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# Synthesis of a Heterocyclic Amine and Acid Receptor

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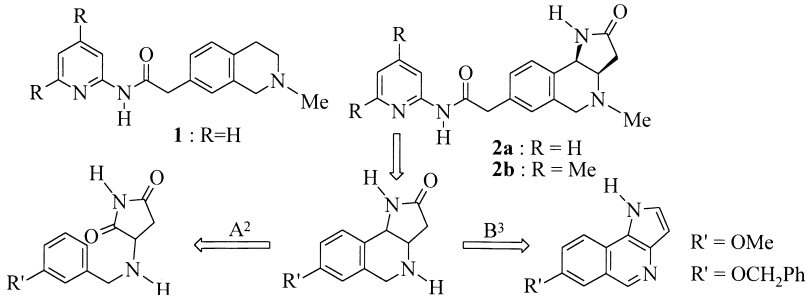
**Abstract**—The synthesis of a molecule able to bind both with an amine and a carboxylic acid is described. This new host consists in a pyrroloisoquinoline structure possessing a side arm with an acetamidopyridine moiety. The pyrroloisoquinoline part was obtained after improvement of the previously published route involving regioselective reduction of appropriate 3-arylalkylaminosuccinimides followed by ring closure using iminium chemistry. The tricyclic structure was then functionalized by cross-coupling reaction under $Pd^0$ catalysis of its triflate derivative with the trimethylsilyl ketene acetal of methyl acetate. The so-obtained ester was then reacted with 2-amino-4,6-dimethylpyridine leading to the targeted host. The association constants of this latter compound with some carboxylic acids and amines were determined by $^1H$ NMR titration. NOESY experiments and molecular modeling calculations were performed in order to precise the actual host–guest interactions. 

## Introduction

In a previous paper, we described the design and synthesis of a heterocyclic molecule able to bind with various amines.[1] This host combined an isoquinoline structure possessing a lone pair for hydrogen bonding with a N–H group and a flexible arm terminated by an acetamidopyridine moiety ensuring the second binding point (Scheme 1). We found it interesting to design also a compound able to bind both with an acid and an amine. For this purpose, we added a five-membered ring possessing a lactam group in order to allow supplementary hydrogen bonding with a carboxylic acid.

The resulting molecule **2a** possesses two heterocyclic nitrogen lone pairs. The CPK model of this host suggested that these two heterocyclic nitrogen lone pairs combined with the two N–H bonds would stabilize the transition state of the reaction between an acid and an amine. We decided then to synthesize this new heterocyclic system using two different methodologies. We have published recently these two routes, the key step of the first one being regioselective reduction of appropriate aminosuccinimides and subsequent ring closure (pathway A)[2] whereas the second consisted in construction of the pyrroloisoquinoline system followed by oxidation leading to the targeted lactam (pathway B).[3] The more convenient route was the first one and it afforded the tricyclic derivatives **4a–c** (Scheme 2). The aim of this paper is to achieve the synthesis of the host molecules **2a**,**b** and to study their binding properties with acids and amines. The main problems were the introduction of the methyl group on the isoquinoline nitrogen and the functional group interconversion leading to the tricyclic ring system substituted by the side chain.




**Scheme 1.**

*Keywords*: molecular recognition; binding constants; molecular modeling; cross-coupling.
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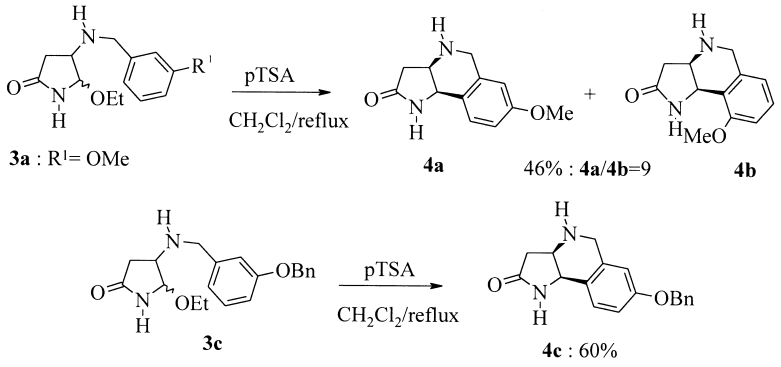



**Scheme 2.**

## Results and Discussion

### Synthesis of the tricyclic phenol

We first tried to introduce the methyl group by reductive amination. This kind of reaction is usually carried out under acidic conditions and classical conditions of the literature led only to low yields of N–Me compound besides large amounts of degradation products ($NaBH_3CN/(HCHO)_n/CH_3COOH$, $NaBH_4/CF_3COOH/(HCHO)_n$[4] or $Zn(BH_4)_2/(HCHO)_n$).[5] The tricyclic structure was rather unstable in acidic medium and we decided to use the neutral conditions of Charles et al.[6] with paraformaldehyde in refluxing methanol (Scheme 3).

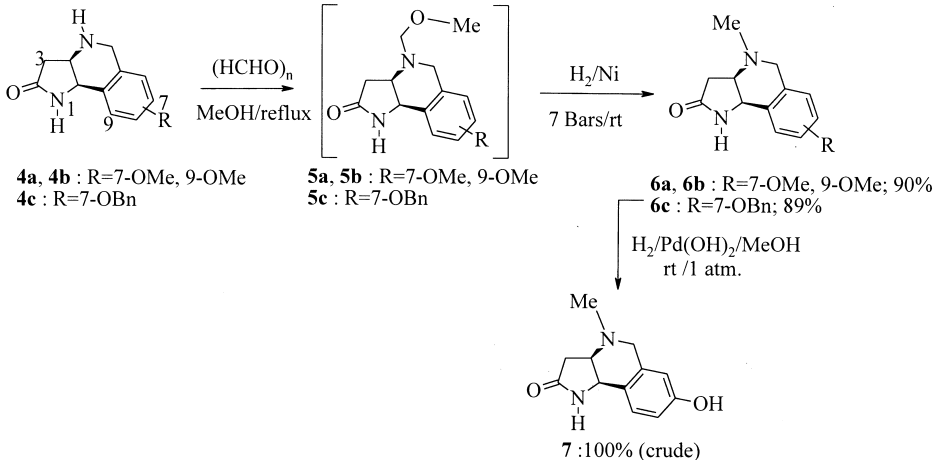
The heterocyclic amines **4a–c** afforded the intermediate ethers **5a–c** isolated as yellow solids. The compounds **5a–c** were in situ reduced in nice yields with hydrogen under Raney nickel catalysis.

Various systems were tried in order to cleave the methoxy group of **6a**,**b** ($NaI/ClSiMe_3$, $Cl_4Si/NaI$, $BCl_3$, $BBr_3$). Whatever the conditions used, only degradation products were formed and it must be pointed out that when the methoxy group was at C-9, no reaction occurred. Alternatively, the benzyloxy derivative **6c** underwent clean cleavage promoted by Pearlman catalyst leading to the desired phenol **7**. The crude phenol obtained after filtration of the catalyst and subsequent removal of the solvent was pure enough to be used without purification. Starting from the appropriate succinimide, this synthesis required four steps and three purifications by flash chromatography. We tried then to improve the overall yield by decreasing the number of purifications. The 4-aminosuccinimide **8**[2] was thus regioselectively reduced under recently published conditions (sodium borohydride in a mixture of methanol and dichloromethane).[7] Under these conditions, the work-up was considerably simplified. The crude hydroxylactam **3d** was not converted into the methoxy derivative but cyclized under *p*-toluenesulfonic acid catalysis leading to the benzyloxypyrroloisoquinoline **4c** in a 30% yield for the two steps starting from **8** (Scheme 4).

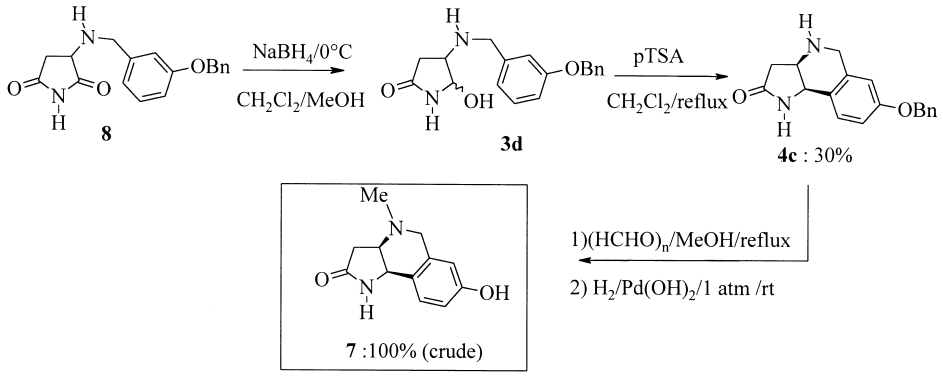
The benzyloxy derivative **4c** was reacted with paraformaldehyde in methanol and the intermediate carbinolamine subsequently reduced with hydrogen under palladium dihydroxide catalysis. The Pearlman's catalyst was reactive enough to cleave in the same pot the benzyloxy group. The required phenol **7** was thus obtained in quantitative yield starting from **4c** and was again pure enough to be used without further purification. So, the tricyclic part was obtained from **8** within three steps and one purification in a nice one-pot procedure.

### Functionalization of the benzene ring

In order to introduce the side chain with a coupling reaction, we selected the triflate group offering large possibilities of



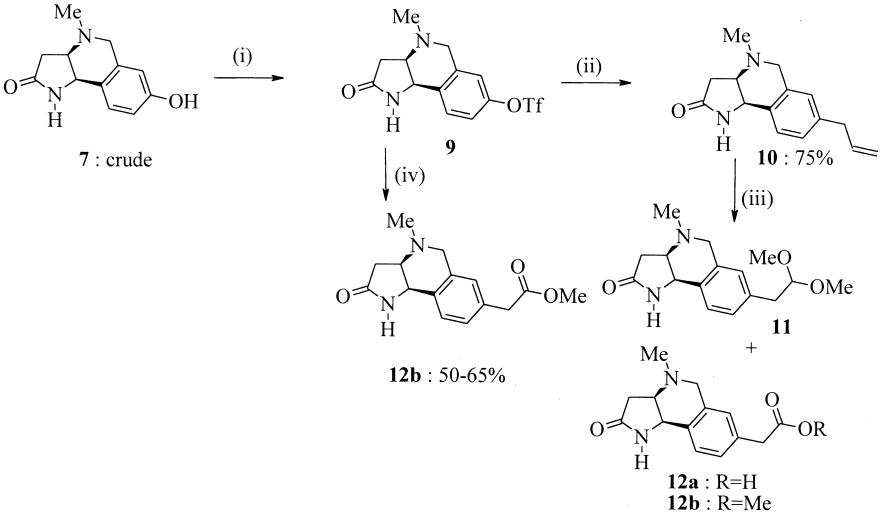

**Scheme 3.**



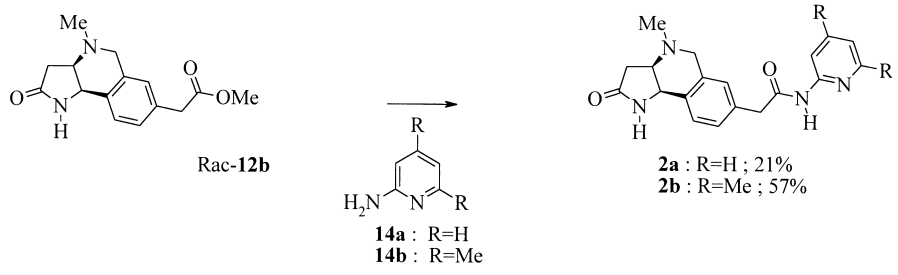

**Scheme 4.** One-pot synthesis of the tricyclic structure.

functionalization of an aromatic ring.[8] We tried first classical conditions with triflic anhydride[9] but only degradation products were observed probably due to the acidity of the medium. Alternatively, when pyridine was used as a solvent, the triflate was obtained in a 61% yield but it could not be purified. In order to use more basic conditions, we tried ditriflimide because it is necessary to activate first the phenol as a phenolate. The triflate **9** was easily isolated (LHMDS, THF, rt) but the yields were not reproducible owing to the low solubility of the phenolate in THF. Finally, the required triflate was obtained in a 84% yield in DMF with triethylamine as a base.

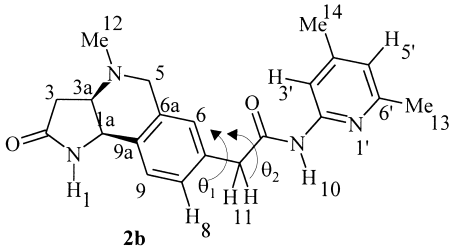
This triflate was reacted with allyltributylstannane under Stille[10] conditions and led to the allyl derivative in a 75% yield (Scheme 5). This allyl group was subsequently oxidized with ozone and a mixture of the acetal **11** and the ester **12b** (with a small amount of the acid **12a**) was isolated. This reaction was not optimized because we found it better to use other coupling reactions. Whereas




**Scheme 5.** (i) 2.2 $PhN(Tf)_2/Et_3N$, DMF/rt. (ii) $CH_2{=}CH{-}CH_2{-}SnBu_3/LiCl$, $DMF/PdCl_2(PPh_3)_2$, 95°C/4 h. (iii) $O_3$/HCl/MeOH. (iv) **13b**/$Pd(PPh_3)_4$/AcOLi/THF reflux.




**Scheme 6.**




**Scheme 7.** Comprehensive numbering of host **2b** for the discussion.

the triflate did not react cleanly under the Reformatski conditions defined by Orsini,[11] the trimethylsilyl ketene acetal of methyl acetate[12] afforded the ester **12b** in variable yields (50 to 65%).[13] An increasing of the amounts of reagent or catalyst did not improve this yield.

The last step of the synthesis involved the conversion of the ester **12b** into the targeted host.

Our previous results in this field showed that this conversion is not so easy.[1] So we decided to check several methods described in the literature (Scheme 6). The complex LAH/2-aminopyridine[14] or $BBr_3$ activation of the ester **12b**[15] led only to tarry material. However, the complex $Me_3Al$/2-aminopyridine[16] afforded the host **2a** in low yield (21%). This compound was not soluble enough in chloroform to undergo NMR binding studies. Fortunately, the more lipophilic 2-amino-4,6-dimethylpyridine led to the more soluble host **2b** in a better yield (57%) by increasing the reaction time. It must be emphasized that an excess of complex (2.4 mol) was required because the isoquinoline nitrogen is probably involved in the complexation process.

## Binding experiments

We first examined the $^1H$ and $^{13}C$ NMR spectra of **2b** in deuteriochloroform. The main features were the following: First of all, a downfield shift was observed for the β proton (7.85 ppm for $H_{3'}$ instead of 6.69 ppm for $H_{5'}$, numbering of Scheme 7) of the pyridine moiety indicating that this proton is close to the carbonyl group. This shift allowed us to assume that the acetylaminopyridine preferred a *trans* conformation. Secondly, the chemical shift of the proton of the lactam group appeared to be very dependent on the concentration. This concentration induced shift could be the consequence of a dimerization process. When a dilution titration[17] was performed over the range of concentrations studied (about 0.02 M), a value of $K_d$=12 $M^{-1}$ for the dimerization was measured. This low value was very interesting because a dimerization process could lead to smaller values for the association constants with guests. However, with binding experiments performed at 0.02 M, this value means roughly that 20–25% of the receptor is present as a dimer or in a higher form. In order to obtain more information on the conformation of **2b** in solution, we performed NOESY experiments on a 500 MHz spectrometer. Lots of cross peaks were observed (Fig. 1, left) and one of them showed a weak correlation between $H_8$ of the benzene ring and one proton of the 6-methylpyridine group. This correlation may be due to a bowl shape of the host. To have an idea of the flexibility of host **2b**, MM2 calculations[18] were carried out with systematic variation of the two dihedral angles $\theta_1$ and $\theta_2$ and assuming a *trans* conformation of the acetamidopyridine moiety (Scheme 7). A number of 362 conformations was obtained with about 20 in the range of 4–4.2 kcal $mol^{-1}$ and a global minimum having an energy of 3.92 kcal $mol^{-1}$ was found (Fig. 1, right). Among the twenty conformers possessing energies close to the global minimum, most of them are folded enough to explain the vicinity of $H_8$ and the methyl connected to $C_{6'}$. However the measured distance between these protons, was too high to explain the observed NOE's. In fact, it is impossible to exclude the contribution of the auto-association process to account this observation.

Binding experiments with some acids and amines were then undertaken using the $^1H$ NMR titration method.[19] It must be pointed out that although dimerization of the receptor is not

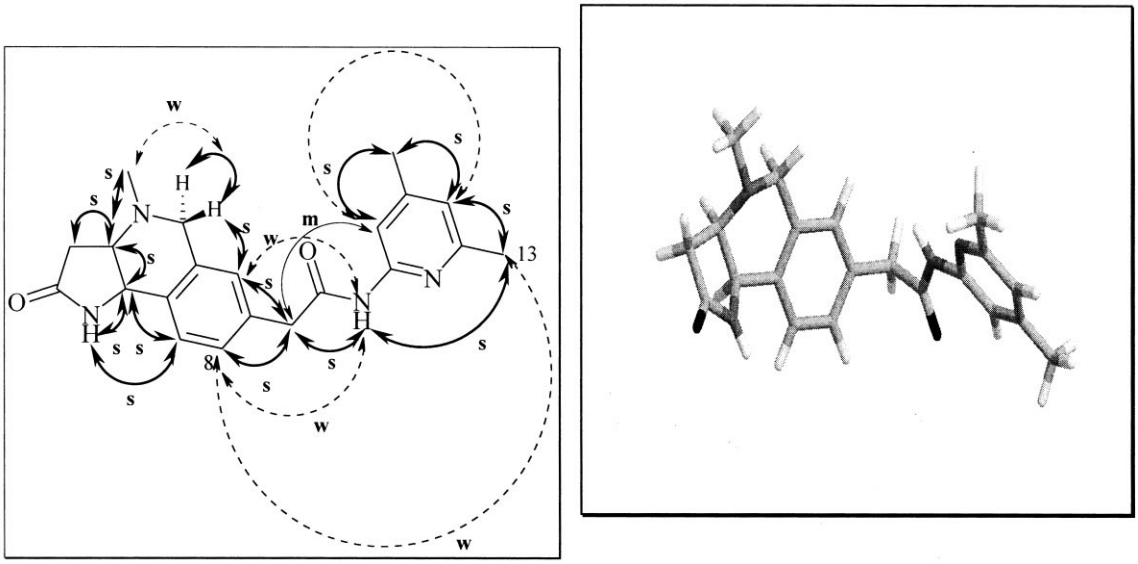



**Figure 1.** Left, observed NOE's in host **2b** and right, more stable conformer of **2b** ($E$=3.94 kcal $mol^{-1}$). Intensity of correlations: w=weak, s=strong, m=medium.

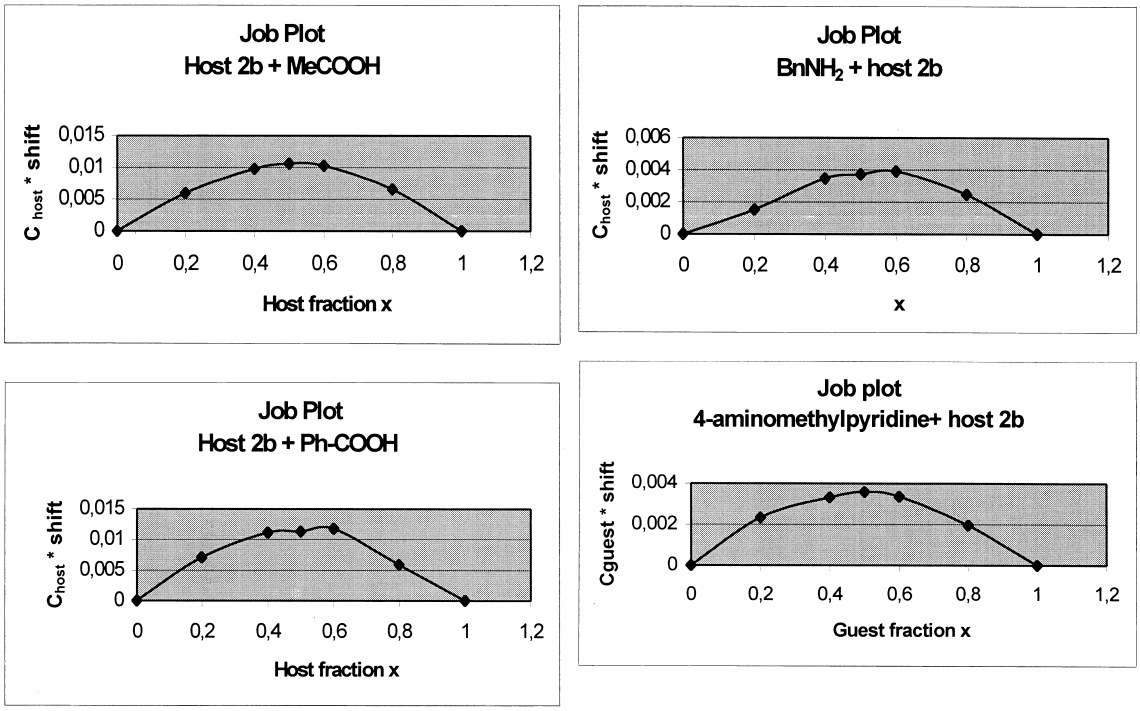


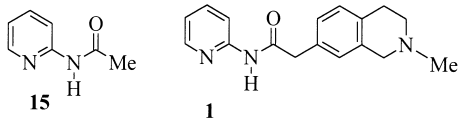

**Figure 2.** Job plots of host **2b** with two carboxylic acids and two amines.

negligible (vide supra), this process was neglected in the calculations. For this reason, the computed values are probably overestimated. The acids used in complexation studies were acetic and benzoic acids. While increasing the concentration of the guest, the signals of the two NH groups of **2b** were shifted downfield until saturation was achieved. (for the carboxamide NH, these saturations occurred at 10.9 ppm in the case of acetic acid and 11.5 ppm for benzoic acid). The complex stoichiometry was determined by Job's method of continuous variation[20] (Fig. 2). Whereas a 1/1 stoichiometry could be assumed with acetic acid (maximum at $x$=0.5), an other geometry could not be discharged with benzoic acid. For the calculation of the associations constants, we found better to use the observed shifts for the signal corresponding to $H_{10}$ not involved in self association of the host (no shift was observed with dilution of the host without guest).

Good values of Ka were obtained (Table 1, 2nd column). For benzoic acid, the association constants with **2b** and 2-acetamidopyridine[21] are similar (Table 1, 3rd column) indicating that the pyridine lone pair and the carboxamide NH are probably involved in the binding process. However, in the case of acetic acid, the measured Ka value is about four fold higher showing the contribution of a supplementary interaction due to the pyrroloisoquinoline unit. The difference between the two acids may be attributed to the bulkiness of the phenyl ring.

On 1/1 complexation, the proximity of benzoic acid into the binding pocket of the receptor **2b** was supported by NOESY experiments where the aromatic protons of this acid and both the methyl pyridine protons and $H_{11}$ of the methylene group showed cross peaks (Fig. 3, lower part and Fig. 4). It must be pointed out that no cross peaks were observed with acetic acid and **2b**, under the same NMR conditions. MM2

**Table 1.** Association constants of **2b** with acids and amines




| Guest | Kass ($M^{-1}$) with **2b** | Kass ($M^{-1}$) with **15** or **1** | $\Delta\delta$ max (ppm) |
|---|---|---|---|
| Acetic acid | 350 | 80[a] | 1.94 |
| Benzoic acid | 240 | 230[a] | 2.66 |
| Benzylamine | 470 | 42[b] | 0.62 |
| 4-Aminomethylpyridine | 190 | 250[b] | 0.34 |
| *n*-Propylamine | 45 | – | 0.44 |

[a] Binding with 2-acetamidopyridine **15**.[21]

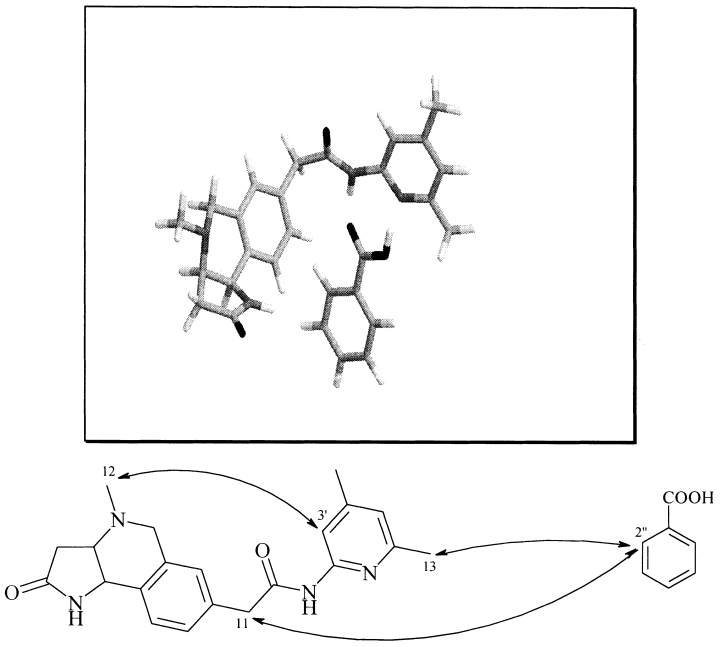



**Figure 3.** Intermolecular observed NOE's and molecular modeling of the binding of benzoic acid with **2b**.

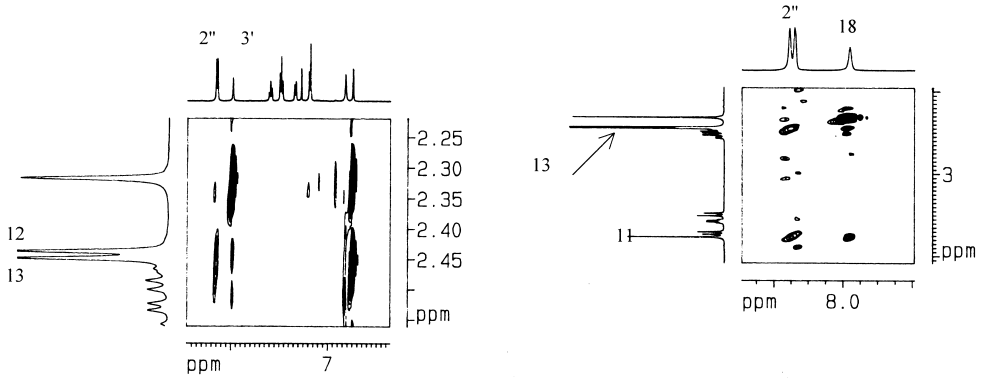



**Figure 4.** 1/1 Complexation of benzoic acid with **2b**. Selected parts of the NOESY spectrum showing cross-peaks.

calculations clearly showed the participation of the pyridine amide in forming the complex as well as the vicinity of the above mentioned protons groups (Fig. 3, high).

Similarly, the complexation of three amines was studied: benzylamine, 4-aminomethylpyridine and *n*-propylamine. While no significative shift of the signals corresponding to the host could be observed, it was possible to monitor the shift of the $NH_2$ protons of the guest by increasing its concentration. The Job plot with 4-aminomethylpyridine was in agreement with a 1/1 complex (Fig. 2, right) and an other geometry could not be discharged with benzylamine. In every case, the calculation process showed a good convergence and Ka values are reported in Table 1 (2nd column). These values are compared to those measured with a simplified amine host (3rd column) previously described by us.[1] With 4-aminomethylpyridine, the Ka is slightly lower than that observed with the simplified receptor **1**. On the contrary, with benzylamine, the association with **2b** was more than ten fold higher than that with **1**. This difference might be attributed to a supplementary interaction between the aromatic parts. This assumption is supported by the low value of Ka with benzylamine with the simplified receptor **1**. On 1/1 complexation, the proximity of benzylamine into the binding pocket of receptor **2b** was also supported by NOESY experiments. Various cross peaks (Fig. 5, high) were observed indicating that the amine group is close to the pyrroloisoquinoline moiety, the methylene group connected to the amide and the pyridine ring. This vicinity was supported by MM2 calculations (Fig. 5). Two possibilities were computed: (1) hydrogen bonding between the lone pair of the amine with the NH amide and between one amine NH with the pyridine lone pair (Fig. 5, left); (2) hydrogen bonding of the first amine NH with the pyridine lone pair and of the second amine NH with the isoquinoline lone pair (Fig. 5, right). However, it was impossible to determine the actual complexation process since the energies of the two possibilities were closely related.

## Conclusion

In this paper, the synthesis of the new heterocyclic host **2b**

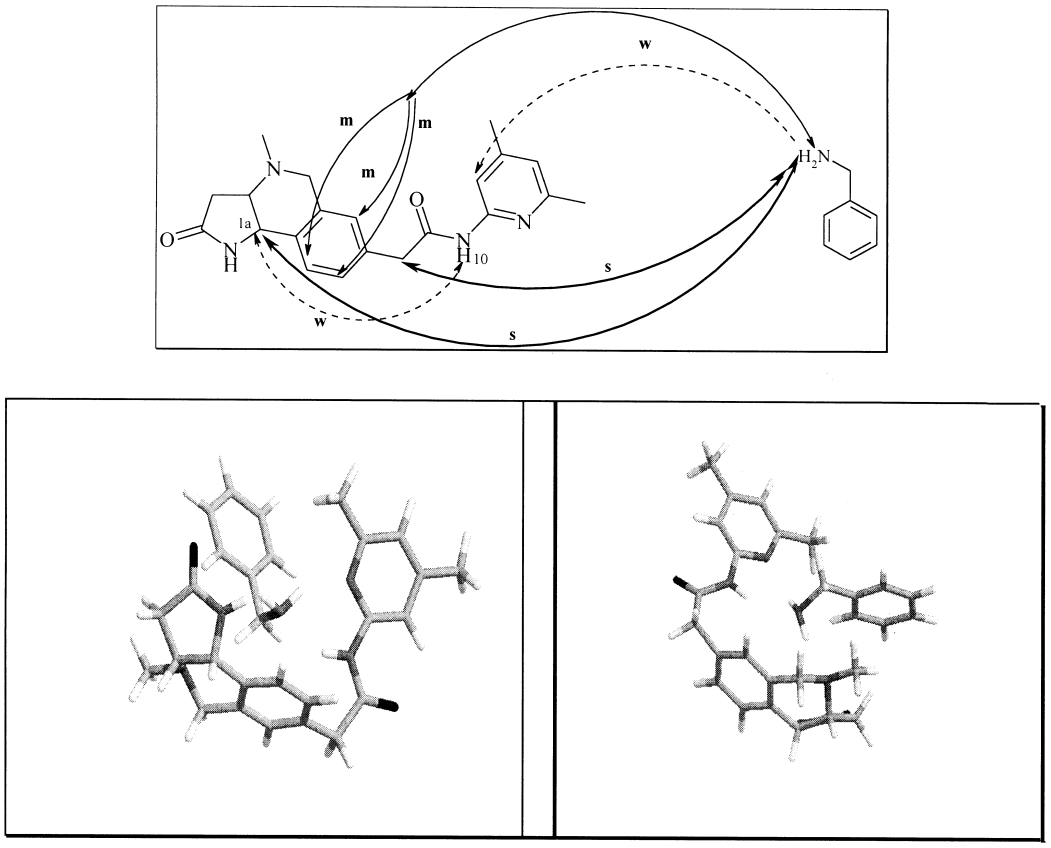



**Figure 5.** Observed intermolecular NOE's and modeling of the two binding modes of benzylamine with **2b.**

has been described. This host possesses a pyrroloisoquinoline structure connected to an acetamidopyridine at the end of a flexible arm. Good association constants were obtained both with some carboxylic acids or amines and NMR experiments associated to molecular modeling seemed to prove that the guests are bound into the pocket resulting from the flexibility of the receptor. We intend now to use the results described in this paper and in our previous reports[1,2] to design a receptor able to promote within a supramolecular process, the reaction between an amine and a carboxylic acid derivative.

## Experimental

The infra-red spectra were recorded on a Beckmann IR 4250 spectrometer. The $^{1}H$ and $^{13}C$ NMR spectra were recorded either on a 200 MHz, a 400 MHz or a 500 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuteriodimethylsulfoxide (DMSO-$d_6$). NOESY experiments were performed on deuteriochloroform solutions at 25°C with the following acquisition parameters: shift width for $F_1$ and $F_2$ 12 ppm; $F_2$ 2048 dots, $F_1$ 512 dots; scan number 32; relaxation time 2 s; mixing time 1 s. Processing parameters: $F_2$ function $\sin^2$, phase angle 90°, 2048 dots; $F_1$ function $\sin^2$, phase angle 90°, 1024 dots. Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless otherwise stated, were used without further purification. Flash chromatographies were performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 $F_{254}$).

**1a,3a,4,5-Tetrahydro-*N*-methyl-7-methoxy-1*H*,3*H*-pyrrolo[3,2-*c*]isoquinolin-2-one (6a).** A solution of the above compound **4a**[2] (0.28 g, 1.27 mmol, obtained after several recrystallizations from a mixture ethyl acetate/cyclohexane), paraformaldehyde (0.2 g, 6.4 mmol) in methanol (12 mL) was heated to reflux for 45 min. After cooling to room temperature, the resulting solution was transferred into a Paar apparatus, under an argon atmosphere. Raney nickel W2 (0.14 g) was then added and the bumb was flushed with hydrogen. The mixture was then vigorously shaked under hydrogen (7 bar) for 5 h. The catalyst was filtered on a celite pad and the filtrate evaporated under reduced pressure. The crude product was purified by flash chromatography on a silica column (AcOEt/EtOH: 1/1). The yield was 0.26 g (90%) of a white solid. Mp 192°C (AcOEt/cyclohexane). TLC: $R_f$=0.25 (AcOEt/EtOH: 1/1). IR ($cm^{-1}$): 3177 (NH lactame); 1696 (C=O lactame); 1276 (C–N). $^{1}H$ NMR ($CDCl_3$): 2.40–2.62 (m, 2H); 2.45 (s, 3H); 3.40–3.60 (m, 1H); 3.49 (d, 1H, $J$=15.0 Hz); 3.74 (d, 1H, $J$=15.0 Hz); 3.78 (s, 3H); 4.77 (d, 1H, $J$=6.5 Hz); 6.62 (d, 1H, $J$=2.6 Hz); 6.84 (dd, 1H, $J$=8.5 and 2.6 Hz); 6.92 (m, 1H); 7.15 (d, 1H, $J$=8.5 Hz). Anal. calcd for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.96; N, 12.06. Found: C, 67.7; H, 6.3; N, 11.9.

**1a,3a,4,5-Tetrahydro-7-benzyloxy-1*H*,3*H*-pyrrolo[3,2-*c*]isoquinolin-2-one (4c).** Sodium borohydride (0.49 g, 12.7 mmol) was added in one portion to a ice-cooled solution of 3-*N*-[(3-benzyloxyphenyl)methyl]aminopyrrolidine-

2,5-dione **8**[2] (3.95 g, 12.7 mmol) in a mixture of dichloromethane (170 mL) and methanol (85 mL). The solution was stirred at 0°C for 90 min. Two other similar amounts of sodium borohydride were added followed by, respectively 90 min and 3 h stirring at 0°C. Water (150 mL was added and the aqueous layer extracted with dichloromethane (5×90 mL). After removal of the solvent, the white solid (intermediate compound **3d**) was taken in dichloromethane (225 mL). After addition of *p*-toluene sulfonic acid monohydrate (4.96 g, 26.1 mmol), the mixture was heated to reflux for 18 h. The resulting solution was cooled to room temperature and washed with an aqueous saturated solution of sodium hydrogencarbonate. The aqueous layer was extracted with dichloromethane (50 mL). The collected organic layers were dried on magnesium sulfate and the solvent was removed under reduced pressure. The crude solid was purified by flash chromatography on silica gel (ethyl acetate/ethanol: 1/1, $R_f$=0.15). The yield was 1.19 g (30%) of a white solid. Mp 208°C (ethyl acetate/cyclohexane). IR ($cm^{-1}$): 3185 (NH amine and lactam); 1696 (C=O lactam). $^1H$ NMR ($CDCl_3$; 200 MHz): 1.68 (m, 1H); 2.32 (dd, 1H, *J*=1.2 and 17.3 Hz); 2.86 (dd, 1H, *J*=7 and 17.3 Hz); 3.80 (m, 1H); 3.93 (s, 2H); 4.56 (d, 1H, *J*=4.9 Hz); 5.07 (s, 2H); 5.89 (m, 1H); 6.70 (d, 1H, *J*=2.5 Hz); 6.90 (dd, 1H, *J*=2.5 and 8.5 Hz); 7.18 (d, 1H, *J*=8.5 Hz); 7.20–7.50 (m, 5H). $^{13}C$ NMR ($CDCl_3$): 39.4 ($C^3$); 46.35 ($C^7$); 53.1 ($C^{4\text{ or }5}$); 54.1 ($C^{4\text{ or }5}$); 70.55 ($C^{14}$); 112.6 ($C^{9\text{ or }11}$); 114.7 ($C^{9\text{ or }11}$); 124.4 ($C^{aromatic}$); 127.8 ($C^{aromatic}$); 128.5 ($C^{aromatic}$); 129.1 ($C^{aromatic}$); 130.8 ($C^{aromatic}$); 138.5 ($C^{aromatic}$); 159.5 ($C^{aromatic}$); 175.9 ($C^2$). A signal corresponding to a quaternary carbon atom could not be observed. Anal. calcd for $C_{18}H_{18}N_2O_2{\cdot}H_2O$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.4; H, 6.15; N, 9.1.

**1a,3a,4,5-Tetrahydro-7-benzyloxy-*N*-methyl-1*H*,3*H*-pyrrolo[3,2-*c*]isoquinolin-2-one (6c).** A solution of compound **4c**[2](0.05 g, 0.17 mmol), paraformaldehyde (0.03 g, 1.9 mmol) in methanol (12 mL) was heated to reflux for 45 min. After cooling to room temperature, the resulting mixture was transferred in a Paar apparatus with Raney nickel W2 (0.08 g). The mixture was then vigorously shaked under hydrogen (7 bar) for 5 h. The catalyst was filtered on a celite pad and the filtrate evaporated under reduced pressure. The crude product was purified by flash chromatography on a silica column ($R_f$=0.15, AcOEt/EtOH: 3/2). The yield was 0.047 g (89%) of a white solid. Mp 202°C (ethyl acetate/cyclohexane). IR ($cm^{-1}$): 3183 (NH lactam); 1698 (C=O lactam); $^1H$ NMR ($CDCl_3$): 2.45 (s, 3H); 2.46 (m, 1H); 2.58 (dd, 1H, *J*=5.3 and 16.8 Hz); 3.49 (d, 1H, *J*=15.7 Hz); 3.41–3.56 (m, 1H); 3.76 (d, 1H, *J*=15.7 Hz); 4.76 (d, 1H, *J*=6.1 Hz); 5.06 (s, 2H); 6.18 (m, 1H); 6.71 (d, 1H, *J*=2.6 Hz); 6.90 (dd, 1H, *J*=8.5 and 2.6 Hz); 7.12 (d, 1H, *J*=8.4 Hz); 7.2–7.4 (m, 5H). Anal. calcd for $C_{19}H_{20}N_2O_2$: C, 73,99; H, 6,55; N, 9,09. Found: C, 73,5; H, 6,3; N, 9,0.

**1a,3a,4,5-Tetrahydro-7-hydroxy-*N*-methyl-1*H*,3*H*-pyrrolo-[3,2-*c*]isoquinolin-2-one (7).** *Starting from the N-methyl compound **6c**:* To a solution of the *N*-methyl compound **6c** (0.205 g, 0.66 mmol) in methanol (25 mL), palladium hydroxide (0.15 g) was added. The mixture was then stirred vigorously at rt under an hydrogen atmosphere for 16 h. The catalyst was filtered on a celite pad and the filtrate concentrated in vacuo. The resulting solid (0.145 g, quantitative yield) was not purified and could be used for the following steps.

*Starting from the N–H compound **4c**:* A solution of the benzyloxy derivative **4c** (2.02 g, 6.90 mmol), paraformaldehyde (1.11 g, 36.2 mmol) in methanol (260 mL) was heated to reflux for 45 min. After cooling at room temperature, palladium hydroxide (1.28 g) was added. The mixture was then stirred vigorously at rt under an hydrogen atmosphere for 16 h. The catalyst was filtered on a celite pad and the filtrate concentrated in vacuo. The resulting solid was not purified and could be used for the following steps. The yield was 1.5 g (100%) of a yellow solid. IR ($cm^{-1}$): 3141 (NH lactam, OH phenol); 1682 (C=O lactame); 1301 (C–N). $^1H$ NMR (DMSO-$d_6$): 2.20–2.30 (m, 2H); 2.25 (s, 3H); 3.19–3.30 (m, 1H); 3.27 (d, 1H, *J*=15.3 Hz); 3.56 (d, 1H, *J*=15.3 Hz); 4.53 (d, 1H, *J*=6.6 Hz); 6.45 (d, 1H, *J*=2.4 Hz); 6.61 (dd, 1H, *J*=8.4 and 2.4 Hz); 7.10 (d, 1H, *J*=8.4 Hz); 8.13 (m, 1H); 9.50 (m, 1H). Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.0; H, 6.2; N, 12.5.

**1a,3a,4,5-Tetrahydro-7-trifluoromethylsulphonyl-*N*-methyl-1*H*,3*H*-pyrrolo[3,2-*c*]isoquinolin-2-one (9).** A solution of the crude tricyclic phenol (0.7 g, 3.2 mmol) **7**, triethylamine (1.1 mL, 8 mmol) and dimethylformamide (21 mL, recently distilled over calcium hydride) was cooled to 0°C under an argon atmosphere. Ditriflimide (2.53 g, 7 mmol) was then added at this temperature. The mixture was stirred at 0°C for 30 min, and then at room temperature for 4 h. After addition of a small amount of water, the solvent was removed under reduced pressure (about 1 Torr). Water (36 mL) was then added and the product extracted with dichloromethane (4×30 mL). The organic layers were dried on magnesium sulfate and the solvent removed under reduced pressure. The resulting crude product was purified by flash chromatography (silica gel ethyl acetate/ethanol: 5/1). The yield was 0.95 g (84%) of a colorless oil changing in a white solid after storage in refrigerator. Mp 117°C. TLC: $R_f$=0.15 (AcOEt/EtOH: 5/1). IR: 3254 (NH lactame); 1697 (C=O lactame); 1423, 1219 (C–N); 1141. NMR $^1H$ ($CDCl_3$, 200 MHz): 2.40–2.60 (m, 2H); 2.47 (s, 3H); 3.54 (d, 1H, *J*=15.5 Hz); 3.50–3.70 (m, 1H); 3.78 (d, 1H, *J*=15.5 Hz); 4.80 d, 1H, *J*=6.7 Hz); 7.04 (d, 1H, *J*=2.4 Hz); 7.18 (dd, 1H, *J*=2.4 and 8.6 Hz); 7.38 (d, 1H, *J*=8.6 Hz); 7.79 (m, 1H). Anal. calcd for $C_{13}H_{13}F_3N_2O_4S$ C, 44.57; H, 3.75; N, 8.00. Found: C, 44.2; H, 3.5; N, 7.8.

**1-Methoxy-1-trimethysilyloxyethylene (13a) and ethyl 2-trimethylsilyl acetate (13b).**[12] A solution of *n*-butyllithium in hexane (2.5 M solution, 8 mL, 20 mmol) was added dropwise to a cooled mixture (−78°C) of freshly distilled diisopropylamine (2.7 mL, 20.5 mmol) in THF (15 mL) under an argon atmosphere. The mixture was stirred for 45 min at −78°C. Methyl acetate (1.6 mL, 20.2 mmol) was then progressively added and the resulting solution stirred for 30 min. Finally, trimethylsilyl chloride (5 mL, 39.4 mmol) was added and the solution stirred again for 30 min at rt. The white solid was filtered and the solvent removed under reduced pressure. The residue was taken in anhydrous diethyl ether, and the solvent was removed after filtration.

The so-obtained liquid was immediately distilled under reduced pressure (38–42°C/15 Torr), and must be used quickly. It must be pointed out that, owing to the volatility of this compound, it was very difficult to evaluate the yield of this reaction. A large amount was lost during the removal of the solvents and the final product was a mixture of the required *O*-silylated compound with the *C*-silylated one. This mixture was used after evaluation of the molar ratio by integration of the NMR spectrum of the crude product and assuming that the *C*-silylated product did not react. Colorless liquid. Bp 38–42°C (15 Torr).

**13a:** $^1$H NMR ($CDCl_3$, 200 MHz): 0.23 (s, 9H); 3.11 (d, 1H, $J$=2.8 Hz); 3.2 (d, 1H, $J$=2.8 Hz); 3.55 (s,3H).

**13b:** $^1$H NMR ($CDCl_3$, 200 MHz): 0.12 (s, 9H); 1.91 (s, 2H); 3.63 (s, 3H).

**Methyl 2-(1a,3a,4,5-tetrahydro-*N*-methyl-1*H*,3*H*-pyrrolo[3,2-*c*]isoquinolin-2-one)-7-yl acetate (12b).** In a three-necked flask were dissolved the triflate **9** (0.835 g, 2.4 mmol), tetrakis triphenylphosphine palladium (0.43 g, 0.36 mmol) and lithium acetate (0.49 g, 7.3 mmol) in tetrahydrofurane (45 mL) under an argon atmosphere. The preceding compound (0.7 g, 4.8 mmol, OSi/CSi=3, 1.5 equiv. in OSi) was added and the reaction mixture was heated to reflux for 16 h. After cooling to rt, an other amount of tetrakis triphenylphosphine palladium (0.056 g, 0.05 mmol) was added and the mixture again heated to reflux for 5 h. The solvent was removed under reduced pressure and the residue was chromatographed on a column containing 42 g of silica gel ($R_f$=0.1, ethyl acetate/ethanol: 5/1). The yield was 0.33–0.43 g (50–65%) of a white solid. Mp (dec) 183°C. IR ($cm^{-1}$): 3410, 3180 (NH lactam); 1736 (C=O ester); 1698 (C=O lactam). $^1$H NMR ($CDCl_3$): 2.45 (dd, 1H); 2.45 (s, 3H); 2.57 (dd, 1H); 3.4–3.6 (m, 1H); 3.50 (d, 1H); 3.59 (s, 2H); 3.68 (s, 3H); 3.74 (d, 1H); 4.76 (d, 1H); 7,01 (s, 1H); 7.16 (d, 1H); 7.22 (d, 1H); 7,49 (m, 1H). Anal. calcd for $C_{15}H_{18}N_2O_3$: C, 65.66; H, 6.63; N, 10.21. Found: C, 65.7; H, 6.4; N, 9.8.

**1a,3a,4,5-Tetrahydro-7-allyl-*N*-methyl-1*H*,3*H*-pyrrolo-[3,2-*c*]isoquinolin-2-one (10).** To a mixture of the triflate **9** (0.078 g, 0,22 mmol), lithium chloride (0.027 g) and tetrakis triphenylphosphine palladium (0.003 g, 0.004 mmol) in freshly distilled dimethylformamide (1.5 mL) under an argon atmosphere, allyltributyltin (85 μL, 0.27 mmol) was added. The solution was heated to reflux for 3 h. After cooling to rt, water (6 mL) was added and the product was extracted with dichloromethane. After drying on magnesium sulfate, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($R_f$=0.1, ethyl acetate/ethanol: 5/1). The yield was 0.04 g (75%) of a white solid. Mp 170°C. IR ($cm^{-1}$): 3171, 3080 (NH lactame); 1699 (C=O lactame). NMR $^1$H ($CDCl_3$): 2.44 (dd, 1H, $J$ hidden by the 6-methyl group); 2.46 (s, 3H); 2.56 (dd, 1H, $J$=5.4 and 16.9 Hz); 3.35 (d, 2H, $J$=6.5 Hz); 3.50 (d, 1H, $J$=15.3 Hz); 3.50–3.60 (m, 1H); 3.76 (d, 1H, $J$=15.3 Hz); 4.78 (d, 1H, $J$=6.7 Hz); 5.08 (m, 2H); 5.93 (m, 1H); 6.50 (m, 1H); 6.94 (s, 1H); 7.09 (d, 1H, $J$=9.4 Hz); 7.15 (d, 1H, $J$=7.5 Hz). Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.33; H, 7.50; N, 11.56. Found: C, 74.25; H, 7.4; N, 11.4.

**2-[7-(1a,3a,4,5-Tetrahydro-*N*-methyl-1*H*,3*H*-pyrrolo-[3,2-*c*]isoquinolin-2-one)]-*N*-(2′-pyridyl) acetamide (2a).** A solution of trimethylaluminum (0.23 mL of 2 M solution, 0.46 mmol) in heptane was added to 2-aminopyridine (0.039 g, 0.42 mmol) in anhydrous tetrahydrofurane (2 mL) under an argon atmosphere. The mixture was then stirred at rt for 3 h. This mixture was then slowly added to a solution of the ester **12b** (0.053 g, 0.19 mmol) in anhydrous THF (3 mL). The flask contents were heated to reflux for 18 h and, after cooling, 1 M aqueous hydrochloric acid (0.46 mL) was carefully added. After one hour stirring at rt, a saturated aqueous solution of sodium hydrogencarbonate (7 mL) was added and the aqueous layer extracted with dichloromethane. The collected organic layers were dried on magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel (the remaining 2-aminopyridine was eluted with pure ethyl acetate and the product with ethyl acetate/ethanol: 5/1, $R_f$=0.1). The yield was 0.013 g (21%) of a white solid. IR ($cm^{-1}$): 3422, 3191 (NH lactame, amide); 1683 (C=O lactame, amide). MS (I.E): 333 [$M^{+\cdot}$]. $^1$H NMR ($CDCl_3$): 2.46 (s, 3H); 2.50 (m, 2H); 3.52 (d, 1H, $J$=15.3 Hz); 3.57 (m, 1H); 3.73 (s, 2H); 3.76 (d, 1H, $J$=15.3 Hz); 4.80 (d, 1H, $J$=6.5 Hz); 6.04 (m, 1H); 7.04 (m, 1H); 7.11 (s, 1H); 7.27 (m, 2H); 7.70 (m, 1H); 8.19 (m, 3H). NMR $^1$H (DMSO-$d_6$): 2.29 (m, 2H); 2.48 (s, 3H); 3.67(s, 2H); 4.64 (d, 1H, $J$=6.8 Hz); 7.06 (s, 1H); 7.06 (m, 1H); 7.19 (d, 1H, $J$=7.8 Hz); 7.29 (d, 1H, $J$=7.9 Hz); 7.73 (m, 1H); 8.02 (d, 1H, $J$=8.3 Hz); 8.29 (s, 2H); 10.67 (m, 1H).

**2-[7-(1a,3a,4,5-Tetrahydro-*N*-methyl-1*H*,3*H*-pyrrolo-[3,2-*c*]isoquinolin-2-one)]-*N*-(4′,6′-dimethyl-2′-pyridyl)-acetamide (2b).** A solution of trimethylaluminum (2 M, 1.3 mL, 2.6 mmol) in heptane was added on a stirred solution of 2-amino-4,6-dimethylpyridine (0.308 g, 2.5 mmol) in anhydrous tetrahydrofurane under an argon atmosphere. The mixture was then stirred for 3 h at rt. The resulting mixture was slowly added on a solution of ester **12b** (0.307 g, 1.1 mmol) in tetrahydrofurane (17 mL). The reaction mixture was heated to reflux for 72 h. After cooling to rt, aqueous hydrochloric acid (1 M solution, 2.6 mL) was added. After one hour stirring at rt, a saturated aqueous solution of sodium hydrogencarbonate (30 mL) was added and the aqueous layer extracted with dichloromethane (5×16 mL). The collected organic layers were dried on magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel (the remaining 2-amino-4,6-dimethylpyridine was eluted with pure ethyl acetate and the product with ethyl acetate/ethanol: 5/1, $R_f$=0.3). The yield was 0.228 g (57%) of a white solid. Mp 147°C (dec). $R_f$=0.15 (AcOEt/EtOH: 5/1). IR ($cm^{-1}$): 3287 (NH lactam, amide); 1700 (C=O lactam, amide). NMR. $^1$H ($CDCl_3$,400 MHz): 2.27 (s, 3H); 2.33 (s, 3H); 2.42 (s, 3H); 2.43 (dd, 1H, $J$=7.0 and 17.0 Hz); 2.50 (dd, 1H, $J$=5.0 and 17.0 Hz); 3.47 (d, 1H, $J$=15.0 Hz); 3.52 (m, 1H); 3.64 (s, 2H); 3.71 (d, 1H, $J$=15.0 Hz); 4.74 (d, 1H, $J$=7.0 Hz); 6.63 (m, 1H); 6.69 (s, 1H); 7.04 (s, 1H); 7.15 (d, 1H, $J$=8.0 Hz); 7.19 (dd, 1H, $J$=8.0 and 1.0 Hz); 7.85 (s, 1H); 8.11 (m, 1H). NMR $^{13}$C (numbering of Scheme 7, $CDCl_3$): 21.23 ($C_{14}$); 23.18 ($C_{13}$); 31.64 ($C_3$); 42.79 ($C_{12}$); 44.10 ($C_{11}$); 53.56 ($C_5$); 53.77 ($C_{1a}$); 59.96 ($C_{3a}$); 111.91 ($C_{3'}$); 120.51 ($C_{5'}$); 127.25 ($C_6$); 128.41 ($C_8$ or $C_9$); 128.54 ($C_8$ or $C_9$); 131.65 ($C_{9a}$); 133.78 ($C_7$); 134.33 ($C_{6a}$); 150.57

($C_{2'}$); 150.73 ($C_{4'}$); 155.71 ($C_{6'}$); 169.61 (C=O amide); 176.32 ($C_2$). Anal. calcd for $C_{21}H_{24}N_4O_2$: C, 69.20; H, 6.65; N, 15.37. Found: C, 69.12; H, 6.67; N, 15.55

*Calculation of binding constants.* Prior to these experiments, $CDCl_3$ was stored on anhydrous potassium carbonate in order to remove any residual acidity from this solvent.

*Dimerization constant of host* ***2b***. A stock solution of the host (0.018235 g) in $CDCl_3$ (1 mL) was prepared with a great accuracy (0.05003 mol $L^{-1}$). An NMR tube (5 mm diameter) was charged with $CDCl_3$ (0.4 mL). Small amounts of the stock solution were then successively added into the NMR tube and the corresponding $^1H$ NMR spectrum was recorded. The changes in the chemical shifts of host were monitored and the dimerization constant was computed according to the method described by Horman and Dreux[17] for caffeine and use of Excel-97®. The added volume of stock solution (mL) and the observed chemical shift of the N–H lactam group (ppm) were the following: 0.1, 5.93; 0.01, 6.02; 0.01, 6.10; 0.01, 6.19; 0.01, 6.24; 0.02, 6.34; 0.02, 6.43; 0.02, 6.50; 0.02, 6.565; 0.05, 6.68; 0.05, 6.77; 0.05, 6.84; 0.1, 6.95; 0.1, 7.02; 0.1, 7.07; 0.1, 7.11

*Job plots.* The continuous variation method of Job[20] was used in order to determine the stochiometry of the complexes. Two solutions in deuteriochloroform (2 mL) of the host and the guest were prepared (the concentrations must be the same, in the range 0.013 mol $L^{-1}$). NMR tubes were then charged with amounts of these two solutions in order to obtain a total volume of 0.5 mL. Volumes (mL) of host and guest solutions were as follows: 0.5, 0; 0.4, 0.1; 0.3, 0.2; 0.25, 0.25; 0.2, 0.3; 0.1, 0.4; 0.5. A signal corresponding to the NH amide of **2b** for binding of acids and $NH_2$ for binding of amines was then monitored. The curves are depicted in Fig. 2.

*Association constants.* An amount of host **2b** was accurately weighed and diluted in deuteriochloroform (0.5 mL) in order to obtain a concentration exactly known of about 0.02 mol $L^{-1}$. The NMR spectrum of **2b** alone was then recorded. The amine or acid guest were accurately weighed and diluted in $CDCl_3$ (5 mL) in order to obtain a concentration exactly known of about 0.3 mol $L^{-1}$. Aliquots of the guest stock solution were successively added and the corresponding NMR spectra recorded: Aliquots of 0.01 mL until achieving host–guest~1, then 0.02 mL aliquots until a total added volume of 0.1 mL, 0.04 mL until a total added volume of 0.3 mL, 0.1 mL aliquots until a total added volume of 1 mL and finally 0.2 mL aliquots until a total added volume of 2 mL. The titration experiment may be stopped when saturation is achieved before adding 0.2 mL aliquots. The chemical shifts of selected protons were measured. Dilution experiments were also performed in order to be sure that the observed shifts were only due to complexation of guest.

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