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Synthesis of 2-[(4-amino or 2,4-diaminophenyl)sulfonyl] derivatives of benzimidazole, benzothiazole and 6-methyluracil as potential antimicrobial agents†

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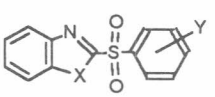
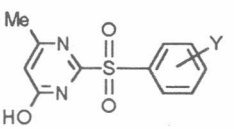
The synthesis of 2-[(4-aminophenyl)sulfonyl] derivatives of benzimidazole **1** benzothiazole **2** and 6-methyluracil **5** has been accomplished *via* $KMnO_4$-oxidation of the corresponding 2-(4-nitrophenyl)thio derivatives to the sulfones followed by dissolved-metal reduction of the nitro group. The synthesis of the 2, 4-diaminophenyl congeners **3, 4** and **6**, on the other hand, has been carried out by initial reduction of the nitro groups in the 2-(2, 4-dinitrophenyl)thio derivatives, followed by acetylation of the produced aminosulfides, oxidation to the acetylaminosulfones and finally deacetylation. The antimicrobial activity of compounds **1-5** against *Escherichia coli* is comparable to that of the antileprotic drug Dapsone.

Only few drugs are available for the treatment and control of human leprosy, a chronic infectious disease caused by *Mycobacterium leprae*[1]. Of these drugs, Dapsone (4, 4'-diaminodiphenylsulfone; DDS) has been found, since 1947, to be the only drug effective in the management of this agonizing illness[2]. However, the possible development of bacterial resistance and the high toxicity of DDS necessitated the search for new antileprotic agents[3]. Several SAR studies have been reported[4-6] on DDS and related compounds with the premise that these diaryl sulfones can have important role as antibacterial and antimalarial agents[7]. Diary sulfones, like sulfonamides, exert their biological action by inhibiting dihydropteroate synthase competitively with respect to the substrate 4-aminobenzoate (PABA)[8]. *ortho*-substitution to the sulfuryl group with electron releasing groups such as NH_2 or OH increases the activity presumably by increasing electron density on the SO_2 group (so as to mimic CO_2^- of PABA[5]) and/or by anchoring the molecule into a pharmacophoric conformation through intramolecular hydrogen bonding[6]. In addition, *ortho*-substitution is reported to inhibit metabolic oxidation of diaminodiaryl sulfones to cytotoxic hydroxylamines[3].





1 X = NH Y = 4-NH_2
2 X = S Y = 4-NH_2
3 X = NH Y = 2,4-diNH_2
4 X = S Y = 2,4-diNH_2
5 Y = 4-NH_2
6 Y = 2,4-diNH_2

The objectives of this study are to synthesize a number of 4-amino or 2, 4-diaminophenylsulfonyl derivatives of benzimidazole, benzothiazole and 6-methyluracil (compounds **1-6**) and to evaluate the antimicrobial activity of these heteroaryl sulfones against *Escherichia coli* in comparison to DDS. Naturally, the replacement of a phenyl group by a heterocyclic ring as in compounds **1-6** can have a pronounced effect on the physiochemical and stereochemical properties of this class of compounds which in turn can affect transport and binding. Part of this effect can be envisioned by a possible variation of electron density on the SO_2

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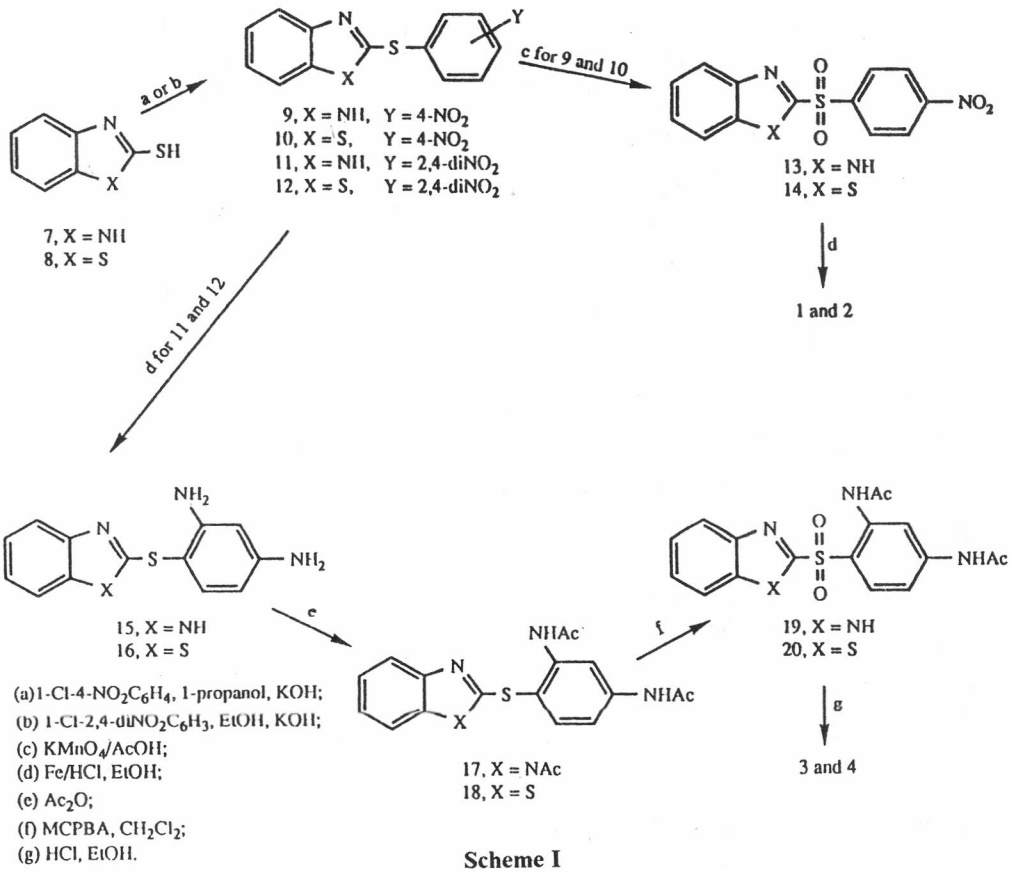


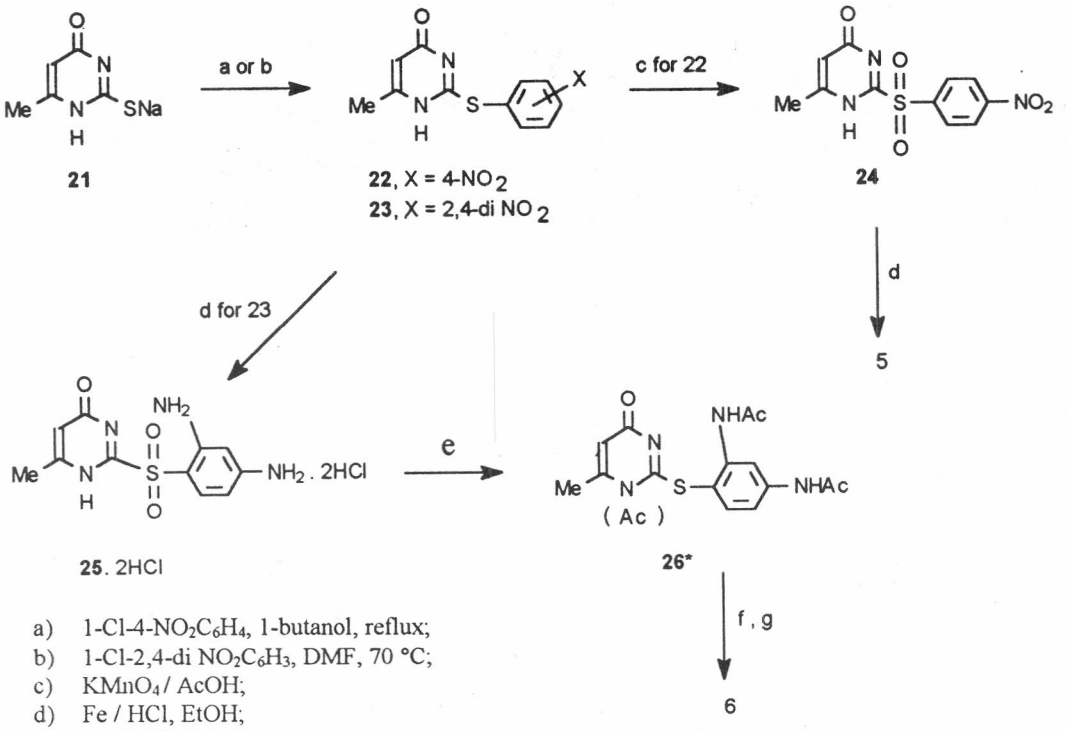
Scheme I

group and by intramolecular hydrogen bonding as described for 2-NH_2 or 2-OH substituent.

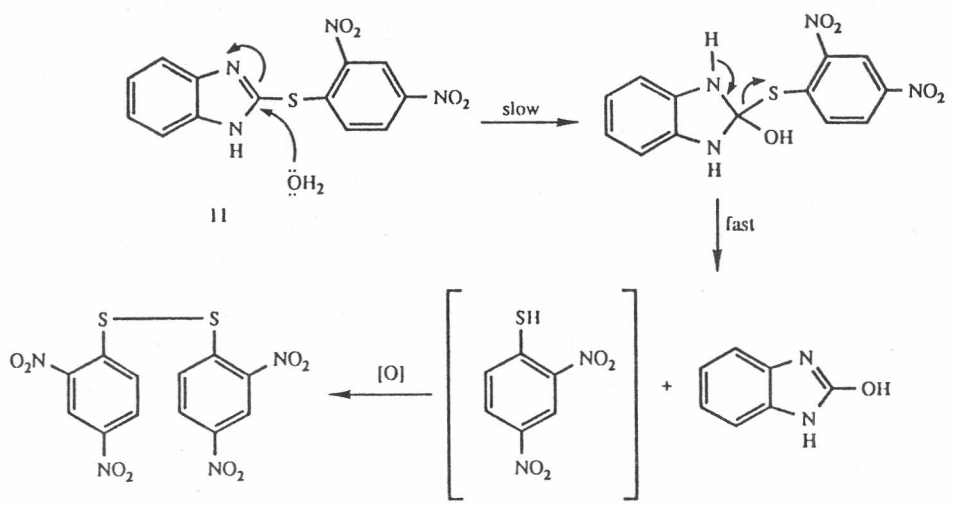
Chemistry

Synthesis of the target compounds **1-6** is illustrated in Schemes I (**1-4**) and II (**5** and **6**). In Scheme I, the reaction of benzimidazole-2-thiol **7** with 1-chloro-4-nitrobenzene in alkaline aqueous *n*-propanol gave 4-nitrophenylthiobenzimidazole **9** in 63% yield[9]. Likewise, the reaction of **7** with 1-chloro-2, 4-dinitrobenzene in ethanolic KOH gave 80% of the dinitro derivative **11**[10,11]. Nitro- and dinitrophenyl thioethers of benzothiazole **10** and **12**, respectively, were prepared similarly[11,12]. Nitrophenyl thioethers **9** and **10** were readily oxidized to the corresponding sulfones **13** and **14**, respectively, using $KMnO_4$/acetic acid[13]. Reduction of **13** or **14** with Fe/HCl in ethanol affected selective reduction of the nitro group to give the desired aminophenyl sulfones **1** and **2**, respectively. On the contrary, their dinitro counterparts **11** and **12** resisted several attempts for oxidation to the corresponding sulfones (using $KMnO_4$/AcOH, H_2O_2/AcOH or MCPBA) probably due to diminishing electron density on the sulfur atom. Accordingly, compounds **11** and **12** were initially reduced (Fe/HCl) to the aminosulfides **15** and **16** protected by acetylation to **17** and **18**, oxidized (MCPBA) to the acetylaminosulfones **19** and **20** and finally deprotected to give the diaminosulfones **3** and **4**, respectively. Acetyl group at N-1 of the intermediate **17** was cleaved possibly during work-up procedures of the oxidation step.

During the unsuccessful attempts for the oxidation of thioethers **11** and **12** to the corresponding sulfones, it was observed that heating (12 hours at 80°C) of **11** in H_2O_2/AcOH resulted in sulfide bond cleavage to give 2-hydroxybenzimidazole (45%) and another side product which was identified (m.p.[14], IR, NMR) as 2, 2', 4, 4'-tetranitrodiphenyldisulfide (48%) (Scheme III). Significantly, identical treatment of **12** resulted in no such cleavage and the benzothiazole thioether was recovered unchanged. It is conceivable that sulfide cleavage resulted from S_NAr type reaction in which the first step (rate determining[15]) is a nucleophilic attack (probably by H_2O) at C-2 of the hetero ring followed by fast departure of the dinitrophenylthiolate anion. In benzimidazole thioether **11**, the first step is accelerated by the strong –I ef-



Scheme II



Scheme III—Proposed mechanism for sulfide bond cleavage in **11** and disulfide formation.

fect of the two nitrogen atoms, a condition which is not quite permissible to the benzothiazole congener. It was also significant to observe that nucleophilic attack occurred at C-2 of the benzimidazole system rather than at C-1 of the phenyl ring as the most electropositive center irregardless to the possibly good-leaving heterothiolate anion. The above observations, in fact, emphasize and demonstrate nucleophilic attack as the rate determining step in S_NAr reactions[15]. Naturally, the presence of an oxidant (H_2O_2) and prolonged heating promoted disulfide production[16].

The above considerations regarding sulfide cleavage and disulfide formation gained further

support as these side reactions became more pronounced during the synthesis of 4-amino- and 2, 4-diaminophenylsulfonyluracils **5** and **6** (Scheme II). In this case, the disulfide production was encountered during several attempts for the preparation and oxidation of 4-nitro- and 2, 4-dinitrophenylthiouracils **22** and **23**, respectively. For example, when 6-methyl-2-thiouracil sodium salt **21** was refluxed in DMF for 1 hr with 1-chloro-4-nitrobenzene, there were quantitative conversions to 4, 4'-dinitrodiphenyldisulfide[16] and 6-methyluracil. Apparently, the more electropostive C-2 of the thiouracil ring constituted a better substrate (than in case of **11**) for nucleophilic attack. In addition, and perhaps more significantly, is the possible stabilization of the Meisenheimer complex brought about by the distribution of the negative charge on the oxygen atom of the carbonyl group. Nevertheless, it was possible to optimize the reaction conditions to obtain 4-nitrophenylthiouracil **22** in 46% yield (together with 20% of the disulfide bt-product) by conducting the reaction in *n*-butanol for 40 hr. Also, thioether **23** was obtained in a good yield when prepared in DMF at 70°C. Oxidation of **22** ($KMnO_4$/AcOH) gave 33% of sulfone **24** in addition to 65% of the disulfide side product. Reduction of **24** provided the aminophenylsulfone **5**. As in the case of dinitrophenyl thioethers **11** and **12**, compound **23** resisted oxidation to the sulfone. In one attempt, it was heated with H_2O_2/AcOH to produce only uracil and disulfide. Therefore, the target compound **6** was obtained *via* the same synthetic approach resorted to for the synthesis of compounds **3** and **4**. ^{1}H NMR analysis of the acetylated product **26** showed that one of the pyrimidine nitrogens was also acetylated; however, the location of the acetyl group (N-1 or N-3) could not be ascertained.

Results and Discussion

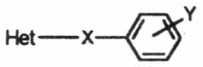
The search for new antileprotic agents is rendered difficult by the current inability to cultivate *M.leprae in vitro*. The most widely used model for screening new drugs is the growth of *M. leprae* in mouse foot pads[17]. However, the bacteriostatic effect of DDS on *E. coli* may be related to its antimycobacterium activity since, in both cases, it was proven that DDS has the same mechanism of action, i.e. inhibition of folate synthesis[18]. Accordingly, the antimicrobial activity of the tested compounds was evaluated against *E.coli* using the agar diffusion method using DDS as standard. The results are expressed as the diameter of inhibition zone as shown in Table I. All the 4-amino- and 2, 4-diaminophenylsulfonyl derivatives **1-5** (compound **6** was not tested) showed antimicrobial activity comparable to that of DDS, irrespective to the nature of the heterocyclic moiety. Unlike diaryl sulfones, the 2, 4-diamino compounds were not more active than the 4-amino compound. Whether this activity was blocked or reversed by PABA (to denote a sulfonamide mechanism[8]) was not investigated. However, to examine the importance of *p*-aminophenylsulfonyl moiety, several other synthetic intermediates in which this moiety was modified were tested. The results (Table I) showed that the antimicrobial activity was maintained in all the tested derivatives (which included diacetylaminophenyl sulfones or sulfides and diamino or dinitrophenyl sulfides). Since these modifications (except acetylation) are known to diminish or abolish the activity in diaryl sulfones[4,6], it is unlikely, therefore, that the activity of **1-5** is associated with the *p*-aminophenylsulfonyl moiety or -for that matter-follows an antifolate mechanism. It is possible, however, that the exhibited antimicrobial activity is related -more closely- to the heterocyclic structure as, for example, some 2-arylthio derivatives of benzimidazole and benzothiazole are reported[9,19] to possess antimicrobial and antifungal activities. It is also conceivable that the activity of the thiouracil derivatives (e.g., compound **22** or **23**) can be brought about by a mechanism which would involve inhibition of protein or nucleic acid biosynthesis[20].

In conclusion, this study showed that replacement of a *p*-aminophenyl moiety in DDS with a heterocyclic structure as in compounds **1-5** maintained an antimicrobial activity against *E. coli* which is equal in potency to DDS but probably of a different mode of action. Further studies on the activity and cytotoxicity of these compounds are worthwhile, in particular with the increasing interest for the use of diaryl sulfones in the chemotherapy of HIV-related infections[21].

Experimental Section

General. Melting points were determined in capillary tubes using a Griffin apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo, Egypt. Infrared spectra were measured on a

Table I — Physical properties and antimicrobial activity of 2-substituted benzimidazole, benzothiazole and 6-methyl-2-uracil derivatives against *E. coli*.



Compd	Het	X	Y	Zone of inhibition (mm)*	Yield (%)	mp °C	Recryst solvent
1	2-Benzimidazolyl	SO_2	4-NH_2	20	54	240	EtOH
2	2-Benzothiazolyl	SO_2	4-NH_2	21	59	209-212	EtOH
3	2-Benzimidazolyl	SO_2	2,4-diNH_2	19	35	>300	EtOH
4	2-Benzothiazolyl	SO_2	2,4-diNH_2	19	50	>300	EtOH
5	6-Me-2-uracilyl	SO_2	4-NH_2	19	30	260-263	EtOH-H_2O
15	2-Benzimidazolyl	S	2,4-diNH_2	20	56	210-211	H_2O
16	2-Benzothiazolyl	S	2,4-diNH_2	19	52	123-125	EtOH
17	1-Ac-2-Benzimidazolyl	S	2,4-diNHAc	19	86	227-229	MeCN
18	2-Benzothiazolyl	S	2,4-diNHAc	18	85	185-187	EtOH-H_2O
19	2-Benzimidazolyl	SO_2	2,4-diNHAc	20	56	240-244	EtOH
20	2-Benzothiazolyl	SO_2	2,4-diNHAc	21	77	135-137	EtOH-H_2O
22	6-Me-2-uracilyl	S	4-NO_2	20	46	255-260	Me_2CO
23	6-Me-2-uracilyl	S	2,4-diNO_2	20	83	211-213	benzene
25.2HCl	6-Me-2-uracilyl	S	2,4-diNH_2	20	49	285-287	EtOH
26	1(3)-Ac-6-Me-2-uracilyl	S	2,4-diNHAc	20	86	223-225	EtOH-H_2O
27	1(3)-Ac-6-Me-2-uracilyl	SO_2	2,4-diNHAc	19	48	305	EtOH
	Dapsone(DDS)			22			

*Average of 2 or more determinations using 20 mg/mL of the test compound or DDS.

Shimadzu IR 435 spectrometer. Proton magnetic resonances (^{1}H NMR) were measured at 90 MHz on a Jeol FX 90 spectrometer using tetramethylsilane as internal standard (chemical shifts are reported in δ ppm). Mass spectra were obtained on a Hewlett Packard 5988 spectrometer.

Benzothiazole-2-thiol was obtained commercially. The following compounds were prepared according to the reported procedures: Benzimidazole-2-thiol[22] **7**, 2-[(4-nitrophenyl)thio]benzimidazole[9] **9**, 2-[(4-nitrophenyl)thio]benzothiazole[12] **10**, 2-[(2, 4-dinitrophenyl)thio]benzimidazole[10] **11**, 2-[(2, 4-dinitrophenyl)thio]benzothiazole[11] **12**, 2-[(4-nitrophenyl)sulfonyl]benzimidazole[13] **13**, 2-[(4-nitrophenyl)sulfonyl]benzothiazole[13] **14** and 6-methyl-2-thioxo-2, 3-dihydro-4(1*H*)-pyrimidinone sodium salt[23] **21**.

m-Chloroperbenzoic acid was always freshly prepared as reported[24].

6-Methyl-2-[(4-nitrophenyl) thio]-4(1*H*)-pyrimidinone 22. To a boiling solution of **21** (1.6g, 0.01 mole) in 1-butanol (50 mL), a solution of 1-chloro-4-nitrobenzene (2.4 g, 0.015 mole) in 1-butanol (25 mL) was added and the mixture refluxed for 40 hr. The hot reaction mixture was filtered to remove any unreacted **21**. The filtrate was concentrated, cooled, scratched and the separated solid crystallized from acetone to give 1.2g (46%) of **22**, m.p. 255-60°C; IR (KBr):3400-2700, 1660-1640 (C=O) 1540, 1340 (NO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): 8.25 (*m*, *J*=7.2 Hz, 4H, ArH), 5.92 (s, 1H, C-5H), 2.16 (s, 3H, CH_3). Anal. Calcd for $C_{11}H_9N_3O_3S$: C, 50.19; H, 3.42; N, 15.96. Found: C, 49.8; H, 3.4; N, 15.5%.

6-Methyl-2-[(2, 4-dinitrophenyl)thio]-4(1*H*)-pyrimidinone 23. To a solution of **21** (3.2 g, 0.02 mole) in dry DMF (30 mL), a solution of 1-chloro-2, 4-dinitrobenzene (4g, 0.02 mole) in dry DMF (5 mL) was added portionwise with stirring at ambient temperature. The mixture was stirred at 70°C for 2 hr, cooled, poured into ice-cold water, filtered and the separated solid crystallized from benzene to give 5.1 g (83%) of **23**, m.p. 211-13°C; IR (KBr): 1690 (C=O), 1520, 1340 (NO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): 12.7 (brs, D_2O exchangeable), 9.28-8.24 (m, 3H, ArH), 6.56 (s, 1H, C-5 H), 2.24 (s, 3H, CH_3); EIMS: m/z 308 (M^+) (3.8%), 262 (M^+–NO_2) (100%); Anal. Calcd for $C_{11}H_8N_4O_5S$: C, 42.85; H, 2.59; N, 18.18. Found: C, 43.2; H, 2.6; N, 18.2%.

6-Methyl-2-[(4-nitrophenyl) sulfonyl]-4 (1*H*)-pyrimidinone 24—To a stirred ice-cold solution of **22** (0.26 g, 0.001 mole) in glacial acetic acid (20 mL), a solution of $KMnO_4$ (0.8 g, 0.005 mole) in H_2O (10 mL) was added portionwise till a permanent pink colour persisted. The reaction mixture was decolourized by a saturated solution of $NaHSO_3$ and diluted with ice-cold water. The separated solid was washed with benzene to remove the side product 4, 4'-dinitrodiphenyldisulfide. The

remaining solid was crystallized from MeOH to give 0.1g (33%) of **24**, m.p. 280-83°C; IR (KBr): 3100 (NH), 1660 (C=O), 1540, 1350 (NO_2), 1350, 1160 (SO_2) cm^{-1}. Anal. Calcd for $C_{11}H_9N_3O_5S$: C, 44.74; H, 3.05; N, 14.23. Found: C; 44.3, H, 3.2; N; 14.3%.

2-[(4-Aminophenyl)sulfonyl]benzimidazole 1, 2-[(4-aminophenyl)sulfonyl]benzothiazole 2 and 6-methyl-2-[(4-aminophenyl)sulfonyl]-4(1*H*)-pyrimidinone 5. To a mechanically stirred boiling mixture of the appropriate 4-nitrophenylsulfonyl derivative **13, 14** or **24** (0.025 mole), iron powder (0.15 mole) and EtOH (150 mL), a solution of HCl (3 mL) in EtOH (10 mL) was added dropwise over a period of 15 min. The mixture was refluxed for an additional period of 3.5 hr, cooled, rendered alkaline with ethanolic KOH (15%) and filtered. The filtrate was concentrated, and the separated solid purified by crystallization to give the respective aminophenylsulfonyl derivatives **1, 2** and **5**.

Compound 1: Yield 54%, mp 240°C (EtOH); IR (KBr): 3380, 3100-2300, 1630 (NH, NH_2), 1350, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 9.4 (s, 1H, NH of benzimidazole, D_2O exchangeable), 8.24-6.4 (m, ArH and NH_2 exchangeable protons); EIMS: m/z 273 (M^+) (71.5%), 209 (M^+–SO_2) (100%). Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.04; N, 15.38. Found: C, 57.2; H, 4.4; N; 15.1%.

Compound 2: Yield 59%, mp 209-12°C (EtOH); IR (KBr); 3450, 3350, (NH_2), 1350, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 8.8-8.4 (m, 2H, ArH), 8.32-7.84 (m, 4H, ArH), 7.2-6.64 (m, 4H, ArH and NH_2 exchangeable protons); EIMS. m/z 290 (M^+) (21.4%), 226 (M^+–SO_2) (100%). Anal. Calcd. for $C_{13}H_{10}N_2O_2S_2$: C; 53.79, H; 3.44; N, 9.65. Found: C, 54.1; H, 3.7; N, 9.9%.

Compound 5: Yield 30%, mp 260-63°C (aqueous EtOH); IR (KBr): 3450, 3250 (NH, NH_2), 1645-1630 (C=O), 1150-1130 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 7.9 (d, J=9 Hz, 2H, ArH), 6.96 (d, J=9 Hz, 2H, ArH), 6.44 (s, 1H, C-5 H), 2.64 (s, 3H, CH_3); EIMS: m/z 265 (M^+) (0.4%), 200 (M^+–SO_2H) (100%). Anal. Calcd for $C_{11}H_{11}N_3O_3S$: C, 49.85; H, 4.15; N, 15.84. Found: C, 50.1; H; 4.3; N, 15.5%.

2-[(2, 4-Diaminophenyl)thio]benzimidazole 15, 2-[(2, 4-diamino-phenyl)thio]benzothiazole 16 and 6-methyl-2-[2, 4-diaminophenyl)thio]-4(1*H*)-pyrimidinone. 2HCl (25. 2HCl). These compounds were prepared from the respective nitro derivatives **11, 12** and **23** following the same procedures as described for the synthesis of compounds **1, 2** and **5**. Compound **25** was isolated as its dihydrochloride salt.

Compound 15: Yield 56%, m.p. 210-11°C (H_2O); IR (KBr): 3550, 3450, (NH, NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): 12.5 (brs, 1H, D_2O exchangeable), 7.84-6.4 (m, 7H, ArH), 6.0 (brs, 2H, D_2O exchangeable, NH_2), 5.04 (brs, 2H, D_2O exchangeable, NH_2); EIMS: m/z 256 (M^+) (97%). Anal. Calcd for $C_{13}H_{12}N_4S$: C, 60.93; H, 4.68; N, 21.87. Found: C, 60.6; H, 4.7; N, 21.4%.

Compound 16: Yield 52%, mp 123-25°C (EtOH); IR (KBr): 3450-3200, (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): 8.4-7.2 (m, 5H, ArH), 6.32 (m, 2H, ArH), 5.6 (s, 2H, D_2O exchangeable), 5.76 (s, 2H, D_2O exchangeable); EIMS: m/z 273 (M^+) (67%). Anal. Calcd for $C_{13}H_{11}N_3S_2$: C, 57.14; H, 4.02; N, 15.38. Found: C, 56.8; H, 3.9; N, 15.4%.

Compound 25. 2HCl: Yield 49%, m.p. 285-87°C (EtOH); IR (KBr): 3400, 3350, 3200 (NH, NH_2) 1660 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): 9.36 (s, 1H), 8.96-5.6 (m, 8H), 2.2 (s, 3H, CH_3); EIMS m/z 216 (M^+–S) (78.7%). Anal. Calcd for $C_{11}H_{12}N_4OS.2HCl$: C, 41.12; H, 4.36; N, 17.44. Found: C, 40.8; H, 4.3; N, 17.1%.

1-Acetyl-2-[(2, 4-diacetylaminophenyl)thio]-benzimidazole 17, 2-[(2, 4-diacetylaminophenyl)thio]benzothiazole 18 and 1(3)-acetyl-6-methyl-2-[(2,4-diacetylaminophenyl)thio]-4(1*H*)-pyrimidinone 26. A mixture of the aminophenylthioether **15, 16** or **25**. 2HCl (0.002 mole) and Ac_2O (0.05 mole) was heated in a boiling water-bath for 1 hr [in case of **25**. 2HCl, anhydrous sodium acetate (0.006 mole) was added to the reaction mixture prior to heating]. The mixture was cooled, poured into ice-cold water and the precipitated solid filtered and purified by crystallization.

Compound 17: Yield 86%, mp 227-29°C (MeCN); IR (KBr):3200 (NH) 1710, 1680 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): 10.64 (brs, D_2O exchangeable), 9.6 (brs, D_2O exchangeable), 8.6-7.4 (m, 7H, ArH), 3.0 (s, 3H, $COCH_3$),2.18(s, 3H, $COCH_3$), 2.08(s, 3H, $COCH_3$). Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65. Found: C, 59.6; H, 4.4; N. 15.0%.

Compound 18: Yield 85%, mp 185-87°C (aqueous EtOH); IR (KBr):3450-3100 (NH), 1680-1660 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): 10.8(s, 1H, NH, D_2O exchangeable), 10.24 (s, 1H, NH, D_2O exchangeable), 8.64-7.44 (m, 7H, ArH), 2.24 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$). Anal. Calcd for

$C_{17}H_{15}N_3O_2S_2$: C, 57.14; H, 4.2; N, 11.76. Found: C, 57.1; H, 4.0; N, 11.8%.

Compound 26: Yield 86%, mp 223-25°C (aqueous EtOH); IR (KBr):3450-3250 (NH), 1695, 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): 9.6 (d, J=9 Hz, 1H, C-6 H of Ph ring), 7.76 (m, 2H, ArH), 6.56 (s, 1H, C-5 H), 2.52 (s, 6H, CH_3 protons) 2.4 (s, 6H, CH_3 protons). Anal. Calcd for $C_{17}H_{18}N_4O_4S$: C, 54.54; H, 4.81; N, 14.97. Found: C, 54.2; H, 4.7; N, 14.9%.

2-{(2, 4-Diacetylaminophenyl)sulfonyl]benzimidazole 19, 2-[(2, 4-diacetylaminophenyl)-sulfonyl]benzothiazole 20 and 1(3)-acetyl-6-methyl-2-[(2, 4-diacetylaminophenyl)sulfonyl]-4(1*H*)-pyrimidinone 27. To a stirred ice-cold solution of the respective acetylaminophenylthioether **17**, **18** or **26** (0.003 mole) in either DMSO (25 mL) (in case of **17**) or CH_2Cl_2 (25 mL) (in case of **18** and **26**), a solution of MCPBA (0.0075 mole) in CH_2Cl_2 (25 mL) was added portionwise over a period of 15 min. The mixture was stirred at room temperature for 48 hr and washed with saturated solutions of $NaHSO_3$ and $NaHCO_3$ and then with water. The organic layer was dried (Na_2SO_4), evaporated and the residue purified by crystallization.

Compound 19: Yield 56% mp 240-44°C (EtOH); IR: 3200 (NH), 1715, 1680-1650 (C=O), 1345, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 10.64 (s, 1H, D_2O exchangeable), 10.24 (s, 1H, D_2O exchangeable), 8.4-7.2 (m, 7H, ArH), 2.2 (s, 6H, $2COCH_3$); EIMS: m/z 371 (M^+–1) (0.4%) 265 (M^+–Ac and SO_2) (100%). Anal. Calcd for $C_{17}H_{16}N_4O_4S$: 54.83; H, 4.3; N, 15.05. Found: C, 54.9; H, 4.7%.

Compound 20: Yield 77%, mp 135-37°C (aqueous EtOH); IR(KBr): 3100-2500 (NH), 1690 (C=O), 1350, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 10.88 (s, 1H, NH, D_2O exchangeable), 10.64 (s, 1H, NH, D_2O exchangeable),, 8.8-7.76 (m, 7H, ArH), 2.2 (s, 6H, 2 $COCH_3$). Anal. Calcd for $C_{17}H_{15}N_3O_4S_2$: C, 52.44; H, 3.85; N, 10.79. Found: C, 52.5; H, 3.5; N, 10.9%.

Compound 27: Yield 48%, mp 305°C (EtOH); IR (KBr) 3400-3150 (NH), 1695-1660 (C=O), 1365 (SO_2) cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_4O_6S$: C, 50.24; H, 4.43; N, 13.79. Found: C, 49.9; H, 4.2; N, 13.5%.

2-[(2, 4-Diaminophenyl)sulfonyl]benzimidazole 3, 2-[(2, 4-diaminophenyl)sulfonyl]benzothiazole 4 and 6-methyl-2-[(2, 4-diaminophenyl)-sulfonyl]-4(1*H*)-pyrimidinone 6. To a boiling solution of the respective acetyl derivative **19**, **20** or **27** (0.001 mole) in EtOH (20 mL) a solution of HCl (2.5 mL) in EtOH (10 mL) was added dropwise. The reaction mixture was refluxed for 3 hr, cooled, rendered alkaline by dropwise addition of EtOH/KOH (15%) and filtered. The filtrate was evaporated and the residue crystallized from EtOH.

Compound 3: Yield 35%, mp >300°C (EtOH); IR (KBr): 3200 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): 8.24-7.0 (m, ArH + NH_2), 6.32(m, D_2O exchangeable); EIMS: m/z 223 (M^+–SO_2H) (100%). Anal. Calcd for $C_{13}H_{12}N_4O_2S$; C, 54.16; H, 4.16; N, 19.44. Found: C, 53.9; H, 4.0; N, 19.1%.

Compound 4: Yield 50%, mp>300°C (EtOH); IR (KBr): 3450-3350 (NH_2), 1350, 1140 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 8.36-7.6 (m); EIMS: m/z 305 (M^+) (2.1%), 240 (M^+–SO_2H) (12.7%). Anal. Calcd for $C_{13}H_{11}N_3O_2S_2$. C, 51.15; H, 3.61; N, 13.77. Found: C, 50.9; H, 3.6; N, 13.3%.

Compound 6 : Yield 54%, mp >300°C (EtOH); IR (KBr): 3400-3200, 1640, 1360, 1160 cm^{-1}; ^1H NMR (DMSO-d_6): 8.8 (d, J≈10 Hz, 1H, C-6 proton of Ph ring), 7.28 (s, 1H, C-3 proton of Ph ring), 7.0 (d, J≈10 Hz, 1H, C-5 proton of Ph ring), 6.4 (s, 1H, C-5 proton of pyrimidine) 5.84 (s, NH_2, D_2O exchangeable), 2.32 (s, 3H, CH_3). Anal. Calcd for $C_{11}H_{12}N_4O_3S$: C, 47.14; H, 4.28; N, 20.0. Found: C, 46.9; H, 4.3; N, 19.8%.

Antimicrobial Activity

Inocula preparation: *Escherichia coli* NCTC 9002 (*E. coli*) was grown in nutrient agar (beef extract, 3.0 g; peptone 5.0 g; agar 15 g/mL) adjusted to *p*H 7.0. A viable cell suspension of *E. coli* after being harvested in sterile saline was adjusted to 10^5-10^6 cells per mL using UV spectrophotometer (Shimadzu UV-160A UV-Vis).

Antimicrobial assay. Tested compounds were dissolved in DMSO to give initial concentration of 20 mg/mL (200 μg/well). Inoculated plates were incubated at 37°C for 24 hr and the antimicrobial activity was recorded by measuring the diameter of zone of inhibition (in mm). Dapsone was used as control and a well impregnated with DMSO was used as negative control.

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