Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(6):423-432

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Topological and Quantum chemical descriptors based Comparative Quantitative Structure-Activity Relationship of benzothiazole derivatives

Bhuwan B. Mishra*, Abhishek Giri, Rajesh K. Singh and Pashupati P. Singh

Department of Chemistry, Maharani Lal Kunwari Post Graduate College, Balrampur(U.P.), India

ABSTRACT

Comparative quantitative structure activity relationship study of twenty five benzothiazole derivatives has been presented. The study is mainly based on two sets of descriptors: topological descriptors and quantum chemical descriptors. For QSAR study, the structures of all the above compounds have been drawn and their geometries have been optimized with the help of CAChe software using PM3 Hamiltonian. The comparative study has shown that the best QSAR is constructed from quantum chemical properties: heat of formation, molecular weight, total energy and LUMO energy. Results emanated from this study show that these descriptors can be used as descriptors of biological activity.

Keywords: Benzothiazole derivatives, topological descriptors, quantum chemical descriptors, QSAR, PM3, CAChe software.

INTRODUCTION

In this work a comparative quantitative structure activity relationship (QSAR)[1] study of twenty five benzothiazoles is presented. The parent skeleton of benzothiazole is shown in Figure-1.

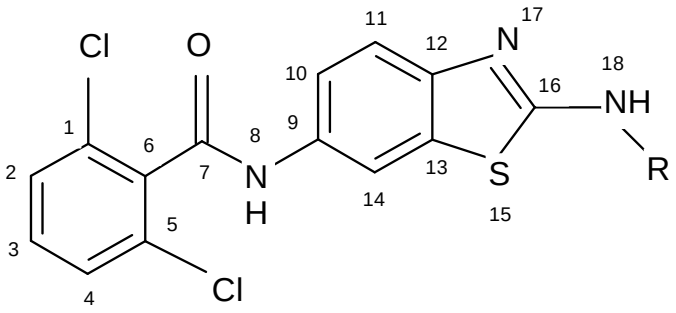


Figure-1.Parent skeleton of benzothiazole

The QSAR study is mainly based on two sets of descriptors. One is based on topological descriptors [2] and the other is based on quantum chemical descriptors.[3]

A. Topological descriptors: Following are the topological descriptors used in the study

1. Connectivity Index (order 0, standard)[4]
2. Valence Connectivity Index (order 0, standard)[4]
3. Shape Index (basic kappa, order 1)[5]
4. Shape Index (basic kappa, order 3)[5]
5. Dipole Moment
6. log P[6]
7. Solvent Accessible Surface Area[7]

B. Quantum Chemical Descriptors: Following are the quantum chemical descriptors used in the study

1. Heat of formation (ΔH_f)[8]
2. Molecular Weight (MW)[9]
3. Total energy (TE)[10]
4. Electronegativity (χ)[11]
5. Absolute Hardness (η)[12]
6. HOMO energy ($\in$HOMO)[13]
7. LUMO energy ($\in$LUMO)[13]

These two sets of descriptors have been used in deriving regression models.[14] The regression models as obtained by topological parameters have been compared with those obtained from quantum chemical parameters.

EXPERIMENTAL SECTION

The study materials of this paper are twenty five benzothiazole derivatives[15] and are presented in Table-1. For QSAR prediction, the structures of all the above compounds have been drawn and their geometries[16] have been optimized with the help of CAChe software[17] using PM3 Hamiltonian.[18] The values of above topological and quantum chemical descriptors have been obtained from same software and the results are included in Table 2 and 3, respectively.

RESULTS AND DISCUSSION

Although a number of topological and quantum chemical descriptors are known, in the present work only seven topological[2] and seven quantum chemical[3] descriptors, which provide better results, have been used. For QSAR prediction of inhibitors we have performed the MLR analysis by using all the topological parameters in one group and quantum chemical parameters all the in another group. Various QSAR models for each set of compounds with each group of descriptors in different combinations have been developed but only five top models of each set are reported here.

Table-1. Derivatives of benzothiazole

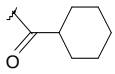
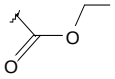
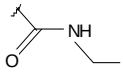
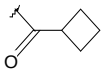
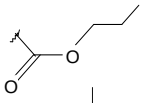
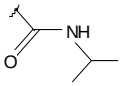
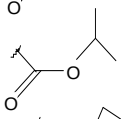
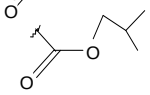
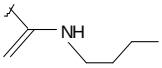
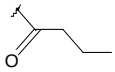
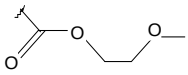
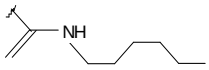
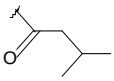
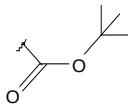
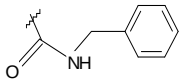
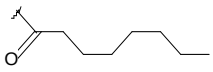
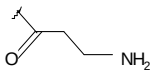
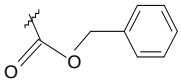
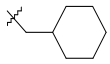
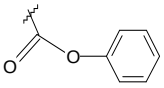
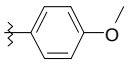
No.	R	-logEC$_{50}$	No.	R	-logEC$_{50}$	No.	R	-logEC$_{50}$
1.		8.09	10.		8.69	18.		7.55
2.		7.99	11.		8.48	19.		7.39
3.		7.75	12.		8.56			
4.		6.36	13.		8.56	20.		7.58
5.		7.65	14.		7.95	21.		6.49
6.		7.90	15.		7.56	22.		6.67
7.		6.82						
8.		5.28	16.		7.00	23.		5.37
9.		7.92	17.		6.00	24.		6.51
						25.		6.06

Table 2. Calculation of various topological descriptors of the compounds with OBA

No.	log P	$^{0}\chi_{t}$	$^{0}\chi^{v}_{t}$	^{1}K	σ	SASA	^{3}K	OBA (–logEC$_{50}$)
C1	4.870	20.380	17.833	21.611	3.839	185.916	5.438	8.090
C2	4.078	18.966	16.419	21.640	3.868	186.296	4.609	7.990
C3	3.682	18.259	15.712	21.738	3.912	187.208	4.224	7.750
C4	2.995	17.267	14.720	22.256	4.992	192.488	4.601	6.360
C5	4.019	18.681	16.135	21.775	3.986	187.588	5.299	7.650
C6	4.350	19.552	17.005	21.612	3.899	186.638	5.758	7.900
C7	5.605	21.510	18.963	22.084	4.998	190.741	7.259	6.820
C9	3.620	17.974	15.129	21.675	3.892	186.562	4.838	7.920
C10	3.963	18.681	15.836	21.388	3.624	183.637	5.299	8.690
C11	4.431	19.389	16.543	21.466	3.890	184.435	5.758	8.480
C12	4.376	19.552	16.706	21.436	3.990	184.131	5.758	8.560
C13	4.834	20.259	17.413	21.436	3.669	184.131	6.250	8.560
C14	3.455	20.096	16.951	21.664	3.881	186.448	6.250	7.950
C15	4.454	20.474	17.629	21.889	4.987	182.930	6.250	7.560
C16	5.397	21.794	18.222	22.890	4.987	190.057	6.533	7.000
C17	5.302	21.087	17.515	22.390	4.559	193.856	6.081	6.000
C18	3.313	18.681	15.927	21.885	5.121	187.968	5.299	7.550
C19	3.726	19.552	16.798	21.872	4.076	189.575	5.758	7.390
C20	5.576	20.096	17.641	21.801	4.019	187.854	6.250	7.580
C21	6.369	21.510	19.055	22.207	4.389	190.994	7.259	6.490
C22	4.747	21.794	18.314	22.199	4.329	191.310	6.533	6.670
C23	5.619	19.510	17.632	22.624	4.778	192.249	5.389	5.370
C24	5.324	18.518	16.641	22.299	4.389	191.918	5.518	6.510

Where C is the compound no., $^{1}\chi_{t}$ is connectivity index (order 1, standard), $^{0}\chi^{v}_{t}$ is valence connectivity index (order 0, standard), $^{1}K_{\alpha}$ is shape index (basic kappa, order 1), σ is dipole moment, SASA is solvent accessible surface area and ^{3}K is shape index (basic kappa, order

3)

Table 3. Calculation of various quantum chemical descriptors of the compounds with OBA

No.	ΔH_f (kcal/mole)	MW	TE (Hartree)	∈HOMO (eV)	∈LUMO (eV)	η	χ	OBA (– logEC_{50})
C1	-31.678	448.366	-208.469	-8.706	-0.771	3.967	4.739	8.090
C2	-32.123	420.312	-207.581	-8.780	-0.825	3.978	4.802	7.990
C3	-24.987	406.286	-207.850	-8.765	-0.830	3.968	4.798	7.750
C4	10.234	380.248	-208.407	-8.779	-0.838	3.971	4.809	6.360
C5	-22.983	408.301	-207.962	-8.771	-0.827	3.972	4.799	7.650
C6	-26.463	422.328	-207.682	-8.775	-0.824	3.975	4.800	7.900
C7	-10.234	464.409	-208.892	-8.776	-0.830	3.973	4.803	6.820
C9	-26.765	396.247	-208.660	-8.891	-0.945	3.973	4.918	7.920
C10	-47.123	410.274	-206.797	-8.858	-0.923	3.967	4.891	8.690
C11	-39.976	424.301	-207.033	-8.875	-0.930	3.973	4.902	8.480
C12	-46.997	424.301	-206.943	-8.855	-0.910	3.973	4.882	8.560
C13	-47.009	438.328	-206.943	-8.858	-0.923	3.968	4.891	8.560
C14	-29.001	440.300	-207.626	-8.889	-0.949	3.970	4.919	7.950
C15	-20.251	438.328	-208.063	-8.812	-0.876	3.968	4.844	7.560
C16	-16.789	472.345	-208.690	-8.981	-0.958	4.012	4.969	7.000
C17	12.008	458.318	-209.810	-8.891	-0.947	3.972	4.919	6.000
C18	-20.987	409.289	-208.074	-8.816	-0.835	3.991	4.826	7.550
C19	-16.998	423.316	-208.253	-8.908	-0.936	3.986	4.922	7.390
C20	-20.990	435.370	-208.040	-8.505	-0.775	3.865	4.640	7.580
C21	5.892	463.424	-209.261	-8.495	-0.779	3.858	4.637	6.490
C22	9.765	471.360	-209.060	-8.645	-0.746	3.949	4.696	6.670
C23	25.994	434.382	-210.516	-8.455	-0.704	3.875	4.579	5.370
C24	10.456	408.345	-209.239	-8.478	-0.710	3.884	4.594	6.510

ΔH_f° is heat of formation, MW is molecular weight, TE is total energy, ∈HOMO is energy of highest occupied molecular orbital, ∈LUMO is energy of lowest unoccupied molecular orbital, η is absolute hardness and χ is electronegativity

3A. QSAR Modeling with Topological Descriptors: Firstly we have been done QSAR study with the help of topological descriptors[2] and various QSAR models in different combinations of descriptors have also been developed but only five top models are reported and are presented as below

I. First QSAR model: The first QSAR model is obtained when multi linear regression analysis is done by taking connectivity index (order 0, standard) as first descriptor, valence connectivity index (order 0, standard) as second descriptor, Shape index (Kappa alpha, order 1) as third descriptor and solvent accessible surface area as fourth descriptor. The regression equation is given below:

$PAT1=0.327217\times {}^{0}\chi_t -0.367639\times {}^{0}\chi^{v}_t -0.98488\times {}^{1}K -0.146137\times SASA+56.275$
rCV^2=0.757041
r^2=0.921985 Eq.1

The values of the predicted activity PAT1 of all the compounds are listed in the Table-4.

II. Second QSAR model: The second QSAR model is obtained when multi linear regression analysis is done by taking connectivity index (order 0, standard) as first descriptor, valence connectivity index (order 0, standard) as second descriptor, dipole moment as third descriptor and solvent accessible surface area as fourth descriptor. The regression equation is given below:

PAT2=0.276387×$^{0}\chi_{t}$ -0.356254×$^{0}\chi^{v}_{t}$ -0.466599× σ -0.206309×SASA+48.8135
rCV^2=0.762696
r^2=0.913327 Eq.2

The values of the predicted activity PAT2 of all the compounds are listed in the Table-4.

III. Third QSAR model: The third QSAR model is obtained when multilinear regression analysis is done by taking log P as first descriptor, connectivity index (order 0, standard) as second descriptor, dipole moment as third descriptor and solvent accessible surface area as fourth descriptor. The regression equation is given below:

PAT3=-0.216619×log P+0.0820541×$^{0}\chi_{t}$ -0.512349× σ -0.196507×SASA+45.9261
rCV^2=0.74055
r^2=0.911394 Eq.3

IV. Fourth QSAR model: The fourth QSAR model is obtained when multi linear regression analysis is done by taking log P as first descriptor, Shape index (Kappa alpha, order 1) as second descriptor, dipole moment as third descriptor and solvent accessible surface area as fourth descriptor. The regression equation is given below:

PAT4=-0.0913334×log P-0.452415×^{1}K -0.317529× σ -0.172×SASA+51.4488
rCV^2=0.598521
r^2=0.91129 Eq.4

The values of the predicted activity PAT4 of all the compounds are listed in the Table-4.

The values of the predicted activity PAT3 of all the compounds are listed in the Table-5.

V. Fifth QSAR model: The fifth QSAR model is obtained when multi linear regression analysis is done by taking valence connectivity index (order 0, standard) as first descriptor, Shape index (Kappa alpha, order 1) as second descriptor, dipole moment as third descriptor and solvent accessible surface area as fourth descriptor. The regression equation is given below:

PAT5=-0.0346735×$^{0}\chi^{v}_{t}$ -0.56486×^{1}K -0.264708× σ -0.170769×SASA+53.6309
rCV^2=0.57125
r^2=0.906937 Eq.5

The values of the predicted activity PAT5 of all the compounds are listed in the Table-4.

Table 4. Predicted activities of compounds as obtained topological descriptors

No.	PAT1	PAT2	PAT3	PAT4	PAT5	OBA
C1	7.934	7.946	8.043	8.030	8.040	8.090
C2	7.907	7.967	8.009	8.015	8.001	7.990
C3	7.706	7.815	7.835	7.836	7.802	7.750
C4	6.465	6.300	6.311	6.413	6.357	6.360
C5	7.597	7.668	7.684	7.700	7.682	7.650
C6	7.861	7.835	7.915	7.934	7.930	7.900
C7	6.717	6.319	6.434	6.551	6.603	6.820
C9	7.984	8.086	7.962	7.988	7.974	7.920
C10	8.665	8.758	8.658	8.674	8.682	8.690
C11	8.443	8.413	8.321	8.374	8.406	8.480
C12	8.510	8.416	8.355	8.413	8.443	8.560
C13	8.482	8.509	8.478	8.473	8.503	8.560
C14	8.036	8.052	8.199	8.031	7.939	7.950
C15	8.203	8.125	8.139	8.092	8.097	7.560
C16	6.389	6.808	6.643	6.327	6.294	7.000
C17	6.355	6.280	6.078	6.044	6.065	6.000
C18	7.509	7.134	7.181	7.289	7.262	7.550
C19	7.252	7.220	7.382	7.312	7.241	7.390
C20	7.441	7.452	7.393	7.489	7.561	7.580
C21	6.525	6.519	6.531	6.576	6.649	6.490
C22	6.853	6.824	6.874	6.692	6.641	6.670
C23	5.800	6.032	6.084	6.116	6.145	5.370
C24	6.209	6.361	6.330	6.471	6.523	6.510

In order to explore the reliability of the proposed model we have used regression coefficient (r^2) and cross-validation coefficient (rCV^2). The regression summary of these models is as shown below

QSAR	rCV^2	r^2	Variable Used	Variable Count
PAT1	0.757041	0.921985	$^0\chi_t$, $^0\chi^v_t$, ^{1}K, SASA	4
PAT2	0.762696	0.913327	$^0\chi_t$, $^0\chi^v_t$, σ, SASA	4
PAT3	0.740550	0.911394	log P, $^0\chi_t$, σ, SASA	4
PAT4	0.598521	0.911290	log P, ^{1}K, σ, SASA	4
PAT5	0.57125	0.906937	$^0\chi^v_t$, ^{1}K, σ, SASA	4

From the above study it is clear that the QSAR model PAT1 has highest predictive powers as it has highest values of r^2 (0.921985) among the five QSAR models

3A. QSAR Modeling with Quantum Chemical Descriptors: After that we have done QSAR study with the help of quantum chemical descriptors[3] and various QSAR models in different combinations of descriptors have also been developed but only five top models are also reported and are presented below

I. First QSAR model: The first QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, molecular weight as second descriptor, total energy as third descriptor and LUMO energy as fourth descriptor. The regression equation is given below:

$PAQ1=-0.0368321\times\Delta H_f^{\circ} -0.00116938\times MW +0.150046\times TE+0.842993 \times \in LUMO + 39.2451$
rCV^2=0.939872
r^2=0.97528 Eq.6

The values of the predicted activity PAQ1 of all the compounds are listed in the Table-5.

II. Second QSAR model: The second QSAR model is obtained when multilinear regression analysis is done by taking heat of formation as first descriptor, molecular weight as second descriptor, total energy as third descriptor and electronegativity as fourth descriptor. The regression equation is given below:

$PAQ2=-0.0368968\times\Delta H_f^{\circ} -0.00124271\times MW+0.150427\times TE-0.603669 \times \chi +41.5391$
rCV^2=0.932379
r^2=0.975231 Eq.7

The values of the predicted activity PAQ2 of all the compounds are listed in the Table-5.

III. Third QSAR model: The third QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, molecular weight as second descriptor, total energy as third descriptor and HOMO energy as fourth descriptor. The regression equation is given below:

$PAQ3=-0.0367686\times\Delta H_f^{\circ} -0.00129337 \times MW +0.150617 \times TE +0.429844 \times \in HOMO +42.4676$
rCV^2=0.926904
r^2=0.974865 Eq.8

The values of the predicted activity PAQ3 of all the compounds are listed in the Table-5.

IV. Fourth QSAR model: The fourth QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, HOMO energy as second descriptor and electronegativity as third descriptor. The regression equation is given below:

$PAQ4=-0.0360544 \times \Delta H_f^{\circ} +0.179285 \times TE-0.601553 \times \in HOMO -1.41398 \times \chi +45.6528$
rCV^2=0.943749
r^2=0.974474 Eq.9

Table 5. Predicted activities of compounds as obtained quantum chemical descriptors

No.	PAQ1	PAQ2	PAQ3	PAQ4	PAQ5	OBA
C1	7.957	7.931	7.911	7.956	7.956	8.090
C2	8.095	8.077	8.066	8.086	8.086	7.990
C3	7.804	7.794	7.787	7.778	7.778	7.750
C4	6.447	6.436	6.436	6.402	6.402	6.360
C5	7.713	7.700	7.692	7.688	7.688	7.650
C6	7.869	7.852	7.842	7.865	7.865	7.900
C7	7.036	7.017	7.008	7.059	7.059	6.820
C9	7.663	7.677	7.690	7.603	7.603	7.920
C10	8.693	8.708	8.715	8.689	8.689	8.690
C11	8.373	8.384	8.391	8.383	8.383	8.480
C12	8.662	8.669	8.671	8.669	8.669	8.560
C13	8.635	8.647	8.652	8.659	8.659	8.560
C14	7.845	7.860	7.871	7.866	7.866	7.950
C15	7.521	7.519	7.520	7.532	7.532	7.560
C16	7.191	7.179	7.181	7.219	7.219	7.000
C17	5.987	5.996	6.010	5.997	5.997	6.000
C18	7.615	7.592	7.581	7.585	7.585	7.550
C19	7.340	7.342	7.349	7.328	7.328	7.390
C20	7.640	7.677	7.686	7.666	7.666	7.580
C21	6.430	6.468	6.481	6.476	6.476	6.490
C22	6.337	6.310	6.295	6.380	6.380	6.670
C23	5.599	5.608	5.608	5.584	5.584	5.370
C24	6.388	6.397	6.396	6.367	6.367	6.510

The values of the predicted activity PAQ4 of all the compounds are listed in the Table-5.

V. Fifth QSAR model: The fifth QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, total energy as second descriptor, HOMO energy as third descriptor and LUMO energy as fourth descriptor. The regression equation is given below:

$PAQ5=-0.0360544\times\Delta H_f^{\circ} +0.179285 \times TE +0.105435 \times \in HOMO +0.706988\times \in LUMO +45.6528$
rCV^2=0.943749
r^2=0.974474 Eq.10

The values of the predicted activity PAQ5 of all the compounds are listed in the Table-5.

In order to explore the reliability of the proposed model we have used regression coefficient (r^2) and cross-validation coefficient (rCV^2). The regression summary of these models is as shown below

QSAR	rCV^2	r^2	Variable Used	Variable Count
PAQ1	0.939872	0.975280	ΔH_f°, MW, TE, $\in$ LUMO	4
PAQ2	0.932379	0.975231	ΔH_f°, MW, TE, χ	4
PAQ3	0.926904	0.974865	ΔH_f°, MW, TE, $\in$ HOMO	4
PAQ4	0.943749	0.974474	ΔH_f°, TE, $\in$ HOMO, χ	4
PAQ5	0.943749	0.974474	ΔH_f°, TE, $\in$ LUMO, $\in$ LUMO	4

From the above study it is clear that the QSAR model no. 1 i.e., PAQ1 has highest predictive powers as it has highest values of r^2 (0.975280) among the five QSAR models.

The top five models of each set of descriptors are given below.

Topological Descriptors			Quantum Chemical Descriptors		
QSAR	r^2	rCV^2	QSAR	r^2	rCV^2
PAT1	0.757041	0.921985	PAQ1	0.939872	0.975280
PAT2	0.762696	0.913327	PAQ2	0.932379	0.975231
PAT3	0.740550	0.911394	PAQ3	0.926904	0.974865
PAT4	0.598521	0.911290	PAQ4	0.943749	0.974474
PAT5	0.57125	0.906937	PAQ5	0.943749	0.974474

The above data show that the best model is provided by the quantum chemical descriptors than topological descriptors. The best model has been selected on the basis of values of correlation coefficient and cross-validation correlation coefficient.

CONCLUSION

The study has shown that the best QSAR (PAQ1) is constructed from quantum chemical properties: heat of formation, molecular weight, total energy and LUMO energy. Results emanated from this study show that these descriptors can be used as descriptors of biological activity.

REFERENCES

[1] C. Hansch; A. Leo, Exploring QSAR. Washington, DC: *American Chemical Society*, **1995**.
[2] P. G. Mezey, *Shape in Chemistry : An Introduction to Molecular Shape and Topology.* VCH Publ.: New York, **1993.**
[3] M. Karelson; V. S. Lobanov; A. R. Katritzky, *Chem. Rev.* **1996**, *96*, 1027.
[4] L. B. Kier; L. H. Hall, *Molecular Connectivity in Chemistry and Drug Research*, Academic Press, New York, **1976**.
[5] L. H. Hall; L. B. Kier, *The Molecular Connectivity Chi Indices and Kappa Shape Indices in Structure-Property Modeling.* Reviews of Computational Chemistry, Volume 2, *D. B. Boyd and K. Lipkowitz, eds.* **1991**.
[6] J. Sangster, *Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry*, in Solution Chemistry. *Chichester: John Wiley & Sons Ltd.* 1997, 2, 178.
[7] B. Lee; F. M. Richards, *J. Mol. Biol.* **1971**, 55, 379.
[8] M. P. Badenes; M.E. Tucceri; C. J. Cobos, *Zeitschrift für Physikalische Chemie* **2000**, 214, 1193.

[9] F. A. Pasha; H. K. Srivastava; P. P. Singh, *Bioorg. & Med. Chem.* **2005**, 13, 6823.
[10] V. K. Sahu; A. K. Soni; P.P. Singh, *Asian J. Chem.* **2010**, 22, 3025.
[11] R. G. Pearson, *Proc. Natl. Acad. Sci. USA.*, **1986**, 83, 8440.
[12] R. G. Parr, R. G. Pearson, *J. Am. Chem. Soc.*, **1983**, 105, 7512.
[13] (a) G. J. Klopman, *Am. Chem. Soc.* **1968**, 90, 223. (b) V. K. Sahu; R. K. Singh, *Clean-soil, air, water*, **2009**, 37, 850.
[14] D. C. Montgomery; E. A. Peck, Introduction to Linear regression analysis 2nd edition. *John Wiley*. New York. **1992**.
[15] M. Yoshida; I. Hayakawa; N. Hayashi; T. Agatsuma; Y. Oda; F. Tanzawa; S. Iwasaki, Koyama; H. Furukawa; S. Kurakatad; Y. Sugano, *Bioorg. Med. Chem. Lett.* **2005,** 15, 3328**.**
[16] (a) W. J. Thiel, *Mol. Struct.* **1988**, 163, 415. (b) Komornicki A.; McIver, J. W. *Chem. Phys. Lett.* **1971**, *10*, 303.
[17] www.CACheSoftware.com
[18] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209.