ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Microwave-Assisted Synthesis and Biological Evaluation of 1, 5-Benzothiazepines as Potential Antihypertensive Agents

Rajini Kanth KN*[a], Rama Rao Nadendla[a], Venkata Rao Vutla[a], Elphine Prabahar A[a] Sathish Kumar M[b] and Valapa Anusha[a]

[a]Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh, India.
[b]Department of Pharmacology, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh, India.

ABSTRACT

A simple, rapid and highly efficient solvent-free synthesis of 2,3-Dihydro-1,5-benzothiazepines (BTZ 01-20) was carried out by the reaction of aryl chalcones with 2-aminothiophenol using silica gel as solid surface and zinc acetate as catalyst. The clean reaction conditions, shorter reaction time and high yields and purity of products are important advantages of this method. All the compounds were identified by melting point, TLC (R_f) and characterized by IR and 1^H-NMR spectral analysis. All the synthesized compounds were screened for antihypertensive activity. Hypertension was induced in male wistar albino rats by using fructose (66%), systolic and diastolic pressure (SBP, DBP) were measured on 16^{th} day of administration of standard and test drugs by noninvasive BP system for rodents. Some of the compounds were found to possess significant antihypertensive activity in rat model.

Keywords: Aryl chalcones, 2-aminothiophenol, Microwave irradiation, 1,5-benzothiazepine, anti-hypertensive activity.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

1,5-benzothiazepines are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds useful in drug research(01). 1,5-Benzothiazepines are one of the three possible benzo-condensed derivatives, viz. 1,4-, 4,1- and 1,5-benzothiazepines[02]. They are of particular interest for discovery of lead molecules because of their diverse biological activities on several targets [03]. The 1,5-benzothiazepine scaffold has been used as cardiovascular modulator [04] such as vasodilator [05], antiarrythmic [06], ACE inhibitors [07] and angiotensin II receptor inhibitors [08]. They also possess anticonvulsant [09,10], anticancer [11], anti-HIV [12], antimicrobial [13], antimalarial [14], antitubercular [15], antiinflammatory [16], antioxidant [17], antiulcer [18] and spasmolytic activities [19]. First molecule used clinically was diltiazem, followed by clentiazem for their cardiovascular action [20,21]. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim and quetiapine fumarate [22,23]. In the present work attempt has been made to develop an environmentally benign synthesis of some newer 1,5-benzothiazepine derivatives using microwave irradiation in the presence of silica gel as solid surface and zinc acetate as catalyst under solvent-free conditions and evaluate them for antihypertensive activity in rat models[24].

MATERIALS AND METHODS

Commercial reagents were used as received without additional purification. Reactants and reagents were procured from reputed companies like Merck, Sigma-Aldrich and Qualigens. Microwave assisted reactions were performed in Raga's Scientific Microwave Synthesizer at power level of 240W. The minimal reaction times were determined by performing sequential series of identical reactions at constant temperature and with continuous heating, but with different irradiation times. Completion of the reaction was observed by TLC after each individual heating period. Thin layer chromatography (TLC) was performed on Merck TLC Silica gel 60 F_{254} aluminium sheets. Melting points were determined using digital melting point apparatus and are uncorrected. The IR spectra were recorded on Bruker Alpha FTIR instrument using KBr pellet method in range of 4000–400 cm^{-1}. The 1^H-NMR spectra were recorded on Varian 300 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as the solvent. In the NMR spectrometry, the abbreviations used for signal coupling are 's' for singlet; 'd' for doublet, 't' for triplet and 'm' for multiplet. The chemical shift values in 1^H-NMR spectra are reported as δ ppm.

General procedure for synthesis of 2,4-Disubstituted-1, 5- benzothiazepines:

Aryl chalcone (0.010 mol) was dissolved in small volume of ethanol in a 50 mL borosil beaker. To this solubilised mass, 2-aminothiophenol (0.015 mol), silica gel (3.0 g) and zinc acetate (2.0g) were added. The resulting mixture was uniformly mixed and air dried to remove the solvent. The absorbed material was irradiated in the microwave synthesizer for 5-6 minutes at 240W power level. The progress of the reaction was monitored with TLC using hexane:ethylacetate (1:4) mobile phase over silica gel 60 F_{254} precoated plates. After completion of the reaction and cooling the mixture to room temperature, it was extracted with ethyl acetate (2x 25mL) and solid compound obtained by evaporation was recrystallized with benzene-ethyl acetate mixture in order to get the product [Figure No.1,2]. Physical characterization data and analytical data of 2,4-Disubstituted-1,5-benzothiazepines were represented in Table No.1-5.

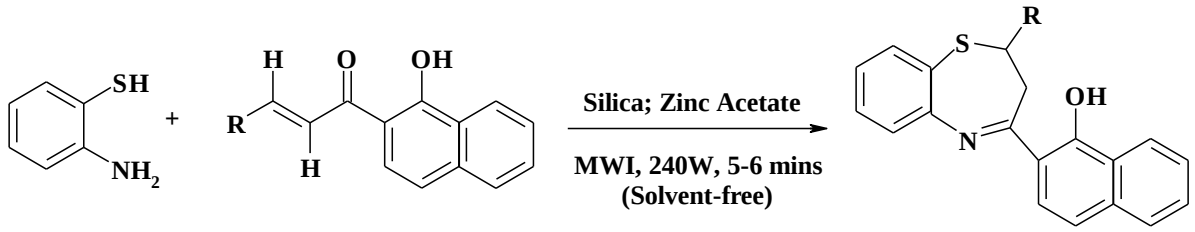


Figure 1: Synthetic route for 1,5-Benzothiazepines

ISSN: 0975-8585

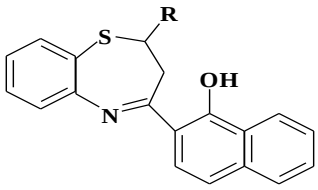
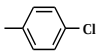
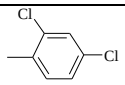
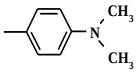
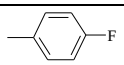
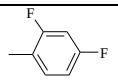
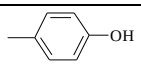
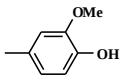
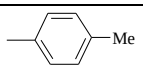
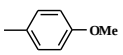
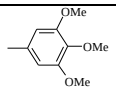
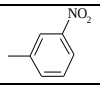
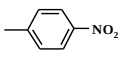


Figure 2: Basic structure of the 1,5-Benzothiazepine derivatives

Table 1: Physical characterization and TLC studies

Compound	R-Group	Mol. Formula	Mol. wt	Yield (%)	M.pt (^{0}C)	R_f
BTZ-01		$C_{25}H_{19}NOS$	381	68	196^{O}C	0.78
BTZ-02		$C_{25}H_{18}NOSCl$	415	75	152^{O}C	0.42
BTZ-03		$C_{25}H_{18}NOSCl$	415	72	214^{O}C	0.71
BTZ-04		$C_{25}H_{17}Cl_2NOS$	450	71	261^{O}C	0.55
BTZ-05		$C_{27}H_{24}N_2OS$	424	76	184^{O}C	0.82
BTZ-06		$C_{25}H_{18}FNOS$	399	75	112^{O}C	0.61
BTZ-07		$C_{25}H_{18}FNOS$	399	66	124^{O}C	0.52
BTZ-08		$C_{25}H_{17}F_2NOS$	417	79	142^{O}C	0.36
BTZ-09		$C_{25}H_{19}NO_2S$	397	56	124 ^{O}C	0.44
BTZ-10		$C_{25}H_{19}NO_2S$	397	75	172^{O}C	0.62

Compound	R-Group	Mol. Formula	Mol. wt	Yield (%)	M.pt (^{0}C)	R_f
BTZ-11		$C_{26}H_{21}NO_3S$	427	72	220 ^{O}C	0.74
BTZ-12		$C_{26}H_{21}NOS$	395	77	210^{O}C	0.32
BTZ-13		$C_{26}H_{21}NO_2S$	411	68	208 ^{O}C	0.70
BTZ-14		$C_{28}H_{25}NO_4S$	471	70	214^{O}C	0.44
BTZ-15		$C_{25}H_{18}N_2O_3S$	426	65	266 ^{O}C	0.60
BTZ-16		$C_{25}H_{18}N_2O_3S$	426	70	224^{O}C	0.52
BTZ-17		$C_{25}H_{18}N_2O_3S$	426	62	280^{O}C	0.63

ISSN: 0975-8585

BTZ-18		$C_{24}H_{18}N_2OS$	382	65	161 ^{O}C	0.71
BTZ-19		$C_{24}H_{18}N_2OS$	382	77	142 ^{O}C	0.72
BTZ-20		$C_{23}H_{17}NO_2S$	371	78	124 ^{O}C	0.44

Table 2: Common IR spectral data of 1,5-Benzothiazepines

Common spectral characteristics of 2,4-Disubstituted-1,5-dihydro benzothiazepine derivatives	1686(C=N), 1625(C=C), 1291(C-N), 1152(C-O), 3342(O-H), 3052 (C-H) and 988 (C-S)

Table 3: IR Spectral Data of 1,5-Benzothiazepines

Compound	Position of absorption band (cm^{-1})
BTZ-01	1615 (C=C), 3047(C-H)
BTZ-02	1610 (C=C), 3071(C-H), 671 (C-Cl)
BTZ-03	1608 (C=C), 3052(C-H), 685 (C-Cl)
BTZ-04	1620 (C=C), 3059(C-H), 702 (C-Cl)
BTZ-05	1608 (C=C), 2937(C-H), 1256 (C-N)
BTZ-06	1612 (C=C), 3091(C-H), 1225 (C-F)
BTZ-07	1611 (C=C), 3028(C-H), 1358 (C-F)
BTZ-08	1617 (C=C), 3068(C-H), 1322 (C-F)
BTZ-09	1602 (C=C), 3022(C-H), 1192 (C-O), 3429 (O-H)
BTZ-10	1612 (C=C), 3089(C-H), 1224 (C-O), 3514 (O-H)
BTZ-11	1610 (C=C), 2990(C-H), 1170 (C-O), 3498 (O-H)
BTZ-12	1614 (C=C), 2981(C-H), 2998 (C-C)
BTZ-13	1625 (C=C), 2944(C-H), 1245 (C-O)
BTZ-14	1610 (C=C), 2938(C-H), 1189 (C-O)
BTZ-15	1601 (C=C), 3018(C-H), 1459 (N=O)
BTZ-16	1614 (C=C), 3029(C-H), 1444(N=O)
BTZ-17	1661 (C=C), 3075(C-H), 1362(N=O)
BTZ-18	1665 (C=C), 1681(C=N)
BTZ-19	1647 (C=C), 1669(C=N)
BTZ-20	1624 (C=C), 1251 (C-O)

Table 4: Common ^{1} H NMR spectral data of 1,5-Benzothiazepines

Common spectral characteristics of 2,4-Disubstituted-1,5-dihydro benzothiazepine derivatives	7.02-7.21 (m, 4H, Ar-H), 7.35-8.08 (m, 6H, Naphthalene), 5.06 (s, Ar = C-OH), 3.81 (t, -CH- , Methine), 2.11 (d, -CH_2-)

Table 5: ^{1} H NMR spectral data of 1,5-Benzothiazepines

Compound	Chemical shift (δ) in ppm
BTZ-01	7.06-7.21 (m, 5H, Ar-H)
BTZ-02	7.22(d, 1H, Ar-H), 7.02(t, 1H, Ar-H), 7.09(t, 1H, Ar-H), 7.06(d, 1H, Ar-H)
BTZ-03	7.21(d, 2H, Ar-H), 7.04(d, 2H, Ar-H)
BTZ-04	7.23(s, 1H, Ar-H), 7.10(d, 1H, Ar-H), 7.06(d, 1H, Ar-H)
BTZ-05	6.54(d, 2H, Ar-H), 6.94(d, 2H, Ar-H), 2.85(s, 6H, -N-CH_3)
BTZ-06	6.92(d, 1H, Ar-H), 7.06(t, 1H, Ar-H), 6.98(t, 1H, Ar-H), 7.10(d, 1H, Ar-H)
BTZ-07	6.82(d, 2H, Ar-H), 7.08(d, 2H, Ar-H)
BTZ-08	6.63(s, 1H, Ar-H), 6.69(d, 1H, Ar-H), 7.02(d, 1H, Ar-H)
BTZ-09	5.04(s, C-OH), 6.68(d, 1H, Ar-H), 6.91(t, 1H, Ar-H), 6.77(t, 1H, Ar-H), 6.95(d, 1H)
BTZ-10	5.01(s, C-OH), 6.68(d, 2H, Ar-H), 6.95(d, 2H, Ar-H)
BTZ-11	5.12(s, C-OH), 3.73(s, 3H,O-CH_3), 6.19(s,1H,Ar-H), 6.24(d, 1H, Ar-H), 6.84(d,1H)
BTZ-12	2.35(s, 3H, CH_3), 7.01(d, 1H, Ar-H), 6.84(d, 1H, Ar-H)
BTZ-13	3.69(s, 3H,O-CH_3), 6.72(d, 2H, Ar-H), 7.01(d, 2H, Ar-H)

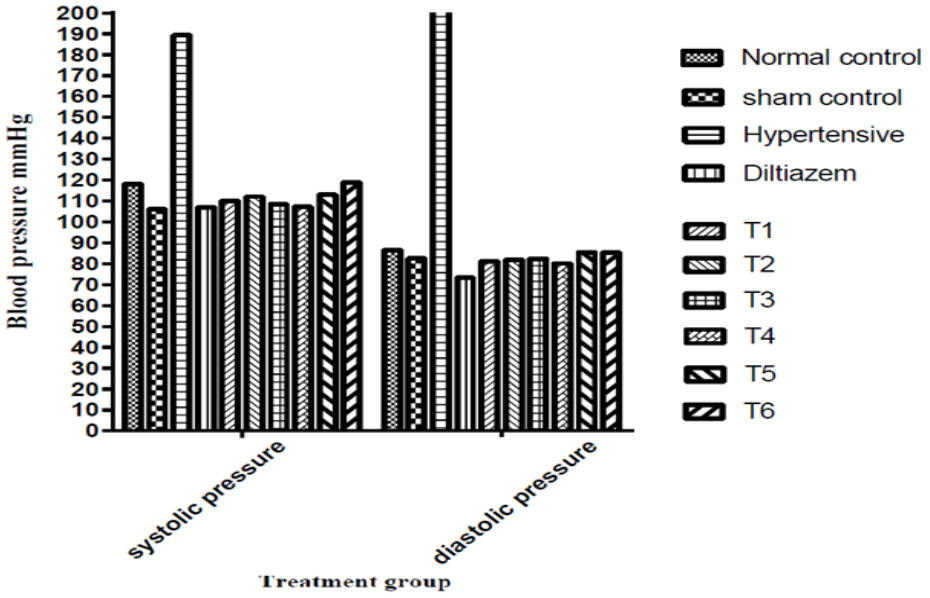
ISSN: 0975-8585

BTZ-14	3.73(s, 9H,O-CH_3), 6.08(s, 2H, Ar-H)
BTZ-15	8.14(d, 1H, Ar-H), 7.34(t, 1H, Ar-H), 7.60(t, 1H, Ar-H), 7.38(d, 1H, Ar-H)
BTZ-16	8.05(s, 1H, Ar-H), 8.01(d, 1H, Ar-H), 7.47(t, 1H, Ar-H), 7.50(d, 1H, Ar-H)
BTZ-17	8.14(d, 2H, Ar-H), 7.36(d, 2H, Ar-H)
BTZ-18	8.62(d, 1H, Ar-H), 7.23(t, 1H, Ar-H), 7.67(t, 1H, Ar-H), 7.29(d, 1H, Ar-H)
BTZ-19	8.60(d, 2H, Ar-H), 7.28(d, 2H, Ar-H)
BTZ-20	7.21(d, 1H, Ar-H), 6.18(t, 1H, Ar-H), 5.88(d, 1H, Ar-H)

PHARMACOLOGICAL STUDIES

Antihypertensive activity

Fructose induced hypertension: The protocol was approved by Institutional Animal Ethics Committee of Chalapathi Institute of Pharmaceutical Sciences (Approval No.43/IAEC/CIPS/2014-15). 60 male wistar albino rats weighing between 200 - 250 gms were used. Prior to the dietary manipulation all rats were fed standard rat chow, containing 60% vegetable starch, 11% fat & 29% protein and maintained on a 12 hour light /dark cycle. In addition, rats were acclimatized to the procedure of blood pressure measurement at 13.00 hour daily for one week. Following the training period, control rats (n=6) were continued on a diet of standard rat chow, where as the experimental groups (n=54) were kept on a diet containing 66% fructose, 12 % fat and 22% protein. The electrolyte content of the two diets was reasonably comparable. The animals were continued on standard rat chow or the fructose diet for 15 days. On day 16 food was removed at 08.00 hour. Rats were weighed & their blood pressure was measured by non - invasive BP system (Pan Lab, Spain) for rodents. The blood pressure parameters were measured in the conscious state of the animals. The mean of 5 consecutive readings were taken as the recorded value of the SBP (systolic blood pressure), and DBP (diastolic blood pressure) of each rat for that day. The average of all parameters on the day 1(before starting the diet) & on the day 16 (day of experiment) were compared to assess the pattern of hypertension induced by fructose diet in rats **(Fig No. 3)** using unpaired student t'test. Animals were allowed normal rat chow and water ad libitum from day 17 onwards.



T_1 = BTZ-04, T_2 = BTZ-05, T_3 = BTZ-08, T_4 = BTZ-11, T_5 = BTZ-17, T_6 = BTZ-19

Figure 3: Anti hypertensive activity of 1,5-Benzothiazepine derivatives

RESULTS AND DISCUSSION

A total of 20 newer 1,5-benzothiazepines were synthesized by microwave-irradiation technique. All the synthesized compounds were obtained in good yields with short reaction times. The power level was also minimal (240W) and chemical transformations could be achieved. The minimal reaction times were

determined by performing sequential series of identical reactions at constant temperature and with continuous heating, but with different irradiation times. Completion of the reaction was observed by TLC after each individual heating period. Spectral data for compounds BTZ-01 to BTZ-20 are consistent with assigned structures. Compounds could be purified using some polar solvents like methanol, ethyl actetate and some using non-polar solvents like hexane, benzene and chloroform. IR and 1^{H}-NMR spectral studies of the compounds BTZ-01 to BTZ-20 reveal the characteristic groups present in the synthesized compounds and were in conformity with the assigned structures.

CONCLUSION

We have synthesized a series of 1,5-benzothiazepine derivatives from aryl chalcones by microwave-assisted solvent-free technique using silica as solid support and zinc acetate as catalyst. The antihypertensive activity of representative compounds was evaluated. Compounds BTZ-04, 05, 08, 11, 17, 19 exhibited anti-hypertensive effect in the form of a significant lowering in systolic, diastolic and mean arterial pressure in the treatment group animals when compared with the disease control group animals.

ACKNOWLEDGEMENTS

The authors profoundly acknowledge UGC-New Delhi for sanctioning minor research grant for this project work. The authors are also thankfull to principal and management, Chalapathi Institute of Pharmaceutical Sciences for providing necessary facilities to carry out the project work. The support rendered by Department of Pharmaceutical Analysis for spectral studies and Department of Pharmacology for animal studies is deeply acknowledged.

REFERENCES

[1] Anshu, D, Ruby S, Dharmendra, S, Ashok. Phosphorus, Sulfur, Silicon Relat. Elem. 2010;185; 2472.
[2] A Levai. J. Heterocycl Chem 1999; 37; 199-214.
[3] GC Morton, JM Salvino, RF Labaudinie`re, TF Herpin. Tetrahedron Lett 2000; 41;3029-3033.
[4] M Sato, T Nagao, I Yamaguchi, H Nakajima, A Kiyomoto. Arzneim.-Forsch 1971; 21;1338-1343.
[5] T Nagao, M Sato, H Nakajima, A Kiyomoto. Chem Pharm Bull 1973; 21; 92-97.
[6] K Yamada, T Shimamura, H Nakajima. Jpn J Pharmacol 1973; 23; 321-328.
[7] J Slade, JJ Stanton, D Ben-David, GC Mazzenga. J Med Chem 1985; 28; 517-1521.
[8] F Micheli, F Degiorgis, A Feriani, A Paio, A Pozzan, P Zarantonello, S Pierfausto. J Comb Chem 2001; 3; 224-228.
[9] Venkata Rao Vutla, Rajendra Prasad Yejella, Ramarao Nadendla and NV Ramarao. Der Pharmacia Lettre 2013; 5 (5); 93-100.
[10] SN Pandeya, Deepak Kumar and Praveen Kumar Verma. Der Pharma Chemica 2012; 4(5); 1853-1855.
[11] KL Ameta, Nitu S Rathore and Biresh Kumar. J Serb Chem Soc 2012; 77(6); 725–731.
[12] G Giuliano, P Luana, A Valeria. Eur J Med Chem 1999; 34(9); 701-709.
[13] PM Sivakumar, S Ganesan, P Veluchamy, M Doble. Chem Biol Drug Des 2010; 76;407.
[14] X Wu, P Wilairat, MN Go. Bioorg Med Chem Lett 2002; 12; 2299.
[15] YM Lin, Y Zhou, MT Flavin, LM Zhou, W Nie, FC Chen. Bioorg Med Chem 2008; 10; 2795.
[16] F Herencia, ML Ferrandiz, A Ubeda, JN Dominguez, JE Charris, GM Lobo, MJ Alcaraz. Bioorg Med Chem Lett 1998; **8;** 1169.
[17] JH Cheng, CF Hung, SC Yang, JP Wang, SJ Won, CH Lin. Bioorg Med Chem 2008; 16; 7270.
[18] H Yamamoto, H Asai. Chem Pharm Bull 1986; 34; 3844-3853.
[19] MJ Kendall, JV Okopski. J Clin Hosp Pharm 1986; 11; 159-174.
[20] M Chaffmann, RN Brogden. Drugs 1985; 29; 387-454.
[21] S Kawakita, M Kinoshita, H Ishikawa, T Kagoshima, R Katori, K Ishikawa, Y Hirota. Clin Cardiol 1991; 14; 53-60.
[22] HM Geyer, N Watzman, JP Buckley. J Pharm Sci 1970; 59; 964-968.
[23] J Hopenwasser, A Mozayani, TJ Danielson, A Harbin, HS Narula, DH Posey, PW Shrode, SK Wilson, R Li, L Sanchez. J Anal Toxicol 2004; 28; 264-268.
[24] Monalisa Jena, J Jena, SB Biswal, Swathi Mishra, Abhisek Pal. Int J Pharm Sci 2013; 5(3);281- 285.