Bioorganic & Medicinal Chemistry Letters 21 (2011) 141–144

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Correlation analyses on binding affinity of substituted benzenesulfonamides with carbonic anhydrase using ab initio MO calculations on their complex structures (II)

Yohei Munei, Kazunori Shimamoto, Masataka Harada, Tatsusada Yoshida, Hiroshi Chuman *

Institute of Health Biosciences, The University of Tokushima Graduate School, 1-78 Shomachi, Tokushima 770-8505, Japan

ARTICLE INFO

Article history:
Received 20 October 2010
Revised 8 November 2010
Accepted 9 November 2010
Available online 2 December 2010

Keywords:
Carbonic anhydrase
Benzenesulfonamide
Dispersion interaction
Fragment molecular orbital (FMO)
Hammett σ
Hydrophobic constant π
Linear expression by representative energy terms (LERE)
Quantitative structure–activity relationship (QSAR)

ABSTRACT

We proposed a novel QSAR (quantitative structure–activity relationship) procedure called LERE (linear expression by representative energy terms)-QSAR involving molecular calculations such as ab initio fragment molecular orbital and generalized Born/surface area ones. We applied LERE-QSAR to two data-sets for the free-energy changes during complex formation between carbonic anhydrase and a series of substituted benzenesulfonamides. The first compound set (Set **I**) and the second one (Set **II**) include relatively small substituents and alkyl chains of different lengths in the benzene ring, respectively. Variation of the inhibitory activity in Set **I** is expressed as the combination of Hammett σ and the hydrophobic substituent constant π in classical QSAR, and variation in Set **II** only by π. LERE-QSAR analyses clearly revealed that effects of σ and π on the activity variations in Sets **I** and **II** are consistently explainable with the energy terms in the LERE formulation, and provide more detailed and direct information as to the binding mechanism. The proposed procedure was demonstrated to provide a quantitative basis for understanding ligand–protein interactions at the electronic and atomic levels.

Carbonic anhydrase (CA) is a ubiquitous metalloenzyme that catalyzes the reversible hydration of CO_2 to bicarbonate. The active site of CA contains a zinc ion (Zn^{2+}), which is essential for the catalysis. The reactions catalyzed by CA play important roles in physiological functions such as CO_2 transport and pH control. Many CA isozymes are important therapeutic targets that are inhibited for treating a range of disorders such as glaucoma, epilepsy, and cancer. Most clinically used CA inhibitors, such as acetazolamide, dorzolamide, and topiramate, have a sulfonamide (SO_2NH_2) group attached to an aromatic ring.[1,2] CA inhibitors having a sulfonamide group exhibit their inhibitory activity toward CA through the formation of a coordination bond between the negatively ionized sulfonamide (SO_2NH^-) and the Zn^{2+} ion in the active site of CA.[3–5]

We recently proposed LERE (linear expression by representative energy terms) analysis involving molecular calculations such as the ab initio fragment molecular orbital (FMO) method,[6,7] and reported a LERE-QSAR (quantitative structure–activity relationship) study on a series of substituted benzenesulfonamides with bovine CA.[8]

$$\Delta G = \Delta G_{\mathrm{bind}} + \Delta G_{\mathrm{sol}} + \Delta G_{\mathrm{dis}} + \Delta G_{\mathrm{others}} \quad (1)$$

ΔG on the left-hand side of Eq. 1 is the overall free-energy change obtained from the observed inhibitory constant K_i $\Delta G = 2.303\,RT \log K_i$. ΔG_{bind}, ΔG_{sol}, and ΔG_{dis} in Eq. 1 are the intrinsic interaction energy between a BSA (benzenesulfonamide) and CA, the solvation free-energy change associated with complex formation, and the dissociation free-energy of BSA, respectively. The free-energy of solvation ΔG_{sol} is further divided into the Born electrostatic (polar) term ($\Delta G_{\mathrm{sol}}^{\mathrm{pol}}$) and a nonpolar term[9] ($\Delta G_{\mathrm{sol}}^{\mathrm{nonpol}} = \gamma\,ASA$, where ASA is the water accessible surface area and γ is taken to be 0.0072 kcal/mol Å^{-2}), which accounts for the cavity formation energy in water. $\Delta G_{\mathrm{others}}$, which represents the sum of free-energy terms such as the deformation energies of a protein and ligand other than ΔG_{bind}, ΔG_{sol}, and ΔG_{dis}, is assumed to be linear with the sum of representative free-energy terms ΔG_{bind}, ΔG_{sol}, and ΔG_{dis} in Eq. 1, and $\Delta G_{\mathrm{others}}$ is expected to work as a penalty term.

$$\Delta G_{\mathrm{others}} = \beta[\Delta G_{\mathrm{bind}} + \Delta G_{\mathrm{sol}} + \Delta G_{\mathrm{dis}}] + const \quad (2)$$

where β <0 and/or $const$ >0.

In addition, ΔG_{bind} is approximately $(1-\alpha)\,\Delta E_{\mathrm{bind}}$ according to the entropy–enthalpy compensation rule.[10–12]

$$T\Delta S = \alpha\Delta H + const \quad (3)$$

where α >0.

* Corresponding author. Tel.: +81 88 633 7257; fax: +81 88 633 9508.
E-mail address: hchuman@ph.tokushima-u.ac.jp (H. Chuman).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.11.050

The value of α on complex formation between CA and BSAs was determined to be 0.65 from the result of Scott et al.[12]

Eq. 4 is derived from Eqs. 1–3.

$$\Delta G = (1+\beta)[(1-\alpha)\Delta E_{\text{bind}} + \Delta G_{\text{sol}} + \Delta G_{\text{dis}}] + const \quad (4)$$

We constructed complexes of bovine CA II (bCA II) and human CA II (hCA II) with a series of BSAs using molecular dynamics (Amber[13]) and ONIOM[14] (our own *n*-layered integrated molecular orbital and molecular mechanics, 2 layers: HF/6-31G* and Amber in this study) calculations based on the crystallographic structures of bCA II (PDB code: 1V9I,[15] 259 amino acid residues) and hCA II (PDB code: 2WEJ,[12] 258 amino acid residues), respectively. The binding energy ΔE_{bind} (=E (complex) − [E (CA) + E (BSA (anion form))]), the solvation energy ΔG_{sol} (=G_{sol} (complex) − [G_{sol} (CA) + G_{sol} (BSA (anion form))]), and the dissociation energy ΔG_{dis} (=[G (BSA (anion form)) + G (H_3O^+)] − [G (BSA (neutral form)) + G (H_2O)]) were calculated with FMO/HF/6-31G,[16] GB/SA generalized Born/surface area,[17] and SCRF–CPCM self-consistent reaction field-conductor-like polarizable continuum model[18] at the B3LYP/6-31+G** level, respectively.

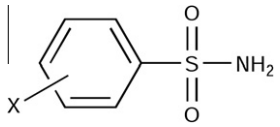
Kakeya et al.[19] reported the inhibitory equilibrium constants K_i of a series of BSAs with bCA II. Table 1(a) lists the K_i values of sixteen compounds selected from Kakeya's dataset (Set **I**). These compounds have relatively small sized substituents at the *para* and/or *meta* positions. We formulated Eq. I-1 for Set **I** compounds with Hammett σ and π, according to Hansch's paper.[20]

$$\log(1/K_i) = 0.946\sigma + 0.177\pi + 5.52 \quad (\text{I-1})$$

n = 16, r = 0.956, s = 0.193, F = 70.3.

The t-value of Hammett σ in Eq. I-1 is considerably large (t = 10.2). However, that of π is much smaller (t = 2.30), although the statistical significance is within the 95% confidence interval.

Table 1
Chemical structure of BSAs with activity and substitution constants



Compound		log (1/K_i)[a]	σ	π
No.	X			
*(a) Set **I** compounds*				
1	4-CH_3NH	4.96	−0.840	−0.470
2	4-NH_2	4.60	−0.660	−1.230
3	4-CH_3O	5.30	−0.268	−0.020
4	4-CH_3	5.49	−0.170	0.560
5	3-CH_3	5.22	−0.069	0.560
6	H	5.12	0.000	0.000
7	4-Cl	5.96	0.227	0.710
8	4-Br	5.96	0.232	0.860
9	3-Cl	5.92	0.373	0.710
10	4-CH_3CO	5.89	0.502	−0.550
11	4-CN	6.19	0.660	−0.570
12	3-NO_2	6.12	0.710	−0.280
13	4-NO_2	6.26	0.778	−0.280
14	3,4-di-Cl	6.52	0.600	1.420
15	3-NO_2, 4-Cl	6.60	0.937	0.430
16	3-CF_3, 4-NO_2	6.66	1.208	0.600
*(b) Set **II** compounds*				
No.	X	log (1/K_i)[b]	σ	π
1	4-CH_3	7.09	−0.170	0.560
2	4-C_2H_5	7.53	−0.150	1.020
3	4-C_3H_7	7.77	−0.150	1.550
4	4-C_4H_9	8.30	−0.150	2.130
5	4-C_5H_{11}	8.86	−0.150	2.670

[a] Taken from Ref. 19.
[b] Taken from Ref. 21.

Thus, it is not clear whether or not the hydrophobic π constant in the classical QSAR equation essentially contributes to the variation of inhibitory activity. We expected that corresponding LERE-QSAR analysis could make this situation clearer. However, π does not show significant correlations with any energy terms in Eq. I-2.

$$\Delta G = (1+\beta)[(1-\alpha)\Delta E_{\text{bind}} + \Delta G_{\text{sol}}^{\text{pol}} + \Delta G_{\text{sol}}^{\text{nonpol}} + \Delta G_{\text{dis}}] + 0.897 \quad (\text{I-2})$$

n = 16, r = 0.954, s = 0.252, F = 142, β = −0.799 (α = 0.65).

Therefore, we carried out LERE-QSAR analysis of the compound set (Set **II**) reported by King and Burgen[21] in order to examine the involvement of the hydrophobic interaction in the binding of BSAs with CA II. In compound Set **II**, the hydrophobic interaction was supposed to be prominently significant, because Set **II** includes compounds having normal alkyl chains (C_nH_{2n+1}, n = 1–5) at the *para* position. For LERE-QSAR analysis of Set **II** compounds, we introduced a dispersion interaction energy term into Eq. 4, because the dispersion interaction energy E_{disp} is supposed to be an essential component of the hydrophobic interaction energy.

$$\Delta G = (1+\beta)[(1-\alpha)(\Delta E_{\text{bind}} + E_{\text{disp}}) + \Delta G_{\text{sol}} + \Delta G_{\text{dis}}] + const \quad (5)$$

We replaced E_{disp} in Eq. 5 by the Lennard–Jones R^{-6} energy term (LJ6) in the Amber force field to save computational time, according to the report of He et al.[22] They reported that E_{disp} can be nicely approximated as S·LJ6, where S is the scaling constant. We determined the scaling constant to be 0.70 from the results of Amber and ab initio MO with CCSD(T)/aug-cc-pVQZ calculations for two complexes, the methane–dimer and formamide–dimer.

Table 1(b) lists the K_i values of Set **II** compounds against hCA II, along with the σ and π substituent constants. The hydrophobic constant π only appears in Eq. II-1, because the σ constants of alkyl groups in Set **II** compounds are nearly constant.

$$\log(1/K_i) = 0.811\pi + 6.62 \quad (\text{II-1})$$

n = 5, r = 0.993, s = 0.0934, F = 215.

Eq. II-1 suggests that the variation of inhibitory activity among Set **II** compounds is governed only by the hydrophobic interaction between the alkyl chain in a BSA and the hydrophobic site in hCA II. Then, we performed LERE-QSAR analysis of Set **II** compounds using Eq. 5, into which the dispersion interaction energy term was introduced as the LJ6 term. Table 2(b) lists the energy terms on the right hand side of Eq. II-2.

$$\Delta G = (1+\beta)[(1-\alpha)(\Delta E_{\text{bind}} + E_{\text{disp}}) + \Delta G_{\text{sol}}^{\text{pol}} + \Delta G_{\text{sol}}^{\text{nonpol}} + \Delta G_{\text{dis}}] + 72.9 \quad (\text{II-2})$$

n = 5, r = 0.967, s = 0.275, F = 43.6, β = 0.233 (α = 0.65).

The π term in Eq. II-1 is nicely expressed by two energy terms, $\Delta G_{\text{sol}}^{\text{nonpol}}$ and E_{disp}, in Eq. II-2 ($\pi = -0.653[\Delta G_{\text{sol}}^{\text{nonpol}} + (1-\alpha)E_{\text{disp}}] - 6.29$, $n = 5$, $r = 0.992$), indicating that π represents the desolvation $\Delta G_{\text{sol}}^{\text{nonpol}}$ and dispersion E_{disp} interaction energies between the alkyl chain in the BSA and the hydrophobic cleft enveloped by hydrophobic residues in hCA II.

After we confirmed that Eq. 5 can reproduce the hydrophobic interaction energy change represented by the π term in Eq. II-1, we applied Eq. 5 to Set **I** compounds and obtained Eq. I-3.

$$\Delta G = (1+\beta)[(1-\alpha)(\Delta E_{\text{bind}} + E_{\text{disp}}) + \Delta G_{\text{sol}}^{\text{pol}} + \Delta G_{\text{sol}}^{\text{nonpol}} + \Delta G_{\text{dis}}] + 2.17 \quad (\text{I-3})$$

n = 16, r = 0.972, s = 0.197, F = 241, β = −0.818 (α = 0.65).

The statistical quality of Eq. I-3 is slightly higher than that of Eq. I-2, where the dispersion interaction energy term E_{disp} is not included. Table 2(a) lists the energy terms in Eq. I-3. Comparison of Eqs. I-2 and I-3 suggests that the energy term E_{disp} does not make a significant contribution to the overall free-energy changes in Set **I**

Table 2
Overall free-energy change ΔG and components of ΔG[a]

Compound		ΔG			ΔE_{bind}	E_{disp}	ΔG_{sol}^{pol}[e]	ΔG_{sol}^{nonpol}[f]	ΔG_{dis}[g]
No.	X	Obsd[b]	Calcd[c]	Calcd[d]					
*(a) Set **I** compounds*									
1	4-CH_3NH	−6.54	−6.20	−6.29	−120.49	−31.56	4.37	−0.42	2.96
2	4-NH_2	−6.07	−6.20	−6.22	−120.40	−30.52	4.55	−0.15	2.46
3	4-CH_3O	−6.99	−6.91	−6.88	−116.46	−30.72	1.54	−0.39	0.82
4	4-CH_3	−7.24	−7.16	−7.13	−116.64	−31.13	0.63	−0.28	0.41
5	3-CH_3	−6.88	−6.99	−7.02	−115.34	−31.91	1.39	−0.33	0.12
6	H	−6.75	−7.27	−7.13	−116.09	−29.47	0.00	0.00	0.00
7	4-Cl	−7.85	−7.86	−7.74	−112.15	−30.74	−3.14	−0.19	−0.94
8	4-Br	−7.85	−7.94	−7.87	−111.95	−31.66	−3.55	−0.24	−0.96
9	3-Cl	−7.80	−7.79	−7.76	−111.66	−31.93	−2.51	−0.26	−1.33
10	4-CH_3CO	−7.76	−7.92	−7.85	−112.24	−31.61	−2.10	−0.59	−1.84
11	4-CN	−8.15	−8.43	−8.28	−108.92	−31.16	−5.45	−0.20	−2.59
12	3-NO_2	−8.07	−7.96	−8.08	−111.14	−34.59	−2.02	−0.38	−2.76
13	4-NO_2	−8.25	−8.42	−8.32	−109.52	−31.84	−4.05	−0.40	−3.53
14	3,4-di-Cl	−8.60	−8.24	−8.25	−108.37	−33.36	−5.07	−0.39	−2.02
15	3-NO_2, 4-Cl	−8.70	−8.27	−8.46	−109.50	−36.13	−3.23	−0.56	−3.45
16	3-CF_3, 4-NO_2	−8.77	−8.75	−8.99	−105.95	−37.63	−5.24	−0.78	−4.87
*(b) Set **II** compounds*									
Compound		ΔG			ΔE_{bind}	E_{disp}	ΔG_{sol}^{pol}[j]	ΔG_{sol}^{nonpol}[k]	ΔG_{dis}[l]
No.	X	Obsd[h]		Calcd[i]					
1	4-CH_3	−9.66		−9.44	−161.22	−29.53	0.00	0.00	0.00
2	4-C_2H_5	−10.27		−10.50	−160.18	−31.68	−0.20	−0.24	−0.03
3	4-C_3H_7	−10.60		−10.83	−159.66	−33.24	−0.02	−0.47	0.11
4	4-C_4H_9	−11.32		−11.35	−159.17	−35.18	0.29	−0.69	0.12
5	4-C_5H_{11}	−12.08		−11.82	−158.78	−36.26	0.28	−0.84	0.13

[a] In kcal/mol.
[b] 2.303 RT log K_i, T = 288 K.
[c] Calculated from Eq. I-2.
[d] Calculated from Eq. I-3.
[e] Relative value from ΔG_{sol}^{pol} (X = H), ΔG_{sol}^{pol} (X = H) = 75.30 kcal/mol.
[f] Relative value from ΔG_{sol}^{nonpol} (X = H), ΔG_{sol}^{nonpol} (X = H) = −2.94 kcal/mol.
[g] Relative value from ΔG_{dis} (X = H), ΔG_{dis} (X = H) = 51.44 kcal/mol.
[h] 2.303 RT log K_i, T = 298 K.
[i] Calculated from Eq. II-2.
[j] Relative value from ΔG_{sol}^{pol} (X = 4-CH_3), ΔG_{sol}^{pol} (X = 4-CH_3) = 130.23 kcal/mol.
[k] Relative value from ΔG_{sol}^{nonpol} (X = 4-CH_3), ΔG_{sol}^{nonpol} (X = 4-CH_3) = −2.96 kcal/mol.
[l] Relative value from ΔG_{dis} (X = 4-CH_3), ΔG_{dis} (X = 4-CH_3) = 51.76 kcal/mol.

compounds. While the π term for Set **II** compounds exhibits excellent correlation (r = −0.992) with the sum of ΔG_{sol}^{nonpol} and E_{disp}, that for Set **I** compounds does not show any significant correlation (r = −0.276). This is probably because more than half of Set **I** compounds have polar substituents such as NH_2 and NO_2. We previously reported that log P of such polar compounds can be expressed by the polar (electrostatic) term ΔG_{sol}^{pol} as well as the nonpolar term ΔG_{sol}^{nonpol}.[23] The effect of π in Eq. I-1 on the overall free-energy change is probably expressed by ΔG_{sol}^{pol} in Eqs. I-2 and I-3, because the variation of ΔG_{sol}^{nonpol} and E_{disp} is smaller than that of ΔG_{sol}^{pol} for Set **I** compounds. The effect of π in Eq. I-1 is adequately expressed by the solvation ($\Delta G_{sol}^{pol} + \Delta G_{sol}^{nonpol}$) and dispersion interaction energy (E_{disp}) terms in Eq. 5. As a result, Eqs. I-2 and I-3 give similar forms of equation with similar statistical qualities.

There are remarkable differences of the intercept (*const*) and absolute value of slope ($|\beta|$) between Eqs. I-3 and II-2. The larger $|\beta|$ and smaller intercept values in Eq. I-3 (β = −0.818 and intercept = 2.17) indicate that ΔG_{others} in Eq. 1 is proportional to the sum of the representative energy terms (ΔG_{others} = −0.858 [ΔG_{bind} + ΔG_{sol} + ΔG_{dis}], n = 16, r = 1.000, where ΔG_{others} is defined as (2.303 RT log K_i) − [ΔG_{bind} + ΔG_{sol} + ΔG_{dis}]), and the smaller $|\beta|$ and larger intercept values in Eq. II-2 (β = 0.233 and intercept = 72.9) indicate that ΔG_{others} can be considered as a positive large constant that does not vary greatly depending on Set **II** compounds (ΔG_{others} = 56.6–57.3). The above comparison suggests that (1) as well as the sum of the representative energy terms, ΔG_{others} in both Sets **I** and **II** represents mainly the electrostatic contribution, and that (2) ΔG_{others} serves as a penalty term in the both sets,

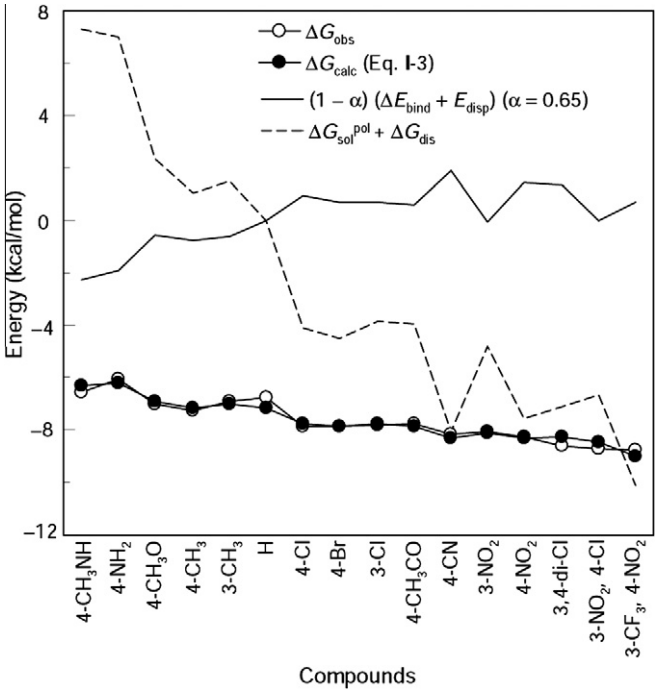


Figure 1. Free-energy changes associated with complex formation of bCA II with Set **I** compounds. (ΔE_{bind} + E_{disp}) and (ΔG_{sol}^{pol} + ΔG_{dis}) are relative energies from those of compound **6** (X = H).

but behaves differently between the two sets, i.e., (β <0, *const* ~0) and (β ~0, *const* >0) for Sets **I** and **II**, respectively, in the assumption of LERE approximation: $\Delta G_{others} = \beta\ [\Delta G_{bind} + \Delta G_{sol} + \Delta G_{dis}] +$ *const* (Eq. 2).

There are nice correlations of Hammett σ with the energy terms ΔE_{bind}, ΔG_{sol}^{pol}, and ΔG_{dis} in Eq. I-3 ($r = 0.969$, -0.911, and -0.996, respectively) and ($\Delta E_{bind} + E_{disp}$) exhibits negative correlation with ($\Delta G_{sol}^{pol} + \Delta G_{dis}$) ($r = -0.900$). As can be seen in Figure 1, the sum of the polar solvation (polar contribution) and dissociation free-energy changes ($\Delta G_{sol}^{pol} + \Delta G_{dis}$) governs the overall free-energy change (ΔG) in Set **I** compounds.

The proposed LERE-QSAR procedure can provide detailed information as to ligand–protein interactions at the electronic and atomic levels,[24] and will be a new powerful tool in the area of drug discovery.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (No. 20590036) from the Ministry of Education, Culture, Sports, Science and Technology. We wish to thank Professor Toshio Fujita (Kyoto University, Japan) for his instructive suggestions.

References and notes

1. Krishnamurthy, V. M.; Kaufman, G. K.; Urbach, A. R.; Gitlin, I.; Gudiksen, K. L.; Weibel, D. B.; Whitesides, G. M. *Chem. Rev.* **2008**, *108*, 946.
2. Supuran, C. T. *Nat. Rev. Drug Disc.* **2008**, *7*, 168.
3. Lindskog, S.; Thorslund, A. *Eur. J. Biochem.* **1968**, *3*, 453.
4. Kanamori, K.; Roberts, J. D. *Biochemistry* **1983**, *22*, 2658.
5. Blackburn, G. M.; Mann, B. E.; Taylor, B. F.; Worrall, A. F. *Eur. J. Biochem.* **1985**, *153*, 553.
6. Nakano, T.; Kaminuma, T.; Sato, T.; Akiyama, Y.; Uebayashi, M.; Kitaura, K. *Chem. Phys. Lett.* **2000**, *318*, 614.
7. Fukuzawa, K.; Mochizuki, Y.; Tanaka, S.; Kitaura, K.; Nakano, T. *J. Phys. Chem. B* **2006**, *110*, 16102.
8. Yoshida, T.; Munei, Y.; Hitaoka, S.; Chuman, H. *J. Chem. Inf. Model.* **2010**, *50*, 850.
9. Bashford, D.; Case, D. A. *Annu. Rev. Phys. Chem.* **2000**, *51*, 129.
10. Krishnamurthy, V. M.; Bohall, B. R.; Semetey, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **2006**, *128*, 5802.
11. Freire, E. *Chem. Biol. Drug Des.* **2009**, *74*, 468.
12. Scott, A. D.; Phillips, C.; Alex, A.; Flocco, M.; Bent, A.; Randall, A.; O'Brien, R.; Damian, L.; Jones, L. H. *ChemMedChem* **2009**, *4*, 1985.
13. Case, D. A.; Cheatham, T. E., III; Darden, T.; Gohlke, H.; Luo, R.; Merz, K. M., Jr.; Onufriev, A.; Simmerling, C.; Wang, B.; Woods, R. J. *J. Comput. Chem.* **2005**, *26*, 1668.
14. Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357.
15. Saito, R.; Sato, T.; Ikai, A.; Tanaka, N. *Acta Crystallogr., Sect. D* **2004**, *60*, 792.
16. Kitaura, K.; Sawai, T.; Asada, T.; Nakano, T.; Uebayasi, M. *Chem. Phys. Lett.* **1999**, *312*, 319.
17. Qiu, D.; Shenkin, P. S.; Hollinger, P. K.; Still, W. C. *J. Phys. Chem. A* **1997**, *101*, 3005.
18. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669.
19. Kakeya, N.; Aoki, M.; Kamada, A.; Yata, N. *Chem. Pharm. Bull.* **1969**, *17*, 1010.
20. Hansch, C. *Il Farmaco* **2003**, *58*, 625.
21. King, R. W.; Burgen, A. S. V. *Proc. R. Soc. Lond. B* **1976**, *193*, 107.
22. He, X.; Fusti-Molnar, L.; Cui, G.; Merz, K. M., Jr. *J. Phys. Chem. B* **2009**, *113*, 5290.
23. Chuman, H.; Mori, A.; Tanaka, H.; Yamagami, C.; Fujita, T. *J. Pharm. Sci.* **2004**, *93*, 2681.
24. Hitaoka, S.; Harada, M.; Yoshida, T.; Chuman, H. *J. Chem. Inf. Model.* **2010**, *50*, 1796.