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Original article

Regioselective reaction: Synthesis, characterization and pharmacological activity of some new Mannich and Schiff bases containing sydnone

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ABSTRACT

A novel series of 1-substituted aminomethyl-3-*[1-(4-isobutylphenyl)ethyl]*-4-(3-aryl-4-sydnonylidene) amino-1,2,4-triazol-5-thiones (**9**), was prepared from the 3-*[1-(4-isobutylphenyl)ethyl]*-4-(3-aryl-4-sydnonylidene) amino 5-mercapto-1,2,4-triazoles (**8**) by aminomethylation with formaldehyde and secondary amine. The structures of Schiff bases (**8**) and Mannich bases (**9**) were characterized on the basis of IR, NMR, mass spectra1 data and elemental analysis. The newly synthesized compounds were screened for their anti-inflammatory and analgesic activities. Mannich bases (**9**) carrying piperidine and morpholine residues showed promising anti-inflammatory and analgesic activity.

1. Introduction

Mesoionic compounds have been studied extensively as possible medicinal agents. It was shown that the structural features possessing partial positive charge on the heterocyclic ring and balanced by a negative charge of an exocyclic atom, they are able to interact with biomolecules such as proteins and DNA. In addition, their overall neutral character enables them to cross biological membranes in vivo [1–3]. Sydnones possessing heterocyclic moieties at the position-4 are also known for a wide range of biological properties [4–7].

A number of mesoionic compounds are reported to possess activities such as anticancer [8–10], anti-inflammatory, analgesic, antimicrobial etc [11–15]. The 1,2,4-triazole and its derivatives were reported to exhibit various pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, antioxidant and anticancer properties [16–20].

Prompted by these observations and in an attempt to synthesize a series of mesoionic compounds with improved biological activity, a new series of Schiff bases (**8**) and Mannich bases (**9**) carrying sydnone moiety were synthesized and evaluated for their anti-inflammatory and analgesic property.

2. Chemistry

3-[1-(4-Isobutylphenyl)ethyl]-4-amino-5-mercapto-1,2,4-triazole (**7**) was prepared by the fusion of 2-[4-isobutylphenyl] propanoic acid (**6**) with thiocarbohydrazide (TCH) [21]. Substituted anilines (**1**) when treated with ethyl chloroacetate in the presence of sodium acetate in ethanol medium gave the corresponding anilino acetic ester. This ester on hydrolysis gave the corresponding anilino acetic acid (**2**). Diazotization of anilino acetic acid (**2**) with sodium nitrite and conc. HCl at 0 °C gave the corresponding N-nitroso compound (**3**). Cyclisation of this N-nitroso compound with acetic anhydride gave 3-arylsydnone (**4**). Formylation of 3-arylsydnones was carried out using $POCl_3$ and N-methylformanilide to give 3-aryl-4-formylsydnones (**5**) (Scheme 1).

Condensation of 3-[1-(4-isobutylphenyl)ethyl]-4-amino-5-mercapto-1,2,4-triazole (**7**) with 3-aryl-4-formylsydnones (**5**) in the presence of catalytic amount of conc. sulphuric acid gave Schiff bases (**8a**–**c**) in good yield (Scheme 2).

Reaction of 3-[1-(4-isobutylphenyl)ethyl]-4-(3-aryl-4-sydnonylidene) amino 5-mercapto-1,2,4-triazoles (**8**) with formaldehyde and secondary amine in ethanol medium gave the N-Mannich bases rather than the S-Mannich bases (Scheme 3). The reaction proceeds via the formation of immonium salt which subsequently attacks the N-1 of triazole giving rise to regioselective N-Mannich base (**9**). The structures of the newly synthesized compounds have been

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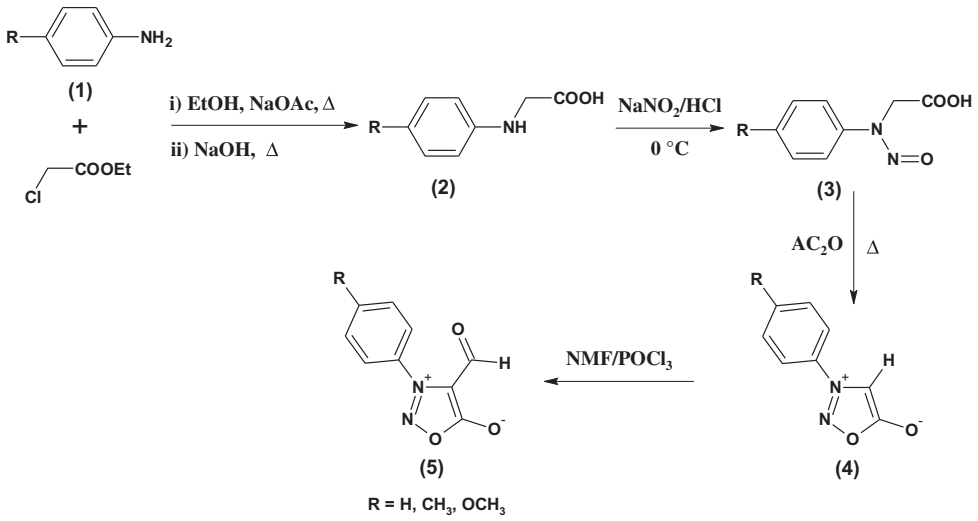


Scheme 1.

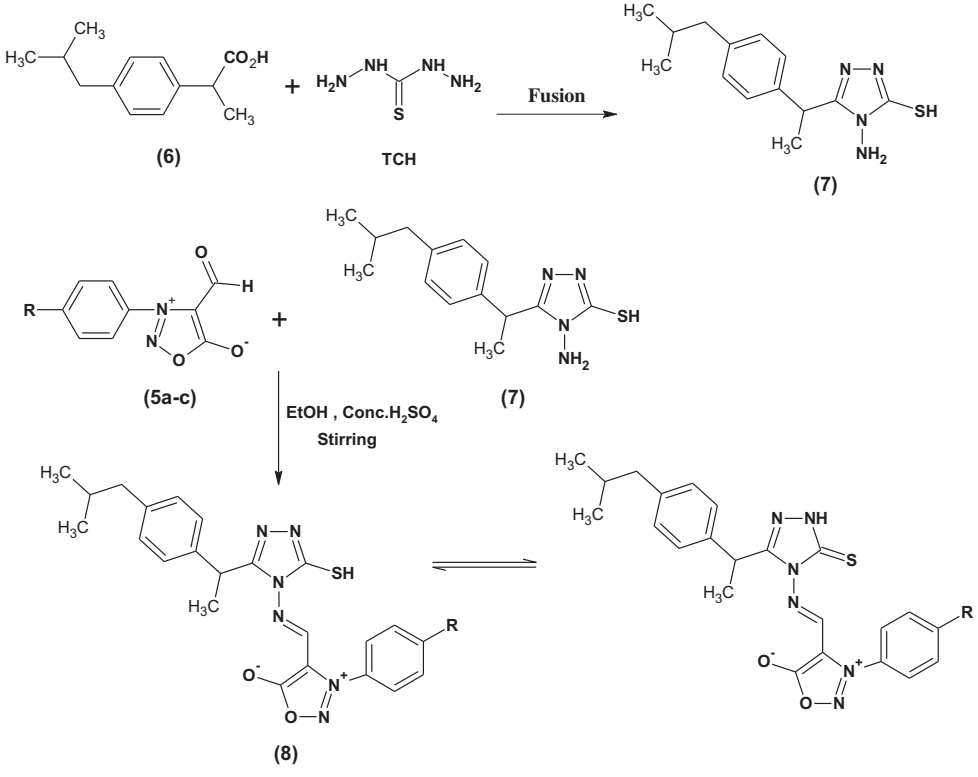
established on the basis of elemental analysis, IR, ^{1}H NMR, mass spectral and ^{13}C NMR data.

3. Pharmacology

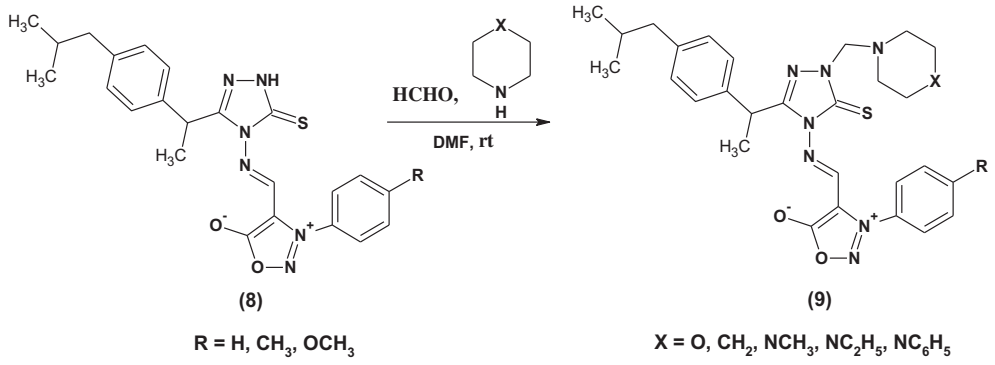
Some of the selected compounds from this series were evaluated for analgesic and anti-inflammatory activities. The anti-inflammatory and analgesic activities of the tested compounds were measured with respect to the control and compared with the standard drugs indomethacin and pentazocine respectively. All the pharmacological data are expressed as mean ± SEM; statistical analysis was applied to determine the significance of the difference between the control group and groups of animals tested with the tested compounds.

3.1. Anti-inflammatory activity

The anti-inflammatory activity was carried out following the method of Winter et al. [22]. The wistar albino rats weighing 150–200 g were selected. The animals were weighed and divided



Scheme 2.



Scheme 3.

into different groups (control, standard and the test groups) of five rats each. The first group of rats was treated with 1 mL of 1% carboxymethyl cellulose suspension orally (control), the second group was administered with a dose of 20 mg/kg of the indomethacin (standard) and the third group was treated with 20 mg/kg of the suspension of the test compounds. After 30 min, the animals were injected with 0.1 mL of 1% carrageenan in normal saline, subcutaneously to the sub-planar region of right hind paw. The paw volume was measured immediately (0 h), after 30 min, 60 min and 120 min using plethysmometer. Values are expressed as mean, by one way ANOVA analysis followed by Dunnett's-*t*-test and results are tabulated in Table 1.

3.2. Analgesic activity

Rats of either sex weighing between 150 and 200 g were used for the experiment. The animals were weighed and divided into different groups (control, standard and the test groups) of five rats each. The first group of rats was treated with control, the second group was administered with a dose of 20 mg/kg of the pentazocine (standard) and the third group was treated with 20 mg/kg of the suspension of the test compounds. In this method heat is used as a source of pain. Animals were individually placed on an analgesiometer, so that the tail lies over the nichrome wire of instrument without touching it (i.e., about 1/8 inch above the nichrome wire) cut off time is 10 s. The end point of the sensation is when rat lifts its tail (i.e. tail flick). Reaction time is noted at an intervals of 30, 60, 90 min after the administration of drug. Values are expressed as mean ± SEM, by one way ANOVA analysis followed by Dunnett's-*t*-test and results are tabulated in Table 2.

4. Results and discussion

4.1. Chemistry

The IR spectra of Schiff bases (**8a**–**c**) the NH absorption band was observed in the range of 3560–3573 cm^{-1}. The band at 1750–1771 cm^{-1} is due to carbonyl stretching of the sydnone moiety and the C=N stretching was observed at 1590–1605 cm^{-1}.

However in the Mannich bases (**9**) the absorption band at 3560–3573 cm^{-1} was not observed there by indicating the formation of N-Mannich bases. The other prominent bands observed are 2900–2954 cm^{-1} for C–H stretching. The sydnone carbonyl absorption band observed at 1770–1793 cm^{-1} and C=N stretching band was seen in the range of 1588–1600 cm^{-1}.

In the ^{1}H NMR spectra of (**8a**–**c**) the NH proton appeared as singlet at δ 13.87–13.0 ppm, presumably due to the existence of thiol–thione tautomerism. The N=CH proton appeared as singlet at δ 10.16–10.10 ppm, whereas in compounds (**9a**–**l**) the signal due to NH proton was absent and the presence of a singlet at δ 5.07–4.94 due to the N–CH_2–N protons confirmed the formation of Mannich bases (**9**).

Table 1
Anti-inflammatory activity data of compounds **8a**–**c** and **9a**–**k**.

Compd.	Edema volume in mL (Mean±SEM)				Percentage reduction (%)			
	0 h	1/2 h	1 h	2 h	0 h	1/2 h	1 h	2 h
Control	0.11 ± 0.005	0.74 ± 0.005	0.76 ± 0.005	0.77 ± 0.02	–	–	–	–
Indomethacin	0.1 ± 0.003	0.31 ± 0.01[b]	0.26 ± 0.005[b]	0.23 ± 0.01[b]	6.06	58.1	65.8	70.1
8a	0.1 ± 0.09	0.49 ± 0.01[a]	0.46 ± 0.01[b]	0.38 ± 0.003[b]	3.03	32.9	39.4	50.2
8b	0.1 ± 0.001	0.45 ± 0.010[b]	0.40 ± 0.014[b]	0.34 ± 0.014[b]	9.09	39.2	46.9	55.4
8c	0.1 ± 0.001	0.38 ± 0.010[b]	0.34 ± 0.011[b]	0.26 ± 0.008[b]	9.09	48.6	55.2	64.0
9a	0.1 ± 0.001	0.42 ± 0.003[b]	0.34 ± 0.005[b]	0.27 ± 0.003[b]	9.09	43.7	55.3	65.3
9b	0.1 ± 0.001	0.40 ± 0.005[b]	0.33 ± 0.012[b]	0.24 ± 0.008[b]	9.09	45.0	56.1	67.9
9d	0.1 ± 0.001	0.45 ± 0.003[b]	0.40 ± 0.008[b]	0.35 ± 0.008[b]	9.09	38.7	46.9	54.5
9e	0.1 ± 0.001	0.53 ± 0.02[a]	0.5 ± 0.011[a]	0.47 ± 0.008[a]	9.09	27.9	34.2	38.5
9f	0.1 ± 0.001	0.43 ± 0.017[b]	0.35 ± 0.008[b]	0.25 ± 0.008[b]	9.09	41.9	53.0	66.6
9g	0.1 ± 0.001	0.45 ± 0.011[b]	0.40 ± 0.008[b]	0.35 ± 0.006[b]	9.09	39.1	46.9	54.1
9h	0.1 ± 0.001	0.47 ± 0.011[b]	0.39 ± 0.017[b]	0.33 ± 0.006[b]	9.09	36.5	48.7	56.2
9i	0.1 ± 0.001	0.50 ± 0.017[a]	0.48 ± 0.017[b]	0.46 ± 0.005[b]	9.09	31.5	35.9	40.2
9j	0.1 ± 0.001	0.37 ± 0.008[b]	0.32 ± 0.008[b]	0.26 ± 0.008[b]	9.09	49.0	57.0	65.8
9k	0.1 ± 0.005	0.42 ± 0.008[b]	0.39 ± 0.005[b]	0.33 ± 0.012[b]	9.09	42.7	48.6	56.2

ANOVA analysis followed by Dunnett's-*t*-test, $n = 5$, values were compared w.r.t. to control.
[a] $P < 0.01$ (significant from the control).
[b] $P < 0.001$ (significant from the control).

Table 2
Analgesic activity data of compounds **8a–c** and **9a–k**.

Compounds	Tail flick latency in secs			
	0 min	30 min	60 min	90 min
Control	3.35 ± 0.028	3.23 ± 0.005	3.34 ± 0.005	3.25 ± 0.005
Pentazocine	3.23 ± 0.017	6.25 ± 0.02[b]	6.95 ± 0.02[b]	7.45 ± 0.02[b]
8a	3.21 ± 0.008	5.76 ± 0.005	6.24 ± 0.005[b]	6.6 ± 0.057[b]
8b	3.25 ± 0.005	4.99 ± 0.101[a]	6.11 ± 0.063[b]	6.92 ± 0.014[b]
8c	3.23 ± 0.033	5.41 ± 0.005[b]	6.30 ± 0.018[b]	7.23 ± 0.020[b]
9a	3.25 ± 0.028	4.92 ± 0.005[a]	6.1 ± 0.057[b]	6.9 ± 0.028[b]
9b	3.17 ± 0.017	4.56 ± 0.008[a]	5.73 ± 0.020[b]	6.8 ± 0.017[b]
9d	3.35 ± 0.005	4.4 ± 0.028[a]	5.39 ± 0.023[b]	6.41 ± 0.020[b]
9e	3.27 ± 0.014	4.19 ± 0.025[a]	5.03 ± 0.044[b]	6.05 ± 0.026[b]
9f	3.24 ± 0.003	5.15 ± 0.028	5.91 ± 0.023[b]	7.12 ± 0.012[b]
9g	3.25 ± 0.035	3.92 ± 0.014[a]	4.31 ± 0.012[a]	5.10 ± 0.008[b]
9h	3.23 ± 0.035	4.52 ± 0.014[a]	5.25 ± 0.028[b]	6.21 ± 0.030[b]
9i	3.28 ± 0.016	4.15 ± 0.028[a]	4.41 ± 0.018[a]	5.35 ± 0.017[b]
9j	3.22 ± 0.031	4.77 ± 0.014[a]	5.92 ± 0.005[b]	6.82 ± 0.012[b]
9k	3.26 ± 0.020	4.61 ± 0.030[a]	5.55 ± 0.028[b]	6.26 ± 0.008[b]

ANOVA analysis followed by Dunnett's-*t*-test, $n = 5$, values were compared w.r.t. to control.
[a] $P < 0.01$ (significant from the control).
[b] $P < 0.001$ (significant from the control).

In the ^{13}C NMR spectra of (**9**) the formation of N-alkyl derivative was indicated by the presence of an N–CH_2–N peak around δ 69.02–68.19 ppm, which is absent in ^{13}C spectra of compound (**8**). In compound (**8**) formation of Schiff base was indicated by the presence of peak in the region of 152.45–152.56 ppm for the –N=CH– carbon. In compound (**8** and **9**) the sydnonyl C-4 signal appeared in the region of δ 139.78–143.21 ppm and C-5 signal appeared at δ 160.50–161.42 ppm.

4.2. Pharmacological screening

The tested compounds showed anti-inflammatory activity ranging from 38.5% to 67.9%, whereas standard drug Indomethacin showed 70.1% inhibition after 2 h (Table 1). Mannich base **9b** displayed the highest anti-inflammatory activity among the set of compounds tested in the present study. Test compounds that exhibited the most potent anti-inflammatory activity were **8c**, **9a**, **9b**, **9f** and **9j**.

The anti-inflammatory activity data showed that the compounds having piperidine **9b** and morpholine **9f** possess highest activity 67.9% and 66.6%. Among the Schiff bases tested for anti-inflammatory activity, **8c** showed 64.0% activity.

Among compounds tested for analgesic activity **8b**, **8c**, **9a**, **9b**, **9f** and **9j** showed activity comparable with that of the standard drug pentazocine. Compounds showing good anti-inflammatory activity also exhibited highest analgesic activity.

5. Conclusion

Sydnones are highly versatile and robust members of the mesoionic class of heteroaromatic compounds. They possess an array of interesting chemical and physicochemical properties, as well as a variety of biological activities. Functionalisation of sydnones in C–H (4th position) position will enhance their biological activity. In this regard we synthesized Schiff and Mannich derivatives possessing sydnone moiety with the objective of developing molecules possessing better anti-inflammatory and analgesic property. It is interesting to note that Schiff base **8c** show good anti-inflammatory and analgesic activity compared to that of **8a** and **8b**, it clearly concluded that presence of electron releasing group in sydnone will enhance the anti-inflammatory and analgesic activity. Among the Mannich bases **9b**, **9a**, **9f** and **9j** showed significant anti-inflammatory and analgesic activity compared to the standard drug. The Mannich derivative possessing piperidine and morpholine will helps to enhance the biological activity.

6. Experimental protocols

Melting points were determined using open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrometer. The ^1H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) NMR spectrometer using TMS as an internal standard. The chemical shifts are expressed in δ scale downfield from TMS and proton signals are indicated as s = singlet, d = doublet, *t* = triplet, *q* = quartet, m = multiplet. The mass spectra were recorded either on a Jeol JMS-D 300 mass spectrometer or API 3000 LC–MS instrument operating at 70 eV.

6.1. General procedure for the synthesis of N-substituted glycines (anilino acetic acid) *2a–c*

A mixture of substituted aniline (**1**) (0.5 mol), ethyl chloroacetate (0.6 mol) and anhydrous sodium acetate (0.6 mol) in 120 mL of ethanol was refluxed in an oil bath for 6 h. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of N-substituted glycine without further purification was used for the next step. To ethyl ester of N-substituted glycine (0.4 mol), sodium hydroxide (0.45 mol) in 200 mL of water was added and refluxed for 0.5 h. After cooling, the reaction mixture was acidified to pH = 2 using hydrochloric acid. The precipitated N-substituted glycine (**2**) was filtered and washed thoroughly with cold water. Further purification was done by recrystallisation from ethanol. The compounds prepared by this procedure are, anilino acetic acid **2a**: m.p. 127–128 °C, yield 70% (lit. [7] 128–129 °C), p-methylanilino acetic acid **2b**: m.p. 163–164 °C, yield 75% (lit. [7] 163–164 °C), p-methoxyanilino acetic acid **2c**: m.p. 142 °C, yield 75% (lit. [7] 144–145 °C).

6.2. General procedure for the preparation of N-nitroso-N-substituted glycines *3a–c*

To a stirred suspension of N-substituted glycine (**2a–c**) (0.1 mol) in 120 mL water at 0 °C, a solution of sodium nitrite (0.1 mol) in water 24 mL was added drop wise during 30 min. The reaction mixture was practically clear after 2 h. It was filtered and acidified with concentrated hydrochloric acid. The precipitated product was filtered, washed with cold water and dried in air. The nitrosoglycines (**3**) prepared by the above method were recrystallised from aqueous ethanol. Compounds prepared according to this procedure are, N-nitroso-N-phenylglycine **3a**: m.p. 101–102 °C, yield 80% (lit. [7] 102–103 °C), N-nitroso-N-(p-tolyl)glycine **3b**: m.p. 98–99 °C, yield 83% (lit. [7] 99–100 °C), N-nitroso-N-(p-anisyl)glycine **3c**: m.p. 120–121 °C, yield 84% (lit. [7] 121 °C).

6.3. General procedure for the preparation of 3-arylsydnone *4a–c*

N-Nitroso-N-substituted glycine (**3a–c**) (0.1 mol) was heated with acetic anhydride (0.5 mol) on a water bath for 2–4 h. The reaction mixture was kept aside at room temperature for overnight. Then it was poured into ice-cold water, filtered and washed with water, 5% sodium bicarbonate solution and again with water. The solid was dried and recrystallised from benzene. Compounds prepared according to this procedure are, 3-phenylsydnone **4a**:

m.p. 134–135 °C, yield 73% (lit. [7] 134–135 °C), 3-(p-tolyl)sydnone **4b**: m.p. 143–144 °C, yield 78% (lit. [7] 144–145 °C), 3-(p-anisyl) sydnone **4c**: m.p. 125–126 °C, yield 75% (lit. [7] 125–126 °C).

6.4. General procedure for the preparation of 3-aryl-4-formylsydnones **5a–c**

N-Methylformanilide (28.4 g, 0.210 mol) and phosphoryl chloride (31.7 g, 0.205 mol) were mixed and after half an hour, 3-arylsydnone (**4a–c**) (0.186 mol) was added portion wise with stirring and cooling so that the temperature was below 45 °C. Hydrogen chloride was evolved vigorously. After standing overnight the dark brown viscous mixture was dissolved in 150 mL of acetone and poured into 750 mL ice water with stirring. The solid obtained was filtered, washed with cold water, dried and recrystallised from ethanol. The compounds prepared according to this procedure are, 3-phenyl-4-formyl sydnone **5a**: m.p. 147–149 °C, yield 53% (lit. [7] 147–150 °C), 3-(p-tolyl)-4-formylsydnone **5b**: m.p. 102–103 °C, yield 60% (lit. [7] 102–103 °C), **5b** further characterized by Single Crystal XRD data [23]. 3-(p-Anisyll)-4-formylsydnone **5c**: m.p. 116–118 °C, yield 59% (lit. [7] 116–119 °C).

6.5. General procedure for the synthesis of 3-[1-(4-isobutylphenyl) ethyl]-4-amino-5-mercapto-1,2,4-triazole **7**

An equimolar mixture of thiocarbohydrazide (TCH) and 2-[4-isobutylphenyl]propanoic acid (**6**) was mixed and heated gently on an oil bath until the evolution of H_2S ceases. The reaction mixture was then cooled to room temperature and poured into ice-cold water and stirred well. It was then filtered, dried and recrystallised from ethanol. Compound prepared according to this procedure is, 3-[1-(4-isobutylphenyl)ethyl]-4-amino-5-mercapto-1,2,4-triazole **7**: m.p. 147–149 °C, yield 60% (lit. [20] 147–150 °C).

6.6. General procedure for the synthesis 3-[1-(4-isobutylphenyl)ethyl]-4-(3-aryl-4-sydnonylidene) amino 5-mercapto-1,2,4-triazoles **8**

To a solution of 3-[1-(4-isobutylphenyl)ethyl]-4-amino-5-mercapto-1,2,4-triazole (**7**) (0.01 mol) in absolute ethanol (25 mL), was added 3-aryl-4-formylsydnone (**5a–c**) (0.01 mol). Concentrated sulphuric acid (0.5 mL) was added to this reaction mixture. The contents were stirred at room temperature for 1–2 h. The solid product separated was collected by filtration. It was dried and recrystallised from ethanol.

6.6.1. 3-[1-(4-Isobutylphenyl)ethyl]-4-(3-phenyl-4-sydnonylidene) amino 5-mercapto-1,2,4-triazole **8a**

Yield 78%, m.p. 215–217 °C; IR (KBr) γ/cm^{-1}: 3562.9 (NH stretching), 2920 (C–H), 1772.7 (sydnone carbonyl), 1592 (–N=CH); ^{1}H NMR (DMSO-d_6): δ 0.84 (d, 6H, J = 6.51 Hz, $(CH_3)_2$), 1.50 (d, 3H, J = 7.26 Hz, CH_3), 1.82–1.78 (m, 1H, CH–$(CH_3)_2$), 2.38 (d, 2H, J = 6 Hz, CH_2), 4.26 (q, 1H, CH), 7.04 (d, 2H, J = 8.22 Hz, 3′, 5′-Ib-Ar-H), 7.15 (d, 2H, J = 8.01 Hz, 2′, 6′-Ib-Ar-H), 7.68–7.84 (m, 5H, Ar-H), 10.10 (s, 1H, N=CH), 13.0 (s, 1H, SH); ^{13}C NMR (DMSO-d_6): δ 19.04 (isobutyl-CH_3), 22.06 (CH_3), 29.47 (isobutyl CH), 34.56 (isobutyl-CH_2), 44.09 (C between triazole and isobutyl phenyl), 125.40 (phenyl C-2 and C-6), 127.22 (isobutyl phenyl C-2 and C-6), 128.96 (isobutyl phenyl C-3 and C-5), 130.08 (phenyl C-3, C-4 and C-5), 132.82 (isobutyl phenyl C-1), 133.16 (isobutyl phenyl C-4), 137.95 (phenyl C-1), 139.76 (sydnonyl C-4), 145.78 (triazole –N=C–), 152.39 (–N=CH–), 161.28 (sydnonyl C=O), 163.66 (C=S); LC–MS (m/z): 449 (M + 1), (M.F. – $C_{23}H_{24}N_6O_2S$); Anal. Calcd for $C_{23}H_{24}N_6O_2S$: C, 61.59; H, 5.39; N, 18.74; S, 7.15. Found: C, 61.56; H, 5.40; N, 18.76; S, 7.15.

6.6.2. 3-[1-(4-Isobutylphenyl)ethyl]-4-[3-(p-tolyl)-4-sydnonylidene] amino 5-mercapto-1,2,4-triazole **8b**

Yield 80%, m.p. 120–124 °C; IR (KBr) γ/cm^{-1}: 3561.9 (NH stretching), 2920 (C–H stretching), 1772.2 (sydnone carbonyl), 1592.4 (–N=C–); ^{1}H NMR (DMSO-d_6): δ 0.82 (d, 6H, J = 6.54 Hz, $(CH_3)_2$), 1.48 (d, 3H, J = 7.26 Hz, CH_3), 2.1–2.3 (m, 1H, CH–$(CH_3)_2$), 2.42 (d, 2H, J = 6 Hz, CH_2), 2.48 (s, 3H, Syd-Ph-CH_3), 4.10 (q, 1H, CH), 7.04 (d, 2H, J = 8.22 Hz, 3′, 5′-Ib-Ar-H), 7.15 (d, 2H, J = 8.01 Hz, 2′, 6′-Ib-Ar-H), 7.49 (d, 2H ortho protons of p-tolyl), 7.71 (d, 2H meta protons of p-tolyl), 10.16 (s, 1H, N=CH), 13.87 (s, 1H, SH); ^{13}C NMR (DMSO-d_6): δ 19.05 (isobutyl-CH_3), 20.84 (CH_3), 22.07 (sydnonyl phenyl CH_3), 29.46 (isobutyl CH), 34.61 (isobutyl-CH_2), 44.09 (C between triazole and isobutyl phenyl), 125.11 (tolyl C-2 and C-6), 127.22 (isobutyl phenyl C-2 and C-6), 129.0 (isobutyl phenyl C-3 and C-5), 130.37 (tolyl C-3 and C-5), 130.72 (isobutyl phenyl C-1 and C-4), 137.90 (tolyl C-1), 139.79 (tolyl C-4), 143.19 (sydnonyl C-4), 146.41 (triazole –N=C–), 152.54 (–N=CH–), 161.49 (sydnonyl C=O), 163.67 (C=S); LC–MS (m/z): 462 (M+), (M.F. – $C_{24}H_{26}N_6O_2S$); Anal. Calcd for $C_{24}H_{26}N_6O_2S$: C, 62.32; H, 5.67; N, 18.17; S, 6.93. Found: C, 62.34; H, 5.67; N, 18.14; S, 6.90.

6.6.3. 3-[1-(4-Isobutylphenyl)ethyl]-4-[3-(p-anisyl)-4-sydnonylidene] amino 5-mercapto-1,2,4-triazole **8c**

Yield 76%, m.p. 110–112 °C; IR (KBr) γ/cm^{-1}: 3562.4 (NH stretching), 2920.4 (C–H), 1773.0 (sydnone carbonyl), 1592.2 (–N=C–); ^{1}H NMR (DMSO-d_6): δ 0.92 (d, 6H, J = 6.54 Hz, $(CH_3)_2$), 1.52 (d, 3H, J = 7.26 Hz, CH_3), 1.80–1.76 (m, 1H, CH–$(CH_3)_2$), 2.36 (d, 2H, J = 6 Hz, CH_2), 3.4 (s, 3H, OCH_3), 4.18 (q, 1H, CH), 7.04 (d, 2H, J = 8.0 Hz, 3′, 5′-Ib-Ar-H), 7.15 (d, 2H, J = 8.01 Hz, 2′, 6′-Ib-Ar-H), 7.30–7.80 (m, 4H, Ar-H), 10.12 (s, 1H, N=CH), 13.0 (s, 1H, SH); ^{13}C NMR (DMSO-d_6): δ 19.04 (isobutyl-CH_3), 22.40 (CH_3), 29.44 (isobutyl CH), 34.60 (isobutyl-CH_2), 44.08 (C between triazole and isobutyl phenyl), 69.02 (sydnonyl phenyl OCH_3), 125.18 (anisyl C-2 and C-6), 127.28 (isobutyl phenyl C-2 and C-6), 129.18 (isobutyl phenyl C-3 and C-5), 130.38 (anisyl C-3 and C-5), 130.86 (isobutyl phenyl C-1 and C-4), 132.70 (anisyl C-1), 142.76 (sydnonyl C-4), 146.12 (triazole –N=C–), 152.44 (–N=CH–), 156.36 (anisyl C-4), 161.42 (sydnonyl C=O), 163.68 (C=S); LC–MS (m/z): 478 (M+), (M.F. – $C_{24}H_{26}N_6O_3S$); Anal. Calcd for $C_{24}H_{26}N_6O_3S$: C, 60.23; H, 5.48; N, 17.56; S, 6.70. Found: C, 60.25; H, 5.52; N, 17.56; S, 6.72.

6.7. General procedure for the synthesis of 1-substituted aminomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-(3-aryl-4-sydnonylidene) amino-1,2,4-triazol-5-thiones (**9**)

A mixture of Schiff bases (**8a–c**) (0.01 mol) and formaldehyde 40% (1.5 mL) in ethanol (20 mL) was taken and to this solution secondary amines (0.01 mol) in DMF (10 mL) was added and stirred at room temperature. The solid product gets separated within half an hour. The stirring was continued for another 4 h. Finally the product was collected by filtration, washed with ethanol and dried. It was further purified by recrystallisation from ethanol.

6.7.1. 1-Morpholinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-(3-phenyl-4-sydnonylidene) amino-1,2,4-triazol-5-thione **9a**

Yield 82%, m.p. 120–122 °C; IR (KBr) γ/cm^{-1}: 2954.08 (C-H stretching), 1778.39 (sydnone carbonyl C=O), 1588.71 (–N=C–); ^{1}H NMR (DMSO-d_6): δ 0.82 (d, 6H, J = 6 Hz, $(CH_3)_2$), 1.52 (d, 3H, J = 6 Hz, CH_3), 1.81–1.76 (m, 1H, CH–$(CH_3)_2$), 2.38 (d, 2H, J = 6 Hz, CH_2), 2.50 (t, 4H, CH_2NCH_2), 3.51 (t, 4H, CH_2OCH_2), 4.20 (q, 1H, CH), 4.97 (s, 2H, NCH_2N), 7.06 (d, 2H, J = 8.0 Hz, 3′, 5′-Ib-Ar-H), 7.17 (d, 2H, J = 8.0 Hz, 2′, 6′-Ib-Ar-H), 7.69–7.86 (m, 5H, Ar-H), 10.16 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.02 (isobutyl-CH_3), 22.80 (CH_3), 29.40 (isobutyl CH), 34.60 (isobutyl-CH_2), 44.06 (C between triazole and isobutyl phenyl), 50.20 (morpholine C-2 and C-6),

66.00 (morpholine C-3 and C-5), 68.10 (C between morpholine and triazole), 125.82 (phenyl C-2 and C-6), 128.12 (isobutyl phenyl C-2 and C-6), 129.52 (isobutyl phenyl C-3 and C-5), 131.24 (phenyl C-3, C-4 and C-5), 133.96 (isobutyl phenyl C-1), 135.05 (isobutyl phenyl C-4), 138.56 (phenyl C-1), 143.16 (sydnonyl C-4), 146.50 (triazole −N=C−), 152.50 (−N=CH−), 161.50 (sydnonyl C=O), 163.60 (C=S); FABMAS (*m*/*z*) − 547.5 (M+), (M.F. − $C_{28}H_{33}N_7O_3S$); Anal. Calcd for $C_{28}H_{33}N_7O_3S$: C, 61.41; H, 6.07; N, 17.90; S, 5.85. Found: C, 61.39; H, 6.08; N, 17.88; S, 5.84.

6.7.2. 1-Piperidinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-(3-phenyl-4-sydnonylidene) amino-1,2,4-triazol-5-thione **9b**

Yield 74%, m.p. 130–132 °C; IR (KBr) γ/cm^{-1}: 2924 (C−H stretching), 1781.96 (sydnone carbonyl), 1589.66 (−N=C−); ^1H NMR (DMSO-d_6): δ 0.82 (d, 6H, J = 4 Hz, $(CH_3)_2$), 1.28 (m, 2H, piperidine CH_2), 1.42 (m, 4H, piperidine $(CH_2)_2$), 1.51 (d, 3H, J = 6 Hz, CH_3), 1.77 (m, 1H, CH−$(CH_3)_2$), 2.38 (d, 2H, J = 4 Hz, CH_2), 2.58 (m, 4H, piperidine CH_2NCH_2), 4.16 (q, 1H, CH), 4.94 (s, 2H, NCH_2N), 7.05 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 7.16 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.72–7.86 (m, 5H, Ar-H), 10.18 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.06 (isobutyl-CH_3), 22.08 (CH_3), 23.40 (piperidine C-4), 25.41 (piperidine C-3 and C-5), 29.49 (isobutyl CH), 34.58 (isobutyl-CH_2), 44.11 (C between triazole and isobutyl phenyl), 51.11 (piperidine C-2 and C-6), 69.02 (C between piperidine and triazole), 125.41 (phenyl C-2 and C-6), 127.18 (isobutyl phenyl C-2 and C-6), 128.98 (isobutyl phenyl C-3 and C-5), 130.04 (phenyl C-3, C-4 and C-5), 132.86 (isobutyl phenyl C-1), 133.14 (isobutyl phenyl C-4), 137.93 (phenyl C-1), 139.78 (sydnonyl C-4), 145.80 (triazole −N=C−), 152.41 (−N=CH−), 161.30 (sydnonyl C=O), 163.68 (C=S); FABMAS (*m*/*z*) − 545.3 (M+), (M.F. − $C_{29}H_{35}N_7O_2S$); Anal. Calcd for $C_{29}H_{35}N_7O_2S$: C, 63.83; H, 6.46; N, 17.97; S, 5.88. Found: C, 63.82; H, 6.48; N, 17.94; S, 5.88.

6.7.3. 1-N-methyl piperazinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-(3-phenyl-4-sydnonylidene) amino-1,2,4-triazol-5-thione **9c**

Yield 63%, m.p. 122–124 °C; IR (KBr) γ/cm^{-1}: 2954.0 (C−H), 1778.9 (sydnone carbonyl), 1588.6 (−N=C−); ^1H NMR (DMSO-d_6): δ 0.83 (d, 6H, J = 6 Hz, $(CH_3)_2$), 1.46 (d, 3H, J = 8 Hz, CH_3), 1.75–1.80 (m, 1H, CH−$(CH_3)_2$), 2.20 (d, 2H, J = 6 Hz, CH_2), 2.38 (t, 4H, CH_2NCH_2), 2.68 (t, 4H, CH_2NCH_2), 3.41 (s, 3H, N−CH_3), 4.18 (q, 1H, CH), 4.96 (s, 2H, NCH_2N), 7.08 (d, 2H, J = 8.10 Hz, 3′, 5′-Ib-Ar-H), 7.18 (d, 2H, J = 8.01 Hz, 2′, 6′-Ib-Ar-H), 7.74–7.88 (m, 5H, Ar-H), 10.16 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.08 (isobutyl-CH_3), 22.12 (CH_3), 29.82 (isobutyl CH), 34.68 (isobutyl-CH_2), 44.20 (C between triazole and isobutyl phenyl), 45.75 (N−CH_3), 49.48 (N-methylpiperazine C-3 and C-5), 54.55 (N-methylpiperazine C-2 and C-6), 68.30 (C between N-methylpiperazine and triazole), 125.82 (phenyl C-2 and C-6), 128.12 (isobutyl phenyl C-2 and C-6), 128.96 (isobutyl phenyl C-3 and C-5), 131.10 (phenyl C-3 and C-5), 131.56 (phenyl C-4), 133.86 (isobutyl phenyl C-1), 135.10 (isobutyl phenyl C-4), 138.46 (phenyl C-1), 141.32 (sydnonyl C-4), 145.72 (triazole −N=C−), 152.46 (−N=CH−), 160.78 (sydnonyl C=O), 163.64 (C=S); FABMAS (*m*/*z*) − 560.2 (M+), (M.F. − $C_{29}H_{36}N_8O_2S$); Anal. Calcd for $C_{29}H_{36}N_8O_2S$: C, 62.12; H, 6.47; N, 19.98; S, 5.72. Found: C, 62.12; H, 6.43; N, 19.92; S, 5.74.

6.7.4. 1-N-ethyl piperazinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-(3-phenyl-4-sydnonylidene) amino-1,2,4-triazol-5-thione **9d**

Yield 66%, m.p. 135–137 °C; IR (KBr) γ/cm^{-1}: 2952.5 (C−H), 1779.0 (sydnone carbonyl), 1588.2 (−N=C−); ^1H NMR (DMSO-d_6): δ 0.80 (d, 6H, J = 6.2 Hz, $(CH_3)_2$), 1.20 (t, 3H, N-ethylpiperazine CH_3), 1.44 (d, 3H, J = 8 Hz, CH_3), 1.74–1.80 (m, 1H, CH−$(CH_3)_2$), 2.20 (d, 2H, J = 6 Hz, CH_2), 2.38 (q, 2H, N-ethylpiperazine CH_2) 2.48 (t, 4H, N-ethypiperazine CH_2NCH_2), 2.68 (t, 4H, N-ethylpiperazine CH_2NCH_2), 4.18 (q, 1H, CH), 4.96 (s, 2H, NCH_2N), 7.10 (d, 2H, J = 8.22 Hz, 3′, 5′-Ib-Ar-H), 7.22 (d, 2H, J = 8.01 Hz, 2′, 6′-Ib-Ar-H), 7.76–7.90 (m, 5H, Ar-H), 10.14 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 18.16 (N-ethylpiperazine CH_3), 19.08 (isobutyl-CH_3), 20.82 (CH_3), 29.84 (isobutyl CH), 34.64 (isobutyl-CH_2), 44.28 (C between triazole and isobutyl phenyl), 49.20 (N-ethylpiperazine CH_2), 49.60 (N-ethylpiperazine C-3 and C-5), 54.50 (N-methylpiperazine C-2 and C-6), 68.26 (C between N-methylpiperazine and triazole), 125.86 (phenyl C-2 and C-6), 126.98 (isobutyl phenyl C-2 and C-6), 129.24 (isobutyl phenyl C-3 and C-5), 131.12 (phenyl C-3, C-4 and C-5), 132.96 (isobutyl phenyl C-1), 134.94 (isobutyl phenyl C-4), 138.28 (phenyl C-1), 142.28 (sydnonyl C-4), 145.74 (triazole −N=C−), 152.48 (−N=CH−), 160.76 (sydnonyl C=O), 163.60 (C=S); FABMAS (*m*/*z*) − 574.1 (M+), (M.F. − $C_{30}H_{38}N_8O_2S$); Anal. Calcd for $C_{30}H_{38}N_8O_2S$: C, 62.69; H, 6.66; N, 19.50; S, 5.58. Found: C, 62.68; H, 6.63; N, 19.52; S, 5.62.

6.7.5. 1-N-phenyl piperazinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-(3-phenyl-4-sydnonylidene) amino-1,2,4-triazol-5-thione **9e**

Yield 70%, m.p. 100–102 °C; IR (KBr) γ/cm^{-1}: 2951.6 (C−H), 1780.6 (sydnone carbonyl), 1589.8 (−N=C−); ^1H NMR (DMSO-d_6): δ 0.84 (d, 6H, J = 6.0 Hz, $(CH_3)_2$), 1.54 (d, 3H, J = 7.26 Hz, CH_3), 1.76–1.80 (m, 1H, CH−$(CH_3)_2$), 2.36 (d, 2H, J = 6 Hz, CH_2), 2.52 (t, 4H, N-phenylpiperazine CH_2NCH_2), 3.16 (t, 4H, N-phenylpiperazine CH_2NCH_2), 4.28 (q, 1H, CH), 5.10 (s, 2H, NCH_2N), 6.78 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 6.92 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.18–7.77 (m, 10H, N-phenyl and sydnonyl Ar-H), 10.06 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.08 (isobutyl-CH_3), 22.10 (CH_3), 29.78 (isobutyl CH), 34.56 (isobutyl-CH_2), 44.14 (C between triazole and isobutyl phenyl), 49.70 (N-phenylpiperazine C-3 and C-5), 50.44 (N-phenylpiperazine C-2 and C-6), 68.48 (C between N-phenylpiperazine and triazole), 125.88 (phenyl C-2 and C-6), 126.90 (isobutyl phenyl C-2 and C-6), 129.46 (isobutyl phenyl C-3 and C-5), 131.10 (phenyl C-3 and C-5), 131.54 (phenyl C-4), 133.86 (isobutyl phenyl C-1), 135.28 (isobutyl phenyl C-4), 138.92 (phenyl C-1), 142.38 (sydnonyl C-4), 145.76 (triazole −N=C−), 152.50 (−N=CH−), 161.20 (sydnonyl C=O), 163.60 (C=S); FABMAS (*m*/*z*) − 623 (M + 1), (M.F. − $C_{34}H_{38}N_8O_2S$); Anal. Calcd for $C_{34}H_{38}N_8O_2S$: C, 65.57; H, 6.15; N, 17.99; S, 5.15. Found: C, 65.54; H, 6.15; N, 17.98; S, 5.13.

6.7.6. 1-Morpholinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-tolyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione **9f**

Yield 80%, m.p. 138–140 °C; IR (KBr) γ/cm^{-1}: 2952.59 (C−H stretching), 1788.20 (sydnone carbonyl), 1589.45 (−N=CH−); ^1H NMR (DMSO-d_6): δ 0.83 (d, 6H, J = 6.6 Hz, $(CH_3)_2$), 1.54 (d, 3H, J = 7.28 Hz, CH_3), 1.75–1.82 (m, 1H, CH−$(CH_3)_2$), 2.39 (d, 2H, J = 7.13 Hz, CH_2), 2.42 (s, 3H, Syd-Ph-CH_3), 2.63 (t, 4H, morpholine CH_2NCH_2), 3.53 (t, 4H, morpholine CH_2OCH_2), 4.19 (q, 1H, CH), 4.99 (s, 2H, NCH_2N), 7.07 (d, 2H, J = 8.13 Hz, 3′, 5′-Ib-Ar-H), 7.19 (d, 2H, J = 8.12 Hz, 2′, 6′-Ib-Ar-H), 7.52 (d, 2H, J = 8.13 Hz, ortho protons of p-tolyl), 7.75 (d, 2H, J = 8.13 Hz, meta protons of p-tolyl), 10.08 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.07 (isobutyl-CH_3), 20.86 (CH_3), 22.09 (sydnonyl phenyl CH_3), 29.48 (isobutyl CH), 34.63 (isobutyl-CH_2), 44.11 (C between triazole and isobutyl phenyl), 50.26 (morpholine C-2 and C-6), 66.00 (morpholine C-3 and C-5), 68.19 (C between morpholine and triazole), 125.11 (tolyl C-2 and C-6), 127.19 (isobutyl phenyl C-2 and C-6), 129.0 (isobutyl phenyl C-3 and C-5), 130.37 (tolyl C-3 and C-5), 130.72 (isobutyl phenyl C-1 and C-4), 137.88 (tolyl C-1), 139.79 (tolyl C-4), 143.21 (sydnonyl C-4), 146.43 (triazole −N=C−), 152.56 (−N=CH−), 161.51 (sydnonyl C=O), 163.69 (C=S); FABMAS (*m*/*z*) − 561 (M+), (M.F. − $C_{29}H_{35}N_7O_3S$); Anal. Calcd for $C_{29}H_{35}N_7O_3S$: C, 62.01; H, 6.28; N, 17.46; S, 5.71. Found: C, 62.00; H, 6.26; N, 17.42; S, 5.68.

6.7.7. 1-Piperidinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-tolyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione ***9g***

Yield 65%, m.p. 146–148 °C; IR (KBr) γ/cm^{-1}: 2950.8 (C–H), 1782.9 (sydnone carbonyl), 1587.6 (–N=CH–); ^{1}H NMR (DMSO-d_6): δ 0.82 (d, 6H, J = 6 Hz, $(CH_3)_2$), 1.26 (m, 2H, piperidine CH_2), 1.42 (m, 4H, piperidine $(CH_2)_2$), 1.50 (d, 3H, J = 6 Hz, CH_3), 1.70–1.80 (m, 1H, CH–$(CH_3)_2$), 2.30 (d, 2H, J = 6 Hz, CH_2), 2.44 (s, 3H, Syd-Ph-CH_3), 2.62 (m, 4H, piperidine CH_2NCH_2), 4.22 (q, 1H, CH), 4.86 (s, 2H, NCH_2N), 7.10 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 7.22 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.62 (d, 2H, J = 8 Hz, ortho protons of p-tolyl), 7.85 (d, 2H, J = 8 Hz, meta protons of p-tolyl), 10.14 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.04 (isobutyl-CH_3), 20.16 (CH_3), 22.43 (sydnonyl phenyl CH_3), 23.44 (piperidine C-4), 25.46 (piperidine C-3 and C-5), 29.50 (isobutyl CH), 34.68 (isobutyl-CH_2), 44.10 (C between triazole and isobutyl phenyl), 50.40 (piperidine C-2 and C-6), 68.90 (C between piperidine and triazole), 125.18 (tolyl C-2 and C-6), 127.24 (isobutyl phenyl C-2 and C-6), 129.18 (isobutyl phenyl C-3 and C-5), 130.38 (tolyl C-3 and C-5), 130.86 (isobutyl phenyl C-1 and C-4), 137.84 (tolyl C-1), 139.92 (tolyl C-4), 143.10 (sydnonyl C-4), 145.78 (triazole –N=C–), 152.46 (–N=CH–), 161.40 (sydnonyl C=O), 163.58 (C=S); FABMAS (m/z) – 559.5 (M+), (M.F. – $C_{30}H_{37}N_7O_2S$); Anal. Calcd for $C_{30}H_{37}N_7O_2S$: C, 64.37; H, 6.66; N, 17.52; S, 5.73. Found: C, 64.38; H, 6.64; N, 17.50; S, 5.70.

6.7.8. 1-N-methyl piperazinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-tolyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione ***9h***

Yield 60%, m.p. 80–82 °C; IR (KBr) γ/cm^{-1}: 2951.31 (C–H stretching), 1783.46 (sydnone carbonyl), 1587.04 (–N=C–); ^{1}H NMR (DMSO-d_6): δ 0.82 (d, 6H, J = 6 Hz, $(CH_3)_2$), 1.48 (d, 3H, J = 8 Hz, CH_3), 1.75–1.81 (m, 1H, CH–$(CH_3)_2$), 2.13 (d, 2H, J = 6 Hz, CH_2), 2.27 (s, 3H, Syd-phenyl-CH_3), 2.35 (t, 4H, CH_2NCH_2), 2.64 (t, 4H, CH_2NCH_2), 3.40 (s, 3H, N-CH_3), 4.18 (q, 1H, CH), 4.99 (s, 2H, NCH_2N), 6.89 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 7.08 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.18 (d, 2H, J = 8 Hz, ortho protons of p-tolyl), 7.75 (d, 2H, J = 8 Hz, meta protons of p-tolyl), 10.07 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.06 (isobutyl-CH_3), 20.80 (CH_3), 22.10 (sydnonyl phenyl CH_3), 29.82 (isobutyl CH), 34.64 (isobutyl-CH_2), 44.20 (C between triazole and isobutyl phenyl), 45.78 (N–CH_3), 49.50 (N-methylpiperazine C-3 and C-5), 54.55 (N-methylpiperazine C-2 and C-6), 68.28 (C between N-methylpiperazine and triazole), 125.28 (tolyl C-2 and C-6), 127.53 (isobutyl phenyl C-2 and C-6), 129.0 (isobutyl phenyl C-3 and C-5), 130.42 (tolyl C-3 and C-5), 130.72 (isobutyl phenyl C-1), 131.02 (isobutyl phenyl C-4), 137.94 (tolyl C-1), 139.92 (tolyl C-4), 141.32 (sydnonyl C-4), 145.70 (triazole –N=C–), 152.46 (–N=CH–), 160.76 (sydnonyl C=O), 163.62 (C=S); FABMAS (m/z) – 574.2 (M+), (M.F. – $C_{30}H_{38}N_8O_2S$); Anal. Calcd for $C_{30}H_{38}N_8O_2S$: C, 62.69; H, 6.66; N, 19.50; S, 5.58. Found: C, 62.69; H, 6.68; N, 19.50; S, 5.54.

6.7.9. 1-N-phenyl piperazinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-tolyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione ***9i***

Yield 62%, m.p. 122–124 °C; IR (KBr) γ/cm^{-1}: 2949.93 (C–H stretching), 1784.46 (sydnone carbonyl), 1600.42 (–N=C–); ^{1}H NMR (DMSO-d_6): δ 0.82 (d, 6H, J = 6.2 Hz, $(CH_3)_2$), 1.54 (d, 3H, J = 8 Hz, CH_3), 1.78–1.74 (m, 1H, CH–$(CH_3)_2$), 2.38 (d, 2H, J = 8 Hz, CH_2), 2.43 (s, 3H, Syd-phenyl-CH_3), 2.50 (t, 4H, N-phenylpiperazine CH_2NCH_2), 3.12 (t, 4H, N-phenylpiperazine CH_2NCH_2), 4.21 (q, 1H, CH), 5.07 (s, 2H, NCH_2N), 6.76 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 6.90 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.16–7.75 (m, 9H, N-phenyl and sydnonyl Ar-H), 10.08 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.08 (isobutyl-CH_3), 20.40 (CH_3), 22.40 (sydnonyl phenyl CH_3), 29.44 (isobutyl CH), 34.62 (isobutyl-CH_2), 44.10 (C between triazole and isobutyl phenyl), 49.68 (N-phenylpiperazine C-3 and C-5), 50.46 (N-phenylpiperazine C-2 and C-6), 68.42 (C between N-phenylpiperazine and triazole), 125.18 (tolyl C-2 and C-6), 127.19 (isobutyl phenyl C-2 and C-6), 129.24 (isobutyl phenyl C-3 and C-5), 130.34 (tolyl C-3 and C-5), 130.62 (isobutyl phenyl C-1), 131.18 (isobutyl phenyl C-4), 137.92 (tolyl C-1), 139.86 (tolyl C-4), 142.30 (sydnonyl C-4), 146.18 (triazole –N=C–), 152.42 (–N=CH–), 161.28 (sydnonyl C=O), 163.56 (C=S); FABMAS (m/z) – 636.3 (M+), (M.F. – $C_{35}H_{40}N_8O_2S$); Anal. Calcd for $C_{35}H_{40}N_8O_2S$: C, 66.01; H, 6.33; N, 17.60; S, 5.04. Found: C, 66.02; H, 6.35; N, 17.58; S, 5.0.

6.7.10. 1-Morpholinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-anisyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione ***9j***

Yield 75%, m.p. 134–136 °C; IR (KBr) γ/cm^{-1}: 2931.20 (C–H), 1792.9 (sydnone carbonyl), 1585.0 (–N=CH); ^{1}H NMR (DMSO-d_6): δ 0.88 (d, 6H, J = 6 Hz, $(CH_3)_2$), 1.56 (d, 3H, J = 6 Hz, CH_3), 1.78–1.84 (m, 1H, CH–$(CH_3)_2$), 2.48 (d, 2H, J = 6 Hz, CH_2), 2.68 (t, 4H, morpholine CH_2NCH_2), 3.58 (t, 4H, morpholine CH_2OCH_2), 3.95 (s, 3H, OCH_3), 4.26 (q, 1H, CH), 4.95 (s, 2H, NCH_2N), 7.10 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 7.30 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.40–7.90 (m, 4H, Ar-H), 10.16 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.04 (isobutyl-CH_3), 22.44 (CH_3), 29.48 (isobutyl CH), 34.60 (isobutyl-CH_2), 44.18 (C between triazole and isobutyl phenyl), 50.38 (morpholine C-2 and C-6), 66.12 (morpholine C-3 and C-5), 68.10 (C between morpholine and triazole), 69.08 (sydnonyl phenyl OCH_3), 125.24 (anisyl C-2 and C-6), 127.56 (isobutyl phenyl C-2 and C-6), 129.20 (isobutyl phenyl C-3 and C-5), 130.38 (anisyl C-3 and C-5), 130.84 (isobutyl phenyl C-1 and C-4), 132.75 (anisyl C-1), 143.16 (sydnonyl C-4), 146.50 (triazole –N=C–), 152.50 (–N=CH–), 156.38 (anisyl C-4), 161.52 (sydnonyl C=O), 163.60 (C=S); FABMAS (m/z) – 578.2 (M + 1), (M.F. – $C_{29}H_{35}N_7O_4S$); Anal. Calcd for $C_{29}H_{35}N_7O_4S$: C, 60.29; H, 6.11; N, 16.97; S, 5.55. Found: C, 60.28; H, 6.13; N, 16.93; S, 5.50.

6.7.11. 1-Piperidinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-anisyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione ***9k***

Yield 72%, m.p. 122–125 °C; IR (KBr) γ/cm^{-1}: 2931.49 (C–H), 1793.16 (sydnone carbonyl), 1585.55 (–N=C–); ^{1}H NMR (DMSO-d_6): δ 0.94 (d, 6H, J = 4 Hz, $(CH_3)_2$), 1.28 (t, 2H, piperidine CH_2), 1.45 (m, 4H, piperidine $(CH_2)_2$), 1.54 (d, 3H, J = 7.26 Hz, CH_3), 1.70–1.80 (m, 1H, CH–$(CH_3)_2$), 2.38 (d, 2H, J = 4 Hz, CH_2), 2.60 (m, 4H, piperidine CH_2NCH_2), 3.85 (s, 3H, OCH_3), 4.20 (q, 1H, CH), 4.95 (s, 2H, NCH_2N), 7.05 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 7.25 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.30–7.80 (m, 4H, Ar-H), 10.10 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.06 (isobutyl-CH_3), 22.42 (CH_3), 23.38 (piperidine C-4), 25.40 (piperidine C-3 and C-5), 29.46 (isobutyl CH), 34.62 (isobutyl-CH_2), 44.10 (C between triazole and isobutyl phenyl), 51.10 (piperidine C-2 and C-6), 68.40 (C between piperidine and triazole), 69.02 (sydnonyl phenyl OCH_3), 125.11 (anisyl C-2 and C-6), 127.19 (isobutyl phenyl C-2 and C-6), 129.0 (isobutyl phenyl C-3 and C-5), 130.37 (anisyl C-3 and C-5), 130.72 (isobutyl phenyl C-1 and C-4), 132.88 (anisyl C-1), 142.78 (sydnonyl C-4), 146.12 (triazole –N=C–), 152.46 (–N=CH–), 156.24 (anisyl C-4), 161.42 (sydnonyl C=O), 163.68 (C=S); FABMAS (m/z) – 575.3 (M+), (M.F. – $C_{30}H_{37}N_7O_3S$); Anal. Calcd for $C_{30}H_{37}N_7O_3S$: C, 62.59; H, 6.48; N, 17.03; S, 5.57. Found: C, 62.57; H, 6.50; N, 17.02; S, 5.59.

6.7.12. 1-N-methyl piperazinomethyl-3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-anisyl)-4-sydnonylidene] amino-1,2,4-triazol-5-thione ***9l***

Yield 70%, m.p. 140–142 °C; IR (KBr) γ/cm^{-1}: 2932.0 (C–H), 1793.0 (sydnone carbonyl), 1584.9 (–N=CH); ^{1}H NMR (DMSO-d_6): δ 0.90 (d, 6H, J = 6 Hz, $(CH_3)_2$), 1.62 (d, 3H, J = 8 Hz, CH_3), 1.78–1.86 (m, 1H, CH–$(CH_3)_2$), 2.40 (d, 2H, J = 6 Hz, CH_2), 2.46 (t, 4H, CH_2NCH_2), 2.68 (t, 4H, CH_2NCH_2), 3.38 (s, 3H, N–CH_3), 3.54 (s, 3H, OCH_3), 4.28 (q, 1H, CH), 5.10 (s, 2H, NCH_2N), 7.12 (d, 2H, J = 8 Hz, 3′, 5′-Ib-Ar-H), 7.30 (d, 2H, J = 8 Hz, 2′, 6′-Ib-Ar-H), 7.50–7.60 (m, 4H, Ar-H), 10.12 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 19.08 (isobutyl-CH_3), 22.12 (CH_3), 29.82 (isobutyl CH), 34.60 (isobutyl-CH_2), 44.14 (C between triazole and isobutyl phenyl), 45.70 (N-CH_3), 49.48

(N-methylpiperazine C-3 and C-5), 54.52 (N-methylpiperazine C-2 and C-6), 68.20 (C between N-methylpiperazine and triazole), 69.10 (sydnonyl phenyl OCH_3), 125.18 (tolyl C-2 and C-6), 127.28 (isobutyl phenyl C-2 and C-6), 129.12 (isobutyl phenyl C-3 and C-5), 130.34 (tolyl C-3 and C-5), 130.86 (isobutyl phenyl C-1 and C-4), 132.70 (tolyl C-1), 141.32 (sydnonyl C-4), 145.70 (triazole −N═C−), 152.46 (−N═CH−), 156.30 (anisyl C-4), 160.68 (sydnonyl C═O), 163.64 (C═S); FABMAS (m/z) − 590 (M+), (M.F. − $C_{30}H_{38}N_8O_3S$); Anal. Calcd for $C_{30}H_{38}N_8O_3S$: C, 60.99; H, 6.48; N, 18.97; S, 5.43. Found: C, 60.97; H, 6.44; N, 18.95; S, 5.48.

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