Synthesis and Antimicrobial Activity of Some New 2-Substituted Benzothiazole Derivatives

B. RAJEEVA, N. SRINIVASULU and S. M. SHANTAKUMAR*

Department of Pharmaceutical Chemistry,
V. L. College of Pharmacy,
Raichur-584103, Karnataka, India.
jeevavlcpl@yahoo.com

Received 8 January 2009; Accepted 10 March 2009

Abstract: Some new 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3- benzothiazole (**3a-j**) were synthesized by refluxing benzothiazolyl carboxyhydrazide with different aryl acids in phosphoryl chloride. Structures of the synthesized compounds were established on the basis of ^1H NMR and Mass spectral data. The anti microbial activity of the synthesized compounds was evaluated by disc diffusion method.

Keywords: 1,3,4-Oxadiazole, Synthesis, Aryl acids and Antimicrobial activity.

Introduction

Substituted 1,3,4-oxadiazole are the heterocyclic system that have been found to exhibit diverse biological activities such as antibacterial¹⁻³, antifungal^{4,5}, anti-inflammatory⁶, analgesic⁷ and anticancer^{8,9} activity. Benzothiazoles are also found to be antimicrobial¹⁰, antifungal^{11,12}, anticancer^{13,14} and anti-inflammatory^{15,16} activity. These biological data prompted us to synthesize some new benzothiazole derivatives containing 1,3,4-oxadiazole ring.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. ^1H NMR were recorded on Varian 200 MHz and Bruker 400 MHz, Mass Spectra were recorded on LCMS Shimadzu spectrophotometer. The physical data of the synthesized compounds were presented in Table 1.

Preparation of ethyl-2-benzothiazole carboxylate (I)

Ethyl-2-benzothiazole carboxylate was synthesized by following method. A mixture of *o*-aminothiophenol (0.1 mol) and diethyl oxalate (0.2 mol) was heated at mild reflux for 4 h, during which the temperature decreases from 147 to 93 °C. After cooling, the mixture was

poured into a solution consisting of 50 mL of conc hydrochloric acid, 150 mL of water and 70 mL of ethanol with stirring, the oil dissolved and a solid formed. The mixture was cooled. The product was filtered and washed with aq. Ethanol, then dried and finally crystallized from pet ether, yield 53%, m.p. 68-70 °C. ¹H NMR (DMSO): δ 1.4 to 1.6 (3H, t, CH₃ of –COOCH₂CH₃), 4.5 to 4.7 (2H, q, CH₂ of –COOCH₂CH₃), 7.5 to 8.3 (4H, m, Ar-H).

Table 1. Characterization of the compounds **3a-j**.

Compound	R	Mol. Formula	Mol. weight	Melting point °C	Yield, %
3a		C ₁₅ H ₉ N ₃ OS	279	170-174	75
3b		C ₁₅ H ₈ BrN ₃ OS	358	116-120	68
3c		C ₁₆ H ₁₁ N ₃ O ₂ S	309	190-194	73
3d		C ₁₅ H ₈ ClN ₃ OS	313	170-174	65
3e		C ₁₄ H ₈ N ₄ OS	280	176-180	68
3f		C ₁₇ H ₁₁ N ₃ OS	305	190-192	61
3g		C ₁₆ H ₉ Cl ₂ N ₃ O ₂ S	378	138-142	60
3h		C ₁₅ H ₇ N ₅ O ₅ S	369	200-202	65
3i		C ₁₇ H ₁₃ N ₃ O ₂ S	323	60-64	62
3j		C ₁₅ H ₉ ClN ₄ OS	328	192-196	66

Preparation of 1, 3-benzothiazole-2-carboxyhydrazide (2)

In to a clean dry 100 mL round bottomed flask, the ethyl-2-benzothiazole carboxylate (**1**) (0.01 mole) was dissolved in ethanol (60 mL). The hydrazine hydrate (0.02 mole) (99%) was added drop by drop with constant stirring and the content were refluxed for 8 h, cooled to room temperature. The solid separated was filtered and washed with water, dried and finally crystallized from ethanol, yield 80%, m.p. 172-174 °C. ¹H NMR (DMSO): δ 4.6 to 4.8 (2H, s, NH₂ of –CONH.NH₂), 7.5 to 8.3 (4H, m, Ar-H), 10.4 to 10.6 (1H, s, NH of –CONH.NH₂).

Preparation of 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3- benzothiazole (3a-j)

A mixture of 1, 3-benzothiazole-2-carboxyhydrazide (**2**) (0.01 mol), appropriate aromatic acid (0.02 mol) and phosphoryl chloride (10 mL) was refluxed on water bath for 6-8 hours. After cooling to room temperature it was poured into the crushed ice with stirring. The solid thus obtained was filtered, washed with water and crystallized from ethanol to give compounds **3a-j** (Scheme 1).

3a: ^1H NMR (CDCl_3): δ 7.5-7.8 (9H, m, Ar-H). **3a** m/z : Molecular ion peak at 279. **3b** ^1H NMR (CDCl_3): δ 7.3-8.2 (8H, m, Ar-H). **3c** ^1H NMR (CDCl_3): δ 3.9 (3H, s, $-\text{OCH}_3$), 7.0-8.2 (8H, m, Ar-H). **3d** ^1H NMR (CDCl_3): δ 7.4-8.2 (8H, m, Ar-H). **3d** m/z : (m^{-1}) Molecular ion peak at 312. **3e** ^1H NMR (DMSO): δ 7.5-8.4 (8H, m, Ar-H). **3f** ^1H NMR (CDCl_3): δ 7.4-8.0 (9H, m, Ar-H), 8.0-8.1 (1H, d, H of $-\text{CH}=\text{CH}$), 8.2-8.4 (1H, d, of $-\text{CH}=\text{CH}$). **3g** ^1H NMR (DMSO): δ 5.7-5.8 (2H, s, $-\text{CH}_2$), 7.1-8.4 (7H, m, Ar-H).

Scheme 1

Antibacterial activity

All the newly synthesized compounds (**3a-j**) 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 $\mu\text{g/mL}$ by disc diffusion method¹⁷ by using DMSO as solvent control and nutrient agar was employed as culture media. After 24 h of incubation at 37 $^\circ\text{C}$, the zone of inhibition were measured in mm. The activity was compared with known antibiotic ciprofloxacin and the data was represented in the Table 2.

Table 2. Antibacterial activity of compounds **3a-j**.

Sample code	*Inhibition of zone diameter in mm			
	<i>B. subtilis</i>	<i>B. pumillis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
	100 µg	100 µg	100 µg	100 µg
3a	14	15	15	14
3b	19	21	20	21
3c	13	15	15	15
3d	20	20	21	20
3e	15	16	15	16
3f	16	16	17	15
3g	21	21	23	20
3h	22	23	20	21
3i	14	16	15	16
3j	15	17	16	15
Ciprofloxacin	24	25	24	24
DMSO	-	-	-	-

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

Conclusion

All the 10 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 **3b**, **3d**, **3g** and **3h** compounds was found to possess 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 V. L. College of Pharmacy, Raichur for providing the necessary facilities to carry out this work. Authors also extend their thanks to IISc Bangalore for providing ^1H NMR spectra analysis.

References

1. Hu G Q, Xie S Q, Xu Q J, Huang W L, Zhang H B and Huang S T, *Yao Xue Xue Bao*, 2005, **40**, 337-339.
2. Karabasanagouda T, Adhikari, Airody V, Shetty and Suchetha N, *Phosp Sulf and Silicon*, 2007, **182**, 2925-2941.
3. Guang F Y, Zu Ming L I U and Xiang H Q, *Chin Chem Lett.*, 2001, **12**, 877-880.
4. Fang L, Luo X O, Song B A, Bhadury P S, Song Y, Jin L H, Weixue and Hu D Y, *Bioorg Med Chem.*, 2008, **16**, 3632-3640.
5. Cai J C, Bao A S, Song Y, Guang F X, Pinaki S B, Lin H Jin, De Y H, Qian Z L, Fang L, Wei X, Ping L and Zhuo C, *Bioorg Med Chem.*, 2007, **15**, 3981-3989.
6. Jakubkiene V, Burbuliene M M, Mekuskiene G, Udrenaite E, Gaidelis P and Vainilavicius P, *IL Farmaco*, 2003, **58**, 323-328.
7. Harish K, Sadique A J, Suroor A K and Mohammad A *Eur J Med Chem.*, 2008, **43**, 2688-2698.
8. Linhong J, Jiang C, Baoan S, Zhuo C, Song Y, Qianzhu L, Deyu H and Ruiqing X *Bioorg Med Chem Lett.*, 2006, **16**, 5036-5040.

9. Ahmed S A, Hamdy M A R, Nadia M M and Mahmoud A E G, *Bioorg Med Chem.*, 2006, **14**, 1236-1246.
10. Kucukbav H, Cetinkaya E and Durmaz R, *Arzneim Forsch*, 1995, **45**, 1331-1334.
11. Pattan S R, Narendra B S N and Angadi J S, *Indian Drugs*, 2002, **39**, 515-517.
12. Ameya A C and Nandini R P, *Molecules*, 2007, **12**, 2467-2477.
13. Caleta I, Grdisa M, Mrvos D S, Cetina M, Tralic K V, Pavelic K and Karminski G *IL Farmaco*, 2004, **59**, 297-305.
14. Geoffrey W, Tracey D B, Patrizia D, Angela S, Dong F S, Andrew D W and Malcolm F G S, *Bioorg Med Chem Lett.*, 2000, **10**, 513-515.
15. Naik P R, Pandeya S N and Pandey A, *Indian J Physiol Pharmacol.*, 1996, **40**, 189-190.
16. Sushilkumar S B and Devanand B S, *J Korean Chem Soc.*, 2003, **47**, 237-240.
17. Cruickshank R, Duguid J P, Marmion B P and Swam H A, *The Practice of Medical Microbiology*; 12th Ed., Churchill Livingstone, London, 1975, p. 544.