RJC

RASĀYAN *J. Chem.*
Vol. 16 | No. 4 |2072-2077| October - December | 2023
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESES AND ANTIMICROBIAL SCREENING OF 8-SUBSTITUTED-2,5-DIHYDRO-2-(2-NITROPHENYL/4-NITROPHENYL)-4-(2-CHLOROPHENYL)-1,5-BENZOTHIAZEPINES

Madhuri Kandalkar, Priyanka Sharma✉ and Sonika Sethi
Department of Chemistry, School of Engineering and Sciences, G D Goenka University, Gurugram, 122102, (Haryana) India
✉Corresponding Author: sharmapriyanka.11@gmail.com

ABSTRACT

1,5-Benzothiazepine, a novel heterocyclic moiety, is under research to assess its intriguing biological properties. Many versatile synthetic approaches allow the incorporation of structural variation within this scaffold. The target benzothiazepines,8-substituted-2,5-dihydro-2-(2-nitrophenyl/4-nitrophenyl)-4-(2-chlorophenyl)-1,5 benzothiazepines, was prepared by reacting, α,β-unsaturated heterocyclyl ketone, 3-(2-nitrophenyl/4-nitrophenyl)-1-(2-chlorophenyl)-2-propenone with 5-substituted-2-aminobenzenethiols, in different reaction conditions via Michael addition mechanism. The current research focuses on the comparative efficacy of synthetic techniques, spectral characteristics, and pharmacological profile of, 8-substituted-2,5-dihydro-2-(2-nitrophenyl/4-nitrophenyl)-4-(2-chlorophenyl)-1,5-benzothiazepines.

Keywords: 1,5-Benzothiazepine, α,β-Unsaturated Heterocyclyl Ketone, Michael Addition, 5-Substituted-2-Aminobenzenethiol, Antimicrobial Activity.

RASĀYAN *J. Chem.*, Vol. 16, No.4, 2023

INTRODUCTION

1,5-Benzothiazepines are significant moiety in pharmacological study because of the several bioactivities.[1-3] These derivatives are of special relevance for lead discovery since they are found active against a number of target families.[4] Diltiazem, clentiazem, and other 1,5-benzothiazepine molecules were the first to be employed in therapeutic settings for their impact on the cardiovascular system.[1-3] Clinically, 1,5-benzothiazepine compounds such as thiazesim, clothiapine, and quetiapine were used for CNS illnesses.[1-4] Considering the usefulness of 1,5-benzothiazepines in drug research, researchers promoted the development of a number of synthetic techniques for their production and chemical modifications. The numerous documented techniques involve inorganic solid supports like alumina, silica gel, clay, exposure to microwave radiation, acetic acid or trifluoroacetic acid, hydrochloric acid, piperidine, diethyl ether, etc.[3,5-10] In continuation of our previous studies, a few more novel 1,5-benzothiazepine moieties were synthesized by reacting one of the reactants, 5-substituted-2-aminobenzenethiols having methyl, chloro, fluoro, and bromo substituents, with second reactant α,β-unsaturated carbonyl system to synthesize 2,4,8-substituted-2,5-dihydro-1,5-benzothiazepines 5a–h in two different reaction conditions (i) dry methanol containing a catalytic quantity of trifluoroacetic acid under reflux for 5-8 hrs and (ii) diethyl ether at room temperature by swirling of 15-20 minutes.

EXPERIMENTAL

Reagents and Instruments

Melting points were determined on the NISCO melting point apparatus as well as in the silicon bath and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with Bruker Advance 400/AvIII HD-300(FT NMR) in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm). Mass spectra were recorded on the water alliance e2695/HPCL-TQD mass spectrometer. Elemental analyses (C, H, N) were measured with Euro Vector E 3000 Elemental Analyzer. Thin layer chromatography (TLC) was conducted on silica gel 'G' coated on aluminium sheet using eluents benzene: ethanol: aq. ammonia (7: 2: 1) for the first method and ethyl acetate: petroleum ether (20: 80) for the second method respectively and inspected in the U.V. cabinet.

Chemicals are research-grade and procured from SRL, CDH, Qualigen, and Spectrochem. The spectral studies and elemental analyses of were conducted at the SAIF, CDRI, Lucknow.

General Procedure

Synthetic Procedure for 3-(2-nitrophenyl)-1-(2-chlorophenyl)-2-propenone, 3a (Scheme-I):

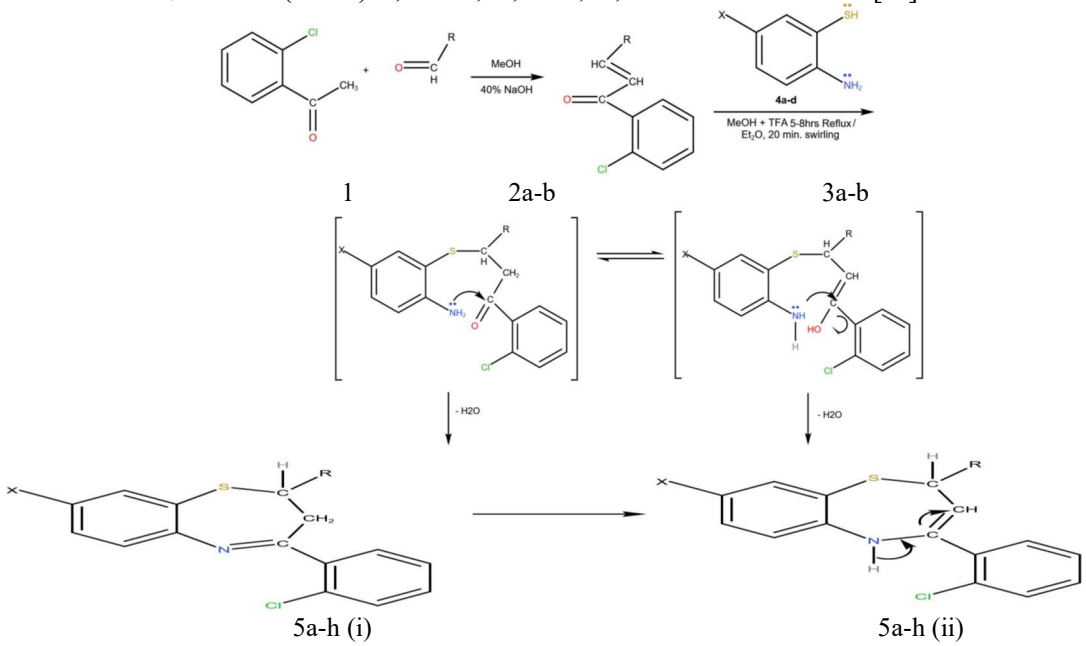
Equimolar amounts of 2-chloroacetophenone, 1, and 2-nitrobenzaldehyde, 2a, were dissolved in dry methanol. 40% NaOH was added in a dropwise manner with continuous agitation on a magnetic stirrer at room temperature, to form a yellow color precipitate of 3-(2-nitrophenyl)-1-(2-chlorophenyl)-2-propenone, 3a.[11,12] The crude product was crystallized from methanol to obtain pure crystals. TLC was used to determine the homogeneity of the compound. Yield 89%, m.pt. 156-158^{0}C.

Synthetic procedure for 3-(4-nitrophenyl)-1-(2-chlorophenyl)-2-propenone, 3b (Scheme-I):

At room temperature, 2-chloroacetophenone, 1, and 4-nitrobenzaldehyde, 2b, were dissolved in equimolar quantities in dry methanol and agitated on a magnetic stirrer. 40% NaOH was added slowly to form, 3-(4-nitrophenyl)-1-(2-chloroacetophenone)-2-propenone, 3b. An orange to red coloured crude product was precipitated out which was crystallized with methanol to get dark yellow crystals. TLC was used to verify the compound's homogeneity. m.pt. 161-163^{0}C, yield 86%. The 5-substituted-2-aminobenzenethiols were synthesized in accordance with literature-reported methods.[10,12]

Synthetic procedure for 8-methyl-2,5-dihydro-2-(2-nitrophenyl)-4-(2-chlorophenyl)-1,5-benzothiazepines, 5a (Scheme-I):

mol of freshly prepared 5-methyl-2-aminobenzenethiol, 4a was reacted with 0.001 mol of 3-(2-nitrophenyl)-1-(2-chlorophenyl)-2-propenone, 3a in dry methanol containing trifluoroacetic acid in catalytic quantity under reflux for 5-8 hrs as first reaction condition. The same reactants were also swirled for 15-20 minutes in diethyl ether at room temperature as a second reaction condition. A crude solid product was obtained in both cases which was crystallized with methanol to produce 8-methyl-2,5-dihydro-2-(2-nitrophenyl)-4-(2-chlorophenyl)-1,5-benzothiazepines, 5a. TLC was used for checking the homogeneity of the compounds, R_f 0.78, m.pt. 96-98^{0}C, Yield 85%. ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H), 3.59 (br, 1H), 7.73 (d, 1H, J=8Hz), 8.26 (d, 1H, J=8Hz), 7.24-7.76 (m, 10H). Anal. Found: C, 64.66; H, 4.20; N, 6.65. Calculated for $C_{22}H_{17}ClO_2SN_2$(408.7) C, 64.75; H, 4.15; N, 6.85% MS: m/z 408 $[M]^+$.



Comp	5a	5b	5c	5d	5e	5f	5g	5h
X	CH_3	Cl	F	Br	CH_3	Cl	F	Br

R	2-nitrophenyl	2-nitrophenyl	2-nitrophenyl	2-nitrophenyl	4-nitrophenyl	4-nitrophenyl	4-nitrophenyl	4-nitrophenyl

Scheme-I

RESULTS AND DISCUSSIONS

Condensation of equimolar quantities of 2-chloroacetophenone, 1 with 2/4-nitrobenzaldehyde, 2a-b was followed by reaction of the resulting α,β-unsaturated carbonyl system, 3-(2-nitrophenyl/4-nitrophenyl)-1-(2-chlorophenyl))-2-propenone, (3a-b) with 5-substituted-2-aminobenzenethiols, 4a-d in acidic and basic conditions (Scheme-I), to obtain 8-substituted-2,5-dihydro-2-(2-nitrophenyl/4-nitrophenyl)-4-(2-chlorophenyl)-1,5-benzothiazepines, 5a-h in 60% to 85% yield in first reaction medium and 60% to 90% yield in second reaction medium. In accordance with the body of known knowledge, the synthetic pathway takes place in two steps. The First step reaction occurs when electrons on a mercapto group of compounds 4a-d make a nucleophilic attack on an activated β-carbon atom of the α,β-unsaturated carbonyl compounds, 3a-b. As a result, an intermediate Michael adduct is produced. The Second step involves the dehydrative condensation between aromatic primary amine and the carbonyl group within the intermediate Michael adduct that leads to the formation of a seven-membered benzo condensed ring system, 5a–h with the elimination of water molecules. The structural determination of the final compounds was ascertained by the mass spectra, ^{1}H and ^{13}C NMR spectral techniques, and microestimation of C, H, and N. The predicted molecular masses for the molecular ion peaks $[M]^{+}$, $[M+2]^{+}$ of final compounds, 5b-h corresponds to the calculated molecular masses: 429, 431; 412, 414; 473, 475; 408, 410; 429, 431; 412, 414 and 473, 475 respectively (Table-I and II). The ^{1}H NMR and ^{13}C NMR spectra represented a broad peak in the region of δ 3.59-4.77 indicating absorption of one proton due to NH. In addition to this, the appearance of two doublets at δ 7.00-8.04 and δ 7.81-8.83 respectively represented the presence of a single proton each at C-2 and C-3 positions. This spectral data ascertained the synthesis of 2,5-dihydro tautomers over 2,3-dihydro derivatives.

Table-I: Physical Constants and Analytical Data of 5b-h

Comp	X	m.pt. (0C)	Rf	Yield (%)		Mol. Formula (Mol. Wt.)	Elemental analysis Found (Calculated.)(%)		
				MeOH+ TFA	Diethyl Ether		C	H	N
5b	Cl	89-91	0.85	84	82	$C_{21}H_{14}Cl_2O_2SN_2$ (429.1)	- (58.72)	- (3.26)	- (6.52)
5c	F	90-92	0.63	61	70	$C_{21}H_{14}ClFO_2SN_2$ (412.7)	61.1 (61.06)	3.51 (3.39)	6.69 (6.78)
5d	Br	108-110	0.81	60	66	$C_{21}H_{14}BrClO_2SN_2$ (473.6)	- (53.2)	- (2.95)	- (5.91)
5e	CH_3	115-117	0.69	82	85	$C_{22}H_{17}ClO_2SN_2$ (408.7)	64.8 (64.75)	4.14 (4.15)	6.88 (6.85)
5f	Cl	120-122	0.82	80	80	$C_{21}H_{14}Cl_2O_2SN_2$ (429.1)	- (58.72)	- (3.26)	- (6.52)
5g	F	112-114	0.71	69	71	$C_{21}H_{14}ClFO_2SN_2$ (412.7)	- (61.06)	- (3.39)	- (6.78)
5h	Br	117-119	0.90	66.00	75.00	$C_{21}H_{14}BrClO_2SN_2$ (473.6)	53.25 (53.2)	2.8 (2.95)	5.94 (5.91)

Table-II: Characteristic ^{1}H NMR ($CDCl_3$, δ Values in ppm, *J* in Hz) Signals of 5b-h

Comp	N-H	C-8-XH	C-3-H	C-2-H	Ar-H
5b	4.77 (br,1H)	-	8.19 (d, 1H, *J*=8)	7.64 (d, 1H, *J*=8)	6.93-8.22 (m, 10H)
5c	3.59 (br,1H)	-	8.22 (d, 1H, *J*=8)	7.56 (d, 1H, *J*=8)	6.72-8.21 (m, 10H)
5d	4.67 (br,1H)	-	7.81 (d, 1H, *J*=8)	7.00 (d, 1H, *J*=8)	6.84-8.86 (m, 10H)
5e	4.38 (br,1H)	2.30 (s, 3H)	8.82 (d, 1H, *J*=8)	7.92 (d, 1H, *J*=8)	7.25-8.85 (m, 10H)
5f	4.39 (br,1H)	-	8.83 (d, 1H, *J*=8)	7.94 (d, 1H, *J*=8)	7.28-7.95 (m, 10H)
5g	4.56 (br,1H)	-	8.80 (d, 1H, *J*=8)	8.04 (d, 1H, *J*=8)	6.93-8.83 (m, 10H)
5h	4.38 (br,1H)	-	8.82 (d, 1H, *J*=8)	7.92 (d, 1H, *J*=8)	7.24-8.85 (m, 10H)

Antimicrobial Screening

All the synthesized compounds, 5a-h were tested for relative bioactivity using the paper-disc method against the microbes including Gram-positive bacteria *Staphylococcus aureus*, the Gram-negative bacterium *Escherichia coli,* and fungus *Candida albicans* at a concentration of 100 µg/disc.[14] To evaluate the relative activity, reference drugs such as *Erythromycin, Amikacin,* and *Fluconazole* were used for Gram-positive bacteria, Gram-negative bacteria, and fungi respectively. The observed Zones of inhibition shown by the reference drugs and the test compounds on incubation of 24h, 48h, and 72h were evaluated (in mm) to calculate the individual Activity Index 5a–h (Table-III).

Activity Index = (Zone of inhibition measured for the test compound)/ (Zone of inhibition measured for reference compound)

Table-III: Antimicrobial Activity of 5a-h (Zone of inhibition in mm)

Compd	Bacteria						Fungi		
	Gram +ve *Staphylococcus aureus*			Gram-ve *Escherichia coli*			*Candida albicans*		
	24h	48h	72h	24h	48h	72h	24h	48h	72h
5a	13 (1.08)	13 (1.08)	12 (1.00)	12 (1.00)	11 (0.91)	11 (0.91)	16 (1.14)	17 (1.21)	16 (1.14)
5b	14 (1.16)	14 (1.16)	13 (1.08)	11 (0.91)	11 (0.91)	10 (0.83)	17 (1.21)	17 (1.21)	17 (1.21)
5c	12 (1.00)	12 (1.00)	11 (0.91)	10 (0.83)	10 (0.83)	9 (0.75)	14 (1.00)	14 (1.00)	13 (0.92)
5d	11 (0.91)	12 (1.00)	12 (1.00)	9 (0.75)	10 (0.83)	10 (0.83)	12 (0.85)	13 (0.92)	13 (0.92)
5e	11 (0.93)	12 (1.00)	10 (0.83)	11 (0.91)	11 (0.91)	12 (1.00)	16 (1.14)	16 (1.14)	15 (1.07)
5f	12 (1.00)	13 (1.08)	12 (1.00)	11 (0.91)	11 (0.91)	10 (0.83)	16 (1.14)	17 (1.21)	16 (1.21)
5g	12 (1.00)	12 (1.00)	11 (0.91)	10 (0.83)	10 (0.83)	9 (0.75)	11 (0.78)	10 (0.71)	10 (0.71)
5h	11 (0.91)	11 (0.91)	11 (0.91)	9 (0.75)	10 (0.83)	8 (0.66)	10 (0.71)	10 (0.71)	10 (0.71)

Activity Index is represented by values in parenthesis.
Erythromycin's zone of inhibition is 12 mm against *S. aureus*.
Amikacin's zone of inhibition is 12 mm against *E. coli*.
Fluconazole's zone of inhibition is 14 mm against *C. albicans*.

For all the newly synthesized compounds, 5a–h, moderate to good activity index was observed within the range of 0.83 to 1.16 against gram-positive bacteria, *S. aureus, and* 0.66 to 1.00 against gram-negative bacteria, *E. coli.* Compounds with chloro and methyl substituents were discovered to have a marginally higher efficacy against *S. aureus* and a marginally lower efficacy against *E. coli*. Most of the synthesized compounds demonstrated good efficiency against the fungus *C. albicans* after being incubated for 24 to 72 hours. With an activity index of 1.21, the chloro-substituted compound showed maximum antifungal activity. Antimicrobial activity at 24 and 48 hours of incubation was found comparable whereas activity index decreased at 72 hours.

CONCLUSION

1,5-Benzothiazepines have been reported to exhibit a wide range of bioactivities, and several publications of the last decade have described the synthesis of analogs of this scaffold. As per the results of our present research, it could be concluded that synthesis of 1,5-benzothiazepine derivatives in reaction condition diethyl ether is an improved approach over another method as the final reaction is completed in very little time. It was also found that methyl and chloro-substituted benzothiazepines are synthesized with higher yield compared to fluoro and bromo-substituted benzothiazepines. Chloro-substituted benzothiazepine derivatives exhibited a remarkably prominent bioactivity over other derivatives followed by methyl-substituted benzothiazepines.

ACKNOWLEDGEMENTS

We are grateful and appreciate the support of the Sophisticated Analytical Instrumental Facility, Central Drug Research Institute, Lucknow, Uttar Pradesh, India for the spectral and analytical examinations. We also appreciate the School of Engineering & Sciences, for providing the necessary facilities and encouragement.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

Madhuri Kandalkar https://orcid.org/0009-0007-6094-2648
Priyanka Sharma https://orcid.org/0000-0002-1685-8269
Sonika Sethi https://orcid.org/0000-0002-9188-7465

REFERENCES

1. V.M. Barot, M.R. Patel and H.B. Naik, *Asian Journal of Chemistry*, **13(1)**, 347(2001).
2. D.S. Ghotekar, R.S. Joshi, P.G. Mandhane, S.S. Bhagat, C.H. Gill, *Indian Journal of Chemistry*, **49B**, 1267(2010).
3. Ch. Prasad, DA. Vasudeva Rao and Mopidevi Venkateswara Rao, *Journal of Global Trends in Pharmaceutical Sciences*, **5(3),** 1769(2014).
4. J.B. Bariwal, K.D. Upadhyay, A.T. Manvar, J.C. Trivedi, J.S. Singh, K.S. Jain and A.K. Shah, *European Journal of Medicinal Chemistry,* **43**, 2279(2008), https://doi.org/10.1016/j.ejmech.2008.05.035
5. N. Bhasker, Y. Prashanthi and S.B.V. Reddy, *Chemical Science Transactions,* **3(1)**, 11(2014), https://doi.org/10.7598/cst2014.549
6. K. Arya and A. Dandia, *Bioorganic & Medicinal Chemistry Letters***, 18(1)**, 114(2008), https://doi.org/10.1016/j.bmcl.2007.11.002
7. M. Haroun, S.S. Chobe, R.R. Alavala, S.M. Mathure, R.N. Jamullamudi, C.K. Nerkar, V.K. Gugulothu, C. Tratrat, M.M. Islam, K.N. Venugopala, M. Habeebuddin, M. Telsang, N. Sreeharsha and M.K.Anwer, *Molecules,* **27(12)**, 3757(2022), https://doi.org/10.3390/molecules27123757

8. S. Pant, P. Sharma, A. Sharma, R. Mishra and U.C. Pant, *Journal of Indian Chemical Society*, **85**, 406(2008), http://doi.org/10.5281/zenodo.5814917
9. S. A. Pathare, E. H. Gade, D. A. Jadhav and M. B. Shinde, *International Journal of Advanced Research,* **4(5)**, 614(2016), http://dx.doi.org/10.21474/IJAR01/515
10. M. Kandalkar and P. Sharma, *Asian Journal of Chemistry*, **35(6)**, 1473(2023), https://doi.org/10.14233/ajchem.2023.27891
11. Khairy AM El-Bayouki, *Organic Chemistry International*, 2013, Article ID 210474, 71 pages. http://dx.doi.org/10.1155/2013/210474
12. A. Levai and J. Jeko, ARKIVOC, **17**, 234(2008).
13. De-Bao Yang, Fang-Ming Liu, Feng Xu, Chun Yang, Jia-Wei Ye, Song-Wei Shen, Ying-Lei Zhou and Wei Li, *Molecular Diversity*, **12(2)**, 103(2008), https://doi.org/10.1007/s11030-008-9082-z
14. A. Bauer, W.M. Kirby, J. Sherris and M. Turch, *American Journal of Clinical Pathology*, **45(4)**, 493(1996), https://doi.org/10.1093/ajcp/45.4_ts.493

[RJC-8498/2023]