Pharmaceutical Chemistry Journal, Vol. 45, No. 12, March, 2012 (Russian Original Vol. 45, No. 12, December, 2011)

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF THIAZOLE, BENZOTHIAZOLE AND PYRIMIDINE DERIVATIVES BEARING SYDNONE MOIETIES

S. T. Asundaria[1] and K. C. Patel[1,*]

Original article submitted June 6, 2011.

The synthesis of sydnone sulfonamides bearing thiazole, benzothiazole and pyrimidine heterocycles is described. The newly synthesized compounds were characterized by IR, NMR and elemental analysis and evaluated for their antibacterial activity against some important Gram-positive and Gram-negative bacterial strains. Most of these compounds showed good to moderate activity against tested microbes.

Key words: Sydnone, thiazole, benzothiazole, pyrimidine, sulfonamide, antimicrobial activity

INTRODUCTION

Mesoionic compounds are of significant interest due to their amazing properties and useful applications. Literature survey disclosed that sydnone is most significant member of the family of mesoionic compounds [1 – 3]. Heterocycles such as thiazole, benzothiazole, and pyrimidine have displayed compliant pharmacological properties [4 – 8]. Sulfonamide derivatives turned out to be useful agents in synthetic and pharmaceutical chemistry [9 – 11]. The combination of a mesoionic ring with various heterocyclic rings such as thiazole, benzothiazole, and pyrimidine by sulfonamide linkage, and the related modification of their biological activity might be interesting.

In our laboratory, we have synthesized and characterized various mesoionic compounds [12 – 15]. To extend the work, the present investigation is centered on the synthesis, spectral analysis, and antimicrobial activity of mesoionic based thiazole, benzothiazole and pyrimidine derivatives as possible antimicrobial agents.

The proposed structures of the synthesized compounds were confirmed by their IR and NMR spectra. Indeed, the IR spectra of compounds **12 – 14** showed absorption between 1328 – 1368, 1187 – 1122 and 3285 – 3258 cm^{-1} for SO_2 (asym.), SO_2 (sym.) and N–H stretching vibraitons, respectively, of sulfonamide group. The absorption band for C–N stretching vibrations of thiazole and benzothiazole ring were observed at 1632 – 1604 cm^{-1}. The carbonyl group of sydnone showed absorption at 1758 – 1735 cm^{-1}. The ^1H NMR spectra of compounds **12 – 14** showed absorption at 10.93 – 11.47 ppm for SO_2NH group. The ^{13}C NMR spectra exhibited characteristic signals of the carbonyl carbon of sydnone around 168.00 ppm. Detailed spectroscopic data for all synthesized compounds are presented in the experimental chemical part.

[1] Department of Chemistry, Veer Narmad South Gujarat University, Surat, 395007, India.
[*] e-mail: shahrukh_sun@rediffmail.com

EXPERIMENTAL CHEMICAL PART

The melting points reported were determined using an electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR instrument. The NMR spectra were recorded on a Brucker Avance II NMR spectrometer. Chemical shifts δ are expressed in ppm. Tetramethyl silane was used as an internal standard for calibration. Elemental analysis was carried out using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. The yields, melting points, and elemental analysis data for the synthesized compounds are summarized in Table 1.

Synthesis of 4-(substituted phenyl)-1,3-thiazol-2-amines (2) (Scheme I)

2,2-Dibromo-1-(substitutedphenyl)ethanone (1). Bromine (0.64 mL, 0.025 mol) in chloroform (20 mL) was added dropwise to the solution of substituted phenylethanone (0.01 mol) in chloroform (20 mL) at room temperature, and the mixture was stirred for about 12 h (until bromine completely disappear from the solution). The precipitates of compound **1** was filtered, washed with sodium bisulfite solution, and recrystallized from methanol.

4-(Substituted phenyl)-1,3-thiazol-2-amine (2). To a solution of 2,2-dibromo-1-(substituted phenyl)ethanone **(1)**

(0.01 mol) in ethanol (10 mL) was added a solution of thiourea (0.76 g, 0.01 mol) in ethanol (10 mL) and the reaction mixture was stirred for 30 min. The solid product was separated and recrystallized from ethanol.

Synthesis of substituted 1,3-benzothiazol-2-amines (4) (Scheme II)

Bromine (1.6 mL) in glacial acetic acid (6 mL) was added to the solution of potassium thiocynate (7.77 g, 0.08 mol) and substituted aniline (0.01 mol) in glacial acetic acid (20 mL) dropwise at a rate such that the temperature would not increase above 30°C. After all the bromine has been added, the solution was additionally stirred for 2 h at room temperature and allowed to stand overnight. The precipitate that settled at the bottom was filtered. The combined filtrate was cooled and neutralized with ammonium hydroxide until complete precipitation. The product was recrystallized from benzene.

TABLE 1. Antibacterial Activity of Compounds **12 – 14**

Compound	Gram-possitive microbes				Gram-negative microbes			
	S.aureus		*B. Subtilis*		*E.coli*		*P. Aeruginosa*	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
12a	10	–	09	–	14	64	08	–
12b	11	128	13	64	06	–	08	–
12c	18	16	16	32	15	32	17	32
12d	09	–	13	64	12	64	12	64
12e	20	16	17	32	18	32	11	64
12f	06	–	10	–	14	64	05	–
12g	13	64	09	–	12	64	14	64
13a	14	64	08	–	10	–	11	128
13b	12	64	06	–	09	–	18	32
13c	17	32	12	64	10	–	11	64
13d	07	–	12	64	09	–	07	–
13e	12	64	09	–	12	64	08	–
13f	15	64	21	16	17	32	18	32
13g	18	32	07	–	06	–	06	–
13h	12	64	08	–	07	–	05	–
13i	21	08	21	16	18	32	09	–
14a	18	16	12	64	06	–	13	64
14b	09	–	20	08	13	64	10	–
14c	08	–	12	64	21	08	09	–
14d	21	08	10	–	22	08	18	32
14e	17	32	09	–	16	32	18	32
14f	06	–	14	64	20	08	21	08
14g	14	64	09	–	08	–	05	–
14h	11	64	13	64	17	32	19	16
14i	13	64	12	64	06	–	09	–
Ciprofloxacin	31	01	35	0.5	38	0.25	41	0.125

Notes: IZ = Inhibition zone (mm) at 200 μg/mL; MIC = Minimum inhibitory concentration

Synthesis of 4-(substituted phenyl)-6-(4-methoxyphenyl)-pyrimidin-2-amines (6) (Scheme III)

To a solution of 4-methoxy acetophenone (0.1 mol, 14.8 g) and substituted aromatic aldehyde (0.1 mol) in methanol (98 mL) was added 20% KOH solution (10 mL). The reaction mixture was stirred overnight at room temperature. After the completion of reaction, it was poured onto ice-cold water, acidified, filtered, and crystallized from ethanol to yield chalcone derivatives **5** with 80 – 95% yield.

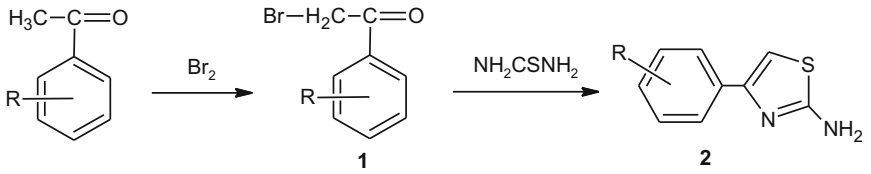
A mixture of chalcone derivatives (0.01 mol), guanidine nitrate (0.015 mole, 1.83 g) and 25% sodium methoxide solution in methanol (28 mL) was refluxed for 6 h. After the completion of reaction, the resultant mixture was cooled to room temperature. Precipitated compound was filtered, washed with water, dried, and crystallized from methanol to yield target pyrimidine derivatives **6** with 88 – 97% yield.

Synthesis of Compounds 12 – 14 (Schemes IV and V)

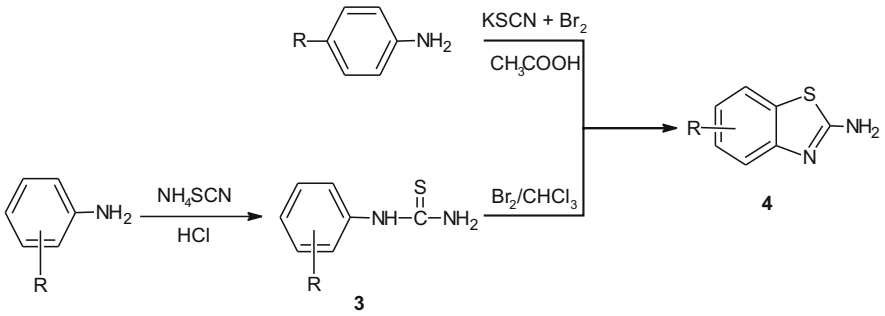
4-{[4-(substituted phenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnones (12). 3-(4-Chlorophenyl)-4-(chlorosulfonyl)sydnone **(11)** (2.95 g, 0.01 mol) was dissolved in acetone at room temperature. A solution of appropriate thiazole derivative (0.01 mol) in acetone was added dropwise to compound **11** solution over a period of 5 h with constant stirring; 0.5 mL of pyridine was added to the well-stirred solution after 1 and 2 h during the reaction. The solution was poured onto ice with stirring. The precipitate was collected by filtration, washed with water, and dried. Recrystallization of the crude product was performed from benzene.

4-[(Substituted-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnones (13). 3-(4-chlorophenyl)-4-(chlorosulfonyl)sydnone **(11)** (2.95 g, 0.01 mol) was dissolved in acetone at room temperature. A solution of appropriate benzothiazole derivative (0.01 mol) in acetone was added dropwise into compound **11** solution over a period of 5 hour with constant stirring; 0.5 mL of pyridine was added to the well-stirred solution after 1 and 2 h during the reaction. The solution was poured onto ice with stirring. The precipitate was collected by filtration, washed with water, and dried. Recrystallization of the crude product was performed from benzene.

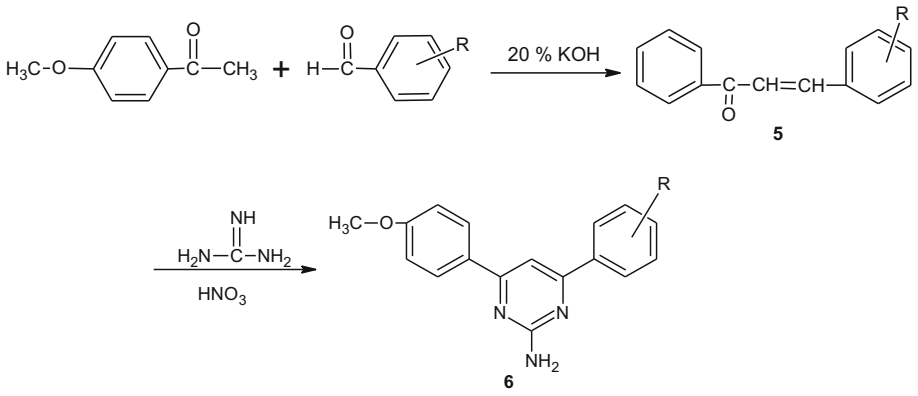
3-(4-Chlorophenyl)-4-{[4-(4-methoxyphenyl)-6-(substituted phenyl)pyrimidin-2-yl]sulfamoyl}sydnones (14). 3-(4-chlorophenyl)-4-(chlorosulfonyl)sydnone (**11**) (2.95 g, 0.01 mol) was dissolved in acetone at room temperature. A solution of appropriate pyrimidine derivative (0.01 mol) in acetone was added dropwise into compound **11** solution over a period of 5 h with constant stirring; 0.5 mL of pyridine was added to the well-stirred solution after 1 and 2 h during the reaction. The solution was poured onto ice with stirring. The precipitate was collected by filtration, washed with water, and dried. Recrystallization of the crude product was performed from benzene.



Scheme I. Synthesis of 4-(substituted phenyl)-1,3-thiazol-2-amines (2).



Scheme II. Synthesis of 2-(amino substituted)benzothiazoles (4).



Scheme III. Synthesis of 4-(substituted phenyl)-6-(4-methoxyphenyl)pyrimidin-2-amines (6).

4-{[4-(2,4-Dichlorophenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (12a). IR (KBr, cm^{-1}) 3268, 1755, 1614, 1328, 1158, 853, 713; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.35 – 7.98 (m, 8H, Ar-H), 11.03 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 108.35, 122.86, 127.53, 128.00, 129.65, 130.35, 130.80, 134.53, 135.12, 135.37, 136.47, 139.00, 154.97, 168.55, 175.42.

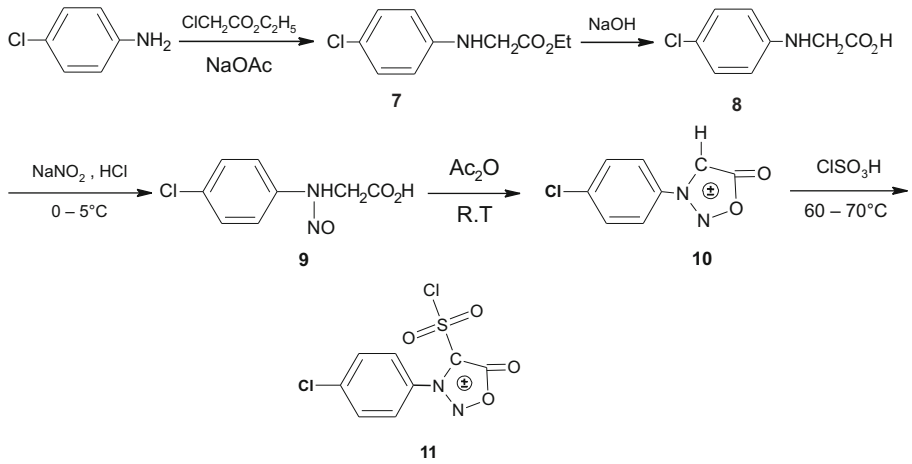
4-{[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (12b). IR (KBr, cm^{-1}): 3266, 2960, 1751, 1607, 1346, 1175, 817, 705; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.26 – 7.79 (m, 9H, Ar-H), 11.16 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 108.33, 122.64, 128.84, 130.35, 130.90, 134.46, 134.64, 134.90, 135.53, 138.47, 152.70, 168.52, 175.39.

4-{[4-(4-Fluorophenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (12c). IR (KBr, cm^{-1}): 3260, 1748, 1627, 1333, 1180, 1098, 823, 727; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.98 – 8.19 (m, 9H, Ar-H), 11.50 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 105.14, 116.00, 126.95, 128.17, 130.74, 131.83, 136.73, 138.72, 140.65, 150.25, 161.94, 167.23, 172.17.

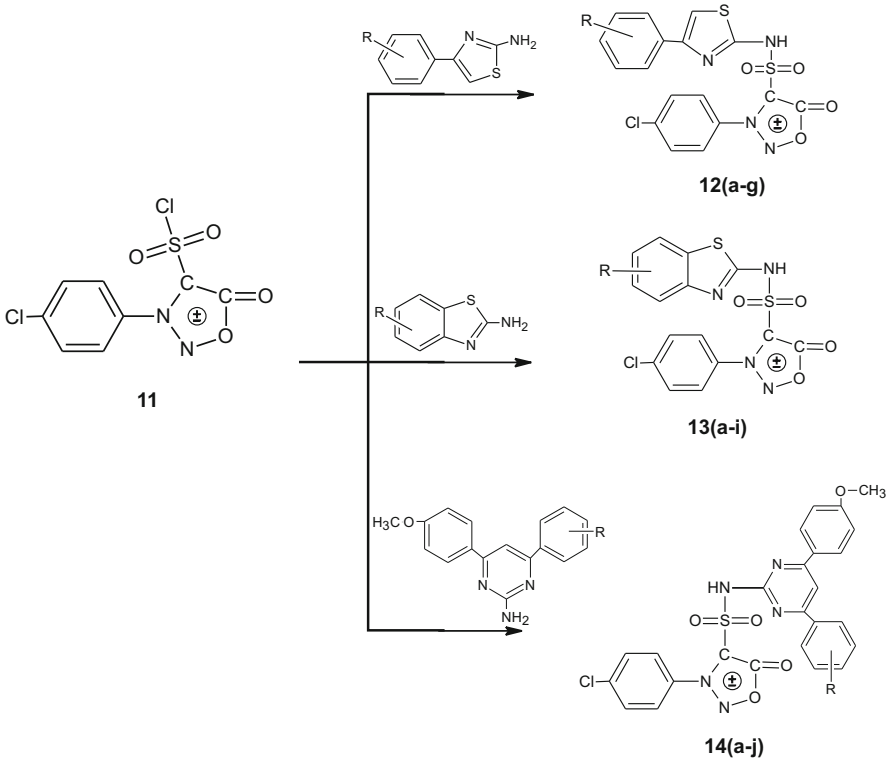
4-{[4-(4-Bromophenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (12d). IR (KBr, cm^{-1}): 3285, 2980, 1738, 1632, 1352, 1177, 713, 596; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.54 – 8.16 (m, 9H, Ar-H), 11.26 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 108.53, 122.06, 123.75, 128.32, 130.75, 132.64, 134.80, 136.38, 135.74, 138.70, 153.00, 168.53, 175.38.

4-{[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (12e). IR (KBr, cm^{-1}): 3264, 2960, 1750, 1610, 1357, 1235, 1165, 846, 736; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 3.56 (s, 3H, OCH_3), 7.36 – 8.11 (m, 9H, Ar-H), 11.16 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 56.75, 105.89, 115.38, 126.50, 126.72, 128.58, 129.47, 130.80, 134.64, 138.73, 151.76, 161.24, 168.55, 174.84.

4-{[4-(4-Methylphenyl)-1,3-thiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (12f). IR (KBr, cm^{-1}): 3274, 2964, 1758, 1620, 1340, 1138, 816, 740; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 2.46 (s, 3H, CH_3), 7.30 – 8.42 (m, 9H, Ar-H), 11.47 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 21.80, 108.33, 122.84, 128.57, 129.60,



Scheme IV. Synthesis of 3-(4-chlorophenyl)-4-(chlorosulfonyl)sydnone (11).



Scheme V. Condensation of 3-(4-chlorophenyl)-4- (chlorosulfonyl)sydnone with thiazole, benzothiazole and pyrimidine derivatives 12 – 14:

(12a) R = 2,4-Cl; (12b) R = 4-Cl; (12c) R = 4-F; (12d) R = 4-Br; (12e) R = 4-OCH_3; (12f) R = 4-CH_3; (12g) R = 2,4-Cl, 5-F; (13a) R = 6-CH_3; (13b) R = 6-NO_2 ; (13c) R = 6-Cl; (13d) R = 6-F; (13e) R = 6-Br; (13f) R = 6-OCH_3 ; (13g) R = 4,6-NO_2; (13h) R = 6-CF_3; (13i) R = 5-CH_3; (14a) R = H; (14b) R = 3-NO_2; (14c) R = 4-NO_2; (14d) R = 4-Cl; (14e) R = 4-F; (14f) R = 4-OCH_3 ; (14g) R = 4-Br; (14h) R = 3-OCH_3; (14i) R = 2,5-Cl.

130.58, 134.16, 135.06, 136.49, 138.49, 140.32, 152.85, 168.36, 175.20.

4-{[4-(5-Chloro-2,4-difluorophenyl)-1,3-thiazol-2-yl]-sulfamoyl}-3-(4-chlorophenyl) sydnone (12g). IR (KBr, cm^{-1}): 3258, 1743, 1617, 1354, 1134, 1114, 847, 732; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 6.84 – 7.46 (m, 7H, Ar-H), 11.08 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 102.50, 108.63, 119.24, 123.15, 130.74, 133.05, 134.53, 135.82, 136.47, 138.42, 154.00, 161.26, 163.47, 168.75, 175.73.

4-[(6-Methyl-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13a). IR (KBr, cm^{-1}): 3277, 2970, 1753, 1614, 1357, 1180, 824, 733; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 2.60 (s, 3H, CH_3), 6.70 – 7.46 (m, 7H, Ar-H), 11.24 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 21.63, 120.15, 122.40, 123.58, 128.84, 130.53, 130.69, 134.28, 135.63, 136.38, 138.85, 152.90, 168.43, 175.28.

4-[(6-Nitro-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13b). IR (KBr, cm^{-1}): 3285, 1748,

1605, 1536, 1358, 1336, 1164, 846, 727; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.46 – 7.90 (m, 7H, Ar-H), 10.93 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 119.16, 119.78, 122.60, 123.80, 130.64, 132.47, 135.58, 136.53, 138.22, 142.53, 168.68, 156.38, 175.63.

4-[(6-Chloro-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13c). IR (KBr, cm^{-1}): 3283, 2960, 1751, 1630, 1352, 1164, 812, 695, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.60 – 8.20 (m, 7H, Ar-H), 11.15 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 120.47, 121.60, 122.10, 125.24, 127.25, 131.00, 133.64, 135.73, 136.27, 138.24, 168.75, 153.80, 175.48.

4-[(6-Fluoro-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13d). IR (KBr, cm^{-1}): 3276, 1750, 1612, 1344, 1173, 1090, 830, 740; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.53 – 8.00 (m, 7H, Ar-H), 11.18 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 108.52, 115.28, 123.46, 123.63, 130.95, 132.04, 135.00, 136.38, 138.79, 152.74, 160.10, 168.15, 174.48.

4-[(6-Bromo-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13e).

IR (KBr, cm^{-1}): 3274, 1756, 1627, 1348, 1157, 828, 727, 632; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.32 – 7.84 (m, 7H, Ar-H), 10.95 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 112.93, 121.50, 122.90, 123.54, 128.63, 131.35, 133.96, 135.40, 136.38, 138.57, 152.73, 168.37, 175.16.

4-[(6-Methoxy-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13f).

IR (KBr, cm^{-1}): 3265, 1754, 1604, 1338, 1264, 1148, 826, 735; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.27 (s, 3H, OCH_3), 6.79 – 7.54 (m, 7H, Ar-H), 10.94 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 57.10, 106.21, 114.64, 119.35, 122.96, 131.37, 132.71, 135.85, 136.73, 138.33, 151.24, 155.85, 168.58, 174.42.

4-[(4, 6-Dinitro-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13g).

IR (KBr, cm^{-1}): 3280, 1745, 1625, 1523, 1368, 1333, 1187, 819, 746; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.65 – 8.90 (m, 6H, Ar-H), 11.34 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 138.23, 131.65, 127.33, 135.54, 138.91, 168.35, 177.12, 151.90, 126.83, 125.97, 145.22, 119.26, 143.74.

4-{[6-(Trifluoromethyl)-1,3-benzothiazol-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (13h). IR (KBr, cm^{-1}): 3265, 1744, 1614, 1334, 1161, 1100, 842, 740; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 7.54 – 8.24 (m, 7H, Ar-H), 11.36 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 121.27, 121.64, 122.80, 123.48, 126.38, 129.93, 130.58, 130.74, 135.78, 136.74, 138.20, 153.54, 168.62, 175.38.

4-[(5-Methyl-1,3-benzothiazol-2-yl)sulfamoyl]-3-(4-chlorophenyl)sydnone (13i). IR (KBr, cm^{-1}): 3273, 2963, 1750, 1610, 1355, 1148, 836, 750; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 2.47 (s, 3H, CH_3), 7.58 – 8.32 (m, 7H, Ar-H), 11.07 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 21.58, 121.37, 122.48, 123.74, 126.85, 130.57, 131.68, 135.55, 135.74, 136.69, 138.45, 168.80, 152.64, 174.95.

3-(4-Chlorophenyl)-4-{[4-(4-methoxyphenyl)-6-phenylpyrimidin-2-yl]sulfamoyl}sydnone (14a). IR (KBr, cm^{-1}): 3257, 2833, 1735, 1675, 1352, 1278, 1122, 836; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 3.83 (s, 3H, OCH_3), 6.80 – 8.03 (m, 14H, Ar-H), 11.34 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 138.53, 131.95, 126.97, 127.70, 136.94, 139.73, 166.37, 169.13, 164.16, 102.12, 161.16, 128.14, 128.71, 128.50, 129.25, 113.64, 160.77, 54.93, 136.37.

3-(4-Chlorophenyl)-4-{[4-(4-methoxyphenyl)-6-(3-nitrophenyl)pyrimidin-2-yl]sulfamoyl}sydnone (14b). IR (KBr, cm^{-1}): 3270, 2839, 1758, 1660, 1536, 1344, 1332, 1264, 1137, 857; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 3.95 (s, 3H, OCH_3), 6.96 – 8.20 (m, 13H, Ar-H), 11.00 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 55.90, 114.63, 115.38, 122.90, 123.38, 125.78, 128.33, 130.10, 130.75, 131.40, 135.46, 135.64, 135.86, 136.48, 138.43, 148.38, 161.50, 163.85, 164.68, 164.83, 168.50.

3-(4-Chlorophenyl)-4-{[4-(4-methoxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl]sulfamoyl}sydnone (14c). IR (KBr, cm^{-1}): 3265, 2835, 1752, 1665, 1524, 1340, 1326, 1237, 1126, 830; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.38 (s, 3H, OCH_3), 7.24 – 7.84 (m, 13H, Ar-H), 11.36 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 55.25, 114.64, 115.47, 122.90, 125.70, 129.63, 129.86, 130.75, 133.16, 135.26, 135.73, 136.49, 138.30, 148.42, 161.35, 163.47, 163.80, 164.00, 168.66.

3-(4-Chlorophenyl)-4-{[4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]sulfamoyl}sydnone (14d). IR (KBr, cm^{-1}): 3260, 2838, 1740, 1647, 1355, 1240, 1153, 830; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.32 (s, 3H, OCH_3), 7.36 – 8.18 (m, 13H, Ar-H), 11.05 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 55.43, 114.65, 115.00, 122.18, 129.46, 130.16, 130.37, 130.67, 132.80, 135.39, 135.48, 135.74, 136.53, 138.42, 159.47, 162.78, 163.48, 163.60, 168.60.

3-(4-Chlorophenyl)-4-{[4-(4-fluorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]sulfamoyl}sydnone (14e). IR (KBr, cm^{-1}): 3281, 2824, 1746, 1652, 1348, 1255, 1147, 1123, 834; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.25 (s, 3H, OCH_3), 7.32 – 8.43 (m, 13H, Ar-H), 11.27 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 56.21, 114.58, 115.28, 116.00, 122.96, 129.58, 130.15, 131.15, 132.85, 135.38, 135.48, 136.63, 138.74, 161.70, 162.64, 163.37, 163.55, 164.62, 168.38.

4-{[4,6-Bis(4-methoxyphenyl)pyrimidin-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (14f). IR (KBr, cm^{-1}): 3272, 2817, 1752, 1675, 1360, 1248, 1152, 830; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.26 (s, 6H, OCH_3), 7.00 – 7.74 (m, 13H, Ar-H), 10.93 (s, 1H, SO_2NH); ^{13}C NMR (100

TABLE 2. Yields, Melting Points, and Elemental Analysis of Compounds **12 – 14**

Cmpd. No.	R	Yield, %	mp, °C	Mol. formula	Elemental analysis (%) found (calcd.)		
					C	H	N
12a	2,4-Cl	82	289	$C_{17}H_9O_4N_4S_2Cl_3$	40.69	1.55	10.98
				(40.53)	(1.80)	(11.12)	
12b	4-Cl	73	246	$C_{17}H_{10}O_4N_4S_2Cl_2$	43.86	2.82	12.19
				(43.51)	(2.51)	(11.94)	
12c	4-F	74	276	$C_{17}H_{10}O_4N_4S_2ClF$	44.78	2.34	12.51
				(45.09)	(2.23)	(12.37)	
12d	4-Br	68	145	$C_{17}H_{10}O_4N_4S_2BrCl$	39.72	2.03	10.77
				(39.74)	(1.96)	(10.90)	
12e	4-OCH_3	78	167	$C_{18}H_{13}O_5N_4S_2Cl$	46.65	2.96	11.96
				(46.50	(2.82)	(12.05)	
12f	4-CH_3	82	233	$C_{18}H_{13}O_4N_4S_2Cl$	48.01	2.54	12.68
				(48.16)	(2.92)	(12.48)	
12g	2,4-Cl, 5-F	87	256	$C_{17}H_8O_4N_4S_2Cl_3F$	39.02	1.46	10.84
				(39.13)	(1.55)	(10.74)	
13a	6-CH_3	89	189	$C_{16}H_{11}O_4N_4S_2Cl$	45.26	3.01	12.98
				(45.44)	(2.62)	13.25)	
13b	6-NO_2	85	245	$C_{15}H_8O_6N_5S_2Cl$	39.89	2.03	15.49
				(39.70)	(1.78)	(15.43)	
13c	6-Cl	82	146	$C_{15}H_8O_4N_4S_2Cl_2$	40.52	1.66	12.51
				(40.64)	(1.82)	(12.64)	
13d	6-F	78	167	$C_{15}H_8O_4N_4S_2ClF$	42.38	1.73	12.90
				(42.21)	(1.89)	(13.13)	
13e	6-Br	76	153	$C_{15}H_8O_4N_4S_2BrCl$	36.82	1.84	11.64
				(36.94)	(1.65)	(11.49)	
13f	6-OCH_3	73	238	$C_{16}H_{11}O_5N_4S_2Cl$	43.58	2.71	12.63
				(43.79)	(2.53)	(12.77)	
13g	4,6-NO_2	83	198	$C_{15}H_7O_8N_6ClS_2$	36.24	1.25	16.71
				(36.12)	(1.41)	(16.85)	
13h	6-CF_3	81	258	$C_{16}H_8O_4N_4S_2ClF_3$	40.53	1.53	11.96
				(40.30)	(1.69)	(11.75)	
13i	5-CH_3	87	168	$C_{16}H_{11}O_4N_4S_2Cl$	45.62	2.78	13.01
				(45.44)	(2.62)	(13.25)	
14a	H	72	195	$C_{25}H_{18}O_5N_5SCl$	56.21	3.48	12.89
				(56.02)	(3.39)	(13.07)	
14b	3-NO_2	79	221	$C_{25}H_{17}O_7N_6SCl$	51.45	3.30	14.14
				(51.69)	(2.95)	(14.47)	
14c	4-NO_2	86	189	$C_{25}H_{17}O_7N_6SCl$	51.56	2.78	14.28
				(51.69)	(2.95)	(14.47)	
14d	4-Cl	82	216	$C_{25}H_{17}O_5N_5SCl_2$	53.01	2.67	11.97
				(52.64)	(3.00)	(12.28)	
14e	4-F	89	258	$C_{25}H_{17}O_5N_5SClF$	53.92	2.85	13.01
				(54.20)	(3.09)	(12.64)	
14f	4-OCH_3	74	168	$C_{26}H_{20}O_6N_5SCl$	54.81	3.62	12.56
				(55.17)	(3.56)	(12.37)	
14g	4-Br	81	249	$C_{25}H_{17}O_5N_5SBrCl$	48.61	2.84	11.51
				(48.84)	(2.79)	(11.39)	
14h	3-OCH_3	69	178	$C_{26}H_{20}O_6N_5SCl$	54.79	3.22	12.68
				(55.17)	(3.56)	(12.37)	
14i	2,5-Cl	62	206	$C_{25}H_{16}O_5N_5SCl_3$	49.32	2.68	11.86
				(49.64)	(2.67)	(11.58)	

MHz, $CDCl_3$; δ, ppm): 56.28, 115.46, 115.94, 123.08, 130.57, 131.76, 134.64, 135.66, 136.85, 138.93, 161.74, 163.30, 164.90, 168.53.

4-{[4-(4-Bromophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]sulfamoyl}-3-(4-chlorophenyl)sydnone (14g). IR (KBr, cm^{-1}): 3268, 2836, 1758, 1668, 1326, 1253, 1137, 836, 578; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.25 (s, 3H, OCH_3), 7.43 – 8.34 (m, 13H, Ar-H), 11.13 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 55.38, 114.57, 115.27, 122.10, 126.15, 129.46, 130.00, 131.64, 131.86, 133.48, 134.90, 135.38, 136.38, 138.53, 161.74, 162.58, 163.47, 163.80, 168.80.

3-(4-Chlorophenyl)-4-{[4-(3-methoxyphenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]sulfamoyl}sydnone (14h). IR (KBr, cm^{-1}): 3263, 2857, 1753, 1670, 1346, 1235, 1140, 848; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.28 (s, 3H, OCH_3), 4.36 (s, 3H, OCH_3), 7.26 – 8.10 (m, 13H, Ar-H), 11.26 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 55.73, 55.80, 111.38, 113.65, 114.75, 115.68, 122.90, 127.29, 128.43, 129.75, 130.77, 135.04, 135.19, 135.38, 136.83, 138.38, 160.34, 162.34, 162.57, 163.38, 163.86, 168.66.

3-(4-Chlorophenyl)-4-{[4-(2,5-dichlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]sulfamoyl}sydnone (14i). IR (KBr, cm^{-1}): 3258, 2864, 1756, 1663, 1310, 1243, 1134, 826; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm): 4.15 (s, 3H, OCH_3), 7.33 – 8.17 (m, 12H, Ar-H), 11.37 (s, 1H, SO_2NH); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 56.28, 114.80, 115.74, 123.54, 125.31, 127.48, 129.46, 130.12, 130.67, 131.42, 134.05, 134.57, 135.17, 135.70, 136.84, 138.57, 161.86, 162.55, 163.03, 164.48, 168.84.

EXPERIMENTAL BIOLOGICAL PART

Antibacterial activity of test compounds **12 – 14** was assessed against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas aeruginosa* by cup plate method. The seed culture was poured on Muller – Hilton agar plate. The cups were completed by scooping out nutrient agar with a sterile cock borer. To these cups, solutions of tested compounds (0.1 mL) were added to each cup using sterile pipettes and these plates were incubated in a refrigerator at 4 – 5°C for 30 minutes so as to allow diffusion of compounds to be tested (this permits the diffusion of compounds without allowing the microbes to grow and gives sharp and clear zones) and subsequently incubated at 37°C for 48 hours. The zone of inhibition if any was measured (in millimeters) for the particular compound against each organism.

Of various compounds synthesized according to scheme V, compound **13i** and **14d** exhibited maximum activity against *S. aureus,* while compound **14b** was most active against *B. subtilis*. Compounds **14c** and **14d** showed maximum activity against *E. coli*, and compound **14f** was most active against *P. aeruginosa*. Compounds **13f and 13i** showed good activity against *B. subtilis* and compound **14h** was found active against *P. aeruginosa*. The rest of the synthesized compounds exhibited moderate to poor activity against test species. On the whole, pyrimidine based sydnone derivatives exhibited excellent activity. The results of antimicrobial activity testing are summarized in Table 2.

In conclusion, various thiazole, benzothiazole and pyrimidine substituted sydnone sulfonamides were synthesized and evaluated for their antibacterial activity. Some of the compounds were found effectively active against tested microorganisms.

ACKNOWLEDGMENTS

The authors express their sincere gratitude to Atul Ltd. (Valsad) for providing some important chemicals.

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