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The Power of MMPA and a Teaching Lesson in Medicinal Chemistry

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Matched molecular pair analysis is used to explore compound property changes resulting from a molecular-shape-conservative replacement of one oxadiazole unit by one of its topological isomers. The exclusive positional interchange of one nitrogen and one oxygen atom in the heteroaromatic five-membered ring within larger molecular contexts has remarkable consequences on compound properties relevant to drug discovery.

Matched molecular pair analysis (MMPA) is a powerful methodology that has been developed in recent years (e.g., see ref 1) to mine large compound and data sets in order to assess changes in compound properties upon selective structural modifications (e.g., see ref 2) and to explore such property changes as a function of structural contexts.[3] Boström et al. from AstraZeneca, Mölndal, Sweden, have used this methodology to explore property changes relevant to medicinal chemistry, observed for pairs of compounds that differ in their molecular structures only in the replacement of a 1,2,4-oxadiazole unit by its topological isomer 1,3,4-oxadiazole.[4] They found substantial and systematic changes in lipophilicity, aqueous solubility, aspects of oxidative metabolism, and hERG channel interaction. This paper is a beautiful illustration of the power of MMPA methodology and a teaching lesson on how minor structural modifications may go a long way in lead optimization.

Replacement of the 1,2,4-oxadiazole by the 1,3,4-oxadiazole unit, keeping the remaining molecular structure unchanged, implies a single formal positional interchange of an oxygen and a nitrogen atom in the five-membered heteroaromatic unit without affecting any aspect of molecular shape (Figure 1). Over 140 matched pairs of this kind could be identified within the nonproprietary part of AstraZeneca's compound and data collection. This compound set appears to be structurally quite diverse and covers a lipophilicity range of approximately 7 log units. Over this entire range a close correlation was found showing that 1,3,4-oxadiazole derivatives were systematically more polar by approximately 1 log D unit than their 1,2,4-counterparts. This is a striking result! Even considering the fact that one may expect 1,3,4-oxadiazole to exhibit a higher dipole moment than the 1,2,4-isomer, as convincingly discussed at the end of the paper by experimental solution-phase data and quantum mechanical computations (for vacuum), the predominance of a polarity difference of a small heterocyclic unit in a larger molecular context of greatly differing overall polarity would have been difficult to predict. Indeed, current ClogP computational tools fall short of predicting this experimental finding adequately.

A subgroup of 25 matched pairs contains basic functionalities in the neighborhood of the oxadiazole unit. One might have anticipated a different degree of basicity modulation by the isomeric heterocycles. Interestingly, however, no pK_a shift or only relatively small pK_a shifts between 0 and $\pm$0.5 for neighboring basic sites are observed going in either direction. Thus, a discussion in terms of log D, measured at pH 7.4, is legitimate; there is no need to resort to intrinsic lipophilicities (log P) of the neutral compounds as calculated from log D and pK_a.

Lipophilicity is a cardinal property in drug discovery. It affects many other compound properties relevant in lead optimization. While there are dominant trends, there are no stringent correlations that would allow other properties to be predicted on the sole basis of lipophilicity. This is very nicely documented and discussed by the authors for representative subsets of these matched pairs for which experimental data for solubility, oxidative metabolism, and hERG interference are available.

The direct correlation between molar aqueous solubility and lipophilicity is poor, clearly indicating that other factors, e.g., crystal packing effects, contribute to solubility. However, by use of matched pair analysis, a remarkable trend emerges indicating that the more polar 1,3,4-oxadiazole derivatives are generally more soluble than their 1,2,4-counterparts.

A subgroup of 34 matched pairs is examined with respect to intrinsic clearance in human liver microsomes, inhibition of recombinant cytochrome (CYP) inhibition, time-dependent CYP inhibition, and CYP reaction phenotyping. This is a rather elaborate analysis that goes way beyond the typical testing of metabolic liability in standard drug discovery efforts and that is typically undertaken only for selected candidates during lead optimization. However, these efforts and discussions are highly valuable. They document that the more polar 1,3,4-oxadiazole derivatives are generally more robust against oxidative metabolism than their matched 1,2,4-counterparts. For various CYP enzymes the inhibitory potency of the less polar 1,2,4-oxadiazole derivatives is typically more pronounced than that of the more polar 1,3,4-conterparts; this is particularly true for CYP3A4 (recognizing lipophilic substrates) and CYP1A2 (recognizing planar heterocycles). Furthermore, while reactive metabolites, resulting in time-dependent CYP inhibition, could be observed for 1,2,4-oxadiazole derivatives, no time-dependent CYP inhibition is generally observed for the matched 1,3,4-counterparts. Finally, interesting changes in the patterns of oxidative attack could be observed for matched pairs by CYP reaction phenotyping, indicating interesting opportunities for lead optimization by switching between the heterocyclic units.

For a subset of seven matched pairs for which hERG channel interference could be experimentally detected at least for one partner of a matched pair, it is found that it is generally the less polar 1,2,4-oxadiazole derivative that displays weak to moderate hERG-channel interference, whereas the corresponding more polar 1,3,4-counterparts consistently display less or no

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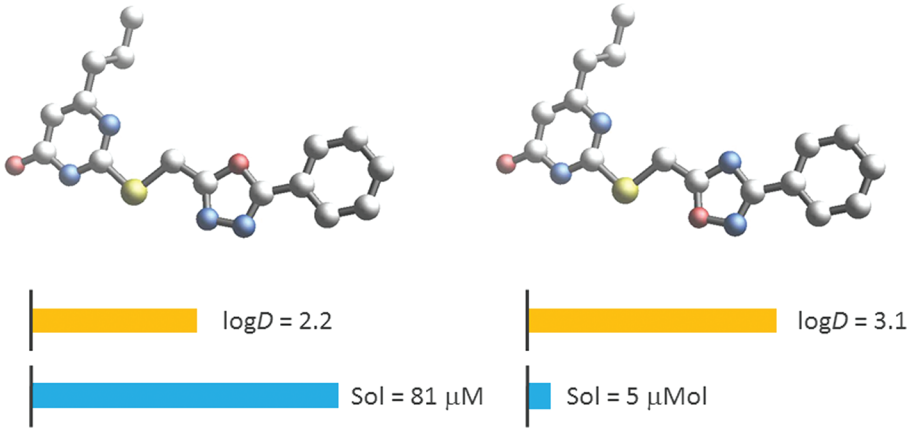

Figure 1. Two compounds of a matched molecular pair differing only in the five-membered heteroaromatic unit: 1,3,4-oxadiazole (left) versus 1,2,4-oxadiazole (right). The two compounds differ markedly in lipophilicity (log *D*) and aqueous molar solubility.

measurable activity. Interestingly, all matched pairs in this subset have a basic functionality in the neighborhood of the oxadiazole unit. As it is well-known that both lipophilicity and the presence of a positive charge at physiological pH contribute to hERG activity, one may be tempted to speculate that these observations may be due also in part to a pK_a-lowering effect of the more polar 1,3,4-oxadiazole unit. However, the finding of little or no changes in pK_a upon switching from 1,2,4- to 1,3,4-oxadiazole derivatives dismisses this interpretation.

The paper by Jonas Boström et al.[4] is a pleasure to read. It beautifully illustrates the power of the molecular matched pair analysis methodology when applied to large compound and data repositories, and it documents an important aspect of heterocyclic chemistry in which a seemingly minor positional interchange of two heteroatoms results in substantial changes in physicochemical and biochemical properties relevant to drug discovery. The careful, detailed, and thorough discussions make this paper a welcome teaching lesson in medicinal chemistry.

This account should not end without mentioning that the authors also report on their successful efforts to improve synthetic access to disubstituted 1,3,4-oxadiazoles. So the authors are kind enough to provide the synthetic tools for others to take up the opportunities clearly outlined in their paper.

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