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Original Article

Synthesis, Antinociceptive, Antiinflammatory and Antiepileptic Evaluation of Some Novel Indeno[1, 2-b] Quinoxalin-11-ylidenamines

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Abstract

A series of novel indeno[1, 2-b]quinoxalin-11-ylidenamines 2-9 have been synthesized via condensation of indane[1, 2-b]quinoxalin-11-one (1) with various primary aromatic amines in presence of AcOH for 3 h. Compound 1 was synthesized by condensation of indane-1,2,3-trione with benzene-1,2-diamine in presence of AcOH. The synthesized compounds were characterized by IR, ^{1}H-NMR, mass spectra and elemental analysis. Compounds 2-9 were screened for anti-nociceptive, anti-inflammatory and antiepileptic activity by AcOH induced writhing method, carrageenan induced paw edema method and maximal electroshock induced convulsion method respectively. Out of the eight synthesized compounds, indeno[1, 2-b]quinoxalin-11-ylidine (4-nitrophenyl)amine (3) exhibited promising anti-inflammatory activity and anti-nociceptive activity. N-(2,4-dinitrophenyl)-N' -(indeno[1,2-b]quinoxalin-11-ylidene)hydrazine (7) showed promising anti-inflammatory activity, anti-nociceptive activity, and antiepileptic activity, whereas N4-indeno[1, 2-b]quinoxalin-11-ylidene biphenyl-4,4'-diamine (8) showed promising anti-inflammatory activity.

Keywords: Indeno[1, 2-b]quinoxalin-11-ylidenamines; Antinociceptive activity; Inflammation; Epilepsy.
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1. Introduction

Quinoxaline derivatives are an important class of benzoheterocycles which has received much attention in recent years owing to their both biological properties and pharmaceutical applications. These derivatives are particularly interesting since some of them showed anti-microbial [1-9], anticancer [10-25], antimalarial [26-31], antiinflammatory [32-33], antinociceptive [34-36], antitubercular [37-39], anthelmintic [40-41], antidiabetic [42] and antiepileptic [43-44] properties. There is no report on the synthesis of indeno[1, 2-b]quinoxalin-11-ylidenamines and hence our research has focused to synthesize new indeno[1, 2-b]quinoxalin-11-ones substituted by aromatic amine moieties in 11 position and to investigate their antinociceptive, anti-

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inflammatory and antiepileptic activities.

2. Materials and methods

2.1. Chemistry

Titled compounds were prepared as shown in Figure1. Melting points were determined by Veego melting point apparatus and are not corrected. Thin layer chromatographic analysis were performed on a Merck grade Aluminum foil GF_{254} plates of 0.25 mm thickness in chloroform: water system (9:1). Spots were visualized under UV light. Infrared spectra were obtained on a Perkin Elmer-1600 series FTIR spectrophotometer using potassium bromide discs. Nuclear magnetic resonance spectra were recorded on Brucker 400 MHz spectrophotometer. Chemical shifts are reported in parts per million (δ) units relative to internal standard tetramethylsilane. Mass spectra were recorded on Joel

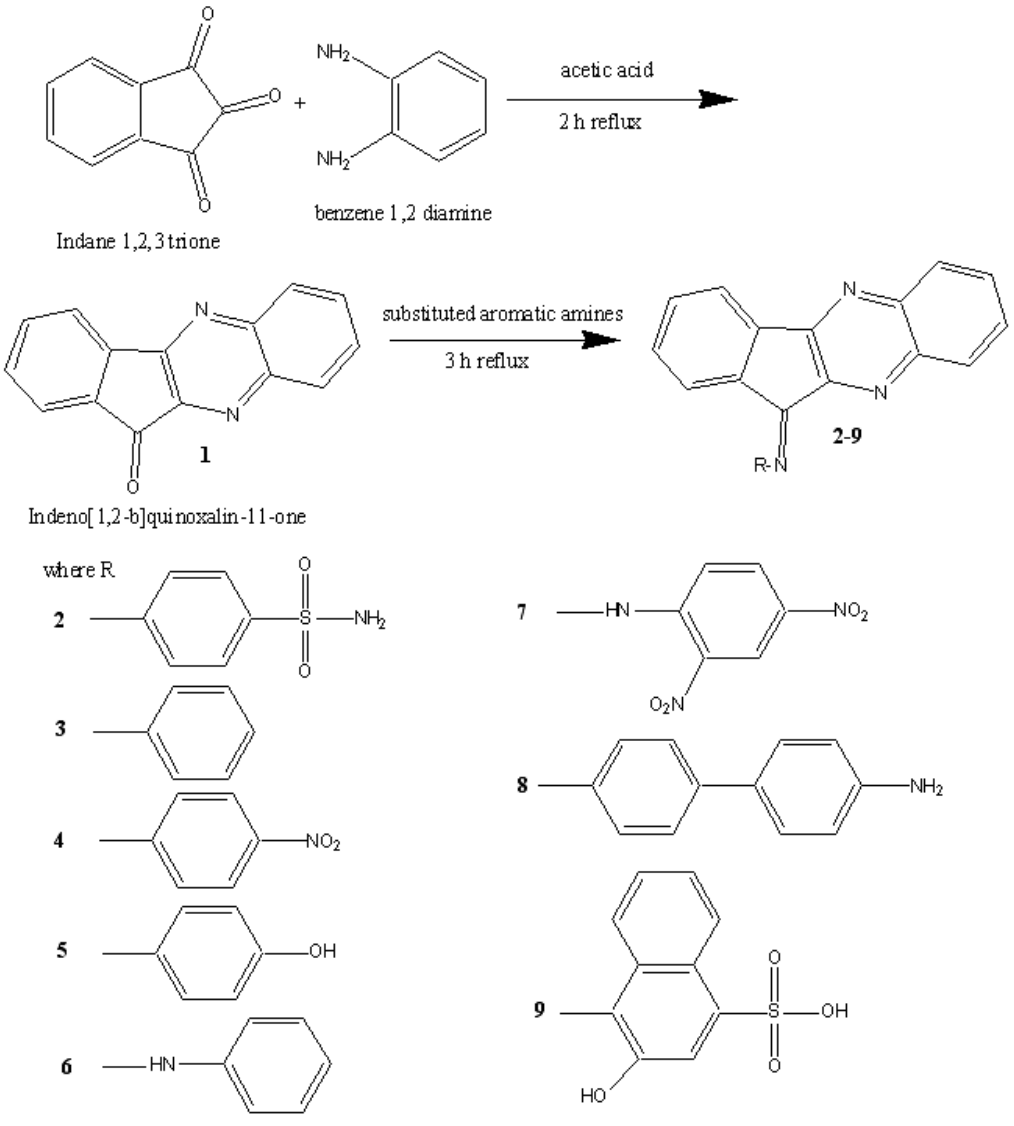

Figure 1. Synthetic scheme of Indeno[1, 2-b] quinox-11-ylideneamines.

Table 1. Effect of synthesized compounds on Rota rod test for mice.

Behaviour			**Effect after 30 min. of administration (mean±SEM) (i.p.)**		
	0.5% v/v Tween 80 suspension	20 $mg.kg^{-1}$	50 $mg.kg^{-1}$	100 $mg.kg^{-1}$	200 $mg.kg^{-1}$
Grip test	No effect	No effect	No effect	No effect	1±0.42*

*p<0.001 represents significant difference when compared with control groups.

JMS-DX 303 mass spectrophotometer. Elemental analysis was performed on Heraceus Carlo Erba 1108 and the analysis indicated by the symbols of the elements was within ±0.4 % of theoretical values.

2.2. Preparation of indeno[1, 2-b] quinoxalin-11-one (1) [45-48]

Equimolar quantities of benzene 1,2-diamine and indan-1,2,3 trione were refluxed in AcOH for 2 h at 100 °C. After 2 h, the mixture was poured into crushed ice and indeno[1,2-b]quinoxalin-11-one (1) obtained was filtered, dried and recrystallized from DMF. The desired product 1 obtained as brown solid in 68% yield: m.p. 107-108 °C. IR: 1725(C=O), 1608, 1506(C=C), 1334, 1189 (C=N), 863, 771, 734 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4) δ: 7.7-8.1(m, 8H, Ar-H). Anal. Calcd for $C_{15}H_8N_2O$: C, 77.58; H, 3.47; N, 12.06; O, 6.89. Found: C, 77.31, H, 3.14; N, 11.86; O, 6.52. EI-MS (m/z) 232.24.

2.3. Preparation of (indeno [1, 2-b] quinoxalin-11-ylideneamino) benzene sulphonamide (2)[49]

Equimolar quantities of compound 1 and 4-aminobenzene sulphonamide were refluxed on a water bath in acetic acid medium for 3 h with continuous stirring. After 3 h, the crude

Table 2. Behavioral study data of the synthesized compounds using actophotometer method.

Treatment	**Dose ($mg.kg^{-1}$)**	**Score (Mean±SEM) (time in s)**
Control	-	275±31*
Phenobarbitone	5	36±70*
2	20	111±32*
	50	83±80*
	100	67±40*
3	20	294±13*
	50	278±17*
	100	240±60*
4	20	217±10*
	50	189±40*
	100	120±20*
5	20	141±10*
	50	120±20*
	100	92±60*
6	20	115±12*
	50	76±40*
	100	56±20*
7	20	44±40*
	50	38±20*
	100	22±90*
8	20	207±10*
	50	168±20*
	100	140±10*
9	20	173±23*
	50	149±30*
	100	120±70*

*p<0.05 represent significant difference when compared with control groups

reaction products were poured into crushed ice and the product obtained was filtered, dried and recrystalized from DMF. The desired product 2 was obtained as a brownish black solid in 64% yield: m.p. 120- 121 °C. IR: 3475, 3380 (N-H), 1609, 1596 (C=C), 1392 (C=N), 1309, 1151 (SO_2), 831, 742 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4) δ: 2 (s, 2H, NH_2), 7.2-7.9 (m, 12 H, Ar-H). Anal. Calcd for $C_{21}H_{14}N_4O_2S$: C, 64.76; H, 3.62; N, 50.35; O, 8.22; S, 8.23 Found: C, 64.42, H, 3.29; N, 50.04; O. 7.99; S, 7.98. EI-MS (m/z) 389.47.

2.4. Preparation of indeno[1, 2-b]quinoxaline-11-ylidene phenylamine (3)

Compound 3 was prepared using the same procedure adopted for compound 2 by reacting equimolar quantities of compound 1 and aniline. The desired product 3 was obtained in 62% yield as a blackish brown solid: m.p. 197-198 °C. IR: 1641, 1619 (C=C),1336, 1182 (C=N), 867 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4) δ: 7.25-8.2 (m, 13 H, Ar-H). Anal. Calcd for $C_{21}H_{13}N_3$: C, 82.07; H, 5.57; N, 13.67; Found: C, 81.88, H, 5.12; N, 13.24. EI-MS (m/z) 307.35.

2.5. Preparation of indeno[1,2-b]quinoxaline-11-ylidene-(4-nitro phenylamine) (4)

Compound 4 was prepared using the same procedure adopted for compound 2 by using equimolar quantities of compound 1 and 4-nitroaniline. The desired product 4 was obtained in 59% yield as black sticky mass. IR: 3438 (N-H), 1619, 1596 (C=C), 1336, 1508 (NO2), 1247 (C=N), 727 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4)) δ: 7.3-8.2 (m, 12 H, Ar-H). Anal. Calcd for $C_{21}H_{12}N_4O_2$: C, 71.59; H, 3.43; N, 15.90; O, 9.08. Found: C, 71.12, H, 3.09; N, 15.56; O, 8.71. EI-MS (m/z) 325.35

2.6. Preparation of (indeno[1, 2-b]quinoxaline -11-ylidene-amino)phenol (5)

Compound 5 was prepared using the same procedure adopted for compound 2 by using equimolar quantities of compound 1 and 4-amino phenol. The desired product 5 was obtained in 60% yield as a black solid: m.p.67-68 °C. IR: 3424 (O-H), 1604, 1506 (C=C), 1376, 1334 (C=N), 1230 (C-O), 771, 734 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4) δ: 5.9 (s, 1H, OH), 6.8-8.3 (m, 12 H, Ar-H). Anal. Calcd for $C_{21}H_{13}N_3O$: C, 77.96; H, 4.05; N, 12.99; O, 4.95. Found: C, 77.58, H, 3.68; N, 12.60; O, 4.56.71. EI-MS (m/z) 323.53.

2.7. Preparation of indeno [1, 2-b] quinoxaline-11-ylidene-N'-phenylhydrazine (6)

Compound 6 was prepared using the same procedure adopted for 2 by using equimolar quantities of 1 and phenylhydrazine. The desired product 6 was obtained in 61% yield

Table 3. Evaluation of anti-nociceptive activity of the synthesized compounds by acetic acid induced writhing method.

Compound	**Dose(mg.kg^{-1})**	**Writhing episodes in 15 min. (mean±SEM)**	**Percentage Protection**
Control	-	53.83±0.00	-
Paracetamol	2.5	09.17±0.83	85
2	20	18.83±0.81*	67
3	20	27.50±0.88*	67
4	20	35.17±0.96*	72
5	20	20.67±0.86*	63
6	20	34.33±0.93*	37
7	20	14.17±0.73*	72
8	20	16.17±0.79*	70
9	20	28.17±0.98*	48

*p<0.001 represent significant difference when compared with control groups

as a brown solid: m.p 185-186 °C. IR: 3434 (NH), 1606, 1502 (C=C), 1334 (C=N), 767 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4) δ: 7 (s, 1H, NH), 7.65-8.25 (m, 13 H, Ar-H). Anal. Calcd for $C_{21}H_{14}N_4$: C, 78.24; H, 3.77; N, 17.38. Found: C, 77.89, H, 3.96; N, 17.01. EI-MS (m/z) 322.37.

2.8. Preparation of N-(2,4-dinitrophenyl)-N'-indeno[1,2-b]quinoxalin-11-ylidene hydrazine (7)

Compound 7 was prepared using the same procedure adopted for 2 by using equimolar quantities of 1 and 2,4-dinitrophenylhydrazine. The desired product 7 was obtained in 65% yield as a brownish red solid: m.p 164-165 °C. IR: 3434 (N-H), 1606, 1502 (C=C), 1552 (NO_2), 1247 (C=N), 757 (aromatic hydrogen) cm^{-1}. ^{1}H-NMR (DMSO-d_4)) δ: 7(s, 1H, N-H), 7.05-8.05 (m, 11H, Ar-H). Anal. Calcd for $C_{21}H_{12}N_6O_4$: C, 61.17; H, 3.18; N, 20.38; O, 15.52. Found: C, 59.78, H, 2.81; N, 19.99; O, 15.14. EI-MS (m/z) 412.36.

2.9. Preparation of Indeno[1, 2-b]quinoxalin-11-ylidene phenylamine (8)

Compound 8 was prepared using the same procedure adopted for 2 by using equimolar quantities of 1 and biphenyl-4,4'-diamine. The desired product 8 was obtained in 63 % yield as a black solid: m.p. 137-138 °C. IR: 3407, 3328 (N-H), 1612 (C=C), 1263 (C=N), 819 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4)) δ: 3.5 (s, 2H, NH2), 6.55-8.1 (m, 16 H, Ar-H). Anal. Calcd for $C_{27}H_{18}N_4$: C, 81.38; H, 4.55; N, 14.06. Found: C, 79.99, H, 4.17; N, 13.68. EI-MS (m/z) 398.49.

2.10. Preparation of 4-(Hydroxy-3-Indeno [1, 2-b] quinoxalin-11-ylidene amino) naphthalene-1-sulphonic acid (9)

Compound 9 was prepared using the same procedure adopted for 2 by using equimolar quantities of 1 and 1-amino-2-naphthol-4-sulphonic acid. The desired product 9 was obtained in 64 % yield as a yellow solid: m.p. 184-185 °C. IR: 3432 (OH), 1506 (C=C), 1334 (C=N), 1189, 1116 (SO_3H), 773, 736 (aromatic) cm^{-1}. ^{1}H-NMR (DMSO-d_4) δ: 2.52 (s, 1H, OH of SO_3H), 3.5 (s, 1H, OH of naphthol), 7.6-8.2 (m, 13 H, Ar-H). Anal. Calcd for $C_{25}H_{15}N_3O_4S$: C, 65.50; H, 2.86; N, 9.17, O, 13.96; S, 6.99. Found: C, 65.12, H, 2.49; N, 8.78; O, 13.58, S.6.58. EI-MS (m/z) 458.47.

2.11. Pharmacological evaluation

The animals used for the studies were in accordance with principles of laboratory animal care and were approved by Institutional animal ethical committee. The antinociceptive evaluation was carried out using acetic acid induced writhing method. Swiss strain albino mice of either sex weighing 25-30 g were used for this study. The antiinflammatory activity evaluation was carried out using carrageenan induced rat paw edema method. Albino rats of Wistar

Table 4. Evaluation of anti-inflammatory activity of the synthesized compounds by carrageenan Induced paw edema method.

Compound	Dose ($mgkg^{-1}$)	Paw volume (mean±SEM)			Percentage inhibition		
		1 h	2 h	3 h	1 h	2 h	3 h
Control	-	0.85±0.00	0.87±0.00	0.87±0.00**	-	-	-
Diclofenac Na	2.5	0.68±0.02**	0.62±0.03**	0.51±0.02**	20.0	28.7	41.3
2	20	0.77±0.03**	0.74±0.02**	0.72±0.01**	9.4	14.9	17.2
3	20	0.75±0.03**	0.73±0.00**	0.72±0.01**	11.7	16.1	17.2
4	20	0.75±0.02**	0.73±0.03**	0.71±0.01**	11.8	16.1	18.3
5	20	0.78±0.03**	0.74±0.02**	0.73±0.01**	8.2	14.1	16.0
6	20	0.80±0.03*	0.75±0.02**	0.73±0.01**	5.8	13.8	16.0
7	20	0.72±0.01**	0.69±0.01**	0.67±0.01**	15.2	20.0	22.2
8	20	0.74±0.03**	0.72±0.00**	0.07±0.01**	12.9	17.2	18.3
9	20	0.79±0.02**	0.70±0.01**	0.72±0.01**	7.5	12.6	17.2

**p<0.001 and *p<0.01 represent significant difference when compared with control groups.

strain weighing 100-200 g of either sex were used for this study.

The antiepileptic evaluation was carried out using maximal electro shock induced seizure method. Swiss strain albino mice of either sex weighing 25-30 g were used for this study. The test compounds were suspended in 0.5 % v/v Tween 80 in water. LD_{50} of the newly synthesized compounds were determined by Miller and Tainter [50] method by administering the compounds intraperitoneally.

2.11.1. Acetic acid induced writhing method [51]

The animals were housed and acclimated under standard laboratory conditions and were supplied with food and water *ad libitum*. The animals were divided into ten groups of six mice each. The control group of animals was administered with 0.5% v/v Tween 80 (0.5 ml) suspension. The standard drug was administered with paracetamol (Micro Labs) i.p. in a dose of 2.5 mg kg^{-1}. Tween 80 suspension (0.5 % v/v) of the test compounds were administered i.p. in a dose of 20 $mg.kg^{-1}$. After 20 min. of the administration of the test compounds and standard, all the groups of mice were given the writhing agent 3 % v/v aqueous acetic acid in a dose of 2 ml kg^{-1} i.p. The total number of writhing produced in these animals were counted visually for 15 min. and the number of writhing produced in treated groups were compared with those in control group. The results recorded in Table 3 are expressed as percentage protection and are analyzed statistically by "student t test".

2.11.2. Anti-inflammatory activity

The antiinflammatory activity was evaluated by carrageenan induced paw edema method [52]. Albino rats of Wistar strain weighing 100-200 g of either sex were divided into ten groups each of six animals. Tween 80 suspension (0.5 % v/v) of the test compounds were administered intraperitoneally in a dose of 20 $mgkg^{-1}$. The control group was given only 0.5% v/v Tween 80 (0.5 ml) suspension. One group was administered with diclofenac sodium (Novartis Laboratories) as standard, i.p. in a dose of 2 mg kg^{-1}. After 30 min. of the administration of test compounds paw edema was induced in albino rats by injecting 0.1 ml of carrageenan (1% v/v in normal saline) suspension, into subplantar region of the left hind paw of each rat. After 1, 2 and 3 h of carrageenan injection, the increase in paw volume was measured by a plethysmometer. The antiinflammatory activity was measured in terms of percentage inhibition of edema and is analyzed statistically by "students t test" and recorded in Table 4.

Table 5. Evaluation of antiepileptic activity of the synthesized compounds by Maximal Electroshock Induced Seizure (MES) method.

Compound	Dose (mg.kg-1)	Duration (mean±SEM, s)			Recovery/ Death
		Extensor	Clonus	Stupor	
Control	-	16.50±0.43	16.50±0.43	16.50±0.43	Death
Phenobarbitone	20	5.67±0.46**	2.17±0.31	1.33±0.21	Recovery
2	20	10.17±0.48**	10.33±0.42	10.33±0.42	Recovery
3	20	15.50±0.43	15.33±0.42	14.33±0.42	Recovery
4	20	15.17±0.37*	10.23±0.41	5.48±0.42	Death
5	20	10.17±0.49**	15.33±0.42	6.33±0.42	Recovery
6	20	10.26±0.39**	30.83±0.60	10.17±0.49	Death
7	20	8.17±0.80**	7.33±0.42	20.50±0.43	Recovery
8	20	13.33±0.56*	10.17±0.49	10.26±0.38	Recovery
9	20	10.27±0.49**	15.46±0.43	5.33±0.42	Recovery

**$p<0.001$ and *$p<0.01$ represent significant difference when compared with control groups.

2.11.3. Anti-epileptic activity [53]

The antiepileptic activity was evaluated by maximal electroshock induced seizure (MES) method. Swiss albino mice weighing 25-30 g of either sex were divided into ten groups each of six animals. The control group of animals was administered with 0.5%v/v Tween 80 (0.5 ml) suspension. One group was administered with phenobarbitone (Nicholas Primal) as standard, i.p. in a dose of 20 $mg.kg^{-1}$. Tween 80 suspensions (0.5 % v/v) of the test compounds were administered i.p. in a dose of 20 mg kg^{-1} for other group of animals. After 1 h of the administration of the test compounds and standard, the animals were given electroshock through ear electrodes of 150 mA for 0.2s by electroconvulsiometer. Onset times for tonic, flexion, extension and clonic phase were noted. The protective index was observed as reduction time of tonic extensor phase and was tabulated in Table 5.

2.11.4. Neurotoxicity screen

Minimal motor impairment was measured in mice by the Rota rod (Techno, India) test. The mice were trained to stay on an accelerating Rota rod of diameter 3.2 cm that rotates at 10 revolutions per min. Previously trained Albino mice were given test compounds i.p. in doses of 20, 50, 100, and 200 $mg.kg^{-1}$. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least one min. in each of the three trials. The results are summarized in Table 1.

2.11.5. Behavioral test

The titled compounds (20 mg kg^{-1} in 0.5 % v/v Tween 80 suspension) were screened for their behavioral effects using actophotometer (Techno, India) by Boissier and Simon method [54]. Albino mice were placed inside the actophotometer after 30 min. of administration of test compounds i.p. The behavior of animals inside the photocell was recorded as a digital score. The control animals were administered with 0.5 ml of Tween 80 (0.5% v/v) suspension. The observations are summarized in Table 2.

3. Results and discussion

3.1. Chemistry

Ketones readily undergo condensation reaction with amines. Indane-1,2,3-trione being a ketone yielded a condensation product indeno[1, 2-b] quinoxalin-11-one with benzene-1,2-diamine. Indeno[1, 2-b] quinoxalin-11-one yielded indeno[1, 2-b] quinoxalin-11-ylidienamines on reaction with various substituted amines.

Infrared spectrum of all eight compounds showed strong absorption bands for C=N group at 1393 cm^{-1} and aromatic absorptions at 1609 cm^{-1} and below 900 cm^{-1}. Compound 2 showed strong absorptions for SO_2 group at 1151 cm^{-1} and N-H group at 3380 cm^{-1}. Compound 4 showed strong absorptions for NO_2 group at 1508 cm^{-1}. Compound 5 showed strong absorptions for OH group at 3424 cm^{-1}. Compound 6 showed absorption band for NH group at 3434 cm^{-1}. Compound 7 showed absorption band for N-H at 3434 cm^{-1} and for NO_2 group at 1552 cm^{-1}. Compound 8 showed absorption band for N-H group at 3428 cm^{-1}. Compound 5 showed strong absorptions for OH group at 3432 cm^{-1} and for sulphonic acid group at 1116 cm^{-1}.

All the eight synthesized compounds showed strong multiplets from δ 7.2-7.9 for aromatic protons. Compounds 2, 6, 7 and 8 showed singlet signals ranging from δ 2 to 7 for NH and NH_2 protons. Hydroxyl protons were detected around δ 5.9 and δ 2.5 for compounds 5 and 9 respectively. Mass spectral data showed expected m/z values for all the eight synthesized compounds.

3.2. Pharmacological evaluation

3.2.1. Neurotoxicity screen

Minimum motor impairment was measured in mouse by Rota rod test showed that all the synthesized compounds have no

effect which was indicated by their ability to maintain the equilibrium on the Rota rod for more than 1 min.

3.2.2. Behavioral test

Compound 7 produced significant decrease in the spontaneous motor activity in mice. This effect was dose dependent and the effect was observed within 30 min. of drug administration. Other compounds except compound 3 also showed good behavioral activity.

3.2.3. Anti-nociceptive activity

3.2.3.1. Acetic acid induced writhing method

Antinociceptive activity was evaluated by acetic acid induced writhing method. All the compounds tested exhibited antinociceptive activity in a dose of 20 $mg.kg^{-1}$. The antinociceptive activity of compounds 4, 7 and 8 is found to be superior compared to other synthesized compounds. The compounds 2, 3 and 5 exhibited moderate antinociceptive activity. The compounds 6 and 9 exhibited negligible anti-nociceptive activity.

3.2.4. Anti-inflammatory activity

The compounds 2, 3, 4, 5, 6, 7, 8 and 9 afforded 16-22% protection against carageenan induced paw edema, where as the standard drug diclofenac sodium (Novartis Laboratories) under similar conditions showed 42% inhibition. Among the compounds tested, compounds 4, 7 and 8 exhibited significant anti-inflammatory activity and compounds 2, 3, 5, 6 and 9 exhibited moderate anti-inflammatory activity.

3.2.5. Anti-epileptic activity

Maximal electroshock induced seizure model was adopted for evaluation of antiepileptic activity. Compound 7 exhibited significant antiepileptic activity by reducing the duration of extensor phase. The compounds 1, 3, 4 and 8 exhibited negligible anti-epileptic activity.

4. Conclusions

A series of indeno[1,2-b]quinoxalin-11-ylidenamines was prepared and demonstrated that these compounds possess good antinociceptive activity tested by acetic acid induced writhing method, antiinflammatory activity tested by carageenan induced paw edema method and antiepileptic activity tested by maximal electroshock method. The most promising compounds having antinociceptive activity were indeno[1,2-b]quinoxalin -11-ylidene-(4-nitrophenyl)amine 4, N-(2,4-dinitrophenyl)-N'-indeno[1,2-b]quinoxalin-11-ylidene hydrazine 7 and N4-indeno[1,2-b]quinoxalin-11-ylidene biphenyl-4, 4'-diamine 8, N-(2,4-dinitrophenyl)-N'-indeno[1,2-b]quinoxalin-11-ylidene hydrazine 7, N4-indeno[1,2-b]quinoxalin-11-ylidene-biphenyl-4,4'-diamine 8 and indeno[1,2-b] quinoxalin-11-ylidene-(4-nitrophenyl) amine 4 exhibited promising antiinflammatory activity.

References

[1] Kotharkar SA, Shinde DB. Synthesis of antimicrobial 2,9,10-trisubstituted-6-oxo-7,12-dihydro-chromeno[3, 4-b]quinoxalines. *Bioorg Med Chem Lett* 2006; 16: 6181-4.

[2] El-Hawash SA, Habib NS, Kassem MA. Synthesis of some new quinoxalines and 1,2,4-triazolo[4, 3-a]-quinoxalines for evaluation of *in vitro* antitumor and antimicrobial activities. *Arch Pharm (Weinheim)* 2006; 339: 564-71.

[3] Khan SA, Saleem K, Khan Z. Synthesis, characterization and in vitro antibacterial activity of new steroidal thiazolo quinoxalines. *Eur J Med Chem* 2007; 42: 103-8.

[4] Corona P, Vitale G, Loriga M, Paglietti G, La Colla P, Collu G, Sanna G, Loddo R. 4-Substituted anilino imidazo[1,2-a] and triazolo[4,3-a]quinoxalines. Synthesis and evaluation of *in vitro* biological activity. *Eur J Med Chem* 2006; 41: 1102-7.

[5] Tandon VK, Yadav DB, Maurya HK, Chaturvedi AK, Shukla PK. Design, synthesis, and biological evaluation of 1,2,3-trisubstituted-1,4-dihydrobenzo[g]quinoxaline-5,10-diones and related compounds as antifungal and antibacterial agents. *Bioorg Med Chem* 2006; 14: 6120-6.

[6] Abid M, Azam A. Synthesis, characterization

and antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives. *Bioorg Med Chem Lett* 2006; 16: 2812-6.

[7] Refaat HM, Moneer AA, Khalil OM. Synthesis and antimicrobial activity of certain novel quinoxalines. *Arch Pharm Res* 2004; 27: 1093-8.

[8] Carta A, Loriga M, Zanetti S, Sechi LA. Quinoxalin-2-ones. Part 5. Synthesis and antimicrobial evaluation of 3-alkyl-, 3-halomethyl- and 3-carboxyethylquinoxaline-2-ones variously substituted on the benzo-moiety. *IL Farmaco* 2003; 58: 1251-5.

[9] Kim SH, Kim TE, Kurasawa Y. Synthesis of 1,3,4-Thiadiazino[5,6-*b*]quinoxalines with Antimicrobial Activity. *J Korean Chem Soc* 2001; 45: 325-33.

[10] Zarranz, B, Aldana, I, Jaso, A, Monge, A.Synthesis and anticancer activity evaluation of new 2-alkylcarbonyl and 2-benzoyl-3-trifluoro methylquinoxaline. 1,4-di-N-oxide derivatives. *Bioorg Med Chem* 2004; 12; 3711-21.

[11] Yan L, Liu FW, Dai GF, Liu HM. An efficient synthesis of quinoxaline derivatives from 4-chloro-4-deoxy-alpha-D-galactose and their cytotoxic activities. *Bioorg Med Chem Lett* 2007; 17: 609-12.

[12] Grande F, Aiello F, Grazia OD, Brizzi A, Garofalo A, Neamati N. Synthesis and antitumor activities of a series of novel quinoxalinhydrazides. *Bioorg Med Chem* 2007; 15: 288-94.

[13] Lenzi O, Colotta V, Catarzi D, Varano F, Filacchioni G, Martini C, Trincavelli L, Ciampi O, Varani K, Marighetti F, Morizzo E, Moro S. 4-amido-2-aryl-1,2,4-triazolo[4,3-a]quinoxalin-1-ones as new potent and selective human A3 adenosine receptor antagonists. synthesis, pharmacological evaluation, and ligand-receptor modeling studies. *J Med Chem* 2006; 49: 3916-25.

[14] Jung JK, Jung EK, Nam-Goong K, Cho JS, Kim HM, Park SG, Yoo YA, Kwon JH, Lee HS. Synthesis and cytotoxic activities of 8-alkyl or 8-aryl-8,9-dihydro-7H-isoindolo[5,6-g] quinoxaline-7,9-diones. *Arch Pharm Res* 2006; 9: 276-81.

[15] Carta A, Loriga M, Piras S, Paglietti G, La Colla P, Busonera B, Collu G, Loddo R. Synthesis of variously substituted 3-phenoxymethyl quinoxalin-2-ones and quinoxalines capable to potentiate in vitro the antiproliferative activity of anticancer drugs in multi-drug resistant cell lines. *Med Chem* 2006; 2: 113-22.

[16] Novellino E, Cosimelli B, Ehlardo M, Greco G, Iadanza M, Lavecchia A, Rimoli MG, Sala A, Da Settimo A, Primofiore G, Da Settimo F, Taliani S, La Motta C, Klotz KN, Tuscano D, Trincavelli ML, Martini C. 2-(Benzimidazol-2-yl) quinoxalines: A novel class of selective antagonists at human A(1) and A(3) adenosine receptors designed by 3D database searching. *J Med Chem* 2005; 48: 8253-60.

[17] Zhao CH, Chen Y, Ding J, Duan WH. Design and synthesis of quinoxaline derivatives and their antitumor activities. *Yao Xue Xue Bao* 2005; 40: 814-9.

[18] Gali-Muhtasib HU, Diab-Assaf M, Haddadin MJ. Quinoxaline 1,4-dioxides induce G2/M cell cycle arrest and apoptosis in human colon cancer cells. *Cancer Chemother Pharmacol* 2005; 55: 369-78.

[19] Liu CH, Wang B, Li WZ, Yun LH, Liu Y, Su RB, Li J, Liu H. Design, synthesis, and biological evaluation of novel 4-alkylamino-1-hydroxymethylimidazo[1,2-a]quinoxalines as adenosine A(1) receptor antagonists. *Bioorg Med Chem* 2004; 12: 4701- 7.

[20] Colotta V, Catarzi D, Varano F, Calabri FR, Lenzi O, Filacchioni G, Martini C, Trincavelli L, Deflorian FM. 1,2,4-triazolo[4,3-a]quinoxalin-1-one moiety as an attractive scaffold to develop new potent and selective human A3 adenosine receptor antagonists: Synthesis, pharmacological, and ligand-receptor modeling studies. *J Med Chem* 2004; 47: 3580-90.

[21] Piras S, Loriga M, Paglietti G, Quinoxaline chemistry. Part XVII. Methyl [4-(substituted 2-quinoxalinyloxy) phenyl] acetates and ethyl N-([4-(substituted 2-quinoxalinyloxy) phenyl] acetyl) glutamates analogs of methotrexate: synthesis and evaluation of *in vitro* anticancer activity. *IL Farmaco* 2004; 59: 185-94.

[22] Zarranz B, Jaso A, Aldana I, Monge A. Synthesis and anticancer activity evaluation of new 2-alkylcarbonyl and 2-benzoyl-3-trifluoromethyl -quinoxaline 1,4-di-N-oxide derivatives. *Bioorg Med Chem* 2004; 12: 3711-21.

[23] Loriga M, Piras S, Paglietti G, Costi MP, Venturelli A. Quinoxaline chemistry. Part 15. 4-[2-Quinoxalylmethylenimino]-benzoylglutamates and -benzoates, 4-[2-quinoxalylmethyl-N-methylamino]-benzoylglutamates as analogues of classical antifolate agents. Synthesis, elucidation of structures and *in vitro* evaluation of antifolate and anticancer activities. *IL Farmaco* 2003; 58: 51-61.

[24] Vekariya NA, Khunt MD, Parikh AR. Synthesis of isoxazoles and quinoxalines as potential anticancer agents. *Ind J Chem* 2003; 42: 421-4.

[25] Piras S, Loriga M, Paglietti G. Quinoxaline

chemistry. Part 14. 4-(2-Quinoxalylamino)-phenylacetates and 4-(2-quinoxalylamino) -phenylacetyl-L-glutamates as analogues-homologues of classical antifolate agents. Synthesis and evaluation of *in vitro* anticancer activity. *IL Farmaco* 2002; 57: 1-8.

[26] Zarranz B, Jaso A, Lima LM, Aldana I, Monge A, Maurel S, Sauvain M. Antiplasmodial activity of 3-trifluoromethyl-2-carbonyl quinoxaline di-N-oxide derivatives. *Brazilian J Pharm Sci* 2006; 42: 357-61.

[27] Zarranz B, Jaso A, Aldana I, Monge A, Maurel S, Deharo E, Jullian V, Sauvain M. Synthesis and antimalarial activity of new 3-arylquinoxaline-2-carbonitrile derivatives. *Arzneimittelforschung* 2005; 55: 754-61.

[28] Guillon J, Grellier P, Labaied M, Sonnet P, Leger JM, Deprez-Poulain R, Forfar-Bares I, Dallemagne P, Lemaitre N, Pehourcq F, Rochette J, Sergheraert C, Jarry C. Synthesis, antimalarial activity, and molecular modeling of new pyrrolo[1, 2a]quinoxalines, bispyrrolo[1,2-a]quinoxalines, bispyrido[3, 2-e]pyrrolo[1,2-a] pyrazines, and bispyrrolo[1, 2-a]thieno[3, 2-e]pyrazines. *J Med Chem* 2004; 47: 1997-83.

[29] Zarranz B, Aldana I, Jaso A, Monge A. Synthesis and antimycobacterial activity of new quinoxaline-2-carboxamide 1,4-di-N-oxide derivatives. *Bioorg Med Chem* 2003; 11: 2149-56.

[30] Seitz LE, Suling WJ, Reynolds RC. Synthesis and antimycobacterial activity of pyrazine and quinoxaline derivatives. *J Med Chem* 2002; 45: 5604-6.

[31] Rangisetty CN, Gupta AL, Prasad P, Srinivas N, Sridhar P, Parimoo A. Veeranjaneyulu. Synthesis of new arylaminoquinoxalines and their antimalarial activity in mice. *J Pharm Pharmacol* 2001; 53: 1409-14.

[32] Lieu F, Ouellet C, Ruediger EH, Belema M, Qiu Y, Yang X, Banville J, Burke JR, Gregor KR, MacMaster JF, Martel A, McIntyre KW, Pattoli MA, Zusi FC, Vyas D. Synthesis and biological evaluation of 4-amino derivatives of benzimidazo-quinoxaline, benzimidazoquinolin, and benzopyrazoloquinazoline as potent IKK inhibitors. *Bioorg Med Chem Lett* 2007; 17: 1233-7.

[33] Singh SK, Saibaba V, Ravikumar V, Rudrawar SV, Daga P, Rao CS, Akhila V, Hegde P, Rao YK. Synthesis and biological evaluation of 2,3-diarylpyrazines and quinoxalines as selective COX-2 inhibitors. *Bioorg Med Chem* 2004; 12: 1881-93.

[34] Ismail MM, Ammar YA, Ibrahim MK, El-Zahaby HS, Mahmoud SS. Synthesis and pharmacological evaluation of novel quinoxalines as potential nonulcerogenic anti-inflammatory and analgesic agents. *Arzneimittelforschung* 2005; 55: 738-43.

[35] Vierfond JM, Legendre L, Martin C, Rinjard P Miocque M. Synthesis, structure activity relationship and pharmacology of thieno-isothiazolo[3,4-b]quinoxalines. *Eur J Med Chem* 1990; 25: 251-5.

[36] Carta A, Piras S, Loriga G, Paglietti G. Chemistry, biological properties and SAR analysis of quinoxalinones. *Mini Rev Med Chem* 2006; 6: 1179-200.

[37] Ortega MA, Aldana I, Jaso A, Monge A, Montoya ME, Sainz Y, Zarranz B. *Anti-Mycobacterium tuberculosis* agents derived from quinoxaline-2-carbonitrile and quinoxaline-2-carbonitrile 1,4-di-N-oxide. *Arzneim Forsch Drug Res* 2002; 52: 113-9.

[38] Aldana OA, Monge I, Zarranz A. Synthesis of New 2-acetyl and 2-benzoyl quinoxaline 1,4-di-N-oxide derivatives as anti-*Mycobacterium tuberculosis agents*. *Eur J Med Chem* 2003; 38: 791-800.

[39] Zanetti LA, Sechi P, Molicotti S, Cannas A, Bua A, Deriu A, Paglietti G. In vitro activity of new quinoxalin 1,4-dioxide derivatives against strains of *Mycobacterium tuberculosis* and other mycobacteria. *Int J Antimicrob Agents* 2005; 25: 179-81.

[40] Sun G, Uretsky NJ, Wallace LJ, Shams G, Weinstein DM, Miller DD. Synthesis of chiral 1-(2'-amino-2'-carboxyethyl)-1,4-dihydro-6,7-quino xaline-2,3-diones: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor agonists and antagonists. *J Med Chem* 1996; 39: 4430-8.

[41] Fisher MH, Lusi A, Egerton JR. Anthelmintic dihydroquinoxalino [2, 3-b]quinoxalines. *J Pharm Sci* 1977; 66: 1349-52.

[42] Bahekar RH, Jain MR, Gupta AA, Goel A, Jadav PA, Patel DN, Prajapati VM, Patel PR. Synthesis and antidiabetic activity of 3,6,7-trisubstituted-2-(1H-imidazol-2-ylsulfanyl) quinoxalines and quinoxalin-2-yl isothioureas. *Arch Pharm* 2007; 340: 359-66.

[43] Bigge CF, Malone TC, Boxer PA, Nelson CB, Ortwine DF, Schelkun RM, Retz DM, Lescosky LJ, Borosky SA, Vartanian MG. Synthesis of 1,4,7,8,9,10-hexahydro-9-methyl-6-nitropyrido[3,4-f]- quinoxaline-2,3-dione and related quinoxalinediones: Characterization of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (and N-methyl-D-aspartate) receptor and anticonvulsant activity. *J Med Chem* 1995; 38: 3720-40.

[44] Ferreri G, Chimirri A, Russo E, Gitto R, Gareri P, De Sarro A, De Sarro G. Comparative

anticonvulsant activity of N-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives in rodents. *Pharmacol Biochem Behav* 2004; 77: 85-94.

[45] Taylor B, Carroll PJ, Joullié MM. Novel compounds from 1,2-indanedione and 3,5-dimethoxyaniline. *Acta Cryst* 1999; 55: 1733-6.

[46] Azizian J, Karimi AR, Kazemizadeh Z, Mohammadi AA, Mohammadizadeh MR. A novel one-pot synthesis of some new interesting pyrrole derivatives. *J Org Chem* 2005; 70: 1471-3.

[47] Deady LW, Desneves J, Ross AC. Microwave-assisted one-pot synthesis of some dicyano-methylene derivatives of indenoquinoxaline and tryptanthrin under solvent free conditions *Tetrahedron* 1993; 49: 9823-32.

[48] Azizian J, Mohammadizadeh MR, Karimi N, Kazemizadeh Z, Mohammadi AA, Karimi AR. One-pot three components synthesis of alkyl indeno [1,2-b]-quinoxalin-11-ylideneacetates in water and under solvent-free conditions. *Heteroatom Chem* 2005; 16: 549-52.

[49] Otomasu HS, Omiya S. Synthesis of condensed quinoxalines. I. On the reaction of 11-oxo-11H-indeno[1,2-b]quinoxaline.*Yakugaku Zasshi* 1969; 89: 607-9.

[50] Miller LC, Tainter ML. Estimation of the ED 50. and its error by means of logarithmic-probit graph paper. *Proc Soc Exp Biol Med* 1944; 57: 261-4.

[51] Witkin LB, Heubner CF, Galdi F, O'keefe E, Spitaletta P, Plummer AJ. Pharmacology of 2-amino-indane hydrochloride (Su-8629): A potent non-narcotic analgesic. *J Pharmacol Exp Ther* 1961; 133: 400-8.

[52] Winter CA, Risley EA, Nuss GW. Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. *Proc Soc Exp Biol Med*. 1962; 111: 544-7.

[53] Dimmock JR, Puthucode RN, Smith JM, Hetherington M, Quail JW, Pugazhenthi U, Lechler T, Stables JP. (Aryloxy)aryl semicarbazones and related compounds: A novel class of anticonvulsant agents possessing high activity in the maximal electroshock screen. *J Med Chem* 1996; 39: 3984-97.

[54] Boissier JR, Simon P. Action of caffeine on spontaneous motility of mouse. *Arch Int Pharmacodyn Ther* 1965; 158: 212-21.