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SYNTHESIS AND BIOLOGICAL INVESTIGATION OF SOME NOVEL SULFONAMIDE DERIVATIVES CONTAINING BENZIMIDAZOLE MOIETY

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ABSTRACT

A new class of potentially biological active sulfonamide derivatives containing Benzimidazole moiety has been synthesized. The newly synthesized compounds were characterized by spectroscopic methods and elemental analysis. Further, the synthesized compounds were evaluated for antibacterial and antioxidant activity. Their antibacterial activity was assigned using the conventional cup plate method and antioxidant activity was assessed using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method. The synthesized compounds exhibited significant antibacterial and antioxidant activities compared to standard compounds.

Keywords: Benzimidazole, Sulfonamide, Antibacterial, Antioxidant.

INTRODUCTION

Infectious diseases caused by bacteria and fungi remain a major global health problem. Recent years have seen increased problems of microbial infection in human as well as in plants. The increasing use and misuse of the existing antimicrobial drugs have resulted in the development of resistant pathogens. [1-2]Therefore, novel antimicrobial agents are needed for effective treatment against infections caused by the pathogenic microbes. Sulfonamides represent an important class of medically important compound, which is present in a number of biologically active molecules, particularly in antimicrobial agents. [3-5] Sulfonamides inhibit conversion of p-aminobenzoic acid (PABA) to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis. Human obtain their folic acid in their diet but bacteria need to synthesize it. Sulfonamide inhibit the growth of bacteria but do not kill them i.e. their action is bacteriostatic. This is the basis for the selective effect of sulphonamides on bacteria and for their broad spectrum of antibacterial activity. In addition Sulfonamide derivatives are extensively used as antitumor, [6-7] antiviral, [8] antimalarial, [9-10] anti-inflammatory,[11]anticancer,[12] anti-carbonic anhydrase,[13] antidiabetic agents[14] and in Alzheimer's diseases. [15] Sulfonamide has also been reported to possess corrosion inhibitory properties. [16] Some sulfonamides were found as potent drugs in treatment of insomnia by antagonizing orexin neural activity. [17] Sulfonamidophenyl porphyrins have been established as potential photo sensitizers. [18] The search for potential pharmacologically active sulphonamides and its derivatives is still of interesting. Benzimidazole is an important motif in many drug and drug intermediates and their derivatives have been showed significant role in various pharmacological activities. [19-22]Various useful synthetic analogs with improved therapeutic properties can be obtained by structural modifications. These evidences boosted us to carry out synthetic work for the titled compounds and evaluate their antibacterial and antioxidant potential.

MATERIALS AND METHODS

Chemicals used were of analytical grade. The reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light. Melting points were taken in open capillaries in a simple 'Neolab'electrical apparatus and are uncorrected. FTIR were recorded on a Schimadzu 8101A spectrophotometer in KBr pellets.^{1}H NMR was recorded on a DPX 300 MHz Brucker spectrophotometer in DMSO with chemical shift in δ ppm. N-alkyl phathalyl-1-amino methyl benzimidazole (Ia and Ib) were synthesized by our earlier reported method. [23]

***Synthesis of 1-methyl [(N-alkyl phthalyl) benzimidazolo]-aryl/4-substituted aryl sulphonamides* (IIa-IIh)**

Equimolar amount of mannich base (Ia, Ib), various aryl sulphonyl chloride and acetic anhydride (each 0.01 mole) were taken in a round bottom flask and refluxed on a sand bath for 6-7 hours in presence of pyridine (10 ml.) The resulted solution was concentrated and then poured into crushed ice. The product so formed was filtered, dried and recrystallized from absolute ethanol. The physical and analytical data are given in Table1.

***Characterization of compounds* (IIa-IIh)**

II_a: FTIR (KBr, Cm^{-1}):1770, 1715 (>C=O, Phthalimido), 1630 (C=N str), 1139(-SO_2, sym.), 1306(-SO_2, asym.), 3203(-NH).^{1}HNMR (DMSO, ppm, 300 MH_Z), 3.33 (s, 2H, CH_2), 8.10(s, broad.1H, NH), 7.65-7.92(m, 13H, ArH).

IIb: FTIR (KBr, Cm^{-1}):1750, 1715 (>C=O, Phthalimido), 1625 (C=N str), 1142(-SO_2, sym.), 1337(-SO_2, asym.),3170(-NH).^{1}HNMR (DMSO, ppm, 300 MH_Z),2.65(s,3H, CH3), 3.32 (s, 2H, CH_2), 8.06(s, broad.1H, NH), 7.40-7.80(m, 12H, ArH).

IIc: FTIR (KBr, Cm^{-1}):1751, 1710 (>C=O, Phthalimido), 1622 (C=N str), 1131(-SO_2, sym.), 1345(-SO_2, asym.)3413(NH, str), 3268(-NH, str.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 3.41 (s, 2H, CH_2), 4.98(s, 2H, Ar-NH2), 7.75(s, Br, 1H, -NH), 7.45-7.86(m, 12H, ArH)

IId: FTIR (KBr, Cm^{-1}):1770, 1720 (>C=O, Phthalimido), 1632 (C=N str), 1148(-SO_2, sym.), 1340(-SO_2, asym.),1521(-N=O, str.),3179(-NH, str).^{1}HNMR (DMSO, ppm, 300 MH_Z), 3.57 (s, 2H, CH_2), 8.15(s, Br,1H, -NH) 7.65-7.92(m, 12H, ArH).

II_e: FTIR (KBr, Cm^{-1}):1765, 1720 (>C=O, Phthalimido), 1622 (C=N str), 1140(-SO_2, sym.), 1305(-SO_2, asym.),3205(-NH).^{1}HNMR (DMSO, ppm, 300 MH_Z), 1.55(d, 3H, CH-CH3),3.69(q,1H, CH-CH3) 3.92(s,2H, N-CH2-NH),7.45-7.82(m, 13H, ArH).

IIf: FTIR (KBr, Cm^{-1}):1752, 1715 (>C=O, Phthalimido), 1620 (C=N str), 1152(-SO_2, sym.), 1335(-SO_2, asym.),3170(-NH).^{1}HNMR (DMSO, ppm, 300 MH_Z),2.64(s,3H, CH3), 3.30 (s, 2H, CH_2), 8.02(s, broad.1H, NH), 7.40-7.82(m, 12H, ArH).

IIg: FTIR (KBr, Cm^{-1}):1750, 1710 (>C=O, Phthalimido), 1622 (C=N str), 1130(-SO_2, sym.), 1340(-SO_2, asym.)3411(NH, str), 3268(-NH, str.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 3.42 (s, 2H, CH_2), 4.96(s, 2H, Ar-NH2), 7.73(s, Br, 1H, -NH), 7.44-7.86(m, 12H, ArH)

IIh: FTIR (KBr, Cm^{-1}):1770, 1722 (>C=O, Phthalimido), 1634 (C=N str), 1148(-SO_2, sym.), 1342(-SO_2, asym.),1522(-N=O, str.),3182(-NH, str).^{1}HNMR (DMSO, ppm, 300 MH_Z), 3.58 (s, 2H, CH_2), 8.18(s, Br,1H, -NH) 7.66-7.92(m, 12H, ArH).

Antibacterial activity: Cup plate method [24] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of IIa-IIh against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumoniae*. The agar media was purchased from HI-media laboratories limited, Mumbai, India. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5mg) was dissolved in 5ml of dimethyl sulfoxide. Benzyl penicillin was employed as reference standard (1000µg/ml) to compare the results. The medium was inoculated at one percent level using 18hrs old cultures of the test organism mentioned above into sterile Petri dishes and allowed to set at room temperature for about 30 minutes. The test and standard solutions were added into cups, left for 90 minutes in a refrigerator for diffusion. After incubation for 24 hours at 37 ºC, the plates were examined for inhibition zones. The results are represented in Table2.

Antioxidant activity: The free radical scavenging activity of sulfonamide derivatives was evaluated by DPPH colorimetric method. [25] DPPH is a stable free radical at room temperature. DPPH radical is scavenged by antioxidants through the donation of a proton and form reduced DPPH.The color changes from violet to yellow after reduction of DPPH and it can be quantified by decrease of absorbance at wavelength 517nm.1 ml of the compounds containing concentration (10-200 µg/ml) was mixed with 3.0ml of 0.1mM solution of DPPH.The mixture was kept in dark for 30 minutes. After a 30 min. incubation period at room temperature, the absorbance was read against blank at 517nm.Ascorbic acid was used as standard antioxidant. The results were expressed as percentage of inhibition, which was calculated

according to the following equation-

$$\% \text{ Inhibition} = \frac{\text{Abs Control- Abs Test}}{\text{Abs control}} \times 100$$

RESULTS AND DISCUSSION

In an in-vitro antibacterial bioassay, the eight compounds were evaluated by Cup plate method using representative standard strains of gram-positive and gram-negative bacteria. The results of antibacterial activity revealed that the compounds (IIa-IIh) exhibited moderate to considerable activity when compared to reference standard benzyl penicillin. The highest activity was observed for the compound IId and IIh for the selective concentration range as shown in figure 2.This may be due to the presence of nitro group on phenyl ring. The antimicrobial potency of the compounds is more against gram-negative bacteria compared to gram-positive bacteria. In-vitro antioxidant activity revealed that compounds IId and IIh showed good radical scavenging activity when compared with the standard drug ascorbic acid. Further Table 3 indicates that radical scavenging activity by DPPH method increases with concentration.

CONCLUSION

All synthesized sulfonamide derivatives shown significant biological activities. In the structure-activity relationship (SAR) studies, it was reported that the incorporation of two different pharmacophores in a single structure enhanced the resulting compounds biological activity. The presence of substituents on aromatic rings also affects the antibacterial activities of compounds. Compounds with resonance electron-withdrawing substitution showed greater activities than those with electron donating substituent group.

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CONFLICT OF INTERESTS

Declared None

Table1: Physical and analytical data of the synthesized compounds (IIa-IIh)

Compd	R	R^1	Yield (%)	M.P. (ºC)	Molecular Formula	Elemental analysis Calcd. %(Found %)				
						C	H	N	O	S
IIa	H	C_6H_5	70	>250	$C_{23}H_{18}O_4N_4S$	61.88 (61.87)	4.04 (4.00)	12.56 (12.54)	14.35 (14.33)	7.17 (7.16)
IIb	H	4-CH_3 C_6H_4	65	>250	$C_{24}H_{17}O_4N_4S$	63.02 (63.01)	3.72 (3.73)	12.25 (12.26)	14.00 (14.01)	7.00 (6.99)
IIc	H	4NH_2 C_6H_4	75	>250	$C_{23}H_{19}O_4N_5S$	59.86 (59.85)	4.12 (4.10)	13.88 (13.90)	15.18 (15.19)	6.94 (6.93)
IId	H	4-NO_2 C_6H_4	65	>250	$C_{23}H_{17}O_6N_5S$	56.21 (56.23)	3.46 (3.45)	14.26 (14.27)	19.55 (19.54)	6.51 (6.50)
IIe	CH_3	C_6H_5	70	>250	$C_{24}H_{20}O_4N_4S$	62.61 (62.60)	4.35 (4.34)	12.17 (12.15)	13.91 (13.90)	6.96 (6.95)
IIf	CH_3	4-CH_3 C_6H_4	65	>250	$C_{25}H_{19}O_4N_4S$	63.69 (63.70)	4.03 (4.05)	11.89 (11.88)	13.59 (13.60)	6.79 (6.80)
IIg	CH_3	4-$NH_2C_6H_4$	70	>250	$C_{24}H_{21}O_4N_5S$	60.63 (60.62)	4.42 (4.43)	13.47 (13.48)	14.73 (14.72)	6.73 (6.72)
IIh	CH_3	4-NO_2 C_6H_4	65	>250	$C_{24}H_{19}O_6N_5S$	57.02 (57.04)	3.76 (3.77)	13.86 (13.84)	19.00 (19.01)	6.34 (6.33)

Table 2: Antibacterial activity

Compound	Zone of inhibition in mm.			
	Gram positive bacteria		Gram negative bacteria	
	Staphylococcus aureus	***Bacillus subtilis***	***Escherichia coli***	***Klebsiella pneumoniae***
IIa	13	14	16	17
IIb	17	16	17	16
IIc	18	17	19	16
IId	22	21	20	19
IIe	15	14	17	17
IIf	16	15	18	18
IIg	17	16	18	18
IIh	20	21	22	20
Control	-	-	-	-
Standard Drug	30	30	32	35

Table3: Antioxidant activity

compound	% inhibition at different concentration(µg/ml)			
	10	**50**	**100**	**200**
IIa	46	58	65	78
IIb	43	51	64	73
IIc	43	52	67	73
IId	59	59	75	90
IIe	44	56	63	72
IIf	44	53	65	78
IIg	46	60	68	82
IIh	57	64	75	88
Standard	65	83	88	90

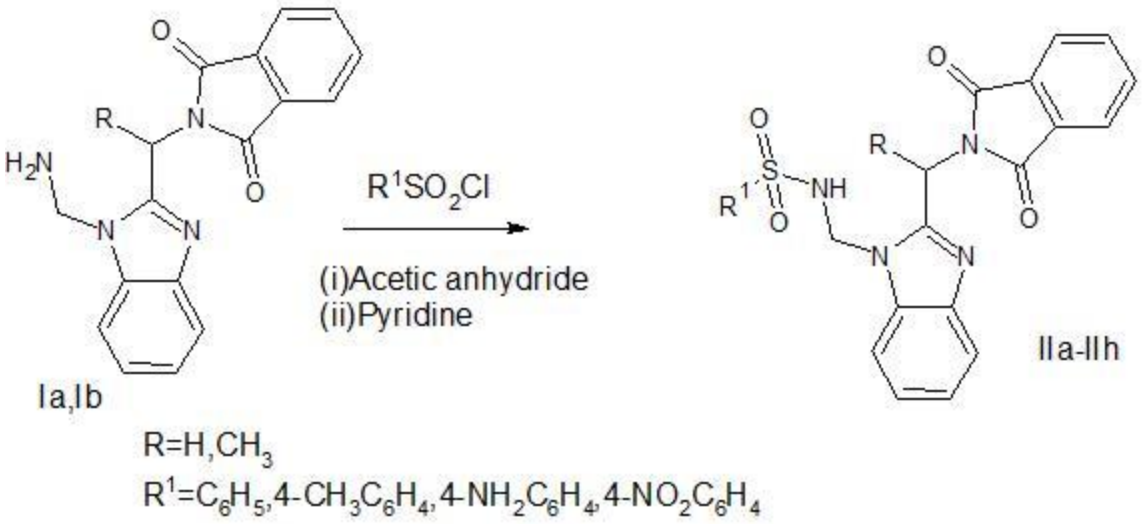

Figure1: Scheme

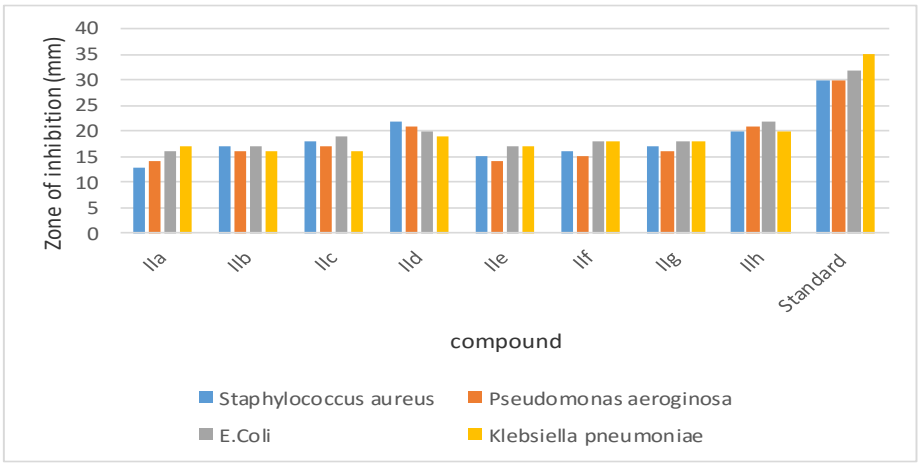

Figure2: Antibacterial activity

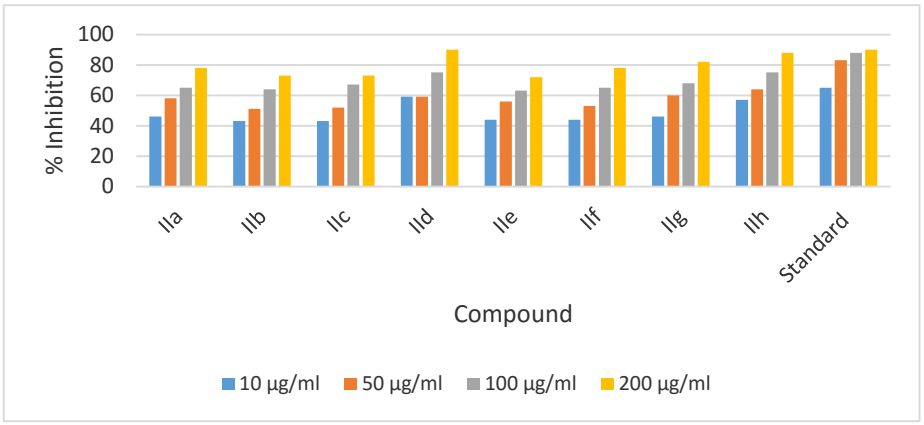

Figure3: Antioxidant activity

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