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# Recognition of insoluble tartaric acid in chloroform

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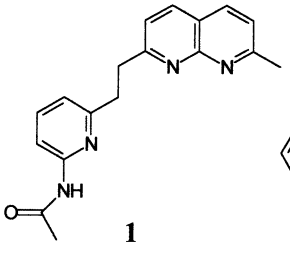
**Abstract**—Simple receptors for the recognition and solubilisation of insoluble tartaric acid in chloroform were designed and synthesised for the first time. Receptors **2** and **3** were successful in solubilising tartaric acid into chloroform forming a 1:1 complex, and were also found to be useful as fluorescent probes for the detection of this substrate. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

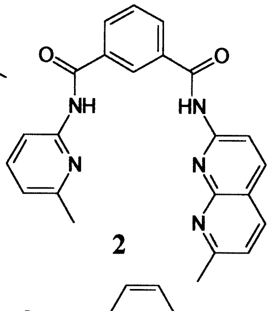
Intermolecular interactions form the basis of specific recognition, reaction, transport and regulation which occur in biological systems.[1] Hydrogen bonding plays a key role in molecular recognition.[2–7] In general, the greater the number of hydrogen bonds contributed by the receptor,[8] the stronger is the complex formed with the guest. The development of synthetic receptors with defined architecture having multiple hydrogen bonding sites for complementary steric match of the guest into the cavity of the receptor is thus of considerable importance.

Synthetic receptors for peptides, amino acid derivatives and hydroxyacids are of prime importance due to the intermolecular interactions involving these small molecules with the peptide backbone in biological systems.[9–18] In continuation of our molecular recognition research,[19–23] we are interested in the design and synthesis of simple receptors as carriers for the transport of biologically important organic substrates (e.g. urea,[21] aminoacids[22,23] and hydroxyacids which are soluble in water but insoluble in organic solvents) into cells. In this regard, tartaric acid is an important bio-active substrate. We report here our efforts to design simple receptors for insoluble tartaric acid which can solubilise it and can be developed as its fluorescent carriers. Lehmann et al. studied the role of hydrogen bonding in the racemic as well as in the enantiomeric forms of tartaric acid.[24] Etter and Hitchcock et al. demonstrated the hydrogen bonding arrangement of (*S*)-1-phenylethyl ammonium hydrogen-L-tartarate.[25,26] Hamilton et al. developed a synthetic receptor that can successfully recognise the two enantiomers[27] of the diacetyltartaric acid derivatives. Kuroda et al. devised a unique trench-type binding site on a porphyrin which specifically recognises tartaric acid derivatives with four-point hydrogen bonding.[28] Lavigne et al. corroborated the recognition of tartrate and malate by their synthetic receptors.[29] Recently Morán et al. reported the recognition of hydroxycarboxylates such as lactic acid or mandelic acids with a macrocyclic receptor.[30] But to our knowledge, no synthetic receptor has been reported till now, for the recognition of tartaric acid itself, which is an insoluble substrate in chloroform.

We report here the efficacy of the simple receptors **1**, **2**, **3** and **4** for tartaric acid binding and solubilisation into chloroform. Receptors **2** and **3**, but not **1** and **4**, were effective in tartaric acid binding. Receptors **2** and **3** have also been found to be useful as fluorescent probes which can offer the specific binding sites for the carboxylic acid functionality of the hydroxyacid at the core of the cavity. They efficiently bind the highly insoluble naturally occurring L-(+)-tartaric acid and solubilise it into chloroform.



**1**



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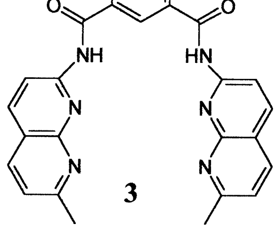

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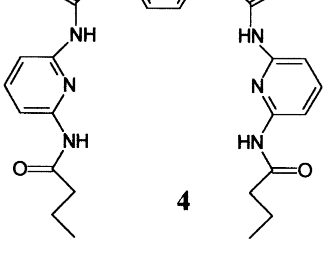

**4**

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*Keywords*: hydroxyacid; fluorescent receptors; molecular recognition; tartaric acid.

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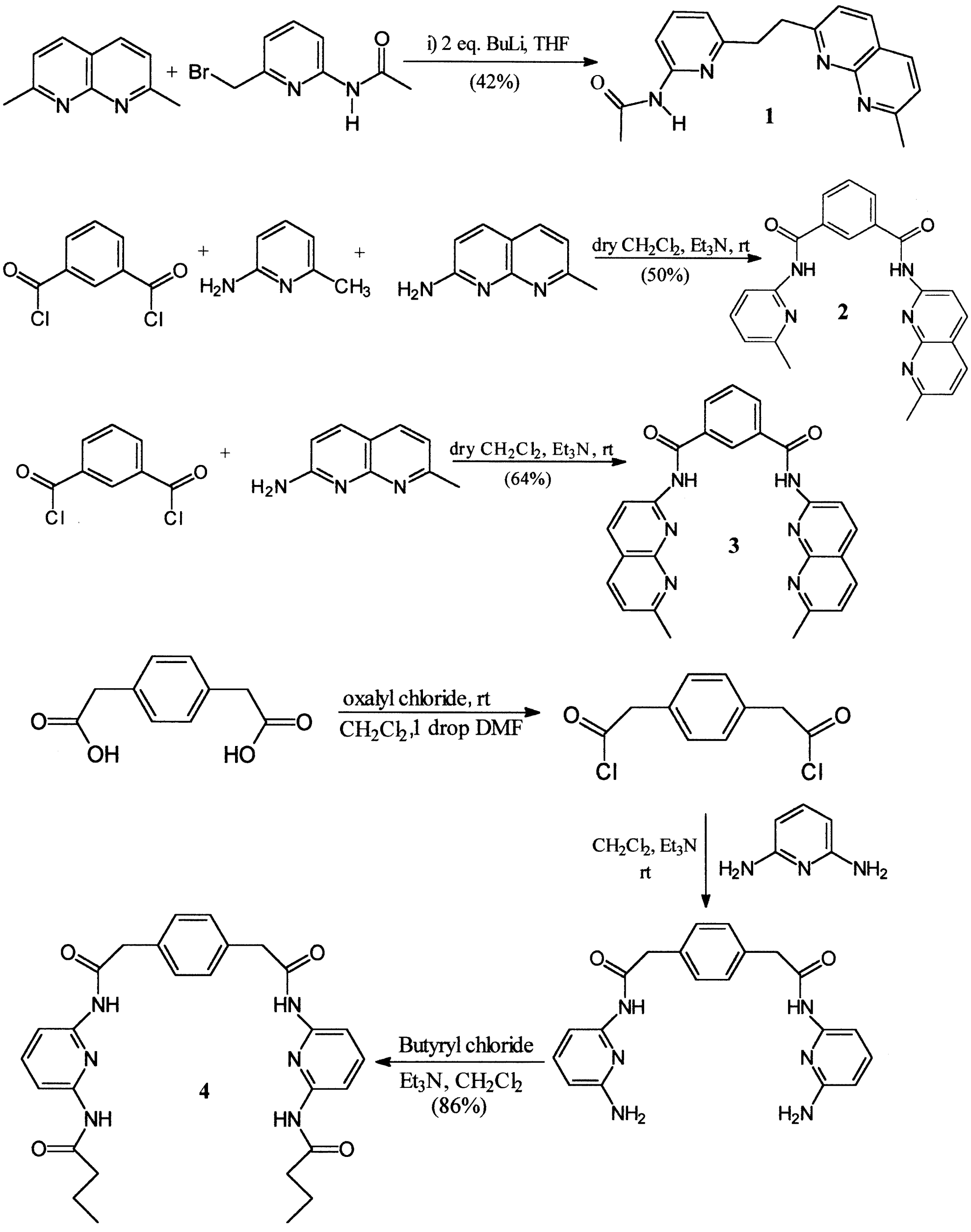


**Scheme 1.**

The synthesis of all the receptors (**1**–**4**) is delineated in Scheme 1. Receptor **1** was synthesised[22] by reaction of 2,7-dimethyl 1, 8-naphthyridine with butyllithium and 2-*N*-acetyl-amino-6-bromomethylpyridine[31] in tetrahydrofuran. Receptor **2** was synthesised by the high dilution reaction of 2-amino-6-methylpyridine and 2-amino-7-methyl-1, 8-naphthyridine with isophthaloyl chloride. Receptor **3** was synthesised by the reaction of isophthaloyl chloride and 2-amino-7-methyl-1, 8-naphthyridine. Receptor **4** was synthesised by the reaction of butyryl chloride with *bis*-monoamide which was obtained by the high dilution coupling of 2,6-diaminopyridine with diacidchloride of 1,4-phenylenediacetic acid.

## 2. Results and discussion

Our previous report comparing two point and three point fixation of monocarboxylic acids with our designed receptors[8] tempted us to study the binding and solubilisation of tartaric acid by our designed receptors **2** and **3**. Receptor **1** does not bind tartaric acid although it has multiple hydrogen bonding sites. This is probably because of its flexibility. This flexibility was reduced by choosing an isophthaloyl spacer between the heterocyclic units which effectively participates in hydrogen bond formation with tartaric acid. Also the 1,4-phenylenediacetyl spacer in receptor **4** is found to be inactive in binding tartaric acid. The complexation and solubilisation of L-(+)-tartaric acid in chloroform were studied by $^1$H NMR, UV and fluorescence experiments with receptors **1**, **2**, **3** and **4**. Receptors **2** and **3** in this regard were only found to be effective to solubilise tartaric acid in chloroform. Receptors **1** and **4** were totally non-interacting showing an almost negligible shift of the amide protons, perhaps due to steric mis-match. The addition of powdered

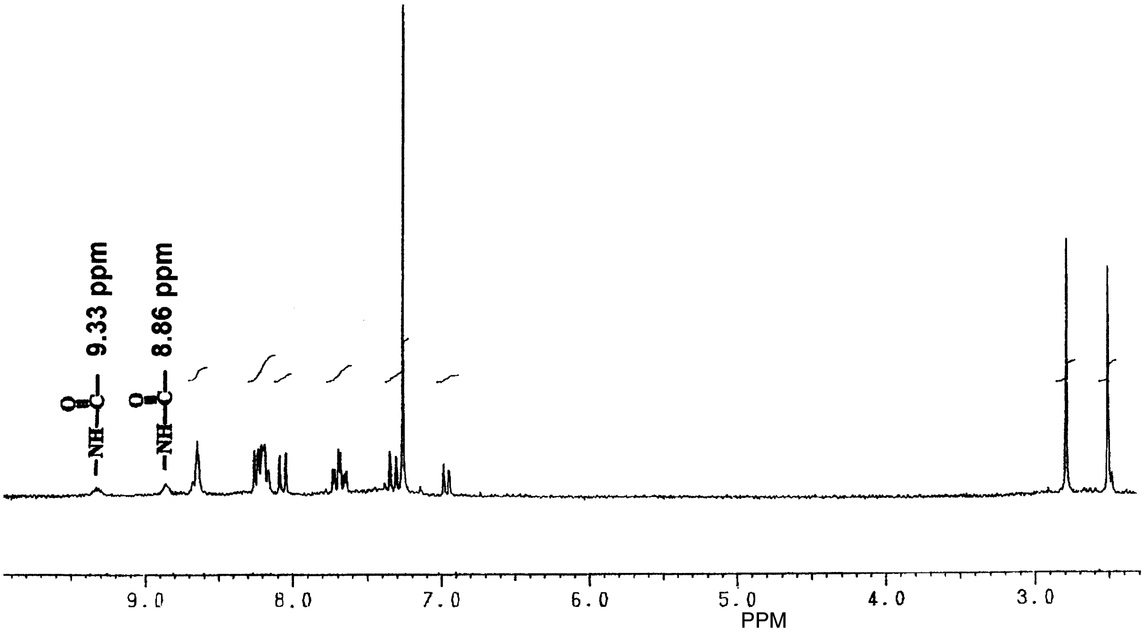
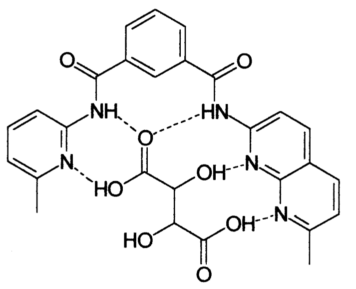


**Figure 1.** $^1$H NMR spectrum of receptor **2**.

L-(+)-tartaric acid into $CDCl_3$ solution of receptor **2** ($1.00\times10^{-2}$ M) led to its facile dissolution, as evidenced by the appearance of the methine protons of tartaric acid at $\delta$ 5.00 ppm (Figs. 1 and 2) and a significant downfield shift of the different amide protons of **2** (from $\delta$ 8.86 to 10.81, $\Delta\delta=1.95$ ppm and $\delta$ 9.33 to 10.96, $\Delta\delta=1.63$ ppm of pyridine and naphthyridine amide protons, respectively) in complex **A**.



**Complex A**

The other receptor **3**[21] is also effective in forming a 1:1 complex with L-(+)-tartaric acid as suggested by the proton integration ratio of the complex in $^1$H NMR. This is also proved by the appearance of the methine protons of tartaric acid at $\delta$ 5.30 ppm in a $CDCl_3$ solution of receptor **3** and a significant downfield shift of the amide protons of the receptor **3** (from $\delta$ 9.44 to 10.70, $\Delta\delta=1.26$ ppm). This may possibly be due to the formation of a tight complex with tartaric acid (complex **B**) either by the formation of higher order

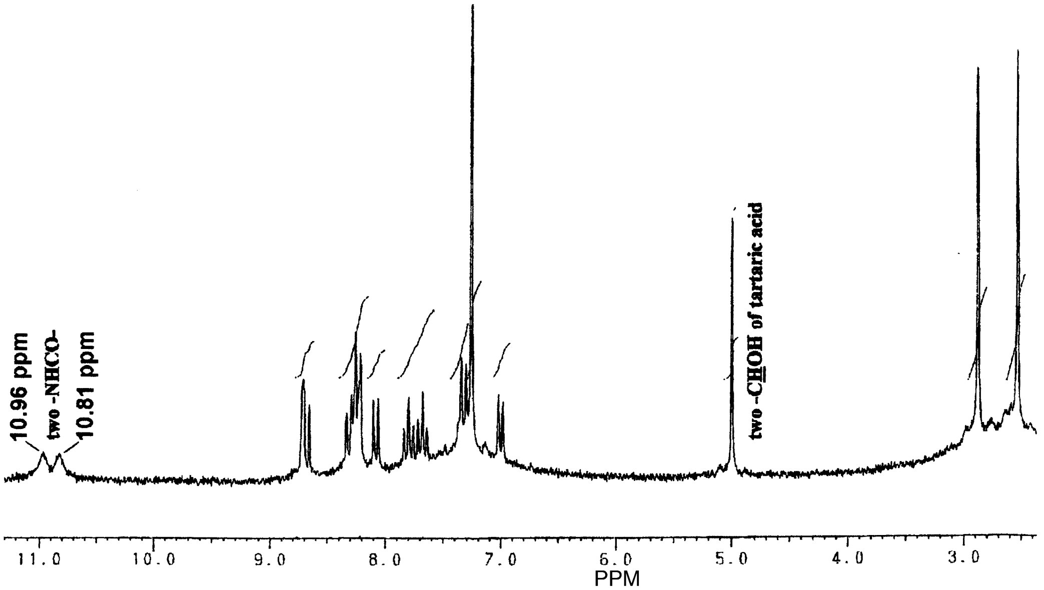


**Figure 2.** $^1$H NMR spectrum of complex **A**.

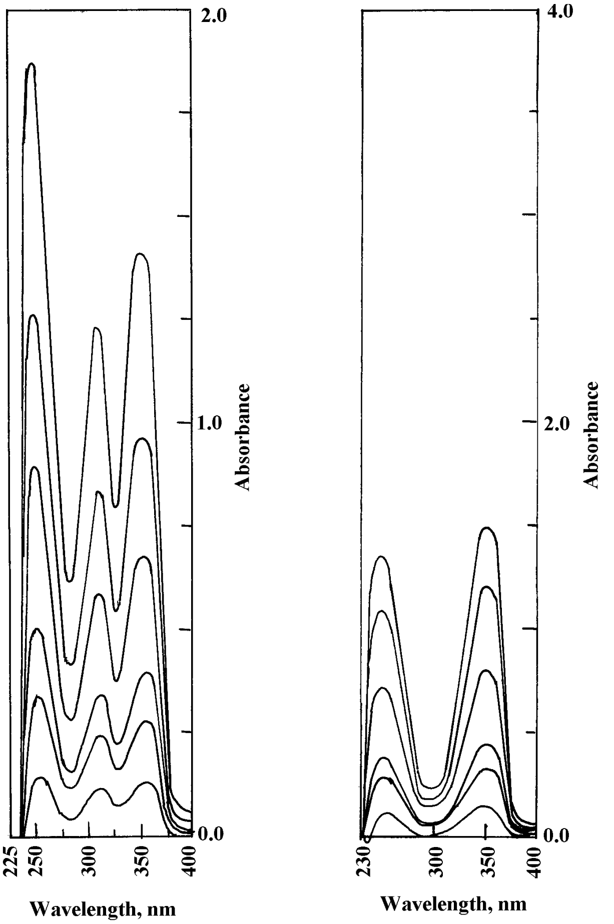
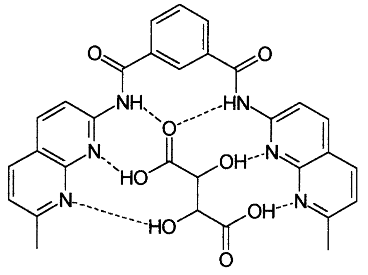


**Figure 3.** (a) UV spectra of complex **A** and its change of absorbance on dilution, (b) UV spectra of complex **B** and its change of absorbance on dilution.



**Complex B**

hydrogen bonds or long range electrostatic interactions with all four hydrogens of carboxyl as well as of the hydroxyl groups of tartaric acid. Effective association of tartaric acid with both **2** and **3** was suggested from the fact that dilution of each 1:1 complex in $CDCl_3$ showed negligible change in NMR spectrum.

The binding constants were evaluated from UV titration experiments at $\lambda_{max}$ 352 nm.[32] Fig. 3a and b show the effect of dilution on the UV spectra of the 1:1 complexes with **2** and **3**, respectively, at 352 nm. For the case of 1:1 complex with **2** in Fig. 3a, on dilution a blue shift of the maximum at $\lambda_{max}$ 249 nm occurs, while a slight red shift of both maxima was observed at $\lambda_{max}$ 310 and 352 nm. Similarly in the case of 1:1 complex in Fig. 3b, on dilution a slight red shift of the maxima of both the peaks at $\lambda_{max}$ 250 and 352 nm is observed. This change in UV–vis spectrum could be used to conveniently study the binding, since the lower concentrations used lead to a more accurate determination of the value of the association constant for tartaric acid. The absorbance effects at the corresponding peak positions are shown graphically in Fig. 4a and b. Receptor **3** shows a moderate binding constant with tartaric acid (Table 1) which is four times greater than **2**. The UV titration experiments using malic and succinic acids as guests with receptors **2** and **3** were also carried out to get further indication of the mode of binding. The relatively lower values of

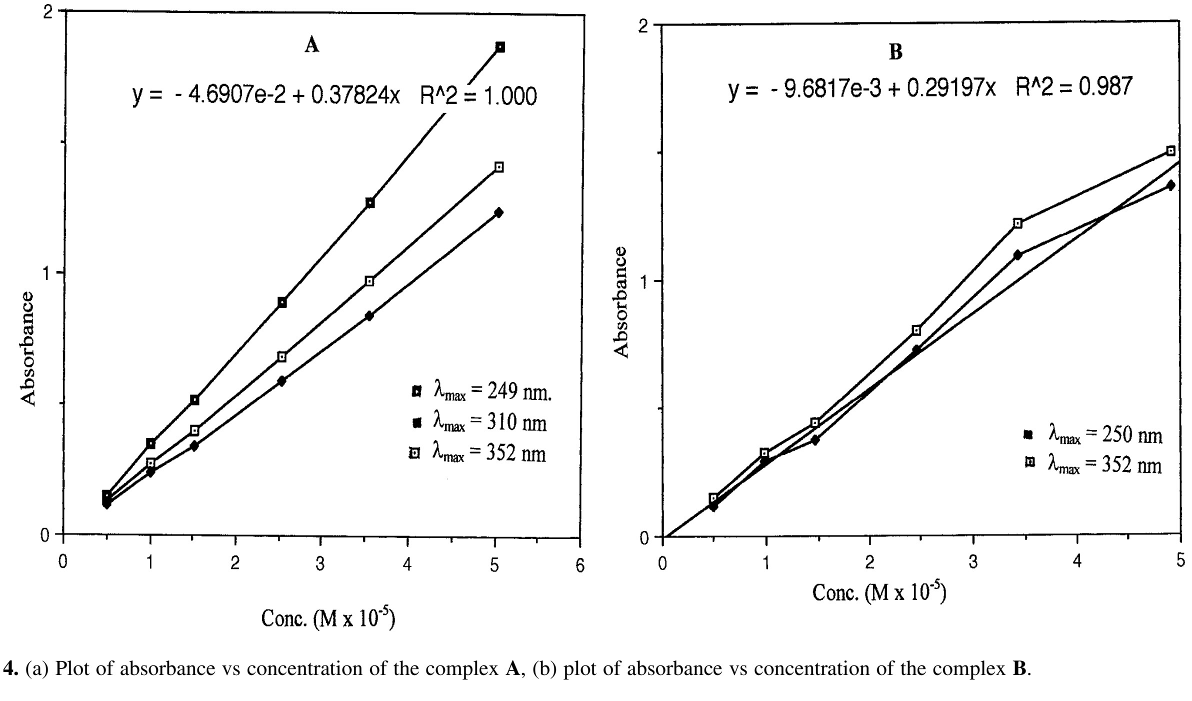


**Figure 4.** (a) Plot of absorbance vs concentration of the complex **A**, (b) plot of absorbance vs concentration of the complex **B**.

**Table 1.** $K_a$ values of L-(+)-tartaric acid, DL-malic acid and succinic acid measured by UV titration

| Acid | Receptor **2** $K_a$ ($M^{-1}$) | Receptor **3** $K_a$ ($M^{-1}$) |
|---|---|---|
| L-(+)-Tartaric acid | $1.6\times10^{4}$ | $7.0\times10^{4}$ |
| *rac*-Malic acid | $1.3\times10^{3}$ | $2.7\times10^{3}$ |
| Succinic acid | $1.0\times10^{3}$ | $1.3\times10^{3}$ |

$K_a$ of tartaric acid with **2** compared to **3** may be due to the smaller number of hydrogen bonds formed with **2** compared to **3** in the 1:1 complexes. The successively lower values of $K_a$ of the acids down the series with **3** may also be due to their lower number of hydrogen bonds during complexation.

This experiment suggests the probable mode of binding could be as shown in complex **B**. Receptors **2** and **3** bind weakly with L-(+)-dibenzoyltartaric acid ($K_a=3.10\times10^{2}$ and $1.5\times10^{2}\ M^{-1}$, respectively)[33] compared to L-(+)-tartaric acid which may be due to the greater steric hindrance in the cavity of **2** and **3** to accommodate the bulky dibenzoyltartaric acid. The binding and solubilisation of tartaric acid in chloroform by receptors **2** and **3** are also corroborated from the enhancement of fluorescence intensity on complexation (Fig. 5). Receptors **2** and **3** were dissolved individually in chloroform and then tartaric acid was added to make the stoichiometry 1:1 in each case. Excitation at 345 nm in both cases gave rise to an emission at 398 nm. On complexation with tartaric acid, the fluorescence emission of **2** and **3** were again observed; however, they showed $\Delta\lambda$ of 15.5 nm (397.50–382.00 nm) and 9.0 nm (394.50–385.50 nm) with the increase in intensity, respectively. This blue shift in fluorescence wavelength indicates the strong hydrogen bonding interactions of **2** and **3** with tartaric acid.

The energy minimisation of receptor **3** with tartaric acid (complex **B**) was performed to visualise the binding interaction between the host and guest by using PCMODEL (Serena software) with standard constant and $E_{min}$ of the 1:1 complex was found to be 35.439 kcal/mol (Fig. 6).

We have thus devised naphthyridine based fluorescent probes **2** and **3** for the solubilisation and detection of insoluble tartaric acid, a substrate of biological significance, in non-competitive organic solvent. This approach can have a direct impact on the development of fluorescent receptors for analytical use to detect insoluble substrates of biological significance.

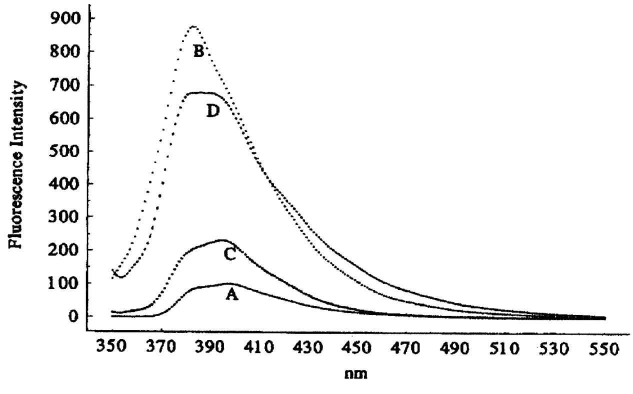


**Figure 5.** Fluorescence emission spectra of (A) receptor **2**, (B) complex **A**, (C) receptor **3**, (D) complex **B**.

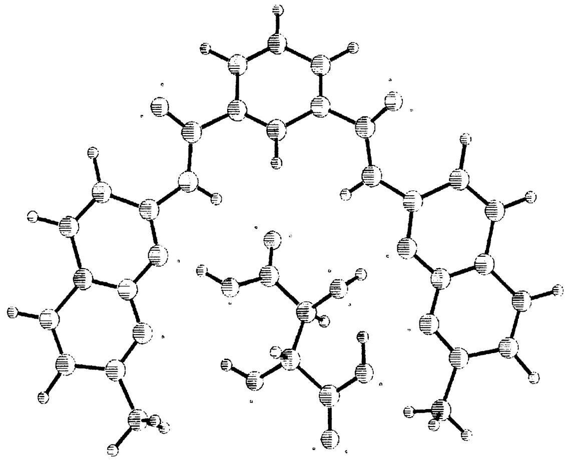


**Figure 6.** Ball and Stick representation of the complex **B**.

## 3. Experimental

### 3.1. General

Melting points (mp) were recorded on a Toshniwal hot-coil stage melting point apparatus and are uncorrected. $^{1}H$ NMR spectra were recorded on a 200 MHz (Bruker) spectrometer. $CDCl_3$ was used as solvent unless otherwise mentioned. $^{13}C$ NMR spectra were recorded in 50 MHz Bruker machine as a solution in $CDCl_3$. IR spectra were recorded for receptors **1**–**3** on Perkin–Elmer 883 and that was recorded for receptor **4** on FTIR-8300 SHIMADZU instrument. Fluorescence studies were carried out on Perkin–Elmer LS 50B and Perkin–Elmer MP F44B machines. UV spectra were recorded using JASCO 7850.

All solvents were dried prior to use. Dichloromethane and triethylamine were distilled from calcium hydride. All reactions were carried out under a nitrogen atmosphere. For preparative thin layer chromatography (PTLC) purification, the layer was formed over a glass plate using water gel-GF254 silica gel.

### 3.2. Fluorescence study

Receptor **2** (0.5 mg, $2.099\times10^{-4}$ M) was dissolved in 6 mL dry chloroform and fluorescence spectrum was recorded exciting at 345 nm wavelength. 3 mL of the solution was taken and to this excess tartaric acid was added and mixed thoroughly, and again the fluorescence spectrum was recorded. Receptor **3** (0.4 mg, $1.488\times10^{-4}$ M) was dissolved in 6 mL dry chloroform and the experiment was performed as for receptor **2**.

### 3.3. UV binding study

Receptor **2** (1.5 mg, $7.5567\times10^{-5}$ M) was dissolved in 50 mL dry chloroform. 25 mL of this stock solution was taken and to this, excess dicarboxylic acid was added and sonicated for 10 min for complexation. The solution of the complex was quickly filtered to remove uncomplexed dicarboxylic acid. The UV spectrum was recorded for uncomplexed receptor and then for the complex. Then the solution of complex was taken in five different volumetric flasks (10 mL) containing 7, 5, 3, 2 and 1 mL of the solution of complex, respectively, and the volume was made up to 10 mL with dry chloroform in each case. The UV spectrum was recorded for each solution and the binding constant was calculated according to Colquhoun et al.[32] Receptor **3** (1.3 mg, $5.8036\times10^{-5}$ M) was dissolved in 50 mL dry chloroform and the experiment was performed as in the case of receptor **2**.

**3.3.1. *N*-{6-[2-(7-Methyl-[1,8]naphthyridin-2-yl)-ethyl]-pyridin-2-yl}-acetamide 1.** To a stirred solution of 2,7-dimethyl-1, 8-naphthyridine (100 mg, 0.63 mmol) in dry THF at −78°C, *n*-BuLi (0.2 mL, 1.5 mmol) was added dropwise under a nitrogen atmosphere. Then the solution was stirred at −78°C for 0.5 h until red colour persists. After that a solution of 2-*N*-acetylamino-6-bromomethyl-pyridine (288 mg, 1.26 mmol) in THF was added dropwise. The red colour gradually disappeared and finally reached to yellowish colour. The solvent was evaporated in vacuo and water was added to the mixture. The aqueous layer was extracted with chloroform, dried over anhydrous sodium sulphate. After evapoartion of the solvent, the crude product was purified by PTLC using 20% ethylacetate in chloroform to afford the title compound as a white solid (0.08 mg, 42%), mp 145°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 8.30 (s, 1H, NH), 8.00 (d of d, 2H, $J$=8, 2 Hz, naphthyridine-4H and -5H), 7.57 (t, 1H, $J$=8 Hz, pyr-4H), 7.34–7.23 (m, 3H, pyr-3H, naphthyridine-3H and -6H), 6.91 (d, 1H, $J$=8 Hz, pyr-5H), 3.42–3.31 (m, 4H, $-CH_2-CH_2-$), 2.79 (s, 3H, naphthyridine-$CH_3$), 2.20 (s, 3H, $CH_3$–CO–). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$: 168.6, 164.9, 162.8, 159.3, 155.5, 150.7, 149.8, 138.7, 136.6, 122.3, 121.7, 119.0, 116.3, 111.2, 38.4, 37.0, 25.4, 24.6. IR (KBr) $\nu_{max}$: 3265, 3058, 2927, 2857, 2354, 1679, 1604, 1538, 1450 cm$^{-1}$. MS (EI, *m/e*) 307 ($M^+$), 117 (100%), 59. Anal. calcd for $C_{18}H_{18}N_4O$: C, 70.59: H, 5.88: N, 18.30. Found C, 70.44: H, 5.91: N, 18.19.

**3.3.2. *N*-(7-Methyl-[1,8]naphthyridin-2-yl)-*N*′-(6-methyl-pyridin-2-yl)-isophthalamide 2.** A solution of 2-amino-7-methylnaphthyridine (100 mg, 0.62 mmol) and triethylamine (0.08 mL) in dry dichloromethane (20 mL) and a solution of 2-amino-6-methylpyridine (70 mg, 0.62 mmol) and triethylamine (0.08 mL) in dry dichloromethane (20 mL) were simultaneously added dropwise separately from two dropping funnels to isophthaloyl chloride (130 mg, 0.62 mmol) in dry dichloromethane (15 mL) under a nitrogen atmosphere during a period of 3 h. The whole mixture was then washed with saturated sodium bicarbonate solution followed by water. The separated organic layer was dried over sodium sulfate. Volatiles were removed under vacuum and the brown solid thus obtained was purified by column chromatography using 5% MeOH in $CHCl_3$, giving the desired product as white solid (120 mg, 50%), mp 126°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 9.33 (s, 1H, NH), 8.86 (s, 1H, NH), 8.65 (s, 2H, *iso*-2H and -4H or -6H), 8.25–8.16 (m, 3H, naphthyridine 3H and 4H, *iso*-4H or -6H), 8.06 (d, 1H, $J$=8 Hz, naphthyridine-5H), 7.68 (t, 2H, $J$=8 Hz, pyr-4H and *iso*-5H), 7.32 (d, 2H, $J$=8 Hz, naphthyridine-6H, pyr-3H), 6.96 (d, 1H, $J$=8 Hz, pyr-5H), 2.78 (s, 3H, naphthyridine-$CH_3$), 2.50 (s, 3H, pyr-$CH_3$). IR (KBr) $\nu_{max}$: 3367, 2921, 1675, 1593, 1448, 1301, 1135 cm$^{-1}$. Anal. calcd for $C_{23}H_{19}N_5O_2$: C, 69.51: H, 4.82: N, 17.62. Found C, 69.17: H, 4.63: N, 17.39.

**3.3.3. *N*,*N*′-Bis-(7-methyl-[1,8]naphthyridin-2-yl)-isophthalamide 3.** The compound was made by coupling of 2-amino-7-methylnaphthyridine (200 mg, 1.24 mmol) with isophthaloyl chloride (130 mg, 0.62 mmol) in presence of triethylamine (0.8 mL) in dry dichloromethane (40 mL) by the above procedure. The compound was isolated as a white solid, yield 64%, mp 130–132°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.44 (bs, 2H, NH), 8.78 (s, 1H, *iso*-2H), 8.54 (d, 2H, $J$=8 Hz, *iso*-4H and 6H), 8.17 (d, 2H, $J$=8 Hz, naphthyridine-3H), 8.14 (d, 2H, $J$=8 Hz, naphthyridine-4H), 8.01 (d, 2H, $J$=8 Hz, naphthyridine-5H), 7.67 (t, 1H, $J$=8 Hz, *iso*-5H), 7.28 (d, 2H, $J$=6.5 Hz, naphthyridine-6H), 2.7 (s, 6H, naphthyridine-$CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$: 165.5, 162.3, 154.0, 153.7, 138.4, 135.9, 133.4, 131.7, 128.6, 126.2, 121.0, 117.9, 114.3, 25.0. IR (KBr) $\nu_{max}$: 3388, 1678, 1598, 1506, 1410, 1300 cm$^{-1}$. MS (EI, *m/e*) 448 ($M^+$, 21%), 186 (100%), 160 (100%). Anal. calcd for $C_{26}H_{20}N_6O_2$: C, 69.64: H, 4.46: N, 18.75. Found C, 69.68: H, 4.38: N, 18.65.

**3.3.4. *N*-[6-(2-{4-[(6-Butyrylamino-pyridin-2-ylcarbamoyl)-methyl]-phenyl}-acetylamino)-pyridin-2-yl]-butyramide 4.** To a stirred solution of 1,4-phenylenediacetic acid (200 mg, 1.02 mmol) in dry dichloromethane (10 mL), oxalyl chloride (0.89 mL) and one drop of dry DMF was added and stirred under a nitrogen atmosphere for 3 h. The volatiles were evaporated and dried. The acid chloride was taken in a round-bottomed flask and dissolved in 15 mL dry dichloromethane and to this the solution of 2,6-diaminopyridine (280 mg, 2.5 mmol) and triethylamine (0.27 mL, 2 equiv.) in dry dichloromethane (25 mL) were added dropwise under a nitrogen atmosphere and stirred overnight. The volatiles were evaporated and the solid were dissolved in dichloromethane and washed with 5% sodium bicarbonate solution. The solvent was evaporated in a rotavapor to yield a white solid (280 mg, 72%). To a solution of the corresponding amine (110 mg, 0.29 mmol) and triethylamine (0.081 mL, 3 equiv.) in dry dichloromethane, butyryl chloride (0.091 mL, 3 equiv.) was added dropwise and stirred overnight under nitrogen. After evaporation of the volatiles the solid was dissolved in dichloromethane and washed with 5% sodium bicarbonate solution. The solvent was evaporated to yield the desired product **4** as a white solid (130 mg, 86%), mp 204°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.90 (d, 2H, $J$=3.2 Hz, pyr-3H), 7.86 (d, 2H, $J$=2.8 Hz, pyr-5H), 7.68 (t, 2H, $J$=8.1 Hz, pyr-4H), 7.60 (bs, 4H, NH), 7.35 (s, 4H, phenyl 2H, 3H, 6H and 5H), 3.73 (s, 4H, phenyl-$CH_2$), 2.30 (t, 4H, $J$=7.4 Hz, $-CH_2CH_2CH_3$), 1.77–1.63 (m, 4H, $-CH_2CH_3$), 0.97 (t, 6H, $J$=7.4 Hz, $-CH_3$). IR (KBr) $\nu_{max}$: 3309.6, 2958.6, 2925.8, 1670.2, 1587.3, 1523.7, 1467.7, 1452.3, 1294.1, 1242.1, 1193.9, 802.3 cm$^{-1}$. Anal. calcd for $C_{28}H_{32}N_6O_4$: C, 65.10: H, 6.24: N, 16.27. Found C, 64.76: H, 6.11: N, 16.10. $^1$H NMR of complex **A** (200 MHz, $CDCl_3$) $\delta$ 10.96 (1H, bs, NH), 10.81 (1H, bs, NH), 8.71 (1H, bs, *iso*-2H), 8.67 (1H, d, $J$=8 Hz, *iso*-4H), 8.35 (3H, m, naphthyridine-3H and -4H, *iso*-6H), 8.07 (1H, d, $J$=8 Hz, naphthyridine-5H), 7.79 (1H, t, $J$=8 Hz, pyr-4H), 7.67 (1H, t, $J$=8 Hz, *iso*-5H), 7.32 (2H, d, $J$=8 Hz, naphthyridine-6H and pyr-3H), 6.98 (1H, d, $J$=8 Hz, pyr-5H), 5.00 (2H, s, methine protons of tartaric acid), 2.87 (s, 3H, naphthyridine-$CH_3$), 2.53 (s, 3H, pyr-$CH_3$). $^1$H NMR of complex **B** (200 MHz, $CDCl_3$) $\delta$ 10.70 (2H, bs, NH), 8.93 (1H, s, *iso*-2H), 8.72 (2H, d, $J$=8 Hz, *iso*-4H and -6H), 8.28 (4H, m, naphthyridine-3H and -4H), 8.10 (2H, d, $J$=8 Hz, naphthyridine-5H), 7.70 (1H, t, $J$=8 Hz, *iso*-5H), 7.64 (2H, d, $J$=8 Hz, naphthyridine-6H), 5.30 (s, 2H, methine protons of tartaric acid), 2.83 (s, 6H, naphthyridine-$CH_3$).

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