Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 41 (2006) 417–422
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://france.elsevier.com/direct/ejmech

Short communication

Synthesis of some new substituted triazolo [4,3-*a*] [1,4] benzodiazepine derivatives as potent anticonvulsants

B. Narayana [a,*], K.K. Vijaya Raj [a], B.V. Ashalatha [a], N. Suchetha Kumari [b]

[a] *Department of Post-Graduate Studies and Research in Chemistry, Mangalore University, Mangalagangotri 574 199, India*
[b] *Department of Biochemistry, K.S. Hegde Medical Academy, Deralakatte 574 162, India*

Received 17 July 2005; received in revised form 10 December 2005; accepted 27 December 2005
Available online 10 February 2006

Abstract

Novel 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines (**5a–f**) were prepared by treating 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione with various aromatic acid hydrazides. The newly prepared compounds were characterized by spectral analysis. Compounds were tested for anticonvulsant activity. Four of the tested compounds such as **5a, 5d, 5e** and **5f** exhibited excellent anticonvulsant activity in comparison with standard drug, diazepam.

Keywords: Synthesis; Triazolo benzodiazepine; Anticonvulsants

1. Introduction

1,4-Benzodiazepine derivatives display tranquilizing, muscle-relaxant, anti-convulsant and sedative effects [1]. Today many benzodiazepines are widely used as daytime sedatives, tranquilizers, sleep inducers, anesthetics, anticonvulsants and muscle relaxants [2]. The use of this class of compounds with therapeutic purposes is not only confined to anxiety and stress conditions, given that minor changes in their structures can produce a host of different biological activities, and novel applications are continuously emerging [3–7]. Five-atom heterocyclic fused benzodiazepine ring systems occupy a prominent place among drugs for treatment of CNS disorders [8]. The introduction of alprazolam, triazolam and midazolam (Fig. 1) in chemotherapy has enhanced the interest in the preparation of novel five-atom heterocyclic fused benzodiazepine ring systems. Numerous analogs of alprazolam, triazolam and midazolam have been described, and they have shown different pharmacological profiles related to those of their parent compounds [9].

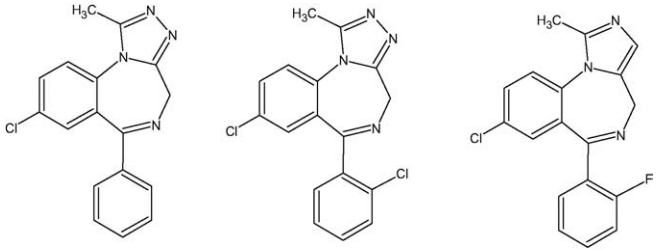


Fig. 1.

Herein, we describe the synthesis of novel 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4H-[1,2,4]triazolo[4,3-*a*][1,4] benzodiazepines, appear to be promising anticonvulsant agents with CNS depressant activity which are analogous to midazolam and alprazolam. The triazole ring increases the basicity of the benzodiazepine system and thereby confers stability to its salts in solution and rapid metabolism. The structure activity studies reveal that electron withdrawing substituents such as chloro and bromo at C-8 confer high activity. Replacement of phenyl group at C-6 by other substituents decreases the potency. Chloro, bromo or fluoro substituents at C′-2 also enhance the potency [8a]. Here we attempted to make structural variation in

* Corresponding author. Tel.: +91 824 228 7262; fax: +91 824 228 7367.
E-mail address: nbadiadka@yahoo.co.uk (B. Narayana).

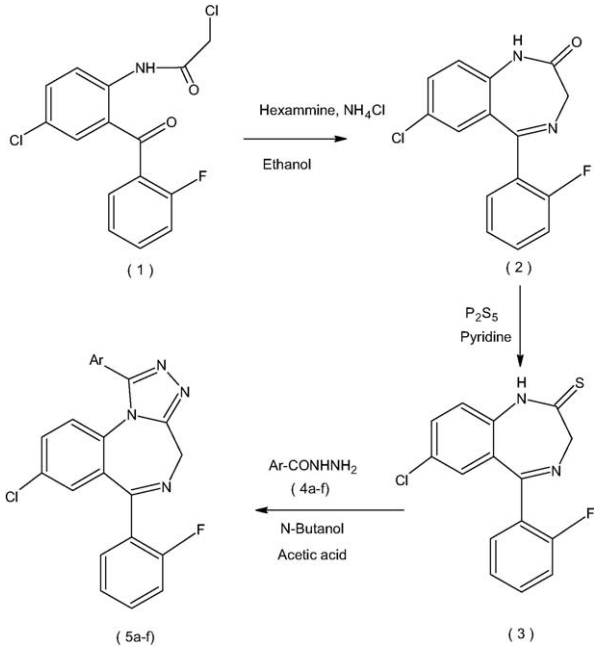
0223-5234/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.ejmech.2005.12.003

the triazole ring by substituting with six potent aromatic ring systems at C-1 and study their anticonvulsant activity. Most common substitution at C-1 described so far in the literature includes only alkyl groups. Since aryl substitution at C-1 has not been studied widely, we therefore concentrated on synthesizing 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo [4,3-*a*][1,4]benzodiazepines and studied their anticonvulsant activity.

2. Chemistry

Various methods are known for the synthesis of 1,4-benzodiazepines [8d,10,11]. In the present study, 2-amino-4-chloro-2′-fluorobenzophenone is converted to 2-(2-chloroacetyl) amino-4-chloro-2′-fluorobenzophenone (1) by treating it with chloroacetyl chloride following a literature reported procedure [8c, 10a]. 2-(2-Chloroacetyl)amino-4-chloro-2′-fluorobenzophenone on treatment with hexamine yielded 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2**). Compound (**2**) on treatment with P_2S_5 in pyridine resulted in the formation of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (**3**). 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (**3**) was then made to react with aromatic acid hydrazides (**4a–f**) by refluxing in *n*-butanol with catalytic amount of acetic acid resulted in the formation of 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4H-[1,2,4]triazolo[4,3-*a*][1,4] benzodiazepine (**5a–f**). Aromatic acid hydrazides (**4a–f**) were prepared by treating the ethyl esters of respective aromatic acids with hydrazine hydrate in methanol. Scheme 1 illustrates the reaction scheme.

The formation of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (2) and 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines (**5a–f**) were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies. The spectral data of each compound is given in the experimental section.



Scheme 1.

3. Anticonvulsant activity

Inbred male albino mice (Swiss strain) weighing between 20–30 g were used in the study. They were housed in groups of three or four mice per cage under standard laboratory conditions for one week before the experiments. The housing conditions were maintained at controlled temperature (23 °C) and humidity (50%). They received standard diet and water ad libitum. The animals were transferred to the laboratory 1 hour before the start of the experiment. The institutional ethical committee approved the study. Studies were carried out by both PTZ animal model and maximal electroshock (MES) test. All the results were statistically analyzed results are expressed as the mean ± S.E.M.

3.1. PTZ animal model [12]

Pentylenetetrazole (PTZ, Sigma Chemicals, USA) was used as convulsant and diazepam (Ranbaxy Laboratories, India) was used as standard drug. PTZ was dissolved in normal saline. Test compounds and standard drug were dissolved in 2% acacia suspension. The mice were divided into eight groups of three each. Group-1 received diazepam, group-2 received **5a**, group-3 received **5b**, group-4 received **5c**, group-5 received **5d**, group-6 received **5e** and group-7 received **5f** at a dose of 4 mg/kg. Each dose was dissolved in 2% gum acacia and delivered orally in a volume of 0.1 ml/10 g body weight. The control group, group-8 received 0.1 ml/10 g of 2% gum acacia orally by gavage feeding.

Convulsion was induced 1 hour after the administration of the standard drug or the test compounds by i.p. injection of PTZ (80 mg/kg) that was dissolved in saline to a volume of 0.1 ml/10 g body weight. The time needed for the development of unequivocal sustained clonic seizure activity involving the limbs (isolated myoclonic jerks or other preconvulsive chewing behavior were not counted) was carefully noted. Duration of seizure was also noted. Seizure free duration for a period of 1 hour was taken as protection. The number of animals protected in each group was recorded and percent protection was calculated.

The animals in the control group exhibited seizures at the dose of PTZ used in the study. The onset of seizure was found to be 119 ± 0.577 s and the mean seizure duration was 311 ± 0.577 s. Diazepam, **5a, 5d, 5e** and **5f** protected the animals from developing convulsions at the dose of 4 mg/kg body weight in comparison with control group. For these compounds, all three mice in the group fail to have seizure and thus go the maximal defined time of 3600 s. Compounds **5b** and **5c** reduced the duration of seizures in comparison with control group. Animals were less active after receiving all of the test compounds than the control mice and great effect was exhibited when compounds **5a, 5d, 5e** and **5f** were given. The tested compounds **5a, 5d, 5e** and **5f** have promising anticonvulsant

Table 2
Anticonvulsant activity of the tested compounds **5a–f** (PTZ animal model)

Group	Drug/test compounds	Dose (mg/kg)	Latency (sec) (mean ± S.E. M)	Protection (%)	Duration of seizure (sec) (mean ± S.E.M)
1	Diazepam	4	3600	100	0
2	**5a**	4	3600	100	0
3	**5b**	4	110 ± 2.886	0	11 ± 0.577
		8	125 ± 0.577	0	8 ± 0.577
		16	123.3 ± 1.666	0	8 ± 2.460
4	**5c**	4	100 ± 2.886	0	14 ± 0.842
		8	110 ± 2.886	0	12 ± 0.842
		16	110 ± 2.886	0	10 ± 0.577
5	**5d**	4	3600	100	0
6	**5e**	4	3600	100	0
7	**5f**	4	3600	100	0
8	2% Gum acacia (Control)	0.1 ml/10 g	119 ± 0.577	0	311 ± 0.577

$N = 3$ in each group.

activity against PTZ induced seizure in mice at a dose of 4 mg/kg in comparison with diazepam at the same dose. The results were given in Table 2. Compounds **5b** and **5c** were evaluated at higher doses of 8 mg/kg and 16 mg/kg. At higher doses both compounds further reduced the duration of seizures in comparison with control group. These results are also included in Table 2.

3.2. Maximal electroshock (MES) test [13]

In the MES tests, the mice were subjected to 50 mA of alternating current from a convulsiometer for 0.2 s through a pair of electrodes attached to each ear. The duration of the tonic hind limb extensor phase, clonic phase and the number of animals protected from convulsions were noted. Phenytoin (40 mg/kg) was used as standard drug. The results are given in Table 3. All the tested compounds showed a reduction in the duration of tonic hind limb extensor phase. Compounds **5a, 5d, 5e** and **5f** reduced the duration of extensor tonus more compared to **5b** and **5c**. A complete abolition of hind limb tonic extension was considered as 100% protection.

4. Discussion

A study of structure activity relationship study revealed that compounds bearing pyridine moiety (**5a** and **5f**), 4-flourophenyl (**5d**) and 2-bromo-5-methoxyphenyl (**5e**) substituents at C-1 had shown excellent anticonvulsant activity in comparison with standard drug diazepam, used in the PTZ animal model. This is in accordance with the structural requirement of CNS depressant drugs. The substitution of pyridine moiety at C-1 enhanced activity in the cases of **5a** and **5f**. Since both **5a** and **5f** contains pyridine at C-1 the higher activity may be attributed to the presence of pyridine ring system. In the case of **5d** and **5e**, the substituents at C-1 were 4-fluorophenyl and 2-bromo-5-methoxy phenyl ring system. The higher activity of **5d** and **5e** might be due to the presence of fluorine and bromine containing ring systems. The same compounds **5a, 5d, 5e** and **5f** were more effective than **5b** and **5c** for shortening the duration of MES-induced tonic seizures too. It can be noted that none of the compounds prevented seizure activity at the doses used, unlike phenytoin that completely prevented MES-induced seizures. Classically, MES has been considered a model of generalized tonic-clonic seizures and pentylenetetrazole a model of absence of seizures. The findings of our studies reveal that the novel compounds might be more effective against absence than generalized tonic-clonic seizures, which is consistent with prior literature for other benzodiazepines in these models. Studies were carried out only at one concentration only; therefore, further studies using larger samples should be done for obtaining conclusive results. Since we limited our studies in a preliminary screening only, the compounds **5a, 5d, 5e** and **5f** could be recommended for further studies including behavioral effect and concentration response studies to find out the advantages of these compounds over known anticonvulsants.

Table 3
Anticonvulsant activity of the tested compounds **5a–f** (MES model)

Group	Drug/test compounds	Duration of tonic hind limb extensor phase (sec)	% of animals protected	Dose of the test compounds (mg/kg)
1	Control	14.24 ± 0.577	0	10 ml/kg
2	**5a**	9.68 ± 0.066	0	4
3	**5b**	11.26 ± 0.067	0	4
4	**5c**	10.48 ± 0.018	0	4
5	**5d**	6.74 ± 0.053	0	4
6	**5e**	7.18 ± 0.012	0	4
7	**5f**	7.14 ± 0.012	0	4
8	Phenytoin	0	100	40

$N = 3$ in each group.

5. Experimental

5.1. 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (2)

2-(2-Chloroacetyl)amino-4-chloro-2′-fluoro benzophenone [8c, 10a] **(1)**, (20 g, 0.061 mol) was dissolved in 340 ml ethanol and 17 g hexamine and 2 g of ammonium chloride was then added. The mixture was refluxed for 4 h. Progress of the reaction was monitored by TLC. 240 ml of ethanol was then

distilled out and cooled the reaction mixture to room temperature. Filtered the insoluble and to the filtrate passed 2.4 g of HCl gas in isopropyl alcohol and adjusted pH to 1.0–1.5 below 25 °C. Stirred the reaction mixture for 1 h and filtered the 2-(2-aminoacetyl)amino-4-chloro-2′-fluorobenzophenone hydrochloride. The hydrochloride was then dissolved in 160 ml water and carefully neutralized with ammonia. Filtered the solid product and washed with chilled water. Yield = 10 g (53.4%), m.p. 221–224 °C ([10a] 223–224 °C), FT-IR (KBr): 3519.8 cm^{-1} and 3350 cm^{-1} (–NH_{str}), 3128.3 cm^{-1} (–CH_{str}), 1697 cm^{-1} (C = O_{str}), 1218.9 cm^{-1} (Ar–F), 1103.2 cm^{-1} (Ar–Cl).

5.2. Preparation of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-thione (3)

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **(3)** (25 g, 0.086 mol) was added to 250 ml pyridine in nitrogen atmosphere. 10.25 g (0.053 mol) of P_2S_5 was then slowly added by maintaining the reaction mass at room temperature. The mixture was then refluxed for 1 h. Progress of the reaction was monitored by TLC. 200 ml of pyridine was then distilled out and cooled the residue to room temperature. A 5% solution of sodium bicarbonate (250 ml) was then added at 30–40 °C and stirred for 12 h. Filtered the sold obtained and washed successively with water, 25 ml methanol and with 50 ml chloroform. The solid was then dried at 70–80 °C. Yield: 17.5 g (66.28%), m.p. 212–214 °C.

FT-IR: (KBr): 3452.3 cm^{-1} (–NH_{str}), 3066.5 cm^{-1} and 2831.3 cm^{-1} (–CH_{str}), 1473 cm^{-1} (–CH_2), 1172.6 cm^{-1} (Ar–F), 1103.2 cm^{-1} (Ar–Cl), 1010.6 cm^{-1} (–C = S)

^{1}H-NMR: ($CdCl_3$) δ 4.77 (s, 2H, –CH_2), δ 7.058 (t, 1H, Ar–H), δ 7.11 (d $_{(J = 6.92)}$, 1H, Ar–H), δ 7.20 (s, 1H, Ar–H), δ 7.23 (d $_{(J = 6.06)}$ 1H, Ar–H), δ 7.45 (dd $_{(J = 6.9,6.01)}$ 2H, Ar–H), δ 7.59 (t, 1H, Ar–H), δ 9.91 (s, 1H, –NH–, exchangeable with D_2O)

^{13}C-NMR: ($CdCl_3$, 75 MHz) 63.06, 116.27 (d, $^2J_{C-F}$ = 21.4), 122.10, 124.51, 124.54, 126.77, 129.83, 130.72, 131.52, 131.94, 132.50, 132.56, 136.72, 159.38,166.08, 200.467

MS: *m*/*z* 304 (M^+100%), *m*/*z* 277(22.3%, $C_{15}H_{13}ClFNO$), *m*/*z* 241(21.4%, $C_{15}H_{15}NS$) *m*/*z* 211(10.1%, $C_{15}H_{17}N$)

Anal. calc. for $C_{15}H_{10}ClFN_2S$, N, 9.19 Found: N, 9.18

6. General method for the preparation of 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4] benzodiazepine (5a–f)

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione **(4)**, (3.047 g, 0.01 mol) was refluxed with corresponding acid hydrazide (0.01 mol) in *n*-butanol in presence of 0.1 ml of acetic acid for 8–12 h. Progress of the reaction was monitored by TLC. Upon completion of the reaction, *n*-butanol was distilled out completely and 25 ml acetone was added. Acetone was then distilled out completely. The solid obtained was purified by flash chromatography with methylene dichloride/ethyl acetate as solvent.

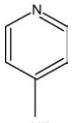
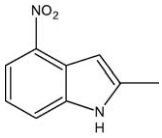
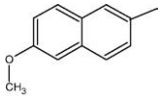
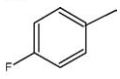
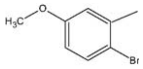
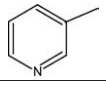
The yield, melting point data of each product is given Table 1. Spectral data of each compound are given below.

6.1. 8-Chloro-6-(2-fluorophenyl)-1-pyridin-4-yl-4H-[1,2,4] triazolo[4,3-a][1,4]benzodiazepine

FT-IR: (KBr): 3041.5 cm^{-1} and 2964.1 cm^{-1} (–CH_{str}), 1614.3 cm^{-1} (–C = N), 1481.2 cm^{-1} (–CH_2), 1097.4 cm^{-1} (Ar–F), 1026.1 cm^{-1} (Ar–Cl).

^{1}H-NMR: ($CdCl_3$): δ 4.18 (d (*J* = 10.44) 1H, –CH_2), δ 5.60 (d (*J* = 10.44) 1H, –CH_2), δ 6.91 (d (6.76) 1H, Ar–H), δ 7.07

Table 1
Characterization data of the compounds **5a–f**

Compound number	Ar	Yield[a] %	Molecular formula	Melting point °C	Nature of crystals[b]
5a		75	$C_{21}H_{13}ClFN_5$	204–206	Pale yellow powder
5b		80	$C_{24}H_{14}ClFN_6O_2$	230–232	Yellow micro crystals
5c		78	$C_{27}H_{18}ClFN_4O$	234–236	Beige powder
5d		75	$C_{21}H_{13}ClF_2N_4$	154–156	Cream microcrystals
5e		78	$C_{23}H_{15}BrClFN_4O$	218–220	Cream microcrystals
5f		68	$C_{21}H_{13}ClFN_5$	178–180	Yellow powder

[a] All the yields are on isolated basis.
[b] All the compounds are purified by column chromatography.

(t, 1H, Ar–H), δ 7.30 (t, 1H, Ar–H), δ 7.37–7.44 (m, 4H, Ar–H), δ 7.49 (m, 1H, Ar–H), δ 7.59 (t, 1H, Ar–H), δ 8.72 (s, 2H, Ar–H)

^{13}C-NMR: ($CdCl_3$, 125 MHz): 46.32, 116.29 (d, $^2J_{C-F}$ = 21.25), 122.19, 124.90, 125.92, 126.86, 126.95, 129.60, 130.84, 131.55, 131.94, 132.96, 133.03, 134.00,134.31, 150.70, 151.33, 157.59, 160.4(d, $^1J_{C-F}$ = 248.8), 165.40

MS: *m/z* 389(M^+, 90%), *m/z* 360(100%, (M – 1)–N_2), *m/z* 340(23%, $C_{19}H_{15}ClFN_3$) *m/z* 326 (10.2%, $C_{19}H_{16}ClFN_2$)

Anal. calc. for $C_{21}H_{13}ClFN_5$; N, 17.97 Found: N, 17.95.

6.2. 8-Chloro-6-(2-fluorophenyl)-1-(4-nitro-1H-indol-2-yl)-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

FT-IR: (KBr): 3041.5 cm^{-1} and 2964.1 cm^{-1} (–CH_{str}), 1614.3 cm^{-1} (–C = N), 1481.2 cm^{-1} (–CH_2), 1097.4 cm^{-1} (Ar–F), 1026.1 cm^{-1} (Ar–Cl).

^{1}H-NMR: ($CdCl_3$): δ 4.2 (d (*J* = 10.4) 1H, –CH_2), δ 5.61 (d (*J* = 10.4) 1H, –CH_2), δ 6.64(s, 1H, Ar–H), δ 7.07 (t, 1H, Ar–H), δ 7.23–7.31 (m, 3H, Ar–H), δ 7.41(s, 1H, Ar–H), δ 7.49–7.52 (m, 3H, Ar–H), δ 7.76 (t, 1H, Ar–H), δ 7.92 (d (*J* = 6.2) 1H, Ar–H), δ 8.24 (d (*J* = 6.37) 1H, Ar–H), δ 10.77 (s, 1H, –NH)

^{13}C-NMR: ($CdCl_3$, 125 MHz): 46.21, 116.35(d, $^2J_{C-F}$ = 21.12), 120.22, 121.14, 124.80, 125.86, 125.93, 126.69, 126.78, 129.40, 129.55, 129.70, 130.89, 131.40, 131.44, 132.37, 132.97, 133.04, 133.32, 134.57, 146.49, 157.331,159.42 (d, $^1J_{C-F}$ = 290), 165.41

MS: *m/z* 472 (M^+, 20%), *m/z* 425 (22.3%, $C_{15}H_{13}ClFNO$), *m/z* 321(76%, $C_{17}H_{12}ClN_5$) *m/z* 286 (10%, $C_{15}H_{11}ClFN_3$) *m/z* 189(100%, $C_9H_7N_3O_2$)

Anal. calc. for $C_{24}H_{14}ClFN_6O_2$; N, 17.77 Found: N, 17.75.

6.3. 8-Chloro-6- (2-fluorophenyl)-1-(6-methoxy-2-naphthyl)-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

FT-IR: (KBr): 3041.5 cm^{-1} and 2964.1 cm^{-1} (–CH_{str}), 1614.3 cm^{-1} (–C = N), 1481.2 cm^{-1} (–CH_2), 1097.4 cm^{-1} (Ar–F), 1026.1 cm^{-1} (Ar–Cl).

^{1}H-NMR: ($CdCl_3$) δ 3.95 (s, 3H, –OCH_3), δ 4.22 (d (*J* = 9.75) 1H, –CH_2), δ 5.62 (d (*J* = 9.72) 1H, –CH_2), δ 6.94 (d (*J* = 6.51), 1H, Ar–H), δ 7.15 (m, 2H, Ar–H), δ 7.25 (m, 2H, Ar–H), δ 7.34 (m, 2H, Ar–H), δ 7.45 (dd (*J* = 6.42,6.36), 1H, Ar–H), δ 7.76 (t, 1H, Ar–H), δ 7.73–7.80 (m, 3H, Ar–H), δ 8.07 (s, 1H, Ar–H)

MS: *m/z* 469 (M^+, 74%) *m/z* 439 (10%, $C_{26}H_{16}ClFNO$), *m/z* 287 (20%, $C_{15}H_{11}ClFN_3$) *m/z* 189(28%, $C_9H_7N_3O_2$)

Anal. calc. for $C_{27}H_{18}ClFN_4O$; N, 11.95, Found: N, 11.94.

6.4. 8-Chloro-6-(2-fluorophenyl)-1-(4-fluorophenyl)-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

FT-IR: (KBr): 3066.6 cm^{-1} and 2925.8 cm^{-1} (–CH_{str}), 1610.5 cm^{-1} (–C = N), 1481 cm^{-1} (–CH_2), 1230.5 (Ar–F), 1103.2 cm^{-1} (Ar–Cl)

^{1}H-NMR: ($CdCl_3$) δ 4.19 (d (*J* = 13.2), 1H, –CH_2), δ 5.58 (d (*J* = 12.9), 1H, –CH_2), δ 6.92 (d (*J* = 9.0), 1H, Ar–H), δ 7.05 (d (*J* = 8.4), 1H, Ar–H), δ 7.13 (dd (*J* = 10.8) 2H, Ar–H), δ 7.45 (m, 2H, Ar–H), δ 7.52 (dd (*J* = 6.6) 2H, Ar–H), δ 7.59 (t, 1H, Ar–H)

^{13}C-NMR: ($CdCl_3$, 75 MHz) 46.40, 116.23 (d, $^2J_{C-F}$ = 22.5), 116.38 (d, $^2J_{C-F}$ = 22.5), 116.38, 116.53, 122.45, 124.84, 125.99, 126.96, 127.11, 129.46, 130.51, 130.63, 130.84, 131.32, 131.96, 132.80, 132.91, 133.78, 154.69(d, $^1J_{C-F}$ = 298.5), 165.43, 165.58; DEPT: 46.4(–ve), 116.08, 116.23, 116.38, 116.53,124.79,125.97,129.43, 130.51, 130.63, 130.81, 131.30, 132.80, 132.90

GCMS: *m/z* 406 (M^+, 26%), *m/z* 404(M-2, 26%) *m/z* 370 (M–F_2, 25%), *m/z* 354, ($C_{20}H_{17}ClFN_3$, 100%)

Anal. calc. for $C_{21}H_{13}ClF_2N_4$; N, 13.77 Found: N, 13.75.

6.5. 1-(2-Bromo-5-methoxyphenyl)-8-chloro-6-(2-fluorophenyl)-4H-[1,2,4]triazolo [4,3-a] [1,4] benzodiazepine

FT-IR (KBr): 3055.0 cm^{-1} and 2926 cm^{-1} (–CH_{str}), 1608. 5 cm^{-1} (–C = N), 1482.2 cm^{-1} (–CH_2), 1297.0 (Ar–F), 1018. 3 cm^{-1} (Ar–Cl)

^{1}H-NMR: ($CdCl_3$) δ 3.82(s, 3H, –OCH_3), δ 4.22 (d (*J* = 13.2), 1H, –CH_2), δ 5.64 (d (*J* = 13.2), 1H, –CH_2), δ 6.85 (d (*J* = 8.4), 1H, Ar–H), δ 6.95 (dd (*J* = 8.7, 9.3), 2H, Ar–H), δ 7.07 (t, 1H, Ar–H), δ 7.16–7.32 (m, 1H, Ar–H), δ 7.45–7.52 (m, 4H, Ar–H), δ 7.67 (t, 1H, Ar–H).

^{13}C-NMR: ($CdCl_3$, 75 MHz) 46.34, 55.70, 116.38 (d, $^2J_{C-F}$ = 22.5), 118.93, 124.64, 129.24, 130.25, 131.58, 132.58, 133.37, 134.29, 157.22 (d, $^1J_{C-F}$ = 288.75) 165.38.

Anal. calc. for $C_{23}H_{15}$ $BrClFN_4O$; N, 11.26 Found: N, 11.20.

6.6. 8-Chloro-6-(2-fluorophenyl)-1-pyridin-3-yl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

^{1}H-NMR: ($CdCl_3$) δ 4.19 (d (*J* = 10.4), 1H, –CH_2), δ 5.61 (d (*J* = 10.4), 1H, –CH_2), δ 6.92 (d (*J* = 6.8), 1H, Ar–H), δ 7.05 (t, 1H, Ar–H), δ 7.30 (t, 1H, Ar–H), δ 7.30 (m, 3H, Ar–H), δ 7.50 (s, 1H, Ar–H), δ 7.74 (s, 1H, Ar–H), δ 7.87(d (*J* = 6.2), 1H, Ar–H), δ 8.72 (d (*J* = 3.2), 1H, Ar–H), δ 8.77 (s, 1H, Ar–H)

^{13}C-NMR: ($CdCl_3$, 125 MHz) 47.21,117.17 (d, $^2J_{C-F}$ = 22.5), 123.74, 124.56, 125.65,126.55, 127.77, 127.86, 130.56, 131.67, 131.88, 132.46, 132.85, 133.72, 133.78, 134.96, 136.59, 149.89, 151.79, 152.18,159.12 (d, $^1J_{C-F}$ = 280), 162.23,166.25

MS: *m/z* 390(M^+, 25%), *m/z* 415 ((M + 2) + Na, 20%), *m/z* 430 (M + K, 18%), *m/z* 355 (M-Cl, 22%), *m/z* 295 ($C_{15}H_{10}ClN_5$, 20%), *m/z* 281 ($C_{14}H_8ClN_5$, 60%), *m/z* 207 ($C_9H_8ClN_4$, 70%), *m/z* 147 ($C_9H_{10}N_2$, 100%).

Anal. calc. for $C_{21}H_{13}ClFN_5$; N, 17.97 Found: N, 17.95.

7. Conclusion

Six novel 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines, which are structural analogues of alprazolam and midazolam were synthesized and characterized by spectral analysis. All the compounds were

screened for anticonvulsant activity by PTZ animal model and MES test. Compounds **5a, 5d, 5e** and **5f** exhibited promising anticonvulsant activity. Since we limited our studies in a preliminary screening only, the compounds **5a, 5d, 5e** and **5f** could be recommended for further studies to find out the advantages of these compounds over known anticonvulsant drugs.

Acknowledgements

The authors are also thankful to the Director, RSIC, Punjab University, Chandigarh and the Head, CDRI Luknow for NMR and Mass analysis. Authors are also thankful to Dr. C.H. Anoop Kumar, Kasturba Medical College, Mangalore, India for his help in carrying out anticonvulsant studies.

References

[1] (a) L.O. Randall, Psychopharmacological Agents, Vol. 3, M. Gordon, Ed. New York, Academic Press (1974) 175–281 b) D.J. Greenblatt, R.I. Shader, Benzodiazepines in Clinical Practice, New York, Raven Press (1974) 183–196 **c**) L.O. Randall, B. Kappell, The Benzodiazepines, S. Garattini, E. Mussini, L.O. Randall, Eds. New York, Raven Press (1973) 27–51 **d**) Benzodiazepines Divided: A Multidisciplinary review, Wiley New York, 1983 **e**) M.G. Block, R.M. DiPardo, B.E. Evans, K.E. Rittle, W.L. Witter, D.F. Veber, P.S. Anderson, R.M. Freidinger, J. Med. Chem, 32 (1989) 13–16.

[2] (a) L.H. Sternbatch, Drugs Affecting the Central Nervous System, Vol. 2, New York, Marcel Dekker (1968) 237–264 b) W. Sneader, Comprehensive Medicinal Chemistry, Vol. 1, C. Hansch, P.G. Sammnes, J.B. Taylor, Eds. Pergamon, London, 65 (1990) **c**) G. Moroz, Journal of Clinical Psychiatry, 65 (2004) 13–18.

[3] J.A. Robol, M.P. Cimarusti, L.M. Simpkins, B. Brown, D.E. Ryono, J.E. Bird, M.M. Asad, T.R. Schaeffer, N.C. Trippodo, N.C, J. Med. Chem. 39 (1996) 494–502.

[4] (a) T. Wang, A.S. Lui, I.S. Cloudsdale, Org. Lett. 1 (1999) 1835–1837 b) F. Novelli, A. Sparatore, B. Tassso, F. Sparatore, Bioorg. Med. Chem. Lett. 9 (1999) 3031–3034 c) S.C. Wilson, P.W. Howard, P.W. Forrow, J.A. Hartley, L.J. Adams, T.C. Jenkins, L.R. Kelland, D.E. Thurston, J. Med. Chem. 42 (1999) 4028–4041.

[5] (a) B. Evans, A. Pipe, L. Clarke, M. Banks, Bioorg. Med. Chem. Lett. 11 (2001) 1297–1300 b) P.G. Wyatt, M.J. Allen, Chilcott, G. Hickin, N.D. Miller, P.M. Woollard, Bioorg. Med. Chem. Lett. 11 (2001) 1301–1305.

[6] (a) I.P. Andrews, R.J. Atkins, R.F. Badham, R.K. Bellingham, G.F. Breen, J.S. Carey, S.K. Etridge, J.F. Haynes, N. Hussain, D.O. Morgan, A.C. Share, S.A.C. Smith, T.C. Walsgore, A.S. Wells, Tetrahedron Lett., 42 (2001) 4915–4917 b) R.G. Sherill, J.M. Berman, L. Birkemo, D.K. Croom, L. Dezube, G.N. Ervin, M.K. Grizzle, M.K. James, M.F. Johnson, K.L. Queen, T.J. Rimele, F. Vanmiddlesworth, E.E. Sugg, Bioorg. Med. Chem. Lett. 11 (2001) 1145–1148.

[7] G.M. Carp, J. Org. Chem. 64 (1999) 8156–8160.

[8] (a) J.A. Vida, Principles of Medicinal Chemistry, M.W. Wolf, A. Burger, Eds.; Wiley, New York (1981)144–170 b) R.I. Frier, Comprehensive Heterocyclic Chemistry, Vol 3, C. Hansch, Ed. Pergamon Press, New York (1990) 539 **c**) J.B. Hester, A.B. Rudzik, B.V. Kamdar, J. Med. Chem, 14 (1971) 1078 d) A. Walser, L.E. Benjamin, T. Flynn, C. Mason, R. Schwarts, R.I. Fryer, J. Org. Chem, 43 (1978) 936–944.

[9] D.P.Carlos, M. Alberto, A. Eduardo, G.Javier, Synthesis, 16 (2004) 2697–2703 (and the references cited in).

[10] (a) L.H. Sternbatch, R. Ivan Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, A. Stempel, J. Org. Chem, 27 (1962) 3788–3796 b) J.B. Hester Jr, D.J. Duchamp, C.G. Chidester, Tetrahedron Lett. 20 (1971) 1609–1612 c) R.I. Frayer, J.V. Earley, N.W. Gilman W. Zally, J. Heteroyclic Chem., 13 (1976) 433–437 d) R.I. Fryer, Z.Q. Gu, C.G. Wang, J. Heterocycl. Chem. 28 (1991) 1661–1669.

[11] (a) G.A. Archer, E. Fells, L.H. Sternbatch, US patent Appl.3422091/1969 b) J.B. Hester Jr, US patent Appl.3987052/1976 c) J.M. Khanna, K. Naresh, K. Chandrahas, M.K. Sharma, P. Sharma, S. Sathyanarayanan, G.P. Singh, US patent Appl. 5792874/1998.

[12] J.A. Vida, Anticonvulsants, in: W.O. Foye, T.L. Lemke, D.A. Williams (Eds.), Principles of Medicinal Chemistry, Williams and Wilkins, London, 1995.

[13] J. Plontnikoff, D.M. Greene, Anticonvulsant action of drugs, J. Pharmacol. Exp. Ther. 119 (1957) 294–299.