Chemistry, Biological Properties and SAR Analysis of Quinoxalinones

A. Carta*, S. Piras, G. Loriga and G. Paglietti

Dipartimento Farmaco Chimico Tossicologico, Facoltà di Farmacia, Università di Sassari, via Muroni 23/a, 07100 Sassari, Italy

Abstract: Quinoxaline derivatives have received much attention in recent years owing to their both biological properties and pharmaceutical applications. In this review we focus the attention on quinoxalin-2(3)-ones and quinoxalin-2,3-diones. These derivatives are particularly interesting since some of them showed antimicrobial (against several bacteria, viruses, fungi, etc), or anticancer activities. Furthermore, others are reported to be potent no-NMDA glutamate receptor antagonists, endowed with anxiolytic, deconditioning, analgesic, antispastic, antiallergic, antithrombotic activities. In this article we also report SAR studies and the most important methods of synthesis of the quinoxalin-2(3)-(*di*)ones.

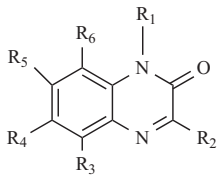
Key Words: Quinoxalin-2(3)-ones, quinoxalin-2,3-diones, AMPA antagonists, Gly_N antagonists, antimicrobial activity, anticancer activity, Pgp antagonists, antiallergic activity, antithrombotic activity, SAR studies, chemical syntheses and reactions.

INTRODUCTION

Quinoxaline derivatives, as quinoxalin-2(3)-ones, quinoxalin-2,3-diones, quinoxaline 1-oxides and quinoxaline 1,4-dioxides, have received much attention in recent years owing to their biological properties [1]. In particular, in the last two decade many 2-oxo and 2,3-dioxo quinoxalines have appeared and their biological activities reported. These derivatives are particularly interesting since some of them are potent no-NMDA glutamate receptor antagonists (AMPA/ Gly_N), whereas others showed antimicrobial, anxiolytic, deconditioning, analgesic, antispastic, antiallergic, antithrombotic anticancer [through their cytotoxicity or antagonizing a membrane transport protein, the P-glycoprotein (Pgp)] activities, or dipeptidyl peptidase-IV (DPP-IV) inhibition.

Antimicrobial Activities

About the antimicrobial properties of the quinoxalinones, Carta *et al.* recently reported the synthesis and biological activities of over 150 quinoxalin-2-ones summarized in Fig. (**1**) [2-6]. Among these, it was observed that compounds bearing a carboxyethyl at C-3 and a CF_3 group or a morpholine ring in the benzo-moiety were moderately active against *E. coli* and *P. aeruginosa* respectively [2], while those with an ethyl at C-3 and a CF_3 group in the benzo-moiety exhibited activity against *P. aeruginosa* [3]. Introduction of a CH_2Br group at C-3 and a CF_3 or a NO_2 group in the benzo-moiety exhibited activity against *S. aureus* and *Candida* spp. respectively [4]. The CF_3 group at both C-3 and the benzo-moiety of quinoxalinones showed to maintain this activity against *C. albicans* and *C. parapsilosis* spp. [4], while a CF_3 group at C-3 and Cl atoms in the benzo-moiety exhibited activity against *S. aureus* [5]. The concomitant presence of a CF_3 group and a Cl atom in the benzo-moiety together with a CH_2Br or a CF_3 group at C-3 promotes a moderate activity against *V. alginolyticus* [6].



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R_1 = H, C_2H_5;
R_2 = COOEt, COOH, -CH(R)COOH, CH_2Br, CF_3, Alkyl, Ph, CH_2Ph;
$R_{3\text{-}6}$ = H, F, Br, Cl, CH_3, NO_2, NH_2, CF_3, OCH_3,, Morpholinyl, Pyperazinyl.

Fig. (1). Quinoxalinones endowed with antimicrobial activity.

Some interesting antiviral quinoxalinones were designed on the basis of the chemical structures of Efavirenz [7-10] and GW-420867X [11-12], two important Non-Nucleoside HIV-1 Reverse Trascriptase Inhibitors (NNRTIs). Patel *et al.* prepared several 3,3-disubstitued quinoxalinones as hybrid structures containing features from both the above NNRTIs [13,14] (Fig. **2**). The synthesized derivatives resulted to be endowed with anti-HIV-1 activity (both on the enzyme inhibition and whole cell antiviral assays) comparable or better than reference compounds (Efavirenz and GW-420867X). In particular when the substituents at the *N*-4 position and in the benzo-moiety (R and X of compound **2** respectively) were a CO_2 alkyl group and halogen respectively, the resulting quinoxalinones showed the best activity but unfortunately they were highly protein bound with a 33- to 50-fold loss in IC_{90} values in the protein binding shift assay. Comparatively, the derivative bearing X=H and R=CO_2Et showed a low protein binding (19-fold loss in IC_{90} value) and a good resistance profile, and its active enantiomer (after resolution of the racemic mixture) was selected for oral pharmacokinetic studies in rhesus monkeys. Unfortunately, poor bioavailability of this derivative, was observed preventing its clinical use.

Another example of quinoxalinones as antiviral agents is reported by German Hoechst A.-G. patent [15] of structure **3** of Fig. (**3**) where 3-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoxalin-2-one (**4**) exhibited MIC = 1 ng/mL against HIV cultured in T-cell.

*Address correspondence to this author at the Dipartimento Farmaco Chimico Tossicologico, Facoltà di Farmacia, Università di Sassari, *via* Muroni 23/a, 07100 Sassari, Italy; Tel: +39-079-228722; Fax: +39-079-228720; E-mail: acarta@uniss.it

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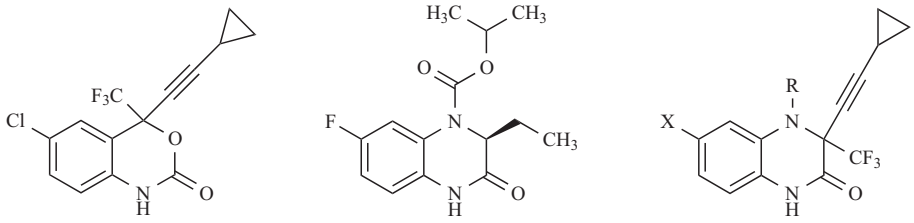
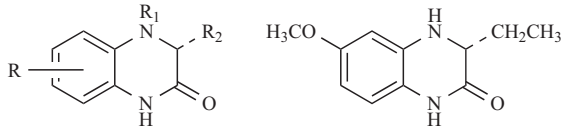


Fig. (2). Structural comparison between 3-cyclopropylethynyl-3-trifloromethyl-quinoxalin-2-ones and others NNRTIs.

Interestingly, the analogous compound bearing the methyl group instead of ethyl one reported by Paglietti *et al*. was devoid of this activity [16].

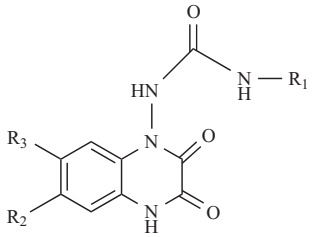


3 **4**

Fig. (3). Quinoxalinones anti-HIV-1.

Dipeptidyl Peptidase-IV (DPP-IV) Inhibition

Dipeptidyl peptidase-IV (DPP-IV) inhibition has been proved to be an effective method for type 2 diabetes pharmacotherapy [17]. DPP-IV is a serine protease which degrades an incretin secreted from the small intestine the glucagons-like peptide-1 (GLP-1). The latter exhibits several biological effects including stimulation of insulin secretion, but the half life of GLP-1 is very short (about 1 min) due to the degradation by DPP-IV. In order to discover novel nonpeptide DPP-IV inhibitors Hwang *et al*. recently reported a brief structure-activity relationship (SAR) study of a series of *N*-ureido- and *N*-thioureido- quinoxalinediones summarized in structure **5** of Fig. (**4**), derived through screening of a chemical library of approximately 32,000 compounds [by High Throughput Screening (HTS) techniques] [18]. DPP-IV enzyme assay was carried out using rat plasma by measuring 7-amino-4-trifluoromethyl-coumarin(AFC) liberated from Ala-Pro-AFC in the presence or absence of a test compound. The *N*-ureido-derivatives were the most potent inhibitors, in particular the nitro group in benzo-moiety (R_2) and the sulfonyl group in ureido part (R_1) seem to increase the potency.



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R_1=SO_2-Aryl, CO-Aryl, Aryl;
R_2=H, Cl, NO_2;
R_3=H, Cl.

Fig. (4). Quinoxalindiones DPP-IV inhibitors.

Deconditioning Activity

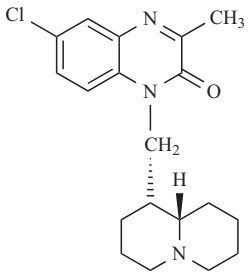
Many quinoxalinones variously substituted on benzene-moiety and bearing different kinds of aminoalkyl chain on position 1 were synthesized by Sparatore and co-workers and evaluated for deconditioning, analgesic and antispastic activities [19-22]. Most of these derivatives showed different degrees of ability influencing the conditioned avoidance response (CAR), particularly in the case of the concomitant presence of a lupinyl substituent on the nitrogen atom in position 1 and a methyl group in position 3. In fact all the 1-lupinyl-3-methyl-6-substituted derivatives exhibited a strong activity in rats at the dosage of 50 mg/Kg s.c.. Furthermore, both 6-chloro-1-lupinyl-3-methylquinoxalinone (**6**) and 1-lupinyl-6-methoxy-3-methylquinoxalinone (**7**) (Fig. **5**) resulted more active than chloropromazine at 2 mg/Kg s.c. [22].

In order to evaluate if the CAR blockade in rats for the above mentioned lupinyl quinoxalinones was caused by either dopamine D_1 or D_2 type receptors blockade, Sparatore *et al*. studied the interaction of **6** with these receptors [23]. Results of this study put in evidence the absence of affinities for D_1 and D_2 receptors. The Authors deduced the good deconditioning activity of this class of quinoxalinones was probably due to interactions with other kinds of receptors (sigma, 5-HT, etc.).

Analgesic and unspecific antispastic properties were also reported by Savelli *et al*. for some 1-*tert*-aminoalkylquinoxalinones, belonging to both the series synthesized by Sparatore's team and new derivatives. The moderate activities (particularly for the antispatic property) and the generally high toxicity exhibited by these compounds did not warrant further investigation [24-26]. In Fig. (**6**) it is summarized the general structure (**8**) of the quinoxalinones endowed with analgesic property.

Antithrombotic Activity

Selective inhibitors of thrombin and coagulation Factor Xa (FXa) are expected to be therapeutically useful in the



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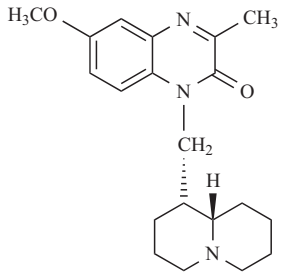
6-chloro-1-lupinyl-3-methylquinoxalinone



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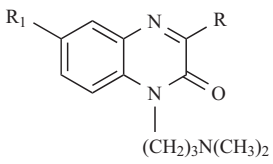
1-lupinyl-6-methoxy-3-methylquinoxalinone

Fig. (5). 1-lupinyl -3-methyl-quinoxalinones endowed with deconditioning activity.



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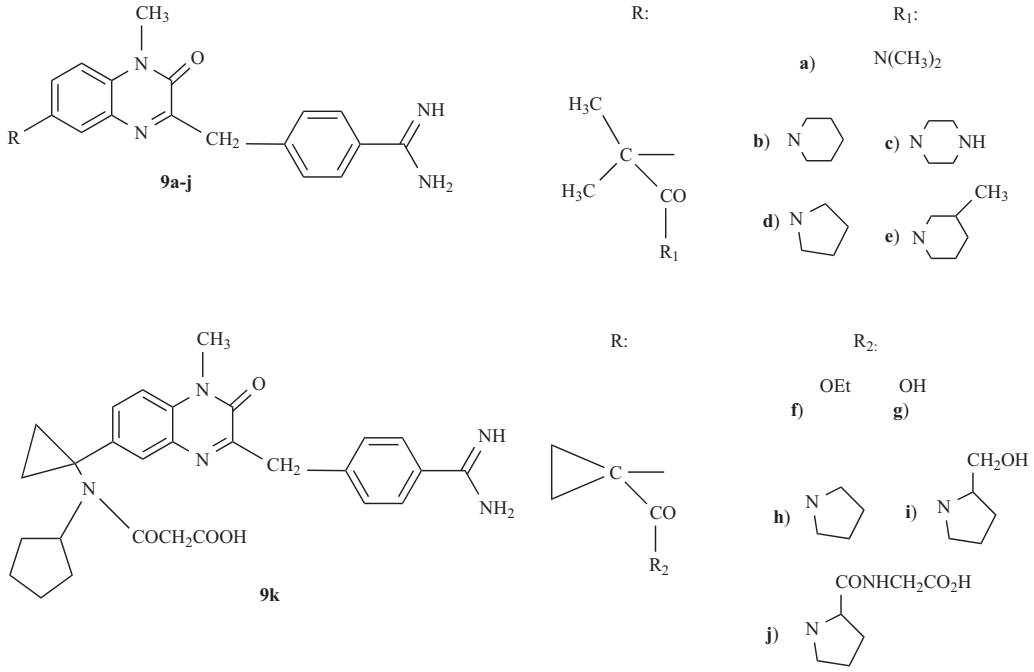
R=CH_3, $CH_2C_6H_5$;
R_1=H, Cl, CF_3, $COCH_3$.

Fig. (6). Quinoxalinones endowed with analgesic activity.

treatment or prophylaxis of thromboembolic diseases. Recent studies by Ries *et al*. [27] and Edmunds *et al*. [28] have put in evidence the importance of the quinoxalinone scaffold for a development of new antithrombotic agents. In Fig. (**7**) are summarized the most interesting structures of quinoxalinone derivatives (**9a-k**) synthesized by Ries *et al*. [27]. These Authors reported μM or nM inhibition values of both the above mentioned coagulation enzymes and a very potent antithrombotic activity in vitro for all the derivatives with the sole exception of the acid (**9g**). In particular the cyclopropyl derivative **9h** inhibited both FXa and trombin with IC_{50} of 84 and 8 nM respectively. Unfortunately, *in vivo* studies highlighted cardiovascular side effects, at therapeutical dosages, for those derivatives bearing cationic groups (compounds **9a-e** and **9h-k**).

In order to improve *in vivo* pharmacokinetic properties it was introduced a negatively charged group [29] at the pyrrolidine ring (compound **9j**) but this determined a dramatic loss of activity, whereas replacement of the cyclopropyl carboxamide moiety with acylated cyclopentyl-aminocycloproyl group provided a potent trombin inhibitor (compound **9k**). Compounds **9j** and **9k** were well tolerated after intravenous (iv) administration to rats but, in the pharmacodynamic stud-



9a-j

9k

Fig. (7). Quinoxalinones inhibitors of thrombin and FXa.

ies, both showed an unfavorable profile, which seemed to be inadequate for therapeutic use.

More success had the studies of Edmunds *et al*. [28], in fact they designed and synthesized a novel and selective quinoxalinone (**10**) inhibitor of FXa coagulation depicted in Fig. (**8**).

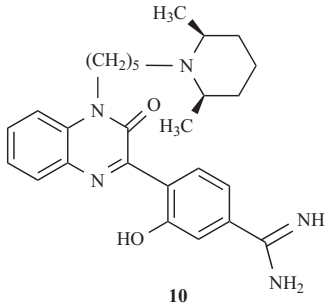


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Fig. (8). Quinoxalinone inhibitor of FXa coagulation.

This compound showed a very interesting in vitro activity with a Ki against FXa of 0.83 nM and an excellent selectivity over similar serine proteases. Molecular modeling and X-ray crystal structure led the Authors to predict binding conformation of this quinoxalinone in FXa. Furthermore, this derivative was tested *ex vivo* in rabbit, dog, and human plasma to determine the effect it had on the standard coagulation parameters. The results of these experiments showed the new quinoxalinone was efficacious in both antithrombotic animal models and it was most effective in human plasma showing species dependent inhibition of FXa.

Anticancer Activity

Since 1980s, some quinoxalinone derivatives were synthesized and tested for anticancer activity, e.g. Sparatore and co-workers prepared some 1-lupinyl derivatives in the aim to assay their activity against lymphocytic leukemia P 388 cell line, unfortunately without appreciable results [30]. More recently (1998-2002), Sanna, Carta *et al*. within a wide study of the biological properties of this nucleus reported the synthesis and anticancer in vitro evaluation of over 130 quinoxalin-2-ones [2-4,6]. Results of those screenings showed that some compounds were endowed with antiproliferative activity (Fig. **9**), in particular the derivate bearing a CH_2Br group at C-3 and a CF_3 group at C-7 (compound **11**) emerged for this activity from the NCI (National Cancer Institute of Bethesda, USA) screening against a panel of about 60 human tumor cell lines [4]. Replacement of the CF_3 with either Cl atoms at C-5 and C-6 (compound **12**), or Cl atom at C-5 and a CH_3O group at C-6 (compound **13**), slightly increases the citotoxicity against MT-4 cells [6].

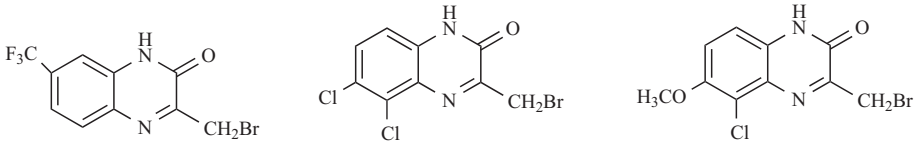
At the same time Smith *et al.* studied the ability of various 3-phenoxymethylquinoxalin-2-ones to antagonize Pgp and MRP1 in drug-resistant cell lines (NCI/ADR and MCF-7/VP, respectively) [31]. Pgp and MRP1 sustain energy-dependent efflux pumps, localized at the cell surface, that prevent the accumulation of certain drugs (such as doxorubicin, the vinca alkaloids vincristine and vinblastine, the topoisomerase II inhibitor etoposide), within cancer cells and are responsible for at least one of the mechanisms that confer multi-drug-resistance (MDR).

The results of this structure-activity study indicate that compounds with carbonyl substitutions of the phenoxy group (ester, amide, or ketone moieties) demonstrate excellent antagonism of Pgp, while having relatively low toxicity toward drug-sensitive cells MCF-7 (breast carcinoma). None of these derivatives antagonized MRP1. In particular, the best combination of both Pgp-selective antagonism and low toxicity was demonstrated by 2-(4-benzyl-3-oxo-3,4-dihydroquinoxalin-2-yl-methoxy)-*N*-phenylbenzamide (**14**) (Fig. **10**). In fact when utilized alone the IC_{50} (concentration required to kill 50% of MCF-7 cells) of **14** was > 54 μM. Whereas, at the concentration of 10 μg/mL, the Pgp antagonism score, calculated as the percentage of NCI/ADR cells surviving in the absence of vinblastine over the percentage of NCI/ADR cells surviving in the presence of vinblastine, was of 12.4; while the MRP1 antagonism score (at the concentration of 10 μg/mL of **14**), calculated as the percentage of MCF-7/VP cells surviving in the absence of vincristine over the percentage of MCF-7/VP cells surviving in the presence of vincristine, was of only 0.9 (Pgp/MRP1 = 13.4).

On the ground of these observations, Carta *et al*. designed a new series of 3-phenoxymethylquinoxalin-2-ones and a series of 3-phenoxymethylquinoxalines (structure **15** and **16** of Fig. **10** respectively) and investigated whether they were able to potentiate the antiproliferative activity of doxorubicin (Doxo), vincristine (VCR) and etoposide (VP16) in human tumor derived cell lines carrying the Pgp (Doxo and VCR), or MRP (VP16) phenotype [32].

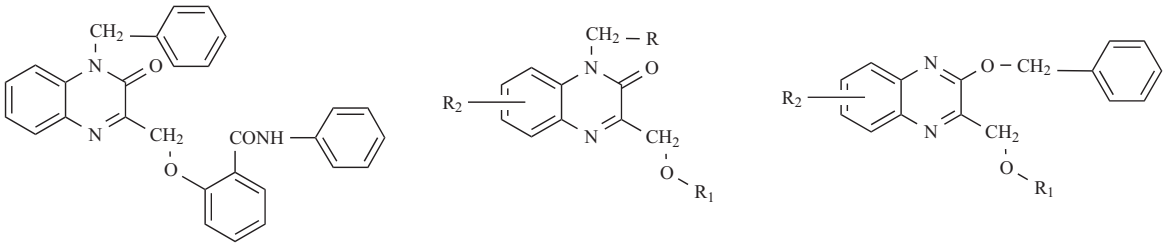
The in vitro antiproliferative activity of these quinoxalinones and quinoxalines was compared to that of **14**, the most interesting Pgp antagonist of the series reported by Smith, either using the drugs alone or in combination with Doxo, VCR or VP16. Test compounds were evaluated in vitro against the wild type nasopharyngeal carcinoma cell line (KB^{WT}), and the following drug resistant subclones.

(i) KB^{MDR}, obtained by transfection of wild type KB cells with a retroviral vector carrying the human MDR-1 gene and maintained under uninterrupted treatment with doxorubicin.



11 **12** **13**

Fig. (9). 3-Bromomethylquinoxaline derivatives endowed with in vitro anticancer activity.



14 **15** **16**

Fig. (10). 2-(4-benzyl-3-oxo-3,4-dihydroquinoxalin-2-yl-methoxy)-N-phenylbenzamide **14**, 3-phenoxymethylquinoxalin-2-ones **15** and 3-phenoxymethylquinoxalines **16**.

(ii) KB^{V20C}, selected under uninterrupted treatment with vincristine. These cells possess an MDR phenotype related to the over-expression of the MDR-1 gene.

(iii) KB^{7D}, selected under uninterrupted treatment with etoposide, a topoisomerase II inhibitor in clinical use. Their drug-resistance is due to the over-expression of the MRP gene, which codes for a membrane glycoprotein (mrp). These cells also express altered levels of topoisomerase II.

The results showed that, when tested alone, several quinoxalinones (**15**) and (**16a**): quinoxaline 2-benzyloxy-3-(2-benzamidephenoxymethyl)-7-trifluoromethylquinoxaline were totally unable to affect cell proliferation against KB^{MDR} (CC_{50} > 100 μM), whereas compound **14** exhibited a moderate cytotoxicity (CC_{50} = 28 μM).

Within the series of quinoxalinones devoided of cytotoxicity several 1,6-dimethyl-3-phenoxymethyl derivatives and the quinoxaline (**16a**), as well as the reference compound **14**, exhibited the ability to potentiate the activity of doxorubicin against KB^{MDR} cells, in a clear dose-dependent manner. Furthermore, both **14** and **16a** were able to potentiate the activity of vincristine against KB^{V20C} cells, but not the etoposide against KB^{7D} cells even when used at a 100 μM concentration. The latter result would confirm the inactivity of this class of molecules against MRP1 efflux pumps. From the comparison of the ability of potentiating the in vitro anticancer activity of **14** and **16a** (against KB^{MDR} and KB^{V20C} cells) towards their citotoxicity (against KB^{MDR} and MT-4 cells) it is possible to put in evidence that **14** exhibited a slightly higher potency than **16a** but this is probably due to higher citotoxicity (Tables **1**-**3**).

Table 1. Antiproliferative Activity, in KB^{MDR} Cells, of 14, and 16a, Alone and in Combination with Doxorubicin

Test Compds	[CC_{50}]			
	*TC alone	Doxorubicin in combination with		
		*TC 1 μM	*TC 10 μM	*TC 100 μM
14	28	0.5 (3)	0.04 (33)	-
16a	>100	0.5 (3)	0.08 (16)	<0.02 (>65)
Doxorubicin	1.3			

***TC** = Test compounds

( ) Fold increase in susceptibility to Doxorubicin

Table 2. Antiproliferative Activity, in KB^{V20C} Cells, of 14, and 16a, Alone and in Combination with Vincristine (VCR)

Test Compds	[CC_{50}]			
	*TC alone	Vincristine in combination with		
		*TC 0.8 μM	*TC 4 μM	*TC 20 μM
14	>100	0.02 (10)	0.003 (67)	0.001 (200)
16a	>100	0.09 (2)	0.01 (20)	0.004 (50)
Vincristine	0.2			

***TC** = Test compounds

( ) Fold increase in susceptibility to Vincristine

Table 3. Antiproliferative Activity of 14, and 16a Against KB^{WT} Nasopharyngeal Carcinoma Cells, KB^{MDR}, KB^{V20C} and KB^{7D} Subclones and MT-4 Cells

Compds	[CC_{50}]				
	KB^{WT}	KB^{MDR}	KB^{V20C}	KB^{7D}	MT-4
14	>100	28	>100	>100	16
16a	>100	>100	>100	>100	>100

However, the potential role of both quinoxaline and quinoxalin-2-one derivatives in the treatment of anticancer therapy requires further clinical evaluation.

Tricyclic Quinoxalinones

Various tricyclic systems bearing the quinoxalinone ring were prepared and tested in order to study their pharmacological activities.

Anxiolytic property was showed in the quinoxalinone system by 3-(5-cyclopropyl-[1,2,4]oxadiazol-3-yl)-5-isopropyl-3,3a-dihydro-5*H*-imidazo[1,5-*a*]quinoxalin-4-one (Panadiplon), an imidazo derivative with a high affinity for benzodiazepine receptor (compound **17** of Fig. **11**) [33-34]. It showed to possess both agonist and antagonist activities and minimal central nervous system depression [34].

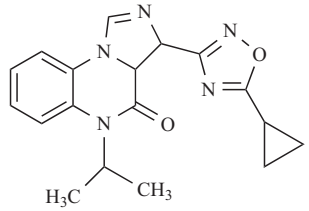


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Fig. (11). Panadiplon.

However, Phase I clinical trials were terminated when hepatic toxicity was observed in some human volunteers in spite of no toxicity observed after oral administration to rats, dogs or monkeys during preclinical safety studies. Furthermore, in subsequent studies a hepatic toxic syndrome in Dutch-belted rabbits and disruption of mitochondrial activities in rabbit and human after administration of panadiplon were observed [35-36].

Antiallergic activity was described for several imidazo- and pyrrolo- quinoxalinone carboxylic acids and esters after both oral (po) and intravenous (iv) administration [37]. All tricyclic quinoxalinones were tested for their ability to inhibit the IgE-mediated Passive Cetaceous Anaphylaxis (PCA) reaction in rats passively sensitized to ovalbumen. Chemical structures are summarized in Fig. (**12**).

In the imidazo[1,2-*a*]quinoxalinones series (**18**), the esters were too insoluble to be tested by iv administration, while their acid counterparts exhibited a good activity, even if lower than that of pyrrolo[1,2-*a*]quinoxalinones (**20**), for both iv and po administration. In particular the iv activity increases with *N*-alkyl chain length to a maximum at *n*-propyl.

In the imidazo[1,5-*a*]quinoxalinones and triazolo[1,5-*a*]quinoxalinones series (**19**), a few derivatives showed reasonable intravenous activity, none of them being orally active.

All the compounds of the pyrrolo[1,2-*a*]quinoxalinones series showed significant activity in the PCA test following either, and in some cases both, iv or po dosing. Several derivatives exhibited activity of the order of 100 times than that disodium cromoglycate (DSCG). In general in this series the maximal activity is restricted to straight-chain alkyl or alkenyl substituents on the 5-nitrogen atom (R_3).

In order to evaluate if an extension of quinoxalinone nucleus with an extra pyridine ring might be profitable to potentiate the antimicrobial and anticancer activities exhibited from the above mentioned quinoxalinones, Carta *et al*. [38] synthesized a series of pyrido[2,3-*g*]quinoxalinones (series **21** and **22**) of Fig. (**13**).

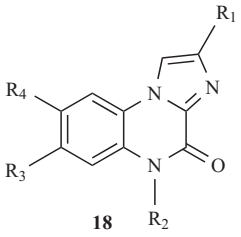
Results of the biological assays showed that all compound, with a few exceptions, exhibited moderate antimicrobial activity, whereas the derivative bearing a bromomethyl group in position 3 (Series **21**, R = CH_2Br) was found to have encouraging in vitro anticancer activity.

QUINOXALINE-2,3-DIONE AMPA/GLY_N RECEPTOR ANTAGONIST

The amino acid L-glutamate is the most important fast excitatory neurotransmitter in neuronal circuits in the mammalian Central Nervous System (CNS) [39-41]. Overexcitation or loss of homeostasis of glutamate receptors may contribute to several neurological disorders and neurodegenerative diseases. This has resulted in major efforts aimed at developing antagonists of glutamate receptors as neuroprotective agents and for the treatment of a variety of neurodegenerative diseases such as global and focal ischemia [40-43], epilepsy [44], Huntington's disease, Alzheimer's disease and Parkinson's disease [45-47] and Acquired Immune Deficiency Syndrome (AIDS)-related dementia [48-49].

Excitatory Amino Acid (EAA) receptors are characterized as ionotropic or metabotropic glutamate receptors [50]. The ionotropic receptors are ligand gated ion channels, whereas the metabotropic receptors are G-protein-linked receptors coupled to secondary messengers such as adenylate cyclase and phospholipase C systems. The ionotropic receptors are further subdivided into two main categories based on the agonists used to characterize them :

The N-methyl D-aspartate (NMDA) and non-NMDA receptors.



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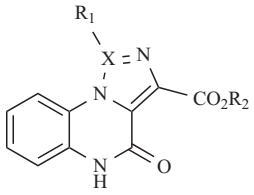
R_1=CO_2Et, CO_2H, CH_2OH, CHO, CONH-tetrazole;
R_2=H, Me, Et, Pr, Bu, CH_2Ph;
R_3=H, Cl;
R_4=H, Cl.

Imidazo[1,2-*a*]quinoxalinones



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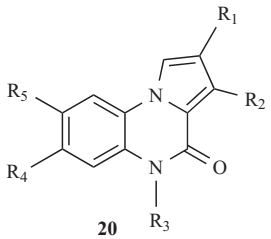
X=C, N;
R_1=H, Me, Et, CH_2Ph;
R_2=H, Me.

Imidazo[1,5-*a*]quinoxalinones and triazolo[1,5-*a*]quinoxalinones



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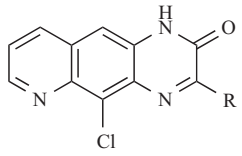
R_1=CO_2Et, CO_2H, CH_2OH, CHO, tetrazole, CONH-tetrazole;
R_2=H, CO_2Me;
R_3=Me, Et, Pr, isopropyl, Bu, pent, ciclopentyl, allyl, Ph;
R_4=H, Cl, Me;
R_5=H, Cl, Me.

Pyrrolo[1,2-*a*]quinoxalinones

Fig. (12). Tricyclic quinoxalinones endowed with antiallergic activity.



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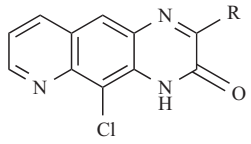

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Fig. (13). Pyrido[2,3-*g*]quinoxalinones.

In terms of therapeutic intervention there are at the least four sites for antagonism of NMDA receptors [51]:

1) Phencyclidine (PCP)-binding sites, located within the channel lumen and accessible in open-channel configurations [52-53]

2) Glutamate-binding sites, where antagonists compete with glutamate to inhibit channel activity [54-55]

3) Glycine coagonist sites (Gly_N), which must be occupied by glycine for glutamate to gate the channel [56-57]

4) Polyamine inhibitory sites [58].

There are also binding sites for Mg^{2+} and Zn^{2+}.

The NMDA receptor requires activation by the coagonists glutamate and glycine, it controls the opening of an ion channel which permits the entry of monovalent (mainly Na^+) and divalent (mainly Ca^{2+}) cations into target cells.

Non-NMDA receptors are comprised of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainate (KA) receptors. The kainate receptors has more specific ligands and distinct pharmacological actions [59], while the AMPA and Gly_N receptor antagonists have similarities in their pharmacophore models and in the commonality of the assay used to evaluate their potentials anticonvulsants and neuroprotectants [60-62].

Much research has focused on the role of NMDA receptors in such "excitotoxic" cell death in recent years, as it seems likely that this mechanism importantly contributes to the permanent damage to the CNS that occurs when there is an excessive release of glutamate following traumatic head or spinal cord injury, stroke, perinatal ischemia, or in hypoglycaemic conditions. The NMDA receptor antagonists have shown to have the potential to protect the CNS from excitotoxic damage in these conditions.

Quinoxaline-2,3-diones CNQX and DNQX (Fig. **14**) were introduced in the 1980s as the first antagonist of the AMPA-subtype of non-NMDA EAA receptor [63] and were subsequently shown to have comparable affinities for the Gly_N site [64-67].

This discovery has greatly facilitated the study of the pharmacology of the AMPA and KA receptors.

In the 1990 Sheardown *et al*. [68] studied a new quinoxalinedione derivative NBQX 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[*f*]quinoxaline (Fig. **15**), which displayed to be

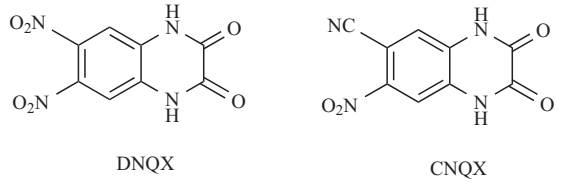


Fig. (14). Quinoxalindione inhibitors of EAA receptors.

more potent than DNQX and CNQX against AMPA (IC_{50} = 0.15 μM), less potent against KA (IC_{50} = 4.8 μM) and inactive against Gly_N (IC_{50} > 100 μM) to rat brain cortical membranes. NBQX being a selective antagonist of AMPA and KA receptors can act as neuroprotectant in global ischemia. On the basis of Structure-Activity Relationships (SAR) studies on the above cited DNQX [69], CNQX [70], NBQX [68], and several new quinoxalinedione derivatives, as PNQX [71], YM-90K [72] etc. an AMPA pharmacophore model was constructed (Fig. **15**) [50].

The most important receptor interaction sites are located in 2, 3, 4 and 6 ring positions and must be conserved for a successful design of new antagonists. The 1, 7 and 8 positions are amenable to modifications that can be used to increase selectivity and potency and to improve the physicochemical properties, including increased aqueous solubility.

The Gly_N pharmacophore model (Fig. **16**) [50] is based on the quinoxaline-2,3-dione derivative ACEA-1021 (see Fig. **24**) [73] and other compounds such as the Merk quinoline–2-carboxylic acid urea [74].

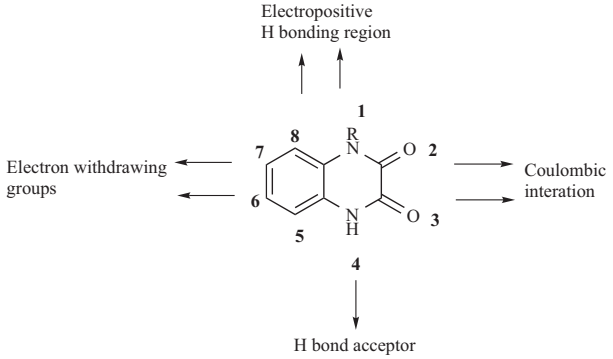


Fig. (16). Pharmacophore model for GlyN antagonists.

Ohmori *et al*. studied the biological effects of the replacement of ciano or nitro group in position 6 with an imidazolyl substituent [72]. The results of these researches showed that these derivatives were endowed with neuroprotective effects, i.e., anti-AMPA-induced toxicity in cultured neurons [75], anticonvulsive activity and antiischemic effects in both global and focal ischemia models [76-78]. In particular, the derivative 7-(imidazol-1-yl)-6-nitro-2,3-quinoxalinedione (YM-90K) (Fig. **17**) showed the most potent activity for the AMPA receptors.

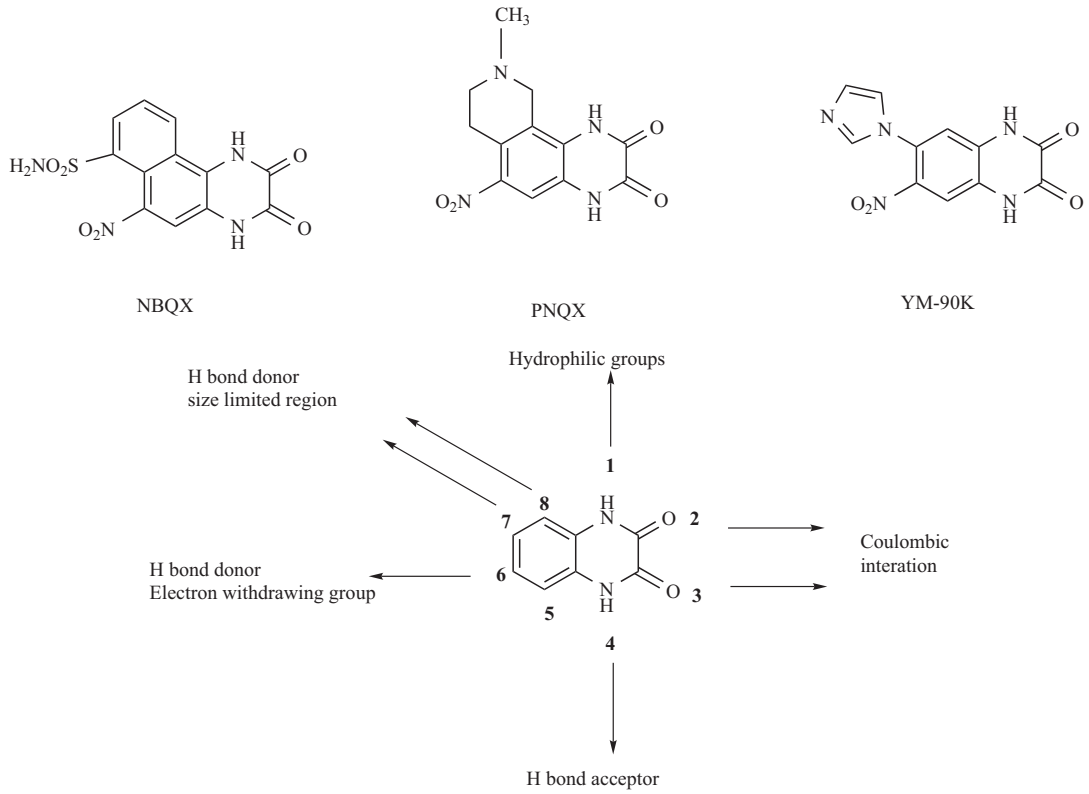


Fig. (15). Pharmacophore model for AMPA antagonists.

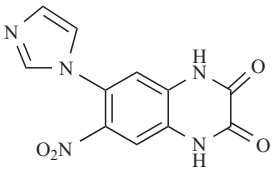
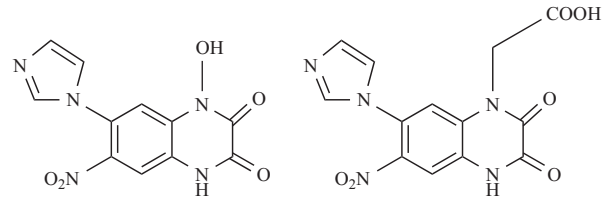


Fig. (17). YM-90K.

YM-90K was a selective antagonist for the AMPA receptor with Ki value of 0.084 μM being approximately equipotent with NBQX (Ki = 0.060 μM), while it showed no inhibitory activity for the NMDA receptor subtype [79]. On focal cerebral ischemic lesion induced by thrombotic middle cerebral artery occlusion (MCAO) in rat, YM-90K administered at various doses as a continuous infusion for 4h reduced the infarct size at 24 h after MCAO in a dose-dependent manner. [80]. Other studies with different model demonstrate that YM-90K provides cerebral neuroprotection against a wide range of ischemic insults. [81-83]. Unfortunately, YM-90K as well as NBQX failed clinical trials because of nephrotoxicity due to their limited solubility in water [84].

Other structure modifications studied from the same Authors of YM-90K concerned the replacement of either the C atoms in position 5 or 7 with N atoms. They demonstrated that the azaquinoxalinedione nucleus functions as a bioisoster for quinoxalinedione in AMPA receptor binding [85-86] and in Glycine site binding [87].

Furthermore, on the basis of SAR studies, Ohmori *et al*. also deduced that the amide proton of the imidazolyl-near side of the quinoxalinedione nucleus is not essential for the receptor binding whereas that of the imidazolyl-far amide does so. In fact the 1-hydroxy derivative of YM-90K (Fig. **18**) showed high affinity for AMPA receptor with Ki value of 0.021 μM [88] which is 3-4 fold greater than that YM-90K and NBQX with Ki = 0.084 μM. and Ki = 0.060 μM respectively, and over 100-fold selectivity for the AMPA receptor than for the NMDA receptor and the glycine site on NMDA receptor. 1-Acetic acid derivative of YM-90K named Zonampanel monohydrate (YM872) (Fig. **18**) is a novel, selective, potent and highly water soluble competitive AMPA receptor antagonist, (Ki = 0.096 μM) while it has very low affinity for other ionotropic glutamate receptors.



1-OH-YM-90K YM872

Fig. (18). YM-90K derivatives.

The solubility of YM872 is approximately 500 to 1000 times higher than that of the other competitive AMPA antagonists: YM-90K, NBQX or CNQX. The neuroprotective efficacy of YM872 was investigated in rats and cats subjected to permanent MCAO. The animals were assessed either histologically or neurologically following ischemia. In rats with MCAO, YM872 significantly reduced, by i.v. infusion, infarct volume measured at 24 h and 1 week after ischemia [89-92].

The evidence for the neuroprotective efficacy of YM872 suggests its therapeutic potential in the treatment of acute stroke in humans [93].

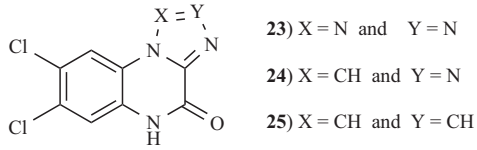
Phase I clinical trial data indicate that this agent can be safely administered in young and elderly subjects. Phase II studies of YM872 in acute ischemic stroke are ongoing [94].

The major elimination route for Zonampanel (YM872) has been reported to be through urine *via* the kidneys.

According to the known pharmacophore of the glycine antagonist-recognition site [95-96] (Fig. **16**), it appeared that there is a lipophylic space in the northern region of the quinoxalinedione molecule which can be occupied by an additional hydrophobic ring system.

Some heterocyclic-fused quinoxalinones were be studied:

1) Tetrazolo [1,5-*a*]quinoxalin-4(5*H*)-ones (series **23**), 1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones (series **24**) and imidazo [1,2-*a*]quinoxalin-4(5*H*)-ones (series **25**) of Fig. (**19**) were found to bind with good affinity to the AMPA receptor and glycine site of NMDA receptor [97].



23) X = N and Y = N

24) X = CH and Y = N

25) X = CH and Y = CH

Fig. (19). Tetrazolo, triazolo and imidazo quinoxalinones.

2) 6,7-Dihydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxaline-2,3-diones (series **26**) and 5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-diones (series **27**) of Fig. (**20**) displayed high affinity for the NMDA-glycine binding site with nanomolar activity [98-99]. In particular, the pyrido derivative SM-18400 is a potent, selective NMDA receptor glycine binding site antagonist; the side chain emanating from the tricyclic ring system was clearly added to improve aqueous solubility and physicochemical properties [100]. This may be useful for treating brain ischemia in humans [101-102].

3) (Imidazol-1-yl)imidazo- and [1,2,4]triazoloquinoxalinones. The derivatives **28a** and **29a** of Fig. (**21**) showed high affinity for AMPA receptors with Ki values of 0.057 and 0.19 μM respectively, in contrast **28b** and **30** showed no or weak affinity for these receptors [103].

On the other hand, introduction of a phosphonate group in *N*-1 position improves solubility and leaves unchanged potency for AMPA receptor [104-109]; ZK 202000 and ZK 200775 (Fig. **22**) showed *in vitro* potency and selectivity very similar to those of NBQX, and protected rodent brain against MCAO and head trauma [110]. ZK 200775 displayed anxiolytic, analgesic, anticonvulsant, muscle relaxant and sedative properties *in vivo*.

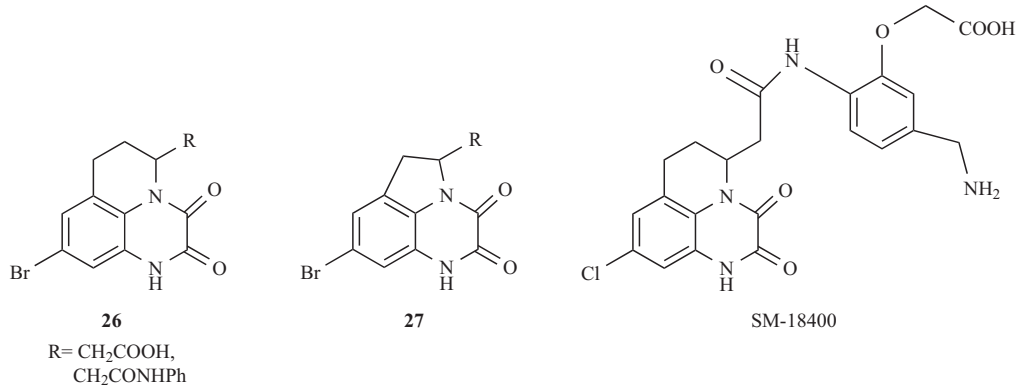


Fig. (20). Pyrido and pyrrolo quinoxalindiones, and SM-18400.

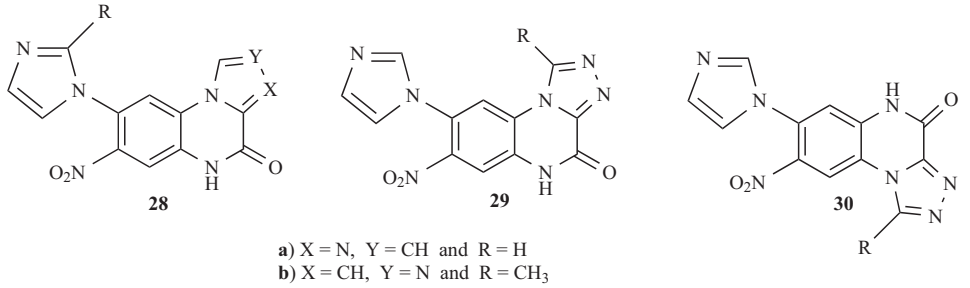


Fig. (21). (Imidazol-1-yl)imidazo- and [1,2,4]triazoloquinoxalinones.

Furthermore, in order to improve the low aqueous solubility (8.6 μg/mL) of the above cited PNQX, a series of novel ring-opened analogues were synthesized and tested. The best of the series was the derivative [(6-ethyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)methylamino]-acetic acid ammonium salt (**31**), reported in Fig. (**23**) [111].

Its aqueous solubility in pH 7.4, 50 mM phosphonate buffer, is 420 μg/mL. It retained AMPA (IC_{50} = 0.14 μM) and Gly_N (IC_{50} = 0.47 μM) receptor affinity shown by PNQX (IC_{50} = 0.63 and 0.37 μM respectively).

Several quinoxalin-2,3-diones were developed by ACEA Pharmaceutical Inc. [112].

Among them the most representatives are ACEA 1021 (Licostinel), which fits the Gly_N pharmacophore model, ACEA 1031, ACEA 1011, ACEA 1328, and ACEA 1416 (Fig. **24**).

The steady-state inhibitory potencies of these molecule were measured with NMDA receptor in cultured rat cortical neurons and non-NMDA receptors expressed in Xenopus oocytes [113].

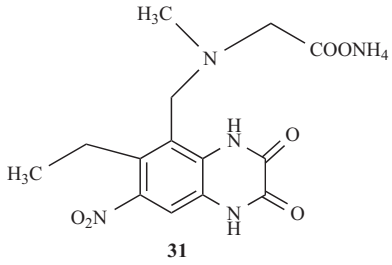


Fig. (23). Soluble derivative of PNQX.

These derivatives were found to be potent and selective Gly_N antagonists. ACEA 1021 has a Kb on NMDA receptor glycine of 0.0059 μM with 254-fold selectivity against on non-NMDA receptor (Kb = 1.5 μM). ACEA 1031 has Kb = 0.0065 μM on NMDA and 0.89 μM on non-NMDA (140-fold selectivity). ACEA 1416 is >400 fold selective for NMDA receptors Gly_N *vs* AMPA receptors, with Kb =0.0079

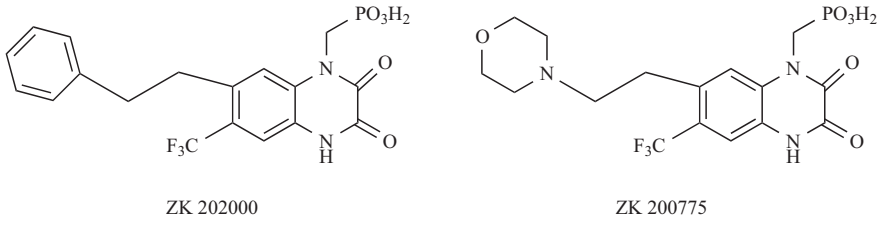


Fig. (22). Soluble quinoxalindiones.

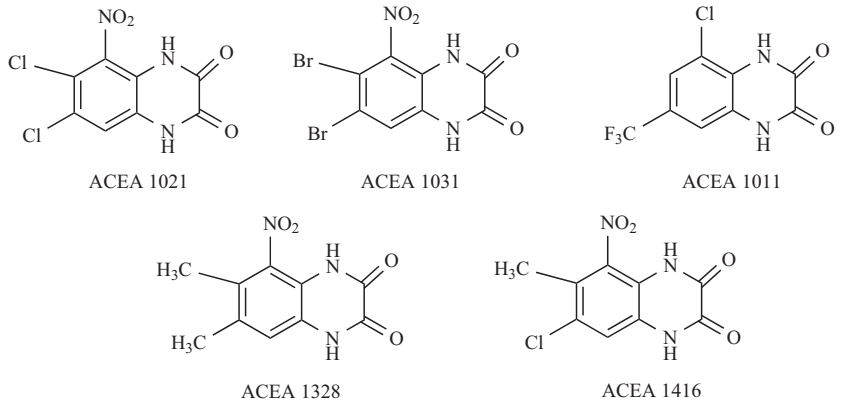


Fig. (24). ACEA series.

μM [114]. Both were moderately potent competitive inhibitors of AMPA and kainate receptor [115]

SAR studies indicate that the replacement of the nitro-group of ACEA1021 and ACEA1416 with a cyano group is positive for the activity (with IC_{50} values of 32 and 26 nM for 5-cyano-6,7-dichloro-, and 5-cyano-7-chloro-6-methyl-quinoxalinediones respectively) while 5-carbonyl derivatives (as carboxy, ester, ketone and amide) showed reduced potency [116].

ACEA 1021 may be a safer and better tolerated neuroprotective agent than many of the previously evaluated NMDA antagonist [117-120]. The beneficial effects of ACEA 1021 were associated with a dose-related fall in body temperature as it has been reported [118]. Another study reports that brain protection was observed even when ACEA 1021 was administered at 2h after the onset of stroke in a robust model of permanent focal cerebral ischemia [121]. Furthermore, ACEA 1021 produced antinociception in the tail-flick and formalin test [122]. Another study showed synergistic antinociceptive effects against tonic pain together with morphine [123]. Intrathecal administration of ACEA1021 decreases incision-induced pain behaviours in rat model of postoperative pain. ACEA1021 blocked spontaneous nociceptive behaviours (SNB) by NMDA, KA and AMPA. This suggests that inhibition of such pain behaviours by it ACEA 1021 is produced by blockade of spinal non-NMDA receptors [124].

Intrathecal administration of morphine and ACEA 2085 (an AMPA antagonist) yielded a dose-dependent increase in the thermal escape latency. A potent synergy was observed with decreased side effects [125-126].

Also both ACEA 1011 and ACEA 1416 showed analgesic properties in animal models of tonic pain [127].

However when NMDA antagonists were examined for their interaction in acute nociception (Thermal escape latency) they had no effects together with morphine, while AMPA antagonists displayed synergy with morphine in the same model [126].

Epilepsy has been considered a potential therapeutic target for ionotropic Glu Receptor (iGluR) antagonists since the demonstration, more than 15 years ago, that NMDA receptor antagonists block seizures in rodent models of epilepsy [128-132].

Some pyrrolyl-quinoxalinediones showed an interesting activity against iGluR. Three derivatives LU 97175, LU 115455 and LU 112313 (Fig. **25**), exerted a potent anticonvulsant effect without inducing motor impairment in the ro-

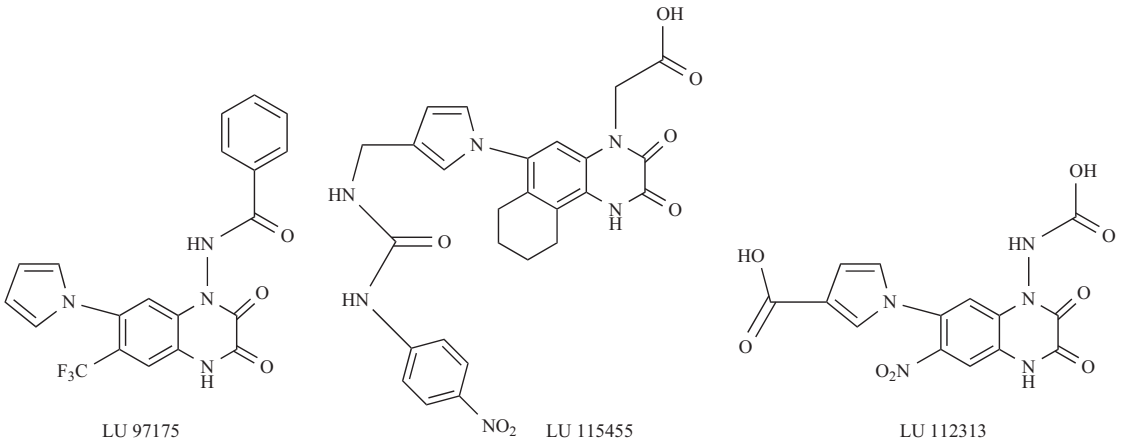


Fig. (25). LU series.

tarod test: this combination of actions is thought to be a prerequisite for selective anticonvulsant drug action [133].

More recently a series of 4,5-dihydro-4-oxo-1,2,4-triazolo [1,5-*a*]-quinoxaline-2-carboxylates (TQXs) has shown to possess a combined Gly/NMDA and AMPA receptor affinity [134]. The introduction of the 8-(1,2,4-triazolo-4-yl)substituent has led to a more potent and selective AMPA receptor antagonist: TQX-173 [135].

TQX-173 (Fig. **26**), showed high affinity for AMPA receptor with a Ki value of 0.14 μM which is several fold greater than that for glycine site (Ki=33.5 μM) and KA receptor (Ki=11.6 μM).

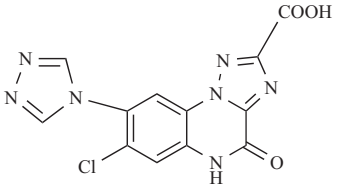


Fig. (26). TQX-173.

Further studies made by Catarzi *et al*. have established that the presence of a N^3-nitrogen-containing heterocycle at position 8 of the TQX framework is an essential feature for potent and selective AMPA receptor antagonists [136-137].

The replacement of the 7-chloro atom with more powerful electron-withdrawing substituents than chlorine (CF_3 or NO_2) has produced some potent and selective AMPA receptor antagonists. For example the derivative analogue of TQX-173 with 7-CF_3 instead of 7-Cl showed value of Ki= 0.095 [138].

CHEMISTRY

A first review of the chemistry of quinoxalin-2-ones and quinoxalin-2,3-diones (strictly named 1*H*-quinoxalin-2-ones and 1*H*,4*H*-quinoxalin-2,3-diones) was reported by Simpson on 1953 [139]. Subsequently, as reported in Fig. (**27**), some spectroscopical studies and aromaticity measurements confirmed the supposed presence of a tautomeric equilibrium between the carbonyl (**a**) and hydroxy (**b**) isomers of the quinoxaline [140-142].

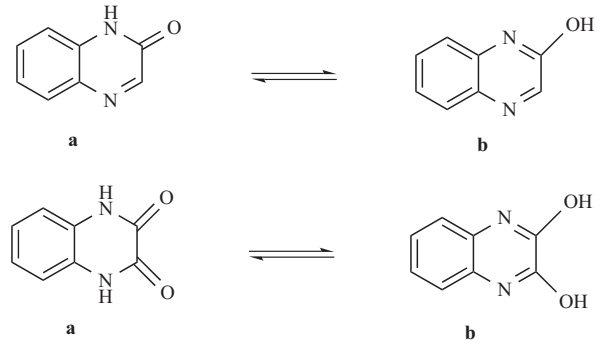


Fig. (27). Tautomeric equilibrium between quinoxalinones and quinoxalines.

Preparations of Quinoxalin-2-ones

Most of quinoxalin-2-one derivatives are easily prepared through a classical simple and direct condensation of the opportune 1,2-diaminobenzene (*o*-phenylenediamine) and sui-table 2-ketoesters or 2-ketocarboxylic acid [2-6, 30, 143-149]. In Fig. (**28**) it is depicted the general scheme of reaction.

In the case of asymmetrically *mono*-substituted 1,2-diaminobenzene (or 6,7-diaminoquinolines) this type of reaction generally affords both the theoretical isomers. In Fig. (**29**) some examples are reported.

4-Chloro-1,2-diaminobenzene (1) reacts with glioxylic acid (2) in refluxing methanol affording a mixture of 7-chloroquinoxalin-2-one (3) and 6-chloroquinoxalin-2-one (4) [150-151]. Likewise 4-methyl-1,2-diaminobenzene (5) and trifluoropyruvic acid hydrate (6) in dioxane gives the expected isomers 3-trifluoromethyl-7-methylquinoxalin-2-one (7) and 3-trifluoromethyl-6-methylquinoxalin-2-one (8) [152]. Finally, 4-fluoro-5-morpholinyl-1,2-diaminobenzene (9) with diethyl ketomalonate (10) in refluxing ethanol affords the isomers 6-fluoro-7-morpholinyl-2-ethoxycarbonylquinoxalin-3-one (11) and 7-fluoro-6-morpholinyl-2-ethoxycarbonylquinoxalin-3-one (12) [2]. In the case of the condensation of 8-chloro-6,7-diaminoquinolines (13) with ethyl 3-methyl-2-oxobutyrate (14), in refluxin ethanolic solution, a mixture of 5-chloro-3-isopropyl-1,2-dihydropyrido[2,3-*g*]-quinoxalin-2-one (15) and 5-chloro-2-isopropyl-3,4-dihydropyrido[2,3-*g*]-quinoxalin-3-one (16) is obtained [36]. Under the above reported neutral conditions the formation of 6-substituted isomers prevails over the 7-ones when the starting diaminobenzene bears an electronwithdrawing group in position 4, while the 7-substituted isomers prevails over the 6-ones for diaminobenzene derivatives bearing electronreleasing group [2-4]. On the other hand, this behaviour is reversed under acidic conditions, as it is reported in a kinetic study on the annelation of heterocycles by Abasolo *et al.* [153] successively confirmed (for reaction in 10% sulfuric acid solution) by Carta *et al.* [4-5].

In addition to the classical reaction with 2-ketoesters or 2-ketocarboxylic acids, the 1,2-diaminobenzene substrates can react with different esters to afford the corresponding quinoxalinones in excellent yield. In Fig. (**30**) are reported some examples: 1,2-diaminobenzene derivative (1) reacts with diethyl dibromomalonate (2) (in methanol at r.t.) to give 2-ethoxycarbonylquinoxalin-3-one (3) [154]; with ethyl 2-bromo-2-methylpropanoate (4) (in DMF and Hunig's base, at 80-100 °C) to give 1*H*,4*H*-3,3-dimethylquinoxalin-2-one (5) [155]; with methyl 2-bromo-2-phenylacetate (6) (in refluxing methyl acetate, KI, K_2CO_3 for 12 h, and then CH_3 ONa and benzene under reflux for 7 h) to give 3-phenylquinoxalin-2-one (7) [156]; with ethyl ethoxycarbonylformamidate (8) (in absolute ethanol at 25 °C) to give 3-aminoquinoxalin-2-one (9) [157-158].

Furthermore, some reports on the solid-phase synthesis of this class of compounds has been recently reviewed by Kamal *et al.* [159].

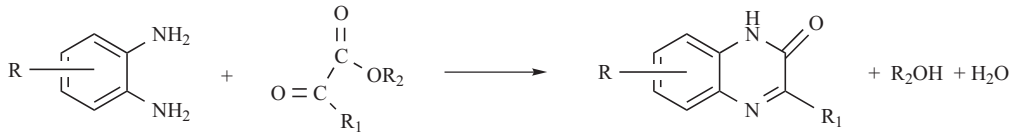


Fig. (28). General scheme of reaction of quinoxalin-2-ones.

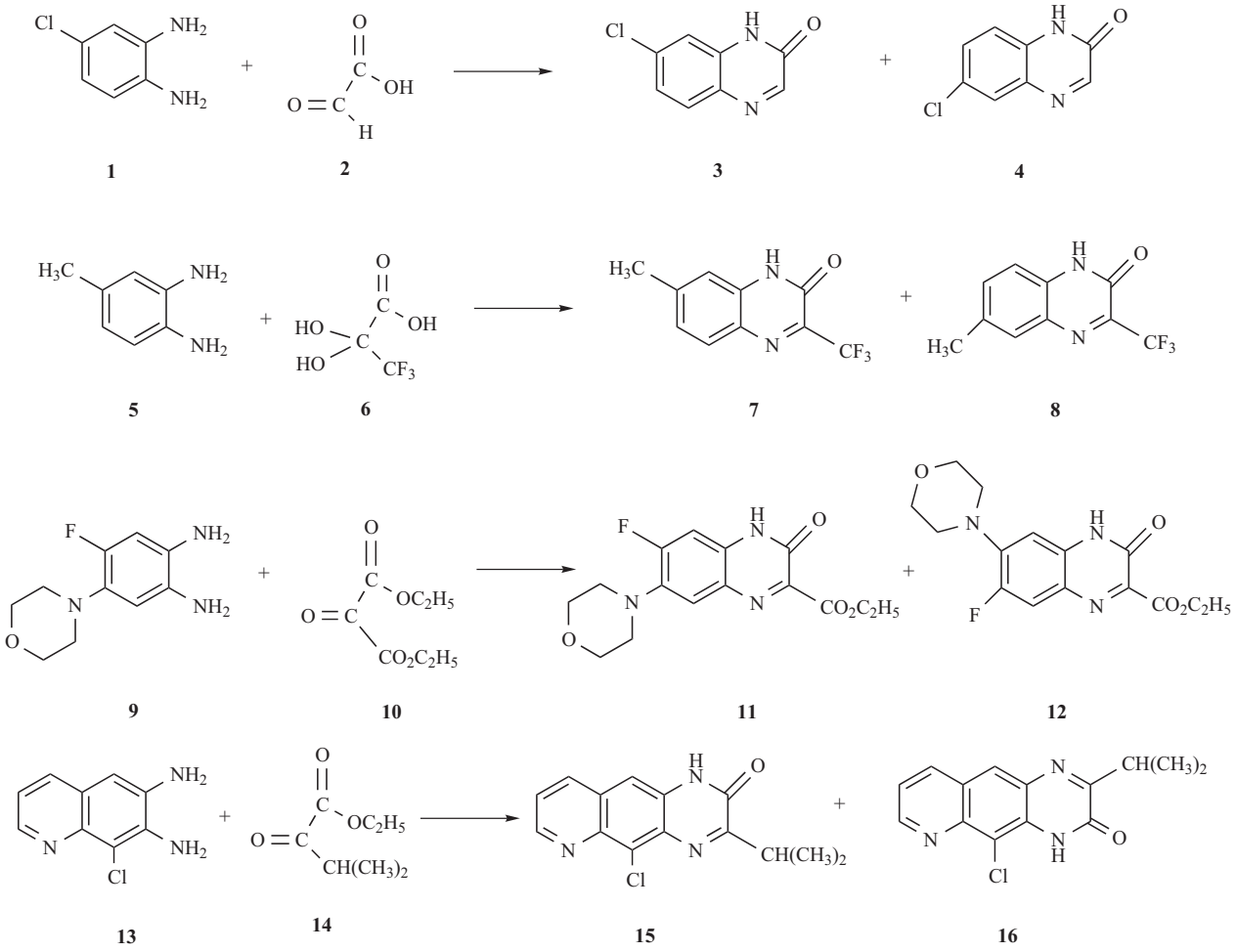


Fig. (29). Reaction of asymmetric o-phenylenediamines.

Several heterocyclic compounds, as furanones, oxazoles, benzoindoles and benzothiopyranes variously substituted, have been condensed with 1,2-diaminobenzenes to afford in good yield interesting quinoxalinone derivatives (Fig. **31**). 1,2-Diaminobenzene derivative (1) reacts with 2-bromomethyl-3-methylmaleic anhydride (2) (in chloroform at -15 °C) to give 2-(2-methyl-3-oxoquinoxalin-2-yl)acrylic acid (3) [160]; with 2,2-*bis*(trifluoromethyl)oxazolin-5-one (4) (in ethyl acetate at r.t.) to give quinoxalin-2-one (5) [161]; with 1-diphenylamino-4,5-dihydro-1*H*-benzo[*g*]indole-2,3-dione (6) (in ethanol and catalytic amounts of *para*toluenesulphonic acid, at r.t. for 120 h) to give the tetrahydronaphtalen-2-yl-quinoxalin-2-one derivative (7) [162]; with 1-diphenylamino-benzothiopyrano[4,3-*b*]pyrrole-2,3-dione (8) (in dichloromethane and traces of HCl, at 20 °C) to give the benzothiopyran-3-yl-quinoxalin-2-one (9) [162].

Quinoxalin-2-ones can be also prepared starting from quinoxaline *N*-oxides. Some preparative routes are briefly described below and depicted in Fig. (**32**). 6-Chloro-2-(piperidin-1-yl)quinoxaline 4-oxide (**1**) and 6-chloro-2-(morpholin-4-yl)quinoxaline 4-oxide (**2**) both react with acetic anhydride affording in good yield 7-chloro-3-(piperidin-1-yl)quinoxalin-2-one (**3**) and 7-chloro-3-(morpholin-4-yl)quinoxalin-2-one respectively (**4**) [163]. Irradiation of aqueous solution of some quinoxaline N-oxides (**5-7**) promotes transposition

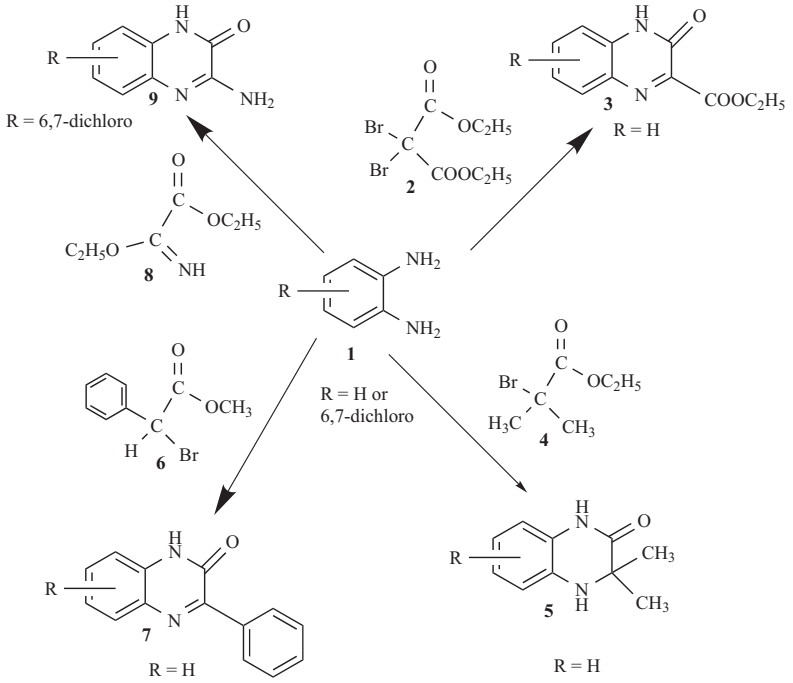


Fig. (30). Synthesis of quinoxalin-2-ones with different synthon esters.

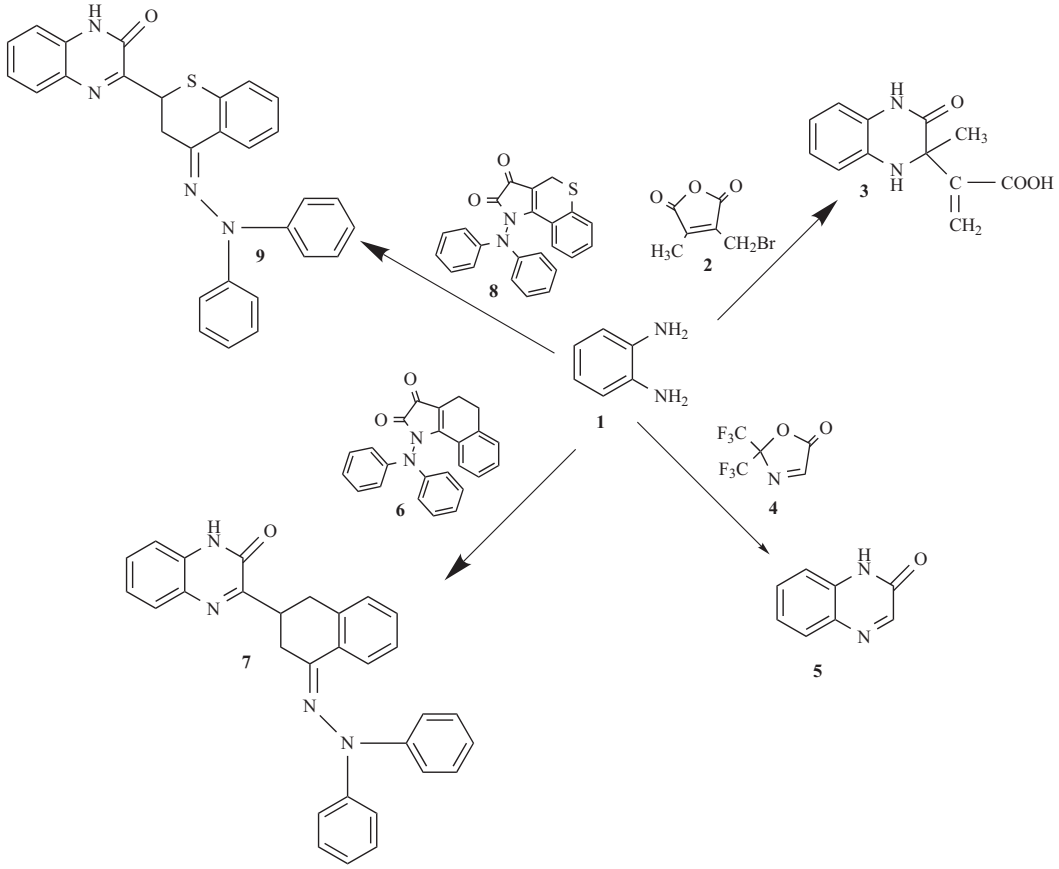


Fig. (31). Synthesis of quinoxalin-2-ones with different heterocycles.

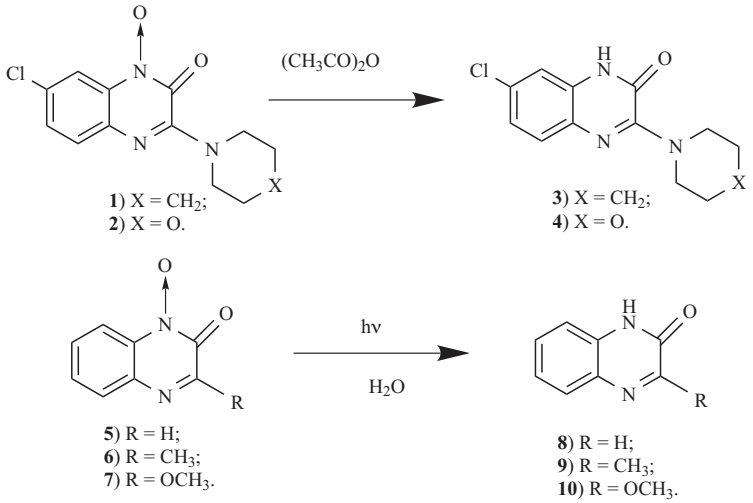


Fig. (32). Synthesis of quinoxalin-2-ones from quinoxaline N-oxides.

of the oxygen atom affording the corresponding quinoxalin-2-ones (**8-10**) [164].

Reactions of Quinoxalin-2-ones

There are numerous articles and patent registrations concerned with these reactions, here we shall simply summarize the main features of the chemical behavior of this nucleus.

Alkylation of quinoxalinones, in the presence of bases, generally affords mixtures of N_1-alkylquinoxalino-2-ones and 2-alkoxyquinoxalines [2, 165-166], but in a few cases only the N_1-alkylquinoxalino-2-ones are obtained [167-168]. Some examples are reported in Fig. (**33**). Methylation of ethyl 6,7-dimethoxy-2-oxo-3-quinoxalinecarboxylate, in dry methanol and ethereal diazomethane, affords in good yield a

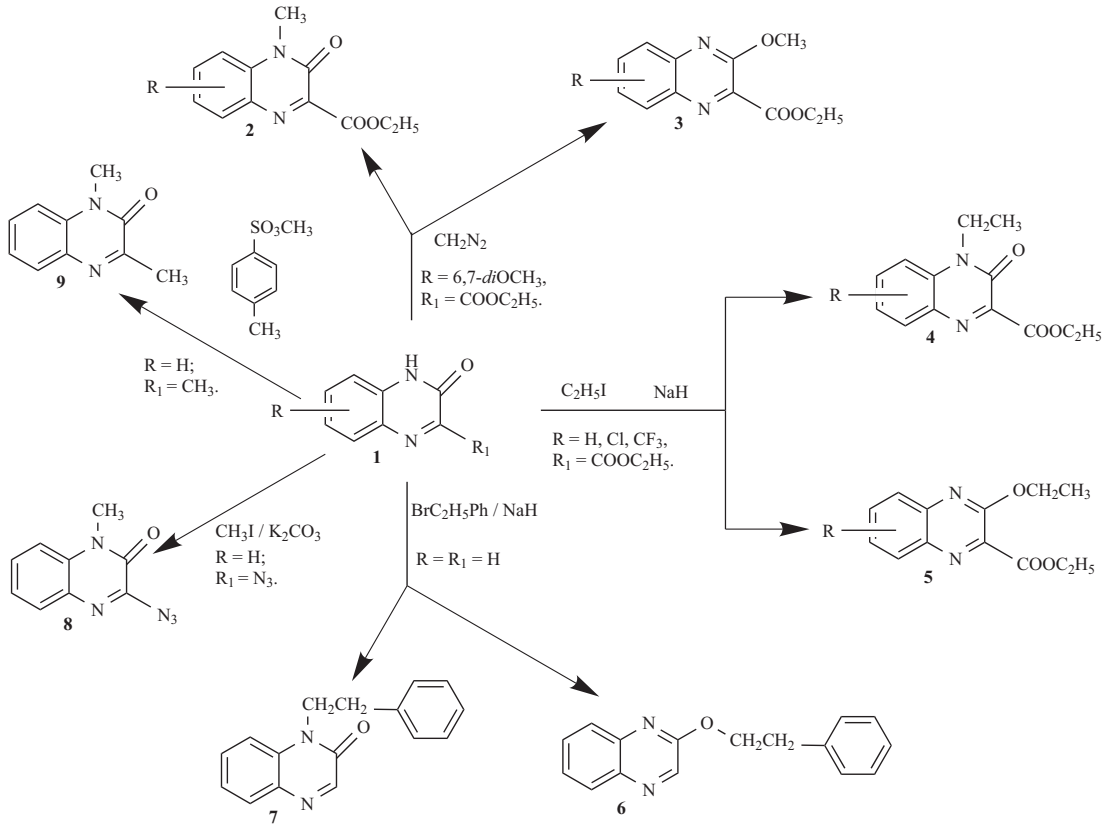


Fig. (33). Alkylation of quinoxalinones.

mixture (about 1:1) of N- and O- methyl derivatives **2** and **3** respectively [166]. Likewise, both ethyl 2-oxo-3-quinoxalinecarboxylates and unsubstituted quinoxalinone react with ethyl iodide and ω-phenylalkylhalogens, under sodium hydride catalysis, affording the corresponding mixtures (**4** and **5**) [2] and (**6** and **7**) [165]. On the other hand, methylation of 3-azidoquinoxalin-2-one and 3-methylquinoxalin-2-one with methyl iodide and methyl *para*toluenesolphonate respectively, both in the presence of potassium carbonate, afford the N_1-alkylquinoxalino-2-ones (**8**) [167] and (**9**) only [168].

Contraction of the pyrazine moiety into 2-methylimidazole derivative occurs when the quinoxalinone system is treated with boiling 50% aqueous hydrazine solution for 24 h [169] (Fig. **34**).

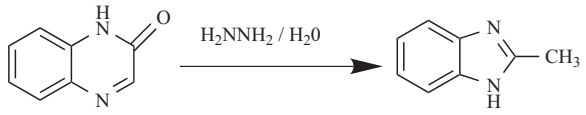


Fig. (34). Ring conctration.

Preparation of Quinoxalin-2,3-diones

Quinoxalin-2,3-diones are prepared by straightforward condensation of a large number of 1,2-diaminobenzene derivatives with many α,β-dicarbonyl derivatives as oxalic acid, dialkyl oxalates, oxalyl halide, and related syntons. Some examples are reported in Fig. (**35**). 1,2-Diamino-4-trifluoromethylbenzene (compound **1** with R = 4-CF_3 and R_1 = H) reacts with dihydrate oxalic acid (at 130 °C for 3 h) to give 6-trifluoromethylquinoxaline-2,3-dione (compound **3** with R = 6-CF_3 and R_1 = H) in good yield [170]. 1,2-Diamino-4,5-dimethylbenzene (compound **1** with R = 4,5-*di*CH_3 and R_1 = H) reacts with diethyl oxalate (in refluxing tetrahydrofurane, under an atmosphere of argon for 3 days) to give 6,7-dimethylquinoxaline-2,3-dione (compound **3** with R = 6,7-*di*CH_3 and R_1 = H) in quantitative yield [171]. 1,2-Diaminobenzenes (compound **1** with R = R_1 = H, R = H, R_1 = CH_3, and other analogs) reacts with oxalyl chloride, in 1,2-dichlorobenzene at 130 °C for 1 h, to afford the corresponding quinoxalin-2,3-diones [172]. Several further *N*-substituted quinoxalin-2,3-diones are prepared starting from the parents *N*-substituted-1,2-diaminobenzenes [173].

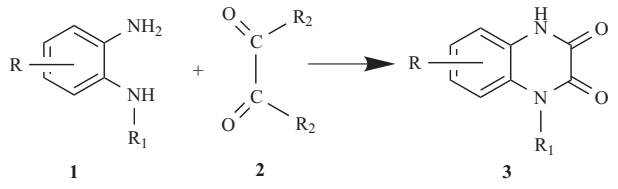


Fig. (35). Scheme of synthesis of quinoxalin-2,3-diones.

Quinoxalin-2,3-diones are also prepared in good yield following different synthetic pathways. In Fig. (**36**) some classified examples are reported. Quinoxaline (**1**) and quinoxalin-2-one (**2**) were oxidized by treatment with ammonium peroxodisulfate [$(NH_4)_2S_2O_8$] and potassium permanganate ($KMnO_4$) respectively, to obtain quinoxalin-2,3-dione (**3**) [174-175]. Furthermore, oxidative nitration of substituted quinoxalin-2-ones (**4**), in THF and $^fHNO_3$, affords the corresponding 5-nitroquinoxalin-2,3-dione derivatives (**5**) [176]. Hydrolysis of 2,3-dichloro-6-methoxyquinoxaline (**6**) with 48% HBr aqueous solution and acetic anhydride gives 6-hydroxyquinoxalin-2,3-dione (**7**) [177]. Likewise, 6-bromomethyl-2,3-dimethoxy-7-methylquinoxaline (**8**) can be hydrolyzed to 6-hydroxymethyl-7-methylquinoxalin-2,3-dione (**9**) and 6-formyl-7-methylquinoxalin-2,3-dione (**10**) with refluxed 1.2 N aqueous solution of HCl and hexamethylenetetramine respectively [178]. Finally, pyridazino[4,5-*b*]quinoxaline-1,4-dione (**11**) in 30% H_2O_2 and acetic acid undergo ring contraction reaction to give quinoxalin-2,3-dione (**3**) [178].

Preparation of DNQX (Fig. 37)

Quinoxalin-2,3-dione (**1**) can be converted into 6-nitroquinoxalin-2,3-dione (**2**) or 6,7-dinitroquinoxalin-2,3-dione (DNQX) by treatment with one or two equivalents of potassium nitrate respectively, in sulphuric acid solution [179].

Preparation of YM-90K (Fig. 38)

The commercially available 2-nitro-5-chloroaniline (**1**) reacts with excess of imidazole (**2**) and potassium hydroxide in DMSO at 80°C for 3 h to give the intermediate 5-(*1H*-imidazol-1-yl)-2-nitroaniline (**3**). Hydrogenation of **3** (at atmosphere pressure) with palladium on carbon affords the diaminoderivative (**4**), which by treatment with oxalic acid in refluxing 4N HCl gives the corresponding imidazolylquinoxalinedione (**5**). Nitration of **5** with $^fHNO_3$ in concentrated H_2SO_4 at room temperature gives the desired compound YM-90K with 53.7 % yield [72].

Preparation of PNQX (Fig. 39)

Nitration of 5-bromoisoquinoline (**1**) with KNO_3 in concentrated H_2SO_4 affords the nitroderivative (**2**) which after N-methylation, using methyl triflate, followed by reduction with sodium cyanoborohydride, gives the corresponding tetrahydroisoquinoline (**3**). Reduction of the nitro group (using deactivated Raney Nickel as catalyst) followed by treatment with acetic anhydride affords the acetamide intermediate (**4**). Nitration of **4** with $^fHNO_3$ in CF_3COOH gives the 7-nitroderivatve (**5**) which by reduction, with H_2 in the presence of 20% palladium on carbon for 4 h, followed by condensation with oxalic acid in HCl affords the quinoxalin-2,3-dione (**6**). Finally, nitration of **6** with KNO_3 in concentrated H_2SO_4 affords the desired PNQX [71].

Preparation of ACEA 1011 and ACEA 1021 (Fig. 40)

Hydrogenation (at 20-30 psi for 3 h) of the commercially available 6-chloro-4-trifluoromethyl-2-nitroaniline (**1**) in methanol with palladium on carbon gives the diamine (**2**) which is condensed with diethyloxalate giving ACEA 1011 [112]. Condensation of the commercially available 4,5-dichlorodiamine (**3**) with oxalic acid in 2N HCl gives the quinoxalinedione intermediate (**4**), which is nitrated with $^fHNO_3$ in concentrated H_2SO_4 at 0°C to affording the desired ACEA 1021 [112].

Preparation of ACEA 1416 (Fig. 41)

The commercially available 3-methyl-4-chlorohalobenzene (**1**) submitted to nitration with KNO_3 in concentrated H_2SO_4 at 0°C affords 4-methyl-5-chloro-2-halonitrobenzene

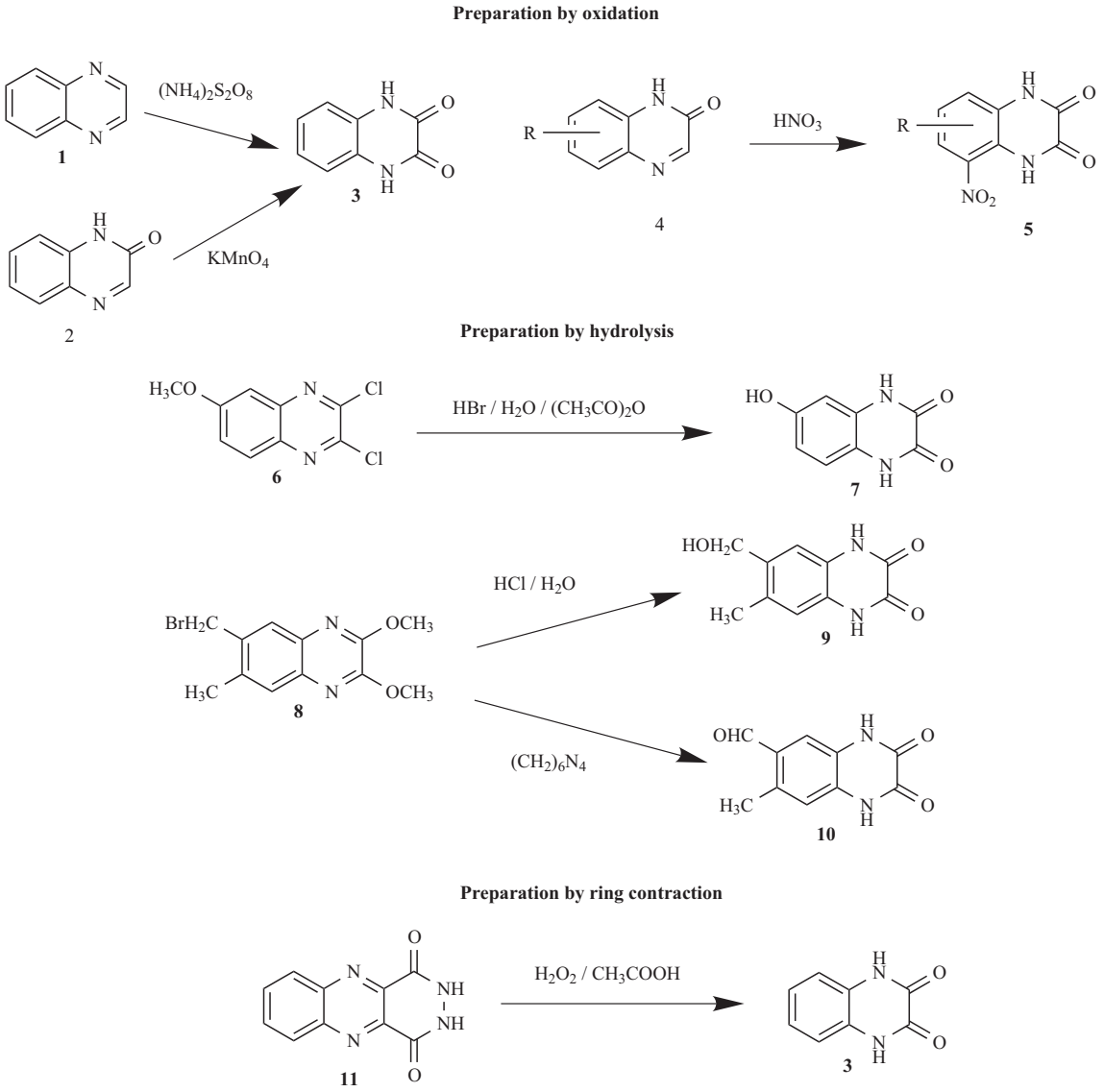


Fig. (36). Scheme of non classic synthesis of quinoxalin-2,3-diones.

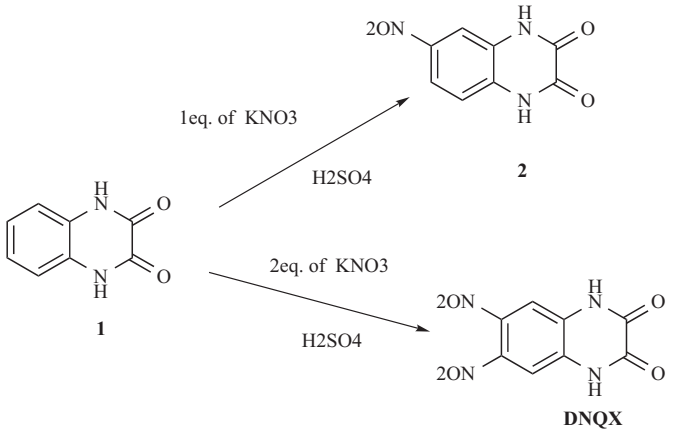


Fig. (37). Synthesis of DNQX.

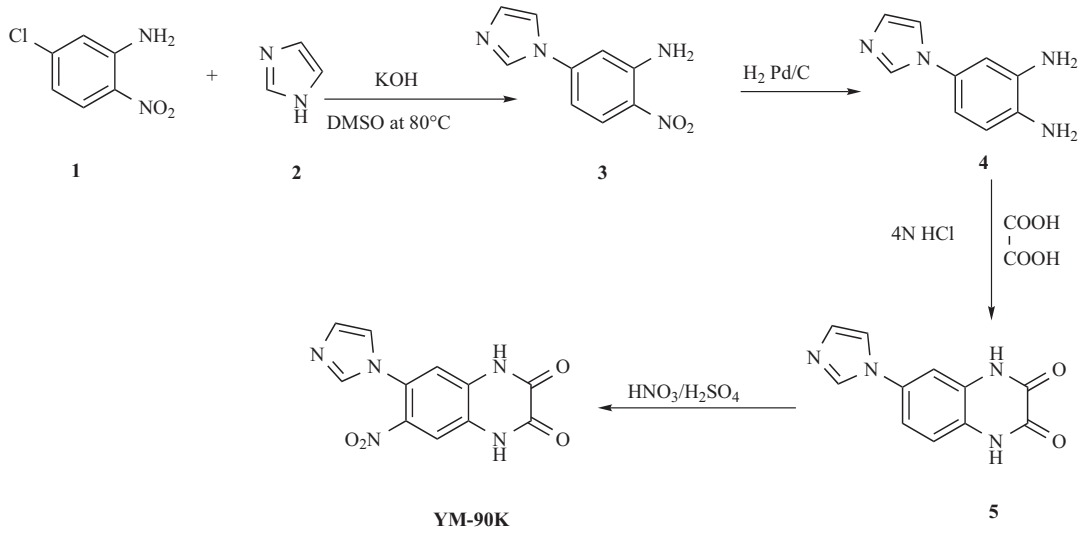


Fig. (38). Synthesis of YM-90K.

(**2**). Nucleophilic aromatic substitution of the halogen in position 2 with sodium glycinate gives the intermediate N-phenylglycinate (**3**), which is treated with $SnCl_2$ in ethanol affording the corresponding aminoderivative which spontaneously cyclizes to give the 3,4-dihydroquinoxalin-2-one (**4**). Nitration of **4** with $^{f}HNO_3$ in trifluoroacetic acid resulted in both nitration and oxidation to give ACEA 1416 [114].

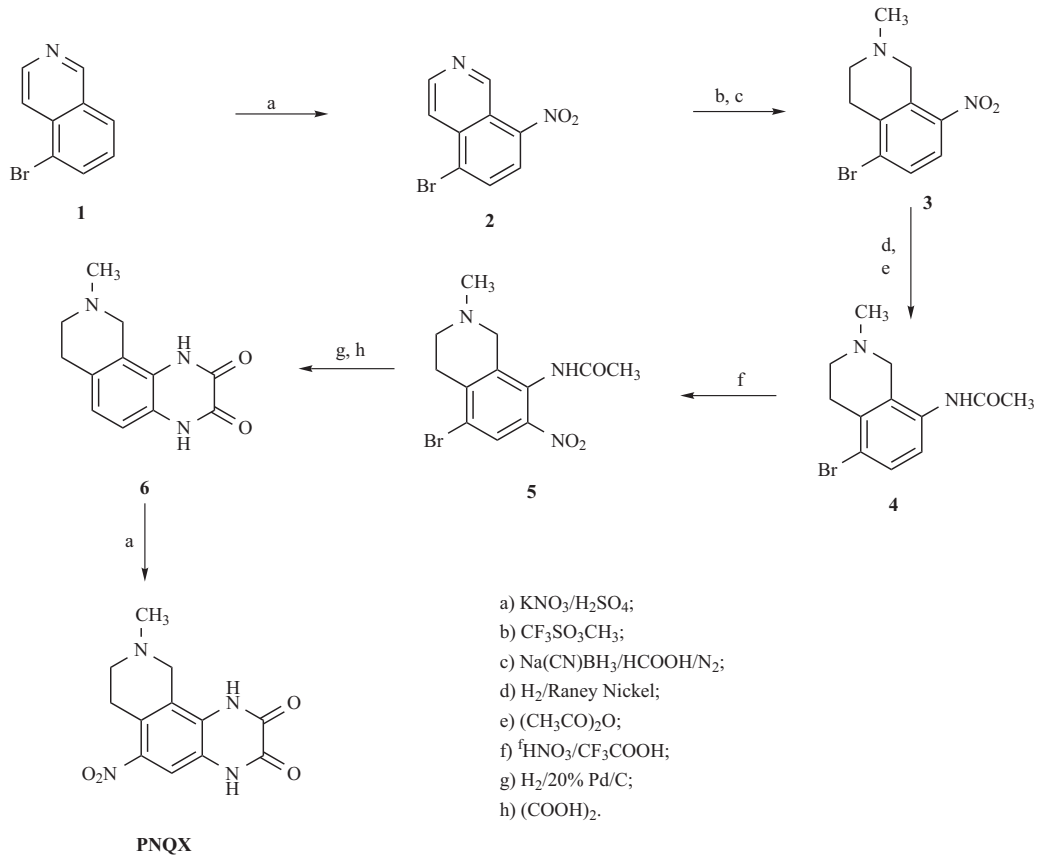


Fig. (39). Synthesis of PNQX.

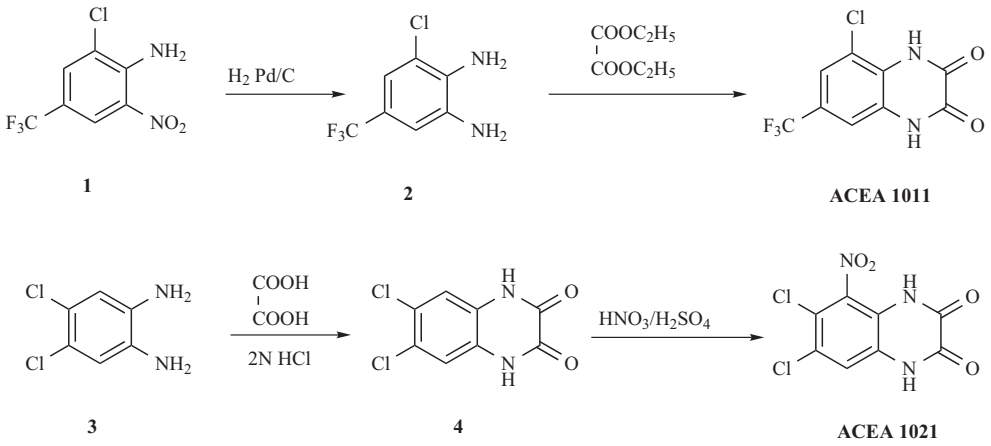


Fig. (40). Synthesis of ACEA 1011 and ACEA 1021.

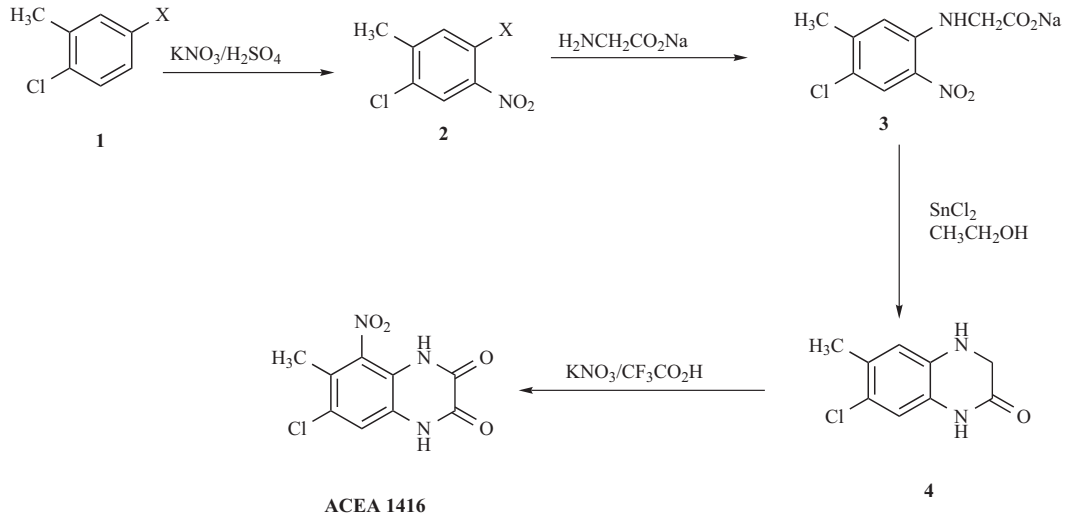


Fig. (41). Synthesis of ACEA 1416.

Reactions of Quinoxalin-2,3-diones

The chemical behavior of quinoxalin-2,3-diones is very similar to that of the quinoxalin-2-ones, little differences are due to the presence of two NH groups. For example, alkylation of quinoxalin-2,3-diones affords only N-alkyl derivatives [95] whereas quinoxalin-2-ones generally affords mixtures of N-alkyl and O-alkyl derivatives [2, 165-166].

Interesting nucleophilic replacement of halogen atoms in the benzo-moiety (further activated by the presence of nitro group) with several azoles are reported in literature for some quinoxalin-2,3-diones [40]. Furthermore, reaction of nitration takes place in good yield on the benzo-moiety of quinoxalin-2,3-diones when they are treated with nitrating mixture (conc. H_2SO_4 and KNO_3 mixture) [72, 112, 180].

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