Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2855–2859

Quantitative structure–activity relationship studies on HEPTs by supervised stochastic resonance

Weimin Guo,* Xiaofang Hu, Ningping Chu and Chunsheng Yin

School of Environmental Science and Technology, Shanghai Jiao Tong University, Shanghai 200240, PR China

Received 28 December 2005; revised 20 February 2006; accepted 7 March 2006
Available online 29 March 2006

Abstract—Quantitative structure–activity relationship studies (QSAR) on HEPTs were performed by using a new approach—supervised stochastic resonance (SSR) in this paper. Errors in physicochemical properties have great effects on variable selection and the predictive capability of QSAR models but errors-in-variables were seldom discussed in QSAR. In this paper, based on the theory of stochastic resonance (SR), SSR was proposed and employed to the problem. In SSR, errors and abundant variables were regarded as noise and the relevant descriptors as signals. In the nonlinear systems involved in the SR, the signal and the noise interact harmonically and the signal was consequently enhanced. Therefore, the correlation between the relevant variables and a specified activity of a series molecule was improved by SSR. It is demonstrated that the obtained QSAR models for HEPT analogues by SSR were comparable to those by published methods in their stability and predictivity. SSR is an efficient and promising approach to QSAR studies.

The aim of quantitative structure–activity relationship (QSAR) studies is to build predictive models for the activities of molecules using their physicochemical properties.[1] In QSAR, numerous descriptors—physicochemical properties are immediately available by using computational and experimental methods. Generally, molecule descriptors can be divided into three main categories, that is, hydrophobic properties, steric parameters, and electric effects, with a 'miscellaneous' group encompassing quite a wide variety of properties and chemical model systems.[2] Computational descriptors derived from quantum chemistry computation and topological indexes are prevalent in QSAR studies for their ready calculation and capability to explain various bioactivities. However, the theoretical simplification and adopted parameters of atoms and chemical bonds bring errors into these descriptors. The errors will spoil the predictive capability of obtained QSAR models and make it difficult to reveal true structure descriptors to explain studied activity. Therefore, errors have great effect in QSAR studies.

However, errors-in-variables do not always bring about negative effects. Based on stochastic resonance (SR), errors can be utilized to improve the correlation between the relevant descriptors and a specified bioactivity. SR is a phenomenon where nonlinear systems produce a strong response to a weak signal with the presence of noise.[3] That means the weak signal is enhanced. In the past decades, SR has been found in various scientific fields.[4–7] Recently, SR was applied in analytical chemistry to amplify weak signals[8,9] and improve the detection limit of analytical methods.[10,11] Cross-validation relationship coefficients of models built by SR for a Selwood's dataset,[12] which contains antifilarial activities of 31 antimycin analogues and 53 descriptors, were also improved 10 percent in average compared with traditional methods.[13,14] SR is a promising powerful tool in analytical chemistry.

In QSAR studies, it is believed that bioactivities were functions of those related descriptors.[1,2,15] Irrelevant descriptors, however, vary independently or randomly with the bioactivity compared with related ones. Therefore, the relevant and irrelevant descriptors can be taken as signals and noise, respectively. In proper nonlinear systems involved in SR, the signal and the noise, which includes errors-in-variables and irrelevant descriptors, interact harmonically to result in the improvement of the descriptors. Thus, the models derived from the

Keywords: Stochastic resonance; HEPT derivatives; Quantitative structure–activity relationship (QSAR).
* Corresponding author. Tel.: +86 021 54748994; fax: +86 021 54740825 608; e-mail: wmguo@sjtu.edu.cn

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.03.019

modified dataset by SR should be more stable and predictive. In the SR, the signals were particularly assigned according to the correlation between variables and a concrete bioactivity, that is, occurrence of the SR was observed by the means of the change of the correlation. Therefore, the proposed algorithm is called supervised stochastic resonance (SSR). The theory and algorithm of SSR are available in Refs. 3,11 and 12 and Supporting information.

The study on anti-HIV-1 products has been a focus for a long time.[16–18] HEPT (1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine) derivatives, whose scheme is shown in Figure 1, have potent anti-HIV-1 activity and inhibit HIV-1 at nanomolar concentration.[19] Therefore, QSAR studies on the analogues were paid general attention.[17,18,20–24] In this work, a group of 80 HEPT analogues were studied by using SSR. The activity data were taken from Ref. 18, in which 107 compounds were studied. Because the observed concentration of the last 28 molecules (number **81**–**107**) was not accurate,[18,23] we merely studied number **1**–**80** molecules. Chemical structures of the 80 compounds studied and their observed and calculated anti-HIV-1 activity are shown in Table 1. The bioactivity was present in logarithm of $1/C$ with C denoting the molar concentration of drug required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1. The overall picture, which emerges from published QSAR studies, shows that the electronic and steric characteristics of the HEPT derivatives have predominant effects on the anti-HIV-1 activity of the analogues.[17–24] Therefore, electronic descriptors and molecule connectivity indexes were used to model the anti-HIV activity of the large group in this work. The former resulted from semiempirical molecule orbit computation by the program of MOPAC with the AM1 Hamilton, which include heat of formation (H_f), total energy (E_t), electronic energy (E_e), core–core repulsion (E_c), ionization potential (E_i), dielectric energy (E_d), HOMO and LUMO energies (HOMO, LUMO) and their difference (ΔE), total dipole contribution (D_t) and 3D components ($D_{x,y,z}$), 3D principal moments of inertia ($I_{a,b,c}$), and net charge of atoms 1–16 ($q_{1\text{-}16}$). In addition, there also were molecular weight (W_M), COSMO area (A_c) and volume (V_c). There totally were 38 quantum chemical descriptors. The latter was calculated by our program developed according to the theory of Kier and Hall.[25] The large group descriptors include path, path/cluster, and chain types to the ninth order since the large substitute functions were thought as important roles in the anti-HIV activity.[21–23] Additionally, the type of chain/path (χ_{ChP}) was used in the work to investigate the effect of the substitution position on the anti-HIV1 activity of the series compound. Therefore, the following connectivity indexes calculated on whole molecule were considered: ${}^{0}\chi$, ${}^{1\text{–}9}\chi_P$, ${}^{4\text{–}12}\chi_{PC}$, ${}^{6}\chi_{Ch}$, and ${}^{7\text{–}14}\chi_{ChP}$, totally 28 topological descriptors.

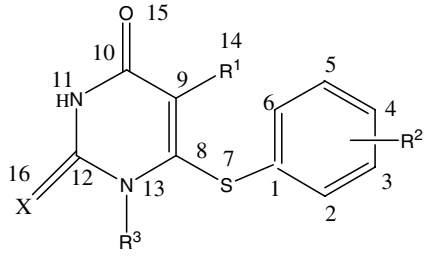

Figure 1. The scheme of HEPT analogues.

Besides these variables, several descriptors used in previous works' models[18,23] were also employed in this work, which include reciprocal of the standard shadow area on YZ plane, $1/S$, ratio of the partial charges on the most positive and the most negative atoms, POS/NEG, square of the number of SP3 carbon atoms of the R^2 substituent, $(\text{NCSP3–R}^2)^2$, number of hydroxyl groups on the R^3 substituent, $(\text{NOH–R}^3)^2$, cub of summation of the positions of R^1 on the C-6 aromatic ring constant, $(\text{NS–R}^1)^3$, the Hansch constant, $\sum\pi(R^1 + R^2)$, the Taft steric constant for ortho substituents, $\text{ES}(2R^1)$, the differential molecular connectivity indexes of zeroth in the acyclic structure, ${}^{0}\Delta\chi(R^3)$, the width parameters of R^1 at the 3-position, $\text{B1}(3R^1)$, the McGowan characteristic volume, V_x, and the index of connectivity level, ${}^{1}\chi_P^N(R^2)$, ${}^{4}\chi_P^N$, which are calculated by dividing the value of the ${}^{1}\chi_P$ (R^2), ${}^{4}\chi_P$ by the number of atoms involved in their calculus, respectively. Finally, a total of 80 descriptors were generated/collected for each molecule.

Before applying SSR to the QSAR study of HEPT analogues, MLR was performed on the compounds present in Table 1. Correlation Eq. 1 was obtained for 80 molecules after the stepwise feature selection mentioned above.

$$\begin{aligned}\log 1/C = {} & 1.69(\pm0.65) - 0.54(\pm0.15)q_6 \\ & - 0.36(\pm0.06)\text{NOH–R}^3 \\ & + 0.75(\pm0.22)\text{POS/NEG} \\ & + 5.75(\pm1.30)^{9}\chi_{ChP} - 2.89(\pm0.47)^{5}\chi_{PC} \\ & + 2.82(\pm0.86)^{6}\chi_{PC} - 2.14(\pm0.45)^{10}\chi_{PC} \\ & - 1.14(\pm0.38)^{8}\chi_{ChP} \\ n = 80;\ & R^2 = 0.8731;\ Q^2 = 0.8368; \\ \text{PRESS} = 23.0463; \quad & F = 60.19. \end{aligned} \tag{1}$$

In this work, all 80 samples were included to develop the QSAR models, while Luco and Ferretti listed the sample 34 as an outlier for their equation.[18] The reason they explained was that the fact that none of their descriptors used to account for the total loss of activity resulting from the substitution at 4-position of the 6-(phenylthio) moiety of HEPT. It seems appropriate to compare the equations with those in references also built by MLR. The statistics of the reported equations for 80 compounds were $n = 79$, $R^2 = 0.901$, $Q^2 = 0.745$ (1 outlier)[18] and $n = 79$, $R^2 = 0.871$, $Q^2 = 0.840$ (1 outlier)[22] and $n = 80$, $R^2 = 0.812$, $F = 52$.[23] It was clear that the statistics of Eq. 1 were comparable with those reported MLR models, especially in cross validation. On the other hand, it should be noticed that high order connectivity

Table 1. Components and their calculated and observed activities

Compound	R^1	R^2	R^3	X	Obsd[a]	Calcd[b]	Calcd[c]
1	Me	2-Me	$CH_2OCH_2CH_2OH$	O	4.15	4.2533	4.2427
2	Me	2-NO_2	$CH_2OCH_2CH_2OH$	O	3.85	3.8625	3.8715
3	Me	2-OMe	$CH_2OCH_2CH_2OH$	O	4.72	4.6492	4.6489
4	Me	3-Me	$CH_2OCH_2CH_2OH$	O	5.59	4.9915	4.9872
5	Me	3-Et	$CH_2OCH_2CH_2OH$	O	5.57	5.1006	5.1030
6	Me	3-*t*-Bu	$CH_2OCH_2CH_2OH$	O	4.92	5.1720	5.1818
7	Me	3-CF_3	$CH_2OCH_2CH_2OH$	O	4.35	4.5964	4.6146
8	Me	3-F	$CH_2OCH_2CH_2OH$	O	5.48	5.0852	5.0833
9[d]	Me	3-Cl	$CH_2OCH_2CH_2OH$	O	4.89	5.0239	5.0154
10	Me	3-Br	$CH_2OCH_2CH_2OH$	O	5.24	5.1280	5.1255
11	Me	3-I	$CH_2OCH_2CH_2OH$	O	5.00	5.3939	5.3930
12	Me	3-NO_2	$CH_2OCH_2CH_2OH$	O	4.47	4.2364	4.2494
13	Me	3-OH	$CH_2OCH_2CH_2OH$	O	4.09	5.1132	5.1160
14	Me	3-OMe	$CH_2OCH_2CH_2OH$	O	4.66	5.0490	5.0534
15	Me	3,5-Me_2	$CH_2OCH_2CH_2OH$	O	6.59	5.8124	5.8092
16	Me	3,5-Cl_2	$CH_2OCH_2CH_2OH$	O	5.89	6.1783	6.1775
17	Me	3,5-Me_2	$CH_2OCH_2CH_2OH$	S	6.66	5.7720	5.7704
18	Me	3-COOMe	$CH_2OCH_2CH_2OH$	O	5.10	5.6166	5.6294
19	Me	3-COMe	$CH_2OCH_2CH_2OH$	O	5.14	5.3420	5.3490
20	Me	3-CN	$CH_2OCH_2CH_2OH$	O	5.00	5.2101	5.2135
21	$CH_2CH{=}CH_2$	H	$CH_2OCH_2CH_2OH$	O	5.60	5.3367	5.3493
22	Et	H	$CH_2OCH_2CH_2OH$	S	6.96	6.6752	6.6947
23	Pr	H	$CH_2OCH_2CH_2OH$	S	5.00	5.6639	5.6796
24[d]	*i*-Pr	H	$CH_2OCH_2CH_2OH$	S	7.23	7.3819	7.4006
25	Et	3,5-Me_2	$CH_2OCH_2CH_2OH$	S	8.11	7.5838	7.5955
26	*i*-Pr	3,5-Me_2	$CH_2OCH_2CH_2OH$	S	8.30	8.8331	8.8669
27	Et	3,5-Cl_2	$CH_2OCH_2CH_2OH$	S	7.37	7.4708	7.4856
28	Et	H	$CH_2OCH_2CH_2OH$	O	6.92	6.3923	6.4094
29	Pr	H	$CH_2OCH_2CH_2OH$	O	5.47	5.2472	5.2599
30[d]	*i*-Pr	H	$CH_2OCH_2CH_2OH$	O	7.20	7.2403	7.2647
31	Et	3,5-Me_2	$CH_2OCH_2CH_2OH$	O	7.89	7.2549	7.2656
32	*i*-Pr	3,5-Me_2	$CH_2OCH_2CH_2OH$	O	8.57	8.4273	8.4508
33	Et	3,5-Cl_2	$CH_2OCH_2CH_2OH$	O	7.85	7.3950	7.4068
34	Me	4-Me	$CH_2OCH_2CH_2OH$	O	3.66	5.2688	5.2747
35	Me	H	$CH_2OCH_2CH_2OH$	O	5.15	5.0496	5.0585
36	Me	H	$CH_2OCH_2CH_2OH$	S	6.01	5.6125	5.6233
37	I	H	$CH_2OCH_2CH_2OH$	O	5.44	5.4494	5.4577
38	$CH{=}CH_2$	H	$CH_2OCH_2CH_2OH$	O	5.69	6.4706	6.4978
39	CH=CHPh	H	$CH_2OCH_2CH_2OH$	O	5.22	4.7224	4.7180
40	CH_2PhH	H	$CH_2OCH_2CH_2OH$	O	4.37	5.9060	5.9150
41	$CH{=}CPh_2$	H	$CH_2OCH_2CH_2OH$	O	6.07	5.4654	5.4728
42[d]	Me	H	$CH_2OCH_2CH_2OMe$	O	5.06	5.0839	5.0945
43	Me	H	$CH_2OCH_2CH_2OAc$	O	5.17	4.9605	4.9727
44	Me	H	$CH_2OCH_2CH_2OCOPhO$	O	5.12	4.6613	4.6366
45	Me	H	CH_2OCH_2Me	O	6.48	6.0851	6.0992
46	Me	H	$CH_2OCH_2CH_2Cl$	O	5.82	5.6344	5.6475
47	Me	H	$CH_2OCH_2CH_2N_3$	O	5.24	5.5133	5.5249
48	Me	H	$CH_2OCH_2CH_2F$	O	5.96	5.4382	5.4495
49	Me	H	$CH_2OCH_2CH_2Me$	O	5.48	5.4617	5.4751
50	Me	H	CH_2OCH_2Ph	O	7.06	6.4580	6.4550
51	Et	H	CH_2OCH_2Me	O	7.72	7.2435	7.2643
52	Et	H	CH_2OCH_2Me	S	7.58	7.2625	7.2850
53	Et	3,5-Me_2	CH_2OCH_2Me	O	8.24	8.2473	8.2654
54	Et	3,5-Me_2	CH_2OCH_2Me	S	8.30	8.0135	8.0289
55	Et	H	CH_2OCH_2Ph	O	8.23	7.5307	7.5383
56	Et	3,5-Me_2	CH_2OCH_2Ph	O	8.55	8.3307	8.3297
57	Et	H	CH_2OCH_2Ph	S	8.09	7.6889	7.6983
58	Et	3,5-Me_2	CH_2OCH_2Ph	S	8.14	8.5398	8.5436
59[d]	*i*-Pr	H	CH_2OCH_2Me	O	7.99	8.1295	8.1490
60	*i*-Pr	H	CH_2OCH_2Ph	O	8.51	8.7177	8.7417
61	*i*-Pr	H	CH_2OCH_2Me	S	7.89	7.3761	7.3980
62	*i*-Pr	H	CH_2OCH_2Ph	S	8.14	8.7238	8.7569
63	Me	H	CH_2OMe	O	5.68	6.6227	6.6482
64	Me	H	CH_2OBu	O	5.33	5.4060	5.4201
65	Me	H	Et	O	5.66	5.7814	5.8027

(*continued on next page*)

Table 1 (*continued*)

Compound	R^1	R^2	R^3	X	Obsd[a]	Calcd[b]	Calcd[c]
66	Me	H	Bu	O	5.92	6.0885	6.1072
67	Et	3,5-Cl_2	CH_2OCH_2Me	S	7.89	8.3615	8.3875
68[d]	Et	H	CH_2O–*i*-Pr	S	6.66	6.8099	6.8267
69	Et	H	CH_2O–*c*-Hex	S	5.79	6.2594	6.2629
70	Et	H	CH_2OCH_2-*c*-Hex	S	6.45	5.8559	5.8508
71	Et	H	$CH_2OCH_2C_6H_4$(4-Me)	S	7.11	7.7767	7.7793
72	Et	H	$CH_2OCH_2C_6H_4$(4-Cl)	S	7.92	7.9244	7.9246
73	Et	H	$CH_2OCH_2CH_2Ph$	S	7.04	7.1794	7.1718
74	Et	3,5-Cl_2	CH_2OCH_2Me	O	8.13	8.2224	8.2407
75	Et	H	CH_2O–*i*-Pr	O	6.47	6.6886	6.7126
76	Et	H	CH_2O–*c*-Hex	O	5.40	6.2403	6.2426
77	Et	H	CH_2OCH_2-*c*-Hex	O	6.35	5.6011	5.5954
78[d]	Et	H	$CH_2OCH_2CH_2Ph$	O	7.02	7.0803	7.0796
79	*c*-Pr	H	CH_2OCH_2Me	S	7.02	6.8185	6.8372
80	*c*-Pr	H	CH_2OCH_2Me	O	7.00	6.6118	6.6284

[a] Ref. 18.
[b] Calculated by Eq. 2.
[c] Calculated by Eq. 3.
[d] Prediction set.

indexes are important roles in Eq. 1. The fact implied that the high order indexes can effectively explain the experimental errors of the anti-HIV1 activity of HEPTs. This should be due to the capability of the high order indexes to identify the different substituted position and the size of the substituents. For instance, in Eq. 1, the chain/path type $^{9}\chi_{ChP}$ is sensitive to the introduction of substituents in 2, 6, and 9. As to the path/cluster type $^{10}\chi_{PC}$, it will contain more terms embracing heteroatoms when the substitution occurs in 2 or 3 than in 4 while the hetero atoms have greater effect on the index values than carbon according to the definition of connectivity indexes. The results obtained by SSR supported the fact further.

After the optimization of SSR, the following correlation Eq. 2 was derived for the components at $a = 1.35640$ and $b = 0.0306$.

$$\begin{aligned}\log 1/C = {} & 81.23(\pm 6.44) + 21.68(\pm 1.05)^{9}\chi_{ChP} \\ & + 18.16(\pm 2.36)^{12}\chi_{PC} - 25.78(\pm 2.17)^{7}\chi_{P} \\ & - 1.71(\pm 0.33)q_4 - 2.27(\pm 0.88)^{6}\chi_{Ch} \\ & + 2.17(\pm 0.60)\mathrm{POS/NEG} \\ n = 80;\ & R^2 = 0.8858;\ Q^2 = 0.8623; \\ \mathrm{PRESS} = 19.4396;\ & F = 93.06. \end{aligned} \quad (2)$$

Obviously, SSR does not only improve the statistics of the model, but simplifies it as well. There are merely six variables in Eq. 2, while eight variables in Eq. 1. The predicted bioactivities are listed in Table 1 and the plot of the predicted values versus observed is shown in Figure 2. Although the correlation coefficient (R^2) of the model was not as good as that obtained by Luco and Ferretti using MLR ($n = 79$, $R^2 = 0.9006$, $Q^2 = 0.7448$),[18] the predictive one (Q^2) was much better than that obtained by them. It was also better than the mean Q^2 obtained by ANN which was 0.7997 calculated by leave six samples out cross-validation procedure.[23] And the results were comparable to those coming from PLS ($n = 79$, $R^2 = 0.8892$, $Q^2 = 0.8593$).[18] It was clear that the high order topological indexes were still an important role effecting the activities of 80 components.

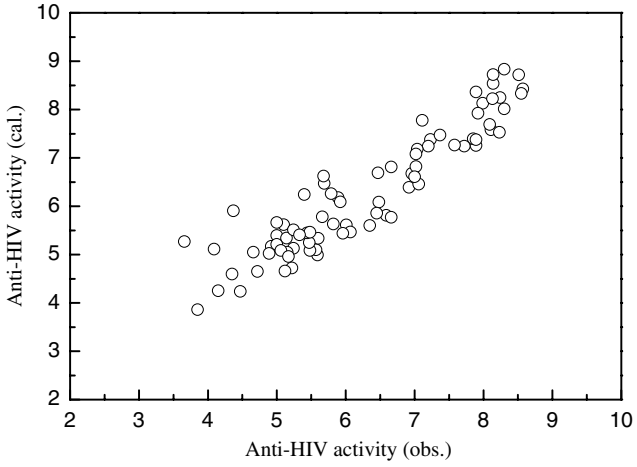

Figure 2. Plot of calculated activity against the experimental values.

In this equation, several high order indexes were also selected in the work and their effects were further emphasized after SR. For the 34th molecules, except for ordinary terms, the path type $^{7}\chi_{P}$ additionally includes a term containing S(7,2) (the first number in parentheses is the atom number in Figure 1 and the second is the connective degree of the atom, and the followings have the same meaning) and N(13,3). While as the substituent was introduced at 3- or 5-position, $^{12}\chi_{PC}$ covers two extra terms embracing O(15,1) and O/S(16,1), respectively. But the substitut-

ed compound at 4-position does not. Additionally, the descriptor POS/NEG was the same important role as in Ref. 23 and the net charge of atom 4 (q_4) is directly effected on by the position of substitute. This was the reason that our equation had stronger ability to explain the observed activity values with satisfying statistics. Apparently, the high order connectivity indexes accompanied by the net charge of atoms can well explain the anti-HIV activities of the 80 HEPTs.

Randomly leaving seven samples out as a prediction set, a new model (Eq. 3) can be obtained by using 73 samples.

$$\begin{aligned}\log 1/C = {} & 81.27(\pm 6.88) + 21.80(\pm 1.17)^{9}\chi_{\mathrm{ChP}} \\ & + 18.47(\pm 2.64)^{12}\chi_{\mathrm{PC}} - 26.04(\pm 2.39)^{7}\chi_{\mathrm{P}} \\ & - 1.73(\pm 0.35)q_4 - 2.40(\pm 1.01)^{6}\chi_{\mathrm{Ch}} \\ & + 2.16(\pm 0.63)\mathrm{POS/NEG} \\ n = {} & 73;\ R^2 = 0.8788;\ Q^2 = 0.8524; \\ \mathrm{PRESS} = {} & 19.5440;\ F = 79.76. \end{aligned} \quad (3)$$

The predicted values of the prediction set are listed in Table 1. The root mean square deviation (rmsd) was 0.1235 for the seven samples. Obviously, the predictive ability of the model was satisfying.

In conclusion, the new approach to QSAR studies—supervised stochastic resonance (SSR) was developed in this work. The conceptions of noise and signal in SR phenomenon were given a new general definition to build the new algorithm. The successful applications of SSR to the QSAR study for the large group of HEPT derivatives implied that the new approach was efficient and feasible. The models obtained by SSR were more stable and predictive than those by ordinary methods. And the essential mechanism of bioactivity may be revealed after SR. It was demonstrated that SSR was a promising approach to QSAR studies not only to build QSAR models but to find the mechanics of bioactivities.

Acknowledgment

This work is supported by the National Natural Science Foundation of China (No. 20075024).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.03.019.

References and notes

1. Hansch, C. *Chem. Rev.* **1969**, *2*, 232.
2. Livingstone, D. J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 195.
3. Gammaitoni, L.; Hanggi, P.; Jung, P.; Marchesoni, F. *Rev. Mod. Phys.* **1998**, *70*, 223.
4. Rao, C. V.; Wolf, D. M.; Arkin, A. P. *Nature* **2002**, *420*, 231.
5. Glass, L. *Nature* **2001**, *401*, 277.
6. Moss, F. *Nature* **1998**, *391*, 743.
7. Zhong, S.; Xin, H. W. *Sci. China, Ser. B.* **2001**, *44*, 17.
8. Wu, X. J.; Guo, W. M.; Cai, W. S.; Shao, X. G.; Pan, Z. X. *Talanta* **2003**, *61*, 863.
9. Pan, Z. X.; Wu, X. J.; Guo, W. M.; Cai, W. S.; Shao, X. G. *Chem. J. Chinese U.* **2003**, *24*, 605.
10. Guo, W. M.; Sun, Y. A.; Wu, X. J.; Cai, W. S.; Shao, X. G.; Pan, Z. X. *Chin. Chem. Lett.* **2003**, *14*, 181.
11. Pan, Z. X.; Guo, W. M.; Wu, X. J.; Cai, W. S.; Shao, X. G. *Chemometr. Intell. Lab. Syst.* **2003**, *66*, 41.
12. Guo, W. M.; Cai, W. S.; Shao, X. G.; Pan, Z. X. *Chemometr. Intell. Lab. Syst.* **2005**, *75*, 181.
13. Selwood, D. L.; Livingstone, D. J.; Comley, J. C. W.; Odowd, A. B.; Hudson, A. T.; Jackson, P.; Jandu, K. S.; Rose, V. S.; Stables, J. N. *J. Med. Chem.* **1990**, *33*, 136.
14. Liu, S. S.; Liu, H. L.; Yin, C. S.; Wang, L. S. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 964.
15. Chiu, T. L.; So, S. S. *J. Chem. Inf. Compu. Sci.* **2004**, *44*, 147.
16. Bajaj, S.; Sambi, S. S.; Madan, A. K. *Bioorg. Med. Chem.* **2005**, *13*, 3263.
17. Bajaj, S.; Sambi, S. S.; Madan, A. K. *Bioorg. Med. Chem.* **2005**, *15*, 467.
18. Luco, J. M.; Ferretti, F. H. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 392.
19. Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Shigeta, S.; Walker, R. T.; Declercq, E.; Miyasaka, T. *J. Med. Chem.* **1992**, *35*, 4713.
20. Zhang, Q. Y.; Xu, L.; Zhang, W. *J. Chem. J. Chinese U.* **2002**, *23*, 1053.
21. Garg, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C. *Chem. Rev.* **1999**, *99*, 3525.
22. Douali, L.; Villemin, D.; Cherqaoui, D. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1200.
23. Jalali-Heravi, M.; Parastar, F. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 147.
24. Chin, T. L.; So, S. S. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 154.
25. Kier, L. B.; Murray, W. J.; Hall, L. H. *J. Med. Chem.* **1975**, *18*, 1272.