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Review Article

Recent advances in the research of quinoxalinone derivatives

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CONTENTS

Abstract

Heterocyclic quinoxalinone (or quinoxalin-2-one) derivatives have been reported to exhibit a wide range of significant biological properties. Recent advances in synthetic methods and the elucidation of their biological activities are reviewed briefly in this paper.

Introduction

Within the family of biologically active heterocyclic templates, the quinoxalinone (or quinoxalin-2-one) core has received much attention in recent years as an important pharmacophore in numerous biologically active compounds. Such compounds are reported to possess diverse biological functions, including inhibition of aldose reductase and kinases. Moreover, the quinoxalinone skeleton is also used as an intermediate in designing novel quinoxalinone derivatives with potential as anticancer, antimicrobial (or antifungal), antithrombotic and anxiolytic agents and glycogen phosphorylase inhibitors, and also as fluoroionophores. Recent advances have attracted the interest of researchers in the discovery of efficient and high-yield synthetic processes. In this context, we will review synthetic methods for the preparation of the quinoxalinone skeleton and derivatives thereof, and their biological functions.

Synthetic methods for quinoxalinone derivatives

Chloroacetyl chloride method

6-Chloro-2(1*H*)-quinoxalinone (**1**) is the key intermediate in the synthesis of the potent herbicide quizalofop-ethyl, which can be obtained via the standard route outlined in Scheme 1. Treatment of 4-chloro-2-nitrophenylamine with chloroacetyl chloride in toluene and subsequent hydrogenation in the presence of Pd/C gives the aniline derivative, which is readily cyclized to the desired compound.

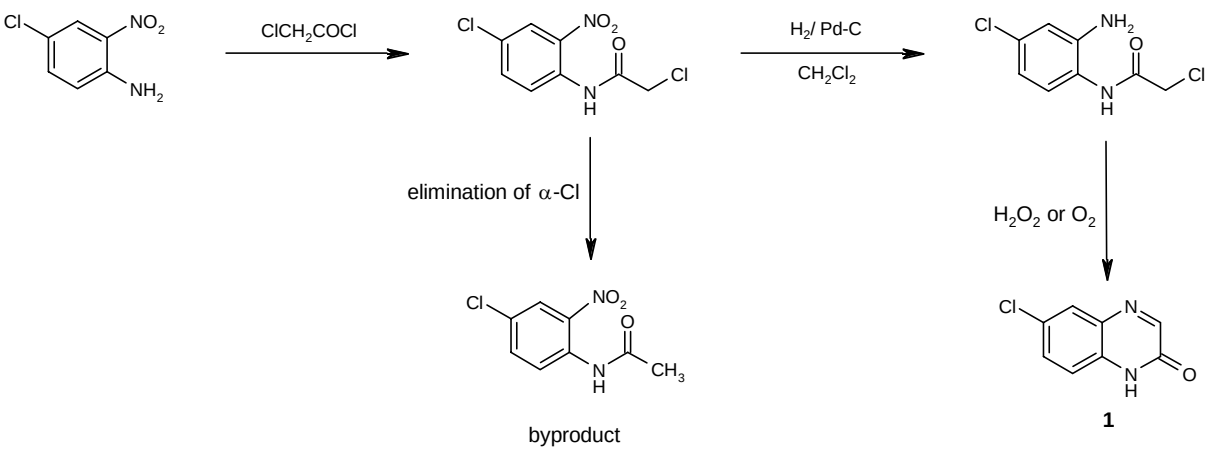
However, the application of this method has been restricted owing to side reactions involving the elimination of α-chloro during the process of catalytic hydrogenation (1). A modified chloroacetyl chloride method for the synthesis of 6,7-disubstituted-1*H*-quinoxalinones (**2**) was therefore investigated in our lab (Scheme 2) (2, 3). This compound can be regioselectively prepared in relatively high yield starting from substituted phenylamines and chloroacetyl chloride, followed by acylation, nitration, reduction, intramolecular alkylation and oxidation steps. By optimizing reduction conditions, the dechlorinated byproduct can be avoided. Moreover, another series of 1,3-dimethyl-1*H*-quinoxalinones can also be easily obtained with satisfactory results by replacing chloroacetyl chloride with 2-chloropropionyl chloride (4, 5).

Amino acid (or amino acid ester) method

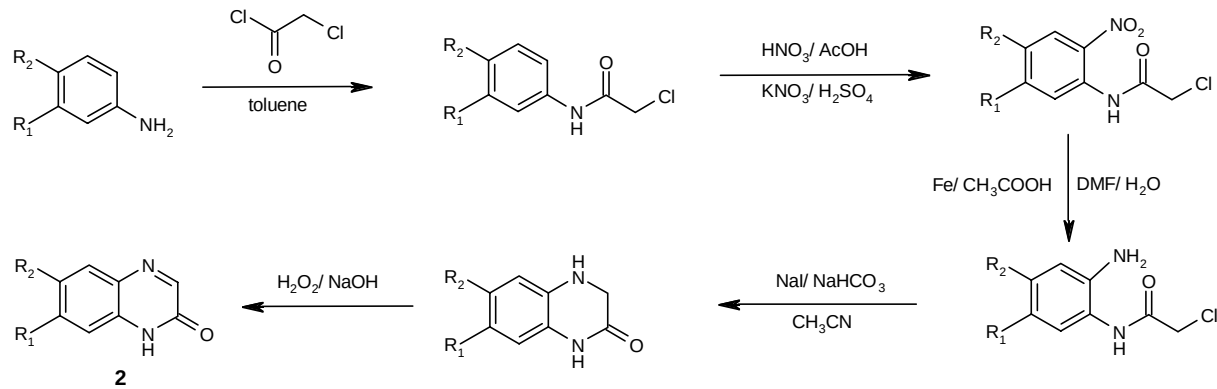
Quinoxalinone derivatives **3** are prepared by treating substituted fluorobenzene with aminoacetic acid (or aminoacetic acid ether), followed by hydrogenation over Raney Ni and cyclization in $AgNO_3$-ammonia solution or reduction with stannum, and finally, oxidation with 30% hydrogen peroxide in the presence of acetic acid (Scheme 3). However, this method is limited by the high cost of $AgNO_3$, low yield, the difficulty of work-up for stannum reduction, etc.

Wu *et al.* reported an improved approach involving economic reduction of the nitro group. A variety of reduction reagents, such as hydrazine/Pd/C, $HCOONH_4$/Pd/C,

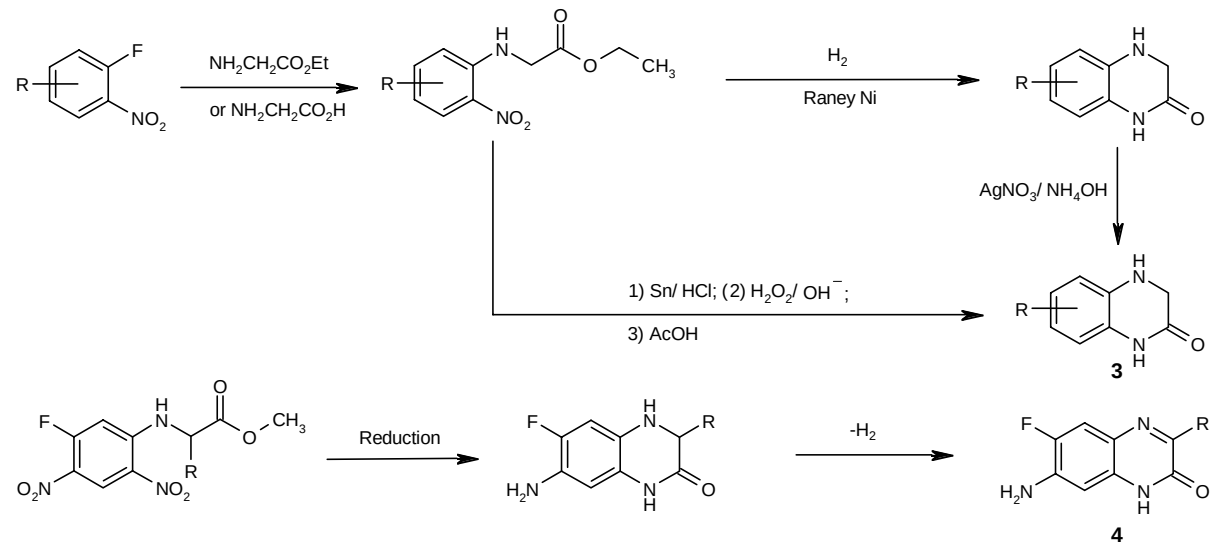
Scheme 1: Synthesis of 6-chloro-2(1*H*)-quinoxalinone



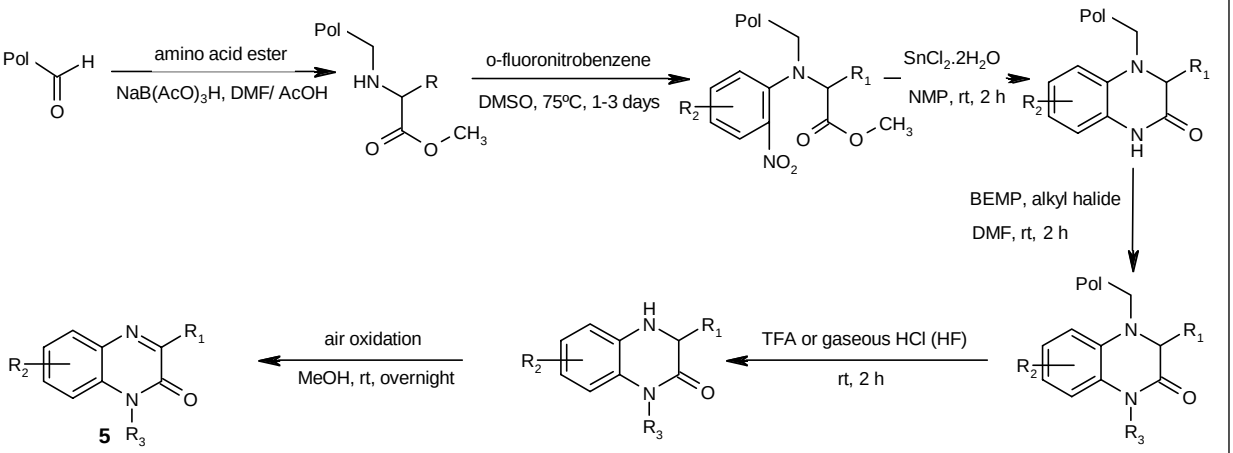
Scheme 2: An improved chloroacetyl chloride method for the synthesis of 6,7-disubstituted-1*H*-quinoxalinones



Scheme 3: The amino acid (or amino acid ester) method for the synthesis of quinoxalinones



Scheme 4: The amino acid ester method with solid-phase synthesis of quinoxalinones



$Na_2S_2O_4$, $SnCl_2$/DMF, $SnCl_2$/HCl and KH_2PO_4/HCOONa/*N*-methyl-2-ketopyrrolidine, were employed to transform the nitro group into an amino group, which can increase reduction yields (6).

Solid-phase quinoxalinone synthesis has developed rapidly over the last decade (7). For example, as shown in Scheme 4, solid-phase synthesis is accomplished by alkylation of the amino acid methyl esters and aldehyde-functionalized polystyrene resin. The resulting resin-bound secondary amines are treated with *o*-fluoronitrobenzenes and then reduced using tin chloride to obtain the dihydroquinoxalinones, which are cleavaged from the resin by TFA or the gaseous reagents HCl or HF, and successively oxidized to quinoxalinone compounds **5** (8).

α-Ketone acid (or aldehyde) ester method

Generally, the quinoxalinone derivatives **6**-**16** can be obtained by treating substituted *o*-phenylenediamine with α-ketone acid, α-aldehyde acid, α-ketone acid ester or α-aldehyde acid ester (Scheme 5). These methods are relatively simple and straightforward approaches for the synthesis of quinoxalinones, although when unsymmetrical substituted *o*-phenylenediamines are used as starting materials, two quinoxalinone isomers, such as **17** and **18**, are formed, which must be separated by HPLC or other techniques to give the optically pure products (9). Because most of the commercially available substituted *o*-phenylenediamines are unsymmetrical, separation of the two isomers must be performed. Also, both *o*-phenylenediamine and α-ketone (α-aldehyde) acid are chemically unstable agents, which also limits the application.

Diketene method

Reaction of substituted *o*-nitroaniline with diketene (4-methyleneoxetan-2-one) in the presence of a catalytic amount of pyridine in benzene (or toluene) affords the key intermediate mono-*N*-oxide, which is treated with $NaBH_4$ to give the corresponding quinoxalinone compound **19** and a small amount of the byproduct 3,4-dihydroquinoxalin-2(1*H*)-one (**20**)**,** which can be easily oxidized with 30% hydrogen peroxide or air to give the desired adduct **19** (Scheme 6). However, certain disadvantages of the diketene method, such as significant lacrimation, high volatilization or polymerization at room temperature, make it inconvenient. Furthermore, the polymerized diketene can also take part in the reaction to give the undesired byproducts. All of these disadvantages greatly affect the reactivity (10).

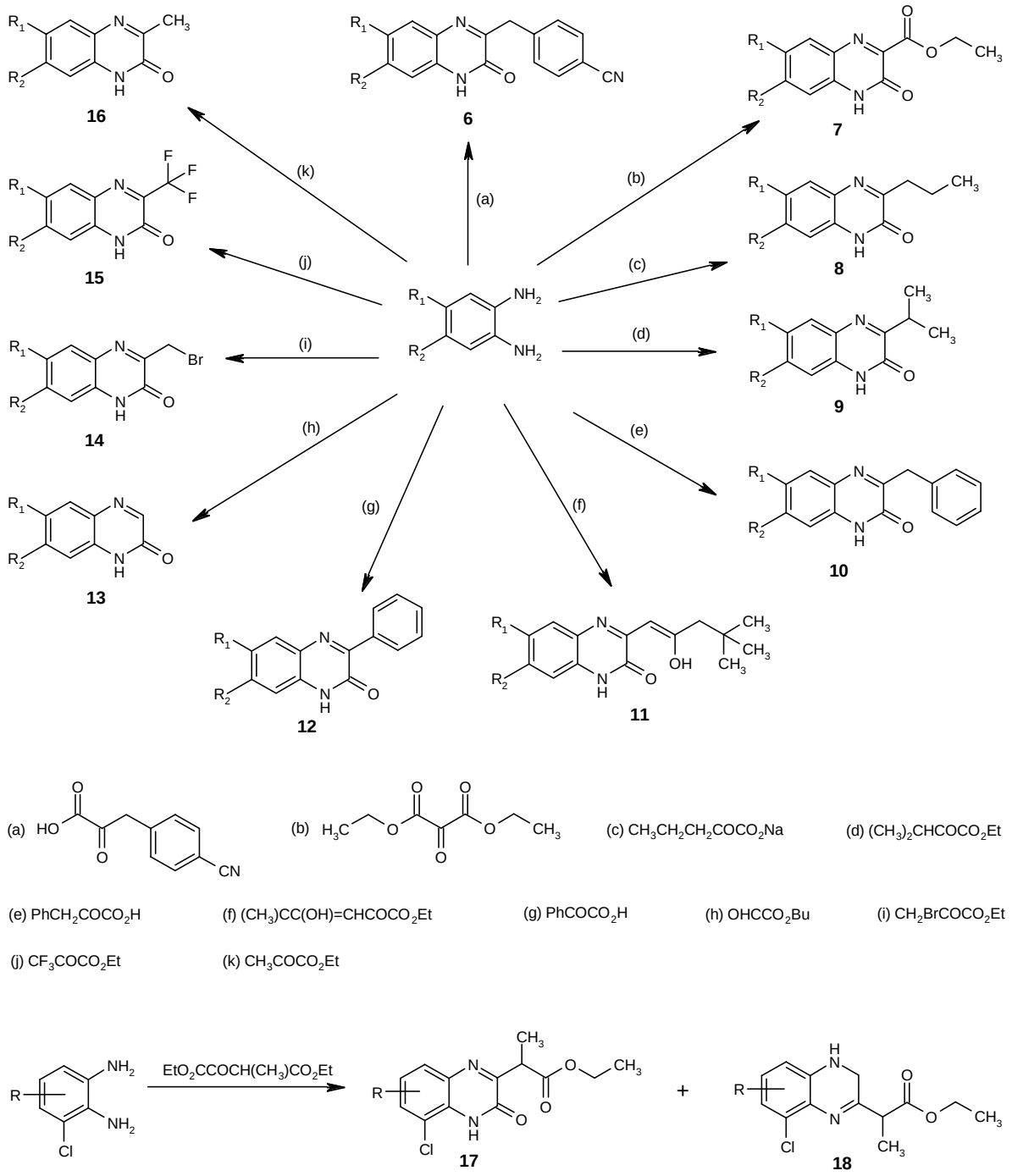
Chloroacetic (or bromoacetic) acid method

A classical synthetic approach involves the condensation of *o*-phenylenediamine and chloroacetic acid in the presence of ammonium carbonate as acid-eliminating agent. The resulting 3,4-dihydroquinoxalin-2(1*H*)-one was oxidized with H_2O_2/NaOH to obtain the desired quinoxalinone **21** (40% overall yield). Because the reaction temperature and decreasing speed of reagents can affect pH fluctuation, the AcOH-NaOH-$NaHCO_3$ buffer solution (pH ≈ 7) is often used as an acid-eliminating agent, and the overall yield increases up to 80%. The bromoacetic acid method is similar to the above, with the difference that the starting material is changed to *o*-nitroaniline, but leads to lower yields (< 20%). Recently, an improved synthesis of quinoxalinone **22** was reported by Willardsen *et al.* from *o*-phenylenediamine in two steps (> 37% overall yield) (Scheme 7). However, prolonged reaction times at high temperatures are required under these circumstances (11).

Cyanomethylation (or cyanoacetylation) method

According to this method (Scheme 8)*, o*-nitroaniline is transformed to the desired quinoxalinone **21** via

Scheme 5: The α-ketone acid (or aldehyde) ester method for the synthesis of quinoxalinone derivatives



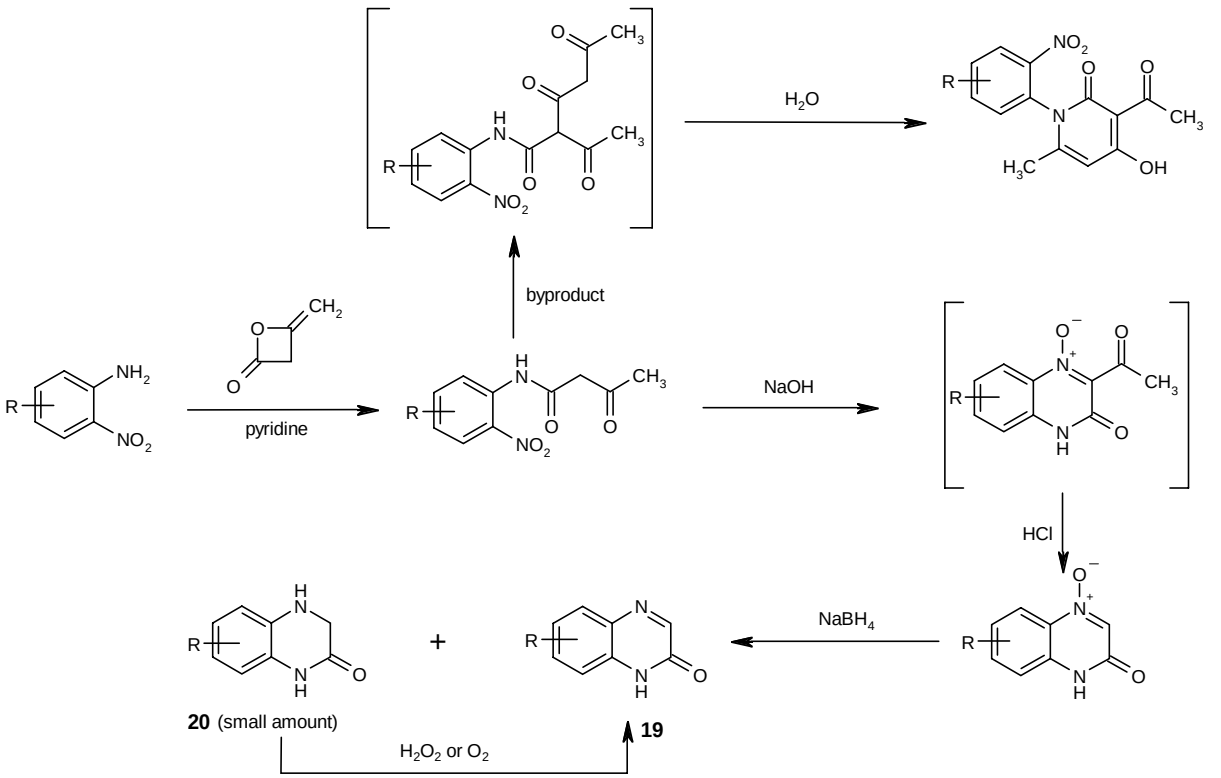
cyanomethylation (or cyanoacetylation), hydrolysis, reduction and oxidation; however, the toxicity of cyanide is disadvantageous for environmental reasons.

Microwave method

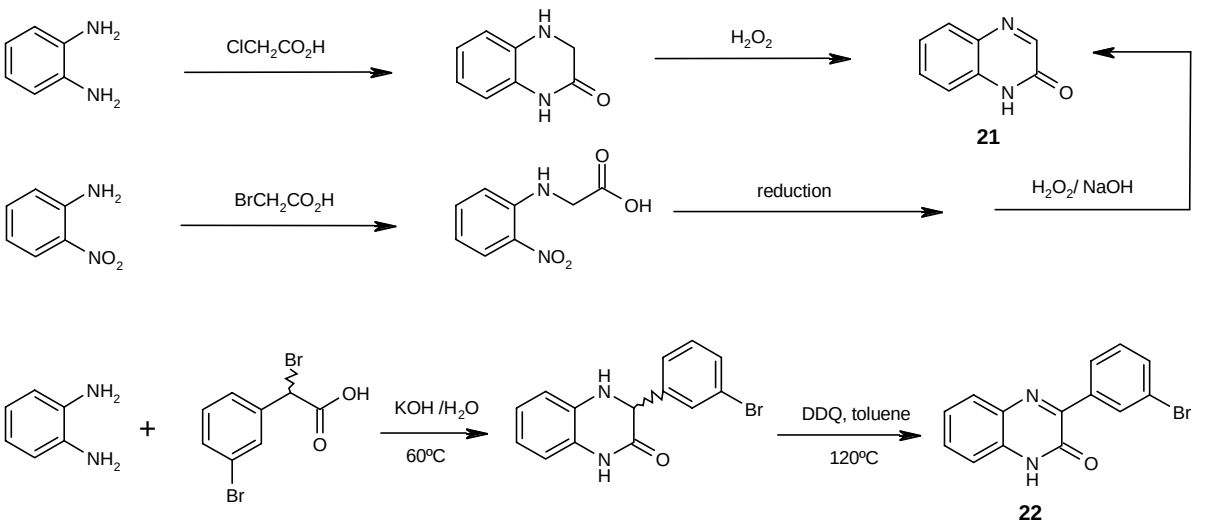
The microwave method is a popular technique for a variety of applications in organic synthesis and functional group transformations because of its low cost, ready availability and high efficiency. Solid-phase quinoxalinone synthesis, as well as classical synthesis, utilizing microwave irradiation is a common method.

Zhang *et al.* (12) employed an improved Ugi/de-Boc/cyclization strategy for the synthesis of quinoxalinone derivatives **23** using both microwave and fluorous technologies. Mixing an *ortho*-*N*-Boc-protected phenyl-

Scheme 6: The diketene method for the synthesis of quinoxalinones



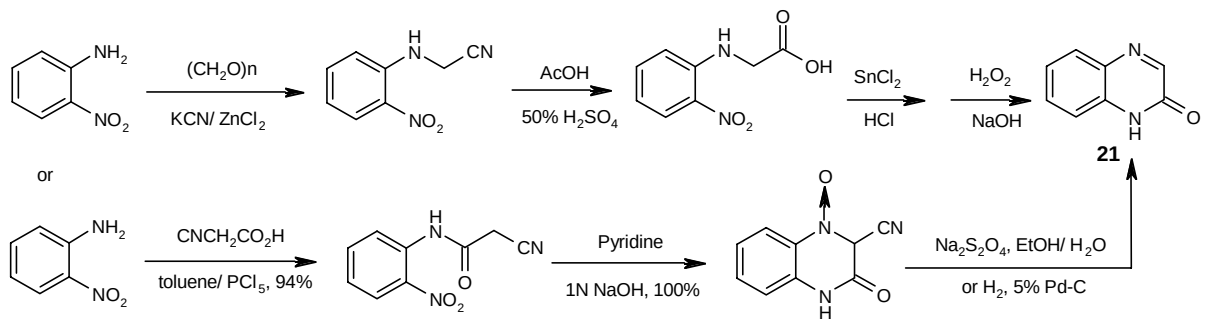
Scheme 7: The chloroacetic (or bromoacetic) acid method for the synthesis of quinoxalinones



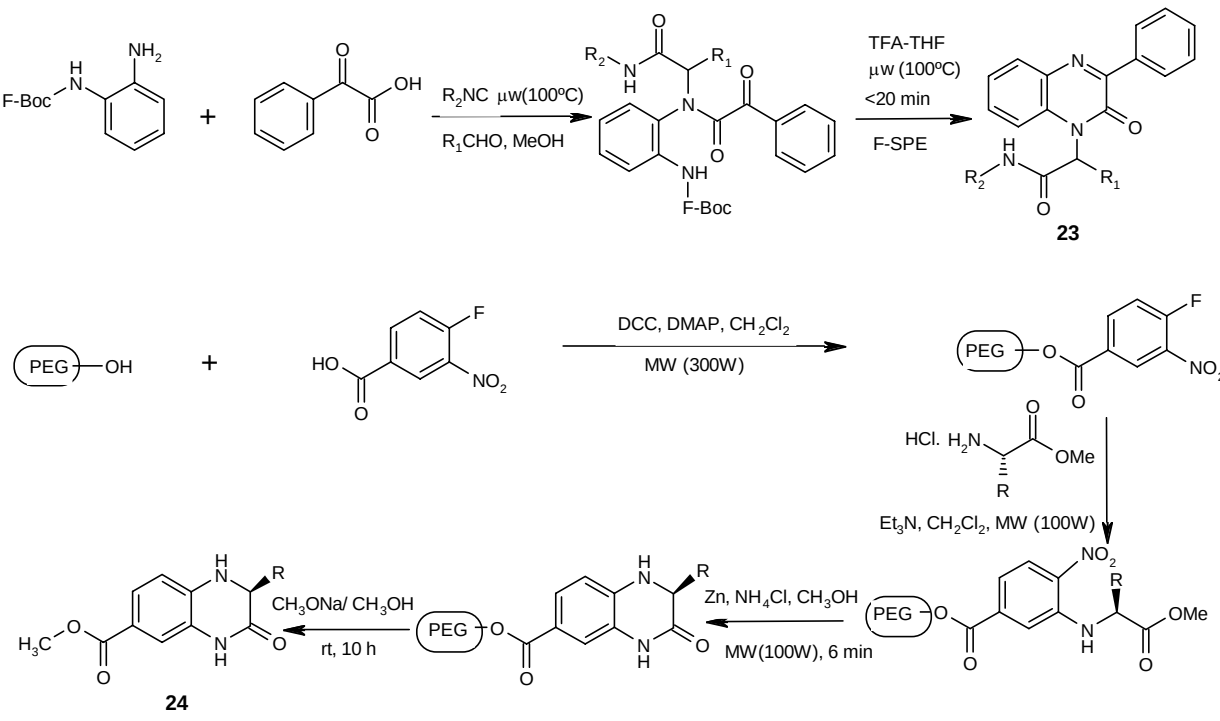
diamine, glyoxylic acid, isonitrile and primary amine gives a novel Ugi quinoxalinone product. Generally, the long reaction time (about 1-2 days) and two-step purification are limiting factors in Ugi synthesis, although in the above microwave-assisted Ugi reactions the purification step was simplified by solid-phase extraction over FluoroFlash™ cartridges and the reaction was completed within 20 min (13).

Tung *et al.* reported chiral libraries of quinoxalinones, which were readily prepared utilizing soluble polymeric support (CH_3O-PEG-OH) through S_NAr reactions and reduction of the nitro group, with concomitant intramolec-

Scheme 8: The cyanomethylation (or cyanoacetylation) method for the synthesis of quinoxalinones



Scheme 9: The microwave method for the synthesis of quinoxalinones



ular cyclization under microwave irradiation. When polymer support was cleaved in CH_3ONa/CH_3OH solution at room temperature, the final enantiomeric quinoxalinone compounds **24** were obtained with excellent yield (70-99%) and purity (73-97%) (Scheme 9) (14).

Quinoxaline-2,3-dione substitution method

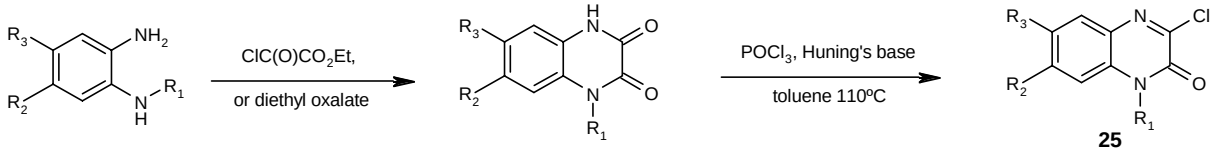
3-Chloro-substituted quinoxalinone derivatives **25** are usually synthesized according to this method from substituted *o*-phenylenediamines in two steps (Scheme 10) (15). The synthetic method is quite convenient under these conditions.

Hexafluoropropylene oxide (HFPO) method

Trifluoroquinoxalinone derivatives **26** can be successfully obtained by treating substituted *o*-phenylenediamine and HFPO in a weakly basic ($NaHCO_3$) solution (Scheme 11) (16). The reaction works well in room temperature and offers the benefit of a relatively short reaction time (only 3 h).

Although several methods are currently available to synthesize the quinoxalinone core and derivatives thereof, more efficient and concise synthetic routes are desirable.

Scheme 10: Quinoxaline-2,3-dione substitution method for the synthesis of quinoxalinones



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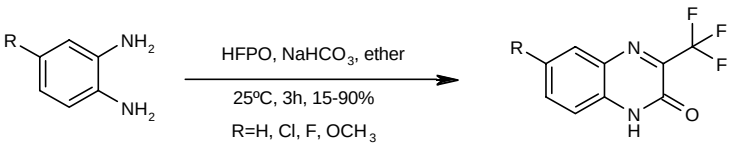
Scheme 11: The hexafluoropropylene oxide method for the synthesis of quinoxalinones



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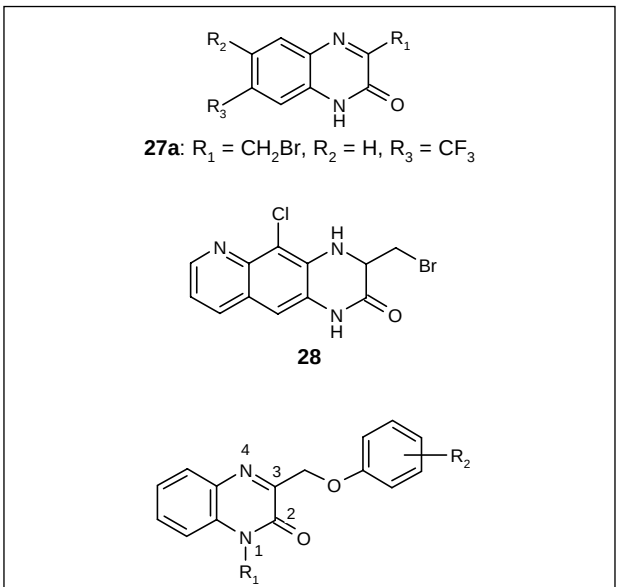
Biological activities of quinoxalinone derivatives

Antitumor activity

Using the National Cancer Institute (NCI) preclinical *in vitro* screening assay, quinoxalinone compounds were found to have anticancer activity. Structure-activity relationship (SAR) analysis of a series of quinoxalinone derivatives **27** (Fig. 1) by Sanna *et al.* revealed that electron-withdrawing groups in the C-3 position, such as NO_2, F, CF_3 or lipid-soluble alkyl, benzyl or phenyl groups, were associated with increased anticancer or antimicrobial activity. In particular, compound **27a** showed broad-spectrum anticancer activity *in vitro* against a subpanel of cell lines, including leukemia, non-small cell lung, colon and CNS cancer and melanoma cell lines, at 100 μM, providing a lead for further research (17, 18). Pyrido[2,3-*g*]quinoxalinones such as **28** (Fig. 1) also exhibited broad-spectrum anticancer activity against different cell lines (IC_{50} = 10.4-19.9 μM) (9).



27a: $R_1 = CH_2Br$, $R_2 = H$, $R_3 = CF_3$

28

29a: R_1 = benzyl, R_2 = 2-C(O)NH-phenyl

Fig. 1. Quinoxalinone derivatives with antitumor activity.

A significant problem in the clinical treatment of cancer is the occurrence of multidrug resistance (MDR). Two transporters closely associated with MDR, P-glycoprotein (P-gp) and multidrug resistance protein 1 (MRP1), have been extensively studied. The overexpression of P-gp, the product of the *MDR1* gene in humans, is considered to be responsible for reducing the efficacy of various cytotoxic drugs used in anticancer chemotherapy (19). Therefore, rationally designed P-gp antagonists may be effective MDR reversal agents. As compared to the classical nonselective modulators, specific P-gp antagonists may be potentially more effective (20).

Lawrence *et al.* (21) demonstrated that the failure of most modulators evaluated in clinical trials could be ascribed to intrinsic toxicity or undesired effects due to reversal of MDR mediated by both P-gp and MRP1. They therefore explored a family of substituted quinoxalinone derivatives **29** (Fig. 1) that selectively antagonized P-gp over MRP1. A qualitative SAR analysis indicated that compounds with carbonyl substitutions of the phenoxy group, such as ester, amide or ketone moieties, exerted an excellent P-gp-antagonist effect, while having relatively low toxicity toward drug-sensitive cells. The most interesting compound was **29a**, with an IC_{50} value of 54 μM, which was about 10-fold lower than that of the other compounds.

It has been found that modulators of P-gp-mediated MDR have several common characteristics: lipophilicity, the presence of an alkaline center (or cation under physiological conditions) and at least two co-planar aromatic rings. Klopman *et al.* (22) discovered that introducing some substituent groups, including –COOH, aniline, a quaternary ammonium salt, –N=CH-CH= and phenol, led to decreased activity. Thus, these substituents should be

avoided in designing MDR modulators. Garrigues *et al.* (23) reported two different but partially overlapping pharmacophore models for binding to P-gp, which indicated the possibility of multiple chemical structure recognition. All the features described above provided a theoretical basis for designing novel modulators of P-gp-mediated MDR.

Anti-HIV activity

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) play a major role in combination therapy for the treatment of human immunodeficiency virus type 1 (HIV-1) infections (24). NNRTIs proved highly active *in vitro*, although they are notorious for rapidly triggering the emergence of drug-resistant HIV-1 variants *in vivo*.

The quinoxalinone derivative S-2720, a reverse transcriptase inhibitor which showed promise in clinical trials, displayed better inhibitory activity than nevirapine, L-697661 and U-88204 (Fig. 2) in HIV-1-infected CEM cell cultures (25). Importantly, S-2720 was associated with little development of HIV-1 resistance mutations at a concentration (0.35 μM) 10-25-fold lower than U-88204 or nevirapine.

HBY-097, a representative second-generation NNRTI, showed a significant inhibitory effect against zidovudine-resistant strains of HIV-1 when administered with lamivudine, and had 50-100-fold greater potency than nevirapine (26). Increased inhibitory effects were observed in HIV-1-infected CEM cell cultures when the novel quinoxalinone clinical candidate from GlaxoSmithKline GW-420867X was combined with the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine and abacavir, and a variety of NNRTIs (efavirenz, UC-781, etc.) (see Fig. 2) (27).

Patel *et al.* (16) reported a series of 3,3-disubstituted quinoxalinone derivatives (**30**) (Fig. 2) as effective NNRTIs containing structural features from both efavirenz and GW-420867X. SAR studies revealed that *N*-allyl-, *N*-cyclopropylmethyl- and *N*-carbalkoxy-substituted compounds displayed activity comparable to or better than efavirenz and GW-420867X (IC_{50} = 108-124 nM).

A research program targeted towards the identification of expanded-spectrum NNRTIs resulted in the DCP series of compounds (Fig. 2), which are analogues of efavirenz with similar or greater potency, and favorable oral bioavailability and pharmacokinetic profiles. Moreover, they showed significant improvements in their overall protein binding-adjusted resistance profile relative to all currently marketed NNRTIs (28).

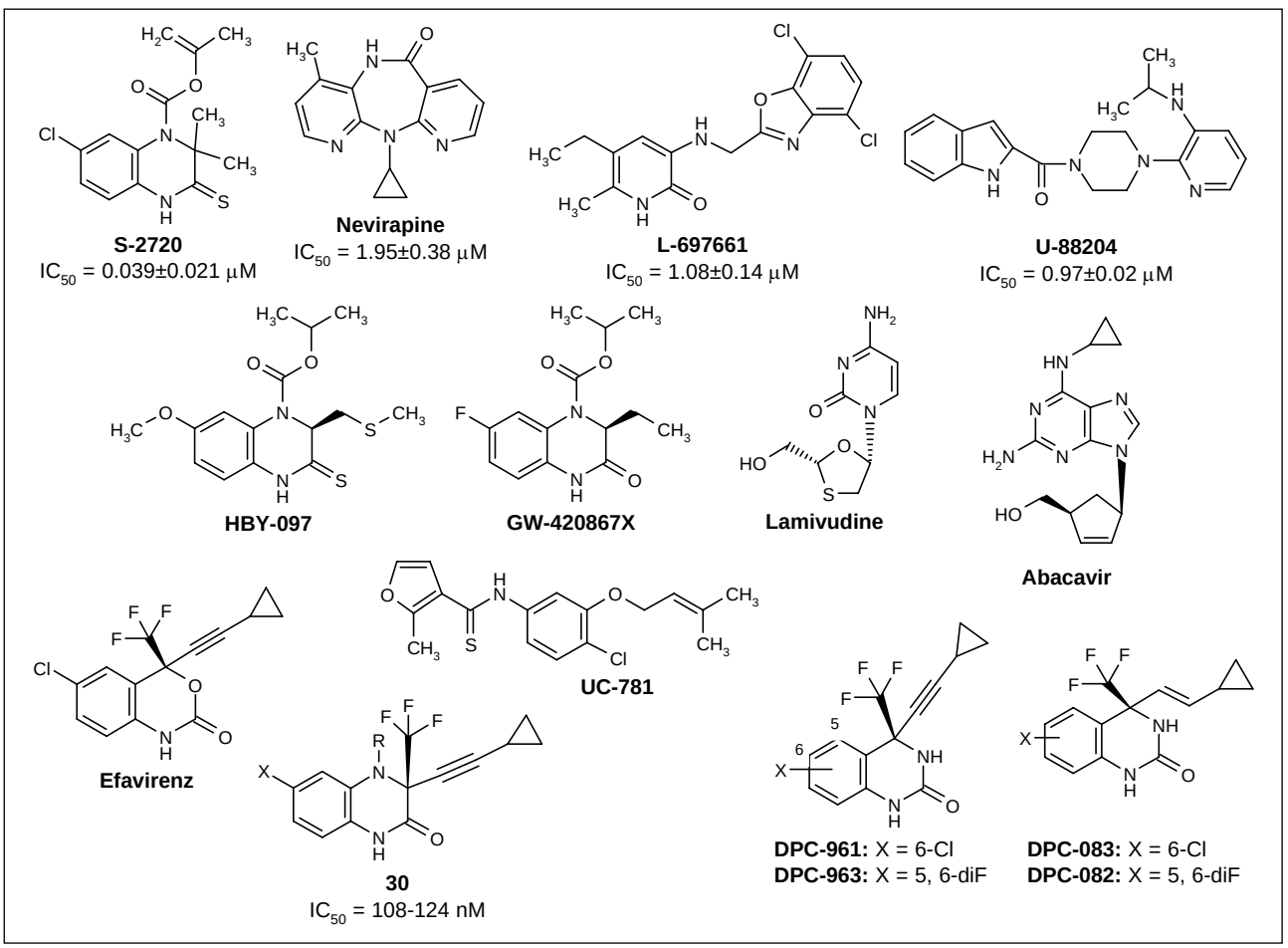


Fig. 2. Quinoxalinone inhibitors of reverse transcriptase as potential anti-HIV agents.

Fluoroionophores

Fluoroionophores are compounds containing both a fluorophore and a crown ether (or an azacrown group), which are linked by one or two bonds or connected by a spacer group. They can change their fluorescence properties upon complexation with an anion, usually a metal or ammonium ion. Selectivity for an ion may be achieved by designing the complexing unit and the total molecular architecture. For example, the quinoxalinone fluoroionophore **31a** (Fig. 3) shows the best selectivity for K^+, with an absorption Φ_f of 0.41 (29). The quinoxalinone compounds DMEQ-Hz, MMEQ-Hz, Br-DMEQ and Br-MMEQ are usually used as fluorescent agents for fluorescent labeling-HPLC determination.

Antithrombotic activity

The central role of the serine proteases factor Xa (FXa) and thrombin in hemostasis makes them important targets for antithrombotic therapy. The Pfizer clinical candidate quinoxalinone compound **32** (IC_{50} = 0.83 nM), a specific inhibitor of FXa, is expected to be therapeutically useful in the treatment of thromboembolic disease (11). In order to develop potent and selective inhibitors of both thrombin and FXa with oral activity, Ries *et al*. synthesized a series of novel coagulation inhibitors (**33**) covering a central quinoxalinone template (Fig. 4) (30). These compounds were found to have nanomolar inhibitory activity against both coagulation enzymes *in vitro*. Moreover, SAR studies revealed that thrombin inhibition was determined by the amide group, while the monocyclic groups such as piperidine, pyrrolidine amide, etc., contributed to FXa inhibition. However, some compounds with promising *in vitro* activity suffered from low tolerability or unfavorable pharmacokinetics, indicating that they were inadequate for therapeutic use. Therefore, further research should be concentrated on the identification of novel compounds with improved pharmacokinetic profiles and oral activity.

Glycogen phosphorylase inhibition

Glycogen phosphorylase is the enzyme responsible for glycogenolysis by catalyzing the breakdown of glycogen to glucose-1-phosphate in the liver and skeletal muscle. Thus, inhibition of this enzyme may be useful for reducing blood glucose levels, providing an adjunctive therapy for type 2 diabetes.

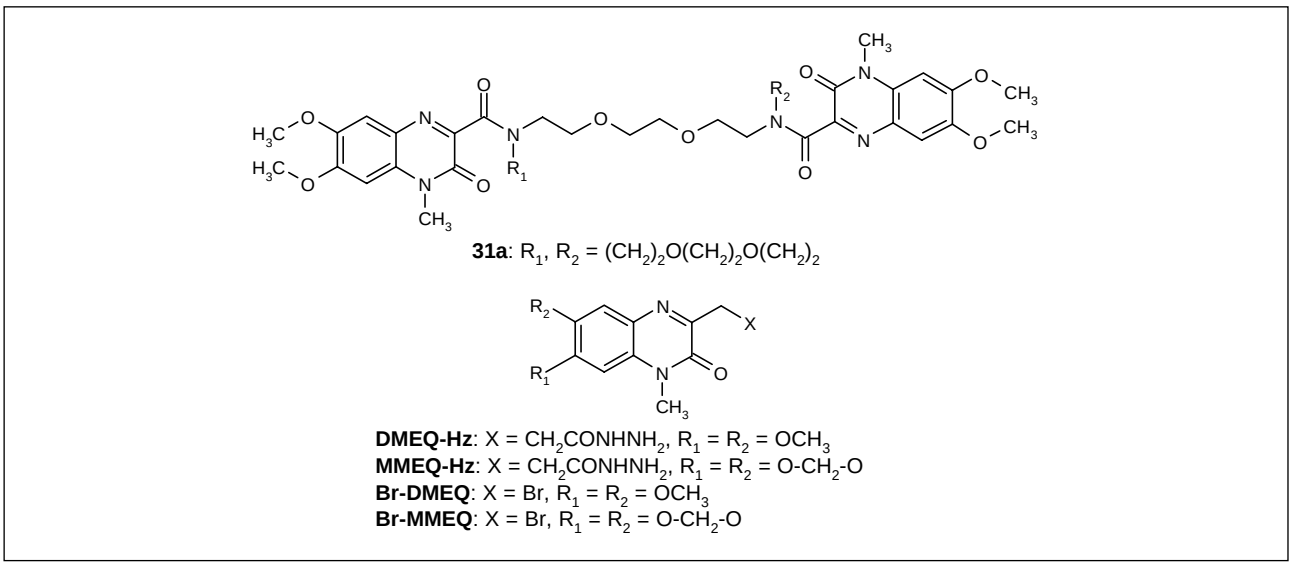


Fig. 3. Quinoxalinone fluoroionophore or fluorescent agents.

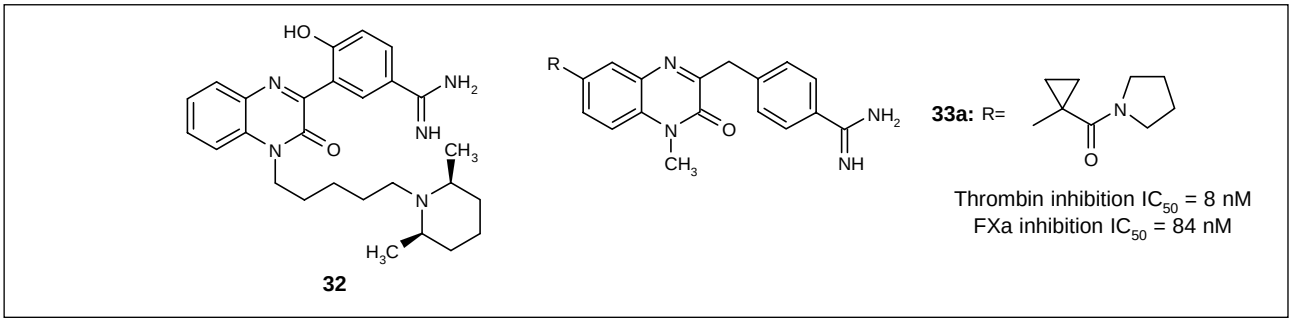


Fig. 4. Quinoxalinone derivatives with antithrombotic activity.

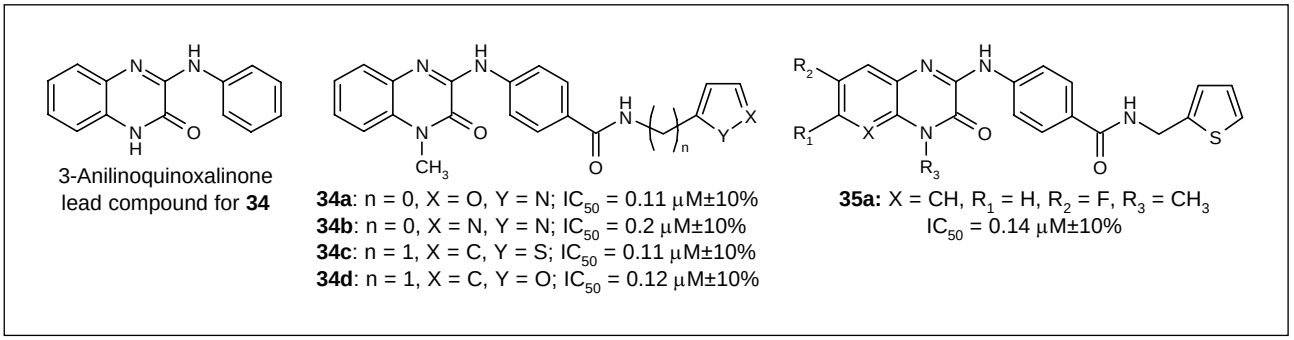


Fig. 5. Quinoxalinone derivatives with glycogen phosphorylase-inhibitory activity.

Based on high-throughput screening (HTS) and a pharmacophore-based electronic database search, a series of quinoxalinone compounds **34** (Fig. 5) were synthesized by modifying the lead 3-anilinoquinoxalinone (IC_{50} = 2 μM) by Dudash *et al.* (15). In particular, compounds **34a-d** showed significant potency (IC_{50} = 0.11-0.2 μM), being about 25 times more potent than the original lead. SAR studies revealed that structural features of the aniline moiety were the most important for inhibitory activity, while the quinoxalinone core was more tolerant to substitution, which provided a clue for designing further derivatives by introducing different substituents at this position. Unfortunately, the *in vitro* activity of most compounds did not translate to inhibition of glycogen phosphorylase *in vivo*, which might be due to the poor aqueous solubility of quinoxalinone compounds, which would ultimately affect their bioavailability. In addition, N-1 substitution (**35**) was reported to provide potential glycogen phosphorylase-inhibitory activity, with IC_{50} values of 0.14-10 μM.

Other activities

The above-mentioned pyrido[2,3-*g*]quinoxalinone **28** (Fig. 6) also proved to have antimicrobial (or antifungal) activities. This compound exhibited high activity against all strains tested, with an MIC of 31.25 μg/ml. Compound **36** (Fig. 6) also showed generally good inhibition against strains of *Staphylococcus aureus* (MIC = 15.6-62.5 μg/ml) and *Candida* (MIC = 31.25-125 μg/ml).

The quinoxalinone compound panadiplon (U-78875) was being developed as a potential new treatment for generalized anxiety disorder and panic disorder, but

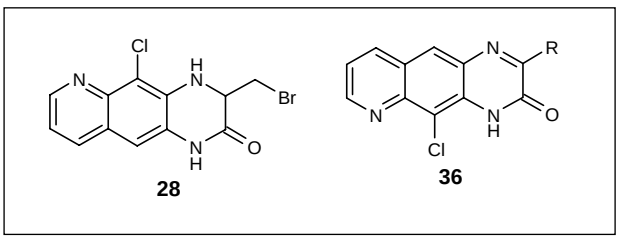


Fig. 6. Pyrido[2,3-*g*]quinoxalinones with antimicrobial activity.

development was discontinued during phase I clinical trials due to unexpected hepatic toxicity in a few human volunteers. A group of researchers (31) studied the mechanism of the hepatotoxicity of panadiplon and its metabolite, cyclopropane carboxylic acid, (CPCA; Fig 7), providing hope for the future development of quinoxalinone anxiolytic or antipanic agents.

Conclusions

The heterocyclic core of the quinoxalinone pharmacophore and derivatives thereof have received increasing attention owing to their diverse biological properties, which have been extensively studied in recent years. A few have shown efficacy in clinical trials. In reviewing their biological applications and SAR studies, we hoped to find clues to develop a new generation of quinoxalinone-based drugs with greater potency, lower toxicity and superior efficacy. On the other hand, in the search for new drugs, an important strategy involves the structural modification of existing quinoxalinone leads possessing significant biological activities. Therefore, there is an urgent need to develop synthetic methods for the quinox-

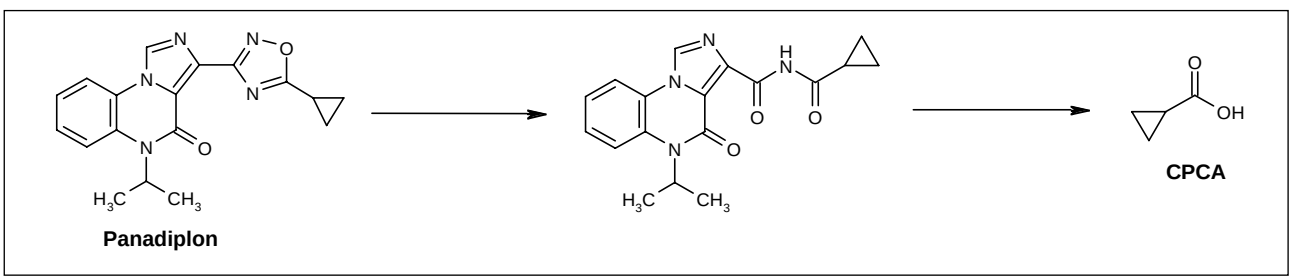


Fig. 7. Panadiplon and its metabolite CPCA.

alinone skeleton or its analogues. Importantly, as a contribution to this field, we have introduced an efficient and improved chloroacetyl chloride method with relatively high yield. We believe that new quinoxalinone drugs will ultimately be developed with further research.

Acknowledgements

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