MORPH: A New Tool for Ligand Design

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A frequently employed strategy in drug discovery efforts is to replace aromatic rings in known active compounds with alternative aromatic moieties to create novel compounds with improved potency and/or adsorption, distribution, metabolism, excretion, and toxicity properties. Here we introduce MORPH, which is a simple software tool for systematically modifying aromatic rings in three-dimensional models of molecules without altering the coordinates of the nonhydrogen atoms in the rings. MORPH works on individual rings as well as fused ring systems and additionally provides the ability to filter out modified compounds which do not contain hydrogen-bond donors or acceptors at specific positions on the rings or contain more or less than the desired number of heteroatoms. The MORPH program and its application to two ligands extracted from cocrystal structures with cyclin-dependent kinase 2 (CDK2)/cyclin A and CDK2 are discussed below.

INTRODUCTION

A common lead optimization technique is to replace aromatic rings in a compound of interest with other aromatic rings in an effort to identify a novel lead with improved potency against the protein target or with better adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. One example of this is the "pyridine scan" in which phenyl rings are replaced with regioisomeric pyridine rings.[1] The ring replacement approach has been employed to great effect in the area of kinase inhibitor drug discovery. For example, the cores of the aminothiazole and aminopyrazole classes of cyclin-dependent kinase 2 (CDK2) and CDK2/cyclin A inhibitors SNS-032[2] (**1**) and PHA-533533 (**2**, Figure 1) and related compounds[3,4] contain the pharmacophore necessary to interact with the acceptor−donor−acceptor motif found in the hinge region of the adenosine triphosphate (ATP) binding site of many kinases[5] but incorporate different heterocycles. Compound **3**, containing an aminoimidazo[1,2-a]pyridine core is a CDK2 inhibitor with an IC_{50} of 0.56 μM,[6] while compound **4**, containing the isomeric aminobenzimidazole core, has been claimed as an inhibitor of Aurora kinases.[7]

During the course of ring modification exercises, participating molecular modelers are frequently asked to suggest which aromatic ring in a molecule should be replaced in order to provide the maximum desired effect and, furthermore, which specific type of ring should be utilized. When the ring to be replaced contains multiple substituents, identification of suitable alternatives becomes a scaffold-hopping exercise in which the potential replacement scaffolds are limited to other aromatic rings.[8] To evaluate different possibilities with either structure-based or some ligand-based methods, the modeler will likely need to generate three-dimensional models of new compounds containing the alternative rings. These can be generated via hand-editing of existing models with the aid of graphics-based software[9] or numerous scaffold-hopping ligand design tools, such as Recore,[10] SHOP,[11−13] and BREED.[14]

In structure-based efforts where the bioactive conformation of the reference ligand is known, it is often desirable to preserve three-dimensional information. Otherwise, new compounds derived from the reference must be fit back onto it or docked into the protein binding site. This increases the complexity of the effort and the probability that, for at least some of the modified compounds, the binding poses may not match the hypothesis for the bioactive conformation (e.g., the conformation of the modified molecule corresponding to the known bioactive conformation of the reference molecule). It is also important for ring replacement analyses to be comprehensive with regard to the substitutions which are evaluated. If hand-editing of models is the method utilized, then care must be taken to avoid overlooking any less common but still synthetically viable rings, and likewise, automated scaffold hopping tools must utilize and completely sample extensive ring databases.

To complement the methods mentioned above, we have developed a simple Python[15] tool utilizing the OEChem[16] library. MORPH identifies aromatic rings in compounds and generates models of new compounds by systematically replacing each carbon, nitrogen, oxygen, or sulfur atom in each ring with carbon, nitrogen, oxygen, and sulfur atoms, adjusting bond orders and numbers and locations of bound hydrogen atoms and determining, via a set of rules, which resultant compounds are both chemically valid and reasonable. The coordinates of nonhydrogen atoms are not altered, thus all models of new compounds generated are superimposed with the model of the original reference compound. Because MORPH systematically modifies element types at each position in a ring, numerous new rings are generated, and scoring, not sampling of different rings, becomes the challenge. One of many possible ways scoring can be addressed is to utilize MORPH for generation of comprehensive ring libraries for scaffold-hopping programs with

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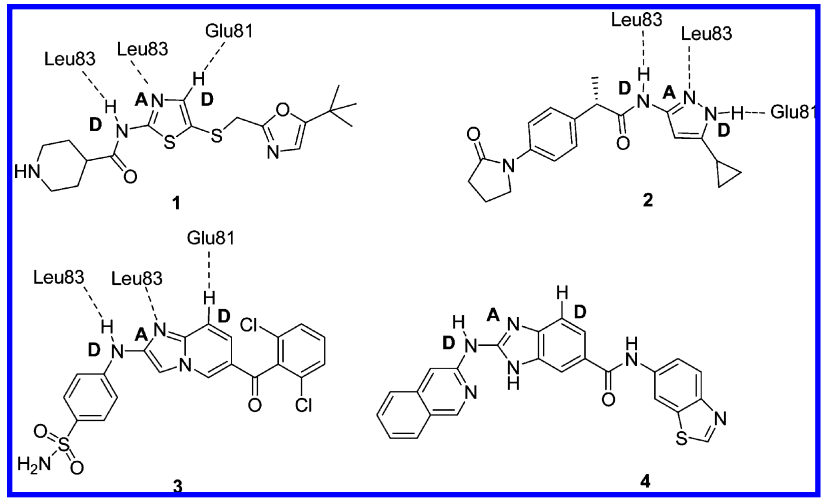


Figure 1. CDK2 inhibitor and clinical candidate SNS-032[2] (**1**) and potent CDK2/Cyclin A inhibitor PHA-533533[4] (**2**) contain aminothiazole and aminopyrazole moieties which form hydrogen-bonding interactions with the CDK2 acceptor−donor−acceptor motif in the ATP binding site. Compound **3** inhibits CDK2, and compound **4** was reported to inhibit at least one Aurora kinase. For **1**−**3**, the moieties acting as hydrogen-bond donors and acceptors complementing the CDK2 hinge acceptor−donor−acceptor motif are labeled D and A, respectively, and hydrogen-bonding interactions with CDK2 Glu81and Leu83 are shown schematically. For **4**, hydrogen-bond donors and an acceptor, which could potentially complement the hinge acceptor−donor−acceptor motif in Aurora kinases, are labeled D and A, respectively.

subsequent scoring of modified compounds, using the scoring functions provided with those tools.[10−14]

MORPH was designed as a model-building tool. Two key features include the ability to limit the analysis to one or more specific rings within a molecule and to filter out generated molecules which do not match specific hydrogen-bond donor−acceptor pharmacophores. The latter functionality is particularly useful when analyzing kinase ligands which interact with the acceptor−donor−acceptor motif in the hinge region of the kinase ATP binding site. This feature is also useful in the absence of structural data when structure−activity relationships (SAR) indicate a requirement for hydrogen-bond donors or acceptors at a specific position in a ring system. Lacking both structural and SAR data, one can use this feature to design sets of compounds which test the importance of donors and acceptors at different ring positions.

MORPH includes the ability for the user to provide upper and lower limits to the numbers of nitrogen, oxygen, sulfur, and total heteroatoms allowed in the modified ring systems. For example, one could specify that only compounds containing one sulfur and no more than two nitrogen atoms in a fused bicyclic ring should be output. The option to automatically filter out compounds which contain undesirable N−N, N−O, and N−S bonds between modified ring atoms and nonring substituent atoms is also provided. Compounds of this type are generated when ring carbon atoms bound to substituents through N, O, or S atoms are changed to nitrogen atoms. Although compounds can be classified by their ability or inability to match a specified hydrogen-bonding pharmacophore, no other scoring metric is provided. Determination of which rings are suitable replacements for the original aromatic ring is left to the user.

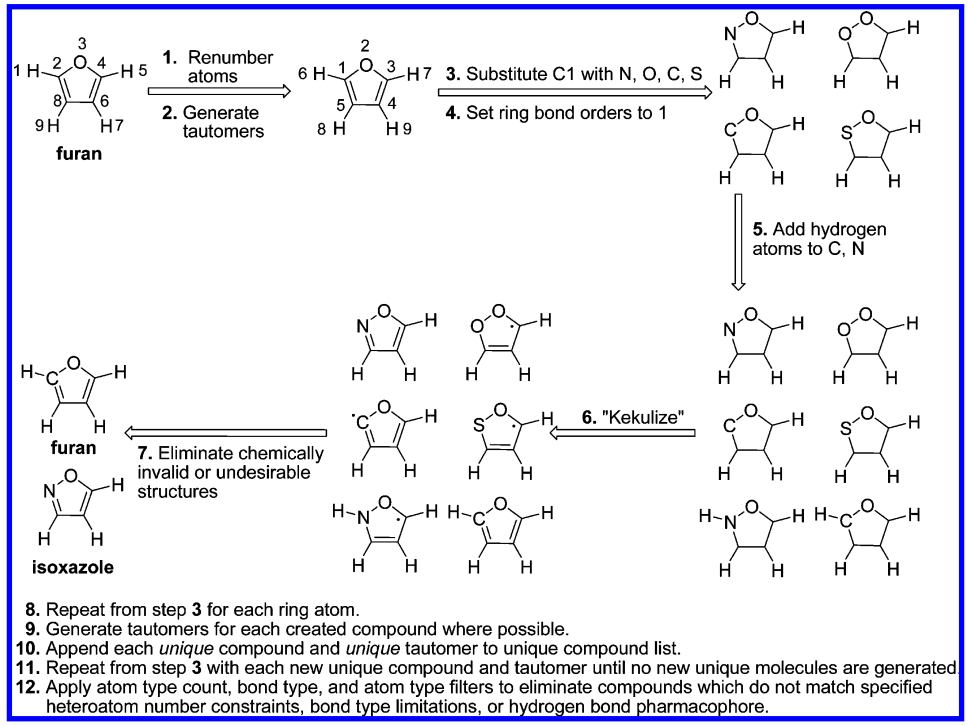
In its current implementation, MORPH is a specialized Linux-based tool which is utilized by members of the Bristol-Myers Squibb (BMS) Research and Development Computer-Assisted Drug Design group. However, it would be relatively straightforward to implement a web interface allowing broader access by other BMS scientists. Although the code for MORPH has not been made publicly available, the description contained herein should allow others with basic Python[15] programming skills, access to the OEChem[16] library of functions available from OpenEye Software, Inc., and with basic organic chemistry knowledge to produce code which performs the same functions as MORPH.

In the following, we describe the MORPH tool, its features and limitations, and its application to two different inhibitors of CDK2 representing distinct chemotypes.

METHODS

The MORPH Algorithm. MORPH is a relatively simple tool coded in the Python[15] programming language that utilizes the OEChem[16] library of functions available from OpenEye Software, Inc. It adjusts atom types, bond orders, and numbers of attached hydrogen atoms in aromatic rings in copies of a query molecule. Scheme 1 depicts the algorithm encoded by the program. In the first stage of processing, a molecule is read from an MDL SDF[17] format file, and the atoms are reordered so that all nonhydrogen atoms precede hydrogen atoms. This is necessary to avoid changing the numbering of nonhydrogen atoms as a result of deleting or adding hydrogen atoms. The nonhydrogen atoms of all compounds generated by MORPH based on a reference molecule will have the same atom numbers as the reference molecule, though the types of elements represented by those atoms will differ. Hydrogen atoms in compounds generated by MORPH will not necessarily have the same atom numbers as in the reference molecule, but this does not impact subsequent processing nor do "gaps" in the sequential numbering of hydrogen atoms, resulting from deletion of hydrogen atoms. Following the reordering, the molecule is analyzed to identify ring systems, and each ring system is further classified as aromatic or nonaromatic. In the current implementation, aromatic rings, such as benzene, imidazole, thiazole, and benzofuran, where the total bond order attributable to ring bonds for each ring carbon atom is equal to three or four are recognized and processed. Aromatic compounds, such as maleimide and pyridone, that contain carbonyl moieties within rings and have ring bond orders of two for the carbonyl carbon atoms are not recognized as

Scheme 1. MORPH Algorithm As Applied to Furan



aromatic and are not further processed. Following this classification, if the user has specified that only certain rings are to be altered, then any others are removed from the list. Next, tautomers of compounds containing five-membered aromatic rings with at least one protonated and one nonprotonated sp^2 nitrogen atom (e.g., imidazole, pyrazole) are generated. The original compound, any tautomers, and a list of rings defined by atom numbers are then passed to the function which performs the atom-type permutations.

In brief, for each molecule passed to it, the ringmorph function systematically modifies the element at each position in each ring to carbon, nitrogen, oxygen, and sulfur, creating a new copy of the original molecule prior to each modification and operating on the copy. Hydrogen atoms are added to the modified ring atoms in copies of the modified molecules. No hydrogen atoms are added to ring oxygen and sulfur atoms, while carbon and nitrogen atoms can have 0 or 1. Following this, bond orders are assigned utilizing the OEChem[16] kekulization function. As the atom permutation procedure is comprehensive, it generates a large number of chemically invalid and "undesirable" structures, such as those with oxygen or sulfur atoms in six-membered rings or two adjacent ring nitrogen atoms each having an attached hydrogen atom. This necessitates use of a series of filters to remove incorrect or unreasonable structures. Finally, a function based loosely on the Hückel $4n+2$ rule[18] is utilized to ensure that antiaromatic compounds are excluded.

Tautomers are generated for each compound returned from the ringmorph function, and the molecule and its tautomers are compared to all other compounds in a list of unique molecules. Compounds not found in the unique molecule list are appended to it. Each compound that is added to the unique molecule list is then subjected to the ringmorph procedure, and this is repeated recursively until no new unique compounds are generated.

To determine uniqueness, the molecular formula for the test compound is compared to the molecular formulas for all other compounds in the unique molecule list. If there are no exact matches, the the test compound is considered unique and added to the list. In each case, where there is an exact match between the molecular formula of the test compound and that of a compound in the unique molecule list, nonhydrogen atoms in the test compound are compared to the corresponding nonhydrogen atoms in the compound from the unique molecule list. Here, corresponding atoms are those having the same sequence numbering in each of the two compounds being compared. If either the atomic numbers or the numbers of attached hydrogen atoms differ for any pair of atoms compared, then the two compounds are considered different. If, using this procedure, the test compound differs from all compounds in the unique molecule list having the same molecular formula, then the test compound is added to the unique molecule list. This definition of uniqueness was used to prevent elimination of symmetry-related conformations of the same compound, which may be nonequivalent in a chiral environment. It also has significant performance advantages over an earlier implementation which utilized interatomic distance comparisons.

Once the full set of modified compounds has been generated, it is filtered to remove compounds not matching any user-defined constraints on the numbers of various types of heteroatoms allowed, compounds containing N−N, N−O, or N−S bonds, if desired, and compounds not matching any user-specified hydrogen-bond donor or acceptor criteria. Here hydrogen-bond donors are defined as any aromatic ring nonhydrogen atom with one attached hydrogen atom (i.e., CH, NH) and acceptors are any aromatic nitrogen atom with no attached hydrogen atoms. Compounds which pass the various filters are written to an MDL SDF format file.[17]

MORPH does not perform energy minimization on the models it creates. Adjustment of bond lengths and angles necessitated by differing connectivity can be achieved in a subsequent energy-minimization step with the modeler's choice of methodology. Since the three-dimensional coor-

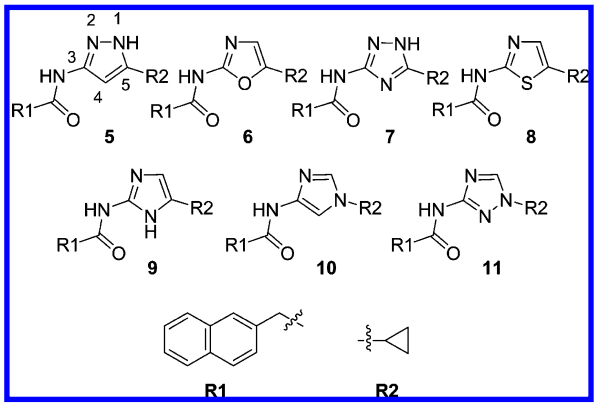


Figure 2. Structure of CDK2/cyclin A inhibitor PNU-292137 (**5**), and compounds **6**−**11** identified through MORPH analysis. The aminoheterocycles in each of these compounds are contained in known kinase inhibitors. Heterocycle atom numbering is shown for compound **5**.

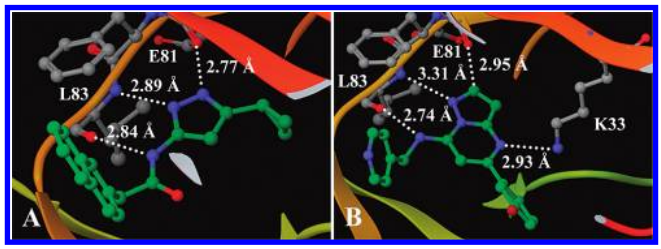


Figure 3. Hydrogen-bonding interactions between **5** (A, left) and **12** (B, right) and CDK2. Figures created from cocrystal structure coordinates (PDB codes 1VYW[3] and 2C68)[23] using Maestro.[20]

dinates of nonhydrogen atoms are not modified by MORPH, the resultant molecules are all superimposed with the original reference molecule. Thus, if the bound conformation/orientation of the reference molecule was used as input for MORPH, then all of the compounds generated would be oriented in the same way, with the same conformation, and could be directly energy minimized within a fixed protein binding site model, eliminating the need for docking. MORPH has substantial utility for ligand design, as highlighted in the following examples.

RESULTS AND DISCUSSION

MORPH Analysis of a 3-Aminopyrazole CDK2/Cyclin A Ligand. PNU-292137 (**5**) shown in Figure 2 is a potent CDK2/cyclin A inhibitor reported by Pevarello and coworkers.[3] The cocrystal structure of this compound with CDK2/cyclin A has been reported (PDB[19] code 1VYW).[3] This structure shows the one-position nitrogen atom of the pyrazole ring donating a hydrogen bond to the backbone carbonyl of Glu81 in CDK2, while the two-position nitrogen accepts a hydrogen bond from the Leu83 backbone NH. The amide NH moiety donates a third hydrogen bond to the backbone carbonyl of Leu83 (Figure 3A). Compound **5** was prepared for analysis with MORPH as follows. First, the PDB[19] file for the complex was read into Maestro,[20] and all atoms except those comprising **5** were deleted. Bond orders were manually assigned, and hydrogen atoms were included using the "add hydrogens" function in Maestro. This model for **5** was then written to an MDL SDF[17] format file with no further refinements.

Starting with **5**, allowing modification of only the five-membered ring and filtering out molecules with N−N, N−O, or N−S bonds, MORPH yielded 44 compounds, including **5**. While this set is extensive, most of these are unlikely to bind with high affinity to the ATP binding sites of any kinases since they lack the correct hydrogen-bonding pharmacophore. With the additional requirements that the atoms at the one- and two-positions of the ring (based on pyrazole numbering) must be hydrogen-bond donors and acceptors, respectively, only 7 compounds including **5** resulted. These are shown in Figure 2. Incorporated within compounds **5**−**11** are the original pyrazole ring as well as oxazole, thiazole, and pairs of isomeric 1,2,4-triazole and imidazole rings. Aminothiazoles are well-known as kinase inhibitors,[21] and SciFinder[22] searches using substructures corresponding to acylated oxazole, both isomeric acylated 1,2,4-triazoles and both isomeric acylated imidazoles, highlighted numerous patents and/or patent applications related to kinases in each case, suggesting that these are at least claimed generically as kinase inhibitors. Each of these possesses the donor−acceptor−donor motif required for binding to the CDK2 backbone. In this relatively simple exercise, MORPH was utilized to identify six other known kinase inhibitor chemotypes starting from one known chemotype. Although this was a retrospective rather than a prospective analysis, and no novel chemotypes were identified, the potential for doing so is clearly illustrated.

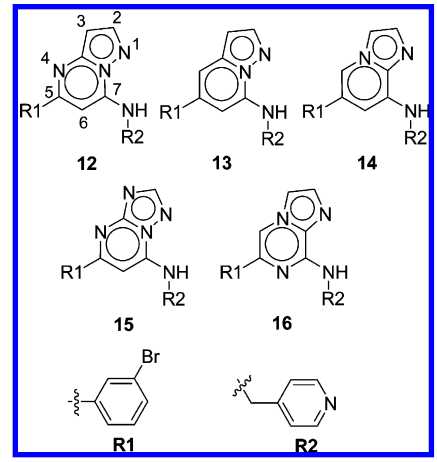


Figure 4. Structures of CDK2 inhibitor **12** and compounds **13**−**16** identified from MORPH analysis which contain [5,6]-fused rings present in reported kinase inhibitors. Heterocycle atom numbering is shown for **12**.

MORPH Analysis of a Pyrazolo[1,5-a]pyrimidine CDK2 Inhibitor. The second example of a MORPH analysis focuses on pyrazolo[1,5-a]pyrimidine CDK2 inhibitors. The IC_{50} of pyrazolo[1,5-a]pyrimidine compound **12** (Figure 4) against CDK2 is 1.8 μM.[24] The cocrystal structure of **12** with CDK2 has also been reported (PDB[19] code: 2C68).[23] When bound to CDK2, **12** forms three hydrogen bonds with the kinase acceptor−donor−acceptor motif; the two-position carbon acts as an aromatic C−H donor for the Glu81 backbone carbonyl oxygen, the one-position nitrogen accepts a hydrogen bond from the Leu83 backbone NH, and the seven-position amino substituent acts as a donor in the interaction with the Leu83 backbone carbonyl oxygen. In addition, the four-position nitrogen is within 3.0 Å of the amino group of Lys33, indicating a probable hydrogen-bonding interaction (Figure 3B).

Preparation of the model of **12** for MORPH analysis was performed as described for compound **5** in the 3-aminopy-

razole example above. Starting from the three-dimensional model of **12**, with changes limited to the central [5,6]-fused ring system, and omitting compounds with N−N, N−O, or N−S bonds, MORPH provided 240 unique compounds. As with the previous example, many of these are unlikely to be suitable kinase inhibitors as they lack the donor−acceptor−donor pharmacophore. Running MORPH with the additional restrictions that compounds must have hydrogen-bond donors at the two-position and acceptors at the one-position (pyrazolo[1,5-a]pyrimidine numbering) to display the required pharmacophore yielded 44 unique molecules. Within this set were four compounds, **13**−**16**, which contain [5,6]-fused ring systems that are incorporated in known kinase inhibitors, and cocrystal structures of close analogs of these compounds with CDK2 have been reported.[23,25] Except for the structure containing the analog of **16**, these cocrystal structures show that the [5,6]-fused ring systems in the compounds form similar interactions with CDK2 compared to that of **12**. When the additional constraint requiring an acceptor at the four-position was added, in order to preserve the hydrogen bond with Lys33, the number of molecules returned was reduced from 44 to 22. Compound **15** was included in this set. This example highlights the ability of MORPH analyses to generate models of compounds from multiple alternative active chemotypes, starting from a known active ligand containing a fused ring system.

The power of hydrogen-bond constraints is illustrated as well. Utilizing the constraints, the set of prospective compounds to be further analyzed was reduced by 91%, from 240 to 22, and all of these compounds have the features required to form hydrogen-bonding interactions with the CDK2 hinge acceptor−donor−acceptor motif and with the amino moiety of Lys33. It should be noted though that not all of these constraints may be necessary, and some potentially active compounds may be eliminated by inclusion of too many. A recent review from Ghose, et al. questioned the importance of multiple hydrogen bonds between the inhibitor and the hinge region of the ATP binding site in kinases based on the fact that the majority of kinase inhibitors approved as drugs form only a single hydrogen bond with a hinge residue.[26] For the examples presented here, our objective was to demonstrate the utility of MORPH in identifying compounds that mimic hydrogen-bonding patterns in reference molecules. Thus, we included constraints based on all of the potential hydrogen bonds between reference ligands and protein utilizing acceptors and both NH and aromatic CH donors. Finally, we emphasize the fact that no ranking of the final 22 compounds was performed by MORPH, and the choice of which one(s) to pursue must be guided by other considerations, such as docking scores, calculated protein−ligand interaction energies, synthetic feasibility, and, most importantly, chemical knowledge and experience.

The preceding two examples highlighted the utility of MORPH for generating new compounds from models of reference ligands in their known bioactive conformations with the application of hydrogen-bonding constraints. Because MORPH generates models of new compounds superimposed with the original reference molecule, it is well-suited for structure-based ligand design work. However, it should be noted that MORPH works equally well with any conformation of the reference model used and does not require any constraints to be applied. Some other potential applications of MORPH include generation of comprehensive databases of aromatic rings for use with other modeling software, ligand-based design work with and without any hypothesis regarding bioactive conformation, and generation of compound sets for probing aromatic ring SAR.

CONCLUSIONS

We have created a new software tool, MORPH, which systematically modifies the nonhydrogen atoms in aromatic ring systems contained in three-dimensional models of compounds to generate new compounds in which none of the coordinates of the nonhydrogen atoms are altered. For structure-based drug design purposes, a model of a reference compound in its bioactive conformation can be extracted from a cocrystal structure and used as input for MORPH, and all of the compounds generated by the analysis will be "pre-docked", facilitating further analysis and comparison. Two examples where MORPH generated structures for multiple known kinase inhibitor chemotypes starting from a model of a single ligand in its bioactive conformation were presented. The ability to impose constraints limiting atom types at specific ring positions to hydrogen-bond donors or acceptors significantly reduces the number of potential structures to be further processed, ensures that all of the resultant compounds contain important elements of binding pharmacophores, and greatly enhances the utility of the program. Although MORPH is well-suited for structure-based ligand design work, its utility extends to other areas of drug design and chemoinformatics as well.

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