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Short communication

Synthesis and pharmacological evaluation of newer substituted benzoxazepine derivatives as potent anticonvulsant agents☆

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Received 22 April 2003; revised and accepted 22 September 2003

Abstract

A series of 2-substitutedphenyl-3-(substitutedphenylamino)methyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (**4a–4p**) and 2-substitutedphenyl-3-substitutedphenylazo-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (**5a–5p**) have been synthesized from 2-substitutedphenyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (**3a–3d**) by the Mannich reaction and diazotization reaction, respectively. All these compounds were screened, in vivo, for their anticonvulsant activity and acute toxicity studies. Compounds **4p** and **5p** were found to be most potent compounds of this series and were compared with the reference drug phenytion sodium, lamotrigine and sodium valproate. The structures of these compounds have been established by IR, ^{1}H NMR and mass spectroscopic data.
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Keywords: Substituted benzoxazepines; Anticonvulsant activity; Acute toxicity

1. Introduction

Compounds containing a fused seven membered heterocyclic ring i.e. benzoxazepines make up a broad class that attracted attention in the past few years owing to its wide range of biological activities especially anticonvulsant [1–4] and CNS depressant activities [5,6]. In view of potential CNS depressant and anticonvulsant activities of benzoxazepine derivatives, we report herein the synthesis of some new 2-substitutedphenyl-3-(substitutedphenylamino)methyl-4-diphenylamino-2,3-dihydro-1,5-benzoxazepines and 2-substitutedphenyl-3-substitutedphenylazo-4-diphenylamino-2,3-dihydro-1,5-benzoxazepines along with their anticonvulsant profile.

2. Chemistry

The synthetic routes of compounds are outlined in Fig. 1. As shown in Fig. 1, the acetylation of diphenylamine yielded *N*-acetyl-diphenylamine i.e. compound **1**, which on further reaction with different substituted aromatic aldehydes yielded their corresponding *N*-substitutedphenyl-*N,N*-diphenyl-propenamides i.e. compounds **2a–2d**. Compounds **2a–2d** on cyclization with 2-aminophenol in the presence of glacial acetic acid gave 2-substitutedphenyl-4-diphenylamino-2,3-dihydro-1,5-benzoxazepines i.e. compounds **3a–3d**. Compounds **3a–3d** further undergoes Mannich reaction with different substituted anilines to afford compounds **4a–4p**. On the other hand, when compounds **3a–3d** reacted with different aryldiazonium salts at 0–5 °C yielded 2-substituted phenyl-3-substitutedphenylazo-4-diphenylamino-2,3-dihydro-1,5-benzoxazepines i.e. compounds **5a–5p**.

The formation of compound **1** was confirmed by the appearance of a sharp singlet at δ 2.56, due to the three protons of $COCH_3$ group and a multiplet of 10 aromatic protons at δ 7.60–6.90 in the ^{1}H NMR spectra. Appearance of a band at 1640 cm^{-1} (C=O) and 1500 cm^{-1} (C–N) in the IR spectrum of compound **1** also supported its structure. Appearance of a band between 1620 and 1625 cm^{-1} (CH=CH) in the IR spectrum of compounds **2a–2d** and appearance of a doublet in between δ 8.60 and δ 8.65 for one proton of =CH–Ar and an another doublet between δ 6.60 and δ

☆ Part of the Ph.D. thesis.
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doi:10.1016/j.ejmech.2003.09.009

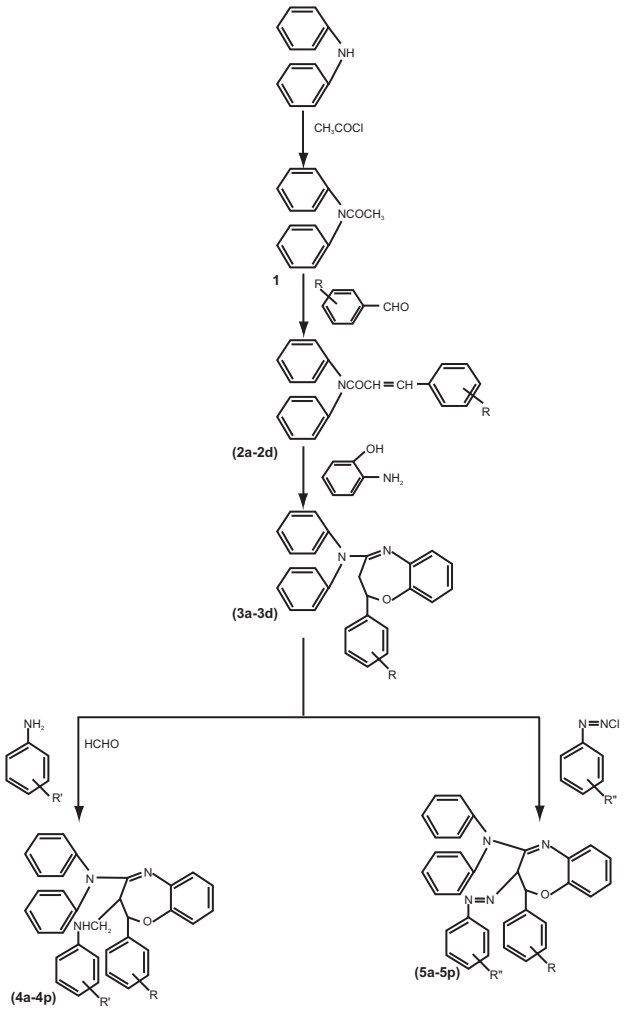

Fig. 1. Route for the synthesis of compounds.

6.68 for one proton of COCH= group in the ^{1}H NMR spectrum, supported their formation. Cyclization of **2a–2d** resulted into compounds **3a–3d**, was confirmed by the presence of a band between 1070 and 1120 cm^{-1} (C–O–C) in the IR spectrum and appearance of a doublet of two protons of C_3–H_2 of oxazepine ring in between δ 3.20 and δ 3.28 along with a triplet of one proton of C_2–H of oxazepine ring between 4.25 and 4.30 in the ^{1}H NMR spectrum. The structure of compounds **4a–4p** was supported by the absence of a triplet between δ 4.25 and δ 4.30 (1H, C_2–H of oxazepine ring) and by the presence of a doublet between δ 4.15 and δ 4.25 (1H, C_2–H of oxazepine) confirms the substitution at the third position of oxazepine ring. Compounds **5a–5p** exhibited a band between 1410 and 1428 cm^{-1} (N=N) in the IR spectrum which confirmed their synthesis.

3. Pharmacological results and discussion

All the newly synthesized compounds were tested in vivo in order to evaluate their anticonvulsant activity. The pharmacological data of all the compounds of this series have been reported in Table 3. These compounds were screened for their anticonvulsant activity against maximal electroshock induced seizures tested at 30 mg kg^{-1} i.p., exhibited substantive anticonvulsant activity. The characteristic feature of this series is the substitution by the different moieties at second and third position of benzoxazepine ring. While evaluating the anticonvulsant activity, it was observed that compound **3a** (having phenyl group at second position of benzoxazepine ring showed least activity (20%) while compound **3d** (having 3-methoxy-4-hydroxy phenyl ring) exhibited maximum response (40%) in comparison to the other substituted compounds.

Further, the next step of this series was characterized by the substitution at the third position of benzoxazepine ring by different arylaminomethylene substitutions. All compounds showed potent anticonvulsant activity, however, compound **4p** (having 2-methoxy phenyl aminomethylene substitution at third position of benzoxazepine ring) have shown most potent response against MES test i.e. 90% protection which is more potent and equipotent than standard drugs phenytoin sodium and lamotrigine. Compounds **4d, 4h** and **4l**, also having the same substitution at third position of benzoxazepine ring, showed better response against MES model i.e. 50%, 50% and 70%, respectively, in comparison to the other substituted derivatives. Moreover, compounds having chloro substituted arylaminomethylene moieties have shown more promising results in comparison to unsubstituted arylaminomethylene moiety (as shown in Table 3).

On the other side, compounds **5a–5p**, substituted with different arylazo moieties at third position of benzoxazepine ring, have shown varying degree (20–80%) of anticonvulsant

Table 1
Physical and analytical data of compounds **1, 2a–2d** and **3a–3d**

Compounds	R	m.p. (°C)	Yield (%)	Recrystallization solvent	Molecular formula	% elemental analysis		
						C calculated (found)	H calculated (found)	N calculated (found)
1	–	102	78	Ethanol	$C_{14}H_{13}NO$	79.62 (79.58)	6.16 (6.20)	6.64 (6.60)
2a	H	95	72	Methanol–water	$C_{21}H_{17}NO$	84.28 (84.24)	5.69 (5.73)	4.68 (4.72)
2b	4-OCH_3	91	70	Ethanol–water	$C_{22}H_{19}NO_2$	80.24 (80.20)	5.78 (5.82)	4.26 (4.22)
2c	4-$N(CH_3)_2$	82	68	Benzene–pet. ether	$C_{23}H_{22}N_2O$	80.70 (80.74)	6.43 (6.39)	8.19 (8.15)
2d	3-OCH_3, 4-OH	80	75	Ethanol	$C_{22}H_{19}NO_3$	76.52 (76.48)	5.51 (5.47)	4.06 (4.10)
3a	H	104	68	Methanol	$C_{27}H_{22}N_2O$	83.08 (83.12)	5.64 (5.60)	7.18 (7.14)
3b	4-OCH_3	100	70	Acetic acid–water	$C_{28}H_{24}N_2O_2$	80.00 (80.04)	5.71 (5.75)	6.67 (6.62)
3c	4-$N(CH_3)_2$	96	74	Ethanol–water	$C_{29}H_{27}N_3O$	80.37 (80.33)	6.24 (6.20)	9.70 (9.74)
3d	3-OCH_3, 4-OH	99	65	Acetic acid–water	$C_{28}H_{24}N_2O_3$	77.06 (77.10)	5.50 (5.54)	6.42 (6.46)

Table 2
Physical and analytical data of compounds **4a–4p** and **5a–5p**

Compounds	R	R′	m.p. (°C)	Yield (%)	Recrystallization solvent	Molecular formula	% elemental analysis		
							C calculated (found)	H calculated (found)	N calculated (found)
4a	H	H	112	70	DMF–water	$C_{34}H_{29}N_3O$	82.42 (82.38)	5.86 (5.90)	8.48 (8.52)
4b	H	2-Cl	115	78	Methanol–water	$C_{34}H_{28}N_3ClO$	77.05 (77.09)	5.29 (5.33)	7.93 (7.97)
4c	H	3-Cl	110	72	Methanol–water	$C_{34}H_{28}N_3ClO$	77.05 (77.00)	5.29 (5.35)	7.93 (7.99)
4d	H	2-OCH_3	120	70	Ethanol–water	$C_{35}H_{31}N_3O_2$	80.00 (80.05)	5.90 (5.94)	8.00 (7.96)
4e	4-OCH_3	H	113	75	Ethanol–water	$C_{35}H_{31}N_3O_2$	80.00 (80.04)	5.90 (5.86)	8.00 (8.04)
4f	4-OCH_3	2-Cl	118	72	Acetic acid–water	$C_{35}H_{30}N_3ClO_2$	75.07 (75.03)	5.36 (5.32)	7.51 (7.55)
4g	4-OCH_3	3-Cl	114	70	Acetic acid–water	$C_{35}H_{30}N_3ClO_2$	75.07 (75.12)	5.36 (5.30)	7.51 (7.47)
4h	4-OCH_3	2-OCH_3	122	68	Methanol–water	$C_{36}H_{33}N_3O_3$	77.84 (77.88)	5.95 (5.99)	7.57 (7.53)
4I	4-$N(CH_3)_2$	H	100	70	DMF–water	$C_{36}H_{34}N_4O$	80.30 (80.26)	6.32 (6.36)	10.41 (10.45)
4j	4-$N(CH_3)_2$	2-Cl	108	72	Benzene–pet. ether	$C_{36}H_{33}N_4ClO$	75.46 (75.50)	5.76 (5.72)	9.78 (9.74)
4k	4-$N(CH_3)_2$	3-Cl	104	68	Methanol–water	$C_{36}H_{33}H_4ClO$	75.46 (75.42)	5.76 (5.80)	9.78 (9.82)
4l	4-$N(CH_3)_2$	2-OCH_3	107	70	DMF–water	$C_{37}H_{36}N_4O_2$	78.17 (78.13)	6.34 (6.30)	9.86 (9.82)
4m	3-OCH_3, 4-OH	H	111	65	Ethanol–water	$C_{35}H_{31}N_3O_3$	77.63 (77.45)	5.73 (5.94)	7.76 (7.80)
4n	3-OCH_3, 4-OH	2-Cl	114	67	Methanol–water	$C_{35}H_{30}N_3ClO_3$	72.98 (72.89)	5.21 (5.85)	7.30 (7.25)
4o	3-OCH_3, 4-OH	3-Cl	116	60	Ethanol–water	$C_{35}H_{30}N_3ClO_3$	72.98 (72.88)	5.21 (5.28)	7.30 (7.34)
4p	3-OCH_3, 4-OH	2-OCH_3	126	62	Benzene–pet. ether	$C_{36}H_{33}N_3O_4$	75.66 (75.70)	5.78 (5.82)	7.36 (7.32)
5a	H	H	118	50	Benzene–pet. ether	$C_{33}H_{26}N_4O$	80.16 (80.20)	5.26 (5.24)	11.34 (11.38)
5b	H	2-Cl	125	52	Methanol	$C_{33}H_{25}N_4ClO$	74.93 (74.97)	4.73 (4.77)	10.60 (10.56)
5c	H	3-Cl	120	55	Ethanol–water	$C_{34}H_{25}N_4ClO$	74.93 (74.89)	4.73 (4.69)	10.60 (10.64)
5d	H	2-OCH_3	123	55	Methanol–water	$C_{34}H_{28}N_4O_2$	77.86 (77.82)	5.34 (5.30)	10.69 (10.66)
5e	4-OCH_3	H	112	53	Acetic acid–water	$C_{34}H_{28}N_4O_2$	77.86 (77.90)	5.34 (5.38)	10.69 (10.64)
5f	4-OCH_3	2-Cl	120	55	DMF–water	$C_{34}H_{27}N_4ClO_2$	73.05 (73.01)	4.83 (4.87)	10.03 (10.08)
5g	4-OCH_3	3-Cl	116	58	DMF–water	$C_{34}H_{27}N_4ClO_2$	73.05 (73.09)	4.83 (4.79)	10.03 (10.07)
5h	4-OCH_3	2-OCH_3	119	50	Ethanol–water	$C_{35}H_{30}N_4O_3$	75.81 (75.85)	5.42 (5.46)	10.11 (10.15)
5i	4-$N(CH_3)_2$	H	126	57	DMF–water	$C_{35}H_{31}N_5O$	78.21 (78.25)	5.77 (5.81)	13.04 (13.08)
5j	4-$N(CH_3)_2$	2-Cl	122	60	DMF–water	$C_{35}H_{30}N_5ClO$	73.49 (73.45)	5.25 (5.29)	12.25 (12.29)
5k	4-$N(CH_3)_2$	3-Cl	128	54	Ethanol–water	$C_{35}H_{30}N_5ClO$	73.49 (73.53)	5.25 (5.21)	12.25 (12.20)
5l	4-$N(CH_3)_2$	2-OCH_3	132	50	Methanol–water	$C_{36}H_{33}N_5O_2$	76.19 (76.23)	5.82 (5.86)	12.34 (12.30)
5m	3-OCH_3, 4-OH	H	125	53	Acetic acid–water	$C_{34}H_{28}N_4O_3$	75.55 (75.51)	5.19 (5.23)	10.37 (10.33)
5n	3-OCH_3, 4-OH	2-Cl	120	57	Benzene–pet. ether	$C_{34}H_{27}N_4ClO_3$	71.02 (71.06)	4.70 (4.75)	9.75 (9.71)
5o	3-OCH_3, 4-OH	3-Cl	124	62	Ethanol	$C_{34}H_{27}N_4ClO_3$	71.02 (70.08)	4.70 (4.81)	9.75 (9.79)
5p	3-OCH_3, 4-OH	2-OCH_3	130	58	Methanol	$C_{35}H_{30}N_4O_4$	73.68 (73.52)	5.26 (5.30)	9.82 (9.86)

activity. However, the effect of different substitution was found to be similar with that of compounds **4a–4p** i.e. compounds **5d, 5h, 5l** and **5p** (having 2-methoxyphenylazo substitution) showed better response i.e. 40%, 40%, 60% and 80%, respectively, in comparison to the other substituted derivatives of this step.

Therefore, considering the compound of this series, it may be concluded that 3-methoxy-4-hydroxyphenylsubstituted benzoxazepine derivatives showed promising anticonvulsant activity. Further, 2-methoxy substituted arylaminomethylene and 2-methoxysubstituted arylazo derivatives have shown more potent response i.e. compounds **4p** and **5p**, respectively. These compounds were tested at three graded doses i.e. 7.5, 15 and 30 mg kg^{-1} i.p. and showed higher protection against MES model than the reference drug phenytoin sodium at all three doses and less potent than standard drug lamtrigine at lower doses (Fig. 2). Being the most potent compound of this series, compounds **4p** and **5p** were compared with reference drug sodium valproate. Compound **5p** have shown more potent anticonvulsant activity than sodium valproate at all three graded doses (20, 40 and 80 mg kg^{-1} i.p.) (Fig. 3) whereas compound **4p** showed less potent and equipotent response than the references drug sodium valproate (Fig. 3).

4. Conclusion

While considering all the newly synthesized compounds of this series together, we may conclude that:

1. Compounds having 3-methoxy-4-hydroxyphenyl substitution at second position of benzoxazepine ring showed better protection against MES test.
2. 2-Methoxyarylamino as well as 2-methoxyarylazo substituted compounds showed more promising results than the other substituted ones.
3. Compounds having arylazo substitution showed better response towards pentylene tetrazole (PTZ) model than arylaminomethylene substituted compounds.
4. Compound substituted with different arylaminomethylene moieties showed potent response against MES model than compounds substituted with different arylazo moieties.

Table 3
Pharmacological data of compounds **3a–3d, 4a–4p** and **5a–5p**

Compounds	Acute toxicity ALD50 (mg kg^{-1} p.o.)	Dose (mg kg^{-1} i.p.)		Anticonvulsant activity (% inhibition)	
		For MES model	For PTZ model	For MES model	For PTZ model
3a	>1000	30	–	20	–
3b	>1000	30	–	30	–
3c	>1000	30	–	30	–
3d	>1000	30	–	40	–
4a	>1000	30	–	40	–
4b	>1000	30	–	30	–
4c	>1000	30	–	40	–
4d	>1000	30	–	50	–
4e	>1000	30	–	40	–
4f	>1000	30	–	30	–
4g	>1000	30	–	40	–
4h	>1000	30	–	50	–
4i	>1000	30	–	50	–
4j	>1000	30	–	50	–
4k	>1000	30	–	60	–
4l	>1000	30	–	70 *	–
4m	>1000	30	–	50	–
4n	>1000	30	–	60	–
4o	>1000	30	–	60	–
4p	>1000	7.5	20	30	20
		15	40	50	30
		30	80	90 *	80 *
5a	>1000	30	–	20	–
5b	>1000	30	–	30	–
5c	>1000	30	–	30	–
5d	>1000	30	–	40	–
5e	>1000	30	–	30	–
5f	>1000	30	–	30	–
5g	>1000	30	–	30	–
5h	>1000	30	–	40	–
5i	>1000	30	–	40	–
5j	>1000	30	–	50	–
5k	>1000	30	–	50	–
5l	>1000	30	–	60	–
5m	>1000	30	–	40	–
5n	>1000	30	–	50	–
5o	>1000	30	–	60	–
5p	>1000	7.5	20	20	30
		15	40	40	50
		30	80	80 *	90 *
P.G. [a]		0.5 ml	0.5 ml	0	0
Phenytoin sodium [b]		7.5	–	20	–
		15	–	50	–
		30	–	80 *	–
Lamotrigine [b]		7.5	–	20	–
		15	–	50	–
		30	–	90 *	–
Sodium valproate [c]		–	20	–	30
		–	40	–	50
		–	80	–	80 *

* $P < 0.001$.
[a] Propylene glycol standard for control group.
[b] Standard drug for SMES pattern test.
[c] Standard drug for PTZ seizure pattern test.

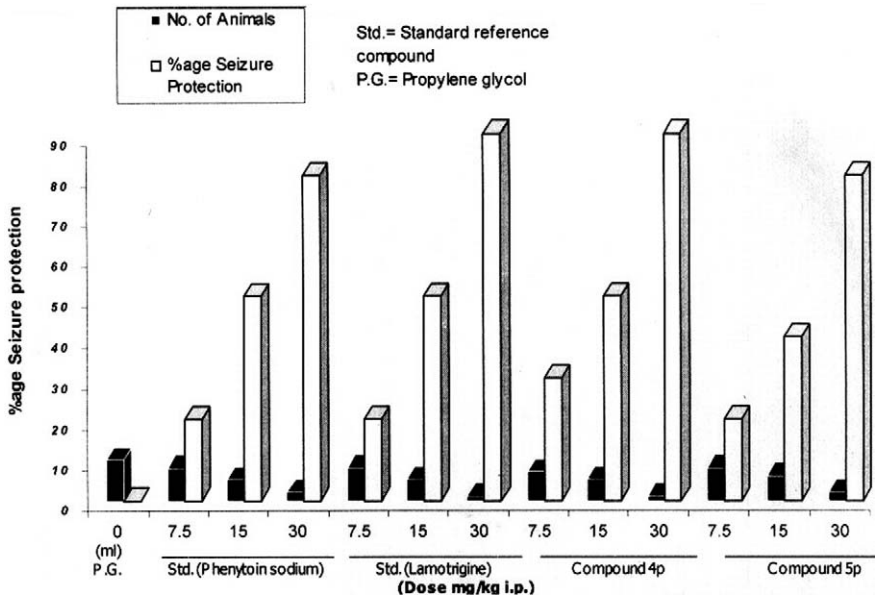

Fig. 2. The bar diagram showing anticonvulsant activity (%age seizure protection) of compounds 4p and 5p their comparison with phenytoin sodium and lamotrigine in supra maximal electroshock pattern test.

5. Experimental

5.1. Chemistry

Melting points were taken in open capillaries with the help of thermonic melting point apparatus and are uncorrected. The purity of the compounds was checked by thin layer chromatography on silica gel-G plates, eluent was a mixture of methanol–benzene in 2:8 proportion and spots were located by iodine. Elemental analysis were performed on CHN analyzer, Carlo Erba 1108 analyzer at the Central Drug Research Institute (Lucknow, India). The IR spectra were recorded on Perkin Elmer 881 FTIR spectrophotometer (ν_{max} in cm^{-1}). The ^1H NMR spectra were recorded in $CDCl_3$ on Brucker DRX-300 FTNMR instrument, mass spectra were determined on JEOL D-300 instrument.

5.1.1. N-*Acetyl-diphenylamine (**1**)*

To the solution of diphenylamine (0.01 mol) in dry chloroform (50 ml), acetyl chloride (0.01 mol) was added drop-by-drop at 0–5°. The reaction mixture was stirred for 4 h at room temperature and then solvent was distilled off. The residue thus obtained was crystallized with ethanol to give compound **1**. Physical, analytical and spectroscopic data are given in Tables 1 and 4, respectively.

5.1.2. N-*Substitutedphenyl*-N,N-*diphenylpropenamide (**2a–2d**)*

The equimolar mixture (0.01 mol) of *N*-acetyl-diphenylamine and different aromatic aldehyde in ethanol (50 ml) was refluxed for 10–12 h in the presence of 2% NaOH solution (2 ml). The reaction mixture was distilled out and poured onto ice in each case. The solution was then

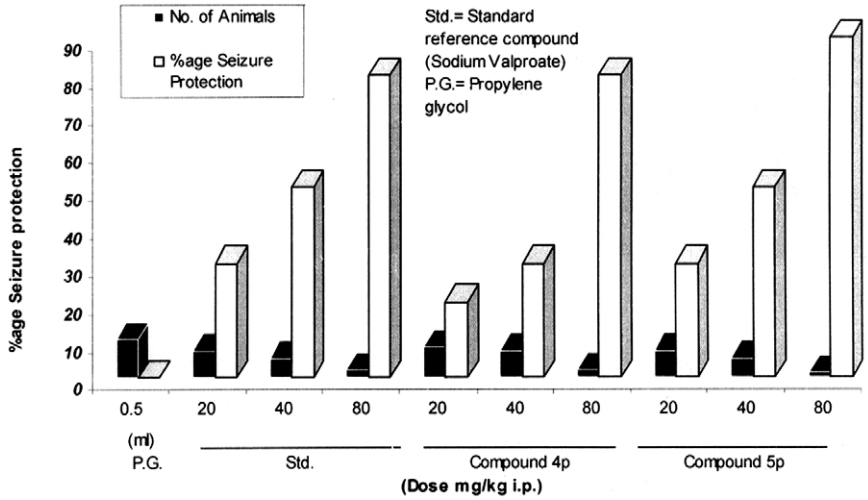

Fig. 3. The diagram showing anticonvulsant activity (%age seizure protection) of compounds 4p and 5p their comparison with sodium valproate in pentylene tetrazol seizure pattern test.

Table 4
Spectral data of compounds **1, 2a–2d, 3a–3d, 4a–4p** and **5a–5p**

Compounds	$[M]^+$ *m/z*	^1H NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
1	211	7.60–6.90 (m, 10H, Ar–H), 2.56 (s, 3H, $COCH_3$)	1640 (C=O), 1575 (C⋯C of aromatic ring), 1500 (C–N)
2a	299	8.60 (d, 1H, =CH–Ar), 7.80–6.85 (m, 15H, Ar–H), 6.65 (d, 1H, COCH=)	1660 (C=O), 1620 (CH=CH), 1580 (C⋯C of aromatic ring)
2b	329	8.65 (d, 1H, =CH–Ar), 7.80–6.90 (m, 14H, Ar–H), 6.65 (d, 1H, COCH=), 3.70 (s, 3H, OCH_3)	1660 (C=O), 1625 (CH=CH), 1578 (C⋯C of aromatic ring)
2c	342	8.62 (d, 1H, =CH–Ar), 7.80–6.92 (m, 14H, Ar–H), 6.68 (d, 1H, COCH=), 1.5 [s, 6H, $N(CH_3)_2$]	1665 (C=O), 1622 (CH=CH), 1580 (C⋯C of aromatic ring)
2d	345	11.30 (s, 1H, OH), 8.60 (d, 1H, =CH–Ar), 7.90–6.85 (m, 13H, Ar–H), 6.60 (d, 1H, COCH=), 3.50 (s, 3H, OCH_3)	3380 (O–H), 1620 (C=O), 1620 (CH=CH), 1575 (C⋯C of aromatic ring)
3a	390	3.25 (d, 2H, C_3–H_2 of oxazepine ring), 7.00–6.35 (m, 19H, Ar–H), 4.25 (t, 1H, C_2–H of oxazepine ring)	1668 (C=N), 1565 (C⋯C of aromatic ring), 1485 (C–N), 1070 (C–O–C)
3b	420	3.20 (d, 2H, C_3–H_2 of oxazepine ring), 7.00–6.38 (m, 18H, Ar–H), 4.25 (t, 1H, C_2–H of oxazepine ring), 3.65 (s, 3H, OCH_3)	1665 (C=N), 1562 (C⋯C of aromatic ring), 1480 (C–N), 1070 (C–O–C)
3c	433	3.28 (d, 2H, C_3–H_2 of oxazepine ring), 7.00–6.40 (m, 18H, Ar–H), 4.28 (t, 1H, C_2–H of oxazepine ring), 1.5 [s, 6H, $N(CH_3)_2$]	1665 (C=N), 1560 (C⋯C of aromatic ring), 1480 (C–N), 1077 (C–O–C)
3d	436	11.20 (ss, 1H, OH), 3.20 (d, 2H, C_3–H_2 of oxazepine ring), 7.00–6.50 (m, 17H, Ar–H), 4.30 (t, 1H, C_2–H of oxazepine ring), 3.55 (s, 3H, OCH_3)	3669 (O–H), 1668 (C=N), 1560 (C⋯C of aromatic ring), 1489 (C–N), 1072 (C–O–C)
4a	495	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.45–6.50 (m, 24H, Ar–H), 4.19 (d, 1H, C_2–H of oxazepine ring), 3.40 (hump, 1H, CH_2NH exchangeable), 1.85 (hump, 2H, $NHCH_2$)	1600 (C=N), 1510 (C⋯C of aromatic ring), 1480 (C–N), 1120 (C–O–C)
4b	530	3.72 (dd, 1H, C_3–H of oxazepine ring), 7.45–6.52 (m, 23H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.43 (hump, 1H, CH_2NH exchangeable), 1.85 (hump, 2H, CH_2NH)	1600 (C=N), 1500 (C⋯C of aromatic ring), 1485 (C–N), 1120 (C–O–C), 680 (C–Cl)
4c	530	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.40–6.48 (m, 23H, Ar–H), 4.20 (d, IH, C_2–H of oxazepine ring), 3.40 (hump, 1H, CH_2NH exchangeable), 1.83 (hump, 2H, CH_2NH)	1610 (C=N), 1520 (C⋯C of aromatic ring), 1480 (C–N), 1122 (C–O–C), 685 (C–Cl)
4d	525	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.43–6.50 (m, 23H, Ar–H), 4.22 (d, 1H, C_2–H of oxazepine ring), 3.40 (hump, 1H, CH_2NH exchangeable), 3.75 (s, 3H, OCH_3), 1.80 (hump, 2H, CH_2NH)	1605 (C=N), 1510 (C⋯C of aromatic ring), 1485 (C–N), 1120 (C–O–C)
4e	525	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.45–6.50 (m, 23H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.70 (s, 3H, OCH_3), 3.45 (hump, 1H, CH_2NH exchangeable), 1.82 (hump, 2H, CH_2NH)	1620 (C=N), 1510 (C⋯C of aromatic ring), 1490 (C–N), 1120 (C–O–C)
4f	560	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.45–6.55 (m, 22H, Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 3.76 (s, 3H, OCH_3), 3.40 (hump, IH, CH_2NH exchangeable), 1.80 (hump, 2H, CH_2NH)	1620 (C=N), 1510 (C⋯C of aromatic ring), 1485 (C–N), 1125 (C–O–C), 685 (C–Cl)
4g	560	3.73 (dd, 1H, C_3–H of oxazepine ring), 7.40–6.50 (m, 22H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.70 (s, 3H, OCH_3), 3.45 (hump, 1H, CH_2NH exchangeable), 1.83 (hump, 2H, CH_2NH)	1625 (C=N), 1520 (C⋯C of aromatic ring), 1482 (C–N), 1125 (C–O–C), 700 (C–Cl)
4h	555	3.72 (dd, 1H, C_3–H of oxazepine ring), 7.35–6.45 (m, 22H, Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 3.77 (s, 6H, 2 × OCH_3), 3.42 (hump, 1H, CH_2NH exchangeable), 1.80 (hump, 2H, CH_2NH)	1620 (C=N), 1500 (C⋯C of aromatic ring), 1485 (C–N), 1120 (C–O–C)
4i	538	3.73 (dd, 1H, C_3–H of oxazepine ring), 7.40–6.68 (m, 23H, Ar–H), 4.18 (d, 1H, C_2–H of oxazepine ring), 3.44 (hump, 1H, CH_2NH exchangeable), 2.80 [s, 6H, $N(CH_3)_2$], 1.82 (hump, 2H, $NHCH_2$)	1605 (C=N), 1530 (C⋯C of aromatic ring), 1510 (C–N), 1300 (C–O–C)
4j	573	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.43–6.68 (m, 22H, Ar–H), 4.18 (d, 1H, C_2–H of oxazepine ring), 3.43 (hump, 1H, CH_2NH exchangeable), 2.85 [s, 6H, $N(CH_3)_2$], 1.80 (hump, 2H, $NHCH_2$)	1620 (C=N), 1525 (C⋯C of aromatic ring), 1500 (C–N), 1300 (C–O–C), 675 (C–Cl)
4k	573	3.72 (dd, 1H, C_3–H of oxazepine ring), 7.45–6.70 (m, 22H, Ar–H), 4.15 (d, 1H, C_2–H of oxazepine ring), 3.45 (hump, 1H, CH_2 NH exchangeable), 2.82 [(s, 6H, $NCH_3)_2$] 1.85 (hump, 2H, NHH CH_2)	1600 (C=N), 1550 (C⋯C of aromatic ring), 1500 (C–N), 1310 (C–O–C), 680 (C–Cl)

(continued on next page)

Table 4
(continued)

Compounds	$[M]^+$ *m/z*	^1H NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
4l	568	3.70 (dd, 1H, C_3–H of oxazepine ring), 7.42–6.70 (m, 22H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.85 (s, 3H, OCH_3), 3.45 (hump, 1H, CH_2NH exchangeable), 2.80 [(s, 6H, $N(CH_3)_2$], 1.82 (hump, 2H, $NHCH_2$)	1600 (C=N), 1545 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1300 (C–O–C)
4m	541	12.70 (ss, 1H, OH), 3.75 (dd, 1H, C_3–H of oxazepine ring), 7.40–6.70 (m, 22H, Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 3.80 (s, 3H, OCH_3), 3.43 (hump, 1H, CH_2NH exchangeable), 1.85 (hump, 2H, $NHCH_2$)	3660 (O–H), 1610 (C=N), 1550 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1300 (C–O–C)
4n	576	12.72 (ss, 1H, OH), 3.75 (dd, 1H, C_3–H of oxazepine ring), 7.45–6.70 (m, 21H, Ar–H), 4.24 (d, 1H, C_2–H of oxazepine ring), 3.80 (s, 3H, OCH_3), 3.40 (hump, 1H, CH_2NH exchangeable), 1.85 (hump, 2H, $NHCH_2$)	3665 (O–H), 1600 (C=N), 1555 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1310 (C–O–C), 680 (C–Cl)
4o	576	12.70 (ss, 1H, OH), 3.73 (dd, 1H, C_3–H of oxazepine ring), 7.40–6.65 (m, 2IH, Ar–H), 4.20 (d, 1H,C_2–H of oxazepine ring), 3.83 (s, 3H, OCH_3) 1.83 (hump, 2H, $NHCH_2$)	3662 (O–H), 1610 (C=N), 1550 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1300 (C–O–C), 685 (C–Cl)
4p	571	12.73 (ss, 1H, OH), 3.70 (dd, IH, C_3–H of oxazepine ring), 7.43–6.68 (m, 21H, Ar–H), 4.22 (d, 1H, C_2–H of oxazepine ring), 3.85 (s, 6H, 2 × OCH_3), 3.40 (hump, 1H, CH_2NH exchangeable), 1.80 (hump, 2H, $NHCH_2$)	3660 (O–H), 1600 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1305 (C–O–C)
5a	494	3.72 (d, 1H, C_3–H of oxazepine ring), 7.25–6.67 (m, 24H, Ar–H), 4.23 (d, 1H, C_2–H of oxazepine ring)	1660 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1425 (N=N), 1330 (C–O–C)
5b	529	3.70 (d, 1H, C_3–H of oxazepine ring), 7.20–6.60 (m, 23H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring)	1600 (C=N), 1555 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1420 (N=N), 1330 (C–O–C), 688 (C–Cl)
5c	529	3.75 (d, 1H, C_3–H of oxazepine ring), 7.15–6.55 (m, 23H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring)	1620 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1410 (N=N), 1300 (C–O–C), 700 (C–Cl)
5d	524	3.75 (d, 1H, C_3–H of oxazepine ring), 7.20–6.60 (m, 23 H, Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 3.79 (s, 3H, OCH_3)	1600 (C=N), 1550 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1425 (N=N), 1330 (C–O–C)
5e	524	3.77 (d, 1H, C_3–H of oxazepine ring), 7.36–6.55 (m, 23H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.85 (s, 3H, OCH_3)	1600 (C=N), 1550 (C⁻⁻⁻⁻Cof aromatic ring), 1495 (C–N), 1420 (N=N), 1300 (C–O–C)
5f	559	3.70 (d, 1H, C_3–H of oxazepine ring), 7.20–6.50 (m, 22H, Ar–H), 4.23 (d, 1H, C_2–H of oxazepine ring), 3.85 (s, 3H, OCH_3)	1620 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1425 (N=N), 1320 (C–O–C); 680 (C–Cl)
5g	559	3.73 (d, 1H, C_3–H of oxazepine ring), 7.30–6.50 (m, 22H, Ar–H) 4.25 (d, 1H, C_2–H of oxazepine ring), 3.80 (s, 3H, OCH_3)	1610 (C=N), 1555 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1428 (N=N), 1325 (C–O–C), 675 (C–Cl)
5h	554	3.72 (d, 1H, C_3–H of oxazepine ring), 7.32–6.50 (m, 22H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.80 (s, 6H, 2 × OCH_3)	1605 (C=N), 1552 (C⁻⁻⁻⁻C of aromatic ring), 1505 (C–N), 1420 (N=N), 1320 (C–O–C)
5i	537	3.70 (d, 1H, C_3–H of oxazepine ring), 7.20–6.60 (m, 23H, Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 2.80 [s, 6H, $N(CH_3)_2$]	1595 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1420 (N=N), 1330 (C–O–C)
5j	572	3.72 (d, 1H, C_3–H of oxazepine ring), 7.25–6.60 (m, 22H, Ar–H), 4.22 (d, 1H, C_2–H of oxazepine ring), 2.80 [s, 6H, $N(CH_3)_2$]	1598 (C=N), 1555 (C⁻⁻⁻⁻C of aromatic ring), 1500 (C–N), 1422 (N=N), 1300 (C–O–C), 680 (C–Cl)
5k	572	3.73 (d, 1H, C_3–H of oxazepine ring), 7.20–6.55 (m, 22H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 2.85 [s, 6H, $N(CH_3)_2$]	1600 (C=N), 1550 (C⁻⁻⁻⁻C of aromatic ring), 1505 (C–N), 1420 (N=N), 1290 (C–O–C), 700 (C–Cl)
5l	567	3.70 (d, 1H, C_3–H of oxazepine ring), 7.25–6.60 (m, 22Hm Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 3.80 (s, 3H, OCH_3), 2.82 [s, 6H, $N(Ch_3)_2$]	1620 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1428 (N=N), 1300 (C–O–C)
5m	540	12.70 [(s, 1H, OH), 3.73 (d, 1H, C_3–H of oxazepine ring), 7.23–6.60 (m, 23H, Ar–H), 4.26 (d, 1H, C_2–H of oxazepine ring), 3.78 (s, 3H, OCH_3)	3660 (O–H), 1600 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1420 (N=N), 1330 (C–O–C)
5n	575	12.75 (s, 1H, OH), 3.70 (d, 1H, C_3–H of oxazepine ring), 7.20–6.53 (m, 22 H, Ar–H), 4.20 (d, 1H, C_2–H of oxazepine ring), 3.77 (s, 3H, OCH_3)	3660 (O–H), 1610 (C=N), 1556 (C⁻⁻⁻⁻C of aromatic ring), 1420 (N=N), 1333 (C–O–C), 700 (C–Cl)
5o	575	12.72 (s, 1H, OH), 3.74 (d, 1H, C_3–H of oxazepine ring), 7.25–6.62 (m, 22 H, Ar–H), 4.23 (d, 1H, C_2–H of oxazepine ring), 3.77 (s, 3H, OCH_3)	3665 (O–H), 1598 (C=N), 1550 (C⁻⁻⁻⁻CC of aromatic ring), 1505 (C–N), 1425 (N=N), 1332 (C–O–C), 675 (C–Cl)
5p	570	12.70 (s, 1H, OH), 3.70 (d, 1H, C_3–H of oxazepine ring), 7.20–6.60 (m, 22 H, Ar–H), 4.25 (d, 1H, C_2–H of oxazepine ring), 3.75 (s, 3H, OCH_3)	3660 (O–H), 1595 (C=N), 1560 (C⁻⁻⁻⁻C of aromatic ring), 1510 (C–N), 1420 (N=N), 1300 (C–O–C)

mixed with benzene and separated by separating funnel. The benzene from an organic layer was distilled off and the residue thus obtained was washed with water several times and finally recrystallized from suitable solvents to afford compounds **2a–2d**. Physical, analytical and spectroscopic data are given in Tables 1 and 4, respectively.

*5.1.3. 2-Substitutedphenyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (**3a–3d**)*

An equimolar mixture (0.01 mol) of ethanolic solution of compounds **2a–2d** and 2-aminophenol was refluxed for 3–4 h in the presence of few drops of glacial acetic acid (1 ml), completion of the reaction was determined by TLC. The solvent was distilled off under reduced pressure and the solid thus obtained was recrystallized by suitable solvents to give compounds **3a–3d**. Physical, analytical and spectroscopic data are given in Tables 1 and 4, respectively.

*5.1.4. 2-Substitutedphenyl-3-(substitutedphenylamino) methyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (**4a–4p**)*

Different aromatic anilines (0.001 mol) and formaldehyde (0.001 mol) were added to the methanolic solution of compounds **3a–3d** (0.001 mol) and refluxed for 4–6 h. The resultant mixture was concentrated, cooled and poured onto ice. Separated solid was filtered and recrystallized from suitable solvents to yield compounds **4a–4p**. Physical, analytical and spectroscopic data are given in Tables 2 and 4, respectively.

*5.1.5. 2-Substitutedphenyl-3-substitutedphenylazo-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (**5a–5p**)*

Aryldiazonium salt solution of different anilines (0.001 mol) was added dropwise with stirring to the ethanolic solution of compounds **3a–3d** (0.001 mol) containing sodium acetate (0.5 g) at 0–5°. The reaction mixture was kept at room temperature for 2 h and poured onto ice cold water. The solid thus obtained was washed several times with water, filtered and then recrystallized by suitable solvents to afford compounds **5a–5p**. Physical, analytical and spectroscopic data are given in Tables 2 and 4, respectively.

5.2. Pharmacology

5.2.1. Acute toxicity

The compounds were investigated for their acute toxicity (ALD_{50}) in albino mice by following the method of Smith [7].

5.2.2. Anticonvulsant activity

5.2.2.1. Supra maximal electroshock seizure (SMES) pattern test. This activity was performed according to the method of Tomon et al. [8] on albino rats of the Charles foster strain of either sex, weighing, between 80 and 120 g. Rats were divided into the groups of 10 animals and pregnancy was excluded in female rats. The rats were treated with the different doses of test drugs or phenytoin sodium 30 mg kg^{-1} i.p. or lamotrigine 30 mg kg^{-1} i.p. After 1 h, they were subjected to the shock of 150 mA by convulsiometer through ear electrodes for 0.2 s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

5.2.2.2. Pentylene tetrazole (PTZ) induced seizures test. It was performed according to the method of Fisher [9]. Albino rats, weighing 100–120, were injected with PTZ in a dose of 70 mg kg^{-1} subcutaneously in scruff of neck. After 2–4 min of PTZ injection animals developed the sequence of excitement, myoclonic jerks, clonic seizures, one or more maximal tonic seizures. Animals exhibiting these seizure patterns were selected and divided into the groups of 10 animals each. Standard drug in this model was sodium valproate (80 mg kg^{-1} i.p.) and was injected 60 min prior to PTZ challenge.

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