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SYNTHESIS OF SOME NEW SUBSTITUTED MERCAPTOMETHYL PYRIMIDINES OF POSSIBLE BIOLOGICAL ACTIVITY

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Abstract

4,6-Diaryl-2-mercaptomethyl pyrimidine derivatives (IIa,b) and (IIIa,b) were prepared. The reaction of IIa with phenylisothiocyanate afforded the corresponding N-phenylthiocarbamoyl derivative (IV) which was used as an intermediate for the synthesis of 1,3,4-thiadiazole (V), 1,3,4-triazole-2-thione-(VII) and 1,3,4-oxadiazole (VI)-5-methyl mercaptopyrimidines. 1,3,4-Triazol-2-thione-5-methylmercaptopyrimidine(VII) was subjected to Mannich reaction. The reaction of 2-amino 1,3,4-thioadiazole-5-methyl mercaptopyrimidine (Vb) with active methylene compounds was also studied structural assignment of the prepared compounds were based on elemental and spectral data.

Some of the prepared compounds were screened in vitro for their antibacterial activity.

Results and Discussions:

As extension of our studies on pyrimidine derivatives[1-4], we intended to prepare 4,6-diaryl-2-mercaptomethyl pyrimidine in order to establish the reactivity of the mercaptomethyl group at the side chain of the pyrimidine nucleus towards some nucleophiles and to give rise to some biologically active heterocycles which might be incorporated to it. It is well known that the introduction of aryl oxymethyl substituent to various heterocycles enhances their biological activities[1,5] and as pyrimidine derivatives possess a pronounced biological activity[4,6] this prompted us to continue our work on the synthesis of nitrogen and sulphur containing heterocycles of biological interest.

Thus, ethyl 2-[2'(4',6'-diaryl) mercaptopyrimidinyl) acetate (I) was prepared by treatment of 4,6-diarylpyrimidine-2-thione[1] with ethylchloroacetate in boiling ethanol containing anhydrous K_2CO_3. The reaction of I with hydrazine hydrate or phenyl hydrazine in boiling ethanol gave the corresponding 2-carbonylhydrazinyl–4,6-diaryl pyrimidines (IIa,b). Also the reaction of I with semicarrbazide/or thiosemicarbazide in boiling pyridine gave the corresponding 2-methyl-mercaptocarbamoyl(IIIa)or-thiocarbamoyl(IIIb)-4,6-diaryl pyrimidines.

The reaction of IIa with phenylisothiocyanate in boiling benzene afforded the corresponding 2-carbonyl-N-phenyl thiocarbonyl-4,6-diarylpyrimidine (IV), (Scheme 1).

Compound (IV) afforded a dipolar cycloaddition in acidic and basic media. Thus, treatment of IV with concentrated H_2SO_4 on cold and for a long period of time (24h) 2[5'(methylmercapto-2-amino-phenyl) 1',3',4'-thiadiazolyl] 4,6-diaryl pyrimidine (Va) afforded the corresponding 5–(4,6–diarylpyrimidine-2-) mercaptomethyl-2-aminophenyl-1,3,4–thiadiazol (Va). Compound (Vb) was obtained by treatment of III with warming sulpuric acid (50%).

Also treatment of IV with boiling alcoholic NaOH gave the corresponding–2[5'(methylmercapto-1,3,4'-triazole-2'thionyl)-4,6-dirayl pyrimidine (VII) (Scheme 1).

Compound (VII) was used for the synthesis of a series of Mannich bases (VIIIa–c) in the presence of the appropriate amine and formaldehyde (37%) in methanol-acetone mixture; (Scheme 1).

Some 5-substituted –1,3,4-oxadiazoles have elicited a good deal of attention as they exhibit antimycobacterial activity[7]. The present work also deals with the synthesis of such nucleus. Thus, treatment of IV with yellow mercuric oxide in boiling ethanol gave 2[5'(mercaptomethyl-2'-aminophenyl)-1',3',4'- oxadiazolyl]-4,6-diaryl pyrimidine(VI); (Scheme 1).

Mass spectrum of (VI) showed a molecular ion peak at m/e 529 (M+3), which underwent further fragmentation process afforded the base peak at m/e 231 (100%).

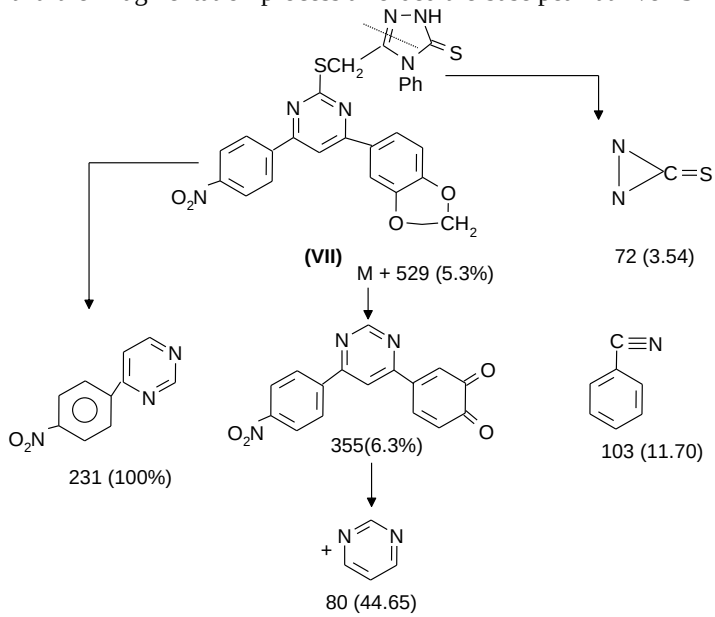
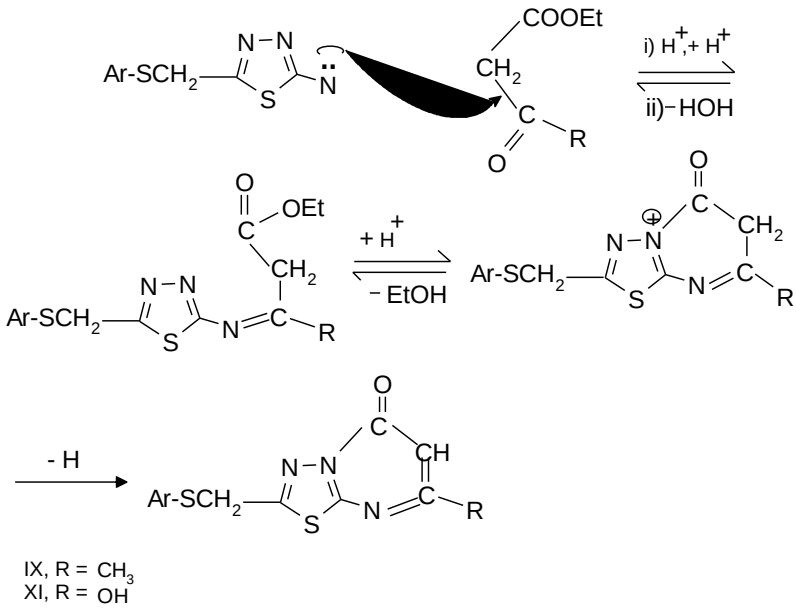


Chart (1)

Compounds (Vb) and (VI) are themselves useful as synthetic intermediates. Thus, treatment of (Vb) with ethyl acetoacetate in the presence of PPA afforded a new heterocyclic product revealed by its NMR spectrum and identified as 7-methyl-2methylmercapto-(4\,6\-diarylpyrimidin)yl-1,3,4-thiadiazolo[3,2-a] pyrimidin–5-one (IX, Scheme 2.



(Chart 2)

Also, the reaction of Va with diethyl[8] malonate gave the ester intermediate derivative (X) which underwent cyclization to the corresponding 7-hydroxy-2-(4,6-diarylpyrimidin)yl-5H-1,3,4-thiadiazolo [3,2-a] pyrimidin-5-one (IX) Scheme 2, .

Experimental

All melting points are uncorrected. The ^{1}H-NMR of the prepared compounds are recorded on a Varian –HAGO spectrophotometer using TMS as internal standard (chemical shifts in δppm) (DMSO-d_6 or $CDCl_3$). Mass spectra on a Jeol JMS-D300 spectrometer at 70eV. IR spectra (KBr) are measured on a Perkin–Elmer infrared spectrophotometer

2-Carbonyl hydrazinyl-4,6-diaryl pyrimidine (IIa,b).

A solution of compound (I)[1] (0.01 mol), hydrazine hydrate or phenylhydrazine (0.01 mol) in ethanol (50ml) was refluxed for 6 hrs. The hot reaction mixture was

filtered off, then cooled. The solid that separated was collected and recrystallized from ethanol to give IIa,b. IR (KBr) 1690-1695 (υC=O)' 1610-1615) (υC=N) and 3180-3370 cm^{-1} (υNH). ^{1}H-NMR (DMSO-d_6): 3.2 (s,2H–OCH_2O), 4.3 (s,1H,NH), 7.2-8.6 (m 8H, Ar-H and cyclic CH=C) and 10.6 (br, 2H, NH_2).

4,6-diaryl-2-mercaptomethylcarbonyl or thiocarbamoyl (IIIa,b).

A mixture of compound (I) (0.01 mol), and semicarbazide/or thiosemicarbazide (0.01 mol) in 30 ml of pyridine was refluxed for 6hrs. The reaction mixture was poured into ice/HCl mixture and the solid that separated was collected, washed well and recrystallized from acetic acid as (IIIa,b) IR (KBr) 3180-3385 (υNH), 1690 (υC=O), 1655 (υC=N), 1620 (υC=C); and 1180 (υC=S, for IIIb); ^{1}H-NMR (IIIb) (DMSO-d_6) δ3.1 (s,2H,OCH_2O), 4.2-5.0 (br, m. 3H, $NHNH_2$), 6.6-7.5 (m, 8H, Ar-H and cyclic CH=C).

2- (Carbonyl-N-Phenyl thiocarbamoyl) mercaptomethyl 4,6-diaryl pyrimidine (IV).

A mixture of IIa(0.01 mol) in benzene (30ml) and phenyl isothiocyanate (0.01mol) was refluxed for 8hrs. The solvent was then removed and the product was washed with petroleum-ether and recrystallized from benzene-petroleum-ether as IV IR (KBr): 3380 (br,υNH), 1680 (υC=O), 1630 (υC=N) and 1180 (υC=S); ^{1}H-NMR ($CDCl_3$) δ3.11 (s,2H, OCH_2O); 6.8-8.3 (m, 13H,Ar-H and cyclic CH=C) and 10.8 (br, 1H, NH-Ph).

2[5'(methylmercapto-2'aminophenyl) 1',3',4'-thiadiazyl] 4,6-diaryl pyrimidine (V_a)

A mixture of IV (0.01 mol) in ice-cold 25 ml (3N) H_2SO_4 was stirred for 1h, then left at room temperature for 24hrs. It was then neutralized with 2N NaOH and the product that separated was collected, washed with water and crystallized from ethanol to give Va. Va; IR(KBr) 3150 (υNH), 1630 (υC=N), 1210 (υC–S); ^{1}HNMR ($CDCl_3$) δ 2.9 (s,2H, S-CH_2), 3.1 (s, 2H, OCH_2O), 6.0 (br, 1H, NHPh), 6.6-8.2 (m, 13H, Ar-H and cyclic CH=C).

5-(4\.6\-diarylpyrimidine-2\-)mercaptomethyl-2-aminophenyl-1,3,4-thiadiazole (Vb).

A mixture of IIIb (0.01 mol) and H_2SO_4(5ml, 50%) was heated on a steam-bath for 1h. It was then cooled and neutralized with 2N NaOH and the product that separated was collected, washed well with water and crystallized from ethanol as Vb. Vb: IR (KBr) 3320 (υNH), 2860 (υCH_2), 1630) υC=N), 1590 (υC=C) and 1210 (υC-S).

^{1}H-NMR of Vb ($CDCl_3$): δ 3.1 (s,2H,SCH_2); 5.0 (b, s,2H,NH_2), 6.6-7.5 (m, 8H, ArH and cyclic CH=C).

2[5'-(mercaptomethyl-2'aminophenyl)-1',3',4'-oxadiazolyl] 4,6-diaryl primidine (VI)

To a suspension of IV (0.01 mol) in 30 ml of absolute ethanol was added 0.01 mol of yellow HgO with stirring. Stirring was continued for 2hr., then the reaction mixture was refluxed for 2hrs filtered with hot and left to cool. The product that separated was collected, washed well with hot water and recrystallized from methanol as VI.

2[5'-(methylmercapto-1',3',4' triazole-2'thionyl]- 4,6-diaryl-pyrimidine (VII)

A mixture of IV (0.01 mol) in ethanol (10ml) was refluxed for 15hrs. together with aqueous NaOH (10ml, 20%). The reaction mixture was cooled, neutralized with ice/10% HCl and extracted with ether. The product that separated after evaporation of ether was crystallized from benzene to give (VII) IR (KBr): 3285 (br, υNH); 2830-3010(υCH); 1630 (υC=N), 1620 (υC=C) and 11% cm^{-1}) (υC=S). ^{1}HNMR (DMSO-d_6); δ3.09 (s, 2H, S-CH_2), 6.8-8.8 (m, 13H, Ar-H and cyclic CH=C), 9.6 (br, 1H of SH, ratio 28.6), 10.2 (br, 1H, NH, ratio 71.4).

Mannich reaction with VII. Formation of 3-substituted amino methyl–5-mercabomethyl(4\',6\'-diarylpyrimidine-2\'-yl)–2-thiones(VIIIa-c).

A solution of VII (0.01 mol) in ice-cold 25 ml acetone was treated with 1ml formaldehyde (37%, w/v) with stirring. Then the appropriate amine namely, and morpholine, diethyl amine, and (0.01 mol) in 25ml of methanol was added dropwise with stirring. The reaction mixture was left to stand for 2hrs. in an ice-bath with occasional shaking . The precipitated Mannich bases were collected and crystallized from ethanol as VIII-a-c.

7-Methyl-2-[2-methylmercapto-4,6-diarylpyrimidinyl]5H-1,3,4-thiadiazolo [3,2-a] pyrimidin–5-one IX).

A mixture of ethyl acetoacetate (0.02 mol) PPA (11.5 g) and Vb (0.005 mol, 1.6 g) was refluxed on a steam-bath for 1hr cooled and neutralized with 2N NaOH. The product that obtained was collected, washed well with hot water and recrystallized from ethanol to give IX.

7-Hydroxy-2-[2-methylmercapto-4,6-diarylpyrimidinyl]-5H-1,3,4-thiadiazolo [3,2-a] pyrimidin-5-one XI).

A mixture of Vb (0.005 mol, 1.6), diethyl malonate (3ml) and *p*-toluene sulphonic acid (0.1g) in dry benzene was heated in an oil-bath at 240°C for 1hr., then cooled. The semi-solid that separated was dissolved in ether then washed well with water. After evaporation of ether, the product corresponding to (X) (m.p. 128°) was refluxed in dry toluene (20ml) containing 0.5 g of *p*-toluene sulphonic acid for 16 hrs. The product that separated was collected, and recrystllaized from benzene as XI.

Antimicrobial Activity

All the synthesized compounds were screened for antimicrobial activity against Gram positive bacterium, Bacillus subtitles; Gram negative bacterium, *Escherichia coli* and a fungus *Aspergillus niger* employing cup diffusion technique[9] using DMF as a solvent control and growth inhibitor was calculated with reference to control.

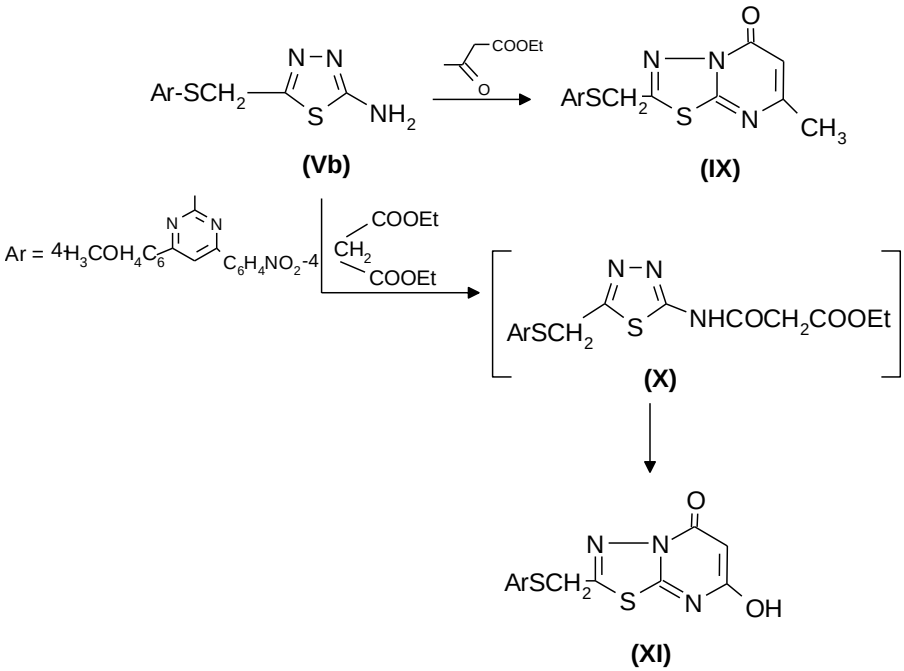
Regarding the results, it was found that compound IX had maximum activity and compounds VIIIa-c exhibited varying degree of growth inhibition. On the other hand, compound IX had exhibited significant antimicrobial activity than VII while compound II-VI exhibited moderate antibacterial activity.

In conclusion, the preliminary screening carried chiefly on the synthesized compounds showed that only derivatives showed that only derivatives, end owed with higher molecular complexity and rigidity such as compounds IX, XI. (table 2).

Table (1) : Physical Data of the Prepared Compounds (II-XI)

Comp. No	Molecular formula (M.wt.)	M.P.ºC Solvent	Yield %	Analysis / calcd / found			
				%C	%H	%N	%S
IIa	$C_{19}H_{15}N_5O_5S$ (425)	144 EtOH	44	53.64 53.7	352 3.5	16.47 16.5	7.52 7.6
IIb	$C_{25}H_{19}N_5O_5S$ (501)	121 EtOH	51	59.88 60.0	3.79 3.8	13.97 14.0	6.38 6.4
IIIa	$C_{20}H_{16}N_6O_6S$ (468)	234 EtOH	62	51.28 51.3	3.41 3.3	17.94 18.0	6.83 6.9
IIIb	$C_{20}H_{16}N_6O_5S_2$ (484)	151 P.E	66	49.58 49.6	3.305 3.3	17.35 17.5	13.22 13.1
IV	$C_{26}H_{20}N_6O_5S_2$ (560)	217 AcOH	74	55.71 55.8	3.57 3.6	15.00 14.9	11.42 11.3
Va	$C_{26}H_{18}N_6O_4S_2$ (542)	183 EtOH	34	57.56 57.6	3.32 3.3	15.49 15.5	11.808 11.9
Vb	$C_{20}H_{14}N_6O_4S_2$ (466)	168 EtOH	41	51.502 51.5	3.004 3.1	18.025 18.7	13.73 13.6
VI	$C_{26}H_{18}N_6O_5S$ (526)	174 MeOH	51	59.31 59.30	3.42 3.41	15.96 15.95	6.08 6.09
VII	$C_{26}H_{18}N_6O_4S_2$ (542)	147 EtOH	59	59.31 59.5	3.42 3.4	15.96 16.0	6.08 6.4
VIIIa	$C_{29}H_{25}N_7O_4S_2$ (599)	171 EtOH	55	58.09 5.1	4.17 4.2	16.36 16.4	10.68 11.0
VIIIb	$C_{31}H_{29}N_7O_4S_2$ (627)	142 EtOH	53	59.33 59.4	4.62 4.6	15.62 15.5	10.207 10.2
VIIIc	$C_{35}H_{35}N_7O_6S_2$ (713)	151 EtOH	49	58.90 58.91	6.45 6.44	18.08 18.09	8.97 8.96
IX	$C_{24}H_{16}N_6O_5S_2$ (532)	205 EtOH	59	54.13 54.1	3.007 3.0	15.78 15.8	12.03 12.1
XI	$C_{23}H_{14}N_6O_6S_2$ (534)	120 B	64	51.68 51.7	2.62 2.6	15.73 15.8	11.98 12.0

Where **:** EtOH **=** ethanol ; P.E. = Petroleum Ether (b.p. 80-110º);
AcOH = Acetic Acid, MeOH = methanol and B = Benzene



(Scheme 2)

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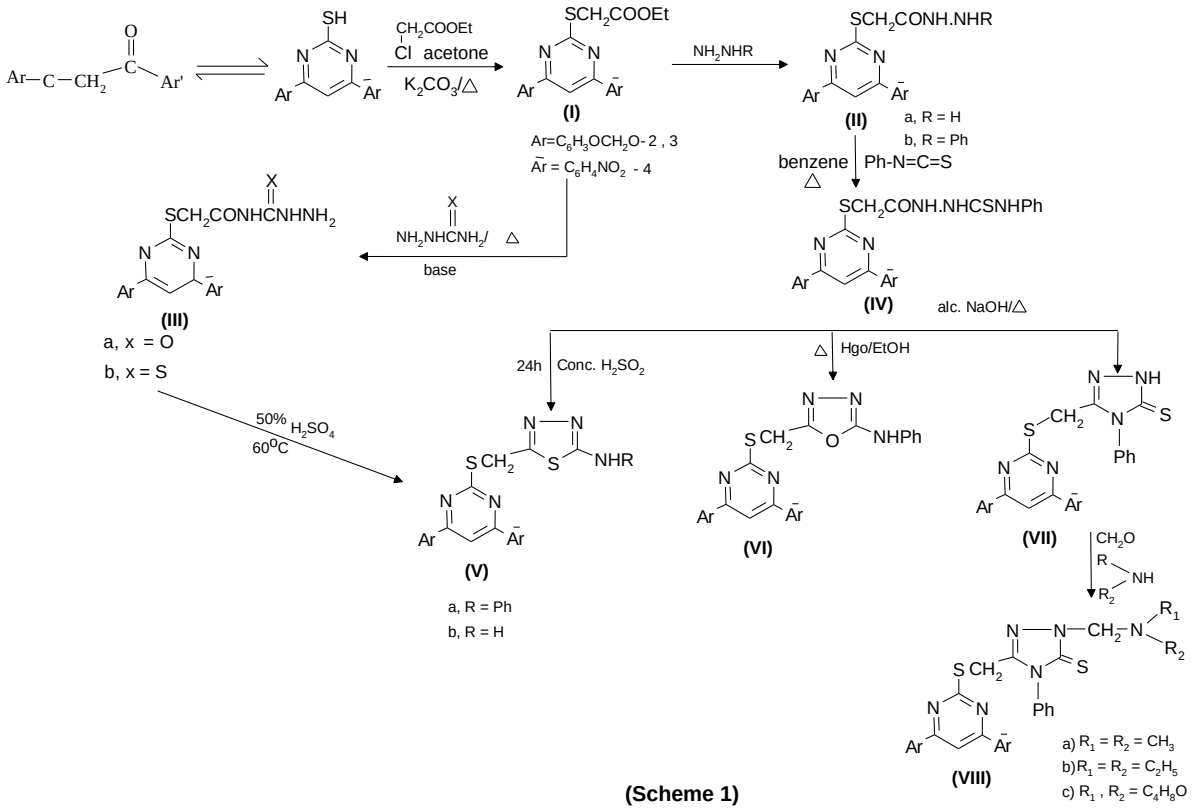
Al-Azhar Bull. Sci. Vol. 17, No. 1 (June.): pp. 161-170 , 2006

Table (2). Antimicrobial activity of some new mercaptomethyl pyrimidine derivatives

Tested organisms	*Staphylococus aureus*			*Bacillus subtilus*			*Salmonella typhi*			*Aspergillus flavus*			*Aspergillus niger*			*Candida albicans*		
Concentration.	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
Comp. No.	(mg/ml)			(mg/ml)			(mg/ml)			(mg/ml)			(mg/ml)			(mg/ml)		
II	++	++	+	+	++	+++	+	++	+++	++	++	+++	0	++	++	+	+	+
III	++	++	+	+	++	++	+	++	++	++	++	++	+	++	++	0	0	0
IV	++	++	+	+	++	+++	+	++	+++	++	++	+++	+	++	++	++	++	++
VI	++	++	+	+	++	+++	+	++	+++	++	++	++	++	++	++	0	+	++
VIIIa	+	++	+	+	++	+++	+	++	+++	++	++	++	+	++	++	0	0	++
VIIIb	+	++	+	+	++	+++	+	++	+++	++	++	++	+	++	++	++	++	0
VIIIc	+	++	+	+	++	+++	+	++	+++	++	++	++	+	++	++	0	+	++
IX	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
XI	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++

* Well diameter : 1 cm (100 µ l of each concentration was tested)
* Inhibition values = 1.1-0.5 cm beyond control = + Inhibition values = 0.6-16.cm beyond control =++
* inhibition values = 1.1-0.5 values = 1.1-1.5 cm beyond control = +++ 0 = not detected


Ar–C–CH2
Ar'
SH
CH2COOEt
Cl acetone
K2CO3/△
SCH2COOEt
(I)
Ar=C6H3OCH2O- 2 , 3
Ar = C6H4NO2 - 4
NH2NHR
SCH2CONH.NHR
(II)
a, R = H
b, R = Ph
benzene
△
Ph-N=C=S
SCH2CONH.NHCSNHPh
(IV)
alc. NaOH/△
SCH2CONHCNHNH2
(III)
a, x = O
b, x = S
NH2NHCNH2/ △
base
50% H2SO4
60°C
24h Conc. H2SO4
△ Hgo/EtOH
(V)
a, R = Ph
b, R = H
(VI)
(VII)
CH2O
R
NH
R2
(VIII)
a) R1 = R2 = CH3
b) R1 = R2 = C2H5
c) R1 , R2 = C4H8O

(Scheme 1)