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Full Length Research Paper

Facile green synthesis of 2, 4-substituted -2, 3- dihydro -1, 5 Benzothiazepine derivatives as novel anticonvulsant and central nervous system (CNS) depressant agents

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The present work reports eco friendly synthesis of 2, 4-substituted -2, 3- dihydro -1,5-benzothiazepine derivatives as novel anticonvulsant and central nervous system (CNS) depressant agents having lesser side effects. Facile, one pot efficient, solvent free microwave-assisted green synthesis of 1, 5-benzothiazepine derivatives by cyclo- condensation of 2-aminothiophenol with 1, 3-substituted-prop-2-en-1-one (2a-h) in the presence of zinc acetate as eco friendly catalyst, was investigated. The products were obtained in shorter reaction time and in better yields as compared with the conventional synthesis. The synthesized compounds (2a-h) and (3a-h) were purified by chromatographic techniques and by recrystallization from suitable solvents. Their anticonvulsant activities were evaluated by the maximal electroshock test and CNS depressant activity was evaluated by sleep deprivation test. The compounds (3a-h) have shown moderate CNS depressant activity and anticonvulsant activity.

Key words: Green synthesis, 1, 5- benzothiazepines, anticonvulsant, central nervous system (CNS) depressant activity.

INTRODUCTION

Epilepsy is the most common primary neurological disorder known, affecting 0.4 to 0.8% of the population and up to 50 million people worldwide (McNamara, 1999; Yogeeswari et al., 2005). Epilepsy is the tendency to experience seizures-intermittent, usually unprovoked and stereotyped episodes that result from abnormal, paroxysmal electric discharge of neurons of the cerebral cortex (Parton and Cockerell, 2003). One of the approaches to analog –based drug discovery is the concept of bioisosteric replacement, which continues to play an important role in bioorganic and medicinal chemistry in designing of novel pharmacological tools. The marketed anticonvulsive drugs such as: Clobezam, clonazepam, diazepam, lorazepam, nitrazpam, and temazepam contain benzodiazepine nucleus (Robertis et al., 1987). 1, 5-benzothiazepines are bioactive molecules of great interest and they are the bioisosters of benzodiazepines (Figure 1). Replacement of nitrogen by sulphur at position 1 in the seven membered rings of benzodiazepines will form benzothiazepine ring and makes it more penetrable in the CNS (Block et al., 2004; David and Thomas, 2002; Tripathi 2004). 1, 5-benzothiazepines are gaining more attention due to their broad range chemotherapeutic applications such as anticonvulsant (Sarroj, 1995), CNS depressant (Nikalje and Pattan, 2007), Ca^{++} channel blockers (Masafumi et al., 1997), anticancer (Sharma et al., 1997), anti fungal (Dandia et al., 2007) and anti-HIV(Giuliano et al., 1999), however they are less explored as anticonvulsants.

Microwave irradiation technique is a powerful tool in 'green organic synthesis'. Its utility in context to 'green chemistry' and for high throughput in combinatorial drug discovery are being fully exploited (Ahluwalia and Kidwai, 2004; Madaan and Guchhait, 2007).

Keeping in view the potential for potent and safer anticonvulsant and CNS active drug molecules, and in continuation of our efforts in search of bioactive molecules

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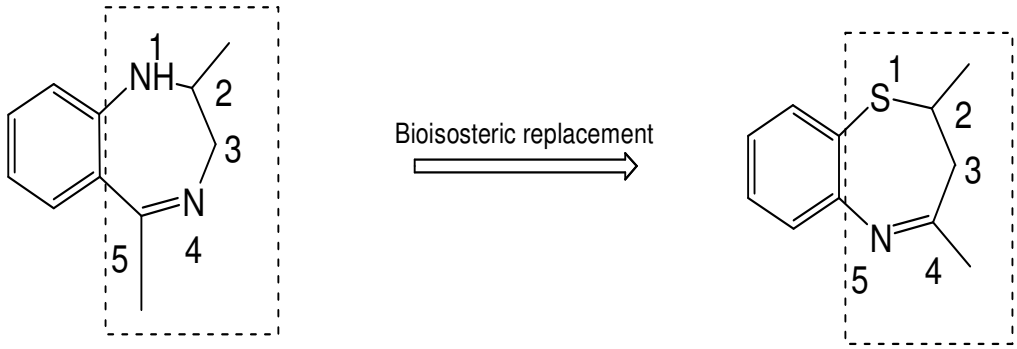


Figure 1. Anticonvulsant compounds designed by bioisosteric replacement.

(Nikalje et al., 2006; Shiradkar et al., 2007), it was thought worthwhile to synthesize substituted 1,5-benzothiazepine derivatives by using green chemistry tools and screen them for CNS activities such as anticonvulsant and CNS depressant.

The principal aim of the present study was to synthesize novel 1, 5-benzothiazepine derivatives by using green chemistry principles, so as to minimize environmental pollution, to save time, to get better yields and to evaluate the synthesized compounds for their CNS activity. The present investigation describes one pot solvent-free synthesis of 1, 5-benzothiazepines by cyclo-condensation of 2-aminothiophenol with 1, 3- substituted-prop-2-en-1-one, using zinc acetate dihydrate as eco friendly catalyst (Pasha and Jayashankara, 2006) that is water soluble.

MATERIALS AND METHODS

In the present work we have used green methodology such as the use of microwave, use of green catalyst and carrying out the reactions in solvent free conditions. The Scheme 1 describes synthesis of intermediates (2a-h) and the final compounds 1, 5-benzothiazepine derivatives (3a-h). The starting compound 2, 6-dichloroacetophenone 1 was obtained by reacting 2, 6-dichloro phenyl acetate with anhydrous aluminium chloride by Fries rearrangement. Condensation of 1 with different aldehydes in presence of alkali gave 1, 3-substituted-prop-2-en-1-one (chalcone) (2a-h). The conventional method of preparation of chalcones by Claisen-Schmidt condensation requires 48 h for completion of reaction where as microwave-assisted synthesis requires only 2 to 7 min and gives better yields.

Finally, when the compounds (2a-h) are cyclo-condensed with 2-aminothiophenol in presence of zinc acetate as eco friendly catalyst, in solvent-free conditions under microwave irradiation, the target compounds (3a-h) that is, 2, 4-substituted-1, 5-benzothiazepines were obtained.

PHARMACOLOGY

The results of pharmacology test of all synthesized compounds and reference drugs are shown in Tables 2 and 3. Compounds exhibited moderate anticonvulsant and CNS depressant activity.

Anticonvulsant activity

Anticonvulsant activity was evaluated by the maximal electroshock method (Vogel, 2002). The animals (rats of Wistar strain) were weighed and were selected for the experiment depending on the weight. The rats were then divided into 7 groups. Group 1 was the control group. Group 2 received 25 mg/kg body weight of phenytoin as standard drug. Groups 3, 4, 5, 6 and 7, received 80 to 150 mg/kg bodyweight of compound 3a to 3h respectively, which were prepared by dissolving in 1% Tween 80. Maximal electroshock (Inco Electroconvulsiometer model #100-3) of 150 mA current for 0.2 s was applied through ear electrodes to induce convulsions in the control and test compound treated animals. The severity of convulsions was assessed by the duration of tonic flexion, tonic extensor, clonus, stupor and recovery phase for each animal.

CNS depressant activity

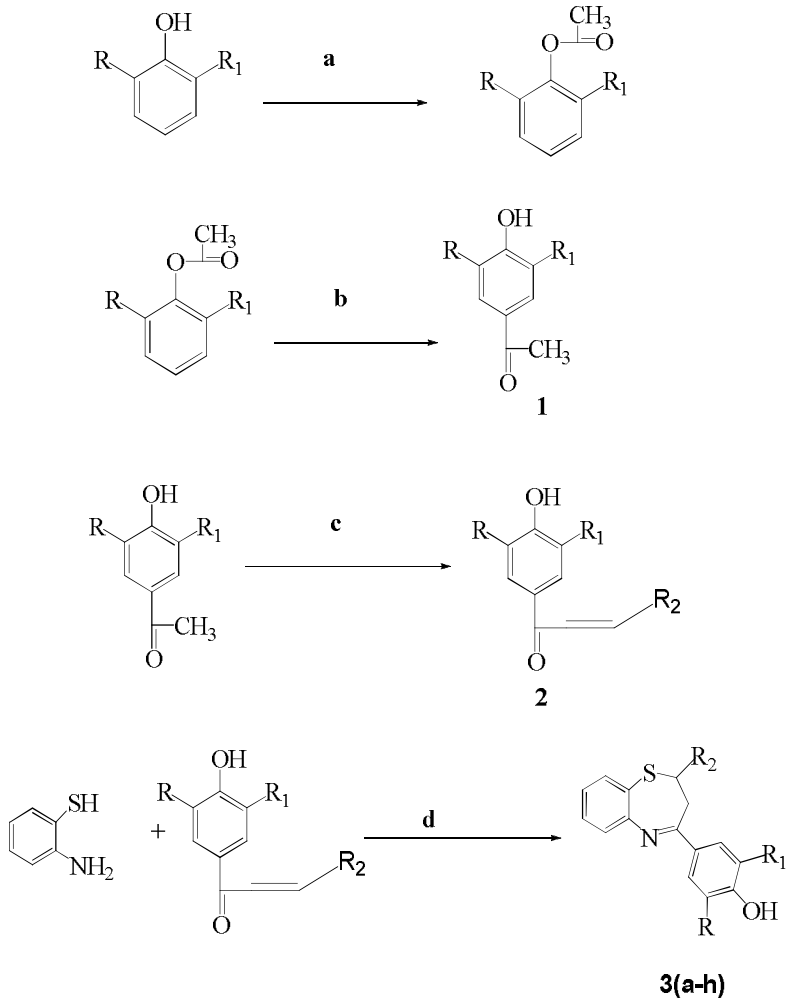
Male Wistar rats weighing in the range of 20 to 25 g were selected from an inbreed strain colony. They were maintained at constant temperatures and relative humidity. Acute toxicity was done by following the sleep deprivation method (Kalonia and Anil, 2007). Diazepam was used as standard drug, 2% CMC suspension was used as control and suspensions of the synthesized compounds were used for screening. The mean sleeping times of the compounds were compared with the standard using one-way ANOVA followed by Scheffe's post analysis to find out the significance. All the synthesized compounds have shown moderate CNS depressant activity.

EXPERIMENTAL PROTOCOLS

All the chemicals used were of Merck make. The reactions were carried out in synthetic microwave oven; CATA R. Melting points was determined in open capillaries using melting point apparatus. IR spectra were recorded by FTIR JASCO 4000, using KBr powder technique. ^{1}HNMR were measured on Brucker advance II 400 NMR spectrotometer in $CDCl_3$, using TMS as internal standard and all the chemical shifts values were given in parts per million relative to tetramethylsilane. Mass spectra were recorded on TOF MS+484. Analyses indicated by the symbols of the elements were within +_ 0.4% of the theoretical values.

Step I: Synthesis of 2, 6-dichlorophenyl acetate

Synthesis was carried out as per the procedure (Furnis et al.,



a. $(CH_3CO)_2O$, 10% NaOH; **b.** Anhy. $AlCl_3$; **c.** R_2CHO, 40% NaOH, EtOH, MW; **d.** Zinc Acetate, MW; R = H, Cl ; R_2 = Aryl, Heteryl

Scheme 1. Synthetic routes of compounds 3(a-h).

2005), (b.p.190°C).

Step II: Synthesis of 3, 5-dichloro-4 hydroxy acetophenone 1

Synthesis was carried out as per the procedure (b.p. 220°C).

Step III: Synthesis of 1, 3-substituted- prop-2-en-1-one (chalcones) 2

By conventional method

Claisen-Schmidt condensation was carried out (Rajendraprasad et al., 2006) in 250 ml beaker, 0.01 M acetophenone or substituted acetophenone, 30 ml of ethanol and 15 ml of 40% KOH was added and the reaction mixture was cooled in ice bath. To this reaction mixture (0.1 M), aldehyde was added with stirring. This mixture was kept for 48 h and then poured on ice and was acidified with dilute HCl. The product thus obtained was filtered, dried and recrystallized with ethanol. Yield and melting point of the product was recorded.

Microwave assisted synthesis of chalcones

Microwave assisted synthesis of chalcones was carried out by solvent phase method (Jhala et al., 2005). Equimolar quantities (0.01 M) of acetophenone and aromatic aldehyde, ethanol (5 ml) and sodium hydroxide (4 ml, 40%) were taken in 100 ml Erlenmeyer borosil flask fitted with condenser. The reaction mixture was subjected to microwave irradiation for 2 to 7 min at power 300 Watt. After completion of reaction, the reaction mixture was cooled to room temperature and was acidified with dilute HCl. The solid obtained was filtered, dried and recrystallized with ethanol. This method gave better yields in shorter times. Yield and melting point of the product was recorded.

2a. 1-(4-Hydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one: Yield 90%, m. p. 125°C; IR (KBr, cm^{-1}) 3207 (aromatic–C=H-str.), 2600 (olefin–CH=CH- str.) 1726 (–C=O), 1545 (NO_2 str.).^{1}H NMR δ($CDCl_3$): 7.8(d,1H,ethylenic), 8.4(d,1H ethylenic), 7.5-8 (m, 9H, phenyl); Mass m/e 253, 131 (M-$C_6H_4NO_2$),122 (M-C_9H_7O).

2b. 1-(4-Hydroxyphenyl)-3-phenylprop-2-en-1-one: Yield 50%, m.p. 65°C; IR (KBr,cm^{-1}) 3406 cm^1 (aromatic–CH=CH- str.), 2436 (olefin-CH=CH- str.), 1625cm^{-1} (–C=O str.); ^{1}H NMR δ ($CDCl_3$): 6.6(d,1H,J=13Hz), 7.5(d,1H,J=13Hz), 7.2-8.1(m,10H,phenyl); Mass m/e 208, 77(M- C_9H_7O),131 (M-C_6H_5).

2c. 3-(2-Hydroxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one: Yield 65% , m.p. 110°C; IR (KBr, cm^{-1}) 3210 (aromatic-CH=CH- str.), 2353(-CH=CH olefin str.), 1782 (–C=O); ^{1}H NMR δ ($CDCl_3$): 5.6(s,aromatic-OH), 7.5(d,1H,J=13Hz), 7.9 (d,1H,J=13 Hz), 6.8-7.8 (m,12H,phenyl); Mass m/e 221,72(M-$C_9H_7O_2$), 216(M-$C_9H_7O_2$),147(M-C_6H_3).

2d. 1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one: Yield 56%, m.p. 75°C; IR (KBr, cm^{-1}) 3129(aromatic–CH=CH- str.). 2436 (olefin–CH=CH-str), 1685 (–C=O); ^{1}H NMR δ($CDCl_3$): 3.73(s, 3H,-OMe) 6.7(d,1H,J=13.5), 6.9(d,1H), 6.7-7.8.(m, 9H, phenyl); Mass m/e 239, 129(M-C_7H_7O), 107(M-C_9H_7O).

2e. 1-(3, 5-Dichloro-4-hydroxyphenyl)-3-(furan-2-yl)prop-2-en-1-one: Yield 60%, m.p. 70°C; IR (KBr, cm^{-1}) ,3221 (aromatic -OH str), 3125(-CH=CH-aromatic str), 2852 (olefin-CH=CH- str), 1720(C=O), 800 (-C-Cl); ^{1}HNMR δ($CDCl_3$): 5.0(s,1H,phenolc OH), 7.5(d, 1H,J=13Hz), 7.9(d,1H,J=13Hz), 6.6(d,1H,=CH), 7.0(d,1H,=CH), 7.8(d,1H,=CH), 7.5(s,2H,phenyl); Mass m/e 283, 67(M-$C_9H_5O_2Cl_2$), 216(M-C_4H_3O), 121(M- $C_6H_3Cl_2$).

2f. 1-(3, 5-Dichloro-4-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one: Yield 70%, m.p. 70°C; IR (KBr, cm^{-1}) 3231 (aromatic-OH str), 3125(aromatic-CH=CH str), 2795 (olefin-CH=CH- str), 1726 (–C=O), 810 (-C-Cl); ^{1}H NMR δ ($CDCl_3$): 3.73 (s,3H,-OMe), 5.9(s,1H, aromatic-OH), 6.8(d,1H,J=14Hz), 7.56(d,1H,J=14Hz), 6.7-7.5 (m,6H,phenyl); Mass m/e 324, 128(M-$C_9H_5O_2Cl_2$), 216(M-C_7H_8O), 162 (M-$C_{10}H_9O_2$).

2g. 1-(3, 5-Dichloro-4-hydroxyphenyl)-3-(thiophen-2-yl) prop-2-en-1-one: Yield 67% , m.p. 65°C; IR (KBr, cm^{-1}), 3221(s, aromatic-OH str.), 3127 (aromatic-CH=CH str.), 2789(olefin -CH=CH- str.), 1782 (–C=O), 798(-C-Cl), 600(-C-S-str.); ^{1}H NMR δ($CDCl_3$): 5.3(s,aromatic-OH), 7.5(d,1H,J=14.3Hz), 7.9(d,1H,J=14.3Hz), 7.3(s,1H,phenyl), 7.5(s,1H, phenyl), 7.3(d,1H,=CH), 7.6(d,1H,=CH), 7.7(d,1H,=CH); Mass m/e 299, 83(M-$C_9H_5O_2Cl_2$), 216(M-C_5H_3S), 162(M-C_7H_5OS).

2h. 1-(3, 5-Dichloro-4-hydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one: Yield 80%, m.p. 90°C; IR (KBr, cm^{-1}), 3321 (-OH str.), 3136(-CH=CH-aromatic str.), 2689(olefin-CH=CH- str.), 1699 (–C=O), 1485 (NO_2 str.), 798 (-C-Cl); ^{1}H NMR δ($CDCl_3$): 5.1(s, 1H, phenolic-OH), 7.8(d,1H, ethylenic J=14.5), 8.4(d,1H,ethylenic J=14), 7.53 (s,2H, phenyl)7.5-8.1 (m, 4H,Ph), Mass m/e 338, 216(M-$C_6H_4NO_2$), 122(M-$C_9H_5O_2Cl_2$).

Step- IV: Synthesis of 2, 4- substituted –2, 3-dihydro- 1,5-benzothiazepin -4yl-phenols 3

Microwave-assisted synthesis

In 50 ml borosil beaker, 0.01 mol of chalcone, 0.01 mol of 2-amino thio phenol (1.27 ml) and pinch of zinc acetate dihydrate, as a catalyst was added. This reaction mixture was irradiated under microwave in solvent-free conditions. This is one pot synthetic step. All these reactions were carried out by microwave irradiation for 3 to 5 min at the power level 700 W and at the temperature 80 to 85°C which was recorded by the temperature probe of the microwave. These compounds were synthesized in solvent-free conditions to avoid unnecessary wastage of solvents. After completion of the reaction, cold water was added to the beaker and the crude product was stirred. The product was filtered, dried and recrystallized from ethanol. The yields and melting points of the compounds thus obtained were recorded. The data is presented in Table 1.

3a. 4-[2-(4-Nitrophenyl)-2, 3-dihydrobenzothiazepin-4-yl] phenol: Yellow solid; yield 75%, m.p. 130°C; IR (KBr, cm^{-1}) 3219,1632,608; ^{1}H NMR δ($CDCl_3$): 3.5 (C_3,dd,splits due to adjacent proton of benzothiazepine of C_2,J=13.59), 5.3(C_2,dd, methine proton, J=13.79), 7-8.1(m.,13H, Ph); Mass m/e359, 122(M-$C_{15}H_{11}SN$), 237(M-$C_6H_4NO_2$), 77(M-$C_{15}H_{10}SN_2O_2$), Anal. $C_{21}H_{16}N_2O_3S$ Cal (%): (C, 67.00; H, 4.28; N, 7.44; O, 12.75; S, 8.52) found (%): (C, 68.10; H, 3.94; N, 7.68; O, 12.75; S, 8.43).

3b. 4-(2-Phenyl-2, 3-dihydrobenzothiazepin-4-yl)-phenol: Brown solid, yield 82%, m.p. 80°C; IR(KBr, cm^{-1}) 3136,1712, 600; ^{1}H NMR δ($CDCl_3$): 3.2(dd , 2H at C_3, J=13.6) 5.3(dd, 1H at C_2 methine proton, J=13.27), 7-7.6(m,14H, phenyl); Mass m/e 314, 77(M-$C_{15}H_{11}SN$), 237(M-C_6H_5), Anal. $C_{21}H_{17}NOS$ cal (%): (C, 76.10; H, 5.17; N, 4.23; O, 4.83 S, 9.96) found (%): (C, 77.95; H, 5.44; N, 4.45; O, 4.90; S, 10.18).

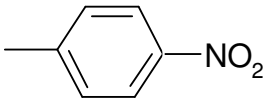
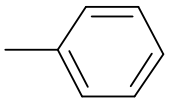
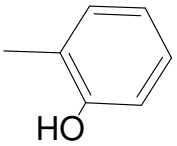
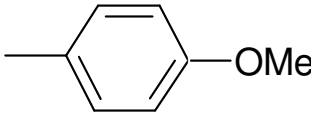
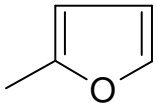
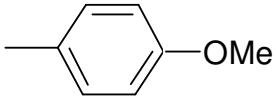
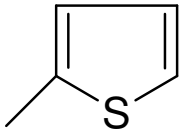
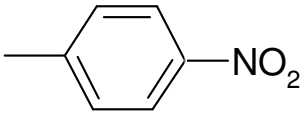
3c. 2-[4-(4-Hydroxyphenyl)-2, 3-dihydrobenzothiazepin-4-yl] phenol: Yellowish- green solid, yield 70%, m.p. 110°C; IR (KBr, cm^{-1}) 3326, 3124, 1622, 604 ; ^{1}HNMR δ($CDCl_3$): 3.7(dd, 2H, CH_2, J=13.8), 5.2(dd, methine proton at C_2, J=13.57), 6.9-7.6(m, 13H), 10.3(s, 1H, aromatic-OH); Mass m/e 328, 235(M-C_5H_5O), 76(M-$C_{15}H_8SNO$). Anal.$C_{21}H_{17}NO_2S$ cal (%): (C, 76.10; H, 5.17; N, 4.23; O, 4.83; S, 9.67) found (%): (C, 76.11; H, 5.18; N, 4.28; O, 4.87; S, 9.65).

3d. 4-[2-(4-Methoxyphenyl)-2, 3-dihydrobenzothiazepin-4-yl]phenol: Brown solid, yield 65%, m.p. 154°C; IR (KBr, cm^{-1}) 3143, 2900, 1678, 604; ^{1}H NMR δ($CDCl_3$): 3.73(s,3H,-OCH_3), 3.7(dd , 2H at C_3, J=13.69) 5.2 (C_2,dd,methine proton, J=13.9), 6.3(m,12H) ; Mass m/e 359, 122 (M-$C_{15}H_{11}SN$), 237(M-$C_6H_4NO_2$), 97 (M-$C_{15}H_{10}SN_2O_2$), 266(M-C_6H_5). Anal. $C_{22}H_{19}NOS$ cal (%): (C, 76.49; H, 5.54; N, 4.05; O, 4.63; S, 9.28 found (%): (C, 76.48; H, 5.55; N, 4.05; O, 4.65; S, 9.29).

3e. 2, 6-Dichloro-4-(2-(furan-2-yl)-2, 3-dihydrobenzothiazepin-4-yl) phenol: Yellow solid, yield 65%, m.p. 110°C ;IR (KBr, cm^{-1}) 3316, 3131 , 2900, 1612, 813, 608; ^{1}H NMR δ($CDCl_3$): 3.5(dd, Splits due to adjacent proton of benzothiazepine of C_2,J=13.69), 5.3(dd, methine proton, C_2 J=13), 6.4(m., 6H), Mass m/e 389, 67(M-$C_{15}H_{11}SNCl_2O$), 322(M-C_4H_3O), 162(M-$C_{13}H_9SNO$). Anal. $C_{19}H_{13}Cl_2NO_2S$ cal (%) (C, 58.47; H, 3.36; Cl, 18.17; N, 3.59; O, 8.20; S, 8.22) found (%): (C, 58.46; H, 3.35; Cl, 18.19; N, 3.59; O, 8.22; S, 8.23).

3f. 2, 6-Dichloro-4-(2-(4-methoxyphenyl)-2, 3-dihydrobenzothiazepin-4-yl) phenol: Brown solid, yield 74%, m.p. 75°C; IR (KBr, cm^{-1}) 3311, 3141, 1612, 810, 607; ^{1}H NMR δ($CDCl_3$): 3.7(s,3H,-OCH_3), 3.8(C3, dd, splits due to adjacent proton of benzothiazepine of C_2, J=14) 5.5(C_2, dd, methine proton, J=14.2), 6.5(m, 10H), 10.3(aromatic-OH); Mass m/e 429, 228(M-

Table 1. Observations for 1,5-benzothiazepines for microwave (MW) and conventional (Conv) method.

Code No.	R	R_1	R_2	Yield (%)		Time	
				MW	Conv.	MW (Min)	Conv. (hour)
3a	H	H		75	69	3.5	4
3b	H	H		82	70	3	4.5
3c	H	H		70	66	5.5	8
3d	H	H		65	57	5	6.5
3e	Cl	Cl		65	72	4	6
3f	Cl	Cl		74	68	3.5	4
3g	Cl	Cl		70	63	5	6.5
3h	Cl	Cl		75	70	4	5

$C_5H_9SNCl_2O$), 322(M-C_7H_7O), 162(M-$C_{16}H_{13}SNO$). Anal. $C_{22}H_{17}Cl_2NO_2S$ cal (%): (C, 61.40; H, 3.98; Cl, 16.48; N, 3.25; O, 7.44; S, 7.45) found (%): (C, 61.41; H, 3.95; Cl, 16.49; N, 3.27; O, 7.46; S, 7.48).

3g. 2, 6-Dichloro-4-(2-(thiophen-2-yl)-2,3-dihydrobenzothiazepin-4-yl) phenol: Brown solid, yield 70%, m. p. 160°C, IR(KBr, cm^{-1}) 3321(aromatic-OH), 3121(aromatic CH=CH str.),1612 (-C=N-str.), 802 (-C-Cl –str.), 604 (-C-S-str.); ^1H NMR δ($CDCl_3$): 3.5(dd , 2H atC_3, J=14), 5.5(dd, 1H at C_2, methine proton, J=14.5), 6.5(m. 6H,phenyl), 6.6(d,1H, =CH thiophene), 6.7(d,1H,=CH thiophene), 6.9(d,1H,=CH thiophene), 10.8(s,1H, Ph-OH). Mass m/e 403, 159(M-C_4H_3S+$C_6H_3OCl_2$), 242(M-$C_6H_3OCl_2$), 162(M-$C_{13}H_8S_2N$), 312(M-C_4H_3S), 293(C_6H_4SN) Anal. $C_{19}H_{13}Cl_2NOS_2$ cal (%): (C, 56.16; H, 3.22; Cl, 17.45; N, 3.45; O, 3.94; S, 15.78) found (%): (C, 56.17; H, 3.23; Cl, 17.47; N, 3.48; O, 3.96; S, 15.79).

3h. 2, 6-Dichloro-4-(2-(4-nitrophenyl)-2, 3-dihydrobenzothiazepin-4-yl) phenol: Brown solid, Yield 75%, m. p. 150°C; IR (KBr, cm^{-1}) 3331(aromatic-OH), 3012(aromatic-C=H str),1672 (-C=N –str.), 801 (-C-Cl-str),603 (-C-S-str.); ^1H NMR δ($CDCl_3$): 3.2(dd , 2H at C_3, J=13.56) 5.3(dd, 1H at C_2, methine proton, J=13.67), 7.34(s,2H,phenyl), 7.0-7.2(m.4H, phenyl), 7.3-8.1(m, 4H, phenyl), 10.0(aromatic-OH). Mass m/e 444, 122(M-$C_{15}H_9SNCl_2O$), 322, (M- $C_6H_4NO_2$), 162(M-$C_{15}H_{10}SN_2O_2$). Anal. $C_{21}H_{14}C_2N_2O_3S$ cal (%): (C, 56.64; H, 3.17; Cl, 15.92; N, 6.29; O, 10.78; S, 7.20) found (%): (C, 56.63; H, 3.15; Cl, 15.93; N, 6.25; O, 10.79; S, 7.21).

Table 2. Anticonvulsant activity of the synthesized compounds.

S/N	Groups	Various phases of convulsions (in Seconds) (Mean± S.E)	
		Flexion	Extensor
1	Control	4.224±0.2412	14.04±0.4343
2	Standard	1.926±0.3615**	0.00±0.0**
3	3a	4.126±0.4533	12.14±0.6666
4	3b	2.138±0.3509**	2.352±1.492**
5	3c	2.590±0.2895*	9.578±0.8534**
6	3d	2.140±0.4532**	3.540±1.526**
7	3e	2.682±0.5040*	10.28±0.3360*
8	3f	3.966±0.1894	10.86±0.4880
9	3g	3.706±0.2826	12.17±1.050
10	3h	3.470±0.4492	11.90±0.5543

Standard: Phenytoin, dose: 25 mg/kg b. w.

Table 3. CNS depressant activity of the synthesized compounds of synthesized compounds.

S/N	Group	Reading
1	Control	342.8±17.47
2	Standard	59.25±10.97**
3	3a	243.0±17.00**
4	3b	115.3±12.24 **
5	3c	306.0±7.561
6	3d	260.0±17.10**
7	3e	241.0±17.18**
8	3f	149.5±11.53**
9	3g	275.0±24.52*
10	3h	376.3±20.58

Standard drug: Diazepam, dose 25 mg/kg b. w.

RESULTS

All the synthesized compounds were obtained in better yield and in shorter span of time than the conventional methods. The structures of the newly synthesized compounds were confirmed by elemental analysis and IR, Mass and ^{1}H NMR spectral data. Spectral data are in accordance with assumed structures. The peculiar pattern of appearance of double doublets for methine proton at C_2 in the range δ 3.2 to 3.8 and methylene protons at C_3 in the range δ 5.2 to 5.5 confirms the formation of imino form of 1,5-benzothiazepine derivatives. The percent yield of the products obtained by conventional method are in the range of 57 to 72%, whereas the percent yield of the products obtained by microwave assisted synthesis are in the range of 65 to 82%. All the compounds were evaluated for their CNS activities and have shown moderate anticonvulsant and CNS depressant activity with lesser side effects.

DISCUSSION

For completion of reaction of final compounds by conventional method given by Hideg and Levai, requires 8 h of refluxing in solvent mixture methanol: acetic acid, where as microwave-assisted synthesis requires only 3 to 5 min irradiation in solvent-free conditions (Dandia et al., 2007); thus microwave method not only saves time but also avoids the use and wastage of solvents and gives better yield of the products, hence is economic. All the compounds were evaluated for their CNS activities that is, anticonvulsant and CNS depressant activity. The Maximal Electro-shock Induced Method investigated the anticonvulsant activities of synthesized compounds, and results from these tests are shown in Table 2. The data for CNS depressant activity, derived by sleep deprivation test, is presented in Table 3. All these compounds are having less potency than the standard drug but here we have tried to prove that 1, 5-benzothiazepine derivatives which are bioisosters of benzodiazepines can be used as anticonvulsant agents and CNS depressant agents and the potency of these molecules can be increased by appropriate substitution.

SAR

Generally, the anticonvulsant activity of organic compound may be increased after the introduction of halogen atom. Therefore, we selected 2, 6-dichlorophenol as starting material to obtain 2, 6-dichloroacetophenone so there must be two chloro substituents in the 1,5-benzothiazepine derivatives. Electron- donor derivatives were also prepared, such as 3d and 3f, containing p-methoxy and p-hydroxy group, respectively and have shown better anticonvulsant activity as compared to other derivatives. Compound 3b containing phenyl group and 3f containing para methoxy

phenyl group have shown better CNS depression as compared to other derivatives. The mechanism of action of these molecules may be the same as that for benzodiazepines; which act on allosteric site of benzodiazepine which facilitates the GABA mediated Cl^- channel opening.

Conclusion

The present study reports the green synthesis of 2, 4-substituted–2, 3-dihydro-1, 5- benzothiazepine derivatives as bioisosteric analogues of benzodiazepines and their evaluation as anticonvulsant agents by the maximal electroshock method and also evaluated as CNS depressant agents by sleep deprivation method.

Four of the synthesized compounds 3h, 3h, 3h and 3h have shown moderate anticonvulsant activity and compounds 3c, 3d, 3e, 3f and 3h have exhibited moderate CNS depressant activity. All the synthesized compounds were evaluated for the toxicity study and are within the toxicity limit. These compounds may serve as lead compound for the search of more powerful selective anticonvulsant and CNS depressant agents.

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