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SYNTHESIS AND ANTIMICROBIAL STUDY OF SOME NOVEL BENZOTHIAZEPINE DERIVATIVES CONTAINING PYRAZOLE MOIETY

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ABSTARCT
In this study, we have developed a synthetic protocol for the synthesis of some novel benzothiazepine derivatives containing pyrazole moiety from various chalcones and 2-aminothiophenol in ethanol under reflux condition. All the synthesized compounds well characterized by IR, NMR and Mass spectral analysis and screened for antimicrobial activities against gram +ve and gram –ve microorganisms. Most of the synthesized compounds show good antimicrobial activity.

KEYWORDS
Chalcones, 2-aminothiophenol, benzothiazepines, pyrazole, antimicrobial activity.

INTRODUCTION

Now a day, a fast growing research field in chemistry is organic synthetic chemistry. In the variety of organic compounds, heterocyclic compounds have been connected with diverse biologically activities. A lot of researchers are interested to study of this because of the bioactivity associated with heterocycles and ease preparation.

The heterocycles compounds containing N- and S-, like thiazepine and their derivatives, show a broad spectrum of biological activity[i-ii]. Benzothiazepine is thiazepine fused with a benzene ring, and it shows diverse biological activities like antimicrobial[iii], antifungal, antibacterial[iv], anti-breast cancer activity[v], anticonvulsant[vi] and acting also as a central nervous system depressant[vii]. The derivatives of benzothiazepine have been found active against diverse families of targets[viii-xiii], Due to this these are of particular interest for lead discovery. Diltiazem[xiv], followed by clentiazem[xv] was the first molecule of 1,5-benzothiazepine used clinically for their cardiovascular action. Several of the derivatives of benzothiazepine were clinically used for quetiapine[xvi], clothiapine[xvii] and CNS disorders[xviii]. Due to the usefulness of 1, 5-benzothiazepines in the drug research which has inspired the development of a broad range of synthetic methods for their preparation and chemical transformations.

EXPERIMENTAL

The required chemicals for the synthesis of the compounds were purchased from Sigma Aldrich and SD Fine chemicals. In liquid paraffin bath, melting points of synthesized compounds were recorded in open capillaries and which are uncorrected. The purity of the synthesized compounds was checked by using TLC, in which silica gel coated plates obtained from Merck as a stationary phase and solvent mixture of ethyl acetate and hexane as a mobile phase. Infrared spectra of synthesized compounds were recorded on Schimadzu-FT-IR Spectrophotometer using potassium bromide pellet technique and the absorption bands are expressed in cm-1. 1H NMR spectra of synthesized compounds were recorded on Varian 400 MHz and Mercury YH 300 MHz instrument in solvents DMSO-d6 and TMS as an internal standard, the chemical shift data were expressed as δ values relative to TMS and in hertz (Hz) coupling constants (J) were expressed. By using electro-spray method (ES), on Macromass mass spectrophotometer (Waters), mass spectra were recorded.

General experimental procedure

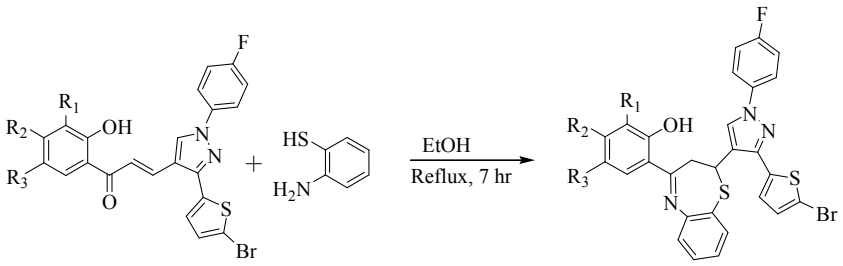
General procedure for the synthesis of 2-((E)-2-(3-(5-bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-4-chlorophenol (2c): Compound 1**c** (0.01 mol) and 2-aminothiophenol (0.01 mol) were mix in 15 ml ethanol in 100ml RBF. The contents of this mixture were heated under reflux for 4 hr. To this reaction mixture, 2ml glacial acetic acid was slowly added and heating continued for further 4 hr. After heating, the contents were cooled to room temperature and poured in to crushed ice. The solid obtained was separated by the filtration. By recrystallzing in ethanol get the product (2c). The compounds **2(a-h)** were prepared following by this general procedure. In **Table 1,** physical data of these synthesized compounds are recorded. Synthesized compounds Structures have been confirmed by IR, ^{1}H NMR and Mass spectra.

IR (2b) (cm^{-1}): 1042(Ar-Br), 1234(C-O), 1517(C=N), 1567(Ar-C=C), 1598(C=N), 3327(Ar-OH).
^{1}H NMR (2b) (DMSO-d_6) δ ppm: 2.1254(s, 3H, -CH_3), 2.2955-2.3011 (d, 1H,-CH_2-), 2.9102-2.9198 (d, 1H, -CH_2-), 3.3124-3.3164(t, 1H, -CH-), 5.5874(s, 1H, Pyrazole-H), 6.9547-6.9874 (dd, 2H, Ar-H), 7.0123-7.1307(d, 1H, Ar-H), 7.1549-7.2098(m, 1H, Ar-H), 7.3697-7.3991 (m, 4H, Ar-H), 7.6728-7.8647(m, 3H, Ar-H), 7.9035-7.9836(m, 1H, Ar-H), 7.9987-8.0021(m, 1H, Ar-H), 12.2619 (s, 1H, Ar-OH).

ES-MS (2b) (m/z): 591.03(M+1), 592.03(M+2).
IR (2c) (cm^{-1}): 752(C-Cl), 1225(C-O), 1510(C=N), 1573(Ar C=C), 1595(C=N), 3381(Ar-OH).
^{1}H NMR (2c) ($CDCl_3$) δ ppm: 2.3211-2.3265 (d, 1H,-CH_2-), 2.8205-2.8264 (d, 1H, -CH_2-), 3.3297-3.3406(t, 1H, -CH-), 5.2654(s, 1H, Pyrazole-H), 6.5897-6.6.6354 (dd, 2H, Ar-H), 6.6589-6.6875(d, 1H, Ar-H), 6.6987-7.2112(m, 1H, Ar-H), 7.2541-7.4325 (m, 4H, Ar-H), 7.5234-7.5614(m, 3H, Ar-H), 7.6478-7.7143(m, 1H, Ar-H), 7.7259-7.7986(m, 1H, Ar-H), 12.5124 (s, 1H, Ar-OH).
ES-MS (2c) (m/z): 610.5 (M+1), 612.5 (M+3).
IR (2g) (cm^{-1}): 1061(Ar-Br), 1227(C-O), 1526(C=N), 1565(Ar-C=C), 1592(C=N), 3412(Ar-OH).
^{1}H NMR (2g) (DMSO-d_6) δ ppm: 2.2964-2.3002 (d, 1H,-CH_2-), 3.1284-3.1321 (d, 1H, -CH_2-), 3.3475-3.3951(t, 1H, -CH-), 5.6023(s, 1H, Pyrazole-H), 6.7984-6.8014(dd, 2H, Ar-H), 6.8751-6.8875(d, 1H, Ar-H), 6.8981-7.1547(m, 1H, Ar-H), 7.3475-7.5478 (m, 4H, Ar-H),

7.6354-7.7841(m, 3H, Ar-H), 7.8245-7.8585(m, 1H, Ar-H), 7.9173-7.9543(m, 1H, Ar-H), 12.1327 (s, 1H, Ar-OH).

ES-MS (2g) (m/z): 654(M+1), 655(M+2), 656(M+3).



1(a-h) **2(a-h)**

Scheme 1: Synthesis of various 2-((E)-2-(3-(5-bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-4-chlorophenol

Table 1: Physical data of compounds 2(a-h)

Comp.	R_1	R_2	R_3	M.P. (^oC)	Yield (%)
2a	**H**	**H**	**H**	76-78	79
2b	**H**	**H**	**CH_3**	80-82	81
2c	**H**	**H**	**Cl**	222-224	61
2d	**Cl**	**H**	**Cl**	206-208	78
2e	**H**	**H**	**F**	68-70	69
2f	**H**	**CH_3**	**Cl**	216-218	86
2g	**H**	**H**	**Br**	220-222	74
2h	**CH_3**	**H**	**CH_3**	72-74	79

RESULT AND DISCUSSION

All benzothiazepines derivatives were synthesized successfully to good yields. On the basis of ^{1}H NMR, Mass, IR spectral analysis, melting point range, all newly synthesized compounds were identified and using disc diffusion method, antimicrobial activity were screened.

Antimicrobial activity: By using paper disc diffusion method, Compounds **1** and **2(a-h)** were screened for their in vitro antimicrobial activity against Salmonella typhi, Enterobacter aerogenes, Escherichia coli, Pseudomonas aerogenosa, Salmonella abony, Shigella boydii, Bacillus subtilis, Bacillus Megaterium, Staphylococcus aureus, Bacillus cereus. Tetracyclin as a reference standard drug. Also antifungal activity was screened against *Candida albicans,* Saccharomyces cerevisiae, Aspergillus niger using Nystatin as standard drug. All the tests were evaluated by using diffusion method and as culture medium Muller Hinton agar was used. On comparing with control, compounds were found to be active. By dissolving 1 mg (1000 ug) in 1 ml of DMSO, test solution was prepared and for testing 0.1 ml (100 ug) of this solution was used. In mm, the zone of inhibition was measured. Microbial data for compounds 2(a-h) are summarized below in **Table 2.**

Table 2: Antimicrobial Analysis Data

	Bacterial pathogens										Fungal pathogen		
	Gram negative pathogen						Gram positive pathogen						
Compounds	Salmonella typhi	Enterobacter aerogenes	Escherichia coli	Pseudomonas aerogenosa	Salmonella abony	Shigella boydii	Bacillus subtilis	Bacillus Megaterium	Staphylococcus aureus	Bacillus cereus	Candida albicans	Saccharomyces cerevisiae	Aspergillus niger
16a	14	22	26	23	21	14	14	24	23	24	25	26	28
16b	12	13	28	19	18	13	17	16	22	13	26	19	24
16c	15	24	30	21	11	16	15	24	29	23	25	29	30
16d	11	11	25	26	26	15	20	11	25	25	25	21	25
16e	14	20	29	23	17	16	14	21	20	21	25	26	26
16f	15	21	30	22	25	15	11	25	21	24	25	25	30
16g	15	21	30	22	25	15	11	25	21	24	25	25	30
16h	13	20	27	21	26	14	13	22	24	25	27	22	28
DMSO	-	-	-	-	-	-	-	-	-	-	-	-	-
STND.	22	30	40	33	38	26	25	36	30	25	42	30	32

*Standard for bacterial pathogens-tetracyclin, for fungal pathogens-nystatin

CONCLUSION

Starting from chalcone we have successfully synthesized benzothiazepines and its derivatives. Most of the synthesized compounds show good antibacterial and antifungal activity.

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REFERENCES:

i. Struga M., Kossakowski J., Koziol A. E., Kedzierska E., Fidecka S., Colla P. L., Ibba C., Collu G., Sanna G., Secc B. and Loddod R., Eur. J. Med. Chem., 44, (2009),4960.

ii. Campiani G., Butini S., Fattorusso C., Trotta F., Gemma S., Catalanotti B., Nacci V., Fiorini I., Cagnotto A., Mereghetti I., Mennini T.,Minetti P., Di Cesare M. A., Stasi M. A., Di Serio S., Ghirardi O., Tinti O. and Carminati P., J. Med. Chem. 48, (2005),1705.

iii. Wang L., Zhang P., Zhang X., Zhang Y., Li Y. and WangY, Eur. J. Med. Chem., 44, (2009), 2815.

iv. Khan A. J., Baseer M. A., Dhole J. M. and Shah S. N., Int. J. Pharma. Sci. Res., 2, No. 10, (2011), 2619.

v. Ameta K. L.,Rathore, N. S. and Kumar B., J. Serb. Chem. Soc.,Vol. 77, No. 6, (2012), 725.
vi. Garg N., Chandra T., Jain A. B. and Kumar A., Eur. J. Med. Chem.,Vol. 45, (2010), 1529.
vii. Nikalje A. P. andVyawahare, D., African J. Pure Appl. Chem.,Vol. 5, No. 12, (2011) 422.
viii. Anjaneyulu A S R, Sudha Rani G, Mallavadhani U V and Murthy Y L N., Ind. J. Het. Chem, 34 B, (1994), 9.
ix. Bala Krishna K and Ganesha Rani, Ind. J. Chem, 42B(10), (2003), 2556.
x. Deshpande A M, Narshinha P A, Arvind A N and Joseph E, Bioorg. Med. Chem, 7(6), (1999), 1237.
xi. Baaterham T J and Highet R J, Australian J.Chem, 17(4), (1964), 428.
xii. Hegert H L and Kurth E F, J. Am. Chem. Soc, 75(7), (1953), 1622.
xiii. Kurokawa J, Adachi-Akahane S, Nagao T, Eur. J. Pharmacol, 325(2-3), (1997), 229.
xiv. Sarro G D, Chimirri A, Sarro A D, Gitto R, Grasso S, Zappala M, Eur. J. Med. Chem, 30(12), (1995), 925.
xv. Saini R K, Joshi Y C, Joshi P. Phosphorus, Sulfur, Silicon Relat. Elem, 183(9), (2008), 2181.
xvi. Maayan S, Ohad N and Soliman K, Bioorg. Med. Chem, 13(2), (2005), 433.
xvii. Yamada S, Mori Y, Morimatsu K, Ishizu Y, Ozaki Y, Yoshioka R, Nakatani T, Seko H, J. Org. Chem, 61(16), (1996), 8586.
xviii. Grandolini G, Perioli L, Ambrogi V., Eur. J. Med. Chem, 34(9), (1999), 701.

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