Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Antimicrobial Evaluation and Efficient Green Synthesis of 8-Substituted-2,5-dihydro-1,5-benzothiazepine Derivatives

Priyanka Sharma✉

Asian Journal of Organic & Medicinal Chemistry

Volume: 4 Year: 2019
Issue: 1 Month: January–March
pp: 32–35
DOI: https://doi.org/10.14233/ajomc.2019.AJOMC-P168

Received: 14 December 2018
Accepted: 5 March 2019
Published: 30 March 2019

ABSTRACT

8-Substituted-2,5-dihydro-1,5-benzothiazepine derivatives have been synthesized by the reaction of 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone with six 5-substiuted-2-aminobenzenethiols in dry ethanol saturated with dry HCl gas and also in the presence of aluminium nitrate as catalyst in dry ethanol. All the newly synthesized compounds were characterized by analytical and spectral data comprising IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass studies. All these compounds have also been evaluated for their antimicrobial assay against the Gram-positive bacteria, *Staphylococcus aureus* and the Gram-negative bacteria, *Pseudomonas aeruginosa* and the fungus, *Candida albicans*. The antifungal activity was found to be more significant than antibacterial activity.

KEYWORDS

1,5-Benzothiazepines, 2-Aminobenzenethiol, Aluminium nitrate, Antimicrobial activity.

INTRODUCTION

1,5-Benzothiazepine class of compounds are important cardiovascular drugs [1-4]. The first well established cardiovascular drug, diltiazem and its further version, clentiazem and siratiazem have methoxyphenyl group as a substituent in 1,5-benzothiazepine nucleus. Two methoxyl group are also present in the analogus benzopyranobenzodiazepine, 'zimet', known for its antineoplastic activity [5] against disease like tumor, leukemia, melanoma B16 and Lewis lung carcinoma. Some bicyclic and tetracyclic 1,5-benzothiazepine having methoxyl group in different proportions were synthesized and reported earlier [6-8]. It was observed that the compound which has maximum number of methoxyl group was found to show maximum antifungal activity. This observation presumed that methoxyl group is functioning as pharmacophore [8]. In literature, 1,5-benzothiazepine having different heterocyclic group are reported to possess analgesic, antihypertensive, vassodepressant, antiulcer and moderate to good antibacterial, antifungal and insecticidal activities [9-12].

The most common strategy for the construction of 1,5-benzothiazepine moiety involves the reaction of 5-substituted-2-aminobenzenethiol with chalcone under thermal conventional synthesis in strong acidic or basic condition [6-8,13,14]. But due to longer reaction time, excess solvent, expensive catalysts and lower reaction yield makes reaction hazardous. In literature,

Author affiliations:

Department of Basic & Applied Sciences, G.D. Goenka University, Gurgaon-122103, India

✉To whom correspondence to be addressed:

E-mail: sharmapriyanka.11@gmail.com

Available online at: http://ajomc.asianpubs.org

various methods [15-17] are reported for the synthesis of 1,5-benzothiazepine, in quest for getting better yield and environmental friendly reaction condition. It was, therefore, thought worthwhile to synthesize bicyclic 1,5-benzothiazepine having methoxyphenyl substitutent along with furyl group under mild condition and also under thermal conventional method to compare the effect on yield and reaction time. The antimicrobial assay was also carried out to find out the effect of methoxyphenyl group on the relative antibacterial and antifungal activity.

EXPERIMENTAL

TLC was used for checking homogeneity of the compounds on silica gel 'G' coated glass plates, using solvent system of benzene:ethanol:aq. ammonia (50 %) in the ratio 7:2:1. The IR spectra were taken in KBr pellets on Shimadzu 8201 PC spectrophotometer. NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) instrument using $CDCl_3$ as solvent and TMS as internal standard. The FAB mass spectra were recorded on JEOL-SX 102/DA-6000 Mass spectrometer/ Data system using Argon/Xenon (6kV, 10 mA) as the FAB gas at room temperature. The accelerating voltage was 10kV and *m*-nitrobenzyl alcohol (NBA) was used as the matrix. Elemental analysis were carried out in Elemental Analyzer, Carlo Erba 1108. The spectral analysis and elemental analysis were carried out at the Sophisticated Analytical Instrumentation Facility (SAIF), Central Drug Research Institute, Lucknow, India. Antimicrobial activity was carried out at Microbiology Department, S.M.S. Medical College, Jaipur, India.

Chalcone, 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone was synthesized and six 5-substituted-2-aminobenzenethiols, the substituents being fluoro, chloro, bromo, methyl, methoxyl and ethoxyl (**1a-f**) were prepared by literature reported methods [6-8,14,16].

1-(2-Furyl)-3-(3,4-dimethoxyphenyl)-2-propenone (3): 3,4-Dimethoxybenzaldehyde (0.01 mol) and 2-acetyl furan (0.01 mol), in equimolar quantities were taken in dry ethanol. Aqueous sodium hydroxide was added in dropwise manner with continuous stirring. The colour of the reaction mixture first turned yellow, finally converted into yellow coloured solid. The crude solid thus separated was recrystallized from dry ethanol to afford 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone, (3). m.p. 90 ºC; yield 86 %; R_f 0.76; ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 3H), 3.93 (s, 3H), 6.88-6.91 (d, 1H), 7.92-7.94 (d, 1H), 7.16-7.82 (Ar, 8H). ^{13}C NMR ($CDCl_3$): δ 56.15 (OCH_3), 110.21 (C6″), 111.35 (C3″), 112.45 (C3′), 119.2 (C2′), 120.78 (C2″), 127.82 (C1″), 129.05 (C2), 144.45 (C3), 147.17 (C4″), 149.17 (C4″), 149.48 (C5″), 153.10 (C1′), 177 (C1), Anal. analysis (%) Calcd. (found) for $C_{15}H_{14}O_3$ (m.w. 242): C, 74.38 (74.48); H, 5.78 (5.62).

8-Fluoro-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (5a): 2-Amino-5-fluorobenzenethiol (**4a**, 0.001 mol, 0.14 g) and 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone (**3**, 0.001 mol, 0.268 g) were taken in dry ethanol saturated with dry HCl gas. The reaction mixture was refluxed for 6 h when colour changed from pale yellow to deep red. The reaction mixture was cooled and solvent is removed by distillation under reduced pressure. The residue obtained after concentration was crystallized from benzene to give crystals of 8-fluoro-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (**5a**).

For mild condition synthesis [18], equimolar quantities of 2-amino-5-fluorobenzenethiol, 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone and aluminium nitrate were taken in dry ethanol. The reaction mixture was refluxed on hot-plate magnetic stirrer for about 2 h. After completion of reaction, the reaction mixture was poured on ice to obtain crude solid. Crude solid thus obtained was washed with excess of water and acetic acid and recrystallized from benzene to give crystals of 8-flouro-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (**5a**). m.p. 100-102 ºC; yield 68 % (conventional) and 75 % (mild condition); R_f 0.69; ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 4.10 (br, 1H), 5.84 (d, 1H, *J* = 7 Hz), 6.10 (d, 1H, *J* = 7 Hz), 6.82-7.76 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 49.32 (C2), 56.15 (OCH_3), 109.27 (C2″), 110.82 (C3″), 111.02 (C2′), 112.24 (C5′), 115.87 (C7), 117 (C3), 117.2 (C9), 117.29 (C6), 128.95 (C6′), 137.37 (C1′), 137.48 (C4), 143 (C4″), 145.35 (C1″), 148.31 (C3′), 149.17 (C4′), 159.77 (C8). ^{19}F NMR: δ-114. Analysis (%) Calcd. (found) for $C_{21}H_{19}NO_3SF$ (m.w. 384): C, 66.66 (65.71); H, 5.48 (4.89); N, 3.46 (3.72); S, 8.10 (8.24).

8-Chloro-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (5b): Following the similar procedures as for compound **5a**, 2-amino-5-chlorobenzenethiol and 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone reacted to give title compound. m.p. 109-100 ºC; yield 71 % (conventional) and 79 % (mild condition); R_f 0.72; ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 4.10 (br, 1H), 5.90 (d, 1H, *J* = 7 Hz), 6.14 (d, 1H, *J* = 7 Hz), 6.76-7.44 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 49.32 (C2), 56.15 (OCH_3), 109.27 (C2″), 110.82 (C3″), 111.02 (C2′), 112.24 (C5′), 117 (C3), 117.29 (C6), 127.84 (C9), 128.75 (C7), 128.95 (C9), 132.70 (C8), 137.37 (C1′), 137.48 (C4), 143 (C4″), 145.35 (C1″), 148.31 (C3′), 149.17 (C4′). Analysis (%) Calcd. (found) for $C_{21}H_{19}NO_3SCl$ (m.w. 400.5): C, 62.92 (63.01); H, 4.74 (4.81); N, 3.49 (3.51); S, 7.99 (8.10). *m/z*, $[M]^+$ and $[M+2]^+$ at 400 and 402.

8-Bromo-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (5c): By similar procedures as for compound **5a**, 2-amino-5-bromobenzenethiol and 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone reacted to give title compound. m.p. 105-07 ºC; yield 63 % (conventional) and 72 % (mild condition); R_f 0.71; ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H), 4.10 (br, 1H), 5.98 (d, 1H, *J* = 7 Hz), 6.12 (d, 1H, *J* = 7 Hz), 6.88-7.22 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 49.32 (C2), 56.15 (OCH_3), 109.27 (C2″), 110.82 (C3″), 111.02 (C2′), 112.24 (C5′), 114.97 (C8), 117 (C3), 117.29 (C6), 128.75 (C7), 128.95 (C6′), 130.33 (C9), 137.48 (C4), 137.37 (C1′), 143 (C4″), 145.35 (C1″), 148.31 (C3′), 149.17 (C4′). Analysis (%) Calcd. (found) for $C_{21}H_{19}NO_3SBr$ (m.w. 445): C, 56.62 (56.71); H, 4.26 (4.14); N, 3.14 (3.02); S, 7.19 (7.21). *m/z*, $[M]^+$ and $[M+2]^+$ at 444 and 446.

8-Methyl-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (5d): On similar lines as for compound **5a**, 2-amino-5-methylbenzenethiol and 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone reacted to give compound **5d**. m.p. 99-100 ºC; yield 60 % (conventional) and 78 % (mild condition); R_f 0.74; ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3H),

3.87 (s, 3H), 4.10 (br, 1H), 5.92 (d, 1H, *J* = 7 Hz), 6.12 (d, 1H, *J* = 7 Hz), 6.90-7.76 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 20.79 (CH_3), 49.32 (C2), 56.15 (OCH_3), 109.27 (C2″), 110.82 (C3″), 111.02 (C2′), 112.24 (C5′), 114.26 (C6), 117 (C3), 127.27 (C7), 128.26 (C9), 128.95 (C6′), 130.39 (C8), 137.37 (C1′), 137.48 (C4), 143 (C4″), 145.35 (C1″), 148.31 (C3′), 149.17 (C4′). Analysis (%) Calcd. (found) for $C_{22}H_{22}NO_3S$ (m.w. 380): C, 69.47 (69.38); H, 5.78 (5.83); N, 3.68 (3.52); S, 8.42 (8.39).

8-Methoxy-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (5e): Following same procedures as for compound **5a**, 2-amino-5-methoxybenzenethiol and 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone reacted to give compound **5e**. m.p. 106-08 ºC; yield 66 % (conventional) and 78 % (mild condition); R_f 0.73; ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H), 3.87 (s, 3H), 4.10 (br, 1H), 5.90 (d, 1H, *J* = 7 Hz), 6.10 (d, 1H, *J* = 7 Hz), 6.90-7.74 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 49.32 (C2), 55.46 (OCH_3), 56.15 (OCH_3), 109.27 (C2″), 110.82 (C3″), 110.85 (C6), 111.02 (C2′), 111.9 (C9), 112.24 (C5′), 113.8 (C7), 117 (C3), 128.95 (C6′), 137.37 (C1′), 137.48 (C4), 143 (C4″), 145.35 (C1″), 148.31 (C3′), 149.17 (C4′), 155.2 (C8). Analysis (%) Calcd. (found) for $C_{22}H_{22}NO_4S$ (m.w. 396): C, 66.66 (66.72); H, 5.55 (5.48); N, 3.53 (3.46); S, 8.08 (8.10).

8-Ethoxy-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(2-furyl)-1,5-benzothiazepine (5f): On the similar lines as for compound **5a**, 2-amino-5-ethoxybenzenethiol and 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone reacted to give compound **5f**. m.p. 102-03 ºC; yield 65 % (conventional) and 80 % (mild condition); R_f 0.75; ^{1}H NMR ($CDCl_3$): δ 1.24 (t, *J* = 7 Hz, 3H), 3.48 (q, *J* = 7 Hz, 2H), 3.87 (s, 3H), 4.10 (br, 1H), 5.90 (d, 1H, *J* = 7 Hz), 6.12 (d, 1H, *J* = 7 Hz), 6.84-7.76 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 14.73 (-CH_3), 49.32 (C2), 56.15 (-OCH_3), 63.69 (-OCH_2-)109.27 (C2″), 110.82 (C3″), 110.85 (C6), 111.02 (C2′), 111.9 (C9), 112.24 (C5′), 113.8 (C7), 117 (C3), 128.95 (C6′), 137.37 (C1′), 137.48 (C4), 143 (C4″), 145.35 (C1″), 148.31 (C3′), 149.17 (C4′), 156.66 (C8). Analysis (%) Calcd. (found) for $C_{23}H_{24}NO_4S$ (m.w. 410): C, 67.31 (67.14); H, 5.85 (5.71); N, 3.41 (3.46); S, 7.80 (7.82).

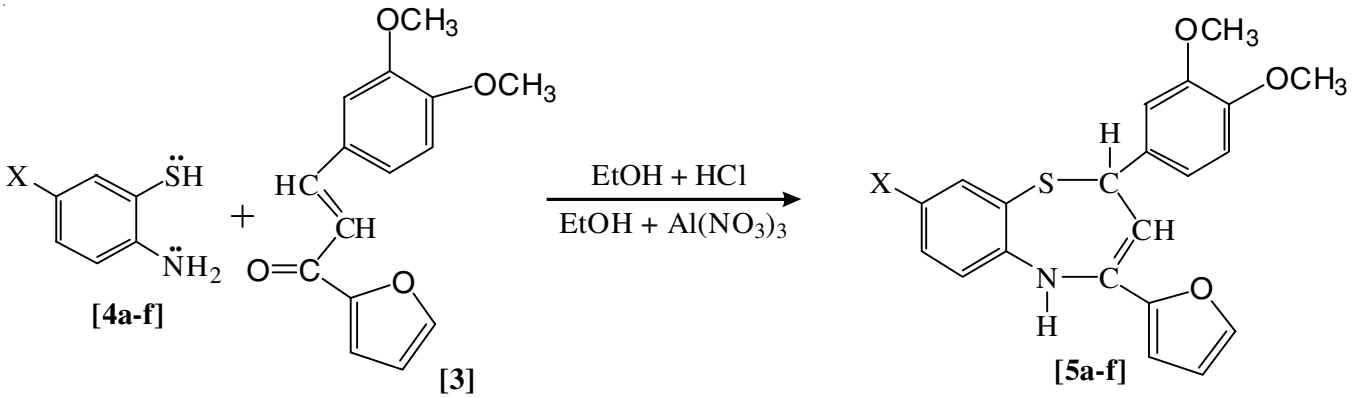
Antimicrobial activity: All the newly synthesized compounds were evaluated for their relative antimicrobial activity against the Gram-positive bacteria, *Staphylococcus aureus* and the Gram-negative bacteria, *Pseudomonas aeruginosa* and against the fungus, *Candida albicans* by using reference compounds gatifloxin, natilmicin and fluconazole, respectively. The paper disc method [18] was used at the concentration of 100 μg/disc. The zone of inhibitions for the test and reference compounds were measured in millimeters in 40 h incubation period and compared to get the results in the form of activity index.

$$\text{Activity index} = \frac{\text{Zone of inhibition exhibited by test compound}}{\text{Zone of inhibition exhibited by the reference compound}}$$

RESULTS AND DISCUSSION

α,β-Unsaturated carbonyl compound, 1-(2-furyl)-3-(3,4-dimethoxyphenyl)-2-propenone was synthesized by the reaction of 3,4-dimethoxyphenyl with 2-acetyl furan in the presence of dry ethanol and NaOH. To obtain a new series of 1,5-benzothiazepine, 8-substituted-2,5-dihydro-4-(2-furyl)-2-(3,4-dimethoxyphenyl)-1,5-benzothiazepines, in mild condition, equimolar quantities of 5-substituted-2-aminobenzenethiols and chalcone were taken in ethanol containing aluminium nitrate in catalytic amount and refluxed with continuous stirring on magnetic stirrer. Final products were obtained in 72-80 % yield. To compare the effect of reaction medium on the reaction, parallel reactions were also set for the same series using dry ethanol saturated with dry hydrogen chloride gas. The final products obtained in 60-71 % yield (**Scheme-I**). TLC was used to check purity of the final products. The results of elemental analysis were found to be satisfactory being within the permissible limit of error.

In the IR spectra of final products (**5a-f**), a broad absorption band was observed at around 3140-3135 cm^{-1} and medium intensity absorptions in the range, 1270-1260 cm^{-1} which may be assigned to secondary amino group ν(N-H) and aralkyl linkage vibrations ν(C-O-C) of methoxyl group. The ^{1}H NMR spectra of all the final products (**5a-f**) showed a doublet at δ 5.84-5.98 (d, 1H, *J* = 7 Hz) and doublet at δ 6.10-6.14 (d, 1H, *J* = 7 Hz) may be due to C-2-H and C-3-H. The downfield absorption of C-2 proton may be accounted due to deshielding zone of aryl ring and attachment of it with electronegative



Compd No.	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**
X	F	Cl	Br	CH_3	OCH_3	OC_2H_5
R	3,4-(OCH_3)$_2$	3,4-(OCH_3)$_2$	3,4-(OCH_3)$_2$	3,4-(OCH_3)$_2$	3,4-(OCH_3)$_2$	3,4-(OCH_3)$_2$

Scheme-I: Synthesis of 8-substituted-2,5-dihydro-1,5-benzothiazepine derivatives

sulphur atom whereas downfield absorption of C-3-H may be due to vinylic proton. Absorption at around δ 6.76-7.76 (m, 10H) as multiplet may be assigned to aromatic protons. Singlets at around δ 3.80-3.95 (s, 3H) in all the synthesized compounds may be assigned to methoxyl protons. A broad singlet at around δ 4.08-4.13 (b, 1H) may be due to secondary amino proton. A singlet at δ 1.88 (s, 3H), may be assigned to three methyl proton. Absorption signals as quartet at around δ 3.48 (q, 2H, J = 7 Hz) may be assigned due to two methylene protons and a triplet at around δ 1.24 (t, 3H, J = 7 Hz), which may be due to three methyl protons, confirmed the presence of ethoxyl group (CH_3-CH_2-O-) protons in the compounds **5f**.

In ^{19}F NMR spectra of compound **5a** absorption signals were found at δ -114.00 and -114.4 respectively, which confirmed the presence of fluorine in the molecules. In the mass spectra of compound **5b**, the presence of molecular ion peaks, *m/z*, $[M]^+$ and $[M+2]^+$ at 400 and 402 correspond to the molecular mass of the product. The intensity of $[M+2]^+$ peak was found nearly one third of the M^+ peak which ascertained the presence of chlorine atom in compound **5b**. The mass spectra of compound **5c** showed molecular ion peaks, *m/z*, $[M]^+$ and $[M+2]^+$ at 444 and 446. The intensity of $[M+2]^+$ peak was found to be nearly equal to the M^+ peak which confirmed the presence of bromine in compound **5c** .

Biological activity: All the synthesized compounds showed significant antifungal activity but did show modeate antibacterial activity against both bacteria. Compound **5e**, methoxyl derivative showed maximum activity against fungus *Candida albicans* and also showed better antibacterial activity than other compounds of the series. Although compound **5f** also showed good antifungal and moderate antibacterial activity. Compound **5c** did not show remarkable antibacterial activity but showed equal relative activity against fungus. Compound **5d**, methyl derivative did not show remarkable antibacterial and antifungal activity (Table-1).

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **5a-f**

Compd. No.	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Candida albicans*
5a	20 (0.90)	16 (0.67)	12 (0.85)
5b	16 (0.72)	18 (0.75)	14 (1.00)
5c	–	15 (0.62)	14 (1.00)
5d	10 (0.45)	–	12 (0.85)
5e	18 (0.81)	20 (0.83)	18 (1.28)
5f	15 (0.68)	18 (0.75)	16 (1.14)
Gatifloxin	22	–	–
Natilmicin	–	24	–
Fluconazole	–	–	14

Zone of inhibitions are given in mm.
Values in parentheses represent activity index.
Concentration of test and reference compounds were 100 µg/disc.

ACKNOWLEDGEMENTS

The author is grateful to Sophisticated Analytical Instrument Facility (SAIF), Central Drug Research Institute, Lucknow , India for providing the elemental analysis and spectral data and also to Dr. Ramesh Mishra, Department of Microbiology, S.M.S. Medical College, Jaipur, India for antimicrobial assay.

REFERENCES

1. F.L. Ansari, F. Iftikhar, Ihsan-ul-Haq, B. Mirza, M. Baseer and U. Rashid, Solid-Phase Synthesis and Biological Evaluation of a Parallel Library of 2,3-dihydro-1,5-benzothiazepines, *Bioorg. Med. Chem.*, **16**, 7691 (2008); https://doi.org/10.1016/j.bmc.2008.07.009.
2. G.R. Mhaske, S.S. Bajod, D.M. Ambhore and S.N. Shelke, Synthesis and Evaluation of Novel 1,5-Benzothiazepine Derivatives as Anti-Inflammatory Agents, *Int. J. Innov. Res. Sci. Eng. Technol.*, **3**, 13208 (2014).
3. K.L. Ameta, N.S. Rathore and B. Kumar, Synthesis and *in vitro* Anti-Breast Cancer Activity of Some Novel 1,5-Benzothiazepine Derivatives, *J. Serb. Chem. Soc.*, **77**, 725 (2012); https://doi.org/10.2298/JSC110715219A.
4. A.P. Nikalje and D. Vyawahare, Facile Green Synthesis of 2,4-Substituted-2,3-Dihydro-1,5-Benzothiazepine Derivatives as Novel Anticonvulsant and Central Nervous System (CNS) Depressant Agents, *African J. Pure Appl. Chem.*, **5**, 422 (2011).
5. W. Ben-Cherif, R. Gharbi, H. Sebai, D. Dridi, N.A. Boughattas and M. Ben-Attia, Neuropharmacological Screening of Two 1,5-Benzodiazepine Compounds in Mice, *C. R. Biol.*, **333**, 214 (2010); https://doi.org/10.1016/j.crvi.2009.09.015.
6. P. Sharma and S. Pant, Syntheses and Antimicrobial Evaluation of Bicyclic 8-Substituted-2,5-dihydro-2-(3,4-dimethoxyphenyl)-4-(4-methylphenyl)-1,5-benzothiazepines, *Int. J. Chem. Sci. Appl.*, **5**, 7 (2014).
7. S. Pant, P. Sharma, A. Sharma, R. Mishra and U.C. Pant, Syntheses of 1,5-Benzothiazepines: Part XXXIV-Syntheses and Antimicrobial Studies of 8-Substituted-2-(4-methoxyphenyl/3,4-dimethoxyphenyl)-2,5-dihydro-4-(2-thienyl)-1,5-benzothiazepines, *J. Indian Chem. Soc.*, **85**, 406 (2008).
8. S. Pant, P. Sharma, B.S. Sharma and U.C. Pant, Syntheses of 1,5-Benzothiazepines: Part XXXIII- Syntheses and Antimicrobial Studies of 10-Substituted-6-(4-methoxyphenyl)-6*H*-6a,7-dihydro-7-(4-methoxyphenyl/3,4-dimethoxyphenyl)[1]benzopyrano[3,4-*c*][1,5]-benzothiazepines, *Indian J. Chem.*, **46B**, 1537 (2007).
9. N. Bhasker, Y. Prashanthi and B V. Subba Reddy, Piperidine Mediated Synthesis of Hetero Chalcones and 8-Substituted-2, 5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1, 5-benzothiazepines as Antibacterial Agents, *Chem. Sci. Trans.*, **3**, 11 (2014); https://doi.org/10.7598/cst2014.549.
10. D.S. Ghotekar, R.S. Joshi, P.G. Mandhane, S.S. Bhagat and C.H. Gill, Synthesis of Some Biologically Important Fluorinated 3-Chlorochromones and 1,5-Benzothiazepines as Antimicrobial and Antifungal Agents, *Indian J. Chem.*, **49B**, 1267 (2010).
11. K.G. Desai and K.R. Desai, Microwave Enhanced Heterocyclization: A Convenient Procedure for Antimicrobial 1,5-Benzothiazepine Compounds, *Indian J. Chem.*, **46B**, 1179 (2007).
12. N. Garg, T. Chandra, Archana, A.B. Jain and A. Kumar, Synthesis and Evaluation of Some New Substituted Benzothiazepine and Benzoxazepine Derivatives as Anticonvulsant Agents, *Eur. J. Med. Chem.*, **45**, 1529 (2010); https://doi.org/10.1016/j.ejmech.2010.01.001.
13. S. Pant, H. Chandra, P. Sharma and U.C. Pant, Syntheses of 1,5-Benzothiazepines: Part XXXII-Syntheses of 8-Substituted-2,5-dihydro-2-(4-pyridyl)-4-(2-thienyl)-1,5-benzothiazepines, *Indian J. Chem.*, **45B**, 1325 (2006).
14. S. Pant, P. Sharma and U.C. Pant, Syntheses of 1,5-Benzothiazepines: Part XXXVI- Syntheses and Antimicrobial Studies of 8-substituted-2-(2-chlorophenyl)-2,5-dihydro-4-(4-chlorophenyl/2-thienyl)-1,5-benzothiazepines, *Phosphorus Sulfur Silicon Rel. Elem.*, **183**, 2974 (2008); https://doi.org/10.1080/10426500802048920.
15. P. Sharma. Biological Evaluation and Microwave Assisted Synthesis of 1,5-Benzothiazepine, *Int. J. Appl. Eng. Res.*, **10**, 27467 (2015).
16. A.V. Chate, R.S. Joshi, P.G. Mandhane and C.H. Gill, An Improved Procedure for the Synthesis of 1,5-Benzothiazepines using Ceric Ammonium Nitrate, *J. Korean Chem. Soc.*, **55**, 776 (2011); https://doi.org/10.5012/jkcs.2011.55.5.776.
17. A.J. Khan, M.Z. Ahmed and M.A. Basser, Aluminium Nitrate-Catalyzed Multi Component, One-Pot Synthesis of 1,5-Benzothiazepines under Mild Conditions, *Int. J. Chem. Stud.*, **1**, 153 (2013).
18. A. Bauer, W.M.M. Kirby, J. Sherris and M. Turck, Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am. J. Clin. Pathol.*, **45**, 493 (1966); https://doi.org/10.1093/ajcp/45.4_ts.493.