Synthesis of Novel Triazolyl/Oxadiazolyl/Thiadiazolyl-Piperazine as Potential Anticonvulsant Agents

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ABSTRACT

Reaction of piperazine with chloroacetylchloride in dry acetone yield compound **1** , which on reaction with hydrazine hydrate yielded compound **2**, which was further reacted with various substituted phenylisothiocyanates in absolute alcohol to afford compounds **3–8** i. e. 2-(carbazolylacetyl)-N-(substitutedphenyl)-hydrazinepiperazinothioamides. Compounds **3–8** on reaction with aqueous NaOH, ethanolic NaOH and conc. H_2SO_4 afford triazoles **9–14**, oxadiazoles **15–20** and thiadiazoles **21–26** respectively. Twenty four newly synthesized compounds were evaluated for their anticonvulsant activity and acute toxicity. The structures of these compounds were established on the basis of analytical and spectral data.

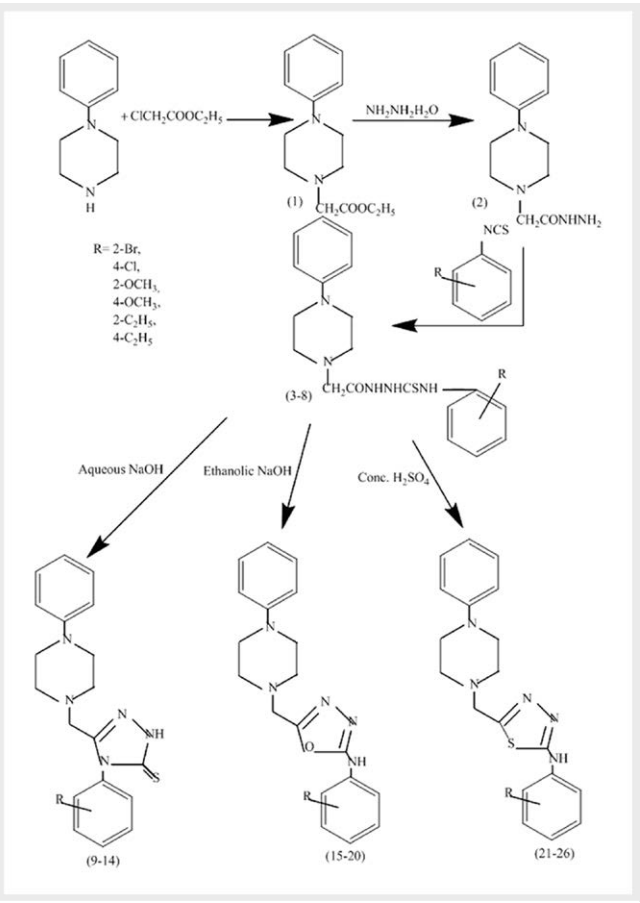
Introduction

Epilepsy is a disorder of brain, in which nerve cells actually in the brain is disturbed, causing seizures. Different groups of pharmacological agents used in the treatment of epileptic seizures are called anticonvulsant agents. Currently available drugs are helpful in approximately 60–70 % patients. Moreover, drugs used for the treatment of epilepsy are associated with a number of adverse reactions causing various side effects. Therefore, the need of the day is to search new chemical entities for the treatment of epilepsy with greater efficacy and fewer side effects.

Heterocyclic compounds forms the backbone for the discovery of many bioactive compounds. Chemical literature survey reveals that piperazine derivatives are biologically versatile compounds which possess potent antifungal [1, 2], antimicrobial [3, 4], antihistamine [5], antipsychotic [6, 7], anticonvulsant [8–10] properties. Moreover, various versatile pharmacophores such as triazoles [11–14], oxadiazoles [15–19] and thiadiazoles [20–22] possess anticonvulsant activity. Several scientists have also elucidated that the modifications at 1st or 4th position in piperazine nucleus by different heterocyclic moieties yielded potent anticonvulsant agents. This fact is utilized in the present work and various new compounds have been synthesized by in- corporating triazoles, oxadiazoles and thiadiazoles at 1st position of piperazine with the aim to synthesize more potent and safer anticonvulsant agents.

Materials and Methods

All the melting points are taken in open capillary and are uncorrected. Analytical thin layer chromatography was performed on silica gel-G plate (0.25 mm thickness) and visualized under UV



▶ **Fig. 1** Synthetic route for the synthesis of compounds **1–26**.

light, and/or by spraying with 5 % solution of phosphomolybdic acid (PMA) in ethanol, followed by charring with a heat gun. The IR spectra were recorded on Beckman Acculab-10 spectrophotometer (γ_{max} in cm^{-1}). ^{1}H-NMR was recorded on Varian NMR 500 instrument at 500 MHz. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal and external standards for ^{1}H-NMR. Mass Shimadzu 2010s mass spectrometer was used for recording mass spetra. Synthetic route for the synthesis of compounds 1 to 26 is depicted in ▶ **Fig. 1**.

Synthesis of N- ethyl phenylpiperazinylacetate (1) : Ethyl chloro acetate (1.0 mole) was added to a solution of phenyl piperazine (1.0 mole) in dry acetone (100ml) in presence of anhydrous K_2CO_3 (8 gm) with constant stirring. The mixture thus obtained was refluxed on a water bath for about 13 hours. The solid mass thus obtained was filtered, dried and recrystallized from ethanol to afford compound 1. The physical and analytical data of compound 1 is given in ▶ **Table 1**. IR ν_{max} (KBr, cm^{-1}):3040 (aromatic C-H), 2130 (C-N), 1680 (C = O ester). ^{1}H-NMR δ ($CDCl_3$ and DMSO-d_6): 3.75 (s, 2H, -NCH_2), 6.69–7.76 (m, 5H, Ar-H), 1.26 (t, 3H, $COOCH_2CH_3$), 4.20 (q, 2H, $COOCH_2CH_3$), 2.62 (m, 5H, 4x-CH_2 of piperazine) (ppm). MS: m/z 248 .

Synthesis of 2-phenylpiperazinyl acetohydrazide (2) : Compound 1 (0.4 mole) was added to hydrazine hydrate (15 ml) taken in round bottom flask. Sufficient quantity of dry ethanol was added to dilute the contents till a clear solution was obtained. The reaction mixture was refluxed for 20–22 hours. After completion of the reaction, excess of ethanol was distilled off till a small volume was left. On cooling, crystals of 2-phenylpiperazinyl acetohydrazides (2) were formed. The crystals so obtained were filtered and recrystallized from methanol. The physical and analytical data of compound 2 is given in ▶ **Table 1**. IR ν_{max} (KBr, cm^{-1}):3030 (aromatic C-H),2128 (C-N), 1690 (C = O), 3370 (NH), 1616. ^{1}H-NMR δ ($CDCl_3$ and DMSO-d_6): 3.70 (s, 2H, -NCH_2), 6.55–7.56 (m, 5H, Ar-H), 8.30 (d, 2H, NH_2), 8.40 (t, 1H, NH), 2.60 (m, 5H, 4x-CH_2 of piperazine) (ppm). MS: m/z 234.

Synthesis of 2-(phenyl piperazinyl acetyl)-N-(2'-bromophenyl)-hydrazinecarbothioamide (3) : A mixture of 2-phenylpiperazinyl acetohydrazide (2) (0.3 mole) and 2-bromophenylisothiocyanate (0.3 mole) in 30 ml of absolute ethanol was refluxed for 5–6 hours. After completion of the reaction, the reaction mixture was concentrated and kept overnight at room temperature. The needle shaped crystals thus obtained were purified by recrystallization with petroleum ether to furnish compound 3. The physical and analytical data of compound 3 is given in ▶ **Table 1**. IR ν_{max} (KBr, cm^{-1}): 3029 (aromatic C-H), 2135 (-CN),1693 (C = O), 3375 (NH), 1130 (C = S), 611 (C-Br). ^{1}H-NMR δ ($CDCl_3$ and DMSO-d_6): 3.70 (s, 2H, -NCH_2), 7.30–8.40 (m, 9H, Ar-H), 8.70 (d, 1H, CONH), 8.74 (d, 1H, NHC = S),8.90 (s, 1H, NH-Ar), 2.62 (m, 5H, 4x-CH_2 of piperazine) (ppm). MS: m/z 448.

Other compounds **(4–8)** of this step were also prepared similarly. Their physical and analytical data are given in ▶ **Table 1**.

Synthesis of 3-(phenyl piperazinyl methylene)-4-(2'-bromophenyl)-1,2,4-triazol-5(4H)-thione (9) : A mixture of compound 3 (0.04 mole) and 30 ml of 2 % NaOH solution was refluxed for 6 hours. After completion of the reaction, the reaction mixture was filtered and the filtrate was neutralized with conc. HCl dropwise till pH was adjusted to 7. The mixture was kept aside for a few minutes. The distinctive precipitate thus obtained was filtered, washed with water and recrystallized from petroleum ether to give compound 9. The physical and analytical data of compound 9 is given in ▶ **Table 1**. IR ν_{max} (KBr, cm^{-1}): 3041 (aromatic C-H), 2160 (-CN), 3440 (NH), 1265 (C = S), 614 (C-Br). ^{1}H-NMR δ ($CDCl_3$ and DMSO-d_6): 4.16 (s, 2H, -NCH_2), 6.83–7.95 (m, 9H, Ar-H), 10.64 (s, 1H, NH of triazole), 8.74 (d, 1H, NHC = S),8.90 (s, 1H, NH-Ar), 2.65 (m, 5H, 4x-CH_2 of piperazine) (ppm). MS: m/z 431.

Other compounds **(10–14)** of this step were also prepared similarly. Their physical and analytical data are given in ▶ **Table 1**.

Synthesis of 5-(phenyl piperazinyl methylene)-2-(2'-bromophenyl)-oxadiazole (15) : A solution of compound 3 (0.04 mole) in 25 ml ethanol and sodium hydroxide solution (4 ml) was cooled under continuous stirring for 30 minutes. To this mixture, iodine in KI (5 %) was added drop-wise till the colour of iodine persisted at room temperature. After that the mixture was refluxed for 2 hours. After completion of the reaction, the mixture was poured onto crushed ice. The solid thus obtained was washed with sodium thiosulphate solution and recrystallized from methanol to give compound 15. The physical and analytical data of compound 15 is given in ▶ **Table 1**. IR ν_{max} (KBr, cm^{-1}): 299 (aromatic C-H), 2180 (-CN), 3460 (NH), 1009 (C-O-C), 613 (C-Br). ^{1}H-NMR δ ($CDCl_3$ and DMSO-d_6): 4.13 (s, 2H, -NCH_2), 6.90–8.05 (m, 9H, Ar-H), 8.83 (s, 1H, NH-Ar), 2.65 (m, 5H, 4x-CH_2 of piperazine) (ppm). MS: m/z 415.

Other compounds **(16–20)** of this step were also prepared similarly. Their physical and analytical data are given in ▶ **Table 1**.

▶ **Table 1** Physical and analytical data of compounds 1-26.

Comp. No.	R	M.P. °C	Recryst. solvent	Yield (%)	Molecular Formula	Calcd. (Found) %		
						C	H	N
1	–	128	Ethanol	80	$C_{14}H_{20}N_2O_2$	67.74 (67.72)	8.06 (8.08)	11.29 (11.31)
2	–	145	Methanol	84	$C_{12}H_{18}N_4O$	61.53 (61.55)	7.69 (7.71)	23.93 (23.95)
3	2-Br	180	pet. ether	76	$C_{19}H_{22}N_5OSBr$	50.89 (50.91)	4.91 (4.89)	15.62 (15.59)
4	4-Cl	185	acetone	78	$C_{19}H_{22}N_5OSCl$	76.66 (76.63)	5.45 (4.47)	17.34 (17.35)
5	2-OCH_3	178	Ethanol	77	$C_{20}H_{25}N_5O_2S$	60.15 (60.12)	6.26 (6.24)	17.54 (17.56)
6	4-OCH_3	177	DMF-water	76	$C_{20}H_{25}N_5O_2S$	60.15 (60.18)	6.26 (6.28)	17.54 (17.52)
7	2-C_2H_5	178	Ethanol	79	$C_{21}H_{27}N_2OS$	70.98 (70.96)	7.60 (7.58)	7.88 (7.90)
8	4-C_2H_5	176	Ethanol	74	$C_{21}H_{27}N_2OS$	70.98 (70.97)	7.60 (7.62)	7.88 (7.91)
9	2-Br	170	pet ether	72	$C_{19}H_{21}N_5SBr$	52.90 (52.87)	4.87 (4.90)	16.24 (16.26)
10	4-Cl	200	Ethanol	74	$C_{19}H_{21}N_5SCl$	58.99 (59.00)	5.43 (5.45)	18.11 (18.09)
11	2-OCH_3	202	DMF-water	72	$C_{20}H_{24}N_5OS$	62.82 (62.79)	6.28 (6.30)	18.32 (18.29)
12	4-OCH_3	205	Methanol	70	$C_{20}H_{24}N_5OS$	62.82 (62.80)	6.28 (6.27)	18.32 (18.31)
13	2-C_2H_5	203	DMF-water	73	$C_{21}H_{26}N_5S$	66.31 (66.29)	6.84 (6.86)	18.42 (18.40)
14	4-C_2H_5	210	acetone	66	$C_{21}H_{21}N_5S$	66.31 (66.33)	6.84 (6.86)	18.42 (18.39)
15	2-Br	215	methanol	73	$C_{19}H_{22}N_5OBr$	54.93 (54.90)	5.06 (5.04)	16.86 (16.84)
16	4-Cl	222	acetone	67	$C_{19}H_{22}N_5OCl$	61.53 (61.55)	5.66 (5.68)	18.89 (18.86)
17	2-OCH_3	218	DMF-water	70	$C_{20}H_{25}N_5O_2$	65.57 (65.55)	6.55 (6.52)	19.12 (19.09)
18	4-OCH_3	214	Ethanol	75	$C_{20}H_{25}N_5O_2$	65.57 (65.60)	6.55 (6.57)	19.12 (19.15)
19	2-C_2H_5	210	acetone	72	$C_{21}H_{27}N_5O$	69.23 (69.20)	7.14 (7.16)	19.23 (19.20)
20	4-C_2H_5	218	pet. ether	71	$C_{21}H_{27}N_5O$	69.23 (69.26)	7.14 (7.13)	19.23 (19.25)
21	2-Br	225	DMF-water	62	$C_{19}H_{22}N_5SBr$	52.90 (52.89)	4.87 (4.90)	16.24 (16.22)
22	4-Cl	226	DMF-water	68	$C_{19}H_{22}N_5SCl$	58.99 (58.97)	5.43 (5.45)	18.11 (18.08)
23	2-OCH_3	224	ethanol	65	$C_{20}H_{25}N_5OS$	62.82 (62.80)	6.28 (6.31)	18.32 (18.30)
24	4-OCH_3	228	DMF-water	64	$C_{20}H_{25}N_5OS$	62.82 (62.85)	6.28 (6.27)	18.32 (18.33)
25	2-C_2H_5	222	methanol	62	$C_{21}H_{27}N_5S$	66.31 (66.28)	6.84 (6.81)	18.42 (18.40)
26	4-C_2H_5	214	ethanol	67	$C_{21}H_{27}N_5S$	66.31 (66.29)	6.84 (6.86)	18.42 (18.44)

C, H, N were within ±0.4%.

Synthesis of 5-(phenyl piperazinyl methylene)-2-(2'-bromophenyl)-thiadiazole (21) : Concentrated sulphuric acid (15 ml) was placed in a conical flask and compound 3 (0.04 mole) was added in small portions over a period of 2 hours with constant stirring while maintaining the temperature at about 0–5 ^{0}C. When the reaction was completed, the mixture was poured onto crushed ice. Precipitated solid thus obtained was filtered, washed with water, dried at room temperature and recrystallized from DMF-water to furnish compound 21. The physical and analytical data of compound 21 is given in ▶ **Table 1**. IR ν_{max} (KBr, cm^{-1}): 299 (aromatic C-H), 2180 (-CN), 3460 (NH), 1009 (C-O-C), 613 (C-Br). ^{1}H-NMR δ ($CDCl_3$ and DMSO-d_6): 4.13 (s, 2H, -NCH_2), 6.90–8.05 (m, 9H, Ar-H), 8.83 (s, 1H, NH-Ar), 2.65 (m, 5H, 4x-CH_2 of piperazine) (ppm). MS: m/z 431.

Other compounds **(22–26)** of this step were also prepared similarly. Their physical and analytical data are given in ▶ **Table 1**.

Pharmacology

Anticonvulsant activity- supra maximal electroshock seizure pattern test (SMES)

Method of Tomen et al. [23] was used for performing the anticonvulsant activity. Rats of Charles Foster strain were used . Rats of both the sex weighing between 90 to 120 grams were used. Activity was performed by dividing the rats into groups. Each group contains 10 animals (rats).The rats were treated with different doses of test drugs and phenytoin sodium 30 mg/kg i.p. The rats were subjected to a shock of 150 M.A. by convulsiometer after 1 hour of drug treatment through ear electrodes for 0.2 s. The presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats. The results are depicted in ▶ **Table 2**

Acute toxicity

Acute toxicity in mice was investigated in mice by following the method of Smith [24] and the results are depicted in ▶ **Table 2**.

Results

Anticonvulsant activity in rats

In the maximal electroshock induced seizure test (MES), out of 24 compounds tested, compounds **9, 15, 21** and **23** exhibited most potent activity with 80%, 80%, 80% and 90% inhibition of seizures respectively. The results are depicted in ▶ **Table 2**.

Acute toxicity in mice

All the compounds **3–26**, were also evaluated for acute toxicity. All compounds showed good value of greater than 1000 mg/kg i.p.

▶ **Table 2** Pharmacological data of compounds (3-26).

Compound	Acute toxicity	Anticonvulsant activity	
	ALD_{50} (mg/kg i.p.)	Dose (mg/kg i.p.)	%inhibition of seizures
3	>1000	30	60**
4	>1000	30	50*
5	>1000	30	60**
6	>1000	30	50*
7	>1000	30	40*
8	>1000	30	40*
9	>1000	30	80***
10	>1000	30	70***
11	>1000	30	70***
12	>1000	30	60**
13	>1000	30	60**
14	>1000	30	60**
15	>1000	30	80***
16	>1000	30	70***
17	>1000	30	70***
18	>1000	30	60**
19	>1000	30	60**
20	>1000	30	60**
21	>1000	30	80***
22	>1000	30	80***
23	>2000	7.5	40*
		15	60**
		30	90***
24	>1000	30	70***
25	>1000	30	60**
26	>1000	30	60**
Phenytoin sodium		30	80***
Propylene glycol		2.0 ml	0

*$p<0.05$, **$p<0.01$, ***$p<0.001$.

thereby suggesting a good safety margin. Compound **23**, exhibit exceptionally high value of ALD_{50} greater than 2000 mg/kg i.p.

Pharmacology

The newly synthesized compounds i. e. compounds (3–8), (9–14), (15–20) and (21–26) were studied for anticonvulsant activity at a dose of 30 mg/kg i.p. These compounds were also evaluated for approximate lethal dose (ALD_{50}). The results of these activities are depicted in ▶ **Table 2**.

Compounds (**3–8**) i.e 2-(phenyl piperazinyl acetyl)-N-(substitutedphenyl)-hydrazinecarbothioamides showed varying degree of protection ranging from 40 % to 60 % against seizures produced by maximal electroshock. Results of anticonvulsant activity shows that compound 3 and compound **5** substituted with bromo and methoxy group respectively at 2nd position of phenyl ring showed appreciable protection of 60 % against convulsions. Compounds **4** and **6** substituted with chloro and methoxy groups respectively at **4** position of phenyl ring showed moderate protection of 50 % against seizures. Compounds **7** and **8** substituted with ethoxy group at 2nd and 4th position of phenylgroup showed least protection of 40 %.

Further, the series was characterized by its trifurcation which leads to the synthesis of triazoles (**9–14**), oxadiazole (**15–20**) and thiadiazoles (**21–26**). Studying the anticonvulsant activity of triazoles (**9–14**) it was noticed that compound 9 having substitution with bromo group at 2nd position of phenyl ring showed good protection of 80 % against seizures which is equipotent to standard drug phenytoin sodiyum (80 %). Compounds **4** and **5** having chloro and methoxy group at 4th and 2nd position of phenyl ring respectively also showed good protection of 70 %. At the same time 60 % inhibition of seizures was shown by compounds **12, 13** and **14** having substitution with 4-methoxy, 2-ethoxy and 4-ethoxy groups on phenyl ring.

Compounds (**15–20**) having different substituted oxadiazole moiety on phenyl piperazine have shown varying degree (50–80 %) of anticonvulsant activity. However, the effect of different substitutions was found to be similar with that of compounds (**9–14**).

Moreover, the compounds (**21–26**) having different substituted thiadiazole moiety on phenyl piperazine ring showed good anticonvulsant response ranging from 60 % to 90 %. Compound **23**, substituted with methoxy group at 2nd position of phenyl ring showed maximum anticonvulsant response of 90 % and was found more potent than standard drug-phenytoin sodium, which provides 80 % inhibition of seizures. Considering the potentiality of this compound, it was studied in detail at three graded dose of 7.5, 15 and 30 mg/kg i.p. and showed protection of 40, 60 and 90 % respectively at these dose levels. Compound **21**, (with bromo group at 2nd position of phenyl ring) also exhibit activity equipotent to standard drug i. e. 80 %. 70 % Inhibition of seizures was shown by compounds 16 and 18 substituted with chloro group and methoxy group respectively at 4th position of phenyl ring. Compounds **25** and **26** substituted with ethoxy group at 2nd and 4th position of phenyl group were found to be least potent (60 %) among thiadiazoles synthesized.

Conclusion

From this study, we may conclude:

1. Compounds with thiadiazole moiety (**21–26**) showed more potent anticonvulsant activity in comparison to their corresponding triazoles (**9–14**) an oxadiazoles (**15–20**).
2. Compounds having bromo group at 2nd position of phenyl group was found to be beneficial for anticonvulsant activity.
3. Presence of methoxy group at 2nd position of phenyl group enhanced anticonvulsant potential when present in thiadiazole, which was not found to enhance activity when present in triazole and oxadiazole.

Conflict of Interest

There is no conflict of interest.

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