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COMPREHENSIVE REVIEW

A review on the synthesis of heteroannulated quinolones and their biological activities

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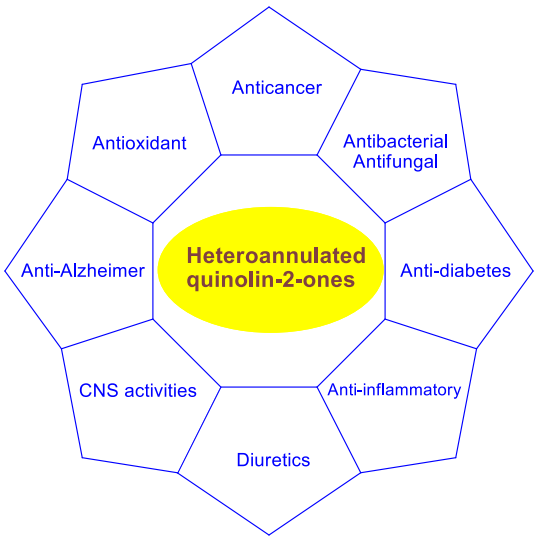
Abstract

The quinoline scaffold has become an important construction motif for the development of new drugs. The quinolones and their heteroannulated derivatives have high importance due to their diverse spectrum of biological activities as antifungal, anti-inflammatory, anti-diabetes, anti-Alzheimer's disease, antioxidant and diuretic activities. This review summarizes the various new, efficient and convenient synthetic approaches to synthesize diverse quinolone-based scaffolds and their biological activities. We also dealt with the important mechanism, the route and type of reactions of the obtained products. The biological activities of some heteroannulated quinolones were also discussed.

Graphic abstract



Keywords Pyrroloquinolones · Thienoquinolones · Oxazoloquinolones · Pyranoquinolones · Furoquinolones · Heteroannulation · Biological activities

Introduction

Nitrogen-containing heterocyclic compounds represent a notable type of anticancer drug candidates, which strongly activate cell apoptosis [1]. Many quinoline-containing compounds have been reported as potential antitumor agents [2, 3]. Quinoline skeletons are important in anticancer drug

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improvement, as their derivatives show significant results through different mechanisms: They may inhibit tumor growth by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration and modulation of nuclear receptor responsiveness [4]. The fused pyranoquinoline moiety is an extremely common structural motif, existing in many naturally occurring or biologically active alkaloids, such as flindersine, atanine, tabouensinium chloride, zanthoxylum simulans, oricine, verprisine and araliopsis tabouensis [5–7]. Figure 3 summarizes Biological activities of heteroannulated quinolones.The unique biological activity of the pyranoquinoline derivatives has made these compounds privileged targets in recent medicinal studies. For instance, compounds that contain a pyranoquinoline nucleus have been frequently used for bactericidal and bacteriolytic activities [8, 9], acetylcholinesterase inhibition [10], antiallergenic [11], anti-inflammatory [12], antimalarial [13], calcium-signaling inhibition [14] and antitumor activities [15–17]. A pyranoquinoline nucleus has been employed in pharmacophores with potential medicinal features against various diseases, like Alzheimer's [18] and psychotropic [19]. This review provides a comprehensive report regarding the methods developed for the synthesis of heteroannulated tricyclic and/or tetracyclic quinolones reported so far. Some of the synthetic strategy is outlined in Fig. 1. The synthetic approaches include Wittig reaction, multicomponent reactions, cyclocondensation reaction, microwave-assisted cyclization, solvent-free reactions and using small chiral organic molecules as catalysts.

Chemistry

Quinoline-2,4-dione 1 occurs in different tautomeric forms between the carbonyl groups and CH_2-3 (Fig. 2). However, X-ray structure analyses of various compounds of that class

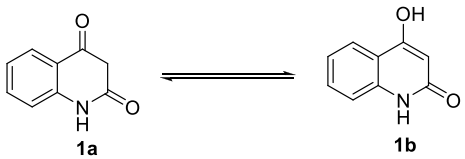


Fig. 2 Two possible common tautomeric structures of quinolin-2,4-dione 1a and 1b

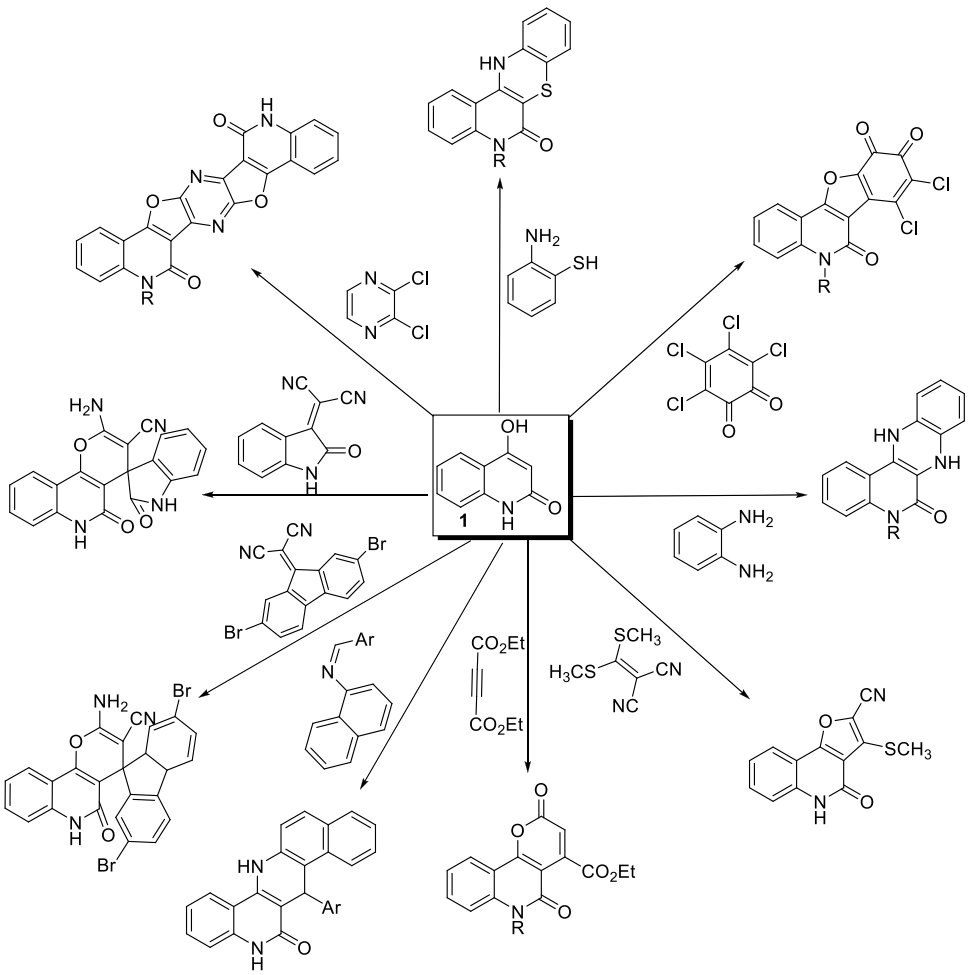


Fig. 1 Synthesis of some heteroannulated quinolones

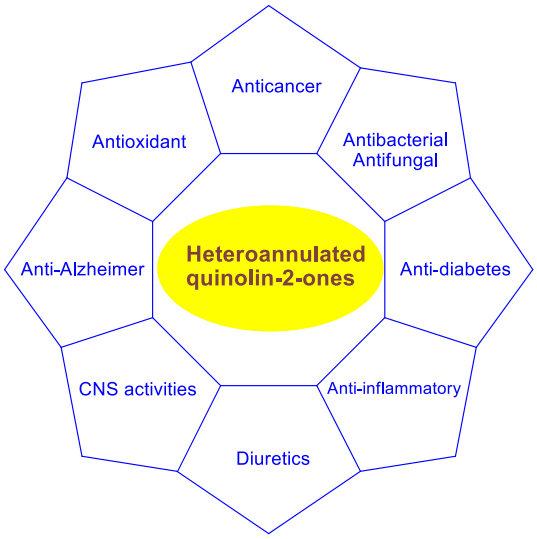
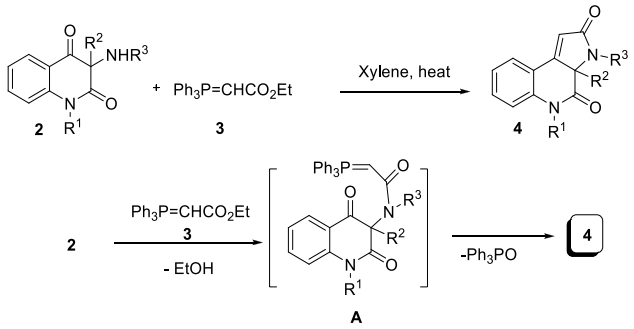


Fig. 3 Biological activities of heteroannulated quinolones



Scheme 1 Synthesis of pyrrolo[3,2-*c*]quinolone derivatives 4

showed that the structure 4-hydroxy-2(1*H*)-quinolone 1b is the most common form [20, 21].

Owing to the high biological impact of heteroannulated quinolones, several synthetic approaches have been developed [22, 23].

Synthesis of quinolones heteroannulated with five-member ring heterocycles

Pyrroloquinolones

The Wittig reaction of 3-aminoquinoline-2,4(1*H*,3*H*)-dione derivatives 2 with ethyl-2-(*tri*-phosphinyl-ylidene)acetate (3) in boiling xylene afforded the pyrroloquinoline-2,4-diones 4 (Scheme 1) [24]. The reaction proceeds via a Michael addition to give intermediate A, followed by a cyclization process, which accompanies by the elimination of EtOH and triphenylphosphine oxide molecules (Scheme 1).

Also, 5-methyl-indolo[3,2-*c*]quinolin-6-one (5a) was successfully synthesized by heating an equimolar mixture of 4-hydroxyquinolone (1) with phenylhydrazine hydrochloride in *p*-toluene sulfonic acid (*p*-TSA) at 120 °C for 6 h either by conventional heating or at 120 °C and 250 watts in the microwave synthesizer for 3 min (Scheme 2) [25].

The first step was successfully carried out by heating equimolar mixture of 4-hydroxy-1-methyl-2-quinolone (**1**) with phenylhydrazine hydrochloride in *p*-TSA at 120 °C for 6 h by conventional heating or at 120 °C and 250 watts in the CEM microwave synthesizer for 3 min, resulting in 90% yield under microwave conditions. The structure of the obtained compound 5a is the same of the alkaloid cryptosanguinolentine, thereby formulating a synthetic route for this alkaloid (Scheme 2) [25]. Fischer indole synthesis of compound 5a may be explained as due to the initial condensation and elimination of H_2O molecule to give intermediate A (Scheme 2). Protonation of A would give B as ene-hydrazine intermediate. Nucleophilic attack of the quinolone activate site (C-3) to the benzene ring followed by rearrangement would give intermediate C. Further nucleophilic attack of the imine to the electrophilic center accompanied by exclusive of proton would give the cyclized intermediate D. Finally, protonation of D would give E, which followed by aromatization process and accompanied with the loss of proton and ammonia would give 5a (Scheme 2).

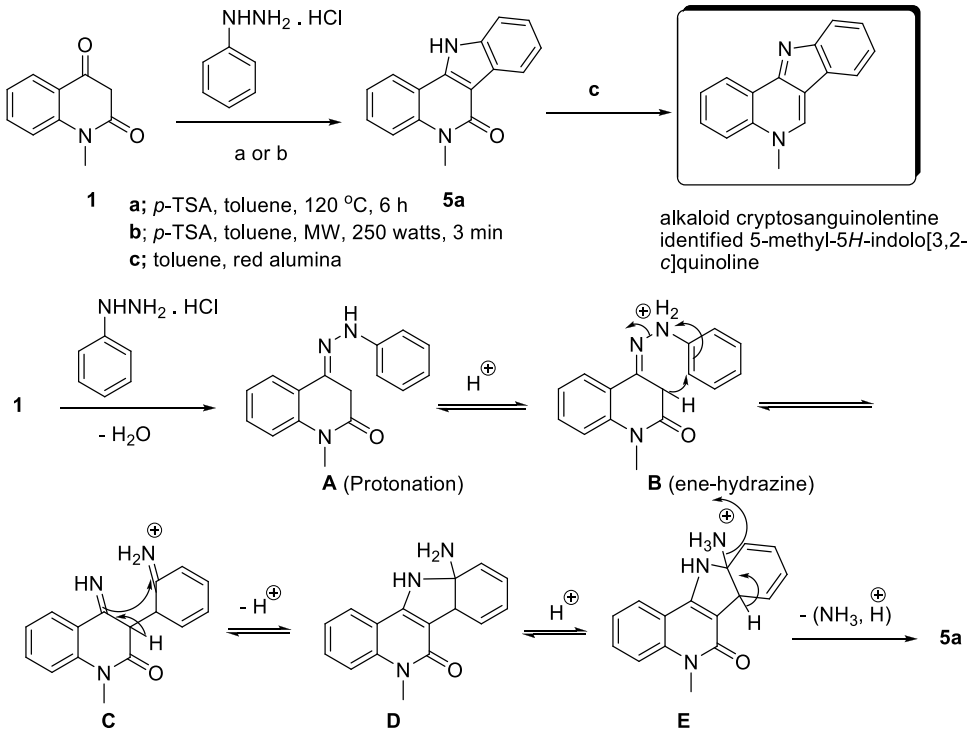
Chen et al. reported a synthesis of pyrroloquinolones 5b,c via compound 6 which was synthesized by refluxing of 4-hydroxyquinolin-2(1*H*)-ones 1 with hydrazine hydrate in ethoxyethanol. Condensation of 6 with cyclohexanone in glacial AcOH at room temperature afforded the corresponding hydrazones 7. Thermal Fischer indolization of 7 followed by dehydrogenation produced the fused desired products 5b,c (Scheme 3) [26]. Compounds 5a,b were evaluated in vitro against a 3-cell lines panel consisting of MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS). The tetracyclic indolo[3,2-*c*]quinolin-2(1*H*)-ones 5a and 5b demonstrated a moderate inhibitory activity with a mean GI50 value of 19.0 and 18.2 µM, respectively.

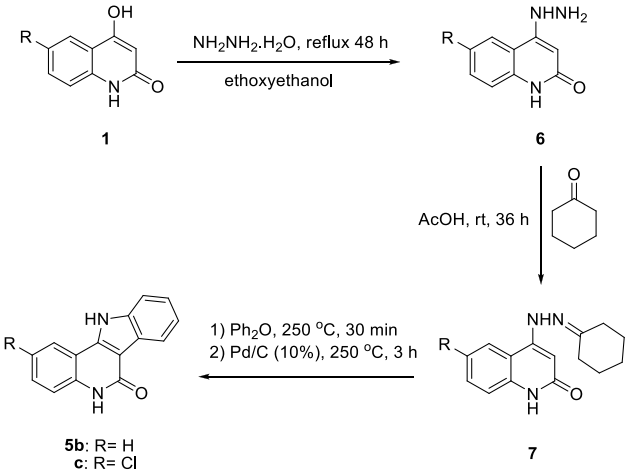
Two different types of pyrroloquinolines were obtained using 2-indolyl-3-peroxyindolenines 8 derived from THβCs and THγCs. In the presence of ascorbic acid, pyrroloquinolines 9 were obtained in 50–97% yields. Reduction of 8 with $NaBH_4$ afforded pyrroloquinolones 10 in 62–99% yields (Scheme 4) [27].

Furoquinolones

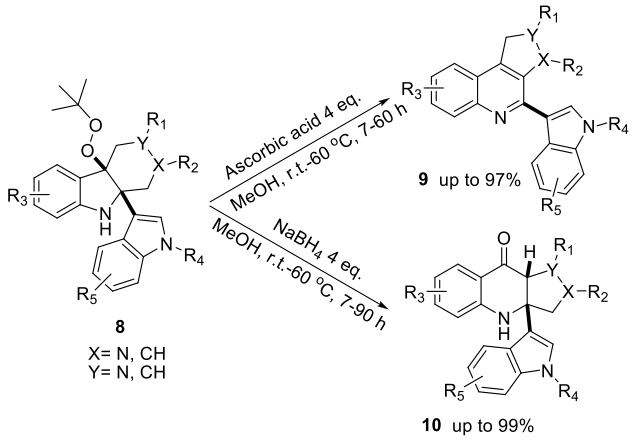
Furo[3,2-*c*]quinolone 12, in 92% yield, was synthesized by the reaction of 4-hydroxyquinolon-3-acetic acid (11) with thionyl chloride (or *N*,*N*'-dicyclohexylcarbodiimide) in refluxed dry carbon tetrachloride for 5 h (Scheme 5) [28].

Scheme 2 Synthesis of alkaloid cryptosanguinolentine 5a





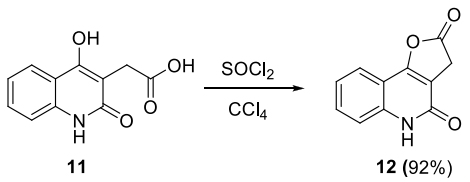
Scheme 3 Synthesis of pyrroloquinolone derivatives 5b,c



Scheme 4 Synthesis of pyrroloquinolone derivatives 9 and 10

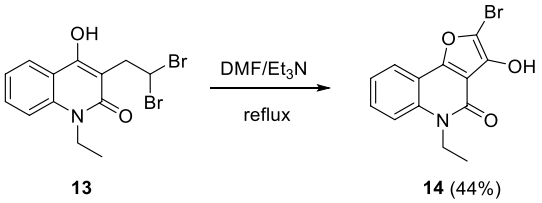
Furthermore, Hassanin and co-workers reported the synthesis of furoquinolone derivative 14, when 3-(2,2-dibromoethyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (13) was dissolved in DMF containing a few drops of triethylamine (Et_3N) and heated under reflux for 4 h (Scheme 6) [29]. The reaction proceeded via a loss of one molecule of HBr to produce 2-bromo-5-ethyl-3-hydroxyfuro[3,2-*c*]quinolin-4(5*H*) –one (14) in 44% yield (Scheme 6) [29].

On the other hand, the reaction of quinolone 1 with α-methylstyrene, cerium ammonium(IV) nitrate (CAN)



Scheme 5 Synthesis of furo[3,2-*c*]quinolone 12

and [bmim][BF_4] in dichloromethane afforded the furoquinolone derivatives 15 and 16 (Scheme 7) [30]. The presence of the ionic liquid not only increases the rate and yield of



13 14 (44%)

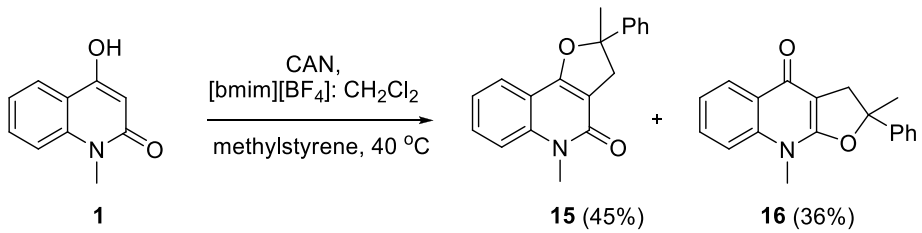
Scheme 6 Synthesis of furo[3,2-*c*]quinolone 14

reactions in dichloromethane but also extends the range of 1,3-dicarbonyl precursors, which can be utilized in these carbon–carbon bond-forming reactions. A similar result has been obtained using manganese(III) acetate in acetic acid although it is interesting to note that the use of Ag_2CO_3/celite only produces the angular isomer 15 [30].

Aly et al. reported the synthesis of furoquinolone derivatives 18a and 18b by the reaction of 4-hydroxyquinolones 1 with 2-[bis(methylthio)methylene]malononitrile (17) in DMF/Et_3N to give two products: 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carbonitriles 18a as major product and 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carboxamides 18b as minor product (Scheme 8) [31]. The mechanism was proposed as that salt formation of intermediate A is due to abstraction of a proton from 1 by Et_3N. Conjugate addition of A to 17, catalyzed by base, would give intermediate B. Elimination of methylthiol from B would give intermediate **C**. Two proposed routes would be: route (a) a nucleophilic attack of the oxygen lone pair to electrophilic carbon assigned as $=C(CN)_2$ accompanied with elimination of HCN molecule would directly proceed to give 18a, or route (b) favorable addition of the oxygen lone pair to the nitrile carbon would give Zwitterion D, which on neutralization would give the expected pyranoquinolone E. Thereafter, ring cleavage and rearrangement of E accompanied by elimination of HCN molecule would give 18a. Partial hydrolysis of 18a under reaction condition would give 18b (Scheme 8).

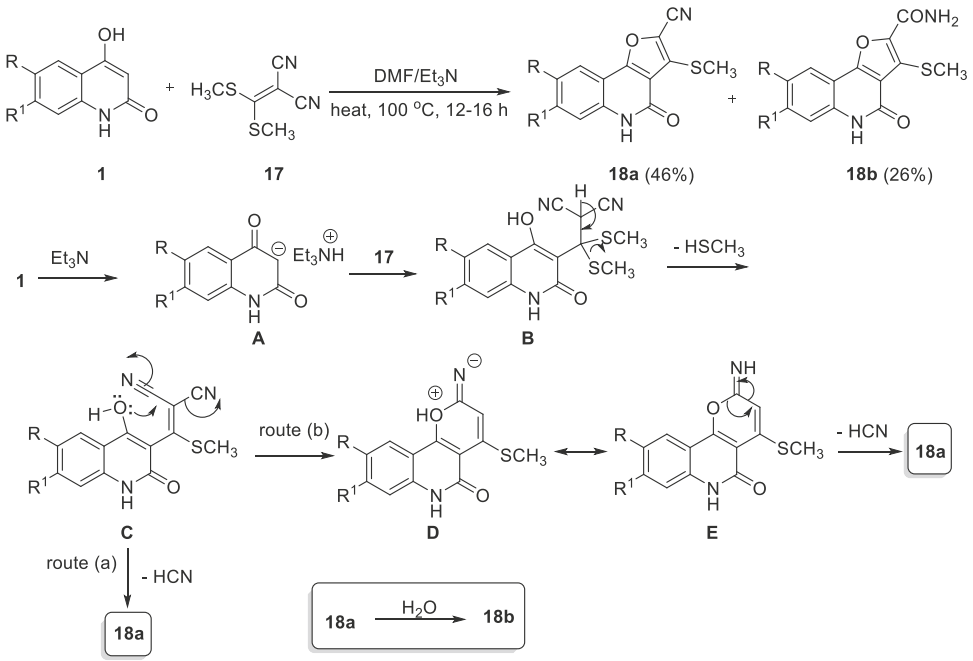
Moreover, Aly et al. reported the synthesis of 7,8-dichlorobenzofuro[3,2-*c*]quinolones 20, in 70–78% yields, by the reaction of the 4-hydroxy-2(1*H*)-quinolone derivatives **1** with 3,4,5,6-tetrachloro-1,2-benzoquinone (*o*-CHL, 19) in tetrahydrofuran (THF) (Scheme 9) [32].

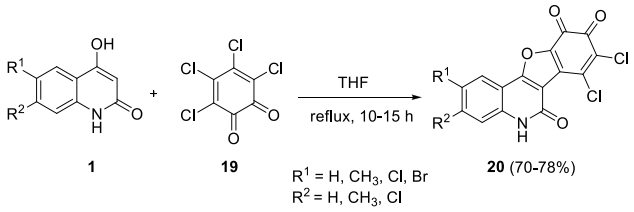
Scheme 7 Synthesis of furoquinolone derivatives 15 and 16



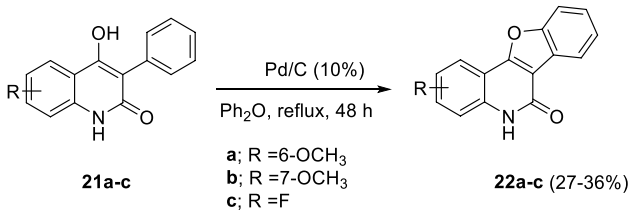
1 15 (45%) 16 (36%)

Scheme 8 Synthesis and mechanism of furoquinolone derivatives 18a,b

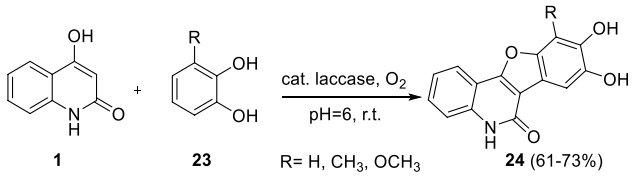




Scheme 9 Synthesis of furoquinolone derivatives 20



Scheme 10 Synthesis of furoquinolone derivatives 22a-c



Scheme 11 Synthesis of furoquinolone derivatives 24

In addition, benzofuro[3,2-*c*]quinolin-6(5*H*)-one derivatives 22a-c were synthesized in 27–36% yields by refluxing of 4-hydroxy-3-phenyl-quinolin-2(1*H*)-ones 21a-c in diphenyl ether in the presence of a catalytic amount of Pd/C (10%) (Scheme 10) [26].

Laccase (Agaricus bisporus)-catalyzed domino reaction of 1 with catechol derivatives 23 using aerial oxygen as the oxidant delivered 10-substituted 8,9-dihydroxybenzofuro[3,2-*c*]quinolin-6(5*H*)-ones 24 in 61–73% yield (Scheme 11) [33]. The reaction condition and the yields of each substituent are demonstrated in Table 1.

Furthermore, Aly et al. demonstrated the synthesis of a series of fused naphthofuro[3,2-*c*]quinolone-6,7,12-trione derivatives 26 by the reaction of quinolone derivatives 1 with 2,3-dichloro-naphthalene-1,4-dione (25) under various conditions (Scheme 12) [34]. Refluxing of the two starting compounds in pyridine was proved as the best condition for preparing compounds 26. Compounds 26 were evaluated for their ability to inhibit ERK1/2 in an in vitro radioactive kinase assay. One of these derivatives inhibited ERK1 with IC50s of 0.5 and 0.19 μM and inhibited ERK2 with IC50s of 0.6 and 0.16 μM, respectively. Kinetic mechanism studies revealed that the inhibitors are ATP-competitive inhibitors [34].

Table 1 Time and yields of each substituent of compounds 24a-c

Entry	23 R	Time (h)	Product 24	Yield (%)a
1	a; R = H	20	a	73
2	b; CH_3	18	b	77
3	c; OCH_3	20	C	61

[a]The reactions were performed with 156 U of laccase from A. bisporus (AbL). The enzyme activity was determined using catechol as the substrate

In 2019, Aly and his co-workers reported that 5,12-dihydropyrazino[2,3-*c*:5,6-*c*]difuro[2,3-*c*:4,5-*c*]diquinoline-6,14(5*H*,12*H*)-dione 28 was synthesized in 60–70% yields by the reaction of 1 with 2,3-dichloropyrazine (27) in DMF and triethylamine at reflux for 20–25 h (Scheme 13) [35]. According to the calculations using Spartan 18: geometries program optimized at the 6-31G* level with B3LYP, it was found that the *Anti*-form of 26 is more stable compared with its *Syn*-form by 2.03 kcal/mol.

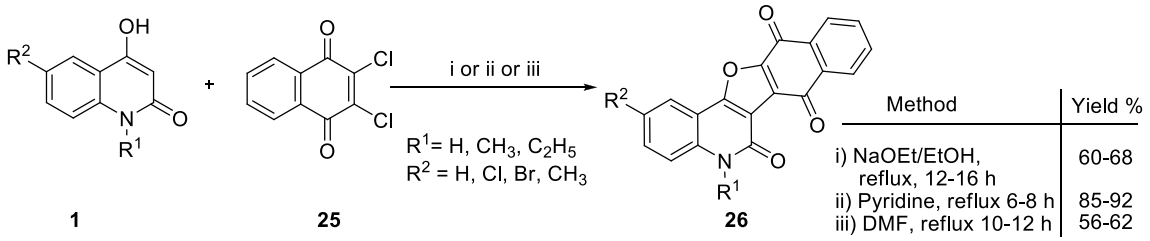
A procedure [36] was reported to prepare furo[3,2-*c*]quinolin-6(5*H*)-ones 22d-f from compounds 29d-f (Scheme 14). The mixture of CuI (10 mol%), 1,10-phenanthroline (12 mol%), benzylamine (1.5 equiv.), KO^{t}Bu (3.0 equiv.) and the respective 4-quinolones 29d-f (1.0 equiv.) in DMF was stirred at 120 °C for 18–24 h. The combined reagent of CuI/$BnNH_2$ increases the nucleophilicity of the oxy-carbonyl that enables an internal intramolecular C–O coupling reaction.

Thienoquinolones

Refluxing a solution of 5-substituted thiophene-3-carboxaldehydes **30** and malonic acid in pyridine produced 5-substituted 3-(3-thienyl)acrylic acids 31, which upon heating with $SOCl_2$ in chlorobenzene underwent cyclization to produce the corresponding 3-chloro-thieno[2,3-*b*]thiophene-2-carbonyl chlorides 32 (Scheme 15) [37]. Thereafter, reaction of 32 with aniline derivatives in refluxing toluene afforded the 3-cholorothieno[2,3-*b*]thiophene-2-carboxamides 33, which were photochemically dehydro-halogenated to give the respective products 34 (Scheme 15) [37].

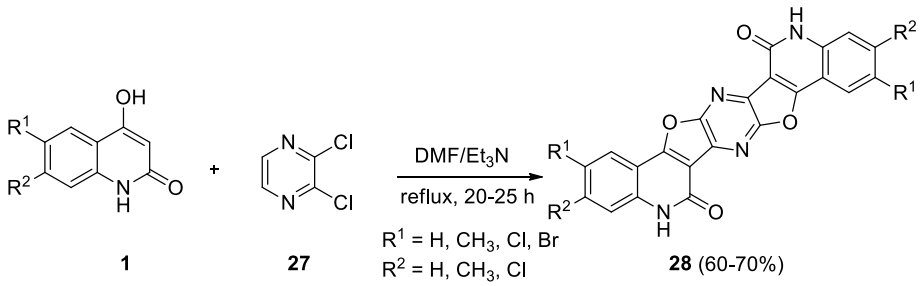
Thienoquinolone 36 was synthesized as shown in Scheme 16. The mixture of 35, di-isopropyl azodicarboxylate (DIAD), $CoCl_2$, sodium pivalate (NaOPiv) and 1,4-dioxane was heated at 130 °C under O_2 for 24 h to afford compound 36 [38]. DIAD was used as a source of releasing CO [38].

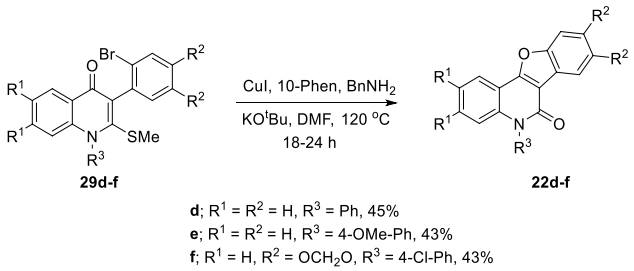
Additionally, when a mixture of 37 (0.2 mmol), L4 (10 mol %), CO_2 (1 atm.), $[RhCl(cod)]_2$ (5 mol%) and *t*-BuOK (6.5 eqv.) was heated in DMF at 150 °C for 24 h, the reaction afforded thieno[3,2-*c*]quinolin-4(5*H*)-one 36 in 70% yield (Scheme 17) [39]. Rh catalyst enhances the



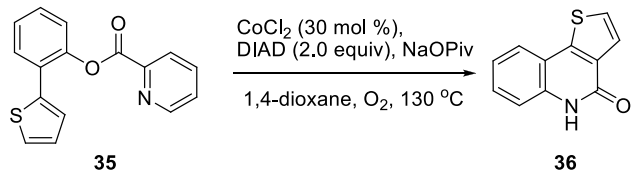
Scheme 12 Synthesis of naphthofuro[3,2-*c*]quinolone-6,7,12-trione derivatives 26

Scheme 13 Reaction of 4-hydoxyquinolones with 2,3-dichloropyrazine 27





Scheme 14 Synthesis of furoquinolone derivatives 22d-f



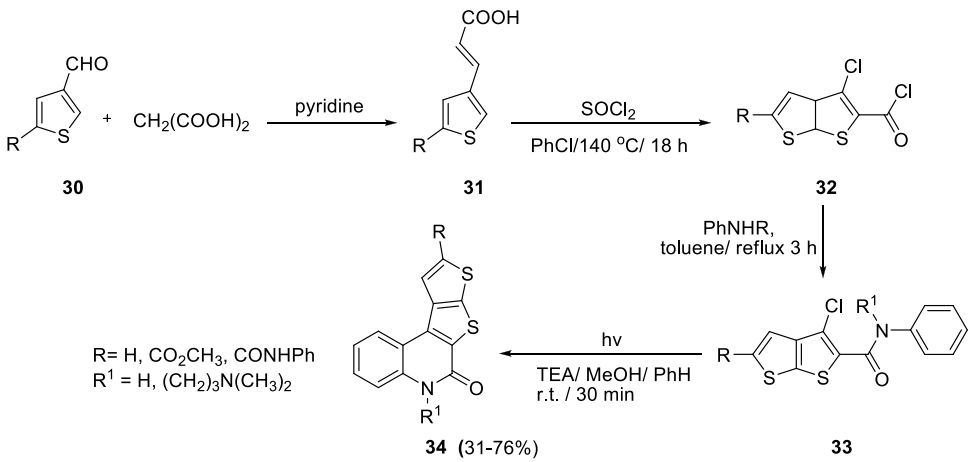
Scheme 16 Synthesis of thienoquinolone 36

nucleophilicity of the C-3 of thiophene, followed by insertion of CO_2 [39].

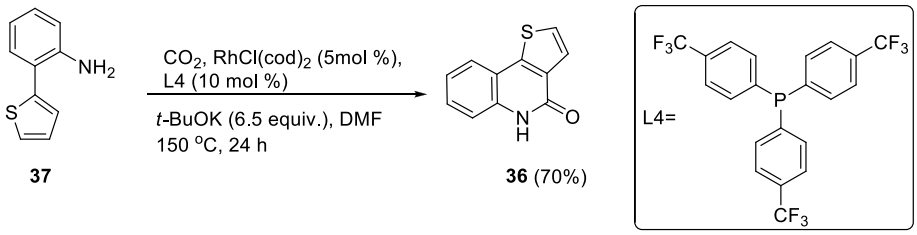
Similarly, Liang and co-workers reported the synthesis of thienoquinolone 36 by treatment of 37 with CO_2 in the presence of a catalyst amount of $Pd(OAc)_2$ and $Cu(TFA)_2$ (Scheme 18) [40].

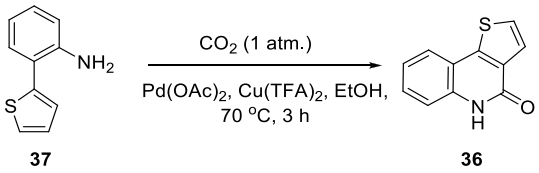
Görlitzer et al. reported the synthesis of methyl 2-(2-nitrophenyl)thiophene-3-carboxylate (38) via Suzuki cross-coupling procedure. Compound 38 was utilized in preparing compound 39 by mixing 38 with 6 ml acetate buffer solution

Scheme 15 Synthesis of thienoquinolone derivatives 34

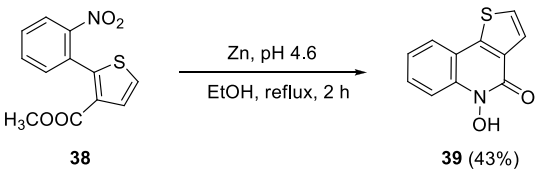


Scheme 17 Synthesis of thienoquinolone 36





Scheme 18 Synthesis of thienoquinolone 36



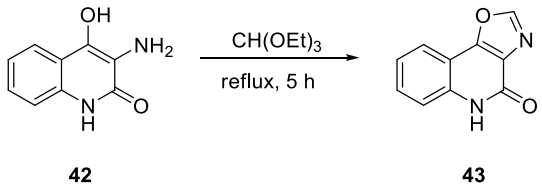
Scheme 19 Synthesis of thienoquinolone 39

pH 4.6 and Zn granules. The mixture was then refluxed in EtOH for 2 h. The desired product was then obtained, which was identified as 5-hydroxy-thieno[3,2-*c*]quinolin-4(5*H*)-one 39 (Scheme 19) [41].

When a solution of (bis(trifluoroacetoxy)iodo)benzene (PIFA) (1.03 mmol) and BF_3-OEt_2 in CH_2Cl_2 was added at 0 °C to a solution of amide 40 (1.0 mmol) in CH_2Cl_2, 5-methoxy-2-methylthieno[2,3-*c*]quinolin-4(5*H*)-one (41) was obtained in 37% yield (Scheme 20) [42]. Interestingly, using TFA instead of BF_3·OEt_2 as the activating agent, the yield was dramatically increased to 91% yield (Scheme 20).

Oxazoloquinolones

Ukrainets and co-workers reported the synthesis of 1,3-oxazoloquinolone 43 by the reaction of 3-amino-1*H*,3*H*-quinoline-2,4-dione (42) with excess triethyl orthoformate under reflux for 5 h (Scheme 21) [43].



Scheme 21 Synthesis of oxazolo[4,5-*c*]quinolone 43

1,3-Oxazoloquinolone 46 was synthesized, in 79% yield, by the reaction of the pyridin-4-yl methylenehydrazide 44 with bromine in glacial acetic acid. A light-orange precipitate 45 was formed immediately, which upon subsequent heating was rapidly decolorized to form compound 46 (Scheme 22) [44].

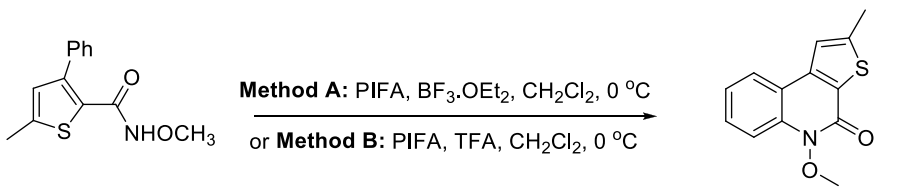
Isoxazoloquinolones

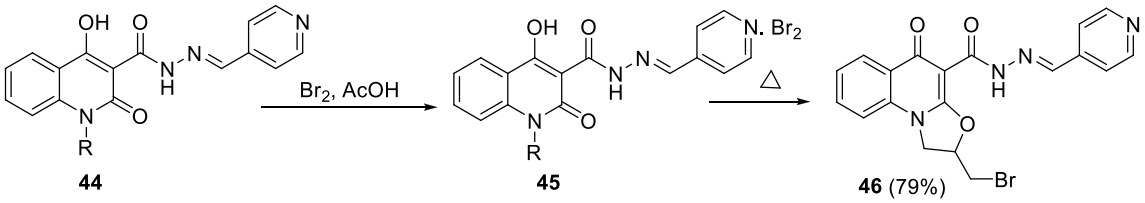
Reaction of 3-arylacryloyl-4-hydroxyquinolin-2(1*H*)-ones 47 with hydroxylamine hydrochloride (1 M) in glacial AcOH at reflux for 19–20 h gave the corresponding 1,2-oxazoloquinolones 48 in 70–81% yields (Scheme 23) [45]. It was noted that increasing the reaction duration increased the obtained yields of products 48 [45].

In a different manner, the regioisomers isoxazolo[4,5-*c*]quinolone (**50**) and oxazolo[4,5-*c*]quinolin-4(5*H*)-one (**51**) were obtained during the reaction of 3-benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (49) in ethylene glycol and hydroxylamine hydrochloride. The reaction mixture was heated at reflux for 4 h (Scheme 24) to produce a mixture of 50 and 51 in 92:8 ratio, which was separated by chromatography [46].

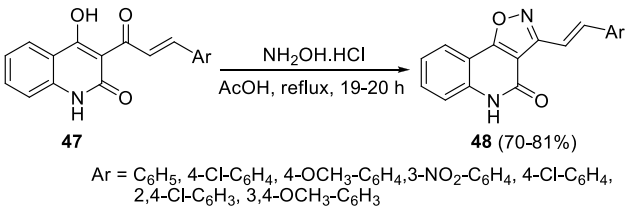
Furthermore, isoxazolo[4,5-*c*]quinolone 53 was obtained, when a solution of [bis(trifluoroacetoxy)iodo]

Scheme 20 Synthesis of thienoquinolone 41

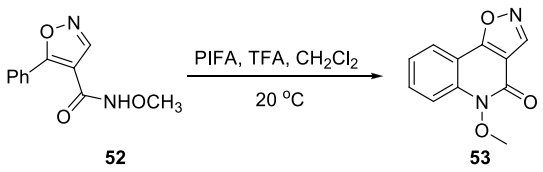




Scheme 22 Synthesis of 1,3-oxazoloquinolone 46



Scheme 23 Synthesis of isoxazolo[4,5-*c*]quinolones 48



Scheme 25 Synthesis of isoxazolo[4,5-*c*]quinolone 53

benzene (PIFA, 1.03 mmol) and trifluoroacetic acid (TFA) in CH_2Cl_2 was added at 20 °C to a solution of amide 52 (1.0 mmol) in CH_2Cl_2. The mixture was stirred for 1 h; work-up and chromatography afforded product 53 (Scheme 25) [42].

Pyrazoloquinolones

Hydrazinolysis of ethyl ester 54 led to the formation of the corresponding hydrazides of 3-(hydrazinyloxy) carbonyl)-4-hydroxyquinolin-2(1*H*)-ones 55 [47], which upon thermolysis afforded 1*H*-pyrazolo[4,3-*c*]quinoline-3,4(2*H*,5*H*)-diones 56 (Scheme 26) [48].

When a suspension of 3-benzoylquinolone 57 and phenylhydrazine in glacial acetic acid was treated with a few drops of concentrated sulfuric acid and heated under reflux for 2 h, the reaction afforded the corresponding product 58 in 72% yield (Scheme 27) [49].

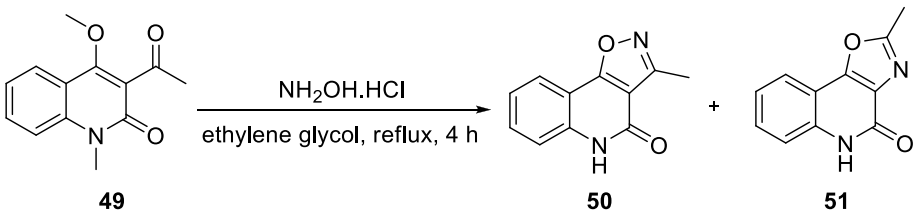
Microwave irradiation of a mixture of 3-acyl quinolin-2-ones 59, phenylhydrazine derivatives and $InCl_3$ in ethanol gave pyrazoloquinolones 60 in 80–95% yields (Scheme 28) [50]. It was found that $InCl_3$ was found to be more effective in providing greater yield of products compared to $Yb(OTf)_3$, $Sc(OTf)_3$, $SnCl_4$, $AlCl_3$, $TiCl_4$, $ZnCl_2$, $FeCl_3$ and $BF_3{\cdot}Et_2O$. Moreover, a comparison of conventional and microwave methods has revealed that the latter method is more efficient compared to former one. Some derivatives of 60 exhibited anti α-glucosidase inhibitory activity with IC_{50} values of 57.5, 60.3, 65.9, 71.9, 80.8, 123.7 and 126.4 µM, respectively, which is quite comparable to the standard drug acarbose (IC_{50} = 115.8 µM) [50].

Feng et al. prepared the 8,9-dihydro-1*H*-pyrazolo[3,4-*f*] quinolin-7(6*H*)-ones 63, in 80–89% yields, by the reaction of 3-phenylisoxazol-5(4*H*)-ones (61), 1*H*-indazol-6-amine (62) and aromatic aldehydes in refluxing EtOH for 8–11 h (Scheme 29) [51].

Addition of hydrazine hydrate to a stirred solution of compound 64 in DMF and at room temperature for 3 h gave the product 65. Upon heating a solution of compound 65 in DMF for 1 h, pyrazoloquinolone 66 was formed in 84% yield (Scheme 30) [52].

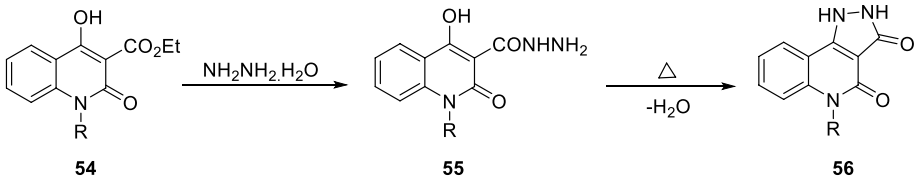
Imidazoquinolones

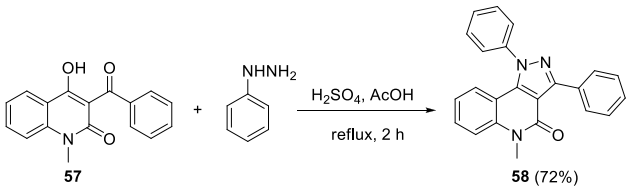
Mrkvicka et al. [53] prepared imidazoquinolone 68 when a mixture of 3-amino-1*H*,3*H*-quinoline-2,4-dione derivatives 67 and potassium thiocyanate in acetic acid was stirred for 5 min. The precipitated product was filtered off to afford the desired product 68 (Scheme 31). The proposed



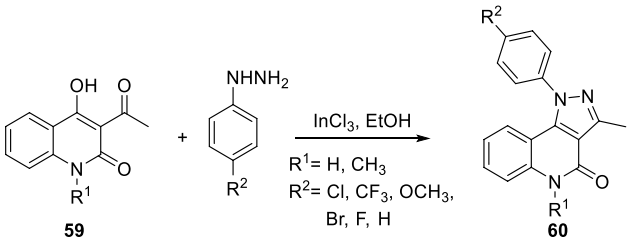
Scheme 24 Synthesis of isoxazolo[4,5-*c*]quinolone 50 and oxazolo[4,5-*c*]quinolone 51

Scheme 26 Synthesis of pyrazoloquinolones 56

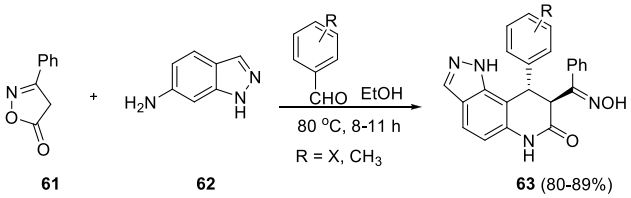




Scheme 27 Synthesis of pyrazolo[4,3-*c*]quinolone 58



Scheme 28 Synthesis of pyrazolo[4,3-*c*]quinolones 60



Scheme 29 Synthesis of pyrazolo[3,4-*f*]quinolones 63

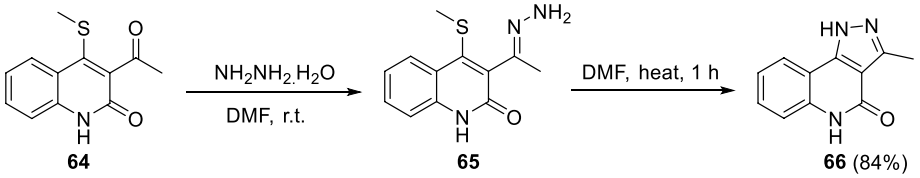
reaction mechanism (Scheme 31) supposes the addition of -aminoketone 67 to isothiocyanic acid. This would give the intermediate A, which cyclizes to give intermediate B and subsequently converts into intermediate C. In an acidic medium, protonation of intermediate C proceeds accompanies with ejection of the benzylic cation to give compound 68 (Scheme 31).

Moreover, a mixture of compounds 71–73 was obtained. When a mixture of 69 in DMF and hydroxylamine was stirred at room temperature, it gave the intermediate 70 [54]. Thereafter, KSCN was added to a solution of compound 70 in AcOH and the mixture was stirred for 3 h at 50 °C, to afford the imidazoquinolones 71–72 (Scheme 32) [55].

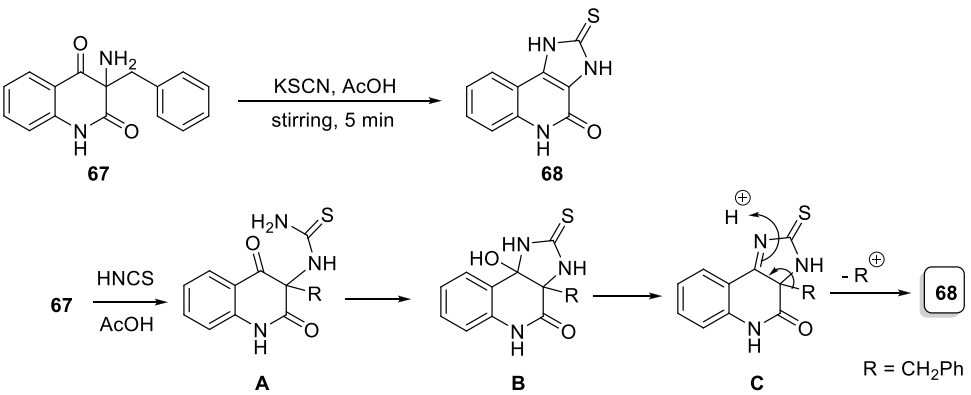
Alkylation of the amide *N*-atom with benzyl and *p*-methoxybenzyl groups of 74 was done by the exposure of NaH and benzyl bromide or *p*-methoxybenzyl chloride, which afforded fully protected derivatives 75a and 75b in 85 and 76% yield, respectively. These intermediates were used as precursors for the intramolecular arylation reaction. Treatment of *N,N*-di-substituted imidazo[1,2-*a*]pyridine-2-carboxamides 75a or 75b with a mixture of K_2CO_3, PPh_3 and $Pd(OAc)_2$ in DMA afforded imidazo[4,5-*c*]quinolone derivatives 76a and 76b (Scheme 33) [56]. The reaction was carried out in the presence of 10 mol % of $Pd(OAc)_2$/20 mol % PPh_3 and K_2CO_3 (2 equiv) in DMA.

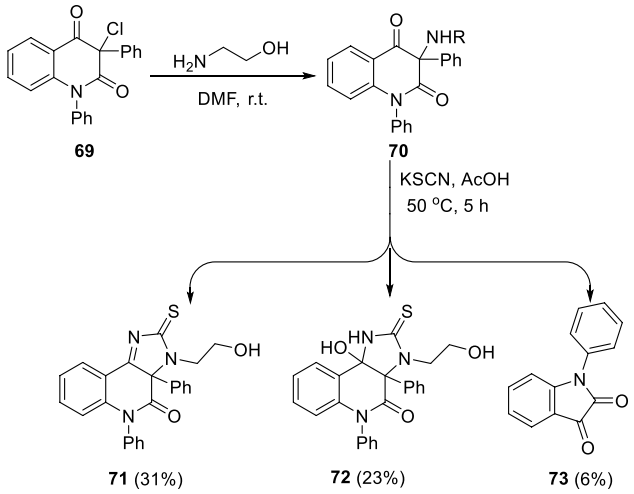
Reagents and conditions: (i) *p*-methoxybenzyl chloride or benzyl bromide, NaH, THF, reflux, 24–36 h (ii) $Pd(OAc)_2$

Scheme 30 Synthesis of pyrazolo[4,3-*c*]quinolin-4(5*H*)-one 66



Scheme 31 Synthesis of imidazo[4,5-*c*]quinolone 68





Scheme 32 Synthesis of imidazoquinolones 71–72

(0.1 eq.), PPh_3 (0.2 eq.), K_2CO_3 (2 eq.), DMA, 100 °C, oil bath.

The 1-butyl-derivative of isatoic anhydride (77) reacted with the anion of ethyl nitroacetate to give 1-butyl-4-hydroxy-3-nitroquinolin-2(1*H*)-one (Scheme 34) [57]. Without purification, the hydroxy group was chlorinated with phosphorus oxychloride under reflux to give 78 (Scheme 34). The chlorine in 78 was readily replaced by primary amines in tetrahydrofuran (THF) at room temperature to provide 79. Hydrogenation of the nitro group in 79, followed by cyclization in refluxing triethyl orthoformate, afforded imidazoquinolones 80 (Scheme 34) [57].

Oxathioloquinolones

[1,3]Oxathiolo-[4,5-*c*]quinoline-2,4(5*H*)-diones 82 were synthesized by the reaction of quinolone 81 with P_2O_5/H_2SO_4 (Scheme 35) [58, 59].

[1–3]Triazoloquinolones

The smooth 1,3-dipolar cycloaddition reaction of heterocyclic nitroalkenes with sodium azide provides a rapid entry into valuable heterocyclic scaffolds with potential biological properties. In 2017, the fused triazole system 84 was synthesized by the reaction of 3-nitroquinolone (83) and sodium azide in DMF. The reaction mixture was subjected to microwave heating for 1 min at 160 °C to give [1–3]triaozlo[4,5-*c*]quinolone (84) in 92% yield (Scheme 36) [60].

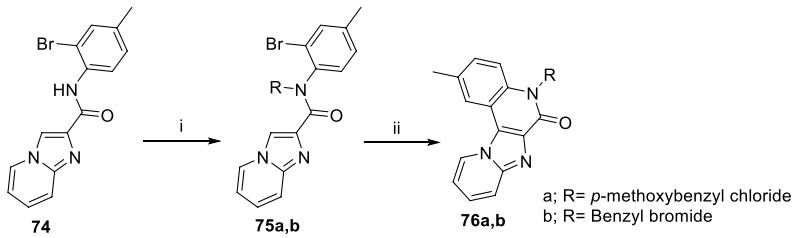
Synthesis of quinolones heteroannulated with six-member ring heterocycles

Pyridoquinolones

Abass and co-workers [61] reported the synthesis of pyridoquinolone 86 by the reaction of 4-hydroxyquinolone derivative 85 with an active methylene reagent such as cyanoacetamide in the presence of tetrabutylammonium bromide (TBAB) and potassium carbonate in DMF. The mixture was heated under reflux for 4 h to afford the corresponding product 86 in 59% yield (Scheme 37) [61]

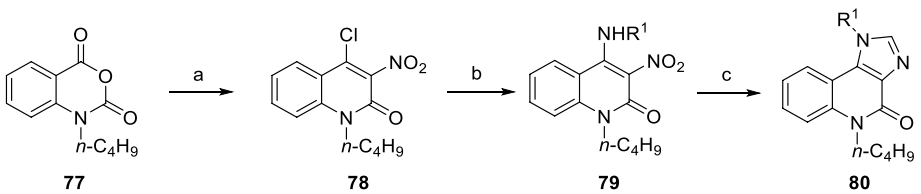
Moreover, Wang et al. reported the synthesis of pyridoquinolones 88 by the reaction of 1 with *N*-benzilidenenaphthalen-2-amine (87) in the presence of triethylbenzyl

Scheme 33 Synthesis of imidazo[4,5-*c*]quinolones 76a,b

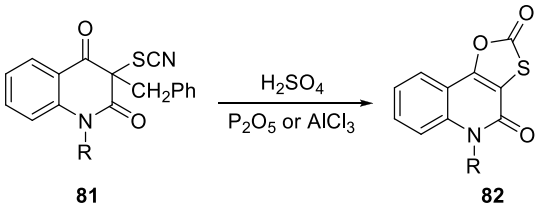


Reagents and conditions; (i) *p*-methoxybenzyl chloride or benzyl bromide, NaH, THF, reflux, 24–36 h (ii) $Pd(OAc)_2$ (0.1 eq.), PPh_3 (0.2 eq.), K_2CO_3 (2 eq.), DMA, 100 °C, oil bath

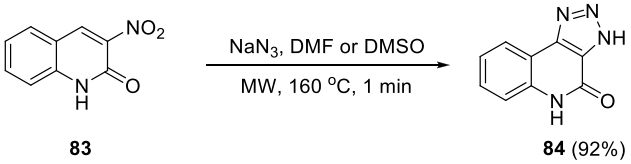
Scheme 34 Synthesis of imidazoquinolones 80



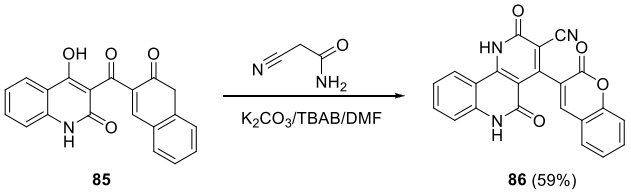
a; (i) $(CH_3)_2NCOCH_3$, $O_2NCH_2CO_2Et$, NaH, 120 °C, (ii) $POCl_3$, heat; (b) THF, R^1NH_2; (c) (i) EtOH, H_2, 10% Pd-C; (ii) $HC(OEt)_3$, heat



Scheme 35 Synthesis of [1,3]oxathiolo[4,5-*c*]quinolones 82

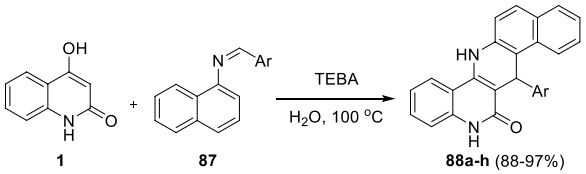


Scheme 36 Synthesis of [1,2,3]triazolo[4,5-*c*]quinolone 84



Scheme 37 Reaction of 4-hydroxyquinolone derivative 85 with cyanoacetamide

ammonium chloride (TEBA) in water at 100 °C (Scheme 38) [62]. Table 2 illustrates the results of the synthesis pyridoquinolones 88a-h in H_2O at 100 °C.

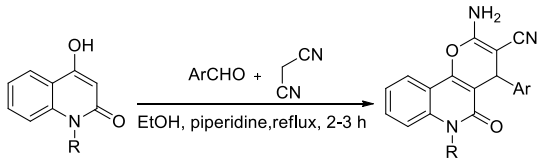


Ar = **a**; 2-Cl-C_6H_4, **b**; 4-Cl-C_6H_4, **c**; 3,4-Cl_2-C_6H_3, **d**; 2,4-Cl_2-C_6H_3, **e**; 4-F-C_6H_5, **f**; 4-Br-C_6H_5, **g**; 4-$OCH_3C_6H_4$, h; 3-ClC_6H_5

Scheme 38 Synthesis of pyridoquinolones 88a-h

Table 2 The results on the reaction of 1 and 87 in water at 100 °C

Entry	Ar	Time (h)	Yields (%)
88a	2-ClC_6H_4	8	94.2
88b	4-ClC_6H_4	8	90.2
88c	3,4-Cl_2C_6H	8	93.2
88d	2,4-$Cl_2C_6H_3$	8	97.0
88e	4-FC_6H_4	8	92.5
88f	4-BrC_6H_4	10	93.5
88 g	4-$CH_3OC_6H_4$	12	91.6
88 h	3-ClC_6H_4	10	87.8



Scheme 39 Synthesis of pyrano[3,2-*c*]quinolin-5-one derivatives 89

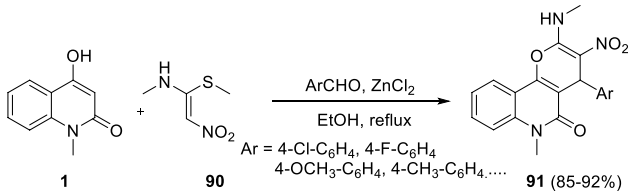
Pyranoquinolones

The three-component reaction of 4-hydroxyquinolin-2(1*H*)-ones **1**, various aldehydes and malononitrile afforded pyrano[3,2-*c*]quinolin-5-one derivatives 89. This reaction can be catalyzed by piperidine, TEBA, ammonium acetate or triethyl amine (Scheme 39) [63–65]

Also, Gunasekaran et al. showed that one-pot reaction of quinolone **1**, (*E*)-*N*-methyl-1-(methylthio)-2-nitro-ethenamine (90) and aromatic aldehydes in the presence of anhydrous $ZnCl_2$ produced 6-methyl-2-(methylamino)-3-nitro-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones 91 in 85–92% yields (Scheme 40) [66]. The reported domino transformation leads to the formation of one ring by creation of two C–C bonds and one C–O bond in a single synthetic operation [66].

In addition, Zhu and co-workers reported the synthesis of pyranoquinolinones 93 when mixtures of **1**, Meldrum's acid (92) and aromatic aldehydes in the presence of *L*-proline were allowed to react in refluxing ethanol (Scheme 41) [67]. It was found that when the reaction was carried out without any catalyst, only a modest amount of product was obtained, even after 5 h (Table 3, entry (1). When the reaction was conducted in the presence of *L*-proline (10 mol%) in ethanol, the target compounds **93** were obtained in very good yield (Table 3, entry 2). Other solvents were also used in this reaction. The results indicated that ethanol provided much better results than acetonitrile, chloroform, acetic acid, *N*,*N*-dimethylformamide (DMF) and water (Table 3, entries 2–7). To optimize the catalyst loading, 5 mol%, 10 mol%, 15 mol% and 20 mol% of *L*-proline were tested in the reactions, respectively (Table 3, entries 2, and 8–10). A 10 mol% loading of *L*-proline was sufficient to efficiently push the reaction forward. Higher amounts of *L*-proline did not lead to significant changes in the reaction yields.

In 2018, Aly, reported the preparation of ethyl 5,6-dihydro-2,5-dioxo-6,9-disubstituted-2H-pyrano[3,2-c]quinoline-4-carboxylates 95 by the reaction of equimolar amounts of 1 and diethyl acetylenedicarboxylate (94) in



Scheme 40 Synthesis of pyrano[3,2-*c*]quinolin-5(6*H*)-ones 91

absolute ethanol containing catalytic amounts of triethylamine (Et3N,Scheme 42) [68].

Reaction of the β-keto acid 96 with isatine was carried out under Knoevenagel reaction conditionsusing fused sodium acetate and glacial acetic acid. The product of this reaction was characterized as2-(indol-3-ylidene)propanoic acid 97 (Scheme 43) [69]. When the product 97 was consequentlytreated with concentrated sulfuric acid, this cyclization took place and compound 98 was formed in88% yield (Scheme 43)

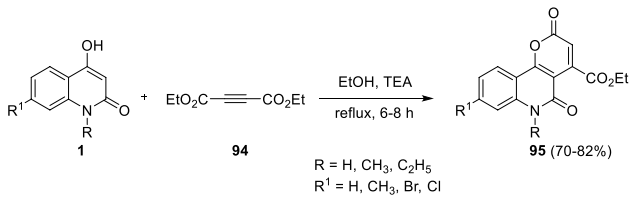
Aly et al. synthesized spiro(indoline-3,4'-pyrano[3,2-*c*]quinoline)-3'-carbonitriles 100 in 85–92% yields by refluxing equimolar amounts of 1 with 2-(2-oxo-1,2-dihydroindol-3-ylidene)-malononitrile (99) in dry pyridine solution (Scheme 44) [20].

When an equimolar mixture of 4-hydroxy quinoline derivatives 1a-f and 2-(2,7-dibromo-9*H*-fluoren-9-ylidene) malononitrile (101) was refluxed for 10–14 h in dry pyridine, the reaction proceeded to afford 2'-amino-2,7-dibromo-5'-oxo-5',6'-dihydrospiro[fluorene-9,4'-pyrano[3,2-*c*]quinoline]-3'-carbonitrile derivatives 102a-f in 77–83% yields (Scheme 45) [70]. Compounds 102b, 102c and 102d inhibited Src kinase activity with IC_{50}'s of 4.9, 5.9 and 0.9 µM, respectively. At the same time, they did not affect the MDM2/p53 interaction in HEK293 cells that have been reported to be affected by some spirocyclic compounds [70].

The 1-alkyl or aryl quinolone derivatives 1a-c were reacted with 2-bromobenzylbromides in refluxing acetone for 4–5 h to afford quinolin-2(1*H*)-ones 103a-c in 80–85% yields (Scheme 46). Upon refluxing 103a-c in benzene-containing tributyltin(IV) chloride (Bu_3SnCl) and sodium cyanoborohydride in the presence of azoisobutyronitrile for 4–5 h, the reaction proceeded to give the tetracyclic pyranoquinolin-7(8*H*)-ones 104a-c (Scheme 46) [71].

Table 3 Optimization of reaction conditions

Entry	Solvents	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	EtOH	No	Reflux	5	45
2	EtOH	*L*-proline (10%)	Reflux	1	91
3	CH_3CN	*L*-proline (10%)	Reflux	2	70
4	$CHCl_3$	*L*-proline (10%)	Reflux	2	63
5	HOAc	*L*-proline (10%)	100	2	80
6	DMF	*L*-proline (10%)	100	2	52
7	H_2O	*L*-proline (10%)	Reflux	4	45
8	EtOH	*L*-proline (5%)	Reflux	2	75
9	EtOH	*L*-proline (15%)	Reflux	1	90
10	EtOH	*L*-proline (20%)	Reflux	1	91

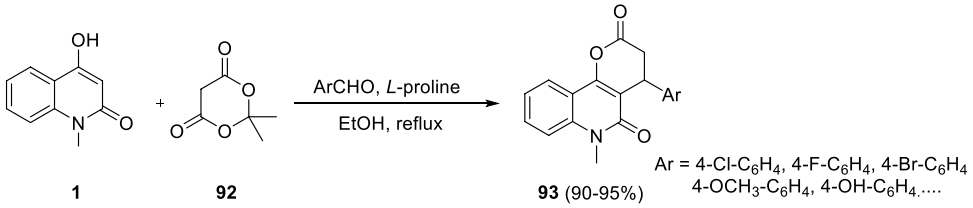


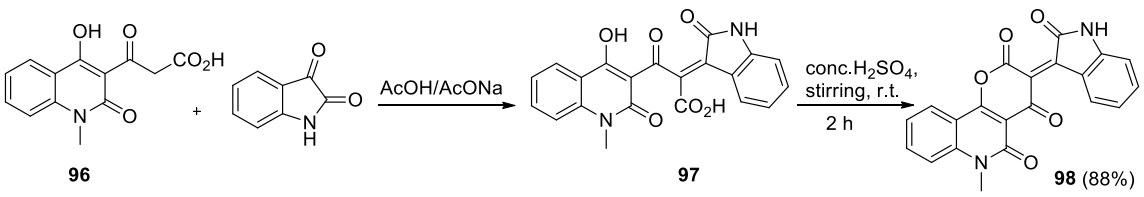
Scheme 42 Synthesis of pyrano[3,2-*c*]quinolones 95

Bu_3SnH-mediated radical cyclizations to the regioselective synthesis of tetracyclic heterocycles 2*H*-benzopyrano[3,2-*c*]quinolin-7(8*H*) ones was described as a general procedure and attractive due to its simplicity. The mechanism was described as due to free radical of the oxidation step in Bu_3SnH-mediated cyclization reaction [71].

Hassanin et al. reported that the reaction of *N*-butylaniline with two equivalents of diethyl malonate, under solvent-free conditions, afforded 4-hydroxypyrano[3,2-*c*]quinoline-2,5(6*H*)-dione 105 which upon thermal condensation with dimethylformamide dimethylacetal

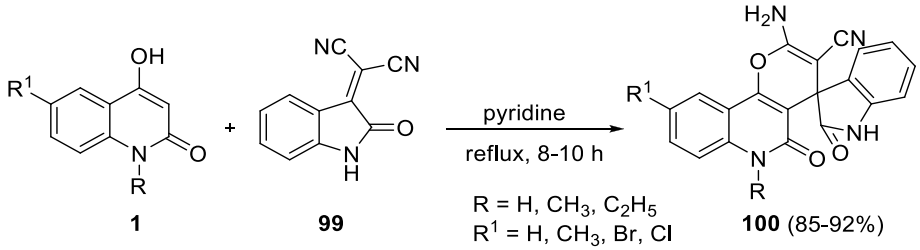
Scheme 41 Synthesis of pyrano[3,2-*c*]quinolones 93



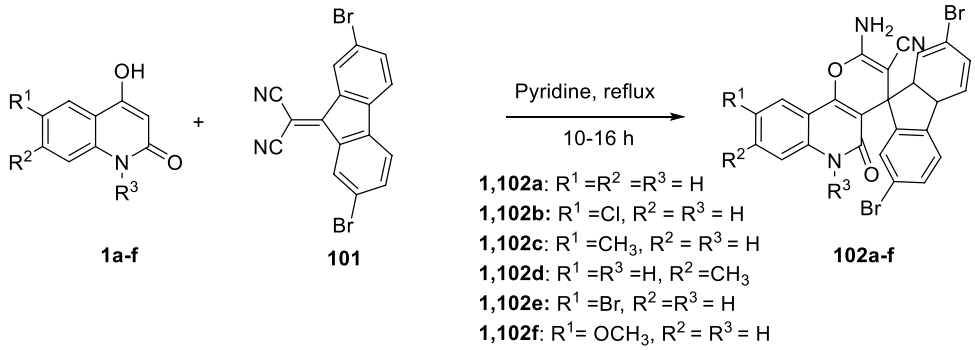


Scheme 43 Synthesis of fused pyranoquinolone 98

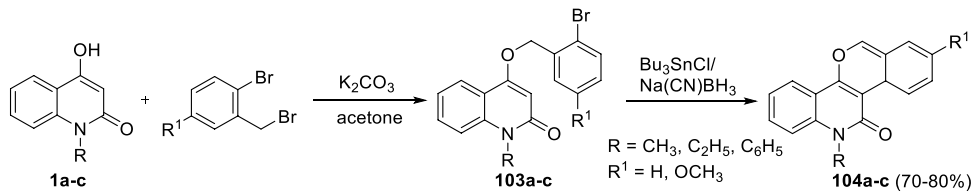
Scheme 44 Synthesis of spiropyrano[3,2-*c*]quinolones 100



Scheme 45 Synthesis of spiropyrano[3,2-*c*]quinolones 102a-f



Scheme 46 Synthesis of pyranoquinolone derivatives 104a-c



(DMF-DMA) afforded compound 106. The reaction of enamine 106 and hydrazine hydrate in boiling absolute ethanol afforded directly the pyranoquinolone 107 in 79% yield (Scheme 47) [72].

Kiamehr and co-workers developed in 2019 an efficient synthesis of tetrahydropyrazolo-[4',3':5,6]pyrano[3,4-*c*]quinolone 110 by the reaction of *N*-acrylated anthranilaldehyde (108), *N*-phenyl pyrazolone (109) and $ZnBr_2$ (50 mol%) in refluxing absolute ethanol for 5 h (Scheme 48) [73]. The reaction was described as domino Knoevenagel/hetero-Diels–Alder (DKHDA) reaction. The products were formed in good yields and with excellent regio- and stereoselectivity in favor of the *cis*-configured isomer [73].

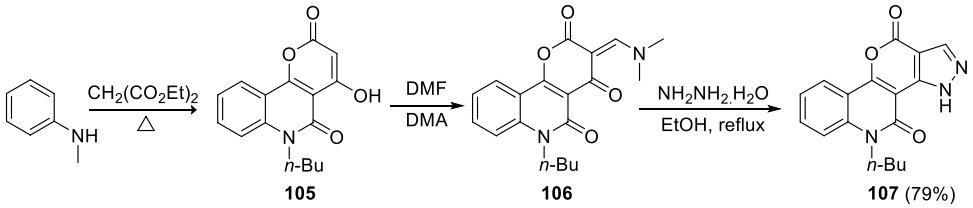
Thiopyranoquinolones

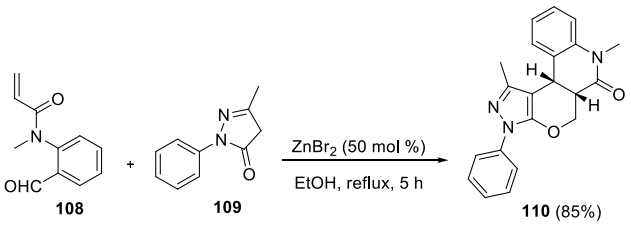
Kiamehr and co-workers reported the synthesis of annulated thiopyranoindolo[3,4-*c*]quinolones 112 by the addition of $ZnBr_2$ (20 mol%) to stirred solutions of *N*-acrylated anthranilaldehydes 108 and indolin-2-thiones 111 in refluxed absolute ethanol for 3 h (Scheme 49) [74].

Thiazinoquinolones

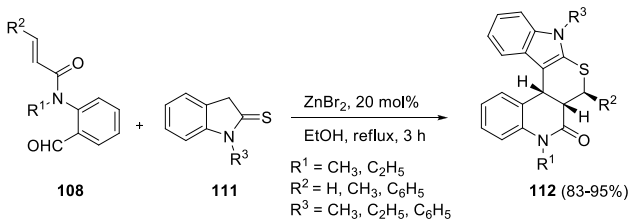
The reaction of 1 with *o*-aminothiophenol in dioxane in the presence of *p*-TSA afforded 5*H*-quinolin[3,4-*b*][1, 4]-benzothiazin-6(12*H*)-one (113) (Scheme 50) [75].

Scheme 47 Synthesis of pyranoquinolones 105–107

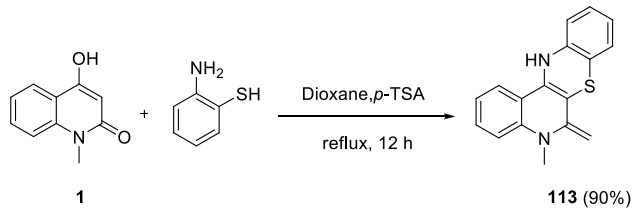




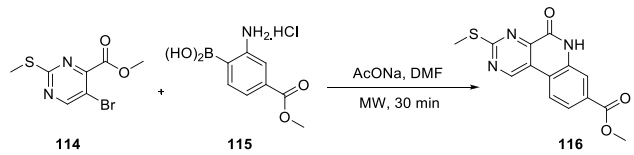
Scheme 48 Synthesis of pyranoquinolone 110



Scheme 49 Synthesis of thiopyranoquinolones 112



Scheme 50 Reaction of quinolone **1** with *o*-aminothiophenol



Scheme 51 Synthesis of pyrimidoquinolone 116

Pyrimidoquinolones

Hodgetts et al. [76] reported the synthesis of pyrimidoquinolones 116 by the reaction of methyl 5-bromo-2-(methylthio)pyrimidine-4-carboxylate (114), 2-amino-4-(methoxycarbonyl)phenyl-boronic acid hydrochloride (115) and sodium acetate in DMF in a microwave vessel (Scheme 51). The mixture was degassed by bubbling nitrogen gas through the solution for 10 min, and the reaction was heated under microwave irradiation at 120 °C for 30 min, to give the expected product 116 (Scheme 51) [76].

Pierre et al. [77] reported the synthesis of pyrimidoquinolone 120, when 4-methyl-3-nitrobenzoic acid (117) was converted to intermediate 118 in four steps. In the following step, the pyrimidine ring 119 was formed by reacting intermediate 118 with acetamidine hydrochloride under basic conditions. Hydrogenation of 119 produced its corresponding intermediate aniline. This intermediate was converted into 120 by intramolecular amide formation using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) in DMF (Scheme 52) [77].

Reagents and conditions: (a) EtOH, HCl, (b) $(CO_2Et)_2$, EtOH, EtONa, 0 °C to r.t., (c) $(EtO)_3CH$, Ac_2O, reflux, (d) pyrrolidine, EtOH, r.t., (e) $MeC(NH_2)=NH.HCl$, dioxane, K_2CO_3, 100°C, (f) 50 psi H_2, Pd/C wet, MeOH, (g) EDCI, DMF, 80 °C.

4-Hydroxy-3-acyl quinolin-2-one (121) was allowed to react with guanidine nitrate and a catalytic amount of sodium acetate in ethanol at reflux. Chromatography afforded compound 122 in 88% yield; compound 120 revealed promising antioxidant activity (Scheme 53) [78].

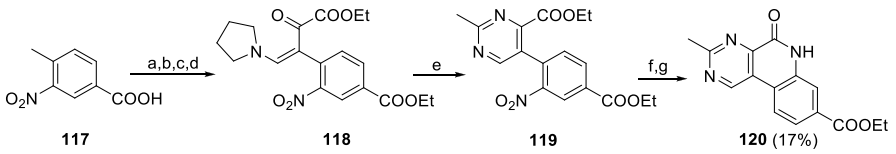
Pyrazinoquinolones

When 3,4-diaminoquinolin-2(1*H*)-one 123 was subjected to chloroacetic acid, pyrazino[2,3-*c*]quinoline-3,5(4*H*,6*H*)-dione 124 was obtained. A similar condensed product, 2,3-dimethylpyrazino[2,3-*c*]quinolin-5(6*H*)-one (125), was obtained from the reaction of 123 with biacetyl (Scheme 54) [79].

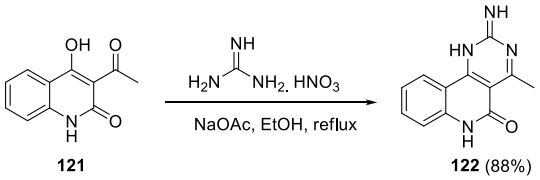
Hamama et al. reported that pyrazinoquinolone 127 was obtained by the reaction of 3-bromo-4-hydroxy-7-methoxyquinolin-2(1*H*)-one (126) with bifunctional nucleophilic reagents such as *o*-phenylenediamine in boiling DMF for 4 h (Scheme 55) [80].

Cincinelli et al. synthesized the pyrazinoquinolone 130 by the reaction of quinolonecarboxylic acid 128 in dry THF, HOBt with aminoacetaldehyde diethylacetal at room temperature to give the intermediate 129. Then, trifluoroacetic acid was added to a suspension of 129 in acetonitrile, and the mixture was heated at reflux for 14 h to give 3*H*-pyrazino[1,2-a]quinoline-4,6-diones (130) (Scheme 56) [81]. It was noted that treatment the reaction of 129a (on the free-NH quinolone), the reaction proceeded smoothly

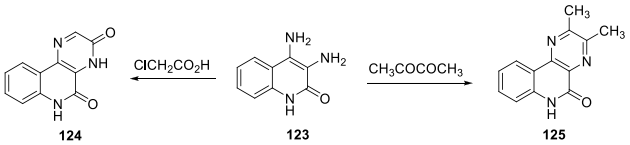
Scheme 52 Synthesis of pyrimidoquinolone 120



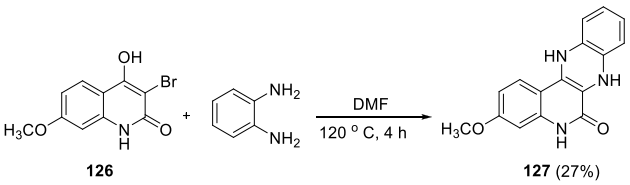
Reagents and conditions: (a) EtOH, HCl (b) $(CO_2Et)_2$, EtOH, EtONa, 0 ºC to r.t. (c) $(EtO)_3CH$, Ac_2O, reflux (d) Pyrrolidine, EtOH, r.t. (e) $MeC(NH_2)$=NH.HCl, dioxane, K_2CO_3, 100 ºC (f) 50 psi H_2, Pd/C wet, MeOH (g) EDCI, DMF, 80 ºC.



Scheme 53 Synthesis of pyrimidoquinolone 122



Scheme 54 Synthesis of pyrazinoquinolones 124,125

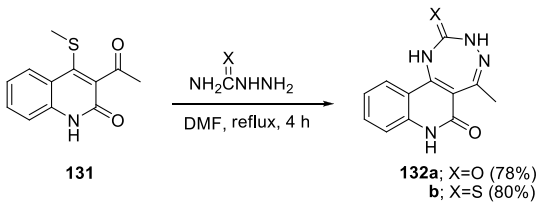


Scheme 55 Synthesis of pyrazinoquinolone 127

to give compound 130a, derived from the attack of *N*-1 to the carbonyl group of the intermediate aldehyde, followed by elimination of two moles of ethanol [81].

Synthesis of quinolones heteroannulated with seven-member ring heterocycles

To a solution of compound 131 in DMF, semicarbazide hydrochloride or thiosemicarbazide was added and the reaction mixture was heated under reflux for 4 h. After cooling to room temperature, the solid precipitate was filtered to give compounds 132a and 132b (Scheme 57) [52].



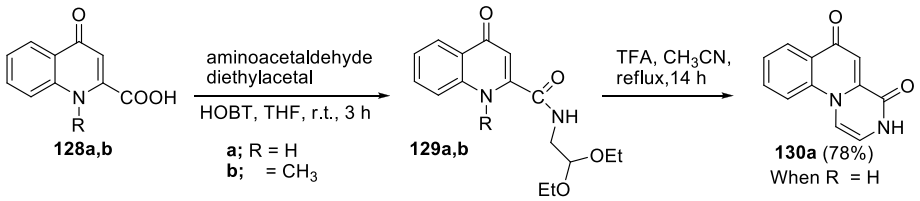
Scheme 57 Synthesis of [1,2,4]triazepino[6,5-*c*]quinolin-6(7*H*)-ones 132a,b

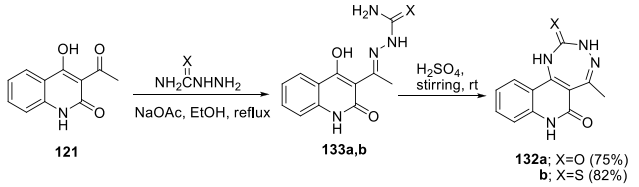
Alternatively, [1, 2, 4]triazepino[6,5-*c*]quinolin-6(7*H*)-ones 132a,b were synthesized by the reaction of 121 with semicarbazide hydrochloride (or thiosemicarbazide) and a catalytic amount of sodium acetate in refluxing ethanol. The formed products 133 were then cyclized with conc. H_2SO_4 at room temperature to give the desired products 132a,b (Scheme 58) [78].

Biological activities of heteroannulated quinolones

2-Quinolone is a common structure in alkaloids [82, 83]. Also, quinolone derivatives have a variety of pharmacological properties [84, 85]. Their derivatives have a relatively simple molecular nucleus that can be subjected to a variety of structural modifications. Quinolone derivatives typically have several advantageous properties, including tissue penetrability, high bioavailability and a relatively low incidence of adverse and toxic effects. They have been shown to be effective in the treatment of a variety of infectious diseases [86]. In recent years, quinolone derivatives have received a great deal of scientific attention in a variety of biological fields.

Scheme 56 Synthesis of pyrazinoquinolone 130





Scheme 58 Synthesis of [1,2,4]triazepino[6,5-*c*]quinolin-6(7*H*)-ones 132a,b

Anticancer activities

Quinoline moieties are important in anticancer drug improvement, as their derivatives show great results through different operations such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration and modulation of nuclear receptor responsiveness [4]. The fused pyranoquinoline moiety is an extremely common structural motif, existing in many naturally occurring or biologically active alkaloids [5, 7, 87].

The natural product Haplamine 134 (Fig. 4), extracted from *Haplophyllum perforatum*, is commonly used in central Asia to treat a variety of diseases, including testicular cancer. Researchers evaluated the haplamine-induced cell death and its major metabolites (*trans/cis*-3,4-dihydroxyhaplamine) 135 (Fig. 4). The IC_{50} values were 52.5, 24.3, 59.7, 41.5, 72 and 32 µM in human pancreatic cancer (Capan1 and Capan2), hepatic cancer (HepG2) and colorectal cancer (LS174T, HT29 and SW620) cell lines, respectively. Meanwhile, the IC_{50} values of *trans/cis*-3,4-dihydroxyhaplamine metabolites 135 (Fig. 4) were both > 200 µM [88].

Kumar et al., in 2018 [89], developed fused quinolone derivatives 136a and 136b (Fig. 5). The obtained compounds were evaluated for their cytotoxic potential in vitro against colon (HT-29, HCT-116, human lung (A549), breast (MCF-7) and prostate (PC-3 and DU145) cancer cell lines. Compound 136a showed promising anti-proliferative activity against lung (A549) cancer cell line with an IC_{50} value of 3.17 ± 0.52 µM. Flow cytometric analyses showed that 136a, in a dose-dependent manner, arrested both the Sub G1 and G2/M phases of the cell cycle. Also, 136b revealed significant inhibition of tubulin polymerization and disruption of microtubule network with an IC_{50} value of 5.15 ± 0.15 µM [89].

Another important example of pharmaceutically active quinolone derivative is the 2-quinolone derivative 137 (Fig. 6), which has revealed anticancer activity in SKBR3 (ER–,PR–,HER2 +), MCF-7 (ER + ,PR + /–,HER2–) and MDA-MB-2 (ER–,PR–,HER2–) cell lines with an IC_{50} value of 23.71, 11.98 and 62.91 uM, respectively. However, 137 showed minor groove binding interaction with DNA at an AT-rich region and induced DNA double-strand breaks [90].

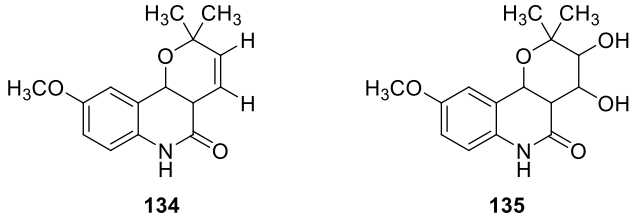


Fig. 4 Structure of Haplamine 134 and *trans/cis* 3,4-dihydroxyhaplamine 135

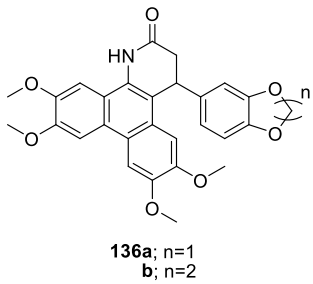
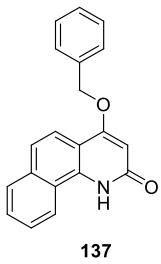


Fig. 5 Structure of compounds 136a,b

Fig. 6 Structure of compound 137



Hamama et al. investigated the antitumor activity of pyrazoloquinolone hybrids 138–140 (Fig. 7). The synthesized derivatives were tested for their cytotoxicity against a very well-known established model EAC (*Ehrlich ascites* carcinoma). The findings revealed that the quinolone moiety is required for the broad spectrum of antitumor activity against the tested cell lines. Introducing a fused pyrazole moiety into quinolone ring system improves the antitumor activity; the tested pyrazoloquinolone hybrids with an IC_{50} ranging of 0.16–0.3 µM were more potent than 5-fluorouracil with an IC_{50} value of 0.54 µM against EAC cells [91].

Aly and co-workers have successfully achieved the synthesis and evaluation of naphthofuro[3,2-*c*]quinoline-6,7,12-dione 26a, pyrano[3,2-*c*]quinoline-6,7,8,13-tetraone (141) and pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (142) (Fig. 8) for their anticancer activities as ERK inhibitors and against BRAF-mutant melanoma. The most potent of these were 26a and 142 which inhibit ERK1 with an IC_{50} value of 0.5 and 0.19 µM and inhibited ERK2 with an IC_{50} value of 0.6 and 0.16 µM, respectively [34].

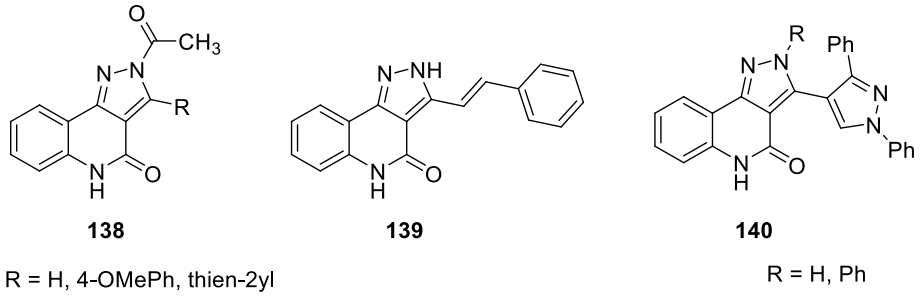


Fig. 7 Structure of compounds 138–140

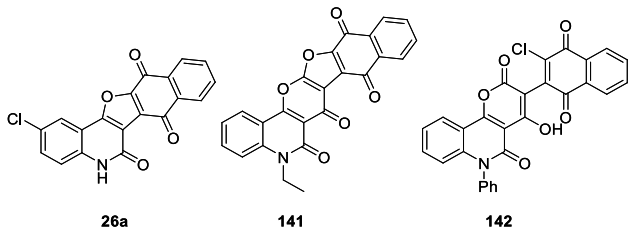


Fig. 8 Structure of compounds 26a, 141 and 142

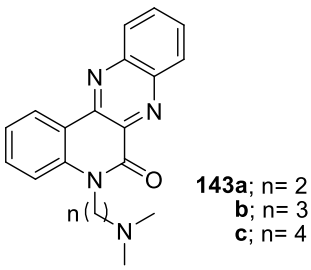


Fig. 9 Structure of compounds 143a-c

In addition, Palluotto et al. designed and synthesized the tetracyclic quinolino[3,4-*b*]quinoxalones 143a-c (Fig. 9). The synthesized derivatives were evaluated for inhibitory activity of topoisomerase IIα (Topo IIα) and cytotoxic characteristics against two human cancer (MCF-7 and HeLa) cell lines. Compounds 143a and 143c, bearing an ethylene and a tetramethylene spacer, respectively, were the most active compounds with an IC_{50} value 35.65 and 34.33 μM, respectively [92].

In 2019, Hassanin et al. synthesized a series of 2,5-dialkyloxazolopyrano[3,2-*c*]quinolones 144a-e (Fig. 10). All the derivatives were tested for cytotoxic activity against a board of three human hepatocellular carcinoma (HepG-2), colon carcinoma (HCT-116) and breast carcinoma (MCF-7) cell lines using 5-fluorouracil as a standard drug. The results indicated that most of the compounds displayed significant activity against all cancer cell lines. Among them, compound 144c has greater inhibitory activity against all three tumor cell lines when compared to other tested compounds with an IC_{50} value of 16.2–28.3 μM, while compound 144e displayed the lowest activity against three tumor cell lines with an IC_{50} value of 118–191 μM. The SAR showed that introduction of longer alkyl chain (R^1) at *N*-position of quinolone improved the anticancer activity. On the other hand, substitution with longer alkyl chain (R^2) at the second position of oxazole ring showed a negative impact on all the cell lines [93].

Furthermore, preparation of pyrroloquinolone derivatives 145 and 146 (Fig. 11) was achieved and was found to possess broad spectrum anticancer activities against a panel of 60 human cancer cell lines with a GI_{50} value ranging from 10.7

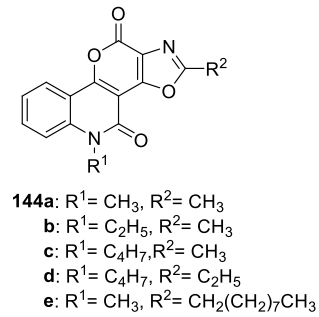


Fig. 10 Structure of compounds 144a-e

to 53.7 μM. The tetracyclic indolo[3,2-*c*]quinolin-2(1*H*)-ones 145 showed a moderate inhibitory activity with a GI_{50} value of 19.0 μM. On the other hand, the isomeric tricyclic 1*H*-pyrrolo[3,2-*c*]quinolin-2(1*H*)-one (146) was less active with a GI_{50} value of 27.5 μM [26].

Some other benzothienoquinolone derivatives 147a-e were synthesized and exhibited promising in vitro anticancer activities against a panel of human cancer cell lines. The SAR of compounds 147a-e (Fig. 12) indicated that introduction of methyl and $(-CH_2)_3$ $N(CH_3)_2$ at (R^1) position of 2-quinolone fragment was essential to the activity. Also, incorporation of mono-imidazolinyl into (R^2) or (R^3) position was benefit to the activity; the derivatives 147c and 147d showed an IC_{50} value ranging from 0.8 to 1.6 μM. Meanwhile, the derivative 147e with the second imidazolinyl moiety showed significant loss of activity with an IC_{50} value of 10 uM. Derivative 147a showed potent activity against

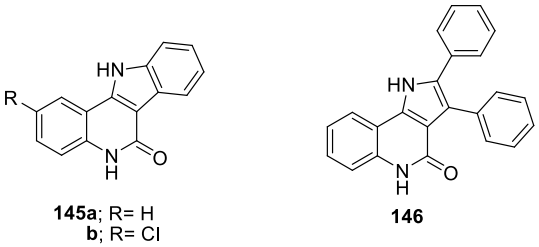


Fig. 11 Structure of compounds 145 and 146

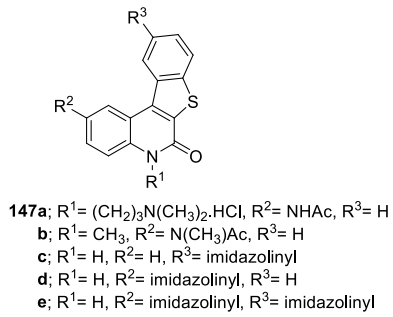


Fig. 12 Structure of compounds 147a-e

HCT116, MCF-7 and H460 cancer cell lines with an IC_{50} value of 0.2, 0.6 and 0.3 μM, respectively [94–97].

Certain benzofuroquinolone 148, indoloquinoline 149 and pyrroloquinolone 150 hybrids (Fig. 13) have been synthesized and evaluated in vitro against breast (MCF7), lung (NCI-H460) and central nervous system (CNS; SF-268) cancer cell lines. According to the findings, cytotoxicity decreases in the order of indoloquinolines > pyrroloquinolones > benzofuroquinolones. Among them, indoloquinoline 149a and its 2-chloro derivative 149b were most active, with mean GI_{50} values of 1.70 and 1.35 μM, respectively. Both 149a and 149b also exhibited excellent selective inhibition against CNS cancer cell line with a GI_{50} value of 0.93 and 0.78 uM, respectively [26].

In addition, tetracyclic quinolino[3,4-*b*]quinoxalones 143 and 151 (Fig. 14) were designed and synthesized. The synthesized derivatives were evaluated for inhibitory activity of topoisomerase IIα(Topo IIα) and the ability to bind and stabilize G-quadruplex structures and cytotoxic characteristics

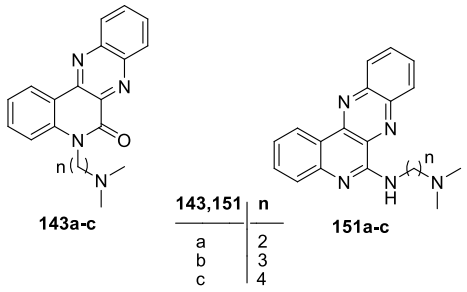


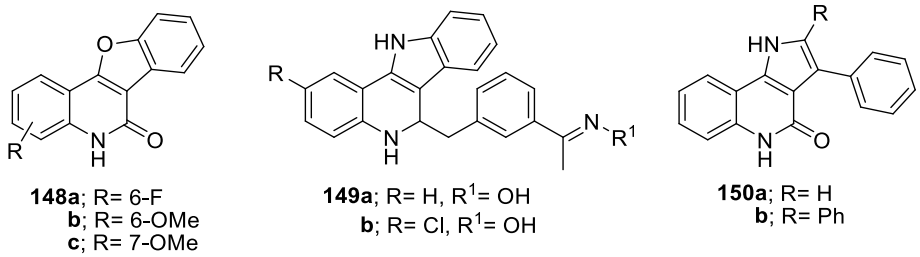
Fig. 14 Structure of compounds 143a-c and 151a-c

against two human cancer (MCF-7 and HeLa) cell lines. Almost all of the agents tested demonstrated a high activity as Topo IIαinhibitors and G-quadruplex stabilizers. Among all the derivatives studied, the quinolino[3,4-*b*]quinoxalines 143b and 151c stand out as the most potential compounds. Hybrid 143b was found to be a selective G-quadruplex sequence binder, while hybrid 151c exhibited the most interesting Topo IIαinhibitory activity with an IC_{50} value of 5.14 μM; both showed high cytotoxic activity with an IC_{50} value of HeLa = 2.04 μM and 2.32 μM, respectively [92].

The 1,3,4-thiadiazino[6,5,4-*i,j*]quinolone 152 and benzimidazo-[2,3:3,4] [1,2,4]triazino[5,6,1-*i,j*]quinolone 153 (Fig. 15) were evaluated for their antitumor activities against 60 cancer cell lines. The SAR demonstrated that in compound 152, *N*,*N*-dimethyl-1,3-diaminopropane pharmacophore was found favorable to the activity. 152 induced virtually complete death (more than 90%) of MCF7 and SF-268 tumor cells. However, substituents had significantly less effect on antitumor activity in compound 153. Thus, introduction of a pyrrolidine fragment led to an increase in percentage death of only two tumor cell lines NCI-H460 and SF-268 [98].

In 2017, the levofloxacin–thiadiazole hybrids 154 and 155 (Fig. 16) revealed significant inhibitory potency against histone deacetylase with an IC_{50} value of 0.046–0.203 and 0.019—0.127 uM, respectively, which were comparable to vorinostat with an IC_{50} value of 0.012–0.044 μM, but far more potent than levofloxacin–thiadiazole hybrids 156 with an IC_{50} value of 11–14.3 μM, suggesting that carboxylic acid at the tail decreased the activity. All hybrids demonstrated promising activities against MGC-803, SW620, NCIH460, PC-3, HepG2 and MCF-7 human cancer cell lines

Fig. 13 Structure of compounds 148a-c, 149a,b and 150a,b



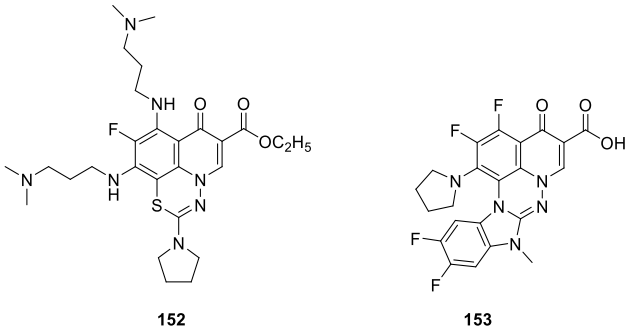


Fig. 15 Structure of compounds 152 and 153

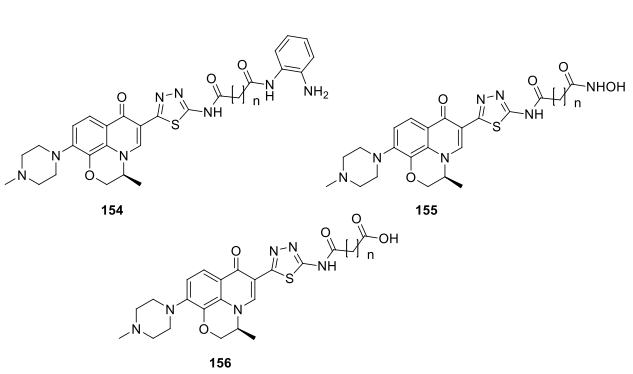


Fig. 16 Structure of compounds 154–156

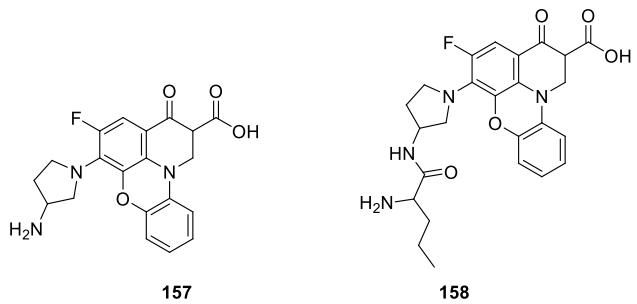


Fig. 17 Structure of compounds 157 and 158

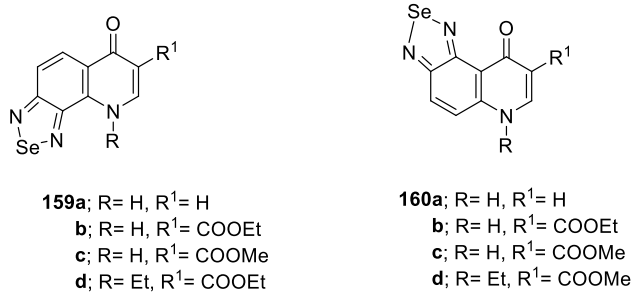


Fig. 18 Structure of compounds 159a-d and 160a-d

with an IC_{50} value range of 0.6–15.9 uM. The anti-proliferative activity of the hybrids was similar with the inhibitory activity against histone deacetylase, and the order was 155 > 154 > 156 [99].

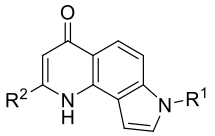
The benzoxazino[2,3,4-*ij*]quinolones 157 (Fig. 17) showed excellent in vitro cytotoxicity with an IC_{50} value range of 0.011–0.59 μM against HT-29, A549, P388 (resistant to doxorubicin) and B16F10 cancer cell lines. Analog 158 was active in vitro with an IC_{50} value range of 0.03–0.49 μM against human cancer cell lines HT-29, A-549, HCT-8, MCF-7 and murine cancer cell lines B16F10 and P388 (resistant to doxorubicin), as well as in vivo against murine and human tumors [100].

The selenadiazoloquinolones 159 and 160 (Fig. 18) exhibited cytotoxic effect toward tumor cells and immunomodulatory activities on RAW 264.7 cell line murine macrophages. Selenadiazoloquinolones 159 and 160 may have a potential use as a novel chemotherapeutic agent with immunomodulatory properties and the ability to induce apoptotic death of cancer cells. Cytotoxic/toxic studies showed that 159 and 160 are not toxic on normal human fibroblast cells BHNF-1 and dimensional skin constructs EpiDerm™ [101–103].

In vitro cytotoxic activities of the pyrroloquinolones 161 (Fig. 19) were tested in a panel of 14 human tumor cell lines, including colon, liver, pancreas, CNS, thyroid, adrenal gland, breast and ovary cancer cells. Compound 161a, which had a methyl group in C-2 position, was inactive, confirming the importance of a 2-phenyl ring for 4-quinolone moiety. For 2-phenyl derivatives, compounds 161c and 161d with an IC_{50} value > 50 μM had low cytotoxic effects against all examined cell lines, implying that strong electron-withdrawing groups such as the nitro group led to loss of activity. The presence of unsubstituted or 3-OCH_3 phenyl ring increased cytotoxic activity, as observed for compounds 161b and 161e with an IC_{50} value of 0.7–10 uM against the majority of tumor cell lines [104].

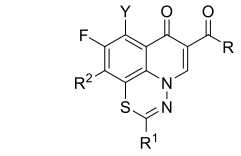
The tri- and pentacyclic fluoroquinolones 162 and 163 (Fig. 20) were evaluated for their anticancer activities against 9 groups, including leukemia, lung, melanoma, CNS, large intestine, renal, ovary, prostate and breast cancer cell lines. The thiadiazinoquinolines 162a-c, containing a cyclohexylamine fragment at position 3, exhibited significant selectivity in comparison with SK-OV-3 cells (the percentage death of tumor cells ranged from 55% to 90%) [98].

On the other hand, various 2,5-dialkyloxazolopyrano[3,2-*c*]quinolone derivatives 164a-j were evaluated for antitumor activity against three human cancer cell lines, namely MCF-7 (breast carcinoma), HepG-2 cells (human hepatocellular carcinoma) and HCT-116 (colon carcinoma) using 5-fluorouracil as a standard drug. Compound 164c and 164f showed higher inhibitory activity against all three tumor cell lines having IC_{50} values in between 6.2 and

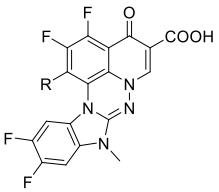


161a; R^1= H, R^2= Me
b; R^1= Me, R^2= Ph
c; R^1= H, R^2= 4-NO_2Ph
d; R^1= H, R^2= 3-NO_2Ph
e; R^1= H, R^2= 3-OMePh

Fig. 19 Structure of compounds 161a-e



162a, R= OEt, R^1= cyclohexylamine, R^2= Y= F
b, R= OH, R^1= cyclohexylamine, R^2= F, Y= H
c, R= OEt, R^1= cyclohexylamine, R^2= F, Y= H



163a, R= pyrrolidin-1-yl
b, R= F

Fig. 20 Structure of compounds 162a-c and 163a,b

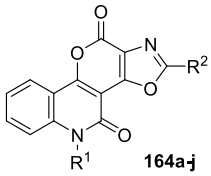
28.3 µg/mL and 28.7 and 43.2 µg/mL, respectively. The SAR study demonstrated that introduction of a longer alkyl chain (164c > 164b > 164a) at the *N*-position of quinolone improved the anticancer activity against all three cell lines. On the other hand, substitution with longer alkyl chain (R^2) at the second position of oxazole ring was shown to be detrimental to activity against all the cell lines (Fig. 21) [105].

11-Substituted 6*H*-indolo[2,3-*b*]quinolines and their methylated derivatives were synthesized and evaluated for anticancer activity. The in vitro anticancer assay indicated that 5-methylated derivatives were more cytotoxic than their respective 6-methylated counterparts. Among them, 11-(4-methoxyanilino)-6-methyl-6*H*-indolo[2,3-*b*]quinoline **165** was the most cytotoxic with a mean GI_{50} value of 0.78 µM and also exhibited selective cytotoxicities for HL-60 (TB), K-562, MOLT-4, RPMI-8226 and SR with GI_{50} values of 0.11, 0.42, 0.09, 0.14 and 0.19 l µM, respectively (Fig. 22) [106].

Antibacterial activities

Quinolones were first synthesized as a by-product of chloroquine; quinolones evolved as a distinct class of synthetic medications [107]. Lescher began researching quinolones as antibacterial drugs in 1962, when he discovered nalidixic acid 166, which has moderate activity against several gram-negative pathogens [108, 109]. Nonetheless, the promising advance in this field resulted during the 1980s when the bioisosteric analog of nalidixic acid was developed, i.e.,

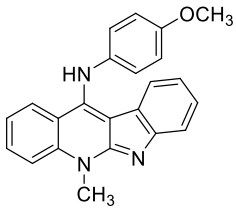
Fig. 21 Structure of compounds 164a-j



164a-j

164a $R^1 = R^2 = CH_3$
b $R^1 = C_2H_5$, R^2 = CH3
c R^1 = *n*-Bu, $R^2 = CH_3$
f R^1 = *n*-Bu, $R^2 = C_2H_5$
h $R^1 = C_2H_5$, R^2 = *n*-Bu
j $R^1 = CH_3$, R^2 = *n*-Bu

Fig. 22 Structure of compound 165

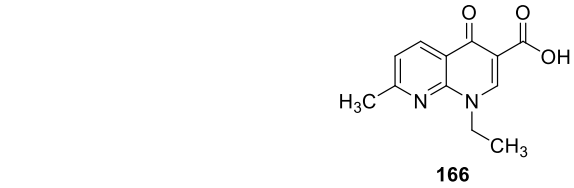


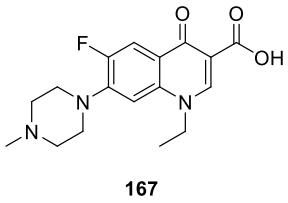
165

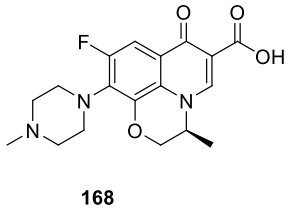
norfloxacin 167 (Fig. 23). It has a combination of fluorine atom at position 6 and a piperazinyl group at position 7 of the 4-quinolone core, which gave the drug antimicrobial activity that is both broad and potent [110]. After the discovery of nalidixic acid, advanced quinolones have developed through extensive research to produce compounds with enhanced activities such as levofloxacin® 168 and rufloxacin® 169 [111]. Several generations of quinolones have been developed on the basis of their antibacterial spectrum which is advancing significantly with each new generation [112].

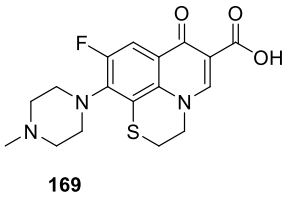
Al-Qawasmeh and co-workers reported the design, synthesis and antimicrobial evaluation of the 9-(substituted)-4-fluoro-6-oxo[1,2,5]thiadiazolo[3,4-*h*]quinoline-5-carboxylic acids 170a-d (Fig. 24). The in vitro antimicrobial activity of these was tested against two gram-positive strains (*B. subtilis* and *S. aureus*) and two gram-negative strains (*E. coli* and *H. influenzae*) using ciprofloxacin as a reference. Among them, the derivatives 170a and 170c demonstrated strong inhibitory activity against various tested bacterial strains with a MIC value of 0.15–3.0 µg/mL compared to ciprofloxacin with a MIC value of 0.03–0.30 µg/mL. The structure activity relationship of antibacterial thiadiazoloquinolones 170a-d revealed that compounds 170a and 170c are twofold less potent than the corresponding cyclopropyl derivative 170b with a MIC value ranging of 0.07–0.3 µg/mL. Therefore, the cyclopropyl moiety on *N*-9 seems to be the most suitable substituent [113].

The levofloxacin hydroxamic acid 171 and the hydrazide derivatives 172 (Fig. 25) showed urease inhibitory activity against *Proteus mirabilis*. The urease inhibitory activity was investigated using the indophenol method. The levofloxacin hydroxamic acid 171 showed the highest activity with an









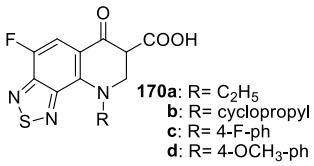
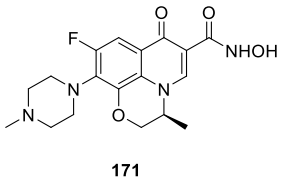


Fig. 24 Structure of compounds 170a-d



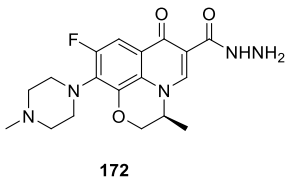
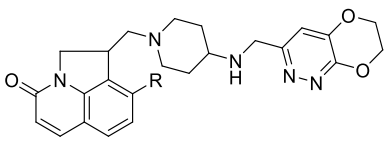


Fig. 25 Structure of compounds 171–172



GSK945237, 173a; R=F
b; R=H
c; R= CH_3

Fig. 26 Structure of compounds 173a-c

IC_{50} value of 2.20 µM compared to *N*-acetyl ciprofloxacin reference with an IC_{50} value of 2.26 µM. Molecular docking studies revealed high spontaneous binding ability of fluoroquinolone hydroxamic acids to the active site of urease [114].

Since infection caused by resistant bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) are on the rise, there is an unmet medical need for novel antibiotics [115]. Bacterial DNA type IIA topoisomerases are suppressed by quinolones, which have been used in the clinic to treat bacterial infections. Unfortunately, these drugs as a class suffer from toxicity concerns; quinolones can cause pathologic lesions in tendon tissue (tendinopathy), limiting their use in females and in teenagers [116–118]. Moreover, target-mediated resistance to fluoroquinolones is on the rise. As a result, the discovery of antibiotics against this target is appealing [119].

Researchers developed the tricyclic GSK945237, 173a-c (Fig. 26), to bind to the topoisomerases in a different manner than the quinolones [120]. These compounds have a mechanism which overcomes concerns of target-mediated resistance for fluoroquinolones [121]. Compound 173a progressed into in vivo efficacy studies, including a rat respiratory tract infection model caused by the quinolone-resistant *S. pneumoniae* TPS3, and showed great efficacy at 50 and 100 mg/kg with a MIC value of 4 µg/mL against *S. pneumoniae* TPS3 when compared to moxifloxacin which was ineffective in this in vivo model [122, 123].

A series of 7-(substituted)pyrrolidino-8-methoxy-isothiazoloquinolone analogues (ITQs) 174 (Fig. 27) was synthesized, and their antibacterial potency against *Escherichia coli*, methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) were compared. Many of these analogues had a MIC value of 0.25 µg/mL against quinolone-resistant MRSA strains [124].

[1,3]Benzothiazino[3,2-*a*]quinoline 175, [3,1]benzothiazino[1,2-*a*]quinoline-6-carboxylic acids 176 and benzothiazoloquinoline acid 177 (Fig. 28) were evaluated for their in vitro antibacterial activity against Gram-positive bacteria including *S. aureus* MPR5 and *S. aureus* ATCC 6538. The MIC values showed total inactivity of derivatives 175 with MIC values of < 128 µg/ml, while a modest antibacterial activity against Gram-positive bacteria was found in the derivatives 176 with MIC values of 2–16 µg/ml. Meanwhile, the benzothiazole derivative 177 is the most active compound with MIC values of 1–16 µg/ml [125].

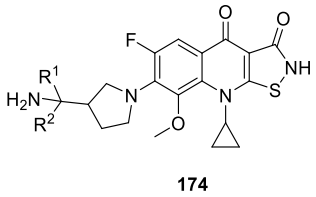


Fig. 27 Structure of compounds 174

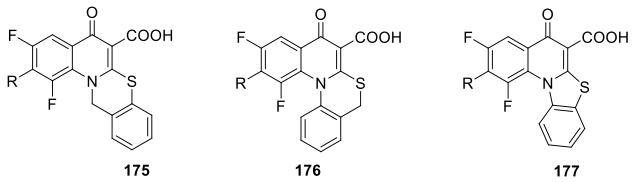


Fig. 28 Structure of compounds 175–177

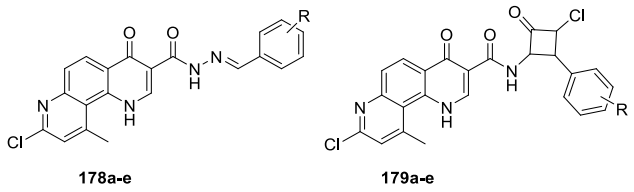
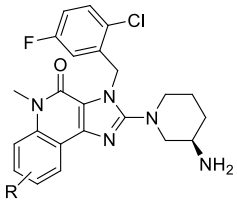


Fig. 29 Structure of compounds 178a-e and 179a-e

Antifungal activities

The pyridoquinolone carbohydrazides 178 and azetidines 179 (Fig. 29) showed considerable antifungal activities against *C. albicans*, *A. clavatus* and *A. flavus* with activity fivefold higher than griseofulvin with a MIC value of 500 µg/ml against *A. flavus* and *A. clavatus*, respectively, but they were less active than nystatin with a MIC value of 100 µg/ml. Among them, compounds 178b and 179e with a MIC value of 100 µg/ml were comparable to nystatin with a MIC value of 100 µg/ml and both showed fivefold more activity than griseofulvin, an MIC value of 500 µg/ml against *C. albicans* [126].

Fig. 31 Structure of compounds 183a-c



Anti-inflammatory activities

The researchers reported on the imidazoquinoline scaffold 180–182 (Fig. 30) that have mPGES-1 inhibitory activity and clear in vitro ADME profile. It was found that changing the quinoline moiety in compound 180 to quinolone derivatives 181 and 182 significantly increased mPGES-1 inhibitory activity. In addition, replacement of the bromine atom of 181 with various substituents led to identification of the phenyl group as the best C(7)-substituent (182) exhibiting high inhibitory action with a favorable in vitro ADME profile. Additionally, compound 182 showed strong mPGES-1 inhibitory activity with an IC_{50} value of 4.1 µM and potent cell-based functional activity with an IC_{50} value of 33 µM with good mPGES-1 selectivity (over 700-fold) [127, 128].

Anti-diabetes

Dipeptidyl peptidase IV (DPP-4) cleaves a wide range of peptides to modulate their biological activity. One of these peptides is the glucagon-like peptide-1 (GLP-1), which released after food ingestion and regulates blood glucose by stimulating insulin production and secretion through its receptor [129]. DPP-4 inhibitors have recently been recognized as effective treatments for type 2 diabetes [130, 131]. A significant number of DPP-4 inhibitors have been created with some approved for the treatment of type 2 diabetes. Researchers have designed and synthesized 2-aminosubstituted imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives 183a-c (Fig. 31), as DPP-4 inhibitor with high selectivity against multiple DPP-4 homologues. Compounds 183a-c showed strong DPP-4 inhibitory activity compared to marketed DPP-4 inhibitors. They also discovered that a carboxyl group at the 7-position (183a) might build a salt bridge with the Lys554 residue. The effect of a carboxyl group at the

Fig. 30 Structure of compounds 180–182

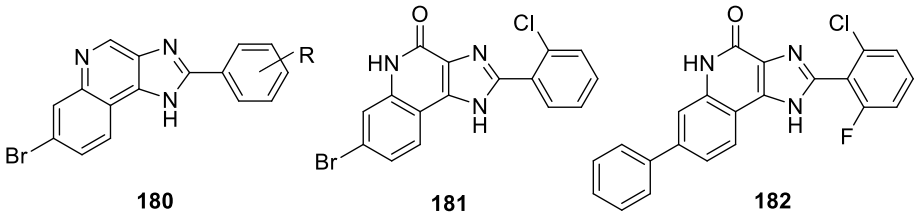
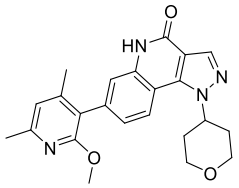


Fig. 32 Structure of compound 184



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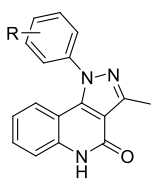
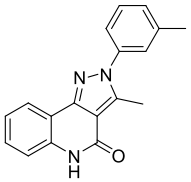


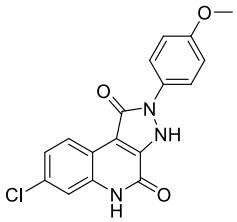
185a; R= 3-Cl
b; R= 3-CH_3



186

Fig. 33 Structure of compounds 185a,b and 186

Fig. 34 Structure of compound 187



187

9-position (183c) was significantly less potent than that of a substituent at the 7-position (183a) or 8-position (183b) [132].

Anti-Alzheimer

Cyclic nucleotide phosphodiesterases (PDEs) play critical roles in regulating the levels of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in the central nervous systems (CNS) and peripheral tissues [133, 134]. PDEs comprise 11 families. Among them, PDE9A is widely abundant in the CNS and has the highest affinity for cGMP [135]. Increased cGMP levels are thought to improve synaptic transmission and long-term potentiation [136]. As a result, selective brain-penetrant PDE9A inhibitors that enhance cGMP level in the CNS would be effective in treating cognitive disruption caused by Alzheimer's disease [137]. A series of pyrazolo[3,2-*c*]quinolone-4(5*H*)-one derivative 184 (Fig. 32) has been discovered with potent PDE9A inhibitory activity [138].

CNS Activities

Since 1982, pyrazoloquinolones have been recognized to have a strong affinity for central benzodiazepine receptors [139]. Cecchi et al. synthesized some pyrazoloquinolin-4-ones bearing an aryl substitution at position 1 or at position 2 and compared them with unsubstituted relatives [140]. The higher affinity of compounds containing phenyl substituents demonstrated the significance of hydrophobic phenyl moiety for the receptor affinity. The structure activity relationships also revealed that the meta-aryl derivative has the highest affinity for the receptor [141]. The binding study on bovine brain membranes has shown that only the 1-aryl-3-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-4-ones 185a,b (Fig. 33) have activity in disrupting specific [^{3}H] Flunitrazepam from its receptor site, whereas the 2-aryl derivative 186 is devoid of activity [142].

Previously, it was reported that antagonists of the *N*-methyl-*D*-aspartate (NMDA) receptor have taken a big hit as prospective therapeutic agents for the treatment of a number of neurodegenerative and neurological disorders: Almost all known antagonists at the glycine site of the *N*-methyl-*D*-aspartate (NMDA) receptor have a low tendency to cross the blood–brain barrier [143–145]. McLeod and his group synthesized 7-chloro-3,5-dihydro-2-(4-methoxyphenyl)-l*H*-pyrazolo[3,4-*c*]quinoline-1,4-(2*H*)-dione (187) (Fig. 34), as the most potent analogue with an IC_{50} value of 3.3 uM [146].

Antioxidant activities

The fused quinolone derivatives 132, 188 and 189 (Fig. 35) were screened for their in vitro antioxidant activities against radical scavenging capacity using 2,2-diphenyl-1-picrylhydrazyl (DPPH), Trolox equivalent antioxidant capacity (TEAC), total antioxidant activity by FRAP, superoxide radical (O_2^-) scavenging activity, metal chelating activity and nitric oxide scavenging activity. Among the compounds screened, 188a and 132b exhibited significant antioxidant activity. Compound 188a was the most active: It achieved 205.2 mmol Fe(II)/g in FRAP test, 3879.2 µmol Trolox/g in TEAC test and 10.7 mg EDTA/g in metal chelating activity [78]

Diuretic activities

Ukrainets et al. reported a series of 2-quinolone hybrids 190a-d (Fig. 36), as diuretics. All compounds were evaluated for diuretic activity using furosemide as a standard drug. The results revealed that among the tested derivatives, compound 190d showed promising diuretic activity (43%) as compared to the standard drug furosemide (104%) although all tested derivatives were less potent as compared to the reference control. Further, SAR study demonstrated that open-chain analogues did not show any diuretic activity, whereas cyclic analogue contributes to diuresis [147].

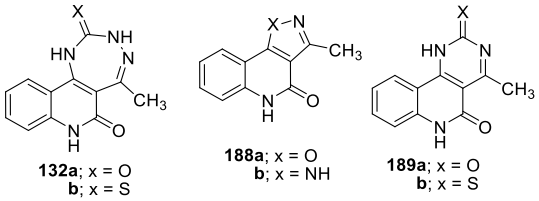
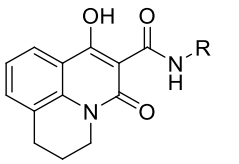


Fig. 35 Structure of compounds 132a,b, 188a,b and 189a,b

Fig. 36 Structure of compounds 190a-d



Conclusion

Quinolones represent a privileged building block for the synthesis of antibiotics used worldwide for the treatment of bacterial and drug-resistant infections. In recent years, large numbers of quinolones and heteroannulated quinolones have been synthesized. Quinolones and their heteroannulated derivatives possess many types of biological activities and have been reported to show significant anticancer activity. Quinolone-based motifs have been explored in different therapeutic areas such as antifungal, anti-inflammatory, anti-diabetes, anti-Alzheimer's disease, CNS, antioxidant and diuretic activities.

Author Contribution Ashraf A Aly contributed to conceptualization, writing, revising and submission; Mohamed Abd El-Aziz performed visualization; Hazem M. Fathy wrote the manuscript; Alan B. Brown revised the manuscript; Yaseen AMM Elshaier performed visualization; Mohamed Ramadan wrote and revised the manuscript.

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Declarations

Conflicts of Interest The authors declare no conflict of interest. The authors declare that they have no known competing interests.

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