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PART I: NOVEL QUINOXALINE DERIVATIVES OF BIOLOGICAL INTEREST

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يشتمل هذا البحث على تحضير سلسلتين من مركبات الكينوكزالين الجديدة: السلسلة الأولى عبارة عن مركبات ٢-مستبدل أمينو-٣-(١-بيرازوليل) كينوكزالين (٤-١١) وذلك بتفاعل ٢-كلورو-٣-هيدرازينو كينوكزالين (١) مع أسيتيل أسيتون وبنزويل أسيتون يلى ذلك معالجة ناتج التفاعل مع بعض الأمينات الثنائية. أما السلسلة الثانية وهى عبارة عن مركبات ٤-(بيبرازينيل)تيترازولو[١و٥-أ] كينوكزالين (١٩-٢٤) فقد أمكن الحصول عليها بتفاعل المركب (١) مع حمض النيتروز ويلى ذلك معالجة الناتج وهو ٤-كلوروتيترازولو[١و٥-أ] كينوكزالين (١٨) مع ١-مشتق ببرازين. وبتفاعل مركب (١) مع حمض بيروفيك فقد أمكن الحصول علي الهيدرازون المقابل والذى بدوره تم حلقنته إلى [١و٢و٤] ترايازينو[٤و٣-أ] كينوكزالين (١٧) مستخدما ثلاثى أوكسيد الفوسفور. وقد تم التعرف على المركبات الجديدة فى هذا البحث بالتحاليل الدقيقة والأشعة تحت الحمراء والرنين النووى المغناطيسى.

تم فى هذا البحث أيضا قياس فاعلية بعض المركبات المشيدة الجديدة كمضادات للاكتئاب وقد أظهرت النتائج السلوكية أو البيوكيميائية فاعلية هذه المركبات وخاصة المركب (٤).

*2-Substituted amino-3-(1-pyrazolyl)quinoxalines **4-11** were prepared by reacting 2-chloro-3-hydrazinoquinoxaline **1** with 1,3-dicarbonyl compounds followed by treatment of the resulting 2-chloro-3-(1-pyrazolyl)quinoxlines **2,3** with the proper 2° amine. Reacting **1** with pyruvic acid or its ethyl ester afforded the corresponding hydrazone. Upon treating the hydrazone **15** with $POCl_3$, the corresponding [1,2,4]triazino[4,3-a] quinoxaline **17** was achieved. Further, a series of 4-(piperazinyl) tetrazolo[1,5-a]quinoxalines **19-24** was prepared by reacting **1** with nitrous acid followed by treatment of the resulting 4-chlorotetrazolo[1,5-a]quinoxalines **18** with 1-substituted piperazines. Biological testing of some of the prepared compounds revealed that these compounds may have antidepressant activity and compound **4** has the most pronounced effect.*

INTRODUCTION

Antidepressants may be conveniently classified into three main categories: the monoamine oxidase (MAO) inhibitors, the tricyclic antidepressants (TCAs) and clinically similar drugs and the serotonin-selective reuptake inhibitors. The main side effects associated with the antidepressant drugs especially MAO inhibitors are their cardiotoxicity, slow of action and anticholinergic effects.[1] These undesirable actions prompted research workers to develop new antidepressants, with the hope to be more safe and rapid in their onset.

In the past few years, attention has been given to quinoxaline derivatives as antidepressant agents.[2-5] Piperazinylquinoxalines were found to inhibit 5-hydroxytryptamine (5-HT), that may be involved in the mechanism of action of antidepressants.[6] Further, [1,2,4]triazolo[4,3-a] quinoxalines have been found to possess antidepressant activity with rapid onset of action.[2-5]

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In the light of the afore-mentioned knowledge, it was designed to synthesize two quinoxaline derivatives, namely, 2-amino-3-(1-pyrazolyl)quinoxalines **4-11** and 4-piperazinyltetrazolo[1,5-a]quinoxalines **19-24** with the aim of evaluating their antidepressant activity.

EXPERIMENTAL

A) Chemistry

Melting points were determined on Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed at the Microanalytical Center, Cairo University. The IR spectra were recorded on Shimadzu IR 435 Spectrophotometer. The PMR were obtained on Jeol FX 90 Q Spectrometer with TMS as internal reference and with solvents as indicated. The chemical shifts are reported in ppm and are given in δ units.

2,3-Dichloroquinoxaline,[5] 2-Chloro-3-hydrazinoquinoxaline[5] **(1)**, and 2-Chloro-[1,2,3.4] tetrazolo[1,5-a]quinoxaline[7] **(18)** were prepared according to reported methods.

2-Chloro-3-(3-methyl-5-substituted-1-pyrazolyl)quinoxalines

General procedure

Equimolecular of 2-chloro-3-hydrazinoquinoxaline **1** (0.79 g, 4 mmole) and the appropriate 1,3-dicarbonyl compound were heated under reflux in ethanol (20 ml) for 3 hr. After cooling, the precipitate was filtered and recrystallized from ethanol.

2-Chloro-3-(3,5-dimethyl-1-pyrazolyl)-quinoxaline (2)

This compound was obtained in yield: 0.8 g (77%), m.p: 112-114°. Anal. Calcd. for $C_{13}H_{11}ClN_4$ (258.5): C, 60.34, H, 4.25, N, 21.66, Found: C, 60.10, H, 3.90, N, 21.90. IR (KBr, ν cm^{-1}): 1665, 1655, 1640 (C=N), 1560, 1480 (aromatic ring stretching), 760 (C-Cl).

2-Chloro-3-(3-methyl-5-phenyl-1-pyrazolyl) quinoxaline (3)

This compound was obtained in yield: 1.0 g (80%,), m.p: 120-122°. Analysis Calcd. for $C_{18}H_{13}ClN_4$ (320.5): C, 67.39; H, 4.05; N, 17.47. Found, C, 67.10; H, 3.70; N, 18.00. IR (KBr, ν cm-1): 1665, 1640 (C=N), 1560, 1500 (aromatic ring stretching), 760 (C-Cl).

2-Substituted amino-3-(3-methyl-5-substituted-1-pyrazolyl)quinoxalines (4-11)

General procedure

A mixture of **2-3** (2 mmole) and the appropriate amine (2.4 mmole) was heated under reflux in ethanol (10 ml) for 6 hr. The reaction mixture was reduced to half its volume under diminished pressure and then poured onto ice-cold water (30 ml). The solution was twice extracted with methylene chloride (20 ml). The organic layer was dried ($MgSO_4$), evaporated under reduced pressure and the residue was recrystallized from CH_2Cl_2/petroleum ether (60/80) (Table I).

PMR (DMSO-d_6, δ = ppm) for compound (4): 2.5 (s, 6H, $2CH_3$), 3.2 (t, 4H, $N(CH_2)_2$), 3.8 (t, 4H, $O(CH_2)_2$), 6.4 (s, 1H, pyrazole C_4-H), 7.6-8.4 (m, 4H, Ar-H).

PMR (DMSO-d_6, δ = ppm) for compound (8): 2.55 (s, 3H, CH_3), 2.9 (t, 4H, $N(CH_2)_2$), 3.5 (t, 4H, $O(CH_2)_2$), 6.75 (s, 1H, pyrazole C_4-H), 7.4-8.5 (m, 9H, Ar-H).

2-Chloro-3-(5-hydroxy-3-methyl-1-pyrazolyl)quinoxaline (12)

A molar equivalent of **1** (0.99 g, 5 mmole) and ethyl acetoacetate (0.65 g, 5 mmole) in ethanol (15 ml), containing two drops of glacial acetic acid, was refluxed for 5 hr. Most of the solvent was evaporated at reduced pressure and the residue was crystallized from ethanol/benzene (2:1) to give pale yellow crystals, yield: 1.0 g (81%), m.p: 265-267°. Anal. Calcd. for $C_{12}H_9ClN_4O$ (260.5): C, 55.27, H, 3.45, N, 21.49. Found, C, 55.20, H, 3.50, N, 21.70. IR (KBr, ν cm^{-1}): 3400-2600 (O-H, hydrogen bonding), 1600, 1480 (aromatic ring stretching). PMR (DMSO-d_6, δ = ppm): 2.7 (s, 3H, CH_3), 7.0 (s, 1H, pyrazole C_4-H), 7.3-8.5 (m, 4H, Ar-H), 12.0 (br s, 1H, OH, D_2O exchange).

Table I: Physical and Analytical Data of 2-Substituted amino-3-(3-methyl-5-substituted-1-pyrazolyl)quinoxalines (4-11).

Compd. No.	R^1	*R^2	M.p. °C	Yield %	Mol. Form. (mol. wt.)	Analysis, % Calcd./Found		
						C	H	N
4	Me	A	135-137	67	$C_{17}C_{19}N_5O$ (309)	66.01 66.50	6.14 6.30	22.65 22.10
5	Me	B	237-239	83	$C_{18}C_{21}N_5$ (307)	70.35 69.90	6.84 6.50	22.80 23.20
6	Me	C	112-113	85	$C_{17}C_{19}N_5$ (293)	69.62 70.10	6.48 6.80	23.89 23.60
7	Me	D	110-111	45	$C_{17}C_{21}N_5$ (295)	69.15 69.30	7.11 6.90	23.72 24.10
8	Ph	A	190-192	75	$C_{22}C_{21}N_5O$ (371)	71.15 71.10	5.66 5.40	18.86 19.20
9	Ph	B	230-232	80	$C_{22}C_{23}N_5$ (369)	74.79 75.20	6.23 6.20	18.97 19.00
10	Ph	C	188-190	85	$C_{22}C_{21}N_5$ (355)	74.36 73.90	5.91 5.70	19.71 20.10
11	Ph	D	107-108	83	$C_{22}C_{23}N_5$ (357)	73.94 73.80	6.44 6.80	19.60 19.70

*A = morpholinyl, B = piperidyl, C = pyrrolidinyl, D = diethylamino

2-Chloro-3-[5-hydroxy-4-(2-hydroxyethyl)-3-methyl-1-pyrazolyl]quinoxaline (13)

A molar equivalent of **1** (0.99 g, 5 mmole) and α-ethoxalyl-γ-butyrolactone (0.64 g, 5 mmole) in ethanol (10 ml), containing two drops of glacial acetic acid, was refluxed for 30 min. Most of the solvent was evaporated at reduced pressure and the residue was crystallized from ethanol/benzene (2:1) to give pale yellow crystals, yield: 1.20 g (82%), m.p: 270-272°. Anal. Calcd. for $C_{14}H_{13}ClN_4O_2$ (304.5): C, 55.17, H, 4.26, N, 18.39. Found: C, 55.30, H, 4.40, N, 18.10. IR (KBr, ν cm^{-1}): 3400-2600 (O-H, hydrogen bonding), 1600 (aromatic ring stretching and C=N). PMR (DMSO-d_6, δ = ppm): 2.6 (s, 3H, CH_3), 3.2-3.8 (broad m., 4H, 2 CH_2), 6.8-8.2 (m, 4H, Ar-H).

2-Chloro-3-[3-ethoxycarbonyl-5-hydroxy-4-(2-hydroxyethyl)-1-pyrazolyl] quinoxaline (14)

A molar equivalent of **1** (0.99 g, 5 mmole) and α-ethoxalyl-γ-butyrolactone (0.93 g, 5 mmole) in ethanol (10 ml), containing two drops of glacial acetic acid, was refluxed for 30 min. Most of the solvent was evaporated at reduced pressure and the residue was crystallized from benzene to give pale yellow crystals, yield: 1.35 (75%), m.p: 150-152°, Anal. Calcd. for $C_{16}H_{15}ClN_4O_4$ (362.5): C, 52.96, H, 4.13, N, 15.44. Found: C, 53.30, H, 3.90, N, 15.60.

IR (KBr, ν cm^{-1}): 3250-2600 O-H, hyderogen bonding), 1760 (C=O ester), 1600 (aromatic ring stretching and C=N). PMR (DMSO-d_6, δ = ppm): 1.4 (t, 3H, CH_3). 3.2-3.8 (m, 4H, $2CH_2$), 4.6 (q, 2H, CH_2), 7.0-8.1 (m, 4H, Ar-H), 13.2 (s, 1H, OH, D_2O exchange).

2-(2-Chloroquinoxalin-3-ylhydra-zono)-propanoic acid (15)

A mixture of equimolecular amounts of **1** (0.99 g, 5 mmole) and pyruvic acid (0.44 g, 5 mmole) in ether (100 ml), containing 5 drops of glacial acetic acid, was stirred at room temperature for 8 hr. The solvent was evaporated at reduced pressure and the separated colourless crystals were filtered and crystallized from CH_2Cl_2/petroleum ether (60/80), yield: 0.70 g (55%), m.p: 168-170°, Anal. Calcd. for $C_{11}H_9ClN_4O_2$ (264.5): C, 49.90, H, 3.40, N, 21.17. Found: C, 50.20, H, 3.60, N, 21.20. IR (KBr, ν cm^{-1}): 3300-2800 (N-H/O-H, hydrogen bonding),1690 (C=O acid), 770 (C-Cl). PMR ($CDCl_3$, δ = ppm): 2.4 (s, 3H, CH_3),7.6-8.3 (m, 4H, Ar-H), 9.10 (s broad, 1H, NH, D_2O exchange).

Ethyl 2(2-Chloroquinoxalin-3-ylhydrazono)-propanoate (16)

An equimolecular mixture of **1** (0.99 g, 5 mmole) and ethyl pyruvate (0.58 g, 5 mmole) in ether (100 ml), containing 5 drops of glacial acetic acid, was stirred at room temperature for 12 hr. The solvent was evaporated at reduced pressure and the separated pale yellow crystals were filtered and crystallized from CH_2Cl_2/petroleum ether (60/80), yield: 1.3 g (87%), m.p: 105-106°, Anal. Calcd. for $C_{13}H_{13}ClN_4O_2$ (292.5): C, 53.33, H, 4.44, N, 19.14. Found: C, 53.50, H, 4.40, N, 19.50. IR (KBr, ν cm^{-1}): 3250 (N-H), 1780 (C=O ester), 1640 (C=N), 760 (C-Cl).

5-Chloro-2-methyl-1-oxo-[1,2,4]triazino[4,3-a]quinoxaline (17)

A mixture of **15** (0.53 g, 2 mmole) and $POCl_3$ (10 ml) was refluxed for 30 min. The excess $POCl_3$ was distilled under diminished pressure and the residue was carefully decomposed with ice cold water. The precipitate was filtered, washed with water, air dried and crystallized from benzene/petroleum ether (60/80) 2:1 ratio, yield: 0.3 g (68%), m.p: > 300°. Anal. Calcd. for $C_{11}H_7ClN_4O$ (246.5): C, 53.54, H, 2.83, N, 22.71. Found, C, 53.70, H, 3.20, N, 22.40. IR (KBr, ν cm^{-1}): 1695 (C=O), 760 (C-Cl). PMR (DMSO-d_6, δ = ppm): 2.6 (s, 3H, CH_3), 8.0-8.3 (m, 3H, Ar-H), 9.7-9.9 (m, 1H, Ar-H at C-10).

2-(4-N-Substituted piperazinyl)-[1,2,3,4]-tetrazolo[1,5-a]quinoxalines (19-24)

A molar equivalent of **18** (0.41 g, 2 mmole) and the appropriate N-substituted piperazine (4 mmole) in DMF (10 ml) was heated under reflux for 1 hr. After cooling, the reaction mixture was poured onto ice-cold water. The obtained product was filtered and recrystallized twice from CH_2Cl_2/petroleum ether (40/60) 2:1 ratio, Table II. IR (KBr, ν cm^{-1}): 2900-2700 (C-H aliphatic), 1590-1510 (aromatic ring stretching), PMR ($CDCl_3$, δ = ppm) for compound **20**: 3.3-3.6 (m, 4H, $N(CH_2)_2$), 4.6-4.8 (m, 4H, $N(CH_2)_2$), 7.2-7.8 (m, 8H, Ar-H).

B) Pharmacological study

a) Behavioral study

Adult albino mice (n = 168) weighing 20-25 g were used. Mice were divided into groups of 12 animals. The test compounds **4**, **8**, **13**, **17** and **21** were suspended in 2% tween 80 and administered orally to groups of 12 mice at dose of 10 mg/kg. One hour after administration of the test compound or the reference compound (amineptine hydrochloride), the mice were subjected to staircase test or open-field test to measure the antidepressant activity. A control group received only the solvent and was run parallel with the treated group.

The staircase test was carried out according to the method of Simiand *et al.*[8] The apparatus consists of a white PVC enclosure with a five identical steps 2.5 cm high, 10 cm wide and 7.5 cm deep. The internal heights are constant along the whole length of the staircase. The box was placed in a room with constant lighting and isolated from external noise. Animals were

Table II: Physical and Analytical data of 2-(4-N-Substituted piperazinyl)- [1,2,3,4]tetrazolo-[1,5-a] quinoxalines (**19-24**).

Compd. No.	R_5	M.p. °C	Yield %	Mol.Form. (mol.wt.)	Analysis, % Calcd./Found		
					C	H	N
19	C_6H_5	212-214	79	$C_{18}H_{17}N_7$ (331)	65.25 64.80	5.13 5.00	29.60 29.60
20	2-Cl-C_6H_4	140-142	65	$C_{18}H_{16}ClN_7$ (365.5)	59.09 59.00	4.37 4.70	26.81 26.30
21	4-Cl-C_6H_4	182-184	60	$C_{18}H_{16}ClN_7$ (365.5)	59.09 58.60	4.37 4.70	26.81 27.20
22	2-EtO-C_6H_4	158-160	55	$C_{20}H_{21}N_7O$ (375)	64.00 63.90	5.60 5.40	26.13 26.10
23	CH_2-C_6H_4	118-119	42	$C_{19}H_{19}N_7$ (345)	66.08 66.40	5.50 5.80	28.40 28.10
24	$(CH_2)_2$-C_6H_4(2-CF_3)	128-130	75	$C_{21}H_{20}F_3N_7$ (427)	59.01 58.80	4.68 5.10	22.95 22.70

placed singly on the floor of the box. The number of steps climbed and rearing were counted over a 3 minutes period. The effect on climbing and rearing represents a definite effect on the behavior of the animal.

The open-field test was done according to the method of DeAngelis.[9] The apparatus consists of a wooden box (60 x 60 x 30 cm) with red sides and white floor. The field was divided into 16 equal squares (15 x 15 cm) by black lines. Two behavioral parameters were measured, ambulation and rearing.

b) Biochemical study

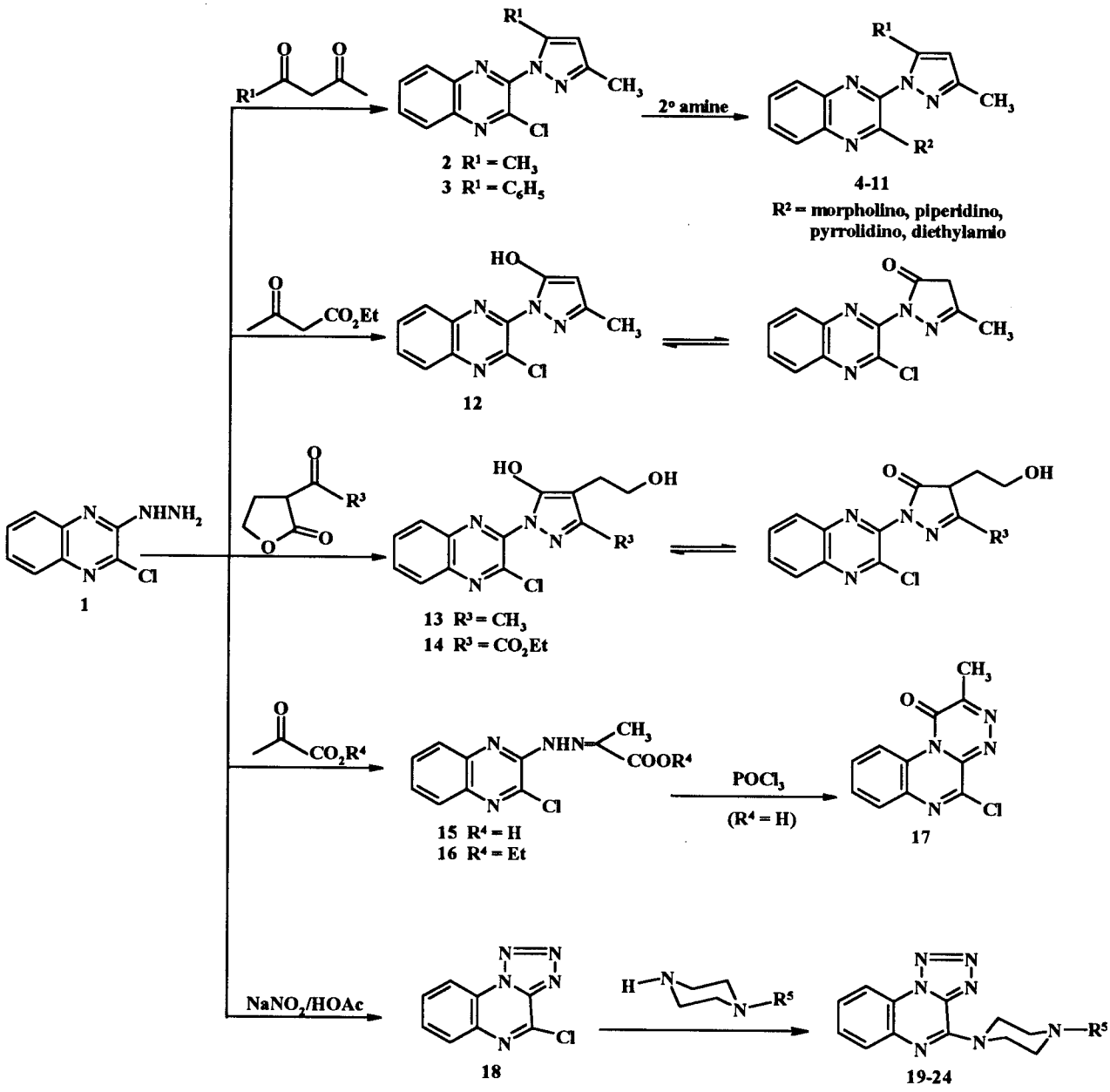
After the behavioral test (staircase) was performed, the animals in each group were decapitated and the brains were removed (in ice/acetone mixture) for the determination of norepinephrine and dopamine in different brain regions, namely: cerebral cortex, thalamus and hypothalamus, midbrain, m, pons and cerebellum. The four regions were separated according to the method described by Glowinski and Iversen.[10] The method reported by Ciarlone[11] was used for the estimation of norepinephrine and dopamine. The norepinephrine was assayed by fluorescence at 380 nm for excitation and 480 nm for emission. The dopamine was assayed spectrofluorometrically at 320 nm for excitation and 475 for emission.

All values in this work are presented as mean ± SEM. Significance of difference between means was tested by student's t-test.[12]

RESULTS AND DISCUSSION

A) Chemistry

Synthesis of the desired quinoxaline derivative was successfully achieved as outlined in Scheme 1. 2-Chloro-3-hydrazinoquinoxalines[5] **1** was prepared by hydrazinolysis of 2,3-dichloroquinoxaline with hydrazine hydrate under the specified conditions. The reaction of **1** with 1,3-dicarbonyl compounds, namely; acetylacetone and benzoylacetone afforded the corresponding 2-chloro-3-pyrazolylquinoxalines **2** and **3** respectively. Amination of the latter compounds with some 2° amines yielded the corresponding 2-substituted aminoquinoxalines **4-11**. The 3-pyrazolyl derivatives **12-14** were obtained by treating of **1** with ethyl acetoacetate, α-acetyl-γ-butyrolactone and α-ethoxalyl-γ-butyrolactone respectively. Compounds **12-14** were expected to exist as an equilibrium mixture of 5-pyrazolinones and 5-hydroxypyrazoles.[13,14]


2 R¹ = CH3
3 R¹ = C6H5
2° amine
4-11
R² = morpholino, piperidino, pyrrolidino, diethylamio
12
13 R³ = CH3
14 R³ = CO2Et
15 R⁴ = H
16 R⁴ = Et
POCl3
(R⁴ = H)
17
NaNO2/HOAc
18
19-24
1

Scheme 1

However, their spectral data were in agreement with 5-hydroxypyrazoles only. The IR spectra which revealed broad O-H stretching absorption bands due to inter- and intramolecular hydrogen bonding around 3400-2600 cm^{-1}. The possibility of tautomerism of these compounds was excluded since no signal for methylene protons was observed in the PMR spectrum of compound **12** and also no signal for methine proton for compounds **13** and **14**. On the other hand, compound **1** was allowed to react with pyruvic acid and its ethyl ester to furnish the corresponding hydrazones **15** and **16** respectively. The cyclization of **15** into 5-chloro-2-methyl-1-oxo-[1,2,4]triazino[4,3-a]quinoxaline **17** was successful only when $POCl_3$ was used as the cyclizing agent. The disappearance of the broad band due to N-H/O-H association in the IR spectrum of **15** and the appearance of multiplet signal integrated for one proton in the position-10 at δ 7.9-9.9 ppm in the PMR spectrum is indicative for success of cyclization. The anomalous high δ value may be attributed to the additional anisotropic effect produced by the C=O group. Moreover, when compound **1** was allowed to react with nitrous acid, 4-chloro-[1,2,3,4]tetrazolo [1,5-a]quinoxaline **18** was obtained in a reasonable yield. Amination of the latter with some 1-N-substituted piperazines afforded the corresponding piperazino-quinoxalines **19-24**.

B) Biological study

Five of the prepared compounds **4**, **8**, **13**, **17** and **21** were tested for antidepressant activity and the results obtained revealed that:

a) Behavioural study

In staircase test, the activity of 12 untreated mice showed that the number of steps climbed (means $\pm$ SEM = 19.6 ± 1.19) and the number of rearing (17.01 ± 0.64) were close to each other. The behaviour of untreated mice was very stable and we did not observe any statistical significant differences in activity from one experiment to another (Table III). Amineptine in a dose of 10 mg/kg, administered orally, significantly decreased the rearing and the steps climbed by 35% and 40% respectively from control value. All the tested compounds produced a parallel reduction in both behavioural variables. Compound **4** produced a marked reduction of rearing and steps climbed (85% and 60%). The majority of non anoxiolytic drugs like imipramine, amitriptylene and amineptine (antidepressants), amphetamine and morphine produced a progressive and simultaneous reduction of both the steps climbed and rearing.

The results using open-field test[9] clearly show that the acute treatment with amineptine or the test compounds induce an increase in locomotor activity and rearing. The mechanism underlying this increase in locomotor activity has been investigated and have demonstrated that amineptine acts specifically on the increase of dopamine release at synaptic level. Amineptine affects the mesolimbic and mesocortical dopaminergic pathways that control mood and behavioral changes, alertness and vigilance.[15,16] The results of the test compounds by open-field test were illustrated in (Table IV). All the test compounds produced a parallel increase in both behavioural variables.

b) Biochemical study

The effect of amineptine and the test compounds on dopamine and norepinephrine content in different brain areas (Table V) showed that amineptine (10 mg/kg) produced a significant increase in dopamine content in cerebral cortex, thalamus and hypothalamus and midbrain by 30%, 80% and 30%, respectively, while test compounds **4**, **8**, **13** and **21** caused a significant increase in dopamine content in thalamus and hypothalamus by 60%, 40%, 30% and 40%, respectively. No significant effect was observed on norepinephrine content in all areas studied.

From the behavioral and biochemical studies for the synthesized compounds, we expect that these compounds may have antidepressant activity and compound **4** has the most pronounced effect.

Table III: Effect of test compounds on rearing and step-climbing activity of mice in the staircase test.

Treatment	Rearing mean ± SEM	Steps-climbed mean ± SEM
Control	17.01 ± 0.64	19.60 ± 1.19
Amineptine (10 mg/kg)	11.10 ± 2.62*	12.00 ± 2.86*
4	2.40 ± 0.31*	8.00 ± 0.89*
8	7.60 ± 1.90*	11.00 ± 1.60*
13	3.75 ± 2.40*	8.16 ± 1.09*
17	5.30 ± 0.60*	9.80 ± 1.08*
21	4.00 ± 0.81*	10.60 ± 1.60*

Each value is the mean of 12 experiments

*Significantly different from control at $P \leq 0.05$

Table IV: Acute effect of test comounds on rearing and ambulation of mice in the openfield test.

Treatment	Rearing mean ± SEM	Steps-climbed mean ± SEM
Control	11.25 ± 0.55	26.00 ± 1.80
Amineptine (10 mg/kg)	30.00 ± 6.80*	114.3 ± 8.20*
4	21.30 ± 4.20*	93.60 ± 4.17*
8	25.60 ± 0.89*	87.66 ± 6.76*
13	17.00 ± 3.11*	59.33 ± 3.73*
17	13.00 ± 2.56*	32.66 ± 6.40*
21	16.60 ± 1.60*	37.38 ± 3.80*

Each value is the mean of 12 experiments

*Significantly different from control at $P \leq 0.05$

Table V: Effect of amineptine (10 mg/kg) and tested compounds (10 mg/kg) on NE, DA contents ($\mu g g^{-1}$ wet wt) in different areas of mouse brain (mean ± SEM, n = 6).

	Mouse Brain Area							
	Cerebral cortex		Thalamus and hypothalamus		Midbrain		Medulla, pons and cerebellum	
	NE	DA	NE	DA	NE	DA	NE	DA
Control	0.32 ± 0.018	0.65 ± 0.04	0.39 ± 0.028	0.50 ± 0.04	0.24 ± 0.018	0.39 ± 0.03	0.17 ± 0.016	0.31 ± 0.021
Amineptine	0.39 ± 0.031	0.84 ± 0.06*	0.34 ± 0.05	0.90 ± 0.051*	0.30 ± 0.02	0.50 ± 0.04*	0.20 ± 0.021	0.35 ± 0.039
4	0.31 ± 0.039	0.74 ± 0.05	0.29 ± 0.031	0.80 ± 0.07*	0.31 ± 0.04	0.50 ± 0.04*	0.18 ± 0.02	0.35 ± 0.05
8	0.29 ± 0.040	0.71 ± 0.04	0.32 ± 0.04	0.70 ± 0.08*	0.29 ± 0.02	0.41 ± 0.039	0.21 ± 0.03	0.34 ± 0.04
13	0.35 ± 0.040	0.69 ± 0.00	0.35 ± 0.035	0.65 ± 0.04*	0.33 ± 0.03	0.40 ± 0.03	0.16 ± 0.04	0.33 ± 0.08
17	0.29 ± 0.030	0.65 ± 0.03	0.36 ± 0.04	0.60 ± 0.18	0.29 ± 0.017	0.33 ± 0.02	0.15 ± 0.08	0.29 ± 0.07
21	0.32 ± 0.040	0.65 ± 0.03	0.38 ± 0.05	0.70 ± 0.069*	0.22 ± 0.018	0.37 ± 0.03	0.18 ± 0.07	0.34 ± 0.06

* Significantly different from control at $P \leq 0.05$.

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