SYNTHESIS OF NOVEL 1, 5-BENZOTHIAZEPINES AS CNS AGENTS

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One pot neat, solvent free green protocol of 1, 5-benzothiazepines is reported here. 1, 3-substituted-prop-2-en-1-one **2a** were synthesized by microwave-assisted Claisen-Schmidt condensation of acetylated α-naphthol with aldehydes in presence of alkali and ethanol.

Synthesis of 2, 3-dihydro-2-substituted-4- (naphthalen-2'-ol)-yl-1, 5-benzothiazepines **3a** was carried out by cyclo condensation of 1, 3-substituted- prop-2-en-1-one **2a** with 2-aminothiophenol in presence of ecofriendly catalyst zinc acetate in the solvent free condition under microwave irradiation. The structures of newly synthesized compounds were confirmed by spectral evidence and the compounds were evaluated for their anticonvulsant and CNS depressant activity. The compounds have shown excellent results.

KEYWORDS: 1,5 benzothiazepines, Green synthesis, CNS activity.

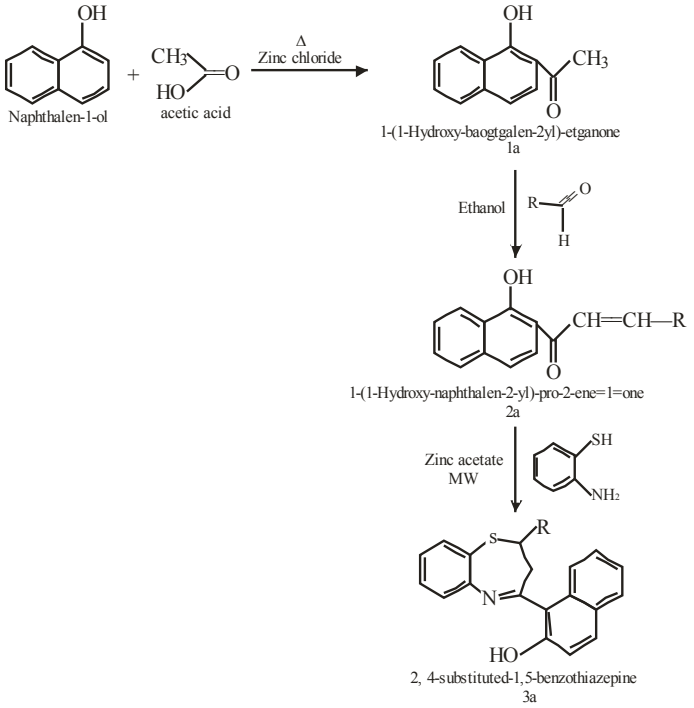
INTRODUCTION

Heterocyclic compounds containing nitrogen and sulphur such as benzodiazepines and benzothiazepines have received considerable attention in recent years. Benzothiazepines have been claimed of various therapeutic activities, but the investigation of their chemistry commenced rather slowly. It is only recently that attention is being directed to the synthetic methods, chemical and biological properties. Benzothiazepines posses wide variety of activities like anticonvulsant [1] CNS depressant [2, 3, 4], Ca^{++} channel blockers [4], anticancer [5], anti fungal [6], anti-HIV [7] and antimicrobial [8] etc. However there are less reports on the CNS action specially anticonvulsant and CNS depressant. 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 the design of novel pharmacological tools as well as new therapeutic agents with optimal pharmacological profile and improved pharmacokinetic properties[9]. Benzothiazepines are bioisosters of benzodiazepines and contain one sulphur in place of nitrogen, thereby enhancing penetration in CNS. Therefore, it was thought worthwhile to synthesize 2, 3-dihydro-2aryl/heteryl substituted-4-(naphthalen-2'-ol)-yl-1, 5-benzothiazepines by using green methodology (Scheme-1) and to screen the synthesized compounds for anticonvulsant and CNS depressant activity. The Green chemistry tools used in the present investigation are neat, solvent-free, microwave-assisted synthesis and use of ecofriendly catalyst. The structures

of all newly synthesized compounds were established by IR, $_1$HNMR, Mass spectral data and elemental analysis. The Characterization data of compounds 3a (1-6) is given in Table 1. These compounds were evaluated for anticonvulsant and CNS depressant activity.

EXPERIMENTAL

The reactions were carried out in synthetic microwave oven CATA R. The melting points of the compounds were determined in open capillary tubes and are uncorrected. The purity of compounds was checked by TLC. IR spectra were recorded by JASCO FTIR (PS-4000, using KBr powder technique. $_1$HNMR spectra were recorded using $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ ppm) on Brucker advance II 400 NMR spectrophotometer. Mass spectra of some of the compounds were scanned on TOF MS + 484.



Scheme-1

Step 1: Acetylation of α-naphthol [10]-1a

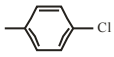
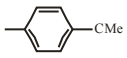
In 80 ml hot glacial acetic acid, 50 gm zinc chloride was added and the reaction mixture was refluxed till it dissolved. Then 30 gm of α-naphthol was added to the reaction mixture and was refluxed for 8hrs. The reaction mixture was cooled and poured in acidulated water. The crude product 1a obtained was filtered, washed with water and recrystallize from ethanol. Yield 98%, m. p. 80°.

IR (cm^{-1}), 3251(aromatic-OH), 3207(-C-H-aromatic –C-H-str.), 1720(-C=O). PMR (δ ppm) 2.55(s, 1H, CH_3), 5.0 (s, 1H, aromatic - OH), 7.39-8.24 (m, 6H, aromatic protons of naphthalene ring); m/e 191,(M-CH_3)179,(M-C_2H_3O)158,(M-$C_2H_4O_2$)132.

Step 2: Synthesis of1, 3-substituted- prop-2-en-1-one-2a Microwave assisted synthesis of prop-2-en-1-one[11]

These compounds can be synthesized by microwave irradiation in solid phase. In this method, acetylated α-naphthol (0.01 mol), aromatic aldehyde (0.011mol) was taken in 5ml of ethanol and poured in 100ml Erlenmeyer borosil flask. To this reaction mixture, (4ml) basic alumina was added. The reaction mixture was thoroughly mixed and irradiated inside a microwave for 2-3 min. at medium level 600 W. After completion of reaction, mixture was cooled and product was extracted with ethan 1.

Table 1: Characterization data of 2, 3-dihydro-2-substituted-4- (naphthalen-2'-ol)-yl -1,5-benzothiazepines 3a (1-6)

Code No. R	Mol. Formula	Mol. Wt.	Yield (%)		Time		M.P	R_f val.
			MW	Conv.	Mw (min)	Conv. (hrs)		
1. 	$C_{25}H_{19}OSN$	381.50	72	65	2.5	5	75	0.76
2 	$C_{25}H_{19}O_2SN$	397.50	88	80	1	2	72	0.81
3. 	$C_{25}H_{18}OClSN$	415.95	78	67	1.5	5.5	80	0.9
4. 	$C_{26}H_{21}O_2SN$	411.53	61	59	1	2.5	99	0.9
5. 	$C_{23}H_{17}NO_2S$	371.46	70	67	2	3	60	0.9
6. 	$C_{23}H_{17}NOS_2$	387.53	60	58	3	4	90	0.8

Conventional Method

In 30 ml ethanol and 15ml KOH (40%), 0.01 mol of acetylated α-naphthol and 0.011mol of various aldehydes were added in separate flasks. Then reaction mixture was kept aside for 24 hrs. On next day crushed ice was added to the reaction mixture and acidified by dil. HCl. The crude product **2a** obtained was filtered and recrystallized by ethanol.

Yield and m. p. of 2a (1-6) is given as: R = Phenyl-yield 75%. m. p. 85_0; R = 2-Hydroxy phenyl- yield 68%, m. p. 80_0 ; R=4-Chlorophenyl-yield 605, m. p. 90_0; R= 4-Methoxyphenyl yield 62%, m. p. 109_0 ; R=Furyl- yield 52% , m. p.50_0 ;R= Thiphenyl-yield65%, m. p. 70_0. IR (cm^{-1}),

3321(aromatic-OH), 3300(aromatic–C-H-str.), 2867(aliphatic-C-H str) 1740(-C=O). PMR (δ ppm): 7.0(d,1H,H_A proton),7.3 (m,10H,aromatic proton),8.2(d,1H,H_B proton); m/e 275,(M-C_7H_6)185,(M-OH) 262,(M-C_9H_7O)144

Step 3: Synthesis of 2, 3-Dihydro-2-substituted-4-(naphthalen-2-ol)-yl-1, 5-benzo-thiazepine-3a

Microwave method

A mixture of 2a (0.01 mol) 1, 3-substituted- prop-2-en-1-one and (0.01 mol, 1.25ml) 2-aminothiophenol and pinch of zinc acetate as catalyst was thoroughly mixed and taken in a clean borosil beaker. The solvent- free reaction mixture was then subjected to microwave irradiation for 2-3 minutes at 80-85$_o$C. The reaction mixture was then allowed to cool to room temperature and then poured cold water in the mixture and stirred vigorously. Product **3a** was washed with water to remove the catalyst filtered, dried and recrystallized by ethanol. Yield

and melting point of synthesized compounds were recorded. (Table1). Conventional synthesis of 2,3-dihydro-2- substituted-4(naphthalen-2-ol)-yl -1,5-benzothiazepine 3a was carried out by following Levai-Hideg method[12,13].

Compound 1 : 2, 3-Dihydro-2-(Phenyl)-4-(naphthalen-2-ol)-yl-1, 5-been zothiazepine

IR (cm^{-1}); 3570(aromatic-OH str.),3510(aromatic -C-H-str),1536(– C=N str), 625(-C-S str) PMR (δ ppm), 3(m,2H, H_A and H_B splits due to adjusant methine proton H_X of C_2), 5.3 (dd,1H, H_X methine proton splits due to adjusant methylene proton H_A of C_3), 6.5(dd,1H, H_X methine proton splits due to adjusant proton H_B of C_3), 6.8 (m,15H,aromatic proton), 8.2(s,1H,aromatic-OH); m/e365,(M- C_6H_5) 288,(M-$_{10}H_7O$)220.

Compound 5: 2,3-Dihydro-2-(Furyl)-4-(naphthalen-2'-ol)- yl -1,5- benzothiazepine

IR (cm^{-1}), 3620(aromatic-OH str.), 3420(aromatic-C-H-str), 1567(- C=N str), 687(-C-S str). PMR(δ ppm), 3.4 (m, 2H, H_A and H_B splits due to adjusant methine proton H_X of C_2),5.6(dd,1H, H_X methine proton splits due to adjusant proton H_A ofC_3), 5.88 (d,1H, =CH-furyl ring), 6.18 (d, 1H, =CH-furyl ring), 7.0(d, 1H, =CH-furyl ring), 7.2-7.8 (m, 10H,aromatic proton), 8.2 (s, 1H,aromatic-OH); m/e 306, (M-C_4H_4O) 238, (M-$C_{10}H_7O$)163.

Pharmacological Screening

All the newly synthesized compounds were evaluated for their anti convulsant and antidepressant activity.

Anticonvulsant activity

Male wistar rats weighing in the range of 20-25gm. were selected for the activity. All newly synthesized compounds were tested for anticonvulsant activity by maximal electro shock method using phenytoin as standard drug at 25mg/kg.

The severity of convulsions was assessed by the duration of tonic flexion, tonic extensor, clonus, stupor and recovery phase for each animal. All the compounds have shown promising anticonvulsant activity. (Table-2)

Table 2. Anticonvulsant activity of 1, 5-benzothiazepine

Comp. No	Time in (seconds) in various Phases of convulsions (Mean±SEM)				
	Flexion	**Extensior**	**Clonus**	**Stupor**	**Recovery**
Control	8.000 ± 0.1511	11.33 ± 0.3331**	3.8833±0.3015 ***	21.57±0.4757**	281±1.847**
Standard	6.300 ± 0.3315	6.345±0.4019**	3.833±0.2029 ***	4.167±0.4777**	99.67±1.574**
1	3.176±0.4832**	8.854± 0.4789**	3.683±0.6581***	3.216±0.4507**	83.27±2.283**
2	3.490±0.4387**	8.453±0.4876**	3.845±0.6128***	3.792±0.5014**	83.67±3.012**
3	3.176±0.4653**	8.798±0.6151**	3.763±0.4125***	3.737±0.4873**	81.59±2.985**
4	3.102±0.2542**	8.997±0.5842**	3.494±0.4297***	2.853±0.4150**	124.5±1.543**
5	3.302±0.2762**	8.897±0.5912**	3.694±0.4197***	2.953±0.4950**	117.5±1.553**
6	3.103±0.2692**	8.907±0.4988**	3.894±0.4797***	2.653±0.4250**	164.5±1.533**

Std drug : Phenytoin (25mg/kg b.w), Dose of compound: 50-100mg/kg

CNS depressant activity

Male Wistar rats weighing in the range of 20-25gm 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. Thiopental sodium (Thiosol ®) 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 compounds have shown excellent CNS depressant activity[9] (Table-3).

Table 3: CNS depressant activity of 2, 3-dihydr o-2-substituted-4(naphthalen-2-ol)-yl -1, 5-benzothiazepine

Compound No.	Reading
Control	342.8±17.47
Standard	59.25±10.97
1	241.0±17.18**
2	149.5±11.53**
3	275.0±24.52*
4	376.3±20.58
5	363.3±19.47
6	276.0±20.32*

Std. drug: Thiosol (25mg/kg b.w), Dose of drug :150-200mg/kg

Conclusion

We have successfully synthesized 2-aryl/heteryl substituted, 4-(naphthalene-2'-ol) -yl-2, 3-dihydro-1, 5-benzothiazepines by using green chemistry techniques. The structures of the synthesized compounds were confirmed by spectral analysis and have shown excellent results as anticonvulsant and CNS depressant agents. Present study revealed that the 1,5-benzothiazepine derivatives possessed a broad spectrum of anticonvulsant activity. All the synthesized compounds were evaluated for the toxicity study and are within the toxicity limit. These compounds may serve as lead compounds for the search of more potent selective anticonvulsant and CNS depressant agents.

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