Research Article

GREEN SYNTHESIS AND PHARMACOLOGICAL SCREENING OF NOVEL 1,5-BENZOTHIAZEPINES AS CNS AGENTS

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ABSTRACT

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.

Key words: 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 possess wide variety of activities like anticonvulsant1, CNS depressant2,3,4, Ca++ channel blockers5, anticancer6, anti fungal7, anti-HIV7 and antimicrobial8 etc. However there are less reports on 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 properties9. 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, 1HNMR, Mass spectral data and elemental analysis. The Characterization data of compounds 3a (1-6) is given in Table1. 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). 1HNMR spectra were recorded using CDCl3 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](image-url)
Step 1: Acetylation of α-naphthol 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 8 hrs. The reaction mixture was cooled and poured in acetaldehyde water. The crude product 1a obtained was filtered, washed with water and recrystallized from ethanol. Yield 98%, m. p. 80°C.

IR (cm⁻¹), 3251 (aromatic- OH), 3207 (–C-H– aromatic –C-H– str.), 1536 (–C=O), 1567 (–C=N str.), 625 (–C–S str.)
PMR (δ ppm), 1H (CH₃ aromatic proton), 1.9 (CH₃ methylene proton splits due to adjacent proton Hα of C₂), 5.5 (dd, 1H, HX methine proton splits due to adjacent proton HB of C₃), 6.6 (d, 1H, α– naphthol aromatic proton), 7.8 (m, 10H, aromatic proton), 8.2 (s, 1H, aromatic–OH); m/e 191, (M+H+) 179, (M+C₄H₄O) 158, (M+C₄H₄O)+ 132.

Step 2: Synthesis of 3-substituted-prop-2-en-1-one 2a
Microwave assisted synthesis of prop-2-en-1-one
These compounds can be synthesized by microwave irradiation in solid phase. In this method, acetylated α-naphthol (0.01 mol), aromatic aldehyde (0.01 mol) was taken in 5 ml of ethanol and poured in 100 ml Erlenmeyer borosil flask. To this reaction mixture, (4 ml) 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 ethanol.

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

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Table 2: Comparison of the activity of test compounds and standard drug in CNS depression test

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Conventional Method
In 30 ml ethanol and 15 ml KOH (40%), 0.01 mol of acetylated α-naphthol and 0.01 mol 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 yields 75%, m. p. 85°C; R= 2-Hydroxy phenyl yields 68%, m. p. 80°C; R= 4-Chlorophenyl yields 62%, m. p. 100°C; R= Furyl yields 52%, m. p. 50°C; R= Thiophenyl yields 65%, m. p. 70°C (cm⁻¹), 3321 (aromatic-OH), 3300 (aromatic-C-H str.), 2867 (aliphatic-C-H str.), 1742 (C=O), PMR (δ ppm): 7.0 (d, 1H, Hα proton), 7.7 (m, 10H, aromatic proton), 8.2 (d, 1H, Hα proton); m/e 275 (M-C₄H₄O) 259, (M-C₄H₄O)+ 244.

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

Step 3: Synthesis of 2,3-Dihydro-2-substituted-4-(naphthalen-2'-ol)-yl -1,5-benzothiazepine - 3a
Microwave method
A mixture of 2a (0.01 mol) 1,3-substituted-prop-2-en-1-one and (0.01 mol, 1.25 ml) 2-aminophenol 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 mins at 80-85°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. (Table 1). Conventional synthesis of 2,3-dihydro-2-substituted-4-(naphthalen-2'-ol)-yl -1,5-benzothiazepine 3a was carried out by following Leiva-Hidieg method 12,13.

Compound 1: 2,3-Dihydro-2-(Phenyl)-4-(naphthalen-2'-ol)-yl -1,5-benzothiazepine
IR (cm⁻¹): 3570 (aromatic-OH str.), 3550 (aromatic-C-H str.), 1536 (C=O str.), 1552 (C=S str.) PMR (δ ppm), 3 (m, 2H, Hα and Hβ, splits due to adjuvant methylene proton Hα of C₂), 5.3 (dd, 1H, Hα, methine proton splits due to adjacent methylene proton Hα of C₂), 6.5(dd,1H, Hα methine proton splits due to adjuvant proton Hα of C₂).

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.

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

CNS depressant activity
Male Wistar rats weighing in the range of 20-25gm were selected from an inbred 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 (Table 2).
REFERENCES

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