International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

QSAR Modeling of 1, 2, 4-Triazole [5,1-i] Purine Derivatives with Adenosine Receptor Subtype

Sukhendra Singh Patel[1] Shailja Sachan[2], Priyanka Dahiya[1], Anand ku. Lakhera [1]
[1]*Department of Chemistry, Awadhesh Pratap Singh University, Rewa (M.P.)*
[2]*Department of chemistry, M. S. Golvalkar college, Rewa(M.P.)*

Submitted: 05-01-2023 Accepted: 13-01-2023

ABSTRACT: In this research paper, the potential of human adenosine A_3 receptor antagonists in the development of prospective therapeutic cloned human adenosine A3 receptor subtype. Quantitative structure –activity relationship (QSAR) studies revealed that the activity is positively influenced by the presence of a aromatic R_2 substituent conjugated with the triazole nucleus contributes significantly to the selectivity. The best QSAR model with good correlation coefficient (r^2=0.94), of high statistical significance (>99.9%) well explained the variance in activity.

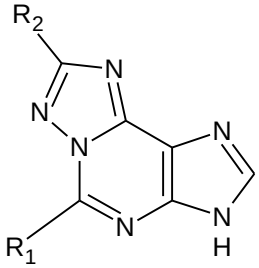
Keywords: QSAR, Adenosine A3 receptor, MLR

I. INTRODUCTION

Adenosine is a physicochemical purine nucleoside that functions as an agonist and activates the A1, A2a, A2b, and A3 G protein-coupled membrane receptors. Almost every cell contains adenosine receptors. Both in peripheral organs and tissues and in the CNS, adenosine is crucial in a variety of pathophysiological situations. Bronchoconstriction, platelet aggregation inhibition, lipolsis inhibition, sedation induction, vasodilation, reduction of heart rate and contractility, and promotion of gluconeogenesis are only a few of the physiological actions that adenosine can mediate[1–5].

Activation of A_3 agonist causes stimulation of phospholipase D and the release of inflammatory mediators such as histamine from mast cells, which are responsible for inflammation and hypotension. A_3 receptors block UV irradiation induced apoptosis in mast like cells[6].

Numerous compounds that act on A3 adenosine receptors have been the subject of quantitative structure activity relationship (QSAR) investigations. Topological, connectedness, lipophilicity, and quantum chemical descriptors are used in QSAR modeling of A3. The 1,2,4 triazolo [5,1-i] purine derivatives' adenosine receptor binding affinity data (Table 1) were employed for the current QSAR study[7–10].Table 1. Structural features, and adenosine receptor binding affinities of 1, 2, 4-triazolo [5,1-i] purine derivatives



S.No.	Structural Features		A_3 binding affinity(pC3)
	R_1	R_2	
1	CH_3	Ph	3.044
2.	C_2H_5	Ph	3.434
3.	n-C_3H_7	Ph	3.216
4.	n-C_4H_9	Ph	3.47
5.	n-C_5H_{11}	Ph	3.427
6.	n-C_6H_{13}	Ph	3.008
7.	Ph	Ph	3.339

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

8.	n-C_4H_9	CH_3	0.06
9.	n-C_4H_9	$PhCH_2$	0.322
10.	n-C_4H_9	3-Pyridyl	2.527
11.	n-C_4H_9	2-Furyl	2.603
12.	n-C_4H_9	Ph(2-Cl)	3.322
13.	n-C_4H_9	Ph(3-Cl)	3.025
14.	n-C_4H_9	Ph(4-Cl)	3.166
15.	n-C_4H_9	Ph(4-F)	3.424
16.	n-C_4H_9	Ph(4-Br)	3.063
17.	n-C_4H_9	Ph(3-CH_3)	3.328
18.	n-C_4H_9	Ph(4-CH_3)	3.333
19.	n-C_4H_9	Ph(4-t-CH_4H_9)	2.653
20.	n-C_4H_9	Ph(4-CF_3)	3.14
21.	n-C_4H_9	Ph(4-Ph)	2.689
22.	n-C_4H_9	Ph(4-OH)	3.5
23.	n-C_4H_9	Ph(3-OCH_3)	3.378
24.	n-C_4H_9	Ph(4-OCH_3)	3.59
25.	n-C_4H_9	Ph(4-OC_2H_5)	3.561
26.	n-C_4H_9	Ph(4-OC_2H_5)	3.381
27.	n-C_4H_9	Ph(3,4,5-OCH_3)$_3$	3.381
28.	n-C_4H_9	Ph(4-SCH_3)	3.189
29.	n-C_4H_9	Ph(4-N(CH_3)$_2$)	3.532

Chemsketch 19 was used to design the chemical structures, which were saved as.mol files. The Dragon program was used to calculate the values of the 29 descriptors shown in Table 2. Indices are 2D descriptors that take into account the internal atomic arrangement of compounds and encode in numerical form information about molecular size, shape, branching, the presence of heteroatoms, and multiple bonds. Indices are a very useful tool for QSAR, taking into account their simplicity and rapidity of computation. This is particularly valuable now as one can analyze structures used for QSAR studies prior to any high throughput synthesis and testing.

Table.2 : Values of molecular descriptors used in the regression analysis

S.No.	pC3	Xt	SNar	PW3	RDCHI	piPC02	piPC09	RCI	IDMT
1	3.044	0.256	15.315	0.356	3.196	4.131	7.804	1.222	4754.597
2	3.434	0.25	16.008	0.358	3.27	4.147	7.858	1.222	5579.584
3	3.216	0.245	16.701	0.347	3.365	4.163	7.891	1.222	6574.373
4	3.47	0.24	17.394	0.34	3.471	4.178	7.919	1.222	7752.072
5	3.427	0.235	18.087	0.335	3.582	4.193	7.931	1.222	9126.322
6	3.008	0.231	18.781	0.331	3.698	4.208	7.937	1.222	10711.07
7	3.339	0.224	19.879	0.349	3.674	4.347	8.322	1.167	9827.603
8	0.06	0.279	12.83	0.34	2.93	3.917	7.032	1.333	3335.597
9	0.322	0.235	18.087	0.332	3.606	4.193	7.681	1.222	9289.8
10	2.527	0.24	17.394	0.34	3.471	4.178	7.919	1.222	7752.072
11	2.603	0.245	16.701	0.344	3.384	4.131	7.792	1.235	6626.943
12	3.322	0.237	17.8	0.347	3.501	4.223	7.99	1.222	8813.071
13	3.025	0.237	17.8	0.34	3.52	4.223	7.978	1.222	8931.617
14	3.166	0.237	17.8	0.34	3.534	4.223	7.997	1.222	9047.161
15	3.424	0.237	17.8	0.34	3.534	4.223	7.997	1.222	9047.161

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

16	3.063	0.237	17.8	0.34	3.534	4.223	7.997	1.222	9047.161
17	3.328	0.237	17.8	0.34	3.52	4.223	7.978	1.222	8931.617
18	3.333	0.237	17.8	0.34	3.534	4.223	7.997	1.222	9047.161
19	2.653	0.228	19.186	0.339	3.725	4.307	8.076	1.222	13721.46
20	3.14	0.228	19.186	0.339	3.725	4.307	8.076	1.222	13721.46
21	2.689	0.211	22.364	0.343	4.078	4.422	8.213	1.167	17818.42
22	3.5	0.237	17.8	0.34	3.534	4.223	7.997	1.222	9047.161
23	3.378	0.233	18.493	0.345	3.605	4.238	8.009	1.222	10317.1
24	3.59	0.233	18.493	0.345	3.63	4.238	8.024	1.222	10551.5
25	3.561	0.228	19.186	0.337	3.738	4.252	8.033	1.222	12278.8
26	3.381	0.224	19.879	0.333	3.851	4.266	8.043	1.222	14243.11
27	3.381	0.22	20.69	0.361	3.82	4.347	8.183	1.222	16499.23
28	3.189	0.233	18.493	0.345	3.63	4.238	8.024	1.222	10551.5
29	3.532	0.23	18.898	0.344	3.689	4.266	8.05	1.222	12110.54

II. MATERIALS AND METHODS

The QSAR analysis was carried out on the set of 35 compounds as shown in table 1, taking the adenosine A_3 agonists pC3 as dependent and different topological parameters as independent parameters. The multiparameter regression analysis was executed on a personal computer using NCSS version 2019. The pearson correlation matrix was constructed to determine the inter-correlation between the physiochemical parameters used in QSAR analysis [11-14]. The correlation matrix that was produced is shown in Table 3. The descriptors that were used by the models are the mean information content based on the vertex degree equality and the edge equality both.

The correlation matrix for the aforementioned indicators is presented in Table 3 and shows that there is significant correlation among the descriptors. From the correlation matrix we can also conclude that of the aforementioned indices is highly correlated with the activity. This means that it is possible to obtain a statistically significant mono-parametric model. Based on the correlation matrix we conclude that only multi-parametric regressions involving combinations of the indices mentioned before may result in a statistically significant regression expression [15-18].

Table 3. Correlation Matrix among biological activity and Indices

	pC3	**Xt**	**SNar**	**PW3**	**RDCHI**	**piPC02**	**piPC09**	**RCI**	**IDMT**
pC3	1.0000								
Xt	-0.4725	1.0000							
SNar	0.4095	-0.9899	1.0000						
PW3	0.2665	0.1145	-0.0899	1.0000					
RDCHI	0.3711	-0.9794	0.9867	-0.2129	1.0000				
piPC02	0.5070	-0.9616	0.9584	0.0635	0.9207	1.0000			
piPC09	0.7563	-0.8828	0.8421	0.1510	0.7890	0.9241	1.0000		
RCI	-0.5557	0.7946	-0.7594	-0.1270	-0.6955	-0.8370	-0.8878	1.0000	
IDMT	0.2813	-0.8990	0.9341	-0.1003	0.9477	0.8721	0.6807	-0.5154	1.0000

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

The DRAGON software has been used for the parameterization of the compounds under study. This software offers several hundreds of descriptors from different perspectives relating to empirical, constitutional and topological indices characteristic to the molecules under multi-descriptor class environment. [19-23].

III. 3. RESULTS AND DISCUSSION

To create relevant QSAR equations, several combinations of independent descriptors with some acceptable association with the adenosine A3 antagonists were tested using stepwise multiple regression analysis. The equations were statistically significant, with a correlation value of more than 0.8 and significant regression coefficient values of more than 99.9ultiple regression analysis was used to create relevant QSAR equations. The equations were statistically significant, with a correlation value more than 0.8 and significant regression coefficient values greater than 99.9%. The number of regression equations with correlation coefficients greater than or equal to the one corresponding to unscrambled response data was tallied. The best model was chosen among the numerous models based on a high F-ratio, a low SE, R, and R2CV.values close to 1.

Model No.1

pC3 = -20.0380(±3.8378)+2.8958(±0.4821)piPC09

N= 29
R^2 = 0.5719
AR2=0.5561
Se =0.5544
F –Ratio = 36.072, Q=1.031

Here and thereafter, N = number of data points, R = correlation coefficient, SE = standard error of estimation, and F = Fischer statistics. Because the piPC09 coefficient in Model No. 1 is high, the piPC09 has a positive correlation with inhibitory activity.

Model No.2

pC3 = -4.4361(±3.5815)+7.5441(±0.8243)piPC09-12.4541(±2.0410)piPC02

N= 29
R^2= 0.8240
AR2=0.8104
Se =0.3622
F –Ratio = 60.855,
Q=0.2749

Topological indices are numerical quantifiers of molecular topology and are sensitive to bonding patterns, symmetry, the content of heteroatoms, and the degree of complexity of atomic neighborhoods. Since the structure of a compound depends on information based on connectivity, it can reveal the role of structural or sub-structural information in a molecule in estimating biological activity.

Model No.3

pC3 = 20.1966(±7.8518)+9.6724(±0.9357)piPC09-22.6869(±3.4680)piPC02+0.0001(±4.9066) IDMT

N= 29
R^2 = 0.8796
AR2=0.8652
Se =0.3055
F –Ratio = 60.885,
Q=2.8755

Model No.4

pC3 = -9.6119(±12.5853)+10.6092(±0.8898)piPC09-20.5196(±3.1565)piPC02

+0.0002(±5.2159)IDMT+52.5167(±18.5037)Xt

N= 29
R^2 = 0.9099
AR2=0.8855
Se =0.2698
F –Ratio = 60.564,
Q= 3.372

The QSAR models 3 and 4 are significant, with positive contributions from piPC09, IDMT, and Xt and an inverse contribution from piPC02 with inhibiton activity. After deleting outlier compound no.10, the final model becomes

Model No.5

pC3 = -4.5673(±10.9772)+10.7846(±0.7694)piPC09-21.6803(±2.7482)piPC02+0.0002(±4.5024)IDMT+46.3697(±16.0819)Xt

N= 28
R^2 = 0.9350
AR2=0.9260
Se =0.2326
F –Ratio = 82.695,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

Q=4.019

The derived equations demonstrated the significance of the dependent variables, particularly the molecular multiple path count of orders 02 and 09, IDMT (total information content on the magnitude of the distance), and Xt (total structure connectivity index). The best model was QSAR model no. 5, which had the greatest regression coefficient (R2 = 0.93) and explained 93.5% of the variation in activity. The model's low standard error of estimate (s) and high F value indicate that it is statistically significant.

Table 4: **Experimental and predicted activities pC3 of the molecules under study**

Compd. No	Obs. pC3	Pred. pC3	Res.
1	3.044	3.059205	-0.01521
2	3.434	3.216705	0.217295
3	3.216	3.235311	-0.01931
4	3.47	3.266068	0.203932
5	3.427	3.171976	0.255024
6	3.008	3.110637	-0.10264
7	3.339	3.710141	-0.37114
8	0.06	0.095152	-0.03515
9	0.322	0.515495	-0.1935
10	2.603	2.874161	-0.27116
11	3.322	3.17457	0.14743
12	3.025	3.073927	-0.04893
13	3.166	3.306878	-0.14088
14	3.424	3.306878	0.117122
15	3.063	3.306878	-0.24388
16	3.328	3.073927	0.254073
17	3.333	3.306878	0.026122
18	2.653	3.054895	-0.40189
19	3.14	3.054895	0.085105
20	2.689	2.245247	0.443753
21	3.5	3.306878	0.193122
22	3.378	3.233839	0.144161
23	3.59	3.452499	0.137501
24	3.561	3.433423	0.127577
25	3.381	3.529025	-0.14802
26	3.381	3.644875	-0.26388
27	3.189	3.452499	-0.2635
28	3.532	3.365138	0.166862

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

Table-1.5- Cross validation statistical parameters

MODEL NO	N	PRESS	SSY	PRESS/SSY	R^2	Adj R^2	R^2_{CV}	PSE	SPRESS
1	29	13.4	5.9865	2.2383	0.5719	0.5561	-1.23	0.1802	0.5544
2	29	3.4125	15.9744	0.2136	0.824	0.8104	0.7864	0.1483	0.1581
3	29	2.5989	16.78806	0.1548	0.8796	0.8652	0.8452	0.1115	0.3055
4	29	1.9025	17.4844	0.1048	0.9019	0.8855	0.8952	0.1016	0.2815
5	28	0.1546	17.997	0.00859	0.9397	0.926	0.9914	0.0579	0.229

We have undertaken a cross validation methodology for deciding the predictive power of the proposed model. It is necessary for a best model to have good statistics but this is not sufficient for good predictive potential.

The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The plot of observed vs predicted activity is shown in Fig. From the plot it can be sheen that MLR model is able to predict the activity of training set quit well (all Points are close to regression line) as well as external.

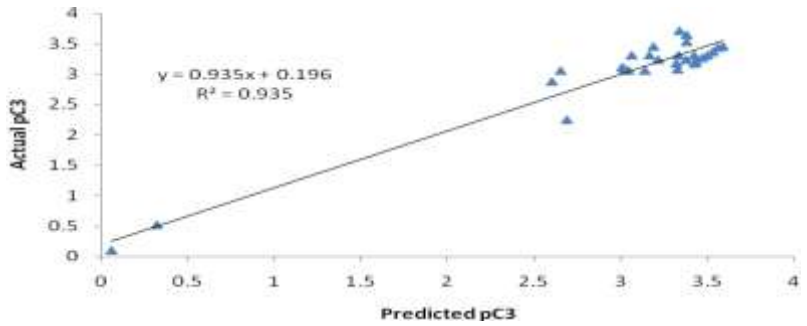


Figure 1: Plot of predicted versus experimentally observed inhibitory activities of under study molecules

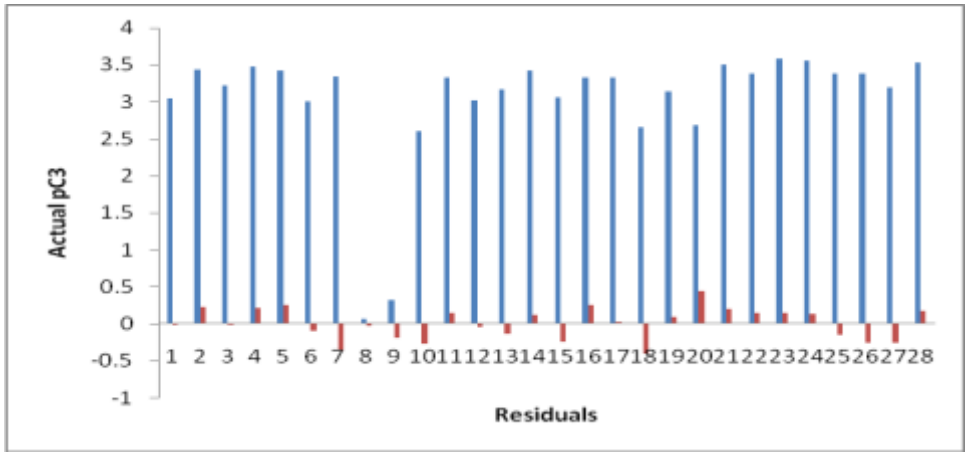


Figure 2: Plot of residual against experimental values of pC3

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 374-381 www.ijprajournal.com ISSN: 2249-7781

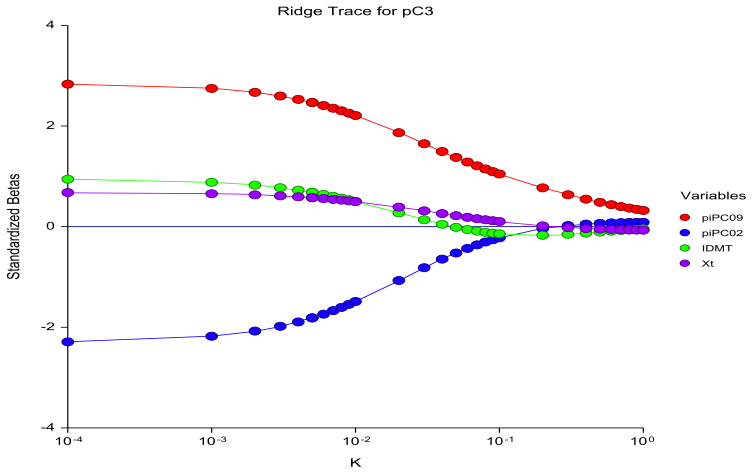


Figure 3. Graph of Ridge Regression

IV. CONCLUSION

We have evaluated the selective binding of 1,2,4-triazolo[5,1-i]purine derivatives with human adenosine A3 receptor subtype

1. Structure activity relationships model indicated that parabolic relation of the A3 receptors binding affinity with the piPc09, IDMT and Xt.
2. The negative coefficient of piPC02 that an aromatic substituent conjugated with the triazole nucleus should be present at R_2 position for the A3 binding affinity.
3. Presence of a 4 substituted phenyl ring at R2 position also increases selectivity as evidenced from the positive coefficients of piPC09, IDMT and Xt.

V. ACKNOWLEDGEMENTS

Dr. V.K. Agrawal, retired professor of chemistry at A.P.S. University, Rewa, provided invaluable advice and inspiration in carrying out this research. Dr. Shailja Sachan, associate professor, Dept. of Chemistry, M. S. Golvalkar College, Rewa, is especially grateful to UGC Bhopal for financial assistance in purchasing the NCSS and E-dragon software utilized in this work, which would not have been feasible without it.

REFERENCES

[1]. Palmer TM., **Drug Dev. Res.,**58(2003)302.
[2]. Lee HT., Gallos, G., **J. Biol. Chem**.,279(2004)19790.
[3]. Chen JF., **Drug Dev. Res**., 58(2003)354.
[4]. Doytchinova I., **Comput. Aided Mol. Des.,** 15(2001)15-29.
[5]. Roy K., **Indian J. Chem**., 42B(2003)1485.
[6]. Roy K., **QSAR Comb. Sci**., 22(2003)614.
[7]. Agrawal VK, Khadikar PV, Supuran CT, **Bioorg. Med. Chem.,** 15 (2007) 6501.
[8]. Elliott M., Janes, NF., Pearson BC., **J. Chem. Soc**., 14(1971)2551-2557.
[9]. Fouque F., Carinci R., **Bull. Soc. Pathol. Exot**., 89(1996) 115-119.
[10]. Agrawal VK, Khadikar PV, Deeb O, Supuran CT, **Chem. Bio. Drug Des.,** 71 (2008) 244.
[11]. Gillett J D., Ross RW., **Ann. Trop. Med. Parasitol**., 49(1955)63-65.
[12]. Gubler D J., **Am. J. Trop. Med. Hyg**.,40(1989)571-578.
[13]. Agrawal VK, Khadikar PV, Deeb O, **Chem. Bio Drug Des.,** 71(2008) 230.
[14]. Katritzky AR., Dobchev DA., Tulp I., **Bioorg. Med. Chem. Lett**., 16(2006) 2306-2311.
[15]. Lee SE., **J. Am. Mosq. Control Assoc**., 16(2000)245-247.
[16]. Malavige GN., Fernando S., Fernando DJ., **Med. J.,** 80(2004) 588-601.
[17]. Agrawal VK, Shrivastava J, Singh J, Shaik B, **Oxid. Commun.,** 31 (2008) 776.
[18]. Agrawal VK, Singh J, Singh S, Khadikar PV, **Oxid. Commun.,** 1 (2009) 28
[19]. Onyango CO., Grobbelaar A., **Emerg. Infect. Dis.,** 10(2004)1668-1670.
[20]. Onyango CO., Ofula VO., Emerg**. Infect. Dis**., 10(2004)1063-1068.
[21]. Park IK., Lee SG., Shin SC., **J. Agric. Food Chem**., 50(2002)1866-1870.

[22]. Philip CB., **Am. J. Trop. Med. Hyg**., 11(1962)697-701.
[23]. Agrawal VK, Singh J, Khadikar PV, **Oxid. Commun.,** 1 (2009) 40.
[24]. Rathnawathie M., Buckle KA., **J. Chromatogr**., 264(1983) 316-320.
[25]. Ribeiro TS., Previato JO., **Bioorg.Med. Chem. Lett**., 14 (2004)3555-3558.
[26]. Rudnick A., **Bull World Health Organ**., 36(1967) 528-532.
[27]. Shaalan EA., Canyon D., Younes MW., **Environ. Int**., 31(2005)1149-1166.
[28]. Soper FL., **Bull.World Health Organ**., 36(1967) 521-527.
[29]. Srivastava JB., **Indian J.Exp. Biol**., 8(1970)224-225.
[30]. Sukumar K., Perich MJ., Boobar LR., **J. Am. Mosq.Control Assoc**., 7(1991)10-237.
[31]. Valero N., **Invest. Clin**., 44**(2003)**269-71.
[32]. Vasconcelos PF., Rosa AP., Rodrigues SG., **Emerg. Infect. Dis.,** 7(2001)565-569.
[33]. Wang Q., Cheng J., **Pest Manag. Sci**., 58(2002)1250-1253.