SYNTHESIS OF *N*-(MORPHOLINOMETHYL) BENZAMIDES AS MOCLOBEMIDE ANALOGS

Hernán Pessoa-Mahana,* Claudio I. Astudillo O., and R. Araya-Maturana

Facultad de Ciencias Químicas y Farmacéuticas, and Departamento de Química Orgánica y Fisicoquímica, Universidad de Chile, Casilla 233, Santiago 1, Chile

ABSTRACT

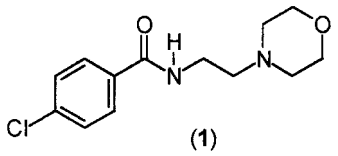
Syntheses of new morpholinomethylbenzamides **6** bearing both electron-withdrawing and electron-releasing groups at the aromatic ring are described. The strategy involved synthesis of hippuric acid ethyl esters **3**, their hydrolysis to hippuric acids **4**, subsequent oxidative decarboxylation to acetate **5** and morpholine addition to provide **6.**

Moclobemide, *p*-chloro-*N*-2-(morpholinoethyl) benzamide (**1**) is a short acting, selective and reversible inhibitor of MAO-A,[1,2] well tolerated, widely available for clinical use, and an effective antidepressant. Monoamine oxidase (MAO) is a flavoprotein of the mitochondrial outer membranes of neuronal cells, involved in the biodegradation of aromatic

*Corresponding author. Fax: 56-2-6782868; E-mail: hpessoa@ll.ciq.uchile.cl

monoamines, including classical neurotransmitters such as serotonin, adrenaline, and dopamine, playing a central role in several psychiatric and neurological disorders.

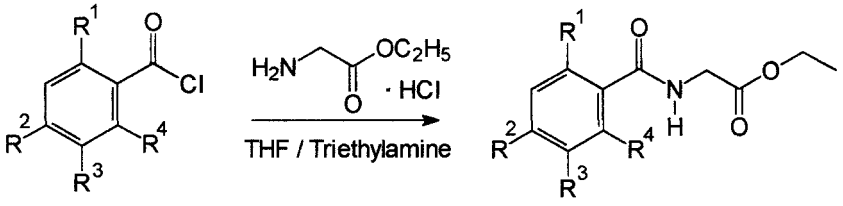
A variety of moclobemide derivatives has been prepared, and studies on structure-activity relationships reveal that both the morpholine and phenyl rings are necessary for antidepressant activity.[3,4] However effects of changes in the aliphatic chain length on biological activity have not been reported. We report herein new and facile syntheses of *N*-(morpholinomethyl) benzamides as moclobemide analogs.



(1)

Several studies regarding the synthesis and reactivity of *N*-(morpholinomethyl) benzamides have been reported.[5,6] Katritzky[7] et al. examined syntheses of monoacylaminals as constituent units of retro-peptide intermediates for obtaining heterocycles.

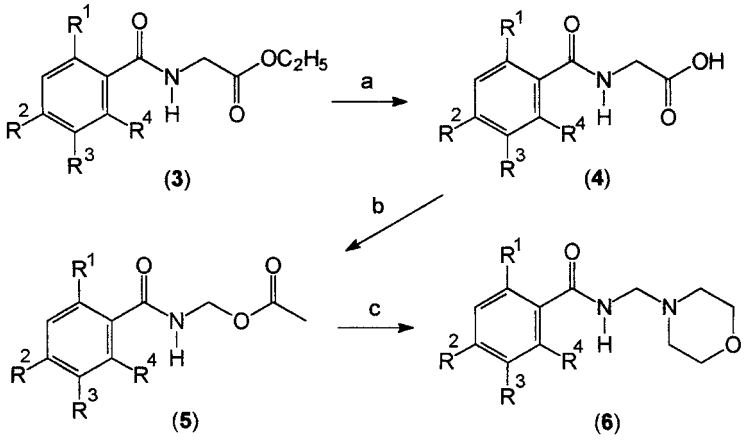
The synthesis of our analogs started with the classical reaction of substituted benzoyl chlorides **2(a–d)** with glycine hydrochloride[8,9] to afford the ethyl esters of hippuric acids **3(a–d)** (Scheme 1).



2 (a-d) **3** (a-d)

a	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=H
b	R^1=OCH_3; R^2=NO_2; R^3=OCH_3 ; R^4=H
c	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=NO_2
d	R^1=H; R^2=Cl; R^3=H; R^4=H

Scheme 1.



Reagents : a) KOH – C_2H_5OH ; H_3O^+ ; b) $Pb(OAc)_4$ – Cu $(OAc)_2$ / CH_3CN; d) Morpholine-Triethylamine / CH_3CN.

Scheme 2.

The hippuric esters **3(a–d)** were subsequently hydrolyzed with methanolic-potassium hydroxide at room temperature, to afford the corresponding hippuric acids **4(a–d)** (Scheme 2). Special care must be taken with the ester **3(d)**, to avoid competitive hydrolysis of the amide which was detected as a side reaction (See Experimental).

The hippuric acids **4(a–d)** were reacted with a mixture of anhydrous lead tetraacetate and cupric acetate, in acetonitrile giving the acetates **5(a–d)**[10] in good yield, (Table 1). This oxidative decarboxylation gave better yields using acetonitrile rather than benzene; when compounds **4(a–d)** were decarboxylated in benzene,[11] their solubilities were low with decreased yields.

In summary we have developed efficient syntheses which afford *N*-(morpholinomethyl) benzamides. Further studies on applications of these compounds will be reported.

EXPERIMENTAL

Melting points were determined on a hot-stage apparatus and are uncorrected. The IR spectra were recorded, on a FT-IR Bruker IFS 55 spectrophotometer for KBr disc and wave numbers are reported in cm^{-1}. The ^1H and ^{13}C NMR spectra were performed on Bruker DRX-300 and AM-200 spectrometers in $CDCl_3$ or DMSO-d_6. Chemical shifts were

Table 1.

Entry	Substrate	Product	Yield (%)
2-a	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=H	**3-a**	85
2-b	R^1=OCH_3; R^2=NO_2; R^3=OCH_3; R^4=H	**3-b**	84
2-c	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=NO_2	**3-c**	79
2-d	R^1=H; R^2=Cl; R^3=H; R^4=H	**3-d**	82
3-a	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=H	**4-a**	85
3-b	R^1=OCH_3; R^2=NO_2; R^3=OCH_3; R^4=H	**4-b**	98
3-c	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=NO_2	**4-c**	95
3-d	R^1=H; R^2=Cl; R^3=H; R^4=H	**4-d**	87
4-a	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=H	**5-a**	91
4-b	R^1=OCH_3; R^2=NO_2; R^3=OCH_3; R^4=H	**5-b**	76
4-c	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=NO_2	**5-c**	78
4-d	R^1=H; R^2=Cl; R^3=H; R^4=H	**5-d**	58
5-a	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=H	**6-a**	71
5-b	R^1=OCH_3; R^2=NO_2; R^3=OCH_3; R^4=H	**6-b**	63
5-c	R^1=OCH_3; R^2=H; R^3=OCH_3; R^4=NO_2	**6-c**	46
5-d	R^1=H; R^2=Cl; R^3=H; R^4=H	**6-d**	52

recorded in ppm (δ) relative to TMS as internal standard. *J* values are given in Hz. EIMS were recorded on VB-12-250 spectrometer.

Microanalyses were carried out on a Fisons EA 1108 analizer. Silica gel Merck 60 (70–230 mesh) and DC-alufolien 60 F_{254} were normally used for column and TLC chromatography respectively.

General Procedure for the Synthesis of Hippuric Ester Derivatives (3)

To a solution of glycine ethyl ester hydrochloride (170 mg, 1.22 mmol), triethylamine (333 mg, 0.45 ml 3.33 mmol) in dry THF (50 ml) at 0°C, benzoyl chloride derivative **2** (1.11 mmol) in THF (10 ml), was slowly added under nitrogen atmosphere . The solution was stirred for 1 h at 0°C and then at room temperature. After 3 h water (100 ml) was added and the mixture was extracted with chloroform (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica gel column (chloroform : ethyl acetate = 1 : 1) or crystallized to give **3**.

2,5-Dimethoxy-hippuric acid ethyl ester (3-a): M.p. 82–83°C; purified by silica gel chromatography, (chloroform : ethyl acetate = 1 : 1) Anal. calcd

for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.37; N, 5.24. Found: C, 57.58; H, 6.55; N, 5.24. IR: 3349, 1755, 1643. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, $J = 7.1$, $OCH_2\underline{CH_3}$), 3.83 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.23–4.31 (m, 4H, $O\underline{CH_2}CH_3$ and NH-$\underline{CH_2}$-CO), 6.95 (d, 1H, $J_o = 8.70$, Ar-3-H), 7.04 (dd, 1H, $J_o = 8.70$, $J_m = 3.40$, Ar 4-H), 7.77 (d, 1H, $J_m = 3.40$, Ar 6-H). ^{13}C NMR (75 MHz $CDCl_3$) δ: 14.6, 42.5, 56.2, 57.0, 61.8, 113.5, 115.9, 120.1, 121.7, 152.5, 154.3, 165.5, 170.6.

2,5-Dimethoxy-4-nitro-hippuric acid ethyl ester (3-b): M.p. 151–152 °C (Ethanol); Anal calcd for $C_{13}H_{16}N_2O_7$: C, 50.0; H, 5.16; N, 8.97. Found: C, 49.79; H, 5.25; N, 9.02. IR: 3339, 1753, 1649. ^{1}H NMR (200 MHz $CDCl_3$) δ: 1.32 (t, 3H, $J = 7.72$, $OCH_2\underline{CH_3}$), 3.97 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.21–4.28 (m, 4H, $O\underline{CH_2}CH_3$ and NH-$\underline{CH_2}$), 7.50 (s, 1H, Ar 6-H), 8.00 (s, 1H, Ar 3-H), 8.56 (br.s, 1H, NH). ^{13}C NMR (75 MHz $CDCl_3$) δ: 14.2, 42.2, 57.1, 57.1, 61.7, 109.2, 117.8, 125.7, 141.0, 147.1, 150.6, 163.1, 169.7; EIMS m/z (%): 312 (M^+, 8), 267 (2), 210 (100), 163 (24).

2,5-Dimethoxy-6-nitro-hippuric acid ethyl ester (3-c): M.p. 86–88°C; (Ethanol). Anal calcd for $C_{13}H_{16}N_2O_7$: C, 50.0; H, 5.16; N, 8.97. Found: C, 49.51; H, 5.39; N, 8.88. IR: 3321, 1740, 1667. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, 3H, $J = 7.40$, $OCH_2\underline{CH_3}$), 3.77 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.11 (d, 2H, $J = 3.2$, NH-$\underline{CH_2}$), 4.17 (q, 2H, $J = 7.40$, $O\underline{CH_2}CH_3$), 7.00 (d, 1H, $J = 6.10$, Ar 3-H), 7.10 (d,1H, $J = 6.10$, Ar 4-H), 7.70 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5, 42.3, 55.7, 57.6, 62.0, 114.7, 116.7, 117.1, 142.6, 145.9, 150.1, 162.0, 170.0.

4-Chloro-hippuric acid ethyl ester (3-d): M.p. 114.5–116°C[8]; (purified by column chromatography, chloroform : ethyl acetate = 2 : 1) Anal. calcd for $C_{11}H_{12}O_3NCl$: C, 54.65; H, 4.96; N, 5.80. Found: C, 54.17; H, 5.06; N, 5.97. IR: 3268, 1747, 1647. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.30 (t, 3H, $J = 7.15$, $OCH_2\underline{CH_3}$), 4.20 (d, 2H, $J = 5.14$, NH-$\underline{CH_2}$), 4.24 (q, 2H, $J = 7.15$, $O\underline{CH_2}CH_3$), 6.86 (s, 1H, NH), 7.39 (d, 2H, $J = 13.3$, Ar 3-H and Ar 5-H), 7.74 (d, 2H, $J = 13.3$, Ar 2-H and Ar 6-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 41.9, 61.8, (2 × 128.6) (2 × 128.8), 132.1, 138.1, 170.1, 173.8.

General Procedure for the Synthesis of Hippuric Acid Derivatives (4)

A solution of the ethyl ester **3** (1.90 mmol.) in KOH 0.5 N : EtOH (1 : 1 v/v), (40 ml) was stirred at room temperature for 3 h (except for the chloro derivative (**3-d**) we use 30 min). The mixture was then diluted with water (50 ml), acidified with HCl 0.1 M and extracted with ethyl acetate, (3 × 50 ml). Organic layers were dried (Na_2SO_4) and the solvent was evaporated under

vacuo. Purification was carried out by chromatographic techniques or crystallization.

2,5-Dimethoxy-hippuric acid (4-a): M.p. 107–108°C (White crystals, column chromatographed, AcOEt). Anal calcd for: $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.86. Found: C, 54.57; H, 5.61; N, 5.96. IR: 3300–2980, 1732, 1615. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.30 (d, 2H, $J = 4.8$, -CH_2-), 6.92 (d, 1H, $J_o = 9.0$ Ar 3-H), 7.02 (d, d, 1H, $J_o = 9.0$, $J_m = 3.0$, Ar 4-H), 7.73 (d, 1H, $J_m = 3.0$, Ar 6-H), 8.75 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.4, 55.9, 56.7, 113.2, 115.6, 120.3, 120.7, 152.3, 154.0, 166.1, 173.3.

2,5-Dimethoxy-4-nitro-hippuric acid (4-b): Yellow crystals (Ethanol) M.p. 197–197.5°C; Anal calcd for $C_{11}H_{12}N_2O_7$: C, 46.48; H, 4.26; N, 9.86. Found: C, 46.67; H, 4.44; N, 9.93. IR: 3379–2850, 3380, 1740, 1613. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.00 (d, 2H, $J = 5.7$, -CH_2-), 7.68 (s, 1H, Ar 6-H or Ar 3-H), 7.70 (s, 1H, Ar 3-H or Ar 6-H), 8.69 (t, 1H, $J = 5.7$, NH), 12.7 (s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 42.1, 57.4, 57.5, 109.6, 116.6, 127.1, 141.2, 145.7, 150.9, 163.6, 171.4.

2,5-Dimethoxy-6-nitro-hippuric acid (4-c): M.p. 233–235°C; Anal calcd for: $C_{11}H_{12}N_2O_7$: C, 46.47; H, 4.26; N, 9.86. Found: C, 46.49; H, 4.57; N, 9.74. IR: 3450, 3350, 1766, 1638, 1532, 1375. ^{1}H NMR (300 MHz DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.05 (d, 2H, $J = 5.3$, -CH_2-), 7.19 (d, 1H, $J = 9.3$ Ar 3-H, or 4-H), 7.25 (d, 1H, $J = 9.3$, Ar 4-H or 3-H), 8.30 (brt, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.4, (2 × 57.1), 115.3, 116.0 118.4, 140.2, 144.5, 150.2, 161.8, 170.6.

4-Chloro-hippuric acid (4-d): White pale crystals (Ethanol). M.p. 141.5–142.5°C Anal. calcd for $C_9H_8NClO_3$: C, 50.58; H, 3.74; N, 6.55. Found: C, 50.88; H, 3.67; N, 6.42. IR: 3600–2850, 3338, 1746, 1685. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.1 (s, 2H, -CH_2-), 7.38 (d, 2H, $J = 8.35$, Ar 3-H, and 5-H), 7.83 (d, 2H, $J = 8.35$, Ar 2-H, and Ar 6-H), 7.94 (br.d., 1H, $J = 4.5$, NH), 9.8–11.2 (br.s., 1H, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.7, (2 × 128.4), (2 × 128.8) 132.3, 137.4, 166.4, 171.7.

General Procedure for the Synthesis of *N*-(Acetoxymethyl) Benzamides (5)

To a solution of carboxylic acid **4** (0.574 mmol), in acetonitrile (40 ml) was added a mixture of anhydrous lead tetraacetate (250 mg, 0.573 mmol) and cupric acetate (104 mg, 0.573 mmol). The mixture was refluxed for 3 h. The reaction mixture was then quenched with water (100 ml), and the resulting solution extracted with ethyl acetate (3 × 50 ml), dried (Na_2SO_4), and

concentrated in vacuo. The products were further purified by silica gel column chromatography.

***N*-(Acetoxymethyl)-2,5-dimethoxybenzamide (5-a):** Pale yellow oil (column chromatographed, AcOEt). Anal calcd for: $C_{12}H_{15}NO_5$: C, 56.90; H, 5.97; N, 5.33. Found: C, 57.03; H, 6.29; N, 5.41. IR: 3380, 1733, 1669. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.46 (d, 2H, $J = 7.18$, -CH_2-), 6.92 (d, 1H, $J_o = 9.0$, Ar 3-H), 7.03 (dd, 1H, $J_o = 9.0$, $J_m = 2.90$, Ar 4-H), 7.76 (d, 1H, $J_m = 2.90$, Ar 6-H), 8.95–9.05 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0, 55.8, 56.6, 64.7, 113.1, 115.9, 120.3, 120.9, 152.2, 153.9, 165.7, 171.8.

***N*-(Acetoxymethyl)-4-nitro-2, 5-dimethoxybenzamide (5-b):** Yellow crystals (column chromatographed, $CHCl_3$/AcOEt = 1 : 1). M.p. 123–124.5°C. Anal. calcd for $C_{12}H_{14}N_2O_7$: C, 48.43; H, 4.73; N, 9.39. Found: C, 48.36; H, 4.85; N, 9.36. IR: 3386, 1747, 1668. ^{1}H NMR (300 MHz,$CDCl_3$) δ: 2.10 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 5.46 (d, 2H, $J = 7.0$, NH-CH_2-O), 7.49 (s, 1H, Ar 6-H), 8.00 (s, 1H, Ar 3-H), 8.93 (br.t, 1H, $J = 7.0$, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.9, 57.1, 57.2, 64.5, 109.4, 118.1, 125.2, 141.2, 147.0, 150.7, 163.8, 171.7.

***N*-(Acetoxymethyl)-6-nitro-2, 5-dimethoxybenzamide (5-c):** Yellow crystals (column chromatographed: AcOEt/$CHCl_3$ 2 : 1). M.p. 124–125°C. Anal calcd. for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 49.09; H, 4.99; N, 9.38. IR: 3357, 1726, 1680, 1539, 1370. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.01 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.17 (d, 2H, $J = 6.9$, -CH_2-), 7.30 (d, 1H, $J = 8.1$, Ar 3-H, or 4-H), 7.37 (d, 1H, $J = 8.1$, Ar 4-H, or 3-H), 9.47 (br.t, 1H, $J = 6.9$, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.1, 57.3, 57.7, 64.2, 116.6, 117.3, 119.9, 139.5, 144.8, 150.1, 163.6, 170.5.

***N*-(Acetoxymethyl)-4-chloro-benzamide (5-d):** M.p. 218–219°C White crystals (column chromatographed AcOEt/$CHCl_3$ = 1 : 2) Anal. calcd for $C_{10}H_{10}NClO_3$: C, 52.74; H, 4.39; N, 6.15; Cl, 15.6. Found: C, 53.46; H, 4.50; N, 5.93. IR: 3328, 1737, 1652. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.1 (s, 3H, CH_3), 5.43 (d, 2H, $J = 7.2$, CH_2), 7.40 (br t, 1H, NH), 7.41 (d, 2H, $J = 8.1$, Ar 2-H, and Ar 6-H), 7.76 (d, 2H, $J = 8.1$, Ar 3-H and Ar 5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 64.7, (2 × 128.7), (2 × 128.9), 131.5, 138.7, 166.4, 172.2.

General Procedure for the Synthesis of *N*-(Morpholinomethyl) Benzamides (6)

To a stirred solution of acetatebenzamide **5** (0.6 mmol) in acetonitrile (20 ml), triethylamine (55.7 mg, 0.080 ml, 0.55 mmol) and Morpholine (48.0 mg, 0.048 ml, 0.55 mmol) were added at 25°C for 4 h. The mixture

was poured into ice-water and extracted with ethyl acetate (3×50 ml). The organic layers were washed with water and dried (Na_2SO_4). Removal of the solvent afforded crude morpholine derivatives **6** which were purified by silica gel column chromatography or crystallization.

2,5-Dimethoxy-*N*-(morpholinomethyl) benzamide (6-a): Pale yellow oil (column chromatographed, AcOEt). Anal. calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 58.12; H, 7.25; N, 9.86. IR: 3391, 1658. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (t, 4H, $J = 4.7$, Morpholine 2-H and 6-H, (N-CH_2)), 3.61 (t, 4H, $J = 4.7$, Morpholine 3-H and 5-H, (O-CH_2)), 3.70 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.22 (d, 2H, $J = 6.30$, NH-CH_2-N), 6.83 (d, 1H, $J = 9.0$, Ar 3-H), 6.90 (dd, 1H, $J_o = 9.0$, $J_m = 3.20$, Ar 4-H) 7.63 (d, 1H, $J_m = 3.20$, Ar 6-H), 8.22 (br t, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: (2×50.1), 55.5, 56.3, 61.24, (2×66.5), 112.7, 115.5, 119.2, 121.4, 151.5, 153.6, 165.5.

2,5-Dimethoxy-4-nitro–*N*-(morpholinomethyl) benzamide (6-b): Yellow crystals (Ethanol). M.p. 116–118°C. Anal. calcd for $C_{14}H_{19}N_3O_6$: C, 51.69; H, 5.89; N, 12.92. Found: C, 51.08; H, 5.98; N, 12.42. IR: 3383, 1669, 1511,1342. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (t, 4H, $J = 4.8$, Morpholine 2-H and 6-H, (N-CH_2)), 3.73 (t, 4H, $J = 4.8$,Morpholine 3-H and 5-H, (O-CH_2)), 3.98 (s, 3H,OCH_3), 4.0 (s, 3H, OCH_3), 4.35 (d, 2H, $J = 6.50$, NH-CH_2-N), 7.51 (s, 1H, Ar 6-H), 8.0 (s, 1H, Ar 3-H), 8.17 (s, broad, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: (2×50.4), (2×57.0), (2×63.1), 66.8, 109.1, 118.0, 126.1, 140.7, 147.2, 150.3, 163.8.

2,5-Dimethoxy-6-nitro-*N*-(morpholinomethyl) benzamide (6-c): Pale yellow crystals (Ethanol). M.p. 169–172°C Anal. calcd for $C_{14}H_{19}N_3O_6$: C, 51.69; H, 5.89; N, 12.92. Found: C, 51.43; H, 5.80; N, 13.02. IR: 3400, 1669, 1535, 1367. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (t, 4H, $J = 4.7$, (Morpholine 2-H and 6-H, (N-CH_2)), 3.72 (t, 4H, $J = 4.7$, (Morpholine 3-H and 5-H), (O-CH_2)), 3.88 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.29 (d, 2H, $J = 6.35$, -NCH_2N-), 7.02 (brt, 1H, NH), 7.07 (d, 1H, $J = 9.24$ Ar 6-H), 7.11 (d, 1H, $J = 9.24$, Ar 3-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: (2×50.3), 57.2, 57.3, 61.7, (2×66.9), 114.3, 115.9, 118.8, 142.0, 146.0, 151.0, 162.5.

4-Chloro-*N*-(morpholinomethyl) benzamide (6-d). Brown pale solid (column chromatographed, $CHCl_3$–AcOEt = 1 : 2). M.p. 70.2–71.3°C. Anal. calcd for $C_{12}H_{15}N_2O_2Cl$: C, 56.58; H, 5.89; N, 11.00. Found: C, 56.37; H, 5.79; N, 10.78. IR: 3304, 1658, 1116. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (t, 4H, $J = 4.4$, Morpholine 2-H and 6-H, (N-CH_2)), 3.73 (t, 4H, $J = 4.4$, Morpholine 3-H and 5-H), (O-CH_2)), 4.29 (d, 2H, $J = 6.1$, -CH_2-), 7.41 (d, 2H, $J = 8.4$, Ar 3-H and 5-H), 7.79 (d, 2H, $J = 8.4$, Ar 2-H and 6-H), 8.29 (br.s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = (2×50.3), 61.5, (2×66.0), (2×128.6), (2×128.8), 132.1, 138.0, 166.9.

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