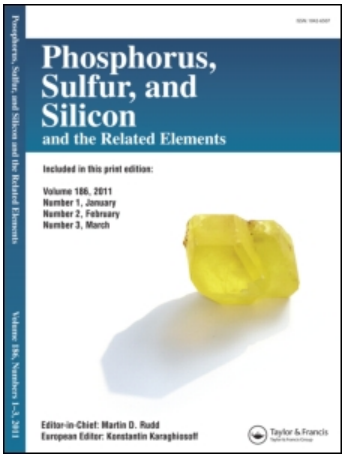

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Synthesis and Biological Study of Some Novel 4-[5-(4,6-Disubstituted-2-thiomethylpyrimidyl)-4'-amino-1,2,4- triazol-3'-yl] thioacetyl-3-arylsydnones

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Synthesis and Biological Study of Some Novel 4-[5-(4,6-Disubstituted-2-thiomethylpyrimidyl)-4′-amino-1,2,4-triazol-3′-yl] thioacetyl-3-arylsydnones

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A series of 4-[5-(4,6-disubstituted-2-thiomethyl pyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]thioacetyl-3-arylsydnones ***7a–i*** *were synthesized by the reaction of 5-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-3-mercapto-1,2-4-triazoles* ***3*** *with 3-aryl-4-bromoacetyl sydnones* ***6*** *in an ethanol medium. The newly synthesized compounds* ***7a–i*** *were screened for their antibacterial activity against* E. coli *and* Serratia marcesens *and for antibacterial activity against* Aspergillus niger *and* Pencillium*. Most of the tested compounds showed significant antifungal activity particularly against* Pencillium *at 10-μg/mL concentration comparable with that of the standard drug Flukanazole.*

Keywords Biological activity; pyrimidine; sydnone; triazoles

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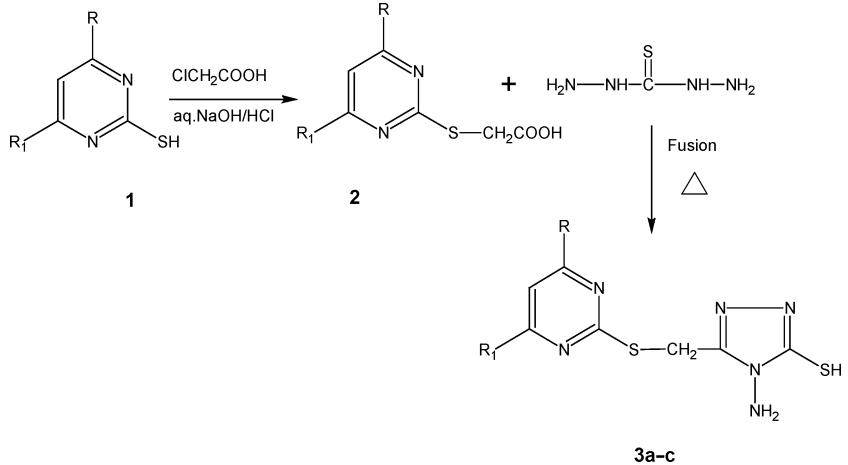
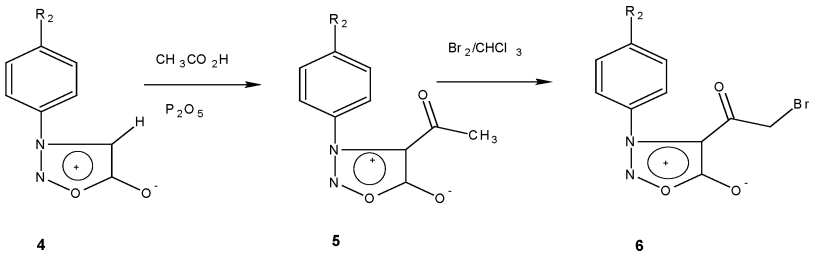
INTRODUCTION

The literature survey shows that a large number of simple, N-bridged, nitrogen- and sulphur-containing heterocyclic compounds carrying a pyrimidine moiety are found to be associated with diverse biological activities. The chemistry of pyrimidine and its derivatives have been studied for over a century due to their diverse biological activities.[1–4] They possess antibacterial,[5] antiviral,[6] antitumor,[7,8] antihypertensive, and anti-inflammatory[9,10] activities. Similarly, 1,2,4-trizoles and their derivatives are found to be associated with diverse pharmacological activities.[11–13] The study of sydnones still remains a field of interest because of their electronic structure and also because of the varied types of biological activity displayed by them. Interest in sydnone has also been encouraged by the discovery that they exhibit various pharmacological activities.[14,15] Keeping in view of these observations, we decided to undertake the synthesis of some novel heterocycles containing pyrimidine, triazole, and sydnone moiety and to evaluate their biological activity.

The synthetic route followed for obtaining the title compound is outlined in Schemes 1, 2, and 3. Thus 4,6-disubstituted-2-thioprymidines **1** on reaction with chloro acetic acid in aqueous sodium hydroxide followed by neutralization with hydrochloric acid gave the pyrimidine thioaceticacid **2**. Fusion of **2** with thiocabohydrazide gave 5-(4, 6-disubstituted-2-thiomethylpyrimidyl)-4-amino-3-mercapto-1,2-4-triazoles, **3a–c** (Scheme 1). Reaction of **3** with bromoacetyl sydnones **6** in an ethanol medium employing sodium acetate as a catalyst gave novel 4-[5-(4,6-disubstituted-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-



SCHEME 1



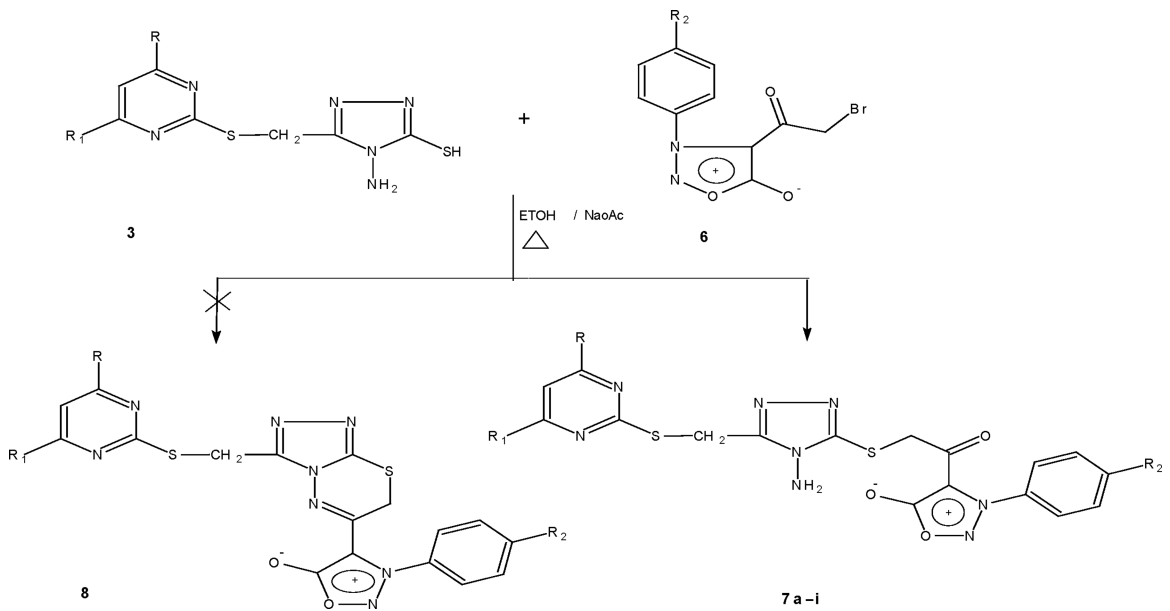
SCHEME 2

3′-yl]-thioacetyl-3-arylsydnone **7a–i** (Scheme 3). Arylsydnones **4**, when reacted with acetic acid in the presence of P_2O_5 in benzene medium,[16] gave 4-acetyl-3-arylsydnones **5**. Bromination of **5** in chloroform medium under irradiation by visible light[17] gave 4-bromoacetyl-3-arylsydnones **6** (Scheme 2). 2-Thio-pyrimidine **1** and arylsydnones **4** were prepared as per the literature procedure,[18,19] respectively.

RESULTS AND DISCUSSION

The structures of the newly synthesized triazoles **3a–c** and 4-[5-(4,6-disubstituted-2-thiomethyl pyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-arylsydnones **7a–i** were established on the basis of analytical and spectral data. The IR spectra of triazoles **3a–c** showed absorption bands in the region 3290–3450 cm^{-1} characteristic of the NH_2 group. The C—H stretching band was observed in the region 2730–2790 cm^{-1}. The C=N absorption band was observed around 1600–1625 cm^{-1}. In a typical example the ^1H NMR spectra of triazole **3b** showed a singlet at δ 2.32 integrating for three protons of the methyl group. The S—CH_2 protons came into resonance at δ 4.36. The NH_2 protons appeared as a singlet at δ 5.11. The 5-H and 6-H protons of pyrimidine appeared as two doublets at δ 6.81 (J = 11 Hz) and δ 8.26 (J = 11 Hz), each integrating for one proton. The SH proton appeared as a singlet at δ 10.5. In the mass spectrum of this compound, the molecular ion peak was observed at m/z 254 (Molecular Formula; $C_8H_{10}N_6S_2$), which is also the base peak, thereby indicating the stability of the triazole.

When these triazoles **3** were reacted with 4-bromoacetyl-3-arylsyndone **6** in an ethanol medium in the presence of sodium acetate as a catalyst, we expected the formation of triazolothiadiazines **8**. However, the reaction resulted in the formation of a novel series of mercaptoacetyl derivatives of sydnones **7** with the elimination of a molecule of HBr. All of our attempts to cyclize these compounds to triazolothiadiazines **8** employing either acidic as well as basic catalysts failed,



SCHEME 3

mainly due to the sensitivity of the sydnone ring toward acids and bases. The IR spectra of compounds **7** showed absorption bands at 3100–3400 cm^{-1} characteristic of the NH_2 group. The absorption band at 1760–1780 cm^{-1} is characteristic of the sydnone carbonyl group, and the absorption peak around 1660–1685 cm^{-1} is due to the carbonyl group of the thioacetyl moiety. In the ^1H NMR spectrum of **7f**, the methyl protons attached to the pyrimidyl group appeared as a singlet at δ 2.4 integrating for three protons. The OCH_3 protons came into resonance at δ 3.9. The S—CH_2 protons appeared as a singlet at δ 4.5. The singlet at δ 4.65 integrating for two protons was assigned for the S—CH_2—C=CO protons. The NH_2 protons appeared as a broad singlet at δ 5.9. The signal due to ortho protons of p-anisyl and the pyrimidine 5H protons mingled together and appeared as a multiplet in the region δ 7.1–7.2 integrating for three protons. The meta-protons of the p-anisyl group appeared as a doublet at δ 7.53, and the pyrimidine —6H proton appeared as a doublet at δ 8.6 integrating for one proton. Further, the mass spectrum of **7f** showed the molecular ion peak at m/z 487 (M^++1) consistent with the molecular formula ($C_{19}H_{18}N_8S_2O_4$), and the cluster of isotope peaks due to S^{34} were also observed at m/z 489 and 491 respectively. Similarly, the spectral details of few other selected compounds are presented in Table II.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin Elmer 577 spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on a Perkin Elmer (Model RB-12) spectrometer using TMS as an internal standard (chemical shifts are reported in δ scale). Mass spectrum was recorded on LC/MS (API 3000, Applied Biosystems, Agilent, USA) operating at 70 eV. C H N analysis was carried out on a Vairo-EL (Elementa) model. Purity of the compounds was checked by TLC on silica gel plates.

Substituted-pyrimidne-2-thioaceticacid 2

2-chloro acetic acid (9.5 g, 0.1 mol) was taken in a round-bottom flask, and 50 mL water was added, cooled, and neutralized by adding a solution of saturated sodium carbonate. A solution of substituted-2-thiopyrimidine (0.1 mol) **1** in aq. sodium hydroxide (8.0 g, 0.2 mol) was added slowly at 15–20°C and stirred at room temperature for 3–4 h. The reaction was monitored by TLC. The contents were cooled and acidified to pH 2–4 using hydrochloric acid. The resulting solids that separated were filtered, washed with water, dried, and recrystallized from ethanol.

5-(4,6-Disubtituted-pyrimidine-2-thiomethyl)-4-amino-3-mercapto-1,2,4-triazole 3

Substitued-pyrimidine-2-thioaceticacid (0.02 mol) **2** and thiocarbohydrazide (2.12 gm, 0.02 mol) were taken in a round-bottom flask and heated under stirring in an oil bath to form a clear solution. Completion of the reaction was monitored by TLC. The contents were cooled to room temperature diluted with water. The solid that separated was filtered, washed with saturated sodium bicarbonate solution, and dried. Further purification was done by recrystallization from ethanol (Scheme 1). The compounds prepared as per this procedure are listed in Table I.

TABLE I Characterization Data of Newly Synthesized 5-(4,6-disubstituted-2-thiomethyl Pyrimidyl)-4-amino-3-mercapto-1,2,4-triazoles (3a–c) and 4-[5-(4,6-disubstituted-2-thiomethyl Pyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3′-arylsydnones 7a–i

Compound No.	R	R_1	R_2	m.p.°C (Yield %)	Mol. Formula (Mol. Weight)	Analysis (%) Found (Calculated) C	H	N
3a	H	H	—	112–114 (74)	$C_7H_8N_6S_2$ (240)	35.09 (35.00)	3.32 (3.33)	34.98 (35)
3b	CH_3	H	—	116–120 (78)	$C_8H_{10}N_6S_2$ (254)	37.72 (37.79)	3.90 (3.93)	33.03 (33.07)
3c	CH_3	CH_3	—	154–158 (75)	$C_9H_{12}N_6S_2$ (268)	40.19 (40.23)	4.45 (4.47)	31.30 (31.34)
7a	H	H	H	158–160 (75)	$C_{17}H_{14}N_8O_3S_2$ (442)	46.10 (46.15)	3.14 (3.16)	25.35 (25.33)
7b	H	H	CH_3	167–169 (65)	$C_{18}H_{16}N_8O_3S_2$ (456)	47.40 (47.36)	3.52 (3.50)	24.51 (24.56)
7c	H	H	OCH_3	190–94 (74)	$C_{18}H_{16}N_8O_4S_2$ (472)	45.81 (45.76)	3.35 (3.39)	23.68 (23.72)
7d	CH_3	H	H	160–164 (75)	$C_{18}H_{16}N_8O_3S_2$ (456)	47.30 (47.36)	3.52 (3.50)	24.61 (24.56)
7e	CH_3	H	CH_3	188–190 (80)	$C_{19}H_{18}N_8O_3S_2$ (470)	48.55 (48.51)	3.80 (3.82)	23.79 (23.82)
7f	CH_3	H	OCH_3	198–200 (85)	$C_{19}H_{18}N_8O_4S_2$ (486)	46.91 (46.87)	3.68 (3.70)	23.08 (23.04)
7g	CH_3	CH_3	H	158–162 (80)	$C_{19}H_{18}N_8O_3S_2$ (470)	48.56 (48.51)	3.79 (3.82)	23.77 (23.82)
7h	CH_3	CH_3	CH_3	172–176 (82)	$C_{20}H_{20}N_8O_3S_2$ (484)	49.55 (49.58)	4.15 (4.13)	23.18 (23.14)
7i	CH_3	CH_3	OCH_3	194–197 (78)	$C_{20}H_{20}N_8O_4S_2$ (500)	48.05 (48.00)	3.98 (4.00)	22.36 (22.40)

TABLE II Selected ^{1}H NMR (δ, ppm) ($CDCl_3$) and MS m/z of the Compounds

3c. 5-(4,6-Dimethyl-pyrimidine-2-thiomethyl)-4-amino-3-mercapto-1,2,4-triazole
δ, 2.45 (s, 6H, 2 × CH_3), 4.5 (s, 2H, S—CH_2), 4.9 (s, 2H, NH_2), 6.75 (s, 1H, pyrimidine-5H) and 10.5 (s, 1H, SH). Mass: m/z, 269 (M^++1) consistent with the molecular formula $C_9H_{12}N_6S_2$.

7d. 4-[5-(4-methyl-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-(p-phenyl) sydnone.
δ, 2.41 (s, 3H, Pyrimidine-CH_3), 3.91 (s, 2H, S—CH_2), 4.68 (s, 2H, S—CH_2—C═O), 5.12 (s, 2H, NH_2), 6.80 (d, 1H, pyrimidine-5H), 7.0–7.82 (m, 5H, Ar—H) and 8.20 (d, 1H, pyrimidine-6H). Mass: m/z, 457(M^++1) consistent with the molecular formula $C_{18}H_{16}N_8O_3S_2$.

7e. 4-[5-(4-methyl-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-(p-tolyl) sydnone
δ, 1.66 (s, 3H, Ar—CH_3), 2.43 (s, 3H, Pyrimidine-CH_3), 3.92 (s, 2H, S—CH_2), 4.64 (s, 2H, S—CH_2—C═O), 5.1 (s, 2H, NH_2), 6.85 (d, 1H, pyrimidine-5H) 7.1 (d, 2H, ortho-protons of p-tolyl) 7.26 (d, 2H meta-protons of p-tolyl) and 8.26 (d, 1H, pyrimidine-6H). Mass: m/z, 471(M^++1) consistent with the molecular formula $C_{19}H_{18}N_8O_3S_2$.

7g. 4-[5-(4,6-Dimethyl-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-(p-phenyl) sydnone
δ, 2.23 (s, 6H, 2 × CH_3 of Pyrimidine), 4.43 (s, 2H, S—CH_2), 4.54 (s, 2H, S—CH_2—C═O), 4.9 (s, 2H, NH_2), 6.76 (s, 1H, pyrimidine-5H) and 7.2–7.76 (m, 5H, Ar—H). Mass: m/z, 471 (M^++1) consistent with the molecular formula $C_{19}H_{18}N_8O_3S_2$.

7h. 4-[5-(4,6-Dimethyl-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-(p-tolyl) sydnone
δ, 1.86 (s, 3H, Ar—CH_3), 2.22 (s, 6H, 2 × CH_3 of Pyrimidine), 4.4 (s, 2H, S—CH_2), 4.53 (s, 2H, S—CH_2—C═O), 4.9 (s, 2H, NH_2), 6.61 (s, 1H, pyrimidine-5H) 7.15 (d, 2H, ortho-protons of p-tolyl) and 7.25 (d, 2H meta-protons of p-tolyl). Mass: m/z, 485 (M^++1) consistent with the molecular formula $C_{20}H_{20}N_8O_3S_2$.

7i. 4-[5-(4,6-Dimethyl-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-(p-anisyl) sydnone
δ, 2.24 (s, 6H, 2 × CH_3 of Pyrimidine), 3.89 (s, 3H, OCH_3), 4.52 (s, 2H, S—CH_2), 4.65 (s, 2H, S—CH_2—C═O), 5.7 (s, 2H, NH_2), 7.25 (d, 2H, ortho-protons of p-anisyl) and 7.54 (d, 2H meta-protons of p-anisyl), 6.66 (s, 1H, pyrimidine-5H). Mass: m/z, 501(M^++1), consistent with the molecular formula $C_{20}H_{20}N_8O_4S_2$.

4-[5-(4,6-Disubstituted-2-thiomethylpyrimidyl)-4′-amino-1,2-4-triazol-3′-yl]-thioacetyl-3-arylsydnone 7

A solution of 5-substituted-4-amino-3-mercapto-1,2,4-triazole **3** (0.01 mol) and appropriate bromoacetyl sydnones **6** (0.01 mol) in ethanol (20 mL) and sodium acetate (0.86 g, 0.001 mol) was refluxed on a water bath for 2–3 h. Completion of the reaction was monitored by TLC. On cooling the contents to room temperature, the solid mass that separated was collected by filtration and recrystallized from ethanol (Scheme 3). The compounds prepared as per this procedure are listed in Table I.

TABLE III Antibacterial Activity of Compounds 7 at 10-μg/mL Concentration (Diameter of Zone of Inhibition in mm)

Compound No.	*E. coli*	*Serratia marcesens*
7a	23	12
7b	16	17
7c	19	11
7d	15	15
7e	11	13
7f	22	15
7g	19	10
7h	10	14
7i	15	14
Tetracyclin (Std.)	25	19

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity in vitro against Gram-positive bacteria *E. coli* and Gram-negative bacteria *Serratia marcesens* by the disk diffusion method.[20] The test compounds were dissolved in N,N-dimethylformamide (DMF) to obtain a solution of 10-μg/mL concentration. The inhibition zones of microbial growth produced by different compounds were measured in millimeters at the end of an incubation period of 48 h at 37°C. DMF alone showed no inhibition zone. Tetracyclin was employed as the reference standard (10 μg) to evaluate the potency of the tested compounds. The results are illustrated in Table III.

TABLE IV Antifungal Activity of Compounds 7 at 10-μg/mL Concentration (Diameter of Zone of Inhibition in mm)

Compound No.	*Aspergillus niger*	*Pencillium*
7a	17	22
7b	22	25
7c	21	22
7d	15	21
7e	15	16
7f	24	18
7g	24	22
7h	19	18
7i	21	29
Flukanozole (Std.)	25	22

Antifungal Activity

Newly synthesized compounds were also screened for their antifungal activity against two species of fungi, *Aspergillus niger* and *Pencillium,* using the disk diffusion method.[20] The test compounds were dissolved in DMF to get a solution of 10-μg/mL concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 37°C. Flukanozole was used as a reference standard, and the results were shown in Table IV. Most of the tested compounds showed significant antifungal activity comparable with that of the standard drug Flukanozole.

CONCLUSION

A new series of pyrimidine- and sydnone-bearing triazoles were reported with a view to evaluate their biological activity. However, the testing results indicated that they are more potent antifungal agents comparable with the standard drug Flukanazole.

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