CHAPTER II
EXPERIMENTAL

Instruments and Equipment

Melting points were determined with a Fishers-Johns melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel (Merck's, Kieselgel 60 F_{254}) and column chromatography was performed on silica gel Merck's silica gel 60 G Art 7734 (70-230 mesh) were used as adsorbents for column chromatography.

The IR spectra were recorded on NICOLET IMPACT 410 FT/IR spectrophotometer. Solid samples were incorporated into a pellet of potassium bromide. Liquid samples were dropped on sodium chloride plates. The ^{1}H- and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal reference on a Fourier Transform Nuclear Magnetic Resonance Spectrometer of Bruker model AC-F 200 which was operated at 200.13 MHz for ^{1}H and 50.32 MHz for ^{13}C nuclei.

Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents used for synthesis were purchased from Fluka Chemical Company or otherwise stated and were used without further purification.

General Procedure for the Synthesis of Amide

Step I :

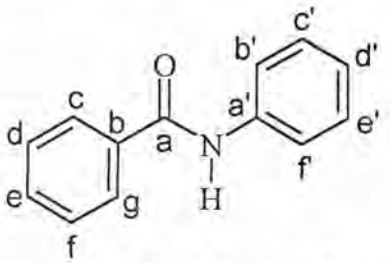
A solution of triphenylphosphine (PPh_3) 2 eq (6 mmol, 1.57 g) in CH_2Cl_2 3 mL was added to a mixture of carboxylic acid 1 eq (3 mmol) and trichloroacetonirile (Cl_3CCN) 2 eq (6 mmol, 0.6 mL) in CH_2Cl_2 3 mL at room temperature. The mixture was stirred for 1 hour.

Step II :

A mixture of amine 1 eq (3 mmol) and 3 eq (9 mmol, 1.25 mL) of triethylamine (Et_3N) was added to the above mixture. The reaction continued stirring

for another 20 minutes at room temperature. When the reaction was completed (monitoring by TLC), the mixture was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, and dried over anhydrous Na_2SO_4. After evaporation, the mixture was separated with column chromatography on silica gel (eluent : hexane-EtOAc 8:2) and recrystallized with CH_2Cl_2 and hexane to yield the desired amide.

Benzanilide Synthesis (Compound **C1**)



The general procedure was followed by using benzoic acid and aniline. After column chromatography separation, benzanilide as white needle crystal 0.44 g (75 %) was obtained, m.p. 164-165 °C (CH_2Cl_2-hexane) (lit.[44] 163 °C), R_f 0.63 (50 % EtOAc/hexane). IR (KBr): 3347, 3056, 1659, 1596, 1436 and 1315 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61 (s, 1H, N*H*) and 7.14-7.87 (m, 10H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 120.3 (2C, Cb′ and Cf′), 124.6 (1C, Cd′), 127.1 (2C, Cc and Cg), 128.8 (2C, Cd and Cf), 129.1 (2C, Cc′ and Ce′), 131.8 (1C, Ce), 135.0 (1C, Cb), 137.9 (1C, Ca′) and 165.9 (1C, Ca).

Study on the Optimum Conditions

1. Influence of Cl_3CCN and PPh_3 Ratio

The ratios of Cl_3CCN and PPh_3 for the synthesis of benzanilide utilizing the general procedure were varied (benzoic acid was fixed at 1 eq). The variations of the Cl_3CCN and PPh_3 ratios are as follows: 1:1, 1:2, 1:3, 1:4, 1:5, 2:0, 2:1, 2:2, 2:3, 2:4, 2:5, 3:1, 4:1, 5:1, 0:2, 3:2, 4:2 and 5:2, respectively. Determine the yield of benzanilide.

2. Influence of Time and Temperature

Employing the above-mentioned general procedure, but the reaction was operated by altering time and temperature in step I.

2.1. Time variation: The reaction was carried out at room temperature (25-30 °C) for 0.5, 1, 1.5, 2 and 3 h, respectively.

2.2. Temperature variation: The reaction was performed by using an ice water bath (0-5 °C) for 0.5, 1, 1.5, 2 and 3 h, respectively.

3. Influence of Solvent System

Solvents for the synthesis of benzanilide according to the general procedure were varied by using chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), ethyl acetate (EtOAc), 1,2-dichloroethane (1,2-DCE), tetrahydrofuran (THF), toluene, acetonitrile, acetone, 1:1 THF-$CHCl_3$, 1:1 acetone-$CHCl_3$, 1:1 ether-$CHCl_3$ and 1:1 methanol (MeOH)-$CHCl_3$ instead of CH_2Cl_2.

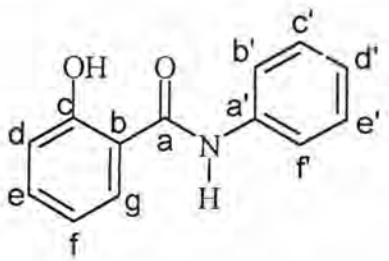
4. Influence of Chlorinated Reagent

Reagents for the synthesis of benzanilide according to the general procedure were altered by employing carbon tetrachloride (CCl_4), trichloroacetic acid (Cl_3CCO_2H), ethyl trichloroacetate (Cl_3CCO_2Et), trichloroethanol (Cl_3CCH_2OH), 2-chloroacetamide ($ClCH_2C(O)NH_2$), trichloroacetamide ($Cl_3CC(O)NH_2$), bromotrichloromethane (Cl_3CBr), trifluoroacetic acid (F_3CCO_2H), hexachloroethane (Cl_3CCCl_3) and hexachloro-2-propanone ($Cl_3CC(O)CCl_3$) in lied of Cl_3CCN.

Carboxylic Acid Variation

In order to overview the scope of this developed procedure, various amides were prepared using general procedure by using aniline as a representative amine reacting with various carboxylic acids, namely salicylic acid, acetylsalicylic acid, 4-methoxybenzoic acid, 4-nitrobenzoic acid, *trans*-cinnamic acid, palmitic acid, 3-bromopropionic acid and phthalic acid. The details and characteristic spectral data are presented as follows.

2-Hydroxy-N-phenylbenzamide (Compound **C2**)



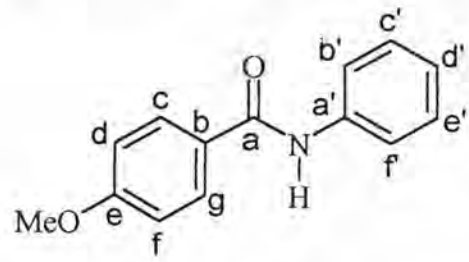
Method A (Compound **C2a**) :

The general procedure was employed using salicylic acid to afford compound **C2** as white plate crystal, 0.35 g (55 %), m.p. 133-135 °C (CH_2Cl_2-hexane) (lit.[44] 135 °C), R_f 0.62 (50 % EtOAc/hexane). IR (KBr): 3675-3356, 3308, 3066, 1688, 1644, 1446 and 1301 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72 (s, 1H, N*H*), 6.52-8.05 (m, 9H, Ar*H*) and 11.98 (s, 1H, O*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 114.6 (1C, Cd), 118.9 (2C, Cb′ and Cf′), 119.0 (1C, Cb), 121.2 (1C, Cf), 125.4 (1C, Cd′), 129.2 (3C, Cg, Cc′ and Ce′), 134.7 (1C, Ce), 136.6 (1C, Ca′), 161.8 (1C, Cc) and 168.4 (1C, Ca).

Method B (Compound **C2b**) :

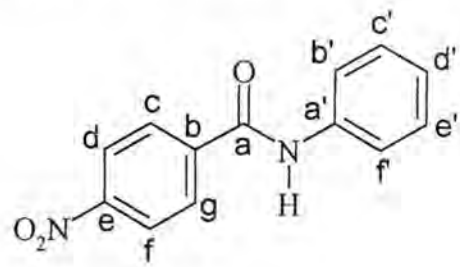
The general procedure was followed starting from acetylsalicylic acid to afford compound **C2**-acetate as white needle crystal, 0.38 g (49 %). The derived *N*-acetylsalicoyl compound was hydrolyzed by dissolving in 0.1 N NaOH and kept at room temperature for 10 minutes. Addition of 0.1 N HCl precipitated the desired compound. The precipitate was recrystallized by a mixture of CH_2Cl_2-hexane to yield white plate crystal, 0.31 g (49 %), m.p. 134-135 °C (CH_2Cl_2-hexane) (lit.[44] 135 °C), R_f 0.62 (50 % EtOAc/hexane). IR (KBr): 3678-3347, 3309, 3063, 1689, 1645, 1447 and 1307 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (s, 1H, N*H*), 6.91-7.92 (m, 9H, Ar*H*) and 11.97 (s, 1H, O*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 114.6 (1C, Cd), 118.9 (2C, Cb′ and Cf′), 119.0 (1C, Cb), 121.3 (1C, Cf), 125.4 (1C, Cd′), 129.2 (3C, Cg, Cc′ and Ce′), 134.7 (1C, Ce), 136.6 (1C, Ca′), 161.8 (1C, Cc) and 168.4 (1C, Ca).

4-Methoxy-N-phenylbenzamide (Compound **C3**)



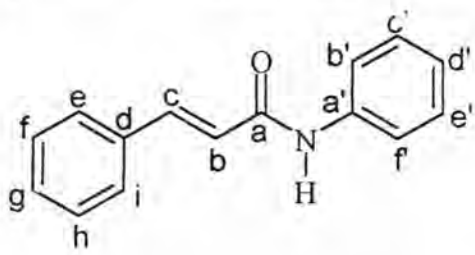
White needle crystal, 0.45 g (66 %), m.p. 171-173 °C (CH_2Cl_2-hexane) (lit.[44] 171 °C), R_f 0.73 (50 % EtOAc/hexane). IR (KBr): 3337, 3052, 2839, 1659, 1596, 1431 and 1315 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59 (s, 1H, N*H*), 3.85 (s, 3H, O*CH*$_3$), 6.95 (d, J = 8.82 Hz, 2H, *H*d and *H*f), 7.12 (t, J = 7.37 Hz, 1H, *H*d′), 7.35 (t, J = 7.47, 2H, *H*c′ and *H*e′), 7.61 (d, J = 7.48 Hz, 2H, *H*b′ and *H*f′) and 7.83 (d, J = 8.89 Hz, 2H, *H*c and *H*g); ^{13}C-NMR ($CDCl_3$) δ (ppm): 55.5 (1C, O*C*H$_3$), 114.0 (2C, Cd and Cf), 120.1 (2C, Cb′ and Cf′), 124.3 (1C, Cd′), 127.1 (1C, Cb), 128.9 (2C, Cc and Cg), 129.1 (2C, Cc′ and Ce′), 138.1 (1C, Ca′), 162.5 (1C, Ca) and 165.2 (1C, Ce).

4-Nitro-N-phenylbenzamide (Compound **C4**)



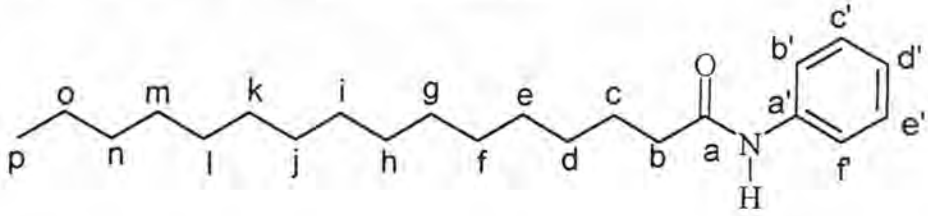
White needle crystal, 0.36 g (49 %), m.p. 213-214 °C (CH_2Cl_2-hexane) (lit.[44] 211 °C), R_f 0.67 (50 % EtOAc/hexane). IR (KBr): 3318, 3081, 1654, 1596, 1528, 1436, 1349 and 1315 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.55 (s, 1H, N*H*), 7.13 (t, J = 7.38 Hz, 1H, *H*d′), 7.37 (t, J = 7.50 Hz, 2H, *H*c′ and *H*e′), 7.76 (d, J = 7.56 Hz, 2H, *H*b′ and *H*f′), 8.17 (d, J = 8.92 Hz, 2H, *H*c and *H*g) and 8.36 (d, J = 8.91 Hz, 2H, *H*d and *H*f); ^{13}C-NMR (DMSO-d_6) δ (ppm): 126.2 (2C, Cb′ and Cf′), 129.3 (2C, Cd and Cf), 129.9 (1C, d′), 134.5 (2C, Cc and Cg), 134.9 (2C, Cc′ and Ce′), 144.4 (1C, Ca′), 146.4 (1C, Cb), 154.9 (1C, Ce) and 169.6 (1C, Ca).

3,N-Diphenyl-2-propenamide (Compound **C5**)



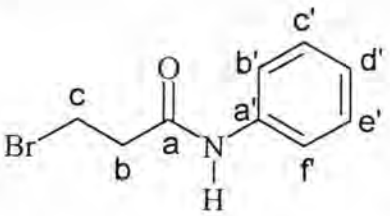
White needle crystal, 0.46 g (68 %), m.p. 154-156 °C (CH_2Cl_2-hexane) (lit.[44] 153 °C), R_f 0.61 (50 % EtOAc/hexane). IR (KBr): 3332, 3047, 1951, 1659, 1620, 1528, 1436 and 1339 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.78 (s, 1H, N*H*), 6.62 (d, J = 15.55 Hz, 1H, HC=C*H*CO), 7.14-7.87 (m, 10H, Ar*H*) and 7.73 (d, J = 15.57 Hz, 1H, C*H*=CHCO); ^{13}C-NMR ($CDCl_3$) δ (ppm): 120.2 (1C, Cb), 121.0 (2C, Cb′ and Cf′), 124.5 (1C, Cd′), 128.0 (2C, Ce and Ci), 128.8 (1C, Cg), 129.0 (2C, Cf and Ch), 129.9 (2C, Cc′ and Ce′), 134.6 (1C, Cd), 138.1 (1C, Ca′), 142.3 (1C, Cc) and 164.4 (1C, Ca).

N-Phenylhexadecanamide (Conpound **C6**)



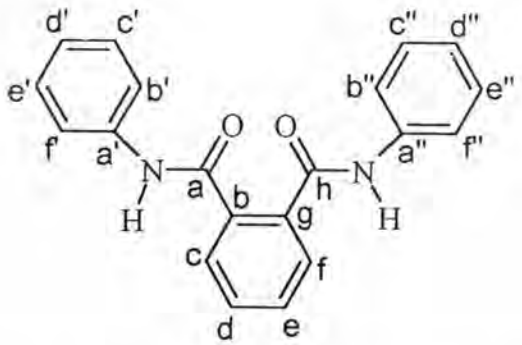
White needle crystal, 0.68 g (68 %), m.p. 88-89 °C (CH_2Cl_2-hexane) (lit.[44] 90 °C), R_f 0.79 (50 % EtOAc/hexane). IR (KBr): 3303, 3056, 2916, 1659, 1601, 1538, 1441 and 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (t, J = 6.23 Hz, 3H, C*H*$_3$), 1.05-1.30 (s (br), 24H, (C*H*$_2$)$_{12}$CH$_3$), 1.54 (s, 1H, N*H*), 1.68-1.75 (m, 2H, C*H*$_2$CH$_2$CO), 2.33 (t, J = 7.41 Hz, 2H, C*H*$_2$CO) and 7.08-7.52 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1 (1C, Cp), 22.7 (1C, Co), 25.7 (1C, Cc), 29.5 (10C, Cd-Cm), 31.9 (1C, Cn), 37.8 (1C, Cb), 119.8 (2C, Cb′ and Cf′), 124.1 (1C, Cd′), 129.0 (2C, Cc′ and Ce′), 138.0 (1C, Ca′) and 171.5 (1C, Ca).

3-Bromo-N-phenylpropanamide (Compound **C7**)



White plate crystal, 0.25 g (37 %), m.p. 120-121 °C (CH_2Cl_2-hexane) (lit.[45] 119-120 °C), R_f 0.54 (50 % EtOAc/hexane). IR (KBr): 3304, 3192, 2979, 1657, 1552, 1441 ans 1310 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61 (s, 1H, N*H*), 2.79 (t, J = 6.43 Hz, 2H, CH_2), 3.86 (t, J = 6.42 Hz, 2H, CH_2Br) and 7.07-7.52 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.6 (1C, Cc), 40.4 (1C, Cb), 120.6 (2C, Cb′ and Cf′), 125.2 (1C, Cd′), 129.6 (2C, Cc′ and Ce′), 140.1 (1C, Ca′) and 174.6 (1C, Ca).

N,N′-Diphenylphthalamide (Compound **C8**)

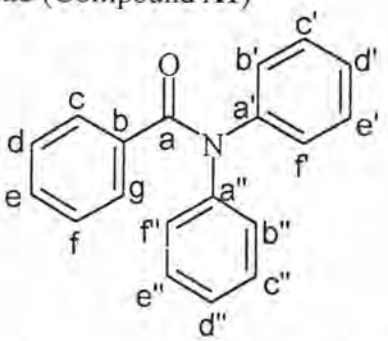


The general procedure was repeated by using phthalic acid and two-fold amounts of reagents: Cl_3CCN, PPh_3, aniline and Et_3N to gain yellow needle crystal, 0.33 g (34 %), m.p. 251-253 °C decomp. (CH_2Cl_2-hexane) (lit.[44] 251 °C decomp.), R_f 0.60 (50 % EtOAc/hexane). IR (KBr): 3463, 3015, 1709, 1589, 1490 and 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54 (s, 2H, N*H*) and 7.39-7.97 (m, 15H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 119.3 (2C, Cb′ and Cf′), 119.5 (2C, Cb″ and Cf″), 123.3(1C, Cd′), 123.4 (1C, Cd″), 127.7 (2C, Cc and Cf), 129.3 (2C, Cc′ and Ce′), 129.5 (2C, Cc″ and Ce″), 131.7 (2C, Cd and Ce), 134.7 (2C, Cb and Cg), 138.9 (1C, Ca′), 139.5 (1C, Ca″), 167.3 (1C, Ca) and 167.4 (1C, Ch).

Amine Variation

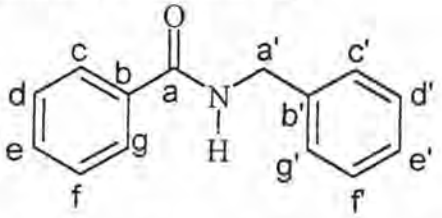
Various amides were prepared using aforementioned general procedure by fixing benzoic acid as a representative carboxylic acid and varied amines, namely *N*-phenylaniline, benzylamine, cyclohexylamine, *i*-butylamine and *n*-butylamine. The details and characteristic spectral data are presented as follows.

N,N-Diphenylbenzamide (Compound **A1**)



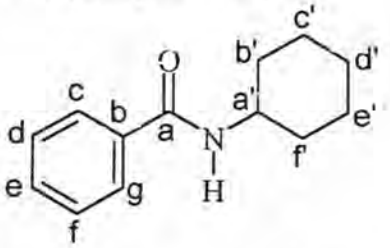
Yellow prism, 0.05 g (7 %), m.p. 177-179 °C (CH_2Cl_2-hexane) (lit.[44] 179-180 °C), R_f 0.32 (CH_2Cl_2). IR (KBr): 3061, 1659, 1601, 1499, 1446 and 1354 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.12-7.46 (m, 15H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 126.3 (4C, Cb′, Cf′, Cb″ and Cf″), 127.5 (2C, Cd′ and Cd″), 127.9 (2C, Cc and Cg), 129.1 (2C, Cd and Cf), 129.5 (4C, Cc′, Ce′, Cc″ and Ce″), 130.2 (1C, Ce), 136.1 (1C, Cb), 143.9 (2C, Ca′ and Ca″) and 170.6 (1C, Ca).

N-Methylphenylbenzamide (Compound **A2**)



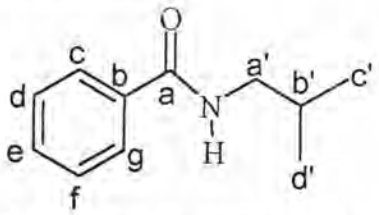
White needle crystal, 0.49 g (77 %), m.p. 103-104 °C (CH_2Cl_2-hexane) (lit.[44] 105-106 °C), R_f 0.51 (50 % EtOAc/hexane). IR (KBr): 3289, 3085-3027, 2926, 1639, 1601, 1593, 1489, 1451 and 1417 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.63 (s, 1H, N*H*), 4.64 (d, J = 5.65 Hz, 2H, C*H*$_2$NH) and 7.24-7.80 (m, 10H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 44.0 (1C, Ca′), 127.1 (1C, Ce′), 127.5 (2C, Cc′ and Cg′), 127.8 (2C, Cc and Cg), 128.5 (2C, Cd′ and Cf′), 128.7 (2C, Cd and Cf), 131.5 (1C, Ce), 134.4 (1C, Cb), 138.4 (1C, Cb′) and 167.6 (1C, Ca).

N-Cyclohexylbenzamide (Compound **A3**)



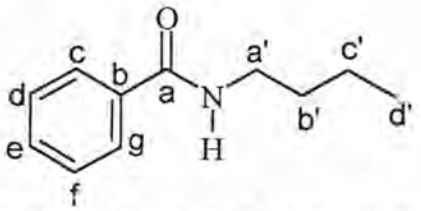
White needle crystal, 0.54 g (89 %), m.p. 147-149 °C (CH_2Cl_2-hexane) (lit.[44] 147 °C), R_f 0.5[illegible] (50 % EtOAc/hexane). IR (KBr): 3313, 3081-3032, 2935, 2853, 1625, 1576, 1489 and 1330 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.12-2.04 (m, 10H, alkyl group), 3.89-4.03 (m, 1H, NHC*H*), 5.94 (s (br), 1H, N*H*) and 7.24-7.77 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.9 (2C, Cc′ and Ce′), 25.6 (1C, Cd′), 33.2 (2C, Cb′ and Cf′), 48.7 (1C, Ca′), 126.8 (2C, Cc and Cg), 128.5 (2C, Cd and Cf), 131.2 (1C, Ce), 135.1 (1C, Cb) and 166.7 (1C, Ca).

N-i-Butylbenzamide (Compound **A4**)



Light yellow liquid, 0.43 g (80 %), R_f 0.44 (50 % EtOAc/hexane). IR (neat): 3588-3192, 3066, 2965-2873, 1644, 1583, 1552, 1485 and 1310 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (d, J = 6.69 Hz, 6H, C*H*$_3$), 1.75-1.89 (m, 1H, C*H*$(CH_3)_2$), 2.06 (s, 1H, N*H*), 3.15 (t, J = 6.85 Hz, 2H, NHC*H*$_2$) and 7.24-7.76 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.2 (2C, Cc′ and Cd′), 28.5 (1C, Cb′), 47.4 (1C, Ca′), 127.0 (2C, Cc and Cg), 128.7 (2C, Cd and Cf), 131.2 (1C, Ce), 134.9 (1C, Cb), and 167.9 (1C, Ca).

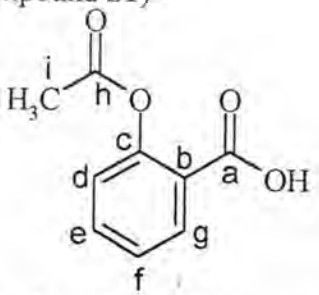
N-n-Butylbenzamide (Compound **A5**)



Deep yellow liquid, 0.33 g (61 %), R_f 0.56 (50 % EtOAc/hexane). IR (neat): 3584-3148, 3066, 2965-2873, 1639, 1601, 1543, 1485 and 1315 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (t, J = 7.11 Hz, 3H, CH_3), 1.23-1.43 (m, 2H, CH_2CH_3), 1.51-1.62 (m, 2H, $NHCH_2CH_2$), 2.24 (s (br), 1H, N*H*), 3.33-3.43 (q, J = 6.86 Hz, 2H, $NHCH_2$) and 7.24-7.76 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.8 (1C, Cd′), 20.1 (1C, Cc′), 31.7 (1C, Cb′), 39.8 (1C, Ca′), 126.9 (2C, Cc and Cg), 128.5 (2C, Cd and Cf), 131.3 (1C, Ce), 134.8 (1C, Cb), and 167.7 (1C, Ca)

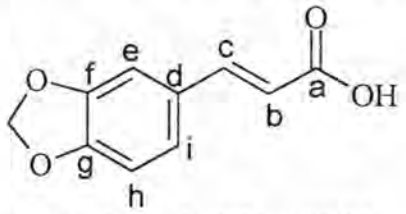
Preparation of Starting Compounds

Acetylsalicylic Acid (Compound **S1**)



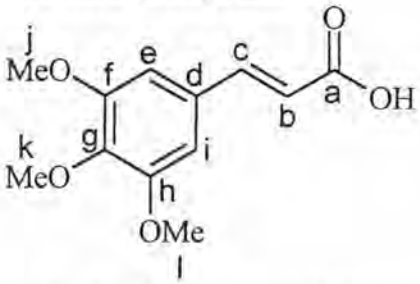
Five drops of concentrated sulfuric acid were added to a mixture of 1 g (0.0725 mol) of dry salicylic acid and 1.4 mL (0.0147 mol) of acetic anhydride. The mixture was warmed on a water bath to about 50-60 °C and stirred for 15 minutes. After that, 15 mL of hot ethanol was added to a mixture. The mixture was poured into 7.5 mL of warm water to precipitate the desired compound. The precipitate was recrystallized by a mixture of ether-hexane to give white needle crystal 2.26 g (85 %), m.p. 133-134 °C (ether-hexane) (lit.[46] 134-136 °C), R_f 0.5 (methanol). IR (KBr): 3308-3544, 1760, 1605, 1460, 1306 and 1185 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.33 (s, 3H, CH_3), 5.08 (s, 1H, O*H*), 7.12 (d, J = 7.95 Hz, 1H, *H*d), 7.33 (t, J = 7.77 Hz, 1H, *H*f), 7.60 (t, J = 7.58 Hz, 1H, *H*e) and 8.09 (d, J = 7.86 Hz, 1H, *H*g); ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.0 (1C, CH_3), 122.2 (1C, Cd), 124.0 (1C, Cb), 126.2 (1C, Cf), 132.5 (1C, Cg), 134.9 (1C, Ce), 151.3 (1C, Cc), 169.8 (1C, Ch) and 170.1 (1C, Ca).

3,4-Dioxymethylene::innamic Acid (Compound **S2**)



After 3,4-dioxymethylenebenzaldehyde 4.50 g (0.03 mol) and piperidine 0.28 mL were added to a solution of malonic acid 3.29 g (0.03 mol) in 5.2 mL of pyridine, the mixture was refluxed for 2 hours. When the reaction was completed (checked by TLC), it was added into a mixture of ice 16 g, conc. HCl 8 mL and water 26 mL for precipitating the desired compound. The solid was filtered and washed with water until no more acid remained (checked by litmus paper). The solid was crystallized by ethanol to give white needle crystal 3.15 g (55 %), m.p. 239-241 °C (EtOH) (lit[44] 242 °C), R_f 0.64 (EtOH). IR (KBr): 3385-2350, 1693, 1625, 1489, 1446, 1320 and 1248 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.33 (s, 1H, *OH*), 6.06 (s, 2H, O*CH*$_2$O), 6.38 (d, J = 15.92 Hz, 1H, CH=C*H*CO), 6.93 (d, J = 8.03 Hz, 1H, *H*h), 7.15 (d, J = 7.90 Hz, 1H, *H*i), 7.36 (s, 1H, *H*e) and 7.49 (d, J = 15.73 Hz, 1H, C*H*=CHCO); ^{13}C-NMR (DMSO-d_6) δ (ppm): 101.5 (1C, O*C*H$_2$O), 106.6 (1C, Ce), 108.4 (1C, Ch), 117.0 (1C, Cb), 124.6 (1C, Ci), 128.6 (1C, Cd), 143.8 (1C, Cc), 148.0 (1C, Cg), 149.1 (1C, Cf) and 167.8 (1C, Ca).

3,4,5-Trimethoxycinnamic Acid (Compound **S3**)



The procedure for the synthesis of Compound **S2** was repeated by employing 3,4,5-trimethoxybenzaldehyde instead of 3,4-dioxymethylenebenzaldehyde. Light yellow needle crystal 2.49 g (35 %) was obtained, m.p. 122-123 °C (EtOH) (lit[44] 127 °C), R_f 0.45 (EtOAc). IR (KBr): 3462-2731, 2861, 1702, 1629, 1504, 1412 and 1344 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (s, 9H, O*CH*$_3$), 6.33 (d, J = 15.92 Hz, 1H, HC=C*H*CO), 6.75 (s, 2H, Ar*H*) and 7.68 (d, J = 15.85 Hz, 1H, C*H*=CHCO); ^{13}C-NMR ($CDCl_3$) δ (ppm): 56.1 (2C, Cj and Cl), 61.0 (1C, Ck), 105.5 (2C, Ce and Ci),

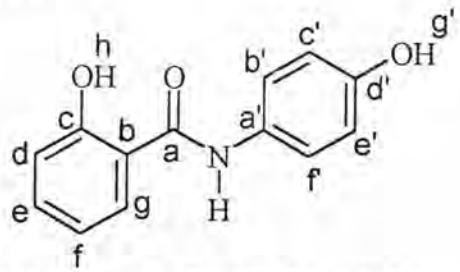
116.5 (1C, Cb), 129.5 (1C, Cd), 140.5 (1C, Cg), 147.0 (1C, Cc), 153.4 (2C, Cf and Ch) and 172.4 (1C, Ca).

General Procedure for the Synthesis of Target Molecules

A mixture of carboxylic acid 1 eq (3 mmol) and Cl_3CCN 1 eq (3 mmol, 0.3 mL) in $CHCl_3$ 3 mL was treated with a solution of PPh_3 2 eq (6 mmol, 1.58 g) in $CHCl_3$ 3 mL at 0-5° C by using ice water bath. After stirred for 2 hours, a mixture of amine 1 eq (3 mmol) and 3 eq (9 mmol, 1.25 mL) of Et_3N was added. The reaction mixture was continued stirring for another 2 hours at room temperature. When the reaction was completed, the mixture was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated to give the crude product which was further purified with column chromatography on silica gel (eluent: hexane-EtOAc 8:2).

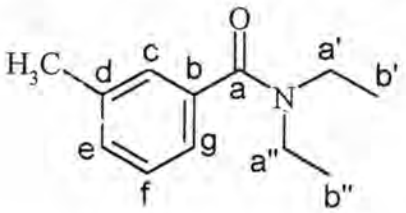
Synthesis of Target Molecules

Osalmid (Compound **T1**)



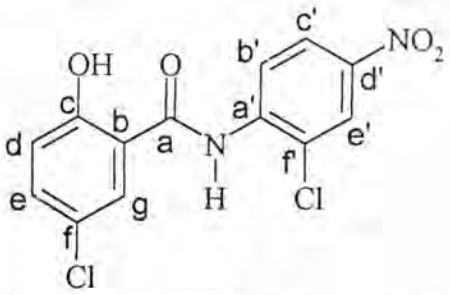
White needle 0.32 g (47 %), m.p. 176-178 °C (MeOH/H_2O) (lit.[47] 178 °C), R_f 0.48 (50 % EtOAc/hexane). IR (KBr): 3601-3352, 3298, 3039, 1615, 1550, 1505, 1445 and 1331 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.78 (s, 1H, *NH*), 6.91 (s, 1H, *Hg'*), 6.97 (d, J = 7.76 Hz, 2H, *Hc'* and *He'*), 7.13 (t, J = 8.10 Hz, 1H, *Hf*), 7.34 (d, J = 8.08 Hz, 1H, *Hd*), 7.42 (t, J = 8.16 Hz, 1H, *He*), 7.69 (d, J = 7.54 Hz, 2H, *Hb'* and *Hf'*), 8.95 (d, J = 8.26 Hz, 1H, *Hg*) and 10.38 (s, 1H, *Hh*); ^{13}C-NMR (DMSO-d_6) δ (ppm): 115.2 (1C, Cd), 115.5 (2C, Cc' and Ce'), 121.0 (1C, Cb), 121.4 (1C, Cf), 121.9 (2C, Cb' and Cf'), 129.4 (1C, Cg), 130.3 (1C, Ca'), 134.5 (1C, Ce), 148.2 (1C, Cd'), 155.4 (1C, Cc) and 167.9 (1C, Ca).

N,N-diethyl-m-toluamide or DEET (Compound **T2**)



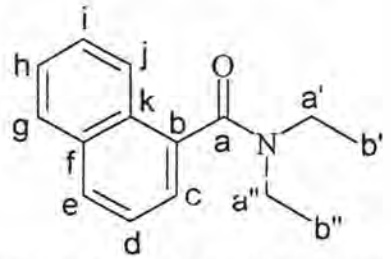
Yellow liquid 0.51 g (89 %), R_f 0.45 (50 % EtOAc/hexane). IR (neat): 3113, 2972, 1629, 1564, 1418 and 1357 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.08 (s (br), 3H, CH_2CH_3), 1.17 (s (br), 3H, CH_2CH_3), 2.30 (s, 3H, $ArCH_3$), 3.21 (s (br), 2H, CH_2), 3.46 (s (br), 2H, CH_2) and 7.01-7.25 (m, 4H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 12.8 (1C, Cb′), 14.1 (1C, Cb″), 21.2 (1C, $ArCH_3$), 39.1 (1C, Ca′), 43.2 (1C, Ca″), 123.0 (1C, Cg), 126.7 (1C, Cc), 128.1 (1C, Cf), 129.7 (1C, Ce), 137.1 (1C, Cb), 138.0 (1C, Cd) and 171.3 (1C, Ca).

Niclosamide (Compound **T3**)



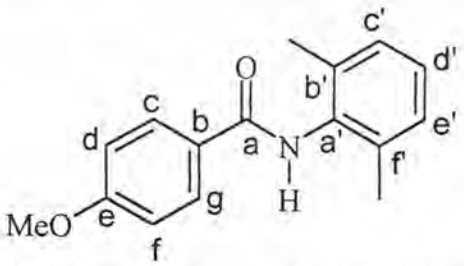
Pale yellow needle crystal 0.39 g (39 %), m.p. 231-232 °C (EtOH/H_2O) (lit.[48] 233 °C), R_f 0.62 (EtOAc). IR (KBr): 3564-3279, 3322, 3081, 1649, 1590, 1523, 1431, 1349, 1315 and 1011 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.57 (s, 1H, N*H*), 6.82 (d, J = 9.09 Hz, 1H, *H*d), 6.98 (d, J = 8.92 Hz, 1H, *H*e), 7.54 (d, J = 8.83 Hz, 1H, *H*b′), 7.71 (s, 1H, *H*g), 7.94 (d, J = 9.08 Hz, 1H, *H*c′), 8.07 (s, 1H, *H*e′) and 10.42 (s, 1H, O*H*); ^{13}C-NMR (DMSO-d_6) δ (ppm): 113.7 (1C, Cd), 114.4 (1C, Cc′), 117.7 (1C, Cb), 119.2 (1C, Cb′), 122.5 (1C, Ce′), 124.3 (1C,Cf), 125.9 (1C, Cf′), 129.1 (1C, Cg), 135.1 (1C, Ce), 144.6 (1C, Ca′), 148.7 (1C, Cd′), 159.6 (1C, Cc) and 164.8 (1C, Ca).

N,N-Diethyl-1-Naphthamide (Compound **T4**)



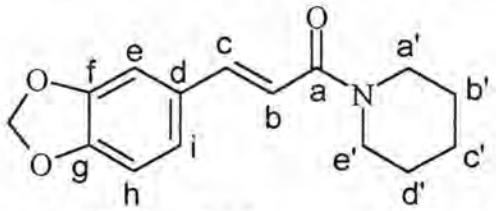
Yellow liquid 0.65 g (95 %), R_f 0.54 (50 % EtOAc/hexane). IR (neat): 3052, 2965, 1644, 1629, 1509, 1475 and 1296 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.97 (t, J = 7.09 Hz, 3H, C*H*$_3$), 1.35 (t, J = 7.09 Hz, 3H, C*H*$_3$), 3.08 (q, J = 7.09 Hz, 2H, C*H*$_2$), 3.54 (s (br), 2H, C*H*$_2$) and 7.35-7.85 (m, 7H, Ar*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.1 (1C, Cb′), 14.3 (1C, Cb″), 39.1 (1C, Ca′), 43.1 (1C, Ca″), 123.2 (1C, Ck), 124.7 (1C, Cj), 125.1 (1C, Cf), 126.4 (1C, Ce), 126.9 (1C, Cd), 128.3 (1C, Cg), 128.7 (1C, Ci), 129.6 (1C, Cc), 133.5 (1C, Ch), 135.1 (1C, Cb) and 170.3 (1C, Ca).

N-(2,6-dimethylphenyl)-4-methoxybenzamide (Compound **T5**)



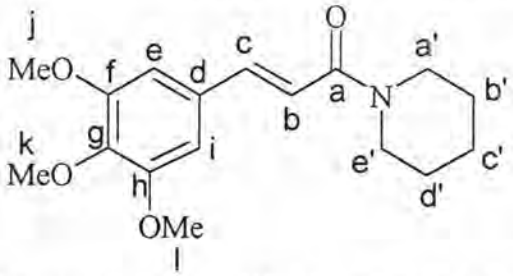
White needle crystal 0.52 g (68 %), m.p. 164-166 °C (CH_2Cl_2/hexane) (lit.[49] 168-170 °C), R_f 0.47 (50 % EtOAc/hexane). IR (KBr): 3250, 3003, 2945, 2834, 1644, 1610, 1533, 1494, 1441 and 1306 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.58 (s, 1H, N*H*), 2.26 (s, 6H, C*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 6.45 (t, J = 6.99 Hz, 1H, *H*d′), 6.83 (d, J = 7.39 Hz, 2H, *H*c′ and *H*e′), 6.96 (d, J = 8.67 Hz, 2H, *H*d and *H*f) and 7.87 (d, J = 8.69 Hz, 2H, *H*c and *H*g); ^{13}C-NMR ($CDCl_3$) δ (ppm): 15.3 (2C, *C*H$_3$), 55.5 (1C, OCH$_3$), 113.9 (2C, Cd and Cf), 123.7 (1C, Cd′), 126.7 (1C, Cb), 127.3 (2C, Cc′ and Ce′), 128.3 (2C, Cc and Cg), 129.1 (2C, Cb′ and Cf′), 135.6 (1C, Ca′), 162.5 (1C, Ca) and 165.4 (1C, Ce).

N-(3,4-Methylenediox;~*innamoyl)piperidide* (Compound **T6**)



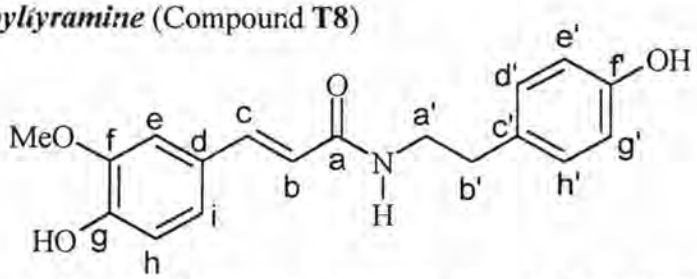
Colorless needle crystal 0.73 g (94 %), m.p. 85-87 °C (CH_2Cl_2/hexane) (lit.[50] 89 °C), R_f 0.30 (50 % EtOAc/hexane). IR (KBr): 3166, 2935, 2857, 1730, 1643, 1601, 1495, 1359 and 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61 (s (br), 6H, Hb′, Hc′ and Hd′), 3.59 (s (br), 4H, Ha′ and He′), 5.93 (s, 2H, OCH_2O), 6.71-6.79 (m, 3H, Ar*H*), 6.98 (d, J = 14.93 Hz, 1H, HC=C*H*CO) and 7.54 (d, J = 15.33 Hz, 1H, C*H*=CHCO); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.5 (1C, Cb′), 25.5 (1C, Cd′), 26.6 (1C, Cc′), 43.2 (1C, Ca′), 46.8 (1C, Ce′), 101.3 (1C, OCH_2O), 106.2 (1C, Ce), 108.2 (1C, Ch), 115.6 (1C, Ci), 123.4 (1C, Cb), 129.7 (1C, Cd), 141.7 (1C, Cc), 148.1 (1C, Cg), 148.7 (1C, Cf) and 165.2 (1C, Ca).

N-(3,4,5-Trimethoxycinnamoyl)piperidide (Compound **T7**)



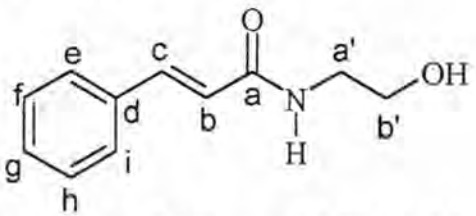
Colorless needle crystal 0.81 g (89 %), m.p. 100-101 °C (CH_2Cl_2/hexane) (lit.[51] 97.5-100 °C), R_f 0.44 (50 % EtOAc/hexane). IR (KBr): 3061, 2931, 2844, 1717, 1639, 1581, 1436 and 1330 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.57 (s (br), 6H, *H*b′, *H*c′ and *H*d′), 3.51 (s (br), 4H, *H*a′ and *H*e′), 3.86 (s, 9H, OCH_3), 6.74 (s, 2H, Ar*H*), 6.93 (d, J = 15.81 Hz, 1H, HC=C*H*CO) and 7.65 (d, J = 15.95 Hz, 1H, C*H*=CHCO); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.5 (1C, Cb′), 25.6 (1C, Cd′), 26.8 (1C, Cc′), 43.4 (1C, Ca′), 47.0 (1C, Ce′), 56.2 (2C, Cj and Cl), 60.4 (1C, Ck), 104.8 (2C, Ce and Ci), 116.9 (1C, Cb), 131.1 (1C, Cd), 133.4 (1C, Cg), 142.3 (1C, Cc), 153.3 (2C, Cf and Ch) and 165.3 (1C, Ca).

N-Feruloyltyramine (Compound **T8**)



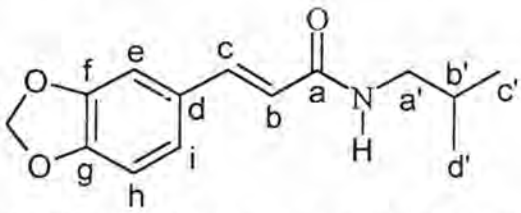
Colorless needle crystal 0.49 g (52 %), m.p. 145-147 °C (CH_2Cl_2/MeOH) (lit[52] 143-145 °C), R_f 0.51 (EtOAc). IR (KBr): 3656-3284, 3329, 3090, 2940, 2848, 1726, 1630, 1596, 1509, 1465, 1417 and 1267 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.17 (t, J = 7.20 Hz, 1H, N*H*), 2.75 (t, J = 7.86 Hz, 2H, *H*b′), 3.01 (q, J = 7.22 Hz, 2H, *H*a′), 3.78 (s, 3H, OC*H*$_3$), 6.34 (d, J = 15.88 Hz, 1H, CH=C*H*CO), 6.71 (d, J = 8.06 Hz, 2H, *H*e′ and *H*g′), 6.80 (d, J = 8.24 Hz, 1H, *H*h), 7.02 (d, J = 7.82 Hz, 2H, *H*d′ and *H*h′), 7.23 (s, 1H, *H*e), 7.45 (d, J = 15.92 Hz, 1H, C*H*=CHCO) and 7.56 (d, J = 8.56 Hz, 1H, *H*i). ^{13}C-NMR (DMSO-d_6) δ (ppm): 32.1 (1C, Cb′), 45.3 (1C, Ca′), 55.6 (1C, O*C*H$_3$), 111.0 (1C,Ce), 115.3(2C, Ce′ and Cg′), 116.2 (1C, Ch), 122.6(1C, Cb), 125.8 (1C, Ci), 127.3(1C, Cd), 129.5 (2C, Cd′ and Ch′), 143.5 (1C, Cc′), 144.0 (1C, Cc), 147.9 (1C, Cg), 149.0 (1C, Cf), 156.1 (1C, Cf′) and 168.3 (1C, Ca).

Idrocilamide (Compound **T9**)



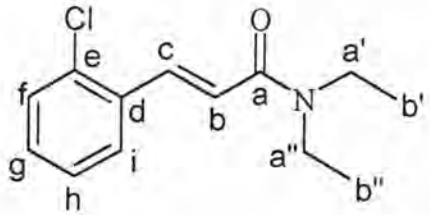
White needle crystal 0.19 g (33 %), m.p. 98-99 °C (MeOH/H_2O) (lit[53] 97 °C), R_f 0.64 (EtOAc). IR (KBr): 3644-3285, 3230, 3057, 2916, 1728, 1637, 1532, 1437 and 1346 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.22 (s (br), 1H, N*H*), 3.35-3.48 (m, 4H, alkyl *H*), 3.95 (s, 1H, O*H*), 6.72 (d, J = 16.16 Hz, 1H, CH=C*H*CO), 7.17 (d, J = 16.53 Hz, 1H, C*H*=CHCO and 7.32-7.76 (m, 5H, Ar*H*); ^{13}C-NMR (DMSO-d_6) δ (ppm): 46.0 (1C, Ca′), 64.5 (1C, Cb′), 120.6 (1C, Cb), 127.8 (2C, Ce and Ci), 128.7 (1C, Cg), 129.3 (2C, Cf and Ch), 135.4 (1C, Cd), 142.4 (1C, Cc) and 165.2 (1C, Ca).

Fagaramide (Compound **T10**)



White needle crystal 0.49 g (69 %), m.p. 119-120 °C (CH_2Cl_2/hexane) (lit[54] 119-120 °C), R_f 0.46 (50 % EtOAc/hexane). IR (NaCl plates): 3289, 3076, 2965, 1643, 1615, 1547, 1494, 1330 and 1243 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.93 (d, J = 6.67 Hz, 6H, C*H*$_3$), 1.57 (s, 1H, N*H*), 1.75-1.88 (m, 1H, C*H*$(CH_3)_2$), 3.19 (t, J = 6.24 Hz, 2H, NHC*H*$_2$), 5.97 (s, 2H, OC*H*$_2$O), 6.19 (d, J = 15.49 Hz, 1H, HC=C*H*CO), 6.77 (d, J = 7.61 Hz, 1H, *H*h), 6.96 (d, J = 7.53 Hz, 1H, *H*i), 6.99 (s, 1H, *H*e) and 7.51 (d, J = 15.56 Hz, 1H, C*H*=CHCO). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.2 (2C, Cc′ and Cd′), 28.6 (1C, Cb′), 47.1 (1C, Ca′), 101.4 (1C, O*C*H$_2$O), 106.3 (1C, Ce), 108.5 (1C, Ch), 118.8 (1C, Ci), 123.8 (1C, Cb), 129.3 (1C, Cd), 140.6 (1C, Cc), 148.2 (1C, Cg), 148.9 (1C, Cf) and 166.1 (1C, Ca).

2-Chloro-N,N-diethyl-cinnamamide (Compound **T11**)



Yellow liquid 0.83 g (70 %), R_f 0.41 (50 % EtOAc/hexane). IR (neat): 3061, 2979, 1639, 1601, 1564, 1465, 1364 and 1046 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.06 (t, J = 7.03 Hz, 3H, *H*b′), 1.13 (t, J = 6.97 Hz, 3H, *H*b″), 3.43 (q, J = 6.99 Hz, 2H, *H*a′), 3.54 (q, J = 6.93 Hz, 2H, *H*a″), 7.13 (d, J = 15.34 Hz, 1H, HC=C*H*CO), 7.35-7.52 (m, 4H, Ar*H*) and 7.79 (d, J = 15.32 Hz, 1H, C*H*=CHCO). ^{13}C-NMR (DMSO-d_6) δ (ppm): 18.3 (1C, Cb′), 20.4 (1C, b″), 45.6 (1C, Ca′), 46.7 (1C, Ca″), 126.9 (1C, Cb), 132.7 (1C, Ch), 133.4 (1C, Ci), 134.9 (1C, Cf), 136.0 (1C, Cg), 138.1 (1C, Ce), 138.5 (1C, Cd), 141.3 (1C, Cc) and 169.3 (1C, Ca).