Asian Journal of Chemistry; Vol. 23, No. 4 (2011), 1829-1832

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Novel and Improved Process for the Preparation of Citalopram

M. PULLA REDDY[1], A.K.S. BHUJANGA RAO[1], V. USHARANI[1,*] and P.K. DUBEY[2]

[1]Natco Research Center, Natco Pharma Ltd. Hyderabad-500 018, India
[2]Department of Chemistry, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500 085, India

*Corresponding author: E-mail: uvattikuti@yahoo.co.in

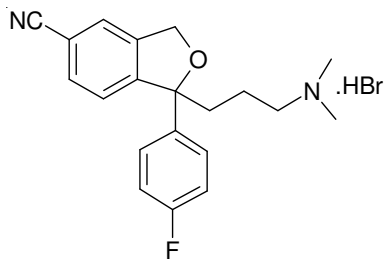
(*Received*: 10 September 2010; *Accepted*: 24 December 2010) AJC-9426

A novel process for the preparation of citalopram (**1**) has been described. The key intermediate 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2**) of citalopram is prepared using novel intermediates. The process involves simple acylation, hydrolysis and reduction, which can be easily adapted to commercial scale.

Key Words: Citalopram hydrobromide, Acylation, Hydrolysis and reduction.

INTRODUCTION

Citalopram hydrobromide (**1a**) is an isobenzofuran derivative, which is used for the treatment of depression. Citalopram hydrobromide was invented by Klaus *et al.*[1]. The chemical name of citalopram is 1-[3-(dimethylamino)propyl-1-(4-flurophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile. Structural formula is given below:

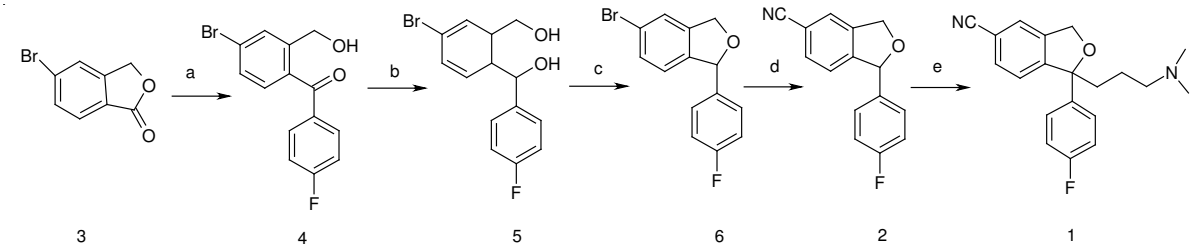


citalopram.Hydrobromide (1a)

A key intermediate (**2**) in the synthesis of citalopram (**1**) is reported by Klaus *et al.*[1,2]. The known process in the literature[1-3] for the preparation of citalopram using this key intermediate (**2**) is presented in **Scheme-I**.

According to the process presented in **Scheme-I**, 5-bromophthalide (**3**) is reacted with *p*-fluorophenyl magnesium bromide to get the benzophenone derivative (**4**) which is reduced with lithium aluminium hydride and the resulting dihydroxy compound (**5**) is cyclized using ortho phosphoric acid to get the phthalane derivative (**6**). The compound (**6**) is reacted with copper cyanide in DMF medium to get the cyano derivative **1**.

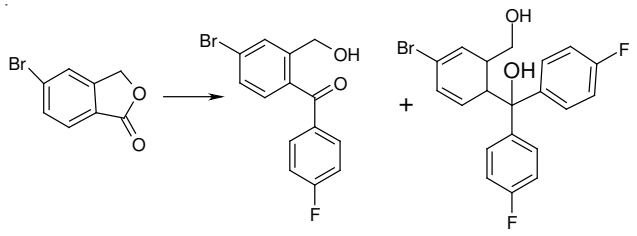
The main draw back in this process is Grignard reaction and the subsequent reduction with $LiAlH_4$ of the benzophenone intermediate. These two reactions could not be easily adapted for commercial scale due to the risk involved in handling of these reagents and low yield in Grignard reaction. Often Grignard reaction is also associated with impurities formation.



Reagents & Conditions: a) 4-fluorophenylmagnesium bromide, ether,THF, rt, 3h, H_2O. b)LAH, ether, reflux, 2h c)60% phosphoric acid, steam, 3h. d)CuCN, DMF, reflux, 4h. e)NaH, DMSO, 3-dimethylaminopropylchloride, rt,1h

Scheme-I

In this particular Grignard reaction, one major impurity (a) *bis*-Grignard product compound (**7**) is formed along with the required product (**5**), as depicted in **Scheme-II**.



3 5 7

Scheme-II

In addition, handling of lithium aluminium hydride on a commercial scale is always risky due to its highly pyrophoric nature and is very expensive. As both the steps involved in making the intermediate (**2**) are very expensive, the process is not an economically viable one.

Keeping in view of the obstacles in commercialization of the above-mentioned process for citalopram intermediate (**2**), we aimed to develop a simple and economical process for the preparation of compound (**2**).

EXPERIMENTAL

Reagent-grade chemicals and solvents were purchased from commercial source and used without further purification. 2-Bromo-4-chlorobenzoic acid was taken from in-house stock. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400-MHz spectrometer. The chemical shifts are reported in δ parts per million (ppm) relative to TMS. The IR spectra were recorded in liquid state as KBr cell and solid state as KBr dispersion using Perkin-Elmer FT-IR spectrometer. The mass spectra were recorded on Waters Quattro Micro LC/MS/MS. Melting points were determined using Mettler Toledo melting point apparatus and are uncorrected. All dry reactions were carried out under moisture-free conditions.

Preparation of 1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-carbonitrile (2)

Preparation of 2-bromo-4-chlorobenzoylchloride (8): Into a 500 mL, three-necked round bottom flask was charged with 2-bromo-4-chlorobenzoic acid (45.0 g, 0.2 mol) and 225 mL of toluene. Thionyl chloride (28.0 g, 0.24 mol) was added to the reaction mixture at room temperature. The reaction mixture was slowly heated to reflux temperature and maintained at reflux tempe-rature for 4 h. Toluene and excess thionyl chloride were distilled off from the reaction mixture and finally applied vacuum to get the required 2-bromo-4-chloro benzoyl chloride as a residue. This was directly used in next step.

Preparation of 2-bromo-4-chloro-4'-fluorobenzophenone (9): Into a clean and dry 500 mL three-necked, round bottom flask was added fluorobenzene (22.0 mL), anhydrous aluminium chloride (14 g, 0.15 mol). 2-Bromo-4-chloro benzoyl chloride (22.6 g, 0.09 mol) in fluorobenzene (22 mL) was added to the reaction mixture at 0-5 ºC. The reaction temperature was slowly raised to 50-60 ºC. Maintained the reaction at 50-60 ºC for 3 h. The reaction mixture was cooled to room temperature and poured into ice-water (200 mL) containing 20 mL of conc. HCl. The reaction mixture was extracted with methylene chloride and the organic layer washed with aqueous sodium bicarbonate. Drying and distillation of solvent gave crude product. The crude compound was distilled under vacuum (200 ºC at 3 mm Hg) to get the required 2-bromo-4-chloro-4'-fluoro benzophenone (20.0 g, 71.5 % yield). A small sample was recrystallized from isopropanol to get the crystalline compound. m.p. 80-81 ºC. IR (KBr, ν_{max}, cm^{-1}): 3081, 1673, 1597, 1582, 1504, 1283, 1243, 1149, 1180, 1044 and 929. ^{1}H NMR (400 MHz, $CDCl_3$); 7.77-7.87 (m, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.40-7.44 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H) and 7.09-7.21 (m, 2H). Mass: [312, M - 1].

Preparation of 2-cyano-4-chloro-4'-fluorobenzophenone (10): Into a 500 mL, three-necked round bottom flask was charged with 2-bromo-4-chloro-4'-fluorobenzophenone (39.0 g, 0.12 mol), copper(I) cyanide (11.7 g, 0.13 mol) and dry DMF (200 mL). The reaction mixture was slowly heated to 110 ºC and maintained at this temperature for 7 h. TLC of the reaction mixture showed the absence of starting bromo compound. The reaction mixture was cooled to room temperature and poured into 500 mL of water. The product was extracted into benzene and the solvent distilled off to get crude compound (35.0 g). The crude product thus obtained was recrystallized from 100 mL of isopropanol to get 25.0 g (78 % yield) of 2-cyano-4-chloro-4'-fluoro benzophenone, as an off white crystalline solid. m.p. 114-5 ºC. IR (KBr, ν_{max}, cm^{-1}): 3075, 2234, 1661, 1599, 1558, 1502, 1286, 1273, 1236, 1153, 932, 854, 842 and 774. ^{1}H NMR (400 MHz, $CDCl_3$); 7.82-7.85 (m, 3H), 7.59-7.70 (m, 2H) and 7.17-7.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 113.36, 115.60, 115.98, 131.14, 131.91, 132.43, 132.81, 132.90, 133.84, 137.77, 139.24, 164.82, 167.38, 191.02. Mass: [260, M + 1].

Preparation of 2-(4-fluorobenzoyl)-4-chlorobenzoic acid (11): Aqueous sulfuric acid (22.5 g, 75 % w/w) and 2-cyano-4-chloro-4'-fluorobenzophenone (10.0 g, 0.04 mol) were charged into a 100 mL, three necked round bottom flask and the contents were heated to 160 ºC and maintained at this temperature for 3 h. TLC of the reaction mixture showed the absence of starting material and reaction mixture was cooled to room temperature before pouring into ice-water (100 mL). Product was extracted into methylene chloride and the organic layer extracted with 30 mL of 10 % aqueous sodium hydroxide solution. The aqueous layer was treated with carbon and filtered. The filtrate was acidified with conc. HCl to get the precipitate. Product was isolated by filtration and dried at 60-70 ºC to get 9.7 g (90 % yield) of off white crystalline solid of 2-(4-fluorobenzoyl)-4-chlorobenzoic acid. A small sample was recrystallized from toluene to get white crystalline solid. m.p. 144-146 ºC. IR (KBr, ν_{max}, cm^{-1}): 3288, 3114, 1721, 1660, 1598, 1564, 1505, 1288, 1262, 1230, 1199, 1152, 1109, 936, 852 and 763. ^{1}H NMR (400 MHz, $CDCl_3$); 8.67 (s, 1H, -COOH), 8.06 (d, *J* = 1.6 Hz, 1H, aromatic), 7.71-7.74 (m, 2H, aromatic), 7.63-7.66 (m, 1H, aromatic), 7.30-7.32 (d, *J* = 8.0 Hz, 1H, aromatic) and 7.08-7.12 (m, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): 115.63, 115.85, 128.89, 129.67, 130.84, 132.00, 133.02, 133.12, 135.86, 140.15, 168.46, 194.79. Mass: [277, M - 1].

Preparation of methyl-2-(4-fluorobenzoyl)-4-chlorobenzoate (12): Into a 250 mL, three-necked, round bottom flask was charged with 100 mL of dry benzene, 10 g (0.036 mol) of 2-(4-fluorobenzoyl)-4-chlorobenzoic acid and 7.0 mL of thionyl chloride. The reaction mixture was heated to reflux temperature and maintained for 3 h. Excess thionyl chloride and benzene were removed from the reaction mass under vacuum and to the crude compound was added 30 mL of methanol and stirred for 2 h at room temperature. Methanol was distilled off from the reaction mixture under vacuum and the residue was recrystallized from ethyl acetate-hexane to get 9.0 g (85.6 % yield) of white crystalline solid, methyl-2-(4-fluorobenzoyl)-4-chlorobenzoate. m.p. 78-80 ºC. IR (KBr, ν_{max}, cm^{-1}): 3074, 2956, 1724, 1671, 1599, 1298, 1147, 931, 823 and 756. ^1H NMR (200 MHz, $CDCl_3$); 8.03 (d, *J* = 2.0 Hz, 1H aromatic), 7.74-7.78 (m, 2H, aromatic), 7.61-7.63 (dd, *J* = 2.0 Hz, 6.4 Hz, 1H, aromatic), 7.33-7.35 (d, *J* = 8.0 Hz, aromatic 1H), 7.09-7.13 (m, 2H, aromatic) and 3.67 (s, 3H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 52.45, 115.67, 128.96, 130.09, 130.65, 131.66, 131.76, 132.37, 133.22, 135.76, 139.52, 164.37, 164.97, 166.91, 194.27; mass: [293, M + 1].

Preparation of 1-(4-chloro-2-hydroxymethylphenyl)-1-(4-fluorophenyl)methanol (13): Into a 250 mL, three-necked, round bottom flask was charged with methyl-2-(4-fluorobenzoyl)-4-chlorobenzoate (5.0 g, 0.017 mol), *t*-butanol (50 mL) and sodium borohydride (3.0 g, 0.08 mol). The reaction mixture was heated to reflux temperature and methanol (10.0 mL) was added in 4 lots over a period of 8 h. After maintaining for 2 h at reflux temperature after the last lot addition, reaction was found to be completed by TLC. The reaction mixture was quenched by adding acetic acid (4.0 mL) and the solvents distilled off under vacuum. To the residue, water (50.0 mL) was added and the product extracted into methylene chloride (3 × 50 mL). Methylene chloride layer dried over sodium sulfate and the solvent distilled off to get 4.0 g (88 % yield) of crude dihydroxy compound, 1-(4-chloro-2-hydroxymethylphenyl)-1-(4-fluorophenyl)methanol as syrup. This was directly used in next step. ^1H NMR (400 MHZ, $CDCl_3$); 6.98-7.28 (m, 7H, aromatic), 5.88 (s, 1H, -CHOH), 4.34-4.53 (m, 2H, $-CH_2OH$) and 3.60 (br, s, 2H, -CHOH-, CH_2OH). ^{13}C NMR (400 MHz, $CDCl_3$): 62.3, 74.0, 116.3, 127.4, 128.5, 129.6, 130.3, 132.2, 139.2, 142.6, 160; mass: [268.5, M + 2].

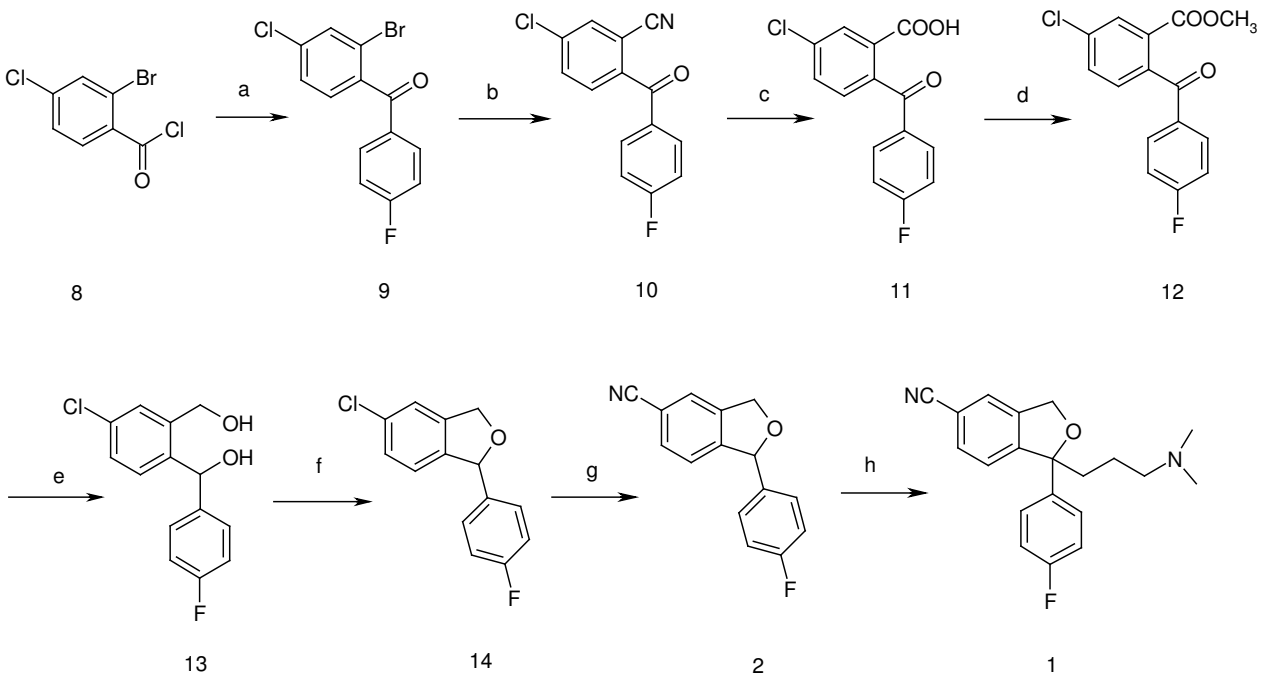
Preparation of 1-(4-fluorophenyl)-1,3-dihydro-5-chloro-isobenzofuran (14): Into a 250 mL, three-necked, round bottom flask was charged with benzene (25 mL), 2.4 g (0.01 mol) of 1-(4-chloro-2-hydroxymethylphenyl)-1-(4-fluorophenyl)methanol and *p*-toluenesulfonic acid (0.63 g, 0.004 mol). The reaction mixture was heated to reflux under azeotropic conditions using Dean Stark apparatus to remove water formed in the reaction. After refluxing for 2 h reaction was found to be completed by TLC. The reaction mixture was cooled to room temperature. Water (100 mL) was added to the reaction mixture and the product extracted into benzene. Benzene layer was washed with 5 % sodium bicarbonate, water (50 mL) and dried over sodium sulfate. Solvent was removed on rotavapour to get 2.0 g (89 % yield) of 1-(4-fluorophenyl)-1,3-dihydro-5-chloro-isobenzofuran as oil. Purity by HPLC was found to be > 96 %. Chromatographic purification over a column of silica gel gave the title compound as pure. IR (KBr, ν_{max}, neat, cm^{-1}): 3072, 2923, 2855, 1605, 1509, 1476, 1419, 1341, 1225, 1156, 1039, 1015, 828, 813, 782 and 699. ^1H NMR (400 MHz, $CDCl_3$): 7.20-7.29 (m, 4H, aromatic), 7.01-7.06 (m, 2H, aromatic), 6. 90-6.92 (d, *J* = 8 Hz, 1H, aromatic), 6.01 (s, 1H, -CHO-) and 5.13-5.29 (m, 2H, $-CH_2O-$). ^{13}C NMR (100 MHz, $CDCl_3$): 72.59, 85.13, 115.40, 115.6, 121.33, 123.35, 127.85, 128.74, 133.72, 137.33, 140.36, 141.16, 161.43, 163.89; mass: [248, M^+].

Preparation of 1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-carbonitrile (2): Into a 250 mL, three-necked round bottom flask was charged with nickel(II) chloride (0.031 g, 0.003 mol), triphenyl phosphine (0.25 g, 0.0012 mol) and acetonitrile (25 mL). The reaction mixture was heated to reflux temperature and treated with 0.2 g of zinc powder. After stirring for 0.5 h at room temperature, a solution of 1-(4-fluorophenyl)-1,3-dihydro-5-chloro- isobenzofuran (1.5 g, 0.006 mol) in acetonitrile (25 mL) was added to the reaction mixture. After stirring for 0.5 h at room temperature, potassium cyanide (0.22 g, 0.003 mol) was added to the reaction mixture and heated the contents to reflux temperature. After maintaining for 8 h at reflux, the reaction mixture was diluted with diisopropyl ether (200 mL) and filtered on hyflow bed. The filtrate was distilled off on rotavapour and the residue chromatographed over a silica gel column to get (86 % yield) of 1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-carbonitrile as off white crystalline solid. m.p. 94-95 ºC. HPLC purity of this material was found to be 95 %. IR (KBr, ν_{max}, cm^{-1}): 3051, 2918, 2809, 2214 1625, 1515, 1480, 1423, 1351, 1161, 1045, 840 and 715. ^1H NMR (400 MHz, $CDCl_3$): 7.54-7.60 (m, 2H, aromatic), 7.25-7.29 (m, 2H, aromatic), 7.04-7.11 (m, 3H, aromatic), 6.16 (s, 1H, -CHO-) and 5.19-5.36 (m, 2H, $-CH_2O-$). ^{13}C NMR (100 MHz, $CDCl_3$): 72.41, 85.19, 111.65, 115.5, 118.55, 123.09, 124.92, 128.63, 131.71, 136.38, 140.25, 146.82, 161.38, 163.83; mass: [239, M + 1].

Preparation of 1-[3-(dimethylamino)propyl}-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrle (1): Into a 250 mL three-necked round bottom flask was charged with DMSO (90 mL), NaH (2.1 g, 60 % dispersion in paraffin oil) under nitrogen atmosphere. A solution of 1-(4-fluorophenyl) -1,3-dihydroisobenzofuran-5-carbonitrile (9.6 g) in DMSO (15 mL) was added to the reaction mixture. After stirring for 10 min at room temperature, a solution of 3-dimethylaminopropyl chloride (5.3 g) in DMSO (2.5 mL) was added to the reaction mixture and the contents were heated to 40 ºC for 50 min. The reaction mixture was poured into ice cold water, extracted with ether (2 × 20 mL). The ether layer was extracted with 10 % aqueous acetic acid. The aqueous acetic acid layer was neutralized with aq. Ammonia and the liberated citalopram base is extracted into isopropyl ether. The extracts were dried and evaporated under vacuum to get 12.6 g of 1-[3-(dimethylamino)-propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrle as an oily residue and is crystallized from isopropyl ether to get crystalline citalopram base (60 % yield).

RESULTS AND DISCUSSION

The present process provides a novel and improved process for the preparation of the compound (**2**) (**Scheme-III**) which



Reagents & Conditions: (a) fluorobenzene, $AlCl_3$, 50-60 ºC, 3 h; (b) CuCN, DMF, 110 ºC, 7 h, (c) H_2SO_4, reflux, 3 h, (d) $SOCl_2$, benzene, MeOH, 2 h; (e) $NaBH_4$, *t*-butanol, reflux, 2 h, (f) PTs-acid, toluene, 2 h, (g) nickel(II)chloride, KCN, triphenylphosphine, Zn, acetonitrile, reflux, 8 h (h), NaH, DMSO, 3-dimethylaminopropylchloride, room temperature, 1 h

Scheme-III

comprises: reacting 2-bromo-4-chlorobenzoyl chloride (**8**) with fluorobenzene in the presence of aluminum chloride to get the benzophenone derivative (**9**), cyanating the resulting benzophenone derivative (**9**) with copper(I) cyanide in a polar solvent medium to get the cyano derivative of (**10**). Hydrolyzing the cyano derivative of **10** to get the benzoic acid derivative of (**11**), esterifying (**11**) with methanol yield compound (**12**), reducing the ester (**12**) with sodium borohydride to get the dihydroxy compound (**13**). Cyclising the diol compound (**14**) in the presence of acid catalyst to get the phthalane derivative (**14**). Cyanating the chloro group present in compound (**14**) to the cyano compound (**2**) can be achieved by conventional method[4].

The present process provides novel compounds **9**, **10**, **11**, **12**, **13**, **14** and process for the same. The present process is described in detail in the experimental section.

Conclusion

The process established in present studies is economical and simple for the preparation of compound (**2**), a key intermediate used in the preparation of citalopram. The process avoids usage of unstable Grignard reagent, pyrophoric and expensive lithium aluminum hydride.

ACKNOWLEDGEMENTS

The authors thank the Management of Natco Pharma Ltd. for supporting this work. The technical service from the analytical division of Natco Research Centre is gratefully acknowledged.

REFERENCES

1. K.P. Boegesoe and J. Perregaard, Pharmaceutically useful (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrosobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof, US Patent 4943590 (1990).
2. K.P. Boegesoe and D.K. Lyngby, Anti-depressive substituted 1-dimethyl-aminopropyl-1-phenyl phthalans, US Patent 4136193 (1979).
3. A.J. Bigler, K.P. Bsgess, A. Toft and V. Hansen, *Eur. J. Med. Chem*., **12**, 289 (1977).
4. H. Petersen and M.H. Rock, PCT Int. Appl., WO 0011926 (2000).