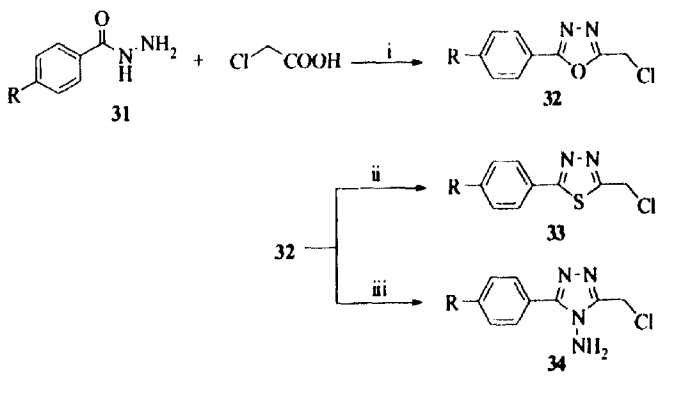
CHAPTER-III

Synthesis and antimicrobial activity of bis(1,3,4-oxadiazolyl / 1,3,4-thiadiazolyl / 1,2,4-triazolylmethylthio)pyrimidines.

CHAPTER III

Chapter III describes the synthesis and antimicrobial activity of 2-(5-phenyl-1,3,4-oxadiazol-2-ylmethylthio)-4-chloro-6-methylpyrimidine, 2-(5-phenyl-1,3,4-thiadiazol-2-ylmethylthio)-4-chloro-6-methylpyrimidine, 2-(5-phenyl-4-amino-1,2,4-triazol-3-ylmethylthio)-4-chloro-6-methylpyrimidine, 2,4-bis(5-phenyl-1,3,4-oxadiazol-2-ylmethylthio)-6-methylpyrimidine, 2,4-bis(5-phenyl-1,3,4-thiadiazol-2-ylmethylthio)-6-methylpyrimidine and 2,4-bis(5-phenyl-4-amino-1,2,4-triazol-3-ylmethylthio)-6-methylpyrimidine.

The 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (**32**) was obtained by the reaction of aryl acid hydrazide (**31**) with chloroacetic acid in the presence of phosphorus oxychloride. The reaction of **32** with thiourea in tetrahydrofuran provided 2-(chloromethyl)-5-phenyl-1,3,4-thiadiazole (**33**). Likewise, 3-(chloromethyl)-5-phenyl-4*H*-1,2,4-triazol-4-amine (**34**) was prepared by the treatment of **32** with hydrazine hydrate in *n*-butanol (Scheme **III.1**).



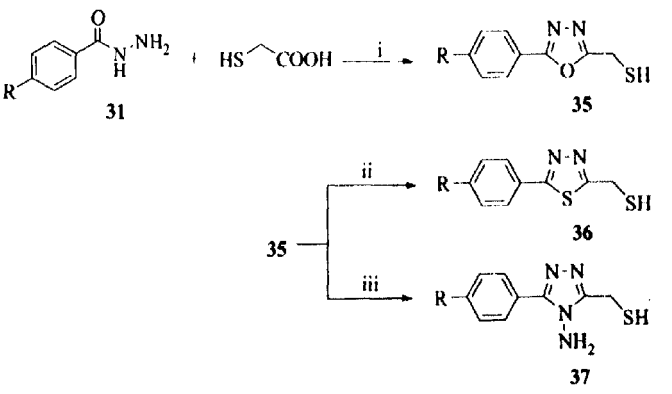
(i) $POCl_3$ /Δ
(ii) NH_2CSNH_2 / THF /Δ
(iii) $NH_2NH_2.H_2O$ / *n*-Butanol /Δ

R = a) H d) 4-Br
b) 4-Me e) 4-OMe
c) 4-Cl f) 4-NO_2

SCHEME III.1

The IR spectra of compounds **32**, **33** and **34** exhibited absorption bands in the regions 1560-1587 cm^{-1} corresponding to C=N. Besides, **34** presented two absorption bands in the regions 3454-3472 and 3358-3372 cm^{-1} due to NH_2. The ^1H NMR spectra of **32a**, **33a** and **34a** showed a singlet at δ 4.90, 4.70 and 4.41 due to methylene protons. Further, **34a** displayed a broad singlet at 5.35 ppm due to NH_2 which disappeared on deuteration.

On the other hand, (5-phenyl-1,3,4-oxadiazol-2-yl)methanethiol (**35**) was prepared by the cyclocondensation of compound **31** with mercaptoacetic acid in the presence of phosphorus oxychloride. Interconvertion of oxadiazole to thiadiazole was effected by treating **35** with thiourea in tetrahydrofuran to get (5-phenyl-1,3,4-thiadiazol-2-ylmethanethiol (**36**). Furthermore, the reaction of **35** with hydrazine hydrate in *n*-butanol furnished (4-amino-5-phenyl-4*H*-1,2,4-triazol-3-ylmethanethiol (**37**) (Scheme **III.2**).



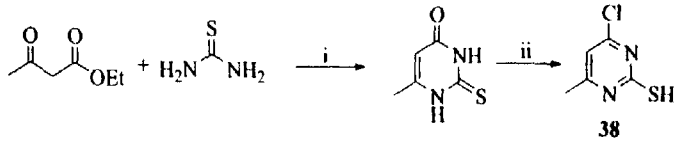
(i) $POCl_3$ /Δ
(ii) NH_2CSNH_2 / THF /Δ
(iii) $NH_2NH_2.H_2O$ / *n*-Butanol /Δ

R = a) H d) 4-Br
b) 4-Me e) 4-OMe
c) 4-Cl f) 4-NO_2

SCHEME III.2

The IR spectra of **35**, **36** and **37** displayed absorption bands in the regions 2550-2600 and 1559-1568 cm^{-1} due to SH and C=N. Apart from these, in **37** broad absorption bands appeared in the regions 3479-3489 & 3347-3364 cm^{-1} were assigned to NH_2. The ^1H NMR spectra of **35a**, **36a** and **37a** presented two singlets at δ 4.35, 4.39, 4.32 and 11.05, 11.10, 11.05 corresponding to CH_2 and SH. The compound **37a** also displayed broad singlet at 5.42 ppm due to NH_2. The signals of SH and NH_2 disappeared on deuteration.

The reaction of ethyl acetoacetate with thiourea in the presence of sodium methoxide produced 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one. This on treatment with phosphorus oxychloride resulted in 4-chloro-6-methylpyrimidine-2-thiol (**38**) (Scheme **III.3**).



38

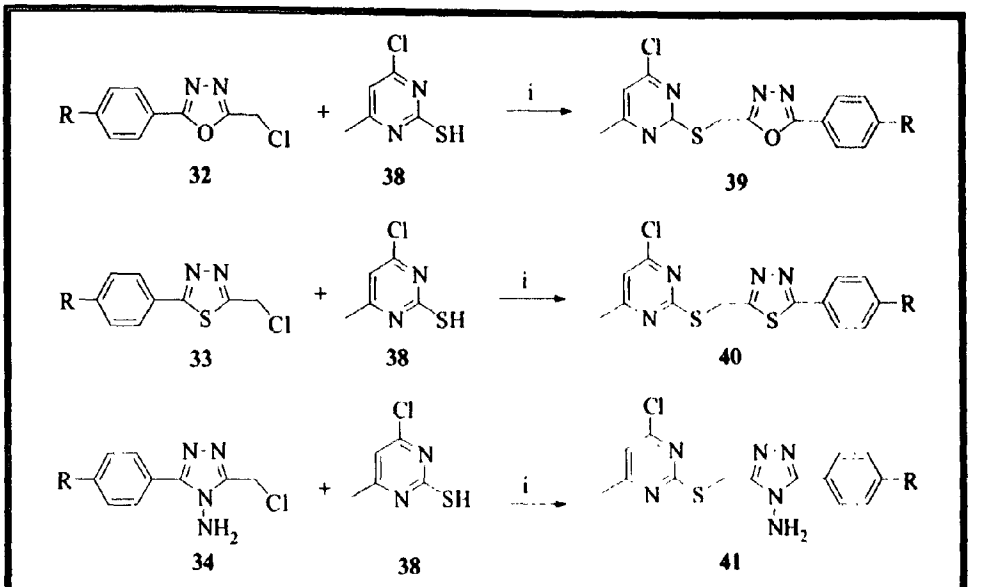
(i) NaOMe / MeOH / Δ
(ii) $POCl_3$ / Diglyme / Δ

SCHEME III.3

The IR spectrum of **38** displayed absorption bands at 2548 (SH), 1623 (C=C) and 1572 cm^{-1} (C=N). The ^1H NMR spectrum of **38** showed three singlets at δ 2.39, 6.70 and 11.08 ppm due to CH_3, C_5-H and SH. The latter signal disappeared when D_2O was added.

The bis heterocyclic compounds methylthio linked bis(oxadiazolyl)pyrimidines, bis(thiadiazolyl)pyrimidines and bis(triazolyl)pyrimidines were prepared as follows. The reaction between compounds **32** and **38** in the presence of triethylamine in tetrahydrofuran afforded 2-(5-phenyl-1,3,4-oxadiazol-2-ylmethylthio)-4-chloro-6-methylpyrimidine (**39**). In a similar way 2-(5-phenyl-1,3,4-thiadiazol-2-ylmethylthio)-4-chloro-6-methyl-pyrimidine (**40**) was obtained by the treatment of **33** with **38**. Likewise 2-(5-phenyl-4-amino-1,2,4-triazol-3-yl-methylthio)-4-chloro-6-methylpyrimidine (**41**) was synthesized by the reaction of **34** with **38**. The compounds **39**, **40** and **41** were also prepared under ultrasonication in an ultrasonic bath operating at a frequency of 35 kHz (Scheme **III.4** & **Table III.1**).

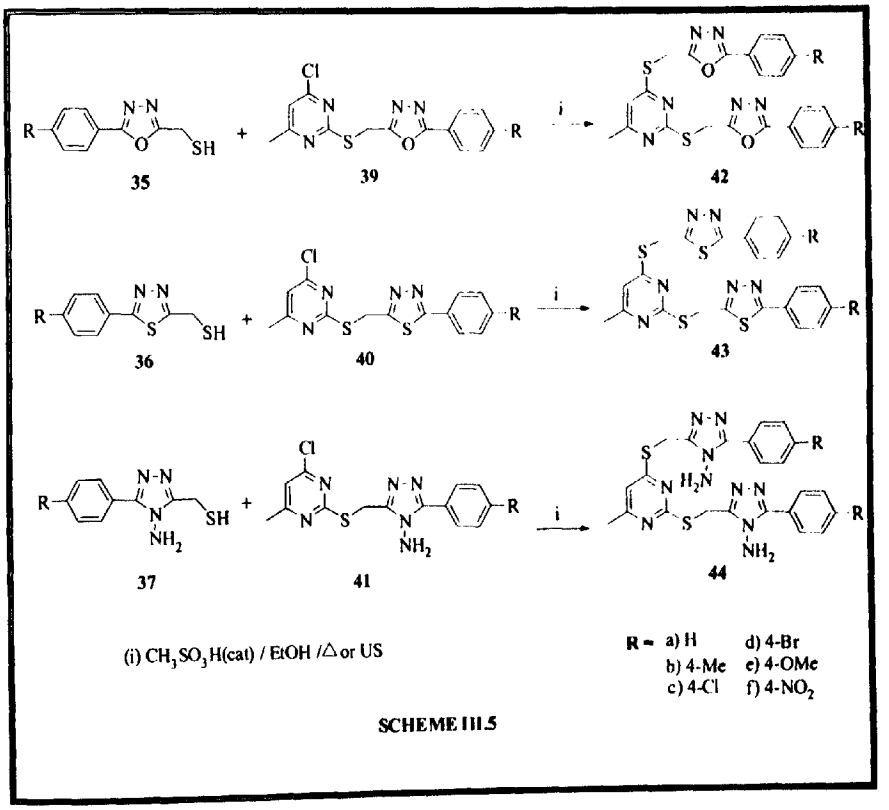
In the IR spectra of compounds **39**, **40** and **41** the absorption bands observed in the regions 1620-1636 and 1562-1586 cm^{-1} were attributed to C=C and C=N. Besides the compound **41** showed an additional band in the regions 3439-3480 & 3334-3371 cm^{-1} due to NH_2 (Table **III.2**). The ^1H NMR spectra of **39a**, **40a** (Fig. **III.1**) and **41a** exhibited three singlets at δ 2.35, 2.45, 2.36 (CH_3); 4.42, 4.51, 4.53 (CH_2) and 7.43, 7.42, 7.35 (C_5-H).



SCHEME III.4

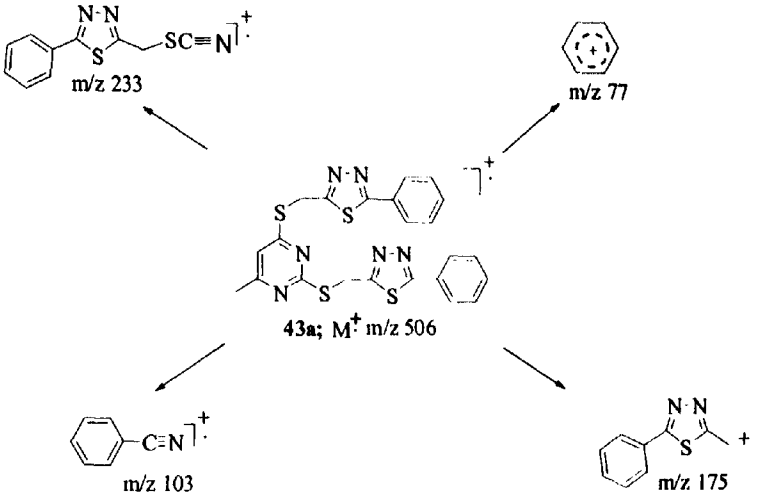
The compound **41a** displayed another singlet at 5.62 ppm due to NH_2 which disappeared on deuteration (Table **III.3**). The ^{13}C NMR spectra of **39a** showed signals at δ 24.9, 34.5, 111.6, 160.4, 162.7, 164.9, 169.8, 173.4; **40a** at (Fig. **III.2**) 25.4, 35.4, 111.3, 160.2, 169.5, 176.8, 168.6, 174.6 and **41a** at 24.5, 36.5, 111.7, 160.8, 148.6, 151.8, 168.4, 173.6 ppm due to CH_3, CH_2, C-5, C-4, C-2'/ C-3', C-5', C-6, C-2, respectively (Table **III.3**).The HRMS mass spectra of **39a** (Fig. **III.3**), **40a** (Fig. **III.4**) and **41a** (Fig. **III.5**) presented M+Na peaks at m/z 341.7718, 357.8374 and 355.8018 corresponding to the chemical compositions, $C_{14}H_{11}ClN_4OS$+Na, $C_{14}H_{11}ClN_4S_2$+Na and $C_{14}H_{13}ClN_6S$+Na, respectively.

Apart from these, 2,4-bis(5-phenyl-1,3,4-oxadiazol-2-ylmethylthio)-6-methyl-pyrimidine (**42**) was prepared by the reaction of **35** with **39** in the presence of a catalytic amount of methanesulfonic acid. Similarly 2,4-bis(5-phenyl-1,3,4-thiadiazol-2-ylmethyl thio)-6-methyl-pyrimidine (**43**) and 2,4-bis(5-phenyl-4-amino-1,2,4-triazol-3-yl-methylthio)-6-methyl-pyrimidine (**44**) were also synthesized by the reaction of **36** with **40** and **37** with **41**. The compounds **42**, **43** and **44** were also prepared under conventional and ultrasonication methodologies (Scheme **III.5** & Table **III.1**). It was observed that all the target compounds were obtained in shorter reaction times with high yield under ultrasonication when compared with the conventional method.



SCHEME III.5

The IR spectra of **42**, **43** and **44** displayed absorption bands in the regions 1618-1645 and 1545-1588 cm^{-1} due to C=C and C=N. The compound **44** also exhibited absorption bands in the regions 3433-3469 & 3326-3356 cm^{-1} due to NH_2 (Table **III.2**). The ^1H NMR spectra of **42a** (Fig. **III.6**), **43a** and **44a** (Fig. **III.7**) presented four singlets at δ 2.34, 2.43, 2.35 (CH_3), 4.41, 4.49, 4.34 (CH_2-C_2'), 4.44, 4.51, 4.39 (CH_2-C_2") and 7.33, 7.40, 7.36 ppm (C_5-H). Moreover, the compound **44a** displayed two broad singlets at 5.48, 5.52 ppm due to two NH_2 groups of triazole rings which disappeared when D_2O was added (Table **III.3**). The ^{13}C NMR spectra of **42a** (Fig. **III.8**) showed signals at δ 24.7 (CH_3), 34.2, (CH_2-C_2') 34.7 (CH_2-C_2"), 114.3 (C-5), 159.7 (C-2'), 161.8 (C-2"), 163.4 (C-5'), 164.2 (C-5"), 165.4 (C-6), 170.5 (C-2), 172.7 (C-4), **43a** at 25.8 (CH_3), 35.2 (CH_2-C_2'), 35.6 (CH_2-C_2"), 115.6 (C-5), 165.7 (C-6), 168.6 (C-2'), 169.5 (C-2"), 171.6, (C-2), 172.5 (C-4), 176.8 (C-5'), 177.5 (C-5") and **44a** (Fig. **III.9**) at 24.2 (CH_3), 36.3 (CH_2-C_2'), 36.9 (CH_2-C_2"), 114.7 (C-5), 148.2 (C-3'), 149.0 (C-3"). 152.2 (C-5'), 152.9 (C-5") 164.5 (C-6), 170.8 (C-2), 172.6 ppm (C-4) (Table **III.3**). In the HRMS mass spectra of **42a** (Fig. **III.10**) and **44a**, the M+Na peaks observed at m/z 497.5486 and 525.6076 are in agreement with their chemical compositions, $C_{23}H_{18}N_6O_2S_2$+Na and $C_{23}H_{22}N_{10}S_2$+ Na. The 70 eV mass spectrum of **43a** (Scheme **III.6** & Fig. **III.11**) exhibited a low intense M^+ peak at m/z 506 corresponding to the molecular formula, $C_{23}H_{18}N_6S_4$. The disintegration of the M^+ in different modes led to the appearance of 2-methyl-5-phenyl-1,3,4-thiadiazole cation (m/z 175), 2-phenyl-5-(thiocyanatomethyl)-1,3,4-thiadiazole (m/z 233) and benzonitrile (m/z 103) radical cations. The phenyl cation (m/z 77) appeared with 100% intensity. Thus different daughter ions formed during the cleavage processes conclusively supports the structure of the compound.



SCHEME III.6

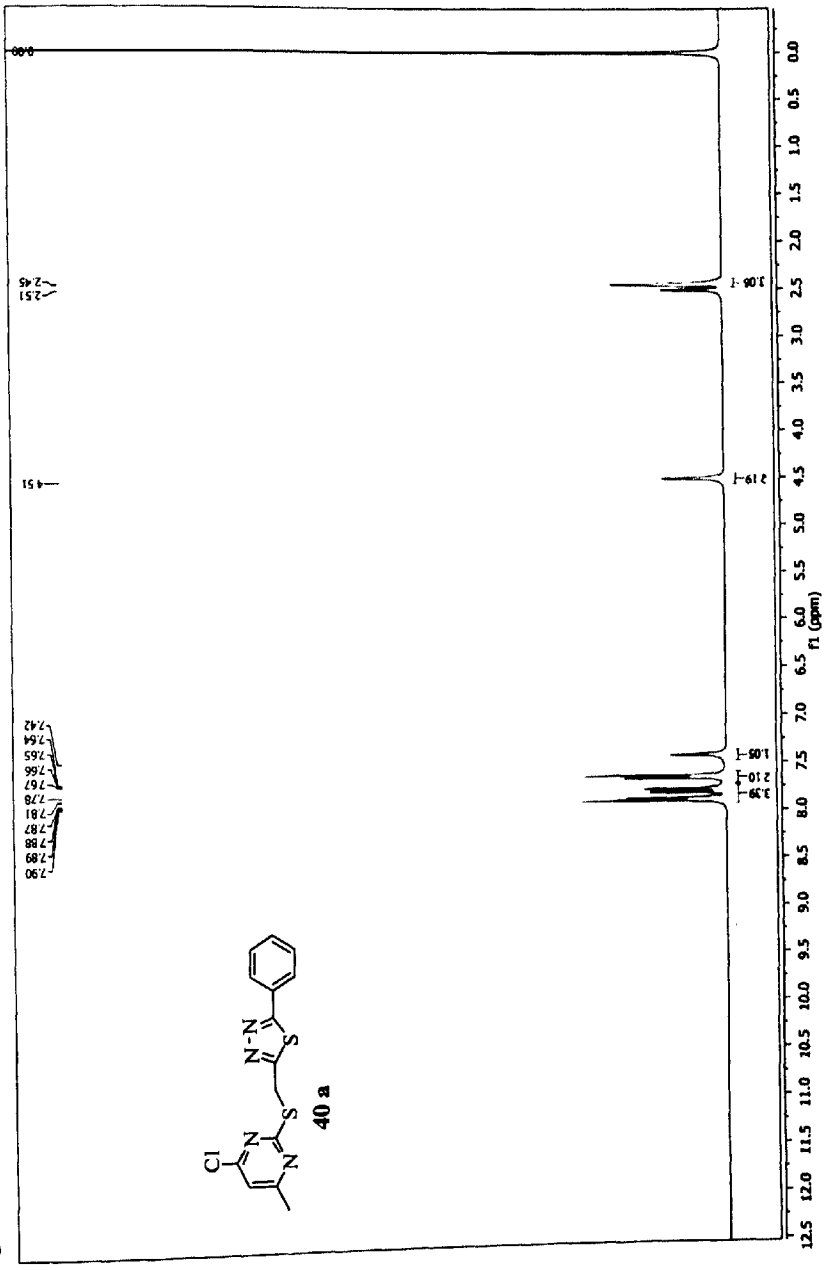


Fig. III. 1

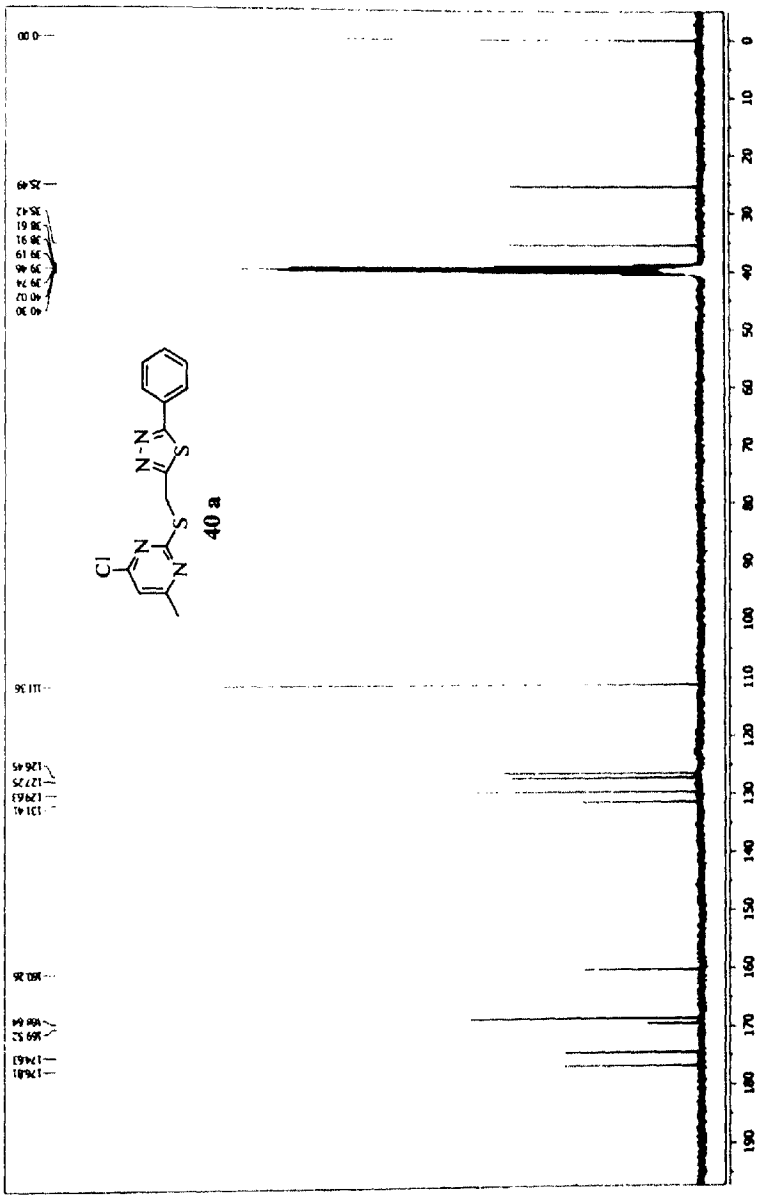
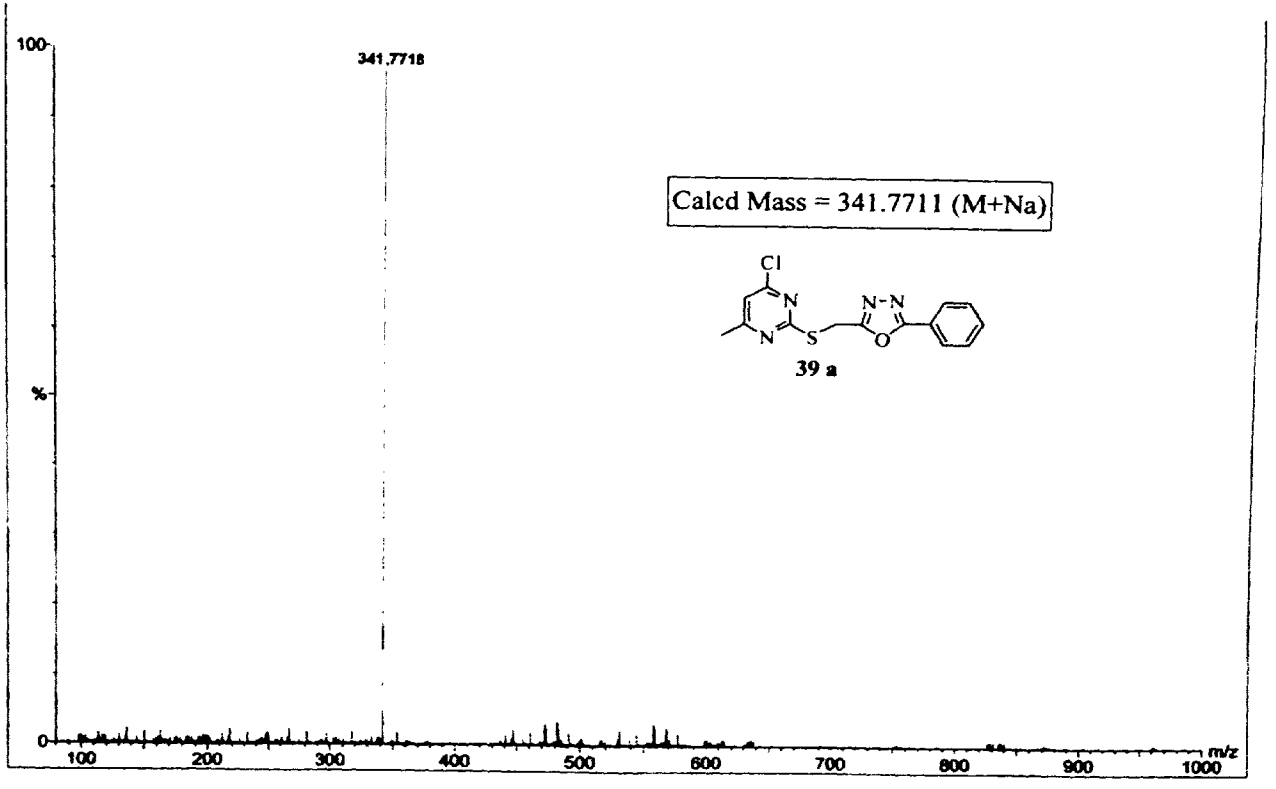


Fig. III. 2

Fig. III.3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%
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100
200
300
400
500
600
700
800
900
1000
m/z
Calcd Mass = 341.7711 (M+Na)
Cl
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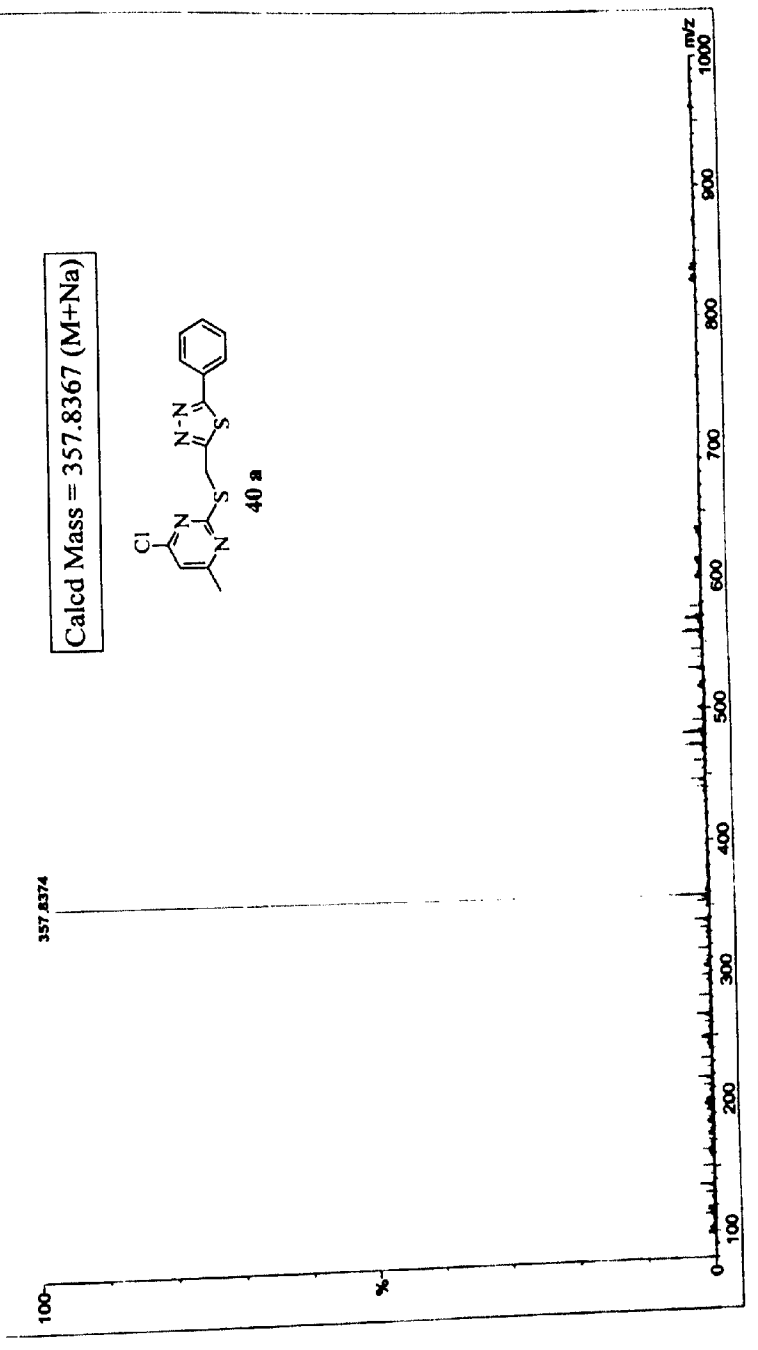
N
S
N-N
O
39 a


Calcd Mass = 357.8367 (M+Na)
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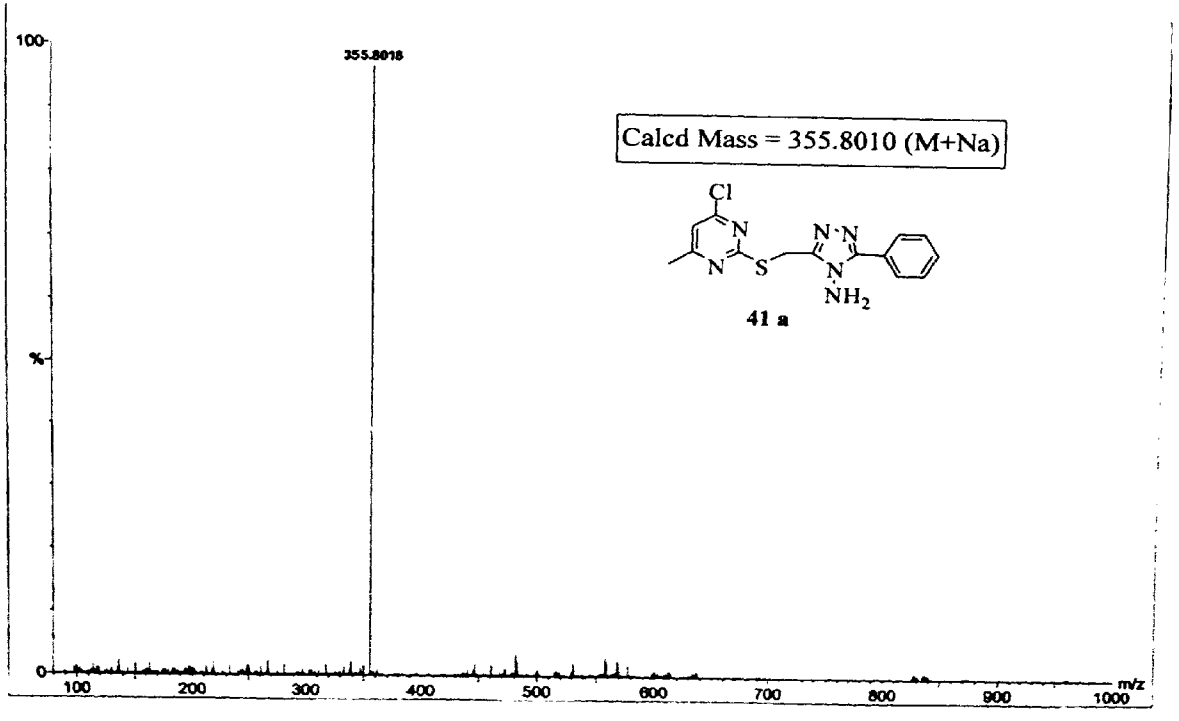
%
0
100
200
300
400
500
600
700
800
900
1000
m/z
Cl
N
N
S
S
N-N
40 a

Fig. III. 4

Fig. III.5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%
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100
200
300
400
500
600
700
800
900
1000
m/z
Calcd Mass = 355.8010 (M+Na)
Cl
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N
S
N
N
N
N
NH2

41 a

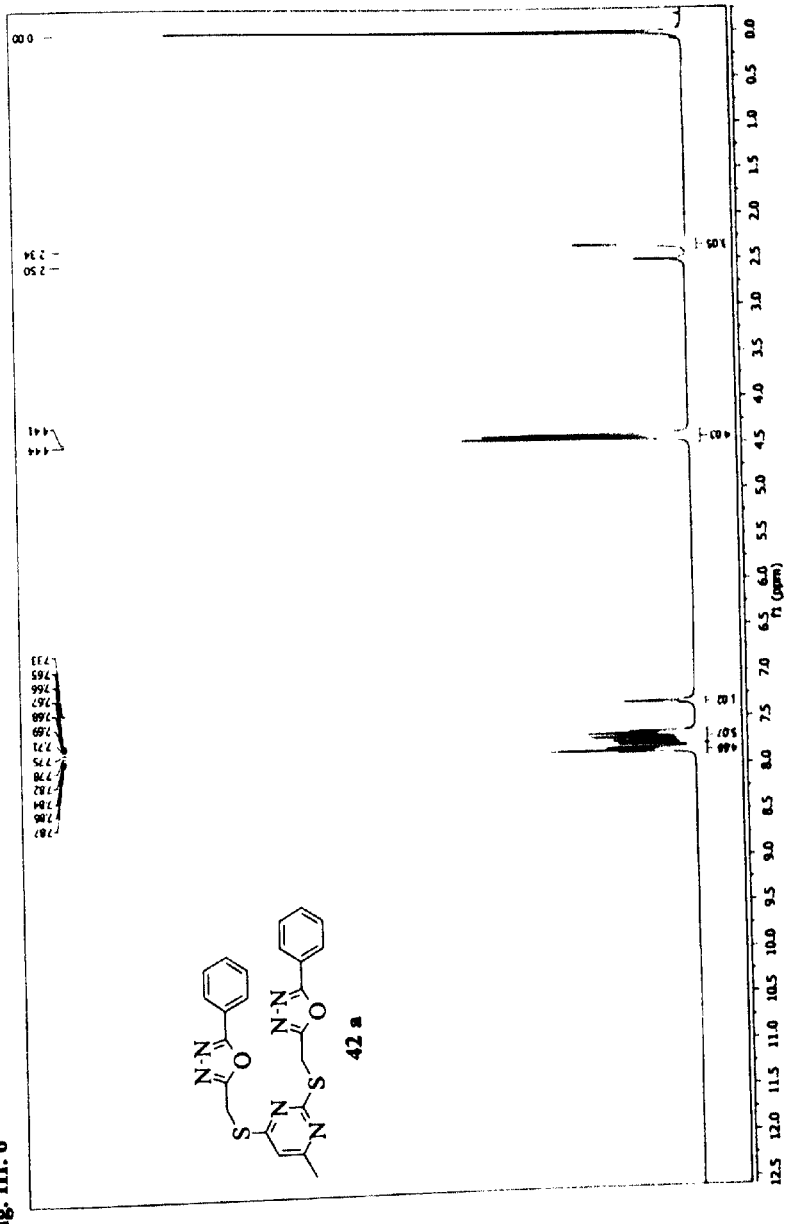


Fig. III. 6

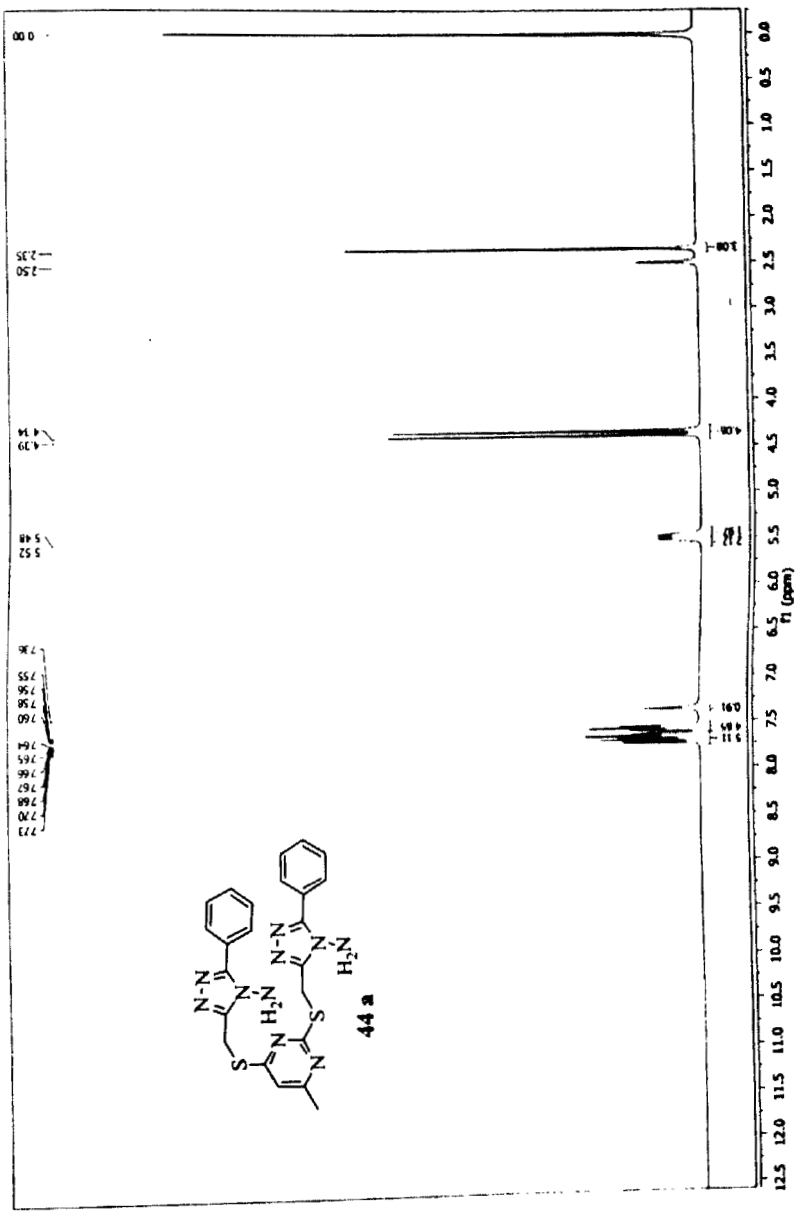


Fig. III. 7

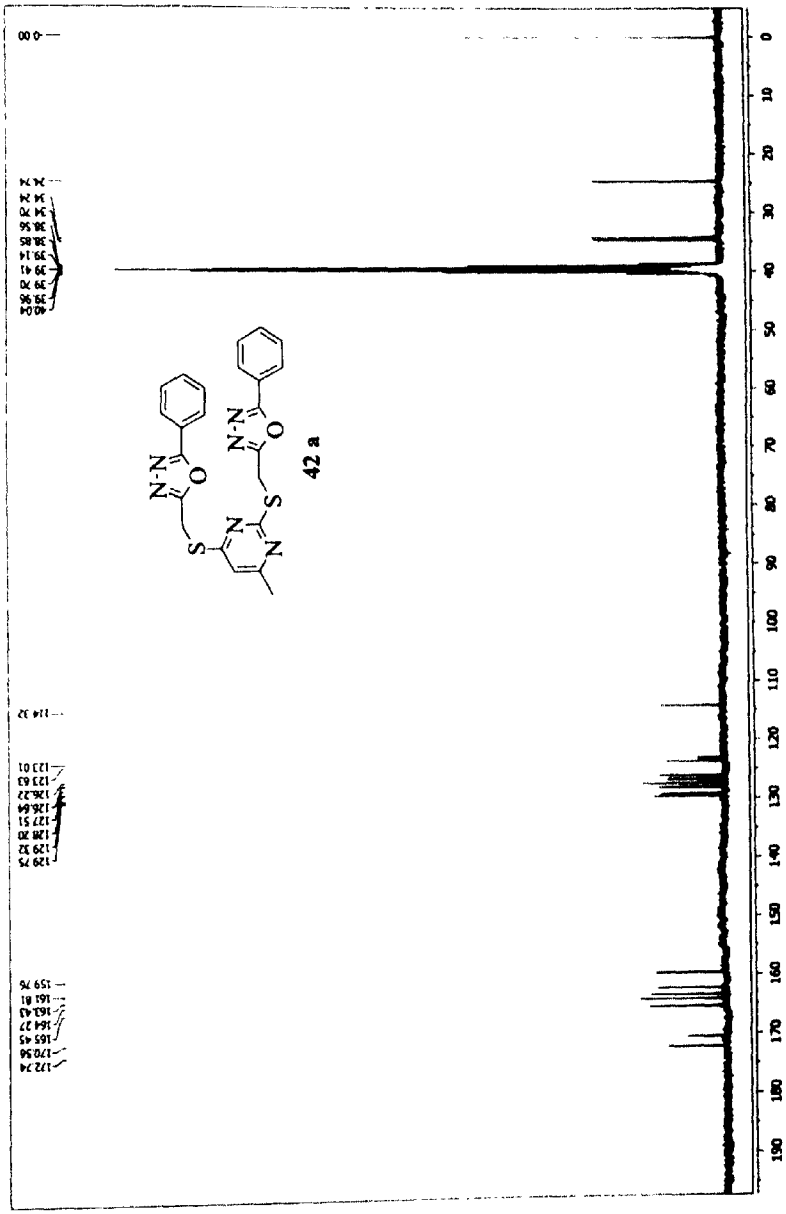


Fig. III.8

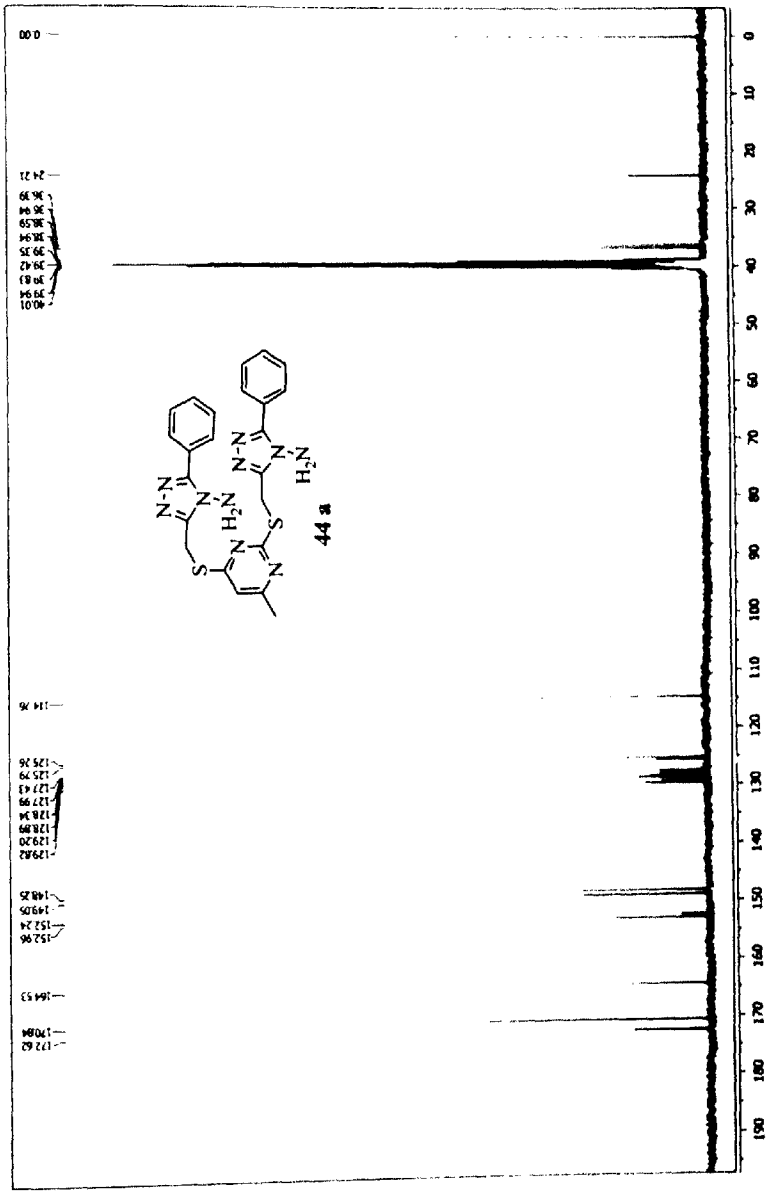
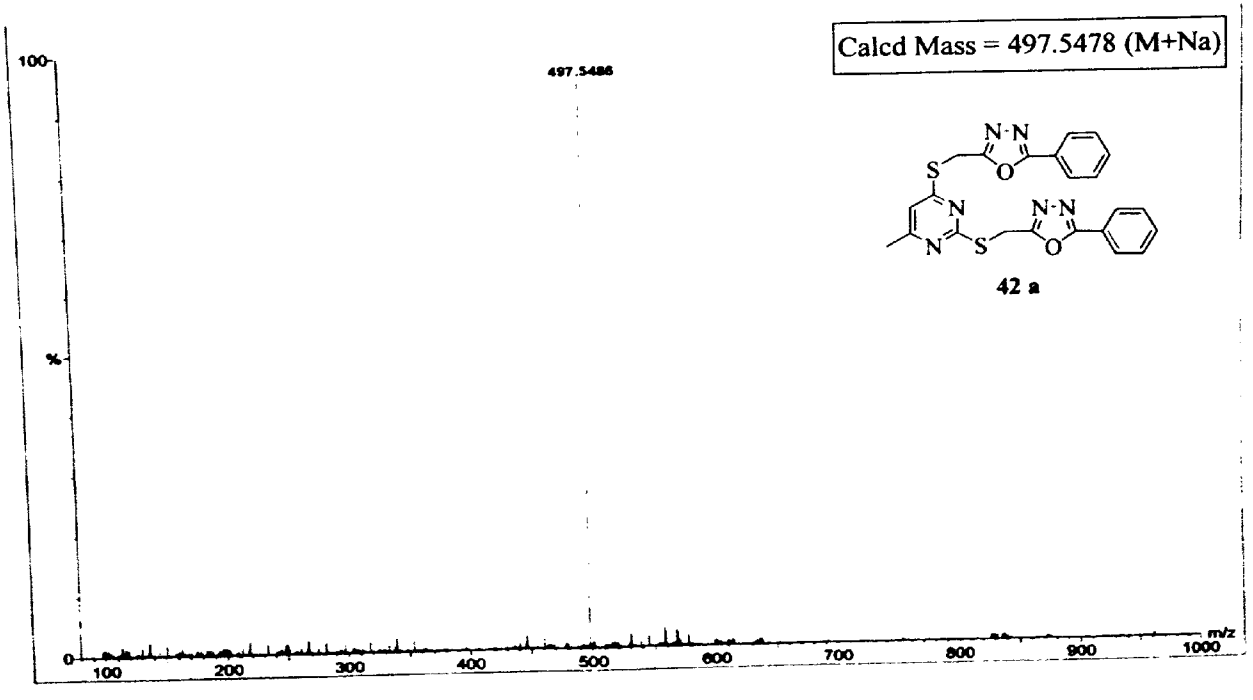


Fig. III. 9

Fig. III.10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%
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100
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300
400
500
600
700
800
900
1000
m/z
42 a

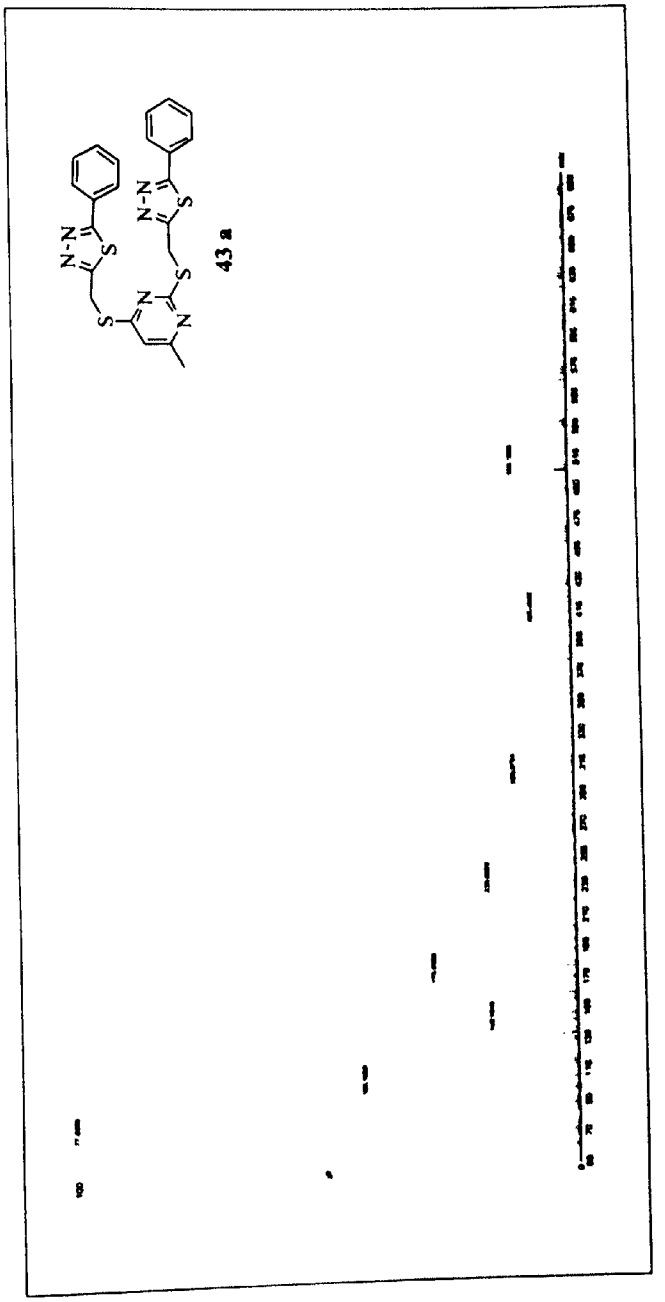


Fig. III. 11

TABLE III.I

Compd. No.	m.p. (°C)	Yield (%)	Mol. formula (Mol. wt.)	Found (Calcd.) %		
				C	H	N
39a	102-104	78 89*	$C_{14}H_{11}ClN_4OS$ (318.78)	52.87 (52.75)	3.50 (3.48)	17.84 (17.58)
39b	121-123	75 87*	$C_{15}H_{13}ClN_4O$ (332.80)	54.23 (54.13)	3.95 (3.94)	16.93 (16.83)
39c	136-138	79 90*	$C_{14}H_{10}Cl_2N_4OS$ 353.2210	47.71 (47.60)	2.87 (2.85)	16.09 (15.86)
39d	160-162	82 92*	$C_{14}H_{10}BrClN_4OS$ (397.67)	42.22 (42.28)	2.52 (2.53)	14.27 (14.09)
39e	128-130	81 91*	$C_{15}H_{13}ClN_4O_2S$ 348.8050	51.78 (51.65)	3.79 (3.76)	16.33 (16.06)
39f	142-144	87 95*	$C_{14}H_{10}ClN_5O_3S$ 363.7760	46.31 (46.22)	2.78 (2.77)	19.46 (19.25)
40a	125-127	76 87*	$C_{14}H_{11}ClN_4S_2$ (334.84)	50.34 (50.22)	3.34 (3.31)	16.99 (16.73)
40b	140-142	78 85*	$C_{15}H_{13}ClN_4S_2$ (348.86)	51.72 (51.64)	3.75 (3.76)	13.25 (16.06)
40c	150-153	74 89*	$C_{14}H_{10}Cl_2N_4S_2$ (369.28)	45.46 (45.53)	2.75 (2.73)	15.34 (15.17)
40d	164-166	79 91*	$C_{14}H_{10}BrClN_4S_2$ (413.73)	40.77 (40.64)	2.48 (2.44)	13.78 (13.54)
40e	145-147	77 84*	$C_{15}H_{13}ClN_4OS_2$ (364.86)	49.49 (49.38)	3.60 (3.59)	15.58 (15.36)

Contd...

40f	156-158	79 90*	$C_{14}H_{10}ClN_5O_2S_2$ (379.83)	44.35 (44.27)	2.64 (2.65)	18.60 (18.44)
41a	117-119	80 88*	$C_{14}H_{13}ClN_6S$ (332.81)	50.58 (50.52)	3.95 (3.94)	25.41 (25.25)
41b	140-142	78 86*	$C_{15}H_{15}ClN_6S$ (346.83)	5.04 (51.94)	4.38 (4.36)	24.46 (25.25)
41c	162-164	81 92*	$C_{14}H_{12}Cl_2N_6S$ (367.25)	45.82 (45.79)	3.31 (3.29)	23.07 (22.88)
41d	155-157	72 89*	$C_{14}H_{12}BrCl_2N_6S$ (411.70)	40.79 (40.84)	2.93 (2.94)	20.26 (20.41)
41e	158-160	74 91*	$C_{15}H_{15}ClN_6OS$ (362.83)	49.78 (44.65)	4.19 (4.17)	23.44 (23.16)
41f	153-155	76 90*	$C_{14}H_{12}ClN_7O_2S$ (377.80)	44.64 (44.51)	3.24 (3.20)	26.23 (25.95)
42a	169-171	79 93*	$C_{21}H_{18}N_6O_2S_2$ (474.55)	58.30 (58.21)	3.84 (3.82)	17.91 (17.71)
42b	178-180	76 92*	$C_{25}H_{22}N_6O_2S_2$ (502.61)	59.86 (59.74)	4.44 (4.41)	16.96 (16.72)
42c	192-194	75 89*	$C_{23}H_{16}Cl_2N_6O_2S_2$ (543.44)	50.96 (50.83)	3.02 (2.97)	15.72 (15.46)
42d	232-234	77 91*	$C_{23}H_{16}Br_2N_6O_2S_2$ (632.34)	43.79 (43.69)	2.27 (2.25)	13.45 (13.29)
42e	183-185	82 90*	$C_{25}H_{22}N_6O_4S_2$ (534.44)	56.28 (56.17)	4.14 (4.15)	15.96 (15. 72)
42f	199-201	85 92*	$C_{21}H_{16}N_8O_6S_2$ (564.55)	49.05 (48.93)	2.89 (2.86)	20.12 (19.85)
43a	181-183	83 90*	$C_{23}H_{18}N_6S_4$ (506.67)	54.62 (54.52)	3.59 (3.58)	16.79 (16.59)

Contd...

43b	187-189	73 88*	$C_{25}H_{22}N_6S_4$ (534.73)	56.27 (56.15)	4.19 (4.15)	15.95 (15.72)
43c	195-197	80 92*	$C_{23}H_{16}Cl_2N_6S_4$ (575.57)	47.94 (47.99)	2.81 (2.80)	14.74 (14.60)
43d	242-244	78 87*	$C_{23}H_{16}Br_2N_6S_4$ (664.48)	41.66 (41.57)	2.45 (2.43)	12.84 (12.65)
43e	190-192	76 92*	$C_{25}H_{22}N_6O_2S_4$ (566.66)	53.12 (52.98)	3.97 (3.91)	15.12 (14.83)
43f	206-208	77 89*	$C_{23}H_{16}N_8O_4S_4$ (596.67)	44.42 (46.30)	2.74 (2.70)	19.03 (18.78)
44a	184-186	72 87*	$C_{21}H_{22}N_{10}S_2$ (502.14)	55.06 (54.96)	4.44 (4.41)	28.08 (27.87)
44b	197-199	80 92*	$C_{25}H_{26}N_{10}S_2$ (530.67)	56.71 (56.58)	4.98 (4.94)	28.13 (26.39)
44c	247-249	76 90*	$C_{23}H_{20}Cl_2N_{10}S_2$ (571.50)	41.94 (41.83)	3.07 (3.05)	21.42 (21.21)
44d	210-212	78 89*	$C_{23}H_{20}Br_2N_{10}S_2$ (660.40)	48.43 (48.34)	3.03 (3.53)	12.62 (12.41)
44e	202-204	74 88*	$C_{25}H_{26}N_{10}O_2S_2$ (562.66)	53.50 (53.36)	4.71 (4.66)	25.18 (24.89)
44f	216-218	79 91*	$C_{23}H_{20}N_{12}O_4S_2$ (592.61)	46.73 (46.61)	3.43 (3.40)	28.61 (28.36)

*Yields under ultrasonication

TABLE III.2

Compd. No.	IR (KBr) cm^{-1}			
	NH_2		C=C	C=N
39a	-	-	1623	1565
39b	-	-	1624	1568
39c	-	-	1631	1566
39d	-	-	1635	1580
39e	-	-	1630	1586
39f	-	-	1632	1579
40a	-	-	1631	1573
40b	-	-	1626	1575
40c	-	-	1635	1572
40d	-	-	1620	1585
40e	-	-	1626	1578
40f	-	-	1636	1575
41a	3446	3338	1635	1562
41b	3439	3334	1629	1578
41c	3470	3360	1632	1552
41d	3453	3341	1629	1564
41e	3461	3352	1623	1578
41f	3480	3371	1633	1575
42a	-	-	1645	1586
42b	-	-	1632	1566
42c	-	-	1640	1575
42d	-	-	1637	1558

Contd...

42e	-	-	1625	1560
42f	-	-	1621	1545
43a	-	-	1619	1566
43b	-	-	1632	1561
43c	-	-	1631	1559
43d	-	-	1632	1582
43e	-	-	1630	1583
43f	-	-	1627	1561
44a	3462	3354	1625	1579
44b	3455	3349	1622	1576
44c	3464	3350	1618	1582
44d	3441	3326	1625	1588
44e	3433	3331	1627	1586
44f	3469	3356	1625	1574

TABLE III.3

Compd. No.	^{1}H-NMR ($CDCl_3$ / DMSO-d_6) δ, ppm	^{13}C NMR($CDCl_3$ / DMSO-d_6) δ, ppm
39a	2.35 (s, 3H, CH_3), 4.42 (s, 2H, CH_2), 7.43 (s, 1H, C_5-H), 7.50-7.96 (m, 5H, Ar- H)	24.9 (CH_3), 34.5 (CH_2), 111.6 (C-5), 160.4 (C-4), 162.7 (C-2'), 164.9 (C-5'), 169.8 (C-6), 173.4 (C-2), 124.5, 126.9, 127.4, 128.4 (aromatic carbons)
39b	2.24 (s, 3H, Ar-CH_3), 2.39 (s, 3H , CH_3), 4.40 (s, 2H, CH_2), 7.42 (s, 1H, C_5-H), 7.68-7.84 (m, 4H, Ar-H),	22.6 (Ar-CH_3), 24.2 (CH_3), 34.0 (CH_2), 111.0 (C-5), 156.7 (C-4), 162.2 (C-2'), 164.3 (C-5'), 168.7 (C-6), 172.6 (C-2), 121.9, 125.4, 126.7, 133.5 (aromatic carbons)
39c	2.41 (s, 3H, CH_3), 4.42 (s, 2H, CH_2), 7.45 (s, 1H, C_5-H), 7.58-7.89 (m, 4H, Ar-H)	25.4 (CH_3), 35.4 (CH_2), 111.7 (C-5), 158.6 (C-4), 163.5 (C-2'), 165.6 (C-5'), 170.6 (C-6), 174.7 (C-2), 123.6, 124.8, 127.2, 135.5 (aromatic carbons)
39d	2.39 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.40 (s, 1H, C_5-H), 7.65-7.73 (m, 4H, Ar-H)	25.0 (CH_3), 35.1 (CH_2), 111.5 (C-5), 158.2 (C-4), 163.1 (C-2'), 165.2 (C-5'), 170.2 (C-6), 174.1 (C-2), 124.7, 127.5, 129.2, 137.6 (aromatic carbons)
39e	2.37 (s, 3H, CH_3), 3.76 (s, 3H, Ar-OCH_3), 4.26 (s, 2H, CH_2), 7.35 (s, 1H, C_5-H), 7.44-7.62 (m, 4H, Ar-H)	23.7 (CH_3), 33.7 (CH_2), 55.4 (Ar-OCH_3), 110.7 (C-5), 156.1 (C-4), 162.7 (C-2'), 164.9 (C-5'), 168.2 (C-6), 172.0 (C-2), 117.5, 119.2, 122.5, 162.3 (aromatic carbons)
39f	2.40 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.47 (s, 1H, C_5-H), 7.96-8.27 (m, 4H, Ar-H)	25.4 (CH_3), 35.8 (CH_2), 111.8 (C-5), 158.9 (C-4), 163.8 (C-2'), 165.7 (C-5'), 171.5 (C-6), 175.8 (C-2), 129.4, 132.4, 134.2, 153.6 (aromatic carbons)

Contd...

40a	2.45 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 7.42 (s, 1H, C_5-H), 7.64-7.90 (m, 5H, Ar-H)	25.4 (CH_3), 35.4 (CH_2), 111.3 (C-5), 160.2 (C-4), 168.6 (C-6), 169.5 (C-2'), 174.6 (C-2), 176.8 (C-5'), 126.4, 127.2, 129.6, 131.4 (aromatic carbons)
40b	2.38 (s, 3H ,CH_3), 2.27 (s, 3H, Ar-CH_3), 4.32 (s, 2H, CH_2), 7.37 (s, 1H, C_5-H), 7.48-7.70 (m, 4H, Ar-H)	23.5 (Ar-CH_3), 25.7 (CH_3), 35.7 (CH_2), 110.0 (C-5), 158.0 (C-4), 168.4 (C-6), 169.2 (C-2'), 174.0 (C-2), 176.4 (C-5'), 127.4, 129.5, 130.9, 131.8 (aromatic carbons)
40c	2.43 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.46 (s, 1H, C_5-H), 7.58-7.87 (m, 4H, Ar-H)	26.5 (CH_3), 35.1 (CH_2), 111.6 (C-5), 158.9 (C-4), 169.2 (C-6), 170.5 (C-2'), 175.5 (C-2), 177.6 (C-5'), 123.1, 129.7, 132.1, 132.5 (aromatic carbons)
40d	2.40 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.42 (s, 1H, C_5-H), 7.72-7.90 (m, 4H, Ar-H)	26.1 (CH_3), 36.2 (CH_2), 111.4 (C-5), 158.4 (C-4), 168.8 (C-6), 170.1 (C-2'), 174.7 (C-2), 177.2 (C-5'), 128.9, 129.3, 131.6, 134.3 (aromatic carbons)
40e	2.32 (s, 3H, CH_3), 3.79 (s, 3H, Ar-OCH_3), 4.30 (s, 2H, CH_2), 7.30 (s, 1H, C_5-H), 7.40-7.71 (m, 4H, Ar-H)	24.2 (CH_3), 33.5 (CH_2), 56.8 (Ar-OCH_3), 110.6 (C-5), 157.4 (C-4), 167.5 (C-6), 168.4 (C-2'), 173.2 (C-2), 175.7 (C-5'), 119.4, 125.8, 128.5, 160.6 (aromatic carbons)
40f	2.47 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 7.48 (s, 1H, C_5-H), 8.02-8.28 (m, 4H, Ar-H)	27.3 (CH_3), 37.2 (CH_2), 111.9 (C-5), 159.5 (C-4), 169.7 (C-6), 170.8 (C-2'), 176.2 (C-2), 178.5 (C-5'), 128.8, 130.9, 132.2, 147.9 (aromatic carbons)
41a	2.36 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 5.62 (bs, 2H, NH_2), 7.35 (s, 1H, C_5-H), 7.57-7.76 (m, 5H, Ar-H)	24.5 (CH_3), 36.5 (CH_2), 111.7 (C-5), 148.6 (C-3'), 151.8 (C-5'), 160.8 (C-4), 168.4 (C-6), 173.6 (C-2), 125.6, 127.8, 128.4, 129.5 (aromatic carbons)

Contd...

41b	2.23 (s, 3H, Ar-CH_3), 2.32 (s, 3H ,CH_3), 4.28 (s, 2H, CH_2), 5.54 (bs, 2H, NH_2), 7.32 (s, 1H, C_5-H), 7.56-7.87 (m, 4H, Ar-H)	22.4(Ar-CH_3), 24.0 (CH_3), 35.4 (CH_2), 110.3 (C-5), 148.0 (C-3'), 151.3 (C-5'), 152.5 (C-4), 168.6 (C-6), 173.6 (C-2), 125.7, 127.5, 129.5, 131.7 (aromatic carbons)
41c	2.41 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 5.62 (bs, 2H, NH_2), 7.43 (s, 1H, C_5-H), 7.65-7.96 (m, 4H, Ar-H)	25.4 (CH3), 36.7 (CH_2), 111.5 (C-5), 149.7 (C-3'), 152.5 (C-5'), 153.4 (C-4), 169.8 (C-6), 174.4 (C-2), 123.4, 129.6, 132.1, 134.5 (aromatic carbons)
41d	2.37 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 5.60 (bs, 2H, NH_2), 7.40 (s, 1H, C_5-H), 7.63-7.78 (m, 4H, Ar-H)	24.7 (CH_3), 36.2 (CH_2), 111.0 (C-5), 149.2 (C-3'), 151.6 (C-5'), 152.6 (C-4), 169.2 (C-6), 173.6 (C-2), 128.7, 128.9, 129.3, 134.2 (aromatic carbons)
41e	2.30 (s, 3H, CH_3), 3.72 (s, 3H, Ar-OCH_3), 4.25 (s, 2H, CH_2), 5.49 (bs, 2H, NH_2), 7.36 (s, 1H, C_5-H), 7.38-7.67 (m, 4H, Ar-H)	24.1 (CH_3), 35.1 (CH_2), 55.2 (Ar-OCH_3), 110.7 (C-5), 147.8 (C-3'), 150.3 (C-5'), 151.4 (C-4), 168.0 (C-6), 172.5 (C-2), 116.5, 122.7, 131.4, 160.7 (aromatic carbons)
41f	2.43 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 5.65 (bs, 2H, NH_2), 7.49 (s, 1H, C_5-H), 8.07-8.38 (m, 4H, Ar-H)	26.6 (CH_3), 37.5 (CH_2), 112.6 (C-5), 150.4 (C-3'), 153.5 (C-5'), 154.6 (C-4), 170.5 (C-6), 175.6 (C-2), 122.4, 127.0, 136.7, 147.2 (aromatic carbons)
42a	2.34 (s, 3H, CH_3), 4.41 (s, 2H, CH_2-C_2'), 4.44 (s, 2H, CH_2-C_2''), 7.33 (s, 1H, C_5-H), 7.65-7.87 (m, 10H, Ar-H)	24.7 (CH_3), 34.2 (CH_2-C_2'), 34.7 (CH_2-C_2''), 114.3 (C-5), 159.7 (C-2'), 161.8 (C-2''), 163.4 (C-5'), 164.2 (C-5''), 165.4 (C-6), 170.5 (C-2), 172.7 (C-4), 123.0, 123.6 126.2, 126.6, 127.5, 128.2, 129.3, 129.7 (aromatic carbons)
42b	2.24 & 2.29 (s, 6H, Ar-CH_3), 2.32 (s, 3H, CH_3), 4.25 (s, 2H, CH_2-C_2'), 4.28 (s, 2H, CH_2-C_2''), 7.30 (s, 1H, C_5-H), 7.45-7.76 (m, 8H, Ar-H)	22.3 & 22.8 (Ar-CH_3), 24.0 (CH_3), 35.0 (CH_2-C_2'), 35.6 (CH_2-C_2''), 113.7 (C-5), 159.4 (C-2'), 160.3 (C-2''), 163.0 (C-5'), 163.8 (C-5''), 165.3 (C-6), 170.1 (C-2), 172.2 (C-4), 121.2, 121.8, 124.6, 125.8, 126.5, 127.2, 132.9, 133.6 (aromatic carbons)

Contd...

42c	2.36 (s, 3H, CH_3), 4.33 (s, 2H, CH_2-$C_{2'}$), 4.36 (s, 2H, CH_2- $C_{2''}$), 7.41 (s, 1H, C_5-H), 7.69-7.95 (m, 8H, Ar-H)	25.6 (CH_3), 36.4 (CH_2-$C_{2'}$), 36.7 (CH_2-$C_{2''}$), 115.6 (C-5), 160.5 (C-2'), 161.7 (C-2"), 162.5 (C-5'), 163.9 (C-5"), 166.5 (C-6), 171.6 (C-2), 173.8 (C-4), 122.7, 123.5, 124.7, 125.2, 127.5, 128.2, 134.8, 135.7 (aromatic carbons)
42d	2.30 (s, 3H, CH_3), 4.29 (s, 2H, CH_2-$C_{2'}$), 4.34 (s, 2H, CH_2-$C_{2''}$), 7.37 (s, 1H, C_5-H), 7.72-7.90 (m, 8H, Ar-H)	25.2 (CH_3), 36.1 (CH_2-$C_{2'}$), 36.5 (CH_2-$C_{2''}$) 114.7 (C-5), 159.6 (C-2'), 161.2 (C-2"), 162.7 (C-5'), 163.0 (C-5"), 166.0 (C-6), 171.0 (C-2), 173.3 (C-4), 124.2, 124.9, 127.2, 127.9, 129.0, 129.8, 137.2, 137.9 (aromatic carbons)
42e	2.29 (s, 3H, CH_3), 3.75 & 3.79 (s, 6H, Ar-OCH_3), 4.22 (s, 2H, CH_2-$C_{2'}$), 4.27 (s, 2H, CH_2-$C_{2''}$), 7.35 (s, 1H, C_5-H), 7.56-7.74 (m, 8H, Ar-H)	23.6 (CH_3), 34.9 (CH_2-$C_{2'}$), 35.0 (CH_2-$C_{2''}$), 54.2 & 54.9 (Ar-OCH_3), 113.0 (C-5), 159.4 (C-2'), 160.1 (C-2"), 162.8 (C-5"), 163.6 (C-5'), 164.2 (C-6), 169.6 (C-2), 171.6 (C-4), 117.2, 117.9, 119.2, 119.8, 122.3, 122.9, 161.1, 162.8 (aromatic carbons)
42f	2.38 (s, 3H,CH_3), 4.34 (s, 2H, CH_2-$C_{2'}$), 4.39 (s, 2H, CH_2-$C_{2''}$), 7.46 (s, 1H, C_5-H), 8.02-8.17 (m, 8H, Ar-H)	25.9 (CH_3), 37.2 (CH_2-$C_{2'}$), 37.6 (CH_2-$C_{2''}$), 116.8 (C-5), 160.7 (C-2'), 161.6 (C-2"), 163.7 (C-5'), 164.5 C-5"), 167.2 (C-6), 171.9 (C-2), 174.5 (C-4), 129.6, 130.2, 132.2, 132.9, 134.1, 134.7, 152.7, 153.8 (aromatic carbons)
43a	2.43 (s, 3H, CH_3), 4.49 (s, 2H, CH_2-$C_{2'}$), 4.51 (s, 2H, CH_2-$C_{2''}$), 7.40 (s, 1H, C_5-H), 7.60-7.78 (m, 10H, Ar- H)	25.8 (CH_3), 35.2 (CH_2-$C_{2'}$), 35.6 (CH_2-$C_{2''}$), 115.6 (C-5), 165.7 (C-6), 168.6 (C-2'), 169.5 (C-2"), 171.6, (C-2), 172.5 (C-4), 176.8 (C-5'), 177.5 (C-5"), 127.2, 128.4, 129.2, 129.8, 130.4, 131.2, 133.4, 133.9 (aromatic carbons)

Contd....

43b	2.29 & 2.32 (s, 6H, Ar-CH_3), 2.38 (s, 3H, CH_3), 4.26 (s, 2H, CH_2-C_2'), 4.28 (s, 2H, CH_2-C_2"), 7.34 (s, 1H, C_5-H), 7.42-7.68 (m, 8H, Ar-H)	21.7 & 22.5 (Ar-CH_3), 25.7 (CH_3), 36.2 (CH_2-C_2'), 37.0 (CH_2-C_2"), 115.0 (C-5), 165.1 (C-6), 168.2 (C-2'), 168.9 (C-2"), 171.2 (C-2), 173.4 (C-4), 175.6 (C-5'), 177.1 (C-5"), 127.3, 127.9, 129.4, 130.1, 130.7, 131.5, 131.9, 132.5 (aromatic carbons)
43c	2.46 (s, 3H, CH_3), 4.35 (s, 2H, CH_2-C_2'), 4.39 (s, 2H, CH_2-C_2"), 7.64-7.88 (m, 8H, Ar-H), 7.45 (s, 1H, C_5-H)	26.4 (CH_3), 37.4 (CH_2-C_2'), 38.6 (CH_2-C_2"), 116.7 (C-5), 166.8 (C-6), 168.6 (C-2"), 170.1 (C-2'), 172.7 (C-2), 174.5 (C-4), 177.5 (C-5'), 178.2 (C-5"), 123.5, 124.3, 129.2, 129.9, 131.6, 132.3, 134.2, 134.8 (aromatic carbons)
43d	2.43 (s, 3H, CH_3), 4.30 (s, 2H, CH_2-C_2'), 4.34 (s, 2H, CH_2-C_2"), 7.41 (s, 1H, C_5-H), 7.71-7.96 (m, 8H, Ar-H)	26.1 (CH_3), 37.2 (CH_2-C_2'), 38.2 (CH_2-C_2"), 116.0 (C-5), 166.2 (C-6), 169.5 (C-2'), 169.7 (C-2"), 172.3 (C-2), 174.0 (C-4), 176.7 (C-5'), 177.3 (C-5"), 127.8, 128.4, 129.2, 129.8, 130.4, 131.6, 133.8, 134.5 (aromatic carbons)
43e	3.78 & 3.81(s, 6H, Ar-OCH_3), 2.32 (s, 3H, CH_3), 4.22 (s, 2H, CH_2-C_2'), 4.26 (s, 2H, CH_2-C_2"), 7.32 (s, 1H, C_5-H), 7.36-7.67 (m, 8H, Ar-H)	25.2 (CH_3), 35.4 (CH_2-C_2'), 36.4 (CH_2-C_2"), 55.3 & 55.9 (Ar-OCH_3), 114.6 (C-5), 164.6 (C-6), 167.4 (C-2'), 168.7 (C-2"), 170.6 (C-2), 172.6 (C-4), 175.4 (C-5'), 176.2 (C-5"), 113.7, 114.6, 125.7, 126.4, 128.2, 128.9, 159.7, 160.4 (aromatic carbons)
43f	2.49 (s, 3H, CH_3), 4.38 (s, 2H, CH_2-C_2'),4.40 (s, 2H, CH_2-C_2"), 7.48 (s, 1H, C_5-H), 8.03-8.25 (m, 8H, Ar-H)	26.9 (CH_3), 38.2 (CH_2-C_2'), 38.7 (CH_2-C_2"), 117.0 (C-5), 167.8 (C-6), 169.4 (C-2'), 170.8 (C-2"), 173.4 (C-2), 174.8 (C-4), 178.3 (C-5'), 178.9 (C-5"), 128.2, 128.9, 130.2, 131.2, 132.4, 133.2, 147.2, 147.8 (aromatic carbons)

Contd...

44a	2.35 (s, 3H,CH_3), 4.34 (s, 2H, CH_2-$C_{2'}$), 4.39 (s, 2H, CH_2-$C_{2''}$), 5.48 (bs, 2H, NH_2), 5.52 (bs, 2H, NH_2-), 7.36 (s, 1H, C_5-H), 7.55-7.73 (m, 10H, Ar- H)	24.2 (CH_3), 36.3 (CH_2-$C_{2'}$), 36.9 (CH_2-$C_{2''}$), 114.7 (C-5), 148.2 (C-3'), 149.0 (C-3''), 152.2 (C-5'), 152.9 (C-5'') 164.5 (C-6), 170.8 (C-2), 172.6 (C-4), 125.2, 125.7, 127.4, 127.9, 128.3, 128.8, 129.2, 129.8 (aromatic carbons)
44b	2.26 & 2.31 (s, 6H, Ar-CH_3), 2.41 (s, 3H ,CH_3), 4.21 (s, 2H, CH_2-$C_{2'}$), 4.23 (s, 2H, CH_2-$C_{2''}$), 5.46 (bs, 2H, NH_2), 5.50 (bs, 2H, NH_2), 7.32 (s, 1H, C_5-H), 7.65-7.96 (m, 8H, Ar-H)	21.2 & 22.6 (Ar-CH_3), 25.1 (CH_3), 33.7 (CH_2-$C_{3'}$), 34.0 (CH_2-$C_{3''}$), 114.2 (C-5), 148.6 (C-3''), 149.2 (C-3'), 152.0 (C-5''), 152.7 (C-5'), 164.0 (C-6), 170.4 (C-2), 171.8 (C-4), 124.6, 125.4, 126.8 127.9, 128.4, 129.2, 131.0, 131.8 (aromatic carbons)
44c	2.43 (s, 3H, CH_3), 4.30 (s, 2H, CH_2-$C_{2'}$), 4.34 (s, 2H, CH_2-$C_{2''}$), 5.53 (bs, 2H, NH_2), 5.58 (bs, 2H, NH_2), 7.44 (s, 1H, C_5-H), 7.74-7.86 (m, 8H, Ar-H)	26.3 (CH_3), 35.5 (CH_2-$C_{3'}$), 35.9 (CH_2-$C_{3''}$), 115.8 (C-5), 149.8 (C-3'), 150.6 (C-3''), 152.0 (C-5'), 153.0 (C-5''), 165.6 (C-6), 171.7 (C-2), 173.5 (C-4), 122.7, 123.5, 128.9, 129.5, 132.2, 132.8, 134.6, 135.2 (aromatic carbons)
44d	2.40 (s, 3H, CH_3), 4.26 (s, 2H, CH_2-$C_{2'}$), 4.29 (s, 2H, CH_2-$C_{2''}$), 5.49 (bs, 2H, NH_2), 5.57 (bs, 2H, NH_2), 7.41 (s, 1H, C_5-H), 7.67-7.86 (m, 8H, Ar-H)	26.0 (CH_3), 35.0 (CH_2-$C_{3'}$), 35.7 (CH_2-$C_{3''}$), 115.3 C-5), 149.1 (C-3'), 150.0 (C-3''), 152.4 (C-5'), 153.3 (C-5''), 165.2 (C-6), 171.2 (C-2), 172.8 (C-4), 128.2, 128.8, 129.4, 129.9, 130.1, 130.7,133.7, 134.5 (aromatic carbons)
44e	2.31 (s, 3H, CH_3), 3.70 & 3.74 (s, 6H, Ar-OCH_3), 4.19 (s, 2H, CH_2-$C_{2'}$), 4.24 (s, 2H, CH_2-$C_{2''}$), 5.41 (bs, 2H, NH_2), 5.48 (bs, 2H, NH_2), 7.30 (s, 1H, C_5-H), 7.47- 7.78 (m, 8H, Ar-H)	24.6 (CH_3), 33.3 (CH_2-$C_{3'}$), 34.5 (CH_2-$C_{3''}$), 54.2 & 55.2 (Ar-OCH_3), 113.7 (C-5), 148.0 (C-3'), 148.8 (C-3''), 150.5 (C-5'), 151.0 (C-5''), 163.6 (C-6), 169.4 (C-2), 171.0 (C-4), 115.6, 116.4, 122.3, 122.9, 1231.2, 131.9, 160.2, 160.8 (aromatic carbons)
44f	2.45 (s, 3H, CH_3), 4.33(s, 2H, CH_2-$C_{2'}$), 4.36 (s, 2H, CH_2-$C_{2''}$), 7.46 (s, 1H, C_5-H), 5.60 (bs, 2H, NH_2), 5.64 (bs, 2H, NH_2), 8.05-8.20 (m, 8H, Ar-H)	26.8 (CH_3), 36.3 (CH_2-$C_{3'}$), 36.8 (CH_2-$C_{3''}$), 116.5 (C-5), 149.3 (C-3'), 150.2 (C-3''), 153.4 (C-5'), 154.7 (C-5''), 164.8 (C-6), 172.5 (C-2), 174.0 (C-4), 121.6, 122.2, 127.2, 127.9, 135.6, 136.4, 147.2, 147.9 (aromatic carbons)

EXPERIMENTAL

2-(Chloromethyl)-5-aryl-1,3,4-oxadiazole (32)

The preparation of this compound involves the following steps.

(i) Esterification of aromatic acid

(ii) Reaction of aromatic ester with hydrazine hydrate

(iii) Cyclocondensation of arylacid hydrazide with chloroacetic acid

i) Preparation of aromatic ester

In a 250 ml round-bottomed flask fitted with a reflux condenser, aromatic acid (0.10 mol), methanol (20 ml) and concentrated sulfuric acid (2 ml) were taken and refluxed on a water bath for 5-7 hrs. The reaction mixture was cooled and poured onto crushed ice. The separated solid was collected on a Buchner funnel, washed with cold water and dried. The crude ester was distilled or recrystallized from methanol to get pure methyl benzoate (87%), b.p. 197-199°C (lit.[310] 199°C); methyl 4-methylbenzoate (79%), m.p. 33-35°C (lit.[310] 34°C); methyl 4-chlorobenzoate (89%), m.p. 40-43°C (lit.[310] 44°C).

ii) Preparation of arylhydrazide (31)

The aromatic ester (0.01 mol), hydrazine hydrate (0.02 mol) and methanol (30 ml) were taken in a 100 ml round-bottomed flask fitted with a reflux condenser and refluxed on a water bath for 8-10 hrs. The contents were cooled and poured onto crushed ice. The solid separated was filtered on a Buchner funnel, washed with cold water, dried and recrystallized from methanol to get pure benzohydrazide (74%), m.p. 110-112°C (lit.[310,314] 112-114°C); 4-methylbenzohydrazide (70%), m.p. 117-119°C (lit.[310,314] 116-118°C); and 4-chlorobenzohydrazide (76%), m.p. 161-163°C (lit.[310,314] 163-165°C).

iii) 2-(Chloromethyl)-5-aryl-1,3,4-oxadiazole (32)

A mixture of arylhydrazide (31) (0.01 mol), chloroacetic acid (0.01 mol) and phosphorus oxychloride (7 ml) was taken in a 100 ml round-bottomed flask fitted with reflux condenser carrying a calcium chloride guard-tube and refluxed for 2-3 hrs. The

excess phosphorus oxychloride was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried and recrystallized from ethanol. The compounds obtained accordingly are given in Table **III.4**.

TABLE III.4

Compd. No.	R	m.p. (°C)	Yield (%)
32a	H	92-94	76
32b	Me	98-100	75
32c	Cl	105-107	78
32d	Br	127-129	71
32e	OMe	110-112	69
32f	NO_2	144-146	73

2-(Chloromethyl)-5-aryl-1,3,4-thiadiazole (33)

The 2-(chloromethyl)-5-aryl-1,3,4-oxadiazole (**32**) (0.01 mol), thiourea (0.04 mol) and tetrahydrofuran (5 ml) were taken in a sealed tube and heated at 120-150°C in an oil bath for 15-18 hrs. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol. All the compounds prepared in a similar way are shown in Table **III.5**.

TABLE III.5

Compd. No.	R	m.p. (°C)	Yield (%)
33a	H	86-88	71
33b	Me	91-93	73
33c	Cl	97-99	74
33d	Br	120-122	70
33e	OMe	100-102	76
33f	NO_2	133-135	72

3-(Chloromethyl)-5-phenyl-4*H*-1,2,4-triazol-4-amine (34)

To a solution of 2-(chloromethyl)-5-aryl-1,3,4-oxadiazole (**32**) (0.01 mol) in *n*-butanol (10 ml) taken in a 100 ml round-bottomed flask fitted with a reflux condenser, hydrazine hydrate (0.06 mol) was added and refluxed for 5-7 hrs. Then, potassium hydroxide (0.04 mol) was added to the reaction media and the precipitate formed was filtered. The solid obtained was acidified with concentrated hydrochloric acid to pH≈3 and washed with water. It was dried and recrystallized from ethanol. The physical data of the compounds synthesized adopting similar procedure is listed in Table **III.6**.

TABLE III.6

Compd. No.	R	m.p. (°C)	Yield (%)
34a	H	129-130	74
34b	Me	153-155	71
34c	Cl	176-178	76
34d	Br	160-162	70
34e	OMe	115-117	72
34f	NO_2	171-173	73

(5-Phenyl-1,3,4-oxadiazol-2-yl)methanethiol (35)

A mixture of arylhydrazide (31) (0.01 mol), mercaptoacetic acid (0.01 mol) and phosphorus oxychloride (7 ml) was taken in a 100 ml round-bottomed flask fitted with a reflux condenser, carrying a calcium chloride guard-tube and refluxed for 2-4 hrs. The excess phosphorus oxychloride was removed under vacuum and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution followed by water, dried and recrystallized from ethanol. The compounds thus obtained are given in Table **III.7**.

TABLE III.7

Compd. No.	R	m.p. (°C)	Yield (%)
35a	H	134-136	70
35b	Me	126-128	68
35c	Cl	152-157	72
35d	Br	146-148	71
35e	OMe	130-132	68
35f	NO_2	180-182	74

(5-Phenyl-1,3,4-thiadiazol-2-yl)methanethiol (36)

In a sealed test tube, a mixture of 5-phenyl-1,3,4-oxadiazol-2-yl)methanethiol (**35**) (0.01 mol), thiourea (0.04 mol) and tetrahydrofuran (5 ml) was taken and heated at 120-150°C in an oil bath for 14-16 hrs. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol. All the compounds prepared in a similar way are presented in Table **III.8**.

TABLE III.8

Compd. No.	R	m.p. (°C)	Yield (%)
36a	H	150-152	69
36b	Me	145-147	70
36c	Cl	167-169	72
36d	Br	156-158	68
36e	OMe	143-145	71
36f	NO_2	176-178	73

(4-Amino-5-phenyl-4*H*-1,2,4-triazol-3-yl)methanethiol (37)

To a solution of 5-phenyl-1,3,4-oxadiazol-2-yl)methanethiol (**35**) (0.02 mol) in *n*-butanol (10 ml) taken in a 100 ml round-bottomed flask fitted with a reflux condenser, hydrazine hydrate (0.06 mol) was added and refluxed for 6-8 hrs. Then, potassium hydroxide (0.04 mol) was added to the reaction media and the precipitate formed was filtered. The solid obtained was acidified with concentrated hydrochloric acid to pH≈3 and washed with water. It was dried and recrystallized from ethanol. The physical data of the compounds prepared in a similar way is listed in Table **III.9**.

TABLE III.9

Compd. No.	R	m.p. (°C)	Yield (%)
37a	H	180-182	70
37b	Me	165-162	72
37c	Cl	196-198	71
37d	Br	189-191	77
37e	OMe	172-174	75
37f	NO_2	202-204	74

4-Chloro-6-methylpyrimidine-2-thiol (38)

A solution of sodium methoxide (0.01 mol) in methanol (20 ml) was taken in a 100 ml round-bottomed flask fitted with a reflux condenser carrying a calcium chloride guard-tube. To this thiourea (0.01 mol) and ethyl acetoacetate (0.01 mol) were added and refluxed for 8 hrs. After completion of the reaction, the contents of the flask were cooled and diluted with acetic acid (5 ml). The resultant solid was separated by filtration, washed with water and dried to obtain 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one. To a suspension of latter compound (0.01 mol) in diglyme (5 ml) taken in a 100 ml round-bottomed flask fitted with a reflux condenser carrying a calcium chloride guard-tube, phosphorus oxychloride (0.035 mol) was added and refluxed for 2 hrs. Then the contents were cooled to room temperature, poured into 10% K_2CO_3 solution (30 ml) and stirred for 1 hr. The solid separated was filtered, washed with water, dried and recrystallized from 2-propanol to get pure 4-chloro-6-methylpyrimidine-2-thiol (67%) m.p. 203-205°C (lit.[315] 204-206°C).

2-(5-Phenyl-1,3,4-oxadiazol-2yl-methylthio)4-chloro-6-methylpyrimidine (39)

Conventional method

In a 100 ml round-bottomed flask fitted with a calcium chloride guard-tube, 4-chloro-6-methylpyrimidine-2-thiol (**38**) (0.01 mol), dry tetrahydrofuran (6 ml) and triethylamine (0.2 ml) were taken and stirred for 1 hr. To this 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (**32**) (0.01 mol) dissolved in dry tetrahydrofuran (5 ml) was added dropwise and continued stirring at room temperature for 13-17 hrs. After completion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice and extracted with dichloromethane. The solvent was removed under reduced pressure and the resultant residue was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The compounds synthesized accordingly are listed in Table **III.10**.

Ultrasound method

To a solution of 4-chloro-6-methylpyrimidine-2-thiol (**38**) (0.01mol) in dry tetrahydrofuran (4 ml) taken in a 100 ml round-bottomed flask fitted with a reflux

condenser carrying a calcium chloride guard-tube, triethylamine (0.2 ml) was added and subjected to ultrasound irradiation for 10-15 min at room temperature. To this, 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (**32**) (0.01mol) in dry tetrahydrofuran (3 ml) was added dropwise and again subjected to ultrasound irradiation at room temperature for 85-90 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were poured onto crushed ice and extracted with dichloromethane. Removal of the solvent under vacuum gave a residue which was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. All the compounds prepared in a similar method are given in Table **III.10**.

TABLE III.10

Compd. No.	R	m.p. (°C)	Yield (%)	
			Conventional method	Ultrasound method
39a	H	102-104	78	89
39b	Me	121-123	75	87
39c	Cl	136-138	79	90
39d	Br	160-162	82	92
39e	OMe	128-130	81	91
39f	NO_2	142-144	87	95

2-(5-Phenyl-1,3,4-thiadiazol-2yl-methylthio)4-chloro-6-methylpyrimidine (40)

Conventional method

A mixture of 4-chloro-6-methylpyrimidine-2-thiol (**38**) (0.01 mol), dry tetrahydrofuran (6 ml) and triethylamine (0.2 ml) was taken in a 100 ml round-bottomed flask fitted with a reflux condenser carrying calcium chloride guard-tube and stirred for 1 hr. To this, 2-(chloromethyl)-5-phenyl-1,3,4-thadiazole (**33**) (0.01mol) dissolved in dry tetrahydrofuran (5 ml) was added dropwise and continued stirring at room temperature for 15-17 hrs. After completion of the reaction, the contents were poured onto crushed ice and extracted with dichloromethane. The solvent was removed *in vacuo*. The resultant residue

was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The compounds thus obtained are shown in Table **III.11**.

Ultrasound method

To a solution of 4-chloro-6-methylpyrimidine-2-thiol (**38**) (0.01mol) in dry tetrahydrofuran (4 ml), taken in a 100 ml round-bottomed flask fitted with a reflux condenser carrying a calcium chloride guard-tube, triethylamine (0.2 ml) was added and subjected to ultrasound irradiation for 3-5 min at room temperature. To this, 2-(chloromethyl)-5-phenyl-1,3,4-thadiazole (**33**) (0.01mol), in dry tetrahydrofuran (3 ml) was added dropwise and again subjected to ultrasound irradiation at room temperature for 100-120 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured onto crushed ice and extracted with dichloromethane. Removal of the solvent under vacuum gave a residue which was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The physical data of the compounds synthesized in a similar way is presented in Table **III.11**.

TABLE III.11

Compd. No.	R	m.p. (°C)	Yield (%)	
			Conventional method	Ultrasound method
40a	H	125-127	76	87
40b	Me	140-142	78	85
40c	Cl	150-153	74	89
40d	Br	164-166	79	91
40e	OMe	145-147	77	84
40f	NO_2	156-158	79	90

5-Phenyl-4-amino-1,2,4-triazol-3yl-methylthio)4-chloro-6-methylpyrimidine (41)

nventional method

A mixture of 4-chloro-6-methylpyrimidine-2-thiol (**38**) (0.01 mol), dry rahydrofuran (6 ml) and triethylamine (0.2 ml) was taken in a 100 ml round-bottomed sk fitted with a reflux condenser carrying a calcium chloride guard-tube was stirred for 1 To this, 2-(chloromethyl)-5-phenyl-1,2,4-triazole (**34**) (0.01 mol), dissolved in dry rahydrofuran (5 ml) was added dropwise and continued the stirring at room temperature 14-15 hrs. After completion of the reaction, the contents of the flask were poured onto ished ice and extracted with dichloromethane. The solvent was removed under reduced ssure and the resultant residue was purified by column chromatography (silica gel, 60-) mesh) using ethyl acetate-hexane (1:3) as eluent. All the compounds obtained adopting similar procedure are given Table **III.12**.

trasound method

To a solution of 4-chloro-6-methylpyrimidine-2-thiol (**38**) (0.01mol) in dry rahydrofuran (4 ml), taken in a 100 ml round-bottomed flask fitted with a reflux ndenser carrying a calcium chloride guard-tube triethylamine (0.2 ml) was added and jected to ultrasound irradiation for 3-5 min at room temperature. To this, 2-loromethyl)-5-phenyl-1,2,4-triazole (**34**) (0.01mol) in dry tetrahydrofuran (3 ml) was led dropwise and again subjected to ultrasound irradiation at room temperature for 85-5 min. The progress of the reaction was monitored by TLC. After completion of the ction, the reaction mixture was poured onto crushed ice and extracted with hloromethane. Removal of the solvent with a rotary evaporator gave a residue which s purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-xane (1:3) as eluent. All the compounds prepared by following the same method are ted in Table **III.12**.

TABLE III.12

Compd. No.	R	m.p. (°C)	Yield (%)	
			Conventional method	Ultrasound method
41a	H	117-119	80	88
41b	Me	140-142	78	86
41c	Cl	162-164	81	92
41d	Br	155-157	72	89
41e	OMe	158-160	74	91
41f	NO_2	153-155	76	90

2,4-Bis(5-phenyl-1,3,4-oxadiazol-2-ylmethylthio)-6-methylpyrimidine (42)
Conventional method

To a solution of 2-(5-phenyl-1,3,4-oxadiazole-2yl-methylthio)4-chloro-6-methyl-pyrimidine (**39**) (0.01 mol) in dry ethanol (4 ml) taken in a 100 ml round-bottomed flask fitted with a reflux condenser carrying a calcium chloride guard-tube and equipped over a heating mantle, (5-phenyl-1,3,4-oxadiazol-2-yl)methanethiol (**35**) (0.011 mol) and a catalytic amount of methanesulfonic acid (0.2 ml) were added. The reaction mixture was heated at 50 °C for 4-5 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, it was allowed to cool, diluted with water (15 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The resultant residue was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. All the compounds prepared in a similar way are shown in Table **III.13**.

Ultrasound method

In a 100 ml round-bottomed flask fitted with reflux condenser carrying a calcium chloride guard-tube, 2-(5-phenyl-1,3,4-oxadiazol-2yl-methylthio)4-chloro-6-methyl-pyrimidine (**39**) (0.01 mol), (5-phenyl-1,3,4-oxadiazol-2-yl)methanethiol (**35**) (0.011 mol), dry ethanol (3 ml) and a catalytic amount of methanesulfonic acid (0.2 ml) were taken and

kept under ultrasonication for 40-50 min at 40 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 The solvent was removed under vacuum and the resultant residue was purified by column chromatography (silica gel,60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The physical data of the compounds thus synthesized is presented in Table **III.13**.

TABLE III.13

Compd. No.	R	m.p. (°C)	Yield (%)	
			Conventional method	Ultrasound method
42a	H	169-171	79	93
42b	Me	178-180	76	92
42c	Cl	192-194	75	89
42d	Br	232-234	77	91
42e	OMe	183-185	82	90
42f	NO_2	199-201	85	92

2,4-Bis(5-phenyl-1,3,4-thiadiazol-2-ylmethylthio)-6-methylpyrimidine (43)
Conventional method

A mixture of 2-(5-phenyl-1,3,4-oxadiazole-2yl-methylthio)4-chloro-6-methylpyrimidine (**40**) (0.01 mol), (5-phenyl-1,3,4-thadiazol-2-yl)methanethiol (**36**) (0.011 mol), dry ethanol and a catalytic amount of methanesulfonic acid (0.2 ml) was taken in a 100 ml round-bottomed flask fitted with reflux condenser, carrying a calcium chloride guard-tube. The reaction mixture was kept under magnetic stirring and heated at 50 °C for 6-7 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool, diluted with water (15 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed with a rotary evaporator. The resultant

residue was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The compounds thus prepared are listed in Table **III.14**.

Ultrasound method

The 2-(5-phenyl-1,3,4-oxadiazole-2yl-methylthio)4-chloro-6-methylpyrimidine (**40**) (0.01 mol), (5-phenyl-1,3,4-thadiazol-2-yl)methanethiol (**36**) (0.011 mol), dry ethanol (3 ml) and a catalytic amount of methanesulfonic acid (0.2 ml) were taken in a 100 ml round-bottomed flask fitted with reflux condenser carrying a calcium chloride guard-tube and kept under ultrasonication for 50-57 min at 40 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The compounds prepared accordingly are given in Table **III.14**.

TABLE *III.14*

Compd. No.	R	m.p. (°C)	Yield (%)	
			Conventional method	Ultrasound method
43a	H	181-183	83	90
43b	Me	187-189	73	88
43c	Cl	195-197	80	92
43d	Br	242-244	78	87
43e	OMe	190-192	76	92
43f	NO_2	206-208	77	89

2,4-Bis(5-phenyl-4-amino-1,2,4-triazol-3-ylmethylthio)-6-methylpyrimidine (44)

Conventional method

In a 100 ml round-bottomed flask fitted with a reflux condenser carrying a calcium chloride guard-tube and equipped over a heating mantle, 2-(5-phenyl-4-amino-1,2,4-triazol-3yl-methylthio)4-chloro-6-methyl-pyrimidine (**41**) (0.01 mol), 4-amino-5-phenyl-4*H*-1,2,4-triazol-3-yl)methanethiol (**37**) (0.011 mol), dry ethanol (7 ml) and a catalytic amount of methanesulfonic acid (0.2 ml) were taken and heated at 50 °C for 5-6 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were allowed to cool, diluted with water (15 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The resultant residue was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The compounds thus prepared are listed in Table **III.15**.

Ultrasound method

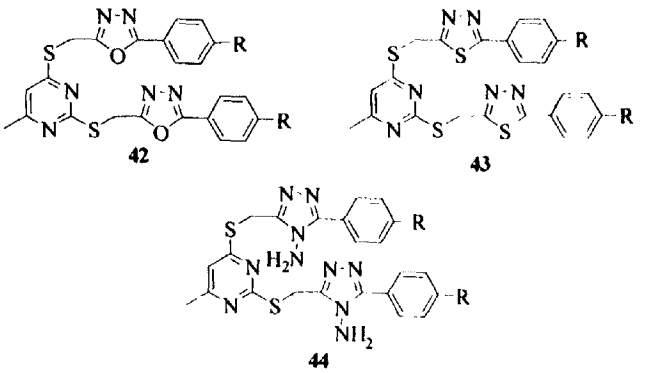
A mixture of 2-(5-phenyl-4-amino-1,2,4-triazol-3yl-methylthio)4-chloro-6-methyl-pyrimidine (**41**) (0.01 mol), 4-amino-5-phenyl-4*H*-1,2,4-triazol-3-yl)methanethiol (**37**) (0.011 mol), dry ethanol (7 ml) and a catalytic amount of methanesulfonic acid (0.2 ml) was taken in a 100 ml round-bottomed flask fitted with a reflux condenser, carrying a calcium chloride guard-tube. The contents were sonicated under ultrasonication bath for 40-65 min at 40 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, it was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The resultant residue was purified by column chromatography (silica gel,60-120 mesh) using ethyl acetate-hexane (1:3) as eluent. The physical data of the compounds thus obtained is given in Table **III.15**.

TABLE III.15

Compd. No.	R	m.p. (°C)	Yield (%)	
			Conventional method	Ultrasound method
44a	H	184-186	72	87
44b	Me	197-199	80	92
44c	Cl	247-249	76	90
44d	Br	210-212	78	89
44e	OMe	202-204	74	88
44f	NO_2	216-218	79	91

ANTIMICROBIAL ACTIVITY

The compounds 2,4-bis(5-phenyl-1,3,4-oxadiazol-2-ylmethylthio)-6-methyl-pyrimidine (**42**), 2,4-bis(5-phenyl-1,3,4-thiadiazol-2-ylmethylthio)-6-methylpyrimidine (**43**) and 2,4-bis(5-phenyl-4-amino-1,2,4-triazol-3-ylmethylthio)-6-methylpyrimidine (**44**) (**Chart**) were tested for antimicrobial activity.



CHART

Methodology

The methodology followed and microorganisms used to study the antimicrobial activity are presented in section **I**.

Results and Discussion

Antimicrobial Activity

The compounds **42-44** were screened for antimicrobial activity at four different concentrations 12.5, 25, 50 and 100 μg/well. The results of antibacterial activity (Table **III.16** & Fig. **III.12**) indicated that all the tested compounds exhibited more antibacterial activity towards Gram-negative bacteria than Gram-positive bacteria.

The bis(thiadiazolyl)pyrimidine (**43**) exhibited greater activity than ıdiazolyl)pyrimidine (**42**) and bis(triazolyl)pyrimidine (**44**). Furthermore compound wed higher antibacterial activity than **42**. The **43c** and **43f** were effective particularly : *P. aeruginosa* at all the tested concentrations. The other compounds showed ıte to good activity whereas the compounds **42e** and **44e** exhibited no activity. s, the compounds possessing electron withdrawing substituents on the phenyl ring /ed greater activity.

All the tested compounds inhibited spore germination against the tested fungi **III.17** & Fig. **III.13**). In general, all the compounds showed higher antifungal y towards *A.niger* than *P.chrysogenum*. The **44c** and **44f** exhibited excellent ıgal activity when compared with the standard drug Ketoconazole at all the tested ıtrations. However **42a, 42c, 42f, 43c, 43d, 43f, 44a** and **44d** showed moderate to ıctivity. On the other hand **42b, 42d, 43b, 44b** and **44e** displayed least activity. The ›unds having chloro, bromo and nitro substituents on the phenyl ring exhibited activity than those with methyl and methoxy substituents.

ıum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration) and Minimum Fungicidal Concentration (MFC)

The minimum inhibitory concentration (MIC), minimum bactericidal concentration) and minimum fungicidal concentration (MFC) values of the compounds tested are in Table **III.18**. MIC is the lowest concentration of an antimicrobial that will inhibit ıible growth of a microorganism (But it is not sure that the microorganisms are ɛtely killed). The MBC/MFC is the lowest concentration of antibiotic required to kill cular bacterium/fungi. The MBC/MFC involves an additional set of steps performed he minimum inhibitory concentration (MIC) is determined. The antimicrobials are / regarded as bactericidal/fungicidal if the MBC/MFC is not greater than four times IC. The compounds **43c, 43f, 44c** and **44f** exhibited low MIC values. The MBC for **43c** and **43f** were 2×MIC particularly against *P. aeruginosa*. However, MFC for compounds **44c** and **44f** were 2×MIC particularly against *A. niger*. The ıre- antimicrobial activity relationship of the synthesized compounds revealed that ›unds having pyrimidine and thiadiazole pharmacophores displayed pronounced

antibacterial activity whereas compounds having pyrimidine and triazole moieties exhibited excellent antifungal activity. Moreover, the compounds having electron withdrawing (nitro, chloro, bromo) substituents on the phenyl ring displayed higher antimicrobial activity than the compounds with electrondonating (methoxy and methyl) substituents.

TABLE III.16

The *in vitro* antibacterial activity of compounds **42, 43** and **44**

Compd. No.	Diameter of zone of inhibition (mm)															
	Gram-positive bacteria								Gram-negative bacteria							
	S. aureus				*B. subtilis*				*P. aeruginosa*				*K. pneumoniae*			
	12.5 μg/ well	25 μg/ well	50 μg/ well	100 μg/ well	12.5 μg/ well	25 μg/ well	50 μg/ well	100 μg/ well	12.5 μg/ well	25 μg/ well	50 μg/ well	100 μg/ well	12.5 μg/ well	25 μg/ well	50 μg/ well	100 μg/ well
42a	-	-	-	-	-	-	-	7±2	7±1	9±2	11±2	14±2	-	7±2	9±1	12±2
42b	-	-	-	-	-	-	-	-	-	8±2	10±2	12±2	-	-	8±2	10±2
42c	-	-	-	-	-	-	7±1	9±3	10±2	12±2	14±2	17±2	10±2	11±2	13±2	16±1
42d	-	-	-	-	-	-	-	8±1	9±2	11±2	13±2	15±2	8±2	10±2	12±2	15±2
42e	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42f	-	7±1	8±3	10±1	9±1	11±2	13±3	15±2	11±2	14±1	16±3	21±1	15±2	17±1	19±3	21±2
43a	10±1	11±2	12±1	13±2	11±2	13±1	15±2	18±1	15±1	19±2	20±2	24±1	20±3	21±2	23±1	26±1
43b	-	-	-	8±2	8±1	10±3	11±2	13±1	10±2	12±2	15±1	19±3	14±1	16±3	18±1	20±2
43c	15±1	17±2	19±1	21±3	21±2	23±1	26±3	29±2	26±2	29±3	32±1	34±2	28±1	30±2	32±3	35±1
43d	11±2	13±1	15±2	17±1	17±1	19±2	21±1	24±3	19±1	23±2	25±2	29±3	24±2	26±1	28±1	31±2

Contd...

43e	-	-	-	-	-	-	-	-	-	-	8±1	10±2	-	-	-	13±2
43f	16±2	18±3	20±1	23±2	22±3	24±1	27±2	31±1	28±2	31±1	33±2	36±3	31±3	33±1	35±2	38±1
44a	8±3	9±1	10±2	12±1	10±2	12±3	14±1	17±1	14±2	16±2	19±1	23±3	17±1	19±3	22±1	24±2
44b	-	-	-	-	-	7±3	9±2	11±3	9±2	11±2	14±2	18±2	12±2	13±1	15±3	18±1
44c	10±2	11±1	13±3	15±1	16±2	18±3	20±1	24±2	18±2	21±1	24±2	27±3	22±2	24±2	26±1	29±2
44d	9±3	10±2	12±1	14±2	15±1	16±2	18±3	20±1	16±1	20±2	22±3	25±2	21±2	23±1	25±2	28±1
44e	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44f	13±1	15±3	17±2	19±3	18±1	20±1	22±2	26±3	23±3	26±2	28±1	31±1	25±1	27±3	29±2	32±1
Chloram-phenicol	30±1	32±3	35±2	37±3	32±2	34±2	36±3	40±1	25±2	27±3	29±1	32±2	38±1	40±2	42±1	44±1
Control (DMSO)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(-) No activity, (±) Standard deviation.

TABLE III.17

The *in vitro* antifungal activity of compounds **42, 43** and **44**

Compd. No.	Diameter of zone of inhibition (mm)							
	A. niger				*P. chrysogenum*			
	12.5 µg/ well	25 µg/ well	50 µg/ well	100 µg/ well	12.5 µg/ well	25 µg/ well	50 µg/ well	100 µg/ well
42a	14±2	16±3	18±2	21±1	8±2	10±2	11±2	13±1
42b	-	-	7±2	9±2	-	-	-	-
42c	18±3	20±1	22±1	25±3	11±2	13±2	15±1	17±2
42d	13±2	15±2	17±2	19±1	-	7±2	9±2	11±3
42e	-	-	-	-	-	-	-	-
42f	20±1	22±1	24±3	27±1	12±2	14±3	16±1	19±2
43a	15±2	17±1	19±3	22±2	9±2	10±2	12±2	14±3
43b	9±2	11±2	13±2	15±1	-	-	-	-
43c	24±2	26±2	28±1	31±3	15±1	17±2	19±2	22±3
43d	22±1	24±1	26±2	30±1	13±2	15±3	17±1	20±2
43e	-	-	-	-	-	-	-	-
43f	27±1	29±2	32±1	35±2	20±2	22±1	24±3	26±2
44a	17±2	19±2	21±3	24±1	11±2	12±2	14±2	16±2
44b	10±2	12±2	14±2	16±2	-	-	8±2	10±2
44c	32±2	33±1	35±1	38±3	21±2	23±1	25±2	29±3
44d	27±1	29±3	31±2	34±2	17±1	19±3	21±1	24±2
44e	-	-	8±2	10±2	-	-	-	-
44f	33±1	35±3	37±2	40±2	23±1	25±3	27±1	31±2
Ketoconazole	29±1	31±3	34±2	37±3	34±3	36±1	37±2	39±3
Control (DMSO)	–	–	–	–	–	–	–	–

(-) No activity, (±) Standard deviation.

TABLE III.18

MIC, MBC and MFC of compounds **43c, 43f, 44c and 44f**

Compd. No.	Minimum inhibitory concentration MIC (MBC / MFC) µg / well					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. niger*	*P. chrysogenum*
43c	50 (200)	25 (100)	6.25 (12.5)	12.5 (50)	12.5 (50)	50 (200)
43f	50 (200)	25 (100)	6.25 (12.5)	12.5 (50)	12.5 (50)	50 (200)
44c	100 (>200)	50 (200)	25 (100)	25 (100)	6.25 (12.5)	25 (100)
44f	100 (>200)	50 (200)	12.5 (50)	25 (100)	6.25 (12.5)	25 (100)
Chloram-phenicol	6.25	6.25	6.25	12.5	-	-
Ketoconazole	-	-	-	-	6.25	12.5

(-) No activity.

Fig. III.12

The *in vitro* antibacterial activity of compounds **42-44.**

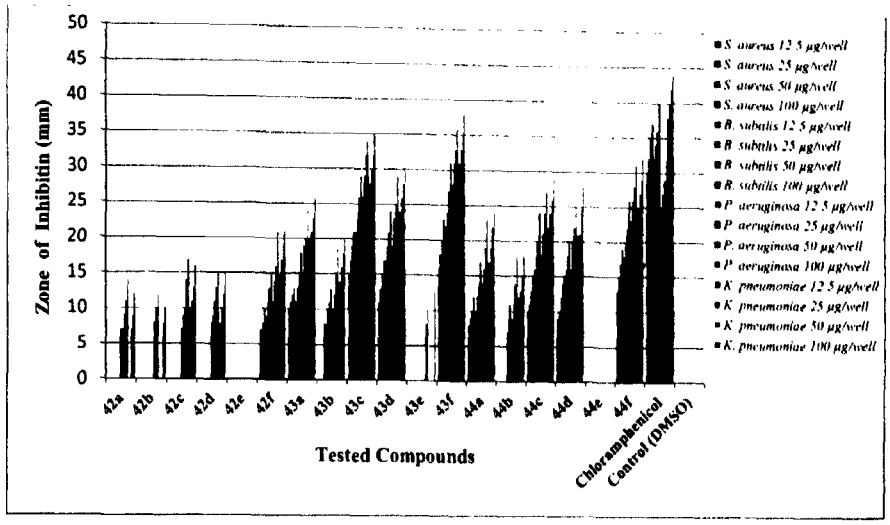


Fig. III.13

The *in vitro* antifungal activity of compounds **42-44.**