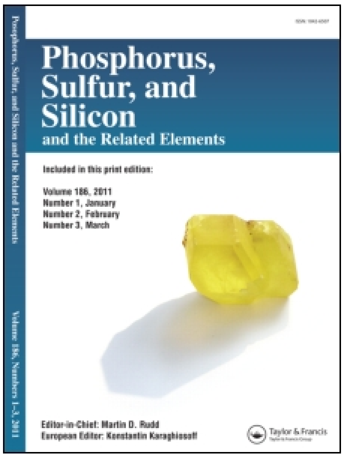

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The One Step Synthesis of 2-(2-Bromo-5- methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo[3,2-*b*]- 1,2,4-triazol-6-(5*H*)-ones and the Evaluation of the Anticonvulsant Activity

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The One Step Synthesis of 2-(2-Bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo[3,2-*b*]-1,2,4-triazol-6-(5*H*)-ones and the Evaluation of the Anticonvulsant Activity

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*A smooth one-step synthesis of 2-(2-bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo[3,2-*b*]-1,2,4-triazol-6-(5*H*)-ones (**4a–n**) is described. The newly prepared compounds are characterized by analytical and IR, ^1H NMR, ^{13}C NMR, and FABMS spectral analysis. A few compounds are screened for anticonvulsant activity. Compounds **4i** and **4n** exhibit promising anticonvulsant activity and are recommended for further studies.*

Keywords Anticonvulsant activity; bromomethoxyphenyl; one step synthesis; thiazolo-triazolones

INTRODUCTION

Multicomponent Reactions (MCRs) are very promising due to their advantages over conventional multistep reactions with respect to speed, time, yield, and reproducibility. Among organic reactions, MCRs are highly convergent[1] and serve as superior tools for diversity-oriented drug syntheses.[2] Recent literature reviews show that one-pot synthesis has importance in the syntheses of various biologically active heterocyclic compounds.[3,4]

Thiazolo[3,2-*b*]-1,2,4-triazole-6-(5*H*)-one derivatives possess biological activity, such as antiinflammatory[5] and vasodilatory[6] activity, as

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well as the antibacterial and antifungal,[7] anticonvulsant,[8] pesticidal,[9] and antiulcer[10] activities.

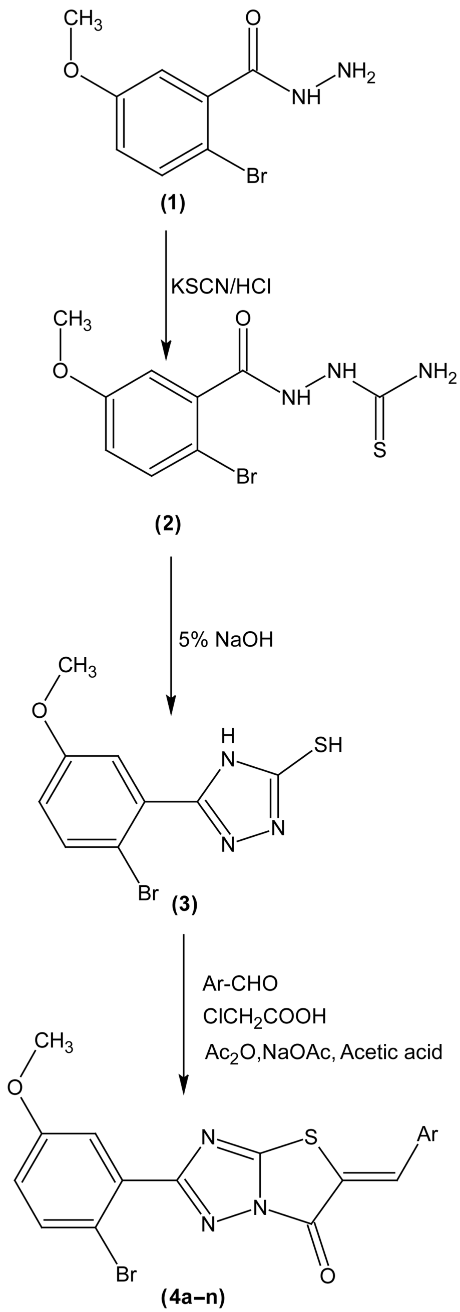
Prompted by these observations, it was contemplated to synthesize a new series of 2-(2-bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo[3,2-*b*]-1,2,4-triazol-6-(5*H*)-ones by the condensation of 5-(2-bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol with appropriate aromatic aldehydes and monochloroacetic acid in the presence of acetic anhydride, acetic acid, and anhydrous sodium acetate in a multicomponent synthesis. The latter provides maximum structural complexity and diversity in a minimum number of steps. In addition, it was the intent to screen them for anticonvulsant activity. The outline of the syntheses is given in Scheme 1.

RESULTS AND DISCUSSION

Chemistry

5-(2-Bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole (**3**) was synthesized by the reaction of 2-bromo-5-methoxybenzoic acid hydrazide (**1**) with potassium thiocyanate and conc. HCl, followed by the cyclization of the resulting 1-(2-bromo-5-methoxybenzoyl) thiosemicarbazide (**2**) with sodium hydroxide,[11] 5-(2-bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol (**3**) was condensed with monochloroacetic acid and aromatic aldehydes in the presence of anhydrous sodium acetate, acetic anhydride, and acetic acid to obtain 2-(2-bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo [3,2-*b*]-1,2,4-triazol-6-(5*H*)-ones (**4a–n**).

The newly synthesized compounds (**4a–n**) were characterized by spectral analysis. The IR spectrum of the compound **4e** showed a series of bands at 3074.8 cm^{-1} to 2837.8 cm^{-1} due to an alkyl and aryl –CH stretch. A band at 1742.5 cm^{-1} was due to a keto group, and a band at 1570.2 and 1514.8 cm^{-1} was due to a –C=N stretch. A band at 1233.9 cm^{-1} was due to an Ar-F stretch. The ^{1}H NMR (δ in ppm) spectrum of **4e** showed a singlet at δ 3.84 is due to –OCH_3 protons. A doublet of a doublet at δ 6.9 (J = 8.7), a doublet at δ 7.47 (J = 3.0), and a doublet at δ 7.54 (J = 8.7) were due to three protons in the aromatic ring bearing the methoxy group. A doublet of doublets at δ 7.65 (J = 8.7) and a multiplet at δ 7.25 were due to 4 protons on the aromatic ring containing a fluorine atom. The multiplet arose due to an F-H coupling. A singlet at δ 8.21 was due to a benzylidene proton. The ^{13}C NMR (δ in ppm) spectrum of **4e** showed peaks at 55.51, 112.53, 116.82, 117.0 (d, $^2J_{C-F} = 22.5$), 118.55, 123.67,128.87, 131.00, 132.98 (d, $^3J_{C-F} = 8.25$), 135.12, 139.49,156.09, 158.87, 159.18, 164.53 (d, $^1J_{C-F} = 87.8$), and 169.60. The FABMS spectrum showed peaks at *m/z* 432 (M^+, I = 60%), and *m/z* 434 (M+2, I = 70%) corresponded to


CH3
O
NH
NH2
Br
(1)
KSCN/HCl
CH3
O
NH
NH
NH2
S
Br
(2)
5% NaOH
CH3
O
H
N
SH
N
N
Br
(3)
Ar-CHO
ClCH2COOH
Ac2O,NaOAc, Acetic acid
CH3
O
N
S
Ar
N
N
Br
O
(4a–n)

SCHEME 1

the molecular formula $C_{18}H_{11}BrFN_3O_2S$. Characterization data of the compounds are given in Table I. Spectral data of other compounds are given in the Experimental section.

Anticonvulsant Activity

Inbred male albino mice (Swiss strain) weighing between 20–30 g were used in the study. They were housed under standard laboratory conditions for one week before experiments were started and were kept in groups of 3–4 per cage at a controlled temperature (23°C) and humidity (50%) with dark–light cycles beginning at 7 a.m. They received a standard diet and water *ad libitum*. Each mouse was used for one seizure test only. Pentylenetetrazole (PTZ, Sigma Chemicals, USA) was used as a convulsant and Diazepam (Ranbaxy Laboratories, India) was used as a standard drug. The studies were carried out at the Department of Chemistry, Mangalore University. The institutional ethical committee (Mangalore University, Karnataka, India) approved the study. The data obtained were analyzed using one-way analysis of variance (ANOVA). $p < 0.05$ was considered as significant. Results are given in Table II.

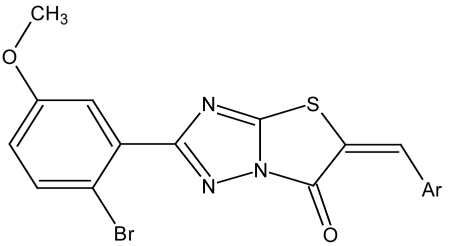
Pentylenetetrazole was dissolved in normal saline. Test and standard drugs were dissolved in 2% gum acacia suspension. Mice were divided into seven groups of three each. Group 1 received diazepam; Group 2 received **4e**; Group 3 received **4f**; Group 4 received **4i**; Group 5 received **4l**; and Group-6 received **4n** at a dose of 4 mg/Kg dissolved in 2% gum acacia in a volume of 0.1 mL/10 g body weight; and Group 7 received 0.1 mL/10 g of 2% gum acacia orally by gavage feeding.

Convulsions were induced[12] one h after the administration of standard and test drugs by injecting PTZ (80 mg/kg) dissolved in saline i.p. in 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 mylonic jerks or other preconvulsive chewing behavior were not counted) was carefully noted. The duration of the seizurewas also noted. A seizure-free duration for a period of one h was taken as protection.

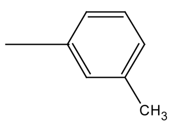
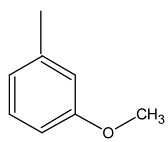
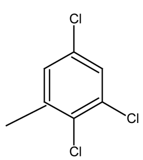
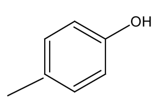
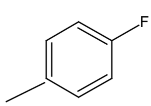
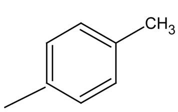
The animals tested in the vehicle group exhibited seizures at the dose of PTZ used in the study. The onset of seizures was found at 119 s, and the meanseizure duration was 259 s. The standard drug diazepam protected the animal from developing convulsions. Although none of the tested compounds protected animals from developing convulsions, **4e** and **4i** increased latency; **4n**, **4i**, and **4f** reduced the duration of seizures, and **4n** and **4i** prevented death.

Out of the tested compounds **4e**, **4f**, **4i**, **4l** and **4n**, the compounds having anticonvulsant action at a dose of 4 mg/kg were **4i** and **4n**, bearing a 3,4-dimethoxybenzene moiety and 2-hydroxyphenyl moiety

TABLE I The Characterization of 2-(2-Bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo [3,2-*b*]-1,2,4-triazol-6-(5*H*)-One (4a–n)

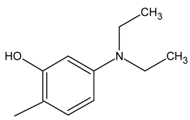
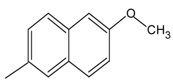
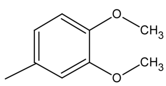
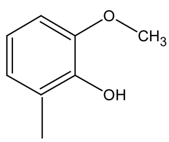
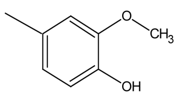
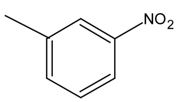
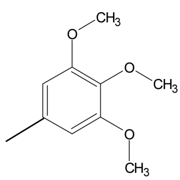
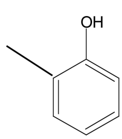


(4a–n)

Compound no.	Ar	Yield[a] %	Molecular formula	M.P.[b] °C	% Nitrogen Calcd.	% Nitrogen Found	Nature of crystals
4a		52	$C_{19}H_{14}BrN_3O_2S$	192–194	9.81	9.60	Yellow crystals
4b		65	$C_{19}H_{14}BrN_3O_3S$	164–168	9.46	9.28	Off-white powder
4c		62	$C_{18}H_9BrCl_3N_3O_2S$	138–142	8.12	8.03	Yellow crystals
4d		68	$C_{18}H_{12}BrN_3O_3S$	178–180	9.77	9.56	Yellow crystals
4e		72	$C_{18}H_{11}BrFN_3O_2S$	228–230	9.72	9.68	Yellow crystals
4f		64	$C_{19}H_{14}BrN_3O_2S$	198–200	9.81	9.67	Off-white crystals

(Continued on next page)

TABLE I The Characterization of 2-(2-Bromo-5-Methoxyphenyl)-5-(3-Arylidene)-1,3-Thiazolo [3,2-*b*]-1,2,4-Triazol-6-(5*H*)-One (4a–n) *(Continued)*

Compound no.	Ar	Yield[a] %	Molecular formula	M.P.[b] °C	% Nitrogen Calcd.	% Nitrogen Found	Nature of crystals
4g		65	$C_{20}H_{17}BrN_4O_3S$	246–248	11.17	11.00	Reddish orange crystals
4h		65	$C_{23}H_{16}BrN_3O_3S$	250–252	8.50	8.34	Yellow crystals
4i		68	$C_{20}H_{16}BrN_3O_4S$	140–144	8.86	8.65	Yellow powder
4j		67	$C_{19}H_{14}BrN_3O_4S$	212–214	9.13	9.01	Off-white crystals
4k		72	$C_{19}H_{14}BrN_3O_4S$	222–224	9.13	9.01	Light yellow crystals
4l		65	$C_{18}H_{11}BrN_4O_4S$	238–240	12.20	12.16	Yellow crystals
4m		61	$C_{21}H_{18}BrN_3O_5S$	212–214	8.33	8.25	Yellow crystals
4n		58	$C_{18}H_{14}BrN_3O_3S$	164–166	9.77	9.63	White crystals

[a]Yields are on an isolated basis.
[b]All compounds are recrystallized in methanol/dimethyl formamide.

TABLE II Anticonvulsant Activity Data of 2-(2-Bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo[3,2-*b*]-1,2,4-triazol-6-(5*H*)-one (4e, 4i, 4f, 4l, 4n)

Group	Drug	Dose (mg/kg)	Latency Mean ± SEM	Duration of seizure mean ± SEM	Mortality
1	Diazepam	4	3598.3 ± 3.6046	0	No
2	**4e**	4	131 ± 1.7016	258 ± 0.4719	Yes
3	**4f**	4	95 ± 0.4719	94 ± 0.4719	Yes
4	**4i**	4	180 ± 0.9438	25 ± 0.4719	No
5	**4l**	4	95.3 ± 0.5449	278 ± 0.9421	Yes
6	**4n**	4	98 ± 0.2724	27 ± 0.4719	No
7	2% gum acacia (Control)	0.1 mL/10 g	94 ± 0.5449	259 ± 0.7209	Yes

$N = 3$ in each group, $p < 0.05$.

respectively. Because as a correct correlation between structure and activity is not clear at present, further studies have to be carried out to establish the proper structure-activity relationship. Since all our inference is based only on a screening test, further investigations using larger samples have to be done to obtain conclusive data.

EXPERIMENTAL

Melting points were taken in open capillary tubes and were uncorrected. The purity of compounds was confirmed by TLC using Merck silica gel 60 F_{254} coated aluminium plates. IR spectra were recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^{1}H NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as internal standard, and ^{13}C NMR spectra were recorded in $CDCl_3$ and in DMSO d_6 on a Varian (75 MHz) spectrometer. FABMS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas.

2-bromo-5-methoxybenzohydrazide was prepared from methyl 2-bromo-5-methoxybenzoate[13] by treating it with hydrazine hydrate in methanol; m.p. 172–174°C. ^{1}H NMR (300 MHz)-δ 3.79 (s, 3H, –OCH_3), δ 6.84 ($dd_{(J=8.8)}$, 1H, Ar-H), δ 6.95 ($d_{(J=2.96)}$, 1H, Ar-H), δ 7.45 ($d_{(J=8.8)}$, 1H, Ar-H), δ 9.26 (bs, 1H, -NH).

The Synthesis of 1-(2-Bromo-5-methoxybenzoyl) Thiosemicarbazide (2)

2-Bromo-5-methoxybenzohydrazide (**1**) (50 g, 0.204 mol), potassium thiocyanate (25 g, 0.267 mol), and 40 mL of conc. HCl in 400 mL of water was refluxed for 4 h. A white solid appeared on cooling and was filtered and dried Yield 51.2 g (74.4%); m.p. 190–192°C. IR (KBr, cm^{-1}): 3280 (NH), 1670 (CONH), 1360 (C=S).

The Synthesis of 5-(2-Bromo-5-methoxyphenyl)-4 *H*-1, 2,4-triazole-3-thiol (3)

1-(2-Bromo-5-methoxybenzoyl)-thiosemicarbazide (50 g, 0.164 mol) was refluxed with 500 mL of 5% sodium hydroxide solution for 4 h and was cooled and filtered. The clear solution was then acidified with conc. HCl to pH 5–6. The solid obtained was filtered and recrystallized (methanol) to give white crystals. Yield, 42 g (89.3%), m.p. > 250; IR (KBr, cm^{-1}): 2575 (SH), 1605 (C=N), 1325 (C=S); ^{1}H NMR (300 MHz,)- δ 3.82 (s, 3H, -OCH_3), δ 7.07 ($dd_{(J=6.6),}$ 1H, Ar-H), δ 7.23 ($d_{(J=2.28)}$, 1H, Ar-H), δ 7.68 ($d_{(J=6.6),}$ 1H, Ar-H), δ 13.66 (s, 1H, -SH), 13.75 (s, 1H,-NH); MS-*m/z* 288 (90%,M+2), *m/z* 286 (80%, M^+), *m/z* 254 (10%, M-SH), *m/z* 176(40%,$C_8H_6N_3S$),*m/z* 154(100%,C_6H_3 Br).

The Synthesis of 2-(2-Bromo-5-Methoxyphenyl)-5-(3-Arylidene)-1,3-Thiazolo[3,2-*b*]-1,2,4- triazol-6-(5*H*)-one(4a–n)

5-(2-Bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol (**1**) (0.003 mol), mono chloroacetic acid (0.045 mol), aromatic aldehyde (0.003 mol), and sodium acetate (0.045 mol) in a mixture of 15 mL acetic anhydride and 30 mL of acetic acid was refluxed for 8 h. The reaction mixture was cooled, and the solid separated was filtered and recrystallized from methanol. All products were isolated in a 58–72% yield.

4a. 2-(2-Bromo-5-methoxyphenyl)-5-(3-methylbenzylidene) [1,3]thiazolo[3,2-b]-1,2,4-triazol-6(5H)-one

^{1}H NMR (300 MHz)- δ 2.35 (s, 3H, -CH_3), δ 3.83 (s, 3H, -OCH_3), δ 6.91 ($dd_{(J=6.63)}$, 1H, Ar-H),δ 7.25 (s, 1H, Ar-H), δ 7.31 ($d_{(J=6.45),}$ 1H, Ar-H), 7.47 ($d_{(J=2.31)}$, 1H, Ar-H), δ 7.60 ($d_{(J=6.63)}$, 1H, Ar-H), δ 7.67 ($dd_{(J=6.48),}$ 2H, Ar-H), 8.24(s, 1H,=CH); MS: *m/z* 474 (80%, M+ 2Na), *m/z* 472 (75%, M-2+2Na), *m/z* 429 (20%,M^+), *m/z* 431 (20%, M+2).

4c. 2-(2-Bromo-5-methoxyphenyl)-5-(2,3,5-trichlorobenzylidene)[1,3]thiazolo[3,2-b]- 1,2,4-triazol-6(5H)-one

IR (KBr, cm^{-1})- 3059 and 3009 (-CH), 1735 (C=O), 1575 (C=N), 735.25 and 700.85 (Ar-Cl); ^{1}H NMR (300MHz)- δ 3.80(s, 3H, -OCH_3), δ 6.91($dd_{(J=8.94)}$, 1H, Ar-H), δ 7.44 (s, 1H, Ar-H), δ 7.50–7.62 (m, 2H, Ar-H), δ 7.67(dd$_{(J=4.91)}$, 1H, Ar-H),8.10 (s, 1H, =CH); MS: *m/z* 552 (80%, M+Cl), *m/z* 550 (90%, M-2+Cl), *m/z* 518 (55%, M^+), *m/z* 476 (30%, M-2).

*4e. 2-(2-Bromo-5-methoxyphenyl)-5-(4-fluorobenzylidene) [1,3]thiazolo[3,2-*b*]-1,2,4-triazol-6-(5*H*)-one*

IR (KBr, cm^{-1})- 3074.8 and 2837.8 (—CH), 1742.5 (C=O),1570.2 and 1514.8 (C=N), 1233.9 (Ar-F); ^{1}H NMR (300MHz)-δ 3.84 (s, 1H, –OCH_3), δ 6.9 (dd$_{(J=8.7)}$, 1H, Ar-H), δ 7.47(d$_{(J=3.0)}$, 1H, Ar-H), δ 7.54 (d$_{(J=8.7)}$, 1H, Ar-H), δ 7.65 (dd$_{(J=8.7)}$, 2H, Ar-H), δ 7.25 (m, 2H, Ar-H), δ 8.21(s, 1H, =CH);^{13}C NMR (75 Hz, ppm):55.51, 112.53, 116.82, 117.0 (d, $^2J_{C-F}$ = 22.5), 118.55, 123.67, 128.87, 131.00, 132.98 (d, $^3J_{C-F}$ = 8.25), 135.12,139.49, 156.09, 158.87, 159.18, 164.53 (d, $^1J_{C-F}$ = 87.8),169.60. DEPT: 55.66, 116.82, 117.0 (d, $^2J_{C-F}$ = 22.5), 118.57,133.01 (d, $^3J_{C-F}$ = 9.75), 135.07, 139.62; MS: *m/z* 432 (60%, M^+), *m/z* 434 (70%, M+2H).

4f. 2-(2-Bromo-5-methoxyphenyl)-5-(4-methylbenzylidene) [1,3]thiazolo[3,2-*b*]-1,2,4-triazol-6(5*H*)-one

IR (KBr, cm^{-1})- 3065.94 and 2939.53 (—CH), 1746.32 (C=O),1598.0 and 1512.43 (C=N); ^{1} H NMR (300MHz)- δ 2.43 (s, 3H,-CH_3) δ 3.84 (s, 1H, –OCH_3), δ 6.89(dd$_{(J=8.7)}$, 1H, Ar-H), δ 7.34 (d$_{(J=7.8)}$, 1H, Ar-H), δ7.47(d$_{(J=3.0)}$,1H, Ar-H), δ 7.52 (d$_{(J=8.4)}$, 2H, Ar-H), δ 7.58 (d$_{(J=9.0)}$, 2H, Ar-H), δ 8.21(s,1H,=CH); ^{13}C NMR (75 Hz, ppm): 21.73, 55.66, 112.40, 116.55,118.5, 122.35, 129.62, 130.35 (2C), 130.95 (2C)135.03,141.14,143.08,156.39, 158.69 (2C), 159.4, 169.33; DEPT: 21.75, 55.66, 116.53,118.52, 130.35, 130.92, 135.05, 141.15; MS: *m/z* 432 (60%, M+4H), *m/z* 431 (20%, M +3H).

4k. 2-(2-Bromo-5-methoxyphenyl)-5-(4-hydroxy-3-methoxybenzylidene)[1,3]thiazolo [3,2-*b*]-1,2,4-triazol-6(5*H*)-one

IR (KBr, cm^{-1})- 3068 and 2940 (—CH), 1746.0 (C=O), 1596.0 and 1512.0 (C=N); ^{1}H NMR (300MHz)- δ 2.35(s, 1H, -OH), δ 3.84 (s, 12H,–OCH_3), δ 3.92 (s, 12H, –OCH_3), δ 6.91 (dd$_{(J=8.8)}$, 1H, Ar-H), δ 7.19 (d$_{(J=3.86)}$, 1H, Ar-H), δ 7.23(s, 1H, Ar-H), δ 7.25 (dd$_{(J=7.0)}$, 1H, Ar-H), δ 7.47(d$_{(J=3.3)}$, 1H, Ar-H), δ 7.59 (d$_{(J=8.8)}$, 1H, Ar-H), δ 8.21 (s, 1H, =CH).

4m. 2-(2-Bromo-5-methoxyphenyl)-5-(3,4,5-trimethoxybenzylidene) [1,3]thiazolo [3,2-b]-1,2,4-triazol-6(5H)-one

IR (KBr, cm^{-1})- 3065.94 and 2939.53 (—CH), 1746.32 (C=O), 1598.0 and 1512.43 (C=N); ^{1} H NMR (300MHz)-δ 3.91 (s, 12H, –OCH_3), δ 6.83 (s, 2H, Ar-H), δ 7.34 ($dd_{(J=7.8)}$, 1H, Ar-H), δ 7.45($d_{(J=3.0)}$, 1H, Ar-H), δ 7.56 ($d_{(J=8.7)}$, 1H, Ar-H), δ 8.14 (s, 1H, =CH);^{13}C NMR (75 Hz, ppm): 55.65, 56.27(2C), 61.11, 108.12 (2C), 112.38, 116.56, 118.50,122.45, 127.60, 130.82, 135.08, 141.06, 141.58, 156.39, 153.75 (2C),156.21, 158.69, 159.15, 169.37; DEPT: 55.66, 55.27(2C), 61.11, 108.11, 116.55, 118.50, 135.08, 141.06; MS: *m/z* 504 (90%, M^+), *m/z* 505 (100%, M+H), *m/z* 506 (100%, M+2H), *m/z* 336 (50%, M-(3xOCH_3+Br)).

CONCLUSION

A new series of 2-(2-bromo-5-methoxyphenyl)-5-(3-arylidene)-1,3-thiazolo[3,2-*b*]-1,2, 4-triazol-6-(5*H*)-ones were synthesized in a multi-component one pot synthesis. A few of the synthesized compounds were screened for their anticonvulsant activity *in vitro*. Among tested compounds **4e**, **4f**, **4i**, **4l**, and **4n**, compounds having an anticonvulsant action at a dose of 4 mg/kg were **4i** and **4n.** These could become candidates for further study. As a correct correlation between structure and activity is not clear at present, more studies have to be carried out further to establish the proper structure-activity relationship.

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