European Journal of Medicinal Chemistry 45 (2010) 857–863

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis and pharmacological screening of potential anticonvulsant agents using hybrid approach

J.G. Ghogare [a], S.V. Bhandari [a,*], K.G. Bothara [b], A.R. Madgulkar [a], G.A. Parashar [a], B.G. Sonawane [a], P.R. Inamdar [a]

[a] Department of Pharmaceutical Chemistry, A.I.S.S.M.S College of Pharmacy, Kennedy Road, Pune-411001, India
[b] Associate Dean, School of Pharmacy & Technology, NMIMS University, Shirpur , Dist.-Dhule , India

ARTICLE INFO

Article history:
Received 30 June 2007
Received in revised form
28 July 2009
Accepted 10 September 2009
Available online 17 September 2009

Keywords:
Hybrid approach
Thiazolidinone
Anticonvulsant and locomotor activity
Thiophene
Benzodiazepine

ABSTRACT

A series of 9H, 10H, 3-[*N*- 4 methyl -2-benzamido thiophen 3-yl carbonyl amino [2-(2′-phenyl 1′-ethylenyl)] 10-(aryl) thiazolidino [4, 5-b] 1, 5 benzodiazepine [**7a**–**7h**] were designed and synthesized to meet the structural requirements essential for anticonvulsant activity. Anticonvulsant activity was determined after intra-peritoneal administration to mice by supramaximal electroshock seizures model and Isoniazide Hydrazone induced seizures model. Motor impairement was determined using acto-photometer and rotarod apparatus. Among the synthesized compounds two [JG **7a** and JG **7e**] compounds exhibited significant anticonvulsant activity after intra-peritoneal administration. Active compounds carry hydroxy substitutent at 2-position and methoxy at 4-position in the phenyl ring at C_5 of benzodiazepine. In present we study conclude that small polar and electron rich groups contribute significantly for anticonvulsant activity while electronegative substitutents showed lesser contribution for anticonvulsant activity.

© 2009 Elsevier Masson SAS. All rights reserved.

1. Introduction

The chemistry and pharmacological applications of condensed diazepines are proved to be the fascinating field of investigation during past few years. Derivatives of 1, 5 benzodiazepine are reported to have tranquilizing, muscle relaxant, anti-convulsant, and sedative actions [1]. Now a days many benzodiazepine derivatives are widely used as daytime sedatives, tranquilizers, sleep inducers, anesthetics, anticonvulsants, and muscle relaxants. The use of this class of compound with therapeutic purposes is not only confined to anxiety and stress conditions but also changes in the structure of benzodiazepine can produce a host of different biological activity. Novel applications of this hybrid category of compounds are continuously emerging [1]. Combined five atom heterocycles and thiazolidinone ring system when fused with benzodiazepine occupy a prominent place amongst drugs for treatment of CNS disorders.

The anticonvulsant activity of benzodiazepines can be correlated to their ability to limit the sustained repetitive firing of neurons, an effect mediated by enhancing γ-amino butyric acid (GABA) mediated synaptic inhibition [2]. GABA a primary neurotransmitter inhibitor of central nervous system, plays an important role in the arrest of convulsions. Many anticonvulsant drugs are reported to act by increasing the GABA level in the brain [3].

Many reports are available on anticonvulsant activity of thiazolidine [4]. Thiophene ring is responsible for CNS depressant action in general and anticonvulsant activity in particular but literature is scarce on significant outcomes of its study. Due to potential clinical applications of 1, 5 benzodiazepine, thiophene and thiazolidine an attempt have been made to discover new, safe and potent chemical entities for the treatment of epilepsy. The aim of this study was to produce more active anticonvulsant drug than currently available anticonvulsant agents without any side effects. In this study combination of thiazolidine nucleus and benzodiazepine was carried out using hybrid approach.

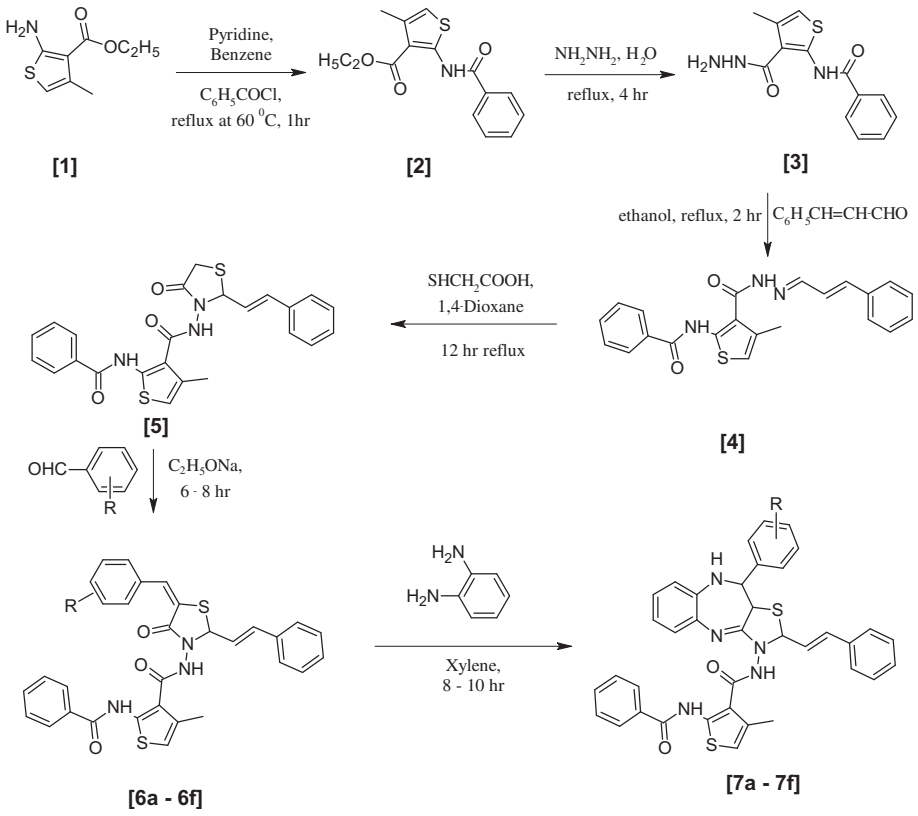
2. Results and discussion

2.1. Chemistry

The synthetic route of compounds is outlined in Scheme 1. The benzoylation of 2-amino 3-carboethoxy 4-methyl thiophene [**1**] yielded 2-benzamido 3-carboethoxy- 4-methyl thiophene [**2**]. Hydrazination of compound [**2**] gave compound [**3**] which on formation of Schiff's base with a cinnamaldehyde yielded derivative

* Corresponding author. Department of Pharmaceutical Chemistry, A.I.S.S.M.S College of Pharmacy, Near RTO, Kennedy Road, Pune-411001, Maharashtra, India.
E-mail address: drugdesign1@gmail.com (S.V. Bhandari).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.09.014



Scheme I. Scheme I Synthetic route for compounds [**7a**–**7f**].

[**4**]. The compound [**4**] was further cyclized with mercptoacetic acid in presence of anhydrous $ZnCl_2$ to afford thiazolidinone derivative [**5**], further compound [**5**] on treatment with different aromatic aldehydes yielded [**6a**–**6f**]. This [**6a**–**6f**] series on further treatment with O-phenylene diamine and xylene as solvent yielded 1, 5 benzodiazepines of compounds [**7a**–**7f**] respectively.

All above reactions were monitored by TLC using precoated TLC plates. The absence of TLC spots for starting materials and appearance of new TLC spots at different Rf values ensured the completion of reaction. The TLC plates were visualized either by iodine vapours or by observing in UV-visible chamber. Structures and purity of anticipated compounds were characterized by physical constant, FTIR spectral studies initially followed by ^1H NMR analysis. All the compounds were characterized by their spectral and elemental analysis. The synthetic route is outlined in Scheme-I.

2.2. Pharmacology

The anticonvulsant activity of the synthesized compounds was determined by evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of isoniazide hydrazone (INH) and electroshock models. Diazepam was considered as a reference standard for anticonvulsant effect in all the models. The synthesized compounds, diazepam or vehicles were administered 30 min before injection of INH 2.5 mg/kg or induction of electroshock (42 mA and 0.2 s). The hind limb tonic extensions were observed in supramaximal electroshock seizures (SMES) model and reduction of seizure were observed in INH model, 30 min later. The compounds were tested at two doses 10 mg/kg and 30 mg/kg intraperitoneally. Among the synthesized compounds two [**7a** and **7e**] were found to be more potent. The graphical representations of compounds [**7a**–**7f**] are shown in Fig. 1 and Fig. 2. The results of pharmacological studies of the synthesized compounds of this series are reported in Table 1.

Spontaneous motor activity was measured using an actophotometer and rotarod instruments. Each animal was placed in the chamber for 1 min to get acclimatized and then activity was measured for duration of 10 min. The compounds were tested at two doses 10 mg/kg and 30 mg/kg intraperitoneally. Compounds having thiazolidine ring at position 2 possess significant anticonvulsant activity. Presence of 4-methoxy in aromatic ring at C_5 of benzodiazepine (**7e**) ring have shown good anticonvulsant activity than 4-fluro derivative against SMES model. Compound **7f** i.e. 4-fluoro at aromatic ring at C_5 of benzodiazepine ring is less potent as compared to **7e** (-4-methoxy derivative) and **7d** (dimethyl amino derivative) in locomotor activity indicating requirement of small, electron rich group at 4-position of aromatic ring at C_5 of benzodiazepine and requirement of thiazolidine at C_2 of benzodiazepine ring. The

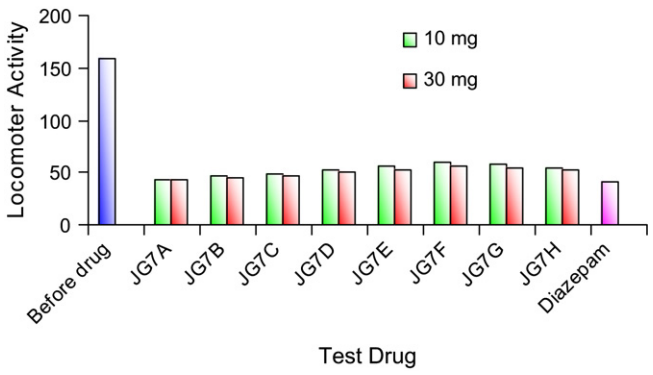


Fig. 1. Comparative locomotor activity of compounds JG_7A-JG_7H with diazepam using actophotometer.

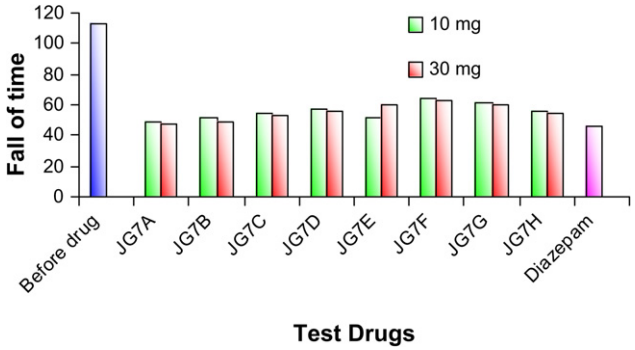


Fig. 2. Comparative locomotor activity (fall of time) of compounds JG_7A-JG_7H with diazepam using rotarod.

pharmacological data of the synthesized compounds of this series is shown in Table 2. The graphical representations of compounds [**7a**–**7f**] are shown in Fig. 3 and Fig. 4.

2.2.1. SMES model

The compounds when screened for their anticonvulsant activity against (SMES) induced seizures, at 10 mg/kg and 30 mg/kg body weight intraperitoneally, exhibited significant anticonvulsant activity. The characteristic feature of this series is presence of thiazolidine nucleus which showed significant contribution to anticonvulsant activity [5]. The results of the compounds **7b**, **7f** showed poor anticonvulsant activity. Compounds **7a**, **7c**, **7d**, **7e** were found to have significant anticonvulsant activity. This could be due to presence of comparatively polar and electron rich groups such as –OH, –Cl, $–N–(CH_3)_2$ and $–OCH_3$. The compounds **7b** and **7f** were less potent in MES model and that might be due to presence of comparatively less polar and electron withdrawing groups.

2.2.2. INH model

In INH model compounds [**7a**, **7c**, **7d**, **7e**] were found to be significantly active and more potent against INH induced convulsions while **7b** and **7f** were found to have poor activity.

2.2.3. Rota rod and actophotometer model

In case of locomotor activity the compounds [**7a**, **7c**, **7d** and **7e**] were more active than [**7b** and **7f**]. This indicated INH induced seizure model was probably less predictive or the mechanism through which these compounds reduced the firing of neurons was different and therefore INH model yielded poor results for the same set of compounds. Compounds [**7a** and **7e**] have been found to be equipotent with standard drug diazepam indicating presence of optimum structural requirements.

In all considering the results of compounds of this series, it could be concluded that all the nuclei viz. thiazolidine, thiophene and 1, 5 Benzodiazepine significantly contributed for the anticonvulsant activity.

Table 1
Anticonvulsant activity of tested compounds [**7a**–**7f**] using SMES model and INH induced seizures.

Group	Drug/test compounds	Dose (mg/kg)	Duration of hind limb extension phase (sec)	Reduction of duration of seizures (sec)
1	Control	–	24.514 ± 0.5245	34.12 ± 0.7444
2	7a	10	13.228 ± 0.9674*	85.50 ± 1.761**
3	7a	30	14.263 ± 0.9436*	87.667 ± 1.211**
4	7b	10	15.328 ± 0.5226*	71.33 ± 1.966*
5	7b	30	14.907 ± 0.3916	78.833 ± 1.169*
6	7c	10	14.540 ± 0.9780***	81.833 ± 1.169*
7	7c	30	13.632 ± 0.5490***	83.33 ± 0.7528*
8	7d	10	13.355 ± 0.8635***	92.33 ± 2.160***
9	7d	30	13.000 ± 0.9220***	95.33 ± 2.338***
10	7e	10	15.328 ± 0.5226***	101.83 ± 5.345***
11	7e	30	14.907 ± 0.3916***	108.50 ± 4.848***
12	7f	10	16.442 ± 0.5917	69.833 ± 1.472
13	7f	30	15.408 ± 0.5578	74.00 ± 0.8944
14	Diazepam	5	8.500 ± 0.5627***	146.67 ± 4.271***

Values are mean ± SEM. Mice were pretreated with test compounds i.p. before the induction of electroshock. Data analyzed by one-way ANOVA followed by Student Newman Keals Multiple Comparison test. $n = 6$ animals in each group. [$p < 0.05$*, $^{**}p < 0.01$, $^{***}p < 0.001$].

Table 2
Locomotor activity of compounds [**7a**–**7f**] using actophotometer and rotarod.

Group	Drug/test compounds	Dose (mg/kg)	Activity score[a] (0.5 h after)	Activity score[a] (fall of time)
1	Control	–	323.33 ± 2.689	323.33 ± 14.977
2	7a	10	54.33 ± 2.155	43.833 ± 4.143*
3	7a	30	52.33 ± 2.261	42.607 ± 3.989*
4	7b	10	51.66 ± 2.217	46.633 ± 4.302
5	7b	30	59.66 ± 2.261	45.167 ± 4.151***
6	7c	10	57.67 ± 2.217	49.00 ± 4.619**
7	7c	30	55.50 ± 2.261	46.197 ± 4.337
8	7d	10	51.00 ± 2.082*	51.500 ± 4.890*
9	7d	30	49.50 ± 1.875*	50.750 ± 4.802*
10	7e	10	48.50 ± 1.875***	55.333 ± 5.155*
11	7e	30	47.50 ± 1.875***	53.00 ± 5.007*
12	7f	10	64.68 ± 2.472	59.333 ± 5.590***
13	7f	30	62.83 ± 2.472	56.833 ± 5.288***
14	Diazepam	5	46.33 ± 2.445***	41.50 ± 4.023***

[a] Each score represents the mean ± SEM of six mice, significantly different from the control score. Data analyzed by one-way ANOVA followed by Student Newman Keals Multiple Comparison test. $n = 6$ animals in each group. [$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$].

3. Conclusions

Considering the pharmacological results of all the newly synthesized compounds, it can be concluded that: compounds having thiazolidine ring at position 2 possesses significant anticonvulsant activity. Presence of 4-methoxy group at aromatic ring at C_5 of benzodiazepine [**7e**] ring had shown good anticonvulsant activity than 4-fluro [**7f**] derivative against MES model. Compound [**7f**] was less potent as compared to **7e** and **7d** in locomotor activity which indicated requirement of small, electron rich group at 4 position of aromatic ring at C_5 of benzodiazepine and requirement of thiazolidine at C_2 of benzodiazepine ring. The compounds were found to be less potent anticonvulsant as compared to diazepam in all models, indicating further investigations of structural features required for anticonvulsant activity and probably the pharmacokinetic profile of these drugs.

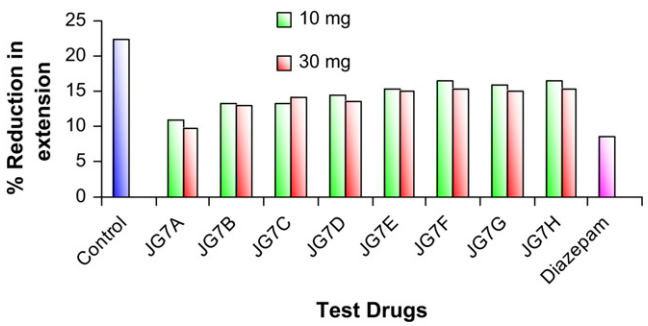
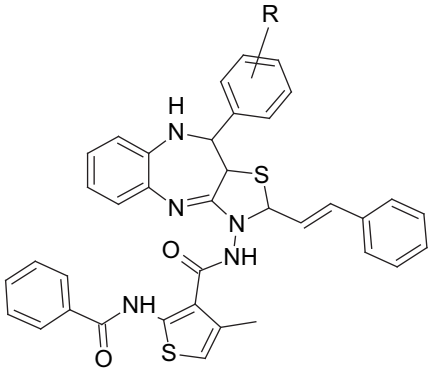


Fig. 3. Anticonvulsant activity (% reduction in extension of hind-limb) of compounds JG_7A-JG_7H in comparison with diazepam using SMES model.

Table 3
Physicochemical data for compounds [**6a–6f**].

Code no	'R'	Molecular formula	Molecular weight	% Yield	Melting point (uncorrected)	Rf
7a	-2- OH	$C_{31}H_{25}N_3S_2O_4$	567	71.57	181–182 °C	0.745
7b	-3-NO_2	$C_{31}H_{24}N_4S_2O_5$	596	73.92	197–198 °C	0.846
7c	-2-Cl	$C_{31}H_{24}N_3S_2O_3Cl$	585.5	76.23	135–136 °C	0.723
7d	-4-N, N $(CH_3)_2$	$C_{33}H_{30}N_4S_2O_3$	594	82.84	134–135 °C	0.501
7 e	-4-(OCH_3)	$C_{32}H_{27}N_3S_2O_4$	581	66.67	163–164 °C	0.788
7 f	-4-F	$C_{31}H_{24}N_3S_2O_3F$	569	80.65	209–210 °C	0.342

General structure of 9H, 10H, 3-[*N*(4-methyl 2-benzamido thiophen-3-yl)]carbonyl amino]2(2-phenyl 1- ethylenyl)10-(substituted aryl) thiazolidino [4,5-b] 1,5 benzodiazepine.



4. Experimental [23]

All the chemicals were analytical grade unless and otherwise stated and procured from LOBA chemicals, Pune, India. Distilled water was used for solution preparation of test compounds, melting points were taken by using melting point apparatus and were uncorrected. Elemental analysis was done by elemental vario EL III Carlo Erba 1108 elemental analyzer. IR spectra recorded on JASCO-FTIR V430+ instrument using KBr pellet technique. ^{1}H NMR spectra were recorded by FT NMR Varian Mercury YH300 spectrophotometer. The protocol for the animal experiments performed was approved by CPCSEA. Test compounds were prepared by dissolving it in distilled water along with Tween 80.

4.1. Synthesis

4.1.1. [(Ethyl 2-(benzamido)-3 carboethoxy 4-methyl thiophene)] [6,7]

Compound [**1**] (0.03 mol), pyridine (0.04 mol) and benzene (0.04 mol), benzoyl chloride (0.03 mol) were taken in a round bottom flask. The reaction mixture was refluxed at 60 °C for 60 min. The resultant reaction mixture was cooled, and poured into ice-cold water. The benzene layer was separated and aqueous layer was again extracted with benzene. The collected benzene extract was washed with 5% Na_2CO_3, followed by water. The produced mixture was dried with anhydrous $MgSO_4$. The benzene layer was separated and concentrated to 1/3 rd volume and the resulting mixture was stirred with *n*-hexane.

The yellow crystalline product [**2**] (Yield 79.14%, m.p.125–126 °C) separated was collected by filtration. IR (KBr): 3234(N–H stretch of amine), 686 (C–S–C bond stretching), 1655 –C═O stretching, 2976 (aromatic C–H stretch).

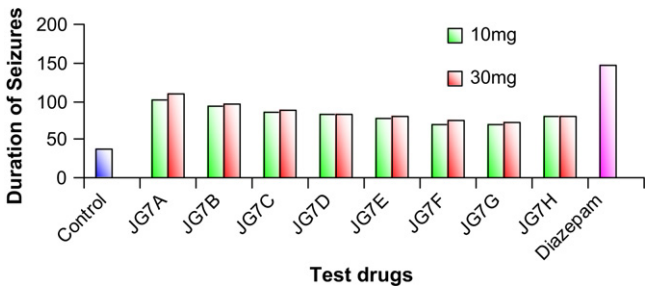


Fig. 4. Anticonvulsant activity (% reduction in seizure) of compounds JG_7A-JG_7H in comparison with diazepam using INH induced seizure.

4.1.2. 2-(Benzamido)-3-hydrazido 4-methyl thiophene- [8]

Compound [**2**] (0.02 mol) and 99% hydrazine hydrate were mixed in 1:3 proportion. The mixture was refluxed for 10 min. To this mixture ethanol was added till both the layers were miscible and was refluxed for 4 h. The mixture was concentrated, allowed to cool at room temperature, and then poured into ice-cold water.

The solid thus obtained was filtered, dried and recystallized from ethanol to get compound [**3**] (Yield 76.46%.m.p., 150–151 °C). IR (KBr): 3325 (–NH stretch), 2919 (–CH_3 stretch), 3216 (–NH–NH_2 stretching).

4.1.3. 2-Benzamido-4-methyl-3-N-[4′-phenylprop-1′, 3′dieneimino] thiophen-3-carboxamide [9]

A mixture of compound [**3**] (0.01 mol) and cinnamaldehyde (0.01 mol) and 2–3 drops of glacial acetic acid in ethanol was refluxed for about 2 h. The solvent was removed under reduced pressure to afford product [**4**] Schiff base.

The product was recrystallized using ethanol (Yield 88.37%, m.p. 239–240 °C). IR (KBr): 3304 (N–H stretch), 1671 (–C═O stretch of CONH), 1546 (C═N stretch), 696 (C–S–C bond stretching), 1576 (–N═N stretch).

4.1.4. 2-Benzamido-4-methyl-N-[2′-(2-phenyl 1-ethylenyl)-4-oxothiazolidin-3-yl] thiophene-3-carboxamide [10]

Schiff Base [**4**] (0.015 mol) was dissolved in sufficient quantity of 1, 4 dioxane (0.015 mol) and mercaptoacetic acid (0.015 mol) and pinch of anhydrous $ZnCl_2$ was added to it. The reaction mixture was refluxed on water bath for 12 h. The solid obtained was triturated with excess of 10% $NaHCO_3$ solution.

Table 4
Physicochemical properties of compounds [**7a**–**7f**].

Code no.	R	Molecular formula	Molecular weight	% Yield	Melting point (uncorrected)	% C	% H	% N
7a	-2-OH	$C_{37}H_{31}N_5S_2O_3$	657	33.18	110–111 °C	66.073 (66.47)	5.472 (5.071)	11.943 (11.456)
7b	-3-NO_2	$C_{37}H_{30}N_6S_2O_4$	686	31.94	218–219 °C	64.983 (64.72)	5.258 (4.918)	12.854 (12.636)
7c	-2-Cl	$C_{37}H_{30}N_5S_2O_2$ Cl	675.5	85.06	220–221 °C	66.748 (66.31)	5.372 (5.11)	9.461 (9.621)
7d	-4-N (CH_3)$_2$	$C_{39}H_{36}N_6S_2O_2$	684	50.00	90–91 °C	70.271 (69.92)	6.564 (6.291)	12.616 (12.358)
7e	-4-(OCH_3)	$C_{38}H_{33}N_5S_2O_3$	671	84.26	240–241 °C	68.126 (68.38)	5.417 (5.05)	10.435 (10.71)
7f	-4-F	$C_{37}H_{30}N_5S_2O_2F$	658	67.09	119–120 °C	68.364 (68.12)	5.475 (5.231)	12.163(12.44)

The precipitate obtained [**5**] was filtered and dried (Yield 71.68%, m.p. 110–111 °C). IR (KBr): 2978 (C–H bond stretch), 1724 (–C═O stretch of CONH), 1536 (C═N stretch), 696 (C–S–C bond stretching), 1576 (–N═N stretch).

4.1.5. 2-Benzamido-4-methyl-N-[2′-(2-pheny1 1-ethylenyl)-5′ (2-hydroxy phenyl) methenyl-4-oxothiazolidin 3-yl] thiophene 3-carboxamide [11]

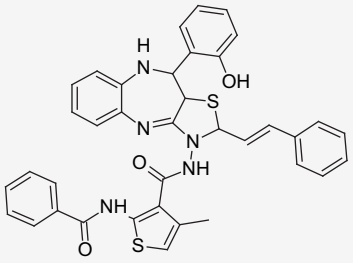
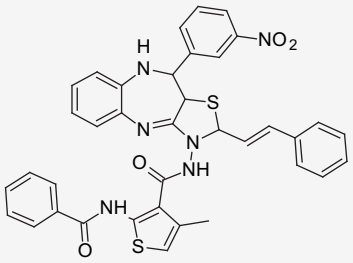
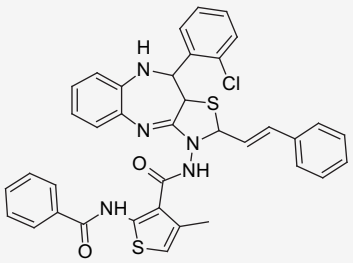
Compound [**5**], (0.002 mol) in presence of sodium ethoxide (0.002 mol) was refluxed in 1, 4 dioxane (50 mL) for about 6–8 h and then cooled. The reaction mixture was poured into ice-cold water. The product precipitated out was filtered, dried and recrystallised using methanol. The resulting compound [**6a**] (Yield 71.57%, m.p.181–182 °C) collected by filtration. Compounds [6b to 6f] were synthesized in a similar way. The details of results obtained are listed in Table 3.

*4.1.6. 9H, 10H, 3[N(4-methyl 2-benzamido thiophen-3-yl)]carbonyl amino] 2(2-phenyl 1- ethylenyl) 10-(2-hydroxy phenyl) thiazolidino [**4**,**5**-**b**] 1,5 benzodiazepine [12]*

A solution of compound [**6a**] was prepared (0.003 mol) in hot xylene and a solution of o-phenylene diamine (0.003 mol) in xylene was prepared separately. Both the solutions were mixed in small proportions and refluxed for 6–10 h using Dean-stark apparatus. Excess solvent was distilled off at reduced pressure to afford product [**7a**].

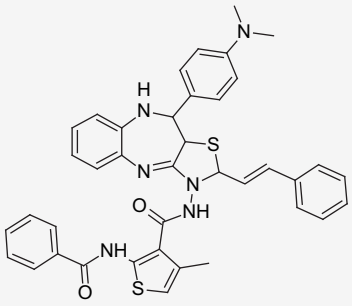
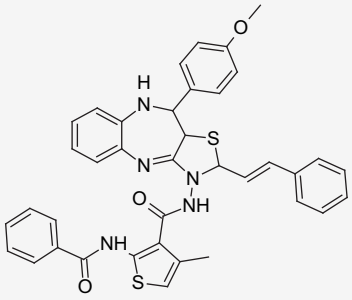
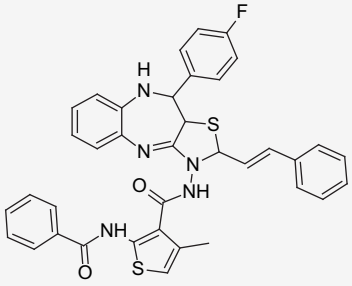
The compound obtained had yield 33.18%. m.p.110–111 °C. Similarly compounds [**7b**–**7f**] were synthesized by reacting with

Table 5
Spectral data of compounds [**7a**–**7f**].

Compound	IR(KBr) Vmax (cm^{-1})	NMR ($CDCl_3$ + DMSO) δ ppm
7a 	3231(N–H stretch of amine),3862(–OH bond stretch), 686(C–S–C bond stretching),1312(–NH bending of thiazolidine ring), 1745(–C═O stretching) 1680 (–C═O stretching of CONH), 1298 (NH in plane)	2.26 (s,3H, –CH3), 7.164 (s,1H ,α –CH of thiophene) 7.252(s,1H, β–CH of thiophene),8.175(s,1H, –NH of benzoyl), 7.807 (s,5H, Ar–H of benzoyl), 3.036 (d,1H, –CH of thiazolidine), 2.574(t,2H,–CH═CH), 7.524 (s,5H,–C_6H_5 of cinnamaldehyde), 2.630 (d, 1H, 9H of 1,5 BZD), 2.653 (t,1H, –CH 10H of 1,5 BZD), 7.524 (s,4H, OPD), 7.501 (s,2H, Ar-H of sallicyldehyde), 3.321(s,1H –OH)
7b 	3351(–NH stretch), 2921(–CH3 stretch) , 2960(C–S–C, cyclic S), 1622(C═C Ar conjugated), 1746(C═O stretching of cyclic amide) 1674 (C═O stretching of primary amide) 1541 (NO_2 stretching), 839 (–C–N stretching) , 1578 (–N–O stretch), 1285(–NH in a plane)	2.274 (s,3H, –CH3), 7.160 (s,1H ,α –CH of thiophene) 7.297(s,1H, β–CH of thiophene),8.202(s,1H, –NH of benzoyl) 4.3 (s,1H,–NO_2)
7c 	3340 (–NH stretch of amine), 3097(aromatic CH stretch), 2924 (–CH_2 stretch) ,1666(–C═O stretch of -CONH), 1288(–N–H in plane, 695 (C–S–C stretching), 745 (C–Cl bond bending)	2.241 (s,3H, -CH3), 7.153 (s,1H ,α –CH of thiophene) 7.231(s,1H, β-CH of thiophene), 3.036 (d,1H, –CH of thiazolidine), 2.574(t,2H,–CH═CH),3.8(s,1H, –Cl), 2.630 (d, 1H, 9H of 1,5 BZD), 2.653 (t,1H, –CH 10H of 1,5 BZD)

(*continued on next page*)

Table 5 (*continued*)

Compound	IR(KBr) Vmax (cm^{-1})	NMR ($CDCl_3$ + DMSO) δ ppm
7d 	3210 (N–H bond stretch), 2963 (C–S–C, cyclic S), 1360 (C–N stretching of ter. Amide), 1665 (–C═O stretch of CONH), 1523 (C═N stretch), 818 (C–S–C bond stretching), 1224(–CH_3 stretch) 757(1,2 disubstitued benzene)	2.273 (s,3H, –CH3), 7.189 (s,1H ,α –CH of thiophene) 7.253(s,1H, β–CH of thiophene),8.027(s,1H, –NH of benzoyl), 7.497 (s,5H, Ar–H of benzoyl),8.339(s,1H, –NH of CONH), 2.778(d,1H, –CH of thiazolidine)2.413 (d, 1H,–CH═CH), 2.660 (t,2H, –CH═CH), 7.524 (s,4H, OPD),1.266 [s,6H, $N(CH_3)_2$]
7e 	3162 (N–H bond stretch of amine), 1674 (–C═O stretch of –CONH),1602 (–═CH aromatic stretch), 1543 (C═NH stretch),1259 (C–N stretching), 682 (C–S–C bond stretching) 1157 (–C═O stretch of aralkyl ether)	7 7.252 (s,1H, β–CH of thiophene ,8.175(s,1H, –NH of benzoyl), 7.807 (s,5H, Ar–H of benzoyl), 3.036 (d,1H, –CH of thiazolidine), 2.574(t,2H,–CH═CH), 7.524 (s,5H,–C_6H_5 of cinnamaldehyde), 2.630 (d, 1H, 9H of 1,5 BZD), 2.653 (t,1H, CH 10H of 1,5 BZD),3.711(s.4H, –OCH_3)
7f 	3361(N–H stretch of amine) , 3090 (aromatic CH stretch), 1676 (–C═O stretch of –CONH), 1603 (–C═CH stretching), 1225 (N-H in a plane), 743 (1,2 disubstitued benzene), 696 (C–S–C bond stretching), 1102 (C–F stretching)	2.281 (s,3H, –CH3), 7.150(s,1H ,α –CH of thiophene) 7.290(s,1H, β–CH of thiophene), ,8.175(s,1H, –NH of benzoyl), 7.807 (s,5H, Ar–H of benzoyl), 3.036 (d,1H, –CH of thiazolidine), 2.574(t,2H,–CH═CH), 7.524 (s,5H,–C_6H_5 of cinnamaldehyde), 2.630 (d, 1H, 9H of 1,5 BZD), 2.653 (t,1H, –CH 10H of 1,5 BZD),4.312(s,1H, –F)

respective aldehydes. The details of results obtained are listed in Table 4. IR (KBr): 3351(–NH stretch), 2921 (–CH_3 stretch), 2960 (C–S–C, cyclic S), 1622 (C═CAr conjugated), 1746 (C═O stretching of cyclic amide) 1674 (C═O stretching of primary amide) 1541 (NO_2 stretching), 839 (–C–N stretching), 1578 (–N═O stretch), 1285 (–NH in a plane). All the data is analyzed by IR (KBr) and NMR, resulting data is shown in Table 5.

4.2. Anticonvulsant activity

4.2.1. SMES pattern test

The SMES pattern test was performed according to the method of Tomon, et.al. [13] using Swiss albino mice of either sex, weighing in the range 30–35 g. Mice were divided into groups of six animals each and mice were treated with two doses of test drugs mainly 10 mg/kg and 30 mg/kg intraperitoneally. Similarly diazepam at 5 mg/kg was given to standard group. After 1 h mice were subjected to the electroshock of 42 mA by electro-convulsiometer through ear electrode for 0.2 s by a techno convulsiometer [14]. Animals which showed positive hind limb tonic extensor response during pre-screening were selected and the test drugs were injected intraperitoneally for ½ h before the supramaximal electroshock. The protective index was defined as the abolition or reduction of the hind limb tonic extension component of seizure. The lesser time for which hind-limb tonic extension was observed, more potent the compound as anticonvulsant.

4.2.2. INH induced seizures

INH induced seizures test was performed on Swiss albino mice weighing 30–35 g. The mice were injected with test drug 10 and 30 mg/kg intraperitoneally. After 30 min, INH injection of dose 250 mg/kg was given intraperitoneally. The animals developed the sequence of excitement, myoclonic jerks, clonic seizures, one or more maximal seizures. Animals exhibiting these seizures pattern were detected and divided into the groups of 6 animals each. The standard drug used in this model was diazepam [15,16].

4.3. Locomotor activity

4.3.1. Using actophotometer

Actophotometer was used to evaluate the locomotor activity [17,18]. The Swiss albino mice weighing in range 30–35 g were

divided into six groups each consisting of six mice. One group received standard diazepam (5 mg/kg) and second i.e. control group received 0.2% tween 80 suspension (0.3 ml/kg, intraperitoneally). The test group received 10 mg/kg and 30 mg/kg of test compounds, [**7a**–**7f**] intraperitoneally. The locomotor activity score of all the animals was noted by placing the animals in the squares area of the instrument for 10 min. The test compounds [**7a**–**7f**] were administered intraperitoneally, and mice tested for activity score after 30 min. The difference in the number of times the animal cuts off the light before and after administration of test compounds was noted and the same parameter was used to compare the locomotor activity of the test compounds with that of standard drug, diazepam.

4.3.2. Using rotarod

Mice were placed on a rod of 10 cm in diameter rotating at a rate of 10 rpm. A group of six mice was used for each compound and average reading was taken. Standard drug diazepam 10 mg/kg was given intraperitoneally [19–22]. The control mice were able to remain on the rod for about 30 min. The mice were treated with synthesized compounds at a dose of 10 mg/kg and 30 mg/kg. The test compounds were suspended in distilled water with the help of tween 80 and injected intraperitoneally. The treated mice were placed on the rod at various time intervals and fall off time was recorded.

Acknowledgments

Authors are grateful to the Head, Department of Sophisticated Analytical Instrument Facilities, CDRI, Lucknow for performing elemental analysis of newly synthesized compounds. We acknowledge the support extended by National Chemical Laboratory, Pune for providing library facilities and University of Pune for analyzing ^{1}HNMR of newly synthesized compounds.

References

[1] B. Narayana, K.K. Vijaya Raj, B.V. Ashalatha, N. SuchethaKumari, Eur. J. Chem. 41 (2006) 417–422.
[2] J.G. Hardman, L.E. Limbard, P.B. Molinoff, R.W. Ruddon, G. Gilman, The Pharmacological Basis of Therapeutics, eleventh ed. McGraw-Hill Co., NewYork, 1996, pp.501–507.
[3] W.O. Foye, Principles of Medicinal Chemistry, third ed. Varghese Publishing House, 1999, pp.185.
[4] D.R. Gahane, V.C. Khapekar, N.J. Gaikwad, Indian J. Pharm. Sci. 14 (1998) 275–279.
[5] S. Misra, S.K. Srivastava, S.D. Srivastava, Indian J. Chem. 36 (1997) 826–830.
[6] N.P. Peet, S. Sunder, R.J. Barbuch, J. Med. Chem. 23 (1986) 123.
[7] M. Gutschow, L. Kuerschner, U. Newmann, M. Pietsch, R. Loser, N. Koglin, K. Eger, J. Med. Chem. 42 (1999) 5437–5447.
[8] B.S. Furniss, A.J. Hannaford, P.W. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, fifth ed. ELBS Publication, 1994, pp.1247.
[9] M.N. Ibrahim, K.J. Hamad, S.H. Al-Joroshi, Asian J. Chem. 18 (2006) 2404–2406.
[10] R.B. Patel, P.S. Desai, K.R. Desai, K.H. Chikhaliz, Indian J. Chem. 45 (2006) 773–778.
[11] K.C. Asati, S.K. Srivastava, S.D. Srivastva, Indian J. Chem. 45 (2006) 526–531.
[12] B. Singh, L.K. Baregama, M. Ahmed, N. Dixit, G.L. Talesara, Indian J. Chem. 43 (2004) 1243–1247.
[13] A.K. Misra, P.C. Dandiya, S.K. Kulkarni, Indian J. Pharmacol. 5 (1973) 449.
[14] A. Almasirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, A. Dalvandi, A. Shafiee, Bio-Org. Med. Chem. Lett 14 (2004) 6057–6059.
[15] E. Ngo Bum, D.L. Dawack, M. Schmutz, A. Rakotonina, S.V. Rakotonirina, Portet, A. Jeker, H.R. Olpe, P. Herrling, Fitoterapia 75 (2004) 309–314.
[16] R. Bernasconi, M. Klein, P. Martin, P. Christen, T. Hafner, C. Portet, M. Schmutz, J. Neural. Transm. 72 (1988) 213–233.
[17] K.K. Agarwal, V. Lata, K. Saxena, A. Srivastava, Kumar, Eur. J. Chem. 41 (2006) 1223–1229.
[18] A. Puratchikody, S. Gopalkrishnan, M. Nallu, Indian J. Pharm. Sci. 67 (2005) 725–731.
[19] S.K. Kulkarni, in: Handbook of Experimental Pharmacology, third ed. Vallabh Prakashan, New Delhi, 1999, p. 117.
[20] M. Zappala, N. Micale, S. Grasso, F.S. Menniti, G.D. Sarro, C.D. Micheli, ARKIVOC (2004) 196–203.
[21] N.W. Dunham, T.S. Miya, J. Am. Pharm. Assoc. Scientific Edition (1957) 208.
[22] V. Jatav, P. Mishra, S. Kashaw, J. Stables, Eur. J. Med. Chem. 43 (2008) 135–141.
[23] R.M. Silverstein, F.X. Webster, Spectrometric Identification of Organic Compounds, sixth ed. John Wiley and Sons, Inc, 2000, pp. 71–144, 168–216.