# Synthesis and structural analysis of copper(II) pyridine amide complexes as HIV-1 protease inhibitors

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***Received (in Cambridge) 26th November 1998, Accepted 16th February 1999***

In an effort to propose original non-peptide HIV-1 protease inhibitors by rational drug design, we have previously reported that the complex diaqua[bis(2-pyridylcarbonyl)amido]copper(II) nitrate dihydrate behaved as a competitive inhibitor of the enzyme ($K_i$ = 480 ± 120 μM). Based on a modeled interaction of this complex with HIV-1 protease, we present here the synthesis and crystallographic structures of two pyridine amide copper(II) coordination complexes, optimized for their interaction with the enzyme active site. The complexes adopted a tetragonally elongated octahedral geometry in the crystal. In both cases, two ligands symmetrically coordinate copper(II) by aromatic nitrogen and amide oxygen atoms, forming an equatorial square plane which may orient the various substituents within the enzyme subsites. As the apical positions form long bonds of 2.423(2) and 2.464(2) Å with copper(II), a statistical analysis was carried out in the Cambridge Structural Database. It gave for 1103 copper(II) complexes a mean copper(II)–oxygen distance of 2.450 ± 0.005 Å in the axial positions, typical of 'long' Cu–O bonds in Jahn–Teller distorted complexes of copper(II). The two compounds showed good inhibition of the HIV-1 protease ($IC_{50}$ = 1.5 and 1.0 μM).

## Introduction

Human type 1 immunodeficiency virus (HIV-1) has become one of the most studied of all viruses due to its massive threat to health on a global scale. Extensive studies are in progress to discover drugs which effectively block its replication. Since 1995, several HIV protease (PR) inhibitors have been approved by the Federal Drug Administration. In association with reverse transcriptase inhibitors, these protease inhibitors are used for the inhibition of viral replication. The compounds that have reached clinical application so far are directed to the active site of HIV-1 PR. These molecules act as transition state analogues and are peptidomimetic, being derived from a peptide base. In order to improve their bioavailability, systematic biological screenings and *de novo* design have been used to propose new non-peptide inhibitors combining both antiviral potency and favourable pharmacokinetic properties.[1,2]

We have used this type of approach to propose *de novo* HIV-1 protease inhibitors and previously discovered a novel non-peptide inhibitor fitting into an original pharmacophore which also included a catalytic water molecule [Fig. 1(*c*)] and a proton acceptor Y interacting directly with residues Ile50/150 of the flaps of the enzyme [Fig. 1(*b*)].[3–6] This complex, diaqua[bis(2-pyridylcarbonyl)amido]copper(II) nitrate dihydrate (SETCEZ),[7] effectively behaved as a competitive inhibitor of the protease, but showed a weak affinity constant ($K_i$ = 480 ± 120 μM).[1]

In search of other metallo-organic compounds with better affinity for HIV-1 PR, we improved the previously developed pharmacophore, focusing on the van der Waals contacts with the four subsites $S_1/S_2$ and $S'_1/S'_2$ of the protease. These subsites are highly hydrophobic anchor points in the enzyme active site and are connected by a $C_2$ symmetry axis. The interaction with these four subsites has been recognized as essential in order for inhibitors to have binding affinity in the nanomolar range[8] (Fig. 2). The three-dimensional structure shows that these important interaction elements in the active site of the enzyme are directed approximately along the axes of an octahedron, with the four subsites forming the equatorial plane while the catalytic water molecule and the proton acceptor Y are located in the axial positions. This observation has been integrated into the pharmacophore in order to design new copper coordination compounds, having such octahedral geometry, favorable for the orientation of their interacting substituents with the protease active site (Fig. 3).[9]

We thus looked for potential ligands containing heteroatoms able to take part in a complexation process with copper(II), bearing substituents which could interact with the enzyme subsites $S_1/S_2$, $S'_1/S'_2$, and which could be synthesized. Among them, compounds *N*-(4-methyl-2-pyridyl)-2,3,6-trimethoxybenzamide (**L1**) and *N*-(2-methoxybenzyl)quinoline-2-carboxamide (**L2**) were selected, synthesized, structurally analyzed after complexation with copper(II) and tested for their activity as HIV-1 protease inhibitors.

## Results and discussion

### Synthesis

[Compounds **L1** and **L2** were obtained by condensation of, respectively, 2-amino-4-methylpyridine with 2,3,6-trimethoxy-

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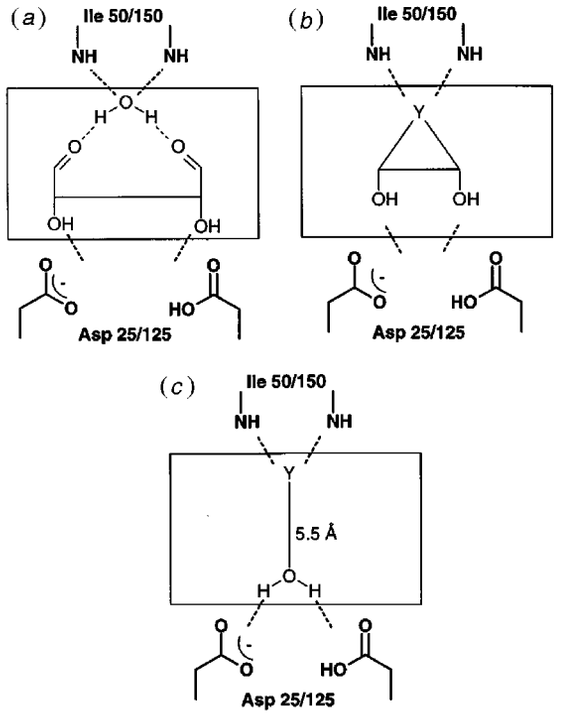



**Fig. 1** Pharmacophores for HIV-1 PR inhibitors. (*a*) Peptidic and peptidomimetic inhibitors. The tetracoordinated water molecule is simultaneously bound to residues Ile50/150 of the protease and to the carbonyl groups of peptidomimetric inhibitors. Hydroxy groups interact with the catalytic residues Asp25/125 (ref. 4–6). (*b*) Nonpeptide inhibitors. The proton acceptor Y mimics the tetracoordinated water molecule (ref. 3). (*c*) Coordination complexes. The pharmacophore includes the water molecule necessary to the protease's hydrolysis process (ref. 1).

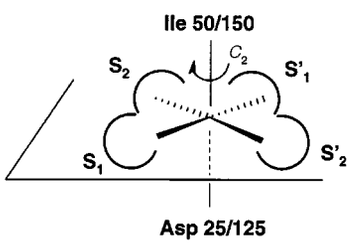



**Fig. 2** HIV-1 PR hydrophobic subsites $S_1/S_2$ and $S'_1/S'_2$ related by $C_2$ symmetry. They constitute, with the catalytic residues Asp25/125 and the flap residues Ile50/150, essentially anchor points in the active site of the enzyme. The directionality of these interaction elements follow approximately the axes of an octahedron.

benzoic acid and 2-methoxybenzylamine with quinolic acid previously activated with oxalyl chloride. Both compounds were obtained in poor yield (about 20%) (Scheme 1). Methanol solutions of copper(II) salts [$Cu(ClO_4)_2$ or $Cu(PF_6)_2$] were added to ligands **L1** and **L2**, previously dissolved in methanol. The solutions obtained were placed into a closed area saturated with $Et_2O$ vapor. After a few hours both compounds formed a complex with copper(II). The molecular structures of the corresponding coordination complexes **C1** and **C2** were analyzed by X-ray diffraction (Scheme 2 and Table 1).

### Structural analysis of (dimethanol)bis[*N*-(4-methyl-2-pyridyl)-2,3,6-trimethoxybenzamide]copper(II) dimethanol diperchlorate (C1)

The complex **C1** contains tetragonally elongated octahedral (dimethanol)bis[*N*-(4-methyl-2-pyridyl)-2,3,6-trimethoxybenzamide]copper(II) cations counterbalanced with $ClO_4^-$ anions (Fig. 4). The $Cu^{II}$ ion is located on an inversion center and is bonded to the ligand by the pyridine N(2)

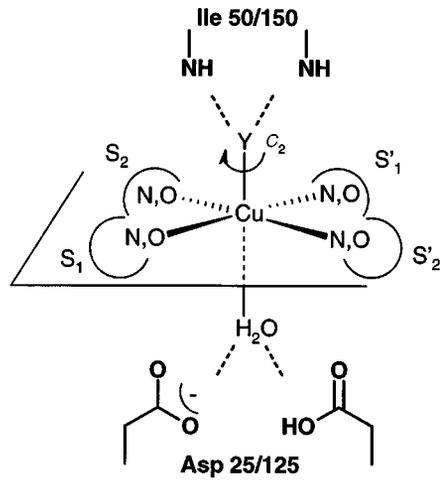
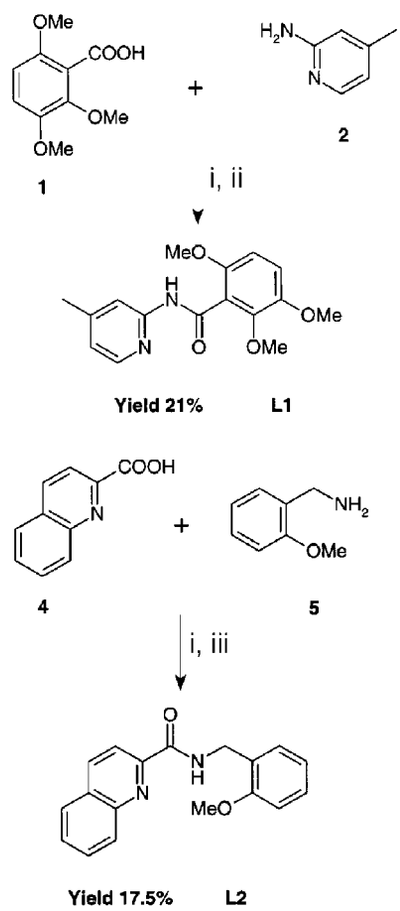



**Fig. 3** Improved pharmacophore for the inhibition of HIV-1 PR by copper(II) coordination compounds with an octahedral geometry able to organize the interaction elements in the shape of the active site of the protease.



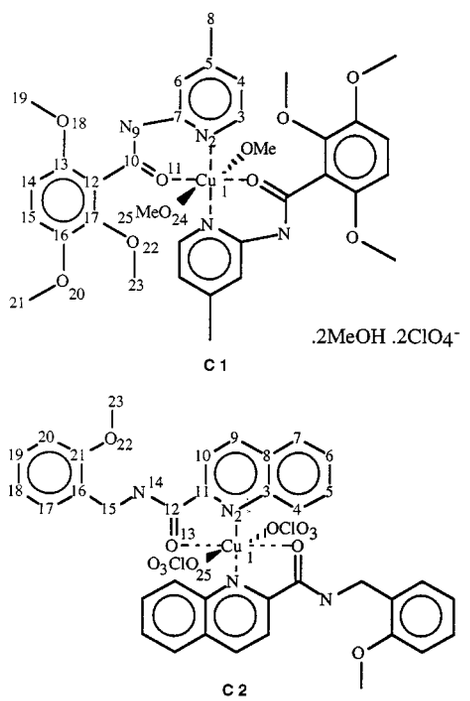

**Scheme 1** Synthesis and molecular structure of ligands **L1** and **L2**. *Reagents and conditions*: i, oxalyl chloride (3.5 equiv.), $CH_2Cl_2$, 0 °C, 90 min; ii, **2** (1 equiv.), $CH_2Cl_2$, room temp., 12 h; iii, **5** (1 equiv.), $CH_2Cl_2$, room temp., 12 h.

[2.011(2) Å] and the carbonyl O(11) [1.955(1) Å] atoms, with a bite angle of 89.17(6)°. The two ligands are in the pseudo-equatorial square plane of the complex while the methanol molecules are located in the axial positions and form long bonds with copper [2.423(2) Å]. The deviation of the $Cu^{II}$ ion from the mean plane N(2)–C(7)–N(9)–C(10)–O(11) is −0.613 Å. The coordinated methanol molecules are hydrogen bridged to adjacent $ClO_4^-$ anions. The amide NH(9) forms a hydrogen bond with the oxygen atom of a free solvent methanol molecule. A single parallel intermolecular π–π interaction is

**Table 1** Crystallographic details[a]

| | C1 | C2 |
|---|---|---|
| Chemical formula | $C_{18}H_{22}ClCu_{0.5}N_2O_5]\cdot CH_3OH\cdot ClO_4$ | $C_{18}H_{16}ClCu_{0.5}N_2O_6$ |
| Formula weight | 497.63 | 423.55 |
| Crystal system | triclinic | triclinic |
| Space group | $P\bar{1}$ | $P\bar{1}$ |
| $\mu$/mm$^{-1}$ | 2.461 | 2.859 |
| $R[F^2 > 2\sigma(F^2)]$ | 0.0473 | 0.0432 |
| $a, b, c$/Å | 10.974(1), 11.421(1), 11.698(1) | 8.544(1), 8.858(1), 13.707(1) |
| $\alpha, \beta, \gamma$ (°) | 114.180(4), 93.573(5), 116.809(6) | 88.050(5), 72.984(5), 64.944(4) |
| $V$/Å$^3$ | 1137.5(2) | 893.8(2) |
| $T$/K | 293(2) | 293(2) |
| $Z$ | 2 | 2 |
| Reflections collected | 4472 | 3518 |
| Observed data [$I > 2\sigma(I)$] | 4229 | 3232 |

[a] Atomic scattering factors from *Acta Crystallogr.*, *Sect. A*, 1995, 441, *International Tables for Crystallography*, vol. C, Mathematical, Physical and Chemical Tables, ed. A. J. C. Wilson, Tables 4.2.6.8 and 6.1.1.4.




**Scheme 2** Molecular structure of complexes **C1** and **C2**.

formed between the methoxybenzyl rings [distance between mean planes (dmp) = 3.410 Å].

### Structural analysis of bis[*N*-(2-methoxybenzyl)quinoline-2-carboxamide]copper(II) diperchlorate (C2)

Two ligands chelate $Cu^{II}$ with a bite angle of 80.85(7)°, *via* the amide O(13) atom and the N(2) atom in the pyridine moiety, forming short bonds of, respectively, 2.096(2) and 1.924(2) Å with $Cu^{II}(1)$ (Fig. 5). The apex perchlorate O(25) atom forms a longer bond of 2.464(8) Å with $Cu^{II}(1)$. The $Cu^{II}(1)$ ion is located on an inversion center. The significant deviation of the angles O(13)–Cu–O(25) [78.03(19)°] and O(13)–Cu–N(2) [80.87(7)°] from the ideal value of 90° is due to the small bite size of the five membered planar chelate ring. The deviation of the $Cu^{II}(1)$ atom from the plane N(2)–C(11)–C(12)–O(13) is 0.274 Å. The molecules are organized in a three-dimensional network in which van der Waals π–π interactions between the aromatic cycles contribute most of the crystallographic cohesion. We also noted that the quinoline rings (dmp = 3.543 Å) as well as the methoxybenzyl rings (dmp = 3.545 Å) are not strictly superposed, but slightly shifted by 0.88 and 1.29 Å, probably in order to optimize the electrostatic contribution to the interaction as has already been described by Hunter and co-workers.[10] A T-shaped π–π intermolecular interaction is also formed between the quinoline and methoxybenzyl rings.[10,11] Moreover, a single hydrogen bond is obtained between the amide NH(14) and a perchlorate oxygen atom of a neighboring molecule.

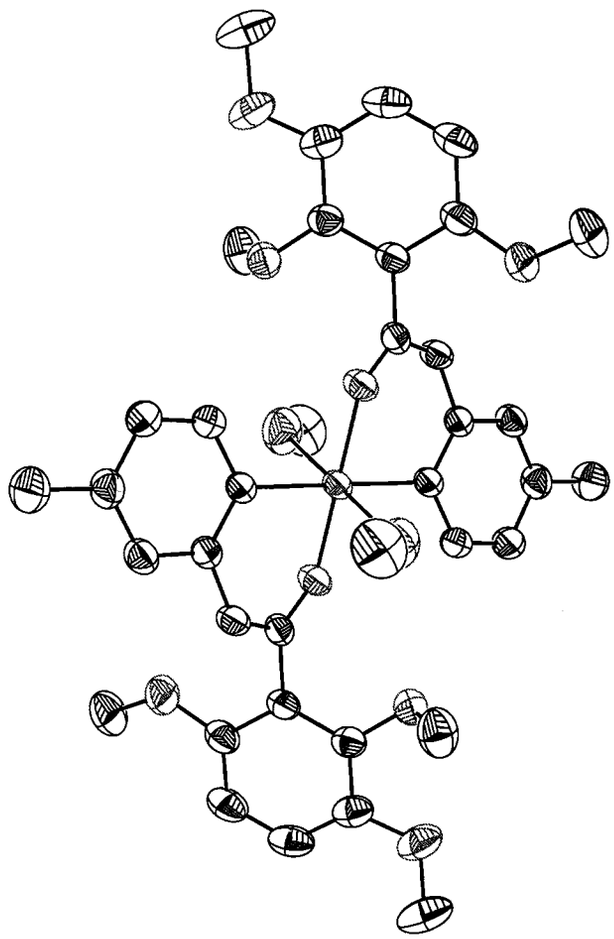


**Fig. 4** Crystal structure of **C1** (for clarity, free solvent molecules and counterions reported in Scheme 2 have been omitted).

### Comparison of the crystal structures

The crystallographic structures of the coordination compounds analyzed in this work reveal that complexes **C1** and **C2** adopt an octahedral geometry, adequate to reach the subsites $S_1/S_2$ and $S'_1/S'_2$ of the protease. Two ligands symmetrically coordinate copper(II) with aromatic nitrogen and amide oxygen atoms. They form an equatorial square plane and orient the substitu-

**Table 2** Bond lengths in Å between copper(II) and the chelating atoms in complexes **C1** and **C2** compared to CSD bond length reference for nitrogen and oxygen bonded to copper(II)

| | C1 | C2 | CSD |
|---|---|---|---|
| $N_{pyridine}$ | 2.011(2) | 2.097(2) | 2.035(2) |
| $O_{amide}$ | 1.955(1) | 1.924(2) | 1.936(5) |
| $O_{apical}$ | 2.423(2) | 2.464(2) | 2.450(5) |

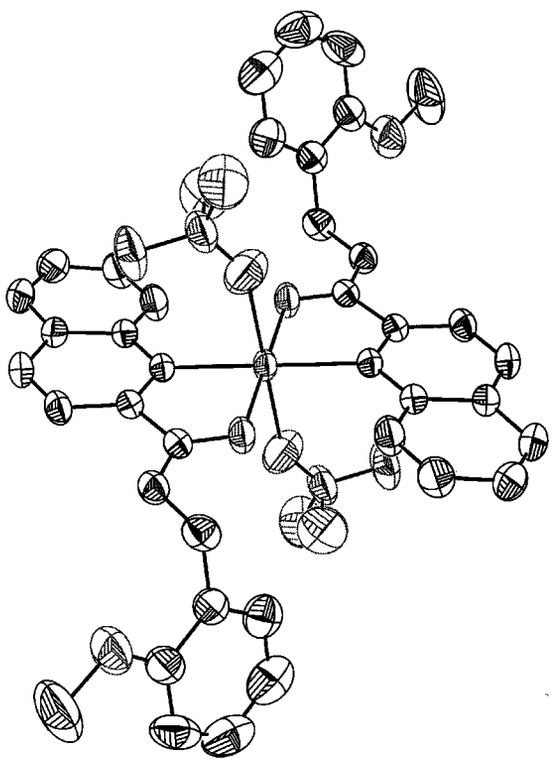


**Fig. 5** Crystal structure of **C2** (for clarity, free solvent molecules and counterions reported in Scheme 2 have been omitted).

ents designed to interact with the hydrophobic pockets $S_1/S_2$ and $S'_1/S'_2$ of the enzyme. **C1** and **C2** display inversion symmetry, with copper(II) being the inversion center.

The environment around copper(II), summarized in Table 2, was further analyzed in terms of bond distances and compared to similar compounds itemized in the Cambridge Structural Database (CSD). The bond distances between the pyridine nitrogen in complexes **C1** and **C2** and copper(II) are typical of $Cu^{II}$–N bonds and close to the mean value of 2.035(2) Å observed for the CSD Cu–$N_{pyr}$ bond distance distribution [Fig. 6(*a*)]. The bond distances between copper(II) and the apical oxygens in the complexes **C1** and **C2** are significantly longer (by *ca.* 0.4 Å) than the bond lengths between copper(II) and oxygen atoms situated in the plane of the complex and range from 2.423(2) to 2.464(2) Å. Two distinct distributions are obtained in the CSD for $Cu^{II}$–O: a thin one centered on shorter bond lengths [1.936(5) Å] and a broader one centered on longer bond lengths [2.316(5) Å] [Fig. 6(*b*)]. Copper(II)–oxygen distances of 2.2–2.4 Å are commonly assumed as typical for 'long' Cu–O bonds in Jahn–Teller distorted complexes of copper(II). This means that the weakly bound axial atoms could be readily dissociated in the enzyme active site and provide sites on $Cu^{II}$ for binding with the catalytic water molecule and proton acceptor Y.

Most of the crystalline cohesion of the complexes **C1** and **C2** is provided by intermolecular van der Waals π–π interactions, given the hydrophobic character of these complexes. Compounds **C1** and **C2** were superimposed and their molecular surfaces computed.[13] These were compared to the molecular

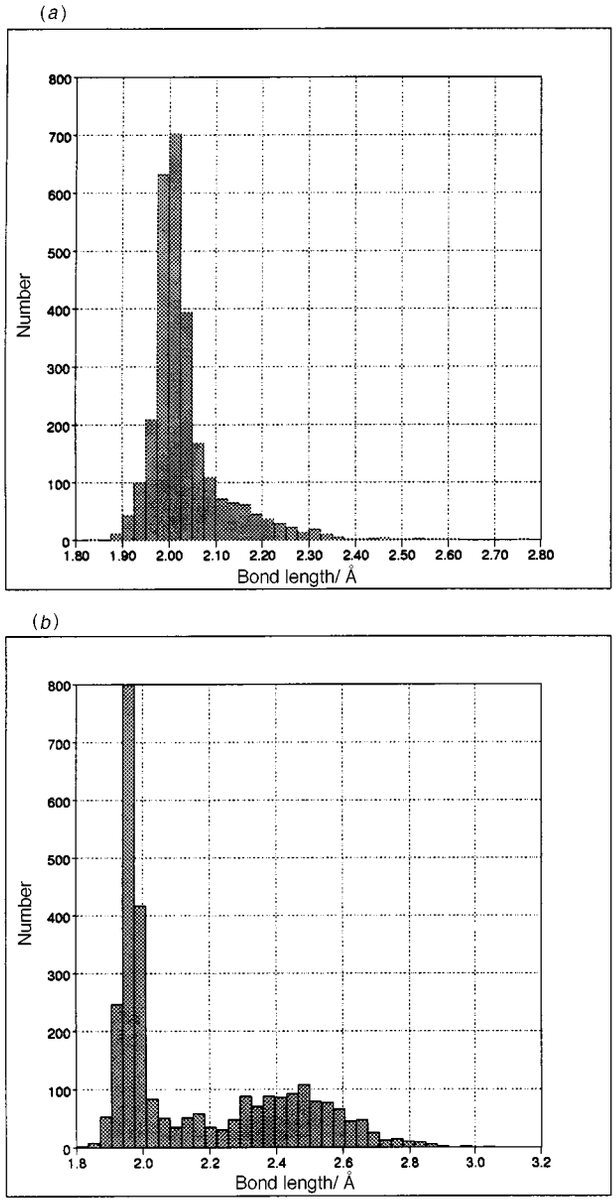



**Fig. 6** Distributions observed for the bond lengths (*a*) $Cu^{II}$–$N_{pyridine}$ and (*b*) $Cu^{II}$–O.

surface obtained from the crystallographic structure of the symmetrical HIV-1 PR peptidomimetic inhibitor L700,417.[14] This inhibitor interacts with the hydrophobic subsites $S_1/S'_1$ and $S_2/S'_2$ of HIV-1 PR through its benzyl and indene groups. Similarly, two symmetrical hydrophobic areas ($H_1/H'_1$ and $H_2/H'_2$) were found around copper(II) which can be related to the hydrophobic subsites $S_1/S'_1$ and $S_2/S'_2$ of HIV-1 PR (Fig. 7). It can further be noted that the amide nitrogen atom involved in hydrogen bonding in the crystalline state of complex **C1** could take part in hydrogen bonding in the active site of the enzyme in analogy to L700,417. As a consequence, the newly synthesized ligands reported here chelate copper(II) in a geometry that places the hydrophobic groups and H-bonding atoms in a way similar to L700,417.

The coordination compounds were tested for their ability to inhibit HIV-1 protease activity. Complexes **C1** and **C2** were found to inhibit the enzyme's activity with an $IC_{50}$ of respectively 1.5 and 1 μM. The inhibition assay was performed as previously described.[15]

## Conclusion

The improvement of the previously described pharmacophore

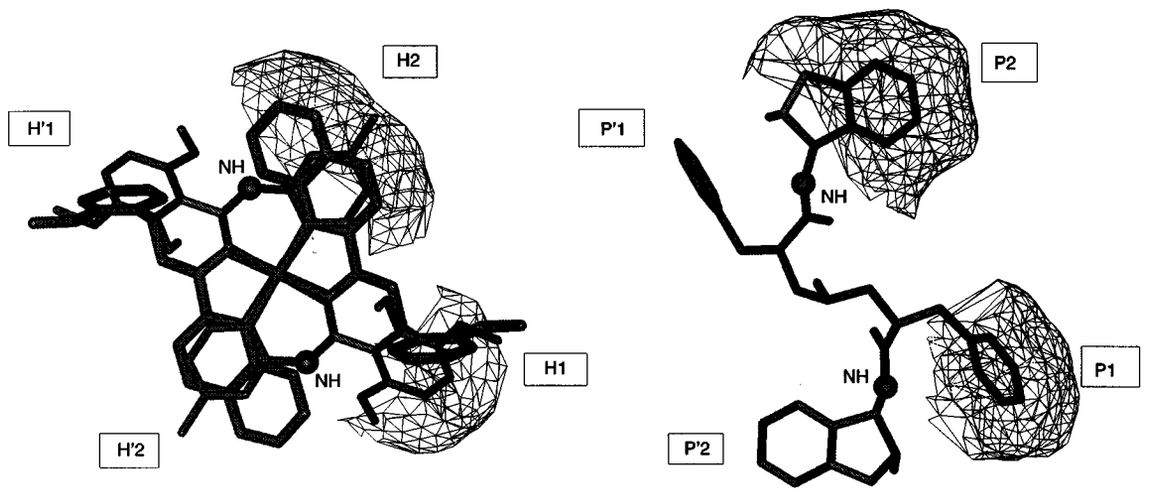



**Fig. 7** (*a*) Superposition of the crystallographic structure of **C1** and **C2** in comparison to (*b*) HIV-1 PR inhibitor L700,417. The hydrophobic areas $H_1/H'_1$ and $H_2/H'_2$ are located similarly to the L700,417 $P_1/P'_1$ and $P_2/P'_2$ groups. For the sake of clarity, the symmetrical $H'_1$, $H'_2$, $P'_1$, $P'_2$ areas and the labile axial molecules have been omitted.

by optimizing the interaction with the hydrophobic subsites of the HIV-1 PR active site led to the design and synthesis of a new family of coordination compounds, active in the micromolar range. The previously tested complex diaqua[bis(2-pyridylcarbonyl)amido]copper(II) nitrate dihydrate had a $K_i$ of only 480 ± 120 μM.[1] Even with such low affinity for the enzyme active site, it demonstrated the validity of the original pharmacophore. This complex was found to interact with the catalytic residues Asp25/125 and the flap resides Ile50/150 but it did not possess substituents large enough to interact with the enzyme hydrophobic subsites $S_1/S'_1$ and $S_2/S'_2$. In the search for more potent compounds that could be considered as 'leads' for the optimization process, we developed in this work octahedral complexes having a proper orientation of the substituents in the enzyme active site, and observed a binding affinity increase by a factor $10^3$. Even with this improvement, the micromolar concentration range is still much too high compared to inhibitors of other families like the peptidomimetic inhibitor L700,417, which possesses substituents complementary to the same subsites $S_1/S'_1$ and $S_2/S'_2$. This molecule also interacts through four additional H-bonds with residues Asp29/129 and Gly 48/148 of the enzyme active site.[6] L700,417 inhibits the enzyme with an $IC_{50}$ of 0.67 nM. More work has to be performed in order to further improve the efficiency of the new family of HIV-1 PR inhibitors. There are several ways to proceed. For example, it is possible to further optimize the interaction of the substituents with the hydrophobic pockets of HIV-1 PR and to add, after molecular modeling of the metallo-organic complexes, functions that will interact with the active site of the enzyme by H-bonding. The positive results obtained with complexes **C1** and **C2** clearly indicate that the use of copper complexes is a potentially fruitful approach for the development of a new family of HIV-1 PR inhibitors which could provide future alternatives to HIV multi-drug treatment.

## Experimental

### *N*-(4-Methyl-2-pyridyl)-2,3,6-trimethoxybenzamide (L1)

To a solution of 2,3,6-trimethyoxybenzoic acid **1** (2 g, 9.4 mmol) in $CH_2Cl_2$ (50 ml), oxalyl chloride was added slowly at 0 °C (2.88 ml, 33 mmol). After stirring at 0 °C for 1 h, the mixture was evaporated at 30 °C, and a solution of 2-amino-4-methylpyridine **2** (1 g, 9.4 mmol) in $CH_2Cl_2$ (50 ml) was added. The mixture was stirred at room temperature for 12 h, and then evaporated. To the oily residue was added 10% aqueous $Na_2CO_3$ (20 ml) and the resulting mixture was extracted with $CH_2Cl_2$ (3 × 20 ml). The organic layers were pooled, washed with brine (40 ml), dried ($MgSO_4$) and evaporated. Column chromatography through silica gel ($CH_2Cl_2$–$Pr^iOH$, 95:5) of the residue gave **L1** (0.6 g, 21%) as a crystalline product: mp 172–174 °C (from $CH_2Cl_2$–$Pr^i_2O$); $\delta_H(CDCl_3)$ 9.07 (1H, br s), 8.26 (1H, s), 7.79–7.77 (1H, d, *J* 5),‡ 6.92–6.87 (1H, d, *J* 9), 6.78–6.75 (1H, d, *J* 5), 6.58–6.54 (1H, d, *J* 9), 3.89 (3H, s), 3.83 (3H, s), 3.72 (3H, s), 2.37 (3H, s); $\delta_C(CDCl_3)$ 164, 151.8, 149.8, 150.7, 147.5, 122, 120.6, 114.9, 114.4, 106.1, 103.1, 61.8, 56.7, 56, 21.4 (Calc. for $C_{16}H_{18}O_4N_2$. $H_2O$: C, 60.0; H, 6.3; N, 8.8. Found: C, 60.1; H, 5.7; N, 8.5%).

### *N*-(2-Methoxybenyl)quinoline-2-carboxamide (L2)

The same procedure was used for the condensation of quinolic acid **4** and 2-methoxybenzylamine **5** **L2** (17.5% yield) was obtained as a crystalline product: mp 112–115 °C; $\delta_H(CDCl_3)$ 8.73 (1H, br s), 8.34–8.2 (2H, m), 8 (1H, d, *J* 8), 7.8 (1H, d, *J* 8), 7.73–7.66 (1H, m), 7.58–7.5 (1H, m), 7.41–7.37 (1H, d, *J* 7), 7.29–7.21 (1H, t, *J* 7.9, 7.7), 6.96–6.85 (2H, m), 4.7 (2H, d, *J* 6), 3.8 (3H, s); $\delta_C(CDCl_3$ 164.4, 157.7, 150.1, 146.5, 137.4, 130.1, 129.8, 129.6, 128.9, 127.9, 127.8, 120.7, 119.0, 110.5, 55.5, 39.3 (Calc. for: $C_{18}H_{16}O_2N_2$: C, 73.9; H, 5.5; N, 9.6. Found: C, 73.8; H, 5.6; N, 9.5%).

### (Dimethanol)bis[*N*-(4-methyl-2-pyridyl)-2,3,6-trimethoxybenzamide] copper(II) dimethanol diperchlorate (C1)

A solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (50 mg in 5 ml of methanol) was added to 58 mg of ligand **L1** previously dissolved in 15 ml of methanol. The green solution obtained was placed into a closed area saturated with $Et_2O$ vapor. After 24 h all the complex **C1** had precipitated.

### Bis[*N*-(2-methoxybenyl)quinoline-2-carboxamide]copper(II) diperchlorate (C2)

A solution of 111 mg of $Cu(ClO_4)_2 \cdot 6H_2O$ dissolved in 5 ml of methanol was added to 90 mg of ligand **L2** previously dissolved in 15 ml of methanol. The green solution obtained was placed into a closed area saturated with $Et_2O$ vapor. After 24 h all the complex **C2** had precipitated.

### X-Ray crystallography

Crystals of **C1** were obtained by slow evaporation of a methanol solution at room temperature. Green cubic crystals grew from the solution but were unstable and required sealing in a

‡ *J* Values are given in Hz.

glass capillary for all X-ray measurements. All data were collected at 293 K using a graphite-monochromated Enraf-Nonius CAD-4 diffractometer with Cu-Kα radiation ($\lambda = 1.54178$ Å). The lattice constants are listed with other relevant crystal data in Table 1. Complete data sets were collected to a maximum $\theta$ limit of 72°. The data were corrected for Lorentz and polarization effects using the in-house program *NONIUS93*, while psi-scan absorption correction was applied. All structures were solved by direct methods using *SIR92*.[16] Refinement on $F^2$ was performed *via* the full-matrix least-squares algorithm of the *SHELXL96* package.[17] Hydrogen atoms were calculated at their standard positions and treated in a rigid model unless they appeared in the Fourier difference map. The compound **C1** perchlorate ion was rotationally disordered over two positions with 60 and 40% occupancies, and was refined with geometric restraints.

Compound **C2** crystallized respectively from a methanol–distilled water solution at room temperature. A green (**C2**) prismatic crystal was used for all X-ray measurements. The crystal structure was obtained using the same procedure as for **C1**. The bound perchlorate ion in compound **C2** was also disordered. The disorder was modelled by including two orientations of the tetrahedra (approximatively 180° rotation around a common Cl–O axis) with 60 and 40% occupancies.§

## Acknowledgements

We wish to thank the EC for grant CT96-0823 and the National Belgian Foundation for Scientific Research (FNRS), IBM-Belgium and the Facultés Universitaires Notre-Dame de la Paix (FUNDP) for the use of the Namur Scientific Computing Facility. The authors would like to thank N. Boggetto, E. de Rosny, B. Norberg and J. Wouters for their help in this study. F. L. and M. L. thank the National Belgian Foundation for Scientific Research (FNRS) and the Industry and Agriculture Research Foundation (FRIA) for financial support.

§ Full crystalline details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/157. See http://www.rsc.org/suppdata/p2/1999/795/ for crystallographic files in .cif format.

## References

1 F. Lebon, E. De Rosny, M. Reboud-Ravaux and F. Durant, *Eur. J. Med. Chem.*, 1998, **33**, 733.
2 M. Markowitz, H. M. Mo, D. J. Kempf, D. W. Norbeck, T. N. Bhat, J. W. Erickson and D. D. Ho, *J. Virol.*, 1995, **69**, 701.
3 P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C. H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe and S. Erickson-Viitanen, *Science*, 1994, **263**, 380.
4 A. L. Swain, M. M. Miller, J. Green, D. H. Rich, J. Schneider, S. B. H. Kent and A. Wlodawer, *Proc. Natl. Acad. Sci. U.S.A.*, 1990, **87**, 8805.
5 M. Jaskolski, A. G. Tomasselli, T. K. Sawyer, D. G. Staples, R. L. Heinrikson, J. Schneider, B. H. Kent and A. Wlodawer, *Biochemistry*, 1991, **30**, 1600.
6 R. Bone, J. P. Vacca, P. S. Anderson and M. K. Holloway, *J. Am. Chem. Soc.*, 1991, **113**, 9382.
7 I. Castro, J. Faus, M. Julve, J. M. Amigo, J. Sletten and T. Debaerdemaeker, *J. Chem. Soc.*, *Dalton Trans.*, 1990, 891.
8 S. Wang, G. W. A. Milne, X. Yan, I. J. Posey, M. C. Nicklaus, L. Graham and W. G. Rice, *J. Med. Chem.*, 1996, **39**, 2047.
9 D. Venkataraman, Y. Du, S. R. Wilson, K. A. Hirsch, P. Zhang and J. S. Moore, *J. Chem. Educ.*, 1997, **74**, 915.
10 C. A. Hunter and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1990, **112**, 5525.
11 M. Luhmer, K. Bartik, A. Dejaegere, P. Bovy and J. Reisse, *Bull. Soc. Chim. Fr.*, 1994, **131**, 603.
12 S. Tsubayama, T. Sakurai, K. Kobayashi, N. Azuma, Y. Kajikawa and K. Ishizu, *Acta Crystallogr.*, *Sect. B*, 1984, **40**, 466.
13 Biosym/Molecular Simulations Inc., San Diego, INSIGHTII package, version 95.0.
14 R. Bone, J. P. Vacca, P. S. Anderson and M. K. Hooloway, *J. Am. Chem. Soc.*, 1991, **113**, 9382.
15 A. Bouras, N. Boggetto, Z. Benatalah, E. de Rosny, S. Sicsic and M. Reboud-Ravaux, *J. Med. Chem.*, in the press.
16 A. Altomare, G. Cascarano, C. Giacovazzo and A. Guagliardi, in Ist. di Ric. per lo Sviluppo di Metodologie Monocristallographiche, CNR, University of Bari, Bari, Italy, 1992.
17 G. M. Sheldrick and T. R. Schneider, 1997, SHELXL: high resolution refinement, *Methods in Enzymology*, 277, ed C. W. Carter, Jr and L. M. Sweet, Academic Press, San Diego, pp. 319–343.

*Paper 8/09270B*