Indian Journal of Chemistry
Vol. 49B, September 2010, pp. 1235-1242

Fungitoxicity and QSAR of 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles[†]

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Received 9 October 2009; accepted (revised) 6 July 2010

Twenty eight 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazoles have been tested *in vitro* against *Rhizoctonia solani, Sclerotium rolfsii, Fusarium oxysporum, Pythium aphanidermatum, Puccinia recondita* and *Bipolaris sorokiniana*. These triazoles have shown very good activity against all the six test fungi, their activity against *P. recondita* and *B. sorokiniana* have been found excellent. The compound, 5-(2-chloro-5-nitrophenyl)-4-amino-3-mercapto-1,2,4-triazole **27** exhibits highest activity (ED_{50} =12 mg mL^{-1}) against *P. recondita* and the compounds 5-(2-chlorophenyl)-4-amino-3-mercapto-1,2,4-triazole **3** and 5-(4-formylphenyl)-4-amino-3-mercapto-1,2,4-traizole **19** (ED_{50} =27 mg mL^{-1}) against *B. sorokiniana.* The quantitative structure activity relationship (QSAR) analyzed using physicochemical parameters for hydrophobic, electronic and steric properties of the molecules by means of multiple regression analysis has revealed different structural requirement for fungicidal activity against different fungi. The position dependent steric effect of the aryl substituents is playing an important role in imparting fungicidal activity against all the test fungi. The positive sign with steric parameter terms indicate that their higher values enhance the fungicidal activity in this series. The other parameters for hydrophobic and electronic effect are also influencing the fungicidal activity differently against different fungi.

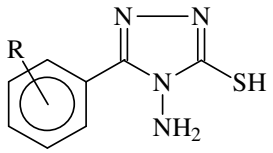
Keywords: QSAR, 1,2,4-triazoles, fungicidal activity, agrochemicals

Among heterocyclic compounds, 1,2,4-triazoles and their derivatives show wide spectrum of bioactivities. Besides various pharmacological activities, these have shown activity as plant protection agents *i.e.* fungicide[1-3], herbicide[3-5], insecticide[6], *etc.* Some of these compounds have been commercialized as excellent fungicides[7]. The increasing importance of 1,2,4-triazoles as agrochemicals prompted the authors to synthesize a new series *viz.* 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazoles. The microwave assisted synthesis of these compounds has been reported earlier[8]. This paper reports the fungicidal activity against some important phytopathogenic fungi and quantitative structure activity relationships of this series of compounds.

Fungicidal activity of 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazoles was studied against six fungi *viz. Rhizoctonia solani, Sclerotium rolfsii, Fusarium oxysporum*, *Pythium aphanidermatum*, *Puccinia recondita* and *Bipolaris sorokiniana*. The inhibition of fungus growth was recorded in case of *R. solani, S. rolfsii, F. oxysporium* and *P. aphanidermatum* and inhibition of spore germination in case of *P. recondita* and *B. sorokiniana.* The ED_{50} (effective dose for 50% inhibition of fungus growth/spore germination) values in mg mL^{-1} **Table I** for the fungicidal activity of these compounds against the six fungi apparently reveal no relationship between structure and fungicidal activity based on electronic nature of the aryl substituents. These triazoles have shown very good activity against all the six test fungi, their activity against *P. recondita* and *B. sorokiniana* have been found excellent as all compounds exhibited ED_{50} below 100 mg mL^{-1} and most of them less than 60 mg mL^{-1}. The compound **27**, 5-(2-chloro-5-nitrophenyl)-4-amino-3-mercapto-1,2,4-triazole exhibited highest activity (ED_{50} = 12 mg mL^{-1}) against *Puccinia recondita* followed by compound **21**, 5-(2,4-dichlorophenyl)-4-amino-3-mercapto-1,2,4-triazole (ED_{50} =18 mg mL^{-1}) and the compounds 5-(2-chlorophenyl)-4-amino-3-mercapto-1,2,4-triazole **3** and 5-(4-formylphenyl)-4-amino-3-mercapto-1,2,4-traizole **19** exhibited highest activity (ED_{50} =27 mg mL^{-1}) against *B. sorokiniana*. The most active compounds against other fungi were, 5-(4-ethoxyphenyl-4-amino-3-mercapto-1,2,4-triazole **13**, *R. solani* (ED_{50}=51 mg mL^{-1}); 5-(5-sulpho-2-hydroxy phenyl)-4-amino-3-mercapto-1,2,4-triazole **26**, *S. rolfsii* (ED_{50}=46 mg mL^{-1}); 5-(4-*t*-butylphenyl)-4-amino-3-

[†]Contribution No. 1009

Table I — Fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles



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Compd	R	m.p. (°C)	ED_{50} (μg mL^{-1}) against test species[a]					
			R.s.	*S.r.*	*F.o.*	*P.a.*	*P.r.*	*B.s.*
1	H	203-205	76	97	57	53	38	29
2	4-NH_2	260-61	97	85	58	59	50	43
3	2-Cl	155-56	76	90	68	66	41	27
4	3-Cl	124-25	105	86	84	83	57	37
5	4-Cl	211-12	89	67	56	54	59	53
6	2-F	127-28	106	68	74	71	59	52
7	4-F	139-40	104	105	65	75	65	59
8	2-OH	202-203	63	90	78	72	33	48
9	4-OH	215-16	99	78	80	81	54	39
10	2-SH	159-60	99	54	47	86	42	32
11	2-OCH_3	218-20	670	81	60	89	48	53
12	4-OCH_3	205-206	85	84	67	73	36	39
13	4-OC_2H_5	158-60	51	71	48	71	51	44
14	2-CH_3	154-55	1082	68	60	81	48	37
15	3-CH_3	159-60	776	83	47	74	53	40
16	4-CH_3	210-13	83	84	45	61	61	65
17	3-NO_2	182-83	970	63	48	72	47	42
18	4-NO_2	215-16	77	64	53	63	50	37
19	4-CHO	164-65	580	63	57	91	53	27
20	4-$C(CH_3)_3$	184-85	115	54	42	68	36	28
21	2,4-Cl_2	209-10	61	59	80	65	18	59
22	2,4-$(OH)_2$	95-96	92	99	59	77	66	40
23	3,5-$(OH)_2$	189-90	487	75	61	115	80	34
24	3,4-$(OCH_3)_2$	174-75	382	60	62	104	53	80
25	5-Cl, 2-OH	207-208	102	57	61	75	32	53
26	5-HSO_3, 2-OH	152-54	409	46	65	67	42	46
27	2-Cl, 5-NO_2	115-16	789	79	52	51	12	57
28	3,5-$(NO_2)_2$, 2-OH	174-75	53	57	64	45	47	86

[a]*R.s.= Rhizoctonia solani*; *P.a.= Sclerotium rolfsii*; *F.o.= Fusarium oxysporum*; *P.a.= Pythium aphanidermatum*; *P.r.= Puccinia recondite*; *B.s.= Bipolaris sorokiniana*

mercapto-1,2,4-triazole **20**, *F. oxysporum* (ED_{50}= 42 mg mL^{-1}) and 5-(3,5-dinitro-2-hydroxyphenyl)-4-amino-3-mercapto-1,2,4-triazole **28**, *P. aphanidermatum* (ED_{50} = 45 mg mL^{-1}).

Quantitative Structure Active Relationship (QSAR)

In order to precisely understand the effect of aryl substituents of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles on their fungicidal activity, quantitative structure activity relationship was analyzed by means of multiple regression analysis using measured –log ED_{50}(M) values (**Table II**) for fungicidal activity against six fungi as dependent variable and various physicochemical parameters for the hydrophobic, electronic and steric properties of each member of a series (**Table III**) as independent variables. The QSAR models for fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles have been developed

for five fungi *viz. S. rolfsii, F. oxysporum, P. aphanidermatum, P. recondita* and *B. sorokiniana* (**Table IV**) and are discussed. A correlation matrix for the parameters used in regression equations is given in **Table V**. Activities of the compounds have also been predicted on the basis of statistically best fit equations and are compared with corresponding observed values (**Table II**). In the regression equations n is the number of compounds included in the correlation, s is the standard deviation, r is the correlation coefficient and Fv_1, v_2 is the F ratio of the correlation where v_1=m and v_2=n-m-1; m is the number of independent variables used in the correlation. The figures in parentheses below the regression coefficient of each parameter are the 95% confidence intervals for the respective constants.

Regression equations (1) to (6) were obtained for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *S. rolfsii*. Eq. 6 which comprises Σπ, ΣF, ΣMR(o), ΣMR(p), ΣL(m) and ΣB1(p) is the statistically best fit and accounts 85.93% (r=0.927) variation in fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *S. rolfsii*. Eq. 6 is significant at 99% level and all the terms in it except Σπ and ΣF are significant at 99% level, Σπ and ΣF terms are significant at 95% level. The $-\log ED_{50}$ (M) values calculated by Eq. 6 for fungicidal activity of triazoles against *S. rolfsii* (**Table II**) are comparable with the observed values. The negative sign with Σπ shows that less hydrophobic is the aryl substituent in triazole more is the fungicidal activity. The negative sign with ΣF also

Table II — Observed *versus* predicted $-\log ED_{50}$ (M) values for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles

Compd.	R (In structure **I**)	$-\log ED_{50}$ (M)									
		S. rolfsii		*F. oxysporum*		*P. aphanidermatum*		*P. recondita*		*B. sorokiniana*	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
1	H	3.30	3.30	3.53	3.48	3.56	3.45	3.71	3.51	3.82	3.74
2	4-NH_2	3.39	3.48	3.55	3.56	3.54	3.50	3.62	3.52	3.68	3.75
3	2-Cl	3.40	3.40	3.52	3.57	3.54	3.45	3.75	3.90	3.93	3.80
4	3-Cl	3.42	3.44	3.43	3.53	3.44	3.61	3.60	3.66	3.78	3.73
5	4-Cl	3.53	3.46	3.61	3.57	3.63	3.53	3.58	3.63	3.63	-
6	2-F	3.49	-	3.45	3.48	3.47	3.45	3.55	3.68	3.61	3.75
7	4-F	3.30	3.35	3.51	3.48	3.45	3.49	3.51	3.52	3.55	-
8	2-OH	3.36	3.41	3.43	3.52	3.46	3.45	3.79	3.63	3.64	3.72
9	4-OH	3.43	3.40	3.41	3.51	3.41	3.48	3.59	3.51	3.73	3.72
10	2-SH	3.62	3.56	3.68	3.64	3.41	3.45	3.73	3.85	3.85	3.77
11	2-OCH_3	3.44	3.53	3.57	3.61	3.40	3.43	3.66	3.64	3.62	3.70
12	4-OCH_3	3.42	3.44	3.52	3.60	3.48	3.48	3.79	3.61	3.76	3.70
13	4-OC_2H_5	3.52	3.49	3.69	3.67	3.52	3.49	3.67	3.71	3.73	3.72
14	2-CH_3	3.48	3.48	3.54	3.57	3.41	3.45	3.64	3.73	3.74	3.74
15	3-CH_3	3.39	3.39	3.64	3.54	3.45	3.56	3.59	3.60	3.72	3.67
16	4-CH_3	3.39	3.39	3.67	3.56	3.53	3.50	3.53	3.56	3.50	-
17	3-NO_2	3.58	3.56	3.70	3.68	3.52	3.58	3.71	3.67	3.75	3.77
18	4-NO_2	3.57	3.50	3.65	3.59	3.58	3.52	3.68	3.72	3.80	3.85
19	4-CHO	3.54	3.49	3.59	3.58	3.38	3.49	3.62	3.67	3.91	3.82
20	4-$C(CH_3)_3$	3.67	3.71	3.77	3.79	3.56	3.60	3.84	3.85	3.94	3.96
21	2,4-Cl_2	3.57	3.56	3.44	-	3.53	3.53	4.09	4.02	3.57	-
22	2,4-$(OH)_2$	3.36	3.46	3.58	3.55	3.47	3.48	3.53	3.62	3.75	3.76
23	3,5-$(OH)_2$	3.48	3.51	3.57	3.58	3.29	-	3.45	3.62	3.82	3.82
24	3,4-$(OCH_3)_2$	3.62	3.66	3.61	3.70	3.39	3.38	3.68	3.78	3.50	3.60
25	5-Cl, 2-OH	3.63	3.60	3.60	3.56	3.51	3.49	3.88	3.78	3.66	3.65
26	5-HSO_3, 2-OH	3.80	-	3.65	-	3.63	-	3.83	-	3.80	-
27	2-Cl, 5-NO_2	3.53	3.56	3.72	3.65	3.73	3.59	4.34	4.11	3.68	3.77
28	3,5-$(NO_2)_2$, 2-OH	3.72	3.68	3.67	3.67	3.82	3.73	3.80	-	3.54	3.48

reveal that less the value of this parameter more is the activity. The positive sign with MR(o) and Σ MR(p) shows the bulky substituents at *ortho* and *para* positions enhances the activity. The positive sign with ΣL(m) and ΣB1(p) shows that the activity increases with increase in length of *meta* substituent and width of *para* substituent in the aryl ring of the triazoles.

Regression Eqs 7 to 9 were obtained for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *Fusarium oxysporum*. Eq. 9 which comprises ΣMR(o), ΣMR(p) and ΣB4(m) terms is the statistically best fit and accounts for 60.68% (r=0.779) variation in fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *Fusarium oxysporum*. Eq. 9 and all the three terms in it are significant at 99% level. The –log ED_{50} (M) values calculated by Eq. 6 (**Table II**) are comparable with the observed values. The positive sign with ΣMR(o), ΣMR(p) and ΣB4(m) shows that bulkiness of *ortho* and *para*-substituent and width of *meta*-substituent enhances the fungicidal activity of the triazoles against *F. oxysporum.*

Regression Eqs 10 to 12 were obtained for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *P. aphanidermatum.* Eq. 12 which comprises ΣB1(m), ΣB1(p) and $(R_M)^2$ terms is significant at 99% level and explains 48.16% (r=0.694) variation in fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *P. aphanidermatum*. The ΣB1(m) term in Eq. 12 is significant at 99% level and the other two terms, ΣB1(p) and $(R_M)^2$ at 95% level. Eq. 12 could not be improved further by addition of any other term and is thus the

Table III — Physicochemical parameters of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles used in QSAR analysis

Compd	R (In structure **I**)	Physicochemical parameters											
		Σπ	Σσ	ΣF	ΣMR(o)	ΣMR(m)	ΣMR(p)	ΣL(m)	ΣB1(o)	ΣB1(m)	ΣB1(p)	ΣB4(m)	R_M
1	H	0.00	0.00	0.00	2.06	2.06	1.03	4.12	2.00	2.00	1.00	2.00	-0.011
2	4-NH_2	-1.23	-0.66	0.00	2.06	2.06	5.42	4.12	2.00	2.00	1.50	2.00	-0.057
3	2-Cl	0.71	0.23	0.41	7.06	2.06	1.03	4.12	2.80	2.00	1.00	2.00	-0.046
4	3-Cl	0.71	0.37	0.00	2.06	7.06	1.03	5.58	2.00	2.80	1.00	2.80	-0.017
5	4-Cl	0.71	0.23	0.00	2.06	2.06	6.03	4.12	2.00	2.00	1.80	2.00	0.000
6	2-F	0.14	0.06	0.43	1.95	2.06	1.03	4.12	2.35	2.00	1.00	2.00	-0.057
7	4-F	0.14	0.06	0.00	2.06	2.06	0.92	4.12	2.00	2.00	1.35	2.00	-0.046
8	2-OH	-0.67	-0.37	0.29	3.88	2.06	1.03	4.12	2.35	2.00	1.00	2.00	-0.017
9	4-OH	-0.67	-0.37	0.00	2.06	2.06	2.85	4.12	2.00	2.00	1.35	2.00	-0.075
10	2-SH	0.39	0.15	0.28	10.25	2.06	1.03	4.12	2.70	2.00	1.00	2.00	-0.034
11	2-OCH_3	-0.02	-0.27	0.26	8.90	2.06	1.03	4.12	2.35	2.00	1.00	2.00	-0.162
12	4-OCH_3	-0.02	-0.27	0.00	2.06	2.06	7.87	4.12	2.00	2.00	1.35	2.00	-0.058
13	4-OC_2H_5	0.38	-0.24	0.00	2.06	2.06	12.47	4.12	2.00	2.00	1.35	2.00	-0.005
14	2-CH_3	0.56	-0.17	-0.04	6.68	2.06	1.03	4.12	2.52	2.00	1.00	2.00	0.026
15	3-CH_3	0.56	-0.07	0.00	2.06	6.68	1.03	5.06	2.00	2.52	1.00	3.04	-0.016
16	4-CH_3	0.56	-0.17	0.00	2.06	1.03	5.65	4.12	2.00	2.00	1.52	2.00	0.047
17	3-NO_2	-0.28	0.71	0.00	2.06	8.39	1.03	5.50	2.00	2.70	1.00	3.44	0.122
18	4-NO_2	-0.28	0.78	0.00	2.06	2.06	7.36	4.12	2.00	2.00	1.70	2.00	0.058
19	4-CHO	-0.65	0.42	0.00	2.06	2.06	6.88	4.12	2.00	2.00	1.60	2.00	0.133
20	4-$C(CH_3)_3$	1.98	-0.20	0.00	2.06	2.06	19.62	4.12	2.00	2.00	2.59	2.00	0.101
21	2,4-Cl_2	1.42	0.46	0.41	7.06	2.06	6.03	4.12	2.80	2.00	1.80	2.00	-0.005
22	2,4-$(OH)_2$	-1.34	-0.74	0.29	3.88	2.06	2.85	4.12	2.35	2.00	1.35	2.00	0.047
23	3,5-$(OH)_2$	-1.34	0.24	0.00	2.06	5.70	1.03	5.48	2.00	2.70	1.00	3.86	0.215
24	3,4-$(OCH_3)_2$	-0.04	-0.15	0.00	2.06	8.90	7.87	6.04	2.00	2.35	1.35	3.87	0.413
25	5-Cl, 2-OH	0.04	0.00	0.29	3.88	7.06	1.03	5.58	2.35	2.80	1.00	2.80	0.349
26	5-HSO_3, 2-OH												-0.115
27	2-Cl, 5-NO_2	0.43	0.94	0.41	7.06	8.39	1.03	5.50	2.80	2.70	1.00	3.44	-0.098
28	3,5-$(NO_2)_2$, 2-OH	-1.23	1.05	0.29	3.88	14.72	1.03	6.88	2.35	3.40	1.00	4.88	-0.046

Table IV — Correlations for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles

Eq. No.	Regression Equation, -log ED_{50} (M)=	n	s	r	Fv_1,v_2 (*)
	Sclerotium rolfsii				
1	3.170 + 0.069ΣL(m) (± 0.054)	26	0.102	0.481	$F_{1, 24}$ = 7.23
2	3.042 + 0.013 ΣMR(p) + 0.084 ΣL(m) (± 0.008) (± 0.046)	26	0.085	0.702	$F_{2, 23}$ = 11.18
3	2.854 + 0.025 ΣMR(o) + 0.019 ΣMR(p) + 0.100 ΣL(m) (± 0.012) (± 0.007) (± 0.035)	26	0.064	0.852	$F_{3, 22}$ = 19.46
4	2.833 - 0.168 ΣF + 0.033 ΣMR(o) + 0.019 ΣMR(p) + 0.101 ΣL(m) (± 0.191) (± 0.014) (± 0.006) (± 0.033)	26	0.061	0.874	$F_{4, 21}$ = 17.00
5	2.623 - 0.202 ΣF + 0.036 ΣMR(o) + 0.011 ΣMR(p) + 0.117 ΣL(m) + 0.127 ΣB1(p) (± 0.175) (± 0.013) (± 0.009) (± 0.033) (± 0.113)	26	0.055	0.903	$F_{5, 20}$ = 17.68
6	2.580 - 0.036 Σπ - 0.203 ΣF + 0.040 ΣMR(o) + 0.012 ΣMR(p) + 0.114 ΣL(m) + 0.157 ΣB1(p) (± 0.031) (± 0.159) (± 0.013) (± 0.008) (± 0.029) (± 0.105)	26	0.049	0.927	$F_{6, 19}$ = 19.35 (3.94)
	Fusarium oxysporum				
7	3.540 + 0.011 ΣMR(p) (± 0.007)	26	0.083	0.525	$F_{1, 24}$ = 9.14
8	3.420 + 0.012 ΣMR(p) + 0.046 ΣB4(m) (± 0.007) (± 0.039)	26	0.075	0.651	$F_{2, 13}$ = 8.45
9	3.320 + 0.019 ΣMR(o) + 0.016 ΣMR(p) + 0.054 ΣB4(m) (± 0.012) (± 0.006) (± 0.033)	26	0.064	0.779	$F_{3, 22}$ = 11.33 (4.82)
	Pythium aphanidermatum				
10	3.209 + 0.135 ΣB1(m) (± 0.099)	26	0.091	0.497	$F_{1, 24}$ = 7.86
11	3.167 + 0.161 ΣB1(m) - 0.954 $(R_{M)}{}^2$ (± 0.097) (± 0.917)	26	0.085	0.611	$F_{2, 23}$ = 6.84
12	2.957 + 0.201 ΣB1(m) + 0.096 ΣB1(p) - 0.997 $(R_M)^2$ (± 0.097) (± 0.093) (± 0.857)	26	0.079	0.694	$F_{3, 22}$ = 6.80 (4.82)
	Puccinia recondita				
13	2.847 + 0.386ΣB1(o) (± 0.208)	27	0.150	0.607	$F_{1, 25}$= 14.62
14	2.561 + 0.016 ΣMR(p) + 0.485 ΣB1(o) (± 0.013) (± 0.206)	27	0.137	0.705	$F_{2, 24}$ = 11.84
15	2.467 + 0.019 ΣMR(m) + 0.020 ΣMR(p) + 0.488 ΣB1(o) (± 0.016) (± 0.013) (± 0.188)	27	0.124	0.775	$F_{3, 23}$ = 11.54
16	2.541 + 0.110 Σσ + 0.022 ΣMR(m) + 0.019 ΣMR(p) + 0.453 ΣB1(o) (± 0.112) (± 0.016) (± 0.012) (± 0.180)	27	0.117	0.815	$F_{4, 22}$ = 10.87 (4.31)
	Bipolaris sorokiniana				
17	3.809 + 0.018 ΣMR(m) (± 0.013)	23	0.100	0.526	$F_{1, 21}$ = 8.02
18	3.808 + 0.087 Σσ - 0.017 ΣMR(m) (± 0.092) (± 0.012)	23	0.094	0.627	$F_{2, 20}$ = 6.48
19	3.773 + 0.131 Σσ + 0.017 ΣMR(m) + 0.064 (Σπ)2 (± 0.079) (± 0.010) (± 0.038)	23	0.075	0.793	$F_{3, 19}$ = 10.74 (5.01)

*Litterature value at 99% level

Table V — Correlation matrix for the parameters used in regression equations

	Σπ	Σσ	ΣF	ΣMR(o)	ΣMR(m)	ΣMR(p)	ΣL(m)	ΣB1(o)	ΣB1(m)	ΣB1(p)	ΣB4(m)	$(\Sigma\pi)^2$	$(R_M)^2$
Σπ	1.000												
Σσ	0.206	1.000											
ΣF	0.169	0.052	1.000										
ΣMR(o)	0.231	0.135	0.571	1.000									
ΣMR(m)	-0.273	-0.133	0.029	-0.014	1.000								
ΣMR(p)	0.329	-0.019	-0.283	-0.363	-0.255	1.000							
ΣL(m)	-0.316	-0.063	-0.090	-0.099	0.926	-0.184	1.000						
ΣB1(o)	0.282	0.189	0.729	0.865	0.088	-0.399	-0.017	1.000					
ΣB1(m)	-0.314	-0.042	-0.079	-0.071	0.885	-0.257	0.952	0.023	1.000				
ΣB1(p)	0.420	0.044	-0.187	-0.292	-0.326	0.809	-0.371	-0.295	-0.413	1.000			
ΣB4(m)	-0.387	-0.085	-0.010	-0.096	0.893	-0.164	0.965	-0.022	0.909	-0.353	1.000		
$(\Sigma\pi)^2$	0.292	-0.251	0.117	-0.056	0.045	0.461	0.002	0.022	0.041	0.614	0.062	1.000	
$(R_M)^2$	-0.148	-0.000	-0.350	-0.086	0.404	0.049	0.494	-0.101	0.284	-0.078	0.423	-0.142	1.000

statistically the best fit possible. The –log ED_{50} (M) values calculated by Eq. 12 (**Table II**) are comparable with the observed values. The Eq. 12 reveals that the fungicidal activity of triazoles increases with increase in width (ΣB1) of *meta* and *para* substituents in aryl ring. The negative sign with $(R_M)^2$ means that both positive and negative values of R_M of the triazoles decreases the fungicidal activity against *P. aphanidermatum.*

Regression Eqs 13 to 16 were obtained for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *Puccinia recondita.* Eq 16 which comprises Σσ, ΣMR(m), ΣMR(p) and ΣB1(o) is the statistically best-fit and accounts for 66.42% (r=0.815) variation in fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *Puccinia recondita.* Eq. 16 and all the terms in it except Σσ are significant at 99% level, the Σσ term is significant at 95% level. The –log ED_{50} (M) values calculated by Eq. 16 (**Table II**) are comparable with the observed values. The positive sign with Σσ shows that electron withdrawing substituents will enhance the fungicidal activity of triazoles. The positive sign with ΣMR(m), ΣMR(p) and ΣB1(o) reveal that bulkiness of *meta* and *para* substituents and width of *ortho* substituents enhances the fungicidal activity of triazoles of this series against *P. recondita.*

Regression Eqs. 17 to 19 were obtained for the fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *B. sorokiniana.* Eq. 19 which comprises Σσ, ΣMR(m) and $\Sigma\pi^2$ is the statistically best-fit and accounts for 62.88% (r=0.793) variation in fungicidal activity of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles against *B. sorokiniana.* Eq. 19 and all the three terms in it are significant at 99% level. The –log ED_{50} (M) values calculated by Eq. 19 (**Table II**) are comparable with the observed values. The positive sign with Σσ and ΣMR(m) shows that electron withdrawing and bulky substituents at *meta* position will enhance the fungicidal activity of triazoles of this series against *B. sorokiniana*. The positive sign with $\Sigma\pi^2$ indicate that the high positive or negative value of Σπ enhances the fungicidal activity against *B. sorokiniana* in this series.

The QSAR models obtained for the fungicidal activity of 5-aryl-4-amino-3-mercapto-1,2,4-triazoles against *S. rolfsii, F. oxysporum, P. aphanidermatum, P. recondita* and *B. sorokiniana* have clearly shown that the position dependent effect of steric parameters of the aryl substituents are playing an important role in imparting fungicidal activity against all the test fungi. The similar position dependent steric effect of the benzene ring substituents on fungicidal activity have been reported earlier in some series of organophosphorus compounds[9,10]. The positive sign associated with each term of the steric parameters indicate that their higher values enhance the fungicidal activity in this series. Besides the steric parameters, hydrophobicity expressed as π in case of *S. rolfsii* and *B. sorokiniana* and R_M in case of *P. aphanidermatum* and the electronic parameters σ in case of *P. recondita* and *B. sorokiniana* and F in case of *S. rolfsii* are also important in contributing to fungicidal activity of the compounds against the respective fungi. The QSAR study has thus revealed different structural requirement for fungicidal activity

Table VI — ^{1}H NMR data of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles

Compd	R (In structure **I**)	^{1}H NMR (δ, ppm)			
		NH_2 (s)	SH(s)	Ar-H(m)	Ar-Substituent-H
1	H	5.14	13.61	7.85-8.15	
2	4-NH_2	5.12	13.92	8.00	
3	2-Cl	4.84	14.00	8.23	
4	3-Cl	5.10	13.91	7.23-7.49	
5	4-Cl	5.70	13.87	7.62-8.11	
6	2-F	5.83	14.10	7.25-7.89	
7	4-F	5.80	13.26	8.00-8.75	
8	2-OH	5.30	13.82	6.80-7.40	
9	4-OH	5.60	13.02	6.80-7.85	
10	2-SH	4.60	13.40	5.50-6.90	
11	2-OCH_3	4.21	13.78	6.83-7.37	3.90, s, -OCH_3
12	4-OCH_3	5.48	13.91	7.01-7.98	3.78, s, -OCH_3
13	4-OC_2H_5	4.45	13.82	7.30-8.00	3,98, m, -OCH_2CH$_3$; 1.81, t, -OCH$_2$CH_3
14	2-CH_3	5.51	13.99	7.52	2.31, s, -CH_3
15	3-CH_3	5.87	14.79	8.02	2.31, s, -CH_3
16	4-CH_3	5.49	13.96	7.21-8.02	2.41, s, -CH_3
17	3-NO_2	5.10	12.50	7.60-8.45	
18	4-NO_2	4.60	12.90	7.50-8.30	
19	4-CHO	4.61	13.68	5.20-5.90	8.15, s, -C*H*O
20	4-C(CH_3)$_3$	4.31	13.00	7.20-8.35	2.58-2.75, s, -C(CH_3)$_3$
21	2,4-Cl_2	5.60	13.75	6.20-6.90	
22	2,4-$(OH)_2$	5.50	13.46	6.20-6.70	
23	3,5-$(OH)_2$	5.80	13.00	5.10-6.51	
24	3,4-$(OCH_3)_2$	5.65	13.01	6.30-8.40	
25	5-Cl, 2-OH	5.55	13.89	6.90-8.00	
26	5-HSO_3, 2-OH	4.15	13.85	6.45-8.10	
27	2-Cl, 5-NO_2	4.23	13.10	7.64-8.40	
28	3,5-$(NO_2)_2$, 2-OH	4.75	13.65	8.05	

of 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazoles against the different fungi.

Experimental Section

4-Amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles I. The compounds, 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles having different substituents in the phenyl ring (**Table I**) were prepared following a four step synthesis scheme starting with aryl acids which were first converted to methyl esters→aryl acid hydrazides→potassium salt of aryl dithiocarbazinic acids→triazoles by the methods reported earlier[8]. In the final step, the preparation of triazoles, besides by using conventional methods, was attempted using microwaves which was found much faster and efficient (Time of reaction: 29-65 s, Yield increase: 2-18%) compared to the conventional methods (Time: 4-10 hr). The structure of triazoles were confirmed by IR and ^{1}H NMR (**Table VI**). The IR spectra (υ_{max} in cm^{-1}) were recorded on a Nicolet FT-IR spectrophotometer, Model Impact-400 using KBr pellets. The ^{1}H NMR spectra (chemical shifts in δ, ppm) were recorded on a Varian EM 360L, 60 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. The IR spectra showed peaks for N-H (3242-3310 cm^{-1}), C=N (1481-1575 cm^{-1}), S-H (2524-2800 cm^{-1}), C-H aromatic (3000-3100 cm^{-1}) and C-C aromatic (1612-1643 cm^{-1}). The ^{1}H NMR of 4-amino-5-substituted aryl-3-mercapto-(4*H*)-1,2,4-triazoles showed characteristic peaks, singlet for –NH_2 (δ 4.15-5.81) and singlet for S-H (δ 12.50-14.79).

Fungitoxicity testing

The fungitoxicity testing of 5-aryl-4-amino-3-mercapto-1,2,4-triazoles was carried out by two methods, spore germination inhibition technique for *Puccinia recondita* and *Bipolaris sorokiniana* and poisoned food technique using potato-dextrose agar (PDA) medium for *Rhizoctonia solani, Sclerotium rolfsii, Fusarium oxysporum* and *Pythium aphanidermatum* as described by Nene and Thapliyal[11]. The inhibition of fungus growth was recorded in case of *R. solani, S. rolfsii, F. oxysporium* and *P. aphanidermatum* and inhibtion of spore germination in case of *P. recondita* and *B. sorokiniana.* The ED_{50} values (mg mL^{-1}) were determined from the respective spore germination/ growth inhibition data by means of BASIC LD_{50} programme version 1:1 (Ref 12) and are given in **Table I**. These were converted to molar activity and its negative logarithm, -log ED_{50} (M) values (**Table II**) were used in QSAR analysis.

Physicochemical parameters

R_M values were used as a measure of hydrophobicity and were experimentally determined. Values for other physicochemical parameters of benzene ring substituents used in the correlation analysis *i.e.* Hansch π values for hydrophobicity, Hammett constant σ for electronic, molar refractivity (MR) and Verloop STERIMOL parameters L, B1 and B4 for steric were taken from literature[13]. For the electronic effect of *ortho*-substituents, σ values of the corresponding *para*-substituents[14] along with Swain-Lupton constant (F) for proximity polar effect suggested by Fujita and Nishioka[15] were taken. The additive nature of all the substituent constants was presumed; the σ and π values of multisubstituents[16], *i.e.* di- and tri-substituted compounds were obtained by adding the values of all ring substituents corresponding to their positions. The values for steric parameters were used as a summation for each position *i.e. ortho*, *meta* or *para*. The values of the various physicochemical parameters used in regression equations of **Table IV** are given in **Table III**.

R_M values: R_M values were obtained by calculations from R_f values, which were determined by reverse phase TLC[17]. Silica gel coated TLC plates (20×20 cm; 250 μm thick) were activated in an oven at 100°C for 2 hr, cooled and then coated with paraffin by developing in a solution of liquid paraffin in *n*-hexane (50 ml L^{-1}). The plates were dried at RT and spotted with test compounds dissolved in DMSO. Nine compounds were spotted on one plate spaced at equal distance from each other. 5-Phenyl-4-amino-3-mercapto-1,2,4-triazole was used as reference standard on all plates. The plates were developed in acetone. The solvent was run 14 cm from the origin. The spots were visualized in iodine. R_f values were measured in three replications. R_M values were then calculated from the average R_f values for each compound, using the formula, $R_M = \log [(1/R_f)-1]$ (Ref. 18).

Structure activity correlations

The structure activity correlations were analyzed by the multiple regression analysis technique[19], using measured -log ED_{50} (M) values for the fungicidal activity of the compounds as dependent variable and the physicochemical parameters for hydrophobic, electronic and steric properties of each member of the series as independent variables. The significance of regression equations was examined by F and Student's t test.

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