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A comparative docking study and the design of potentially selective MMP inhibitors

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Summary

As part of a program aimed at the design and synthesis of constrained MMP inhibitors, a survey of the reported X-ray and NMR structures of MMP/inhibitor complexes was performed, revealing mutations of key amino acids at different subsites between MMPs. A comparative study of fully automated docking programs AutoDock and DOCK in closely approximating the X-ray crystal structures of ten selected MMP inhibitors was performed. AutoDock proved to be highly reliable, efficient and predictive for a set of inhibitors with less than six atom types.

Introduction

The matrix metalloproteinases (MMPs) are involved in the alteration of natural biological components such as collagen leading to serious or even fatal pathologies like arthritis or cancer. As a result they have become a target of prime interest in search of effective inhibitors as drug candidates [1–4]. This is illustrated by the growing number of reports in this area as exemplified by the development of inhibitors such as Batimastat (1) [5] and CGS 27023A (2) [6] (Figure 1).

The number of available high resolution X-ray crystal structures of enzyme/inhibitor complexes has dramatically increased in recent years. For instance, the structures of complexes of **1** [7], **2** [8], or **3** [9] with MMPs have been resolved. This structural information has become an important tool in designing potential inhibitors at the early lead generation stage. The advent of molecular modeling, in conjunction with increasingly powerful graphics workstations has also been an important source of information for structure-based molecular design of small molecule drugs [10]. Comparative Molecular Field Analysis and related programs (CoMFA [11], CoMSIA [12]), Receptor Surface Model program (RSM [13, 14]), and molecular dynamics [15] have been extremely useful in determining the best molecular shape and ligand complementarity for a receptor or an enzyme of unknown tertiary structure, eventually leading to the synthesis of 'designed' small molecules for biological testing.

The two major challenges in inhibitor design for example are the prediction of the change in binding energy upon complex formation within the active site of the enzyme, and the conformational search to allow for the flexibility of both partners. For instance, fast empirical scoring functions have been implemented in *de novo* design programs such as LUDI [16–19], or docking programs such as Hammerhead [20, 21]. DOCK [22–30], and similarly FLOG [31], evaluate the shape complementarity using spheres to characterize the binding site, and they use a grid to evaluate the electrostatic and van der Waals contribution to binding. Indeed, grid-based energy evaluation (GRID [32–35], GREEN [36], LEGEND [37, 38]), and direct force field evaluation of the energy (MCSS [39–42]), have been widely used.

To avoid getting trapped in local minima, the conformational sampling has to be complete. This prob-

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lem was initialy tackled using the ellipsoid algorithm [43] or the distance geometry concept [44]. More common conformational search methods were introduced such as the Monte Carlo simulated annealing method (AutoDock 2.4 [45–47]), genetic algorithm and evolutionary programming (AutoDock 3.0 [47], GOLD [48, 49], DIVALI [50], PRO_LEADS [51] and others [52–53]), Tabu search (PRO_LEADS [51]) and other Monte Carlo methods (MCMM [54], MCDOCK [55]). Building up the ligand within the binding site has also been envisaged. MCSS uses multiple replications of functional groups that are linked using a bank of skeletons [39–42]. A related atom by atom construction is proposed in LEGEND [37, 38]. FlexX [56], Hammerhead [20, 21] and DREAM++ [57] select an anchor, dock it and perform an incremental construction from this atom or group of atoms. Molecular graphs or lattices (atoms are nodes and bonds are edges) were also envisaged to construct molecules (HIPPO [58, 59], Builder [60]) or to map binding sites [61]. This concept was extended to docking graphs (DOCK [30]).

Studies in our laboratories have led to the discovery of acyclic sulfonamides such as **4** [62, 63] as potent MMP inhibitors *in vitro* (Figure 1). This activity was rationalized based on the NMR structure assingments for a preferred mode of binding for a related sulfonamide with MMP-3 [8]. Our initial attempts to prepare constrained analogs incorporating cyclopropane [8], cyclohexene [64], and tetrahydrofuran derivatives [64] resulted in inactive compounds. We thus became interested in the prospects of utilizing molecular modeling to predict the preferred bioactive conformation of *de novo* designed inhibitors. We reasoned that a good agreement between the structure of an enzyme-inhibitor complex determined by X-ray crystallography, and one proposed by molecular modeling utilizing appropriate docking techniques would be promising for the design of novel inhibitors.

An overview of the existing data and a comparative study of the readily available programs seemed necessary. To date, the reported docking methods are not universally applicable in providing agreement with X-ray structural information. Indeed, due the poorly defined solvent exposed S_1 and S_2' pockets of MMPs, the manual docking of an inhibitor and its binding mode is difficult to predict. We chose to explore the suitability of GRID 17.0 [32–35] in mapping the binding site, and DOCK 4.0 [22–30] and AutoDock, [45–47] in reproducing the binding mode of MMP inhibitors whose enzyme-inhibitor complex structures

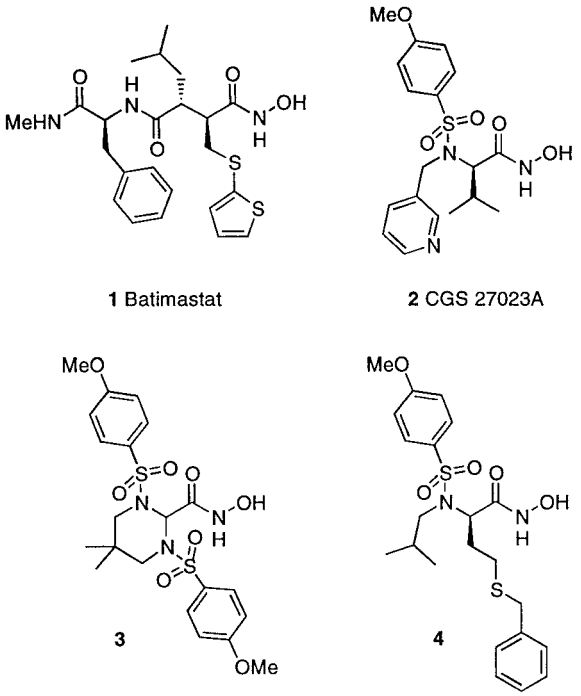

Figure 1. Selected MMP inhibitors.

have been reported by X-ray crystallography. We compared the results provided by these programs for a selected group of known MMP inhibitors that had several degrees of conformational freedom, with the corresponding X-ray enzyme-inhibitor crystal structures. Preliminary studies in our laboratory had shown that AutoDock was a reliable program for the *de novo* design of constrained analogs in which the P1 functionality was diversified [66]. During the course of our work, a comparative study of constrained inhibitors based on MMP-3 as a target was reported [67].

Material and methods

General

Molecular modeling was performed on a Silicon Graphics Octane 2 workstation equipped with a 360 MHz R12000 processor running IRIX (version 6.5). The molecules were manipulated using InsightII® version 95.0 [68] and Macromodel® version 5.5 [69].

Metalloproteinase-inhibitor complex structures and docking

The cartesian coordinates of thirty-six MMP-inhibitor complexes were retrieved from the Brookhaven Protein Databank (PDB) and the water molecules were removed. PDB codes: **MMP-1**: 3AYK, 1FBL, 1HFC, 1TCL, 966C; **MMP-2**: 1QIB (free catalytic site); **MMP-3**: 1B3D, 1B8Y, 1BIW, 1BQO, 1CAQ, 1CIZ, 1HFS, 1SLM, 1SLN, 1UEA, 1UMT, 1USN, 2USN, 3USN; **MMP-8**: 1A85, 1A86, 1JAN, 1JAO, 1JAP, 1JAQ, 1KBC, 1MMB, 1MNC, 1BZS; **MMP-9**: 1MMP, 1MMQ, 1MMR; MMP-13: 456C, 830C, 1CVX.

Of these, the compounds for which enzyme-inhibitor X-ray structures were known at resolutions ranging from 1.7 Å to 2.3 Å were selected for the comparative docking studies (Figure 2). Our choice was guided by their structural and functional diversity featuring sulfonamide, phosphonylamide and amide functions as H-bond acceptors, several common lipophilic moities, charged groups, and thiols, hydroxamic or carboxylic acids as zinc binding sites. In addition, 6 to 17 torsions were considered to further test the validity of the conformational search methods.

Polar hydrogens were added and visually inspected. Atom types and charges were added using AMBER [70, 71]. The force field to model the zinc ion was parametrized according to Guida [72] and Merz [73]. The atomic partial charges of the inhibitors were calculated using the semi-empirical MNDO method implemented in the MOPAC® program.

Modeling metal ion chelation

DOCK and AutoDock consider the metal ions as spherical atoms, and the geometries of coordination cannot be predicted. These parameters can be obtained using GOLD [48, 49]. It is noteworthy that the distorted trigonal bipyramidal coordination of the zinc atom involving three histidines in the MMPs and the binding group in the ligand would require a complex set of geometric parameters. Consequently, we assumed that the electrostatic treatment of the zinc-ligand interaction would be adequate and that the overall scoring function would not be offset.

Computational methods

GRID version 17.0: The MMP-3 binding site was mapped using Dry (hydrophobic probe), O= (sulfonamide oxygen), O (carbonyl oxygen), N1 (amide hydrogen) and OH2 (water) as probes, 2 planes per Ångström (NPLA= 2), and considering the flexibility of the side chains (MOVE = 1).

DOCK version 4.0: The binding site was represented by spheres following Kuntz' protocol and visually inspected. Preliminary optimization showed that an average of 40–50 spheres per cluster was ideal. Grid maps with $61 \times 61 \times 61$ points centered on the binding site with a grid point spacing of 0.375 were computed. Prior to docking, parameters for aryl sulfonamides were added in the flex.defn and flex_drive.tbl files used to generate preferred torsion values during the conformational search. The overview of the X-ray structures of sulfonamides showed that preferred torsion values for the dihedral angle C_{ar}-C_{ar}-S(O_2)-N were roughly 90 and -90. (flex.defn: name sulfone-arom, drive_id 64, minimize 0, definition S (2 O [*]) C.ar; flex_drive.tbl: drive_id 64, positions 2, torsions -90 90). During the docking runs, the ligand flexibility was alternatively considered by multiple anchor docking (with an anchor size of 3 atoms) or simultaneous search using 'torsion drive' in both cases. Minimization of the torsions and ligand were concurrently performed. We also looked at multiple orientations using alternatively site point directed automated matching or random search, and up to 1000 orientations were produced. Inter- and intramolecular scores were computed after bump filtering. The adjustement of the docked conformers was refined by 250 minimization steps with optimized initial translation, rotation and torsion values corresponding to 2 Å, 0.2 unit and 20°, respectively. Finally, the resulting conformers were ranked according to the energy scores, and the RMSD (Root Mean Square Deviation) relative to the crystal structure was measured.

AutoDock 3.0: AutoDock was used with the Lamarckian genetic algorithm as search method. Initial attempts with simulated annealing showed the inefficiency of this method of conformational search for flexible ligands. The macromolecules and the ligands were prepared following the original publication protocols [47]. The energy scoring grid size and spacing were identical to the ones used with DOCK ($61 \times 61 \times 61$, 0.375) including solvation parameters in the scoring function. The initial population was constituted by 100 random individuals. Step sizes of 1 Å for translation and 50° for rotation were chosen and a maximum number of 600 000 to 1 700 000 energy evaluations (100 000 per torsion) and 27 000 generations was considered. The mutation, crossover and elitism default parameters were kept. The pseudo-

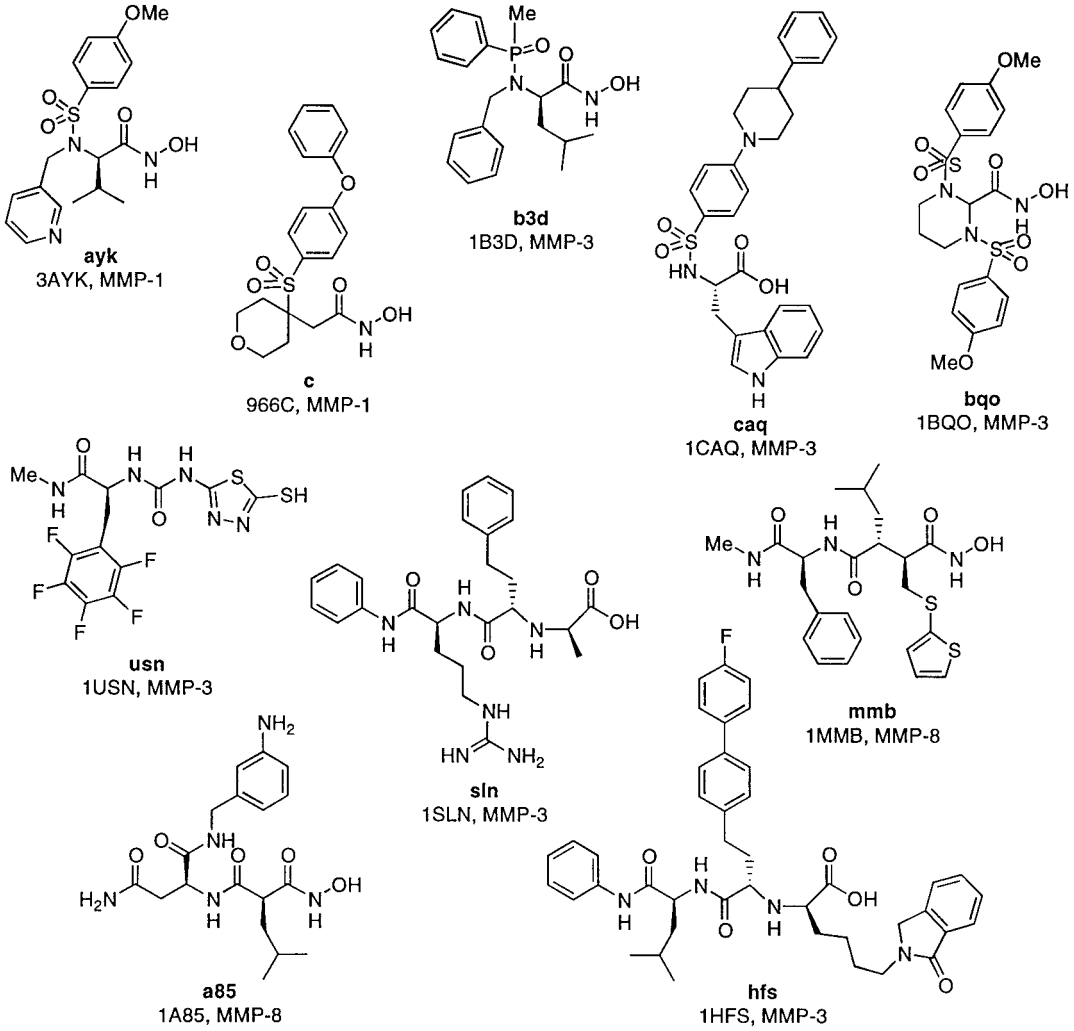

Figure 2. Selected inhibitors for the comparative docking study with PDB codes for MMP-inhibitor crystal structures.

Solis and Wets local search method was included with the default parameters. Three sets of ten runs were performed on each system and the results compared.

Results and discussion

Available X-ray and NMR data and GRID mapping

The crystal structures of six MMPs were superposed and only slight deviations were observed in their ribbon diagrams. Inspite of mutations of specific amino acid residues in the active sites of the MMPs, their relative positions were found to be very similar. Figure 3a and Table 1 clearly show this similarity as well as the relevant mutations.

The composite picture of inhibitor binding sites of six relevant MMPs shown in Figure 3a is useful for the design of new potentially selective inhibitors. Closer scrutiny shows that probing S_1' would be useful for providing selective inhibitors for MMP-2, MMP-3, MMP-8 and MMP-13 versus MMP-1 and MMP-9. For instance, the arginine side-chain in MMP-1 shortens the long narrow pocket formed in MMP-3. In fact, this property has already been exploited in connection with docking studies to effectively afford selective inhibitors by elongating the P_1' subsite [74, 75]. Less probed, the S_1 pocket in different MMPs can be more hydrophobic due to several combinations of Tyr/Phe, or less hydrophobic as when Ser/Phe are present (Table 1).

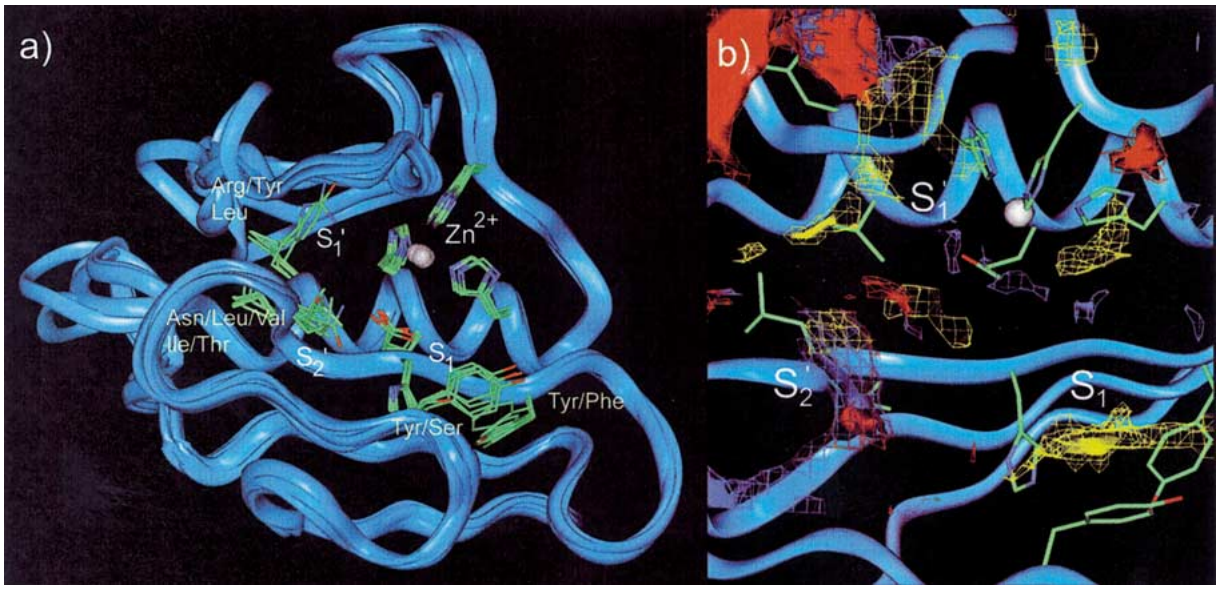

Figure 3. (a) Superposition of MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-13. (b) GRID mapping of the catalytic site of MMP-3, represented by a ribbon diagram, catalytic zinc atom shown as a gray ball and the relevant side-chains as sticks. Isosurfaces for hydrophobic probe (yellow), sulfonamide oxygen (red), amide NH (blue).

Table 1. Relevant side chain mutations.

Pocket	MMP-1	MMP-2	MMP-3	MMP-8	MMP-9	MMP-13
S_1	Ser^{172}/Phe^{185}	Tyr^{155}/Phe^{168}	Tyr^{155}/Tyr^{168}	Ser^{151}/Phe^{164}	Tyr^{172}/Phe^{185}	Tyr^{176}/Phe^{189}
S_1'	Arg^{214}	Leu^{197}	Leu^{197}	Leu^{193}	Tyr^{214}	Leu^{218}
S_2'	Asn^{180}	Leu^{163}	Val^{163}	Ile^{159}	Thr^{180}	Leu^{184}

A GRID study of the binding site confirmed the higher hydrophobicity of the S_1 pocket in MMP-2, MMP-3, MMP-9 and MMP-13 involving Tyr/Tyr or Tyr/Phe combinations. Figure 3b illustrates this observation with MMP-3 where the most hydrophobic region of the S_1 site appeared in this pocket (yellow surface). The use of other probes in GRID, such as amide nitrogen or oxygen and sulfonamide oxygen did not provide additional relevant information.

We next embarked on a comparative study to evaluate the ability of DOCK and AutoDock to reproduce the conformation and binding mode of a given inhibitor, as in its original co-crystal structure with different MMPs. For each of the ten structures (Figure 2), the inhibitor (ligand) was removed from the binding site, then docked back into the enzyme using DOCK and AutoDock separately. The conformation and functional group orientations of the resulting docked structures were compared to the original enzyme-inhibitor complex structure.

DOCK

'Simultaneous search' and 'multiple anchor' methods are implemented in DOCK to handle the flexibility of the ligands. Docking methods such as 'automated matching' and 'random search' are also available. Initial attempts to obtain good results from a 'simultaneous search' method were not successful. Five of the ten inhibitors led to RMSDs above 6 Å compared to the crystallographic structures. In contrast, the 'multiple anchor' method that considers the ligands as a series of fragments was more successful. The reproducibility of the two docking methods was confirmed by executing triplicate runs for each. Table 2 summarizes the RMSD and energy values for the docked structures using 'automated matching' (columns 2–4) and 'random search' (columns 5–7). Ideally, the smallest RMSD as found by the program and used to create the superposed structures in Figure 4, would approximate the parameters from the X-ray bound structure.

Table 2. RMSD and energies from docking study with DOCK compared to X-ray structures.

Compound	RMSD, Å and energy score (kcal mol^{-1})					
	Automated matching			Random search		
b3d	1.24	1.30	1.22	0.77	0.53	1.22
	(−25.4)	(−22.5)	(−24.0)	(−24.2)	(−17.4)	(−21.9)
c	0.66	0.62	5.81	8.21	7.72	8.76
	(−32.9)	(−39.2)	(−26.6)	(−28.8)	(−28.2)	(−26.5)
a85	4.49	6.46	4.61	6.54	6.49	4.61
	(−36.0)	(−38.4)	(−36.7)	(−38.6)	(−36.1)	(−33.8)
bqo	10.30	7.29	12.8	9.32	7.36	9.02
	(−37.2)	(−40.7)	(−38.6)	(−46.3)	(−46.6)	(−45.4)
caq	1.10	0.68	2.10	1.63	1.25	1.51
	(−46.6)	(−49.6)	(−46.3)	(−46.3)	(−47.0)	(−47.5)
Ayk[a]	1.97	2.10	2.17	2.11	2.19	2.12
	(−37.8)	(−33.9)	(−39.4)	(−36.7)	(−37.3)	(−40.2)
mmb	6.02	3.12	2.76	6.48	2.96	3.11
	(−26.4)	(−27.1)	(−26.2)	(−26.6)	(−25.4)	(−25.7)
sln	6.74	7.09	1.72	9.67	1.78	1.47
	(−40.8)	(−38.4)	(−39.3)	(−42.3)	(−41.0)	(−39.3)
usn	0.74	2.29	1.58	1.50	2.18	1.60
	(−35.7)	(−31.9)	(−33.7)	(−33.2)	(−35.2)	(−32.5)
hfs	2.51	1.86	0.95	3.62	10.12	2.54
	(−35.2)	(−35.2)	(−41.2)	(−34.3)	(−33.5)	(−42.9)

[a]NMR structure.

Only the two lowest RMSD values were considered for each structure.

DOCK predicted the binding mode of six of the ten inhibitors as seen in the good congruence of docked and X-ray crystal structures for **b3d, c, ayk, usn, caq** and **hfs** (Figure 4, panels a–d, f, j). In these cases the RMSDs from the X-ray structures were reasonable ($\sim$ 1–2 Å) although the value for the energies given by 'automated matching' and 'random search' were different sometimes. This may be due to the low convergence of the method using anchoring and subsequent reconstruction of the ligand, as well as inadequate prediction of zinc chelation by modeling. Docked structures of **mmb** presented high RMSDs, but the main chain was in the correct orientation and conformation compared to the X-ray structure (Figure 4, panel e). DOCK failed to reproduce the chelation of the hydroxamic acid in **a85** to the zinc cation, and proposed a reverse mode of binding (RMSD $>$ 6 Å, Table 2 and Figure 4, panel g). DOCK was also unable to handle **bqo** and **sln**, showing significant differences in RMSD values compared to the X-ray structure (Figure 4, panels i, h). Finally, the ability of DOCK to predict the binding mode of **hfs**, with the highest number of degrees of freedom of the side-chains compared to the other ligands using the automated matching method proved to be surprisingly good.

AutoDock 3.0

We next tested the ability of AutoDock to match the X-ray crystal structures of the same ten inhibitors discussed above (Figure 2). Using the simulated annealing approach, AutoDock was unable to handle the flexibility of the test inhibitors. Neither large number of steps nor high temperature succeeded in attaining the desired levels of convergence. This is not unexpected since AutoDock recommends 10 deg of freedom or less.

We then turned our attention to the genetic algorithm approach known to be faster and more efficient. AutoDock, whose upper limit is six atom types could not handle usn due to the presence of seven atom types. The other nine systems were computed with the Lamarckian genetic algorithm search method. Ten runs were separately performed on each system and these sets were iterated three times to evaluate their reproducibility. The analysis of the data was performed

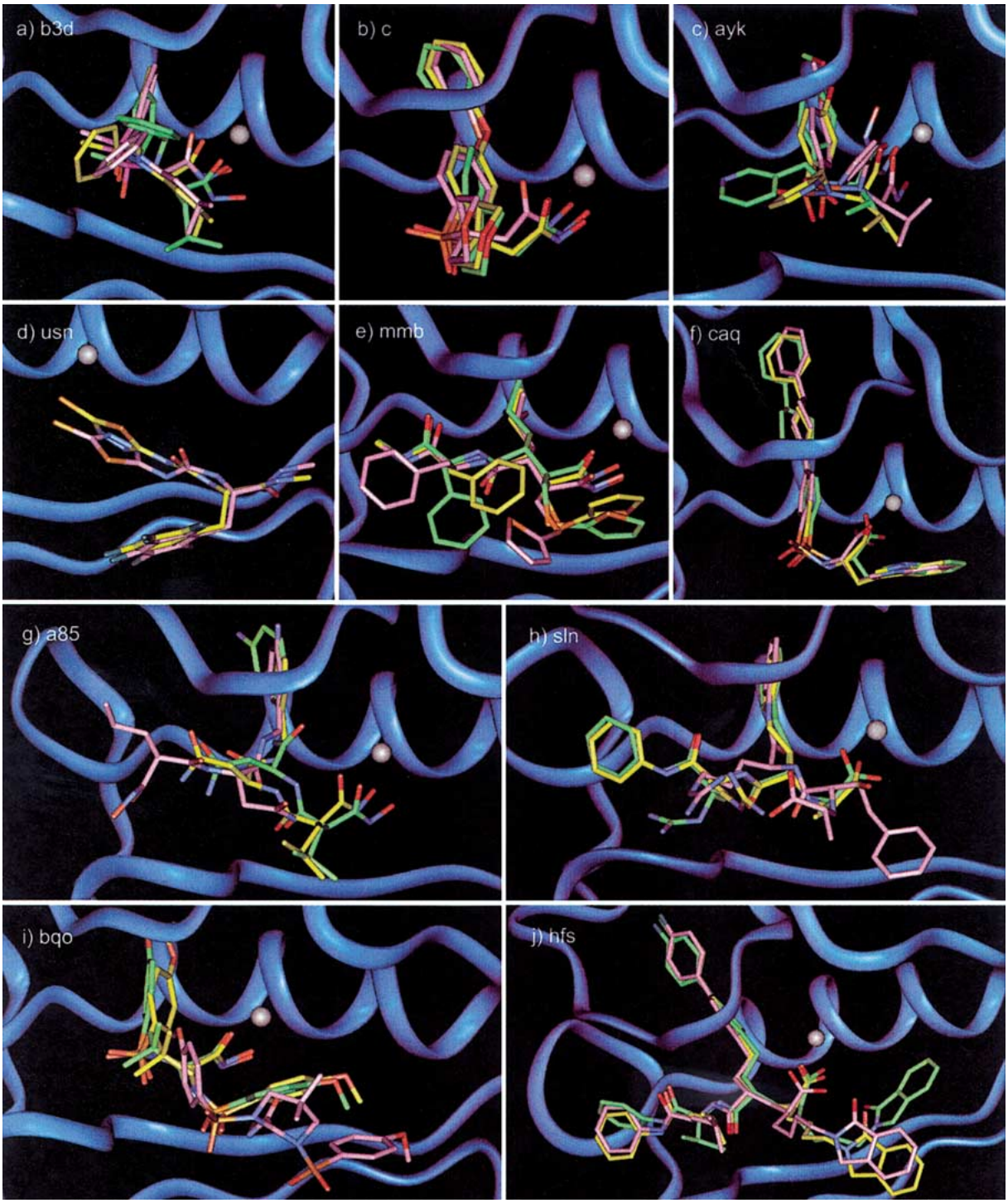

Figure 4. MMP/inhibitor complexes: crystallographic structure (yellow), proposed docked structures by AutoDock (green) and DOCK (pink); AutoDock structure is not shown for **usn** (panel d).

Table 3. RMSD and energy values from docking study with AutoDock.

Compound	RMSD, Å (energy score, kcal mol^{-1})		
b3d	1.38	0.83	0.90
	(−11.2)	(−11.2)	(−10.9)
c	0.70	0.55	0.64
	(−2.7)	(−2.6)	(−2.7)
a85	1.14	1.37	1.94
	(−13.8)	(−14.2)	(−13.9)
bqo	0.78	1.19	0.97
	(+3.6)	(+4.0)	(+3.7)
caq	0.64	0.73	2.47
	(−10.5)	(−10.6)	(−10.5)
ayk	2.93	2.12	1.80
	(−6.0)	(−6.1)	(−5.8)
mmb	1.04	1.02	1.39
	(−12.7)	(−12.8)	(−12.7)
sln	1.51	1.68	1.65
	(−15.1)	(−15.2)	(−15.1)
usn	–	–	–
hfs	1.10	1.88	1.65
	(−17.9)	(−18.0)	(−18.3)

by evaluation of the RMSD and visual comparison of the obtained coordinates relative to the crystallographic coordinates used as reference. Table 3 lists the RMSD of the best of each set. It is worthy to note that whatever the system, all three docked energies are in the same range. Moreover, the third set did not add more information, thus indicating that the convergence conditions were indeed attained.

Most of the proposed binding modes were associated with a RMSD lower than 2 Å (81%), with more than a fourth of these being below 1 Å compared to the X-ray structure (Figure 4). Even with a high RMSD for **ayk** and **a85**, they were docked in the correct orientation (Figure 4, panels c, g). The expected interaction of **hfs** in the S_1 pocket was reproduced only once while the bicyclic side-chain of **caq** showed a slightly different torsion angle in one set (Figure 4, panels j, f). These results reflect the efficiency of the scoring function in AutoDock to reliably predict the binding modes of metalloproteinase inhibitors. Although AutoDock did not consider geometric coordinates around the zinc atom, interaction either by a hydroxamic acid or a carboxylic acid was nevertheless reproduced in the bound ligands.

Conclusion

This study was instigated by the desire to design and predict the binding conformations of MMP inhibitors without extensive synthetic efforts such in the preparation of large libraries. We embarked on a modeling study starting with the survey of the existing structural information and GRID studies of the binding site of such enzymes as a prelude for a systematic docking program. In order to validate the reliability of such dockings, we undertook a comparative study of fully automated docking programs such as DOCK and AutoDock for ten known MMP inhibitors whose X-ray crystal structures with different enzymes were known. AutoDock proved to be reliable, efficient and accurate in predicting binding modes that closely approximated the conformations observed in X-ray co-crystals of MMPs with nine of the ten selected inhibitors. Based on these results, we have successfully designed a series of MMP inhibitors in which the interactions of P_1 substituents with the S_1 site were explored to greater advantage. Results pertaining for these studies will be published elsewhere [63, 66].

Acknowledgements

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