Binding interactions between 3-aryl-1,2,4-oxadiazol-5-ones and a trisimidazoline base

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The use of 1,2,4-oxadiazol-5-ones, a recently developed class of bioisosteric replacements for carboxylic acids in medicinal chemistry, as binding ligands in supramolecular complexes is reported and has been exemplified by the formation of non-covalent complexes between acidic 3-aryl-1,2,4-oxadiazol-5-ones and an imidazoline base, 1,3,5-tris(4,5-dihydroimidazol-2-yl)benzene **1**. The X-ray crystal structure of complex **6d** illustrates how the carbonyl oxygen and the nitrogen atom in the position α to the carbonyl group of the heterocyclic ligand are hydrogen-bonded to the NH groups of tris(imidazoline) **1**. A combination of ^{1}H NMR dilution studies and electrospray mass spectrometry-based competition experiments shows that 1,2,4-oxadiazol-5-ones bind more strongly to receptor **1** than a comparable benzoate.

Introduction

Tetrazoles and 1,2,4-oxadiazol-5-ones are heterocyclic acids that have attracted a lot of interest in medicinal chemistry. The 1,2,4-oxadiazol-5-one heterocycle is a relative newcomer among binding groups in modern drug design. It has already become a promising bioisosteric[1] replacement for carboxylic acids, for example, in non-peptide angiotensin II receptor antagonists[2] (for lowering blood pressure) and in cholecystokinin antagonists[3] (for the treatment of certain neuropsychiatric disorders). While pK_a values† tend to be comparable, tetrazoles and 1,2,4-oxadiazol-5-ones are more lipophilic than carboxylic acids.[1] The change in water solubility, binding affinity, metabolic rate and bioavailability become important in the optimisation of pharmacological properties during the development of new drugs.
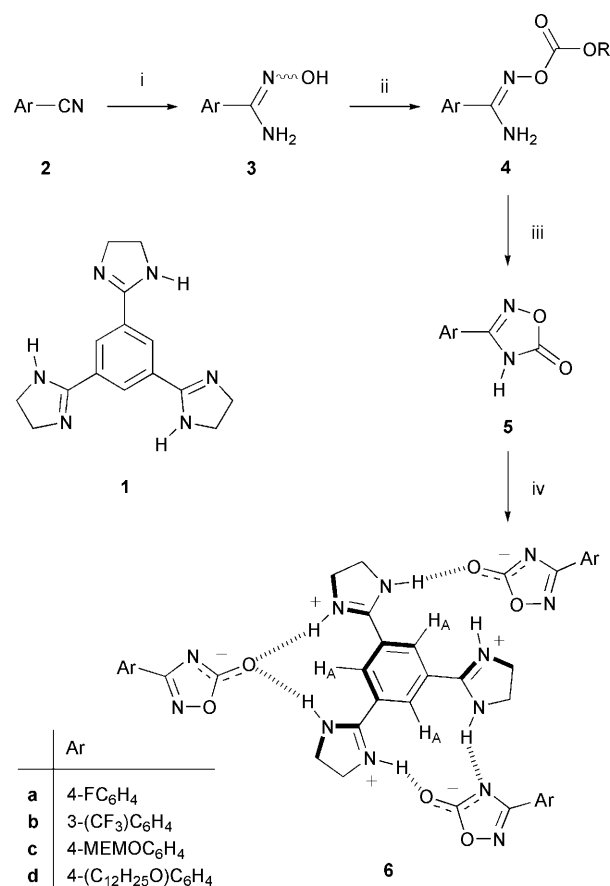
Their effectiveness as ligands should make acidic heterocycles promising binding groups in supramolecular chemistry, too. While studying non-covalent complexes with amidine bases, we have recently been able to demonstrate that the replacement of carboxylic acids by tetrazoles in complexes with heterocyclic amidine **1** causes subtle changes in the binding mode that affect the properties of the complexes both in the solid and solution phase.[4] Following a preliminary report on the complexation of other acidic heterocycles,[5] we now describe details of the synthesis, crystal structure and solution binding studies of non-covalent complexes between several 1,2,4-oxadiazol-5-ones and the relatively simple trisimidazoline receptor **1**.

Results and discussion

Synthesis

The 3-step synthesis of 1,2,4-oxadiazol-5-ones is outlined in Scheme 1.[6,7] Nucleophilic addition of hydroxylamine to aromatic nitriles **2** gave amide oximes **3** which were esterified with ethyl chloroformate or 2-ethylhexyl chloroformate ‡ and cyclised

	Ar
a	4-FC$_6$H$_4$
b	3-(CF$_3$)C$_6$H$_4$
c	4-MEMOC$_6$H$_4$
d	4-(C$_{12}$H$_{25}$O)C$_6$H$_4$

Scheme 1 *Reagents and conditions*: i, NH$_2$OH·HCl, Na$_2$CO$_3$, EtOH–H$_2$O, reflux; ii, EtOCOCl or 2-ethylhexyl chloroformate, NEt$_3$, CHCl$_3$, 25 °C; iii, xylene, reflux; iv, **1** (0.33 equiv.), EtOH, reflux.

† Two structurally related antihypertension drugs, one with a 1,2,4-oxadiazol-5-one and another with a tetrazole group, were reported to have pK_a values of 6.1 and 5.3, respectively.[6a,b]

‡ Compared to the ethyl carbonate derivative, a 2-ethylhexyl carbonate had a much higher solubility in non-polar solvents which, in the absence of other solubilising groups, proved advantageous during column chromatography.
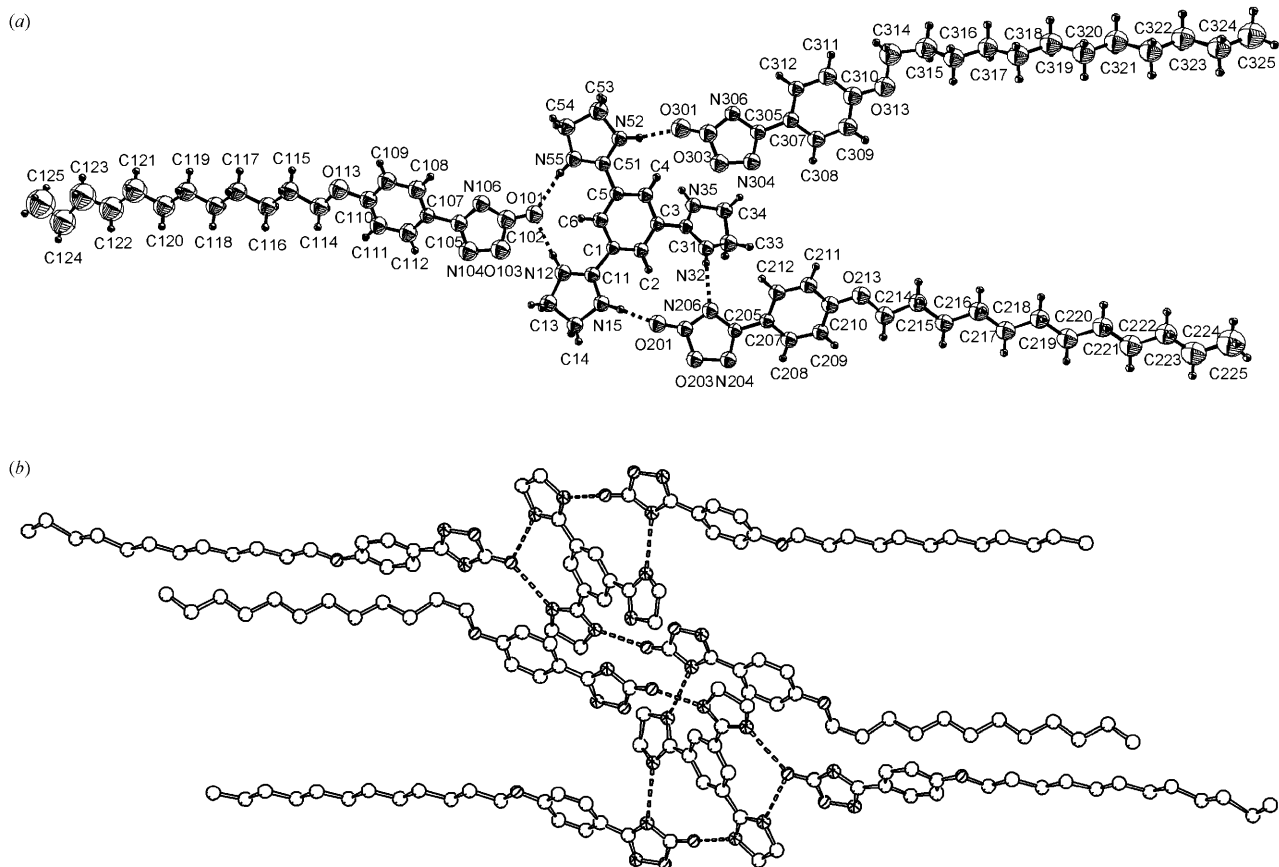
Fig. 1 (*a*) Crystal structure of **6d**. (*b*) Hydrogen bonding between two adjacent molecules of **6d** (hydrogen atoms are omitted for clarity).

to the 3-aryl-1,2,4-oxadiazol-5-ones **5a–d** in refluxing xylene. When trisimidazoline base **1** was dissolved with 3 equiv. of a 1,2,4-oxadiazol-5-one in hot EtOH, the 1 : 3 salts **6** crystallised in analytical purity upon cooling. Complexes **6a–d** were characterised by ^{1}H and ^{13}C NMR, IR, electrospray MS and elemental analysis. The preparation of complexes with related heterocycles followed an analogous procedure.

Crystal structure

Slow evaporation of a methanolic solution of complex **6d** gave needles suitable for X-ray analysis. The most striking feature of the crystal structure is that all three oxadiazolone ligands bind differently (Fig. 1a). One of the ligands shows a bifurcated hydrogen bond between its carbonyl-O atom and two imidazolinium-NH groups (O101 · · · N12, O101 · · · N55). Another oxadiazolone binds through its carbonyl-O201 to N15-H; in addition, ring nitrogen N206 (which is adjacent to the ligand's carbonyl group) is hydrogen-bonded to N32-H of another nearby imidazoline. In contrast to previous crystal structures of **1**–carboxylic acid[8a,9] and **1**–tetrazole[4] complexes, the trisimidazoline core of **6d** displays notable deviations from planarity. As a result of the way all imidazoline groups twist out of the plane of the trisimidazoline's central benzene ring, the third oxadiazolone ligand forms just one intramolecular hydrogen bond (O301 · · · N52). A second H-bond exists to an adjacent molecule (N306 · · · N35*), and two complexes in the crystal thus assemble to a centrosymmetric H-bonded dimer (Fig. 1b). Hydrogen bond lengths and angles are compiled in Table 1.

To the best of our knowledge, the crystal structure of **6d** is the first of a 1,2,4-oxadiazol-5-one that is not *N*-substituted.[10] It illustrates two types of H-bonding patterns that are possible for oxadiazolone ligands, even though the observed binding arrangement may have been in part due to crystal packing

effects enforced by the long dodecyloxy side chains. Hydrogen bonds are observed between the NH groups of protonated **1** and the deprotonated heterocycle, involving exclusively the latter's exocyclic oxygen and the ring nitrogen N[4] adjacent to the carbonyl group. Neither ring oxygen O[1] nor ring nitrogen N[2] of the oxadiazolone act as H-bond acceptors.

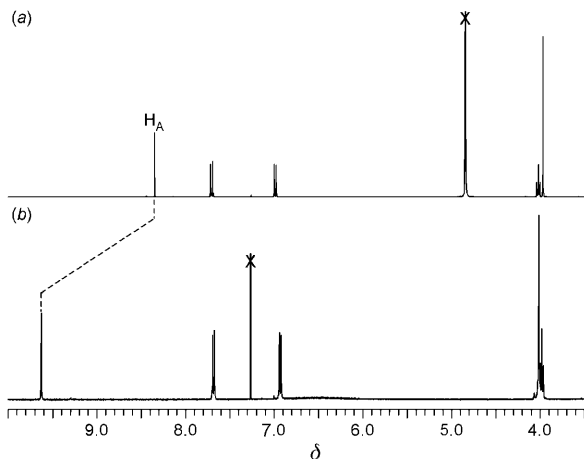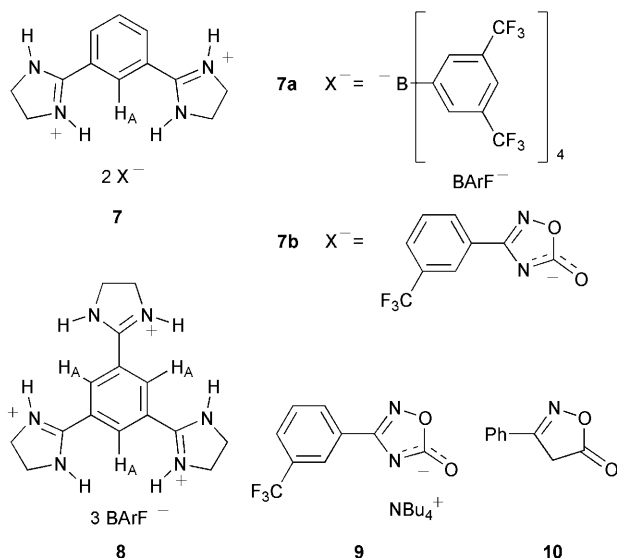### Complexes of 1 with related heterocycles

Related heterocycles would be expected to show similar binding modes. 3-Phenylisoxazol-5-one (**10**)[11] and 5-methylisoxazol-3-ol (**11a**)[12] (with pK_a values of 4.01 and 5.85, respectively, in water) are both acidic enough for salt formation, yet their respective complexes with **1** tended to be rather waxy, difficult to crystallise and prone to thermal decomposition. In contrast, saccharin **14** (with a pK_a of 1.6 in water)[13] gave a complex with **1** that was easily isolated and remained thermally stable up to its melting point of 324 °C. Judging from the crystal structure of **6d**, the lack of a nitrogen atom adjacent to the carbonyl group in ligand **10** might readily explain the compound's failure to give a stable complex. However, why isoxazol-3-ols **11a–b** caused similar problems despite the isoxazole ring nitrogen's known ability to act as a hydrogen-bond acceptor (*cf.* various crystal structure of muscimol analogues)[14] is unclear at the moment. As will be shown later on, such difficulties in preparation or isolation do not necessarily correlate with low binding affinities.
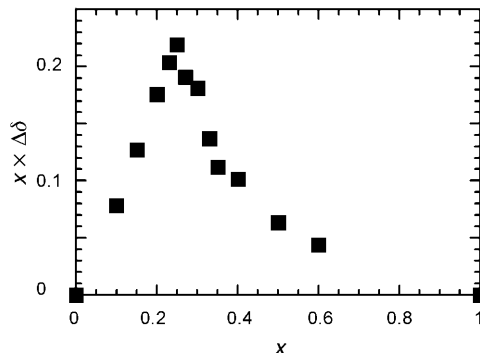
IR and ^{1}H NMR spectra

All oxadiazolones gave rise to one or two characteristic IR bands between 1775 cm^{-1} and 1820 cm^{-1}.[7] In contrast, the C=O stretching frequency of the deprotonated heterocycle **9** as well as of complexes **6a–d** was reduced to about 1695 cm^{-1}, indicating a weakening of the carbonyl bond owing to delocalisation of the negative charge.

Table 1 Hydrogen bond geometries

X ⋯ HN hydrogen bond	X ⋯ N distance/Å	X ⋯ HN distance/Å	X ⋯ HN angle/°
O101 ⋯ **H–N12**	2.86	2.02	163
O101 ⋯ **H–N55**	2.99	2.14	166
O201 ⋯ **H–N15**	2.68	1.82	168
N206 ⋯ **H–N32**	2.86	2.09	148
O301 ⋯ **H–N52**	2.68	1.83	166
N306 ⋯ **H–N35***	2.85	2.01	162

Fig. 2 ^{1}H NMR spectra (40 MHz, 25 °C) of **6d** in different solvents: (a) in CD$_3$OD; (b) in CDCl$_3$. Solvent and water signals are marked by 'X'.

Fig. 3 Job plot for the protonated tris(imidazoline) **8** binding deprotonated oxadiazolone **9**. The mole fraction x of **8** is defined as [**8**]/ ([**8**]+[**9**]). The total concentration in CDCl$_3$–CD$_3$CN (6 : 1)§ was maintained at 10^{-3} M, and the change in the H$_A$ NMR chemical shift $\Delta\delta = \delta_{observed} - \delta_0$ was determined for various compositions (δ_0 is the chemical shift of the H$_A$ singlet in **8**). The maximum of the Job plot was observed for a mole fraction of 0.25 as would be expected for a 1 : 3 complex.

by vapour-pressure osmometry measurements in chloroform (complex **6d**, see Experimental) and by Job's method[16] of continuous variation (Fig. 3).

Binding studies

Fast exchange,[17b] certainly on the NMR timescale, led to scrambling between different binding modes in chloroform. Association constants in CDCl$_3$ were too large to be measured accurately by NMR methods. To avoid complications from multiple equilibria between 1 : 1 and higher complexes, we resorted to a model system consisting of an equimolar mixture of bisimidazoline **7a**—with non-coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF$^-$) counter-anions—and the tetrabutylammonium salt of a deprotonated oxadiazolone (**9**) in a more competitive solvent mixture (CDCl$_3$–CD$_3$OD, 97 : 3). Under these conditions complexation of a second anion was suppressed, and binding could be evaluated by simple 1 : 1 host–guest complex formation. An association constant K_a of 1990 ± 150 M^{-1} was derived by following the change in the H$_A$ chemical shift of **7a** during a typical ^{1}H NMR dilution experiment (Fig. 4).[18] The deviation from planarity of the trisimidazoline core, which is evident from the crystal structure, suggests at first that the binding mode for oxadiazolones may be less favourable than for benzoates. Nevertheless, the K_a value of a deprotonated oxadiazolone (**9**) binding to bisimidazoline **7a** in CDCl$_3$–CD$_3$OD (97 : 3) was determined to be about twice as large as for 4-*tert*-butylbenzoate ($K_a = 990 \pm 230$ M^{-1})[8] and slightly less than that of 5-(4-*tert*-butylphenyl)tetrazolate ($K_a = 2470 \pm 400$ M^{-1}) in the same solvent mixture.[4]

Electrospray mass spectra

During the last years electrospray ionisation (ESI) mass spectrometry has been recognised as an up-and-coming method

The ^{1}H NMR spectrum of a protonated trisimidazoline with non-coordinating counter-anions (*e.g.*, **8**) displays a singlet at $\delta_H \approx 8.6$ for the aromatic H$_A$ protons in both polar and non-polar solvents. The chemical shift changes considerably upon complex formation with carboxylate ($\delta_H \approx 10.1$ in CDCl$_3$)[8] or tetrazolate ligands ($\delta_H \approx 9.9$ in CDCl$_3$).[4] Likewise, in the case of 1,2,4-oxadiazol-5-ones, no evidence for a 1 : 3 complex is found in methanolic solution, whereas the H$_A$ singlet of chloroform-soluble **6c–d** undergoes a downfield shift of about 1 ppm to $\delta_H \approx 9.6$ that is indicative of complexation (Fig. 2). Similar diagnostic downfield shifts of aromatic proton signals have been reported for isophthalamide receptors upon binding of barbiturates, halide anions and acetate.[15] In all these cases, ^{1}H NMR downfield shifts correlate with close contacts between ligand and aromatic receptor, which are also recognised in the crystal structure of complex **6d** (selected O ⋯ H distances: O101 ⋯ H–C6 2.18 Å, O201 ⋯ H–C2 2.39 Å, O301 ⋯ H–C4 2.59 Å). A 1 : 3 complex stoichiometry was confirmed
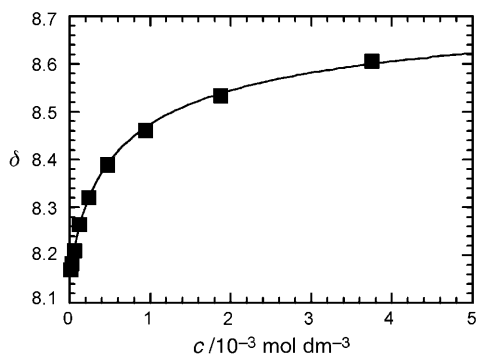
Fig. 4 Changes of the chemical shift of the H_A signal upon dilution of an equimolar solution containing **7a** and **9** in $CDCl_3$–CD_3OD (97 : 3) at 25 °C. The curve represents the calculated isotherm for 1 : 1 binding.

for the high-throughput screening of combinatorial inhibitor libraries in the presence of natural enzymes or receptors [19,20] and, in one recent case, it has been successfully applied to the study of synthetic complexes consisting of hydrogen-bonded dimers of calixarene tetraureas.[21] The method is based on the notion that non-covalent complexes containing tightly bound inhibitors give rise to stronger ion peaks in the mass spectrum than more weakly bound ligands, always provided that the enzyme–inhibitor [or receptor–(ant)agonist] complex is charged, which is the case in most biochemical studies. Even though the ions are transferred from solution into the vacuum of the mass spectrometer, solution binding constants and intensities of mass ion peaks generally correlate quite well.

Electrospray ionisation mass spectra were performed in MeOH [or MeOH–MeCN (1 : 1)] in which the 1 : 3 complexes were mostly dissociated and only the best ligands were expected to show some residual binding to **1**. Fig. 5a displays the positive ion ESI mass spectrum of complex **6b**. Not surprisingly, protonated tris(imidazoline) **1** is the most abundant ion. Although a neutral 1 : 3 complex—if it is present at all—eludes detection, charged fragments of the complex are easily identified. The dominant ions of interest are a singly protonated 1 : 1 adduct of **1** and oxadiazolone **5b**; a protonated 1 : 2 complex of **1** and **5b**; and a doubly charged 1 : 1 adduct (**1·5b + 2 H⁺**) at a lower mass-to-charge ratio. In comparison, the ESI mass spectrum of a complex of **1** with 4-*tert*-butylbenzoic acid (**12**)[8] likewise shows a 1 : 1 adduct (**1·12 + H⁺**), but no ion originating from a 1 : 2 complex can be detected (Fig. 5b). A number of additional ions have to be attributed to singly and doubly charged cluster ions that involve neutral species. Except in the case of a tetrazole (*e.g.*, **13**) complex, where a whole series of cluster ions were of the type **1 + n 13 + 2 H⁺** (with *n* = 1–7), these ions were generally present in comparatively small amounts.

Competition experiments

The straightforward assignment of ions in the ESI mass spectrum of complex **6b** (Fig. 5a) promised that even mixtures of complexes should be analysable by ESI-MS, at least in principle. This way, we intended to check our previous results from NMR dilution experiments by an independent method, which promised to be not only faster but also more widely applicable, especially in cases (*e.g.*, **11a**) when a tetrabutylammonium salt could not be obtained for NMR titration studies. In particular, a single competition experiment would greatly facilitate the comparison between two ligands under identical conditions.[20,22,23]

The absence of unexpected or overlapping ion peaks in the mass regions of interest made it possible to directly compare differences in ion abundance, and hence in binding, of 1 : 1 and 1 : 2 adducts provided that equimolar mixtures of the two complexes were used. Assignment of individual ions was possible since in a mixture of a complex of **1** with a 1,2,4-
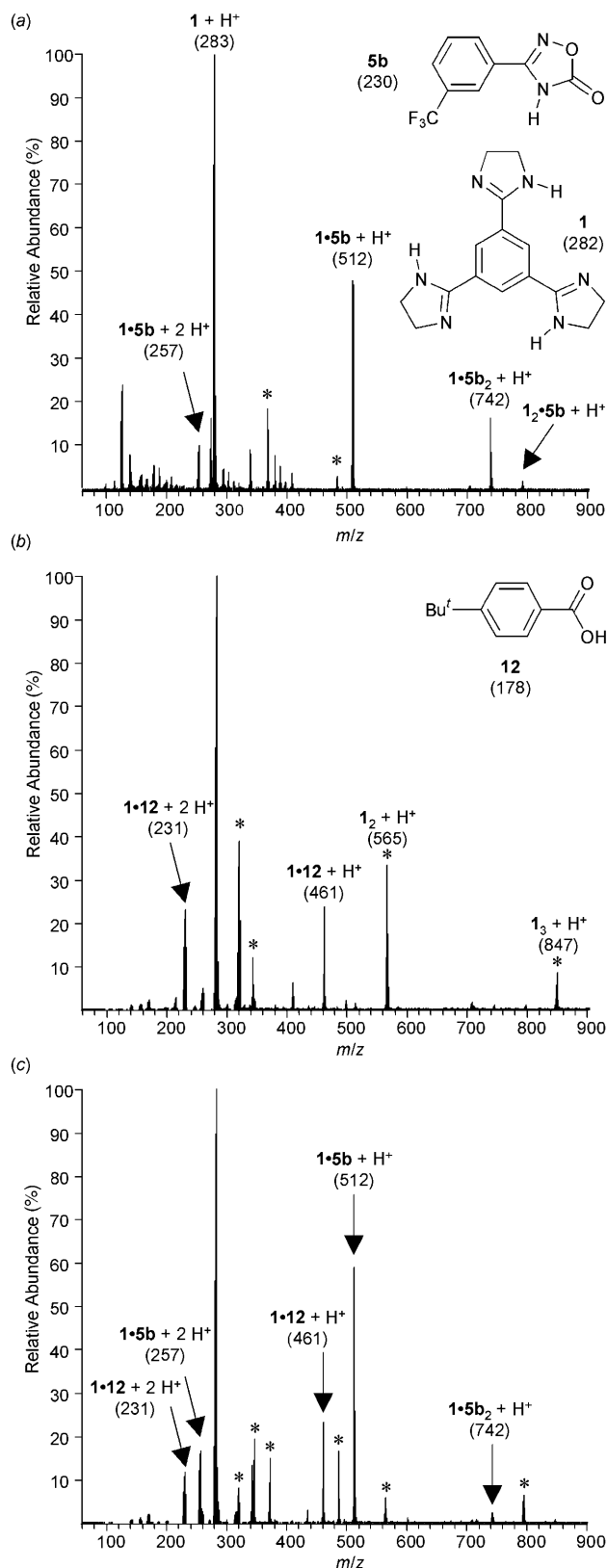
Fig. 5 (*a*) Electrospray mass spectrum of complex **6b** in MeOH–MeCN (1 : 1). (*b*) Electrospray mass spectrum of a complex of **1** with 4-*tert*-butylbenzoic acid (**12**) in MeOH. (*c*) An electrospray mass spectrum of a mixture containing equimolar amounts of complex **6b** and a complex of **1** with 4-*tert*-butylbenzoic acid (**12**) in MeOH. Peaks marked by an asterisk denote singly and doubly charged cluster ions involving neutral species.

oxadiazol-5-one (**5b**) or a carboxylic acid (**12**)[8] the masses of the base (**1**) and the two ligands (**5b** and **12**) are sufficiently different. Fig. 5c shows that ions of the respective singly and doubly protonated 1 : 1 complexes are readily identified, and in

Fig. 6 Ligands used in electrospray MS binding studies, arranged according to the intensity of the mass ion peak of their 1 : 1 adduct with protonated **1**
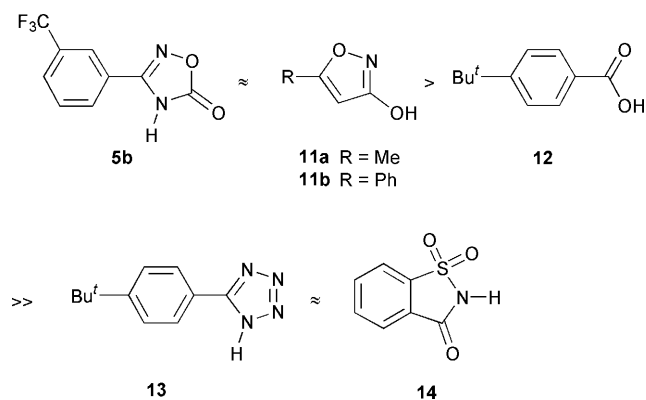
both cases oxadiazolone-containing ions are more abundant than the corresponding complexes of the benzoate. Despite the weak intensities of ions corresponding to protonated 1 : 2 complexes, the oxadiazolone-containing complex is still recognised at $m/z = 742$, whereas the corresponding benzoate complex (expected at $m/z = 639$) is not observed. Doubly protonated 1 : 1 adducts (at $m/z = 231$ and 257), too, show an intensity difference between the two ligands, although less pronounced. Some additional ions could be attributed to singly or doubly protonated oligomers and clusters of **1** and **5b**; these cluster ions were, however, comparatively small and not of interest for this investigation.

By combining two to three complexes at a time, we have been able to derive information about the binding affinity of various ligands directly from the intensities of the protonated 1 : 1 adducts with trisimidazoline **1**. Although these results remained qualitative, it could be construed that the best ligands were **5b** and **11b**, followed by benzoic acid **12** (Fig. 6). Both tetrazole **13** and saccharin **14** gave very weak ion peaks for 1 : 1 complexes in any of the competition experiments. From this, it is evident that of the two ligands, **5b** and **12**, the oxadiazolone binds more strongly than the benzoate.

These findings correlate well with solution studies; there are some minor discrepancies which can be attributed to changes in solvent and binding system. Isoxazolol **11b** turns out to be a ligand with a binding affinity comparable to oxadiazolone **5b**. Against our expectations, tetrazole **13** performed poorly in comparison, mainly owing to non-specific associations;[17a] however, a quantitative study should take into account that **13** was included in a series of mixed cluster ions so that the total intensity of tetrazole-containing ions may be more representative than the monitoring of just one arbitrarily chosen peak (*i.e.*, the monoprotonated 1 : 1 complex).¶ Saccharin showed very weak binding; possibly, its larger acidity makes its complex with **1** more salt-like, thereby preferring to dissociate in a more polar solvent. There is a rough inverse correlation between ion abundance of the 1 : 1 complexes and the pK_a of the ligand: the two least acidic ligands depicted in Fig. 6 (isoxazolol **11b** and oxadiazolone **5b**) were found to show the strongest binding, whereas saccharin with the highest acidity of the heterocycles investigated gave rather weak ion peaks for its complex with **1**. Unlike our NMR binding studies in chloroform-rich solvents (in which hydrogen bonding and electrostatic interactions dominate), ESI-MS seems to measure the relative amounts of

ion pairs that are solvent-separated. In all probability solvatophobicity may well be a major factor, and the greater lipophilicity of some of the heterocyclic acids compared to a carboxylate will have to be considered. It has been previously reported that 1,2,4-oxadiazol-5-ones are more lipophilic than tetrazoles,[6] which in turn have a higher lipophilicity than carboxylic acids.[1] Care is therefore needed once solution binding constants in non-polar solvents and abundances of mass ion peaks in electrospray mass spectra [in polar solvents like MeOH or MeOH–MeCN (1 : 1)] are correlated. Although the respective conclusions for oxadiazolones *vs.* carboxylates seem to agree quite well, the example with the tetrazole ligand (which binds strongly in non-polar solvents, but apparently does not give rise to an intense ion peak for its 1 : 1 complex in the electrospray mass spectrum) demonstrates that there are limits to the method.

All in all, the results emphasise a potential of the ESI-MS technique for comparing supramolecular receptor–ligand interactions in a manner similar to that used for rapid screening assays aimed at identifying lead structures in the development of new pharmaceutical drugs.

Conclusion

Following their launch in medicinal chemistry, 1,2,4-oxadiazol-5-ones have proven to be interesting acidic heterocycles that can replace carboxylic acids as ligands in supramolecular complexes. It could be deduced from ¹H NMR dilution studies and competition experiments by electrospray MS that a 3-aryl-substituted 1,2,4-oxadiazol-5-one binds more strongly to basic receptor **1** than a comparable benzoate.

Recent reports have indicated that both the carboxy terminus of angiotensin and the acid group of tetrazole-based antagonistic drugs are known to interact with a protonated lysine and a histidine—two basic amino acids—at the angiotensin II receptor binding site.[24] We note that, like the natural receptor, protonated **1** with its *meta*-positioned imidazoline substituents has pairs of cationic hydrogen bond donor groups in close proximity. Our structural studies featuring oxadiazolone complex **6d** demonstrate how, in the presence of two nearby NH hydrogen bond donor sites, a 1,2,4-oxadiazol-5-one forms hydrogen bonds principally through the exocyclic carbonyl oxygen and, at least in two out of three cases, the nitrogen α to the carbonyl group. The simple model suggests several possible binding modes for this ligand. It provides valuable information about the binding affinity of a heterocyclic acid that has become increasingly important as a pharmacophore in modern drug design.

Experimental

General

All solvents were distilled prior to use. Melting points: Olympus BH-2 polarisation microscope with Linkam TMS91 programmable sample heater. DSC: Mettler TC 11, DSC821e. NMR: Varian VXR 300, Bruker DPX 400, DRX 500. TMS was used as standard in the NMR measurements. The multiplicities of ¹³C signals were determined by DEPT experiments. IR: Bruker Vector 22 FT-IR. EI-MS: Varian MAT 311 A (70 eV). CI-MS: Finnigan INCOS 50. TLC: aluminium sheets with silica gel 60F₂₅₄ (Merck). Chromatography: ICN silica gel 32–63 (ICN Biomedicals). VPO: Knauer vapour-pressure osmometer; number-average molar masses M_n were determined in chloroform (concentration range of 20–50 mg g⁻¹). Elemental analyses: Pharmazeutisches Institut der Heinrich-Heine-Universität Düsseldorf.

General procedure for 3-aryl-1,2,4-oxadiazol-5-ones 5

All 3-aryl-1,2,4-oxadiazol-5-ones were prepared by an adapted

¶ Previous studies have demonstrated that the formation of larger aggregates is also observed in non-polar solvents in which complexes between tetrazoles and **1** have a strong tendency to self-associate.[4] The completely planar structure of such tetrazole complexes was found to be responsible for promoting π-stacking and salt-packing interactions. The tendency of tetrazoles to produce series of charged cluster peaks containing neutral tetrazole molecules has been noted in a different context before.[29]

3-step procedure similar to a literature route.[6a] The corresponding nitrile precursor **2** (35 mmol) was dissolved in EtOH (130 cm³). A solution of hydroxylamine hydrochloride (70 mmol) and Na_2CO_3 (105 mmol) in water (40 cm³) was added and refluxed for 5–8 hours. The solvent was then removed *in vacuo*. After addition of water (200 cm³), an insoluble solid could be collected by suction filtration. The crude amide oxime **3** (20 mmol) was dissolved in CHCl₃ (50 cm³), treated with NEt₃ (27 mmol) and ethyl chloroformate (21 mmol) or 2-ethylhexyl chloroformate, and stirred at room temperature for 1–2 days. The mixture was washed with ice-cold brine, the organic phase was dried over Na_2SO_4, CHCl₃ was removed *in vacuo*, and the residue was dried. Cyclisation to the 1,2,4-oxadiazol-5-one **5** occurred upon heating a solution of the usually crude carbonate ester (13 mmol) in xylene (150 cm³) to reflux for 6–8 h. After removal of xylene by vacuum distillation, the crude product was further purified by recrystallisation or column chromatography as indicated.

3-(4-Fluorophenyl)-1,2,4-oxadiazol-5(4H)-one 5a. Prepared in two steps from the commercially available 4-fluorobenzamide oxime (Aldrich) and 2-ethylhexyl chloroformate. Yield: 84%, colourless solid, mp 206–210 °C (from xylene) (Found: C, 53.6; H, 2.5; N, 15.5. $C_8H_5FN_2O_2$ requires C, 53.3; H, 2.8; N, 15.55%); ν_{max} (KBr)/cm⁻¹ 1817 (CO), 1737, 1608, 1527, 1486, 1232, 1171, 957, 852, 763; δ_H(500 MHz, CDCl₃–DMSO-d_6, 7 : 1) 7.18–7.22 (2 H, m), 7.86–7.89 (2 H, m); δ_C(125 MHz, CDCl₃–DMSO-d_6, 7 : 1) 116.3 ($^2J_{CF}$ 22), 128.5 ($^3J_{CF}$ 9) (CH), 119.9, 156.6, 160.5, 164.6 ($^1J_{CF}$ 253) (ipso-C, C=O, C=N); *m/z* (EI, 70 eV) 181, 180 (M⁺, 14, 100%), 137 (97), 121 (64), 109 (68).

3-(Trifluoromethyl)benzamide oxime 3b. Yield: 96%, colourless solid, mp 92 °C (after sublimation at 70 °C/10⁻⁴ mbar) (Found: C, 47.1; H, 3.6; N, 13.7. $C_8H_7F_3N_2O$ requires C, 47.1; H, 3.5; N, 13.7%); ν_{max} (KBr)/cm⁻¹ 3359, 2993, 1753, 1643, 1633, 1401, 1324, 1168, 1130, 1074; δ_H(500 MHz, CDCl₃–DMSO-d_6, 5 : 2) 5.66 (2 H, br s), 7.53 (1 H, t, *J* 7.8), 7.62 (1 H, br d, *J* 7.8), 7.94 (1 H, br d, *J* 7.8), 8.01 (1 H, br s), 9.80 (1 H, br s); δ_C(125 MHz, CDCl₃–DMSO-d_6, 5 : 2) 122.2, 125.2, 128.7, 129.0 (CH), 124.0 (q, $^1J_{CF}$ 271), 129.6 (q, $^2J_{CF}$ 31), 134.2, 150.1 (ipso-C, C=N); *m/z* (CI, NH₃) 239 (M + NH₃ + NH₄⁺, 12%), 222 (M + NH₄⁺, 95), 206, 205 (M + H⁺, 25, 100), 189 (54).

N^2-(Ethoxycarbonyloxy)-3-trifluoromethylbenzamidine 4b. Yield: 99%, colourless solid, mp 98 °C (Found: C, 47.8; H, 4.1; N, 10.1. $C_{11}H_{11}F_3N_2O_3$ requires C, 47.8; H, 4.0; N, 10.1%); ν_{max} (KBr)/cm⁻¹ 3361, 1753, 1632, 1400, 1324, 1168, 1130; δ_H(500 MHz, CDCl₃) 1.38 (3 H, t, *J* 7.2), 4.35 (2 H, q, *J* 7.2), 5.14 (2 H, br s), 7.57 (1 H, t, *J* 7.8), 7.74 (1 H, br d, *J* 7.8), 7.91 (1 H, br d, *J* 7.8), 7.95 (1 H, br s); *m/z* (CI, NH₃) 311 (M + NH₃ + NH₄⁺, 11%), 294 (M + NH₄⁺, 68), 277 (M + H⁺, 38), 206 (49), 189 (100).

3-[3-(Trifluoromethyl)phenyl]-1,2,4-oxadiazol-5(4H)-one 5b. Yield: 71% (after chromatography with CH₂Cl₂–Et₂O, 6 : 1), mp 185–186 °C (decomp.) (Found: C, 46.8; H, 2.0; N, 11.9. $C_9H_5F_3N_2O_2$ requires C, 47.0; H, 2.2; N, 12.2%); ν_{max} (KBr)/cm⁻¹ 1815 (CO), 1736, 1351, 1338, 1308, 1179, 1138, 695; δ_H(500 MHz, CDCl₃–DMSO-d_6, 7 : 1) 7.69 (1 H, t, *J* 7.9), 7.82 (1 H, br d, *J* 7.9), 8.09 (1 H, br d, *J* 7.9), 8.19 (1 H, br s); δ_C(125 MHz, CDCl₃–DMSO-d_6, 7 : 1) 123.1, 128.4, 129.4, 129.9 (broadened signals) (CH), 123.4 (q, $^1J_{CF}$ 271), 124.6, 131.2 (q, $^2J_{CF}$ 33), 156.4, 160.3 (ipso-C, C=N, C=O); *m/z* (EI, 70 eV) 230 (M⁺, 90%), 187 (100), 171 (32), 145 (37), 139 (30), 109 (40), 75 (35); R_f (CH₂Cl₂–Et₂O, 6 : 1) 0.1. A solution of **5b** (200 mg, 0.869 mmol), aqueous NBu₄OH (40%, 0.3 cm³, 0.5 mmol) and NaOH (70 mg, 1.7 mmol) in water (10 cm³) was extracted with CH₂Cl₂ (3 × 10 cm³). The combined organic extracts were washed with brine (10 cm³) and water (10 cm³), dried (Na₂SO₄), and concentrated *in vacuo* to afford tetrabutylammonium salt **9**

(198 mg, 48%) as a colourless amorphous solid (Found: C, 63.5; H, 8.6; N, 8.7. $C_{25}H_{40}F_3N_3O_2$ requires C, 63.7; H, 8.6; N, 8.9%); ν_{max} (KBr)/cm⁻¹ 1695 (CO), 1383, 1326, 1169, 1122; δ_H(500 MHz, CDCl₃) 0.98 (12 H, t, *J* 7.3), 1.41 (8 H, sextet, *J* 7.4), 1.60–1.67 (8 H, m), 3.25–3.29 (8 H, m), 7.48 (1 H, t, *J* 7.7), 7.58 (1 H, br d, *J* 7.7), 8.20 (1 H, br d, *J* 7.7), 8.28 (1 H, br s).

4-(2-Methoxyethoxymethoxy)benzonitrile 2c. The compound was prepared as described in a method by Kremers and Meijer for the treatment of hydroxymethylmalonates with MEM chloride.[25] A solution of MEM chloride (26.2 g, 210 mmol), 4-hydroxybenzonitrile (22.5 g, 190 mmol) and diisopropylethylamine (39 cm³) in dry CH₂Cl₂ (275 cm³) was stirred at room temperature until TLC analysis (with hexane–ethyl acetate, 2 : 1) indicated that conversion was complete. The reaction mixture was then washed with saturated aqueous NaHCO₃ (3 × 150 cm³), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was distilled twice (Kugelrohr, 170–180 °C/0.02 mbar) to furnish a light yellow liquid (36.0 g, 92%) (Found: C, 63.0; H, 6.6; N, 6.7. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3; N, 6.8%); ν_{max} (film)/cm⁻¹ 2226, 1605, 1508, 1239, 1173, 1106, 983, 841; δ_H(500 MHz, CDCl₃) 3.36 (3 H, s), 3.53–3.56 (2 H, m), 3.81–3.83 (2 H, m), 5.32 (2 H, s), 7.11, 7.58 (2 × 2 H, AA′XX′); δ_C(125 MHz, CDCl₃) 59.0, 116.8, 133.9 (CH, CH₃), 68.1, 71.4, 93.2 (CH₂), 105.1, 119.1, 160.6 (CN, ipso-C); *m/z* (CI, NH₃) 242 (M + NH₃ + NH₄⁺, 34%), 225 (M + NH₄⁺, 100).

3-[4-(2-Methoxyethoxymethoxy)phenyl]-1,2,4-oxadiazol-5(4H)-one 5c. Prepared in 3 steps from **2c** (using the ethyl carbonate route) without purification of the intermediates. Yield: 42% (after column chromatography with CH₂Cl₂–MeOH, 15 : 1), mp 120–122 °C (Found: C, 54.4; H, 5.2; N, 10.5. $C_{12}H_{14}N_2O_5$ requires C, 54.1; H, 5.3; N, 10.5%); ν_{max} (KBr)/cm⁻¹ 1781 (CO), 1614, 1475, 1239, 1100, 1085, 995; δ_H(500 MHz, CDCl₃) 1.36 (2 H, t, *J* 7.1), 3.38 (3 H, s), 3.56–3.59 (2 H, m), 3.83–3.86 (2 H, m), 4.32 (2 H, q, *J* 7.1), 5.33 (2 H, s), 7.17, 7.75 (2 × 2 H, AA′XX′); δ_C(125 MHz, CDCl₃) 59.0, 117.0, 127.8 (CH, CH₃), 68.1, 71.6, 93.2 (CH₂), 115.8, 156.9, 160.6, 162.3 (ipso-C, C=N, C=O); *m/z* (CI, NH₃) 301 (M + NH₃ + NH₄⁺, 41%), 284 (M + NH₄⁺, 100), 225 (35); R_f (CH₂Cl₂–MeOH, 15 : 1) 0.35.

4-Dodecyloxybenzamide oxime 3d. Prepared from **2d**.[26] Yield: 83%, colourless solid (Found: C, 70.6; H, 10.0; N, 8.2. $C_{19}H_{32}N_2O_2$ requires C, 71.2; H, 10.1; N, 8.7%); ν_{max} (KBr)/cm⁻¹ 2920, 2852, 1653, 1611, 1520, 1395, 1253, 827; δ_H(500 MHz, DMSO-d_6) 0.85 (3 H, t, *J* 6.6), 1.20–1.44 (18 H, m), 1.70 (2 H, quintet, *J* 7.2), 3.96 (2 H, t, *J* 6.3), 5.68 (2 H, s), 6.90, 7.58 (2 × 2 H, AA′XX′), 9.42 (1 H, s); δ_C(125 MHz, DMSO-d_6) 14.3, 114.2, 127.0 (CH, CH₃), 22.4, 25.9, 29.0, 29.1, 29.1, 29.35, 29.39, 31.6, 67.8 (CH₂), 114.2, 150.9, 159.6 (ipso-C, C=N); *m/z* (CI, NH₃) 338 (M + NH₄⁺, 7%), 323, 322, 321 (M + H⁺, 17, 22, 100), 305 (23); R_f (CH₂Cl₂–MeOH, 9 : 1) 0.46.

4-Dodecyloxy-N^2-(ethyloxycarbonyloxy)benzamidine 4d. Yield: 92%, colourless solid (after chromatography with hexane–ethyl acetate, 2 : 1) (Found: C, 67.6; H, 9.4; N, 6.9. $C_{22}H_{36}N_2O_4$ requires C, 67.3; H, 9.2; N, 7.1%); ν_{max} (KBr)/cm⁻¹ 2919, 1757, 1628, 1258; δ_H(500 MHz, CDCl₃) 0.88 (3 H, t, *J* 6.9), 1.25–1.48 (18 H, m), 1.35 (3 H, t, *J* 7.1), 1.78 (2 H, tt, *J* 7.2 and 6.6), 3.90 (2 H, t, *J* 6.5), 3.90 (2 H, q, *J* 7.1), 5.10 (2 H, s), 6.86, 7.59 (2 × 2 H, AA′XX′), 9.42 (1 H, s); *m/z* (CI, NH₃) 410 (M + NH₄⁺, 8%), 394, 393 (M + H⁺, 16, 100); R_f (hexane–ethyl acetate, 2 : 1) 0.26.

3-(4-Dodecyloxyphenyl)-1,2,4-oxadiazol-5(4H)-one 5d. Yield: 12%, colourless solid (after column chromatography with CH₂Cl₂–Et₂O, 2 : 1), mp 166 °C (Found: C, 69.4; H, 8.7; N, 8.0. $C_{20}H_{30}N_2O_3$ requires C, 69.3; H, 8.7; N, 8.1%); ν_{max} (KBr)/cm⁻¹ 2921, 2852, 1819 (CO), 1780, 1733, 1616, 1250; δ_H(500 MHz,

CDCl$_3$) 0.88 (3 H, t, J 7.0), 1.20–1.40 (16 H, m), 1.43–1.50 (2 H, m), 1.77–1.85 (2 H, m), 4.02 (2 H, t, J 6.6), 7.01, 7.71 (2 × 2 H, AA′XX′), 10.91 (1 H, br s); δ_C(125 MHz, CDCl$_3$) 14.5, 115.7, 128.2 (CH, CH$_3$), 23.1, 26.4, 29.4, 29.7, 29.94, 29.97, 30.02, 30.04, 32.3, 68.8 (CH$_2$), 114.7, 114.8, 129.8, 157.4, 162.95, 162.99 (*ipso*-C, C=N, C=O); *m/z* (CI, NH$_3$) 364 (M + NH$_4^+$, 100%), 305 (35); R_f (CH$_2$Cl$_2$–Et$_2$O, 2 : 1) 0.67.

General procedure for the preparation of the complexes

Imidazoline base **1**[27] and 3-aryl-1,2,4-oxadiazol-5(4*H*)-one **5** (3 equiv.) were dissolved in hot ethanol (*ca.* 12–20 cm^3 per mmol **5**). After filtration of the hot solution and concentration, the crude product was crystallised from the solvent (mixture) indicated for each complex and thoroughly dried at 50–100 °C/ 10^{-5} mbar.

Complex 6a. Yield: 47% (from EtOH), off-white solid, mp 227–230 °C (Found: C, 56.8; H, 4.2; N, 20.3. C$_{39}$H$_{33}$F$_3$N$_{12}$O$_6$ requires C, 56.9; H, 4.0; N, 20.4%); ν_{max} (KBr)/cm^{-1} 1655 (CO), 1604, 1420, 1385, 1222, 600; δ_H(500 MHz, CDCl$_3$–CD$_3$OD, 7 : 1) 4.00 (12 H, s), 7.11–7.22 (6 H, m), 7.76–7.86 (6 H, m), 8.54 (3 H, s).

Complex 6b. Yield: 66% (from EtOH), colourless needles, mp 206–207 °C; ν_{max} (KBr)/cm^{-1} 1677 (CO), 1578, 1406, 1385, 1325, 1286, 1127, 696; δ_H(500 MHz, CDCl$_3$–DMSO-d$_6$, 7 : 1) 3.92 (12 H, s), 7.64 (3 H, br t, J 7.8), 7.75 (3 H, br d, J 7.8), 8.09 (3 H, br d, J 7.8), 8.15 (3 H, br s), 8.72 (3 H, s).

Complex 6c. Yield: 74% (from EtOH), colourless solid, mp 154–155 °C (Found: C, 56.5; H, 5.5; N, 15.3. C$_{51}$H$_{60}$N$_{12}$O$_{15}$ requires C, 56.7; H, 5.6; N, 15.55%); ν_{max} (KBr)/cm^{-1} 1674 (CO), 1658, 1611, 1425, 1386, 1228, 986, 983; δ_H(500 MHz, CDCl$_3$) 3.35 (9 H, s), 3.52–3.57 (6 H, m), 3.80–3.84 (6 H, m), 3.97 (12 H, s), 5.29 (6 H, s), 7.08, 7.69 (2 × 6 H, AA′XX′), 9.60 (3 H, s).

Complex 6d. Yield: 47% (from EtOH), colourless crystals, DSC: K$_1$/83 (ΔH 118 J g^{-1})/K$_2$/186 (ΔH 60 J g^{-1})/I (Found: C, 68.2; H, 8.4; N, 12.65. C$_{75}$H$_{108}$N$_{12}$O$_9$ requires C, 68.5; H, 8.7; N, 12.7%); ν_{max} (KBr)/cm^{-1} 2923, 2852, 1660 (CO), 1653, 1611, 1424, 1381, 1250; δ_H(500 MHz, CDCl$_3$, 10^{-2} M) 0.88 (9 H, t, J 6.9), 1.22–1.48 (54 H, m), 1.78 (6 H, tt, J 6.7 and 7.1), 3.94 (12 H, s), 3.97 (6 H, t, J 6.6), 6.92, 7.68 (2 × 6 H, AA′XX′), 9.59 (3 H, s), 10.5 (6 H, br s); δ_H(500 MHz, CD$_3$OD, 10^{-2} M) 0.89 (9 H, t, J 6.9), 1.27–1.51 (54 H, m), 1.79 (6 H, tt, J 6.7 and 7.1), 3.96 (12 H, s), 4.03 (6 H, t, J 6.6), 7.00, 7.72 (2 × 6 H, AA′XX′), 8.35 (3 H, s); δ_C(125 MHz, CDCl$_3$) 14.1, 114.6, 127.8, 134.2 (CH, CH$_3$), 22.7, 26.0, 29.2, 29.35, 29.42, 29.58, 29.61, 29.64, 29.67, 31.9, 45.5, 68.2 (CH$_2$), 121.1, 125.9, 160.9, 163.3, 166.7, 174.2 (*ipso*-C, C=N, C=O); M_n (VPO, CHCl$_3$, 33 °C) 1520 g mol^{-1} (against benzil as standard; C$_{75}$H$_{108}$N$_{12}$O$_9$ requires 1322), 1530 g mol^{-1} (against polystyrene 2000 as standard).

Complex 7b. From 1,3-bis(4,5-dihydro-1*H*-imidazol-2-yl)benzene[8b,27] and **2b** (2 equiv.). Yield: 76% (from CH$_3$CN), colourless crystals, mp 192–194 °C (decomp.) (Found: C, 53.3; H, 3.4; N, 16.65. C$_{30}$H$_{24}$F$_6$N$_8$O$_4$ requires C, 53.4; H, 3.6; N, 16.6%); ν_{max} (KBr)/cm^{-1} 1696 (CO), 1677, 1388, 1330, 1281, 1121, 696; δ_H(500 MHz, CDCl$_3$–DMSO-d$_6$, 7 : 2) 3.95 (8 H, s), 7.62 (2 H, br t, J 7.8), 7.67 (1 H, t, J 7.9), 7.71 (2 H, br d, J 7.8), 8.10 (2 H, br d, J 7.8), 8.13 (2 H, dd, J 7.8 and 1.7), 8.17 (2 H, br s), 8.60 (1 H, t, J 1.7).

Complex 7c. From 1,3-bis(4,5-dihydro-1*H*-imidazol-2-yl)benzene[8b,27] and **2d** (2 equiv.). Yield: 66% (from EtOH), colourless crystals, mp 192–194 °C (decomp.) (Found: C, 69.1; H, 8.4; N, 12.3. C$_{52}$H$_{74}$N$_8$O$_6$ requires C, 68.8; H, 8.2; N, 12.35%); ν_{max} (KBr)/cm^{-1} 2920, 2852, 1658 (CO), 1611, 1425, 1388, 1248; δ_H(500 MHz, CDCl$_3$) 0.88 (6 H, t, J 6.9), 1.23–1.48

(36 H, m), 1.75–1.81 (4 H, m), 3.97 (2 H, t, J 6.7), 3.99 (8 H, s), 6.91, 7.72 (2 × 4 H, AA′XX′), 7.10 (1 H, t, J 7.9), 8.33 (2 H, dd, J 7.9 and 1.3), 9.08 (1 H, br s).

Complex with 10. Yield: 48% (from EtOH), waxy, light yellow solid, mp 123 °C (Found: C, 65.7; H, 5.3; N, 16.4. C$_{42}$H$_{39}$N$_9$O$_6$ requires C, 65.9; H, 5.1; N, 16.5%); ν_{max} (KBr)/cm^{-1} 3126, 2968, 1611, 1576, 1475, 1417, 1290, 745, 698; δ_H(500 MHz, CDCl$_3$–DMSO-d$_6$, 5 : 2) 3.99 (12 H, s), 4.74 (3 H, br s), 7.36–7.42 (6 H, m), 7.63–7.68 (6 H, m), 7.78–7.82 (3 H, m), 8.78 (3 H, s).

Complex with 11a.[12] Yield: 45% (from propan-2-ol). The light yellow waxy solid decomposed rapidly upon standing, probably owing to the high volatility of **11a**; δ_H(500 MHz, CDCl$_3$) 2.22 (9 H, d, J 0.8), 4.06 (12 H, s), 5.47 (3 H, q, J 0.8), 9.19 (3 H, s), 10.25 (6 H, br s).

Complex with 11b.[28] Yield: 19% (from EtOH), yellow solid (Found: C, 63.6; H, 5.3; N, 15.5. C$_{42}$H$_{39}$N$_9$O$_6$·1.5 H$_2$O requires C, 63.6; H, 5.3; N, 15.9%); δ_H(500 MHz, CDCl$_3$) 4.17 (s, 12 H), 6.09 (s, 3 H), 7.36–7.43 (m, 9 H), 7.66–7.70 (m, 6 H), 9.64 (s, 3 H).

Complex with 14. Yield: 75% (MeOH), colourless needles, mp 324 °C (Found: C, 51.8; H, 4.0; N, 15.1. C$_{36}$H$_{33}$N$_9$O$_9$S$_3$ requires C, 52.0; H, 4.0; N, 15.15%); ν_{max} (KBr)/cm^{-1} 3131b, 2969b, 1642, 1611, 1572, 1287, 1153, 603; δ_H(300 MHz, DMSO-d$_6$) 4.12 (12 H, s), 7.56–7.71 (12 H, m), 8.80 (3 H, s), 11.0 (6 H, br s).

Electrospray ionisation mass spectrometry

ESI mass spectra were recorded on a single quadrupole Thermoquest Automass LC/GC benchtop mass spectrometer. Samples were introduced as 0.5–1 mM solutions in HPLC-grade methanol at flow rates of 15 μL min^{-1} *via* a Rheodyne inlet (main solvent stream MeOH–H$_2$O, 1 : 1). Representative conditions for the positive ion mode were as follows: heated capillary temperature 180 °C; cone voltages were set to 8 V to avoid excessive dissociation of the non-covalent complexes; at least 15 scans were averaged to improve the signal-to-noise ratio. For competition experiments a solution containing 3 μmol of each complex in CD$_3$OD was prepared and the ratio of the components was determined by ^{1}H NMR spectroscopy and, if necessary, adjusted by addition of the minor component until integration confirmed an equimolar mixture within an acceptable error limit (±10%). The solvent was then allowed to evaporate and the residue was redissolved in methanol (5 mL).

X-Ray crystal structure analysis of 6d ‖

Formula C$_{75}$H$_{110}$N$_{12}$O$_{10}$, $M = 1339.75$, colourless crystal 0.20 × 0.10 × 0.05 mm (from MeOH), $a = 8.775(6)$ Å, $b = 14.312(3)$ Å, $c = 30.069(7)$ Å, $\alpha = 85.76(2)°$, $\beta = 81.87(4)°$, $\gamma = 85.32(4)°$, $V = 3718(3)$ Å^3, $\rho_{calcd} = 1.197$ g cm^{-3}, $\mu = 6.42$ cm^{-1}, empirical absorption correction *via* ψ scan data (0.882 ≤ T ≤ 0.967), $Z = 2$, triclinic, space group $P\bar{1}$ (No. 2), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 8233 reflections collected ($-h$, ±k, ±l), [(sin θ)/λ] = 0.50 Å^{-1}, 7581 independent and 2053 observed reflections [$I \geq 2$ $\sigma(I)$], 392 refined parameters, $R = 0.096$, $wR^2 = 0.204$, max. residual electron density 0.52 (-0.30) e Å^{-3}. Owing to the weakly diffracting crystal and the resulting amount of observed reflections all atoms were refined with isotropic thermal parameters; hydrogens at solvent water molecule were not found, others were calculated and refined riding. Data set was collected with an Enraf Nonius CAD4 diffractometer, equipped with a sealed tube generator. Pro-

grams used: data collection, EXPRESS;[30] data reduction, MolEN;[31] structure solution, SHELXS-97;[32] structure refinement, SHELXL-97;[33] graphics (with unsystematical numbering schemes), DIAMOND[34] and SCHAKAL.[35]

Acknowledgements

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