Some new 3-substituted-4-amino-5-mercapto-4(*H*)-1,2,4-triazoles as nonsteroidal antiinflammatory agents

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Certain new 3-[(((α-phenyl/methyl)benzylidene)amino)oxy] methyl/ethyl-4-amino-5-mercapto-1,2,4-triazoles **4a-d**, have been prepared starting from α/β-[((α-(phenyl/methyl)benzylidene) amino)oxy] acetic/propionic acid esters **1a-d**. The esters **1a-d**, are converted into the corresponding hydrazides **2a-d**, by refluxing them with 99% hydrazine hydrate. The potassium salts of dithiocarbazinates **3a-d**, are obtained by stirring hydrazides **2a-d** with alcoholic potassium hydroxide and carbon disulphide. Potassium salts of dithiocarbazinate **3a-d**, when refluxed with two fold excess of hydrazine hydrate, afford the parent triazoles **4a-d**. The structures of the compounds have been characterised by elemental and spectral (IR, 1HNMR and mass) analysis. All the newly synthesised 1,2,4-triazoles have been screened for antiinflammatory activity by carrageenan induced rat paw edema and cotton pellet induced granulation tissue formation methods. The same compounds have also been screened for their ulcerogenic liability and antimicrobial activity against *E. coli, B. cirroflagellosus, A. niger* and *R. bataticola*. Some of the newly synthesised compounds have been evaluated for antituberculosis activity against Mycobacterium tuberculosis H37Rv strain as well.

1,2,4-Triazoles are associated with diverse pharmacological activities[1-5]. Previous experimental and theoretical studies[6] in the field of adrenergic drugs have indicated that at least in the case of these type of drugs, the "methylene amino oxy methyl moiety" (=C=N-O-CH$_2$-, MAOMM) can be considered as a "biostere"[7] of either aryls (Ar) or other aromatic groups (Figure 1)[6]. These results suggested that it might be possible to effect the substitution of an Ar with the MAOM moiety in drugs other than adrenergics in which the Ar group seems to be a prerequisite for eliciting biological activity.[8].

Encouraged by these observations and established pharmacological activities such as antidepressant[9], 5-HT-uptake inhibition[9],
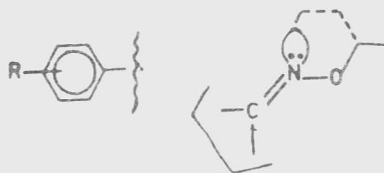

Figure 1 —Representation of the biosterism between Ar and MAOMM

antianginal[9], β-adrenoreceptor blocking[10,11], blood pressure lowering[12,13], hypocholesterolemic[14,15], antiamoebic[16], diuretic[17], hypotensive[18,19], antiinflammatory[20,21] and antiulcer[22] activities of compounds with MAOMM, it was contemplated to incorporate the MAOM moiety at the third position of the triazole moiety. To enable further evaluation of the potential usefulness of 1,2,4-triazoles and in continuation of our search for 1,2,4-triazoles as pharmacologically active heterocycles[23-25], we report herein the synthesis of some new 3-[(((α-phenyl/methyl)benzylidene)-amino)oxy]methyl/ethyl-4-amino-5-mercapto-1,2,-4-triazoles **4a-d** with a view to achieve better antiinflammatory and least ulcerogenecity. The same compounds were also screened for their antimicrobial activity against *E. coli, B. cirroflagellosus, C. albicans, R. bataticola* and antituberculosis activity against *M. tuberculosis H37Rv* strains. The synthetic route for the title compounds is depicted in Scheme I.

In the present investigation, α-[(((α-phenyl/methyl)benzylidene)amino)oxy] ethyl acetates **1a-b** were prepared by refluxing oximes with
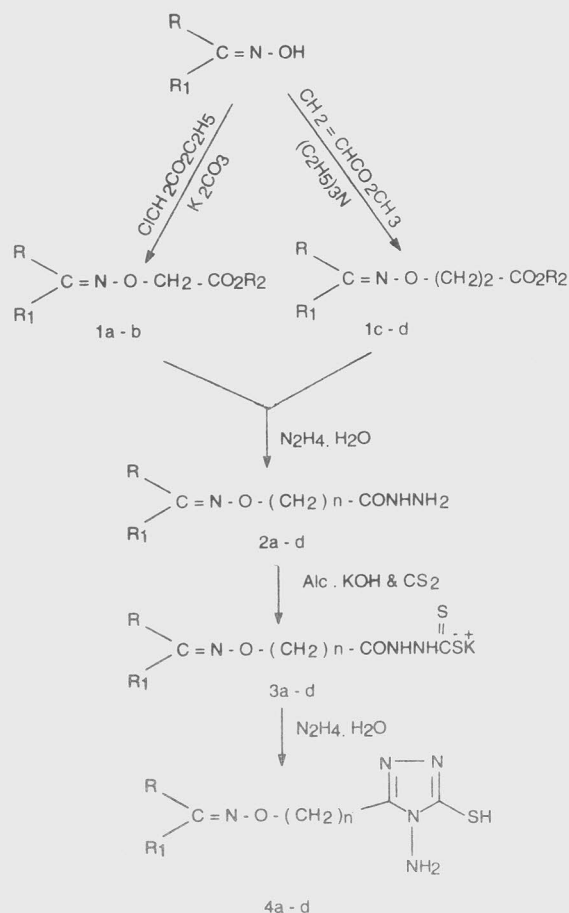
Where , R = C_6H_5 ; R_1 = C_6H_5 ; CH_3 ; R_2 = C_2H_5 , CH_3 ; n = 1,2.

Scheme I

methyl β-[(((α-phenyl/-methyl)-benzylidene)-amino)-oxy] propionates **1c-d**. Ethyl/methyl esters of α/β-[(((α-phenyl/methyl) benzylidene)amino)oxy]-acetic/propionic acids **1a-d** (Table I), were converted to the corresponding α/β -[(((α-phenyl/methyl)benzylidene)amino)oxy]acetic/propionic acid hydrazides **2a-d** (Table II), by refluxing with hydrazine hydrate (99%) in abs. ethanol. Potassium salts of α/β-[(((α-phenyl/methyl)-benzylidene) amino) oxy] acetyl/propionyl dithiocarbazinates **3a-d** were obtained by stirring hydrazides **2a-d** with alcoholic potassium hydroxide and carbon disulphide. Potassium salts of **3a-d** on reaction with two fold excess of hydrazine hydrate yielded 3-[(((α-phenyl/-methyl)benzylidene)amino)oxy] methyl/ethy!-4-amino-5- mercapto-4(H)-1,2,4- triazoles **4a-d** (Table III). The structures of the newly synthesised compounds were confirmed by elemental and spectral (IR, ^{1}HNMR and mass) analysis.
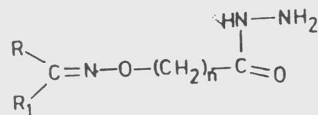
Pharmacological evaluation

After establishing the physicochemical properties of triazoles **4a-d**, the compounds were subjected to pharmacological screening.
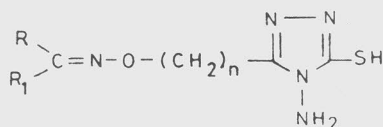
(i) *Acute toxicity study.* Newly synthesised triazoles **4a-d** were first subjected for acute toxicity study in order to determine their LD_{50}. The study was carried out according to the method of Miller and Tainter[26]. The test samples **4a-d**, failed to produce any mortality even up to the dose of 900 mg/100 g b.w., by oral route of administration. When all the test samples **4a-d**, were administered

ethyl chloroacetate in presence of anhyd. potassium carbonate and acetone. Oximes on condensation with methyl acrylate in the presence of catalytic amount of triethylamine furnished

Table I—Physicochemical data of ethyl/methyl esters of α/β-[(((α-phenyl/methyl)benzylidene)
amino)oxy] acetic/propionic acids **1a-d**

$$R\diagdown C = N - O - (CH_2)_n - \overset{\overset{O}{\|}}{C} - OR_2$$
$$R_1 \diagup$$

Compd	R	R_1	R_2	N	m.p., (°C)	Yield (%)	Mol. Formula	Analysis (%) Calc. (Found)		
								C	H	N
1a	C_6H_5	C_6H_5	C_2H_5	1	116-18	70	$C_{17}H_{17}NO_3$	72.07 (71.90)	6.05 (5.90)	4.94 (4.75)
1b	C_6H_5	CH_3	C_2H_5	1	oil	58	$C_{12}H_{15}NO_3$	65.14 (65.01)	6.83 (6.53)	6.33 (6.00)
1c	C_6H_5	C_6H_5	CH_3	2	96-97	73	$C_{18}H_{19}NO_3$	72.70 (72.56)	6.44 (6.32)	4.71 (4.55)
1d	C_6H_5	CH_3	CH_3	2	oil	60	$C_{13}H_{17}NO_3$	66.36 (66.21)	7.28 (7.06)	5.95 (5.80)

Table II—Physicochemical data of hydrazides of α/β-[(((α-phenyl/methyl)benzylidene) amino)oxy]acetic/propionic acids **2a-d**

$$R\diagdown \atop R_1 \diagup C=N-O-(CH_2)_n-C=O, \quad C \text{ with } HN-NH_2$$

Compd	R	R₁	n	m.p., (°C)	Yield (%)	Mol. formula	Analysis (%) Calc. (Found)		
							C	H	N
2a	C_6H_5	$C_{6w}H_5$	1	110-11	74	$C_{15}H_{15}N_3O_2$	66.90 (66.90)	5.61 (5.58)	15.60 (15.57)
2b	C_6H_5	CH_3	1	Oil	60	$C_{10}H_{13}N_3O_2$	57.95 (57.93)	6.32 (6.28)	20.27 (20.24)
2c	C_6H_5	C_6H_5	2	87-89	70	$C_{16}H_{17}N_3O_2$	67.82 (67.80)	6.04 (6.01)	14.83 (14.80)
2d	C_6H_5	CH_3	2	oil	59	$C_{11}H_{15}N_3O_2$	59.71 (59.69)	6.83 (6.80)	18.99 (18.96)

Table III—Physicochemical data of 3-[(((α-phenyl/methyl)benzylidene)amino)oxy] methyl/ethyl-4-amino-5-mercapto-4(H)-1,2,4-triazoles **4a-d**

$$R\diagdown \atop R_1 \diagup C=N-O-(CH_2)_n - \text{triazole} -SH, \quad NH_2$$

Compd	R	R₁	n	m.p., (°C)	Yield (%)	Mol. formula	Analysis (%) Calc. (Found)		
							C	H	N
4a	C_6H_5	C_6H_5	1	220-21	35	$C_{16}H_{15}N_5OS$	59.06 (59.02)	4.64 (4.60)	21.52 (21.49)
4b	C_6H_5	CH_3	1	105-06	37	$C_{11}H_{13}N_5OS$	50.18 (50.00)	4.98 (4.94)	26.59 (26.54)
4c	C_6H_5	C_6H_5	2	218-19	39	$C_{17}H_{17}N_5OS$	60.16 (60.00)	5.05 (5.01)	20.63 (20.59)
4d	C_6H_5	CH_3	2	221-22	35	$C_{12}H_{15}N_5OS$	51.97 (51.94)	5.45 (5.42)	25.25 (25.22)

intraperitoneally, only compound **4d**, showed increased toxicity and a mortality rate of 83 percent at a dose of 40 mg/100 g b.w. Remaining compounds **4a**, **4b** and **4c** did not show mortality at the same dose. LD_{50} of the compound **4d**, by intraperitoneal route is 31.62±1.40/100 g b.w.

(ii) *Antiinflammatory activity*. The antiinflammatory activity of triazoles **4a-d** was studied by the following methods: (a) carrageenan induced rat paw edema method due to winter *et al.*[27], and cotton pellet induced granulation tissue formation method due to Meir *et al*[28],

All the results and statistical data like SE and p for all the three doses 10, 20 and 40 mg/100 g b.w., are recorded in Tables IV and V.

(iii) *Ulcerogenic liability*. After removing the cotton pellets the abdomen of all the animals were opened and the naked eye examination of the various viscera was done for any ulcer formation on the inner surface of the stomachs.

There were no ulcerogenic changes, except mild congestion of the stomachs from compounds treated groups. But one to two necrohaemorrhagic spots were observed on the inner surface of the stomachs from the ibuprofen treated group.

Biological evaluation

(i) *Evaluation of antimicrobial activity*. Some of the newly synthesised compounds were evaluated for their antimicrobial activity against Gram negative bacterium *Escherichia coli*, Gram positive bacterium *Bacillus cirroflagellosus* and fungi *Aspergillus niger, Rhizoctonia bataticola*, by cup plate method[29].

Table IV—Results of antiinflammatory activity of compounds **4a-d**, by carrageenan induced method

Time (hr)		Untreated control group	Ibuprofen treated Group	Compd **4a** Treated Group	Compd **4b** Treated Group	Compd **4c** treated group	Compd **4d** treated group
			Dose = 10 mg/100 g.b.w.				
1st hr	Mean edema	39.3	20.00	20.80	19.40	20.60	20.90
	% Inhibition	-	48.88	46.82	50.61	47.41	46.73
	SE	2.07	1.74	6.08	8.679	4.06	2.93
	p	-	<0.001	>0.02	<0.001	>0.001	<0.001
IIIrd hr	Mean edema	37.10	15.00	18.30	17.69	17.20	19.30
	% Inhibition	-	59.47	50.53	52.29	53.39	47.85
	SE	6.57	2.37	2.81	4.79	4.45	3.23
	p	-	>0.010	>0.020	>0.050	>0.050	>0.050
Vth hr	Mean edema	33.20	15.50	18.50	18.60	19.20	23.90
	% Inhibition	-	53.13	44.02	43.97	41.88	27.77
	SE	7.46	3.76	2.63	2.58	4.49	4.01
	p	-	>0.050	>0.050	>0.100	>0.100	<0.051
			Dose=20 mg/100 g.b.w.				
Ist hr	Mean edema	39.3	19.50	18.00	18.50	17.10	19.40
	% Inhibition	-	50.33	53.97	52.90	56.45	50.41
	SE	2.07	1.91	4.41	8.28	2.04	1.40
	p	-	<0.001	>0.001	>0.0013	<0.001	<0.001
IIIrd hr	Mean edema	37.10	14.30	15.00	15.74	15.00	18.30
	% Inhibition	-	61.25	59.31	57.56	59.52	50.50
	SE	6.57	2.01	1.60	3.88	3.95	2.60
	p	-	>0.010	>0.010	>0.020	>0.020	>0.020
Vth hr	Mean edema	33.20	15.00	17.80	16.09	18.70	19.90
	% Inhibition	-	54.69	45.95	51.52	43.38	39.96
	SE	7.46	4.11	5.01	3.77	5.63	4.90
	p	-	>0.050	<0.050	>0.100	>0.100	>0.100
			Dose=40 mg/100 g.b.w.				
Ist hr	Mean edema	39.3	15.10	16.80	14 57	16.90	15.20
	% Inhibition	-	61.57	57.04	62.90	56.89	61.10
	SE	2.07	3.57	5.51	6.52	3.35	2.10
	p	-	<0.001	>0.001	<0.001	<0.001	<0.001
IIIrd hr	Mean edema	37.10	11.40	15.30	11.51	14.70	12.40
	% Inhibition	-	69.05	58.64	68.90	60.21	66.37
	SE	6.57	2.78	3.40	1.77	4.95	2.40
	p	-	>0.001	>0.020	>0.001	>0.020	>0.001
Vth hr	Mean edema	33.20	12.40	13.60	12.73	16.40	14.00
	% Inhibition	-	62.39	58.79	61.60	50.30	57.65
	SE	7.46	0.94	3.56	2.94	6.30	3.39
	p	-	>0.020	>0.050	>0.050	>0.100	<0.050

No. of animals used=6 albino rats

(ii) *Evaluation of Antituberculosis activity.* Some of the newly synthesised compounds were tested for their antituberculosis activity against *M. tuberculosis H37Rv* by Bactec 460 radiometric system at Southern Research Institute, Frederick Research Center, Frederick MD.

(iii) *In vitro evaluation of antituberculosis activity.* Primary screening of *in vitro* antituberculosis activity was conducted at a concentration of 12.5 μg/mL against *Mycobacterium tuberculosis H37Rv* in BACTEC 12B medium using the BACTEC 460 radiometric system. The antituberculosis activity of

Table V—Results of antiinflammatory activity of compounds **4a-d** using
cotton pellet induced granulation tissue formation method

	Untreated control group	Ibuprofen treated group	Compd **4a** Treated Group	Compd **4b** treated group	Compd **4c** treated group	Compd **4d** treated group
			(Gain in mean weight in milli grams)			
			DOSE=10 mg/100g b.w.			
Mean	13.16	11.85	12.53	11.98	12.58	11.43
% Inhibition	-	9.99	4.81	8.99	4.43	13.16
SE	0.3664	0.1896	0.214	0.432	0.258	0.270
p	-	<0.02	>0.010	>0.010	>0.010	>0.001
			DOSE=20 mg/100g b.w.			
Mean	13.16	11.08	12.08	11.53	12.08	11.13
% Inhibition	-	15.82	8.23	12.41	8.23	15.44
SE	0.3664	0.342	0.049	0.489	0.076	0.216
p	-	>0.001	>0.020	>0.001	>0.020	>0.001
			DOSE=40 mg/100g b.w.			
Mean	13.16	10.52	11.90	10.92	11.80	10.82
% Inhibition	-	20.13	9.62	17.09	10.38	17.85
SE	0.3664	0.098	0.226	0.260	0.372	0.457
p	-	<0.001	>0.020	<0.001	>0.010	>0.001

No. of animals used=6 albino rats.

all the newly synthesised compounds are compared with the standard, Rifampin (which has 96% inhibition at a MIC of 0.031 µg/mL).

Results and Discussion

In the carrageenan induced rat paw edema method triazoles **4a-d**, exhibited significant antiinflammatory activity comparable with that of the standard ibuprofen (Table IV).

The antiinflammatory activity of the compounds **4a-d**, is dose dependent and is maximum at the end of the third hour. At 40 mg/100 g b.w., all the compounds **4b**, **4d**, **4c**, and **4a** exhibited antiinflammatory activity in the order of 68.90, 66.37, 60.21, 58.64% respectively, whcih are comparable to the activity shown by ibuprofen (69.05%). Cotton pellet granulation tissue formation studies indicated that, both triazoles **4a-d** and ibuprofen have exhibited moderate degree of antiinflammatory activity. The activity in this method of testing is also dose dependent. Compounds **4b** and **4d** exhibited the activity in the order of 17.85 and 17.09% respectively, which are comparable to the activity exhibited by ibuprofen

(20.13%). However the remaining compounds **4a** and **4c** exhibited moderate to minimum antiinflammatory activity (Table V).

During the present investigation all the triazoles **4a-d**, have shown lesser degree of ulcerogenecity as compared to the standard ibuprofen.

Amongst all the compounds screened for antimicrobial activity, the hydrazides **2a-d**, exhibited better antibacterial activity against *E. coli*, (153.33-359.04%, relative percent inhibition with respect to the standard cotrimoxazole) and antifungal activity against *R. bataticola* (153.33-247.61%, relative percent inhibition with respect to the standard Fluconazole) than the parent triazoles **4a-d** (76.19-282.86% and 100-182.05 respectively). However, both hydrazides and triazoles exhibited moderate antimicrobial activity against *B. cirroflagellosus* (23.80-166.96%) and *A. niger* (20.72-78.76) respectively. Amongst the various compounds screened for antituberculosis activity against *Mycobacterium tuberculosis, H37Rv,* only compound **4b**, exhibited 78 percent inhibition, in comparison to Rifampin, which has 96 percent inhibition at a concentration of 0.031 µg/mL. Remaining compounds exhibited minimum

to moderate antituberculosis activity (24-35%) against the same strain.

Structure activity relationship

From the results of antimicrobial screening the following structure activity relationship (SAR) are generalized.

From the above observations, we notice that the replacement of C_6H_5 by CH_3 group in the methylene amino oxy methyl moiety, MAOMM, did not appear to alter the antimicrobial and antiinflammatory activity appreciably. Hence, it is concluded that the biologically active biostere 'Methylene Amino Oxy Methyl Moiety (MAOMM), is responsible for the significant antiinflammatory and antimicrobial activities of the compounds.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr, were recorded on a Perkin Elmer spectrophotometer and ^{1}HNMR spectra on varian 300 MHz NMR spectrometer using TMS as an internal standard (chemical shifts in δ ppm). Mass spectra were recorded on Finnig Mat 8230 spectrometer. The starting materials benzophenone oxime and acetophenone oximes (lit. m.p. 142 °C and 59 °C respectively), were prepared by literature methods.[30,31] The observed melting points were consistant with the melting points reported in the literature.

General procedure for the preparation of ethyl esters of α-[(((α-phenyl/methylbenzylidene)-amino)oxy]acetic acids 1a-b. A mixture of benzophenone oxime (0.1 mole) and anhyd. K_2CO_3 (13.8 g, 0.1 mole) were treated with acetone (35 mL) and the resulting mixture was stirred at reflux temperature for 3 hr. To the stirred suspension ethyl chloroacetate (12.25 g, 0.1 mole) in acetone (15 mL) was added and refluxing was continued for 8 hr. The excess of acetone was removed *in vacuo* and the residual mass poured onto crushed ice. The solid separated was filtered, washed thoroughly with water, dried and crystallised from ethanol. **1a**: IR: 1590 (>C=N), 940 (=N-O), 2965 (CH_2), 1660 cm^{-1} (>C=O).

General procedure for the preparation of methyl esters of β-[(((α-phenyl/methyl)benzy-lidene)-amino)oxy]propionic acids 1c-d. To a well stirred solution of benzophenone oxime (0.1 mole) and triethyl amine (3 mL) in abs. ethanol (40 mL), methyl acrylate (8.9 g, 0.1 mole) was added and the resulting reaction mixture was refluxed for 9 hr. After evaporation *in vacuo*, the residual mass was poured over crushed ice. The solid separated was filtered, washed with water and crystallized from ethanol. **1c**: IR: 1605 (>C=N-), 935 (=N-O-), 2950 (CH_2), 1675 cm^{-1} (>C=O).

General procedure for the preparation of hydrazides of α/β-[(((α-phenyl/methyl)benzyli-dene) amino)oxy]acetic/propionic acids 2a-d. To a solution of ester **1a-d** (0.05 mole) in abs. ethanol (50 mL) was added hydrazine hydrate 99%, (2.25 g, 0.05 mole) dropwise with cooling. The resulting reaction mixture was refluxed for 6 hr. Concentration *in vacuo* left residue, which was poured onto crushed ice. The solid separated was filtered, washed with water, dried and crystallised from ethanol **2a**: IR: 1580 (>C=N-), 970 (=N-O-), 2950 (CH_2), 1685 (>C=O-) 3200 and 3120 (-NH_2)- 3300 cm^{-1} (-NH-); **2c**: IR: 1600 (>C=N), 950 (=N-O-), 2930 (CH_2), 1690 (>C=O), 3225 and 3115 (-NH_2-), 3325 cm^{-1} (-NH-).

General procedure for the preparation of potassium α/β-[(((α-phenyl/methyl)benzyli-dene)amino)oxy]acetyl/propionyl dithiocarba-zinates 3a-d. To a well stirred clear solution of KOH (3.36 g, 0.06 mole) in abs. ethanol (15 mL), was added hydrazide **2a-d** (0.04 mole), with stirring and cooling in ice. To this, carbon disulphide (3.72 g, 0.06 mole) was added in small portions. The reaction mixture was stirred continuously for 12 hr and diluted with anhyd. ether (200 mL). The potassium dithiocarbazinate that separated was filtered, washed several times with anhyd. ether and dried *in vacuo*. The potassium salt obtained in quantitative yield, was moisture sensitive and hence used directly for the preparation of the corresponding triazole without further purification.

General procedure for the preparation of 3-[(((α-phenyl/methyl) benzylidene) amino)oxy]-

methyl/ethyl-4-amino-5-mercapto-4(*H*)-1,2,4-tri-azoles 4a-d. To a solution of potassium dithiocarbazinate, **3a-d** (0.04 mole) in water (10 mL), was added hydrazine hydrate 99% (4.0 g, 0.08 mole) and the reaction mixture was refluxed for 3 hr. The colour of the mixture turned from red to green, with the evolution of hydrogen sulphide gas (lead acetate paper test and odour). The clear solution was treated with decolorising charcoal, filtered, cooled in ice and then carefully acidified with acetic acid. The precipitated solid was filtered, washed with water, dried and crystallized from abs. ethanol. **4a**: IR: 960 (=N-O-), 2960 (CH_2), 1610 (>C=C<), 1580 (>C=N-), 1470 (>C-N-), 1265 and 1175 (>C=S), 3200 and 3125 (NH_2), 3120 cm^{-1} (-NH-); **4b**: IR: 940 (=N-O-), 2965 (CH_2), 1605 (>C=C<), 1595 (>C=N-),1490 (>C-N-), 1275 and 1190 (>C=S), 3225 and 3115 (NH_2), 3280 cm^{-1} (NH-): **4a** : ^{1}HNMR (DMSO-d_6): 5.18 (s, 2H, CH_2), 5.62 (s, 2H, NH_2, D_2O-exchangeable), 13.78 (br.S, 1H, -NH-C=S, D_2O-exchangeable), 7.33-7.47 (m, 10H, ArH); **4c** : ^{1}HNMR (DMSO-d_6): 3.75 (t, 2H, -O-CH_2CH$_2$), 2.25 (t, 2H, -O-CH$_2$$CH_2$), 5.72 (s, 2H, NH_2, D_2O-exchangeable), 13.75 (s, 1H, -NH-C=S, D_2O-exchangeable), 7.20-7.80 (m, 10H, ArH), **4a** : MS: (m/z, Rel. Abund): 325 (M$^+$, 10), 275 (25), 205 (100), 134 (50), 77 (90).

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