Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 2307–2315
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Mini-review

Ligand binding to nucleic acids and proteins: Does selectivity increase with strength?

Hans-Jörg Schneider*

FR Organische Chemie, Universität des Saarlandes, D 66041 Saarbrücken, Germany

Received 17 November 2007; received in revised form 30 January 2008; accepted 8 February 2008
Available online 29 February 2008

Abstract

The possible relation of strength and selectivity of ligand binding to biomacromolecules and its theoretical limitation is discussed and illustrated with some examples. It is shown that a linear correlation between selectivity and affinity may be expected on the basis of thermodynamic principles, which also imply that multivalency is as important for selectivity as for affinity enhancement. That strictly linear correlations are often not observed is, apart form statistical problems, mostly due to interactions which may remain constant only at some sites but can differ significantly at other sites, which, e.g., dominate the affinity. Nevertheless, some drugs exhibit in line with theory at the same time a peak affinity and selectivity, such as etonitazene with different opioid receptors. Double-stranded nucleic acids feature relative stable and uniform structures and therefore show relatively good correlations with simple polyamines as ligands and RNA or DNA model receptors. Metalloproteins possess strong binding centers with additional discrimination sites, and can exhibit linear correlations, at least with structurally related metalloproteinases and their inhibitors.

Keywords: Drug interactions; Proteins; Nucleic acids; Selectivity; Affinity correlations; Molecular recognition

1. Introduction

Complex formation by intermolecular interactions is the basis of most biological functions. Strength and selectivity of such supramolecular complexations are therefore of paramount importance in life and medical sciences. Efficient ligands with non-covalent interactions require high affinity as well as high selectivity, both in synthetic host–guest complexes and in natural systems. Although drug action is not simply ruled by optimization of receptor occupancy [1] all available models rely on high and selective binding between drug and receptor. The question to which degree binding strength and selectivity correlate with each other is of obvious significance in synthetic supramolecular as well as in biological or pharmaceutical chemistry [2], but has only recently been reviewed for relatively simple host–guest complexes [3]. Affinity together with selectivity data in particular of drug receptor complexes is used as valuable basis for QSAR approaches, but little attention has been paid until now to their possible interdependence. As will be seen one rarely finds quantitative linear correlations between the two parameters. A recent principal component analysis (PCA) of many inhibitor affinity data with two metalloproteins has for instance revealed families with strong and selective as well as unselective complexations and *vice versa* [4]. Force field interaction energies (GRID), knowledge-based statistical potentials (DrugScore), and PCA analysis can on the basis of many, mostly X-ray derived structures reveal important insight into the specificity requirements of, e.g., matrix metalloproteinases (MMPs) [5]. Other promising approaches towards selectivity prediction rely not on structures of the biological targets but on patterns of chemical similarity between many ligands [6]. The present review aims to illustrate with some representative biopolymer associations how far affinity–selectivity correlations can hold, which recently [3] were analysed for low molecular weight supramolecular complexes.

* Tel.: +49 682 302 3209.
E-mail address: ch12hs@rz.uni-sb.de

0223-5234/$ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.02.011

2. Some fundamental aspects

Emil Fischer's lock and key model requires an optimal geometric fit between effector and receptor molecules, which we will basically assume to be given in the following discussion although mismatch may actually contribute to selectivity. An optimal geometric fit – which can of course optimize by an induced fit, although at the expense of some additional strains – will usually result in an optimal number n of interactions between acceptor and donor functions of host and guest. Theoretically one can then expect that indeed both affinity and selectivity of a receptor R with either ligand i or ligand j will increase to the same degree; this follows quantitatively from the equations describing changes in free energy of complexation:

$$K_{\mathrm{Ri}}/K_{\mathrm{Rj}} = \exp\left[\left(\Delta G_{\mathrm{Ri}} - \Delta G_{\mathrm{Rj}}\right)/RT\right] \quad (1)$$

Biological receptors and most synthetic host compounds use a number n of interactions; this chelate effect leads to correspondingly enhanced affinity $\Delta G_{\mathrm{total}}$, which usually can be described by adding the single binding increments $\Delta\Delta G$. With $\Delta G_{\mathrm{total}} = n\Delta\Delta G_{\mathrm{n}}$ one obtains

$$K_{\mathrm{Ri}}/K_{\mathrm{Rj}} = \exp\left[n\left(\Delta\Delta G_{\mathrm{j}} - \Delta\Delta G_{\mathrm{i}}\right)/RT\right] \quad (2)$$

This characterizes how the presence of multiple binding sites (the chelate effect) not only enhances affinity but also selectivity in supramolecular complexes. Hence, if there is only one kind of interaction, such as in complexation of spherical guest compounds (halides, metal ions, etc.) one expects linear correlations between total binding strength and selectivity, which indeed is observed (cf. Fig. 1).

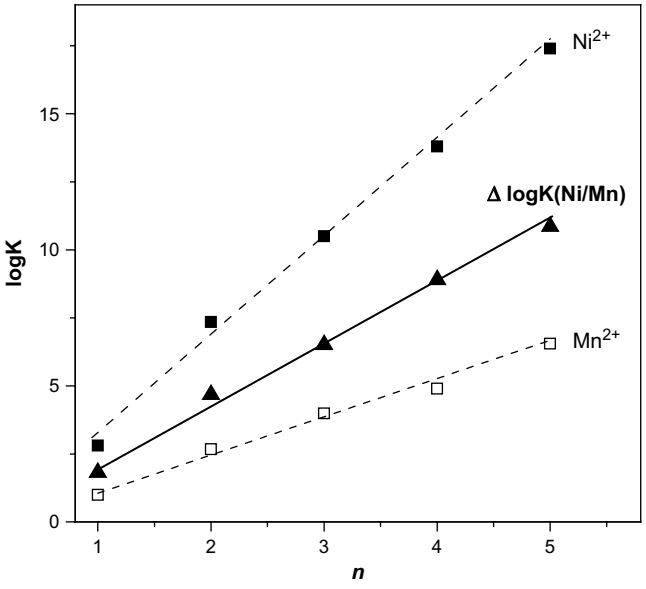


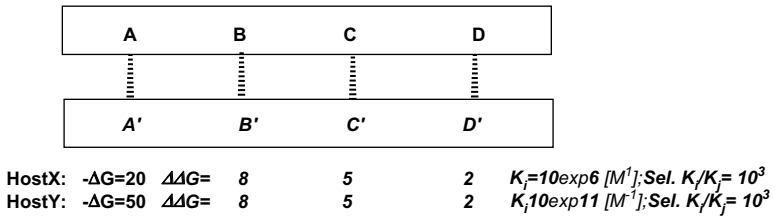
Fig. 1. Logarithms of stability constants of Mn^{2+} and Ni^{2+} complexes with linear polyamine ligands $H_2N(CH_2CH_2NH)_{n-1}H$ as a function of total number n of nitrogen donor atoms. As n increases from 1 to 5 the selectivity of binding of Ni^{2+} over Mn^{2+} increases in terms of $K_{\mathrm{Ni}}/K_{\mathrm{Mn}}$ by nine orders of magnitude [3]. Reprinted with permission from Royal Society of Chemistry.

3. Limitations of linear selectivity–affinity correlations in complexes with biological macromolecules

If all binding sites in a biomacromolecule complex contribute to selectivity and affinity to the same degree one could expect linear correlations as in Fig. 1. The usual situation in biological complexes, however, is that interactions of different nature and strength contribute, often at one binding site A, which can, e.g., dominate the affinity, and at further binding sites B, C, D, etc. which may control selectivity. Scheme 1 illustrates how two complexes may differ by a factor of, e.g., 10 exp 5 in strength, but will retain the same selectivity between guest molecules i and j as long as the secondary discriminating interactions at the sites B, C, D, etc. remain constant. Only if single contributions, such as ΔG_{A} remain the same in, e.g., two complexes: **X** and **Y** we can expect a linear selectivity–affinity correlation to hold. In many cases, however, the primary interaction ΔG_{A} can change with the occupation of the second binding sites, which is the major reason why complexes with natural, strongly anisotropic substrates will often not exhibit a simultaneous increase or decrease of binding selectivity and affinity. It can even happen that the discrimination factors ΔG_{B}, ΔG_{C}, ΔG_{D}, etc., including geometric mismatch, can actually counteract the primary binding contribution ΔG_{A}, with the consequence of an increased selectivity with decreasing total complexation free energy. Obviously, the requirement of a constant, affinity-dominating contribution ΔG_{A} is only met in complexes with structurally related receptors; on the other hand, discrimination between those targets is of particular interest for practical applications. The total free energy ΔG_{t} involved in associations with efficient ligands, such as inhibitors usually amounts to values, which exceeds the differences necessary for a selectivity ratio of, e.g., $K_{\mathrm{Ri}}/K_{\mathrm{Rj}} = 100$ by orders of magnitude, as will be exemplified below with some metalloproteinase inhibitors. As consequence even percentage-wise minor alterations of ΔG_{A} at the affinity-dominating site can have the same impact on selectivity as relatively larger changes at the weaker discrimination sites, thus making strictly linear correlations between ΔG_{t} and $\Delta\Delta G$ again less likely.

It should be stressed that the rules derived above from fundamental principles hold independent of the nature of participating non-covalent interactions, notwithstanding that, e.g., hydrogen bonds usually provide for higher selectivity than, e.g., salt bridges. It can happen that a perfect interaction at a single discrimination site may lead to larger selectivity than less discriminating interactions at multiple sites. Nevertheless, an increased ligand size will usually provide for more interactions and hence, in line with Eq. (2), to higher selectivity. For enzyme–substrate complexes specificity is defined by substrate competition, measured by the value of $k_{\mathrm{cat}}/K_{\mathrm{m}}$, and thus evades a simplified thermodynamic analysis as given above for reversible complexations.

In a first approach one will check if there is a correlation between binding free energies (or $\log K$ values) of several ligands with a receptor **X** or **Y**; if there is a fairly linear correlation one can conclude that a similar binding mechanism



Scheme 1. Schematic illustration of complexes with same selectivity but different affinities: the discriminating binding free energy difference $\Delta\Delta G$ between to guest molecules i and j with two host molecules **X** and **Y** is the same; only the primary interaction ΔG differ (all ΔG values in kJ/mol).

with both **X** and **Y** prevails. One can hope then to see a linear selectivity–affinity log K_x *vs.* log K_y correlation; for the slope $m = 1$ the sensitivity of the ligands of course is the same in all complexes. Unfortunately, if the sensitivity is very different, and the selectivity therefore high, the slope is small, and the quality of the correlation will decrease solely due to statistical reasons. Another problem is that the available experimental data are often not well-defined association constants, but, e.g., IC_{50} values; then one has to use data taken under the same conditions, such as concentration. In view of the limitations it will be rarely possible to obtain linear selectivity–affinity correlations in biological complexes; instead one can try to just find examples were the principle of parallel decreased or increased binding strength and selectivity holds.

4. Associations with nucleic acids

Selective binding of natural or synthetic ligands to nucleic acids is of great medicinal importance, not only for, e.g., tumor therapy but also for selective modulation of gene expression as a promising future alternative to targeting proteins which stem from aberrant gene transcription [7]. Compared to the structural diversity of proteins nucleic acids exhibits relatively uniform binding characteristics which could lead to more transparent correlations between affinity and selectivity, particular if there is a uniform binding mechanisms. Association of polyamines with double-stranded DNA is essentially due to ion pairing with the phosphates. Fig. 2 illustrates that as consequence there is a relatively linear correlation for the selectivity between DNA and RNA-like polymers, with poly-A·polyU as RNA and poly(dA)·poly(dT) as DNA model. The preference of RNA over DNA is due to a deeper RNA groove with higher negative charge density [8]. In line with this, a simple synthetic hexamine (“TAL”) has recently been shown to exhibit the largest known discrimination between RNA and DNA-like double-strands [9]. The particular high charge density in this ligand makes it so efficient that it lies above the correlation line of other amines and surpasses significantly the selectivity of the most discriminating natural antibiotic.

Many natural antibiotics, such as the minor groove binders' neomycin, gentamycin, kanamycin, streptomycin and spectinomycin bind much better to RNA than to DNA [8]. The melting points with RNA increase regularly with the number n of basic nitrogen functions, with $\Delta T = 7\ ^\circ C$ for $n = 3$ to $\Delta T = 33\ ^\circ C$ for $n = 6$ (measured with a ligand to polymer ratio of $r = 0.3$ in MES buffer with 0.1 M NaCl), in line with Fig. 1 [10]. The DNA polymer, however, shows almost no binding (negligibly small $\Delta T < 1\ ^\circ C$), remarkably *independent* of the total affinity. One complication is that the particular location of the $NH_2/NH_3^+/OH$ groups within aminoglycosides can also modulate their RNA binding properties by affecting the conformational preferences and flexibility of these drugs [11].

Complexes of five well known *minor groove binders* (Hoechst33258, Hoechst33342, DAPI, netropsin, berenil) with different 12mer-duplexes' sequences [12] also show no linear correlation; e.g., the binding constant ratio K_A/K_B for a duplex with *dAdAdAdA* to a *dAdTdAdT* repeat units is for the strongest complexes with the Hoechst33258 ligand (with *dAdAdAdA* duplex $K_A = 1.2 \times 10^7$) $K_A/K_B = 2.4$; for Hoechst33342 one observed $K_A = 6.6 \times 10^6$ and $K_A/K_B = 3.7$, with berenil ($K_A = 2.1 \times 10^5$) the ratio is with $K_A/K_B = 0.32$ even reversed. Similarly, binding constant ratios K_A/K_B for a *5′-dAdAdAdA-3′* to a *5′-dAdTdAdT-3′* duplex are for distamycin $K_A/K_B = 4.4$ ($K_A = 1.7 \times 10^7$), whereas for the stronger complex with netropsin ($K_A = 35 \times 10^7$) the ratio is reversed ($K_A/K_B = 0.28$) [13]. The investigation of DNA

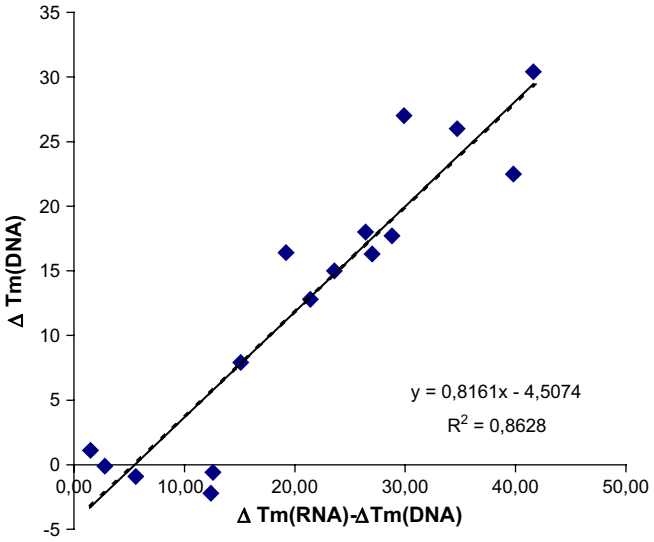


Fig. 2. Selectivity of polyamine binding to DNA/RNA as function of affinity towards RNA; measured as melting point changes ΔT with polyU·polyA as RNA, and poly(dA)·poly(dT) as DNA model, correlation coefficient $R^2 = 0.8628$ [3].

interactions with diphenylfuran dications has shown that the binding mode for unfused aromatic cations can change completely depending on substituent position and DNA sequence [14]. Similar observations emerge from studies with 4,4′-bispiperidine and related derivatives [10], which show preference for polyA·polyU, indeed increasing as theoretically expected with enhanced affinities, but a reversed preference for DNA-like polymers as soon as phenylrings are incorporated into the ligands.

Oligoamides consisting of pyrrole–imidazole combinations can bind DNA double-strand sequences in the minor groove with spectacular subnanomolar affinity and remarkable sequence selectivity (Fig. 3). Alkylation of adenine, mostly in pure A/T tracts, is brought about by the electrophilic cyclopropyl residues of the ligands [15]. Most recently hairpins containing base selective heterocycles, such as hydroxybenzimidazole and oxazole, and/or chlorothiophene rings were shown by DNase footprinting to reach affinities approaching 10^{-10} M [16]. The remarkable sequence selectivities which can be reached with peptide nucleic acids (PNAs) [17], partially also with amide-type ligands [8] can only be mentioned here.

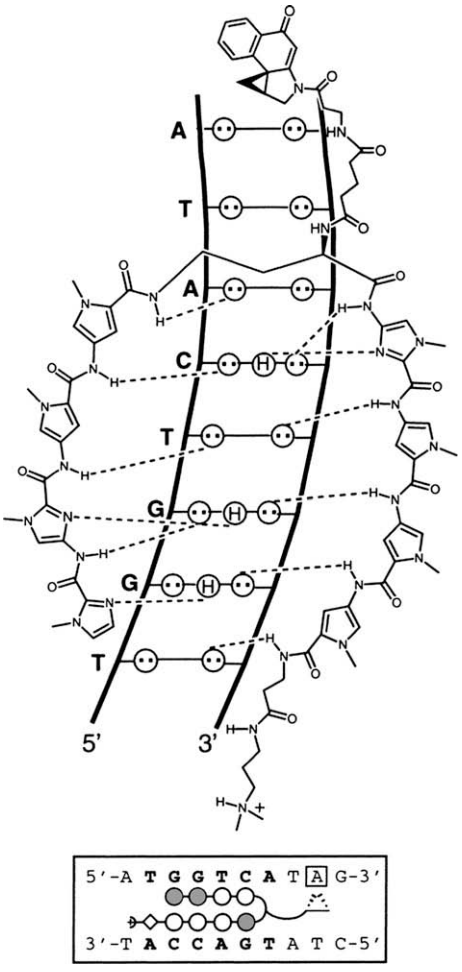
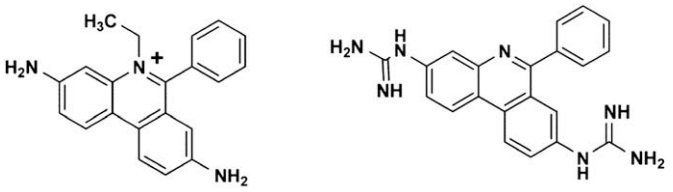


Fig. 3. Hairpins of pyrrole–imidazole combinations binding selectively to ds-DNA with subnanomolar affinity. Reprinted with permission from Ref. [15]. Copyright (2000) American Chemical Society.

Macrocyclic polyamines exhibit either rather distinct preference for RNA or DNA models, depending on position of aromatic moieties within the ring system and the size of macrocycle, with no clear dependence of ΔT_m on the total affinity. It has been shown also by NMR and modeling studies that the binding mechanisms of such ligands vary from "normal" groove binding to incorporation of nucleobases which can flip out of the double helix [18]. The results demonstrate how high selectivities (favoring, e.g., DNA-over RNA polymers with $\Delta\Delta T_m = 33$ °C) can be reached by using different binding mechanisms with properly designed synthetic ligands, whereas inverse preferences of similar magnitude are observed for RNA either with natural antibiotics, or even more with simple synthetic polyamines (see Fig. 2), then with the theoretically expected correlation to the total affinity.



Intercalation into double-stranded nucleic acids [19] usually is dominated by stacking forces which essentially depend on the size of aromatic surfaces, and thus is not very selective with respect to the nature of the nucleobases or aromatic ligands. Most classical monointercalators prefer binding to DNA-like double-strands [20], with melting points ΔTm for polydA·dT ranging from 11 to 22 °C and for the RNA-type polyA·U polymer from 1 to 13 °C . There is no systematic selectivity increase with binding strength increase, e.g., the melting point differences are for mitoxanthrone $\Delta\Delta T_m = 11$ °C (ΔT_m(DNA) 23 °C), but for adriamycin $\Delta\Delta T_m = 12$ °C with ΔT_m(DNA) = only 13 °C, or for coralyne $\Delta\Delta T_m = 16$ °C with ΔT_m(DNA) = 18 °C. Few intercalators show the opposite preference for RNA-type double-strands, such as ethidium bromide (EB), with $\Delta T_m = 17$ °C for polyA·U and $\Delta T_m = 7$ for polydA·dT (all melting points at a ratio of 0.3 mol of ligand to nucleic acid bases) [20]. Small structural variations, such as an exchange of the EB amine groups for guanidinium substituents (ligand DB950) can lead to preferential interactions with the groove phosphates, and a much more pronounced, even sequence-selective minor groove binding with AT-containing double-strands [21]. This illustrates how changes in binding mode obviously render any selectivity–affinity relations even between structurally quite similar ligands impossible.

Bisintercalators can lead to somewhat enhanced selectivities, e.g., for C:G sequences [19,22]. Significantly enhanced affinity and selectivity with respect to the nucleobase sequence of the double-strand can be achieved by appending large intercalators to oligonucleotides. The intercalator then determines essentially the total affinity, and the oligonucleotide by, e.g., Hoogsteen hydrogen bonds the selectivity (Fig. 4). This is an obvious illustration of the separation between primary and secondary interactions shown in Scheme 1. A related

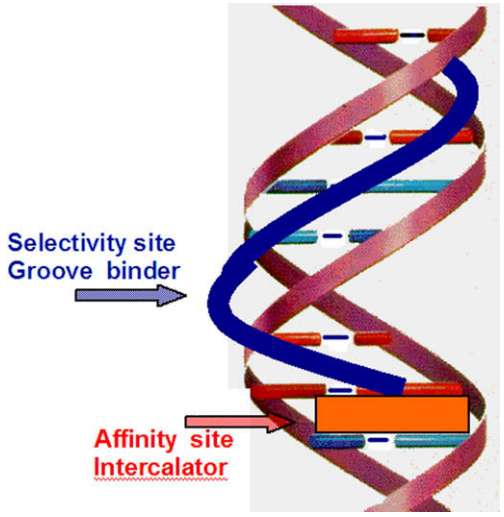


Fig. 4. Selection site (groove binding) and affinity site (intercalation) at double-stranded DNA.

approach is using unspecific polyamine binding for enhancing affinity to nucleic acids [23].

5. Protein complexes

Protein complexes are usually characterized by a multitude of interaction sites and the occupation of a single site can considerably change the binding properties of others. In consequence, linear correlations between affinity and selectivity will be rather exception than rule. As mentioned above enzymes pose particular problems with, e.g., serine protease k_{cat}/K_m depends only on the binding and acylation steps $k1$, $k-1$, and $k2$; any increase of k_{cat}/K_m stems from an increase in k_{cat} rather than from a decrease in K_m; hence specificity is primarily determined by the acylation step. Moreover, the specificity of ester hydrolysis may be dominated by substrate association in solution prior to action with the enzyme [24]. Specificity in some serine protease reactions was also ascribed to induce fit mechanisms and allosteric interactions [24]. The understanding of the structural mechanisms for the specificity of serine protease has been characterized to be still at an introductory stage [25]. In protein tyrosine phosphatases, e.g., two binding sites have been identified; specific and high-affinity bidentate inhibitors bind simultaneously to the active site and to a second adjacent site [26]. For kinases a five-point pharmacophore has been identified for the discrimination between nonselective so-called frequent hitters, which still may have <2 μM affinity and selective ligands [27]. Structural investigation of nuclear hormone receptors indicates induced conformational changes in the tertiary protein structure, which affects the ligand-specific receptor/cofactor interactions [28].

In many *metalloproteins*, interactions between the metal ion and complementary ligand parts provide high affinity, whereas selectivity is achieved by interactions of other ligand parts within neighbouring protein pockets. It has been noted that, e.g., three inhibitors of metalloproteinases (MMPs) obey the rule of increasing selectivity with affinity, but three other do not [29]; side effects of MMP in clinical trials inhibitors have been ascribed to lack of specificity [30]. MMP complexes with strong, nanomolar, inhibitors; with the specificity residing mainly in a pocket close to the catalytic Zn^{2+} ion (Fig. 5A) illustrate this situation [31]. The binding free energies with a series of related inhibitors with different substituents R_1, R_2 and R_3 (Fig. 5B) and one MMP structure have been analysed [31] on the basis of X-ray derived structures with a force field and docking program [32]; a pairwise comparison between single ligands showed semiquantitative agreement with experimental $\Delta\Delta G$ values, although sizeable entropic contributions complicate the prediction. The affinity differences between structurally related different ligands are semiquantitatively predictable; peak selectivity against different MMP proteinases is observed for the strongest ligand in some, but not all cases.

A large number of data from more than 90 metalloproteinase inhibitors have been compiled recently for a chemometrical study with respect to affinity and selectivity [4]. The best linear correlation with $R^2 = 0.966$ is observed if only seven, chemically related inhibitors are compared (Fig. 6a), with a, however, small selectivity difference, as the slope is close to one. In consequence, there is no linear correlation between the parameters for selectivity and affinity. The first 14 inhibitors of the data provided in Ref. [4], which structurally are still related, show a good correlation of $\log(1/IC_{50})$ values between the receptors MMP 3 and MMP 8 ($R^2 = 0.95$), but again almost the same sensitivity (slope = 1.1, Fig. 6b). Other inhibitors show a poor correlation of $\log(1/IC_{50})$ values between MMP 3 and MMP 8 (for all 90 compounds $R^2 = 0.835$); the sensitivity, however, is generally higher of the MMP 8 in comparison to the

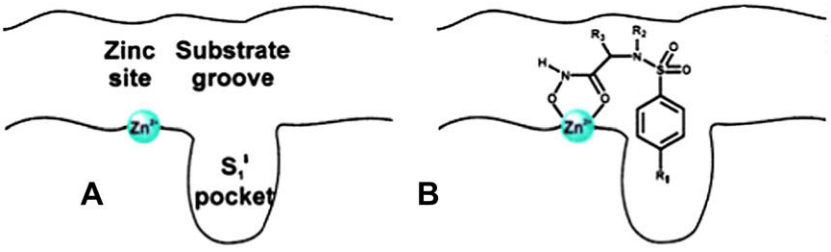


Fig. 5. Metalloproteinases (MMPs): strong binding site at Zn, discrimination at a separate selection site. Reprinted with permission from Ref. [31]. Copyright (2007) American Chemical Society.

MMP 3 receptor (slope = 0.86, Fig. 6c). As expected there is no visible linear correlation between selectivity and affinity if all 90 inhibitors are analysed indiscriminately. In spite of this nearly same sensitivity, however (slope close to one) nine of the structurally related first 14 inhibitors exhibit the theoretically expected increase of the selectivity with decreasing IC_{50} values.

6. Opioid receptors: correspondence of large affinity and selectivity

The μ, κ and δ type of opioid receptors have been studied intensively with a wide range of morphine-related drugs and peptides; in particular occupation of the δ receptor is known to lead to a manifold of other than analgesic reactions [33]. Indeed the largest selectivity of, e.g., $K_\kappa/K_\mu = 11.650$ has been found for a ligand of particularly high affinity: etonitazene, the most potent benzimidazole-type opioid currently known, exhibits a potency 1000–1500× of morphine, with $K_{i\mu} = 0.01$ or 0.02 nM, depending on presence of Na ions (Scheme 2) [34]. Peptides in particular bind to these receptors via multiple binding pockets [35], which by themselves may not differ much in their single affinity contributions. This may explain why one can barely observe here linear selectivity–affinity correlations. Naltrindole shows $K_i = 0.2$ nM and $K_\mu/K_\delta = 120$ a moderate selectivity, but some naltrindole analogs exhibit $K_\mu/K_\delta = 1900$ with a, however, larger $K_{i\delta} = 7$ nM [36]. With a series of carbamate morphinane analogs [37] a moderately linear correlation ($R^2 = 0.86$) between log $K_{i\delta}$ and log $K_{i\mu}$ can be deduced (Fig. 7); the slope as measure of relative sensitivity is with a value of 0.85 within the scatter so close to one that there is no Δlog K − selectivity correlation of ratios between the log K_i values.

7. Correlations between artificial and biological receptors

Finally, a question of interest also with respect to drug design is to which degree one could possibly draw conclusions

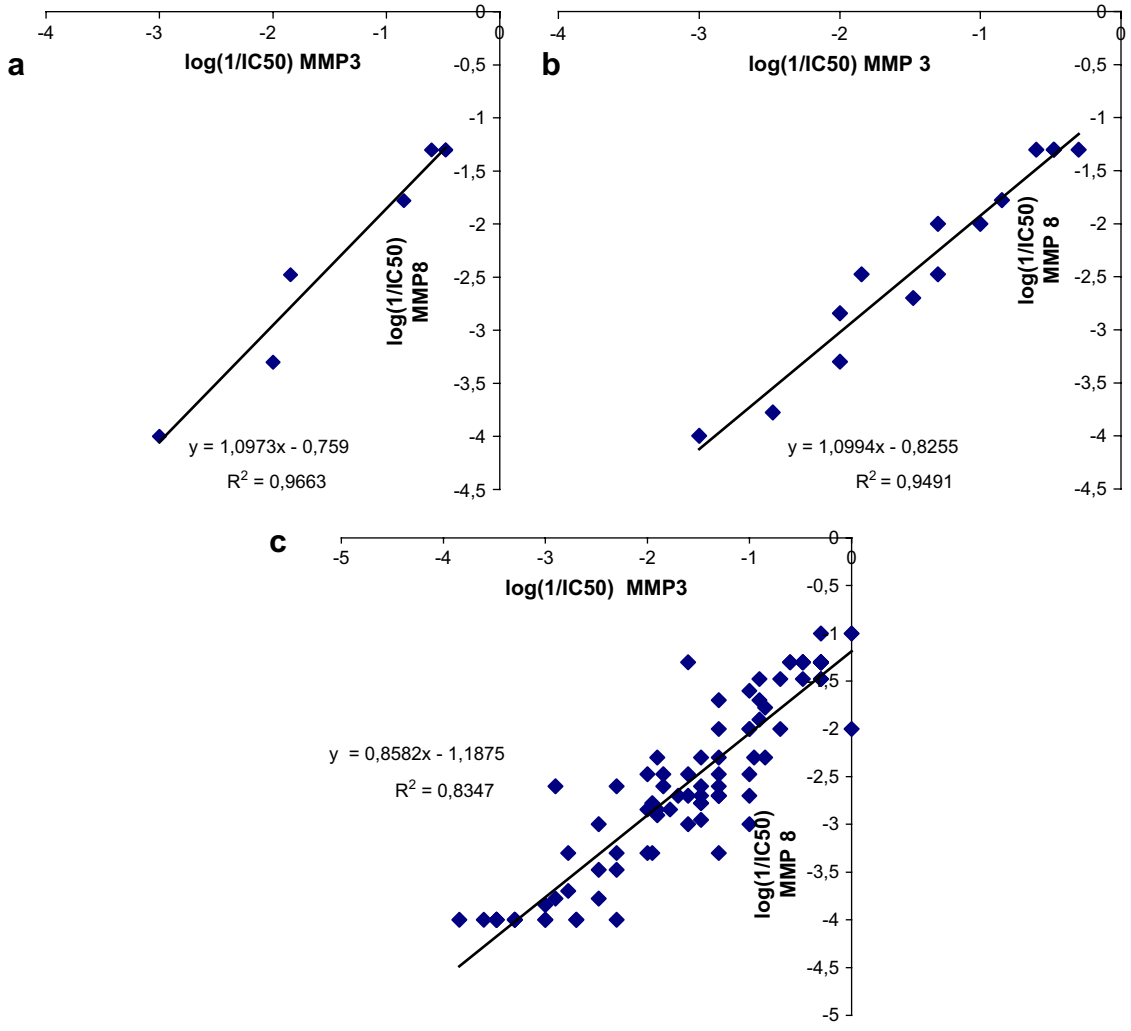
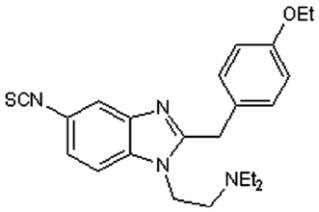
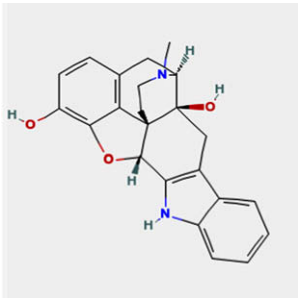


Fig. 6. Correlations with metalloproteinase inhibitors; always with log(1/IC_{50}) of ligands with metalloproteinase MMP 3 or metalloproteinase MMP 8 (data from Ref. [4]); IC_{50} values in nanomolar concentrations. Fig. 6a: log(1/IC_{50}) of MMP 8 *vs.* those with MMP 3 for the first seven structurally related inhibitors from Ref. [4]; Fig. 6b: same for the first 14 structurally related inhibitors from Ref. [4]; Fig. 6c: same for all 90 inhibitors.

Etonitazene



Naltrindole



Oxymorphindole

	K_i μ receptor	K_i κ receptor	K_i δ receptor	Selec. K_κ/K_μ	Selec. K_δ/K_μ
Etonitazene[a]	0.01 (or 0.02)	235	176	23500 (or 11650)	17600 (or 8800)
Naltrindole[b]	27	30	0.22	1.1	0.008
Oxymorphindole[b]	66	2170	0.80	33	0.012

[a]Data: Ref. [34]; K_i [nM] with rhesus monkey brain membrane receptors; K_i in presence of Na ions (with μ receptor 0.01 in absence of Na ions).
[b]Data: Ref. [36]; K_i [nM] with rat brain membrane receptors.

Scheme 2. Examples of opioid receptor ligands with particularly large affinity and selectivity.

from affinity values obtained with artificial small host compounds to those with biopolymers. Fig. 8 shows as an example [3] the affinity differences of 1-alkanols as function of the ligand chain length in comparison between the cyclodextrins as small host, and the urinary protein MUP-1 as large biological receptor [38]. Obviously, the selectivity is determined by the same hydrophobic binding mechanism, with a typical affinity increase with each additional methylene group in the alcohols. The binding constants with the protein are about 100 times higher than those with the cyclodextrins; Fig. 8 illustrates once more that in line with the theoretical prediction the selectivity is simultaneously increased, with a factor of 7 in binding constant per additional methylene group in comparison to only threefold increase with cyclodextrin.

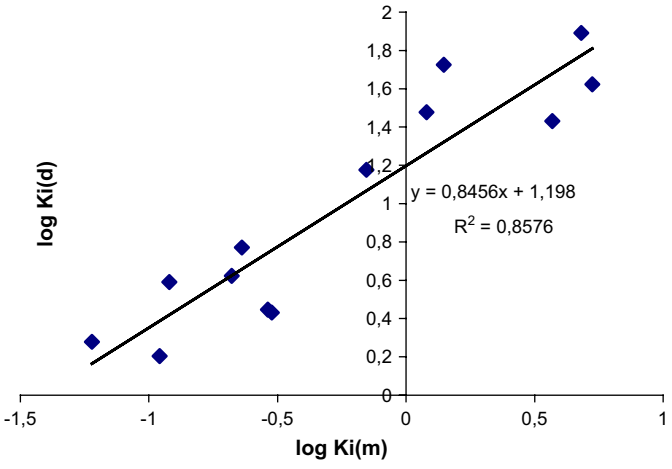


Fig. 7. Correlation between log $K_{i\delta}$ and log $K_{i\mu}$ for morphinane analogs (data from Ref. [37]).

8. Conclusions

Correlations between binding strength and selectivity can be derived on the basis of first principles, in particular as consequence of multivalency in supramolecular complexes which not only increases affinity but at the same time selectivity. In addition to the disturbances by mutual interactions between binding sites and the statistical problems mentioned above the major problem in establishing explicit quantitative linear selectivity–affinity correlations with biopolymer complexes is the usually much higher total binding free energy ΔG_{total}

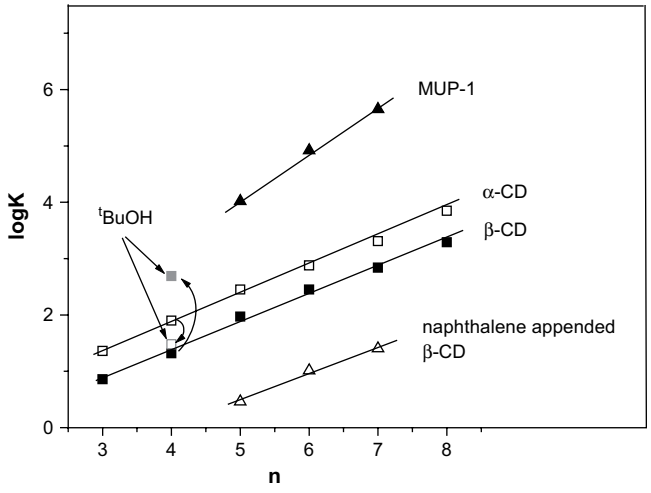


Fig. 8. Logarithms of binding constants of 1-alkanols (CH_3–$(CH_2)_{n-1}$–OH) to α- and β-cyclodextrins (open and solid squares, respectively) and to the MUP-1 protein (solid triangles), values for naphthalene appended β-CD are also shown (open triangles), as well as binding constants for *tert*-butanol. Reprinted with permission from Royal Society of Chemistry.

in comparison to the energy difference $\Delta\Delta G$ with different ligands. In particular for inhibitor complexes the total ΔG often amounts to over 50 kJ/mol, whereas $\Delta\Delta G = 10$ kJ/mol is enough to warrant already a significant selectivity ratio of $K_{iv}/K_{iy} = 100$. Thus, the maximal selectivity difference observed for just two compounds out of the abovementioned 90 high-affinity metalloproteinase inhibitors is $\Delta\log = 2.0$; with about nine inhibitors $\Delta\log$ is 1.5, for all others $\Delta\log$ is between 0.2 and 0.5. In consequence, alterations at the primary interaction site – e.g., the metal binding site – by few percent will have the same order of magnitude as the ones at the secondary binding site which determines the selectivity. Even though explicit linear correlations will be rather exception than rule, the examples given for the opioid complexes (Scheme 2) illustrate that in line with the theoretical prediction a ligand of very large *in vitro* affinity and biological activity can also exhibit a particularly high selectivity. Binding affinity correlations between complexes with small synthetic hosts and biological receptors can shed light on the underlying binding mechanisms and can be helpful for the design of more selective ligands.

Acknowledgement

Helpful discussions are acknowledged with Professor A. Yatsimirski, UNAM Mexico.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2008.02.011.

References

[1] For an brief overview on drug action theories see e.g. A. Korolkovas, Essentials of Medicinal Chemistry, second ed. Wiley, New York, 1988, p. 171.
[2] A. Fersht, Structure and Mechanism in Protein Science, W.H. Freeman & Co, New York, 1999;
W. Saenger, Principles of Nucleic Acid Structure, Springer, New York, 1988.
[3] H.-J Schneider, A. Yatsimirski, Chem. Soc. Rev. (2008) 263–277.
[4] H. Matter, W. Schwab, J. Med. Chem. 42 (1999) 4506–4523.
[5] B. Pirard, H. Matter, J. Med. Chem. 49 (2006) 51–69.
[6] M.J. Keiser, B.L. Roth, B.N. Armbruster, P. Ernsberger, J.J. Irwin, B.K. Shoichet, Nat. Biotechnol. 25 (2007) 197;
for the leadlikeness approach see e.g. M.M. Hann, T.I. Oprea Curr. Opin. Chem. Biol. 8 (2004) 255
[7] (a) M. Demeunynck, C. Bailly, W.D. Wilson, DNA and RNA Binders, Wiley-VCH, Weinheim, 2002;
(b) G.M. Blackburn, M.J. Gait, Nucleic Acids in Chemistry and Biology, Oxford University Press, Oxford, New York, Tokyo, 1990;
(c) M. Waring (Ed.), Sequence-specific DNA Binding Agents, Royal Society of Chemistry, Cambridge, 2006;
(d) J.P.G. Wakelin, Med. Res. Rev. 6 (1986) 275–340;
(e) W.C. Tse, D.L. Boger, Chem. Biol. 11 (2004) 1607;
(f) P.B. Dervan, A.T. Poulin-Kerstien, E.J. Fechter, B.S. Edelson, Top. Curr. Chem. 253 (2005) 1–31;
(g) P.B. Dervan, Bioorg. Med. Chem. 9 (2001) 2215–2235.
[8] (a) B.S. Reddy, S.K. Sharma, J.W. Lown, Curr. Med. Chem. 8 (2001) 475–508;
(b) S. Neidle, Nat. Prod. Rep. 18 (2001) 291–309.
[9] N. Lomadze, H.-J. Schneider, M.T. Albelda, E. Garcia-Espana, B. Verdejo, Org. Biomol. Chem. 4 (2006) 1755–1759.
[10] M. Ke Li, C.T. Fernandez-Saiz, A. Rigl, K.G. Kumar, A.W.C. Ragunathan, D.W. McConnaughie, H.-J. Boykin, H.-J. Schneider, W.D. Wilson, in: S. Hecht (Ed.), Strategies for RNA Recognition, Bioorg. Med. Chem. (1997) 1157–1172.
[11] F. Corzana, I. Cuesta, F. Freire, J. Revuelta, M. Torrado, A. Bastida, J. Jiménez-Barbero, J.L. Asensio, J. Am. Chem. Soc. 129 (2007) 2849–2865.
[12] Data: F. Rosu, V. Gabelica, C. Houssier, E. De Pauw Nucleic Acids Res. 30 (2002) e82.
[13] Data: D.L. Boger, B.E. Fink, S.R. Brunette, W.C. Tse, M.P. Hedrick J. Am. Chem. Soc. 123 (2001) 5878–5891 and references cited therein.
[14] B. Nguyen, C. Tardy, C. Bailly, P. Colson, C. Houssier, A. Kumar, D.W. Boykin, W.D. Wilson, Biopolymers 63 (2002) 281–297.
[15] Ref. [7e] and A.Y. Chang, P.B. Dervan, J. Am. Chem. Soc. 122 (2000) 4856–4864;
P.B. Dervan, A.T. Poulin-Kerstien, E.J. Fechter, B.S. Edelson, DNA Binders and Related Subjects, vol. 253, 2005, p. 1 ff; P.B. Dervan, B.S. Edelson, Curr. Opin. Struct. Biol. 13 (2003) 284–299.
[16] M.R.M. Doss, M.A. Marques, S. Foister, D.M. Chenoweth, P.B. Dervan, J. Am. Chem. Soc. 128 (2006) 9074–9079.
[17] P.E. Nielsen, Acc. Chem. Res. 32 (1999) 624;
P.E. Nielsen, Mol. Biotechnol. 26 (2004) 233;
P.E. Nielsen, Drug–Nucleic Acid Interactions, vol. 340, 2001, p. 329;
A. Porcheddu, G. Giacomelli, Curr. Med. Chem. 12 (2005) 2561;
V.A. Kumar, K.N. Ganesh, Acc. Chem. Res. 38 (2005) 404.E. Uhlmann, Biol. Chem. 379 (1998) 1045;
Z.V. Zhilina, A.J. Ziemba, S.W. Ebbinghaus, Curr. Top. Med. Chem. 5 (2005) 1119.
[18] (a) M. Fernandez-Saiz, H.-J. Schneider, J. Sartorius, W.D. Wilson, J. Am. Chem. Soc. 118 (1996) 4739–4745;
(b) M. Fernandez-Saiz, F. Werner, T.M. Davis, H.-J. Schneider, W.D. Wilson, Eur. J. Org. Chem. (2002) 1077–1084.
[19] L.P. Wakelin, M.J. Waring, in: C. Hansch (Ed.), Comprehensive Medicinal Chemistry, Elsevier, New York, 1990, pp. 703–724;
W.D. Wilson, in: K. Nakanishi, D. Barton (Eds.), Comprehensive Natural Products Chemistry, Elsevier, New York, 1999, pp. 427–476.
[20] W.D. Wilson, L. Ratmeyer, M. Zhao, L. Strekowski, D. Boykin, Biochemistry 32 (1993) 4098–4104.
[21] C. Bailly, R.K. Arafa, F.A. Tanious, W. Laine, C. Tardy, A. Lansiaux, P. Colson, D.W. Boykin, W.D. Wilson, Biochemistry 44 (2005) 1941–1952.
[22] S. Dawson, J.P. Malkinson, D. Paumier, M. Searcey, Nat. Prod. Rep. 24 (2007) 109–126.
[23] P.M. Cullis, L. Merson-Davies, M.J. Sutcliffe, R. Weaver, Chem. Commun. (1998) 1699–1700;
P.M. Cullis, L. Merson-Davies, R. Weaver, J. Am. Chem. Soc. 117 (1995) 8033–8034.
[24] L. Hedstrom, Chem. Rev. 102 (2002) 4501–4523;
see also A. Vindigni, Comb. Chem. High Throughput Screen. 2 (1999) 139.
[25] H. Czapinska, J. Otlewski, Eur. J. Biochem. 260 (1999) 571–595.
[26] Z.-Y. Zhang, Annu. Rev. Pharmacol. Toxicol. 42 (2002) 209–234.
[27] A.M. Aronov, M.A. Murcko, J. Med. Chem. 47 (2004) 5616–5619.
[28] R. Kumar, E.B. Thompson, Steroids 64 (1999) 310–319;
recent review: J.B. Biggins, J.T. Koh Curr. Opin. Chem. Biol. 11 (2007) 99.
[29] N. Borkakoti, J. Mol. Med. 78 (2000) 261–268.
[30] L.M. Coussens, B. Fingleton, L.M. Matrisian, Science 295 (2002) 2387–2392.
[31] I. Bertini, V. Calderone, M. Fragai, A. Giachetti, M. Loconte, C. Luchinat, M. Maletta, C. Nativi, K.J. Yeo, J. Am. Chem. Soc. 127 (2007) 2466–2475.
[32] G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, J. Comput. Chem. 19 (1998) 1639–1662.
[33] (a) D.S. Fries, Opioid Analgesics, in: W.O. Foye, T.L. Lemke, D.A. Williams (Eds.), Principles of Medicinal Chemistry, Williams &

Wilkins, Baltimore, 1995, pp. 453–479;
(b) J.V. Aldrich, Narcotic Analgesics, in: D.J. Abraham (Ed.), Burger's Medicinal Chemistry & Drug Discovery, vol. 6, Wiley, New York, 2003, pp. 329–481;
see also D.N. Dhawan, F. Cesselin, R. Raghubir, T. Reisine, P.B. Bradley, P.S. Portoghese, M. Hamon, Pharmacol. Rev. 48 (1996) 567–592.
[34] P.J. Emmerson, M.R. Liu, J.H. Woods, F. Medzihradsky, J. Pharmacol. Exp. Ther. 271 (1994) 1630–1637.
[35] F. Meng, M.T. Hoversten, R.C. Thompson, L. Taylor, S.J. Watson, H. Akil, J. Biol. Chem. 270 (1995) 12730–12736.
[36] A. Coop, R.B. Rothman, C. Dersch, J. Partilla, F. Porreca, P. Davis, A.E. Jacobson, K.C. Rice, J. Med. Chem. 42 (1999) 1673–1679.
[37] X.M. Peng, B.I. Knapp, J.M. Bidlack, J.L. Neumeyer, Bioorg. Med. Chem. Lett. 17 (2007) 1508–1511.
[38] R. Malham, S. Johnstone, R.J. Bingham, E. Barratt, S.E.V. Phillips, C.A. Laughton, S.W. Homans, J. Am. Chem. Soc. 127 (2005) 17061–17067.