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SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITY OF NEW SERIES OF BENZOXAZOLE DERIVATIVES

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ABSTRACT

In the present research work, the title compounds were synthesized from 4-hydroxy benzaldehyde (1) on treatment with $Al(NO_3)_3$ in the mixture of acetic acid and acetic anhydrides afforded 3-nitro,4-hydroxybenzaldehyde (2), on treatment of 4-hydroxybenzohydrazide gave 4-hydroxy-*N*'-[(*Z*)-(4-hydroxy-3-nitrophenyl)methylidene] benzohydrazide (3) and heating with chloramines-T afforded 4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]-2-nitrophenol (4) on reduction afforded 2-amino-4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenol (5) and refluxed with appropriate aliphatic acid yielded the corresponding 4-[5-(2-substituted-1,3-benzoxazol-5-yl)-1,3,4-oxadiazol-2-yl] phenol. 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, some of the derivatives of benzoxazole containing heterocyclic ring have been prepared and their bio-potential have been evaluated.

Key words: Benzoxazole derivatives, 1, 3, 4-oxadiazol, Anti-microbial activity.

INTRODUCTION

Compounds bearing benzoxazole moiety are reported to possess a number of interesting biological activities such as antihistaminic[1], antifungal[2], cyclooxygenase inhibiting[3], antitumor[4], antiulcer[5], anticonvulsant[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, we have reported here the synthesis of novel benzoxazole derivatives to evaluate their antimicrobial activity.

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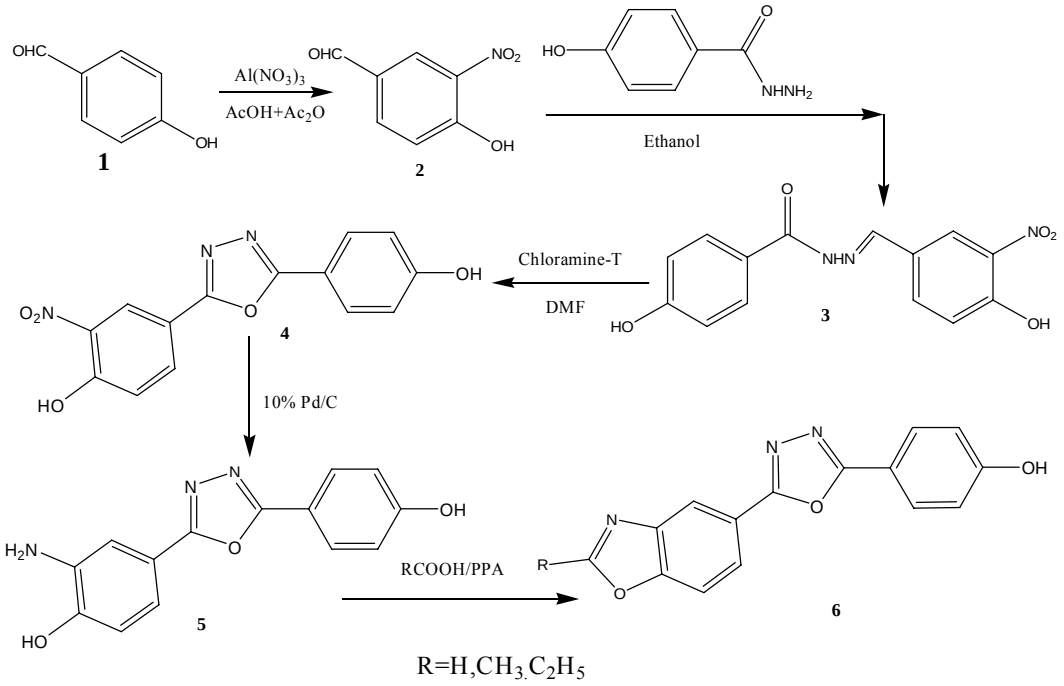
EXPERIMENTAL

Materials 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 DMSO and $CDCl_3$ as a 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 4-hydroxy-3-nitrobenzaldehyde (2)

To a solution of aluminium nitrate (40 g) in acetic acid-acetic anhydride (1 : 1) mixture (160 mL), 4-hydroxybenzaldehyde (1), (40 g) was added in small portions,

maintaining the temperature between 30-45°C for 2 hr. The reaction completion was monitored by TLC, The resulting solution was slowly poured into ice-cold water under stirring to get a yellow precipitate. It was filtered washed with small quantity of methanol and purified by recrystallization from alcohol to get a yellow crystalline solid.

Yield: 44.3 g (81%), m.p. 138-140°C.

IR (KBr): 3433 cm^{-1} (OH), 3233 cm^{-1} (Ar-CH), 1686 cm^{-1} (C=O), 1533, 1331 cm^{-1} (NO_2), 1610 cm^{-1} (Ar C=C), 3084 cm^{-1} (Ar-H).

^1H NMR: ($CDCl_3$) 7.3 (s, 1H), 8.0-8.3 (dd, 2H), 8.9 (s, 1H).

Preparation of 4-hydroxy-N'-[(Z)-(4-hydroxy-3-nitrophenyl) methylidene] benzo-hydrazide (3)

A mixture of a 4-hydroxy-3-nitrobenzaldehyde (2) (0.1 mol), 4-hydroxy carbonyl hydrazone (0.11) and catalytic amount of acetic acid in a ethanol (150 mL) was heated to reflux for 3-4 hours. The reaction completion was monitored by TLC. The reaction mixture was distilled off to get residue, dissolved the above residue in a mixture of ethanol and water, cooled to precipitate. The resulting solid product was filtered, washed with water and recrystallized from ethanol.

Yield: 27.4 g (91%), m.p. 181-183°C.

IR (KBr): 3297 cm^{-1} (NH-N), 1730 cm^{-1} (C=O), 1626 cm^{-1} (CONH), 1596 cm^{-1} (C=N), 3084 cm^{-1} (Ar–H), 877 cm^{-1} (C=C),

^1H NMR: ($CDCl_3$) 6.92-7.1 (m, 1 H), 7.73 (m, 3 H), 8.3-8.4 (m, 1 H).

Preparation of 4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]-2-nitrophenol (4)

A mixture of a 4-hydroxy-N'-[(Z)-(4-hydroxy-3-nitrophenyl) methylidene] benzohydrazide (3) (80.2 mmol) and chloramine-T (80.2 mmol) in a DMF (200 mL) was heated to reflux for 3-4 hours. The reaction completion was monitored by TLC, the reaction mixture was cooled and treated with ice-cold water. The resulting solid product was filtered, washed with water and recrystallized from ethanol.

Yield: 20.53 g (85%), m.p. 177-179°C. m/z (+ve ion): 302.0

IR (KBr): 1605 cm^{-1} (C=N), 3053 cm^{-1} (Ar–H), 1053 cm^{-1} (C-O-C).

^1H NMR: ($CDCl_3$) 6.8-7.2 (m, 3H), 7.4-7.6 (m, 3H), 8.4 (br, 2H).

Preparation of 2-amino-4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenol (5)

A solution of 4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]-2-nitrophenol (4) (12 g) in a methanol (250 mL) subjected to reduction with 10% Pd/C (1.2 g), reaction completion monitored by TLC. Filtered the reaction mixture through ceilite bed, concentrated to get crude solid and the solid recrystallized from ethanol to furnish fine solid.

Yield: 10.0 (80%), m.p. 158-160^{o}C.

IR (KBr): 3320, 3430 cm^{-1} (NH_2), 1605 cm^{-1} (C=N), 3053 cm^{-1} (Ar–H), 1052 cm^{-1} (C-O-C).

^{1}H NMR: ($CDCl_3$) 4.8 (br, 1H), 6.7-6.9 (m, 3H), 7.4-7.5 (m, 3H), 8.5 (br, 2H).

Preparation of 4-[5-(2-2-substituted-1, 3-benzoxazol-5-yl)-1, 3, 4-oxadiazol-2-yl] phenol (6a-6c)

A mixture of 2-amino-4-[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] phenol (5) (9.28 mmol) and appropriate aliphatic acid (formic acid, acetic acid and propionic acid) and catalytic amount of polyphosphoric acid was heated to reflux for 4 hrs. Reaction completion was monitored by TLC. The reaction mixture was cooled and poured into crushed ice with stirring, the product thus separated was filtered under suction and washed with cold water. The products were recrystallised from ethanol.

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

(a) 4-[5-(1,3-benzoxazol-5-yl)-1,3,4-oxadiazol-2-yl] phenol (6a)

Yield 1.94 g (75%), m.p. 138-140^{o}C.

(b) 4-[5-(2-methyl-1,3-benzoxazol-5-yl)-1,3,4-oxadiazol-2-yl] phenol (6b)

Yield 2.17 g (80%), m.p. 168-170^{o}C.

(c) 4-[5-(2-ethyl-1,3-benzoxazol-5-yl)-1,3,4-oxadiazol-2-yl] phenol (6c)

Yield 2.1 g (74%), m.p. 191-193^{o}C.

6a: IR (KBr): 1574 cm^{-1} (C=N), 3053 cm^{-1} (Ar-H), 1042 cm^{-1} (C-O-C).

^{1}H NMR: ($CDCl_3$) 7.9 (s, 1H), 7.4-7.58 (m, 6H), 6.9-7.0 (m, 2H), 8.65 (br, 1H).

6b: IR (KBr): 1569 cm^{-1} (C=N), 3059 cm^{-1} (Ar-H), 1059 cm^{-1} (C-O-C), 3000 cm^{-1} (CH).

^{1}H NMR: ($CDCl_3$) 7.7 (s, 1H), 7.4-7.5 (m, 4H), 6.9-7.0 (m, 2H), 2.46 (s, 3H).

6c: IR (KBr): 1610 cm^{-1} (C=N), 3094 cm^{-1} (Ar–H), 1043 cm^{-1} (C-O-C), 1654 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.4-7.5 (m, 5H), 6.8-7.0 (m, 2H), 2.5(q, 2H), 1.3 (t, 3H).

Table 1: Physical data of compounds

Compd.	R	M.P. (^oC)	Yield (%)	Molecular formula
2	--	138-140	81%	$C_7H_5NO_4$
3	--	181-183	91%	$C_{14}H_{11}N_3O_5$
4	--	177-179	85%	$C_{14}H_9N_3O_5$
5	--	158-160	80%	$C_{14}H_{11}N_3O_3$
6a	H	138-140	75%	$C_{15}H_9N_3O_3$
6b	CH_3	168-170	80%	$C_{16}H_{11}N_3O_3$
6c	C_2H_5	191-193	74%	$C_{17}H_{13}N_3O_3$

Biological activity

The activity was determined using disc diffusion method by measuring zone of inhibition in mm. All the three compounds, 6a, 6b and 6c were screened in vitro at concentration of 5 μg/disc for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* and *acillus subtilis*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Antifungal evaluation was carried out against *Candida albicans* and *Aspergillus niger* at concentration of 5 μg/disc. Standard antibacterial drug ciprofloxacin (10 μg/disc) was also tested under similar conditions against these organisms. All synthesized compounds exhibited significant antibacterial activities and moderate anti-fungal activities. Each experiment was done in triplicate and the average reading was taken.

Table 2: Antimicrobial activity data

Compound	MIC (Conc. μg/mL)			
	Staphylococcus aureus	***Escherichia coli***	***Pseudomonas aeruginosa***	***Candida albicans***
6a	28	14	14	10
6b	14	10	15	10
6c	21	13	19	11
Ciprofloxacin	26	28	25	-

Standard: Streptomycin

RESULTS AND DISCUSSION

In the present investigation, (6a-6c) compounds were synthesized. All the above compounds (6a-6c) were synthesized from 4-hydroxy benzaldehyde. 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.

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