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Synthesis and Anticonvulsant Activity of Novel 2- and 3-[4-(Trisubstituted Pyridyl)-phenylamino]- and 2-[3- and 4-(Trisubstituted Pyridyl)-phenoxy]-quinoxaline Derivatives

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A series of novel quinoxaline derivatives linked to a pyridine moiety through phenylamino or phenoxy residue was synthesized and evaluated as candidate anticonvulsants. The synthesis was achieved through reaction of 2,3-dichloroquinoxaline (**1**) with an equimolar amount of 4-aminoacetophenone to give compound **2** which is considered as an important synthon for the construction of a pyridine ring *via* several synthetic routs. Some compounds were synthesized through formation of the intermediate α,β–unsaturated compounds which, in turn, were allowed to react with malononitrile to give the corresponding alkoxypyridines (**8-17**). Compounds **18-21** were synthesized by a one-pot simple reaction between **2**, the appropriate aldehyde, and malononitrile in sodium alkoxide solution. Moreover, they can be synthesized through reaction of compound **2** and arylidenemalononitrile in sodium alkoxide. The phenoxy analogues were prepared by reaction of **1** with 4-hydroxyacetophenone or 3-hydroxybenzaldehyde to give **22** and **27**, respectively. These compounds, in turn, were allowed to react with malononitrile and the proper carbonyl compound in presence of sodium alkoxide in a one-pot reaction technique to give the target compounds. Biological evaluation of the prepared compounds showed that some of them are potent anticonvulsant agents. The detailed synthesis, spectroscopic and biological data are reported.

(keywords: quinoxaline derivatives, alkoxypyridines, phenylamino and phenoxyquinoxalines, anticonvulsant activity).

Introduction

Despite the availability and optimal use of several antiepileptic drugs, 20-30 % of patients with epilepsy still experience inadequate seizure control. While absence (petit mal) seizures are well-treated in most instances, significant therapeutic improvement is still needed for the treatment of partial-complex (focal) and generalized tonic-clonic (grand-mal) seizures.[1,2] Moreover, antiepileptic drugs may cause burdening adverse effects, such as sedation, teratogenecity, gastrointestinal disturbances, and hepatotoxicity.[3-5] Consequently, new antiepileptic drugs with fewer side effects and lower toxicity are needed.

Many antiepileptic drugs have important structural similarities; the most common structural elements appear to be a nitrogen heterocyclic system with at least one carbonyl group and an aromatic substituent linked to the heterocycle. Moreover, several physicochemical properties, such as lipophilicity, have been associated with anticonvulsant action [6-8] and are related to the ability of the drug to pass the blood brain-barrier in order to reach the site of action. The choice of these compounds appear particularly interesting because there are some suggestions in literature that quinoxaline,[9-11] pyridine[12-14] and aryloxyaryl[15] derivatives show remarkable anticonvulsant activity.

In the course of our approach in synthesizing a new type of anticonvulsant quinoxaline derivatives, we synthesized new compounds in which a quinoxaline moiety, referred to as the proximal ring, substituted in the 2 or 3-position by chloro, oxo and alkoxy groups and attached in the 2 or 3-position to a substituted phenyl moiety, referred to as a distal ring, *via* -NH- or -O-linkage. Whereas the phenyl ring was substituted with formyl, acetyl and substituted propenoyl

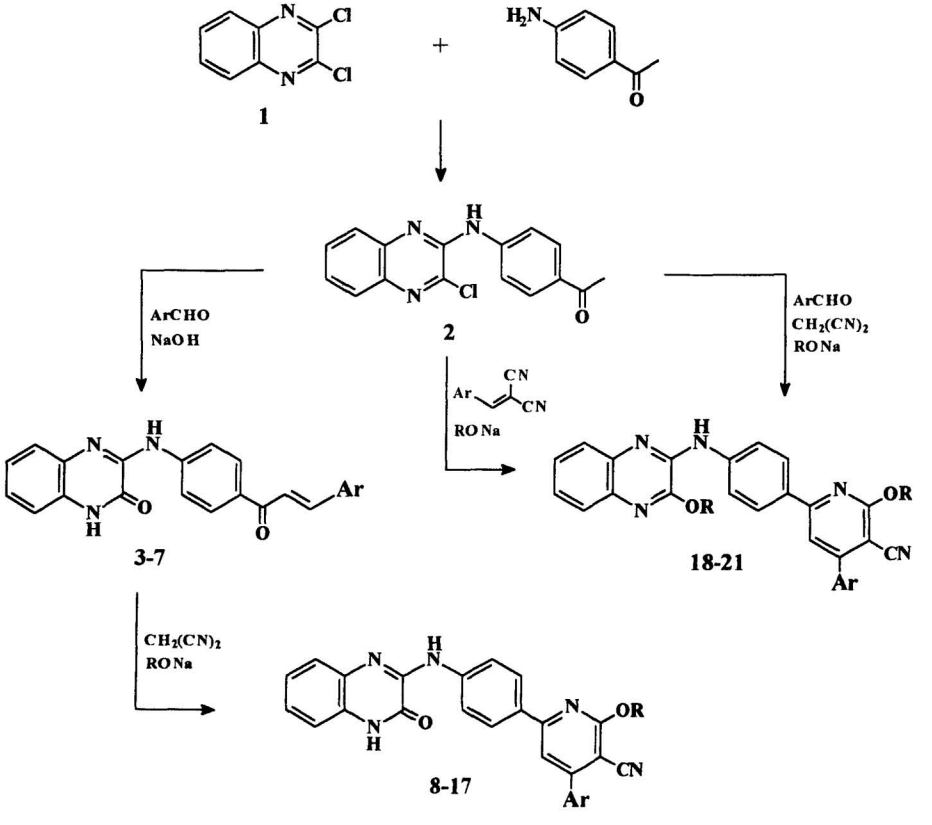
moieties. Moreover, attempts were made to clarify the situation and to test whether modulation of alkoxypyridine moiety could eventually lead to better anticonvulsants with prolonged duration of action.

As a continuation to our previous work[16] on the synthesis of new quinoxaline derivatives and the study of their potential biological activities, we report in this paper the synthesis of a new series of 3-[4-(4,5,6-trisubstituted-2-pyridyl)-phenylamino]-2-oxo-1,2-dihydroquinoxalines **8-17**, 3-alkoxy-2-[4-(4,5,6-trisubstituted-2-pyridyl)-phenylamino]-quinoxalines **18-21**, 3-alkoxy-2-[4-(4,5,6-trisubstituted 2-pyridyl)-phenoxy]-quinoxalines **23-26** and 3-alkoxy-2-[3-(2,3,6-trisubstituted-4-pyridyl)-phenoxy]-quinoxalines **28-31** in order to ascertain which structural features and the attendant functionalities are necessary for their anticonvulsant activities.

Results and Discussion

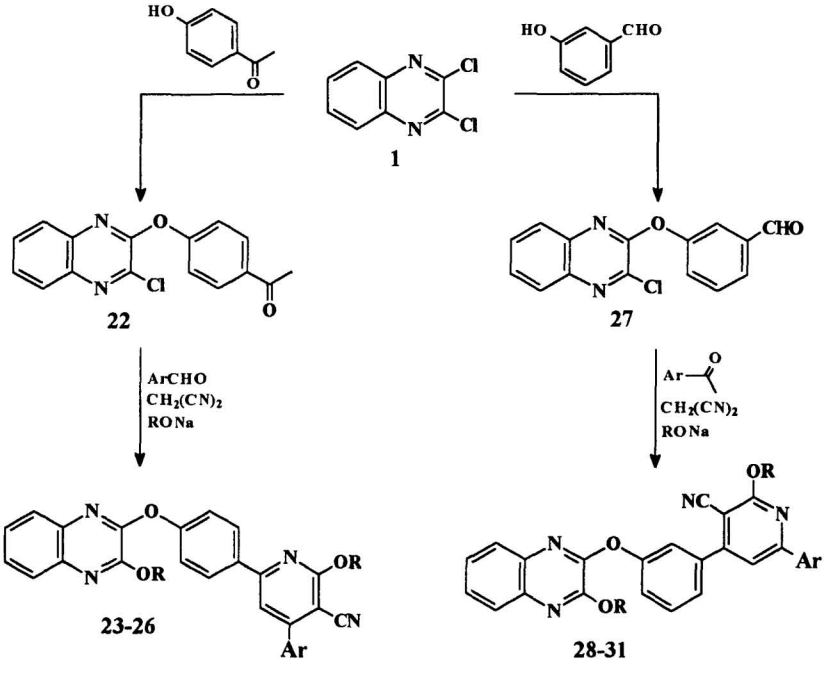
The synthetic approaches to the title compounds were straightforward as illustrated in Schemes I

Scheme I



and II. Reaction of 2,3-dichloroquinoxaline **1**[17] with an equimolar amount of 4-aminoacetophenone in ethanol afforded 2-(4-acetylphenylamino)-3-chloroquinoxaline (**2**). Compound **2** was considered an important synthon for the construction of pyridine ring. The synthesis of 2-alkoxypyridines by the reaction of α,β-unsaturated ketones with malononitrile in sodium alkoxide-alcohol system was reported to give yields of 55-70%.[18] A modified synthesis of 2-alkoxypyridines has been achieved through the reaction of arylidenemalononitriles and aryl methyl ketones at ambient temperature in sodium alkoxide-alcohol system.[19,20] In the present work, 3-[4-(4,5,6-trisubstituted-2-pyridyl)-phenylamino]-2-oxo-1,2-dihydroquinoxalines **8-17** have been synthesized *via* Claisen-Schmidt condensation of **2** and the appropriate aldehyde to afford the corresponding 3-[4-(3-aryl-propenoylphenylamino)-2-oxo-1,2-dihydroquinoxalines **3-7**. The latter was transformed into the desired alkoxypyridines **8-17** (Scheme I) by reaction with malononitrile in sodium alkoxide-alcohol system at ambient temperature. The 3-chloro atom in compound **2** was hydrolyzed to the corresponding oxo derivative by the effect of sodium hydroxide solution used for the formation of the α,β-unsaturated carbonyl compounds, which was confirmed by the presence of ir bands at 1665-1670 cm^{-1} corresponding to COCH=CH and CONH. 3-Alkoxy-2-[4-(4,5,6-trisubstituted-2-pyridyl)-phenylamino]-quinoxalines **18-21**, were synthesized following the two synthetic strategies illustrated in Scheme I. Briefly, a one-pot simple reaction between **2**, the appropriate aldehyde and malononitrile in sodium alkoxide-alcohol system (Method a) gave the target compounds **18-21** in high yields (70-75%).

Scheme II



Moreover, these compounds can be synthesized by condensation of the appropriate aldehyde with malononitrile in base-catalyzed reaction, yielding the corresponding arylidenemalononitrile,[21,22] which was then reacted with compound **2** at room temperature in sodium alkoxide solution (Method b) to give the provided alkoxy-pyridines **18-21** in good yields (65-69%). The formation of alkoxypyridines **8-21** (Scheme I) is assumed to proceed *via* Michael addition of malononitrile to the methyl carbon of the aryl methyl ketone, β-carbon of α,β-unsaturated carbonyl compound to form Michael adduct, followed by cyclization in successive steps and Dimroth rearrangement leading to the formation of alkoxypyridines.

Table 1: Physicochemical data of the new compounds.

Comp.	Ar	R	Mp °C	Yield% (a/b)	Rec. Sol.[c]	Mol. Form.
3	4-Cl-Ph	-	>300	62	E	$C_{23}H_{16}ClN_3O_2$
4	4-Br-Ph	-	250-252	65	M	$C_{23}H_{16}BrN_3O_2$
5	4-NO_2-Ph	-	>300	58	Ac	$C_{23}H_{16}N_4O_4$
6	2,4-$(OMe)_2$-Ph	-	295-297	64	Ac	$C_{25}H_{22}N_3O_4$
7	3,4-$(OMe)_2$-Ph	-	275-277	61	E	$C_{25}H_{22}N_3O_4$
8	4-Cl-Ph	Me	>300	70	Ac	$C_{27}H_{18}ClN_5O_2$
9	4-Cl-Ph	Et	>300	58	A	$C_{28}H_{20}ClN_5O_2$
10	4-Br-Ph	Me	>300	66	M	$C_{27}H_{18}BrN_5O_2$
11	4-Br-Ph	Et	>300	60	E	$C_{28}H_{20}BrN_5O_2$
12	4-NO_2-Ph	Me	>300	55	Ac	$C_{27}H_{18}N_6O_4$
13	4-NO_2-Ph	Et	>300	62	Ac	$C_{28}H_{20}N_6O_4$
14	2,4-$(OMe)_2$-Ph	Me	>300	66	A	$C_{29}H_{23}N_5O_4$
15	2,4-$(OMe)_2$-Ph	Et	>300	68	A	$C_{30}H_{25}N_5O_4$
16	3,4-$(OMe)_2$-Ph	Me	>300	67	E	$C_{29}H_{23}N_5O_4$
17	3,4-$(OMe)_2$-Ph	Et	>300	65	E	$C_{30}H_{25}N_5O_4$
18	4-Cl-Ph	Me	>300	(72/68)	E	$C_{28}H_{20}ClN_5O_2$
19	4-Cl-Ph	Et	>300	(70/69)	E	$C_{30}H_{24}ClN_5O_2$
20	3,4-$(OMe)_2$-Ph	Me	230-232	(73/65)	Ac	$C_{30}H_{25}N_5O_4$
21	3,4-$(OMe)_2$-Ph	Et	170-172	(75/65)	Ac	$C_{32}H_{29}N_5O_4$
23	4-Cl-Ph	Me	210-212	72	E	$C_{28}H_{19}ClN_4O_3$
24	4-Cl-Ph	Et	145-147	69	E	$C_{30}H_{23}ClN_4O_3$
25	4-Br-Ph	Me	258-260	73	M	$C_{32}H_{27}ClN_6O$
26	4-Br-Ph	Et	>300	72	A	$C_{34}H_{32}N_6O$
28	4-Cl-Ph	Me	240-242	75	Ac	$C_{32}H_{27}N_7O_3$
29	4-Cl-Ph	Et	183-185	74	A	$C_{22}H_{12}Cl_2N_4O$
30	4-Br-Ph	Me	275-277	76	Ac	$C_{22}H_{12}BrClN_4O$
31	4-Br-Ph	Et	126-128	73	E	$C_{22}H_{15}ClN_6O$

[a]Yield of method a; [b]Yield of method b, respectively; [c]Rec. Sol., A: Aqueous acetic acid, Ac: Acetone, E: Ethanol, M: Methanol.

On the other hand, compound **2** was used as a precursor for the preparation of phenoxy derivatives (**23-26** and **28-31**) (Scheme II). The general synthesis of these compounds was carried out in a fashion similar to that applied for preparation of the trisubstituted pyridyl phenylaminoquinoxaline derivatives (**18-21**). Treatment of compound **1** with 4-hydroxyacetophenone or 3-hydroxybenzaldehyde gave the corresponding 4- and 3-substituted phenoxyquinoxaline derivatives **22** and **27**, respectively. Reaction of **22** or **27** directly with the appropriate aldehyde or substituted acetophenone and malononitrile in sodium alkoxide solution at room temperature yielded the corresponding compounds **23-26** and **28-31,** respectively.

Anticonvulsant Screening

Biological evaluation of the quinoxaline derivatives was conducted. The test compounds were assessed for their ability to treat two types of induced convulsion, maximal electroshock-induced convulsion (MES) and subcutaneous pentylenetetrazole-induced convulsion (scPTZ). The comp-

Table 2: Anticonvulsant testing data of the quinoxaline derivatives in mice.

Comp.	Time h	Percentage Reduction					
		MES			ScPTZ		
		30	100	300	30	100	300
2	½	0	20	20	0	0	0
	2	0	0	20	0	0	0
4	½	60	60	80	0	40	60
	2	20	40	40	20	40	40
5	½	40	40	60	0	40	40
	2	0	40	20	0	20	20
6	½	20	40	60	0	20	40
	2	0	20	40	0	0	20
8	½	60	60	80	20	20	40
	2	40	40	60	0	0	20
10	½	80	100	80	40	20	40
	2	40	60	60	0	20	20
11	½	60	80	80	40	40	20
	2	20	40	40	0	0	20
18	½	80	80	80	0	20	20
	2	40	60	60	0	20	20
23	½	80	60	80	0	40	20
	2	60	60	60	0	20	20
25	½	80	100	100	60	60	40
	2	60	80	100	40	60	40
26	½	60	60	80	40	20	40
	2	60	40	60	20	20	40
30	½	80	80	100	60	40	40
	2	80	80	100	60	40	60
Phenytoin	½	100	100	100	-	-	-

[a]Mice were injected with doses of 30, 100, and 300 mg/kg of compounds intraperitoneally in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) and were examined after ½ and 2 hours.

ounds were given intraperitoneally to albino mice at three dose levels, 30, 100, and 300 mg/kg applying a procedure previously reported.[23,24] Phenytoin was used as a reference standard. The anticonvulsant screening data are shown in Table 2. Two different linkers to the quinoxaline ring were explored to determine the structural requirements for activity. However, as the data in Table 2 indicate, compounds containing the amine and ether linkers, represented by **18** and **23**, respectively, exhibit more or less comparable anticonvulsant activities. As could be seen in Table 2, lengthening of the simple carbonyl group of compound **2** into aryl enone functionality was fruitful. Thus, compounds **4**, **5**, and **6** show good activity particularly against MES-induced convulsion. However, in the chalcone series, to investigate the effect of substituents on the terminal phenyl ring on biological activity, different derivatives were synthesized where that substituent was varied. Except for the bromophenyl analogue **4**, which is the most active in this series, the other analogues display comparable activities against MES-induced convulsion. This finding indicates that in this series of compounds, the electronic properties of the substituent can vary and still provide favorable activity. Moreover, the increased activity of the bromophenyl derivative might be due to coupling with a distal hydrophobic binding site. Several analogues of compounds were synthesized with a pyridine nucleus to examine its utility in providing desirable activity against convulsion. However, compounds that contain the pyridine moiety generally displayed an increased anticonvulsant activity as compared to those with chalcone structure. Furthermore, changing the 2-oxo group in compound **8** with an alkoxy group as in **18** resulted in a modest increase in the anticonvulsant activity (Table 2). In general, the ethoxy group at the pyridine and quinoxaline rings resulted in a slight drop in the anticonvulsant activity when compared to the analogous methoxy derivatives. This trend can be seen for both ether and amine linkers. On the other hand, in ether linker series, the pyridine nucleus was built up at either the 3- or 4-position of the phenyl ring with concomitant change of the position in pyridine ring attached to the phenyl ring. However, this structural modification provided no substantial change in anticonvulsant activity. In these series of anticonvulsant agents, compounds **25** and **30** possessing *p*-bromophenyl structure with heterocyclic system bearing methoxy groups display the best overall therapeutic profile against both types of induced convulsion.

On the basis of the previous SAR, generally, in the pyridine and enone series, compounds did not possess a polar group on the phenyl ring exhibit better anticonvulsant activities. The most active members of this series have pyridine nucleus attached through an ether or amine linker to the quinoxaline moiety. In addition, methoxy groups as well as bromophenyl residue are needed to afford the maximal anticonvulsant activity.

Experimental

A. Synthesis

Melting points were determined on a Fischer-Johns apparatus and are uncorrected. IR spectra were carried out on a PYE UNICAM SP 1000 spectrophotometer on KBr disk (ν in cm^{-1}). ^{1}H-nmr spectra were recorded on a Varian EM-360 (90 MHz) instrument using TMS as internal standard (chemical shifts in ppm, δ units). The results of elemental analyses (C,H,N) were within $\pm$ 0.4% of the theoretical values. Thin-layer chromatography was performed on silica gel GLF plates, 250 microns.

***2-(4-Acetylphenylamino)-3-chloroquinoxaline* (2)**. A mixture of 2,3-dichloroquinoxaline (**1**) (1.99 g, 0.01 mol), 4-aminoacetophenone (2.02 g, 0.015 mol), and absolute ethanol (10 ml) was heated

under reflux for 6 h. On cooling, the separated precipitate was collected by filtration, dried, and recrystallized from acetone to give 2.23 g (75%) of **2**: mp 220-222 °C. ir (cm^{-1}): 3450 (NH), 1690 (CO). ^{1}H-nmr (DMSO-d_6): 2.35 (s, 3H, CH_3), 8.72 (br s, 1H, NH; D_2O exchangeable), 7.14-8.22 (m, 8H, Ar-H).

3-[4-(3-Arylpropenoyl)-phenylamino]-2-oxo-1,2-dihydroquinoxalines **(3-7)**. A mixture of compound **2** (2.97 g, 0.01 mol) and the appropriate aldehyde (0.01 mol) in ethanolic sodium hydroxide solution (10%, 25 ml) was stirred at ambient temperature for 12 h and allowed to stand overnight. The precipitated solid was collected by filtration, dried, and recrystallized from the suitable solvent. ir, **3**: 3456 (NH), 2960 (=CH), 1665, 1660 (CO). **5**: 3450 (NH), 2980 (=CH), 1668, 1662 (CO). **7**: 3375 (NH), 2982 (=CH), 1675, 1670 (CO). ^{1}H-nmr (DMSO-d_6), **3**: 5.82 (s, 2H, CH=CH), 7.21-8.46 (m, 12H, Ar-H), 8.87 (br s, 1H, NH; D_2O exchangeable), 12.67 (br s, 1H, NH; D_2O exchangeable). **5**: 5.94 (s, 2H, CH=CH), 7.14-8.22 (m, 12H, Ar-H), 9.07 (br s, 1H, NH; D_2O exchangeable), 12.28 (br s, 1H, NH; D_2O exchangeable).

3-[4-(6-Alkoxy-4-aryl-5-cyano-2-pyridyl)-phenylamino]-2-oxo-1,2-dihydroquinoxalines **(8-17)**. To a cooled freshly prepared sodium alkoxide solution (0.017 mol, 0.39 g of sodium in 150 ml absolute ethanol), malononitrile (1.12 g, 0.017 mol) was added with stirring. The appropriate α,β-unsaturated ketone **3-7** (0.017 mol) was then added while stirring at 60 °C for 10 h. The reaction mixture was left overnight, the obtained product was collected by filtration, dried, and recrystallized from the suitable solvent. ir, **8**: 3450 (NH), 2220 (CN), 1668 (CO). **11**: 3420 (NH), 2225 (CN), 1668 (CO). **17**: 3395 (NH), 2225 (CN), 1665 (CO). ^{1}H-nmr (DMSO-d_6), **8**: 4.82 (s, 3H, CH_3), 7.22-8.31 (m, 13H, Ar-H), 8.79 (br s, 1H, NH; D_2O exchangeable), 12.58 (br s, 1H, NH; D_2O exchangeable). **11**: 1.01 (t, 3H, CH_3), 4.62 (q, 2H, CH_2), 7.41-8.23 (m, 13H, Ar-H), 8.78 (br s, 1H, NH; D_2O exchangeable), 12.91 (br s, 1H, NH; D_2O exchangeable).

3-Alkoxy-2-[4-(6-alkoxy-4-aryl-5-cyano-2-pyridyl)-phenylamino]-quinoxalines **(18-21).**
Method a. To a cooled freshly prepared sodium alkoxide solution (0.04 mol, 0.92 g of sodium in 150 ml absolute methanol or ethanol) was added a mixture of compound **2** (5.95 g, 0.02 mol), malononitrile (1.32 g, 0.02 mol), and the appropriate aldehyde (0.02 mol) in absolute methanol or ethanol (40 ml), respectively, with continuous stirring for 8-10 h. The precipitated solid was collected by filtration, dried, and recrystallized from the suitable solvent. ir, **18**: 3385 (MH), 2220 (CN). **20**: 3411 (NH), 2221 (CN). **21**: 3530 (NH), 2223 (CN). ^{1}H-nmr (DMSO-d_6), **18**: 3.92 (s, 6H, CH_3), 7.11-8.19 (m, 13H, Ar-H), 8.91 (br s, 1H, NH; D_2O exchangeable). **20**: 3.75 (s, 6H, CH_3), 4.12 (s, 6H, CH_3), 7.00-8.12 (m, 12H, Ar-H), 8.66 (br s, 1H, NH; D_2O exchangeable).
Method b. Substituted benzylidenemalononitrile (0.02 mol) was added while stirring to a cooled freshly prepared sodium alkoxide solution (0.04 mol, 0.92 g of sodium in 150 ml absolute ethanol or methanol). Compound **2** (5.95 g, 0.02 mol) was then added and stirring was continued at ambient temperature for 8 h. The precipitate was collected by filtration, dried, and recrystallized from the suitable solvent.

2-(4-Acetylphenoxy)-3-chloroquinoxaline **(22).** A mixture of 2,3-dichloroquinoxaline (**1**) (1.99 g, 0.01 mol), 4-hydroxyacetophenone (1.36 g, 0.01 mol), and anhydrous potassium carbonate (3.18 g, 0.03 mol) in absolute ethanol (50 ml) was stirred for 20 h. The reaction mixture was allowed to stand overnight at room temperature, the solid separated was collected by filtration and recrystallized from ethanol to yield 1.97 g (66%) of **22**, mp 138-140 °C. ir: 1667 (CO). ^{1}H-nmr (DMSO-d_6): 2.42 (s, 3H, CH_3), 7.12-8.10 (m, 8H, Ar-H).

3-Alkoxy-2-[4-(6-alkoxy-4-aryl-5-cyano-2-pyridyl)-phenoxy]-quinoxalines **(23-26).** These compounds were prepared as described in method a for preparation of compounds **18-21** except that compound **22** (5.97 g, 0.02 mol) was used instead of compound **2**. ir, **23**: 2219 (CN). **25**: 2221 (CN). ^{1}H-nmr (DMSO-d_6), **23**: 4.11 (s, 6H, CH_3), 7.23-8.12 (m, 13H, Ar-H). **25**: 4.25 (s, 6H, CH_3), 7.12-8.22 (m, 13H, Ar-H). **26**: 1.12 (t, 6H, CH_3), 4.19 (q, 4H, CH_2), 7.10-8.23 (m, 13H, Ar-H).

3-Chloro-2-(3-formylphenoxy)-quinoxaline **(27).** This compound was prepared by the same procedure described for preparation of compound **22** except that 3-hydroxybenzaldehyde (1.22 g, 0.01 mol) was used instead of 4-hydroxyacetophenone. The product was recrystallized from aqueous acetone to yield 1.65 g (58%) of **27**, mp 160-162 °C. ir: 2739, 2827 (=CH), 1700 (CO). ^{1}H-nmr (DMSO-d_6): 7.11-8.04 (m, 8H, Ar-H), 9.10 (s, 1H, CHO).

3-Alkoxy-2-[3-(2-alkoxy-6-aryl-3-cyano-4-pyridyl)-phenoxy]-quinoxalines **(28-31).** Compounds **28-31** were prepared by the same procedure described for preparation of compounds **23-26** except that compound **27** (5.69 g, 0.02 mol) was used instead of **22** and substituted acetophenone (0.02 mol) was used instead of the substituted aldehydes. ^{1}H-nmr (DMSO-d_6), **28**: 4.19 (s, 6H, CH_3), 7.22-8.34 (m, 13H, Ar-H). **31**: 1.10 (t, 6H, CH_3), 4.11 (q, 4H, CH_2), 7.13-8.16 (m, 13H, Ar-H).

B. Anticonvulsant Screening

Maximal electroshock seizure test and pentylenetetrazole test were carried out for testing anticonvulsant activities using groups of albino mice in the 20-25 g weight range, 5 mice each. Each compound suspended in 0.5% carboxymethylcellulose (CMC) was administered intraperitoneally at three dose levels (30, 100, and 300 mg/kg).

Maximal electroshock seizures (MES) were induced 30 min after administration of the compound by application of a 60-Hz current of 50 mA for 0.2 s *via* corneal electrode into the eyes. The protection was defined as the abolition of hind-leg tonic maximal extension component of the seizure.

The subcutaneous pentylenetetrazole seizure threshold test (sc-PTZ) was carried out by an intraperitoneal administration of pentylenetetrazole (85 mg/kg). Animals were observed over 2 h. Failure to observe the generalized clonic seizure is defined as protection.

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