International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

**Original Article** **CODEN: IJPNL6**

# SYNTHESIS, SPECTRAL STUDIES AND ANTI-BACTERIAL ACTIVITY OF 8-SUBSTITUTED-4-(2,4-DIHYDROXYPHENYL)-2-(4-CHLOROPHENYL)-2,5-DIHYDRO-1,5-BENZOTHIAZEPINES

Prerna Jain*, B.S. Sharma

Dept. of chemistry, govt. R.R. Auto. P.G. Autonomous College, Alwar, Rajasthan, India-301001

***Corresponding author e-mail:** lect.prernajain@gmail.com

***Received on: 03-10-2015; Revised on: 19-11-2015; Accepted on: 21-12-2015***

**ABSTRACT**

A new series of 1,5-benzothiazepine compounds have been synthesized by the reaction between equimolar quantities of 5-substituted-2-aminothiophenol and 1-(2,4-dihydroxyphenyl)-3-(4-chlorophenyl)-2-propenone, in the presence of absolute alcohol saturated with dry HCl gas. The reaction progress is monitored by TLC. Structure of compound is ascertained by Spectral and by elemental analysis.

**Keywords:** 1,5-benzothiazepine ; 1-(2,4-dihydroxyphenyl)-3-(4-chlorophenyl)-2-propenone ; anti-bacterial activity; 5-substituted-2-aminothiophenol.

## INTRODUCTION

1,5-benzothiazepine scaffold is extremely versatile in a large no. of drugs therefore it attracted chemists in the field of drugs and pharmaceutical research. Benzothiazepine compounds are widely used as anticonvulsant[1], anti-spasmodic[2], neurolaptic[3], antidepressive[4], antibacterial[5], anti-ulcer[6] as well as anti-inflammatory[7] agents. The I generation drug Diltiazem[8] having 1,5-benzothiazepine nucleus with 4-methoxy group at position 2, acetoxy at position 3,oxo at 4. The prodigious applications of diltiazem such as blood platelet aggregation inhibitor[9], anti thrombotic[10], anti ischemic[11], anti arrhythemic[12], Calcium channel modulator[13], anti-hypertensive[14] etc have captivate the chemists to synthesize more improved version of it. Thus endeavour of researchers had launched Clentiazem[15] in which Cl is present at position 8 and an isopropyl at position 5. Clentiazem exhibits more curative uses as anti-coagulant[9], anti-arteriosclerotic[16] etc. From short summary of literature it was concluded that inclusion of chlorine as chlorophenyl substituent in benzothiazepine nucleus intensify the biological activities such as vasodepressant[17], analgesic[18] etc. This biological profile of 1,5-benzothiazepine incited us to synthesize new benzothiazepine derivatives containing chlorophenyl groups. The work has been done and presented in this communication.

## MATERIALS AND METHODS

The m.p. of all the synthesized compounds were determined in open capillary tubes and are precise. The reaction progress is monitored by TLC on silica gel G using solvent system benzene: ethanol; ammonia(7:2:1). The IR spectra were taken in KBr pellets using Perkin-Elmer RX1 FT IR spectrometer. The $H^1$ NMR spectra were recorded on Bruker Avance 400 (FT NMR) using $CDCl_3$ as solvent. The mass spectra were recorded on JMS-T100LC, Accu TOF (DARTMS) spectrometer. The Elemental and Spectral analysis have executed at CDRI, lucknow.

**Synthesis of 1-(2,4-dihydroxyphenyl)-3-(4-chloro phenyl) -2-propenone:** 2,4-dihydoxy acetophenone

(0.01 mol, 1.51 g) and p-chlorobenzaldehyde (0.01 mol., 1.40 gm) were dissolved in 20 ml ice cold ethanol in round bottom flask placed in ice bath. To this 50 % NaOH solution was added with vigorous stirring for about 30 minutes. The reaction mixture was kept overnight then diluted with ice cold water and neutralized with dilute HCl. The creamy yellow crude product was obtained which was washed with cold water and dried. The yellow crystals of 1-(2,4-dihydroxyphenyl)-3-(4-chlorophenyl)-2-propenone were obtained. (m.p. $138^0$C lit. 134-$137^0$C, yield 89%).

**8-methoxy-4-(2,4-dihydroxyphenyl)-2-(4-chloro phenyl)-2,5-dihydro-1,5-benzothiazepine**:
2-amino-5-methoxybenzothiol (0.001mol, 0.139gm) and 1-(2,4dihydroxyphenyl)-3-(4-chlorophenyl)-2-propenone (.001 mol, 0.274 gm) were dissolved in 50 ml dry ethanol and saturated with dry HCl gas. The reaction mixture was refluxed for about five hours when colour change from pale yellow to deep red. The reaction mixture was reduced under diminished pressure to obtain crude solid which was crystalized by ethanol to give red brown coloured crystals of 8-methoxy-4-(2,4-dihydroxyphenyl)-2-(4-chlorophenyl) -2,5-dihydro-1,5-benzothiazepine 5d. (m.p $135^0$, yield 72%). On the above pattern all the compouds were prepared. The analytical and spectral data of 5a to f are given in table I & II respectively.

## RESULTS AND DISCUSSIONS

To achieve the synthesis of targeted compound, the methodology is as follows;
**Step-I** Synthesis of 1-(2,4-dihydroxyphenyl)-3-(4-chlorophenyl)-2-propenone (3) is carried out by the condensation of 2,4-dihydroxtacetophenone (1) and 4-chlorobenzaldehyde (2). (Scheme I)
**Step-II** An equimolar quantity of chalcone and 5-substituted-2-aminothiophenol was refluxed in dry ethanol saturated with dry HCl gas. The red brown coloured crystals of 8-substituted-4-(2,4-dihydroxyphenyl)-2-(4-chlorophenyl)-2,5-dihydro-1,5-benzothiazepines were separated out and crystallized with ethanol. The structure of the final products was determined by IR, $H^1$NMR, Mass Spectra and Elemental Analysis.
The reaction between 5-substituted-2-aminothiophenol and chalcone initialise by nucleophilic attack of the lone pair of sulphydryl electrons on the β-carbon of chalcone . It gives ketoamine which tautomerizes to the inolic form which on dehydration and cyclisation yields final product 8-substituted-4-(2,4-dihydroxyphenyl)-2-(4-chlorophenyl)-2,5-dihydro-1,5-benzothiazepine(5a-f).

**Spectral Analysis:** The absence of absorption band in the region 1685-1645$^{cm-1}$confirmed the absence of C=O group. However broad absorption around 3145-3130$cm^{-1}$was obtained which may due to secondary amino group. Peak near 3400-3300 $cm^{-1}$ confirms the presence of OH group. Band near 790-775 $cm^{-1}$ ascribed to C-Cl stretching. The $H^1$-NMR spectra of all final product (5a-f) showed one proton doublet at δ=6.45-7.35 (d, 1H, J=7 Hz) which may be assigned to $C_2$-H and other doublet around δ= 7.05-8.20 (d, 1H, J=7 Hz) integrating for 1 proton may be ascribed to $C_3$-H. The broad absorption signal in the region 3.85-4.30 (br, 1H) may be due to NH. The multiplet at around 6.52 to 8.15 (m,10H) may be assigned to aromatic ring. The absorption at 11.5-12.4 as a singlet may be assigned to OH group. In the spectra of 5d peak at δ=3.54 as a singlet may be assigned to 3 protons of $OCH_3$ group. The peak at δ 2.45 as a singlet integrated for 3 protons indicates the presence of $CH_3$ group in 5f. In spectra of compound 5e, the signal at 3.85 as quartet integrated for 3H and triplet at δ 1.90 integrated for 2H with same J=6 Hz may be assigned to $OC_2H_5$ group. The mass spectra of compounds 5c showed molecular ion peaks $[M]^+$ and $[M+2]^+$ peak at 440.4 and 442.4 correspond to the molecular mass of the product. Both the peaks were found to be nearly of equal intensity which confirms the presence of Bromine in 5c.

**Anti-bacterial activity:** Compound 5a-5f were investigated for their invitro anti-bacterial activity against E.coli and Ps. Aeruginosa using paper disc method[19]. Ampicillin and amikacin was used as a standard drug for E.coli and pseudomonas aeruginosa respectively. The concentration of compound used was 100 µg/disc. The zone of inhibition for all compounds was measured after 24 hours of incubation at optimum temperature.

## CONCLUSION

The compounds 5a, b, c, d, f showed anti-bacterial activity almost equal to the reference drug Amikacin against Ps.Aeruginosa and compounds 5a, b, d, e, f showed anti-bacterial activity almost equal to the reference drug Ampicillin against E.Coli..

## ACKNOWLEDGMENT

The authors wish to thank Principal R.R. Govt. College Alwar and Dr. Saroj Garg (Head Dept.of chemistry) for providing necessary facilities. One of them (BSS) is grateful to UGC New Delhi for the award of a minar research project. Authors are grateful to CDRI Lucknow for analytical and spectral work. Authors are also thankful to Curewell Diagnostics, Alwar to conduct anti-microbial activity.

**Table-1**

**Characteristic data of compound 5a-5f**

| Compd | X | m.p $^0$C | Yield (%) | $R_f$ | Mol.formula (mol.wt.) | Elemental analysis Calcultd(found)% | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| 5a | F | 132 | 82 | 0.72 | $C_{21}H_{15}O_2SNF$ (379.5) | 66.40 (65.98) | 3.95 (3.23) | 3.68 (3.56) |
| 5b | Cl | 157 | 85 | 0.74 | $C_{21}H_{15}O_2SNCl$ (396) | 63.63 (62.45) | 3.78 (3.67) | 3.53 (3.56) |
| 5c | Br | 116 | 79 | 0.65 | $C_{21}H_{15}O_2SNBr$ (440.5) | 57.20 (56.65) | 3.40 (3.56) | 3.17 (3.12) |
| 5d | $OCH_3$ | 135 | 72 | 0.68 | $C_{22}H_{18}O_3SN$ (391.5) | 67.43 (66.76) | 4.59 (4.23) | 3.57 (3.25) |
| 5e | $OC_2H_5$ | 145 | 69 | 0.64 | $C_{23}H_{20}O_3SN$ (405.5) | 68.06 (67.920 | 4.93 (4.46) | 3.45 (3.23) |
| 5f | $CH_3$ | 139 | 78 | 0.71 | $C_{22}H_{18}O_2SN$ (375.5) | 70.30 (68.93) | 4.79 (3.94) | 3.72 (3.62) |

**Table-2**

| Comp. No. | IR | $^1$H-NMR | | | | |
|---|---|---|---|---|---|---|
| | N-H | N-H (br, 1H) | $C_2$-H (d, 1H, J7) | $C_3$-H (d, 1H, J7) | O-H (s,1H) | Ar Protons (m, 10H) |
| 5a | 3135 | 3.95 | 6.45 | 7.05 | 11.4 | 6.54-7.90 |
| 5b | 3140 | 3.98 | 6.99 | 7.10 | 11.9 | 7.20-7.85 |
| 5c | 3134 | 4.04 | 7.30 | 7.80 | 12.3 | 7.10-8.10 |
| 5d | 3136 | 4.02 | 7.35 | 8.10 | 12.1 | 7.29-7.99 |
| 5e | 3138 | 4.02 | 6.89 | 7.10 | 11.7 | 6.99-7.86 |
| 5f | 3141 | 4.25 | 7.15 | 7.12 | 11.8 | 7.11-7.99 |

**Spectral data of compd 5a-f**

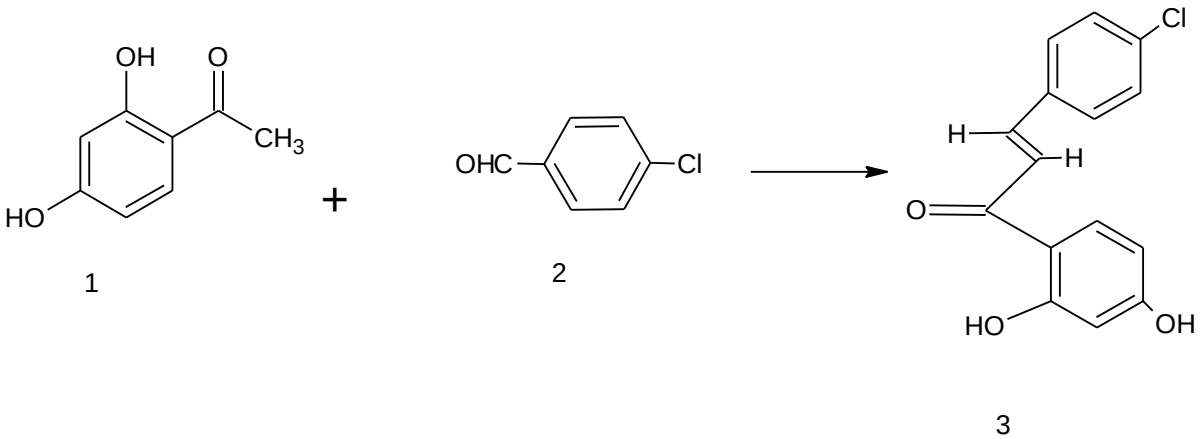
**Table -3**

**Antibacterial studies of compds 5a-f**

| Compound | Zone of inhibition(mm) | |
|---|---|---|
| | E.coli | Ps.aeruginosa |
| 5a | 15 | 19 |
| 5b | 16 | 18 |
| 5c | 14 | 15 |
| 5d | 13 | 20 |
| 5e | 09 | 19 |
| 5f | 14 | 17 |

*Zone of inhibition of ampicillin= 18mm*
*Zone of inhibition of amikacin = 21mm*

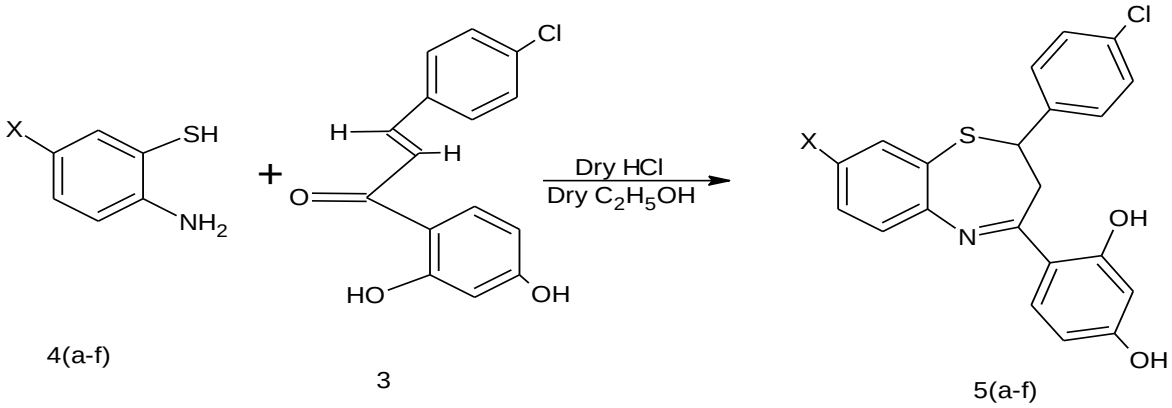
(I)




1 2 3

scheme-1

(II)




4(a-f) 3 5(a-f)

scheme-2

**REFERENCES**


1. Sarro GD, Chimirri A, Sarro AD, Gitto R, Grasso S & Zappala M, Eur J Med Chem,1995; 30: 925.
2. Krapcho J, US Patent, 3361 750, 1968.
3. Renz JB, Jean P & Winkler H, France Patent, 1535 533 (Cl. 07d, A, 61K), 1968.
4. Geyer HM, Watzman N, Buckley JP, J Pharmacol Sci, 1970 ;59:964. Bernstein J, Brit patent,1198 825,1970
5. Sharma AK, Singh G, Yadav AK & Prakash L, Molecules,1997;2:129.
6. Ohno S, Izumi K, Mizukoshi K, Kato K & Hori M, Chem Pharm Bull, 1983;5:1780.
7. Mohmad Imran & Khan Suroor A, Asian J Chem, 2004;16:543.
8. kantoci D,murray ED,quiggle DD & wechter WJ, j med chem, 1996;39:1196.
9. Weiss K, Fitscha P, Gazso A, Gludovacz D & Sinzinger H. Prog Clin Biol Res, 1989; 301:353.
10. Myers AK, Forman G, Duarte APT, Penhos J & Ramwell P, Proc Soc Exp Biol Med, 1986; 183:86.
11. Kuzelova M, Svec P, Cesk Farm,1993; 42:124.
12. Alonzo D,Allert J, Thomas H, Darbenzio A, Raymond R & Joseph SC, J Cardivasc Pharmacol,1993;21: 677.
13. Vaghy LP,Williams SJ & Schwartz A,Am J Cardiol, 1987; 59: 9A.
14. Burris J, Weir M, Oparil S, Weber S,Cady W,Stewart W & JAMA, J Aaam Med Assoc, 1990; 263:1507.
15. Kinoshita K, Yammamura M &Matsuoka Y, Pharmacol Biochem Behav,1995;50(4):509.
16. Shimizu N (Dep Geriatr Med, Tokkyo Med Coll, Tokkyo Japan), Tokkyo Ika Daigaku Zasshi, 47 (1980) 440; Chem Abstr,111 (1989) 187170f.
17 Itoh K, Mori M, InadaY, Nishikawa K, Kawamatsu V & Sugihara H, Chem Pharm Bull, (1986); 34(4), 3747. Chem. Abstr., 106, 122593r (1987).
18. Murako Pharmaceutical Co. Ltd., Jpn. Kokai Tokkyo Koho JP 81, 127, 367 [Cl.CO7D281/10] (1981); Chem. Abstr., 96, 85601b (1986).
19. Bauer A, Kirby WMM, Sherris J &Turck M, Amer J. Clin. Pathol, 1966; 45(4): 493.