J Mol Model (2008) 14:797–805
DOI 10.1007/s00894-008-0320-1

ORIGINAL PAPER

The use of local surface properties for molecular superimposition

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Received: 7 February 2008 / Accepted: 18 April 2008 / Published online: 24 May 2008

Abstract This study employed surface-based properties for use in the superimposition of three series of molecules. The properties used were derived from semiempirical molecular orbital calculations and can be related to the physics of intermolecular interactions. In each case, the superimposition of the compounds was within 0.6 Å of the experimental overlay. The superimposition cases presented differing levels of involvement of electrostatic interactions, and in only one case did shape similarity provide the best overlay. Two test compounds were applied to an example exploring non-nucleoside HIV-1 reverse transcriptase inhibitors and only one of these compounds overlaid in the same manner as their crystal structure complexes. This served to highlight the need for molecules to occupy the same region of space when employing this technique. Nevertheless, the method can be used to generate pharmacophores and ultimately could be used to interrogate databases for molecules that match the key surface properties, thus allowing scaffold hopping.

Keywords Semiempirical molecular orbitals · Molecular-field similarity · Non-nucleoside HIV-1 reverse transcriptase inhibitors · Human thrombin inhibitors · Dihydrofolate reductase inhibitors

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Introduction

One of the concepts underlying medicinal chemistry is that molecules exhibiting similar patterns of biological activity and that bind to the same active site must also possess a high level of overall similarity in chemical and/or structural characteristics. The chemical characteristics that govern this similarity encompass their gross physicochemical properties (e.g. size, lipophilicity) as well as the location of key molecular features, which in turn determine molecular field information (i.e. steric, electrostatic and hydrophobic). Similarity in this sense does not therefore, simply refer to conventional 2D structure matching. Given that we seek to establish a chemical similarity in 3D space, chemists often try to develop pharmacophores [1] that embody the fundamental functional group requirements for biological activity at a macromolecular target. Where structural information is absent for a biological target, pharmacophores are extremely useful as they can be exploited for drug design and database searching (reviewed in [2]).

Although not the case today, traditional modelling methods often aimed to emphasise structural comparisons to explain biological activity. While this can help with closely related compounds it is unable to deal with diverse molecules, which then stifles drug design activities seeking to scaffold-hop and explore novel chemical structures. Most medicinal chemists are now aware of techniques that can compare molecules using field-based information concerning shape and electrostatic features. Indeed, field-based parameters provide a better description of a compound with regard to binding properties.

Among these field-based methods has been the development of XED (extended electron distribution) charges, which has been used successfully for molecular modelling [3–5]. To achieve this, XEDs were encoded into a

molecular mechanics force field where appropriate partial charges were distributed around atom centres. Application to a series of well known intermolecular interactions allowed Vinter et al. to adequately reproduce these experimental observations (e.g. aromatic–aromatic π-stacking, etc.) [5, 6]. Vinter and co-workers further developed their XED charges to generate field points around molecules to represent energy extrema of the molecular electrostatic, steric and hydrophobic fields [7]. In this way, molecules could be compared easily without the need for choosing structural alignments, thus facilitating database searching for molecules that match these field points [8]. The ultimate aim of the method is to allow "scaffold hopping", where structurally diverse compounds that match the field information are identified and screened for activity, resulting in new lead compounds [4].

Of course, modelling methods that exploit field information have been examined by many groups. For example, previous studies have used a variety of techniques and have focussed on either hydrogen bonding atoms, molecular electrostatic potential or electron densities and steric matching [9–12]. These methods aim to assess similarity by projecting one or more properties of molecules onto a surface or into space. CoMFA will not be discussed here; suffice to say that this method is very sensitive to molecular alignment and success is dependent on optimising the superimposition of compounds being studied [13]. Flexibility is also an important aspect to consider and other groups have incorporated this into their superimposition/similarity software [14–17]. By far the best summary of the requirements of software intended for comparing molecular similarity was presented as a list by Miller and co-workers when they described their SQ method [10]. Key among this list was the need to produce superimpositions including those that are not obvious and non-intuitive as well as being able to deal with diverse structures. To adequately describe all the relevant studies in this area is beyond the scope of this paper and we shall consider only one further method.

Recently, Clark and his team have employed semiempirical molecular orbital (MO) information to calculate a series of local molecular properties suitable for use in quantitative structure-activity relationship (QSAR) studies, molecular superimposition and database searching [18–21]. These properties are encoded onto a molecular surface that is described by spherical harmonics [22] and include the molecular electrostatic potential (MEP), local ionisation energy (IE_L), local electron affinity (EA_L), local polarisability (α) as well as the molecular surface itself [20, 21]. A number of quantitative structure-property relationship (QSPR) studies have exploited these properties to look at physicochemical properties where the effect of conformation is less critical [19, 23–26]. The properties themselves are intended to be related to the physical theory of intermolecular interactions. The next logical use for these properties is to apply them to the examination of compounds that elicit similar biological activities and to compare molecular superimpositions to known experimental molecular overlays. Broadly speaking, the properties encompass Coulombic, van der Waals' and donor–acceptor interactions. While Vinter chose to incorporate these concepts into his molecular mechanics package, Clark has since argued that sufficient computational power now exists to contemplate semiempirical MO calculations on larger sets of compounds [21]. MO methods also have the advantage of circumventing the need to parameterise functional groups for XED charges. The software generated by Clark and his collaborators (ParaSurf and ParaFit) has been implemented in a range of packages, and these were made available for this study (Cepos InSilico, Erlangen, Germany). These software packages have already been used for molecular alignments using examples common to the ones described in this study [27]. This current work extends these investigations with the technique by quantitating the molecular alignments against experimental data as well as introducing further superimposition examples.

If ParaSurf is able to adequately model intermolecular interactions and provide advantages over existing techniques, then a range of modelling problems need to be tackled and assessed. Moreover, the software needs to be trialled in order to fully understand its capabilities as well as helping in its overall development. We therefore investigated three modelling scenarios varying in complexity and in the structural diversity of the compounds. They also differed in the level of interactions with their associated targets with regard to the number of ionic, hydrogen bond and electrostatic contacts. Importantly, we have the experimental overlay for all three superimposition cases detailing how each compound is bound to their relevant protein targets.

The first example was the classic and simple modelling conundrum concerning the binding mode of the pteridine rings of dihydofolic acid [28] and methotrexate [6, 27, 29] to dihydrofolate reductase (DHFR). Here, the binding mode of methotrexate is upside down relative to dihydofolic acid, which is an unexpected result if one simply compares the 2D structures of the compounds. The second example looks at two human thrombin inhibitors, which involves an ionic interaction with the binding site. In addition, these structurally diverse compounds interact with the enzyme, sharing key hydrogen bonds and hydrophobic interactions [10, 30]. The final case was intended to be challenging, so we adopted a superimposition originally described by Mestres and co-workers [12]. This modelling task used three non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) that show substantial structural diversity; only one of these compounds makes a hydrogen bond with the binding site. Once again, the crystal structures were

available [31–33] for comparison to the computational superimposition.

Methods

Three modelling scenarios were attempted in this study where information was available for the crystal structure of the ligands bound to their target protein. The PDB [34] codes for each example are given below.

Escherichia coli DHFR

The molecules of interest for DHFR were methotrexate (4DFR [29]) and dihydrofolic acid (1RF7 [28]). For this particular example, our attention was placed solely in the orientation of the pteridine rings and only fragments of the original molecules were employed (Fig. 1). This approach was undertaken to be consistent with the study of Vinter and Saunders [6].

Thrombin (human)

The classic thrombin inhibitors NAPAP (1DWD [30]) and PPACK (1DWE [30]) were selected for comparison, which corresponds to the molecules chosen by Miller and co-workers [10]. In this case, the entire molecules were employed and the guanidine and amidine groups were modelled as the charged (+1) species (Fig. 1). PPACK was modelled as the aldehyde to maintain consistency with the Miller et al. study [10].

Non-nucleoside HIV-1 reverse transcriptase inhibitors

In this final case, three molecules representing ligands studied by Mestres and co-workers were used [12]. Only

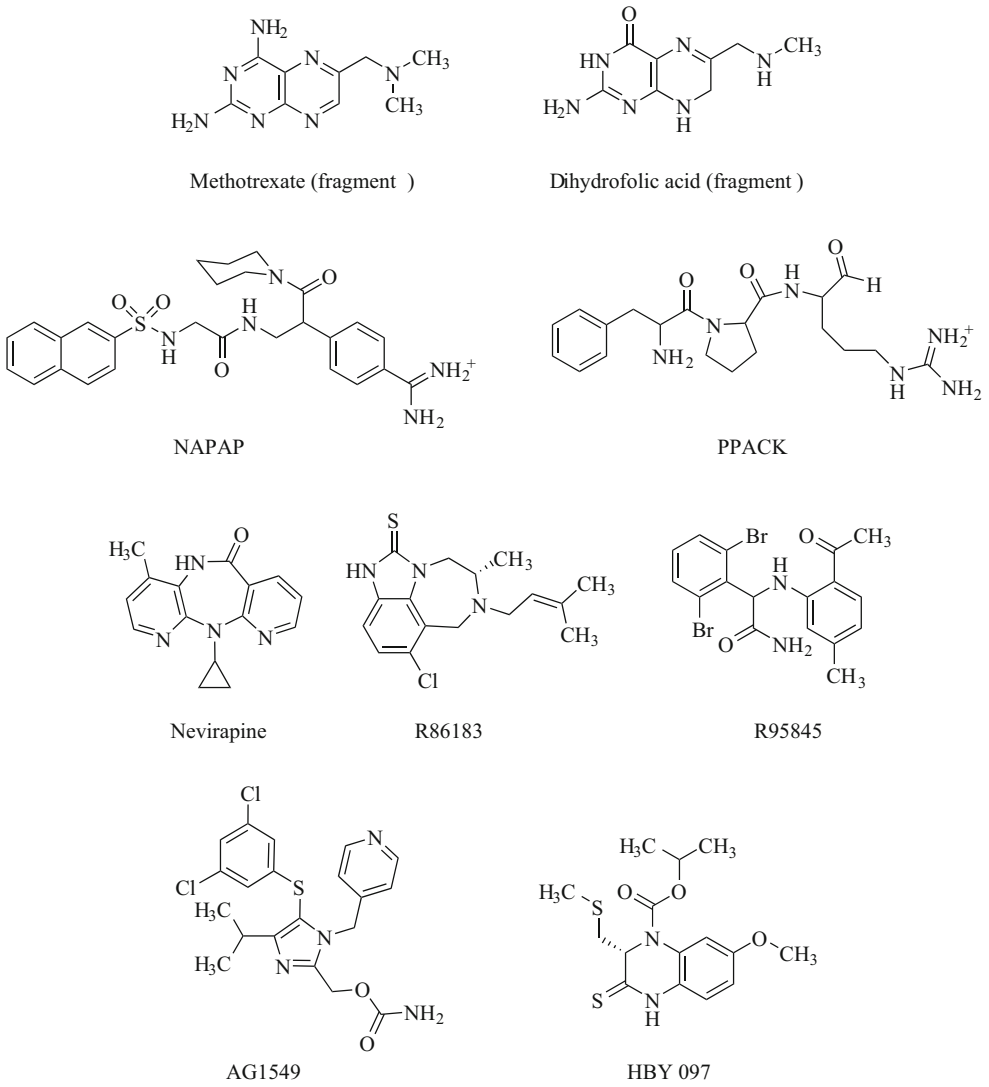

Fig. 1 Structures of the compounds used in this study

Table 1 Comparison of the superimposition of the dihydrofolate reductase (DHFR) ligands to their experimental overlay. *MEP* Molecular electrostatic potential, IE_L local ionisation energy, EA_L local electron affinity

Local property	RMS (Å)
Shape	0.96
MEP	>2
EA_L	0.58
IE_L	0.94
α	1.92

one of these compounds makes a hydrogen bond with the binding site, which corresponds to a difficult superimposition task where obvious ionic and hydrogen bond clues are largely missing. The three compounds studied were nevirapine (3HVT [31]), the TIBO analogue R86183 (1HNV [33]) and the α-APA analogue R95845 (1HNI [32]) (Fig. 1). Two further compounds, AG1549 (1EP4 [35]) and HBY 097 (1BQM [36]), were used as test compounds. For these compounds, separate experiments were conducted where the protein structures were individually fitted as above to 3HVT, 1HNV and 1HNI for pairwise comparisons. The experimental overlay of the three ligands with the test compounds thus gave six superimpositions, and an RMS fit was determined for these six analyses using the IE_L parameter.

Superimposition of protein structures

Within Sybyl [37], residues within 4 Å of the bound ligand were identified and used for superimposition purposes for each of the three cases. The alpha carbons of the residues common to each compound were superimposed, except in the NNRTI example where a residue was chosen if it was within 4 Å of two of the three inhibitors.

Experimental binding mode

Having been superimposed, the ligands were extracted into a common file to represent the experimental overlay of the compounds. This was, in effect, close to the ideal overlay given the differences observed in the protein structures themselves. Each compound was also curated to amend atom and bond types as well as adding hydrogen atoms. Care was taken not to alter the conformation.

MOPAC 6.0, ParaSurf, ParaFit

Molecular orbital information was calculated for each molecule using the MOPAC 6.0 program [38, 39] using the 1SCF keyword to avoid geometry optimisation. Following this, ParaSurf was used to generate molecular surfaces and a series of local properties. Finally ParaFit was used to superimpose sets of compounds using each of the properties generated by ParaSurf in turn. For the NNRTI series, each molecule was used as a template to compare against the other two compounds. The test compound (AG1549) was compared against R86183. Once the superimposition of the molecules was generated, an RMS value was determined, in most cases by a comparison to their experimental overlay using all heavy atoms.

Results

Dihydrofolate reductase

The two proteins (4DFR and 1RF7) were superimposed using the alpha carbons of residues within 4 Å of the ligands, resulting in an RMS fit of 0.39 Å. Fragments of the ligands were superimposed using each of the four properties generated by the ParaSurf package as well as their molecular shape. Table 1 shows the RMS fit between the ParaFit superimposition and the experimental overlay. The best overlay employed EA_L, while both shape and IE_L also gave good results. Local polarisability (α) and MEP were unable to demonstrate the classic 'flip' of the methotrexate pteridine ring relative to dihydrofolic acid. Figure 2 shows the experimental overlay in comparison to the best overlay using EA_L.

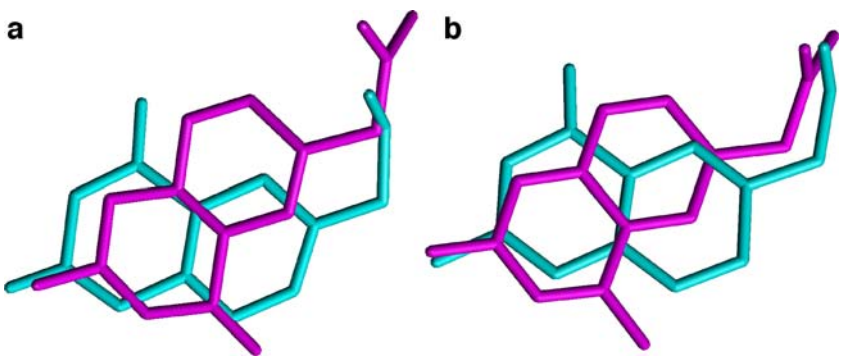

Fig. 2 Diagram showing the experimental overlay of the substructures of dihydrofolic acid (*cyan*) and methotrexate (*magenta*) (**a**) and their overlap using local electron affinity (EA_L) (**b**)

Table 2 Comparison of the superimposition of the human thrombin ligands to their experimental overlay

Local property	RMS (Å)
Shape	0.52
MEP	0.72
EA_L	>2
IE_L	0.74
α	0.57

Thrombin (human)

Superimposition of the two proteins (1DWD and 1DWE) gave a good overlay near the active site, with an RMS of 0.31 Å. The entire structures of the ligands were used for superimposition in this case and Table 2 shows a comparison of the ParaFit and experimental overlays. Only one property (EA_L) failed to adequately superimpose the compounds, while both shape and α demonstrated the best fit showing similar accuracy. Figure 3 shows the superimposition of the two compounds using the α parameter.

Non-nucleoside HIV-1 reverse transcriptase inhibitors

As there are three crystal structures in this analysis, a choice of template protein structure was needed. Given that there were no clear measures as to which protein would best serve this role, some obvious caution is needed when interpreting the results as differing numbers would be obtained using each protein as the template. The RMS fit of the three proteins given in Table 3 shows that 1HNI differed the least from the other two proteins as well as having the highest resolution. This protein was used as the template and it should be remembered that the resulting comparisons would differ slightly should the other proteins be employed for this purpose. For the ligands themselves, a 3×5 matrix of results was generated ,where each ligand was used in turn as the template for the four properties and shape comparison. The results showed, however, that the same overlay (or one extremely similar) was obtained regardless of which molecule was selected as the template. As a consequence, Table 4 simply shows the results for each local property, illustrating that IE_L gave the best overlay followed by shape similarity. EA_L, MEP and α were unable to adequately overlay the compounds. Figure 4 shows the best superimposition using the IE_L property.

Two test compounds were included in this assessment, and, given the success outlined above, the IE_L property was used. Experiments on the first compound, AG1549 (1EP4), were unable to reproduce its bound configuration using all three of the NNRTI ligands as the template. The degree of overlap of AG1549 with the three ligands was quite small, demonstrating that this compound does not share much of the binding site common to the original set of three compounds. The second molecule was selected so that its binding orientation was in closer to proximity to the three NNRTIs. In this case, HBY 097 fitted well when nevirapine and R86183 were used as the templates (RMS 0.62 Å and 0.39 Å, respectively) but failed when R95845 was used. Figure 5 demonstrates the excellent fit of HBY 097 with R86183 using the IE_L parameter.

Discussion

Intermolecular interactions are driven primarily by three properties/forces [40]. The first of these covers electrostatic interactions and is usually modelled using Coulomb's law. Typically, the MEP can be used for Coulomb interactions and this has been adopted for use on molecular surfaces by Clark's group [20]. There are two aspects to van der Waals interactions comprising steric repulsion and dispersion forces. Steric repulsion can be modelled simply by way of a molecular surface, which has been applied for ParaSurf in the form of a spherical harmonic representation [41]. Dispersion forces on the other hand have been modelled using the parameter α [18], and have been applied particularly to non-polar molecules [19]. The final area that needs to be described adequately is donor/acceptor interactions. Two particular properties have been established to help model this aspect of intermolecular interactions. The

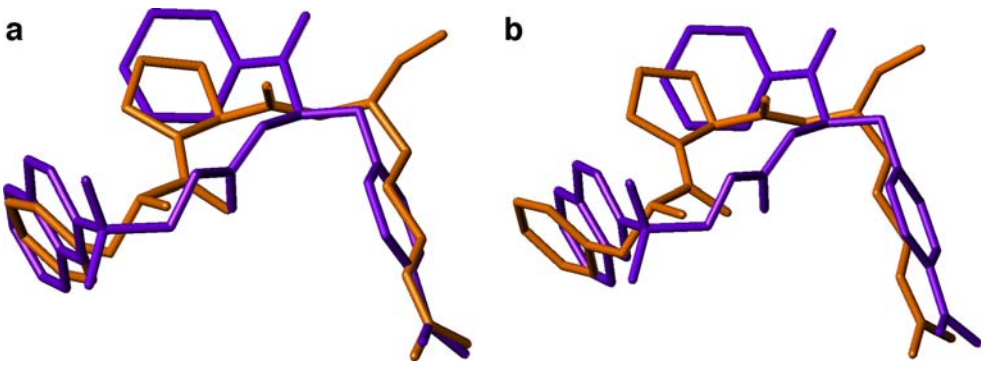

Fig. 3 Diagram showing the experimental overlay of NAPAP (*purple*) and PPACK (*orange*) (**a**) and their overlap using α (**b**)

Table 3 RMS fit and experimental resolution (Å) of active site residues for the non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) case

Protein	1HNI	1HNV	3HVT	Resolution
1HNI	0.0			2.8
1HNV	0.35	0.0		3.0
3HVT	0.53[a]	0.75	0.0	2.9

[a] Superimposition was performed without Val 179 as this residue showed a large degree of movement between the two complexes

first was described by Murray and Politzer [42], who developed the property IE_L, which effectively describes the electron donor ability of a molecule. To cater for electron acceptor behaviour, Clark's group [18] introduced the EA_L descriptor and have found it to be of utility in predicting chemical reactivity. In short, the properties that Clark's group have developed in conjunction with their molecular surfaces adequately describe the key requirements for intermolecular interactions. While they have been applied to the modelling/QSPR of physicochemical properties, a concerted series of experiments towards biological applications was warranted.

Taking an overall assessment of the three cases presented in this study, it is clear that both the molecular surface (i.e. shape) and IE_L consistently reproduce the experimental overlay. While not necessarily always the best parameter, they were within 0.4 Å of the best overlay. For the DHFR case, the EA_L parameter gave the best result. This parameter is known to be associated with electron acceptor behaviour, and a quick examination of the interactions between methotrexate and dihydrofolic acid and the binding site show some common hydrogen bonds and charge-assisted hydrogen bonds. These interactions are largely hydrogen bond donor in nature from the perspective of the ligands. The finding that the EA_L parameter gave the best overlay is in accord with the experimental hydrogen bonds when we consider that a hydrogen bond donor can be regarded as an electron acceptor. Importantly for this study we chose to select crystal structures from the same organism so that assessments could be made to the computational overlays. This is not a perfect overlay given that there are some differences in the location of the alpha carbons of the residues that interact with the ligands (RMS 0.39 Å). Nevertheless, this allows us to compare the crystal overlay with the computational one in a quantitative manner, which is in contrast to a number of previous studies.

Table 4 Comparison of the superimposition of the NNRTI ligands (nevirapine, R86183 and R95845) to their experimental overlay

Local property	RMS (Å)
Shape	0.80
MEP	>2
EA_L	>2
IE_L	0.47
α	>2

Recently, Hudson and co-workers [27] also successfully investigated the alignment of the heterocyclic rings in dihydrofolate and methotrexate using ParaSurf and related software. One concern of theirs was to explore the tautomeric state of the dihydrofolate ring. They concluded that the keto form was the likely bioactive configuration, and that tautomerism in general is a problem that plagues these types of analyses. Encouragingly, this current study was in agreement with that of Hudson et al. [27]; however, it differed slightly in the molecular fragments used as we retained a short alkyl amino side-chain to coincide with the work of Vinter [6].

Our second analysis sought not only to explore the entire structure of the ligands but also to select compounds diverse in structure. As in the DHFR case, the thrombin inhibitors made interactions largely with the same set of residues for each molecule (e.g. Asp189 and Gly216), and the protein structures were from human origin to allow direct comparison and superimposition. Once again, molecular shape was able to reproduce the overlay and α also provided a good fit (Table 2). Given that α is said to be associated with non-polar molecules [19], this appears a strange result as both compounds have been modelled as the charged species. The most encouraging aspect of this result was that four of the five properties were able to closely reproduce the experimental overlay.

The final case was the most challenging given the lack of obvious electrostatic interactions with the binding site. Only one molecule, R86183, made a hydrogen bond with the binding site. This was one of the reasons that attracted Mestres and co-workers [12] to study these compounds. Since their study, many other complexes have been solved and more recent work has sought to develop pharmacophores based on a larger set of compounds [43]. The main difference between these two research projects was that Daeyaert et al. focused on the hydrogen bond requirements of NNRTIs such that all their compounds had two hydrogen bonding groups as an absolute requirement. Like Mestres, we faced the dilemma of which protein and ligand to use as

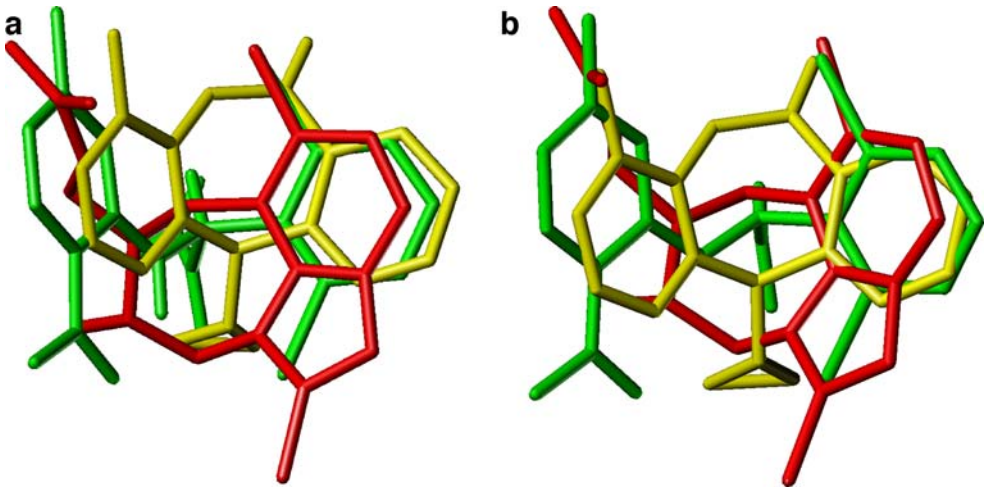

Fig. 4 Diagram showing the experimental overlay of nevirapine (*yellow*), R86183 (red) and R95845 (*green*) (**a**) and their overlap using IE_L (**b**)

a template [12]. We were fortunate, as the computational superimposition did not seem to depend on which ligand was used. While this did not pose a problem in the current study, the possibility remains that in other cases it would be a challenge and more work is needed to investigate this. The results demonstrated that shape and IE_L alone were able to reproduce the experimental overlay. Given that these three molecules make very few hydrogen bonds with the enzyme, the success with a parameter that best describes hydrogen bond donor behaviour is certainly intriguing.

The beauty of a pharmacophore, or indeed any overlay that can reproduce experimental binding orientations, is that it can potentially be used for database searching. Armed with the success of the IE_L descriptor for the NNRTI case, we applied the method to two test compounds. The first (AG1549) was not successful and this compound was specifically selected as it accepts only a single hydrogen bond with the enzyme. Thus, it was largely in keeping with the overall nature of our three NNRTI trial molecules. An examination of the degree of overlap of AG1549 with the three original compounds showed that it bound mostly to alternative regions of the binding site. This highlighted the probable need for molecules to be occupying the same regions of the binding site for the method to work and, as such, a second compound was sought to test the model. HBY 097 was structurally diverse with respect to the other NNRTIs studied but retained a thioamide motif in common with R86183, which makes similar hydrogen bonds with the binding site. Here, the problem of which template to use served to highlight where good results were obtained for two of the three template compounds. Having said that, the result was impressive given the structural diversity of the compounds and given that the result was extremely close to the experimental overlay. On this occasion, HBY 097 had a large degree of overlap with the three trial compounds, which contrasts significantly to AG1549.

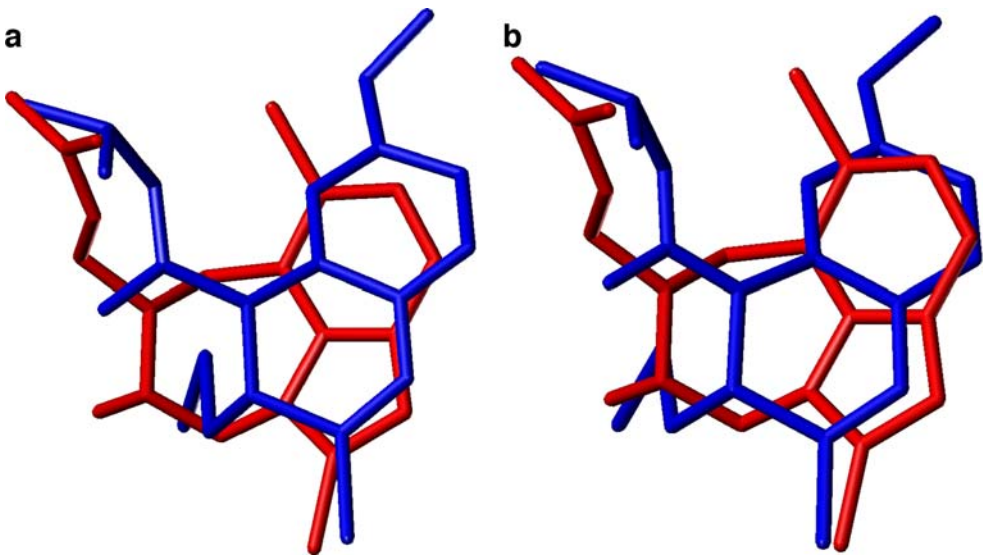

Fig. 5 Diagram showing the experimental overlay of HBY 097 (*blue*) and R86183 (*red*) (**a**) and their overlap using IE_L (**b**)

Summary

Taken together, ParaSurf and ParaFit have shown that they can be applied successfully to predicting the binding orientation of compounds to macromolecular targets. For all of the three cases studied, successful overlays were found within 0.6 Å of the experimental superimposition. Moreover, the binding orientation of a test compound applied to the NNRTI model was reproduced successfully. The current study not only encourages further work to use the technique for database searching (i.e. for scaffold-hopping), it also raises a series of questions that will require more research. The first of these concerns conformational flexibility where, as in the current study, the compounds have been used in their bound configuration. This is a fundamental need given that, in a real-world drug discovery setting, the bioactive conformation would not be known [27]. The simple solution is to undertake conformational searches for the ligands under consideration and to apply the similarity measures available in the ParaFit software [41]. Another need is to allow partial matching where ligands do not necessarily fully overlap in the binding site. This is being addressed and will be extremely useful when implemented (T. Clark, personal communication). Also of interest is the matter of multiple compound comparisons where a consensus is needed when dealing with more than two molecules regarding matching of key surface property features. Finally, tautomerism is also influential and will need to be considered in future developments [27].

As mentioned above, the property that best reproduced the experimental overlays was not common to all three cases. While shape and IE_L worked well, it was somewhat surprising that MEP did not perform well, nor was there an apparent match between the best property and the nature of the interactions with the binding site. Most interesting of all is that, in the hands of Clark's group, they too find that IE_L is consistently useful in their modelling research (T. Clark, personal communication). Certainly this parameter deserves further study given its global success in this current study. Finally, once further research is completed to refine these methods, it would be useful to develop a visual summary of molecular superimpositions to detail to medicinal chemists the important features that govern the resulting overlay of ligands. This would allow them to grasp the pharmacophoric nature of the overlap, which would help them in drug design matters. Of course, an interface to database searching will facilitate the ultimate purpose of this software, which is to find novel ligands to scaffold hop into new areas of chemistry.

Acknowledgements The author would like to thank Professors Tim Clark and Dave Ritchie for their helpful comments and access to their software packages. Thanks also go to Daniel Rametta, whose undergraduate project contributed to this manuscript.

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