Steric inhibition of Hydrogen bonding in molecular recognition of dicarboxylic acids: Di-topic receptors containing nitro group designed to behave like monotopic receptors

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Contents

1. General

Chromatographic separations were performed on silica gel (100-200 mesh). The petroleum ether used has a boiling range of 60-80°C. All the melting points were determined on a hot coil stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on 400 MHz spectrometers. For NMR spectra, $CDCl_3$ and d_6-DMSO were used as solvents using TMS as an internal standard. Chemical shifts are expressed in δ-units and coupling constants in Hz.

2. General procedure for UV-vis and fluorescence titration

Stock solutions of the receptors (receptor **1**, **2**, **3**, **4** and **5**) were taken in the order of ca. 1.0×10^{-5} M in $CHCl_3$ and the 1×10^{-3} M guest carboxylic acid solutions in $CHCl_3$. The solutions of guests were added in increasing μL volume to avoid the dilution effect and the possible dilution is taken into account for the calculation of binding constant, i.e. volume correction has been done. All the acids were dissolved in $CHCl_3$ in order of ca.1.0×10^{-3} M concentration and sonicator was used for dissolving some of the acids. Then the guest solution is added to the receptor solution (taking 2 mL in UV-vis cuvette) and continuous decrease of absorbance in UV-vis spectra was recorded for each time. For each of the gusts volume added in μL are 5, 5, 10, 10, 10, 10, 20, 25, 25, 50, 50 and so on for the rest. Association constants were calculated by plotting 1/[G] versus 1/ΔI (ΔI= change of intensities of the absorbance spectrum during titration and the [G] is the concentration of guest). Sigmaplot 12.3 version (Sigmaplot for windows, Version 12.3, Dundas Software, Germany) has been use to perform all the non-linear regression and thereby calculation of the binding constants. All the errors have been calculated from the same software during fitting. The binding constants were determined following the equation f= y0+ax, where "y0" is the intercept and "a" is the slope. Binding constant *Ka* determined by the ratio of "y0" and "a", i.e. *Ka*= y0/a. The binding curves i.e the curve obtained from the plot of the changes of absorbance vs the ratio of concentrations of guest and host were fitted with sigmoidal 3 parameters fitting process following the standard equation f=y0+a/(1+exp(-(x-x0)/b))^c, where a, b and c are constants.

3. 1/[G] versus 1/ΔI fits for the calculation of binding constant values

Nonlinear Regression Tuesday, August 19, 2014, 11:16:21 AM

Data Source: Data 1 in Notebook3
Equation: Standard Curves, Linear Curve
f = y0+a*x

R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.9972	0.9945	0.9939	0.0072

	Coefficient	Std. Error	t	P
y0	-14.8408	0.6825	-21.7438	<0.0001
a	0.0421	0.0010	40.2765	<0.0001

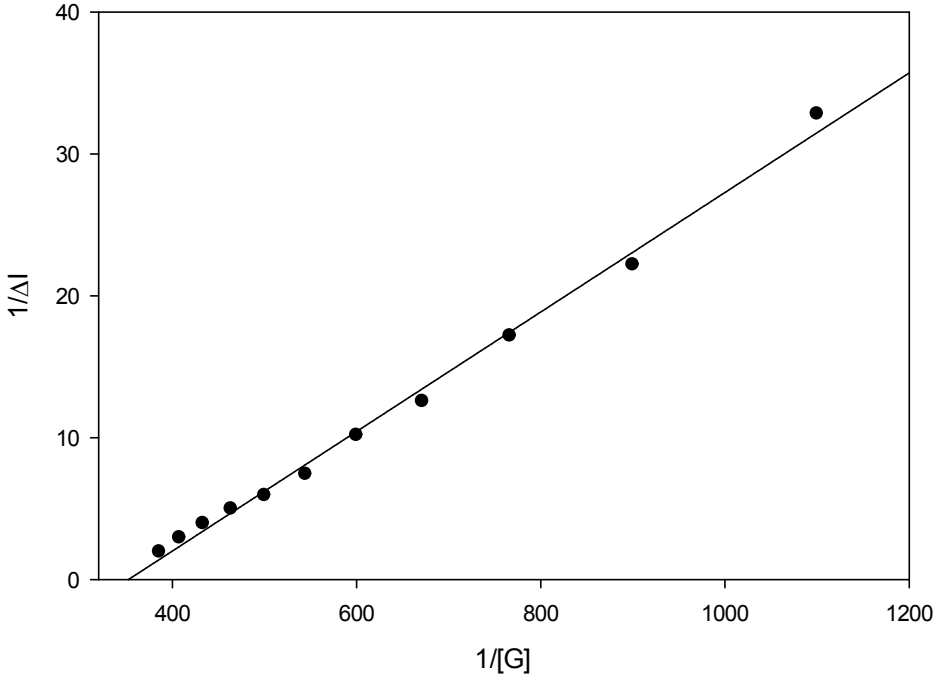


Figure S1: Non-linear fit of the plot of 1/[G] versus 1/ΔI for the titration of macrocycle **4** with adipic acid.

Nonlinear Regression Tuesday, August 19, 2014, 11:06:06 AM

Data Source: Data 1 in Notebook2
Equation: Standard Curves, Linear Curve
f = y0+a*x

R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.9952	0.9904	0.9893	0.00775

	Coefficient	Std. Error	t	P
y0	-11.0261	0.7068	-15.5998	<0.0001
a	0.0033	0.0001	30.4769	<0.0001

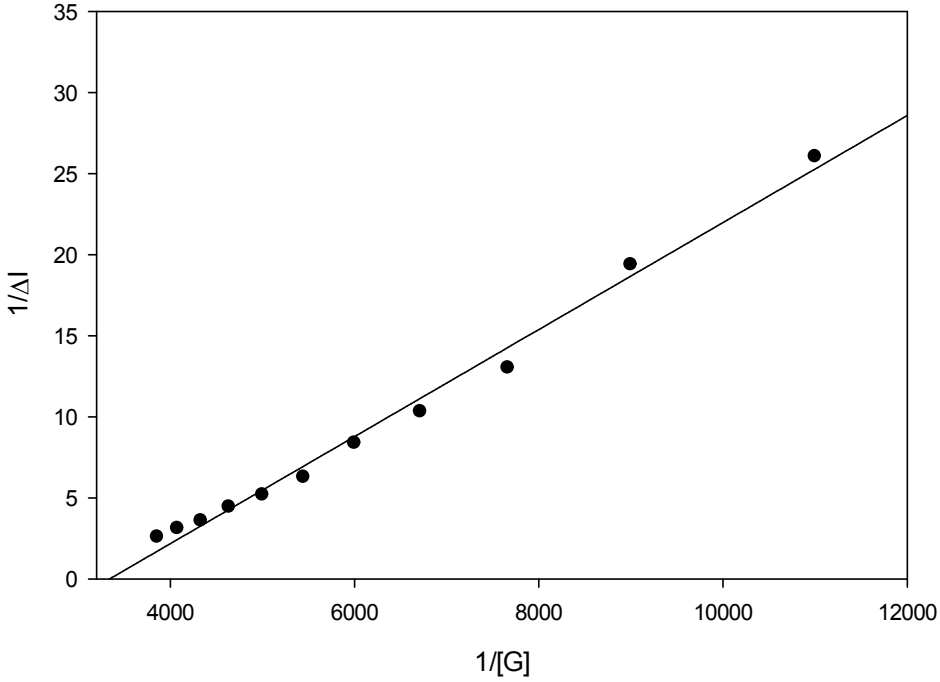


Figure S2: Non-linear fit of the plot of 1/[G] versus 1/ΔI for the titration of macrocycle **4** with DL-malic acid.

Nonlinear Regression Tuesday, August 19, 2014, 11:25:17 AM

Data Source: Data 1 in Notebook4
Equation: Standard Curves, Linear Curve
f = y0+a*x

R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.9977	0.9955	0.9950	0.0222

	Coefficient	Std. Error	t	P
y0	-37.9315	1.5681	-24.1890	<0.0001
a	0.0983	0.0021	46.9574	<0.0001

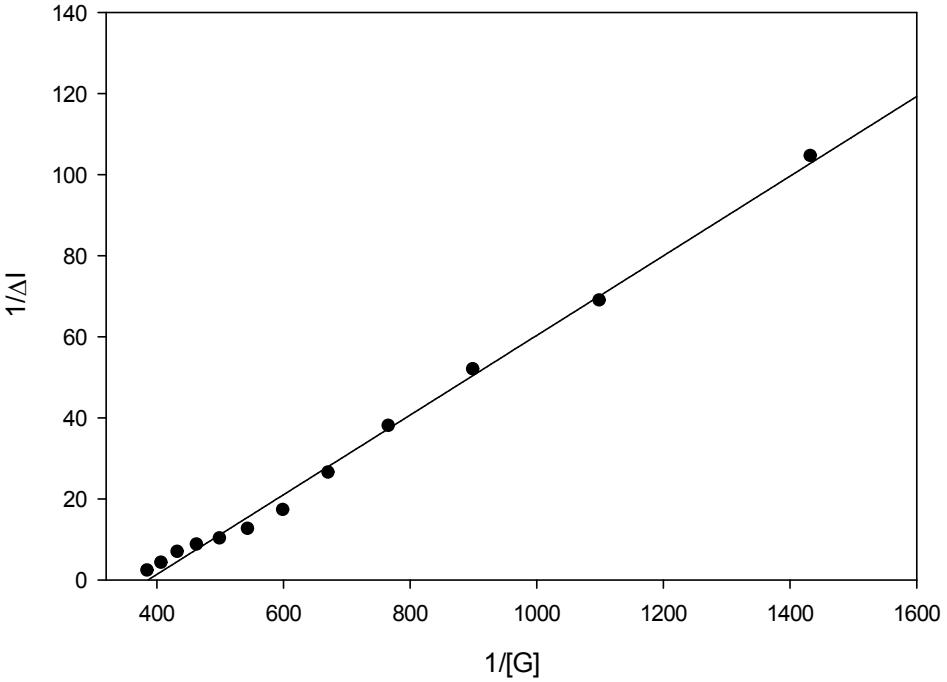


Figure S3: Non-linear fit of the plot of 1/[G] versus 1/ΔI for the titration of macrocycle **5** with adipic acid.

Nonlinear Regression Tuesday, August 19, 2014, 10:29:06 AM

Data Source: Data 1 in Notebook1
Equation: Standard Curves, Linear Curve
f = y0+a*x

R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.9952	0.9904	0.9894	0.01

	Coefficient	Std. Error	t	P
y0	-37.2555	2.3284	-16.0007	<0.0001
a	0.0092	0.0003	30.5125	<0.0001

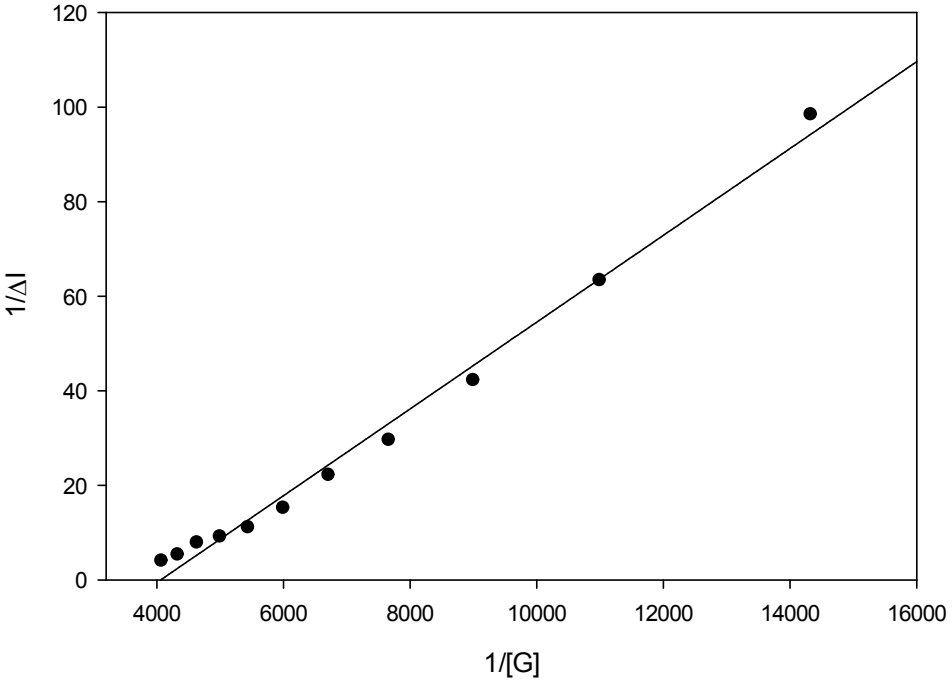


Figure S4: Non-linear fit of the plot of 1/[G] versus 1/ΔI for the titration of macrocycle **5** with DL-malic acid.

4. [G]/[H] versus ΔI fits

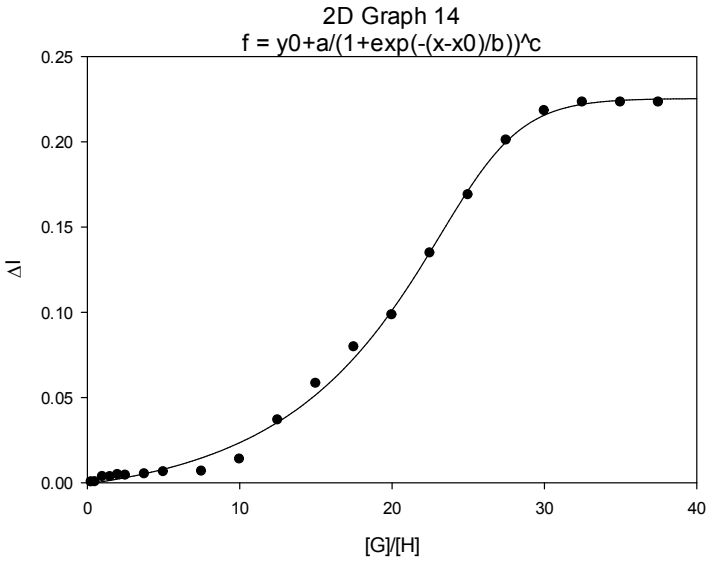


Figure S5: Exponential fit of the plot of [G]/[H] versus ΔI for the titration of macrocycle **4** with adipic acid.

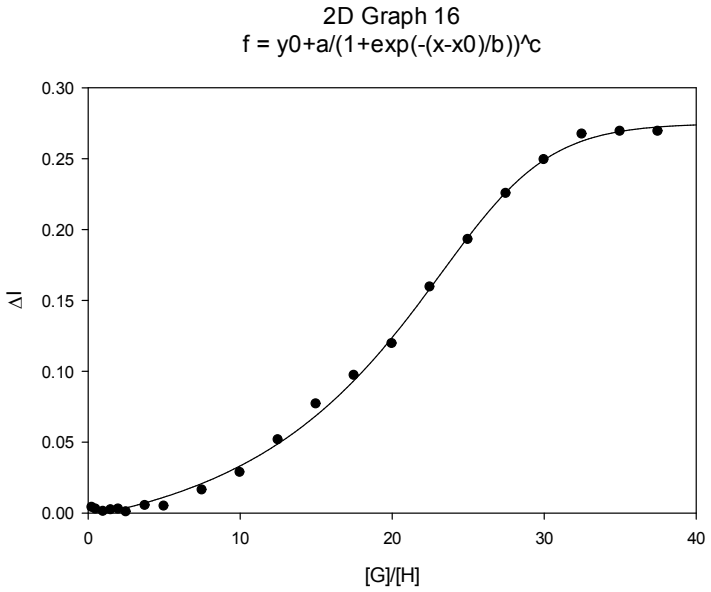


Figure S6: Exponential fit of the plot of [G]/[H] versus ΔI for the titration of macrocycle **4** with DL-malic acid.

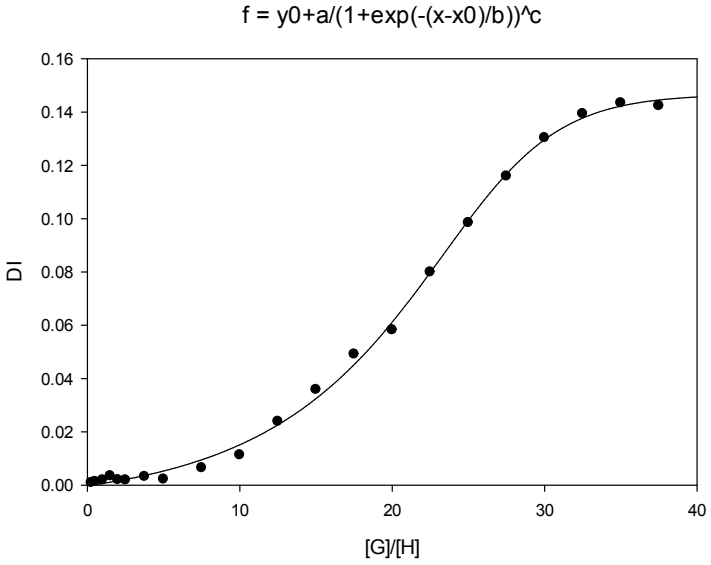


Figure S7: Exponential fit of the plot of [G]/[H] versus ΔI for the titration of macrocycle **5** with adipic acid.

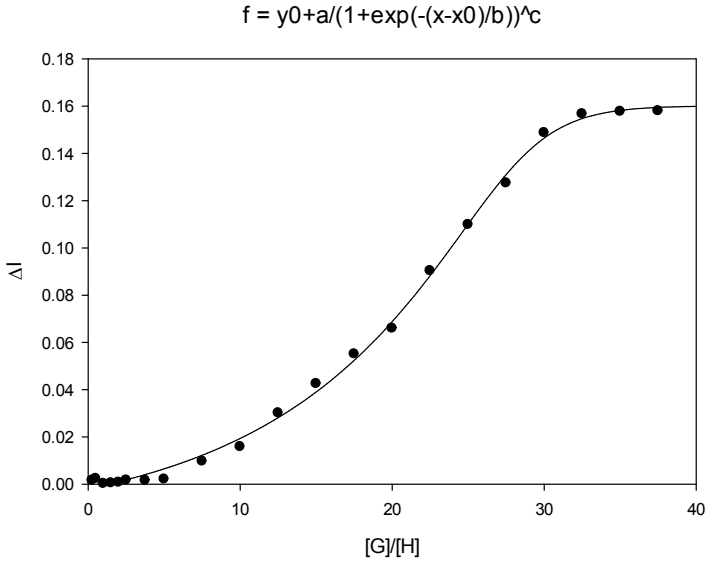
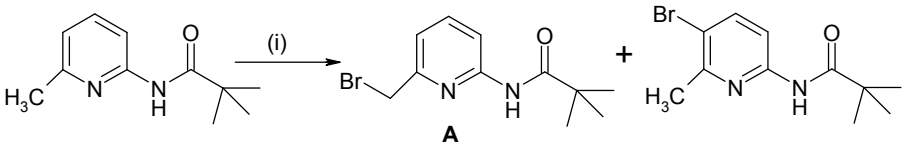


Figure S8: Exponential fit of the plot of [G]/[H] versus ΔI for the titration of macrocycle **5** with DL-malic acid.

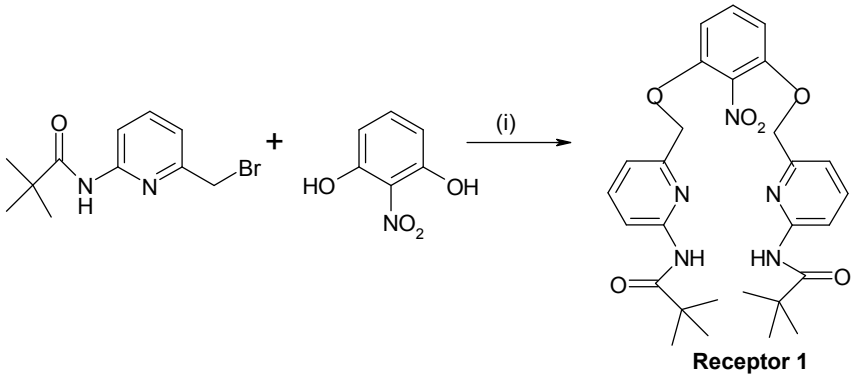
4. Synthetic scheme:

Synthesis of the receptors [receptor **1**, receptor **2** and receptor **3**]

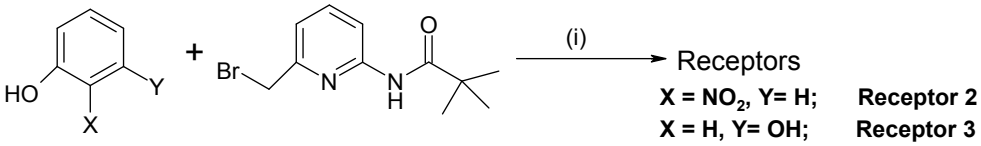
N-(6-Bromomethyl-pyridin-2-yl)-2, 2-dimethyl-propanamide[5f] (**4**) has been synthesized in our laboratory using NBS and AIBN used in catalytic amount and the whole mixture was refluxed in dry CCl_4. Then reaction of **5**, **6** and **7** with compound **3** yielded receptors **1**, **2** and **3** respectively (schemes 1-2).



Scheme 1. Reagents and conditions: (i) NBS, AIBN, hυ, CCl_4, reflux, 6 h, 60%.



Reagents and condition: (i) K_2CO_3, dry acetone, TBAB, r.t., 14 h.



Scheme 2. Reagents and condition: (i) Dry K_2CO_3, dry acetone, TBAB, r.t, 15 h.

Synthetic scheme of receptor 1: 2-Pivaloylamino-6-bromomethylpyridine (600 mg, 1 mmol), 2-nitroresorcinol (170 mg, 0.5 mmol), potassium carbonate (1.07 g, 3.5 mmol) and n-tetrabutylammonium bromide (TBAB) (0.14 g, 0.2 mmol) were taken in a 50 ml r.b. containing 15 ml acetone. The mixture was stirred at r.t. for 14 h. After completion of the reaction acetone was distilled out and the crude product was purified by column chromatography using 50% ethyl acetate in petroleum ether as eluent to yellowish solid, receptor **1** (0.35 g, yield 58.3 %). M.pt.184-186^oC; ^1H NMR of receptor **1** ($CDCl_3$, 500 MHz): δ (ppm) 8.16(d, 2H, *J*= 8.3 Hz), 7.96(s, 2H), 7.72(t, 2H, *J*= 7.94 Hz), 7.26-7.23(m,

1H, *J*= 8.5 Hz), 7.17(d, 2H, *J*= 7.5 Hz), 6.63(d, 2H, *J*= 8.57 Hz), 5.15(s, 4H), 1.34(s, 18H); ^{13}C NMR of receptor **1** ($CDCl_3$; 125 MHz): δ 177.0, 153.9, 151.0, 150.7, 139.4, 132.8, 131.2, 116.8, 112.9, 106.4, 71.0, 39.8, 27.5; Mass $[M+H]^+$ (FIA) calcd. for $C_{28}H_{34}N_5O_6$ is 535, found 535.4.

Preparation of receptor 2

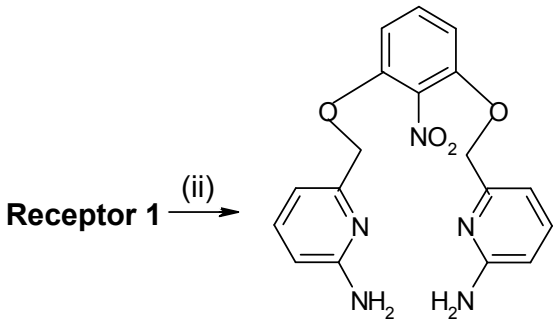
Receptor **2** was synthesized using the similar procedure as stated in the case of receptor **1**. N-(6-Bromomethyl-pyridin-2-yl)-2, 2-dimethyl-propanamide, **A** (2.46 g, 9.08 mmol), resorcinol (500 mg, 4.54 mmol), K_2CO_3 (1.57 g, 11.35 mmol) and TBAB (80 mg, 0.25 mmol) were taken in a round bottomed flask. Dry acetone (18 ml) was added to it and stirred for 20 h at r.t. Acetone was distilled out and the crude was extracted with $CHCl_3$ (20 mL x 4), which was then dried over anhydrous Na_2SO_4 and concentrated under vacuum. This crude was purified by column chromatography using silica gel (100-200 mesh) and EtOAc (10 %) in petrolium ether as eluent to afford semi-solid substance (350 mg, 15.7%). ^{1}H NMR of receptor **2** ($CDCl_3$; 500 MHz): δ 8.17(d, 2H, *J*= 8.3 Hz), 8.01(bs, 2H), 7.71(t, 2H, *J*= 7.9 Hz), 7.22-7.17(m, 3H), 6.65-6.58(m, 3H), 5.04(s, 4H), 1.34(s, 18H); ^{13}C NMR of receptor **2** ($CDCl_3$; 125 MHz): δ 177.1, 159.6, 155.2, 151.2, 139.2, 130.1, 117.2, 112.9, 107.6, 102.3, 70.3, 39.8, 27.5; Mass $[M+H]^+$ (FIA) calcd. for $C_{28}H_{34}N_4O_4$ is 490, found 490.4.

Preparation of receptor 3

N-(6-Bromomethyl-pyridin-2-yl)-2, 2-dimethyl-propanamide, **A** (855 mg, 3.16 mmol), 2-nitrophenol (400 mg, 2.87 mmol), K_2CO_3 (590 mg, 4.28 mmol) and TBAB (80 mg, 0.25 mmol) were taken in a round bottomed flask. Dry acetone (15 ml) was added to it and stirred for 12 h. at r.t. Acetone was distilled out and the crude was extracted with $CHCl_3$ (20 mL x 4), which was then dried over anhydrous Na_2SO_4 and concentrated under vacuum. This crude was purified by column chromatography using silica gel (100-200 mesh) and EtOAc (10%) in pet. ether as eluent to afford white solid (400 mg, 42.3%).

^{1}H NMR of receptor **3** ($CDCl_3$; 500 MHz): δ 8.18(d, 1H, *J*= 8.5 Hz), 7.96(bs, 1H), 7.89(d, 1H, *J*= 8.1 Hz), 7.75(t, 1H, *J*= 7.9 Hz), 7.51(t, 1H, *J*= 7.9 Hz), 7.34(d, 1H, *J*= 7.6 Hz), 7.71-7.05(m, 2H), 5.21(s, 2H), 1.35(s, 18H); ^{13}C NMR of receptor **3** ($CDCl_3$; 125

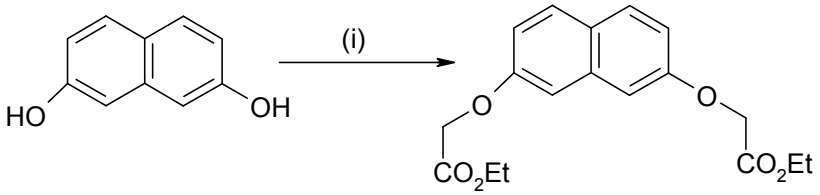
MHz): δ 177.0, 153.9, 151.6, 151.0, 140.1, 139.4, 134.2, 125.8, 120.9, 116.9, 114.9, 112.9, 71.1, 39.8, 27.5; Mass $[M+H]^+$ (FIA) calcd. for $C_{17}H_{19}N_3O_4$ is 330, found 330.2.



Compond B

R*eagents and condition*: (ii) 4(N) KOH in 1:1 EtOH: H_2O, 10 h.

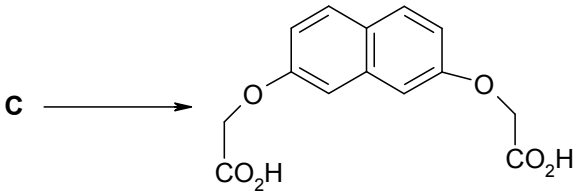
Compound B. Compound A (300 mg, 0.56 mmol) was hydrolysed using 4(N) KOH in 1:1 EtOH in H_2O under refluxing condition for 10 h. After completion of the reaction crude was purified over column chromatography using 70% ethyl acetate in petroleum ether as eluent to obtain off white colored compound B (130 mg, 63 %).



C

Reagents and condition: (i) Ethylchloro acetate, K_2CO_3, dry acetone, r.t., 10 h.

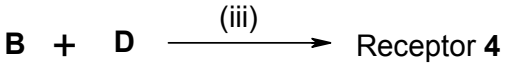
Compound C. 2,7-Dihydroxynaphthalene (3 g, 18.75 mmol), ethylchloro acetate (4.59 g, 37.5 mmol), K_2CO_3 (5.18 g, 37.5 mmol), n-tetrabutylammonium bromide (161 mg, 02 mmol) and dry acetone (20 ml) was stirred at r.t. for 10 h in 10 ml r.b. Compound C separated after purification with $CHCl_3$ (100-200 mesh silica gel) as white solid (2.2 g, 35 %).



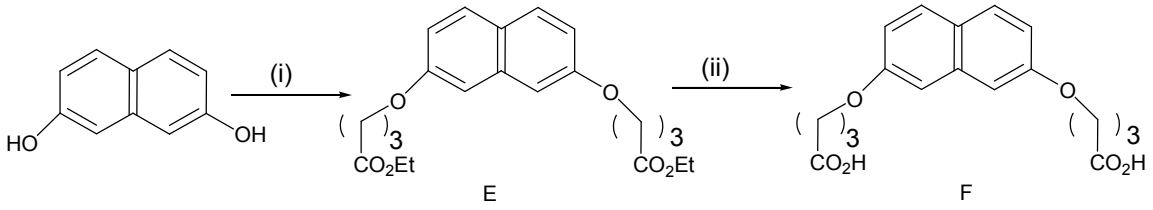
D

Reagents and condition: 4 (N) KOH in 1:1 EtOH : H_2O, 12 h.

Compound D. Compound C (2 g, 6.02 mmol) on base hydrolysis using 4 (N) KOH at reflux produces compound D as off-white solid (1 g, 60%) after acidification with glacial acetic acid.



Procedure for the preparation of receptor 4: Compound B (66mg, 0.18 mmol) and compound D (50 mg, 0.18 mmol) were reacted under high dilution technique in 1:1 dry CH_2Cl_2 and dry THF to afford receptor **4** as white solid (8 mg, 7.6 %). ^{1}H NMR of receptor **4** (1 % DMSO in $CDCl_3$, 500 MHz): δ (ppm): 8.90(s, 2H), 8.12(bs, 2H), 7.84(d, 2H, *J*= 8.9 Hz), 7.68(t, 2H, *J*= 7.9 Hz), 7.23(d, 2H, *J*= 8.9 Hz), 7.15(s, 2H), 7.11(d, 2H, *J*= 7.4 Hz), 6.65(d, 2H, *J*= 8.6 Hz), 4.81(s, 4H); ^{13}C NMR of receptor **4** ($CDCl_3$; 125 MHz): δ 167.7, 157.3, 153.9, 150.6, 150.2, 139.3, 132.4, 129.0, 128.8, 118.2, 116.2, 113.1, 107.1, 106.2, 68.1; Mass (HRMS) $[M+H]^+$ calcd. for $C_{32}H_{26}N_5O_8$ is 608.1776, found 608.1765.

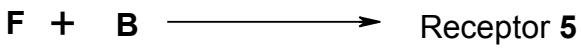


Reagents and condition: Ethyl-4-bromobutyrate, K_2CO_3, dry acetone, TBAB, 10 h.

Compound E. 2,7-Dihydroxynaphthalene (2g, 12.5 mmol),ethyl-4-bromobotyrate (4.8 g, 25 mmol), K_2CO_3 (3.45 g, 25 mmol) and TBAB (50 mg) were taken in 100 ml r.b. in 30 ml dry acetone and was allowed to stir at r.t. for 10 h. The crude obtained in this reaction

was purified using $CHCl_3$ as eluent (100-200 mesh silica gel) to get white solid (2.1 g, 43 %).

Compound F. Compound E (1g, 2.58 mmol) was subjected to bade hydrolysis using 4 (N) KOH in 1:1 EtOH in H_2Owhich yielded after acidification with glacial acetic acid white solid Compound F (400 mg, 37 %).



Reagents and condition: Dry CH_2Cl_2, dry THF, Et_3N, high dilution, r.t.

Procedure for the preparation of receptor 5: Compound F (50 mg, 0.14 mmol) and Compound B (51 mg, 0.14 mmol) were subjected to react in high dilution technique to afford white solid receptor **5** (15 mg, 16.3 %) which was purified by preparative chromatography using 2% MeOH in $CHCl_3$

^{1}H NMR of receptor **5** (2% DMSO in $CDCl_3$, 500 MHz): δ 8.77(s, 2H), 8.09(s, 2H), 7.64(t, 2H, *J*= 7.9 Hz), 7.58(d, 2H, *J*= 8.8 Hz), 7.07(d, 2H, 7.5 Hz), 6.96(d, 2H, *J*= 8.8 Hz), 6.93(s, 2H), 6.62(t, 1H, *J*= 8.4 Hz), 6.46(d, 2H, *J*= 8.6 Hz), 5.07(s, 4H), 4.07-4.05(m, 12H); ^{13}C NMR of receptor **5** (1% DMSO in $CDCl_3$; 125 MHz): 167.7, 157.3, 143.9, 150.6, 150.2, 139.3, 132.4, 129.0, 128.8, 118.2, 116.2, 113.1, 107.1, 106.2, 68.2, 38.7, 29.7, 23.7; Mass (HRMS) $[M+H]^+$ calcd.for $C_{36}H_{34}N_5O_8$ 664.2402, found 664.2397.

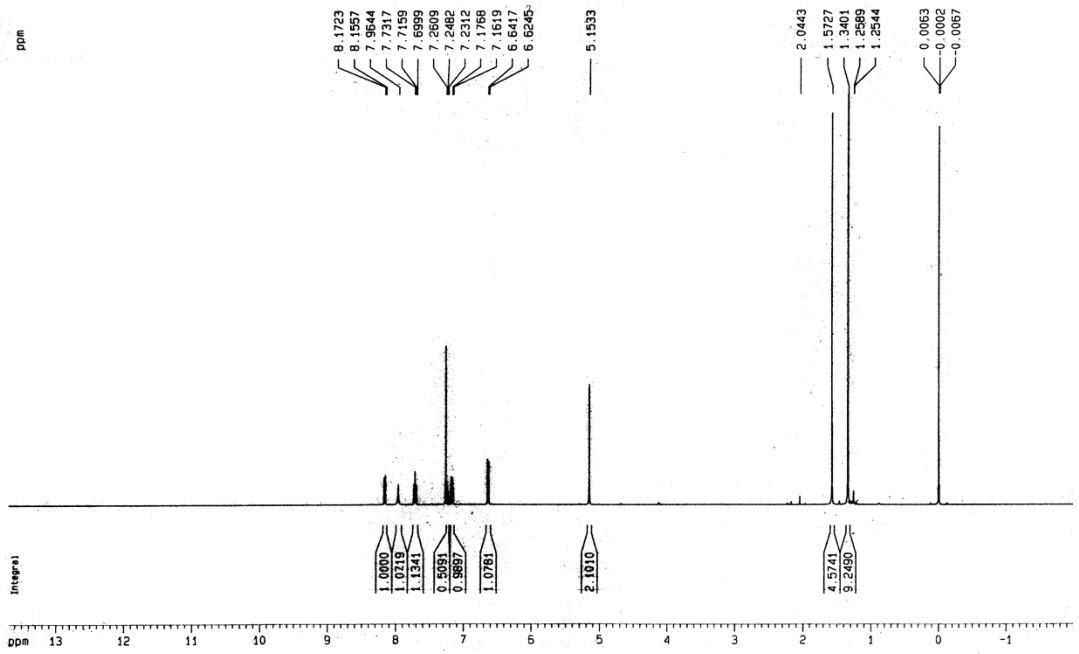
5. Table of crystallographic data of receptor 1

Table 1: Crystallographic data and structure refinement parameters of receptor **1**.

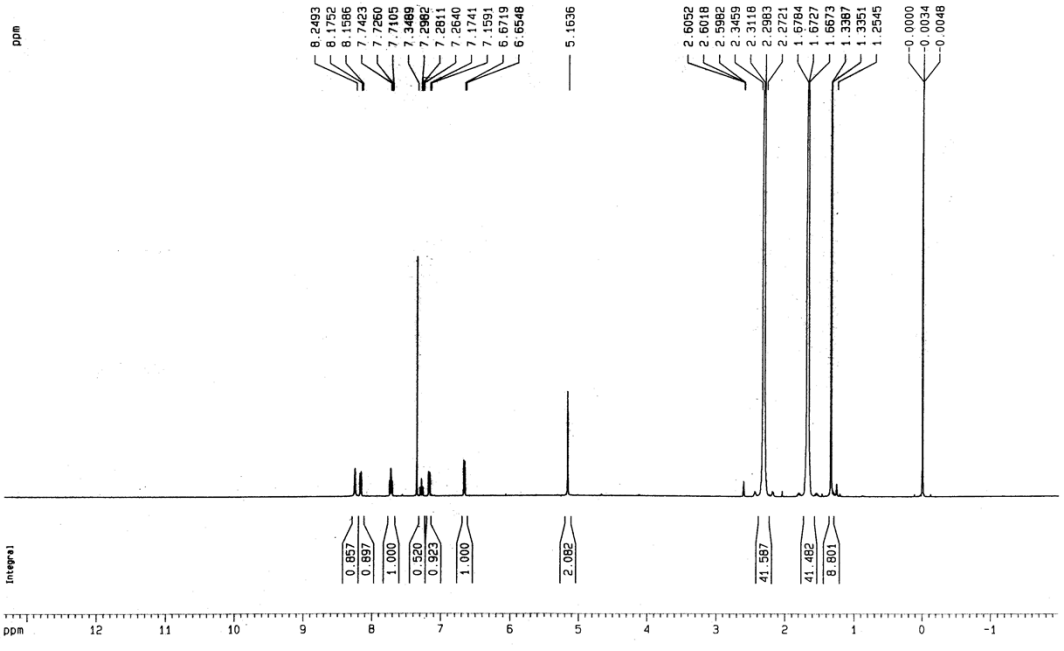
CCDC	**764388**
Empirical formula	C_{28} H_{33} N_5 O_6
Formula Weight	535.59
Crystal System	Monoclinic
Space group	C2/c (No. 15)
Temperature (K)	100
a [Å]	21.4456(4) Aº
b [Å]	11.4678(2) Aº
c [Å]	11.4003(3) Aº
α [º]	90
β [º]	107.9100(10)
γ [º]	90
Z	4
V [$Å^3$]	2667.85(10)
D_{calc} [g/cm^3]	1.334
F(000)	1136
μ / mm^{-1}	0.095
2θ [º]	2.0-35.2
Crystal Size [mm]	0.20 x 0.20 x 0.77
Radiation [Aº] Mo-Kα	0.71073
Index ranges	-34≤ h ≤ 34
	-18≤ k ≤17
	-18≤ l ≤ 17
Reflections collected	23672
Unique reflections	5910
Observed reflections	4176
R_1 [I > 2σ(I)]	0.046
R, wR2, S	0.0532, 0.1566, 1.06

6. Spectra of receptors

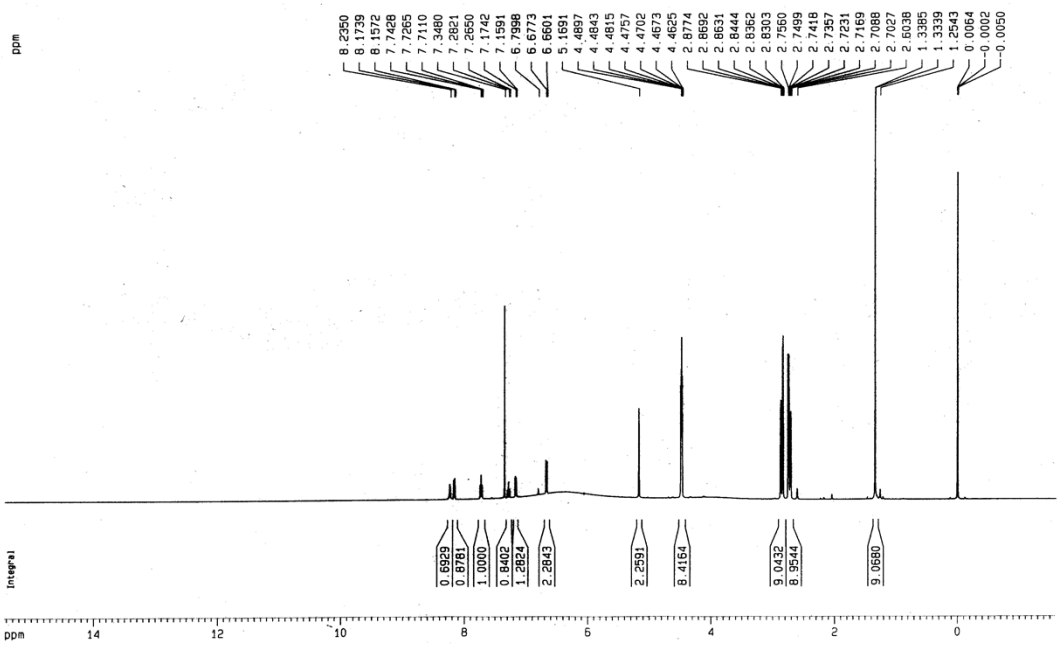
^{1}H nmr of receptor 1 in $CDCl_3$



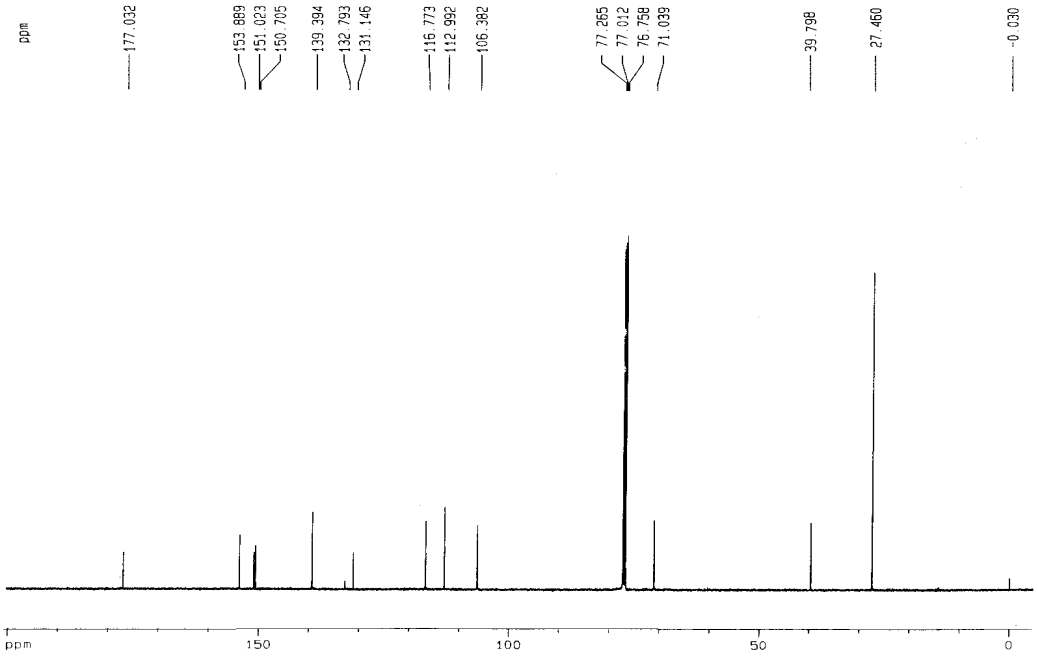
(1:1) nmr of receptor 1 with adipic acid



(1:1) nmr of receptor 1 with DL-malic acid

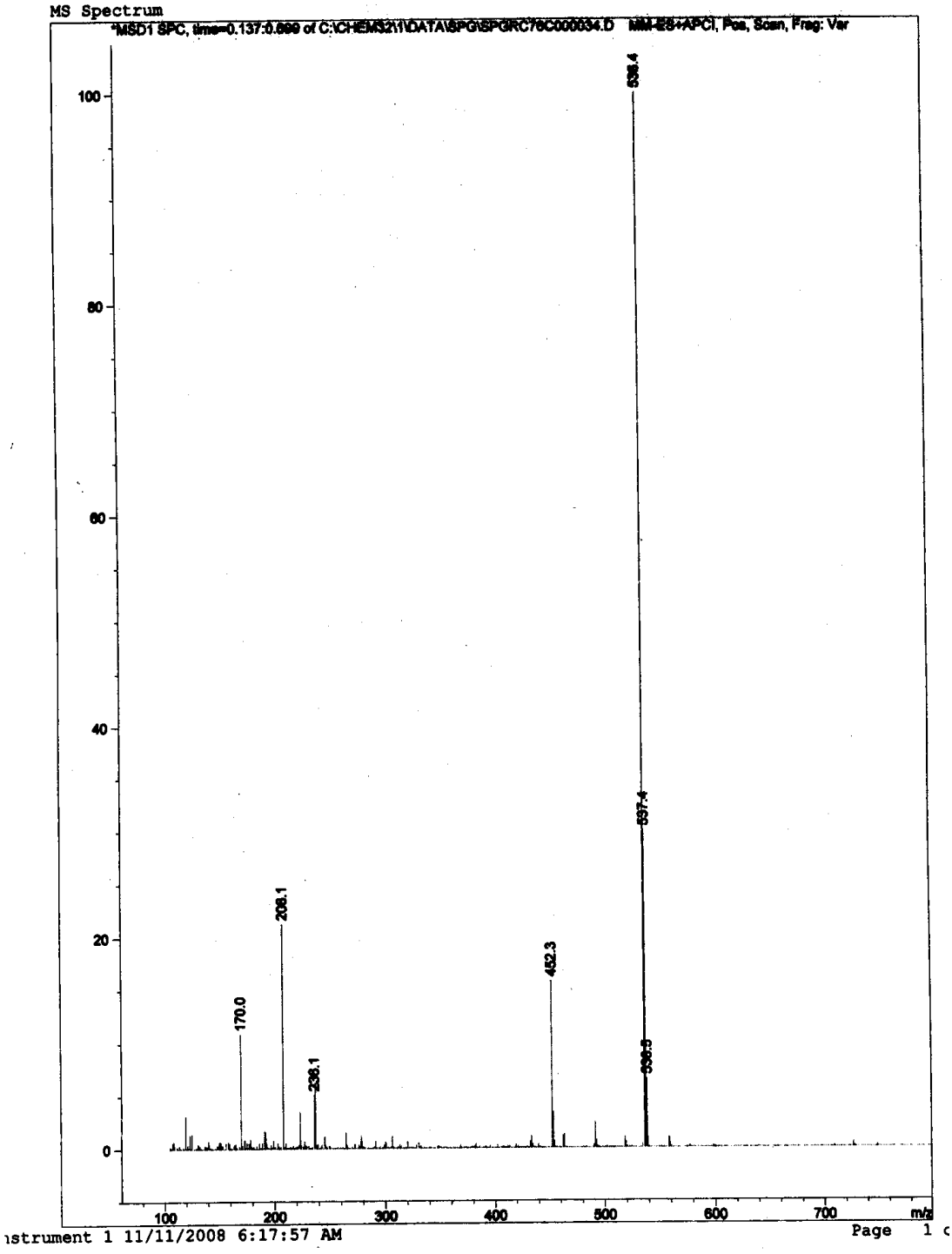


^{13}C nmr of receptor 1 in $CDCl_3$

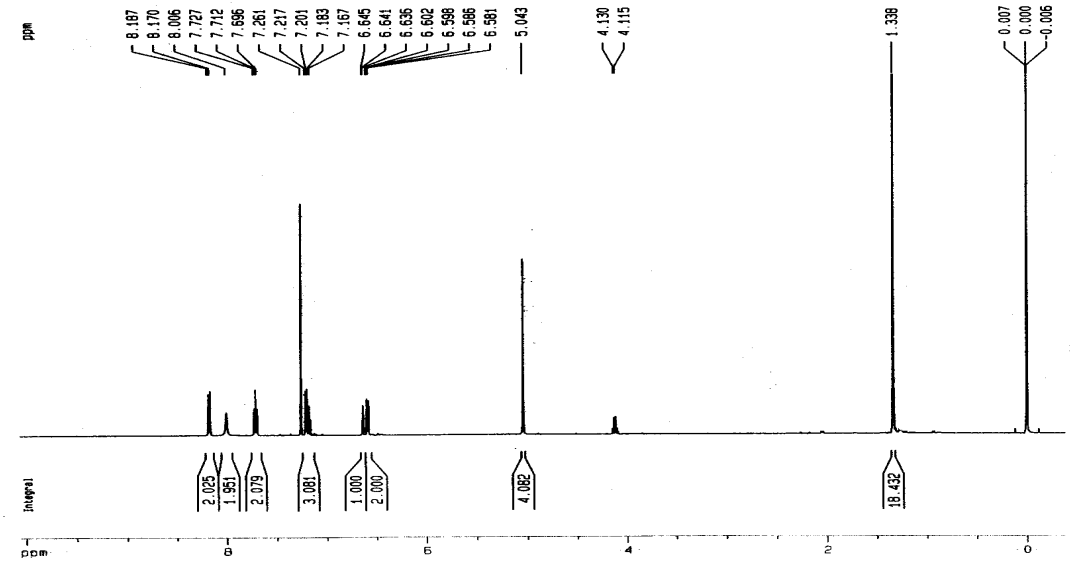


Mass (FIA) of receptor 1

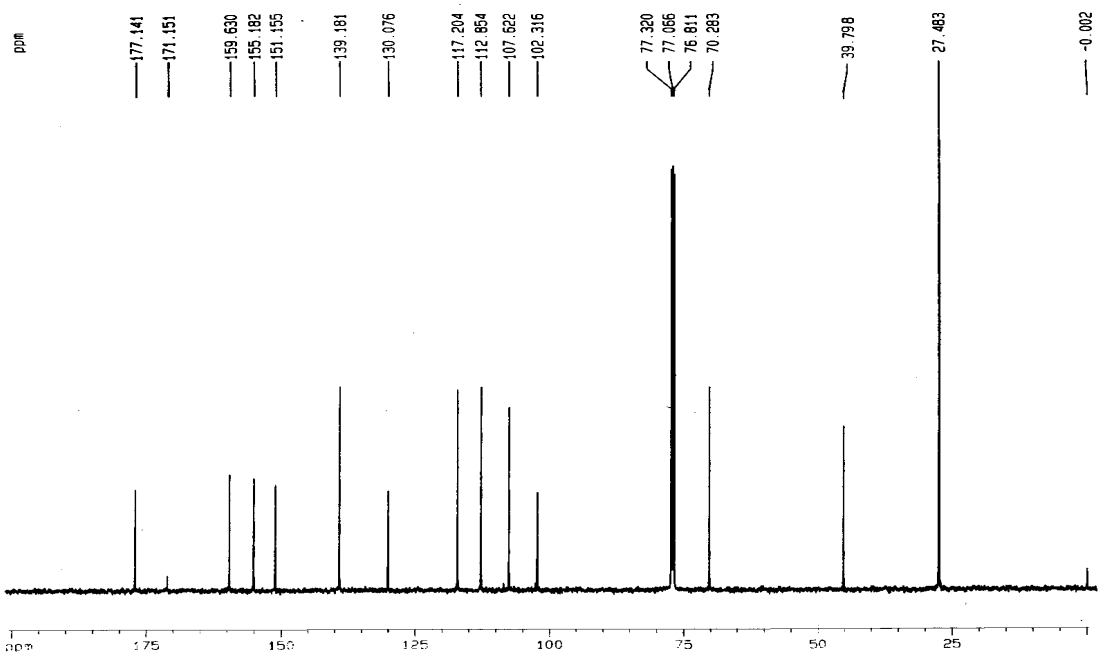
$[M^{+}+H]^{+}$ calculated for $C_{28}H_{34}N_5O_6$ is 536 and found 536.4.



^{1}H nmr of receptor 2 in $CDCl_3$

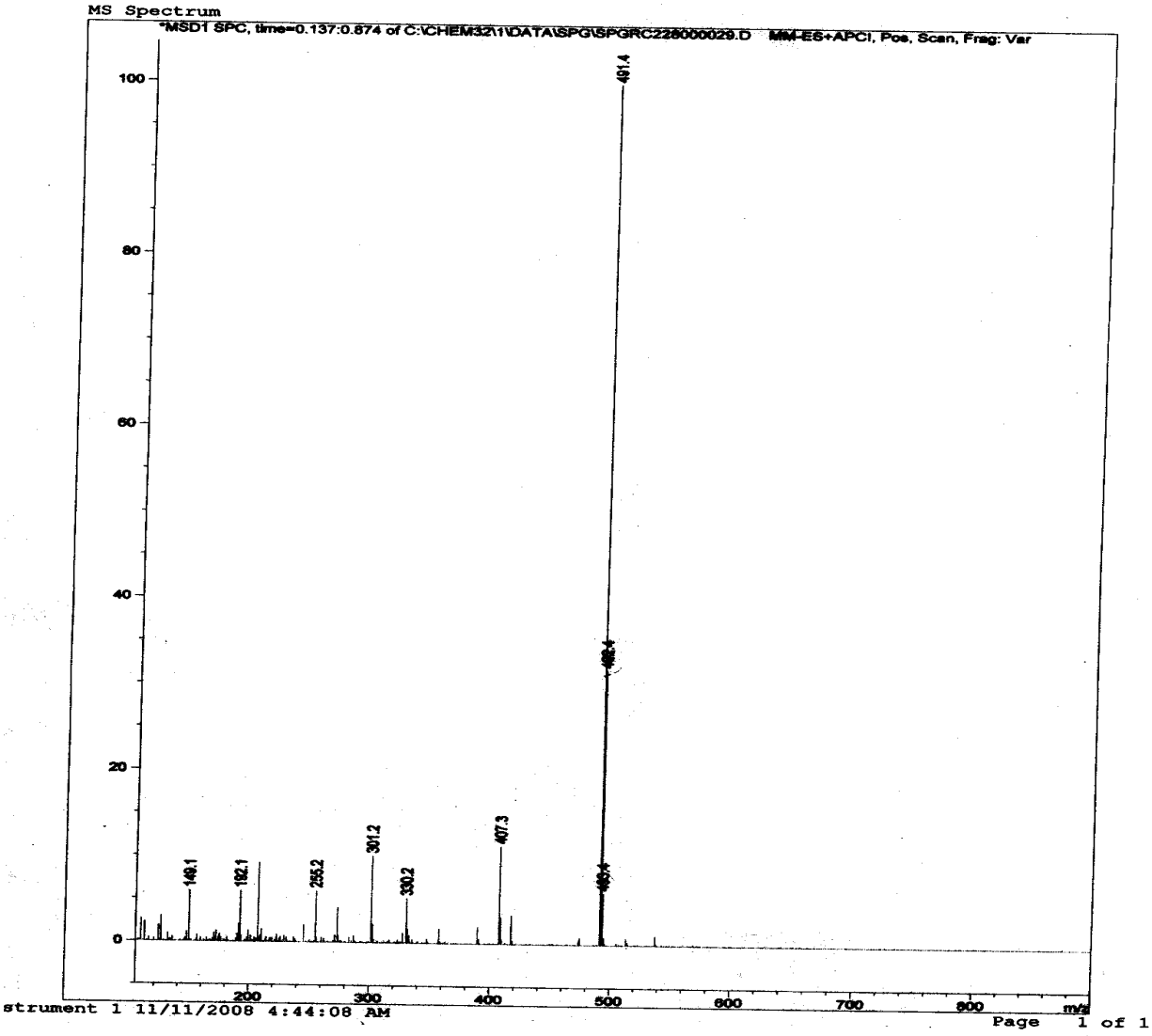


^{13}C nmr of receptor 2 in $CDCl_3$

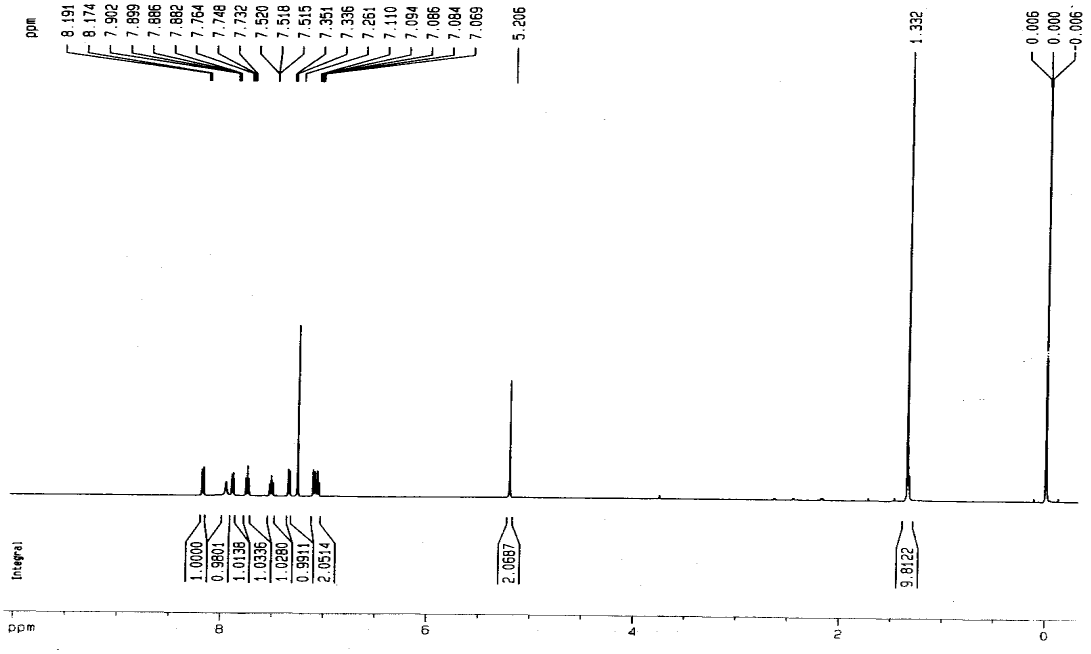


Mass (FIA) of receptor 2

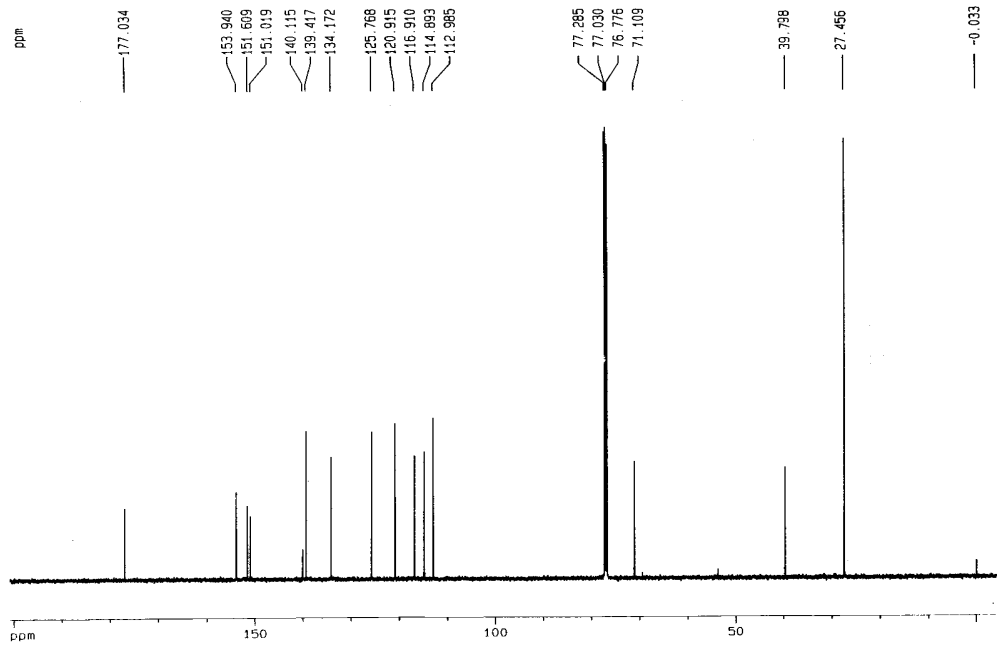
$[M^{+}+H]^{+}$ calculated for $C_{28}H_{35}N_4O_4$ is 491 and found 491.4.



^{1}H nmr of receptor 3 in $CDCl_3$

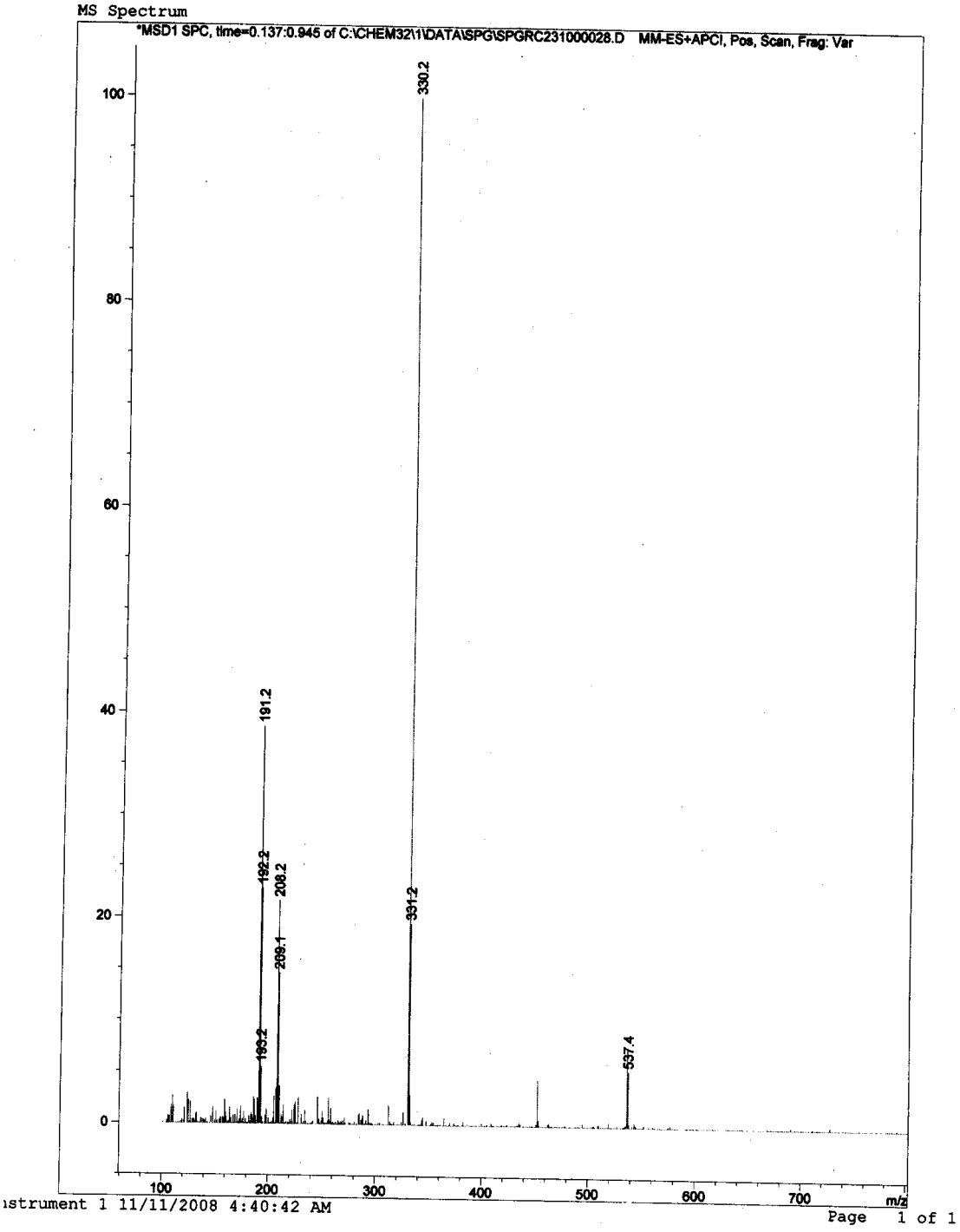


^{13}C nmr of receptor 3 in $CDCl_3$

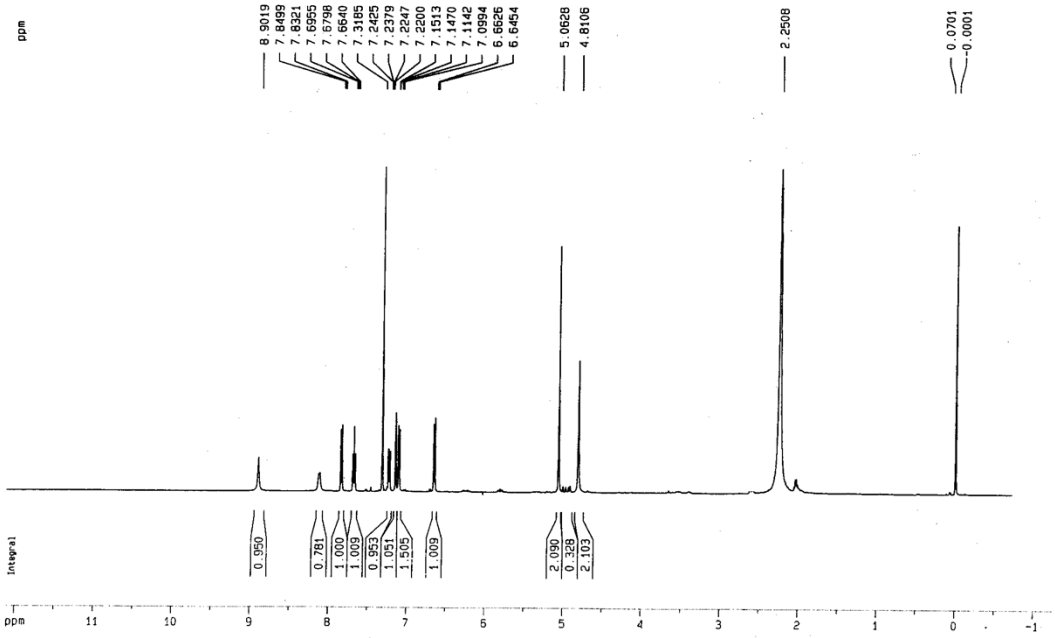


Mass (FIA) of receptor 3

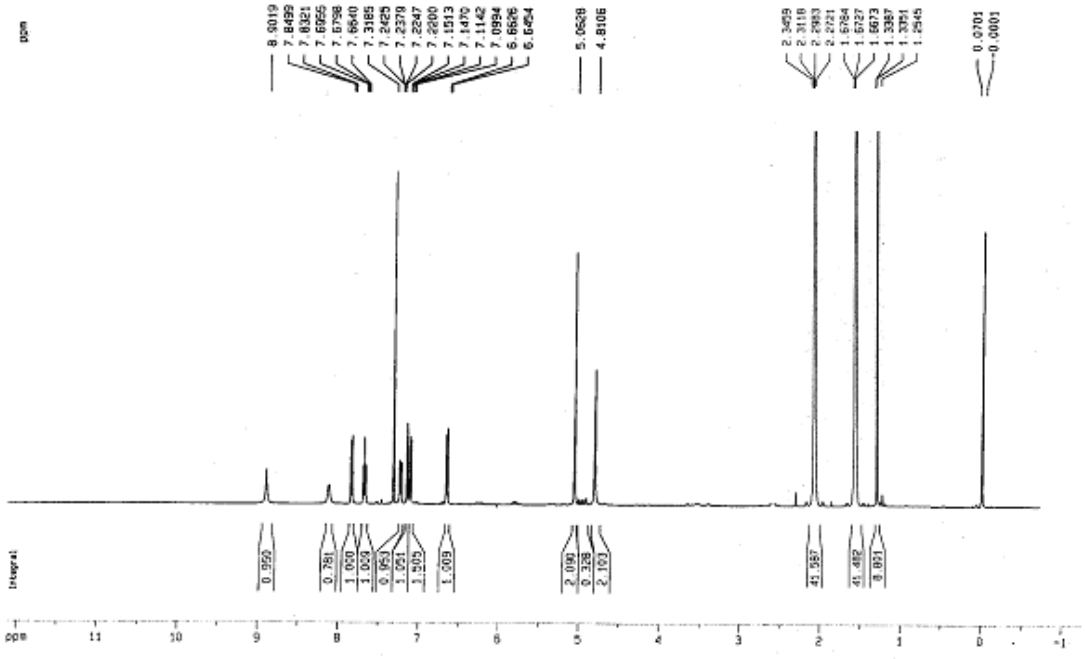
$[M^{+}+H]^{+}$ calculated for $C_{17}H_{19}N_3O_4$ is 330 and found 330.2.



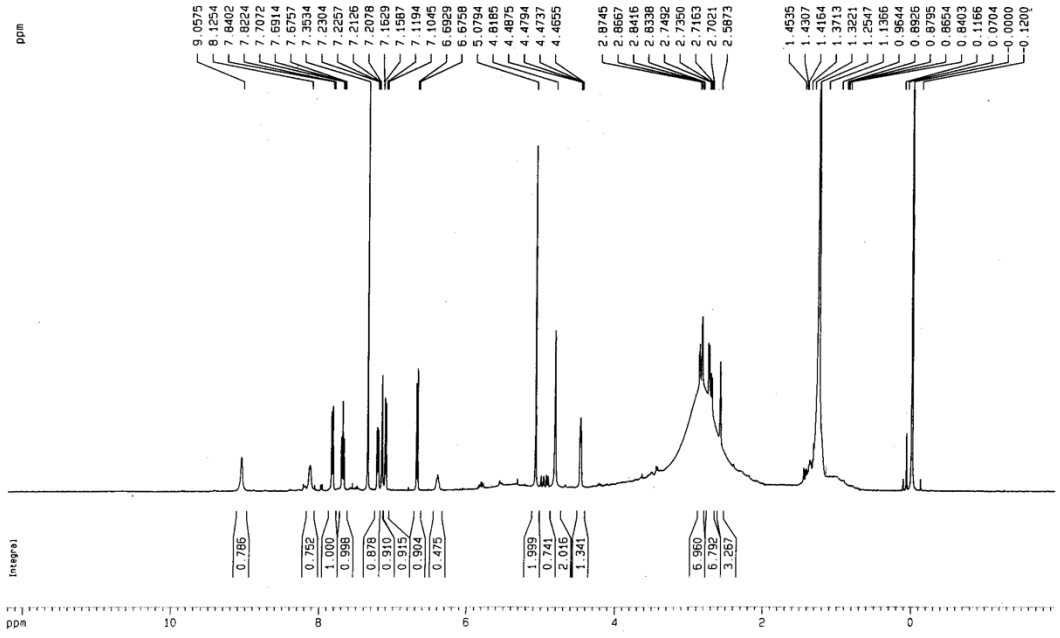
^{1}H nmr of receptor 4 in 1% DMSO+$CDCl_3$



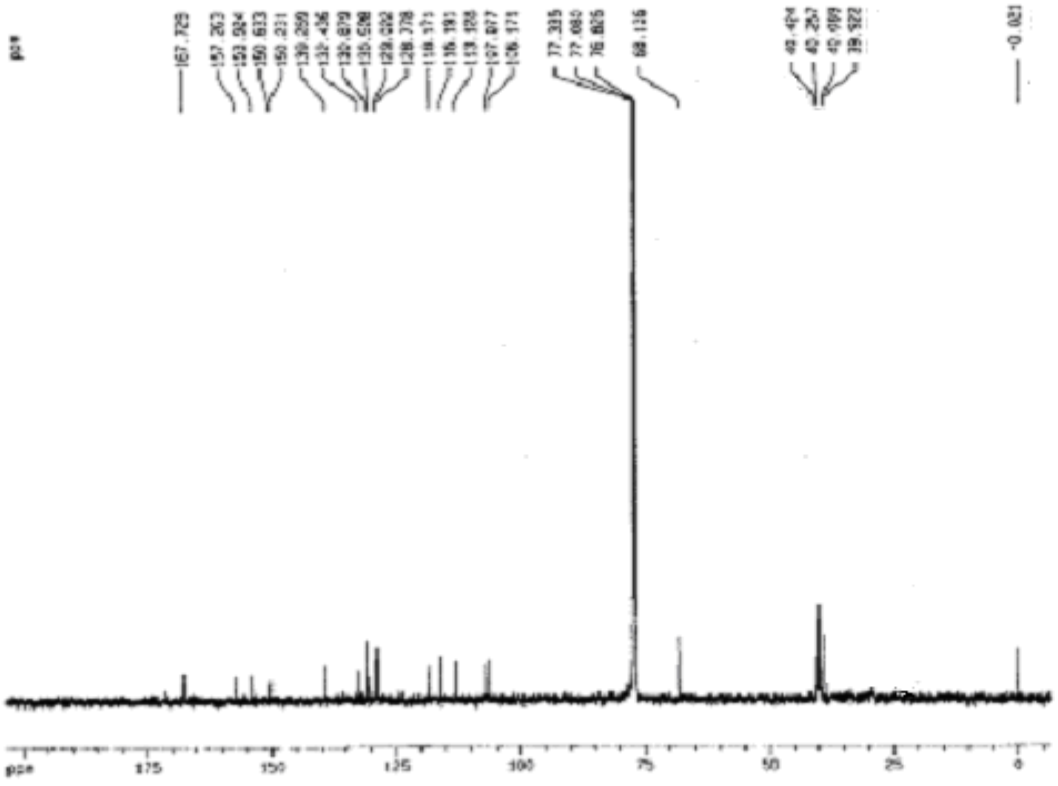
(1:1) nmr of receptor 4 with adipic acid



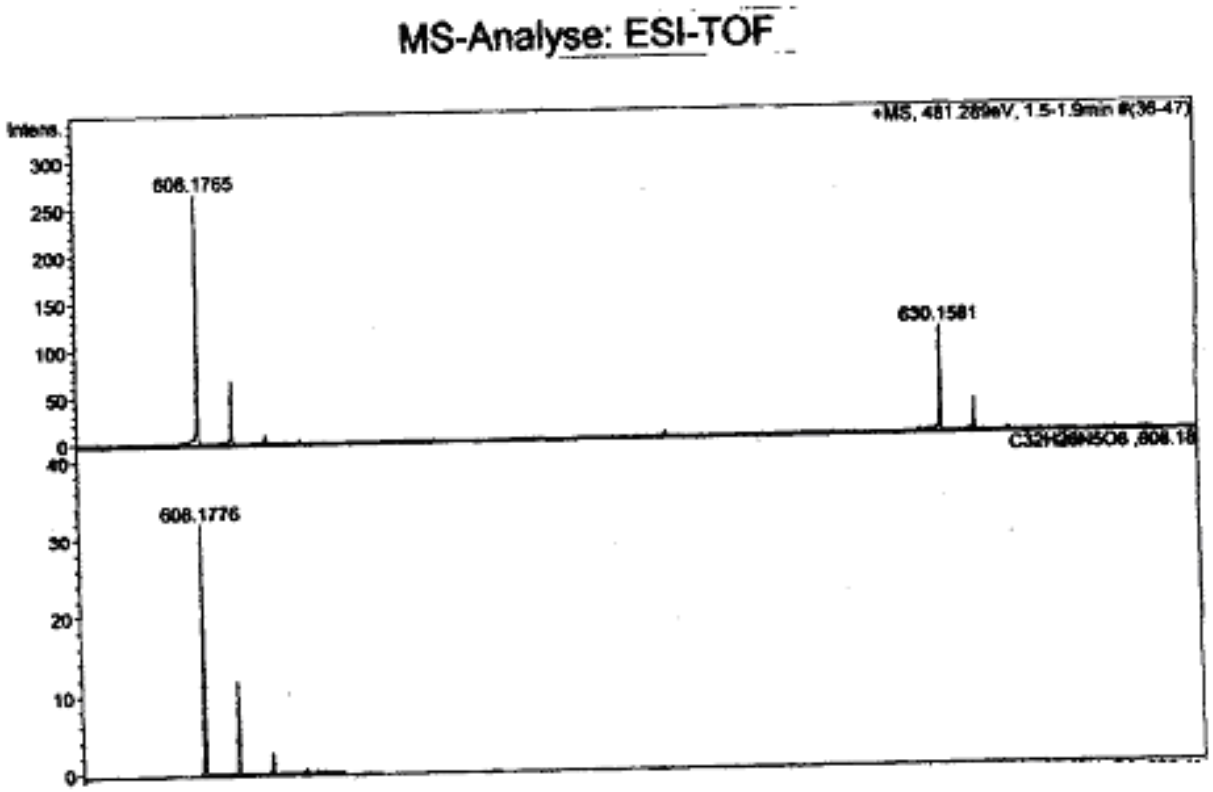
(1:1) nmr of receptor 4 with DL-malic acid



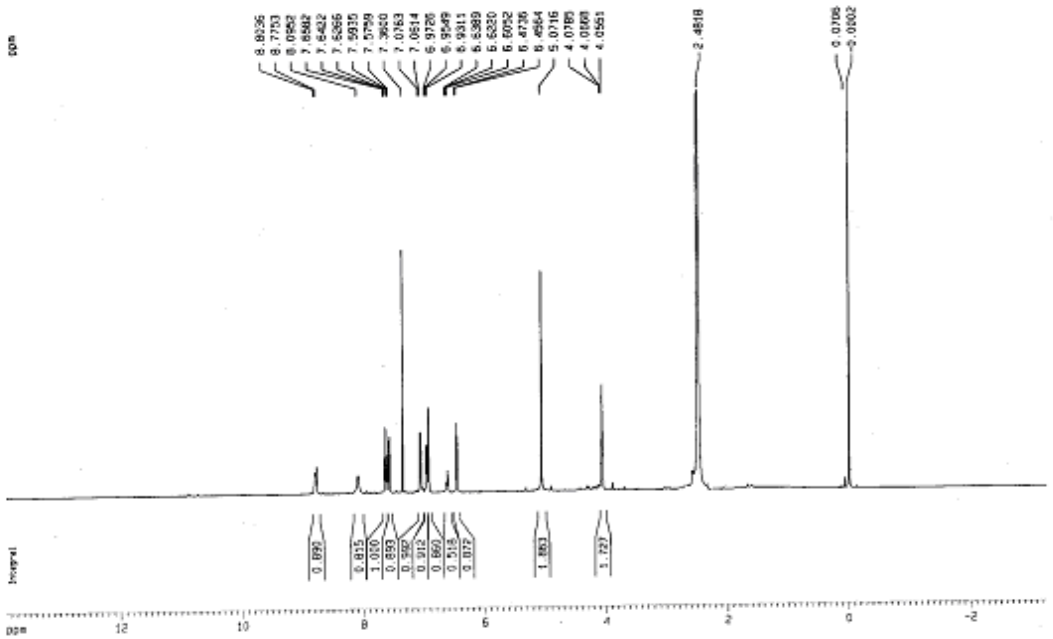
^{13}C nmr of receptor 4 in 1% DMSO+$CDCl_3$



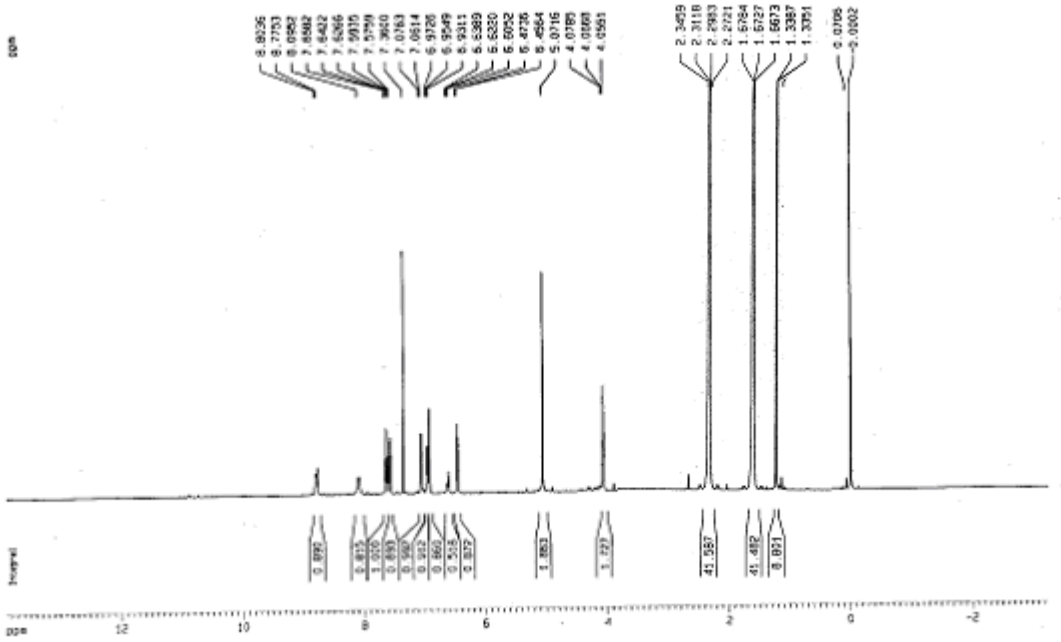
HRMS mass spectra of receptor 4



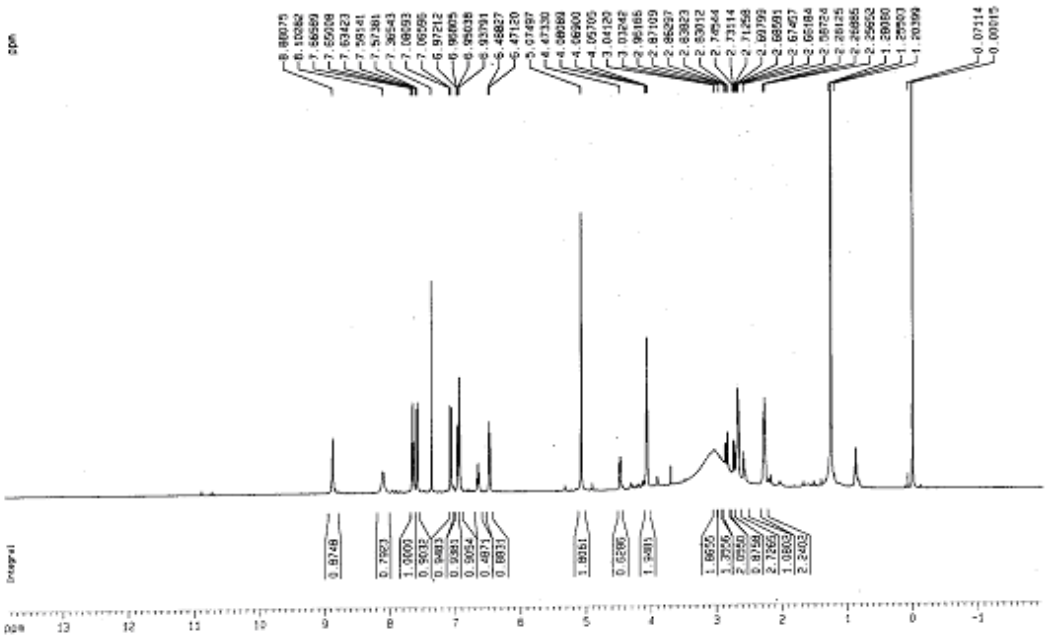
^{1}H nmr of receptor 5 in 1% DMSO+$CDCl_3$



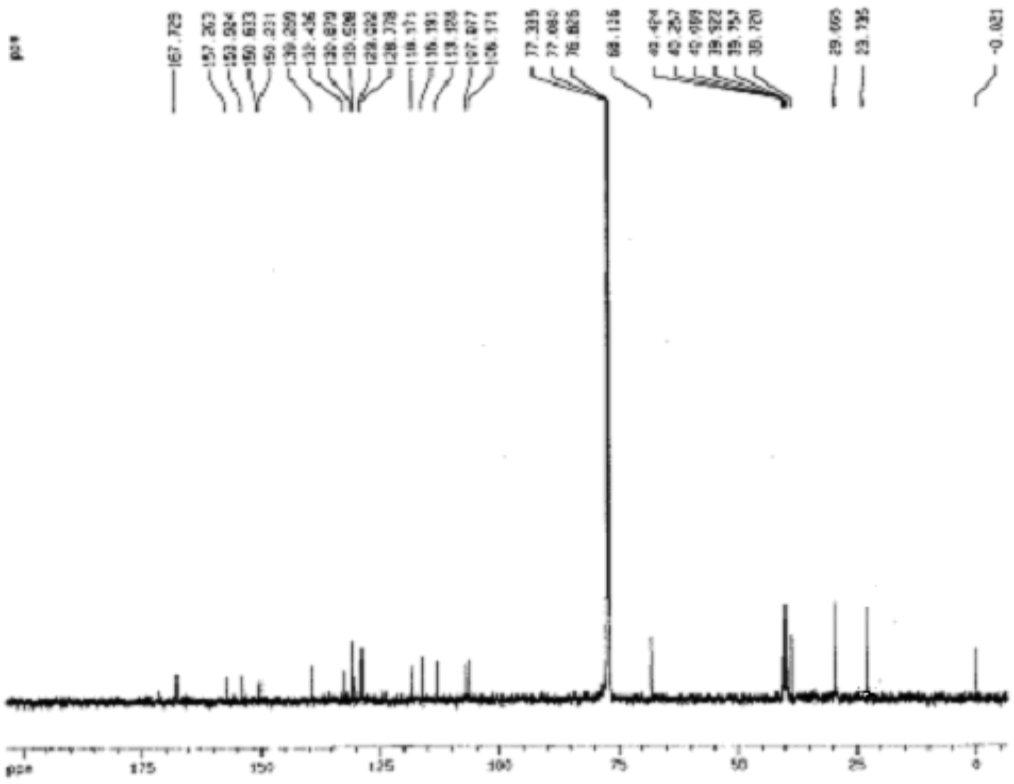
^{1}H nmr of (1:1) complex of receptor 5 with adipic acid in 1% DMSO+$CDCl_3$



^{1}H nmr of (1:1) complex of receptor 5 with DL-malic acid in 1% DMSO+$CDCl_3$



^{13}C nmr of receptor 5 in 1% DMSO in $CDCl_3$



HRMS mass spectra of receptor 5