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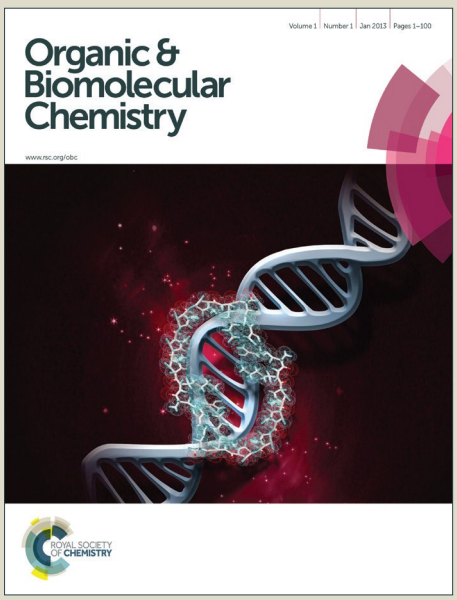

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ARTICLE

The Influence of Intramolecular Sulfur–Lone Pair Interactions on Small-Molecule Drug Design and Receptor Binding

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Sulfur–lone pair interactions are important conformational control elements in sulfur-containing heterocyles that abound in pharmaceuticals, natural products, agrochemicals, polymers and other important classes of organic molecules. Nonetheless, the role of intramolecular sulfur–lone pair interactions in the binding of small molecules to receptors is often overlooked. Here we analyze the magnitudes and origins of these interactions for a variety of biologically relevant small molecules using quantum chemical and automated docking calculations. In most cases examined in this study, the lowest energy conformation of the small molecule displays sulfur–lone pair close contact. However, docking studies, both published and new, often predict that conformations without sulfur–lone pair contacts have the best binding affinity for their respective receptors. This is a serious problem. Since many of these predicted bound conformations are not actually energetically accessible, pursuing design (e.g., drug design) around these binding modes necessarily will lead, serendipity aside, to dead end designs. Our results constitute a caution that one best not neglect these interactions when predicting the binding affinities of potential ligands (drugs or not) for hosts (enzymes, receptors, DNA, RNA, synthetic hosts). Moreover, a better understanding and awareness of sulfur–lone pair interactions should facilitate the rational modulation of host–guest interactions involving sulfur-containing molecules.

Introduction

Sulfur atoms in complex organic molecules often reside near oxygen or nitrogen lone pairs. While this statement may seem counterintuitive given that sulfur atoms also bear lone pairs and chemists are conditioned to avoid contorting molecules into shapes where lone pair/lone pair repulsion can occur, its validity is supported by extensive experimental and theoretical studies.[1-15] Here we shine light on the importance of intramolecular sulfur–lone pair interactions for the binding of small molecules, such as drugs, to receptors, such as enzymes, offering both a caution and a recommended procedure for properly modeling the binding of ligands where such effects might be at play.

Theoretical studies agree that sulfur lone pair/oxygen or nitrogen lone pair interactions are repulsive; however, compensatory favorable interactions can sometimes lead to net attraction between sulfur atoms and oxygen or nitrogen atoms bearing lone pairs.[1-15] Arguments for both favorable electrostatic interactions (dipole/dipole) and orbital interactions ($X_{lp} \leftrightarrow \sigma^*_{S-Y}$) have been made, although the relative importance of each depends on the specific molecule (and also on the specific theoretical approach used to assign an energy value to each interaction).[1-15] Analogies have also been made to halogen bonding,[16,17] leading to the use of the term "chalcogen bonding" to refer to favorable interactions between sulfur (and other chalcogens) with lone pairs.[9]

Results and Discussion

Although the optimization of sulfur–lone pair interactions occasionally has been applied in drug design,[1,18-24] to our knowledge, commercial force fields and energy functions used for automated docking have not included explicit terms accounting for favorable sulfur–lone pair interactions.[14] This has led to reports in which binding modes are predicted that involve conformations of small molecules lacking sulfur–lone pair interactions, even though other conformations with sulfur–lone pair interactions would likely be significantly lower in energy.[25-37] For example, the lowest energy conformation of compound **1** (a caspase-3 inhibitor),[25] shown in Figure 1, is one that exhibits a sulfur–lone pair interaction on one side of the molecule and a hydrogen-bonding interaction on the opposite side. A conformation lacking the sulfur–lone pair interaction, which corresponds to that reported in a previous docking study,[25] is higher in energy by 11 kcal/mol. Compound **2** (an antimicrobial agent),[26] also presented in Figure 1, was found to have a 10 kcal/mol preference for a conformation that puts the sulfur atom near an oxygen atom over a conformation having a nitrogen atom near an oxygen atom—the latter again a conformation reported in a previous docking study.[26]

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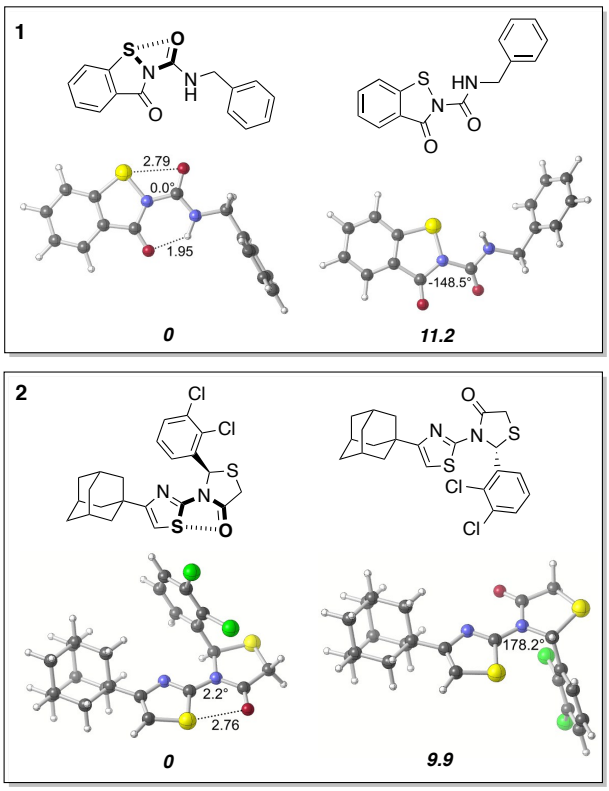

Figure 1. Conformational energy differences for 1 and 2. Configurations with sulfur–lone pair interactions are lower in energy than those lacking them. Free energies (gas phase) shown in kcal/mol were computed at M06-2X/6-31+G(d,p). Select distances shown in Ångstroms.

Using OpenEye[45] docking software, we subjected optimized structures of **1** and **2** to a thorough conformational search then docked them into crystal structures of their protein targets. As shown in Figure 2, conformations of **1** with and without sulfur–lone pair interactions were found to occupy similar regions of the active site and essentially no difference in docking scores was found. However, in that quantum chemical calculations predict that conformations with sulfur–lone pair interactions are energetically preferred; these are the ones that should be considered biologically relevant.[22,52] Analysis of **2** led to slightly different results. The best binding mode where the substrate lacks a sulfur–lone pair interaction was predicted to be favored over the best binding mode where the substrate does have a sulfur–lone pair interaction. However, the predicted conformation is not biologically accessible since it is 10 kcal/mol higher in energy than the low scoring conformation. Again, neclecting sulfur–lone pair interactions, i.e., not taking into account the energies of conformers with and without such interactions, leads to faulty predictions of preferred binding modes.

For these examples, X-ray crystal structures with the small molecules in question bound are not available. Consequently, we examined systems for which crystal structures with ligands displaying intramolecular sulfur–lone pair interactions are available to compare the energies of bound conformations possessing sulfur–lone pair interactions to alternative conformations lacking them. For example, compound **VO2**

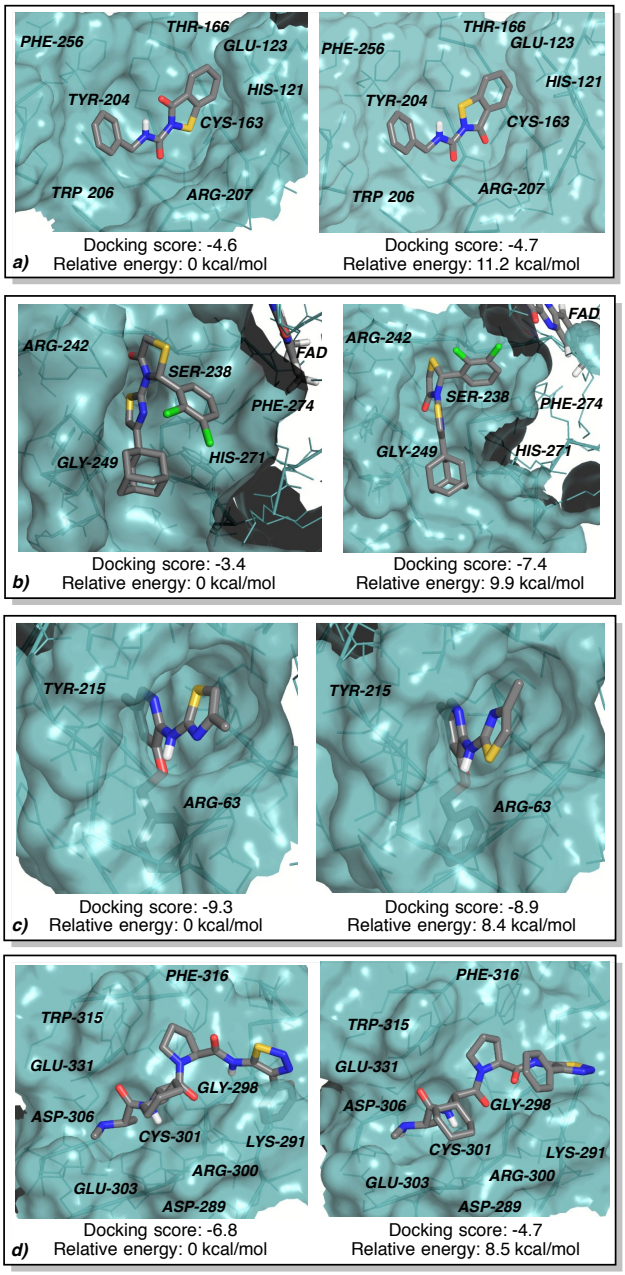

Figure 2. Predicted binding modes, docking scores, and relative energies of 1, 2, VO2, and PRD. Results from automated docking and quantum chemical calculations for conformations with and without sulfur–lone pair close contacts for **a**) **1** in caspase-3 enzyme (PDB ID: 3H0E), **b**) **2** in MurB (PDB ID: 1HSK), **c**) **VO2** in glucokinase (PDB ID: 4MLH), and **d**) **PRD** in cIAP1/XIAP chimeric BIR3 domain (PDB ID: 3UW4).

bound to glucokinase (PDB ID: 4MLH),[38] adopts a conformation with a sulfur–lone pair close contact (Figure 3). Quantum chemical calculations indicate that this corresponds to a low energy conformation of **VO2**; conformations without sulfur–lone pair interactions were found to be higher in energy (e.g., Figure 3). Another example, compound **PRD** bound to the cIAP1/XIAP chimeric BIR3 domain (PDB ID: 3UW4),[39] again shows that the bound conformation, which has a sulfur–lone

pair interaction, is lower in energy than conformations lacking this interaction (e.g., Figure 3).

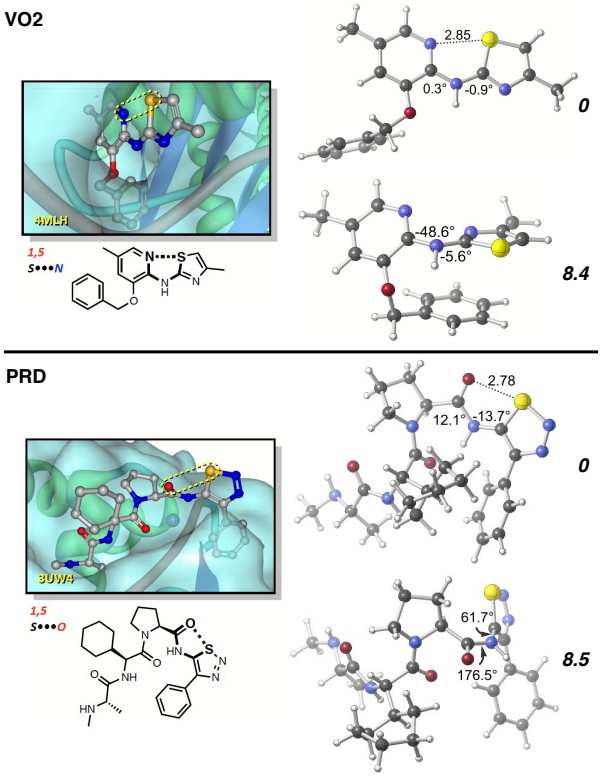

Figure 3. X-ray crystal structures and relative energies of inhibitors VO2 and PRD. X-ray crystal structures of **VO2** and **PRD** bound in their respective active sites display intramolecular sulfur–lone pair close contacts. Conformations of **VO2** and **PRD** found in the X-ray crystal structures were optimized using M06-2X/6-31+G(d,p). Free energies shown in kcal/mol and select distances shown in Ångstroms.

Work to understand the origins of sulfur–lone pair interactions has predominantly focused on donor-acceptor orbital interactions between the lone pair of an oxygen or nitrogen atom and the σ* antibonding orbitals of S–Y bonds.[1-15] Using NBO 6.0, the magnitudes of such interactions were quantified for truncated versions of compounds **1**, **2**, **VO2**, and **PRD** as shown in Figure 4. As described above, the preferred conformer of **1** has both a sulfur–lone pair interaction and an N–H•••O hydrogen bond. Based on NBO analysis, $O_{lp} \leftrightarrow \sigma^*_{S-N}$ and $O_{lp} \leftrightarrow \sigma^*_{S-C}$ interactions are favorable while lone pair/lone pair repulsion is unfavorable by a slightly greater amount. On the opposite side of **1** is a hydrogen bond that is net attractive by 3.44 kcal/mol. Overall, favorable sulfur–lone pair and hydrogen bonding donor-acceptor orbital interactions outweigh filled/filled interactions (additional electrostatic interactions may also contribute to the free energy difference between the two conformations of **1**).

Analysis of compounds **2**, **VO2**, and **PRD** show that sulfur–lone pair donor-acceptor orbital interactions again play key roles, but other donor-acceptor orbital interactions do, as well. In short, the lone pair/lone pair repulsion associated with having a sulfur atom near to an O/N atom is generally counterbalanced by favorable $O/N_{lp} \leftrightarrow \sigma^*_{S-Y}$ interactions, i.e., although favorable sulfur–lone pair interactions do not dominate, neglecting them would lead to erroneous predictions about conformational preferences.

We also carried out docking calculations for **VO2** and **PRD**, for which crystal structures are available and which have sulfur–lone pair close contacts in their bound conformations.

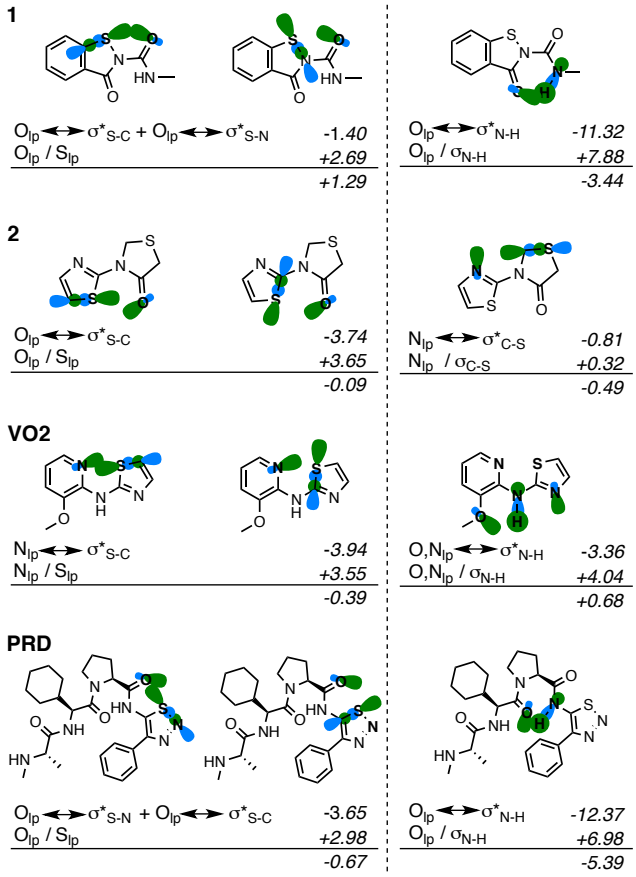

Figure 4. Natural bond orbital (NBO) interactions and their role in sulfur–lone pair interactions. Core structures of compounds **1**, **2**, **VO2**, and **PRD** with intramolecular sulfur–lone pair interactions were used to quantify donor-acceptor orbital interactions via NBO calculations using M06-2X/6-31+G(d,p) level of theory. Favorable donor–acceptor interactions counterbalance the effect of lone pair/lone pair repulsion between sulfur and a heteroatom. Energies shown in kcal/mol.

These calculations predicted that the best conformations of **VO2** with and without sulfur–lone pair close contacts have similar binding affinities (Figure 2c). Again, based on such docking studies alone, one could not correctly identify the ideal docking pose of this compound. Docking calculations did predict that a conformer of **PRD** with a sulfur–lone pair close contact binds best (Figure 2d), but it is likely that this prediction resulted primarily from shape considerations.

In some cases, conformations of molecules containing sulfur–lone pair interactions are not significantly lower in energy than conformations lacking these interactions. Examples are shown in Figure 5. These molecules, a histone methyltransferase inhibitor (**3**)[27] and a folate receptor inhibitor (**4**)[28], were discovered, in part, using automated docking studies. In these cases, no strong favorable interactions occur on the side of each thiophene opposite to the sulfur atom in

conformations containing sulfur-oxygen close contacts, nor do strongly favorable or unfavorable interactions occur upon rotation of the thiophene ring by ~180° (e.g., S is not a good hydrogen-bond acceptor[40]). Although we have discussed some useful guidelines, such as these, for making predictions about

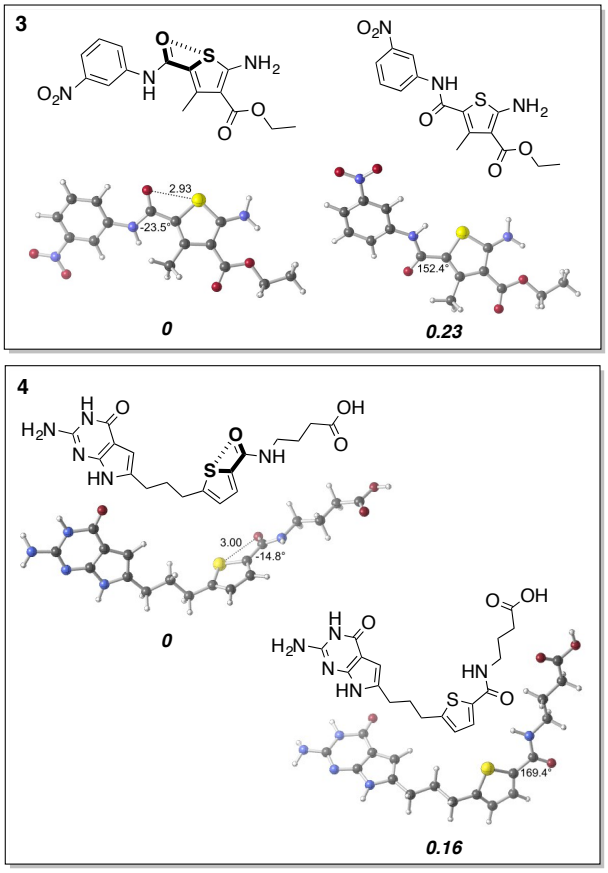

Figure 5. Conformational energy differences of 3 and 4. Small molecule leads that do not exhibit an energetic preference for a conformation with a sulfur–lone pair interaction. Some cases are difficult to predict without quantum chemical calculations. Free energies (gas phase) shown in kcal/mol computed at M06-2X/6-31+G(d,p). Select distances shown in Ångstroms.

conformational preferences, it is still difficult to make firm predictions without quantum chemical studies.

Methods

All quantum chemical calculations were performed using Gaussian 09[41] with the M06-2X/6-31+G(d,p)[42,43] level of theory in the gas phase (relative energies may be different to some extent in solvent, but large differences are not expected; see Supplementary Information for results from test calculations). Separate calculations using the MP2 method also were carried out to confirm that differences were not observed in the energetic preferences for conformations of **1** (results of these calculations can be found in the Supplementary Information). Natural bonding orbital calculations to quantify the magnitude of donor-acceptor and filled/filled orbital interactions were completed using NBO6.0[44] with the keywords E2PERT=0.1 and STERIC=0.1. Structures were truncated to their "core" structures in order to model more general motifs found in pharmaceutical compounds. The OpenEye Suite was used for conformer generation, receptor creation, and receptor-conformer library docking.[45] Drawings of optimized structures were produced using CYLView[46] and images of docking results were produced using PyMol.[47]

Receptor and ligand preparation. Optimized structures were used to initiate the docking studies using the OpenEye Suite.[45] Docking studies involved conformer generation using OMEGA[48] (conformers were sorted based on whether a sulfur-lone pair interaction was present or not), receptor creation using published crystallographic data in FRED Receptor, control experiments of natural ligands in their respective active sites, and docking of small molecule drugs using FRED.[49] Information on receptor creation of each active site generated such as box volume, inner/outer contour size, and constraints imposed (if any) can be found in Supplementary Table 1.

Receptor-conformer library docking. The default scoring function in OpenEye, Chemgauss4, was used and the top ten (lowest-scoring) poses were analyzed. The Chemgauss4 scoring function uses Gaussian potentials to measure ligand poses in the active site based on shape, protein-ligand hydrogen bonding, ligand–solvent hydrogen bonding, and metal–chelator interactions.[46] After each conformer generates a pose and receives a score, an overall score and ranking is generated (in this case, the top 10 poses are ranked). Docking poses found using OpenEye were similar to those reported previously using other molecular docking tools.[25,26] Images shown in Figure 2 depict similar receptor orientations as shown in previous reports.

Conclusions

These results lead us to the following recommendations for carrying out docking computations using energy/scoring functions that do not account for favorable sulfur–lone pair interactions. (1) Perform a conformational analysis of the small molecule to be docked in which conformer energies are computed using a suitably reliable quantum chemical method. (2) Dock conformers within 5 or so kcal/mol of the lowest energy conformer, since it is unlikely that a protein that binds a small molecule will, through intermolecular interactions, selectively pay an energy price larger than this.[22] (3) When ranking small molecules on the basis of docking scores, be they binding energies or not, do not neglect energy differences for conformers computed with quantum chemistry. These guidelines are relevant not only to the assessment of designs for potential pharmaceuticals, but to the design of any host–guest system with the potential for sulfur–lone pair interactions.[50,51,52] Neglecting sulfur-lone pair interactions in making quantitative or qualitative predictions about conformations and binding modes, even if these interactions are not net favorable energetically, is ill advised.

Acknowledgements

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References

1 B. R. Beno, K. S. Yeung, M. D. Bartberger, L. D. Pennington and N. A. Meanwell, *J. Med. Chem.* 2015, **58**, 4383-4438.
2 R. C. Reid, M.-K. Yau, R. Singh, J. Lin and D. P. Fairlie, *J. Am. Chem. Soc.* 2014, **136**, 11914-11917.
3 D. A. Rogers, J. D. Margerum and G. M. Wyman, *J. Am. Chem. Soc.* 1957, **79**, 2464-2468.
4 G. S. Egerton, *Nature* 1959, **183**, 389-390.
5 I. Jalsovszky, Ö. Farkas, J. Rábai and A. Kucsman, *J. Molec. Struc. (Theochem)* 1996, **365**, 93-102.
6 Y. Nagao, T. Hirata, S. Goto, S. Sano, A. Kakehi, K. Iizuka and M. Shiro, M. *J. Am. Chem. Soc.* 1998, **120**, 3104-3110.
7 M. Iwaoka, S. Takemoto and S. Tomoda, *J. Am. Chem. Soc.* 2002, **124**, 10613-10620.
8 U. Adhikari and S. Scheiner, *J. Phys. Chem. A* 2012, **116**, 3487-3497.
9 P. Politzer, J. S. Murray and T. Clark, T. *Phys. Chem. Chem. Phys.* 2013, **15**, 11178-11189.
10 E. V. Sadchikova, V. A. Bakulev, J. O. Subbotina, D. L. Privalova, W. Dehaen, K. Van Hecke, K. Robeyns, L. Van Meervelt and V. S. Mokrushin, *Tetrahedron* 2013, **69**, 6987-6992.
11 S. Tsuzuki and N. Sato, *J. Phys. Chem. B* 2013, **117**, 6849-6855.
12 F. Zhou, R. Liu and H. Zhang, *New J. Chem.* 2015, **39**, 1611-1618.
13 S. P. Thomas, D. Jayatilaka and T. N. Guru Row, *Phys. Chem. Chem. Phys.* 2015, **17**, 25411-25420.
14 X. Zhang, Z. Gong, J. Li and T. Lu, *J. Chem. Inf. Model.* 2015, **55**, 2138-2153.
15 R. E. Rosenfield, Jr., R. Pathasarathy and J. D. Dunitz, *J. Am. Chem. Soc.* 1977, **99**, 4860-4862.
16 K. E. Riley and P. Hobza, *Phys. Chem. Chem. Phys.* 2013, **15**, 17742-17751.
17 M. C. Ford and P. S. Ho, *J. Med. Chem.,* DOI: 10.1021/acs.jmedchem.5b00997.
18 G. J. Yu, C. L. Yoo, B. Yang, M. W. Lodewyk, L. Meng, T. T. El-Idreesy, J. C. Fettinger, D. J. Tantillo, A. S. Verkman and M. J. Kurth, *J. Med. Chem.* 2008, **51**, 6044-6054.
19 S. Lin, S. T. Wrobleski, J. Hynes, Jr., S. Pitt, R. Zhang, Y. Fan, A. M. Doweyko, K. F. Kish, J. S. Sack, M. F. Malley, S. E. Kiefer, J. A. Newitt, M. McKinnon, J. Trzaskos, J. C. Barrish, J. H. Dodd, G. L. Schieven and K. Leftheris, *Bioorg. Med. Chem. Lett.* 2010, **20**, 5864-5868.
20 J. M. Knapp, A. B. Wood, P. –W. Phuan, M. W. Lodewyk, D. J. Tantillo, A. S. Verkman and M. J. Kurth, *J. Med. Chem.* 2012, **55**, 1242-1251.
21 K. C. Coffman, H. H. Nguyen, P. –W. Phuan, B. M. Hudson, G. J. Yu, A. L. Bagdazarian, D. Montgomery, M. W. Lodewyk, B. Yang, C. L. Yoo, A. S. Verkman, D. J. Tantillo and M. J. Kurth, *J. Med. Chem.* 2014, **57**, 6729-6738.
22 L. Ye, B. Hu, F. El-Badri, B. M. Hudson, P. –W. Phuan, A. S. Verkman, D. J. Tantillo and M. J. Kurth, *Bioorg. Med. Chem. Lett.* 2014, **24**, 5840-5844.
23 L. D. Pennington, M. D. Bartberger, M. D. Croghan, K. L. Andrews, K. S. Ashton, M. P. Bourbeau, J. Chen, S. Chmait, R. Cupples, C. Fotsch, J. Helmering, F. –T. Hong, R. W. Hungate, S. R. Jordan, K. Kong, L. Liu, K. Michelsen, C. Moyer, N. Nishimura, M. H. Norman, A. Reichelt, A. C. Siegmund, G. Sivits, S. Tadesse, C. M. Tegley, G. Van, K. C. Yang, G. Yao, J. Zhang, D. J. Lloyd, C. Hale and D. J. St. Jean, *J. Med. Chem.*, DOI: 10.1021/acs.jmedchem.5b01367.
24 An intermolecular example: H. V. Le, D. D. Hawker, R. Wu, E. Doud, J. Widom, R. Sanishvili, D. Liu, N. L. Kelleher and R. B. Silverman, *J. Am. Chem. Soc.* 2015, **137**, 4525-4533.
25 D. Liu, Z. Tian, Z. Yan, L. Wu, Y. Ma, Q. Wang, W. Liu, H. Zhou and C. Yang, *Bioorg. Med. Chem*. 2013, **21**, 2960-2967.
26 E. Pitta, E. Tsolaki, A. Geronikaki, J. Petrović, J. Glamočlija, M. Soković, E. Crespan, G. Maga, S. S. Bhunia and A. K. Saxena, *Med. Chem. Commun.* 2015, **6**, 319-326.
27 F. Meng, S. Cheng, H. Ding, S. Liu, Y. Liu, K. Zhu, S. Chen, J. Lu, Y. Xie, L. Li, R. Liu, Z. Shi, Y. Zhou, Y. –C. Liu, M. Zheng, H. Jiang, W. Lu, H. Liu, C. Luo, *J. Med. Chem.* 2015, **58**, 8166-8181.
28 L. K. Golani, C. George, S. Zhao, S. Raghavan, S. Orr, A. Wallace, M. R. Wilson, Z. Hou, L. H. Matherly and A. Gangjee, *J. Med. Chem.* 2014, **57**, 8152-8166.
29 S. S. Sulthana, S. A. Antony, C. Balachandran and S. S. Shafi, *Bioorg. Med. Chem. Lett.* 2015, **25**, 2753-2757.
30 S. Massari, G. Nannetti, J. Desantis, G. Muratore, S. Sabatini, G. Manfroni, B. Mercorelli, V. Cecchetti, G. Palù, G. Cruciani, A. Loregian, L. Goracci and O. Tabarrini, *J. Med. Chem.* 2015, **58**, 3830-3842.
31 H. Zhao and A. Caflisch, *Bioorg. Med. Chem. Lett.* 2014, **24**, 1523-1527.
32 S. –K. Yang, J. S. Kang, P. Oelschlaeger and K. –W. Yang, *ACS Med. Chem. Lett.* 2015, **6**, 455-460.
33 L. Wu, M. Lu, Z. Yan, X. Tang, B. Sun, W. Liu, H. Zhou and C. Yang, *Bioorg. Med. Chem.* 2014, **22**, 2416-2426.
34 M. Schiedel, T. Rumpf, B. Karaman, A. Lehotzky, J. Oláh, S. Gerhardt, J. Ovádi, W. Sippl, O. Einsle and M. Jung, *J. Med. Chem.*, DOI: 10.1021/acs.jmedchem.5b01517.
35 D. H. Pandya, J. A. Sharma, H. B. Jalani, A. N. Pandya, V. Sudarsanam, S. Kachler, K. N. Klotz and K. K. Vasu, *Bioorg. Med. Chem. Lett*. 2015, **25**, 1306-1309.
36 S. A. Starosyla, G. P. Volynets, S. S. Lukashov, O. B. Gorbatiuk, A. G. Golub, V. G. Bdzhola and S. M. Yamoluk, *Bioorg. Med. Chem*. 2015, **23**, 2489-2497.
37 T. Tomašič, S. Katsamakas, Ž. Hodnik, J. Ilaš, M. Brvar, T. Solmajer, S. Montalvão, P. Tammela, M. Banjanac, G. Ergović, M. Anderluh, L. P. Mašič and D. Kikelj, *J. Med. Chem.* 2015, **58**, 5501–5521.
38 R. J. Hinklin, S. A. Boyd, M. J. Chicarelli, K. R. Condroski, W. E. Jr. Dewolf, P. A. Lee, W. Lee, A. Singh, L. Thomas, W. C. Voegtli, L. Williams and T. D. Aicher, *J Med. Chem.* 2013, **56**, 7669-7678.
39 J. A. Flygare, M. Beresini, N. Budha, H. Chan, I. T. Chan, S. Cheeti, F. Cohen, K. Keshayes, K. Doerner, S. G. Eckhardt, L. O. Elliott, B. Feng, M. C. Franklin, S. F. Reisner, L. Gazzard, J. Halladay, S. G. Hymowitz, H. La, P. LoRusso, B. Maurer, L. Murray, E. Plise, C. Quan, J. –P. Stephan, S. G. Young, J. Tom, V. Tsui, J. Um, E. Varfolomeev, D. Vucic, A. J. Wagner, H. J. A. Wallweber, L. Wang, J. Ware, Z. Wen, H. Wong, J. M. Wong, M. Wong, S. Wong, R. Yu, K. Zobel and W. J. Fairbrother, *J. Med. Chem*. 2012, **55**, 4101-4113.
40 F. H. Allen, C. M. Bird, R. S. Rowland and P. R. Raithby, *Acta Cryst.* 1997, **B53**, 696-701.
41 Gaussian 09, Revision B.01, M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2009**. (Full reference in the Supplementary Information)
42 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc. 2008,* **120**, 215-241.
43 Y. Zhao and D. G. Truhlar, *Acc. Chem. Res. 2008,* **41***,* 157-167.

44 NBO 6.0. Glendening, E. D. *et al*. (Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, 2013); http://nbo6.chem.wisc.edu/
45 OEChem, version 4.1.2, OpenEye Scientific Software, Inc., Santa Fe, NM, USA, www.eyesopen.com, 2010.
46 CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).
47 The PyMOL Molecular Graphics System, Version 1.7.4.4 Schrödinger, LLC.
48 J. Bostrom, *J. Comp.-Aid. Mol. Design*. 2001, **15**, 1137-1152.
49 M. R. McGann, H. R. Almond, A. Nicholls, J. A. Grant and F. K. Brown, *Biopolymers*, 2003, **68**, 76-90.
50 M. Iwaoka and N. Isozumi, *Molecules*, 2012, **17**, 7266-7283.
51 D. Pal and P. Chakrabarti, *J. Biomol. Struct. Dyn.* 2001, **19**, 115-128.
52 B. Kuhn, W. Guba, J. Hert, D. Banner, C. Bissantz, S. Ceccarelli, W. Haap, M. Körner, A. Kuglstatter, C. Lerner, P. Mattei, W. Neidhart, E. Pinard, M. G. Rudolph, T. Schulz-Gasch, T. Woltering, and M. Stahl. *J. Med. Chem*., Article ASAP. DOI: 10.1021/acs.jmedchem.5b01875