. *In Vitro* and *in Vivo* Pharmacological Characterization of JTE-907, a Novel Selective Ligand for Cannabinoid CB_2 Receptor. *J. Pharmacol. Exp. Ther.* 2001 **296**:420-425.

[130]. A. RIVKIN, Y. R. KIM, M. T. GOULET, N. BAYS, A. D. HILL, I. KARIV, S. KRAUSS, N. GINANNI, P. R. STRACK. 3-Aryl-4-hydroxyquinolin-2(1H)-one Derivatives as Type I Fatty Acid Synthase Inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 2006, **16**(17): 4620-4623. DOI: 10.1016/j.bmcl.2006.06.014. ISSN 0960894x.

[131]. R. STORER, D. W. YOUNG, D. R. TAYLOR, J. M. WARNER. Isolation and Synthesis of N-Methyl-4,7,8-trimethoxy-2-quinolone from *Spathelia sorbifolia* L. *Tetrahedron*. 1973, **29**(12): 1721-1723. DOI: 10.1016/0040-4020(73)80118-8. ISSN 00404020.

[132]. S. C. CHHABRA, R. L. A. MAHUNNAH, E. N. MSHIU. Plants Used in Traditional Medicine in Eastern Tanzania. VI. Angiosperms (*Sapotaceae* to *Zingiberaceae*). *Journal of Ethnopharmacology*. 1993, **39**(2): 83-103. DOI: 10.1016/0378-8741(93)90024-Y. ISSN 03788741.

[133]. E. ZIEGLER, K. GELFERT. Synthesen von Heterocyclen, 24. Mitt.: Über 4-Hydroxy-carbostyrile. *Monatshefte fuer Chemie*, 1959, **90**(6): 858-865.

[134]. N. SHOBANA, P. YESHODA, P. SHANMUGAM. A Convenient Approach to the Synthesis of Prenyl-, Furo- and Pyrano-quinoline Alkaloids of the *Rutaceae*. *Tetrahedron*. 1989, **45**(3): 757-762. DOI: 10.1016/0040-4020(89)80106-1. ISSN 00404020.

[135]. I. M. Isak, E. S. LEE, S. J. CHOI, J. Y. LEE, Y. C. KIM. Structure–activity Relationships of Heteroaromatic Esters as Human Rhinovirus 3C Protease Inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 2009, **19**(13): 3632-3636. DOI: 10.1016/j.bmcl.2009.04.114. ISSN 0960894x.

[136]. T. ISHIDA, S. KIKUCHI, T. YAMADA. Efficient Preparation of 4-Hydroxyquinolin-2(1 H)-one Derivatives with Silver-Catalyzed Carbon Dioxide Incorporation and Intramolecular Rearrangement. *Organic Letters* . 2013, **15**(14): 3710-3713. DOI: 10.1021/ol401571r. ISSN 1523-7060.

[137]. S. KAFKA, A. KLÁSEK, J. POLIS, J. KOŠMRLJ. Syntheses of 3-Aminoquinoline-2,4(1*H*,3*H*)-diones. *Heterocycles*. 2002, **57**(9): 1659 – 1682. DOI: 10.3987/COM-02-9522.

[138]. O. RUDOLF, V. MRKVIČKA, A. LYČKA, M. ROUCHAL, A. KLÁSEK. Reaction of Some 2-Quinolone Derivatives with Phosphoryl Chloride: Synthesis of Novel Phosphoric Acid Esters of 4-Hydroxy-2-quinolone. *Journal of Heterocyclic Chemistry*. 2013, **50**: E100-E110. DOI: 10.1002/jhet.1082.

[139]. E. ZIEGLER, R. SALVADOR, T. KAPPE. Synthesen von Heterocyclen, 41. Mitt.: Über cyclische Dichlormalonyl-Verbindungen. *Monatshefte fuer Chemie.* 1962, **93**: 1376-1381.

[140]. W. STADLBAUER, R. LASCHOBER, H. LUTSCHOUIG, G. SCHINDLER, T. KAPPE. Halogenation Reactions in Position 3 of Quinoline-2,4-dione Systems by Electrophilic Substitution and Halogen Exchange. *Monatshefte fuer Chemie*. 1992, **123**(6): 617 – 636.

[141]. C. FOURNIER, J. DECOMBE. *Bulletin de la Societe Chimique de France*. 1967, 3367-3370.

[142]. C. FOURNIER, J. DECOMBE. *Comptes Rendus des Seances de l'Academie des Sciences, Serie C: Sciences Chimiques.* 1967, **265**: 1169.

[143]. V. N. DROZD, V. N. KNYAZEV, N. L. NAM, V. P. LEZINA, T. Y. MOZHAEVA, V. L. SAVELEV. *Russian Journal of Organic Chemistry*. 1993, **29**(4): 653 – 658.

[144]. E. ZIEGLER, R. SALVADOR, T. KAPPE. Synthesen von Heterocyclen, 50. Mitt.: Über Dibrommalonyl-Verbindungen. *Monatshefte fuer Chemie*. 1963, **94**: 941-949.

[145]. S. KAFKA, S. HAUKE, A. SALCINOVIC, O. SOIDINSALO, D. URANKAR, J. KOŠMRLJ. Copper(I)-Catalyzed [3+ 2] Cycloaddition of 3-Azidoquinoline-2,4(1H,3H)-diones with Terminal Alkynes. *Molecules*. 2011, **16**(12): 4070-4081. DOI: 10.3390/molecules16054070. ISSN 1420-3049.

[146]. R. LASCHOBER, W. STADLBAUER. Synthesis of 3-Heptyl- and 3-Nonyl-2,4(1H,3H)-quinolinediones. *Liebigs Annalen der Chemie*. 1990, **1990**(11), 1083-1086. DOI: 10.1002/jlac.1990199001195. ISSN 01702041.

[147]. I. V. UKRAINETS, S. G. TARAN, O. A. EVTIFEVA, O. V. GOROKHOVA, N. I. FILIMONOVA a A. V. TUROV. 4-Hydroxy-2-quinolones. 26. Bromination of 3-Substituted 2-Oxo-4-hydroxyquinolones. *Chemistry of Heterocyclic Compounds*. 1995, **31**(2): 176-179. DOI: 10.1007/BF01169675. ISSN 0009-3122.

[148]. S. KAFKA. *Nepublikované výsledky*.

[149]. A. KLÁSEK, A. LYČKA, I. MIKŠÍK, A. RŮŽIČKA. Reaction of 3-Phenyl-3-aminoquinoline-2,4-diones with Isothiocyanates. Facile Access to Novel Spiro-linked 2-Thioxoimidazolidine-oxindoles and Imidazoline-2-thiones. *Tetrahedron*. 2010, **66**(11): 2015-2025. DOI: 10.1016/j.tet.2010.01.041. ISSN 00404020.

[150]. B. C. CHEN, P. ZHOU, F. A. DAVIS, E. CIGANEK. A-Hydroxylation of Enolates and Silyl Enol Ethers. *Organic Reactions*. DOI: 10.1002/0471264180.or062.01. ISBN 0471264180.

[151]. W. STADLBAUER, T. KAPPE. *Zeit. Naturfor.* **1982**, *37*, s. 1196 – 1200.

[152]. W. STADLBAUER, H. LUTSCHOUNIG, G. SCHINDLER, T. WITOSZYNSKYJ, T. KAPPE. Synthesis of 3-Nitro- and 3-Aminoquinoline-2,4-diones. An Unexpected Route to 3-Hydroxyquinoline-2,4-diones. *Journal of Heterocyclic Chemistry*. 1992, **29**(6): 1535-1540. DOI: 10.1002/jhet.5570290627. ISSN 0022152x.

[153]. S. KAFKA, K. PROISL, V. KAŠPÁRKOVÁ, D. URANKAR, R. KIMMEL, J. KOŠMRLJ. Oxidative Ring Opening of 3-Hydroxyquinoline-2,4(1H,3H)-diones into N-(α-Ketoacyl)anthranilic Acids. *Tetrahedron* . 2013, **69**(51): 10826-10835. DOI: 10.1016/j.tet.2013.10.092. ISSN 00404020.

[154]. R. M. MAHRAN, W. M. ABDOU, M. M. SIDKY, H. WAMHOFF. *Synthesis*. 1987, **5**: 506 – 508.

[155]. BAEYER a HOMOLKA. *Chemische Berichte*. 1883, **16**: 2216.

[156]. T. KAPPE, E. ZIEGLER. Synthesen von Heterocyclen, 53. Mitt.: Zur Chemie der Chlornitromalonyl-Verbindungen. *Monatshefte fuer Chemie*. 1964, **95**: 415-419.

[157]. STATE OF OREGON, ACTING BY AND THROUGH THE OREGON STATE BOARD OF HIGHER EDUCATION, ACTING FOR AND ON BEHALF OF THE OREGON HEALTH SCIENCES UNIVERSITY AND THE UNIVERSITY OF OREGON, ACEA

PHARMACEUTICALS, INC., THE REGENTS OF THE UNIVERSITY OF CALIFORNIA. Glycine Receptor Antagonists Pharmacophore. US 5597922 A1, 1997.

[158]. N. AHMED, K. G. BRAHMBHATT, I. P. SINGH, K. K. BHUTANI. Efficient Chemoselective Alkylation of Quinoline 2,4-diol Derivatives in Water. *Journal of Heterocyclic Chemistry*. 2011, **48**(1): 237-240. DOI: 10.1002/jhet.364. ISSN 0022152x.

[159]. J. REISCH, A. BATHE. Acetylenchemie, 5. Mitt. PTC-Umsetzung von 4-Hydroxychinolin-2-on und Indolin-2-on mit 3-Bromprop-1-in. *Archiv der Pharmazie*. 1987, **320**(8): 737-742. DOI: 10.1002/ardp.19873200812. ISSN 0365-6233.

[160]. H. NISHIMURA, Y. NAGAI, T. SUZUKI, T. SAWAYAMA. Synthesis of 4-Hydroxy-2(1*H*)-quinolone Derivatives. *Yakugaku Zasshi*. 1970, **90**: 818-825.

[161]. C. M. SEONG, W. K. PARK, C. M. PARK, J. Y. KONG, N. S. PARK. Discovery of 3-Aryl-3-methyl-1H-quinoline-2,4-diones as a New Class of Selective 5-HT6 Receptor Antagonists. *Bioorganic & Medicinal Chemistry Letters*. 2008, **18**(2): 738-743. DOI: 10.1016/j.bmcl.2007.11.045. ISSN 0960894x.

[162]. L. TAIMR, M. PRUSÍKOVÁ, J. POSPÍŠIL. *Angewandte Makromolekulare Chemie*. **190**(1): 53-65. DOI: 10.1002/apmc.1991.051900104. ISSN 00033146.

[163]. T. PROVDER, J. BAGHDACHI. Smart coatings II. *American Chemical Society*. 2009, **14**: 337. ISBN 0841272182.

[164]. W. S. MOON, J. C. KIM, K. H. CHUNG, E. S. PARK, M. N. KIM, J. S. YOON. Antimicrobial Activity of a Monomer and its Polymer Based on Quinolone. *Journal of Applied Polymer Science*. 2003, **90**(7): 1797-1801. DOI: 10.1002/app.12813. ISSN 0021-8995.

[165]. Fluorescence Properties of 6-Methoxy- and 6,7-Dimethoxyquinoline-3,4-dicarbonitriles. 14th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-14) 1-30 November 2010. Dostupné z: http://boch35.uni-graz.at/~sta/lecture/066/poster/poster.html.

[166]. A. M. KELTERER, G. URAY, W. M. F. FABIAN. Rational Design of Long-wavelength Absorbing and Emitting Carbostyrils Aided by Time-dependent Density Functional Calculations. *Computational and Theoretical Chemistry*. 2015, **1055**: 25-32. DOI: 10.1016/j.comptc.2014.12.006. ISSN 2210271.

[167]. R. B. TOCHE, M. A. KAZI, S. P. PATIL, S. B. KANAWADE, M. N. JACHAK. Synthesis of Quinolone Substituted Pyrazoles, Isoxazoles and Pyridines as a Potential Blue Luminophors. *Journal of Fluorescence*. 2010, **20**(5): 1129-1137. DOI: 10.1007/s10895-010-0654-9. ISSN 1053-0509.

[168]. R. P. DHANAPAL, T. PERUMAL, M. DAMODIRAN, C. RAMPRASATH, N. MATHIVANAN. Synthesis of Quinoline Derivatives for Fluorescent Imaging Certain Bacteria. *Bioorganic & Medicinal Chemistry Letters*. 2012, **22**(20): 6494-6497. DOI: 10.1016/j.bmcl.2012.08.039. ISSN 0960894x.

[169]. Z. WU, P. SHAO, S. ZHANG, X. LING, M. BAI. Molecular Imaging of Human Tumor Cells that Naturally Overexpress Type 2 Cannabinoid Receptors Using a Quinolone-based Near-infrared Fluorescent Probe. *Journal of Biomedical Optics*. 2014, **19**(7): 076016. DOI: 10.1117/1.JBO.19.7.076016. ISSN 1083-3668.

[170]. H. S. JUNG, J. H. HAN, T. PRADHAN, S. KIM, S. W. LEE, J. L. SESSLER, T. W. KIM, C. KANG, J. S. KIM. A Cysteine-selective Fluorescent Probe for the Cellular Detection of Cysteine. *Biomaterials* . 2012, **33**(3): 945-953. DOI: 10.1016/j.biomaterials.2011.10.040. ISSN 01429612.

[171]. A. KOWALSKA, J. KOLIŃSKA, R. PODSIADŁY, J. SOKOŁOWSKA. Dyes Derived from 3-Formyl-2(1 H)-quinolone - Synthesis, Spectroscopic Characterisation, and their Behaviour in the Presence of Sulfhydryl and Non-sulfhydryl Amino Acids. *Coloration Technology*. 2015, **131**(2): 157-164. DOI: 10.1111/cote.12140. ISSN 14723581.

[172]. G. PARAMAGURU, R. V. SOLOMON, S. JAGADEESWARI, P. VENUVANALINGAM a R. RENGANATHAN. Tuning the Photophysical Properties of 2-Quinolinone-Based Donor-Acceptor Molecules through N - versus O -Alkylation: Insights from Experimental and Theoretical Investigations. *European Journal of Organic Chemistry* . 2014, **2014**(4): 753-766. DOI: 10.1002/ejoc.201301085. ISSN 1434193x.

[173]. S. PILLAI, M. KOZLOV, S. A. E. MARRAS, L. N. KRASNOPEROV, A. MUSTAEV. New Cross-Linking Quinoline and Quinolone Derivatives for Sensitive Fluorescent Labeling. *Journal of Fluorescence*. 2012, **22**(4): 1021-1032. DOI: 10.1007/s10895-012-1039-z. ISSN 1053-0509.

[174]. S. KUKLA, V. CIMROVÁ, D. VÝPRACHTICKÝ. Terbium Binding in Highly Luminescent Polymer Complexes. *Collection of Czechoslovak Chemical Communications*. 2006, **71**(9): 1333-1349. DOI: 10.1135/cccc20061333. ISSN 0010-0765.

[175]. D. VÝPRACHTICKÝ, V. CIMROVÁ, S. KUKLA, P. PAVLAČKOVÁ. Efficient Donor for Terbium Luminescence Based on Polymer Ligand Containing Quinolinone Fluorophore. *Macromolecular Chemistry and Physics*. 2006, **207**(3): 318-326. DOI: 10.1002/macp.200500454. ISSN 1022-1352.

[176]. D. VÝPRACHTICKÝ, F. MIKEŠ, J. LOKAJ, V. POKORNÁ, V. CIMROVÁ. Resonance Energy Transfer from Quinolinone Modified Polystyrene-block-poly(styrene-alt-maleic anhydride) Copolymer to Terbium(III) Metal Ions. *Journal of Luminescence*. 2015, **160**: 27-34. DOI: 10.1016/j.jlumin.2014.11.023. ISSN 00222313.

[177]. M. IKBAL, R. BANERJEE, S. ATTA, A. JANA, D. DHARA, A. ANOOP, N. D. P. SINGH. Development of 1-Hydroxy-2(1 H)-quinolone-Based Photoacid Generators and Photoresponsive Polymer Surfaces. *Chemistry - A European Journal*. 2012, **18**(38): 11968-11975. DOI: 10.1002/chem.201104065. ISSN 09476539.

[178]. N. RAJENDIRAN, T. BALASUBRAMANIAN. Dual fluorescence of N-Phenylanthranilic Acid: Effect of Solvents, pH and β-Cyclodextrin. *Spectrochimica Acta Part*

A: Molecular and Biomolecular Spectroscopy. 2007, **68**(3): 867-876. DOI: 10.1016/j.saa.2006.12.072. ISSN 13861425.

[179]. Y. F. QIAO, D. U. Lin, J. ZHOU, Y. HU, L. LI, B. LI, Q. H. ZHAO. Synthesis, Structures, and Fluorescent Properties of Azo Anthranilic Acid and its Cu(II), Co(II), and Ni(II) Complexes. *Journal of Coordination Chemistry*. 2014, **67**(15): 2615-2629. DOI: 10.1080/00958972.2014.948870. ISSN 0095-8972.

[180]. S. TEP, M. HINCAPIE, W. S. HANCOCK. A MALDI-TOF MS Method for the Simultaneous and Quantitative Analysis of Neutral and Sialylated Glycans of CHO-expressed Glycoproteins. *Carbohydrate Research*. 2012, **347**(1): 121-129. DOI: 10.1016/j.carres.2011.10.005. ISSN 00086215.

[181]. K. R. ANUMULA. New High-performance Liquid Chromatography Assay for Glycosyltransferases Based on Derivatization with Anthranilic Acid and Fluorescence Detection. *Glycobiology*. 2012, **22**(7): 912-917. DOI: 10.1093/glycob/cws067. ISSN 0959-6658.

[182]. Y. ISHIBASHI, Y. NAGAMATSU, S. MEYER, A. IMAMURA, H. ISHIDA, M. KISO, N. OKINO, R. GEYER, M. ITO. Transglycosylation-based Fluorescent Labeling of 6-Gala Series Glycolipids by Endogalactosylceramidase. *Glycobiology*. 2009, **19**(7): 797-807. DOI: 10.1093/glycob/cwp051. ISSN 0959-6658.

[183]. J. LARSEN, E. M. ESPINOZA, V. I. VULLEV. Bioinspired Molecular Electrets: Bottom-up Approach to Energy Materials and Applications. *Journal of Photonics for Energy*. 2015, **5**(1): 055598. DOI: 10.1117/1.JPE.5.055598. ISSN 1947-7988.

[184]. A. KIKUCHI, K. SHIBATA, R. KUMASAKA, M. YAGI. Excited States of Menthyl Anthranilate: a UV-A Absorber. *Photochem. Photobiol. Sci*. 2013, **12**(2): 246-253. DOI: 10.1039/C2PP25190F. ISSN 1474-905x.

[185]. J. JIA, Q. C. XU, R. C. LI, X. TANG, Y. F. HE, M. Y. ZHANG, Y. ZHANG, G. W. XING. Tetrahydroindazolone Substituted 2-Aminobenzamides as Fluorescent Probes: Switching Metal Ion Selectivity from Zinc to Cadmium by Interchanging the Amino and Carbamoyl Groups on the Fluorophore. *Organic & Biomolecular Chemistry*. 2012, **10**(31): 6279. DOI: 10.1039/c2ob25852h. ISSN 1477-0520.

[186]. J. JIA, Z. Y. GU, R. C. LI, M. H. HUANG, C. S. XU, Y. F. WANG, G. W. XING, Y. S. HUANG. Design and Synthesis of Fluorescent Sensors for Zinc Ion Derived from 2-Aminobenzamide. *European Journal of Organic Chemistry*. **2011**(24): 4609-4615. DOI: 10.1002/ejoc.201100388. ISSN 1434193x.

[187]. A. WANG, Y. BAI, H. GAO, S. WANG. A Tetracycline-selective Fluorescent Biosensor Using Anthranilic Acid Immobilized on a Glutaraldehyde-coated Eggshell Membrane. *Anal. Methods*. 2015, **7**(16): 6842-6847. DOI: 10.1039/C5AY01047K. ISSN 1759-9660.

[188]. A. MURUGESAN, B. MEENARATHI, L. KANNAMMAL, S. PALANIKUMAR, R. ANBARASAN. Synthesis, Characterization and Drug Delivery Activity of

Poly(anthranilicacid) Based Triblock Copolymer. *Synthetic Metals*. **189**: 143-151. DOI: 10.1016/j.synthmet.2014.01.015. ISSN 03796779.

[189]. I. V. KALINOVSKAYA, A. N. ZADOROZHNAYA, V. E. KARASEV. The Dispersity and Distribution of Luminophors in High-pressure Polyethylene. *Russian Journal of Physical Chemistry A*. 2008, **82**(12): 2156-2158. DOI: 10.1134/S0036024408120327. ISSN 0036-0244.

[190]. H. PANG, W. G. ZHANG, S. M. ZHAO. The Electroluminescent Devices Based on Benzoxazinone as Strong Fluorescent Material. *Advanced Materials Research*. 2011, **380**: 339-343. DOI: 10.4028/www.scientific.net/AMR.380.339. ISSN 1662-8985.

[191]. DELTACHEM (QINGDAO) CO.,LTD . 2010. Dostupné z: http://www.deltachem.net/enProductList.aspx?id=22

Karel Proisl

Syntézy nových sloučenin vycházející ze 4 hydroxychinolin-2(1*H*)-onů potenciálně využitelných k úpravě vlastností nebo k ochraně materiálů

Syntheses of Novel Compounds Based on 4-Hydroxyquinolin-2(1*H*)-ones Potentially Applicable for Properties Modification or Protection of Materials

Vydala Univerzita Tomáše Bati ve Zlíně,
nám. T. G. Masaryka 5555, 760 01 Zlín.

Náklad: 5 výtisků

Sazba: Karel Proisl

Publikace neprošla jazykovou ani redakční úpravou.

Rok vydání 2017