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Molecular Recognition: Connection and Disconnection of Hydrogen bonds, a case study with dimeric and highly associated Monocarboxylic acids with Simple Receptors

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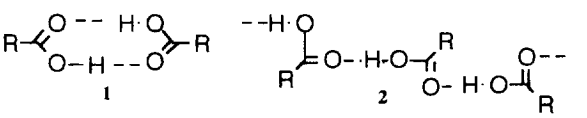
Abstract The new receptor (**5**) having mixed diamide moieties is a simple synthetic model which binds carboxylic acids by three point hydrogen bonds involving pyridine nitrogen, pyridine amide as well as the flexible aliphatic amide moieties. This is in contrast to the receptor (**6**) which makes only two point hydrogen bonds. Binding studies of the simple pyridine amide (**3**) making two hydrogen bonds with a number of dimeric and highly associated monocarboxylic acids are also reported. Receptor (**9**) shows higher binding constant with ibuprofen compared to (**3**). Copyright © 1996 Published by Elsevier Science Ltd

INTRODUCTION

In the area of molecular recognition the design and synthesis of molecules to mimic biological events is a field of current interest. This has strong relevance to enzyme models and drug design. For designing molecules to recognise other specific molecules, the prime factor is the consideration of the specific interaction between the functional groups of host and guest by hydrogen bonds. To have such type of hydrogen bondings between the functional groups of hosts and guests, the knowledge of hydrogen bondings amongst the independent host or guest system causing selfassociation is essential for successful heteroassociation of the host and guest. The other equally important factor is the consideration of intramolecular hydrogen bonds within the host[1] itself so that the cavity is not collapsed and the hydrogen bonding groups are freely available for host-guest association.

The report of molecular recognition of dicarboxylic acids,[2] amino acids,[3] acylamino acids[4] and carboxylate anion[5,6] prompted us to recognise monocarboxylic acid itself which is of current interest.[7,8] The binding of carboxyl or carboxylate groups is involved in many biological recognition processes. In peptide recognition by vancomycin, amide-carboxylate binding is crucial.[6] Carboxyl group has also been incorporated in the design of receptors for strong complexation with adenine.[9] A large number of drugs like antibiotics, analgesics and anti-inflammatory agents have -COOH, -$CH(CH_3)COOH$ or -CH_2COOH moieties.

Monocarboxylic acids are known to be present in dimeric (**1**) or highly associated forms (**2**).[10] Gandour[11] pointed out the stereoelectronic features of carboxyl oxygens. The *syn*-planar structure is more stable than the *anti*-planar one and in formic acid the *syn* -planar form is more favoured by 8 kJ mol^{-1}.[12-14] Acetic acid exists in the gas phase as a dimer except at low pressure.[15] Unlike most carboxylic acids like propionic acid which exists as cyclic hydrogen bonding dimer, acetic acid crystals contain infinite chains of O-H...O-H bonding monomers. The lowest member formic acid forms infinite hydrogen-bonded chains rather than dimers in the solid state.[10] The chain like arrangement is also proved by measurement of the dielectric polarisation of solid formic acid.[10]

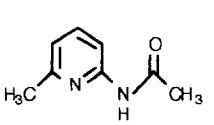


1 2

In this paper we wish to report the systematic design and synthesis of a number of flexible receptors for the binding studies of a series of monocarboxylic acids employing hydrogen bonding.

RESULTS AND DISCUSSION

Previously it was shown that the two point fixation of monocarboxylic acids with the derivative of 2-amino-6-methylpyridine normally shows weak binding ($2x10^2$ M^{-1}).[2] This is also in accordance with our systematic binding studies of the simple pyridine amide **3** with a series of hitherto unreported monocarboxylic acids which exist in highly selfassociated forms (Table 1). To enhance the binding of the simple pyridine amide moiety with associated carboxylic acids, we designed the flexible receptors **5** and **6** to examine the participation of the aliphatic amide moiety to form three hydrogen bonds.



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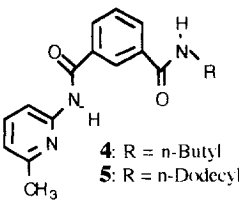
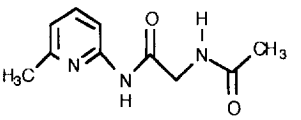


4: R = n-Butyl
5: R = n-Dodecyl



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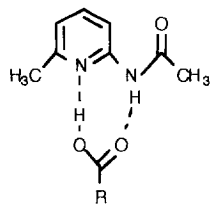
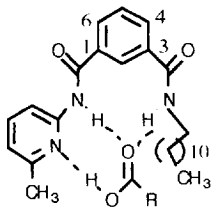
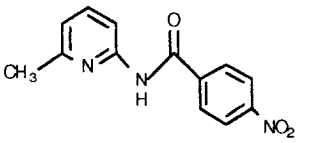


Complex 7
Two point H-bonding



Complex 8
Three point H-bonding



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7a. R = H
7b. R = CH_3
7c. R = C_2H_5
7d. R = C_6H_5
7e. R = 4-CH_3O-C_6H_4
7f. R = 4-$CH_3CH(CH_3)CH_2$-C_6H_4-$CH(CH_3)$

8a. R = H
8b. R = CH_3
8c. R = C_2H_5
8d. R = C_6H_5
8e. R = 4-CH_3O-C_6H_4
8f. R = 4-$CH_3CH(CH_3)CH_2$-C_6H_4-$CH(CH_3)$

NMR titrations in $CDCl_3$ show moderate binding[16] and formation of 1:1 complex with a number of aliphatic (including ibuprofen) and aromatic acids with the simple receptor **3** and the new mixed amide receptor **5** (Tables 1 and 2). Formic acid, on complexation with receptor **3**, shows a downfield shift ($\Delta\delta$ 0.18 ppm in 1:1 complex) of the hydrogen attached to the carboxylic carbon besides the significant shift of the pyridine amide proton supporting hydrogen bond formation as shown in complex **7a** but no proton transfer.[17] The dimeric state of the carboxylic acid (selfassociation constant is of the order of 0.01-5 L M^{-1})[2] which is resonance stabilised is slightly converted to the monomer only at high dilution. Thus the new organisation of hydrogen bonds with the receptors shows that heterodimerisation is possible at the dilution of the titration experiments overcoming the selfassociation of monocarboxylic acids.

Table 1 Binding constants with **3**

substrate acid[S]	[RS]* complex	K_a, M^{-1}	ΔG at 25°C kcal/mol
Formic	**7a**	0.50×10^2	-2.31
Acetic	**7b**	0.80×10^2	-2.59
Propionic	**7c**	0.75×10^2	-2.55
Benzoic	**7d**	2.30×10^2	-3.20
Anisic	**7e**	6.60×10^2	-3.84
Ibuprofen	**7f**	1.00×10^2	-2.72

*[RS] = receptor-substrate complex

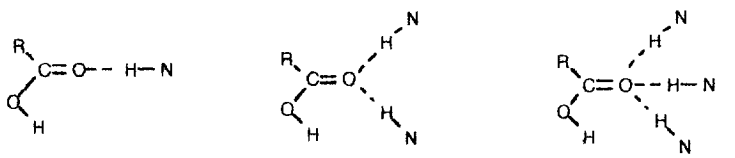
Table 2 Binding constants with **5**

substrate acid [S]	[RS]* complex	K_a, M^{-1}	ΔG at 25°C kcal/mol
Formic	**8a**	0.70×10^2	-2.51
Acetic	**8b**	2.20×10^2	-3.19
Propionic	**8c**	1.70×10^2	-3.04
Benzoic	**8d**	1.34×10^2	-2.90
Anisic	**8e**	1.65×10^2	-3.02
Ibuprofen	**8f**	2.80×10^2	-3.33

*[RS] = receptor-substrate complex

The low value of binding constant of formic acid as shown in the Table 1 with receptor **3** suggests probably stronger selfassociation compared to acetic and propionic acids and also to ibuprofen. The binding constants of receptor **5** with the carboxylic acids by formation of an extra hydrogen bond are not, however, much increased as expected[3] (approximately three times for acetic acid and ibuprofen but negligibly for formic acid) (Tables 1 and 2).

The number of hydrogen bond contacts with the carboxyl carbonyl group may be represented as (a) one (b) two and (c) three as shown below. Among these three forms, (b) is more pronounced due to the minimum nonbonded lone pair repulsion provided there is no adverse steric environment.[18]



(a) (b) (c)

Comparing the binding constants in Tables 1 and 2, it is apparent that with an increase in the number of hydrogen bonds from receptor **3** (Complex **7**) to receptor **5** (Complex **8**), the values for aliphatic acids increase whereas for aromatic acids they decrease. In case of aliphatic carboxylic acids (acetic, propionic and ibuprofen), the higher binding constants with receptor **5** compared to receptor **3** suggest a better steric fit for all the possible hydrogen bonds compared to the aromatic acids. This suggests the possibility of an adverse steric environment in case of aromatic acids in the binding pocket to attain a hydrogen bonded structure like (b). Though anisic acid is weaker than benzoic acid, it shows stronger binding with receptors **3** and **5**. This may be due to the enhanced electron density on the carbonyl oxygen of the carboxyl group by electron donating resonance effect of the *p*-methoxy group in anisic acid.

Interestingly in the alternative receptor **6**, the flexible aliphatic amide (glycinamide) proton undergoes negligible shift compared to the large downfield shift of the pyridine amide proton on complexation with carboxyl group indicating the involvement of pyridine amide only in the two point hydrogen bond formation unlike the unique three point hydrogen bondings with receptor **5** having isophthaloyl spacer between the pyridine amide and aliphatic amide moieties.

The formation of complexes **8(a-f)** of carboxylic acids with receptor **5** indicates the participation of both aliphatic and aromatic amide protons as shown by the significant $\Delta\delta_{max}$ values of both the amide protons as

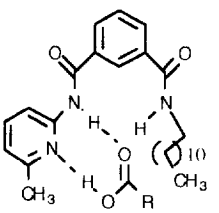
shown in Table 3. Previous studies have shown that the isophthaloyl amide protons can make two point hydrogen bonds with the barbital 2-carbonyl in the binding cavity of the receptor.[19]

Table 3 Chemical shift changes on complexation with receptor **5**

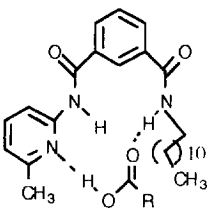
substrate acid[S]	[RS]* complex	$\Delta\delta_{max}$ for the amide protons aliphatic (ppm)	aromatic (ppm)
Formic	**8a**	0.73	1.50
Acetic	**8b**	0.69	1.53
Propionic	**8c**	0.71	1.30
Benzoic	**8d**	0.71	1.60
Anisic	**8e**	0.64	1.43
Ibuprofen	**8f**	0.68	1.42

*[RS] = receptor-substrate complex

The considerable downfield chemical shift changes of both the aliphatic and aromatic amide protons in receptor **5** is indicative of three point hydrogen bondings on complexation with carboxylic acids. However, in solution, the equilibration between the two 2-point binding structures [Complex (**10**) and Complex (**11**)] cannot be ruled out.



Complex 10
Two point H-bonding
R=H, CH_3, C_2H_5, C_6H_5, 4-CH_3O-C_6H_4
4-$CH_3CH(CH_3)CH_2$-$C_6H_4CH(CH_3)$



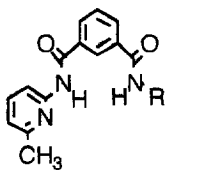
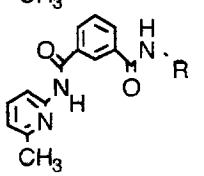
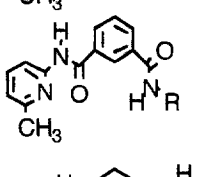
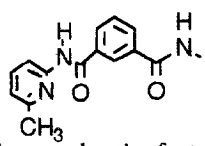
Complex 11
Two point H-bonding
R=H, CH_3, C_2H_5, C_6H_5, 4-CH_3O-C_6H_4
4-$CH_3CH(CH_3)CH_2$-$C_6H_4CH(CH_3)$

In solid state IR studies of complex of carboxylic acids with receptor **3**, the reduced OH stretching bands observed at low frequencies (2480 - 2510 cm^{-1} and 1890 - 1910 cm^{-1}) characteristically show that the carboxylic acid hydrogen is bonded to the aromatic ring nitrogen.[20] The participation of the pyridine amide as well as the aliphatic amide protons of receptor **5** in forming the complex with carboxylic acids is also evident from the decreasing absorption frequencies of both the NH (from 3306 to 3250 cm^{-1}) and carboxylic OH stretching (from 2510 - 2540 cm^{-1} and 1880 - 1900 cm^{-1}).

To have an idea of the flexibility of receptor **5**, we performed some calculations on different conformations using the DTMM program[21] which revealed little difference in different forms. The different energy minimised[21] conformations of receptor **5** have comparable energy values (Table 4). The preferred orientation required for optimum complexation with carboxyl group is shown in Fig.1.

For binding experiments the receptor **5** was preferred to **4** because of its increased solubility in chloroform. Increased hydrophobicity of **5** may also have some role in blocking the access of any trace of water that may inherently be present in the system into the binding pocket of the receptor.

Table 4.§ Energy values for different conformations of **5**

CONFORMATIONS		E_{min} (kcal/mol)	Distance (in A) N-N	NH-NH	CO-CO
	*syn*	56.60	4.96	3.21	5.04
	anti	55.23	4.98	3.23	5.04
	*syn*	56.20	6.50	6.32	5.05
	anti	54.39	6.50	6.32	5.05
	*syn*	56.55	6.49	6.30	5.04
	anti	55.15	6.49	6.31	5.04
	*syn*	57.51	7.36	7.30	5.04
	anti	55.58	7.35	7.28	5.04

§ *syn* and *anti* refer to the orientation of the pyridine N lone pair with respect to the pyridine amide H keeping the aliphatic amide moiety fixed as shown. R = dodecyl

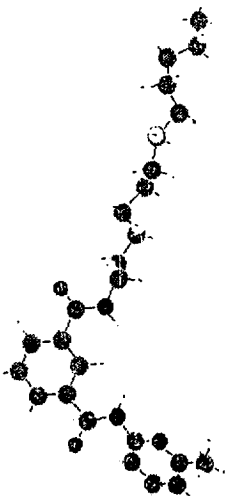


Fig.1. Preferred conformation of receptor **5**

Positive NOE effects of both H-2 and H-4 as well as H-2 and H-6 were observed on respective irradiation of the aliphatic amide and aromatic amide protons suggesting conformational equilibrium of the free receptor **5** in $CDCl_3$ solution.

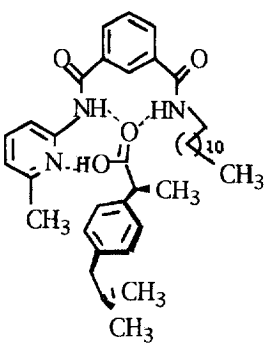


Fig 2. Proposed model of the bound complex of ibuprofen with receptor **5.**

On complexation, the proximity of ibuprofen into the binding pocket of the receptor **5** (Fig.2) was supported by NOESY experiments where the aromatic protons of ibuprofen and the pyridine methyl protons showed cross peak. The involvement of both pyridine amide and the aliphatic amide protons of **5** in the formation of 1:1 complex **8f** with ibuprofen was supported by appreciable downfield shifts (Fig. 3) of $\Delta\delta$ 1.0 ppm and 0.47 ppm respectively.

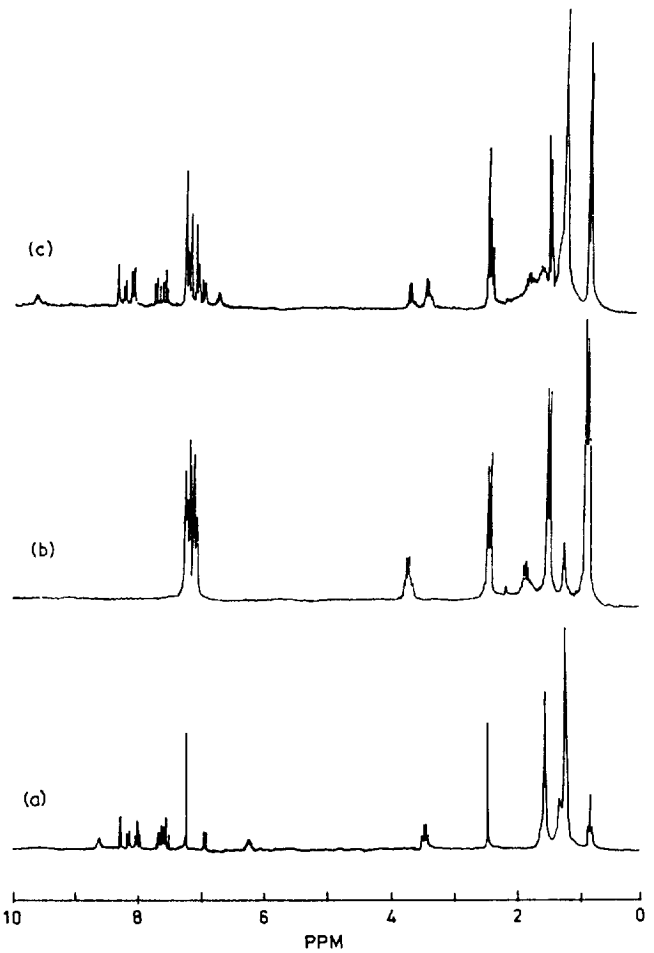


Fig 3 (a) ^{1}H NMR spectrum of receptor **5** (b) ^{1}H NMR spectrum of guest ibuprofen (c) ^{1}H NMR spectrum of complex **8f**.

Complexation with a non-macrocyclic and flexible receptor **5** thus demonstrates that hydrogen bonding can induce the conformational organisation directed to favour all the three possible hydrogen bonds with the carboxyl group mimicking to some extent the binding of vancomycin [22] with carboxylate ion.

The receptor **9** having a *p* -nitrobenzamide moiety somewhat enhances the binding constant with ibuprofen (K_a =1.5 x10^2 M^{-1}) compared to **3** which may be due to some increased acidity of the amide hydrogen of the host and weak aromatic p-stacking interaction between the *p* -nitrophenyl of host and phenyl

ring of ibuprofen in **Complex 12**. This is recognized from ^{1}H NMR by upfield shift of the corresponding protons of *p* -nitrophenyl and phenyl ring by 0.1 ppm.

The titration and binding constant curves of ibuprofen with receptors **5** and **9** are represented in Fig 4.

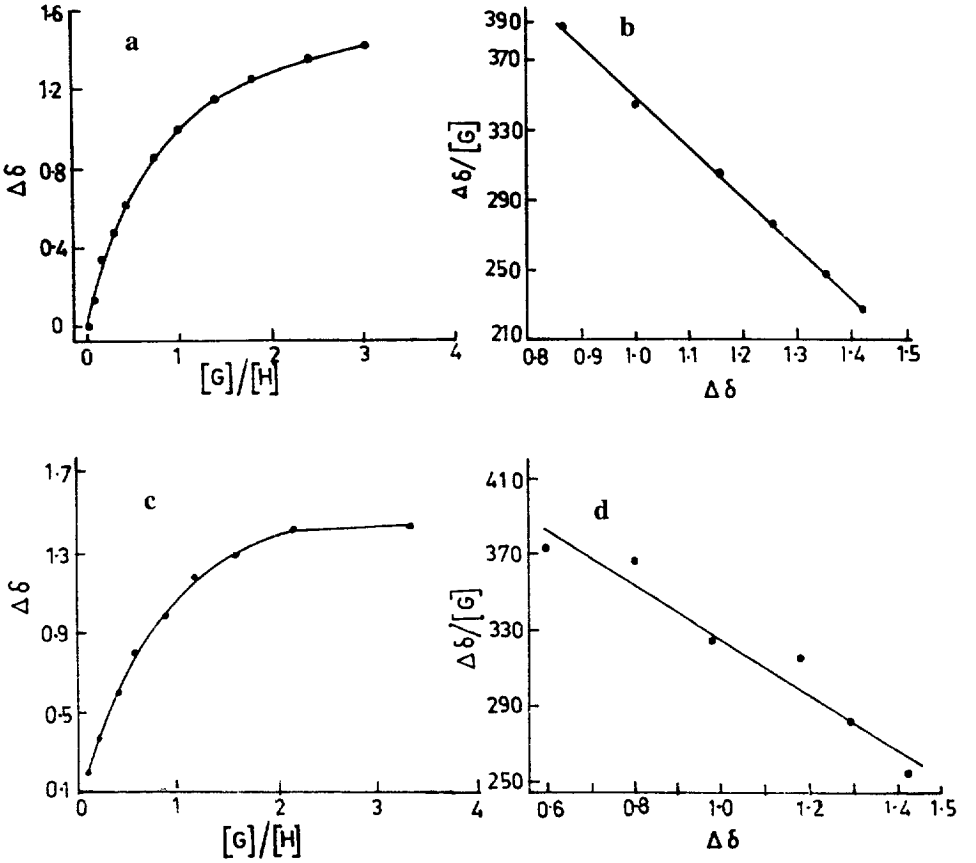
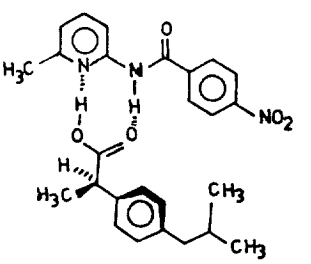


Fig. 4. (a) Titration curve for ibuprofen with receptor **5** (b) Binding constant curve for ibuprofen with receptor **5** (c) Titration curve for ibuprofen with receptor **9** (d) Binding constant curve for ibuprofen with receptor **9**



Complex 12

The receptor **5** was synthesised by high dilution reaction of 2-amino-6-picoline and dodecylamine with isophthaloyl chloride. The receptor **6** was obtained simply by DCC coupling of 2-amino-6-picoline with acetylglycine.

In summary, we have shown that the simple flexible model receptor **5** is capable of making three hydrogen bonds with carboxylic acid. This is in contrast to two hydrogen bonds with receptor **6** indicating the importance of suitable placement of the hydrogen bonding groups in the design of receptors. These binding experiments with receptors **3** and **5** with monocarboxylic acids give an insight into the connection and disconnection of hydrogen bonds that accompany heterodimerisation over selfdimerisation or selfassociation at the dilution of NMR titration. To enhance the binding constant further work is in progress with a macrocycle which can hold rigidly both the amide moieties to make three point hydrogen bonds with carboxylic acids.

EXPERIMENTAL SECTION

General.

All solvents were dried prior to use. Methylenechloride, triethylamine were distilled from calcium hydride. Tetrahydrofuran was distilled from benzophenone ketyl. All reactions were carried out under nitrogen. Silica gel chromatography was performed using 60-120 mesh. IR spectra were recorded on Perkin-Elmer model-883. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 200. Analyses were obtained from Indian Association for Cultivation of Science, Calcutta. Melting points were recorded in open capillaries and are uncorrected.

1-[[(6-Methylpyrid-2-yl)amino]carbonyl]-3-[(dodecylamino)carbonyl]benzene(5): A solution of 2-amino-6-methylpyridine (159 mg, 1.47 mmol) and triethylamine (0.2 ml) in dry methylenechloride (50 ml) and a solution of dodecylamine (273 mg, 1.47 mmol) and triethylamine (0 2 ml) in dry methylenechloride (50 ml) were simultaneously added dropwise separately from two dropping funnels to isophthaloyl diacid chloride (300 mg, 1.47 mmol) in dry methylenechloride (40 ml) under nitrogen during a period of 8 h. The whole mixture was then washed with saturated sodium bicarbonate followed by water. The separated organic layer was dried over sodium sulfate and evaporated to dryness. The crude mixture was purified by preparative layer chromatography [chloroform-ethylacetate (90:10)] to afford the receptor (**5**) which was made analytically pure by passing again through a short silicagel column as white solid (250 mg, 40%), mp 108 °C, IR (KBr) cm^{-1}: 3306, 2923, 2855, 1641, 1590, 1530; ^{1}H NMR ($CDCl_3$): d 9.03 [s, 1H, NH (pyr. amide)], 8.38 (s, 1H, isophth-2H), 8.24 (d, J = 8 H_Z,1H, pyr-3H), 8.04 (d of d, J =8 H_Z, 2H, isophth-4,6 H), 7.72 (t, J = 8 H_Z, 1H, isophth-5H), 7.58 (t, J = 8H_Z, pyr-4H), 6.98 (d, J = 8 H_Z, 1H, pyr-5H), 6.42 (bs, 1H, NH, aliphatic amide), 3.48 (q, 2H, J = 6.6 H_Z, 2H, -NHC**H**$_2$), 2.52 (s, 3H, pyr-CH_3), 1.77-1.68 (m, 2H, NHCH$_2$C**H**$_2$),1.65-1.62 (m, 2H, NHCH$_2$CH$_2$C**H**$_2$), 1.32-1.26(m, 16H, $(CH_2)_8$, 0.88 (t, J =6.3H_Z,,CH_3) ^{13}C ($CDCl_3$): 166.12, 164.98, 154.92, 150.22, 141.06 (CH), 135.51, 133.57, 131.79 (CH), 130.30 (CH), 129.37 (CH), 125.39 (CH), 119.63 (CH), 111.89 (CH), 40.39 (CH_2), 31.91 (CH_2), 29.61-29.10 (7 CH_2 unresolved), 27.06 (CH_2), 22.74 (CH_2), 22.67 (CH_3), 14.09 (CH_3). MS, m/e calcd. for $C_{26}H_{37}N_3O_2$: 423.288578, found 423.291494 (M^+, 20%), 394(100%). Anal. calcd. for $C_{26}H_{37}N_3O_2$: C, 73.70; H, 8.82; N, 9.92. Found: C, 73.54; H, 8.67; N, 10.16.

2-(*N*-acylglycinamido)-6-methylpyridine(6): To a stirred solution of acetylglycine in anhydrous methylenechloride(10 ml) and dicyclohexylcarbonyldiimide(880 mg, 4.27 mmol) and 4-DMAP was added

dropwise a solution of 2-amino-6-methylpyridine(460 mg, 4.27 mmol) in dry methylenechloride under nitrogen at 0 °C. After completion of addition the mixture was left overnight stirring at room temperature under nitrogen. The precipitated dicyclohexyl urea was then filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in methylenechloride, washed thoroughly with saturated sodium bicarbonate solution followed by water and then dried (sodium sulfate). The solvent was removed under reduced pressure and the product was purified by silica gel chromatography [petroleum ether : ethylacetate (90: 10)] to afford the product, (570 mg, 60%), mp 145-6 °C; IR (KBr), cm^{-1} 3337, 3042, 1642, 1552, 1452. ^1H NMR ($CDCl_3$): δ 8.27 [s, 1H, NH(pyr. amide];7.94(d, J = 8 H_Z, 1H, pyr-3H); 7.60(t, J = 8 H_Z, 1H, pyr-4H); 6.92(d, J = 8H_Z, 1H, pyr-5H); 6.28(s, 1H, NH, glycinamide); 4.11(d, J = 6 H_Z, 2H, CH_2NHCO); 2.45(s, 3H, pyr-CH_3); 2.09(s, 3H, $NHCOCH_3$). ^{13}C : 170.65, 167.64, 156.91, 150.26, 139.82, 119.56, 111.13, 44.05, 23.89, 22.96. MS, m/e M^+ 207 (65%), 164 (M^+ -.CH_3CO, 35%), 135 (m/e164 -CO-H^+). Anal. calcd. for $C_{10}H_{13}N_3O_2$. C, 57.95; H, 6.34; N, 20.28. Found: C, 57.63, H, 6.11; N, 20.16.

6-methyl-2-(4-nitrobenzoylamino)pyridine(9): To a stirred solution of isophthaloyldiacidchloride(1.71 g, 9.24 mmol) in dry methylenechloride(30 ml) was added dropwise 2-amino-6-methylpyridine (1g, 9.24 mmol) and triethylamine(1.3 ml) at room temperature under nitrogen. The mixture was left overnight under stirring and water(20 ml) was added. The organic layer was washed with water followed by saturated sodium bicarbonate solution and dried(sodium sulfate). After evaporation of the solvent the product was further purified by silica gel chromatography(2.14 g, 90%), mp 128 °C, IR (KBr), cm^{-1}: 3543, 3341, 1658, 1605, 1523, 1452. ^1H NMR ($CDCl_3$): δ 8.55(s, 1H, NH); 8.36(d, 2H, J = 8H_Z); 8.12(m, 3H); 7.67(t, 1H, J = 8H_Z); 6.97(d, 1H, J = 8H_Z); 2.48(s, 3H). M^+ 257 (30%).

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