INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME 1, 3-BENZTHIAZOLES DERIVATIVES

Deshmukh R*[1], Thakur AS[1], Jha AK[1] and Deshmukh R[2]

[1]Shri Shankaracharya Institute of Pharmaceutical Science, Bhilai, Chhattisgarh, India
[2]Department of Biotechnology, IIT Guwahati, Assam, India.

*Corresponding Author: ravitasd@gmail.com

ABSTRACT

The enhancement of bacterial resistance of pathogens to currently available antibiotics constitutes a serious public health threat. So, there is constant need of new antibacterial agent having novel mechanism to act against the harmful pathogens. The present study deals with antimicrobial evaluation of some substituted benzothiazole were synthesized by reacting substituted aniline with potassium thiocyanide it forms N-substituted-benzothiazol-2-yl) amines this upon reacting with DMF, CS_2 it forms N-Substituted dimethyl benzo[d]thiazol-2-yl) carbonodithioimidate finally on reacting with o-phenylenediamine it forms N-Substituted (benzo[d]thiazol-2-yl)-1H-benzo[d]imidazol-2-amine. All the synthesized compounds were screened for antibacterial activity against the representative panel of Gram-positive and Gram-negative bacteria strains. The biological screening identified compounds 3c and 3h as the most active ones showing an interesting antibacterial activity. It was also found that compounds 3c, 3e, 3f, 3h showed very good antibacterial activity whereas the other entire compound showed mild to moderate antibacterial activity as compared to standard drug.

Keywords: Antibacterial, Gram negative micro-organism, Gram positive micro-organism.

INTRODUCTION

The enhancement of bacterial resistance of pathogens to currently available antibiotics constitutes a serious public health threat. So, intensive efforts are underway worldwide to develop new antimicrobial agents[1-4]. On the basis of exhaustive literature review it has been found that benzothiazole nucleolus posses good potential to act as antibacterial agent[5-7]. Compounds containing substituted benzothiazole moiety have shown a variety of useful pharmacological actions and many of these have gained very wide importance in research[8-11].

So in present study, some substituted benzothiazole were synthesized and subjected to antibacterial evaluation. Also the benzothiazole derivatives represent an extensive group of heterocyclic compounds, several of which have already found application in the medical sphere as medicines[12]. Substituted imidazole are the heterocyclic system that have been found to exhibit diverse biological activities such as antibacterial[13-15], antifungal[16,17], anti-inflammatory[18], analgesic[19], and anticancer[20,21],

activity. Benzothiazoles are also found to be antimicrobial[22], antifungal[23,24], anticancer[25,26], and anti-inflammatory[27,28] activity. These biological data prompted us to synthesize some new benzothiazole derivatives containing imidazole ring.

In the present study we reported here the synthesis and antimicrobial activity of several N-Substituted (benzo[d]thiazol-2-yl)-1H-benzo[d]imidazol-2-amine. Incorporation of imidazole moiety into the second position of the benzothiazole ring may result in compounds having better antimicrobial activity.

Experimental Studies

Method and Materials

The melting points were determined in open capillary tubes in a Hicon melting point apparatus. The elemental analyses (C, H, N) of all compounds were performed on the CHNS Elimentar (Analysen systime, GmbH) Germany Vario EL III. All the Fourier transform infra red (FTIR) spectra were recorded in KBr pellets on a Jasco FT/IR 410 spectrometer. The 1H NMR spectra were taken on a Bruker 400 Ultra shieldTM (400 MHz) NMR spectrometer. Chemical shifts (d) are expressed in parts per million relative to tetramethylsilane (TMS) as an internal standard. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on silica gel G (Merck) coated plates by using toluene: ethylacetate: formic acid (5:4:1) as solvent system. Iodine chamber and UV lamp were used for the visualization of TLC spots.

Synthesis

General Procedure for Synthesis of N-substituted-benzothiazol-2-yl)amines (I a-h)

A mixture of substituted aniline (0.01 mol) and potassium thiocyanate (0.01 mol) in glacial acetic acid was cooled and stirred. To this solution, bromine (0.01 mol) was added drop wise at such a rate to keep the reaction temperature below 10 °C throughout the addition. Stirring was continued for additional 3 h and the separated hydrochloride salt was filtered, washed with acetic acid and dried. It was dissolved in hot water and neutralized with aqueous ammonia solution (25 %). The precipitate obtained was filtered, washed with water, dried and recrystallized to afford the N-substituted-1,3-benzothiazol-2-amine.

General Procedure for Synthesis of N-Substituted dimethyl benzo[d]thiazol-2-yl) carbonodithioimidate (II a-h)

To stirred cold solution of I (0.05 mol) in DMF (25cm3), 20 M-NaOH (5 cm3), carbon disulfide (8 cm3), and methyl iodide (0.05 mol) were added and the stirring was continued for additional 4 h. The mixture was poured into cold water and the formed solid was crystallized from benzene.

General Procedure for Synthesis of N-Substituted (benzo[d]thiazol-2-yl)-1H-benzo[d]imidazol-2-amine (III a-h)

A mixture of II (0.04 mol) and o-phenylenediamine (0.04 mol) in DMF (30 cm3) was refluxed for 8h. After cooling, the formed solid was crystallized from ethanol.

Spectral Analysis

***N-(benzo[d]thiazol-2-yl)-1H-benzo[d] imidazol-2-amine* (3a)**

IR($CDCL_3$)- NH (3339), Ar=C-H(3020), C=N(1610), CN(1453), CS(1259), ^{1}H NMR (DMSO): 6.29-6.54 (8H of Ar-H), 3.5, 4.0 (2H, NH, exchangeable).

***N-(7-chlorobenzo[d]thiazol-2-yl)-1H-benzo[d] imidazol-2-amine* (3b)**

IR NH(3325), 3034(Ar=C-H) 1597(C=N),1465(C-N), 1255(C-S),916, 780(C-Cl), ^{1}H NMR (DMSO): 5.93-6.17 (8H of Ar-H), 4.0, 5.0 (2H, NH, exchangeable).

***N-(6-chlorobenzo[d]thiazol-2-yl)-1H-benzo[d] imidazol-2-amine* (3c)**

IR- NH(3330), 3036(Ar=CH), 1602(C=N),1470(C-N), 1262(C-S), 920, 785(C-Cl), ^{1}H NMR (DMSO): 6.83.-7.20 (8H of Ar-H), 4.5, 5.0 (2H, NH, exchangeable).

***2-(1H-benzo[d]imidazol-2-ylamino)benzo[d] thiazol-6-ol* (3d)**

IR- NH (3339), Ar=C-H(3020), C=N(1610), CN(1453), CS(1259), O-H Stretching(3466), ^{1}H NMR (DMSO): 7.10-7.42 (8H of Ar-H), 2.0, 4.0 (2H, NH, exchangeable).

***N-(6-nitrobenzo[d]thiazol-2-yl)-1H-benzo[d] imidazol-2-amine* (3e)**

IR- NH(3338), 3033(Ar=C-H) 1617(C=N), 1480(C-N),1266(C-S), 1359(C-NO_2), ^{1}H NMR (DMSO): 7.22-7.90 (8H of Ar-H), 3.0, 4.0 (2H, NH, exchangeable).

***N2-(1H-benzo[d]imidazol-2-yl)benzo[d] thiazole-2,6-diamine* (3f)**

IR- NH (3339), Ar=C-H(3020), C=N(1610), CN(1453), CS(1259) ,N-H Stretching of amine(3375) , ^{1}H NMR (DMSO): 6.84-6.52 (8H of Ar-H), 3.0, 4.5(2H, NH, exchangeable).

***N-(6-methylbenzo[d]thiazol-2-yl)-1H-benzo [d]imidazol-2-amine* (3g)**

IR- NH (3339), Ar=C-H(3020), C=N(1610), CN(1453), CS(1259), (2839.22) C-H Stretching in CH_3, ^{1}H NMR (DMSO): 6.28-6.95 (8H of Ar-H), 3.3, 4.6 (2H, NH, exchangeable).

***N-(6-methoxybenzo[d]thiazol-2-yl)-1H-benzo [d]imidazol-2-amine* (3h)**

IR- NH(3320), 3034(Ar=C-H) 2951(C-CH_3), 1625 (C=N), 1470(C-N), 1260 (C-S), 1291 (C-O), ^{1}H NMR (DMSO): 6.39-6.72 (8H of Ar-H), 3.0, 5.0 (2H, NH, exchangeable).

Antibacterial Activity

All the newly synthesized compounds (**3a-h**) were evaluated for *in vitro* antibacterial activity against gram positive and gram negative bacterial strains such as *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aureginosa* at concentration 100 µg/mL by disc diffusion method[29] by using DMSO as solvent control and nutrient agar was employed as culture media. After 24 h of incubation at 37°C, the zone of inhibition was measured in mm. The activity was compared with known antibiotic ciprofloxacin and the data was represented in the Table 2.

RESULTS AND DISCUSSION

The results of antimicrobial evaluation suggest that all the compounds have very good potential to act as antibacterial agents. Compound 3c, 3e 3f, 3h showed very good activities against the entire test microorganism. All synthesized compounds are more active against gram positive microorganism as compared to gram negative one. Compound having substitution in the p-position **(3c)** are more active than m-substitution **(3b).** Compound 3c and 3h has highest antibacterial activity against all the test microorganisms. The zone inhibition is described in Table 2.

Table 1: Characterization of Compounds

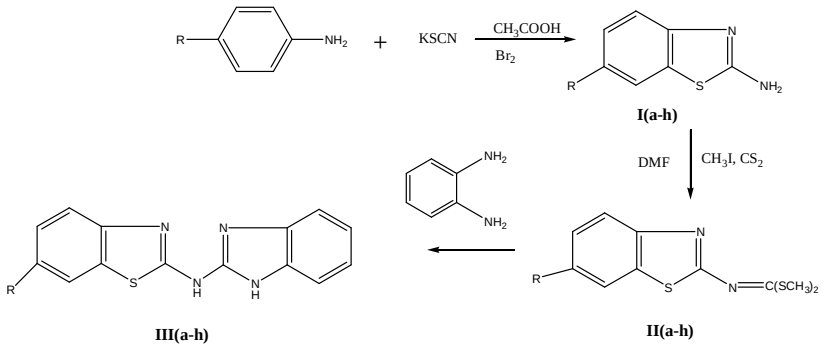
Compound	R	Mol. Formula	Mol. Weight	Melting Point °C	Yield %	C	H	N
3a	H	$C_{14}H_{10}N_4S$	266.32	210	55	63.14	3.78	21.04
3b	m-Cl	$C_{14}H_9ClN_4S$	300.77	206	61	55.91	3.02	18.63
3c	P-Cl	$C_{14}H_9ClN_4S$	300.77	202	57	55.92	3.00	18.65
3d	p-OH	$C_{14}H_{10}N_4OS$	282.32	178	61	59.59	3.57	19.85
3e	p-No_2	$C14H_9N_5O_2S$	311.32	196	63	54.01	2.10	22.50
3f	p-NH_2	$C_{14}H_{11}N_5S$	281.34	232	54	59.77	3.94	24.89
3g	P-CH_3	$C_{15}H_{12}N_4S$	280.35	220	59	64.26	4.31	19.98
3h	P-OCH_3	$C_{15}H_{12}N_4OS$	296.35	236	64	60.79	4.08	18.91

Table No 2: Antibacterial Activity of Compounds 3a-h.

Compound Code	*Inhibition of zone diameter in mm			
	B. subtilis	*B. pumillis*	*E. coli*	*P. aeruginosa*
	100 µg	100 µg	100 µg	100 µg
3a	16	15	14	15
3b	17	16	15	17
3c	20	23	19	21
3d	17	16	16	15
3e	20	22	19	21
3f	21	23	22	21
3g	16	17	15	16
3h	21	20	19	22
Ciprofloxacin	20	23	25	24
DMSO	_	_	_	_

*****Each value is an average of three independent determination ± Standard deviation. Note: '-' denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 mm and above good activity.*

Fig. 1: Scheme 1



CONCLUSION

All the 08 newly synthesized compounds were screened for antibacterial activity studies at a concentration of 100 µg/mL using DMSO as a control and ciprofloxacin used as standard against gram positive and gram negative bacteria. The data in the Table 2 indicates that among the synthesized compounds **3c, 3e, 3f** and **3h** compounds was found to posses a broad spectrum activity. However, the activities of the tested compounds are much less than those of standard antibacterial agents used.

ACKNOWLEDGEMENTS

The authors are thankful to the Management of SSIPS, Bhilai (C.G.) for providing the necessary facilities to carry out this work. Authors also extend their thanks to BIT, Mesra and CDRI, Lucknow for providing IR spectra and 1H NMR spectra analysis respectively.

REFERENCES

1. Bax R, Mullan N and Verhoef J. International Journal of Antimicrobial Agents. 2000;16(1):51-59.
2. Matsushita M and Janda KD. Bioorganic & Medicinal Chemistry. 2002;10(4):855-867.
3. Devitt DM and Rosenberg. Trends in Microbiology. 2001; 9(12): 611-617.
4. Trias J and Gordon E. 1997;8(6):757-762.
5. Carratala J, Alcaide F and Fernandez SA. Clin Infect Dis. 1995;20:1169-1173.
6. Sogn DD, Evans R and Shepherd GM. Arch Intern Med. 1992;152(5):1025-1032.
7. Bayles KW. Trends Microbiol. 2000;8:81274-81278.
8. Baumgartner JD and Glauser MP. Arch Intern Med. 1983;143:1868-1873.
9. Haas DW, Stratton CW, Griffin JP and Weeks L. Clin Infect Dis. 1995;20:671-676.
10. John CC. Clin Infect Dis. 1994;18:188-193.
11. Schaad UB, Suter S and Gianella AB. New Engl J Med. 1990;322:141-147.
12. Kashiyama E and Hutchinson I. Chua MS Journal of Medical Chemistry. 1999;42:4172–4184.
13. Hu GQ, Xie SQ, Xu QJ, Huang WL, Zhang HB, Huang ST and Yao Xue XB. 2005;40: 337-339.
14. Karabasanagouda T, Adhikari, Airody V, Shetty and Suchetha N. Phosp Sulf and Silicon. 2007;182:2925-294.
15. Guang FY, Zu Ming LIU and Xiang HQ. Chin Chem Lett. 2001;12:877-880.
16. Fang L, Luo XO, Song BA, Bhadury PS, Song Y, Jin LH, Weixue and Hu DY. Bioorg Med Chem. 2008;16(7):3632-3640.
17. Cai JC, Bao AS, Song Y, Guang FX, Pinaki SB, Lin HJ, De YH, Qian ZL, Fang L, Wei X, Ping L and Zhuo C. Bioorg Med Chem. 2007;15(12):3981-3989.
18. Jakubkiene V, Burbuliene MM, Mekuskiene G, Udrenaite E, Gaidelis P and Vainilavicius P. IL Farmaco. 2003;58(4):323-328.

19. Harish K, Sadique AJ, Suroor AK and Mohammad A. Eur J Med Chem. 2008;43:2688-2698.
20. Linhong J, Jiang C, Baoan S, Zhuo C, Song Y, Qianzhu L, Deyu H and Ruiqing X. Bioorg Med Chem Lett. 2006;16(19):5036-5040.
21. Ahmed SA, Hamdy MAR, Nadia MM and Mahmoud AEG. Bioorg Med Chem. Novel 5-(2-Hydroxyphenyl)-3-Substituted-2,3-dihydro-1,3,4-Oxadiazole-2-thione Derivatives. Promising Anticancer Agents. 2006;14(4):1236-1246.
22. Kucukbav H, Cetinkava E and Durmaz R. Arzneim Forsch. 1995;45:1331-1334.
23. Pattan SR, Narendra BSN and Angadi JS. Indian Drugs. 2002;39:515-517.
24. Ameya AC and Nandini RP. Molecules, Synthesis and Biological Activity of N-Substituted-3-chloro-2-azetidinones. 2007;12(11):2467-2477.
25. Caleta I, Grdisa M, Mrvos DS, Cetina M, Tralic KV, Pavelic K and Karminski G. ILFarmaco. Synthesis, Crystal Structure and Antiproliferative Evaluation of Some New Substituted Benzothiazoles and Styrylbenzothiazoles,2004;59(4);297-305.
26. Geoffrey W, Tracey DB, Patrizia D, Angela S, Dong FS, Andrew DW and Malcolm FGS. Bioorg Med Chem Lett. Antitumour benzothiazoles. The synthesis and antitumour Activity of Benzothiazole Substituted Quinol Derivatives. 2000;10(5):513-515.
27. Naik PR, Pandeya SN and Pandey A. Indian J Physiol Pharmacol. 1996;40:189-190.
28. Sushilkumar SB and Devanand BS. J Korean Chem Soc. 2003;47:237-240.
29. Cruickshank R, Duguid JP, Marmion BP and Swam HA: The Practice of Medical Microbiology: 12th ed.; Churchill Livingstone, London, 1975; 544-565.