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# Oxadiazoles in Medicinal Chemistry

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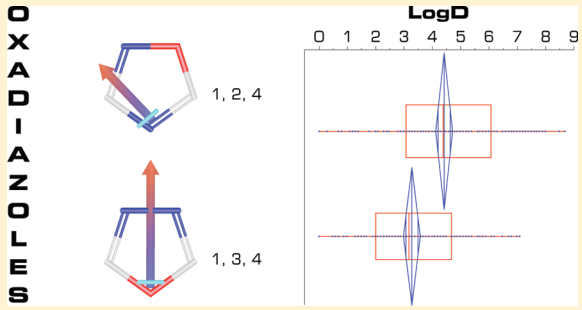
Supporting Information

**ABSTRACT:** Oxadiazoles are five-membered heteroaromatic rings containing two carbons, two nitrogens, and one oxygen atom, and they exist in different regioisomeric forms. Oxadiazoles are frequently occurring motifs in druglike molecules, and they are often used with the intention of being bioisosteric replacements for ester and amide functionalities. The current study presents a systematic comparison of 1,2,4- and 1,3,4-oxadiazole matched pairs in the AstraZeneca compound collection. In virtually all cases, the 1,3,4-oxadiazole isomer shows an order of magnitude lower lipophilicity (log *D*), as compared to its isomeric partner. Significant differences are also observed with respect to metabolic stability, hERG inhibition, and aqueous solubility, favoring the 1,3,4-oxadiazole isomers. The difference in profile between the 1,2,4 and 1,3,4 regioisomers can be rationalized by their intrinsically different charge distributions (e.g., dipole moments). To facilitate the use of these heteroaromatic rings, novel synthetic routes for ready access of a broad spectrum of 1,3,4-oxadiazoles, under mild conditions, are described.




## INTRODUCTION

Compounds containing heterocyclic ring systems are of great importance both medicinally and industrially. As an example, five-membered ring heterocycles containing two carbon atoms, two nitrogen atoms, and one oxygen atom, known as oxadiazoles (Figure 1a), are of considerable interest in different areas of medicinal and pesticide chemistry and also polymer and material science.[1] The level of interest is clearly shown, as over the past 9 years the number of patent applications containing oxadiazole rings has increased considerably (100%), to a total of 686 (Figure 1b). Within drug discovery and development, a number of compounds containing an oxadiazole moiety are in late stage clinical trials, including zibotentan (**1**) as an anticancer agent[2] and ataluren (**2**) for the treatment of cystic fibrosis[3] (Figure 2). So far, one oxadiazole containing compound, raltegravir (**3**),[4] an antiretroviral drug for the treatment of HIV infection, has been launched onto the marketplace. It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes,[5] obesity,[6] inflammation,[7] cancer,[8] and infection.[9]

Oxadiazole rings have been introduced into drug discovery programs for several different purposes. In some cases, they have been used as an essential part of the pharmacophore, favorably contributing to ligand binding.[10] In other cases, oxadiazole moieties have been shown to act as a flat, aromatic linker to place substituents in the appropriate orientation,[11] as well as modulating molecular properties by positioning them in the periphery of the molecule.[12] It has also recently been shown that significant differences in thermodynamic properties can be achieved by influencing the water architecture within the aldose reductase active site by using two structurally related oxadiazole regioisomers.[13] Finally, oxadiazoles have been used as replacements for carbonyl containing compounds such as esters, amides, carbamates, and hydroxamic esters.[14−16]

Oxadiazole rings can exist in different regioisomeric forms; two 1,2,4-isomers (if asymmetrically substituted), a 1,3,4-isomer, and a 1,2,5-isomer (Figure 1). The 1,2,5-regioisomer is significantly less common (Figure 1) and orients the side chains ($R^1$ and $R^2$, Figure 1) in different positions relative to the other three isomers. The two 1,2,4- and the 1,3,4 regioisomeric oxadiazoles all present the $R^1$ and $R^2$ side chains with essentially the same exit vector arrangement, thus placing the side chains in very similar positions. The consequence is that matched pairs will show the same overall molecular shapes and are thus expected to bind in a similar fashion.[17] Moreover, oxadiazoles display interesting hydrogen bond acceptor properties, and it will be shown that the regioisomers display significantly different hydrogen bonding potentials.

While searching for new inhibitors of an enzyme in an in-house drug discovery program, we were interested in synthesizing the 1,3,4- and the two 1,2,4-oxadiazole regioisomers in an efficient manner to explore if and how different electronic effects influenced ligand binding, while maintaining the directionality of the substituents. Interestingly, the 1,3,4-regioisomer showed an improved lipophilicity profile, as well as more favorable ADME properties. To probe whether this was a general effect, we searched the entire AstraZeneca compound collection for sets of oxadiazole containing compounds that only differed in their regioisomeric form. A data set was obtained and was subject to thorough analysis. A rationalization for the significant differences between oxadiazole regioisomers

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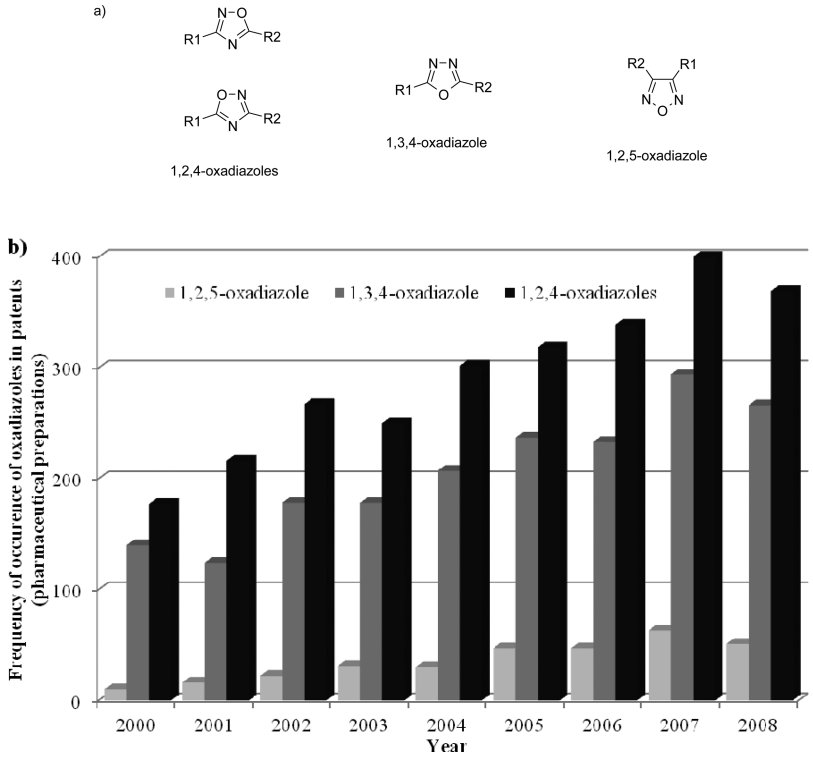



**Figure 1.** (a) Oxadiazole rings can exist in different regioisomeric forms. One 1,3,4-isomer and one 1,2,5-isomer and two 1,2,4-isomers (if asymmetrically substituted). (b) The number of patent applications containing oxadiazoles has increased significantly between 2000 and 2008. The 1,2,5-regioisomer is less common than the other regioisomers.

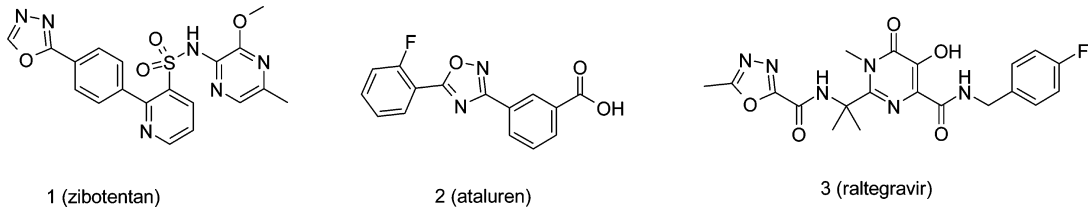


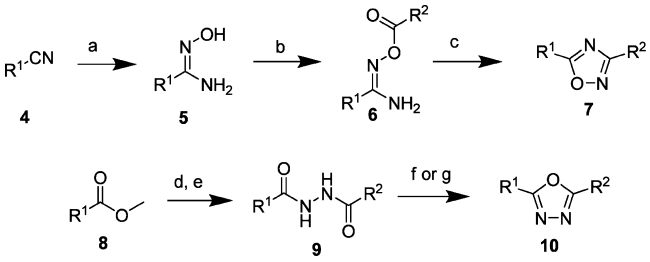

**Figure 2.** Structures of oxadiazole containing compounds in late stage clinical development (**1** and **2**) or launched drug (**3**).

using high-level quantum molecular calculations is presented. Finally, a novel, fast, and mild synthetic approach to attain structurally diverse 1,3,4-oxadiazoles is described.

## ■ CHEMISTRY

The preparation of the 1,2,4-oxadiazole (**7**) as well as the 1,3,4-isomer (**10**) is well described in the literature; see Scheme 1.[18]

**Scheme 1. Common Cyclization Reactions of Oxadiazoles**[a]




[a]Reagents and conditions: (a) EtOH, $NH_2OH$; (b) acylating reagent, DIPEA, DCM; (c) pyridine, reflux; (d) hydrazine hydrate, rt; (e) acylating reagent, DIPEA, DCM; (f) $POCl_3$, 100 °C; (g) 2-chloro-1,3-dimethylimidazolinium chloride, triethylamine, DCM, room temp, 16 h.

1,2,4-Oxadiazoles (**7**) are most frequently prepared from nitriles (**4**) or other amidoxime precursors. After acylation of **5** to the *O*-acylamidoxime **6**, cyclization is mainly achieved by heating at ca. 100 °C or in the presence of coupling reagents.[18] One of the most common building blocks for the synthesis of 1,3,4-oxadiazoles (**10**) are hydrazide derivatives (**9**), which can be cyclized under various conditions. Most of the preparation methods involve strong acidic conditions at elevated temperatures, which narrows the convenient access of derivatized 1,3,4-oxadiazoles.[18,19]

Milder reaction conditions can be achieved via the generation of phosphonium intermediates or by using 2-chloro-1,3-dimethylimidazolinium chloride (DMC), leading to activation of the monoacylhydrazide moiety, followed by cyclization to give the 1,3,4-oxadiazole (**10**). Such methods, however, generally require longer reaction times to go to completion. None of the existing protocols were considered sufficiently robust to generate a wide variety of oxadiazoles at low temperature with short reaction times to optimize the accessibility of the 1,3,4-isomers. The oxophilicity of the phosphonium agent is often used to initiate the dehydration process. A mild method for the dehydration of acylhydrazides (**9**) using $PPh_3$ under Mukaiyamás redox-condensation is known to generate 1,3,4-oxadiazoles (**10**) with some limitations depending on the substitution pattern.[20] Kelly



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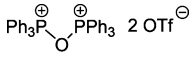
and co-workers have investigated the dehydrocyclization of thiazolines by employing the $P^V$-reagent **11** (Figure 3).[21] Their

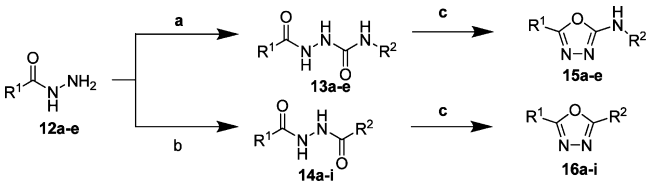


**11**

**Figure 3.** The $P^V$-reagent **11**, employed for dehydrocyclization of thiazolines.[21]

method tolerates the presence of protective groups which are stable under mild acidic conditions, such as esters and carbamates, and showed excellent stereocontrol. Our interest was focused on the feasibility of utilizing this procedure to generate 1,3,4-oxadiazoles with a variety of substitution patterns. To investigate the scope of the reaction, fast and easy access to diverse building blocks with varying functionalities was needed. Hence, starting from acylhydrazides as versatile starting materials, aminosemicarbazoles or 1,2-diacylated hydrazides are readily accessed by reaction with isocyanates or acylating agents, respectively (Scheme 2). After generation of the bistriphenylphosphonium

**Scheme 2. Preparation of 1,3,4-Oxadiazoles Using Phosphonium Salt 11**[a]



[a]Reagents and conditions: (a) $R^2NCO$ (1 equiv), ethanol, room temp; (b) $R^2COCl$ (1.1 equiv), triethylamine (1.5 equiv), DCM, room temp; (c) $Ph_3PO$ (3 equiv), $Tf_2O$ (1.5 equiv), DCM, 0 °C to room temp.

ditriflate **11**, the cyclization proceeds by dehydration of the hydrazides (**13** and **14**) in a one-pot procedure at room temperature.

Reaction times are typically in the range 1−30 min with a tendency of longer reaction times for electron deficient $R^1$-substituents. Yields are moderate to good (Table 1), with

**Table 1. Syntheses of Aminooxadiazoles 15a−e and Oxadiazoles 16a−i**

| acylhydrazide | $R^1$ | $R^2$ | product | yield[a] |
|---|---|---|---|---|
| **13a** | phenyl | phenyl | **15a** | 72% |
| **13b** | phenyl | ethyl | **15b** | 77% |
| **13c** | 3-pyridyl | ethyl | **15c** | 49% |
| **13d** | *n*-propyl | phenyl | **15d** | 52% |
| **13e** | 5-bromothiophen-2-yl | phenyl | **15e** | 82% |
| **14a** | phenyl | phenyl | **16a** | 96% |
| **14b** | phenyl | *p*-tolyl | **16b** | 82% |
| **14c** | phenyl | *p*-chlorophenyl | **16c** | 68% |
| **14d** | phenyl | benzyl | **16d** | 70% |
| **14e** | *p*-chlorophenyl | ethyl | **16e** | 84% |
| **14f** | phenyl | 3-pyridyl | **16f** | 78% |
| **14g** | 4-hydroxyphenyl | ethyl | **16g** | 26% |
| **14h** | 5-bromothiophen-2-yl | *iso*-propyl | **16h** | 52% |
| **14i** | phenyl | *N,N*-dimethyl-4-aminophenyl | **16i** | 78% |

[a]The yields are based on isolated compounds.

the exception of the phenol substituted compound **16g**, possibly due to reaction of the phosphonium salt **11** with the phenol precursor **14g**.

Attempts were made to understand the necessity of the reagents in the cyclization step (c) in Scheme 2. Carrying out the reaction in the absence of triphenylphosphine oxide (just triflic anhydride) did not yield any oxadiazole products, in contrast to the described procedure by Liras et al.[22] However, it was found that the triphenylphosphine oxide can be replaced with diphenyl-2-pyridylphosphine oxide, which is readily available by oxidation of the 2-pyridylphosphine.[23] Despite some loss in reaction yields (approximately 20−50%), the use of this reagent can be advantageous, particularly in a parallel setting where HPLC purification of the compounds is automated and there is a risk for coelution of the product with triphenylphosphine oxide.

## ■ COMPUTATIONAL RETRIEVAL OF MATCHED PAIRS

The current work describes differences between the most common oxadiazole regioisomers, the 1,2,4- and 1,3,4- oxadiazoles, and not the 1,2,5-oxadiazoles. That is, the focus is on regioisomers which differentiate only by ring atom positions and not in the relative position of their corresponding $R^1$ and $R^2$ substituents. The data set of 1,2,4-oxadizole and 1,3,4-oxadiazole matched pairs was generated in an automated fashion as follows. The AstraZeneca corporate collection was queried for all 1,2,4-oxadiazole containing compounds, where the attachment atoms of $R^1$ and $R^2$ were allowed to be either carbon, nitrogen, or hydrogen (Figure 1), using the pattern matching function (OESubSearch) implemented in the OEChem Python Toolkit.[24] In a subsequent step, each 1,2,4-oxadiazole containing molecule was transformed into the corresponding 1,3,4-oxadiazole matched pair using the OEChem reaction processing function (OEUniMolecularRxn), as shown in Figure 4.[24] The SMILES strings for the transformed structures were standardized (canonicalized) and used to search the AstraZeneca corporate collection, to computationally efficiently identify all exact matched pairs. In this study, exact matched pairs are defined as pairs of molecules only differing by oxadiazole regioisomers; the remaining parts ($R^1$ and $R^2$) of the molecules are identical within a matched pair. There are many methods for molecular manipulations and for performing matched molecular pairs analysis (MMPA).[25] The advantage of the query-based approach described herein is that it is tailored to provide detailed insights on one specific transformation, in contrast to other MMPA methods.[25] Figure 4 depicts a schematic overview of the process of retrieval of all oxadiazole matched pairs in the AstraZeneca corporate collection.

## ■ DATA SET

The entire AstraZeneca compound collection was used as a source for the systematic retrieval of a comprehensive data set of exact matched pairs of 1,2,4- and 1,3,4-oxadiazole regioisomers (Figure 4). This resulted in 770 exact matched pairs. A subset of 148 of the 770 pairs displayed satisfactory purity and quantity, and was found to be externally known and thus available for public disclosure. The 148 matched pairs include 282 compounds and define the data set used in the current study. There are 16 triplets in the data set, meaning that the 1,3,4-regioisomer and both of the two corresponding 1,2,4-regioisomers are present.



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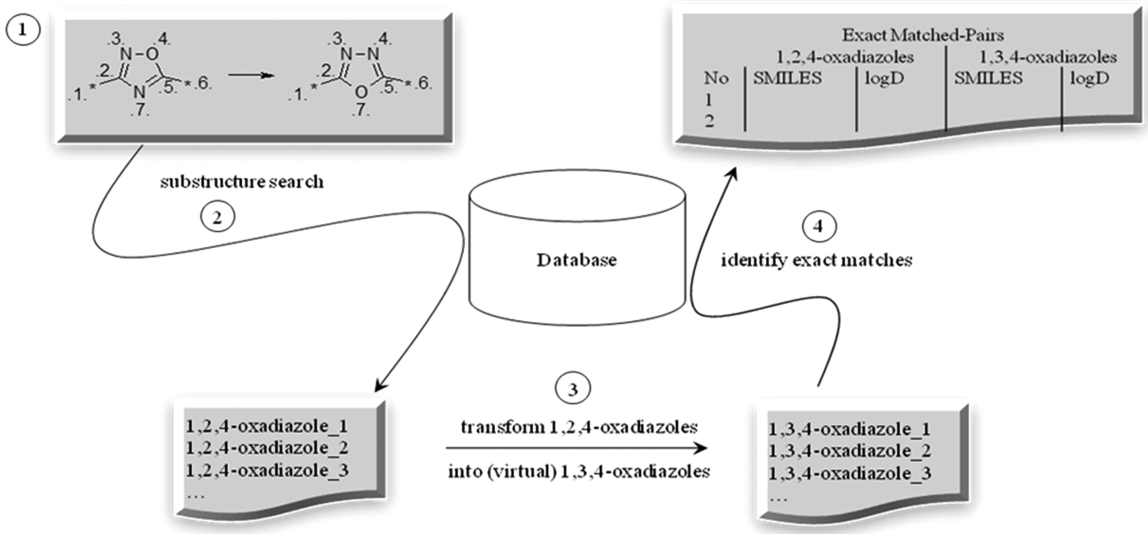


**Figure 4.** Automated procedure used to identify all regioisomeric oxadiazole matched pairs in the AstraZeneca corporate collection. Step 1. A python script, using the OEChem tool-kit, is used to process a MDL reaction (.rxn) file, and the 1,2,4-oxadiazole substructure is used to search a database containing molecules (step 2), with their associated data (e.g., log *D*, solubility, *HLM CLint*, cytochrome P450, hERG inhibition, etc). The molecules in the database matching the 1,2,4-oxadiazole query pattern are transformed to (virtual) 1,3,4-oxadiazole compounds using the OEChem reaction processing function (step 3) and are subsequently used to search the standardized SMILES strings stored in the database by computational efficient string comparisons (step 4). All exact molecular matches are recorded and stored in a tabulated format.

The structural diversity of the compounds in the data set is reflected in their activity against different target proteins. The data set was matched against GVKBio's Medicinal Chemistry and Target Databases[26] containing SAR data extracted from medicinal chemistry journals and patents; 82 compounds were identified that are claimed for 16 target proteins, belonging to several different target-classes (e.g., enzymes, GPCR, and ion channels). In addition, the molecules in the data set were evaluated against five calculated physicochemical properties widely used in medicinal chemistry (ClogP, molecular weight, the number of rotatable bonds, and the number of hydrogen bond acceptors and donors). The compounds essentially show the same characteristics as compounds with typical druglike properties. It should also be mentioned that the data set covers molecules with different ionization states at physiological pH; 253 neutral, 25 basic, and 4 acidic compounds. The data set was also subjected to a near-neighbor analysis, and the 282 compounds were found to cover several different structural series: 25 clusters according to lingo similarities,[27] using the recommended similarity cutoff of 0.5.[28]

In summary, an exhaustive and systematic matched pair analysis of AstraZeneca's corporate compound collection resulted in a set of 148 1,2,4-oxadiazole and 1,3,4-oxadiazole matched pairs. The relatively large and unbiased set spanned a broad spectrum of physical and chemical properties and should therefore allow general conclusions to be drawn. The lipophilicity (log *D*) values were determined for all compounds by a HPLC LC/MS method.[29] Aqueous solubility, hERG inhibition, p$K_a$ values, cytochrome P450 (CYP) inhibition, metabolic stability (*HLM CLint*), time-dependent inhibition (TDI), and CYP Reaction Phenotyping (CRP) data are reported for a significant number of example compounds. The data set, including results as well as detailed descriptions for the experimental methods, can be found in the Supporting Information.

## ■ RESULTS AND DISCUSSION

Our interest in the observed differences in physicochemical and pharmacological properties between a small set of 1,2,4- and 1,3,4-oxadiazole regioisomers in an internal drug discovery project prompted us to embark on a more general analysis. Thus, all oxadiazole matched pairs were extracted from the AstraZeneca compound collection to provide a larger data set. The main goal was to develop a better understanding for the generality of the observed differences and attempt to rationalize the observed effects.

**Oxadiazole Isomers Influence on Lipophilicity.** The role of lipophilicity in determining the overall quality of candidate drug molecules has recently been described as of paramount importance.[30] For example, lipophilicity has been shown to significantly impact oral bioavailability,[31] lead to increased promiscuity,[32] and increase the risk of toxicity.[33] Lipophilic compounds are also likely to be rapidly metabolized, to show low solubility, and to display poor oral absorption.[34] As a consequence, medicinal chemists generally follow the mantra "reduce lipophilicity" when encountering any such issue.[35] A common design strategy to reduce lipophilicity is to introduce polar atoms, while maintaining the overall molecular shape of lead molecules, in order to improve the odds of retaining the affinity to the target protein. This approach has, for example, been successfully shown in terms of affording "me-too" drugs.[36]

The lipophilicity of compounds is often assessed by calculations, and as such ClogP[37] calculations are typically first in line when choosing a method. Chemical series in drug discovery projects often include charged moieties, and this is a potential drawback when using log *P* calculations, since they do not explicitly take account of different ionic states and their potential influence on compound lipophilicity. On the other hand, log *D* calculations are designed to account for pH dependencies and are, thus, frequently used when predicting lipophilicity for ionizable compounds.



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Lipophilicity is a deceptively simple system to model compared to other systems encountered in drug discovery (such as blood brain barrier penetration or whole organs). Despite a large amount of experimental data available, it is still not a trivial task to achieve precise predictions.[38] This is illustrated in Figure 5, where experimentally determined log *D* values are plotted against calculated ClogP values (Figure 5a) or ACD log*D*7.4[39] values (Figure 5b) for the current data set of oxadiazoles ($N = 282$). The high correlation coefficient ($R^2 = 0.85$) for ClogP is satisfactory, and most compounds are correctly ranked. However, the correlation deviates from the 1:1 line, which results in less accurate predictions for lipophilic compounds. Thus, the higher the logD, the less predictive the ClogP model becomes. The accuracy in the ACD log*D*7.4 predictions is suboptimal. For example, compounds where the experimentally determined log *D* values are around 3.0 show a range of four log units in the predictions (Figure 5b). Given this lack of precision, it is clear that further method development efforts are desirable to better predict log *D* values. A recent example that is markedly different to linear models using fragment-based parametrized approaches to modeling log *D* is matched molecular pairs analysis.[40] The idea of matched molecular pairs analysis is to systematically identify pairs of molecules with minor structural differences and to determine the difference in property change associated, rather than predicting their absolute values.[40]

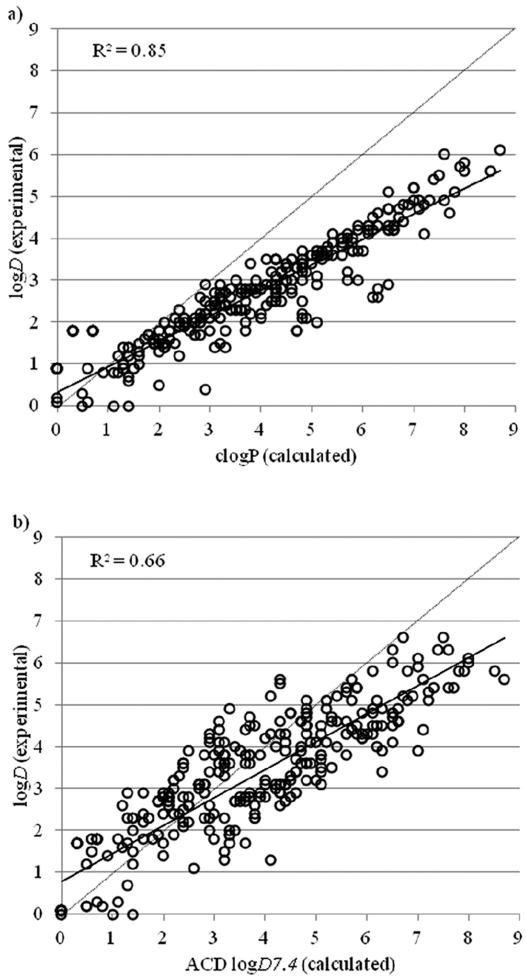


**Figure 5.** Experimentally determined log *D* values plotted against calculated ClogP values (a) and ACDlog*D*7.4 values (b) for the data set of oxadiazoles. The correlation coefficients ($R^2$) are 0.85 and 0.66, respectively. The higher the experimentally determind log *D*, the less predictive the ClogP model is. The ACD log*D*7.4 predictions deviate from experiments to a relatively large extent. The 1:1 lines are shown for clarity.

When comparing the experimentally determined log *D* values for the data set of 148 oxadiazole matched pairs, a remarkable correlation is revealed, as shown in Figure 6a. The correlation coefficient ($R^2$) is as high as 0.97. The 1,3,4-oxadiazole regioisomers consistently show lower log *D* values, as compared to their 1,2,4-oxadiazole matched pair. The box-plot in Figure 6b shows that the median log *D* difference for the regioisomers is 1.2 log *D* units. This important information can be successfully employed when designing compounds with the aim of lowering lipophilicity.

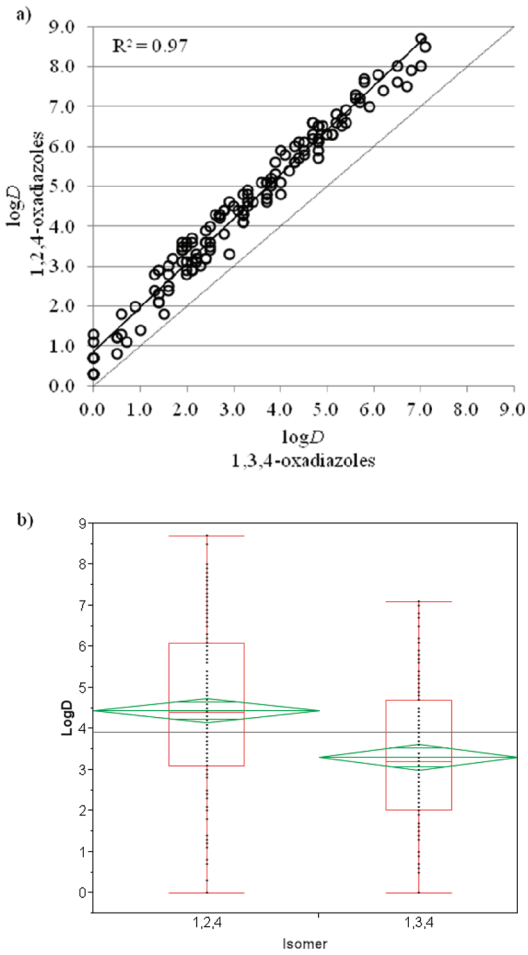


**Figure 6.** (a) Experimentally determined log *D* values plotted for the matched-pairs of 1,2,4- and 1,3,4-oxadiazoles. The 1,3,4-regioisomer is, in all cases, less lipophilic. The 1:1 line is shown for clarity. (b) A box-plot displaying the log *D* differences between the regioisomers. The median log *D* value for the 1,2,4-isomers is 4.4, whereas it is 3.2 for the 1,3,4-isomers.

It should be noted that, although not as pronounced, a similar correlation to the one shown in Figure 6a is obtained when using calculated ClogP values; 1,3,4-oxadiazole regioisomers are consistently predicted to be lower in lipophilicity ($\Delta$ClogP = 0.86). The corresponding correlation plot for ACD log*D*7.4 predictions shows a mixed picture; almost half of the regioisomeric pairs are erroneously predicted to have the same



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value. The ACD log*D*7.4 mispredictions are independent of molecular charge (i.e., neutral or charged species at physiological pH) and do not pick up the observed difference in log *D* within a matched pair to a satisfactory level of detail.

The differences in log *D* between the 1,3,4- and the 1,2,4-regioisomers seem to be general and wide-ranging; no significant difference is observed between the oxadiazole compounds with aliphatic and aromatic substituents. Furthermore, little or no difference in log *D* is observed between the two 1,2,4 regioisomers in the 16 triplets in the data set. The different regioisomers affect the basicity of nearby ionizable functional groups to a very similar extent, as evidenced by experimentally determined p$K_a$ values for a subset of test compounds (*vide infra*).

**Oxadiazole Isomers Influence on Aqueous Solubility.** Drug discovery compounds with low solubility carry a higher risk of failure due to the fact that insufficient solubility may, for example, compromise pharmacokinetic and pharmacodynamic properties and/or mask other undesirable properties. In some cases, poor solubility can stop promising drugs from reaching the market,[41] and regulatory authorities currently require additional investigations on low soluble compounds when the aim is oral administration.

As noted above, lipophilicity can influence many other molecular properties,[30] and perhaps the most obvious connection exists between lipophilicity and solubility. For example, aqueous solubilities are often reported to be adversely influenced by lipophilicity.[42] Poor aqueous solubility can also be the result of solid phase contributions, such as strong intermolecular interactions, making dissolution energetically unfavorable. There are several experimental approaches available to tackle the issue of poor aqueous solubility. For example, appropriate formulation work, formation of pro-drugs, polymorph selection, and the generation of salts (of acidic and basic drugs) can be used to overcome solubility related problems. However, these approaches can be expensive and do not guarantee success. Thus, the preferred approach to improve solubility is by molecular design, in particular at the early stage of a drug discovery program. The design strategy of improving solubility has successfully been used in the context of "me-too" drugs,[36] where it has been shown that minor atomic variations (e.g., matched pairs) can cause drastic changes in solubility and, thus, result in significant therapeutic advantages.[43]

To assess the extent to which the aqueous solubilities, for the present set of oxadiazole containing compounds, depend on their experimentally determined log *D* values, a subset of the data set ($N$ = 116, 55 matched pairs) was investigated. Figure 7 displays the measured log *D* values versus the measured aqueous solubility values. The correlation is poor, and it is evident that other factors than log *D* (e.g., intermolecular interactions) influence the aqueous solubility for this set of oxadiazole containing compounds. Although a linear relationship is not observed, Figure 7 reveals a trend; the more soluble compounds (−log solubility <4.5) also include all the hydrophilic compounds (log *D* < 2.0).

A number of lipophilic compounds display high solubility. A significant fraction of these compounds include a charged moiety. The charge is hypothesized to compensate for the high lipophilicity and thus lead to high solubility.

The observed differences in lipophilicity between the oxadiazole regioisomeric pairs are reflected in their aqueous solubility measurements (Figure 8). That is, in the majority of the 56 matched pairs, the 1,3,4-oxadiazole regioisomers display a higher aqueous solubility than their 1,2,4 isomers, and there is only one single example where the 1,2,4-oxadiazole isomer is more soluble than its regioisomeric partner (Figure 8). As indicated above, the difference in aqueous solubility can only be observed for the more lipophilic compounds (log *D* > 2.0). Figure 9 shows an illustrative example where 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)methylsulfanyl]-4-propyl-1H-pyrimidin-6-one (**17**) is sixteen times more soluble than the more lipophilic

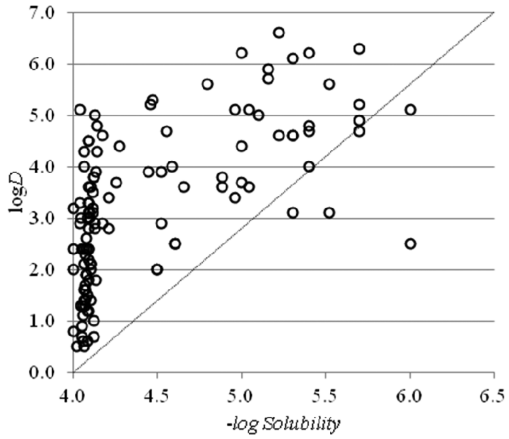


**Figure 7.** Experimentally determined log *D* values plotted against molar solubility values for the set of oxadiazoles ($N$ = 116). The correlation coefficient is low ($R^2$ = 0.4), indicating that other factors than lipophilicity (log *D*) are important for the aqueous solubility of the compounds. The 1:1 line is shown for clarity.

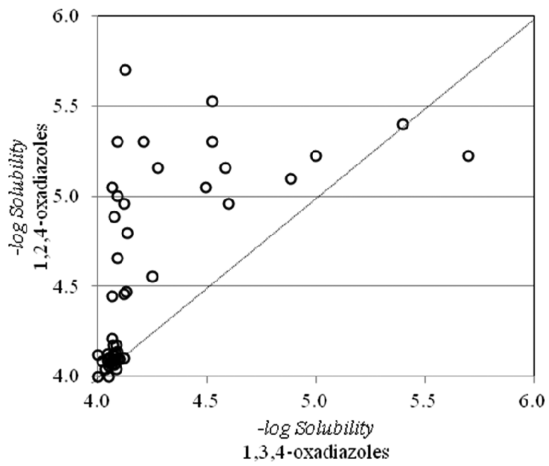


**Figure 8.** Experimentally determined molar solubility values plotted for the matched-pairs. The 1,3,4-oxadiazoles are in general more soluble. The 1:1 line is shown for clarity.

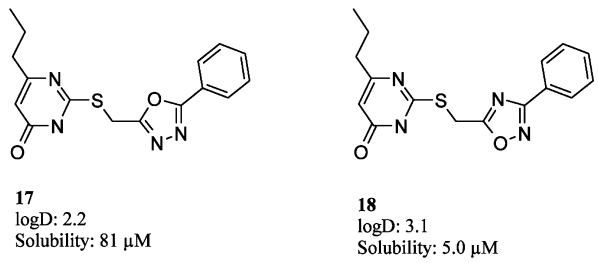


**Figure 9.** Matched pair example where the less lipophilic 1,3,4-oxadiazole containing compound **17** is sixteen times more soluble than the corresponding 1,2,4-oxadiazole **18**.



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2-[(3-phenyl-1,2,4-oxadiazol-5-yl)methylsulfanyl]-4-propyl-1H-pyrimidin-6-one (**18**).

In the majority of matched pairs (36 out of 55), the difference in aqueous solubility between the regioisomers is within the experimental error. Since the difference in log *D* is more than one log unit for most of these pairs, they consequently do not adhere to the commonly observed lipophilicity/solubility trend. This may be due to different crystal packing effects. Unfortunately, the estimation of crystal lattice energies remains to be the main challenge in the prediction of solubilities.[44] However, in an attempt to shed some light on this matter, the Cambridge Structural Database (CSD) was examined.[45] A larger fraction of compounds were found to match the 1,3,4-oxadiazole substructure, as compared to compounds matching the 1,2,4-oxadiazole substructure, 183 and 114, respectively. This relationship is opposite of what one would expect considering the frequency of occurrence of oxadiazole regioisomers in patent applications (Figure 1). When performing the same substructure search in SciFinder,[46] the frequency of occurrence is also reversed (1,2,4-oxadiazoles, 491 994; 1,3,4-oxadiazoles, 381 252). A speculative conclusion is that 1,3,4-oxadiazoles are more likely to crystallize and that the two effects (lipophilicity and intermolecular interactions) can cancel each other out. But there could, of course, be many other reasons for this observation. For example, it could be a direct consequence of the stronger dipole interactions (*vide infra*) between the more polar 1,3,4-oxadiazole units in the crystal. One single matched pair of oxadiazoles could be found (CSD reference codes: UJUVIE and UJUVOK). The nature of the crystal packing for this particular example was not sufficient to provide a general rationalization of 1,2,4- and 1,3,4-oxadiazoles and their difference in aqueous solubility.[47]

**Oxadiazole Isomers Influence on Metabolic Stability and CYP450 Inhibition.** A frequently occurring challenge in drug discovery projects is to balance target potency and metabolic stability. Low metabolic stability is associated with issues such as high hepatic clearance, short half-life, and poor *in vivo* exposure. A typical design strategy to improve compounds metabolic stability is to reduce lipophilicity by incorporating polar atoms while retaining affinity to the target protein. A different design approach is to block metabolically labile positions or to incorporate metabolically stable functional groups, which can in fact be of lipophilic nature.[48]

Metabolic intrinsic clearance (*CLint*) data measured in human liver microsomes (*HLM*) for 68 oxadiazole containing compounds (34 matched pairs) were determined to investigate if significant effects in metabolic stability were observed in the entire data set as well as between the oxadiazole regioisomers. Although the metabolic stability of a molecular subunit clearly depends on the structural context in which it is embedded, the overall lipophilicity of a compound can often serve as an indicator of metabolic stability. However, in this data set, no correlation was obtained when comparing *HLM CLint* versus log *D* values (data not shown). The matched pair analysis, however, reveals a trend for the regioisomers. That is, in more than half of the pairs (19 out of 34), the 1,3,4-oxadiazoles show better metabolic stability, in terms of lower *HLM CLint* values (Figure 10).

The higher intrinsic clearance for the 1,2,4-regioisomers could originate from a higher metabolic instability of the 1,2,4-oxadiazole moiety. However, since the oxadiazole is not the primary site of metabolism (as observed by an in-house metabolite identification assay in *HLM*), it seems likely that the molecular recognition of the metabolizing enzymes for

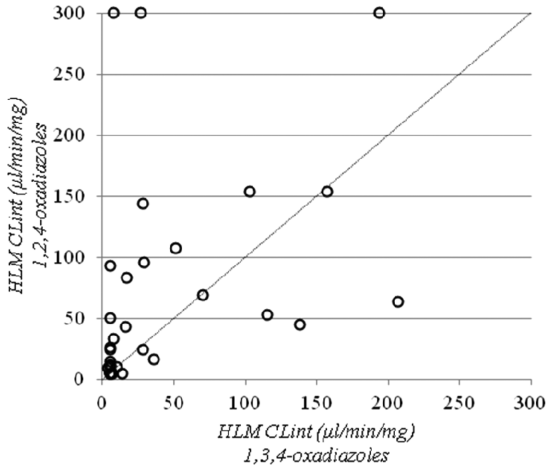


**Figure 10.** Experimentally determined *HLM CLint* values plotted for the matched-pairs. The 1,3,4-oxadiazoles are in general more stable. The 1:1 line is shown for clarity.

compounds containing the 1,2,4-oxadiazole versus the 1,3,4-oxadiazole moiety differs. Since cytochrome P450 (CYP) enzymes play a major role in *HLM* metabolism, we hypothesized that compounds containing the 1,3,4-oxadiazole moiety either bind more weakly to the most common CYP enzymes and are therefore less metabolized or, alternatively, bind more strongly to the CYP enzymes, leading ultimately to stronger inhibition and a decrease in *CLint* values.

To investigate both hypotheses, recombinant CYP inhibition data was collected for a set of 33 matched pairs. In none of the matched pairs was a strong CYP inhibition (<1.0 $\mu$M) observed. Figure 11 displays the frequency of occurrence data for binned $IC_{50}$ values for six common cytochrome P450 enzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) for the 1,2,4- and 1,3,4-oxadiazole containing compounds.

In all cases, save one (CYP2C8), the 1,2,4-oxadiazole containing compounds display a larger fraction of high-affinity compounds. The observed data is in line with the general characteristics of human P450 substrates.[49] That is, oxadiazole regioisomeric differences are observed at CYP3A4, which is known to favor lipophilic molecules, and at CYP1A2, which is associated to favor planar heterocyclic compounds (Figure 11).[49] Overall, this indicates that 1,2,4-oxadiazole derivatives are more frequently recognized by cytochrome P450 enzymes, leading to a higher metabolic turnover in *HLM*. While the parent compounds in general did not show strong CYP inhibition, it is possible that their putative metabolites could lead to CYP inhibition. By investigating time-dependent inhibition (TDI) for the different CYP enzymes, it is possible to rule out the formation of reactive metabolites leading to strong CYP inhibition, which in turn could result in an apparent increase in metabolic stability. Table 2b shows that, in general, the 1,3,4-oxadiazoles display either no TDI or the same TDI profile as their 1,2,4-regioisomeric matched pairs (Figure 12). These findings support the hypothesis that the increase in metabolic stability for the 1,3,4-regioisomers is originating from weaker coordination to the CYP enzymes rather than stronger CYP inhibition by the parent compound or possible reactive metabolites. Assuming a dissimilarity in coordination strength of the different regioisomers, we were interested if a regioisomeric swap of the oxadiazole scaffold could influence the overall CYP recognition pattern. Thus, to investigate the possible changes in the contributions of different CYP enzymes to the total metabolic



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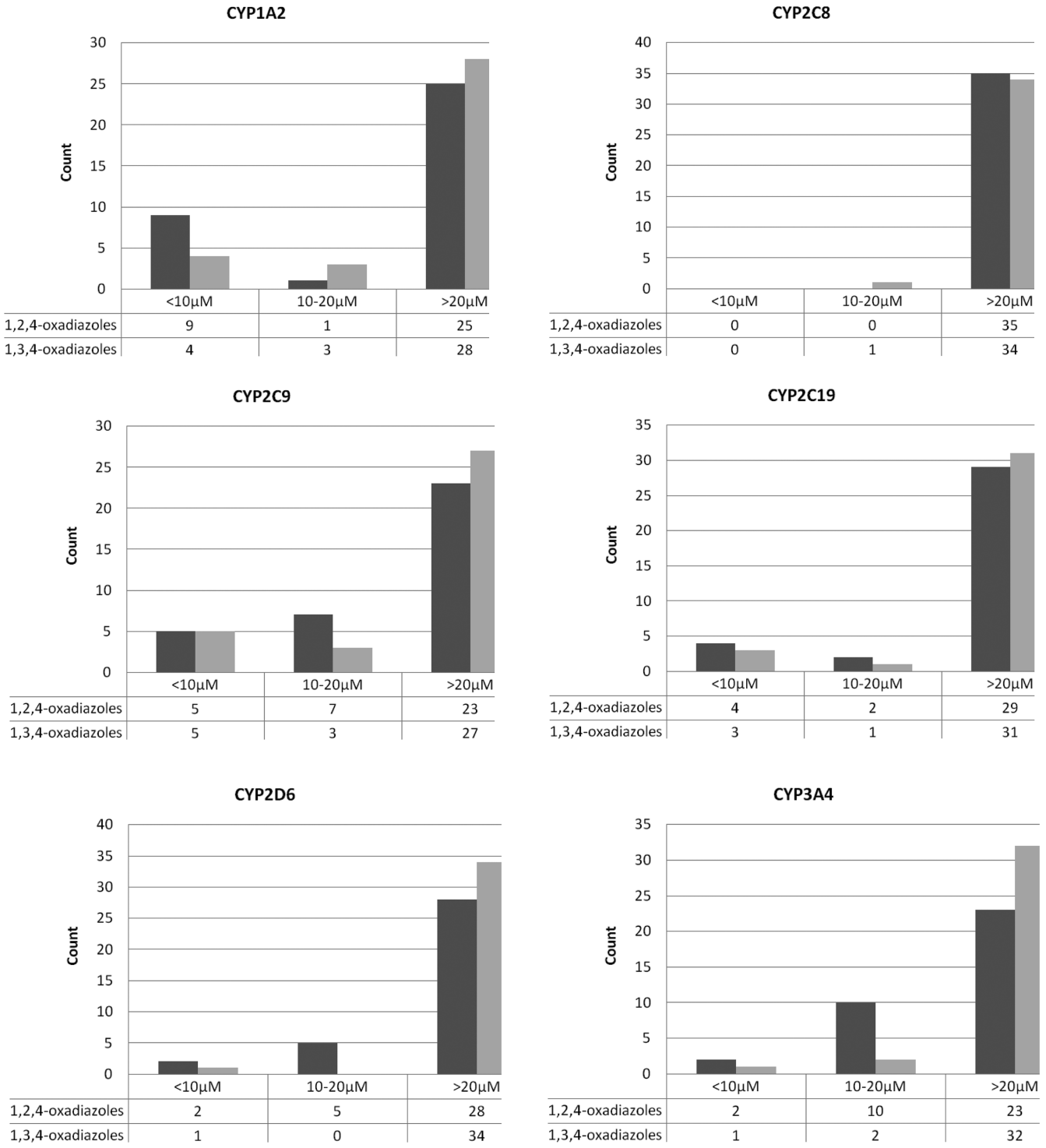


**Figure 11.** Diagrams showing the frequency of occurrence data for binned IC50 values for the six most common cytochrome P450 enzymes, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, for 1,2,4- and 1,3,4-oxadiazole containing compounds. In all cases, except one (CYP2C8), the 1,2,4-oxadiazole compounds show a larger fraction of high-affinity compounds. CYP inhibition values show the inhibition of metabolic degradation of the corresponding substrate by human recombinant cytochrome P450s at 37 °C (the percent of inhibition is determined at five different concentrations and is reported as $IC_{50}$).

clearance, a CYP reaction phenotyping (CRP)[50] study was performed on five matched pairs. Most interestingly, a substantial change in the CRP profile for some of the matched pairs was observed, underlining the ability to influence molecular recognition of CYP enzymes through minimal structural changes (Tables 2 and 3). This is a significant piece of information, since it is desirable for a compound to be cleared by more than one excretion route and elimination pathway to reduce the risk of drug−drug interactions (DDI).

**Oxadiazole Isomers Influence on hERG Inhibition.** Lipophilic compounds often show greater promiscuity with unintended effects on other biological targets and are therefore generally more liable to side effects than hydrophilic compounds. One such example of an unwanted side effect is the



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**Table 2. *HLM Clint* and CYP Inhibition Data for Five Matched Pairs[a]**

| | | CYP | | | | | |
|---|---|---|---|---|---|---|---|
| no. | hMics Clint ($\mu$L/min/mg) | 3A4 $IC_{50}$ ($\mu$M) | 2D6 $IC_{50}$ ($\mu$M) | 2C8 $IC_{50}$ ($\mu$M) | 2C9 $IC_{50}$ ($\mu$M) | 2C19 $IC_{50}$ ($\mu$M) | 1A2 $IC_{50}$ ($\mu$M) |
| **19** | >300 | 14.2 | >20 | >20 | >20 | >20 | >20 |
| **20** | 8 | >20 | >20 | >20 | >20 | >20 | >20 |
| **21** | 93 | 14.6 | 9.4 | >20 | 2.2 | 1.3 | >20 |
| **22** | <5.0 | >20 | 5.7 | >20 | 1.7 | 9.8 | >20 |
| **23** | 83 | 10.2 | 10 | >20 | 17.6 | 1.2 | 2.4 |
| **24** | 17 | >20 | >20 | >20 | >20 | 1.3 | >20 |
| **25** | 50 | >20 | >20 | >20 | >20 | >20 | >20 |
| **26** | <5.0 | >20 | >20 | >20 | >20 | >20 | >20 |
| **27** | 9 | >20 | 10.2 | >20 | NV | >20 | >20 |
| **28** | 4 | >20 | >20 | >20 | >20 | >20 | >20 |

[a]*HLM CLint* values were determined as the rate of disappearance in human liver microsomes, measured from 45 min incubation with human hepatic liver microsomes (1 mg/mL at 37 °C). CYP inhibition values show the inhibition of metabolic degradation of the corresponding substrate by human recombinant cytochrome P450s at 37 °C (the percent of inhibition is determined at five different concentrations and reported as $IC_{50}$).

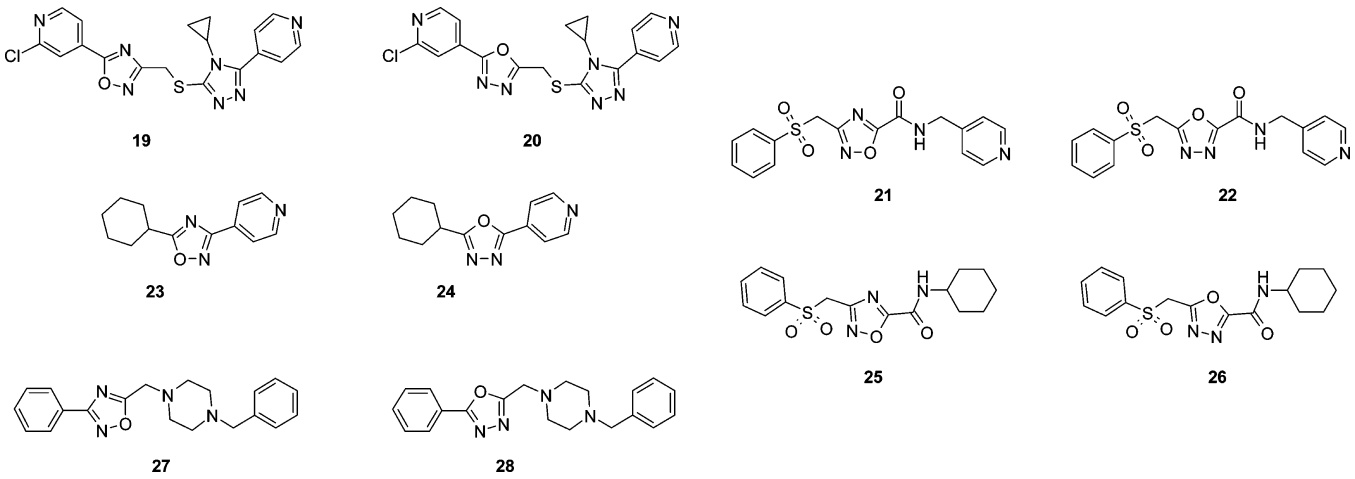


**Figure 12.** Structures of the five matched-pairs discussed in the metabolic stability and CYP450 inhibition section. The data associated with compounds **19**−**28** are shown in Tables 2 and 3

**Table 3. Time-Dependent Inhibition (TDI) and CYP Reaction Phenotyping (CRP) Data for Five Matched Pairs.[a]**

| | TDI | | | | | | CRP | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | 3A4 (%) | 2D6 (%) | 1A2 (%) | 2C9 (%) | 2C19 (%) | 2C8 (%) | 3A4 (%) | 2D6 (%) | 1A2 (%) | 2C9 (%) | 2C19 (%) | 2C8 (%) |
| **19** | 30 | <11 | <10 | <19 | <12 | <14 | 99.5 | 0.0 | 0.2 | 0.0 | 0.1 | 0.2 |
| **20** | <7 | <11 | <10 | <19 | <12 | <14 | 100 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **21** | 42 | <11 | <10 | <19 | <12 | <14 | 99.8 | 0.1 | 0.0 | 0.1 | 0.1 | 0.0 |
| **22** | <7 | <11 | <10 | <19 | <12 | <14 | 0.0 | 100 | 0.0 | 0.0 | 0.0 | 0.0 |
| **23** | <7 | <9 | <7 | <19 | <12 | <13 | 17.7 | 8.6 | 29.5 | 4.7 | 38.0 | 1.5 |
| **24** | <7 | <11 | <10 | <19 | 13 | <14 | 11.7 | 1.1 | 68.5 | 2.4 | 14.8 | 1.5 |
| **25** | <7 | <9 | <7 | <19 | <19 | <13 | 91.5 | 0.1 | 0.2 | 0.3 | 7.9 | 0.0 |
| **26** | <7 | <9 | <7 | <19 | <12 | <13 | 52.2 | 2.4 | 0.0 | 0.0 | 45.4 | 0.0 |
| **27** | 9 | <9 | <7 | <19 | <12 | <13 | 92.1 | 2.3 | 1.5 | 1.0 | 2.2 | 0.9 |
| **28** | NT | NT | NT | NT | NT | NT | 92.0 | 1.7 | 0.0 | 1.2 | 3.2 | 1.5 |

[a]TDI shows the %-inhibition of human recombinant cytochrome P450s with/without NADPH after 30 min preincubation at 37 °C. TDI is performed at two test concentrations (10 and 50 $\mu$M). Only results for the 50 $\mu$M concentration are shown here. CRP data is expressed as the percent contribution to the metabolism from each CYP isoform, relative to the other isoforms included in the test, at 37 °C.

inhibition of the hERG potassium ion channel. Inhibition of the hERG channel causes a slower outflow of potassium ions, lengthening the time required to repolarize the cell, which can trigger Torsades de Pointes (TdP) and arrhythmia. Results from *in vitro* hERG assays are therefore often used as a predictor of a compound producing cardiac arrhythmic side effects, and this has resulted in a number of drugs being withdrawn from the market.[51] Inhibition of the hERG ion-channel is thus often seen as a major concern and represents a significant regulatory hurdle for new molecular entities in drug development. There are several derivative studies suggesting the use of simple rules for overcoming hERG inhibition in drug design.[52] The most recurrent rule suggests that hERG inhibition can be reduced by decreasing lipophilicity.[53]



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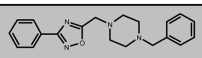
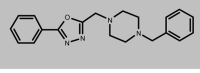
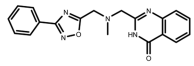
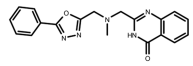
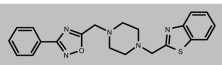
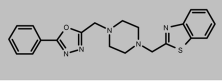
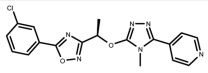
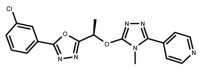
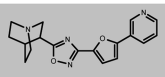
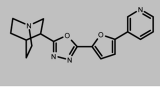
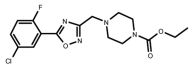
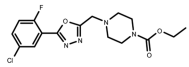
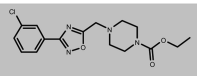
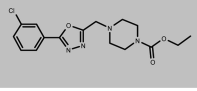
**Table 4. Molecular Structures, Experimental log *D*, pKa, hERG Inhibition, and Calculated ClogP**

| No | Structure | Oxadiazole isomer | hERG[a] (μM) | log*D* | ClogP | pKa |
|---|---|---|---|---|---|---|
| 27 |  | 1,2,4 | 12.7 | 5.1 | 3.6 | 6.7 |
| 28 |  | 1,3,4 | 27.3 | 3.6 | 2.7 | 6.7 |
| 29 |  | 1,2,4 | 26.2 | 3.1 | 1.4 | 2.1 |
| 30 |  | 1,3,4 | >33 | 2.0 | 0.5 | 2.3 |
| 31 |  | 1,2,4 | 13 | 5.3 | 3.6 | 4.4 |
| 32 |  | 1,3,4 | 30 | 3.9 | 2.7 | 4.4 |
| 33 |  | 1,2,4 | 11.6 | 3.0 | 2.4 | 3.4 |
| 34 |  | 1,3,4 | 21.5 | 2.3 | 1.5 | 3.7 |
| 35 |  | 1,2,4 | 6.4 | 0.7 | 1.8 | 8.8 |
| 36 |  | 1,3,4 | 20.2 | <0.0 | 0.9 | 9.1 |
| 37 |  | 1,2,4 | 31 | 4.3 | 3.5 | 4.0 |
| 38 |  | 1,3,4 | >33 | 3.2 | 2.6 | 3.5 |
| 39 |  | 1,2,4 | 15.5 | 4.8 | 3.3 | 3.4 |
| 40 |  | 1,3,4 | >33 | 3.3 | 2.4 | 3.5 |

[a]Patch clamp assay using IonWorks technology in hERG-expressing CHO cells.

Inhibition data against the hERG channel was collected for a set of 11 oxadiazole matched pairs. The hERG $IC_{50}$ patch clamp assay used was run in the IonWorks high-throughput mode (see Supporting Information).[53] The values for both oxadiazole regioisomers in four of the 11 matched pairs were determined to be above the highest assay concentration (>33 $\mu$M). These four pairs were excluded from the comparison. Table 4 shows that in the remaining seven matched pairs the 1,2,4-oxadiazoles display higher affinity toward the hERG receptor than their 1,3,4-oxadiazole partner. As previously shown (Figure 6), the 1,2,4-oxadiazoles are in general one log unit more lipophilic than their 1,3,4-regioisomer matched pair, and this is thus also the case for these 11 matched pairs. The results shown in Table 4 are in line with the finding by Jamieson et al., who stated that "*should compounds have ClogP values <3 and still exhibit hERG potency then structural modification is required, and on average 1 log unit reduction in ClogP leads to 0.8 log unit reduction in hERG activity*".[52]

Although this hERG data set is on the smaller side and the differences in affinities are not vast, a pattern is emerging. The more lipophilic 1,2,4-isomers are also more potent against the hERG channel. Moreover, experimentally measured $pK_a$ values for the seven matched pairs in Table 4 illustrate that the oxadiazole regioisomers do not have a significant effect on the basicity of nearby ionizable functional groups; the $pK_a$ values are nearly identical within a matched-pair. This is an interesting observation in itself, since most ligands that inhibit the hERG channel include a basic nitrogen likely to be protonated at physiological pH.[52] Consequently, it seems not advisible to use various oxadiazole regioisomers in the design strategy of reducing hERG inhibition by lowering the $pK_a$ (and thus reducing the proportion of molecules in their protonated form). It could therefore be concluded that the increase in hERG inhibition observed for the 1,2,4 regioisomers is most likely driven by lipophilicity.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**Dipole Moments and Minimized Molecular Electrostatic Potentials.** An attempt to rationalize the observed difference in profile between the 1,2,4 and 1,3,4 regioisomers was conducted. Experimentally determined dipole moments in solution (benzene), which provide information on molecular electronic distributions, were found for two compounds in our matched pair data set: the diphenyl substituted 1,3,4-oxadiazole (**16a**) and the corresponding diphenyl substituted 1,2,4-oxadiazole (**41**).[54] The reported dipole moment for compound **16a** is 3.5 D, whereas it was reported to be significantly lower for compound **41**, 1.8 D.[54] High-level *ab initio* calculations (LMP2/cc-pVTZ(-f)) are in excellent agreement with the experimental results; the dipole moment for the 1,3,4-oxadiazole **16a** is calculated to be 3.1 D as compared to 1.8 D for the 1,2,4-oxadiazole matched pair **41** (Figure 13). It is proposed that the different charge distributions can be used to rationalize why 1,3,4-oxadiazole containing compounds show improved molecular properties as compared to their 1,2,4-regioisomeric matched pairs. The greater the dipole moment, the greater is the polarity, and this is the reason for the lower lipophilicity as well as the increased solubility of **16a** (log *D*, 4.0; solubility, 26 $\mu$M), as compared to that of **41** (log *D*, 5.9; solubility, 7 $\mu$M).

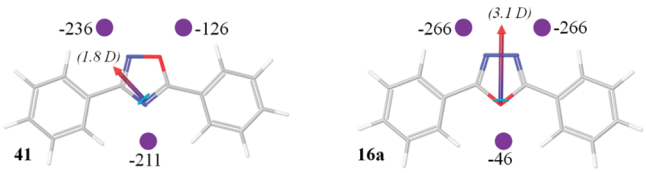


**Figure 13.** Illustration showing that the 1,3,4-oxadiazole containing compound **16a** displays a significantly larger dipole vector than its 1,2,4-oxadiazole matched pair **41**: 3.1 and 1.8 D (LMP2/cc-pVTZ-(-f)), respectively. The two nitrogens in compound **16a** display stronger calculated hydrogen bond acceptors (large negative $V_{min}$ values). These electronic effects are believed to be the reason for the fact that compound **16a** is significantly less lipophilic and more soluble than compound **41**.

A second type of calculation was performed. Hydrogen bond acceptor and donor strengths have previously been linked to lipophilicity and can be studied at the atomic level of detail using quantum mechanical calculations.[55−57] More specifically, the value of the electrostatic potential at a minimum ($V_{min}$) has been found to be an effective predictor of hydrogen bond acceptor strength.[55−57] Figure 13 also shows the calculated hydrogen bond acceptor strengths (described in kcal/mol). It can be seen that the hydrogen bond acceptor strengths differ in magnitude as it moves around between the heterocyclic atoms. The two nitrogen atoms in the 1,3,4-oxadiazole are calculated to be very favorable hydrogen bond acceptors (in terms of low negative values), whereas the oxygen atom is predicted to be a comparably poorer hydrogen bond acceptor. In comparison, the nitrogens in the 1,2,4-oxadiazole are not as strong hydrogen bond acceptors, but the oxygen is calculated to be slightly better than that in the 1,3,4-oxadiazole case. These calculated results support the case that electrostatic differences are responsible for the discrepancy in lipophilicity between oxadiazole regioisomers. The calculations are also in line with the very recent work by Leach et al., who assessed the difference in hydrogen bond accepting potentials both with measurements ($\Delta$ log *P*) and with calculations.[58]

## CONCLUSIONS

Oxadiazoles can exist in different regioisomeric forms and are frequently occurring motifs in druglike molecules, often used as bioisosteres for ester and amide functionalities. The most common regioisomeric forms are the two 1,2,4-isomers and the 1,3,4-isomer. These isomers are geometrically virtually identical, thus orienting possible substituents into the same space.

Novel computational methods were used to search the AstraZeneca corporate collection and to retrieve all exact matched pairs of 1,2,4-oxadiazole and 1,3,4-oxadiazole regioisomers. 148 such matched pairs were identified, spanning structural and biological space, allowing for an in-depth analysis and the ability to draw general conclusions. Several parameters frequently used for decision-making in drug discovery were experimentally determined. The subsequent analysis revealed systematic trends, regardless of substitution patterns. That is, in virtually all cases, the 1,3,4-oxadiazole isomer shows an order of magnitude lower lipophilicity (measured log *D*), as compared to the 1,2,4 isomer. This favorable effect is also observed in increased aqueous solubility, a decrease of hERG inhibition, and improved metabolic stability of the 1,3,4-oxadiazole isomers. Moreover, it is suggested that the 1,2,4-derivatives coordinate more frequently to the heme-moiety in cytochrome P450 enzymes, leading to a higher metabolic turnover in *HLM*. Changes between regioisomers can also significantly affect the profile of CYP recognition responsible for metabolism of the parent compound. These observations provide the medicinal chemist with a tool to shift the CRP pattern and influence potential drug−drug interactions.

The distinct profile difference between the 1,2,4- and 1,3,4-oxadiazole regioisomers is likely to be caused by their intrinsically different charge distributions, as evidenced by experiment and high level quantum mechanical calculations.

The observations reported herein can successfully be employed when designing compounds with the aim of lowering lipophilicity, by only making minor structural modifications. The results presented can also be used to further develop computational approaches to improve the accuracy of calculated predictions (e.g., log *D*).

Finally, novel chemistry has been developed, allowing straightforward high-throughput synthesis of a diverse array of substituted 1,3,4-oxadiazoles, under mild conditions.

## EXPERIMENTAL SECTION

**Computational Methods for Dipoles and Electrostatic Potentials.** The minimized electrostatic potentials ($V_{min}$) were calculated using the Gaussian 09 program[59] as described by Kenny et al. (HF/6-31G*).[57] The dipole moments were calculated with the Jaguar program[60] using the cc-pVTZ(-f) basis set at the LMP2 level of theory (*in vacuo*).

**Synthetic Chemistry.** *General Methods.* Preparative HPLC was performed using a reversed-phase C-18 column (FractionLynx III; mobil phase, gradient 5−95% acetonitrile in 0.2% $NH_3$, pH 10; column, Xbridge Prep C18 5 $\mu$m OBD 19 mm × 150 mm), with the above-mentioned gradient at a flow rate of 20.0 mL min$^{-1}$. Product collection was carried out by mass triggered fraction collection on [M + 1]. Reversed-phase HPLC was performed using a C-18 column (Acquity; mobil phase, gradient 2−95% acetonitrile, pH 10; column, Acquity BEH C18, 1.7 $\mu$m, 2.1 mm × 100 mm) with the above-mentioned gradient at a flow rate of 1.0 mL min$^{-1}$. Purity was determined by UV percentage of the observed mass peak using reversed-phase HPLC (instrument, Acquity; mobil phase, gradient 2−95% acetonitrile, pH 10; column, Acquity BEH C18, 1.7 $\mu$m, 2.1 mm × 100 mm). All compounds reported have UV purity >95%, and all yields are based on the isolated product.



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The $^1$H NMR spectra were recorded on a Varian Inova 600 spectrometer operating at a magnetic field of 14.1 T equipped with a 5 mm $^1$H{$^{13}$C, $^{15}$N} triple resonance gradient probe, a Varian Inova 500 spectrometer operating at a magnetic field of 11.7 T equipped with a 5 mm $^1$H{$^{13}$C} gradient probe or a Varian Inova 400 spectrometer operating at a magnetic field of 9.4 T equipped with a 5 mm autoswitchable multi nuclei gradient probe.

*Typical Preparation Procedure for 1,3,4-Oxadiazoles.* Trifluoromethanesulfonic anhydride (50 μL, 0.3 mmol) was added slowly to a solution of triphenylphosphine oxide (167 mg, 0.6 mmol) in dry $CH_2Cl_2$ (2 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and then adjusted to room temperature, followed by addition of the acylated semicarbazide (0.2 mmol). The reaction was monitored by LCMS. The reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The resultant crude product was purified by automated HPLC (mobil phase, gradient 5−95% acetonitrile in 0.2% $NH_3$, pH 10; column, Xbridge Prep C18 5 μm OBD 19 mm × 150 mm).

*2,5-Diphenyl-1,3,4-oxadiazole (**16a**).* $^1$H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 2H), 7.37−7.62 (m, 3H), 8.14 (s, 2H).

*2-(4-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (**16b**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 7.56−7.67 (m, 6H), 8.06−8.16 (m, 4H). APCI MS *m/z*: 223.1 (M + 1).

*2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**16c**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 3.00 (s, 6H), 6.84 (d, 2H), 7.55−7.02 (m, 2H), 7.89 (d, 2H), 8.03−8.08 (m, 2H). APCI MS *m/z*: 266 (M + 1).

*2-Benzyl-5-phenyl-1,3,4-oxadiazole (**16d**).* $^1$H NMR (400 MHz, $CDCl_3$) δ 4.26 (s, 2H), 7.21−7.30 (m, 1H), 7.30−7.39 (m, 4H), 7.39−7.54 (m, 3H), 7.98 (dd, 2H). APCI MS *m/z*: 237.1 (M + 1).

*2-(4-Chlorophenyl)-5-ethyl-1,3,4-oxadiazole (**16e**).* $^1$H NMR (400 MHz, $d_6$-DMSO) δ 1.28 (td, 3H), 2.89 (qd, 2H), 7.61 (dd, 2H), 7.94 (dd, 2H). APCI MS *m/z*: 209.0 (M + 1).

*2-Phenyl-5-(pyridine-3-yl)-1,3,4-oxadiazole (**16f**).* $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40−7.64 (m, 4H), 8.07−8.19 (m, 2H), 8.42 (dt, 1H), 8.77 (dd, 1H), 9.29−9.39 (m, 1H). APCI MS *m/z*: 265.1 (M + 1).

*4-(5-Ethyl-1,3,4-oxadiazol-2-yl)phenol (**16g**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 1.27 (t, 3H), 2.87 (q, 2H), 6.86−6.93 (m, 2H), 7.74−7.81 (m, 2H).

*2-(5-Bromothiophen-2-yl)-5-propan-2-yl-1,3,4-oxadiazole (**16h**).* $^1$H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, 6H), 3.21 (hept, 1H), 7.08 (t, 1H), 7.43 (d, 1H). APCI MS *m/z*: 273.0 (M + 1).

*2-(N,N-Dimethyl-4-aminophenyl)-5-phenyl-1,3,4-oxadiazole (**16i**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 7.58−7.66 (m, 3H), 7.67−7.72 (m, 2H), 8.09−8.16 (m, 4H). APCI MS *m/z*: 257 (M + 1).

*Typical Preparation Procedure for 2-amino-1,3,4-oxadiazoles.* Trifluoromethanesulfonic anhydride (50 μL, 0.3 mmol) was added slowly to a solution of triphenylphosphine oxide (167 mg, 0.6 mmol) in dry $CH_2Cl_2$ (2 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and then adjusted to room temperature, followed by addition of the aminosemicarbazole (0.2 mmol). The reaction was monitored by LCMS. The reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The resultant crude product was purified by automated HPLC (mobil phase, gradient 5−95% acetonitrile in 0.2% $NH_3$, pH 10; column, Xbridge Prep C18 5 μm OBD 19 mm × 150 mm).

*N,5-Diphenyl-1,3,4-oxadiazol-2-amine (**15a**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 6.95−7.05 (m, 1H), 7.29−7.39 (m, 2H), 7.53−7.57 (m, 3H), 7.57−7.62 (m, 2H), 7.83−7.91 (m, 2H). APCI MS *m/z*: 238.1 (M + 1).

*N-Ethyl-5-phenyl-1,3,4-oxadiazol-2-amine (**15b**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 1.11−1.23 (m, 3H), 3.24 (qd, 2H), 7.45−7.52 (m, 3H), 7.72 (t, 1H), 7.76−7.80 (m, 2H). APCI MS *m/z*: 190.1 (M + 1).

*N-Ethyl-5-(pyridin-3-yl)-1,3,4-oxadiazol-2-amine (**15c**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 1.14 (dt, 3H), 3.25 (qd, 2H), 7.53 (ddd, 1H), 7.85 (t, 1H), 8.13 (ddd, 1H), 8.65 (dt, 1H), 8.95 (dt, 1H). APCI MS *m/z*: 191.1 (M + 1).

*N-Phenyl-5-propyl-1,3,4-oxadiazol-2-amine (**15d**).* $^1$H NMR (600 MHz, $d_6$-DMSO) δ 0.93 (t, 3H), 1.66 (tq, 2H), 2.61−2.78 (m, 2H), 6.94 (ddd, 1H), 7.29 (dd, 2H), 7.51 (dd, 2H), 10.30 (s, 1H). APCI MS *m/z*: 204.1 (M + 1).

*5-(5-Bromothiophen-2-yl)-N-phenyl-1,3,4-oxadiazol-2-amine (**15e**).* $^1$H NMR (400 MHz, $d_6$-DMSO) δ 6.98 (t, 1H), 7.28−7.38 (m, 3H), 7.42 (d, 1H), 7.50−7.59 (m, 2H), 10.71 (s, 1H). APCI MS *m/z*: 322.0 (M + 1).

## ■ ASSOCIATED CONTENT

### Supporting Information

The oxadiazole matched pair data set, including all measured data reported in the article, together with a detailed description of the experimental methods used to measure log *D*, solubility, hERG inhibition, p$K_a$ values, CYP inhibition, *HLM CLint*, TDI, and CRP. This material is available free of charge via the Internet at http://pubs.acs.org.

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