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SYNTHESIS OF N-SUBSTITUTED BENZOTHIAZOLE-6-SULFONAMIDE DERIVATIVES FOR POTENT ANTIBACTERIAL ACTIVITY

Alok singh thakur*[1], A.K. Jha[1]
Shri Shankaracharya Institute of Pharmaceutical Science, Bhilai, Chhattisgarh, India.
Email: alokthakur1985@yahoo.com

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Abstract

All the newly synthesized benzothiazole derivatives have shown considerable antibacterial activity. Here the comparison between urea and thiourea molecule have been attempted to contributing for the activity. After the synthesis and its evaluation it is found that the thiourea moiety **(3f-3j)** better compliment the activity of sulfonamide present along with the benzothiazole molecule. It is also concluded after the study the presence of chloride **(3c-3h)** give better activity as compare to nitro, methoxy like functional atom.

Keywords: benzothiazole, thiourea, sulfonamide, antibacterial.

Introduction

Benzothiazole heterocyclic ring is a potent lead for the various pharmacological activities. Since the numerous derivatives of such lead have been established for the treatment of various diseases still there is further challenges have been remain to improvise for launching newer derivatives. Different substitutions and combinations on benzothiazole moiety on different position are found to posses different activity, like anticancer[1], anticonvulsant[2], anti-inflammatory[3], antimicrobial[4], diuretic activity[5], anthelmintic activity[6] etc. are inspired to prepare new molecular combination with the benzothiazole. In the present effort it was trying to fuse the sulfonamide moiety with the phenyl ring of benzothiazole heterocyclic ring. For such purpose the simple synthetic procedure are acknowledged for the idea of synthesis.

The combination of the sulfonamide moiety responsible for the generation of very potent lead and the other combination along with the urea of thiourea pharmacophore again provide the idea for establishing this moiety as

potential lead for the various pharmacological activities. More over the urea and thiourea are molecule with explore the scope for the fusion of other functional moiety to improve the activity.

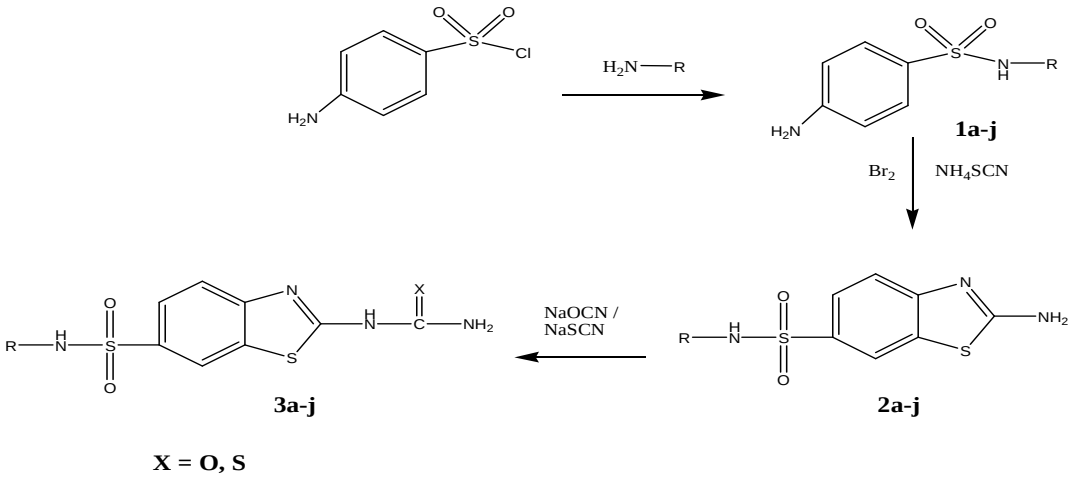

Table-1: Physicochemical properties of compound (3a-j).

Compound	R	X	Yield (%) Approx	M.P. (^{0}c)	Elemental analysis (%N)
3a	C_6H_5-	O	86	186	16.42
3b	4-NO_2-C_6H_4-	O	76	188	17.21
3c	4-Cl-C_6H_4-	O	74	174	14.20
3d	4-CH_3-C_6H_4-	O	78	162	14.98
3e	4-CH_3O-C_6H_4-	O	81	184	14.31
3f	C_6H_5-	S	84	172	14.78
3g	4-NO_2-C_6H_4-	S	80	182	16.96
3h	4-Cl-C_6H_4-	S	72	178	14.36
3i	4-CH_3-C_6H_4-	S	75	168	14.88
3j	4-CH_3O-C_6H_4-	S	78	176	14.12

Experimental

Melting points were determined with open capillary and are uncorrected. Proton NMR spectra were taken in $CDCl_3$ and recorded at 300 MHz in Bruker DRX-300. Chemical shifts (δ) were measured in ppm with respect to TMS. FTIR

spectra recorded on instrument simadzu 2100 S and Perkin Elmer BX. MS were obtained on a JEO JMC-300 instrument. Elemental analysis performed on Elementar Vario EL III.

General procedure for the preparation of following:

***4-amino-N-substituted benzenesulfonamide* (1a-j)[7]**

Substitute amine (0.1 mol) was taken in a 250-mL conical flask and sodium hydroxide solution (2N) was added slowly till the entire solid get dissolved and the mixture become distinctly alkaline. The reaction mixture was stirred on a magnetic stirrer and the temperature was maintained at 70 ^{0}C using hot water-bath. Para amino benzenesulphonylchloride (0.15 moles) was added in small portions with constant stirring and sodium hydroxide (2N) was added time-to-time to keep the reaction mixture alkaline. The reaction was continued until a clear homogeneous solution resulted and thin layer chromatography showed the reaction was complete. After the reaction was over, it was allowed to cool to room temperature and filtered to separate undissolved solid matter, if any. The filtrate was acidified with concentrated hydrochloric acid and saturated with sodium chloride. The product was extracted with three 50 mL portions of ethyl acetate. Ethyl acetate layer was washed with brine solution (15 mL) and dried overnight over anhydrous sodium sulphate. The solvent was distilled off to get the desired product. Product was purified by recrystallization with suitable solvent.

***2-amino-N-substituted benzothiazole-6-sulfonamide* (2a-j)**

Equimolar quantities of substituted aniline (0.02mol) and ammonium thiocyanate (0.02mol) were dissolved in ethanol containing 2ml of Conc. Hydrochloric acid. To this bromine in glacial acetic acid (2.7ml, 0.05mol) was added and the reaction mixture was refluxed for 1hr. Then, it was cooled in ice-water mixture. The precipitate obtained, strained well, filtered washed with cold water and dried. Products were crystallize with ethanol.

***2-urea/thiourea-N-substituted benzothiazole-6-sulfonamide* (3a-j)[8]**

To the solution of sodium cyanate/ thiocyanate (0.01 mol) in minimum quantity of water, glacial acetic acid (5 mL) was added. This solution was heated with 2-amino-N-substituted benzothiazole-6-sulfonamide (2a-j) previously dissolved in alcohol, till the contents of mixture become turbid and volume remained half of the original volume. The

content was poured on crushed ice. The solid obtained was filtered off and dried. The product become purified by crystallization with suitable solvent.

Table-2: Spectroscopical study of compounds (3a-3j).

Compound No.	FTIR (KBr, cm^{-1})	1H-NMR (DMSO-d6) δ (ppm)	Mass (EI) m/z
3a	3315 (NH), 3090 (CH–Ar), 1600 (C=O), 1462 (C=N), 1271 (C–N),	4.48 (s, 1H, $NHSO_2$) , 6.28 (m, 3H, NHCONH), 6.46–7.06 (m, 5H, Ar–H), 8.29-8.55 (m, 3H, Ar–H).	**348**
3b	3365 (NH), 2924 (CH–Ar), 1631 (C=O), 1436 (C=N), 1245 (C–N), 1405 (C–NO_2).	4.04 (s, 1H, $NHSO_2$) , 6.02 (m, 3H, NHCONH), 6.76–7.76 (m, 4H, Ar–H), 8.34-8.11 (m, 3H, Ar–H).	**394**
3c	3216 (NH), 2994 (CH–Ar), 1612 (C=O), 1478 (C=N), 1214 (C–N), 814 (C–Cl),	4.21 (s, 1H, $NHSO_2$) , 6.03 (m, 3H, NHCONH), 6.38–7.12 (m, 4H, Ar–H), 8.20-8.75 (m, 3H, Ar–H).	**383**
3d	3314 (NH), 2910 (CH–Ar), 1647 (C=O), 1432 (C=N), 1222 (C–N), 2924 (CH–Aliph.)	4.27 (s, 1H, $NHSO_2$) , 6.16 (m, 3H, NHCONH), 6.32–6.74 (m, 4H, Ar–H), 8.36-8.68 (m, 3H, Ar–H), 2.32 (s, 3H, CH_3).	**363**
3e	3365 (NH), 2924 (CH–Ar), 1631 (C=O), 1436 (C=N), 1245 (C–N), 2919 (CH–Aliph.).	4.51 (s, 1H, $NHSO_2$) , 6.25 (m, 3H, NHCONH), 6.38–6.62 (m, 4H, Ar–H), 8.15-8.52 (m, 3H, Ar–H), 3.41 (s, 3H, OCH_3).	**378**
3f	3345 (NH), 3040 (CH–Ar), 1477 (C=N),1263 (C–N), 719 (C–S–C).	4.01 (s, 1H, $NHSO_2$) , 2.02- 3.89 (m, 3H, NHCONH), 6.36–6.52 (m, 5H, Ar–H), 8.26-8.65 (m, 3H, Ar–H).	**365**
3g	3293 (NH), 3011 (CH–Ar), 1415 (C=N),1284 (C–N), 708 (C–S–C), 1405 (C–NO_2).	4.28 (s, 1H, $NHSO_2$) , 2.12-4.27 (m, 3H, NHCONH), 6.27–6.86 (m, 4H, Ar–H), 8.13-8.31 (m, 3H, Ar–H).	**409**
3h	3362 (NH), 3042 (CH–Ar), 1420 (C=N),1286 (C–N), 771 (C–S–C), 814 (C–Cl),	4.29 (s, 1H, $NHSO_2$) , 2.08-4.05 (m, 3H, NHCONH), 6.08–6.88 (m, 4H, Ar–H), 8.09-8.54 (m, 3H, Ar–H).	**398**
3i	3277 (NH), 3031 (CH–Ar), 1424 (C=N),1252 (C–N), 765 (C–S–C), 2924 (CH–Aliph.)	4.54 (s, 1H, $NHSO_2$) , 2.36-3.98 (m, 3H, NHCONH), 6.42–6.79 (m, 4H, Ar–H), 8.25-8.75 (m, 3H, Ar–H), 2.47 (s, 3H, CH_3).	**380**
3j	3274 (NH), 3033 (CH–Ar), 1427 (C=N),1204 (C–N), 708 (C–S–C), 2919 (CH–Aliph.).	4.61 (s, 1H, $NHSO_2$) , 2.58-4.30 (m, 3H, NHCONH), 6.18–6.25 (m, 4H, Ar–H), 8.41-8.82 (m, 3H, Ar–H), 3.31 (s, 3H, OCH_3).	**395**

Antibacterial Activity

The compounds were evaluated for the antibacterial activity by the disc diffusion method by using DMSO as solvent. The nutrient agar culture media was used as for in vitro evaluation after incubation at 37^0C for 24 hrs. the zone of inhibition were measured in mm. synthesized compounds were evaluated against gram positive and gram negative bacterial strains such as *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aureginosa.* The activity was compared with known antibiotic ciprofloxacin. The data are compiled in the table as follows.

Table-3: Antibacterial activity of compounds 3a-j.

Compounds	Inhibition of zone diameter in mm (at 150 µg concentration)			
	B. subtilis	*B. pumillis*	*E. coli*	*P. aeruginosa*
3a	12	15	16	14
3b	17	18	20	15
3c	15	17	18	16
3d	13	12	14	12
3e	15	14	15	15
3f	13	16	20	18
3g	18	19	18	20
3h	21	20	18	19
3i	17	18	16	18
3j	17	17	18	18
Ciprofloxacin	24	24	23	24
Control	-	-	-	-

Result and Discussion

All the synthesized compounds are active against the bacterial strain. The activity might be enhancing due to presence of sulfonamide group along with the benzothiazole and urea moiety. According to the evaluation, thiourea moiety (**3f-3j**) contributing for considerable activity as compare to the molecule having urea in its structure. Further the presence of different electronegative atoms along with the sulfonamide moiety shown the variation in activity, all this suggest the importance of presence of different functional atoms. More over the presence of chloride moiety **(3c and 3h)** give the more satisfactory result as compare to other functional group.

Conclusion

After the thorough evaluation it is found that the lead molecule benzothiazole can be potentiate by the addition of some other functional moiety as the sulfonamide here along with urea and thiourea. Further the synthesized molecules have great potential for the further study and evaluation of different activity in future.

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Corresponding Author:

Alok Singh Thakur*,

Shri Shankaracharya Institute of Pharmaceutical Sciences,

Bhilai, Chhattisgarh,

India, 490020.

Email: *alokthakur1985@yahoo.com*