http://www.e-journals.net

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
Vol. 4, No.1, pp 14-20, January 2007

Synthesis and Antibacterial Activity of Some New Phenothiazine Derivatives

PAWAN KUMAR SWARNKAR, P. KRIPLANI, G. N.GUPTA and K.G.OJHA*

Department of Pure and Applied Chemistry,
Maharshi Dayanand Saraswati University,
Ajmer, Rajasthan (India) 305009.
E-mail: chiya_f@yahoo.co.in

Received 24 July 2006; Accepted 8 September 2006

Abstract: A series of some new phenothiazine derivatives were synthesized with the objective for evaluation as antimicrobials. The title compounds were prepared by a five step synthesis scheme. 2-Amino-6-substituted benzothiazoles (**1**) on diazotization afford 6-substituted benzothiazolyl-2-diazonium chlorides (**2**). Reaction of **2** with cold solution of β-naphthol in dilute NaOH furnishes α-(2-diazo-6-substituted benzothiazolyl)- β-sodionaphthoxides (**3**) which on acidification with concentrated HCl gives α-(2-diazo-6-substituted benzothiazolyl)-β-naphthols (**4**). Reaction of **4** with p-substituted anilines gives α-(2-diazo-6-substituted benzothiazolyl)-β-(*p*-substituted anilino) naphthalenes (**5**). This synthesis besides by using conventional methods was also attempted using microwave. Fusion of **5** with sulphur in presence of iodine results in α-(2-diazo-6-substituted benzothiazolyl)-6- substituted [2, 3-b] benzophenothiazines(**6**). The structures of all these compounds have been supported by elemental analysis and their spectral studies. All synthesized compounds were tested for their antibacterial activity using standard drugs.

Keywords: Phenothiazines, benzothiazole, antibacterials, microwave irradiation.

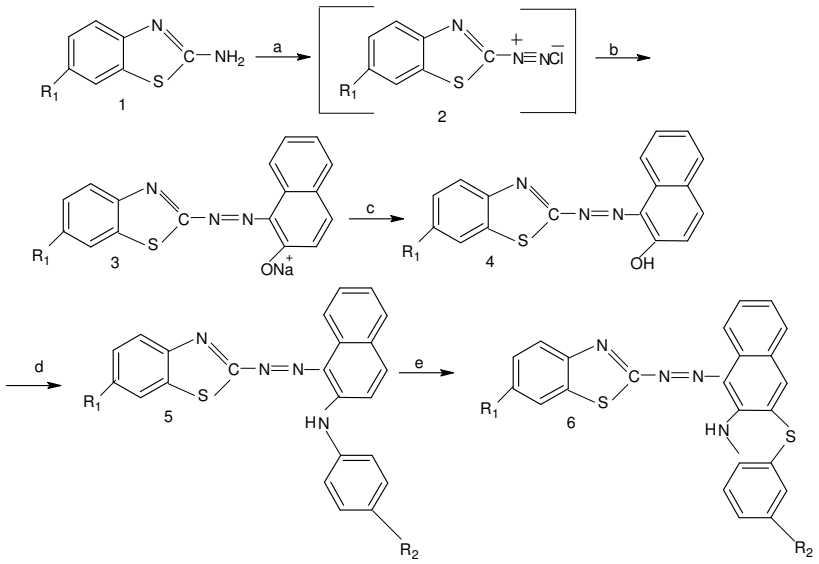
Introduction

Phenothiazine derivatives constitutes an important class of thiazines hetrocyclic ring system and possess potent biological activities as neuroleptics[1], tranquilizers[2], analgesic[3], antimalarian[4], anticancer[5], CNS- activity[6], antiviral[7] and antibacrerials[8]. Furthermore a wide spectrums of biological activities including antibacterial[9], antitumor[10], antituberculotic[11] and

insecticides[12] have been reported in different benzothiazole derivatives. Benzothiazoles have also shown significant effects against cancer[13]. Similarly diazo compounds also shows a biological activity such as such as antibacterial[14], antiviral[15], antifungal[16], In view of the activities exhibit by benzothiazoles, diazo compounds and phenothiazines, we have taken up the environmentally benign and economic synthesis of some new phenothiazine derivatives. Microwave mediated reaction have emerged as a powerful technique to promote a variety of chemical reactions. The growing number of publications in micro-wave- assisted synthesis includes virtually all type of chemical reactions such as additions, cycloadditions, substitutions, eliminations and fragmentations etc[17,18]. Applications of microwave methodology in Heterocyclic chemistry in terms of enhancements in the rate of reaction and in yields are striking[19, 20].

Experimental

All the melting points are uncorrected. The purity of synthesized compounds has been checked by thin layer chromatography. IR spectra are recorded on FT-IR Perkin-Elmer (Spectrum RX1) spectrophotometer (ν_{max} in cm^{-1}) using KBr disc.^{1}H NMR spectra are recorded in $CDCl_3$ on a Bruker DRX-300 MHz using TMS as internal standard. The chemical shifts are reported as parts per million (ppm). Microwave synthesis was carried out in a domestic microwave oven model L.G. MS-194W, 230-50 Hz., 800W.



Scheme 1. Reagents and condition: **(a)** $NaNO_2$ / HCl, 0^oC, **(b)** β- Naphthol / dil. NaOH, 0^o – 5^o C, **(c)** Conc. HCl , **(d)** p- substituted aniline / EtOH, anhyd. $ZnCl_2$ heating on steam-bath , reflux, 5hr., **MWI** for 1.5-2.0 minutes **(e)** S, I_2 / heating on oil bath.

Synthesis of substituted 2- aminobenzothiazoles (1)

These compounds were synthesized by methods reported earlier [21, 22].

Synthesis of 6-substituted benzothiazolyl-2-diazonium chlorides (2)

A solution of compound **1** (0.001mole) in 5N HCl (20ml) was cooled to 0^0C. To this solution was added a cold solution of sodium nitrite (1.0gm) drop wise with constant

stirring. When the addition was complete, the resultant reaction mixture was left in ice- chest for 1hr. It was used as such for further reaction.

Synthesis of α-(2-diazo-6-substituted benzothiazolyl)- β-sodionaphthoxides (3)

To the ice cold solution of compound **2**, a cold solution of β-naphthol(0.05mole) in dilute NaOH was added drop wise with constant shaking. A dark red dye resulted which darkened on adding more alkaline solution of β-naphthol. When the addition was complete, the resultant reaction mixture was vigorously stirred and filtered off. It was dried and used for further reaction as such.

Synthesis of α-(2-diazo-6-substituted benzothiazolyl)- β-naphtholes (4)

A saturated solution of compound **3** (0.002mole) in water was neutralized with concentrate HCl. A solid separated out which was allowed to stand at room temperature for 30min. It was filtered off and washed with water. The compounds thus prepared, were recrystallised from redistilled ethanol.

Synthesis of α-(2-diazo-6-substituted benzothiazolyl)- β-(p-substituted anilino) naphthalenes (5)

A mixture of compound **4** and p-substituted aniline (equimoler amount) containing anhydrous $ZnCl_2$ (1gm) in absolute ethanol (50ml) was heated under reflux for 5hr on a steam bath. The solvent was distilled off and the residual solid was washed with water. It was dried in vacuo and recrystallised from methanol.

Microwave synthesis of α-(2-diazo-6-substituted benzothiazolyl)- β-(p- substituted anilino) naphthalenes (5)

A mixture of compound **4** and p-substituted aniline (equimolar amount) in minimum quantity of anhydrous ethanol were taken in RB flask, which was placed in microwave oven and a reflux condenser was attached. The contents were subjected to microwave irradiation. The reaction was completed in 1.5 – 2 minutes (monitored with T.L.C.). The solid obtained washed with distill water, dried in vaccuo and recrystallised from ethanol.

Synthesis of α-(2-diazo-6-substituted benzothiazolyl)-6- substituted [2, 3-b] benzophenothiazines(6)

Heating of mixture of compound **5** (0.001mole), sulphur (0.002mole) and iodine (1% weight of reaction mixture) in an oil-bath for 2hr afforded a dark green solid which was cooled and washed repeatedly with water. It was dried and recrystallised from benzene as light green crystalline mass.

Characterization data of all the synthesized compounds are summarized in Table 1**.**

Antibacterial activity

All the synthesized compounds (**5a-6d)** were tested against gram positive bacteria *S. aureus* and gram negative bacteria *E.coli, Pseudomonas aeruginosa* and *Klebsiella* species using paper disc method. The zone of inhibition was measured in mm. The standard drugs used were streptomycine and ceftazidime. The compounds were tested at 200µg/ml concentration. The observations show that compound 6a, $6c_2$, $6c_1$ were found more effective against *E.coli*, *Klebsiella* species and *S. aureus* respectively as compared to streptomycine and the compound $6c_2$, $6c_2$, $5c_2$ more effective against *E.coli*, *Klebsiella* species and *Pseudomonas aeruginosa* respectively as compared to ceftazidime. The results of activity summarized in Table 2.

Table 1. Physico-chemical data of synthesized compounds (C.M. = Conventional method, M.W. = Microwave)

Compounds	R_1	R_2	Reaction Period		Yield (%)		M.P. ^0C	Elemental analysis Cal./(Found) %		
			C.M h	M.W min	C.M.	M.W.	M.W./ C.M.	C	N	S
4a	Br	-			62	-	116	53.13 (53.09)	10.93 (10.85)	8.34 (8.28)
4b	CH_3	-			70	-	92	67.68 (67.60)	13.15 (13.18)	10.03 (10.12)
4c	OCH_3	-			51	-	135	64.46 (64.42)	12.52 (12.48)	9.56 (9.62)
4d	NO_2	-			49	-	105	58.27 (58.18)	15.99 (15.91)	9.15 (9.09)
5a	Br	Cl	6-7	1.5	58	85	198(d) 195(d)	55.94 (55.88)	11.34 (11.38)	6.49 (6.52)
5b	CH_3	Cl	6-7	2.0	68	88	221 219	67.20 (67.28)	13.06 (13.12)	7.47 (7.52)
$5c_1$	OCH_3	Cl	6-7	1.5	48	95	156 155	64.78 (64.72)	12.59 (12.52)	7.20 (7.18)
$5c_2$	OCH_3	F	6-7	1.0	46	90	161 160	67.27 (67.18)	13.07 (13.12)	7.48 (7.42)
5d	NO_2	OCH_3	6-7	2.0	52	72	112 110	63.28 (63.32)	15.37 (15.31)	7.03 (6.98)
6a	Br	Cl			58	-	201	52.73 (52.68)	10.69 (10.62)	12.24 (12.18)
6b	CH_3	Cl			56	-	>280	62.80 (62.76)	12.20 (12.24)	13.97 (13.92)
$6c_1$	OCH_3	Cl			46	-	172	60.68 (60.52)	11.79 (11.82)	13.50 (13.53)
$6c_2$	OCH_3	F			42	-	181	62.86 (62.78)	12.21 (12.16)	13.98 (14.01)
6d	NO_2	OCH_3			62	-	122	59.36 (59.28)	14.42 (14.48)	13.20 (13.22)

Results and Discussion

The structures of all the synthesized compounds have been supported by elemental analysis and their spectral studies. Compounds **(4)** shows IR absorption bands at 1605-1635(-N=N, stretching), 3340-3450 (-O-H streching). Compound **(5)** they show sharp IR bands at 1580-1600 (NH bending) and broad IR bands at 3400-3440 cm^{-1}(NH Streching). The presence of sharp bands at 1380-1395 cm^{-1}(-C-S), confirms the structure of compounds **(6).**

Table 2. The zone of inhibition in mm of the compound as well as standard drugs tested for antibacterial activity.

S.No	Compounds	R_1	R_2	Zone of Inhibition (mm)			
				E.Coli	*Klebsiella Spp.*	*Pseudomonas aeruginosa*	*S.aureus*
1	5a	Br	Cl	19	20	12	08
2	5b	CH_3	Cl	11	09	16	13
3	$5c_1$	OCH_3	Cl	21	18	09	07
4	$5c_2$	OCH_3	F	22	24	23	16
5	5d	NO_2	OCH_3	19	15	15	12
6	6a	Br	Cl	23	21	10	21
7	6b	CH_3	Cl	19	17	21	13
8	$6c_1$	OCH_3	Cl	22	24	18	26
9	$6c_2$	OCH_3	F	26	27	22	21
10	6d	NO_2	OCH_3	21	19	14	15
11	Streptomycine			22	23	25	20
12	Ceftazidime			24	26	21	26

Spectral analysis of compounds 4a-4d, 5a-5d, 6a-6d

Compound 4a: M.F.$C_{17}H_{10}N_3OSBr$,IR(KBr)ν_{max} in cm^{-1} 878(C-Br), 1370(C-S), 1662(C=N), 1605(-N=N),1470,1580(ArC=C),3402.5(-O-H),^{1}HNMR(300MHz,$CDCl_3$):δ 5.65(s,1H,-OH), 7.30-8.0.(m,9H,ArH).

Compound 4b: M.F.$C_{18}H_{13}N_3OS$, IR(KBr)ν_{max} in cm^{-1}1380(C-S),1658(C=N), 1635(-N=N), 1490,1608(ArC=C), 2995(-CH_3), 3340(-O-H), ^{1}HNMR(300MHz,$CDCl_3$):δ2.45(s,3H,CH_3), 5.09(s,1H,-OH), 7.2-7.8(m,9H, ArH).

Compound 4c: M.F.$C_{18}H_{13}N_3O_2S$,IR(KBr) ν_{max} in cm^{-1} 1598(C=N),1360(C-S),1620(N=N), 1470,1490,1540(ArC=C),3350(-O-H),1364(-OCH_3),^{1}HNMR(300MHz,$CDCl_3$) δ 3.65(s,3H,-OCH_3),5.15(s,1H.-OH), 7.4-7.80(m,9H, ArH).

Compound 4d: M.F. $C_{17}H_{10}N_4O_3S$, IR (KBr) ν_{max} in cm^{-1} 1590(C=N),1370(C-S), 1610(N=N), 1440,1535(ArC=C), 3440(-O-H), 1540,1360(NO_2) 1457,1545(ArC=C),^{1}HNMR (300MHz,$CDCl_3$):δ5.4(s,1H,-OH),7.2-8.3(ArH)

Compound 5a: M.F. $C_{23}H_{14}N_4SClBr$, IR (KBr)ν_{max} in cm^{-1}864(C-Cl),846(C-Br),1310(C-S), 1630(C=N),1610(-N=N),3402(-NH str.) 1465,1540(ArC=C), ^{1}HNMR (300MHz,$CDCl_3$): δ 8.2(s,1H,-NH), 7.20-7.8(m,13H,ArH).

Compound 5b: M.F. $C_{24}H_{17}N_4SCl$, IR (KBr) ν_{max} in cm^{-1}852(C-Cl),1305(C-S),1642(C=N), 1622(-N=N), 2950(CH_3), 1470,1541(ArC=C), 3415(N-Hstr.), ^{1}HNMR (300MHz,$CDCl_3$): δ 2.39(s,3H, -CH_3), 8.35(s,1H,NH),7.32-7.90(m,13H, ArH).

Compound $5c_1$: M.F.$C_{24}H_{17}N_4OSCl$, IR(KBr)ν_{max} in cm^{-1}1605(C=N)1340(C-S), 1630(N=N), 848(C-Cl), 1365(-OCH_3)1460-1535(ArC=C),3410(N-Hstr.), ^{1}HNMR (300MHz,$CDCl_3$): δ 3.62(s,3H, -OCH_3), 8.3(s,1H,NH),7.40-8.20(m,13H, ArH),

Compound $5c_2$: M.F. $C_{24}H_{17}N_4OSF$, IR (KBr) ν_{max} in cm^{-1} 1660(-C=N), 1325(-C-S), 1640(-N=N), 1435,1560(ArC=C), 3435(N-Hstr.),1105(C-F), 1370(-OCH_3), ^{1}HNMR (300MHz,$CDCl_3$): δ 3.70((s,3H,-OCH_3),7.26-8.10(m,8H,ArH),8.35(s,1H,NH).

Compound 5d: M.F. $C_{24}H_{17}N_5O_3S$**,** IR (KBr) ν_{max} in cm^{-1} 1580(-C=N),1385,1505(-NO_2), 1330(-C-S), 1660(-N=N), 1465,1540(ArC=C), 3415(N-Hstr.), 1360(-OCH_3), ^{1}HNMR (300MHz,$CDCl_3$): δ 3.8((s,3H,-OCH_3),7.28-8.00(m,13H,ArH),8.54(s,1H,NH).

Compound 6a: M.F.$C_{23}H_{12}N_4S_2ClBr$, IR(KBr) ν_{max} in cm^{-1}1383(C-S), 1495-1605(ArC=C), ^{1}HNMR (300MHz,$CDCl_3$): δ 8.4(s,1H, NH), 7.45-7.90(m,11H, ArH).

Compound 6b:M.F.$C_{24}H_{115}N_4S_2Cl$, IR(KBr) ν_{max} in cm^{-1}1395.5(C-S), 1485-1610(ArC=C), 3490(-NHstr.), ^{1}HNMR (300MHz,$CDCl_3$): δ 2.45(s,3H, -CH_3), 7.20-7.90(m,11H, ArH), 8.34(s,1H,-NH).

Compound 6c$_1$: M.F.$C_{24}H_{15}N_4OS_2Cl$, IR (KBr) ν_{max} in cm^{-1} 1390(-C-S), 3460(-NH str.), 1510-1630(ArC=C), ^{1}HNMR (300MHz,$CDCl_3$): δ 3.85(s,3H,-OCH_3),8.50(s,1H,-NH),7.30-7.90(m,11H,ArH).

Compound 6c$_2$: M.F.$C_{24}H_{15}N_4OS_2F$, IR (KBr) ν_{max} in cm^{-1} 1380(-C-S), 3450(-NH str.), 1430-1540(ArC=C), ^{1}HNMR (300MHz,$CDCl_3$): δ 3.50(s,3H,-OCH_3),8.24(s,1H,-NH),7.30-8.10(m,11H,ArH).

Compound 6d: M.F.$C_{24}H_{15}N_5O_3S_2$, IR (KBr) ν_{max} in cm^{-1} 1385(-C-S), 3440(-NH str.), 1435-1550(ArC=C), ^{1}HNMR (300MHz,$CDCl_3$): δ 4.10(s,3H,-OCH_3), 8.42(s,1H,-NH),7.10-8.20(m,11H,ArH).

Conclusions

During our synthesis, we have used microwave methodology for the synthesis of α-(2-diazo-6-substituted benzothiazolyl)-β-(p-substituted anilino) naphthalenes. Microwave- assisted organic synthesis have fascinated the chemist due to its useful ness with reduction of reaction time, environmental friendly methodology etc. Compound (**6c$_2$**) was effective against *E.Coli, Klebsiella*, compound (**5c$_2$**) was effective against *Pseudomonas aeruginosa* and compound (**6c$_1$**) was effective against *S. aureus.*

Acknowledgement

Authors are thankful to Head, Department of Pure and Applied Chemistry, M.D.S University, Ajmer for providing necessary laboratory facilities , to the Director, CDRI Lucknow for providing elemental analysis, spectral data and to Head , department of Microbiology, J.L.N. Medical College, Ajmer for providing antibacterial screening facility. Authors also express thanks to CSIR New Delhi India for providing JRF to one of them (P. Kriplani).

References

1. Makareeva E N, lozovskaya E L and Sapezhinskii I.I., *Biofizika,* 1998, **43(2),** 181.
2. Kulkarni K G and Fingerman M, *Gen. Pharmacol*., 1986, **17 (6)**, 671.
3. Singh S, Peshin P K and Krishnamurthy D, *Indian Vet. J*., 1994, **71(10)**, 983.
4. Bristol – Myres Co. Belg., 1976, **838**, 243.
5. Krishna R and Mayer L D, *Pharm. Pharmacol commun*., 1999, **5(8)**, 511.
6. Collier H O, *J Nature*, 1940, **146**, 232.
7. Ddhlbom R and Ekstramd T, *Arch. Intern. Pharmacodynamics*. 1966, **159**, 70.
8. Dave A M, Bhatt K N, Vandania N K and Trivedi P B, *J. Indian Chem. Soc.* 1998, **65 (5)**, 365.
9. Ansari A S and Banerji J C B, *J. Indian Chem.Soc*. 1998, **75**, 108.

10. Bradshaw T D, Stevens M F G and Westwell A D, Current Medicinal Chemistry. 2001, **8 (2)**, 203.
11. Waisser K, Dolezal M, Sidoeva E and Odlerova Z, *J. Drasta. Chem. Abstr*. 1989, **110**, 128063e.
12. Pathak V N, Yadav S S and Srivastava R C, *Indian Sci. Abstr*., 1994, **30**, 17.
13. Wells G, Bradshaw T D, Diana P, Seaton A, Shi D F, Westwell A D and Stevens M F G, *Bioorg.& Med. Chem. Lett*., 2000, **10**, 513
14. Amir M, Alamkhan S and Drabo S, *J. Indian Chem. Soc*., 2002, **79**, 280.
15. Pandey V K and Negi H S, *Indian J. Chem*. 2003, **42(B)**, 206.
16. Dhingra V, Bhatwadekar R and Pendse S, *Asian J. Chem*. 1993, **5**, 515.
17. Nuchter M, Ondruschka B, Bonrath W and Gum A, *Green Chem*., 2004, **6**, 128.
18. Wathey B, Tierney J, Lidstrom P and Westman J, *Drug Discovery Today,* 2002, **7**,373.
19. Alterman M and Halberg A, *J. Org. Chem*., 2000, **65**, 7984.
20. Katritzky AR and Singh S K, *J. Org. Chem*., 2002, **67**, 9077.
21. Gupta R R and Ojha K G, *Synth. Commun*. 1979, **9 (6)**, 457.
22. Gupta R R, Ojha K G and Kumar M, *J. Heterocycl. Chem*. 1980, **17**, 1325.