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Regioselective reaction: Synthesis of novel Mannich bases derived from 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-5-mercapto-1,2-4-triazoles and their antimicrobial properties

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A new series of 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-5-mercapto-1,2-4-triazoles have been synthesized. These triazoles on reaction with aldehydes in the presence of acid catalyst forms Schiff's bases. These Schiff's bases can exist both in the thiol as well as in the thione tautomeric form. However when these compounds are subjected to Mannich reaction, N-Mannich bases **7a-f** are obtained rather than the S-Mannich bases. The structures of the new compounds have been confirmed by spectral and analytical data. Few of these Mannich bases have been evaluated for their possible antifungal and antibacterial activity. Most of the tested compounds show significant antifungal and antibacterial activity.

Keywords: 1,2,4-Triazoles, pyrimidines, Schiff bases, Mannich bases

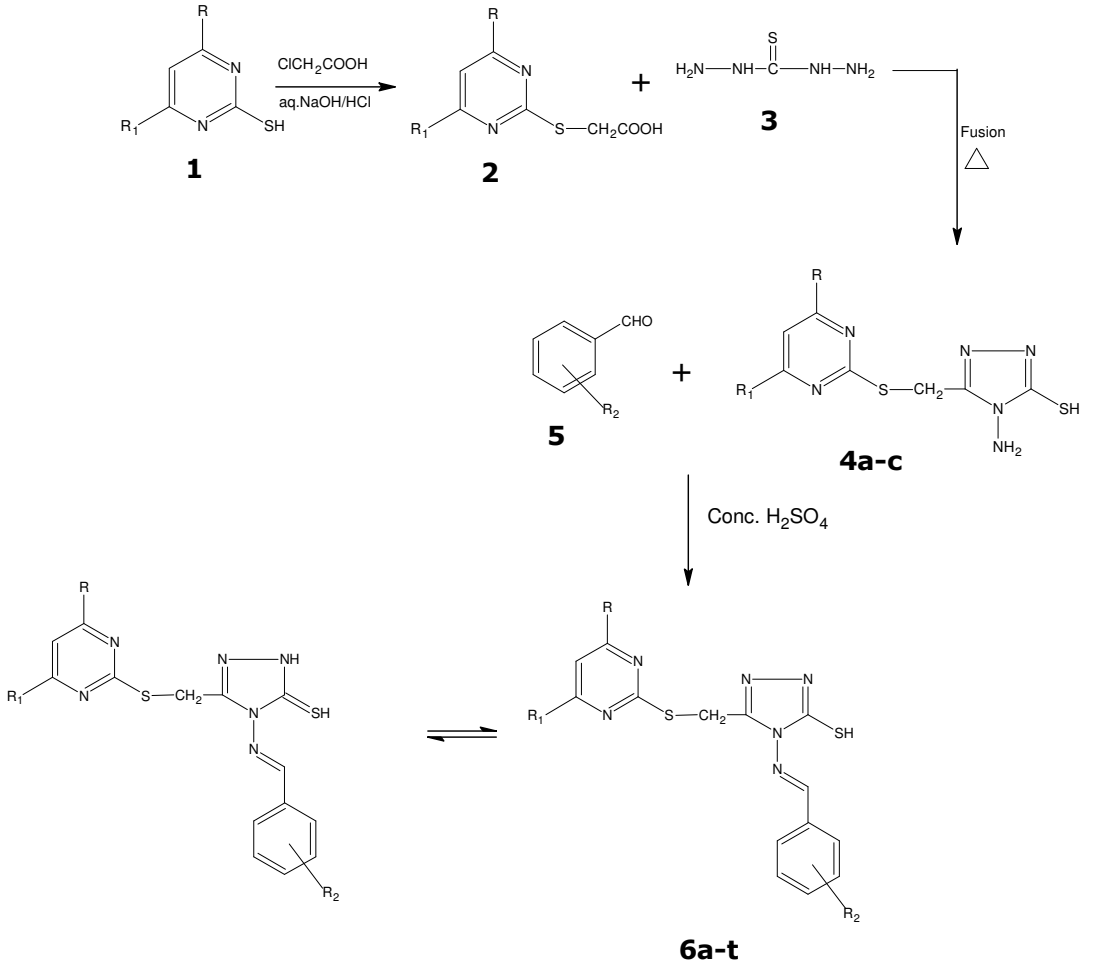
Literature survey shows that large number of heterocyclic compounds carrying pyrimidine moiety are found to be associated with diverse biological activities such as insecticidal, antimicrobial, antiviral[1-3] etc. Pyrimidines are of great importance in fundamental metabolism. Pyrimidine derivatives are also known to possess analgesic and anti-inflammatory activity[4]. Various analogous of thiopyrimidines such as 2-thiouracil and 2,4-dithiouracil possess systemic fungicidal activity. 1,2,4-Triazoles are found to be associated with diverse pharmacological activities[5-7]. In recent years Mannich bases have gained importance because of their technological applications in polymer industry especially as paints and surface-active reagents. These are also used in the field of pharmaceutical products, as anti-neoplastic drugs, analgesic drugs, and antibiotic drugs, etc.[8-11] Fascinated by the varied biological activity of pyrimidine derivatives it was contemplated to synthesize a new series of pyrimidine triazoles, their hydrazones and Mannich bases.

Results and Discussion

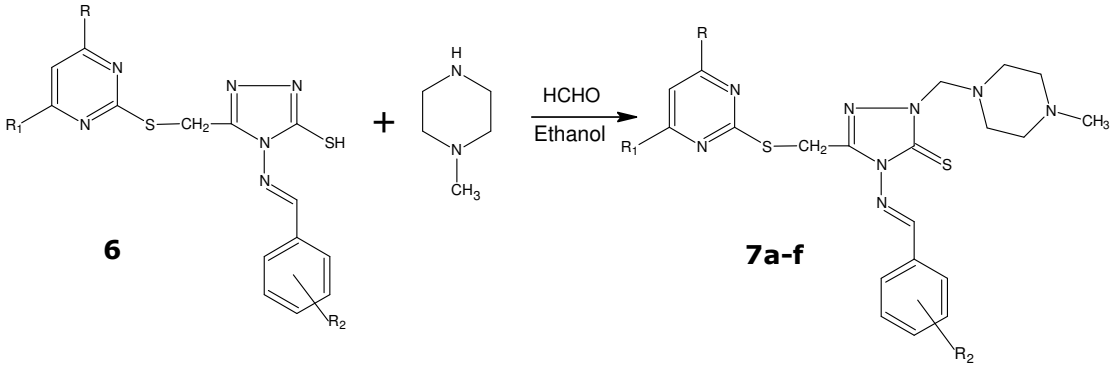
The synthetic route followed for obtaining the title compound is outlined in **Schemes I** and **II** Thus 4,6-disubstituted-pyrimidine-2-thiol[12,13] **1** on reaction with chloroacetic acid in aqueous sodium hydroxide followed by neutralization with hydrochloric acid gave the pyrimidine-2-thioacetic acid **2**. Fusion of **2** with thiocarbohydrazide **3** gave 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-5-mercapto-1,2-4-triazoles **4a-c**. Reaction of 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-5-mercapto-1,2-4-triazoles **4a-c** with various aldehydes **5** in ethanol medium in the presence of sulphuric acid catalyst gave 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-(substituted arylidine)amino-5-mercapto-1,2-4-triazole **6a-t (Scheme I)**.

These triazole thiones **6a-t** can exist both in the thiol as well as in the thione tautomeric form. However the Mannich reaction of these compounds with N-methylpiperazine in ethanol medium in the presence of formaldehyde resulted in the formation of N-Mannich bases **7a-f** rather than the S-Mannich bases, there by indicating that the reaction is highly regiospecific (**Scheme II**).

The structures of the newly synthesized 3-(4, 6-disubstituted-2-thiomethyl pyrimidyl)-4-amino-5-mercapto-1,2-4-triazoles **4a-c**, 3-(4,6-disubstituted-2-thiomethyl pyrimidyl)-4-(substituted arylidene)-amino-1,2,4-triazole-5-thiones **6a-t** and 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-(substituted-arylidene)-amino-2-(N-methylpiperazinomethyl)-1,2, 4-triazole-5-thiones **7a-f** were established on the basis



Scheme I



Scheme II

of analytical and spectral data. The characterization data of triazoles **4a-c**, Schiff bases **6a-t** and Mannich bases **7a-f** were given in **Table I** and **Table II** respectively.

The IR spectra of triazoles **4a-c** showed absorption bands in the region of 3290-3450 cm^{-1} characteristic of the NH_2 group. The C-H stretching band was observed in the region of 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 **4b** showed a singlet at δ 2.33 integrating for three protons of the methyl group. The S-CH_2 protons came

Table I — The characterization data of triazoles **4a-c**, Schiff bases **6a-t**

Compd	R	R_1	R_2	m.p. (°C) (Yield %)	Mol. Formula (Mol.Wt)	Analysis (%) Found (Calcd)		
						C	H	N
4a	H	H	-	112-14 (74)	$C_7H_8N_6S_2$ (240)	35.09 (35.00	3.32 3.33	34.98 35)
4b	CH_3	H	-	116-20 (78)	$C_8H_{10}N_6S_2$ (254)	37.72 (37.79	3.90 3.93	33.03 33.07)
4c	CH_3	CH_3	-	154-58 (75)	$C_9H_{12}N_6S_2$ (268)	40.19 (40.23	4.45 4.47	31.30 31.34)
6a	CH_3	H	*p*-Chloro phenyl	180-82 (80)	$C_{15}H_{13}N_6S_2Cl$ (376)	47.81 (47.87	3.42 3.45	22.38 22.34)
6b	CH_3	H	*p*-Nitro phenyl	198-201 (74)	$C_{15}H_{13}N_7O_2S_2$ (387)	46.56 (46.51	3.33 3.35	25.29 25.32)
6c	CH_3	H	*o*-Anisyl	210-13 (78)	$C_{16}H_{16}N_6OS_2$ (372)	51.55 (51.61	4.34 4.30	25.60 25.58)
6d	CH_3	H	*p*-N,N-Dimethyl phenyl	220-22 (90)	$C_{17}H_{19}N_7S_2$ (385)	52.94 (52.98	4.96 4.93	25.41 25.45)
6e	CH_3	H	3,4-Dimethoxy phenyl	180-84 (75)	$C_{17}H_{18}N_6O_2S_2$ (402)	50.77 (50.74	4.42 4.47	20.89 20.89)
6f	CH_3	H	3,4,5-Trimethoxy phenyl	168-70 (65)	$C_{18}H_{20}N_6O_3S_2$ (432)	50.07 (50.00	4.60 4.63	19.44 19.44)
6g	CH_3	H	2-Nitro-4,5-dimethoxy phenyl	242-46 (74)	$C_{17}H_{17}N_7O_4S_2$ (447)	45.69 (45.63	3.75 3.80	21.96 21.92)
6h	CH_3	H	2,3,5-Trichloro phenyl	200-03 (75)	$C_{15}H_{11}N_6S_2Cl_3$ (444)	40.40 (40.45	2.45 2.47	18.88 18.91)
6i	CH_3	H	6-Methoxy-naphthyl	198-200 (70)	$C_{20}H_{18}N_6OS_2$ (422)	56.84 (56.87	4.29 4.26	19.87 19.90)
6j	CH_3	H	8-Quinolinyl	220-23 (650)	$C_{18}H_{15}N_7S_2$ (393)	54.94 (54.96	3.85 3.81	24.96 24.93)
6k	CH_3	CH_3	*p*-Chloro phenyl	160-62 (75)	$C_{16}H_{15}N_6S_2Cl$ (390)	49.29 (49.23	3.81 3.84	21.50 21.53)
6l	CH_3	CH_3	*p*-Nitro phenyl	238-40 (72)	$C_{16}H_{15}N_7O_2S_2$ (401)	47.92 (47.88	3.71 3.74	24.47 24.43)
6m	CH_3	CH_3	*o*-Anisyl	226-28 (71)	$C_{17}H_{18}N_6OS_2$ (386)	52.79 (52.84	4.68 4.66	21.79 21.76)
6n	CH_3	CH_3	*p*-N,N-Dimethyl phenyl	218-21 (65)	$C_{18}H_{21}N_7S_2$ (399)	54.18 (54.13	5.24 5.26	24.59 24.56)
6o	CH_3	CH_3	3,4-Dimethoxy phenyl	234-36 (60)	$C_{18}H_{20}N_6O_2S_2$ (416)	51.96 (51.92	4.78 4.80	20.22 20.19)
6p	CH_3	CH_3	3,4,5-Trimethoxy phenyl	195-97 (75)	$C_{19}H_{22}N_6O_3S_2$ (446)	51.20 (51.12	4.95 4.93	18.80 18.83)
6q	CH_3	CH_3	2-Nitro-4,5-dimethoxy phenyl	248-52 (70)	$C_{18}H_{19}N_7O_4S_2$ (461)	46.81 (46.85	4.14 4.12	21.27 21.25)
6r	CH_3	CH_3	2,3,5-Trichloro phenyl	214-17 (74)	$C_{16}H_{13}N_6S_2Cl_3$ (458)	41.87 (41.92	2.80 2.83	18.38 18.34)
6s	CH_3	CH_3	6-Methoxy-naphthyl	202-05 (75)	$C_{21}H_{20}N_6OS_2$ (436)	57.72 (57.78	4.60 4.58	19.21 19.26)
6t	CH_3	CH_3	8-Quinolinyl	231-33 (70)	$C_{19}H_{17}N_7S_2$ (407)	55.96 (56.01	4.19 4.17	24.03 24.07)

Solvent for recrystallization: Ethanol

Table II — Characterization data of 3-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-(substituted-arylidene)-amino-1-(N-methyl-piperazinomethyl)-1,2,4-triazole-5-thiones (Mannich bases) **(7a-f)**

Compd	R	R_1	R_2	m.p. (°C) (Yield %)	Mol. formula (Mol. wt)	Analysis (%) Found (Calculated)		
						C	H	N
7a	CH_3	H	*p*-Chloro phenyl	162-66 (70)	$C_{21}H_{25}N_8ClS_2$ (488)	51.69 (51.63	5.10 5.12	22.91 22.95)
7b	CH_3	H	*p*-Nitro phenyl	158-62 (65)	$C_{21}H_{25}N_9O_2S_2$ (499)	50.55 (50.50	5.03 5.01	27.20 27.25)
7c	CH_3	H	2-Nitro-4,5-dimethoxy phenyl	152-54 (65)	$C_{23}H_{29}N_9O_4S_2$ (559)	49.32 (49.37	5.21 5.18	22.57 22.54)
7d	CH_3	CH_3	*p*-Chloro phenyl	150-52 (70)	$C_{22}H_{27}N_8ClS_2$ (502)	52.64 (52.59	5.35 5.37	22.28 22.31)
7e	CH_3	CH_3	*p*-Nitro phenyl	175-78 (75)	$C_{22}H_{27}N_9O_2S_2$ (513)	51.51 (51.46	5.25 5.26	24.58 24.56)
7f	CH_3	CH_3	2-Nitro-4,5-dimethoxy phenyl	168-70 (60)	$C_{24}H_{31}N_9O_4S_2$ (573)	50.21 (50.26	5.40 5.41	22.02 21.99)

Solvent for recrystallization: Ethanol

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 and δ 8.26 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.

Condensation of 3-(4,6-disubstituted-2-thiomethyl pyrimidyl)-4-amino-5-mercapto-1,2,4-triazoles **4a-c**, with appropriate aldehyde **5** in ethanol medium employing concentrated sulphuric acid catalyst gave the respective hydrazones **6** (**Table I**). In the IR spectrum of **6f** C-H stretching absorption was observed at 2937 cm^{-1} and the C=N absorption band was seen at 1587 cm^{-1}. Further evidence in support of the proposed structure was obtained by recording the proton NMR. The ^1H NMR spectrum of compound **6f** the methyl protons came into resonance as a singlet at δ 2.43 integrating for three protons, while the signal due to the three methoxy protons appeared as a singlet at δ 3.92 integrating for nine protons. The S-CH_2 protons came into resonance as a singlet at δ 4.64 integrating for two protons. The pyrimidine C_5-H and C_6-H protons appeared as two doublets at δ 6.86 and 8.37 integrating for one proton each. The C_1 and C_6 aromatic protons appeared as two singlets at δ, 7.10 and 7.26 integrating for one proton each. The –N=CH proton resonated as a singlet at δ 10.25 while the signal due to SH proton appeared as a broad singlet at δ 13.6.

Further the Mannich reaction of these hydrazones **6** with N-methylpiperazine and formaldehyde in ethanol medium gave the corresponding N-Mannich bases **7a-f** rather than the S-Mannich derivatives. Formation of N-Mannich base was confirmed by analytical and spectral studies. In a typical example the ^1H NMR spectrum of Mannich base **7b** (DMSO-d_6) the pyrimidinyl methyl protons appeared as singlet at δ 2.26 integrating for three protons. The signal due to piperazine protons appeared as a singlet at δ 2.439 integrating for eight protons. The N-methyl protons came into resonance as a singlet at δ 2.839 integrating for three protons. The signal due to S-CH_2 protons appeared at δ 4.64 integrating for two protons while the N-CH_2 protons resonated as a singlet at δ 5.12 integrating for two protons.

The pyrimidine C_5-H proton appeared as a doublet at δ 6.83, while the pyrimidine C_6-H came into resonance as doublet at δ 8.36 each integrating for one proton. The *ortho* and *meta* protons of *p*-nitro phenyl appeared as two doublets centered at δ 7.69 and 8.13 each integrating for two protons. The azomethine proton appeared as a singlet at δ 11.32 integrating for one proton. Further the mass spectrum of this compound showed the molecular ion peak at *m/z* 499 in agreement with the molecular formula $C_{21}H_{25}N_9O_2S_2$. The peak at *m/z* 453 is due to the loss of NO_2 radical from the molecular ion. The peak at *m/z* 388 (M^++1) is due to the loss of CH_3-NCH_2N-$CH^{\bullet}$ radical from the molecular ion.

Table III — Antibacterial activity data of compounds **6a-g** and **7a-f** at 10 µg/mL concentration
(Diameter of zone of inhibition in mm)

Compd	*Pseudomonas aeruginosa*	*Serratia marcesens*	*Staphylococcus aureus*	*Escherichia coli*
6a	19	19	17	16
6b	21	16	17	17
6c	21	14	15	14
6d	14	13	16	15
6e	17	14	20	13
6f	20	20	20	14
6g	16	17	16	15
7a	17	15	14	13
7b	20	19	13	12
7c	22	17	15	16
7d	18	17	16	16
7e	20	16	19	15
7f	17	23	15	12
Tetracyclin (Std)	25	25	25	25

Table IV — Antifungal activity data of compounds **6a-g** and **7a-f** at 10 µg/mL concentration
(Diameter of zone of inhibition in mm)

Compd	*Aspergillus niger*	*Pencillium*	*Aspergillus fumigatus*	*Candida albicans*
6a	19	20	22	15
6b	21	21	19	10
6c	20	21	19	11
6d	18	20	23	15
6e	17	19	15	16
6f	22	19	18	14
6g	22	20	14	10
7a	15	18	11	13
7b	23	23	15	14
7c	21	24	16	19
7d	12	19	14	19
7e	18	16	19	23
7f	13	17	23	15
Flukanozole (Std)	25	25	25	19

Antimicrobial studies

Antibacterial activity

Among the newly synthesized Schiff bases a few selected Schiff bases and all the Mannich bases were screened for their antibacterial activity *in vitro* against Gram-positive bacteria namely *E.coli, Staphylococcus aureus* and Gram-negative bacteria namely *Serratia marcesens and Pseudomonas aeruginosa* by disk diffusion method[14]. The test compounds were dissolved in N, N-dimethyl formamide (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 hr at 37°C. DMF alone showed no inhibition zone. *Tetracyclin* was employed as the reference standard (10 µg/mL) to evaluate the potency of the tested compounds. The results are illustrated in the **Table III**.

Antifungal activity

The same set of Schiff bases and the Mannich bases were also screened for their antifungal activity against two species of fungi, *Aspergillus niger* and *Pencillium,* using the disk diffusion method[14]. 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 hr 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*.

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at 10 µg/mL concentration. However the activity was less compared to the standard drugs.

Experimental Section

Melting points of the newly synthesized compounds 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 $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. All chemical shift values are reported in δ scale downfield from TMS. Mass spectrum was recorded on LC/MS (API 3000, Applied Biosystems) operating at 70 eV. C H N analysis was carried out on a Vairo-EL (Elementa) model. Homogeneity of the compounds was checked by TLC on silica gel plates.

5-(4,6-Disubtituted-pyrimidine-2-thiomethyl)-4-amino-3-mercapto-1,2,4-triazole 4. Substitued-pyrimidine-2-thioaceticacid (0.02 mole) **2** and thiocarbohydrazide **3** (2.12 g, 0.02 mole) were taken in a round bottom flask and fused 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 and diluted with water. The solid separated was filtered, washed with saturated sodium bicarbonate solution and dried. Further purification was done by recrystallization from ethanol.

4a: 3-(Pyrimidine-2-thiomethyl)-4-amino-5-mercapto-1,2,4-triazole. ^{1}H NMR: δ 4.47 (s, 2H, S-CH_2), 5.63 (s, 2H, NH_2), 7.26 (t, 1H, pyrimidine-5H), 8.6 (d, 2H, pyrimidine-4H and 5H) and 13.59 (s, 1H, SH); Mass: *m/z* 240 (M^++) consistent with the molecular formulae $C_7H_8N_6S_2$.

4c: 3-(4,6-Dimethyl-pyrimidine-2-thiomethyl)-4-amino-5-mercapto-1,2,4-triazole. ^{1}H NMR: 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 10.50 (s, 1H, SH); Mass: *m/z* 269 (M^++1) consistent with the molecular formulae $C_9H_{12}N_6S_2$.

General procedure for the the preparation of hydrazones 6a-t.

A solution of substituted Triazole **4a-c** (0.01 mole) and appropriate aldehyde **5** (0.01 mole) in ethanol (20 mL) and conc. Sulphuric acid (0.5 mL) was refluxed on a water bath for 2-3 hrs. Completion of the reaction was monitored by TLC. On cooling the contents to room temperature, the solid mass separated was collected by filtration washed with water and thoroughly dried. Further purification was done by recrystallization from ethanol (**Table I**).

Spectral data of the few compounds were given below.

3-(4-Methyl-2-thiomethyl pyrimidyl)-4-(2-nitro-4,5-dimethoxy benzylidene)-amino-1,2,4-triazole-5-thione (6g). ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3 of pyrimidine), 4.1 (s, 6H, 2 × OCH_3), 4.65 (s, 2H, S-CH_2), 7.0 (d, 1H, pyrimidine-5H), 7.5 (s, 1H, C_2-H of phenyl), 7.7 (S, 1H, C_5-H of phenyl), 8.3 (d, 1H, pyrimidine-6H), 10.0 (s, 1H, N=CH) and 13.02 (br, 1H, SH).

3-(4-Methyl-2-thiomethyl pyrimidyl)-4-(6-methoxy-napthylidene)-amino-1,2,4-triazole-5-thione 6i. ^{1}H NMR: (DMSO-d_6): δ, 2.435 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 4.505 (s, 2H, S-CH_2), 6.90 (d, 1H, pyrimidine-5H), 7.78 - 8.27 (m, 6H, biphenyl), 8.38(d, 1H, pyrimidine C_6-H) and 10.10 (s, 1H, N=CH) and 13.86 (br, 1H, SH); Mass: *m/z,* 422 ($M^{+\bullet}$), M.F ($C_{20}H_{18}N_6OS_2$).

3-(4,6-Dimethyl-2-thiomethyl pyrimidyl)-4-(*p*-nitro-benzylidene)-amino-1,2,4-triazole-5-thione (6l). ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 6H, 2 × CH_3), 4.63 (s, 2H, S-CH_2), 6.94 (s, 1H, pyrimidine C_5-H), 8.045 (d, 2H, *ortho* protons of *p*-nitro phenyl), 8.175 (d, 2H, *meta* protons of *p*-nitro phenyl), 10.987 (s, 1H, N=CH) and 14.0 (br, 1H, SH); Mass: *m/z* 403($M^{+\bullet}$), M. F. ($C_{16}H_{15}N_7O_2S_2$).

3-(4,6-Dimethyl-2-thiomethyl pyrimidyl)-4-(2-nitro-4,5-dimethoxy-benzylidene)-amino-1,2,4-triazole-5-thione (6q). ^{1}H NMR: ($CDCl_3$): δ 2.39 (s, 6H, 2 × CH_3), 4.036 (s, 6H, 2 × OCH_3), 4.63 (s, 2H, S-CH_2), 6.7 (s, 1H, pyrimidine C_5-H), 7.6(s, 1H, aryl C_6-H), 7.7 (s, 1H, aryl C_3-H) and 10.09 (s, 1H, N=CH) and 13.7 (br, 1H, SH); Mass: *m/z* 461, M.F ($C_{18}H_{19}N_7O_4S_2$).

General procedure for the synthesis of 4-[3-(4,6-disubstituted-2-thiomethyl pyrimidyl)-4-(substituted aryl)amino-1-(N-methyl piperazinomethyl)-1,2-4-triazole-5-thione 7a-f. A solution of Schiff bases 6 (0.01mole) in absolute ethanol (20 mL) taken on a round bottom flask was treated with formaldehyde 40% (3.0 mL). To this, N-methyl piparazine (1.0g, 0.01 mole) in ethanol (10 mL) was added with stirring and the reaction mixture was stirred overnight. The precipitated Mannich base was collected by filtration and dried. Further purification was done by recrystallization from ethanol to give compounds 7a-f. Characterization data of these compounds are given in **Table II**.

3-(4,6-Dimethyl-2-thiomethyl pyrimidyl)-4-(2-nitro-4,5-dimethoxy-benzylidene)-amino-1-(N-methylpiperazinomethyl)-1,2,4-triazole-5-thione, 7f. ^{1}H NMR: ($CDCl_3$): δ 2.25 (s, 3H, CH_3 of Piparazine), 2.38 (s, 6H, CH_3 of pyrimidine), 2.40 (t, 4H, CH_2 of piperazine), 2.42 (t, 4H, CH_2 of piperazine), 3.5 (s, 6H, 2-OCH_3), 4.68 (s, 2H, S-CH_2), 4.74 (s, 2H, N-CH_2), 7.0 (s, 1H, Pyrimidine-5H), 7.5(s, 1H, C_2-proton of phenyl), 7.6 (S, 1H, C_5-proton of phenyl) and 10.5 (s, 1H, N=CH); Mass: *m/z* 573(M+)

($C_{24}H_{31}N_9O_2S_2$) and 528 (M^+-NO_2), 461 loss of N-methyl piperazino methyl radical.

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