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Synthesis and Biological Evaluation of Schiff's Bases of Some New Benzothiazole Derivatives as Antimicrobial Agents

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Abstract: A series of Schiff's base of several benzothiazole derivatives have been synthesized. *para*-nitro benzothiazole carboxylic acid was synthesized by Jacobson synthesis[1]. It was then reduced to para amino benzothiazole carboxylic acid with ammonium chloride and iron metal. The resulting product was then condensed with various aromatic or heterocyclic aldehydes in the presence of concentrated sulphuric acid as a catalyst using ehanol as solvent to yield different Schiff bases. The structure of synthesized compounds was characterized by IR, ^{1}H NMR and Mass spectral data. Purity of the individual compound was confirmed by TLC. Then, each product was evaluated for their in vitro growth inhibiting activity against several microbes. All the compounds have shown significant antibacterial activity with the reference standard Ampicillin and Ketoconazole

Key Words: *Benzothiazole, Schiff's bases, Jacobson synthesis, antimicrobial activity.*

Introduction:

Development in biological evaluation of heterocyclic molecules has undergone manifold changes and the advancement in molecular biology has eased the design of new molecules based on their mechanism of action. Proposed work is based upon the development of newer analogues of benzothiazoles followed by their biological evaluation. Benzothiazoles have been reported with good biological activities ranging from antiparasitic[2], anti-inflammatory[3], antitumour[4], p56lck inhibition[5], immunosupressive[6,7] anti- tubercular activity[8] etc. With this background, we thought to develop newer analogues of the nucleus-benzothiazole expecting better biological activity owing to rationale in design of the target molecules. Synthesis of the basic nucleus is well established and the proposed derivatives can be synthesized based upon the literature available about the reaction involved or the new methods developed as per the requirement. Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number of 2-aminobenzothiazoles were intensively studied as central muscle relaxants. Since then medicinal chemists have not taken active interest in this chemical family. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole[9] was discovered. Riluzole (6-trifluoromethoxy-2-benzothiazolamine, PK-26124, RP-25279, Rilutek) was found to interfere with glutamate neuro transmission in biochemical, electro- physiological and behavioral experiments. After that benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity. Although they have been known from long ago to be biologically active[10-12], their varied biological features are still of great scientific interest. Benzothiazoles show antitumor activity, especially the phenyl-substituted benzothiazoles[13-15], while

condensed pyrimido benzothiazoles and benzothiazolo quinazolines exert antiviral activity[16]. Recently, Racane *et al.*[17] have described the synthesis of bis-substituted amidino benzothiazoles as potential anti HIV agents. Substituted 6-nitro- and 6-aminobenzothiazoles[18] show antimicrobial activity. We have given below a brief account of various alterations conducted on benzothiazole ring and their associated biological activities.

Material and methods

General experimental:

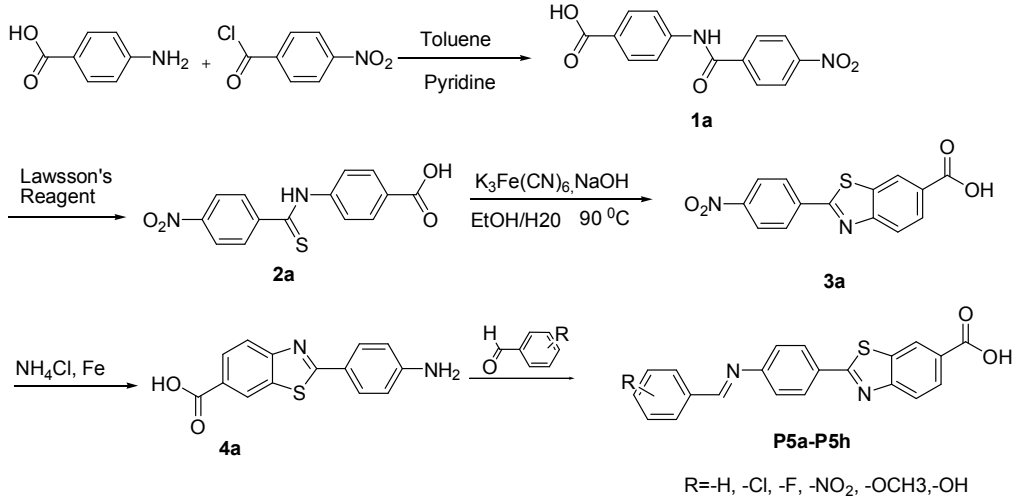
All reactions were carried out under prescribed laboratory conditions, All reactions requiring anhydrous conditions, were conducted inflame dried apparatus. The solvents and reagents used in the synthetic work were of laboratory reagent grade and were purified by distillation and crystallization technique, wherever necessary and their melting points were checked with the available literature. Melting points of synthesized compounds were determined by melting point apparatus. NMR spectra were recorded on BRUKER-spectrospin 400MHz spectrometer in $CDCl_3$, Tetra methyl silane (TMS; δ = 0.00 ppm) served as internal standards for ^1H NMR. The corresponding residual non-deuterated solvent signal ($CDCl_3$: δ = 77.00 ppm) was used as internal standards for ^{13}C NMR. IR spectra were measured using a JASCO FT/IR-410 spectrometer, and Perkin-Elmer FT/IR Spectrum BX, GX. Mass spectra were measured with Micromass Q-Tof (ESI-HRMS). Column chromatography was conducted on Silica gel 230-400 mesh (Merck) and preparative thin-layer chromatography was carried out using SILICA GEL GF-254. Spectras were obtained from IISC Bangalore.

Procedure:

1. Synthesis of N-(4-Carboxy phenyl)-4- nitro phenyl benzamide (1a) : To a solution of Para amino benzoic acid (11.5 g, 62.6 mmol) in dichloro methane (100 ml) was added pyridine (40 ml) followed by addition of mixture of *para*-nitro benzoyl chloride (8 ml, 68.9 mmol) in toluene (30 ml). Then, the mixture was heated at reflux for 5 hrs, after this toluene was removed under vacuum, 100 ml water was added then product was extracted with dichloromethane (3×100ml) and dichloromethane layer was rinsed with 1M HCl (200 ml) followed by washing with 20% 100ml aqueous solution of sodium carbonate. The organic layer was then dried over sodium sulphate (Na_2SO_4) and concentrated to produce benzamide derivative **1a** as a purple crystalline solid. The compound was recrystallised from dichloromethane and hexane. Yield = 86 %.

2. Synthesis of N-(4- Carboxy phenyl)-4-nitrophenyl thio benzamide (2a): To a solution compound **1a** (1.0 g) in 40 ml dry toluene was added lawesson's reagent (0.6 molar eq). The mixture was heated under an atmosphere of nitrogen at reflux for 2 hrs, after which it was concentrated and purified by column chromatography to give yellow crystals. Yield 85 %

Chemistry: Scheme I

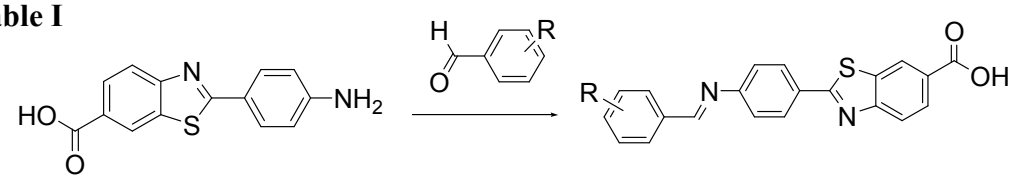


3. Synthesis of 6-carboxy-2-(P-nitrophenyl) benzothiazole (3a): To the compound **2a** (0.1g) in 0.5 ml ethanol was added 1.5 M 7 ml NaOH. The solution was cooled in an ice-bath and freshly prepared aqueous potassium ferricyanide (2-3 molar equivalents) was added. The reaction mixture was stirred at room temperature for 24 hr; then, the mixture was neutralized with 1M HCl and extracted with ethyl acetate (3×75ml). The organic layer was dried over Na_2SO_4. Then organic layer was removed in vacuum and the residue is purified by recrystallisation from ethanol or ethyl acetate: hexanes to give white needles. Yield 79%.

4. Synthesis of 6-carboxy-2-(*p*-aminophenyl) benzothiazole (4a): To 6-carboxy-2-(*p*-nitrophenyl)-benzothiazole **3a** (5g, 25 mmol) in 20ml ethanol : 10ml water was added iron powder (4.1g, 75 mmol) (325 mesh) and ammonium chloride (0.7g, 12.5 mmol). The reaction was stirred at 85 ^oC for one hr, cooled to room temperature, and filtered through celite. The filter cake was then washed with 100ml toluene and the filtrate and filtrate was washed with water (2 ×100 ml). The toluene layer was dried over $MgSO_4$ or Na_2SO_4 and concentrated to a solid that was triturated with hexane (25 ml). The solid was separated by filtration. Yield = 86% .

5. General procedure for the synthesis of Schiff bases of benzothiazole (P5a-P5h): 6-carboxy-2-(P-aminophenyl) benzothiazole **4a** (0.025 moles) was dissolved in 20 ml ethanol, followed by dropwise addition of
substituted aromatic aldehyde (0.030 moles) dissolved in 10ml ethanol at room temperature. The reaction mixture was stirred for 24 Hr at room temperature. Then, ethanol was evaporated and product was recrystallized from ethyl acetate: hexane mixture.
Table I indicates yield and M.P. of various compounds synthesized

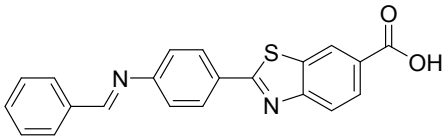
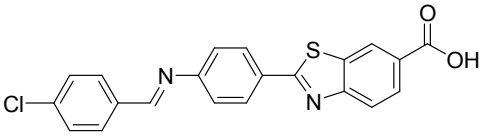
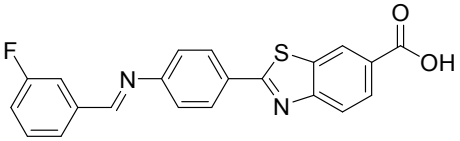
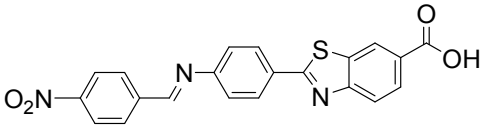
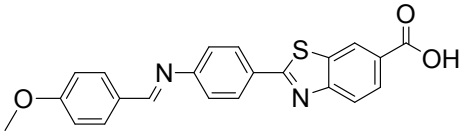
Table I

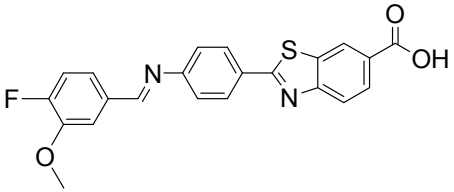
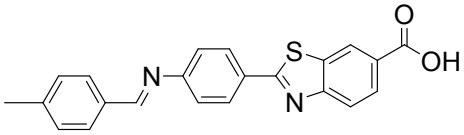
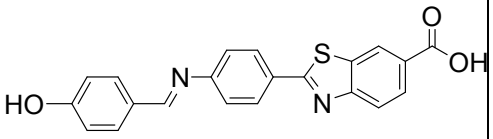


R=-H, -Cl, -F, -NO_2, -OCH3,-OH

Sr No.	Code	-R	Physical nature	% Yield	M.P.
1	P5a	-H	Light orange crystals	71	230-232
2	P5b	*para*-Cl	Yellow-orange crystals	67	245-258
3	P5c	*meta*-F	Light orange crystals	70	260-263
4	P5d	*para*-NO_2	Orange crystals	68	235-238
5	P5e	*para*-OCH_3	Yellow crystals	65	285-288
6	P5f	4-F, 3-OCH_3	Yellow-white crystals	75	305-307
7	P5g	*para*-CH_3	Yellow-white crystals	74	265-268
8	P5h	*para*-OH	Yellow crystals	78	250-252

Table 2: Spectral data of synthesized compounds.

SR NO.	code	Structure	IR	*HR-ESIMS*	NMR ^{1}H and ^{13} C
01	P5a		1745(C=O), 1635(C=N), 1710(C=C)	Calculated for $C_{21}H_{14}N_2O_2S$ (358.41306) found 358.40292	**^{1}H:** δ 7.4-8.6 (m, 12H, aromatic) **^{13}C:** δ 120, 121.7, 123.2, 125.6, 128.5, 128.7, 128.9, 129.6,132.5, 135.7, 135.8, 153.9, 160, 166.6, 168, 182.
02	P5b		1751(C=O), 1638(C=N), 1714(C=C)	Calculated for $C_{21}H_{13}ClN_2O_2S$ (392.85812) found 392.03863.	**^{1}H:** δ 7.47-8.6 (m, 11H, aromatic) **^{13}C:** δ 120.3, 121.7, 123.2, 125.6, 128.5, 128.7, 129, 130, 134.7, 135.8, 137.9, 153.9, 160.4, 166.6, 168, 182.6.
03	P5c		1745(C=O), 1636(C=N), 1715(C=C)	Calculated for $C_{21}H_{13}FN_2O_2S$ (376.40352) found 376. 4038.	**^{1}H:** δ 7.31-8.5 (m, 11H, aromatic) **^{13}C:** δ 116.8, 117.6, 120.1, 121.2, 123.5, 125.7, 126.5, 128.5, 128.8, 130.2, 135.8, 138.5, 153.4, 160.0, 162.3, 165.6, 166, 168.0, 186.1.
04	P5d		1749(C=O), 1628(C=N), 1713(C=C)	Calculated for $C_{21}H_{13}N_3O_4S$ (403.41062) found 403. 40668.	**^{1}H:** δ 7.62-8.6 (m, 11H, aromatic) **^{13}C:** δ 120.6, 121.3, 123.3, 125.6, 128.1, 128.7, 128.9, 130.1, 135.8, 143.5, 150.0, 153.3, 160.0, 163.3, 166.6, 168., 187.6.
05	P5e		1742(C=O), 1630(C=N), 1712(C=C)	Calculated for $C_{22}H_{16}N_2O_3S$ (388.43904) found 388.4123.	**^{1}H:** δ 3.5 (s, 3H, -CH3) δ 7.04-8.5 (m, 11H, aromatic) **^{13}C:** δ 56, 114.6, 120.3, 121.4, 123.2, 125.1, 128.7, 128.9, 131.2, 135.8, 143.5, 153.3, 160.0, 163.2, 166.3, 168., 214.7.

06	P5f		1747(C=O), 1632(C=N), 1715(C=C)	Calculated for $C_{22}H_{15}FN_2O_3S$ (406.4295) found 406.07874	**^{1}H:** δ 3.91(s, 3H, -CH3) δ 7.3-8.6 (m, 10H, aromatic) **^{13}C:** δ 56.8, 112.6, 116.0, 116.2, 121.2, 123.3, 124.4, 125.7, 128.2, 133.5, 135.8, 151.0, 153.3, 156.3, 159.2, 163.5, 166.6., 168.0.
07	P5g		1745(C=O), 1630(C=N), 1712(C=C)	Calculated for $C_{22}H_{15}FN_2O_3S$ (406.4295) found 406.07874	**^{1}H:** δ 2.14(s, 3H, -CH3), δ 6.9-10.4 (m, 11H, aromatic). **^{13}C:** δ 21.1, 120.0, 121.3, 125.0, 128.0, 128.4, 129.5, 130.1, 143.6, 156.3, 161.1, 162.4, 163.0, 167.7
08	P5h		1748(C=O), 1630(C=N), 1716(C=C) 3330(-OH)	Calculated for $C_{21}H_{14}N_2O_3S$ (374.41246) found 374.40322	**^{1}H:** δ 5.0(s, 1H, -OH) δ 6.8-8.5 (m, 11H, aromatic) **^{13}C:** δ 115.7, 120.1, 121.2, 121.2, 123.2, 125.6, 128.1, 128.9, 131.4, 135.8, 153.9, 159.3, 162.3, 163.3, 166.0, 168.0, 186.1

Biological Evaluation:

In vitro antimicrobial study: Benzothiazoles show a wide spectrum of chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles.

Synthesized compounds were screened for their *in-vitro* antibacterial activity against *P.aeruginosa, E.coli, S.aureus, B.subtilis* at 100 µg/ml and *in-vitro* antifungal activity against *Candida albicans and Aspergillus niger* activities at 100 µg/ml concentration. Standard antibacterial ampicillin and standard antifungal ketoconazole were also screened under similar conditions for comparison. DMSO was used as a solvent control. The culture media was nutrient agar and method employed was cup plate method[19]. All the compounds showed varying degree of antibacterial activity. All the compounds were far less active than the standard drug taken.

Results and discussion:

Amongst the synthesized compounds several compounds exhibit antifungal and anti-bacterial activity. Compounds **P5c, P5e, P5f, P5g, P5h** have shown significant antibacterial activity against *S .aureus, B. Subtilis*. Compound **P5g** was most significant against *E.coli, S .aureus* and *B. Subtilis.* We were pleased to observe significant activity of compound **P5e, P5f** and **P5g** against *Candida albicans* and *Aspergillus niger*. While other compound shown less significant activity against bacteria and fungi.

All the compounds were confirmed by the IR, NMR and Mass spectroscopy.

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Table 3: Results of Anti-bacterial activity

Sl.No	code	Diameter of zone of inhibition (in mm)			
		P.aeruginosa	***E.coli***	***S.aureus***	***B.subtilis***
01	**P5a**	09	09	12	11
02	**P5b**	10	10	11	10
03	**P5c**	12	10	14	13
04	**P5d**	14	11	15	12
05	**P5e**	16	11	16	14
06	**P5f**	18	14	16	14
07	**P5g**	17	16	18	18
08	**P5h**	15	12	11	14
09	**Ampicillin**	21	20	22	20
10	**DMSO**	-	-	-	-

Table 4: Results of Anti-fungal activity

Sl.No	Code	Diameter of zone of inhibition (in mm)	
		Candida albicans	***Aspergillus niger***
01	**P5a**	07	07
02	**P5b**	08	07
03	**P5c**	07	08
04	**P5d**	10	09
05	**P5e**	12	12
06	**P5f**	12	13
07	**P5g**	13	14
08	**P5h**	09	11
09	**Ketoconazole**	16	18
10	**DMSO**	-	-

References

1. Hntchinson Jan; Mei-sze Chua; Browne, H. L.; Stevans, F. G., J.Med.Chem. 2001, 44, 1446-1455.
2. Alaimo, R. J.; Pelosi, S. S., J. Med. Chem. 1974, 17, 775-776.
3. Singh, S. P. Vaidya, R. K. Ind. J. of Chem. 1986, 25, 288-291.
4. Schnur, R. C.; Anton, F. J.; Kajiji, F. S.; Pollack, V. A., J.Med.Chem. 1991, 34, 914-918.
5. Das, J.; Joel, C.B.; John.W., United States Patent. 2002, US 2002/0123484
6. Paget. Kisner.; Stone.; Dilong. J.Med.Chem. 1960, 10, 1016-1018.
7. Hugershoff, A., Ber. 1901, 34, 3130.
8. Leon, K., J.Am.Chem.Soc. 1951,73, 4007-4010.
9. Bryson, M., Fulton, B. and Benfield, P., Drugs, 1996, 52, 549.
10. Lacova, M., Chovancova, J., Hyblova, O. and Varkonda, S., Chem. Pap., 1991, 45, 411.
11. Chulak, I., Sutorius, V. and Sekerka, V., Chem. Pap., 1990, 44, 131.
12. Papenfuhs, T., Ger. Offen. De., 1987, 3, 528.
13. Bradshaw, T.D., Bibby, M. C., Double, J.A., Fichtner, I., Cooper, P.A.,Alley, M.C., Donohue, S., Stinson, S.F., Tomaszewjski, J.E., Sausville, E.A. and Stevens, M.F.G., Mol. Cancer. Therapeutics, 2002, 1, 239.
14. Bradshaw, T.D., Chua, M.S., Browne, H. L., Trapani, V., Sausville, E. A. and Stevens, M. F.G., Brit. J. Cancer., 2002, 86, 1348.
15. Hutchinson, I., Jennings, S.A., Vishnuvajjala, B. R., Westwell, A.D. and Stevens, M.F.G., J. Med. Chem., 2002, 45, 744.
16. El-Sherbeny, M.A., Arzeneim-Forsch., 2000, 50, 843.
17. Racane, L., Tralic-Kulenovic, V., Fiser-Jakic, L., Boykin, D.W. and Karminski-Zamola, G., Heterocycles, 2001, 55, 2085.
18. Mahmood-ul-Hasan, Chohan, Z.H. and Supuran, C.T., Main Group Met. Chem., 2002, 25, 291.
19. R. Cruichshank, J.P.Duguid, B.P.Marmoin and H.A.Swan, The Pracice of Medical Microbiology, Vol 2, 12th Eddition, Churchill livingstone, London (1975) p.190.

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