Synthesis and Bioassay of Amino-pyrazolone, Amino-isoxazolone and Amino-pyrimidinone Derivatives

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Novel amino-pyrazolone, amino-isoxazolone and amino-pyrimidinone derivatives were prepared from ethyl 4-phenylsulfonyl-2-(2′-phenylsulfonylethyl)-2-cyanobutyrate (1), ethyl 4-arylsulfonyl-3-aryl-2-cyanobutyrate (7) and ethyl 4-arylmethylsulfonyl-3-aryl-2-cyanobutyrate (8). The lead molecules have been tested for their antimicrobial activity and antioxidant property.

Key words amino-pyrazolone; amino-isoxazolone; amino-pyrimidinone; antimicrobial activity; antioxidant property

Heterocyclic compounds particularly five and six membered heterocycles have attracted the attention of pharmaceutical community over the years due to their therapeutic value. A number of barbiturate and thiobarbiturate derivatives exhibit anticonvulsant, anaesthetic, sedative and hypnotic properties.[1—5] In fact, phenobarbital and mephobarbital[6] are used for clinical treatment of epilepsy. Barbiturates still are used world wide in hospitals as injection narcotics.[7,8] Besides this, pyrazole and isoxazole derivatives possess bacteriostatic, antidiabetic, analgesic, antiarrhythmic, anti-inflammatory, antifungal and antiviral properties.[9—14] Celecoxib, a pyrazole derivative, and valdecoxib, an isoxazole derivative are now being used as anti-inflammatory drugs.[15] A continuoes effort is maintained in our laboratories for the development of biologically potent heterocycles. The present communication deals with the synthesis of amino substituted pyrimidine, thioxopyrimidine, pyrazoline and isoxazoline derivatives from Michael adducts by cyclocondensation with different nucleophiles.

Chemistry

The Michael adduct, ethyl 4-phenylsulfonyl-2-(2′-phenylsulfonylethyl)-2-cyanobutyrate (**1**) is prepared by the addition of ethyl cyanoacetate to vinyl sulfone in the presence of Trition-B in benzene. However, ethyl 4-arylsulfonyl-3-aryl-2-cyanobutyrate (**7**) and ethyl 4-arylmethylsulfonyl-3-aryl-2-cyanobutyrate (**8**) are obtained by the reaction of aryl styryl sulfones and benzyl styryl sulfones with ethyl cyanoacetate in the presence of K_2CO_3 in methyl ethyl ketone.[16] The cyclocondensation of **1**, **7** and **8** with hydrazine hydrate in the presence of piperidine in ethanol afforded 5-amino-4,4-bis-(2′-phenylsulfonylethyl)-pyrazol-3-one (**2**), 5-amino-4-(2′-arylsulfonyl-1′-arylethyl)-pyrazol-3-one (**9**) and 5-amino-4-(2′-arylmethylsulfonyl-1′-arylethyl)-pyrazol-3-one (**10**). Similarly, 3-amino-4,4-bis-(2′-phenylsulfonylethyl)-isoxazol-5-one (**3**), 3-amino-4-(2′-arylsulfonyl-1′-arylethyl)-isoxazol-5-one (**11**) and 3-amino-4-(2′-arylmethylsulfonyl-1′-arylethyl)-isoxazol-5-one (**12**) are obtained by treating **1**, **7** and **8** with hydroxylamine hydrochloride. Likewise, six membered heterocycles, 6-amino-5,5-bis-(2′-phenylsulfonylethyl)-2-hydroxypyrimidine-4-one (**4**), 6-amino-5-(2′-arylsulfonyl-1′-arylethyl)-2-hydroxypyrimidine-4-one (**13**), 6-amino-5-(2′-arylmethylsulfonyl-1′-arylethyl)-2-hydroxypyrimidine-4-one (**14**), 6-imino-5,5-bis-(2′-phenylsulfonylethyl)-1,3-dimethylpyrimidine-2,4-dione (**5**), 6-imino-5-(2′-arylsulfonyl-1′-arylethyl)-1,3-dimethylpyrimidine-2,4-dione (**15**) and 6-imino-5-(2′-arylmethylsulfonyl-1′-arylethyl)-1,3-dimethylpyrimidine-2,4-dione (**16**) are obtained by the cyclocondensation of **1**, **7** and **8** with urea and 1,3-dimethylurea, respectively. In addition, 6-amino-5,5-bis-(2′-phenylsulfonylethyl)-2-mercaptopyrimidine-4-one (**6**), 6-amino-5-(2′-arylsulfonyl-1′-arylethyl)-2-mercaptopyrimidine-4-one (**17**) and 6-amino-5-(2′-arylmethylsulfonyl-1′-arylethyl)-2-mercaptopyrimidine-4-one (**18**) are prepared by refluxing the compounds **1**, **7** and **8** with thiourea. Summary of the reactions involved in the synthesis is given in Charts 1 and 2.

The IR spectra of **2**—**6** and **9**—**18** displayed an absorption band at 3435—3475 and 3345—3370 cm^{-1} for NH_2 and at 1125—1145 and 1310—1340 cm^{-1} for SO_2. Apart from these compounds **4**—**6** and **13**—**18** exhibited an absorption band at 1645—1682 cm^{-1} (C=O of pyrimidine ring) while **6**, **17** and **18** exhibited a band at 2545—2560 cm^{-1} (SH). Besides the compounds **2**—**4**, **6**, **9**—**14**, **17** and **18** showed an absorption band at 1600—1620 cm^{-1} (C=N). In the ^{1}H-NMR spectra of **2**—**6** the methylene protons displayed multiplets at 1.83—2.01, 2.11—2.23 for C_1'-H and 2.80—3.05 ppm for C_2'-H. However, a singlet is observed at 2.70—2.74 ppm due to *N*-methyl protons in **5**. The compounds **2**, **3**, **4** and **6** exhibited a broad singlet at 5.77—5.97 ppm for NH_2. Also the compounds **2** and **5** showed a broad singlet at 9.18—9.96 ppm for NH. The signals due to NH_2 and NH disappeared on deuteration. The ^{1}H-NMR spectra of **9**—**12** displayed a doublet at 4.29—4.44 ppm for C_4-H while **13**—**18** at 4.31—4.35 ppm for C_5-H. The compounds **9**—**18** showed a multiplet in the region 4.08—4.29 ppm for C_1'-H, two double doublets at 3.01—3.13 and 3.68—3.78 ppm for C_2'-H. a broad singlet at 5.77—5.91 ppm is observed for NH_2 in **9**—**14**, **17** and **18**. The compounds **10**, **12**, **14**, **16** and **18** showed a sharp singlet at 4.25—4.35 ppm for benzylic protons.

Antimicrobial Testing The compounds **2**—**6** and **9**—**18** were tested for *in vitro* antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, the Gram-negative bacteria *Klebsiella pneumoniae*, *Proteus vulgaris* and fungi *Fusarium solani*, *Curvularia lunata* and *Aspergillus niger*. The primary screen was carried out by agar disc-diffusion method[17] using nutrient agar medium. The minimal inhibitory concentration for the most active

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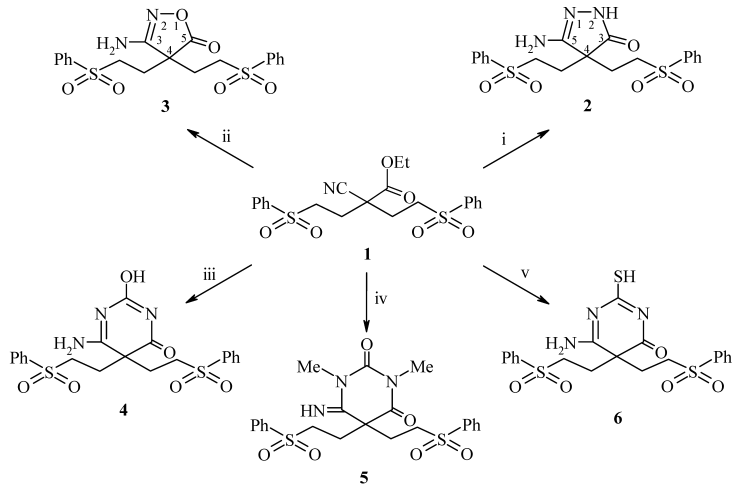
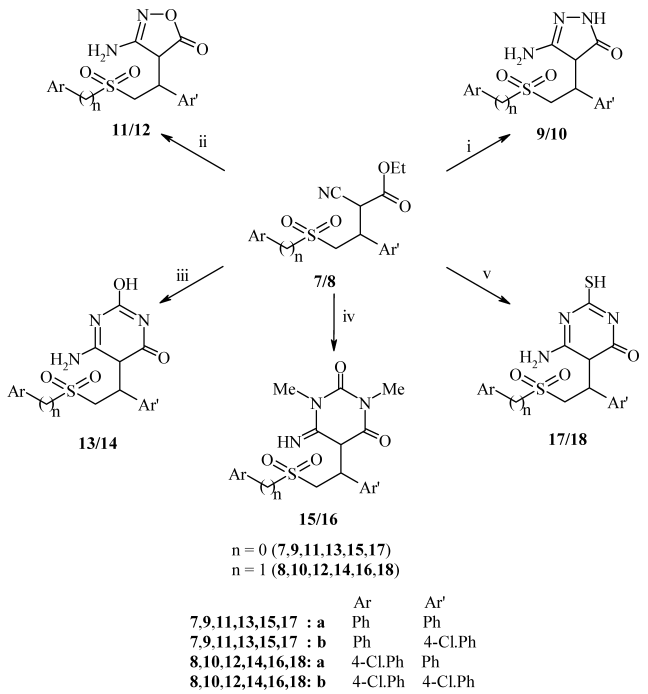


(i) $NH_2NH_2.H_2O$, Piperidine, EtOH, reflux, 6-8 h, 85%
(ii) $NH_2OH.HCl$, Piperidine, EtOH, reflux, 4-5 h, 65% (iii) NH_2CONH_2, Piperidine, EtOH, reflux, 6-9 h, 66%
(iv) MeNHCONHMe, Piperidine, EtOH, reflux, 6-10 h, 64% (v) NH_2CSNH_2, Piperidine, EtOH, reflux, 7-12 h, 68%

Chart 1



n = 0 (**7**,**9**,**11**,**13**,**15**,**17**)
n = 1 (**8**,**10**,**12**,**14**,**16**,**18**)

	Ar	Ar'
7,**9**,**11**,**13**,**15**,**17** : **a**	Ph	Ph
7,**9**,**11**,**13**,**15**,**17** : **b**	Ph	4-Cl.Ph
8,**10**,**12**,**14**,**16**,**18**: **a**	4-Cl.Ph	Ph
8,**10**,**12**,**14**,**16**,**18**: **b**	4-Cl.Ph	4-Cl.Ph

(i) $NH_2NH_2.H_2O$, Piperidine, EtOH, reflux, 6-8 h, 78-86%
(ii) $NH_2OH.HCl$, Piperidine, EtOH, reflux, 4-5 h, 67-73% (iii) NH_2CONH_2, Piperidine, EtOH, reflux, 6-9 h, 66-70% (iv) MeNHCONHMe, Piperidine, EtOH, reflux, 6-10 h, 62-65%
(v) NH_2CSNH_2, Piperidine, EtOH, reflux, 7-12 h, 65-75%

Chart 2

compounds **2** and **10a** against the same microorganisms used in the preliminary screening was carried out using microdilution susceptibility method.[18] Chloramphenicol and ketoconazole were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs were given in Tables 1, 2 and 3.

The results of the compounds of preliminary antibacterial testing are shown in Table 1. The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. Among them 5-amino-4,4-bis-(2′-phenylsulfonylethyl)-pyrazol-3-one (**2**), 3-amino-4,4-bis-(2′-phenylsulfonylethyl)-isoxazol-5-one (**3**), 5-amino-4-[2′-(4-chlorophenylmethylsulfonyl)-1′-(phenyl)-

Table 1. Antibacterial Activity of **2**—**6** and **9**—**18**

Compound	Concentration (μg)	Zone of inhibition (mm)			
		Gram (+)ve		Gram (−)ve	
		Staphylococcus aureus	*Bacillus subtilis*	*Klebsiella pneumoniae*	*Proteus vulgaris*
2	100	34	36	29	27
	200	39	38	33	31
3	100	28	26	25	29
	200	32	30	26	31
4	100	16	14	15	16
	200	18	17	18	18
5	100	14	13	11	12
	200	17	15	14	15
6	100	20	17	18	16
	200	23	21	20	19
9a	100	19	16	18	19
	200	23	18	20	20
10a	100	32	37	33	31
	200	37	39	36	34
11a	100	17	19	17	16
	200	20	22	20	18
12a	100	27	28	27	26
	200	31	33	29	29
13a	100	14	16	12	14
	200	16	17	15	17
14a	100	29	30	24	26
	200	32	34	28	29
15a	100	15	14	14	16
	200	18	16	17	19
16a	100	12	11	16	14
	200	15	13	18	17
17a	100	15	15	14	12
	200	18	17	16	15
18a	100	18	20	16	16
	200	21	22	20	18
Chloramphenicol	100	35	38	37	42
	200	41	44	42	45

ethyl]-pyrazol-3-one (**10a**), 3-amino-4-[2′-(4-chlorophenylmethylsulfonyl)-1′-(phenyl)ethyl]-isoxazol-5-one (**12a**) and 6-amino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl]-2-hydroxypyrimidine-4-one (**14a**) exhibited high activity (24—39 mm) on both gram (+)ve and gram (−)ve bacteria. In fact, compounds **2** and **10a** showed pronounced activity (36—39 mm) towards gram (+)ve bacteria. The compounds, 6-amino-5,5-bis-(2′-phenylsulfonylethyl)-2-mercaptopyrimidine-4-one (**6**), 5-amino-4-(2′-phenylsulfonyl-1′-phenylethyl)-pyrazol-3-one (**9a**), 3-amino-4-(2′-phenylsulfonyl-1′-phenylethyl)-isoxazol-5-one (**11a**) and 6-amino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl)-2-mercaptopyrimidine-4-one (**18a**) displayed moderate to high activity towards gram (+)ve bacteria (16—23 mm) and moderate activity (16—20 mm) towards gram (−)ve bacteria. On the other hand, 6-amino-5,5-bis-(2′-phenylsulfonylethyl)-2-hydroxypyrimidine-4-one (**4**), 6-imino-5,5-bis-(2′-phenylsulfonylethyl)-1,3-dimethylpyrimidine-2,4-dione (**5**), 6-amino-5-(2′-phenylsulfonyl-1′-phenylethyl)-2-hydroxypyrimidine-4-one (**13a**), 6-imino-5-(2′-phenylsulfonyl-1′-phenylethyl)-1,3-dimethylpyrimidine-2,4-dione (**15a**), 6-imino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl]-1,3-dimethylpyrimidine-2,4-dione (**16a**) and 6-amino-5-(2′-phenylsulfonyl-1′-phenylethyl)-2-mercaptopyrimidine-4-one (**17a**) exhibited least activity against both bacteria.

Table 2. Antifungal Activity of **2**—**6** and **9**—**18**

Compound	Concentration (μg)	Zone of inhibition (mm)		
		Fusarium solani	*Curvularia lunata*	*Aspergillus niger*
2	100	22	21	19
	200	25	24	22
3	100	24	24	18
	200	26	27	20
4	100	18	16	15
	200	22	19	17
5	100	21	18	17
	200	23	20	21
6	100	24	19	18
	200	26	22	21
9a	100	19	22	17
	200	21	24	21
10a	100	28	25	20
	200	31	27	23
11a	100	24	23	17
	200	27	25	20
12a	100	29	27	22
	200	32	31	24
13a	100	17	16	14
	200	20	21	17
14a	100	18	21	16
	200	20	23	19
15a	100	16	18	15
	200	20	22	17
16a	100	20	19	16
	200	23	21	19
17a	100	16	17	15
	200	19	19	16
18a	100	27	25	24
	200	29	29	27
Ketoconazole	100	38	41	36
	200	42	44	39

Antifungal Testing All the test compounds inhibited the spore germination of tested fungi *Aspergillus niger*, *Fusarium solani* and *Curvularia lunata*. Results of the investigation presented in Table 2 revealed that all the compounds except **4**, **13a**, **15a** and **17a** possess relatively high inhibitory effect on *Fusarium solani* and *Curvularia lunata* than on *Aspergillus niger*. Further, the compounds having amino-pyrazolone and amino-isoxazolone units displayed greater activity.

The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (Table 3). The structure–antimicrobial activity relationship of the synthesized compounds revealed that the compounds having amino-hydroxypyrimidinone and *N*,*N*-dimethyliminopyrimidinedione exhibited least activity when compared with compounds having amino-pyrazolone and amino-isoxazolone moieties. Besides, the compounds having benzyl sulfonyl group were the most active. The maximum activity was observed with the compounds **2** and **10a** having amino-pyrazolone unit (Table 3).

Antioxidant Testing The compounds **2**—**6** and **9**—**18** are tested for antioxidant property by nitric oxide[19,20] and DPPH[21] methods. The compounds **2**, **3**, **10a** and **12a** exhibited high antioxidant property in both nitric oxide and DPPH

Table 4. Antioxidant Property of **2**—**6** and **9**—**18**

Compound	% Inhibition at 100 μM	
	Nitric oxide method	DPPH method
2	82.25	84.74
3	91.18	93.65
4	34.33	38.10
5	29.21	24.75
6	41.15	44.52
9a	40.62	41.34
10a	93.65	91.22
11a	42.57	41.26
12a	96.42	94.38
13a	24.78	24.78
14a	40.16	40.89
15a	22.18	28.61
16a	34.62	37.83
17a	28.36	31.22
18a	42.44	41.56

Table 3. Minimum Inhibitory Concentration of **2** and **10a**

Compound	Minimal inhibitory concentration (MIC), μg/ml						
	S. aureus	*B. subtilis*	*K. pneumoniae*	*P. vulgaris*	*F. solani*	*C. lunata*	*A. niger*
2	100	100	200	200	100	100	100
10a	25	25	50	100	100	50	50
Chloramphenicol	6.25	6.25	6.25	12.5	—	—	—
Ketoconazole	—	—	—	—	12.5	6.25	6.25

methods at 100 μM concentration (Table 4).

Conclusion

A new class of amino-pyrazolone, amino-isoxazolone, and amino-pyrimidinone derivatives were prepared from Michael adducts 4-phenylsulfonyl-2-(2′-phenylsulfonylethyl)-2-cyanobutyrate (**1**), ethyl 4-arylsulfonyl-3-aryl-2-cyanobutyrate (**7**) and ethyl 4-arylmethylsulfonyl-3-aryl-2-cyanobutyrate (**8**) by cyclocondensation with appropriate nucleophiles. The antimicrobial testing showed that compounds having amino-pyrazolone and amino-isoxazolone possess greater antibacterial activity.

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 3 : 1). The IR spectra were recorded on a Thermo Nicolet infrared spectrophotometer, model Nicolet IR-200 in KBr pellets. The ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra were recorded in $CDCl_3$/DMSO-d_6 (1 : 0.4) on a Varian EM-360 spectrometer with TMS as an internal standard. The elemental analyses were performed by using perkin-elmer 240c elemental analyzer. The mass spectra were recorded on Finnigan Mat 1210 B and Waters Micromass Quattro Micro API at 70 eV with an emission current of 100 μA. The antioxidant property was carried out by using Shimadzu UV-2450 spectrophotometer. The compounds ethyl 4-phenylsulfonyl-2-(2′-phenylsulfonylethyl)-2-cyanobutyrate (**1**), ethyl 4-arylsulfonyl-3-aryl-2-cyanobutyrate (**7**)/ethyl 4-arylmethylsulfonyl-3-aryl-2-cyanobutyrate (**8**) were prepared according to the literature procedure.[16)]

General Procedure of Synthesis of 5-Amino-4,4-bis-(2′-phenylsulfonylethyl)-pyrazol-3-one (2)/5-Amino-4-(2′-arylsulfonyl-1′-arylethyl)-pyrazol-3-one (9a—b)/5-Amino-4-(2′-arylmethylsulfonyl-1′-arylethyl)-pyrazol-3-one (10a—b) A mixture of **1**/**7**/**8** (0.01 mol), hydrazine hydrate (0.015 mol), EtOH (20 ml) and piperidine (5 ml) was refluxed for 6—8 h. The solution was cooled and poured onto crushed ice containing conc. HCl. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The solid obtained was recrystallized from MeOH.

5-Amino-4,4-bis-(2′-phenylsulfonylethyl)-pyrazol-3-one (**2**): White crystals; yield 85%, mp 209—211 °C; IR (KBr) cm^{-1}: 3475, 3369 (NH_2), 3209 (NH), 1638 (C=O), 1607 (C=N), 1146, 1309 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.90—2.00 (m, 2H, C$_1'$-H), 2.13—2.23 (m, 2H, C$_1'$-H), 2.83—3.04 (m, 4H, C$_2'$-H), 5.91 (bs, 2H, NH_2), 7.57—7.85 (m, 10H, Ar-H), 9.96 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 25.3 (C-1′), 49.3 (C-4), 50.0 (C-2′), 158.1 (C-5), 171.9 (C-3), 126.7, 128.3, 132.8, 137.5; MS *m*/*z*: 435 ($M^{+\cdot}$). *Anal.* Calcd for $C_{19}H_{21}N_3O_5S_2$: C, 52.40; H, 4.86; N, 9.65; Found C, 52.52; H, 4.82; N, 9.75.

5-Amino-4-(2′-phenylsulfonyl-1′-phenylethyl)-pyrazol-3-one (**9a**): White crystals, yield 80%, mp 201—202 °C; IR (KBr) cm^{-1}: 3475, 3369 (NH_2), 3209 (NH), 1639 (C=O), 1607 (C=N), 1309, 1146 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.07 (dd, 1H, C$_2'$-H, *J*=4.3, 14.1 Hz), 3.70 (dd, 1H, C$_2'$-H, *J*=9.4, 14.0 Hz), 4.22—4.27 (m, 1H, C$_1'$-H), 4.33 (d, 1H, C$_4$-H, *J*=5.1 Hz), 5.82 (bs, 2H, NH_2), 7.11—7.84 (m, 10H, Ar-H), 9.89 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 52.3 (C-2′), 54.6 (C-1′), 61.8 (C-4), 157.1 (C-5), 174.7 (C-3), 125.9, 126.4, 127.2, 128.9, 129.7, 131.2, 136.8, 138.8; MS *m*/*z*: 343 ($M^{+\cdot}$). *Anal.* Calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24; Found C, 59.55; H, 4.95; N, 12.18.

5-Amino-4-[2′-phenylsulfonyl-1′-(4-chlorophenyl)ethyl]-pyrazol-3-one (**9b**): White solid, yield 86%, mp 212—214 °C; IR (KBr) cm^{-1}: 3355, 3449 (NH_2), 3200 (NH), 1626 (C=O), 1614 (C=N), 1315, 1139 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.04 (dd, 1H, C$_2'$-H, *J*=4.5, 14.3 Hz), 3.72 (dd, 1H, C$_2'$-H, *J*=9.5, 14.1 Hz), 4.23—4.29 (m, 1H, C$_1'$-H), 4.35 (d, 1H, C$_4$-H, *J*=5.2 Hz), 5.87 (bs, 2H, NH_2), 7.14—7.99 (m, 9H, Ar-H), 9.78 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 53.1 (C-2′), 54.8 (C-1′), 62.7 (C-4), 156.7 (C-5), 175.0 (C-3), 126.3, 127.1, 127.6, 128.5, 129.2, 133.2, 137.4, 138.5; MS *m*/*z*: 377 ($M^{+\cdot}$). *Anal.* Calcd for $C_{17}H_{16}ClN_3O_3S$: C, 54.04; H, 4.27; N, 11.12; Found C, 53.97; H, 4.24; N, 11.08.

5-Amino-4-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl]-pyrazol-3-one (**10a**): White crystals; yield 78%, mp 206—208 °C; IR (KBr) cm^{-1}: 3364, 3471 (NH_2), 3204 (NH), 1635 (C=O), 1603 (C=N), 1313, 1142 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.03 (dd, 1H, C$_2'$-H, *J*=4.1, 14.0 Hz), 3.76 (dd, 1H, C$_2'$-H, *J*=9.2, 13.8 Hz), 4.18—4.25 (m, 1H, C$_1'$-H), 4.31 (s, 2H, Ar-CH_2), 4.33 (d, 1H, C$_4$-H, *J*=5.4 Hz), 5.91 (bs, 2H, NH_2), 7.19—7.32 (m, 9H, Ar-H), 9.84 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 53.3 (C-2′), 53.9 (C-1′), 58.2 (Ar-CH_2), 62.4 (C-4), 154.2 (C-5), 175.3 (C-3), 127.4, 128.1, 128.9, 129.5, 131.2, 131.3, 139.7; MS *m*/*z*: 391 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_3S$: C, 55.17; H, 4.63; N, 10.72; Found C, 55.11; H, 4.65; N, 10.80.

5-Amino-4-[2′-(4-chlorophenylmethanesulfonyl)-1′-(4-chlorophenyl)-ethyl]-pyrazol-3-one (**10b**): Light yellow solid; yield 82%, mp 216—218 °C; IR (KBr) cm^{-1}: 3358, 3446 (NH_2), 3208 (NH), 1633 (C=O), 1620 (C=N), 1327, 1133, (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.07 (dd, 1H, C$_2'$-H, *J*=4.2, 14.2 Hz), 3.79 (dd, 1H, C$_2'$-H, *J*=9.3, 13.9 Hz), 4.21—4.26 (m, 1H, C$_1'$-H), 4.28 (s, 2H, Ar-CH_2), 4.34 (d, 1H, C$_4$-H, *J*=5.3 Hz), 5.84 (bs, 2H, NH_2), 7.07—7.33 (m, 8H, Ar-H), 9.87 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 54.1 (C-2′), 56.4 (C-1′), 58.9 (Ar-CH_2), 63.6 (C-4), 155.8 (C-5), 176.2 (C-3), 125.4, 126.4, 128.1, 129.5, 130.7, 132.1, 133.7, 139.2; MS *m*/*z*: 425 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{17}Cl_2N_3O_3S$: C, 50.71; H, 4.02; N, 9.86; Found C, 50.80; H, 4.06; N, 9.82.

General Procedure of Synthesis of 3-Amino-4,4-bis-(2′-benzenesulfonylethyl)-isoxazol-5-one (3)/3-Amino-4-(2′-arylsulfonyl-1′-arylethyl)-isoxazol-5-one (11a—b)/3-Amino-4-(2′-arylmethylsulfonyl-1′-arylethyl)-isoxazol-5-one (12a—b) To a solution of **1**/**7**/**8** (0.01 mol) in EtOH (20 ml), hydroxylamine hydrochloride (0.01 mol) and piperidine (5 ml) were added and refluxed for 4—5 h. The solution was cooled and poured onto crushed ice, acidified with conc. HCl. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave crude product which was purified by recrystallization from MeOH.

3-Amino-4,4-bis-(2′-phenylsulfonylethyl)-isoxazol-5-one (**3**): White solid, yield 65%, mp 178—180 °C; IR (KBr) cm^{-1}: 3467, 3356 (NH_2), 1646 (C=O), 1610 (C=N), 1322, 1139 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.85—1.98 (m, 2H, C$_1'$-H), 2.16—2.21 (m, 2H, C$_1'$-H), 2.87—3.05 (m, 4H, C$_2'$-H), 5.86 (bs, 2H, NH_2), 7.41—7.98 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 24.3 (C-1′), 46.7 (C-4), 50.3 (C-2′), 156.9 (C-3), 174.6 (C-5), 125.7, 129.5, 131.2, 138.5; MS *m*/*z*: 436 ($M^{+\cdot}$). *Anal.* Calcd for $C_{19}H_{20}N_2O_6S_2$: C, 52.28; H, 4.62; N, 6.42; Found C, 52.43; H, 4.64; N, 6.53.

3-Amino-4-(2′-phenylsulfonyl-1′-phenylethyl)-isoxazol-5-one (**11a**): White crystals, yield 68%, mp 184—186 °C; IR (KBr) cm^{-1}: 3435, 3349 (NH_2), 1636 (C=O), 1612 (C=N), 1333, 1135 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 3.05 (dd, 1H, C$_2'$-H, *J*=4.3, 14.1 Hz), 3.68 (dd, 1H, C$_2'$-H, *J*=9.5, 14.0 Hz), 4.24—4.28 (m, 1H, C$_1'$-H), 4.37 (d, 1H, C$_4$-H, *J*=5.0 Hz), 5.77 (bs, 2H, NH_2), 7.08—7.85 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 54.5 (C-2′), 56.2 (C-1′), 63.3 (C-4), 159.2 (C-3), 175.4 (C-5), 124.2, 125.3, 126.7, 127.5, 129.1, 131.4, 137.2, 138.3; MS *m*/*z*: 344 ($M^{+\cdot}$). *Anal.* Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13; Found C, 59.39; H, 4.65; N, 8.05.

3-Amino-4-[2′-phenylsulfonyl-1′-(4-chlorophenyl)ethyl]-isoxazol-5-one (**11b**): White solid, yield 73%, mp 189—191 °C; IR (KBr) cm^{-1}: 3441, 3352 (NH_2), 1621 (C=O), 1619 (C=N), 1337, 1141 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 3.04 (dd, 1H, C$_2'$-H, *J*=4.4, 14.2 Hz), 3.68 (dd, 2H, C$_2'$-H, *J*=9.6, 14.2 Hz), 4.08—4.19 (m, 1H, C$_1'$-H), 4.44 (d, 1H, C$_4$-H, *J*=5.2 Hz), 5.87 (bs, 2H, NH_2), 7.18—7.39 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 53.5 (C-2′), 58.7 (C-1′), 64.8 (C-4), 158.3 (C-3), 176.2 (C-5), 127.3, 127.4, 127.5, 128.2, 128.7, 136.7, 140.3, 142.7: MS *m*/*z*: 378 ($M^{+\cdot}$). *Anal.* Calcd for $C_{17}H_{15}ClN_2O_4S$: C, 53.90; H, 3.99; N, 7.39; Found C, 54.01; H, 4.04; N, 7.46.

3-Amino-4-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl]-isoxazol-5-one (**12a**): Light yellow solid, yield 67%, mp 195—197 °C; IR (KBr) cm^{-1}: 3444, 3359 (NH_2), 1642 (C=O), 1603 (C=N), 1331, 1128 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 3.08 (dd, 1H, C$_2'$-H, *J*=4.5, 14.4 Hz), 3.74 (dd, 1H, C$_2'$-H, *J*=9.7, 14.3 Hz), 4.21—4.27 (m, 1H, C$_1'$-H), 4.29 (d, 1H, C$_4$-H, *J*=5.1 Hz), 4.34 (s, 2H, Ar-CH_2), 5.88 (bs, 2H, NH_2), 7.02—7.63 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 54.2 (C-2′), 57.8 (C-1′), 58.8 (Ar-CH_2), 62.9 (C-4), 158.3 (C-3), 173.7 (C-5), 126.3, 127.5, 128.7, 129.4, 129.9, 131.8, 139.2; MS *m*/*z*: 392 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36; N, 7.13; Found C, 55.15; H, 4.32; N, 7.09.

3-Amino-4-[2′-(4-chlorophenylmethylsulfonyl)-1′-(4-chlorophenyl)-ethyl]-isoxazol-5-one (**12b**): Colourless crystals, yield 70%, mp 200—202 °C; IR (KBr) cm^{-1}: 3453, 3343 (NH_2), 1631 (C=O), 1606 (C=N), 1338, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 3.03 (dd, 1H, C$_2'$-H, *J*=4.6, 14.5 Hz), 3.71 (dd, 1H, C$_2'$-H, *J*=9.8, 14.4 Hz), 4.19—4.25 (m, 1H, C$_1'$-H), 4.31 (d, 1H, C$_4$-H, *J*=5.3 Hz), 4.35 (s, 2H, Ar-CH_2), 5.91 (bs, 2H, NH_2), 7.03—7.45 (m, 8H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 53.8 (C-2′), 54.9 (C-1′), 57.7 (Ar-CH_2), 62.4 (C-4), 159.1 (C-3), 174.2 (C-5), 125.2, 126.4,

127.3, 129.5, 131.8, 131.9, 133.5, 140.3; MS *m/z*: 426 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{16}Cl_2N_2O_4S$: C, 50.59; H, 3.77; N, 6.56; Found C, 50.50; H, 3.75; N, 6.60.

General Procedure of Synthesis of 6-Amino-5,5-bis-(2′-phenylsulfonylethyl)-2-hydroxypyrimidine-4-one (4)/6-Amino-5-(2′-arylsulfonyl-1′-arylethyl)-2-hydroxypyrimidine-4-one (13a—b)/6-Amino-5-(2′-arylmethylsulfonyl-1′-arylethyl)-2-hydroxypyrimidine-4-one (14a—b) The compound **1**/**7**/**8** (0.01 mol) was dissolved in EtOH (10 ml). To this urea (0.01 mol) in EtOH (10 ml) and piperidine (5 ml) were added and refluxed for 6—9 h. The contents were cooled, poured onto crushed ice containing conc. HCl and extracted with ethylacetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* gave crude product which was purified by recrystallization from MeOH.

6-Amino-5,5-bis-(2′-phenylsulfonylethyl)-2-hydroxypyrimidine-4-one (**4**): White needles, yield 66%, mp 270—272 °C; IR (KBr) cm^{-1}: 3458, 3362 (NH_2), 3335 (OH), 1635 (C=O), 1604 (C=N), 1335, 1145 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.92—2.01 (m, 2H, C_1'-H), 2.15—2.22 (m, 2H, C_1'-H), 2.85—3.01 (m, 4H, C_2'-H), 5.94 (bs, 2H, NH_2), 6.84 (s, 1H, OH), 7.42—7.85 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 24.7 (C-1′), 47.2 (C-5), 49.1 (C-2′), 157.4 (C-6), 161.2 (C-2), 178.7 (C-4), 125.8, 127.3, 131.6, 136.2; MS *m/z*: 463 ($M^{+\cdot}$). *Anal.* Calcd for $C_{20}H_{21}N_3O_6S_2$: C, 51.82; H, 4.57; N, 9.07. Found C, 51.70; H, 4.60; N, 9.14.

6-Amino-5-(2′-phenylsulfonyl-1′-phenylethyl)-2-hydroxypyrimidine-4-one (**13a**): Colourless crystals, yield 66%, mp 284—286 °C; IR (KBr) cm^{-1}: 3442, 3365 (NH_2), 3328 (OH), 1635 (C=O), 1609 (C=N), 1334, 1142 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.11 (dd, 1H, C_2'-H, J=4.4, 14.3 Hz), 3.79 (dd, 1H, C_2'-H, J=9.4, 14.4 Hz), 4.17—4.22 (m, 1H, C_1'-H), 4.33 (d, 1H, C_5-H, J=5.4 Hz), 5.86 (bs, 2H, NH_2), 6.92 (bs, 1H, OH), 7.11—7.82 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 52.7 (C-2′), 53.6 (C-1′), 63.9 (C-5), 158.8 (C-6), 162.5 (C-2), 176.3 (C-4), 125.3, 125.9, 126.7, 127.4, 129.1, 131.3, 137.8, 138.3; MS *m/z*: 371 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31; Found C, 58.30; H, 4.66; N, 11.41.

6-Amino-5-[2′-(4-chlorophenylsulfonyl)-1′-phenylethyl]-2-hydroxypyrimidine-4-one (**13b**): White solid, yield 68%, mp 268—270 °C; IR (KBr) cm^{-1}: 3379, 3453 (NH_2), 3315 (OH), 1625 (C=O), 1612 (C=N), 1328, 1130 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.07 (dd, 1H, C_2'-H, J=4.5, 14.4 Hz), 3.74 (dd, 1H, C_2'-H, J=9.5, 14.5 Hz), 4.21—4.26 (m, 1H, C_1'-H), 4.31 (d, 1H, C_5-H, J=5.4 Hz), 5.89 (bs, 2H, NH_2), 6.87 (bs, 1H, OH), 7.04—7.87 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 52.1 (C-2′), 54.9 (C-1′), 64.5 (C-5), 159.2 (C-6), 163.4 (C-2), 175.7 (C-4), 125.1, 126.9, 128.1, 129.4, 130.4, 131.8, 137.9, 140.1; MS *m/z*: 405 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{16}ClN_3O_4S$: C, 53.27; H, 3.97; N, 10.35.;Found C, 53.22; H, 4.00; N, 10.30.

6-Amino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl]-2-hydroxypyrimidine-4-one (**14a**): White crystals, yield 70%, mp 262—264 °C; IR (KBr) cm^{-1}: 3360, 3445 (NH_2), 3331 (OH), 1637 (C=O), 1601 (C=N), 1328, 1146 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.05 (dd, 1H, C_2'-H, J=4.2, 14.1 Hz), 3.67 (dd, 1H, C_2'-H, J=9.2, 14.1 Hz), 4.14—4.21 (m, 1H, C_1'-H), 4.26 (s, 2H, Ar-CH_2), 4.33 (d, 1H, C_5-H, J=5.2 Hz), 5.78 (bs, 2H, NH_2), 6.93 (bs, 1H, OH), 7.09—7.46 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 53.8 (C-2′), 55.2 (C-1′), 59.8 (Ar-CH_2), 63.3 (C-5), 158.7 (C-6), 162.7 (C-2), 174.2 (C-4), 126.1, 126.9, 127.0, 127.7, 129.3, 131.3, 137.8, 140.4; MS *m/z*: 419 ($M^{+\cdot}$). *Anal.* Calcd for $C_{19}H_{18}ClN_3O_4S$: C, 54.35; H, 4.32; N, 10.01; Found C, 54.44; H, 4.33; N, 10.08.

6-Amino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-(4-chlorophenyl)-ethyl]-2-hydroxypyrimidine-4-one (**14b**): White crystals, yield 69%, mp 280—282 °C; IR (KBr) cm^{-1}: 1134, 1325 (SO_2), 1610 (C=N), 1630 (C=O), 3324 (OH), 3372, 3443 (NH_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 3.09 (dd, 1H, C_2'-H, J=4.3, 14.2 Hz), 3.77 (dd, 1H, C_2'-H, J=9.3, 14.2 Hz), 4.19—4.24 (m, 1H, C_1'-H), 4.32 (d, 1H, C_5-H, J=5.3 Hz), 4.25 (s, 2H, Ar-CH_2), 5.86 (bs, 2H, NH_2), 6.89 (bs, 1H, OH), 7.04—7.39 (m, 8H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 54.2 (C-2′), 54.4 (C-1′), 58.5 (Ar-CH_2), 64.9 (C-5), 158.7 (C-6), 161.8 (C-2), 173.8 (C-4), 125.4, 126.1, 127.3, 128.7, 129.8, 131.7, 134.2, 138.1; MS *m/z*: 453 ($M^{+\cdot}$). *Anal.* Calcd for $C_{19}H_{17}Cl_2N_3O_4S$: C, 50.23; H, 3.77; N, 9.25; Found C, 50.29; H, 3.80; N, 9.20.

General Procedure of Synthesis of 6-Imino-5,5-bis-(2′-phenylsulfonylethyl)-1,3-dimethylpyrimidine-2,4-dione (5)/6-Imino-5-(2′-arylsulfonyl-1′-arylethyl)-1,3-dimethylpyrimidine-2,4-dione (15a—b)/6-Imino-5-(2′-arylmethylsulfonyl-1′-arylethyl)-1,3-dimethylpyrimidine-2,4-dione (16a—b) A mixture of **1**/**7**/**8** (0.01 mol), 1,3-dimethylurea (0.01 mol), EtOH (15 ml) and piperidine (5 ml) was taken and refluxed for 6—10 h. The contents were diluted with ice-cold water, acidified with conc. HCl and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded crude product which was purified by recrystallization from MeOH.

6-Imino-5,5-bis-(2′-phenylsulfonylethyl)-1,3-dimethylpyrimidine-2,4-dione (**5**): White powder, yield 64%, mp 273—275 °C; IR (KBr) cm^{-1}: 3215 (NH), 1634 (C=O), 1612 (C=N), 1327, 1133 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.88—1.96 (m, 2H, C_1'-H), 2.11—2.20 (m, 2H, C_1'-H), 2.70 (s, 6H, N-CH_3), 2.80—2.96 (m, 4H, C_2'-H), 7.44—7.87 (m, 10H, Ar-H), 9.18 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 23.8 (C-1′), 28.9 (N-CH_3), 29.2 (N-CH_3), 42.5 (C-5), 49.4 (C-2′), 158.4 (C-2), 164.2 (C-6), 178.0 (C-4), 126.6, 130.1, 132.5, 136.3; MS *m/z*: 491 ($M^{+\cdot}$). *Anal.* Calcd for $C_{22}H_{25}N_3O_6S_2$: C, 53.75; H, 5.13; N, 8.55; Found C, 53.89; H, 5.15; N, 8.67.

6-Imino-5-(2′-phenylsulfonyl-1′-phenylethyl)-1,3-dimethylpyrimidine-2,4-dione (**15a**): White solid, yield 64%, mp 287—288 °C; IR (KBr) cm^{-1}: 3212 (NH), 1641 (C=O), 1603 (C=N), 1326, 1137 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 2.73 (s, 6H, N-CH_3), 3.02 (dd, 1H, C_2'-H, J=4.1, 14.0 Hz), 3.75 (dd, 1H, C_2'-H, J=9.6, 14.3 Hz), 4.15—4.21 (m, 1H, C_1'-H), 4.34 (d, 1H, C_5-H, J=5.1 Hz), 7.05—7.87 (m, 10H, Ar-H), 9.21 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 27.9 (N-CH_3), 28.5 (N-CH_3), 52.8 (C-2′), 54.1 (C-1′), 64.3 (C-5), 159.7 (C-2), 163.2 (C-6), 176.5 (C-4), 125.5, 126.4, 126.8, 127.8, 129.5, 131.3, 138.5, 141.2; MS *m/z*: 399 ($M^{+\cdot}$). *Anal.* Calcd for $C_{20}H_{21}N_3O_4S$: C, 60.13; H, 5.30; N, 10.52. Found C, 60.24; H, 5.28; N, 10.60.

6-Imino-5-[2′-phenylsulfonyl-1′-(4-chlorophenyl)ethyl]-1,3-dimethylpyrimidine-2,4-dione (**15b**): White solid, yield 67%, mp 266—267 °C; IR (KBr) cm^{-1}: 3217 (NH), 1634 (C=O), 1607 (C=N), 1313, 1128 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 2.71 (s, 6H, N-CH_3), 3.06 (dd, 1H, C_2'-H, J=4.3, 14.3 Hz), 3.78 (dd, 1H, C_2'-H, J=9.7, 14.4 Hz), 4.16—4.23 (m, 1H, C_1'-H), 4.32 (d, 1H, C_5-H, J=5.2 Hz), 7.01—7.88 (m, 9H, Ar-H), 9.18 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 28.4 (N-CH_3), 29.1 (N-CH_3), 53.2 (C-2′), 54.7 (C-1′), 65.2 (C-5), 158.6 (C-2), 162.4 (C-6), 175.3 (C-4), 126.5, 127.1, 127.9, 129.2, 130.5, 132.5, 138.8, 140.3; MS *m/z*: 433 ($M^{+\cdot}$). *Anal.* Calcd for $C_{20}H_{20}ClN_3O_4S$: C, 55.36; H, 4.65; N, 9.68; Found C, 55.30; H, 4.70; N, 9.74.

6-Imino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-phenylethyl]-1,3-dimethylpyrimidine-2,4-dione (**16a**): White solid, yield 62%, mp 270—272 °C; IR (KBr) cm^{-1}: 3232 (NH), 1640 (C=O), 1615 (C=N), 1324, 1125 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 2.74 (s, 6H, N-CH_3), 3.08 (dd, 1H, C_2'-H, J=4.5, 14.5 Hz), 3.71 (dd, 1H, C_2'-H, J=9.5, 14.6 Hz), 4.21—4.25 (m, 1H, C_1'-H), 4.28 (s, 2H, Ar-CH_2), 4.35 (d, 1H, C_5-H, J=4.9 Hz), 7.06—7.33 (m, 9H, Ar-H), 9.21 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 27.8 (N-CH_3), 28.1 (N-CH_3), 52.4 (C-2′), 55.3 (C-1′), 56.8 (Ar-CH_2), 63.8 (C-5), 157.4 (C-2), 163.2 (C-6), 174.9 (C-4), 125.1, 125.7, 126.6, 127.4, 128.3, 131.7, 133.8, 139.9; MS *m/z*: 447 ($M^{+\cdot}$). *Anal.* Calcd for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; N, 9.38; Found C, 56.41; H, 4.94; N, 9.45.

6-Imino-5-[2′-(4-chlorophenylmethylsulfonyl)-1′-(4-chlorophenyl)ethyl]-1,3-dimethylpyrimidine-2,4-dione (**16b**): Light yellow solid, yield 64%, mp 250—252 °C; IR (KBr) cm^{-1}: 3225 (NH), 1636 (C=O), 1604 (C=N), 1318, 1132 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 2.73 (s, 6H, N-CH_3), 3.13 (dd, 1H, C_2'-H, J=4.7, 14.6 Hz), 3.74 (dd, 1H, C_2'-H, J=9.6, 14.4 Hz), 4.11—4.17 (m, 1H, C_1'-H), 4.27 (s, 2H, Ar-CH_2), 4.34 (d, 1H, C_5-H, J=5.0 Hz), 7.12—7.41 (m, 8H, Ar-H), 9.18 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 28.9 (N-CH_3), 29.4 (N-CH_3), 53.3 (C-2′), 54.8 (C-1′), 57.3 (Ar-CH_2), 64.2 (C-5), 157.0 (C-2), 162.6 (C-6), 175.3 (C-4), 126.4, 126.9, 127.2, 129.3, 130.4, 131.3, 133.6, 138.7; MS *m/z*: 481 ($M^{+\cdot}$). *Anal.* Calcd for $C_{21}H_{21}Cl_2N_3O_4S$: C, 52.29; H, 4.39; N, 8.71; Found C, 52.21; H, 4.43; N, 8.68.

General Procedure of Synthesis of 6-Amino-5,5-bis-(2′-phenylsulfonylethyl)-2-mercaptopyrimidine-4-one (6)/6-Amino-5-(2′-arylsulfonyl-1′-arylethyl)-2-mercaptopyrimidine-4-one (17a—b)/6-Amino-5-(2′-arylmethylsulfonyl-1′-arylethyl)-2-mercaptopyrimidine-4-one (18a—b) To a solution of **1**/**7**/**8** (0.01 mol) in EtOH (20 ml), thiourea (0.01 mmol) and piperidine (5 ml) were added and refluxed for 7—12 h. The reaction mixture was cooled, poured onto crushed ice containing conc. HCl and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed with rotary evaporator. The resulted solid was purified by recrystallization from MeOH.

6-Amino-5,5-bis-(2′-phenylsulfonylethyl)-2-mercaptopyrimidine-4-one (**6**): White solid, yield 68%, mp 269—271 °C; IR (KBr) cm^{-1}: 3462, 3357 (NH), 2558 (SH), 1630 (C=O), 1616 (C=N), 1338, 1142 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.35 (s, 1H, SH), 1.83—1.94 (m, 2H, C_1'-H), 2.14—2.22 (m, 2H, C_1'-H), 2.89—3.05 (m, 4H, C_2'-H), 5.97 (bs, 2H, NH_2), 7.37—

7.86 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 22.9 (C-1′), 43.2 (C-5), 49.1 (C-2′), 163.8 (C-6), 179.1 (C-4), 187.5 (C-2), 127.2, 129.4, 133.4, 137.5; MS *m/z*: 479 ($M^{+\cdot}$). *Anal.* Calcd for $C_{20}H_{21}N_3O_5S_3$: C, 50.09; H, 4.41; N, 8.76.; Found C, 50.00; H, 4.39; N, 8.84.

6-Amino-5-(2′-phenylsulfonyl-1′-phenylethyl)-2-mercaptopyrimidine-4-one (**17a**): White crystals, yield 65%, mp 285—287 °C; IR (KBr) cm^{-1}: 3462, 3357 (NH), 2557 (SH), 1638 (C=O), 1610 (C=N), 1325, 1137 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.38 (s, 1H, SH), 3.01 (dd, 1H, C_2'-H, *J*=4.6, 14.4 Hz), 3.75 (dd, 1H, C_2'-H, *J*=9.7, 14.5 Hz), 4.14—4.21 (m, 1H, C_1'-H), 4.31 (d, 1H, C_5-H, *J*=5.2 Hz), 5.77 (bs, 2H, NH_2), 7.11—7.84 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 52.0 (C-2′), 53.4 (C-1′), 63.7 (C-5), 162.9 (C-6), 178.3 (C-4), 186.8 (C-2), 125.2, 126.0, 126.6, 127.5, 128.4, 132.3, 137.6, 140.2; MS *m/z*: 387 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{17}N_3O_3S_2$: C, 55.79; H, 4.42; N, 10.84; Found C, 55.73; H, 4.45; N, 10.93.

6-Amino-5-[2′-phenylsulfonyl-1′-(4-chlorophenyl)ethyl]-2-mercaptopyrimidine-4-one (**17b**): White crystals, yield 70%, mp 276—278 °C; IR (KBr) cm^{-1}: 3450, 3338 (NH), 2545 (SH), 1645 (C=O), 1606 (C=N), 1316, 1134 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.35 (s, 1H, SH), 3.08 (dd, 1H, C_2'-H, *J*=4.8, 14.2 Hz), 3.77 (dd, 1H, C_2'-H, *J*=9.8, 14.3 Hz), 4.16—4.22 (m, 1H, C_1'-H), 4.37 (d, 1H, C_5-H, *J*=5.1 Hz), 5.85 (bs, 2H, NH_2), 7.05—7.96 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 53.1 (C-2′), 55.8 (C-1′), 62.9 (C-5), 163.7 (C-6), 176.2 (C-4), 187.4 (C-2), 125.5, 126.3, 127.2, 129.6, 131.5, 132.2, 138.9, 140.6; MS *m/z*: 421 ($M^{+\cdot}$). *Anal.* Calcd for $C_{18}H_{16}ClN_3O_3S_2$: C, 51.24; H, 3.82; N, 9.96; Found C, 51.32; H, 3.86; N, 10.04.

6-Amino-5-[2′-(4-chlorophenylsulfonyl)-1′-phenylethyl]-2-mercaptopyrimidine-4-one (**18a**): White crystals, yield 75%, mp 204—206 °C; IR (KBr) cm^{-1}: 3457, 3351 (NH), 2543 (SH), 1634 (C=O), 1608 (C=N), 1321, 1131 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.32 (s, 1H, SH), 3.05 (dd, 1H, C_2'-H, *J*=4.7, 14.5 Hz), 3.74 (dd, 1H, C_2'-H, *J*=9.4, 14.4 Hz), 4.18—4.23 (m, 1H, C_1'-H), 4.29 (s, 2H, Ar-CH_2), 4.33 (d, 1H, C_5-H, *J*=5.3 Hz), 5.78 (bs, 2H, NH_2), 7.04—7.37 (m, 9H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 52.9 (C-2′), 54.7 (C-1′), 57.6 (Ar-CH_2), 63.7 (C-5), 162.7 (C-6), 175.5 (C-4), 185.9 (C-2), 125.3, 126.6, 127.1, 128.6, 129.5, 131.7, 133.9, 141.5; MS *m/z*: 435 ($M^{+\cdot}$). *Anal.* Calcd for $C_{19}H_{18}ClN_3O_3S_2$: C, 52.35; H, 4.16; N, 9.64; Found C, 52.43; H, 4.18; N, 9.60.

6-Amino-5-[2′-(4-chlorophenylsulfonyl)-1′-(4-chlorophenyl)ethyl]-2-mercaptopyrimidine-4-one (**18b**): White solid, yield 72%, mp 254—256 °C; IR (KBr) cm^{-1}: 3441, 3345 (NH), 2559 (SH), 1642 (C=O), 1614 (C=N), 1330, 1138 (SO_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.37 (s, 1H, SH), 3.02 (dd, 1H, C_2'-H, *J*=4.9, 14.3 Hz), 3.71 (dd, 1H, C_2'-H, *J*=9.5, 14.1 Hz), 4.21—4.26 (m, 1H, C_1'-H), 4.28 (s, 2H, Ar-CH_2), 4.30 (d, 1H, C_5-H, *J*=5.4 Hz), 5.85 (bs, 2H, NH_2), 7.10—7.41 (m, 8H, Ar-H); ^{13}C-NMR ($CDCl_3$+DMSO-d_6) δ: 52.6 (C-2′), 53.8 (C-1′), 57.9 (Ar-CH_2), 62.4 (C-5), 163.5 (C-6), 176.4 (C-4), 186.7 (C-2), 125.3, 126.2, 127.4, 128.4, 130.8, 131.7, 133.8, 141.3 (aromatic carbons); MS *m/z*: 469 ($M^{+\cdot}$). *Anal.* Calcd for $C_{19}H_{17}Cl_2N_3O_3S_2$: C, 48.51; H, 3.64; N, 8.93. Found C, 48.57; H, 3.63; N, 8.98.

Antimicrobial Testing The compounds **2**—**6** and **9**—**18** were dissolved in DMSO at different concentrations of 100, 200 and 800 μg/ml.

Antibacterial and Antifungal Assays Preliminary antimicrobial activities of compounds **2**—**6** and **9**—**18** were tested by agar disc-diffusion method. Sterile filter paper discs (6 mm diameter) moistened with the test compound solution in DMSO of specific concentration 100 μg and 200 μg/disc were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 °C and the diameter of the growth inhibition zones were measured after 24 h. in case of bacteria and after 48 h in case of fungi.

The MICs of the compounds assays were carried out using microdilution susceptibility method. Chloramphenicol was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The test compounds, chloramphenicol and ketoconazole were dissolved in DMSO at concentration of 800 μg/ml. The twofold dilution of the solution was prepared (400, 200, 100, 50, 25, 12.5, 6.25). The microorganism suspensions were inoculated to the corresponding wells. The plates were incubated at 36 °C for 24 and 48 h for bacteria and fungi, respectively. The minimum inhibitory concentrations of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no turbidity (*i.e.* no growth) of inoculated bacteria/fungi.

Antioxidant Testing The compounds **2**—**6** and **9**—**18** are tested for antioxidant property by nitric oxide and DPPH methods.

Assay for Nitric Oxide (NO) Scavenging Activity Sodium nitroprusside (5 μM) in phosphate buffer pH 7.4 was incubated with 100 μM concentration of test compounds dissolved in a suitable solvent (dioxane/methanol) and tubes were incubated at 25 °C for 120 min. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 ml of incubation solution was taken and diluted with 0.5 ml of griess reagent (1% sulfanilamide, 0.1% *N*-naphthylethylenediamine dihydrochloride and 2% *o*-phosphoric acid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthylethylenediamine dihydrochloride was read at λ 546 nm. The experiment was repeated in triplicate.

Reduction of 1,1-Diphenyl-2-picrylhydrazyl (DPPH) Free Radical (DPPH Method) The nitrogen centered stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at λ 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties.

The solutions of test compounds (100 μM) were added to DPPH (100 μM) in dioxane/ethanol. The tubes were kept at an ambient temperature for 20 min and the absorbance was measured at λ 517 nm. The difference between the test and the control experiments was taken and expressed as the per cent scavenging of the DPPH radical.

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