Int. J. Chem. Sci.: 10(2), 2012, 619-626
ISSN 0972-768X
www.sadgurupublications.com

SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITY OF NOVEL SUBSTITUTED BENZOXAZOLE DERIVATIVES

G. BALASWAMY, K. SRINIVAS[*], P. PRADEEP and M. SARANGAPANI[a]

Department of Chemistry, Kakatiya University, WARANGAL (A.P.) INDIA
[a]University College of Pharmaceutical Sciences, Kakatiya University, WARANGAL (A.P.) INDIA

ABSTRACT

In view of the fact that a large number of derivatives of benzoxazole have been found to exhibit a wide variety of pharmacological activities. In the current research work, the title compounds were synthesized from 2-substituted benzoxazole-5-carbohydrazide **(1)** on treatment with equimolar quantities of anhydrides afforded 1-[(2-substituted-1,3-benzoxazol-5-yl)carbonyl]-1,2-dihydropyridazine-3,6-dione **(2)**, of 1-[(2-substituted-1,3-benzoxazol-5-yl) carbonyl] tetrahydropyridazine-3,6-dione **(3)** and 2-[(1,3-benzoxazol-5-yl)carbonyl]-2,3-dihydrophthalazine-1,4-dione **(4)**. The identification and characterization of all the synthesized compounds were confirmed by elemental analysis, melting point, Thin layer chromatography, FT-IR, ^{1}H NMR and mass spectral data. All the compounds were screened for antimicrobial activity. In view of interesting biological activities and pharmacological importance associated with benzoxazole derivatives hence, the some of the derivatives of benzoxazole containing heterocyclic ring have been prepared and their bio-potential have been evaluated.

Key words: Benzoxazole derivatives, Dihydropyridazine, Tetrahydropyridazine, Dihydrophthalazine, Anti-microbial activity.

INTRODUCTION

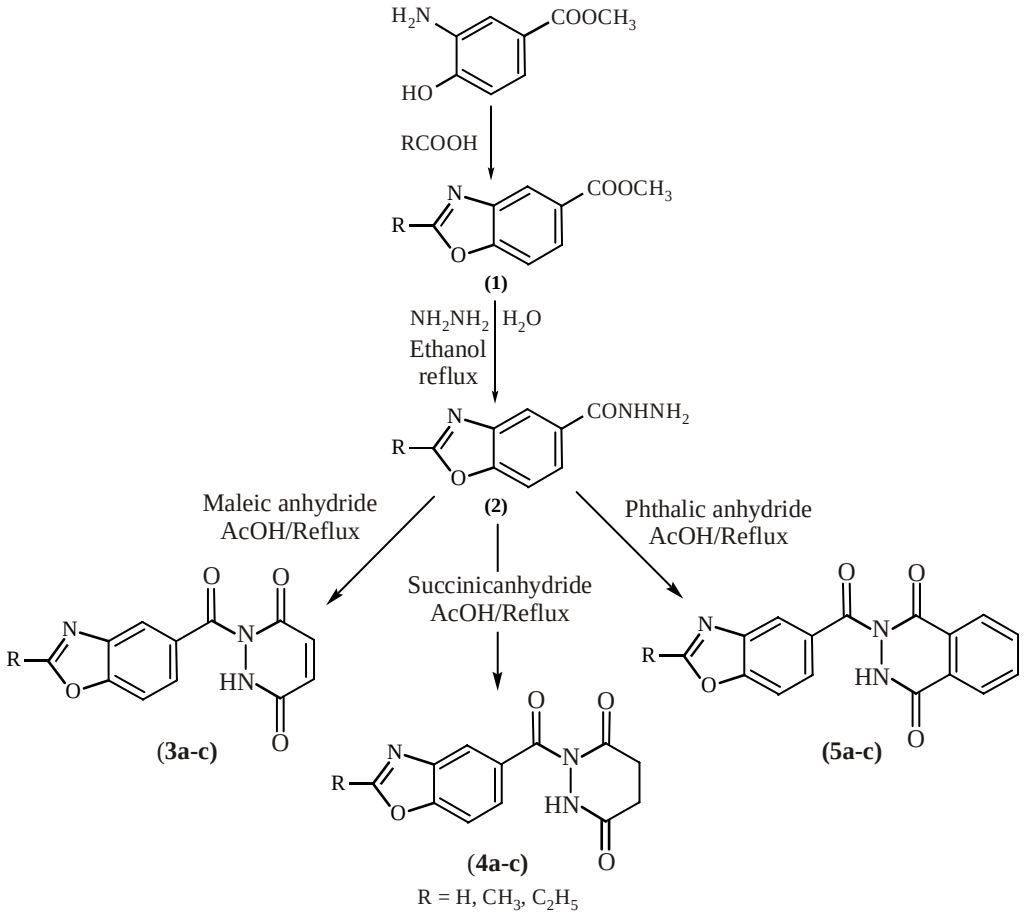
The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. Benzoxazoles have been reported to show a broad spectrum of biological activities. Notable among these are antihistaminic[1], antifungal[2], cyclooxygenase inhibiting[3], antitumor[4], antiulcer[5], anti-convulsant[6], hypoglycemic[7], anti-inflammatory[8,9] and cytotoxic activity[10,11]. In the present work three different heterocycles[12,13] were incorporated to benzoxazole moiety. All the compounds were screened for antimicrobial activity.

[*]Author for correspondence; E-mail: katla_org@yahoo.co.in

EXPERIMENTAL

Material and methods

All the reagents and solvents used were of laboratory grade. The melting points of synthesized compounds were determined by open capillary method and were uncorrected. The purity and homogeneity of compounds were checked using TLC technique. IR spectra[14] of compounds were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer. ^{1}H-NMR[15] spectra were recorded on Bruker Avance-300 MHz spectrophotometer using $CDCl_3$ as solvent at Indian Institute of Chemical Technology (IICT), Hyderabad. Mass spectra of the synthesized compounds were recorded on liquid chromatography mass spectrometer at Indian Institute of Chemical Technology (IICT), Hyderabad. The compounds were also subjected to C, H, N and S analysis (Thermo Finnigan) at IICT (Hyderabad).



Scheme

Preparation of 2-subtituted benzoxazole-5-carboxylic acid methyl ester (1)

A mixture of 3-amino-4-hydroxy-benzoic acid methyl ester (0.1 mol) and appropriate aliphatic acid (formic acid, acetic acid and propionic acid) was heated to reflux for 4 h. The reaction mixture was cooled and poured in to crushed ice with stirring. The product thus separated was filtered under suction and washed with cold water. The products were recrystallised by using methanol as a solvent.

Preparation of 2-substituted benzoxazole-5-carboxylic acid hydrazide (2a-c)

A mixture of a 2-subtituted benzoxazole-5-carboxylic acid methyl ester **(1)** (0.085 mol) in alcohol (150 mL) and hydrazine hydrate (99%, 0.212 mol) was heated under reflux on water bath for 8 hours. The alcohol was evaporated till 40 mL remained and cooled. The product precipitated was filtered and washed with small amount of cold alcohol and followed by cold water repeatedly and dried. The following three compounds were synthesized by using the above procedure.

(a) Benzoxazole-5-carboxylic acid hydrazide (2a)

Yield 12.0 g (80%), m.p. 108-110°C**.**

(b) 2-Methyl-benzoxazole-5-carboxylic acid hydrazide (2b)

Yield 12.2 g (75%), m.p**.** 144-146°C.

(c) 2-Ethyl-benzoxazole-5-carboxylic acid hydrazide (2c)

Yield 12.9 g (74%), m.p. 138-140°C.

Preparation of 1-[(2-substituted-1,3-benzoxazol-5-yl) carbonyl]-1,2-dihydro pyridazine -3,6-dione (3a-c)

A 11.29 mmol of 1,3-benzoxazole-5-carbohydrazide dissolved in 20 mL of acetic acid and 11.29 mmol of maleic anhydride added to the above and content refluxed for 6 hrs and the reaction monitored by TLC (Methanol : EtOAc/6 : 4), quenched in to the ice under stirring to get the solid, filtered the solid, washed the solid with chilled water and recrystallized from minimum amount of methanol to get the white crystalline powder.

The following three compounds were synthesized by using the above procedure.

3a: IR (KBr): 3320 cm^{-1} (NH), 1730 cm^{-1} (C=O), 1630 cm^{-1} (C=N), 3084 cm^{-1} (Ar–H), 877 cm^{-1} (C=C); **^{1}H NMR:** ($CDCl_3$) 7.71-7.85 (m, 3H), 8.4 (s, 1H), 8.8 (m, 1H), 2.5-2.7 (m, 2H).

3b: IR (KBr): 3324 cm^{-1} (NH), 1730 cm^{-1} (C=O), 1627 cm^{-1} (C=N), 3090 cm^{-1} (Ar–H), 838 cm^{-1} (C=C), 2900 cm^{-1} (CH); **^{1}H NMR:** ($CDCl_3$) 7.7 (d, 1H), 7.95 (m, 1H), 8.0 (s, 2H), 2.5-2.7 (m, 5H).

3c: IR (KBr): 3325 cm^{-1} (NH), 1732 cm^{-1} (C=O), 1634 (C=N), 2890 cm^{-1} (C–H), 3010 cm^{-1} (Ar–H), 900 cm^{-1} (C=C); **^{1}H NMR:** ($CDCl_3$) 8.0-8.4 (m, 4H), 7.3-7.5 (m, 2H), 3.0 (q, 2H), 1.3 (t, 3H).

Preparation of 1-[(2-substituted-1,3-benzoxazol-5-yl) carbonyl] tetrahydropyridazine-3,6-dione(4a-c)

A 11.29 mmol of 1,3-benzoxazole-5-carbohydrazide dissolved in 20 mL acetic acid and 11.29 mmol of succinic anhydride added to the above and content refluxed for 8 hrs and the reaction monitored by TLC (Methanol : EtOAc/6 : 4), quenched in to the ice under stirring to get the solid, filtered the solid, washed the solid with chilled water and recrystallized from minimum amount of methanol to get the white powder.

The following three compounds were synthesized by using the above procedure.

4a: IR (KBr): 3320 cm^{-1} (NH), 1732 cm^{-1} (C=O), 1625 cm^{-1} (C=N), 3025 cm^{-1} (Ar–H), 1640 (C=C) 3100 (CH); **^{1}H NMR:** ($CDCl_3$) 7.6-7.85 (m, 4H), 8.4 (s, 1H, 2.6-2.7 (m, 4H).

4b: IR (KBr): 3290 cm^{-1} (NH), 1734 (C=O), 1630 cm^{-1} (C=N), 3084 cm^{-1} (Ar–H), 1640 cm^{-1} (C=C) 3000 cm^{-1} (CH); **^{1}H NMR:** ($CDCl_3$) 7.7- 7.95 (m, 3H), 8.65 (m, 1H), 2.60-2.70 (m, 7H).

4c: IR (KBr): 3320 cm^{-1} (NH), 1738 cm^{-1} (C=O), 1626 cm^{-1} (C=N), 3094 (Ar–H), 1654 cm^{-1} (C=C); **^{1}H NMR:** ($CDCl_3$) 8.0-8.3 (m, 4H), 3.0 (q, 2H), 2.6-2.7 (m, 4H), 1.3 (t, 3H).

Preparation of 2-[(2-substituted-1,3-benzoxazol-5-yl) carbonyl]-2,3-dihydrophthalazine-1,4-dione(5a-c)

A 11.29 mmol of 1,3-benzoxazole-5-carbohydrazide dissolved in 20 mL of acetic acid and 11.29 mmol of phthalic anhydride added to the above and content refluxed for 8 hrs and the reaction monitored by TLC (Methanol : EtOAc/6 : 4), quenched in to the ice under stirring to get the solid, filtered the solid, washed the solid with chilled water and recrystallized from minimum amount of methanol to get the white crystalline powder.

The following three compounds were synthesized by using the above procedure.

5a: IR (KBr): 3390 cm^{-1} (NH), 1730 cm^{-1} (C=O), 1630 cm^{-1} (C=N), 3085 cm^{-1} (Ar–H), 835 (C=C); **^{1}H NMR:** ($CDCl_3$) 7.6-7.9 (m, 7H), 8.5 (s, 1H), 8.8 (m, 1H).

5b: IR (KBr): 3390 cm^{-1} (NH), 1732 cm^{-1} (C=O), 1625 cm^{-1} (C=N), 3094 cm^{-1} (Ar–H), 900 cm^{-1} (C=C), 3000 cm^{-1} (CH); **^{1}H NMR:** ($CDCl_3$) 7.4-7.9 (m, 7H), 8.6 (s, 1H), 8.8 (m, 1H) 2.65 (s, 3H).

5c: IR (KBr): 3270 cm^{-1} (NH), 1730 cm^{-1} (C=O), 1620 cm^{-1} (C=N), 3025 cm^{-1} (Ar–H), 900 cm^{-1} (C=C); **^{1}H NMR:** ($CDCl_3$) 7.6-8.3 (m, 8H), 3.1 (q, 2H), 2.65 (t, 3H).

Table 1: Physical data of compounds

Compound	R	M.P. (^{o}C)	Yield (%)	Molecular formula
3a	H	185-187	85%	$C_{12}H_7N_3O_4$
3b	CH_3	190-192	84%	$C_{13}H_9N_3O_4$
3c	C_2H_5	198-200	80%	$C_{14}H_{11}N_3O_4$
4a	H	170-172	78%	$C_{12}H_9N_3O_4$
4b	CH_3	205-207	80%	$C_{13}H_{11}N_3O_4$
4c	C_2H_5	223-225	75%	$C_{14}H_{13}N_3O_4$
5a	H	220-222	82%	$C_{16}H_9N_3O_4$
5b	CH_3	225-227	86%	$C_{17}H_{11}N_3O_4$
5c	C_2H_5	234-236	84%	$C_{18}H_{13}N_3O_4$

Biological activity

The synthesized compounds were screened for antimicrobial activity by zone of inhibition method. Antibacterial activity was observed for all the compounds using four strains of Gram (+ ve) and Gram (-ve) bacteria. The strains used were *Staphylococcus Aureus, Bacillus pumilis, Proteus mirabilis* (+ve) and *Escherchia Coli* (-ve).The concentrations taken were 600 µg/mL, 900 µg/mL. By the analysis of antimicrobial data found that, compounds 3c and 4c were found to be more active against *Escherchia Coli* (-ve) organism and 3b is more active against *Bacillus pumilis* used. The remaining compounds showed moderate and low activity against organisms.

Table 2: Antimicrobial activity data

Compound	Conc. (µg/mL)	Zone of inhibition (*in mm*)			
		Escherichia coli	***Bacillus pumilis***	***Proteus mirabilis***	***Staphylococcus aureus***
3a	600	2.23	5.92	2.65	NA
	900	4.5	10.69	4.29	NA
3b	600	1.98	7.42	4.32	6.62
	900	3.75	14.80	8.49	12.0
3c	600	3.26	6.10	2.12	5.03
	900	6.50	11.20	4.28	10.2
4a	600	1.15	2.26	5.52	5.69
	900	2.78	5.25	10.25	11.2
4b	600	2.26	3.35	4.95	3.65
	900	4.90	6.25	10.25	7.25
4c	600	3.36	5.21	5.59	4.56
	900	6.85	10.29	11.25	8.67
5a	600	2.01	4.52	2.21	4.98
	900	3.45	8.60	4.55	9.20
5b	600	2.06	5.26	5.50	3.30
	900	4.25	10.25	10.55	6.25
5c	600	2.25	4.56	4.95	5.92
	900	4.25	8.25	9.52	11.25
Std	600	3.06	7.25	12.82	10.34
	900	6.14	14.50	20.34	20.01

Standard: Streptomycin

RESULTS AND DISCUSSION

In the present investigation, (3a-5c) compounds were synthesized.

All the above compounds (3a-5c) were synthesized from 2-substituted benzoxazole-5 carboxylic acid hydrazides with corresponding anhydride and using the solvent acetic acid

at reflux over a period of 4-8 hrs to obtain the 1-[2-substituted (1,3-benzoxazol-5-yl) carbonyl] tetrahydropyridazine-3,6-dione,1-[2-substituted(1,3-benzoxazol-5-yl)carbonyl]-1,2-dihydropyridazine-3,6-dione and 2-[2-substituted (1,3-benzoxazol-5-yl)carbonyl]-2,3-dihydrophthalazine-1,4-dione.

The purity and homogeneity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected), thin-layer chromatography.

The chemical structures were confirmed by infra-red absorption spectra of all the synthesized compounds. The aromatic Ar–H stretching for all the derivatives was found to be at the range of 3000-3200 cm^{-1}. The presence of N-H stretching was confirmed by the peaks at the range 3290-3390 cm^{-1}. Also some ^{1}H NMR spectra were useful for some protons in the compounds such as δ 7.30-8.0 indicates the presence of phenyl ring protons and mass spectrum of the compounds gives mass of compounds.

ACKNOWLEDGEMENT

Authors are thankful to Kakatiya University, Warangal, Andhra Pradesh, India for providing necessary support for this research work.

REFERENCE

1. Y. Kastura, Y. Tnoue and S. Nishino, Chem. Pharm. Bull, **40(6)**, 1424 (1992).
2. Y. Ismail, O. lkay and T. Özlem, Acta Biochimica Polonica, **47**, 481-486 (2000).
3. R. Shrinivasa, P. Rao and P. Kumar, Bioorganic and Medicinal Chemistry Letters, 13: 657- 660 (2003).
4. S. Aiello, G. Wells, E. Ston and H. Kadri, J. Med. Chem., **51**, 5135-5139 (2008).
5. Y. Kastura, Y. Tnoue and S. Nishino, Chem. Pharm. Bull., **40(6)**, 1424-1438 (1992).
6. N. Siddiqui, M. Sarafaroz, M. Alam and W. Ahsan, Polish Pharmaceiutical Society, Acta Poloniae Pharmaceiutica-Drug Res., **65(4)**, 449-455 (2008).
7. K. Arakova, M. Inamasu and M. Masumoto, Chem. Pharm. Bull., **45(12)**, 1984 (1997.).
8. S. Sondhi, N. Singh, A. Kumar and O. Lozach, Bioorg. Med. Chem., **14(11)**, 3758-3765 (2006).
9. S. S. Unlu and Kupeli E. Baytas, Archives Der Pharmazie, **336(6-7)**, 310 (2003).

10. N. N. Eshbha and H. M. Dalama, Pharmazie, **40**, 320 (1985).

11. Venkateshwar Rao Jupally and Sarangapani Manda, Int. J. Chem. Sci., **5(5)**, 2161-2168 (2007).

12. M. E. Abd El-Fattah, Indian, J. Heterocyclic Chem., **8**, 111-116 (1998).

13. S. Arunkumar and N. Ramalaxmi, Indian, J. Heterocyclic Chem., **16**, 29-32 (2006).

14. R. M. Silverstein and T. C. Morrill, Spectrophotometric Identification of Organic Compounds, Edn. 4th John Wiley and Sons, New work., 192 (1981).

15. R. M. Silverstein and T. C. Morrill, Spectrophotometric Identification of Organic Compounds., Edn. 4th John Wiley and Sons, New work., 312 (1981).

Accepted : 03.12.2011