International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF NOVEL ARYL SULFONE DERIVATIVES

Shipra Bhati

Department of Chemistry, The Oxford College of Engineering, (Affiliated to Visvesvaraya Technological University, Belagavi, Karnataka), Bommanahalli, Bangalore-560 068, Karnataka, India

***Corresponding author e-mail:** shiprabhati@yahoo.com

ABSTRACT

A series of some new aryl sulfone derivatives containing benzimidazole moiety were synthesized. The compounds were characterized by means of IR,^{1}HNMR and elemental analysis. The compounds were evaluated for antibacterial activity against both gram positive and gram negative organisms with standard benzyl penicillin. Synthesized compounds exhibited significant biological activity.

Keywords: Benzimidazole, Sulfone, Antibacterial.

INTRODUCTION

Hetero cycles are important structural unit found in a wide range of biologically active compounds. Benzimidazoles are a class of hetero cyclic compounds with a broad spectrum of biological activities.[1-3]. Various useful synthetic analogs with improved therapeutic properties can be obtained by structural modifications. Sulfones are a major class of organo sulfur compounds that have been extensively used as versatile intermediates in organic synthesis.[4,5] Sulfones are very well known for their chemotherapeutic properties. Sulfones have been used in the treatment of trachoma,malaria and taxoplasmosis.[6,7] The aryl sulfones are common structure in valuable molecules in field such as pharmaceuticals,agrochemicals and polymer science.[8]Diaryl sulfones have been reported to inhibit HIV-1 reverse transcriptase[9,10] and diphenyl sulfones is useful as an intermediate for synthesis of 4,4'-diamino diphenyl sulphones (Dapsone) which is effective for leprosy treatment.[11] Cyclic sulfones have also been investigated as the key sub unit and scaffold for the construction of biologically active molecules such as protease and β-lactamase inhibitors.[12,13] The biological profile of sulfones derivatives is very extensive.[14-19]The present communication reports the synthesis of some new sulfone derivatives incorporating the bioactive benzimidazole nuclei.

MATERIAL & METHOD

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 phthalyl benzimidazoles (Ia-Ib) were synthesized by reported method.[20]

Synthesis of 4-(N-methyl phthalyl benzimidazolo)-thiophenol (IIa)-Equimolar amount of N-methyl phthalyl benzimidazoles and 4-chloro thiophenol(each 0.01 mole) were taken in round bottom flask,a pinch(0.1gm) anhydrous K_2CO_3 was added and the contents were refluxed for 6-8 hours using 1,4-dioxane (10 ml.) as solvent. The resultant solution was decanted leaving the unreacted K_2CO_3 in the flask,and then poured into crushed ice. The solution was kept overnight in the refrigerator. On cooling a solid mass separated out which was filtered and dried.

Yield:72%.m.p.225ºC,MolecularFormula:$C_{22}H_{15}O_2N_3S$,FTIR (KBr, Cm^{-1}):1750, 1715 (>C=O, Phthalimido), 1630 (C=N str), 2560(-SH).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.42 (s, 1H,SH), 7.45-7.83(m, 12H, ArH).

Synthesis of [4'-(N-methyl phthalyl benzimidazolo) -phenyl]-2 tolyl sulphides (IIIb)- Equimolar amount of 4-(N-methyl phthalyl benzimidazolo)-thiophenol (IIa) and o-tolyl chloride(each 0.01 mole) were taken in round bottom flask. A pinch (0.01 gm) anhydrous K_2CO_3 was added and the contents were refluxed for 6-8 hours in presence of dry acetone (10 ml)as the solvent. The resultant solution was decanted ,excess acetone was distilled off and the solution was cooled. A solid mass separated out which was filtered, dried and recrystallized from acetone.

Yield:70%.m.p.230ºC,MolecularFormula:$C_{29}H_{21}O_2N_3S$,FTIR (KBr, Cm^{-1}):1751, 1710 (>C=O, Phthalimido), 1632 (C=N str), 722(-CS).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.48(s, 3H,C-CH3), 7.40-7.78(m, 16H, ArH).

Synthesis of [4'-(N-methyl phthalyl benzimidazolo)-phenyl]-2 tolyl solfones (IVb)-0.01 mole of [4'-(N-methyl phthalyl benzimidazolo)-phenyl]-2 tolyl sulphides (IIIb) was dissolved in minimum amount of glacial acetic acid (5-7 ml.).After dissolution 5-7 ml. Of H_2O_2 was added dropwise to the above solution with constant magnetic stirring for half an hour. The reaction mixture was then kept at room temperture for 30 minutes. It was then further stirred on the magnetic stirrer for the next half an hour and poured dropwise with constant shaking into crushed ice. The resultant solution was then left overnight in the refrigerator. The product so formed was filtered and dried to give sulfones.

The other derivatives were synthesized following same procedure. The physical and analytical data are given in Table1.

IV_a:FTIR (KBr, Cm^{-1}):1770, 1715 (>C=O, Phthalimido), 1630 (C=N str), 1138(-SO_2,sym.), 1305(-SO_2,asym.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.55 (s, 2H, CH_2), 7.65-7.92(m, 17H, ArH).

IV_b:FTIR (KBr, Cm^{-1}):1765, 1720 (>C=O, Phthalimido), 1632 (C=N str), 1139(-SO_2,sym.), 1305(-SO_2,asym.),2932(-CH,alkyl str.vibration).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.57(s, 2H, CH_2), 7.67-7.82(m, 16H, ArH).

IVc:FTIR (KBr, Cm^{-1}):1750, 1715 (>C=O, Phthalimido), 1625 (C=N str), 1520 (-NO2),1137(-SO_2,sym.), 1306(-SO_2,asym.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.60 (s, 2H, CH_2), 7.60-7.90(m, 16H, ArH).

IVd:FTIR (KBr, Cm^{-1}):1751, 1710 (>C=O, Phthalimido), 1525 (C=N str), 1520(-NO2)1140(-SO_2,sym.), 1305(-SO_2,asym.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.56 (s, 2H, CH_2), 7.62-7.88(m, 15H, ArH)

IVeFTIR (KBr, Cm^{-1}):1768, 1715 (>C=O, Phthalimido), 1632 (C=N str), 1140(-SO_2,sym.), 1302(-SO_2,asym.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.55 (s, 2H, CH_2), 7.65-7.92(m, 17H, ArH).

IV_f:FTIR (KBr, Cm^{-1}):1764, 1720 (>C=O, Phthalimido), 1634 (C=N str), 1142(-SO_2,sym.), 1307(-SO_2,asym.),2934(-CH,alkyl str.vibration).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.58(s, 2H, CH_2), 7.66-7.84(m, 16H, ArH).

IVg:FTIR (KBr, Cm^{-1}):1752, 1713 (>C=O, Phthalimido), 1630(C=N str), 1522(-NO2)1139(-SO_2,sym.), 1309(-SO_2,asym.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.62 (s, 2H, CH_2), 7.62-7.92(m, 16H, ArH).

IVh:FTIR (KBr, Cm^{-1}):1750, 1715 (>C=O, Phthalimido), 1530 (C=N str), 1525(-NO2)1138(-SO_2,sym.), 1310(-SO_2,asym.).^{1}HNMR (DMSO, ppm, 300 MH_Z), 2.54 (s, 2H, CH_2), 7.58-7.78(m, 15H, ArH).

ANTIBACTERIAL ACTIVITY

Cup plate method [21,22]using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of IVa-IVh against Bacillus subtilis, Staphylococcus aureus, Eischerria coli and Pseudomonas aeroginosa. 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 petridishes 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 were represented in Table2.

RESULTS AND DISCUSSION

The results of antibacterial activity revealed that the compounds (IVa-IVh) exhibited moderate to considerable activity when compared to reference standard benzyl penicillin. In addition it was found that IVh showed maximum activity against gram positive organism B.subtilis and this may be due to the presence of nitro group. Moreover it was also

observed that the compounds IVd and IVh showed remarkable activity against gram positive and gram negative organisms. Against Staphylococcus aureus compound IVb,IVc,IVf showed moderate activity while Compound IVh showed maximum activity against E-coli. Compounds IVa,IVb,IVe,IVf and IVg showed moderate activity against P.aeroginosa.

CONCLUSION

All synthesized arylsulfone derivatives shown significant activity against selected bacterial strains. Structure activity relationship have shown that the compounds having electron withdrawing nitro group enhanced antibacterial activity.

ACKNOWLEDGEMENT

The author is thankful to SAIF(Sophisticated Analytical Instrument Facility),CDRI(Central Drug research Institute),Lucknow for FTIR and ^{1}H NMR analysis. Thanks are also due to Head, Department of Chemistry, J.N.V. University,Jodhpur for providing laboratory facilities.

Table1 :Physical and analytical data of compounds (IVa-IVh)

Compd.No.	R	R_1	Yield (%)	M.P. (ºC)	Molecular Formula	Elemental analysis Found % (Calcd.%)				
						C	H	N	O	S
IVa	H	C_6H_5	70	>250	$C_{28}H_{19}O_4N_3S$	68.11 (68.15)	3.28 (3.85)	8.50 (8.51)	12.97 (12.98)	6.47 (6.49)
IVb	H	2-CH_3 C_6H_4	65	>250	$C_{29}H_{21}O_4N_3S$	68.64 (68.63)	4.13 (4.14)	8.29 (8.28)	12.63 (12.62)	6.28 (6.31)
IVc	H	3-$NO_2C_6H_4$	75	>250	$C_{28}H_{18}O_6N_4S$	62.44 (62.45)	3.31 (3.34)	10.38 (10.40)	17.84 (17.84)	5.93 (5.94)
IVd	H	2,4-$(NO_2)_2$ C_6H_3	65	>250	$C_{28}H_{17}O_8N_5S$	57.61 (57.63)	2.90 (2.91)	12.01 (12.00)	21.94 (21.95)	5.47 (5.48)
IVe	CH_3	C_6H_5	70	>250	$C_{29}H_{21}O_4N_3S$	68.64 (68.63)	4.13 (4.14)	8.29 (8.28)	12.61 (12.62)	6.30 (6.31)
IVf	CH_3	2-CH_3 C_6H_4	65	>250	$C_{30}H_{23}O_4N_3S$	69.08 (69.09)	4.38 (4.41)	8.05 (8.06)	12.29 (12.28)	6.12 (6.14)
IVg	CH_3	3-$NO_2C_6H_4$	70	>250	$C_{29}H_{20}O_6N_4S$	63.03 (63.04)	3.61 (3.62)	10.15 (10.14)	17.38 (17.39)	5.80 (5.79)
IVh	CH_3	2,4-$(NO_2)_2$ C_6H_3	65	>250	$C_{29}H_{19}O_8N_5S$	58.27 (58.29)	3.17 (3.18)	11.73 (11.72)	21.45 (21.44)	5.35 (5.36)

Table 2: Antibacterial activity

Compound	Zone of inhibition in mm.			
	Bacillus subtilis	Staphylococcus aureus	E.Coli	Pseudomonas aeroginosa
IVa	12	18	12	15
IVb	11	15	16	17
IVc	16	15	14	19
IVd	20	20	23	21
IVe	14	19	13	16
IVf	14	17	17	17
IVg	18	19	19	17
IVh	29	24	28	23
Standard Drug	30	26	32	28

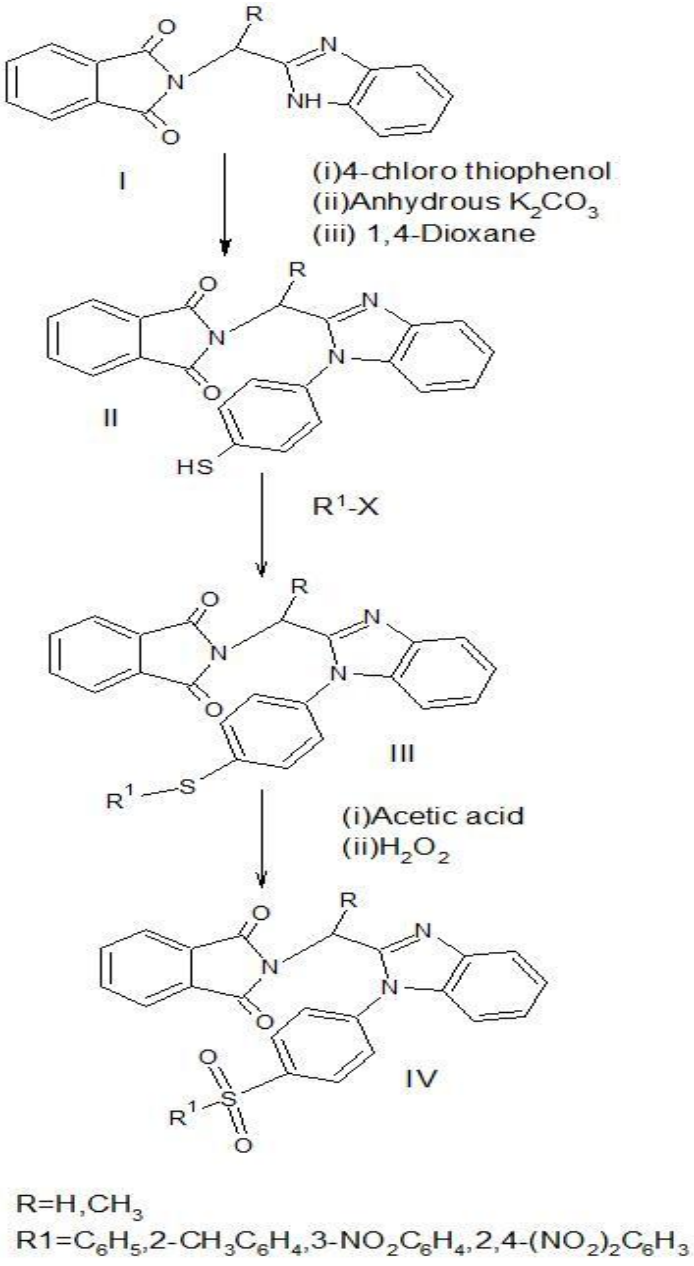

Figure 1:Scheme

REFERENCES

1. Kumar D,Jacob MR,Reynolds MB,Kerwin SM,Biorg Med Chem Lett ,2002;10:3997-4004.
2. Suganthi K,Kannan M,Velrajan G,Indian J Heterocyclic Chem,2005;15:173-80.
3. Kavali JR ,Badami BV , Indian J Heterocyclic Chem,2003;12(3):249-52.

4. Schank K,Patai S,Rappoport Z,Stirling C,In The Chemistry of Sulphones and Sulphoxides,2nd ed.,New York;John Wiley and Sons:1988.
5. Simpkins NS,Sulphones in Organic Synthesis,Pergamon;Oxford:1993.
6. Illiader P,Meshnick SR,Macreadie IG,Antimicrob Agents Chemother,2005;49:41-5.
7. Artico M,Silvestri R,Massa S,J Med Chem,1996;39:522-30.
8. Trost BM,Shen HC,Surivet JP,J Am Chem Soc,2004;126:12565-79.
9. Neamati N,Mazumder A,Zhao H,Sunder S,Burke TR,Scbultz RJ,Pommier Y,Antimicrob Agents Chemothes,1997;41:385-9.
10. Regina LG,Coluccia A,Pisalelli F,Bergamini A,Sinistro A,Cavazza A,Maga G,Samvele A,Zanoli S,Novellino E,Artico M,Silvestri R,J Med Chem,2007;50(20):5034-8.
11. Repichet S,Le Roux C,Hernandez P,Dubac J,Desmurs JR,J Org Chem,1999;64:6479-82.
12. Richter HGGF,Angebm P,Hubschwerlen C,Kania M,Page MGP,Specklin JL,Winkler FK,J Med Chem,1996;39:3712-22.
13. Buynak JD,Vogeti L,Chen H,Org Lett ,2001;3:2953-56.
14. Guruswamy B,Arul RK,Venkat M,Chaitanya SRK,Subrahmanya S,Darsi,PK,Eur J Chem,2013;4(4):329-35.
15. Li P,Shi Li,Yang X,Yang L,Chen XW,Wu F,Shi QC,Xu WM,He M,Hu DY,Sang BA,Bioorg Med Chem Lett,2014;24(7):1677-80.
16. Veinberg G,Shestakova I,Vorona M,Kanepe I,Lukevics E,Bioorg Med Chem Lett,2004;14(1):147-50.
17. Korzynski MD,Borys KM,Bialek J,Ochal Z,Tetrahedron Lett,2014;55(3):745-8.
18. Prajapati LM,Parmar VK,Patel MJ,Patel JR,Der Pharma Chemica,2011;3(6):53-61.
19. Dunny E,Doherty W,Paul,Evans,Paul JG,Malthouse,Nolan D,Knox AJS,J Med Chem,2013;56(17):6638-50.
20. Rajpurohit S,Sah P , Asian J Chem,2005;17(2):949-54.
21. Zavrsnik D, Muratovic S, Makuc D ,Molecules, 2011; 16(7): 6023–40.
22. Banty AL, The Antimicrobial Susceptibility Test: Principle and Practice, Illus,Lea Febiger(eds),Philadelphia;PA:USA:1976.