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Synthesis and in-vitro antimicrobial evaluation of some novel phthalyl substituted aryl sulphones and sulphonamides

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ABSTRACT

A new series of phthalyl substituted Sulphones (**$IV_{a–f}$,VI**) and Sulphonamides (**$VIII_{a–b}$**) were synthesized from phthalimide. First Phthalimide was converted to a thiophenol on treating with 4-chloro thiophenol (**II**), which when reacted with various aryl halides gave subsequent sulphides (**III_{a-f},V**). Further oxidation with hydrogen peroxide gave the title compounds (**IV_{a-f},V**). The sulphonamides were synthesized from mannich bases by reating with aryl sulphonyl chlorides (**$VIII_{a-b}$**).Spectral techniques of IR, ^{1}HNMR, Mass and elemental analysis were used to characterize the synthesized compounds. All the synthesized compounds (**$IV_{a–f}$,VI**) and (**$VIII_{a-b}$**) were screened for their antibacterial activity against the pathogenic strains *E. coli, S. aureus* and *S. typhii* while antifungal activity was evaluated against *A. niger, Penicillium sp*. and *C. albicans*.

Keywords: Phthalimide, Sulphones, Sulphonamides, Antibacterial and Antifungal activity.

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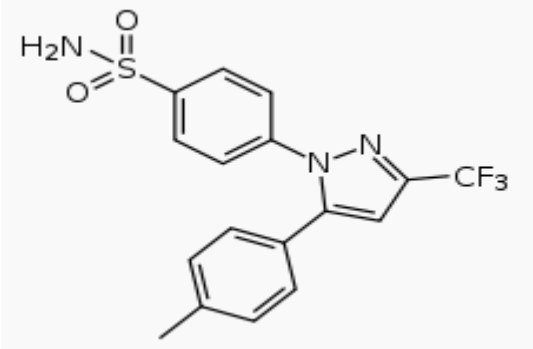
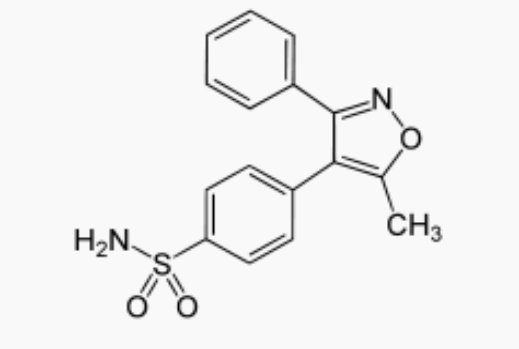
INTRODUCTION

The chemistry of heterocyclic compounds has attracted attention in recent times due to its increasing importance in the field of pharmaceuticals and industries. Sulfones, sulfonamides and amino sulfones are very well known for their chemotherapeutic importance.Sulfonamides and sulfones have been used in the treatment of leprosy, trachoma, malaria, and taxoplasmosis [1-6].

Sulfones are a major class of organosulfur compounds [7] that have been extensively used as versatile intermediates in organic synthesis.[8] The importance of the sulfone functional group in synthetic organic chemistry warrants significant interest in the development of new methodologies related to the introduction of the sulfone functionality into an organic molecule as well as the further synthetic transformation of the sulfone intermediate, and, when desirable and possible, its eventual elimination from the target. The sulfonamide group is also found in many therapeutic agents, including drugs for the treatment of bacterial and viral infections.[9] More recently, it has been found to be a key constituent of a new class of cyclooxygenase inhibitors such as Celecoxib[10] and Valdecoxib.[11]



Celecoxib



Valdecoxib

Among sulfones, aryl sulfones are widely used in medicinal chemistry and found on several drugs, including the recently developed selective COX-2 inhibitor Vioxx.[12] Many methodologies exist for the preparation of aryl sulfones. Among these methods figure the oxidation of corresponding sulfides,[13] the reaction of organolithium or Grignard reagents with sulfonate esters[14] and the sulfonylation of arenes,[15] which are attractive methods because of their simplicity.

Based on these reports, we thought to apply this methodology for the preparation of aryl sulfones

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MATERIALS AND METHODS

Experimental

General procedures

All the melting points were taken in open capillary tubes and are uncorrected IR (KBr) spectra were recorded on FTIR RX 1 Perkin–Elmer Spectrophotometer. ^{1}HNMR were determined on Bruker DRX 400 MHz Spectrophotometer with DMSO as the solvent. Mass was recorded on a JEOL–ACCUT of JMS–T100LC Mass Spectrometer having a DART source.

Synthesis of 4-(1',3'-dioxo-1',3'-dihydro-(2'H)-isoindol-2'-yl)-thiophenol (II)

Equimolar amount of phthalimide (**I**) and 4-chloro thiophenol(each 0.01 mole) were taken in a round bottom flask, a pinch (0.1 gm) anhydrous K_2CO_3 was added and the contents were refluxed for 6-8 hours using 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 :81%, m.p.- 204° C, $C_{14}H_9O_2NS$, IR(KBr): 1751,1710 (>C=O, phthalimido), 3018(-CH, aromatic stretching vibration), 2565(-SH) cm^{-1}, ^{1}HNMR: δ2.40 (s,1H,SH), δ 7.09-7.82 (m,8H,ArH), % Calc. C-65.88, H- 3.53, N- 5.49, S- 12.55, Obs. C- 65.81, H- 3.49, N- 5.43, S- 12.62, MS (EI) : m/z: 254

Synthesis of [4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-aryl/(2/3/4/2,4-substituted aryl)/benzyl sulphides (III_{a-f}) and (V)

Equimolar amount of intermediate (**II**) and various aryl halides (each 0.01 mole) were taken in a round bottom flask. A pinch (0.1 gm) anhydrous K_2CO_3 was also added and the contents were then refluxed on a water bath for 6-7 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.

[4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-phenyl sulphides (III_a)

Yield-72%, m.p. 228° C, $C_{20}H_{13}O_2NS$,IR(KBr):1750,1700(>C=O, phthalimido), 720(-C-S) cm^{-1}, ^{1}HNMR: δ 7.43-7.81 (m,13H, ArH), % Calc. C-72.52, H-3.93, N-4.22, S-9.67,Obs. C-72.56, H-3.87, N-4.18, S-9.74. MS (EI) : m/z: 330

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-2-tolyl sulphide (III_b)

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Yield-70%, m.p.-224° C, $C_{21}H_{15}O_2NS$,IR(KBr) :1751,1715(>C=O, phthalimido), 718 (-C-S), 2930(-CH, alkyl stretching vibration) cm^{-1} , ^{1}HNMR: δ 2.50 (s,3H,C-CH3),7.32-7.98 (m,12H,ArH), % Calc C-73.04, H-4.35, N-4.06, S-9.28,Obs. C-73.11, H-4.40, N-3.99, S-9.21. MS (EI) : m/z:344

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-4-tolyl sulphide (III_c)

Yield-69%, m.p.-228° C, $C_{21}H_{15}O_2NS$,IR(KBr) :1751, 1715(>C=O, phthalimido), 718 (-C-S), 2945(-CH, alkyl stretching vibration) cm^{-1},% Calc. C-73.04, H-4.35, N-4.06, S-9.28, Obs. C-72.95, H-4.32, N-4.13, S-9.34. MS (EI) : m/z:344

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-3-nitrophenyl sulphide (III_d)

Yield-68%, m.p. -232° C, $C_{20}H_{12}O_4N_2S$, IR(KBr): 1749,1710(>C=O, phthalimido), 722(-C-S), 1520(-NO_2) cm^{-1}, % Calc. C-63.83, H-3.19, N-7.45, S-8.51,Obs. C-63.79, H-3.25, N-7.51,S-8.47. MS (EI) : m/z:375

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-4-nitrophenyl sulphide (III_e)

Yield-67%, m.p.-230° C, $C_{20}H_{12}O_4N_2S$, IR(KBr): 1749,1710(>C=O, phthalimido), 722 (-C-S), 1520 (-NO_2) cm^{-1}, %Calc. C-63.83, H-3.19, N-7.45, S-8.51, Obs. C-63.77, H-3.22, N-7.51, S-8.44. MS (EI) : m/z:375

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-2,4-dinitrophenyl sulphide (III_f)

Yield-69%, m.p-236° C, $C_{20}H_{11}O_6N_3S$,IR(KBr): 1751,1710(>C=O, phthalimido), 725 (-C-S), 1525(-NO_2) cm^{-1} , % Calc.- C-57.01, H-2.61, N-9.98, S-7.60, Obs. C-57.08, H-2.54, N-9.90, S-7.65. MS (EI) : m/z :420

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-benzyl sulphide (V)

Yield-68% , m.p-226° C, $C_{21}H_{15}O_2NS$, IR(KBr) :1750,1700(>C=O, phthalimido), 720(-C-S), 2845(-CH, stretching vibration) cm^{-1}, % Calc. C-73.04, H-4.35, N-4.06, S-9.28, Obs. C-73.09, H-4.40, N-4.00, S-9.32. MS (EI) : m/z:344

Synthesis of [4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-aryl/(2/3/4/2,4-substituted aryl)/benzyl sulphones (IV_{a-f} and VI).

0.01 mole of (**III $_{a-f}$ or V**) 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 temperature for 30 minutes. It was then further stirred on the magnetic stirrer for next half an hour and then 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 sulphones.

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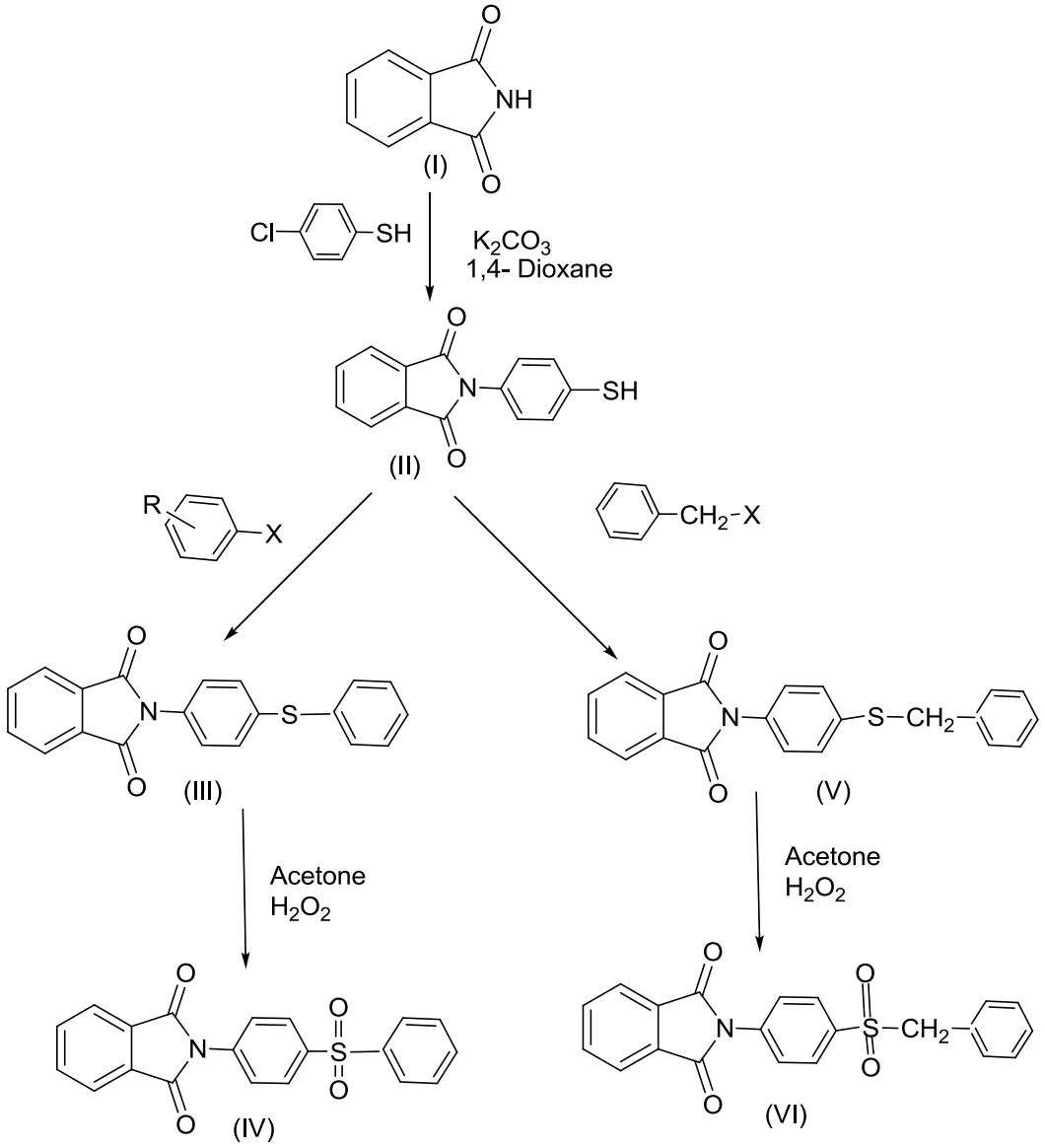

SCHEME 1

[4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-phenyl sulphone (IV_a)

Yield-66%, m.p.-226° C, $C_{20}H_{13}O_4NS$, IR(KBr) :1750,1700(>C=O, phthalimido), 1139 (-SO_2, sym.), 1306(SO_2, asym) cm^{-1}, % Calc. C-66.12, H-3.58, N-3.86, S-8.82, Obs. C-66.17, H-3.64, N-3.91, S-8.71. MS (EI) : m/z:362

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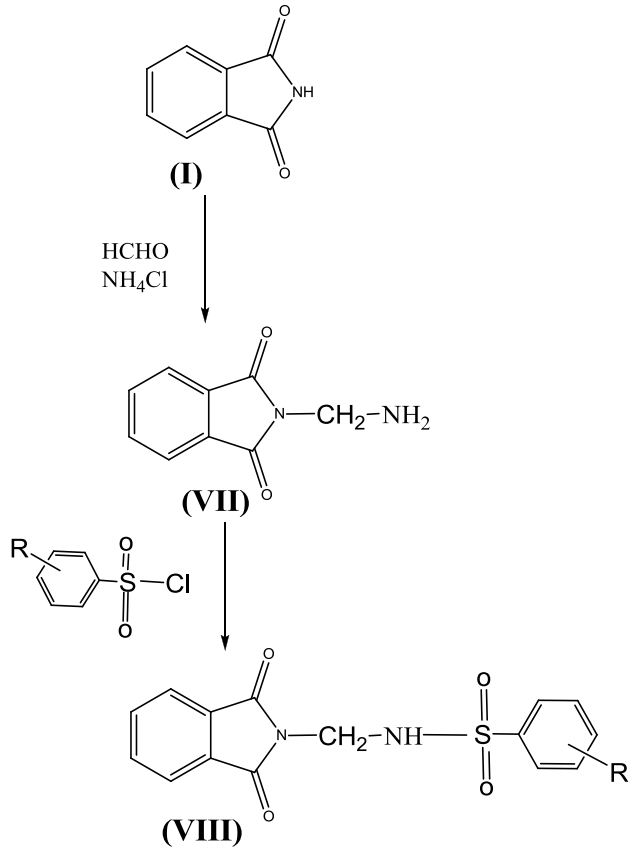

SCHEME 2

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-2-tolyl sulphone (IV_b)

Yield-68%, m.p.-224° C, $C_{21}H_{15}O_4NS$, IR(KBr) : 1751,1750(>C=O, phthalimido), 1138 (-SO_2, sym.), 1307(SO_2, asym), 2920 (-CH,alkyl stretching vibration) cm^{-1}, % Calc. C-66.84, H-3.98, N-3.71, S-8.49, Obs. C-66.78, H-3.92, N-3.78, S-8.41. MS (EI) : m/z:376

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-4-tolyl sulphone (IV_c)

Yield-68%, m.p.-236° C, $C_{21}H_{15}O_4NS$, IR(KBr) : 1751,1715(>C=O, phthalimido), 1138 (-SO_2, sym.), 1307(SO_2, asym), 2930 (-CH, alkyl stretching vibration) cm^{-1}, %Calc. C-66.84, H-3.98, N-3.71, S-8.49, Obs. C-66.79, H-4.02, N-3.64, S-8.53. MS (EI) : m/z:376

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-3-nitrophenyl sulphone (IV_d)

Yield-65%, m.p. -232° C, $C_{20}H_{12}O_6N_2S$, IR(KBr): 1749,1710(>C=O, phthalimido), 1137 (-SO_2, sym.), 1307(SO_2, asym), 1520 (-NO_2) cm^{-1}, % Calc. C-58.52, H-2.94, N-6.86, S-7.84, Obs. C-58.89, H-2.99, N-6.80, S-7.89. MS (EI) : m/z:407

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-4-nitrophenyl sulphone (IV_e)

Yield-65%, m.p.-228° C, $C_{20}H_{12}O_6N_2S$, IR(KBr):1749,1710(>C=O, phthalimido), 1137 (-SO_2, sym.), 1307(SO_2, asym), 1520 (-NO_2) cm^{-1} , % Calc. C-58.82, H-2.94, N-6.86, S-7.84, Obs. C-58.88, H-2.89, N-6.93, S-7.76. MS (EI) : m/z:407

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-2,4-dinitrophenyl sulphone (IV_f)

Yield-69%, m.p-226° C, $C_{20}H_{11}O_8N_3S$, IR(KBr) : 1751,1710(>C=O, phthalimido), 1138 (-SO_2, sym.), 1306(SO_2, asym), 1525 (-NO_2) cm^{-1}, ^{1}HNMR: δ 7.27-7.83 (m,11H,ArH), % Calc- C-52.98, H-2.43, N-9.27, S-7.06, Obs. C-53.00, H-2.37, N-9.35, S-7.01. MS (EI) : m/z:452

4'-(1'',3''-dioxo-1'',3''-dihydro-(2''H)-isoindol-2''-yl)-phenyl]-benzyl sulphone (VI)

Yield-68% , m.p-220° C, $C_{21}H_{15}O_4NS$, IR(KBr) : 1750,1700(>C=O, phthalimido), 1139 (-SO_2, sym.), 1306(SO_2, asym), 2855 (-CH stretching vibration) cm^{-1}, ^{1}HNMR: δ3.36 (s,2H,S-CH_2), 7.39-7.96 (m,13H,ArH) % Calc. C-66.84, H-3.98, N-3.71, S-8.49, Obs. C-66.91, H-4.01, N-3.75, S-8.40 MS (EI) : m/z:376

Synthesis of (1,3-dioxo-1,3-dihydro-(2H)-isoindol-2-yl)-amino ethane (Mannich base)(VII)

Equimolar amount of phthalimide (**I**) , ammonium chloride and formaldehyde (0.01M) were taken and the contents were refluxed on a water bath at 65-70°C for 4-5 hours in presence of absolute ethanol (10ml)as solvent. The resultant solution was concentrated and then kept in a refrigerator overnight .On cooling, a solid mass separated out which was filtered, dried and recrystallized from absolute ethanol. Yield-85%, m.p. -232° C, Mol. Formula-$C_9H_8O_2N_2$, IR(KBr): 1749,1710(>C=O, phthalimido), 3012(CH, aromatic stretching vibrations),3412(NH_2) cm^{-1}, ^{1}HNMR: δ 2.96 (s,broad,2H,NH_2), 3.36(s,2H,N-CH_2-NH_2),7.23-7.81(m, 4H, ArH), % Calc. C-61.36, H-4.54, N-15.90, Obs. C-61.42, H-4.48, N-15.85. MS (EI) : m/z: 175

Synthesis of [(1',3'-dioxo-1',3'-dihydro-(2'H)-isoindol-2'-yl)-methyl]-aryl/4-substituted aryl sulphonamides ($VIII_{a,b}$) (Mannich base)

Equimolar amount of Mannich base (**VII**), various aryl sulphonyl chlorides 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 resultant solution was concentrated and then poured into crushed ice. The product so formed was filtered and dried and recrystallized from absolute ethanol.

[(1',3'-dioxo-1',3'-dihydro-(2'H)-isoindol-2'-yl)-methyl]-benzene sulphonamides ($VIII_a$)

Yield- 86%, m.p-222° C, $C_{15}H_{12}O_4N_2S$, IR(KBr): 1750,1715(>C=O, phthalimido), 1139 (-SO_2, sym.), 1306(SO_2, asym), 3203 (-NH), 2915 (-CH, alkyl stretching vibration) cm^{-1}, ^{1}HNMR: δ 3.33

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(s,2H,N-CH_2-NH), 5.10 (s,broad,1H,-NH-) 7.15-7.88(m,9H,ArH) % Calc. C-56.96, H-3.80, N-8.86, S-10.13, Obs. C-57.01, H-3.85, N-8.80, S-10.06. MS (EI) : m/z:315

[(1',3'-dioxo-1',3'-dihydro-(2'H)-isoindol-2'-yl)-methyl]-4-tolyl sulphonamide ($VIII_b$)

Yield-85%, m.p-226° C, $C_{16}H_{14}O_4N_2S$, IR(KBr) : 1745,1710(>C=O, phthalimido), 1142 (-SO_2, sym.), 1310 (SO_2, asym), 3203 (-NH), 2920 (-CH, alkyl stretching vibration) cm^{-1}, ^{1}HNMR: δ 2.47 (s,3H,C-CH_3), 3.38 (s,2H,N-CH_2-NH), 5.15 (s,broad,1H,-NH-), 7.09-7.82 (m,8H,ArH) % Calc. C-58.18, H-4.24, N-8.48, S-9.70, Obs. C-58.11, H-4.18, N-8.52, S-9.65. MS (EI) : m/z: 329

Antimicrobial Screening

Antimicrobial screening of the sulphones and sulphonamides were done following the disc diffusion technique.[16] All the compounds **(IV_{a-f},VI)** and (**$VIII_{a-b}$**) were screened for their *in vitro* antibacterial activity against *S. aureus*, *E. coli* and *S. typhi* at 250 µg/disc with Streptomycin as the standard drug. Antifungal activity was conducted against *Aspergillus niger*, *Penicillium sp.* and *Candida albicans* at a concentration of (500 µg/disc) using Gentamycin as the standard drug. The zone of inhibition was recorded in mm after incubation of plates for 24 hrs. (antibacterial) and 72 hrs. (antifungal) at 37 °C.

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RESULT AND DISCUSSION

The IR spectral data showed characteristic bands at 1751,1710and 2565 cm^{-1} in compound (**II**) which were identified as the stretching vibrations for the >C=O of the phthalimido and SH group, confirming the formation of the thiophenol. The PMR data also showed a singlet at δ 2.40, integrating for one proton of mercapto group. Presence of C-S linkage was indicated by a band observed at 720 cm^{-1} in compound **III_a** hence confirming the joining of the aryl halide with –SH group while the PMR spectra showed an aromatic multiplet between δ 7.43-7.81 integrating for 13 protons. Oxidation of compound **III_a** with hydrogen peroxide showed the absence of C-S band at 720 cm^{-1} but two new modes at 1139 and 1306 cm^{-1} were observed in compound **IV_a,** which were identified as the symmetric and asymmetric SO_2 vibration.

Antimicrobial activity

The antimicrobial data reveals that compounds **IV_{d-f}** and **$VIII_b$** were found to be active against *E. coli* while **IV_b**, **IV_c**, and **$VIII_a$** showed moderate activity. *E.coli* proved to be a resistant strain against **IVa** and **VI** respectively**.** All the derivatives except **IV_b, IV_c** and **$VIII_a$** inhibited the growth of both *S. aureus* and *S. typhii*, whereas **IV_b** and **IV_c** showed no activity.

Against *A. niger*. **IV_f** and **$VIII_b$** were highly active with the development of only one fungal colony while the other derivatives were moderately active.The other derivatives were moderately active against *Penicillium sp.* except **IV_b, VI** and **$VIII_a$**, while **IV_f** was the only derivative active against both *A. niger* and *Penicillium sp.***.** Similar behavior was observed

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against *C. albicans* as the test strain. Most of the derivatives showed moderate activity whereas **IV_b ,IV_c, VI** and **$VIII_a$** were inactive.

Table 1 : Antibacterial activity of compounds (IV_{a-f},VI) and ($VIII_{a-b}$)

S.No.	Compound No.	*S. aureus*	*E. coli*	*S. typhii*
1	**IV_a**	+	-	+
2	**IV_b**	-	+	-
3	**IV_c**	-	+	-
4	**IV_d**	-	++	+
5	**IV_e**	+	++	+
6	**IV_f**	+	++	+
7	**VI**	+	-	+
8	**$VIII_a$**	-	+	-
9	**$VIII_b$**	+	++	+

Control : DMSO (negative); Reference Standard : Streptomycin (20-25mm)
(+++): Highly active (20-24mm)
(++): Active (15-19mm)
(+): Moderately active (8-12mm)
(-): Inactive (< 8mm)

Table 2 : Antifungal activity of compounds (IV_{a-f},VI) and ($VIII_{a-b}$)

S.No.	Compound No.	*A.Niger*	*Penicillium sp.*	*C. albicans*
1	**IV_a**	-	+	+
2	**IV_b**	+	-	-
3	**IV_c**	+	+	-
4	**IV_d**	+	+	+
5	**IV_e**	+	+	+
6	**IV_f**	++	++	+
7	**VI**	+	-	-
8	**$VIII_a$**	+	-	-
9	**$VIII_b$**	++	+	+

Control : DMSO (negative); Reference Standard : Gentamycin (No growth, no fungal colony)
(+++): Highly active (No growth, no fungal colony)
(++): Active (0-20% growth, one fungal colony)
(+): Moderately active (20-40% growth, 2-3 fungal colony)
(-): Inactive (>40%, Heavy fungal colonies)

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