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Synthesis and Biological Activity of Some New β-Lactame Derivatives

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Abstract: ***Methyl 5-amino- 3- methylthio-1- phenyl-pyrazole -4- carboxylate 1 was reacted with different aldehydes namely, benzaldehyde, anisaldehyde , p- nitrobenzaldehyde, p-chlorobenzaldehyde and p-bromobenzaldehyde in the presence of glacial acetic acid at refluxed temperature afforded the corresponding Schiff- bases 2(a-e) ,which on reaction with each of chloroacetyl chloride and thioglycolic acid gave the corresponding β-lactam derivatives 3(a-e) and thiazolidines 4(a-e) respectively . N-alkylation of pyrazole derivative 6 was achieved by reaction with chloroacetyl amino acetophenone 5 in refluxing toluene, while the reaction of purified semicarbazone 7 with each of thionyl chloride and selenium dioxide gave the corresponding1,2,3- thiadiazole 8 and 1,2,3-selenadiazole 9 derivatives. The antibacterial and antifungal activities of some synthesized compounds have been discussed.***

Keywords: Pyrazole; thiazolidine; semicarbazone; β-lactam; thiadiazole ;selenadiazole ;Schiff- bases; antibacterial and antifungal activities

1. Introduction

It has been reported that pyrazoles [1-3] act as selective serotonin re-uptake inhibitors corticotrophin releasing factor (CRF), as cardiovisculator, and they are effective in the treatment of a range stress related diseases such as depression, anxiety and headache [4-6]. Also pyrazoles show analgesic, antinociceptive activity [7] .They are platelet aggregation inhibitors [8] and enhance phagocytes of leukocytes. They are also used as drugs for treatment of pancytopenia, thrombocytopenia and erythropenia. This promoted us to synthesize of some new pyrazole derivatives likely to possess biologically active new compounds.

2. Results and Discussion

As a continuation of our recent studies[10-12] aimed to synthesis some biologically active pyrazole compounds , we reported here on the synthesis and the biological activity of some new pyrazoles incorporated with heterocyclic moieties such as B- lactame , 4-thiazolidinone, 1,2,3- thiadiazoles, and 1,2,3-selensdiazoles derivatives.

In order to fulfill this aim, it was necessary to prepare methyl 5-amino- 3- methylthio-1- phenyl-pyrazole -4-carboxylate **1** as starting materials of this work through the reaction of 2, 2-bis (methylmercapto)-1- cyano –1-methylcarboxy acrylic acid with phenyl hydrazine in refluxing absolute ethanol and few drops of triethyl amine [13]. The structure of the pyrazole derivative **1** was confirmed from its analytical and spectral data. Treatment of methyl 5-amino- 3- methylthio-1- phenyl-pyrazole -4-carboxylate **1** with different aldehydes namely, benzaldehyde, anisaldehyde , p- nitrobenzaldehyde, p-chlorobenzaldehyde and p-bromobenzaldehyde in the presence of glacial acetic[14] acid at refluxed temperature afforded the corresponding Schiff bases **2(a-e).** Beside the elemental and spectral analysis the structure of Schiff bases was established via their reaction with different reagents to give new expected biologically active heterocycles annulated to pyrazole derivatives. The structure of compounds **2(a-e)** was confirmed from their correct analytical data, their IR spectra which, showed the absence absorption bands correspond to amino group and showed bands at 1615and 1725 Cm^{-1} assigned to (C=N) and (C=O of ester) respectively.

In the view of the fact that the antibiotic activity of penicillin and cephalosporin-c is mainly due to the attached -β lactam ring structure, it was of interest to incorporate lactam ring to the well known antimicrobial pyrazole derivatives and evaluate the pharmacological activity. Thus, the cyclocondensation of Schiff bases **2(a-e)** with chloroacetyl chloride was carried out in dry benzene[15] in the presence of triethyl amine as catalyst gave the corresponding methyl-5-(3-chloro-2-oxo-4-arylazetidinyl)-3-methylthio-1-phenylpyrazolo-4- carboxylate **3(a-e)** . The structure of compounds **3(a-e)** was confirmed from their correct analytical data, their IR spectra which, showed and showed absorption bands at 1725 Cm^{-1} assigned to C=O of ester groups IR spectra showed the absence of the absorption bands correspond to CH=N group. While reaction of Schiff- bases **2(a-e)** with thioglycolic acid in refluxing dry benzene [16] gave the corresponding methyl-5-[4-oxo-2-aryl-(1,3-thiazolidin-3-yl)]-3-methylthio-1-phenylpyrazolo-4- carboxylate **4(a-e)**.

N-alkylation of pyrazole derivative **6** was achieved by reaction with chloroacetyl amino acetophenone **5** in refluxing toluene [17] afforded the methyl 5-(2-(4-(1-(2-carbamoylhydrazono)ethyl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate **6.** IR spectrum of compound **6** pectrum showed absorption bands at 3280-3220Cm^{-1}(NH), 1670Cm^{-1}correspond to (C=O) , 1725 Cm^{-1}(C=O) of ester group and at1605Cm^{-1}correspond CH-N group . Chemically, the structure of the above compound was

supported through the reaction of compound **6** with semicarbazide hydrochloride and sodium acetate in refluxing ethanol to give the corresponding Methyl 5-(2-(4-(1-(2-carbamoylhydrazono)ethyl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate **7** which is considered as useful intermediate [18] for preparation of heterocyclic compound. IR spectrum of compound **7** showed absorption bands at 3440-3340 Cm^{-1} referred to amide group ,3280-3220Cm^{-1}(NH), 1670Cm^{-1}correspond to (C=O) , 1725 Cm^{-1}(C=O) of ester group and at1625Cm^{-1}correspond CH=N group. In addition , selenadiazole derivatives have marked broad spectrum antibacterial and antifungal activities so, it was of interest to prepare 1,2,3- selenadiazole derivative via the reaction of purified semicarbazone **7** with selenium dioxide according to Lalazari's synthesis[19] gave the corresponding corresponding methyl 5-(2-(4-(1,2,3-selenadiazol-4-yl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate **8**. IR spectrum of compound **8** showed absorption bands at 3440-3340 Cm^{-1} referred to amide group ,3280-3220Cm^{-1}(NH), 1670Cm^{-1}correspond to (C=O) , 1725 Cm^{-1}(C=O) of ester group and at1625Cm^{-1}correspond CH=N group).

It has been reported that thiadiazoles have antimicrobial and antifungal activities, while 1,2,3- thiadiazoles 4-caboxylic acid derivatives have sedative and hypotensive properties, this promoted us to prepare 1,2,3- thiadiazoles through the reaction of the semicarbazone **7** with thionyl chloride[20] to give corresponding methyl 5-(2-(4-(1,2,3-thiadiazol-4-yl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate **9.** . IR spectrum of compound **9** showed absorption bands at 3440-3340 Cm^{-1} referred to amide group ,3280-3220Cm^{-1}(NH), 1670Cm^{-1}correspond to (C=O) , 1725 Cm^{-1}(C=O) of ester group and at1625Cm^{-1}correspond CH=N group.

3. Antimicrobial Activity

The antimicrobial activity of the synthesized compounds **2a,R=H ,2c, R=p-NO_2, 2c,R=p-NO_2, 3a,R=H, 3c,R=p-NO_2, 3c,R=p-NO_2, 4c,R=p-NO_2, 8** and **9** was determined *in vitro* against a variety of bacteria and fungi. Comparative studies between the activity of our prepared compounds and standard drug were also carried out. The compounds were dissolved in DMF, and activity mentioned on 1000ppm. Agar plates were surface inoculated uniformly from fresh broth culture of the gram +ve and gram –ve bacteria and fungi. The Gram +ve bacteria were *Bacillus stablius* and Micrococcus *Luteus* the Gram –ve bacteria were *Serratia Rhodnii* and the fungi were *Penicillium Purperogenum, Trichoderma Viridi* and *Penicillium Funiculosum* .Flucanazole and Etraconazole were used as standard for antibacterial and antifungal activity respectively. The antimicrobial activity of the selected compounds are listed in Table 1 and Table 2 while the characterization and physical data are listed in Table 3.

Table 1: Results of antibacterial screening of selected compounds (expressed as diameter of the inhibition zone in mm):

Compd.	*Serratia Rhodnii (-ve)*	*Escherichia Coli (-ve)*	*Bacillus Subtilis* (+ve)	*Micrococcus Luteus (+ve)*
2a,R=H	13	8	-	13
2c,R=p-NO_2	11	8	12	8
3a,R=H	7	-	-	-
3c,R=p-NO_2	11	12	8	-
4a,R=H	7	-	12	8
4c,R=p-NO_2	4	12	11	-
8	5	6	9	9
9	8	-	5	13

While and the fungi were (*Penicillium Purperigenum, Trichoderma Viridi* and *Penicillium Funiculosum* .Flucanazole and Etraconazole were used as standard for antibacterial and antifungal activity respectively.

Table 2: Results of antifungal screening of selected compounds (expressed as diameter of the inhibition zone in mm):

Compd.	*Penicillium Purperigenum*	*Trichoderma Viridi*	*Penicillium Funiculosum*
2a,R=H	5	5	3
2c,R=p-OCH_3	3	3	5
3a,R=H	6	7	7
4c,R=p-NO_2	7	2	3
4a,R=H	2	5	5
8	3	5	7
9	3	5	6

4. Experimental

All melting points are uncorrected. IR spectra were recorded on Perkin-Elmer spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra ($CDCl_3$) were carried out on a Hitachi Perkin-Elmer *VA60* spectrometer using TMS as internal reference (chemical shifts inδ, ppm).

Methyl -5-amino- 3- methylthio-1- phenyl-pyrazole -4-carboxylate 1:
A mixture of 2, 2-bis (methylmercapto)-1- cyano –1-methylcarboxy acrylic acid (0.01mol) with phenyl hydrazine (0.01mol) and few drops of triethylamine in refluxing absolute ethanol (25 ml) was heated under reflux for one hour. The precipitate obtained by cooling was filtered off, dried and recrystallized from pet. ether (40-60) to give faint yellow crystals .

Methyl -5-(aza-2-arylphenyl-vinyl) 3- methylthio-1-phenyl-pyrazole -4- carboxylate 2(a-e):
A mixture of methyl 5-amino- 3- methylthio-1- phenyl-pyrazole -4- carboxylate **1** (0.01 mol) and the appropriate aldehydes namely, benzaldehyde, anisaldehyde , p-nitrobenzaldehyde, p-chlorobenzaldehyde and p-bromobenzaldehyde (0.01 mol) in the presence of glacial acetic acid (50 ml) under reflux for 3 hours afforded the corresponding Schiff bases **2(a-e).** The precipitate obtained by cooling was filtered off, dried and recrystallized from the proper solvents.

^{1}H-NMR spectrum of **2a** showed signals at δ =2.2 (s, 3H, S-CH_3), 3.6 (s, 3H, OCH_3), 7.4-8.0(m, 10H aromatic protons) and 8.5(s, 1H, CH=N).and for **2b** at δ =2.2 (s, 3H, S-CH_3), 3.3 (s, 3H,$COOCH_3$),3.8(s, OCH_3) 7.4-8.0(m, 9H aromatic protons) and 8.5(s, 1H, CH=N).

Methyl-5-(3-chloro-2-oxo-4-arylazetidinyl)-3-methylthio-1-phenyl pyrazolo-4- carboxylate 3(a-e):
To a well stirred solution of Schiff bases **2(a-e)** (0.01 mol) and triethylamine (0.02 mol) in dry benzene (50 ml) mono chloroacetylchloride (0.01 mol) was added at room temperature .The mixture was stirred for 10 hours and left at room temperature for 7 days .The precipitated triethylamine hydrochloride was filtered off and washed with dioxan .The filtrate was evaporated under reduced pressure and the residue obtained was washed with dil.HCl , wash with water , dried and recrystallized from the proper solvents to give lactams **3(a-e).**

^{1}H-NMR spectrum of **3b** showed signals at δ = 2.6 (s, 3H, S-CH_3), 3.5 (s, 3H, OCH_3 of ester), 3.8 (s, 3H, OCH_3 of anisaldehyde), 5.0(d,1H,CH-N),5.4(d, 1H,CH-Cl) and 7.1-7.8.0(m, 9H aromatic protons).

Methyl-5-[4-oxo-2-aryl-(1, 3-thiazolidin-3-yl)]-3-methylthio-1-phenylpyrazolo-4- carboxyl ate 4(a-e).
To a solution of Schiff bases **2(a-e)** (0.01 mol) in dry benzene (50 ml) thioglycolic acid (0.01 mol) was added, the mixture was refluxed using water separator. The excess benzene was evaporated and the residue obtained was dried and recrystallized from the proper solvents to give thiazolidines **4(a-e).**

^{1}H-NMR spectrum of **4a** showed signals at δ = 2.3 (s, 3H, S-CH_3), 3.1 (s, 3H, OCH_3 of ester), 3.9(s, 2H, CH2), 6.4(s, 1H, CH of thaizolidine) and 7.3-7.8(m, 10H aromatic protons).

Chloroacetyl amino acetophenone 5:
Chloroacetyl amino acetophenone was prepared according to the reported method [17].

Synthesis of methyl 5-(2-(4-(1-(2-carbamoylhydrazono)ethyl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate 6:
A mixture of chloroacetyl amino acetophenone **5** (0.01 mol) and the aminopyrazole **1** (0.01 mol) in dry toluene (50 ml) was refluxed for three hours. The precipitated amino hydrochloride was filtered off and extracted with dil.HCl, neutralized with sodium bicarbonate and the precipitated solid filtered, wash with water, dried and recrystallized from ethanol to give faint yellow crystals.

^{1}H-NMR spectrum of **6** showed signals at δ = 2.3 (s, 3H,S-CH_3) 2.5 (s, 3H, CO-CH_3), 3.9(s,3H,$COOCH_3$), 5.4(d, 2H,CH_2-CO),6.9(br,1H,NH-CH_2) and 7.1-7.8(m, 9H aromatic protons) and 10.5(br, 1H,NH).

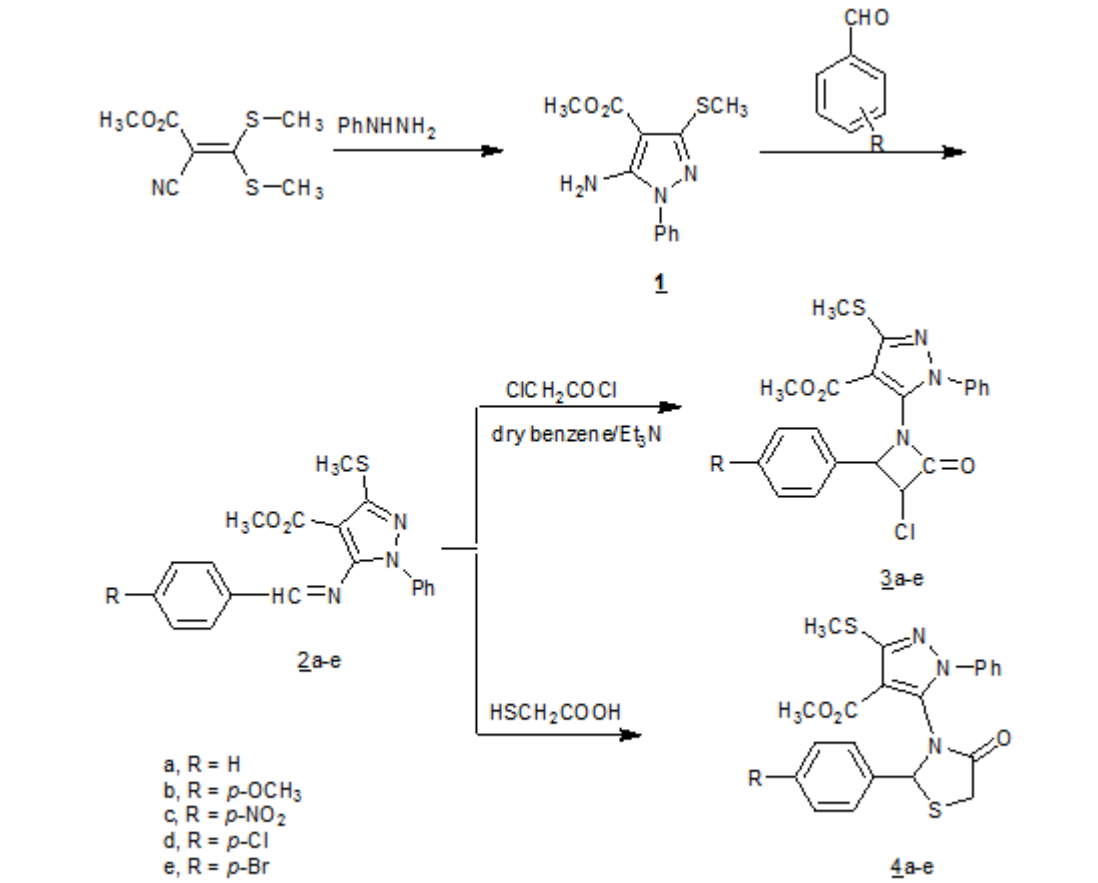
Synthesis of methyl 5-(2-(4-(1-(2-carbamoylhydrazono)ethyl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate 7:
A mixture of compound 6 (0.01 mol) with semicarbazide hydrochloride(0.01 mol) and sodium acetate(0.03 mol) was refluxed ethanol(30 ml).The mixture was poured upon ice cold water and the solid obtained was washed with water, filtered, dried and recrystallized.

^{1}H-NMR spectrum of **7** showed signals at δ = 2.2 (s, 3H, N=C-CH_3), 2.5 (s, 3H,S-CH_3), 3.9(s,3H,$COOCH_3$), 5.4(d, 2H,CH_2-CO),6.2(br,2H,NH_2) , 6.9(br,1H,NH-CH_2), 7.2-7.9(m, 9H aromatic protons) and 10.5(br, 2H,NH).

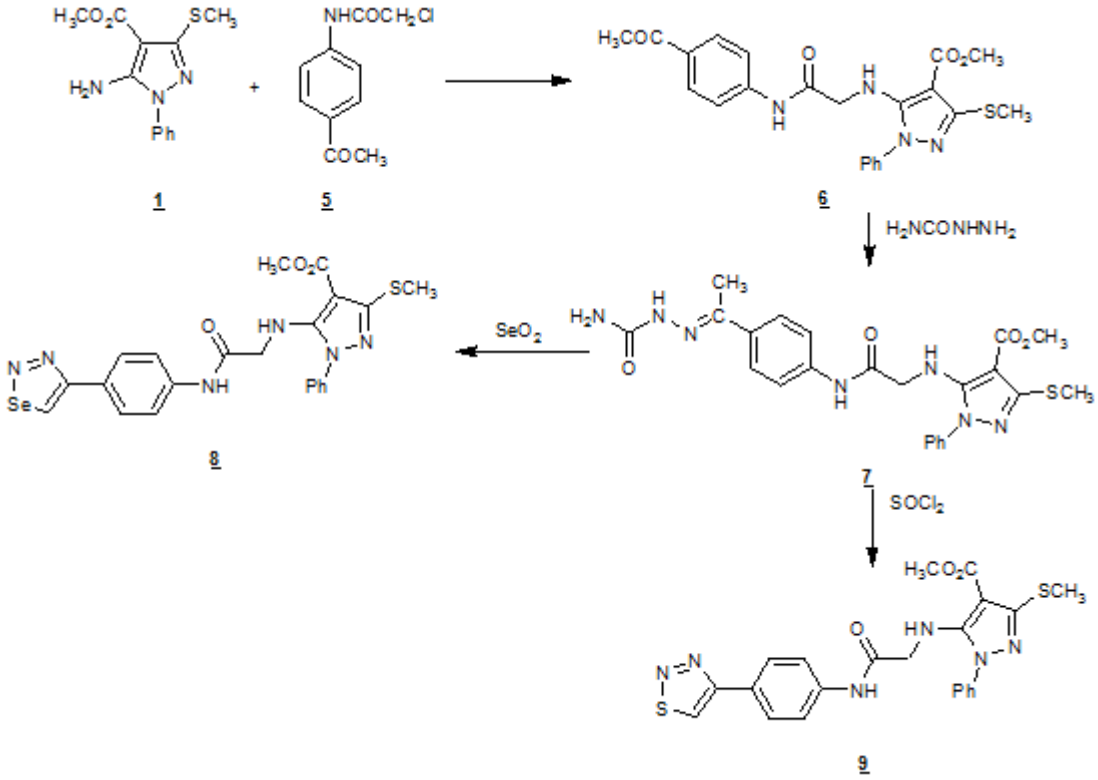
Synthesis of methyl 5-(2-(4-(1,2,3-selenadiazol-4-yl)phenylamino)-2-oxoethylamino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate 8 :
The powdered semicarbazone **7** (0.01 mol) was dissolved in 30 ml of boiling glacial acetic acid then a finely powdered selenium dioxide (0.01 mol) was added in potions while stirring and heating on a water bath for 2 hours , the residue was triturated with ethanol, and the solid separated was filtered, dried and crystallized .

^{1}H-NMR spectrum of **8** showed signals at δ = 2.6 (s, 3H,S-CH_3), 3.8(s,3H,$COOCH_3$), 5.1(d, 2H,CH_2-CO) 5.6(s, 1H,CH-selensdiazole), 6.9(br,1H,NH-CH_2), 7.1-7.9(m, 9H aromatic protons) and 10.2(br, 1H,NH).

Synthesis of methyl 5-(2-(4-(1,2,3-thiadiazol-4-yl)phenylamino)-2-oxoethyl amino)-3-(methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylate 9.
Thionyl chloride (9ml) was gradually added to the semicarbazone **7** (0.01 mol)and the mixture was gently heated ,then left overnight at room temperature .An ice – cold saturated solution of $NaHCO_3$ was added . The solid separated was washed with water filtered, dried and crystallized. The^{1}H-NMR spectrum of 9 showed signals at δ = 2.6 (s, 3H,S-CH_3), 3.8(s,3H,$COOCH_3$), 5.1(d, 2H,CH_2-CO), 6.9(br,1H,NH-CH_2), 7.2-8.0(m, 9H aromatic protons), 8.1(s, 1H,CH-selensdiazole) and 10.2(br, 1H,NH).



Scheme 1



Scheme 2

Table 3: Charactization and physical data.

Compd.	M.P °C Solvent	Yield %	Mol. Formula/ M.Wt	Analyses Calcd/Found (%)			
				C	**H**	**N**	**S**
1	115 Pet.Eth. (40-60)	85	$C_{12}H_{13}N_3O_2S$ (263.3)	54.74 54.71	4.98 4.91	15.96 15.91	12.18 12.11
2a	180	57	$C_{19}H_{17}N_3O_2S$ (351.25)	64.96	4.84	11.96	9.13

	E			64.90	4.69	11.54	9.10
2b	179 E.	55	: $C_{20}H_{19}N_3O_3$ S (381.45)	62.97 62.90	5.02 4.97	11.02 11.00	8.41 8.21
2c	190 E	59	$C_{19}H_{16}N_4O_4$ S (396.42)	57.57 57.50	4.07 4.00	14.13 14.00	8.09 8.01
2d	186 E	79	: $C_{19}H_{16}ClN_3O_2S$ (385.87)	59.14 59.10	4.18 4.10	10.89 10.76	8.31 8.21
2e	150 M	65	$C_{19}H_{16}BrN_3O_2S$ (429.01)	53.03 53.00	3.75 3.70	9.76 9.66	7.45 7.40
3a	260 Diox.	55	$C_{21}H_{18}ClN_3O_3S$ (427.08)	58.94 58.90	4.24 4.11	9.82 9.71	7.49 7.38
3b	230 Diox.	57	$C_{22}H_{20}ClN_3O_4S$ (457.09)	57.70 57.69	4.40 4.25	9.18 9.11	7.00 6.90
3c	250 Diox.	66	$C_{21}H_{18}Cl\ N_3\ O_3S$ (472.06)	53.34 53.32	3.62 3.61	11.85 11.77	6.78 6.70
3d	243 Diox.	60	$C_{21}H_{17}\ Cl_2N_3O_3S$ (462.35)	54.56 54.51	3.68 3.76	9.08 9.00	6.93 6.85
3e	261 Diox.	79	$C_{21}H_{17}BrCl\ N_3O_3S$ (506.80)	49.78 49.68	3.35 3.42	8.29 8.25	6.33 6.21
4a	220 E	75	$C_{21}H_{19}N_3O_3\ S_2$ (425.33)	59.30 59.26	4.47 4.40	9.87 9.79	15.07 15.00
4b	145 E.	70	$C_{19}H_{16}N_4O_4\ S_2$ (396.25)	58.03 58.01	4.61 4.58	9.22 9.12	14.08 14.01
4c	230 E	69	$C_{21}H_{18}N_4O_5\ S_2$ (470.33)	53.62 53.59	3.82 3.78	11.91 11.87	13.63 13.59
4d	254 pet.eth.	76	$C_{21}H_{18}N_3O_3\ S_2$ (459.83)	54.85 54.78	3.91 3.85	9.13 9.09	13.94 13.83
4e	275 B	78	$C_{21}H_{18}N_3O_3\ S_2Br$ (504.23)	50.01 49.98	3.57 3.51	8.33 8.27	12.72 12.66
6	238 Bu	73	$C_{22}H_{22}N_4O_4$ S (438.28)	60.28 60.18	5.02 5.00	12.87 12.66	7.31 7.27
7	143 E	78	$C_{23}H_{25}N_7O_4$ S (495.28)	60.77 60.70	5.04 5.00	19.79 19.71	6.46 6.40
8	135 Pet.eth.	88	$C_{22}H_{20}N_6O_3$ SSe(482.58)	54.70 54.66	4.14 4.10	17.39 17.29	6.62 6.59
9	232 B	77	$C_{22}H_{20}N_6O_3S_2$ (480.50).	54.94 54.90	4.16 4.11	17.48 17.41	6.65 6.62

E=ethanol, Diox= Dioxan , B= Benzene, Bu= Butanol, Pet.eth.=petroleum ether, M Methanol.

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