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A Simple and Efficient Procedure for Synthesis of Agomelatine

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A simple and efficient process for the large scale preparation of agomelatine, an antidepressant drug is described. Agomelatine was synthesized from 7-methoxy-1-tetralone in five steps. The route reported employs readily, commercially viable starting materials, reagents and potentially be utilized for the process of synthesis of agomelatine.

Keywords: Knoevenagel condensation, Decarboxylation, Esterification, Aromatization, Reductive acetylation, Agomelatine.

INTRODUCTION

Depression is a common illness worldwide, with an estimated 350 million people affected. It is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. By 2020, according to the WHO report, depression will be the second disease next to ischemic heart disease and become one of the major contributors to the global disease burden [1,2]. The current antidepressant drugs in clinic can generally be classified into several categories, which include tricyclic antidepressant, monoamine oxidase inhibitors, selective serotonin, serotonin norepinephrine, noradrenaline and dopamine-noradrenaline reuptake inhibitors (Fig. 1) [3-5]. Agomelatine is a melatonin analog represents a new class of antidepressants. It is a potent melatonergic agonist (MT1 and MT2) and also has 5-hydrotryptamine 2C (5-HT$_{2C}$) antagonist properties. In particular, a great deal of pre-clinical and clinical data indicated that agomelatine has a comparable antidepressant efficacy to other well as established antidepressants [6-10]. Furthermore, there are no increases in specific side effects such as sexual disfunction and body weight gains, which are common with some classes of antidepressants [11-13]. Agomelatine as the first known antidepressant that works *via* a non-monoaminergic mechanism of action was approved for the treatment of major depression in Europe in 2009.

Agomelatine was first synthesized by Yous *et al.* [14] in a multistep synthetic route starting from (7-methoxy-1-naphthyl) acetic acid. The majority of the known literature procedures involve the preparation of 7-methoxy-1-naphthylacetonitrile synthesis of agomelatine from naphthyl glyoxylic acid as an alternate starting material have been reported as a feasible approach [15]. Before attempting modifications to improve the yields and substrate scope in the process development of agomelatine [16], recently facile route for agomelatine starting from 8-aminonaphthalene-2-ol by sequential diazotization, iodination, formylation, Henry reaction, further reduction of the double bond and finally *N*-acetylation key chemistry issues related to selective reduction of acid derivatives and nitriles with excess reducing reagent under high pressure conditions need to be addressed. Accordingly, the development of new and simple routes utilizing alternate starting materials is necessary. Several modifications of the original procedure, mostly aiming at industrial scale synthesis, have been published later in the patent literature [17].

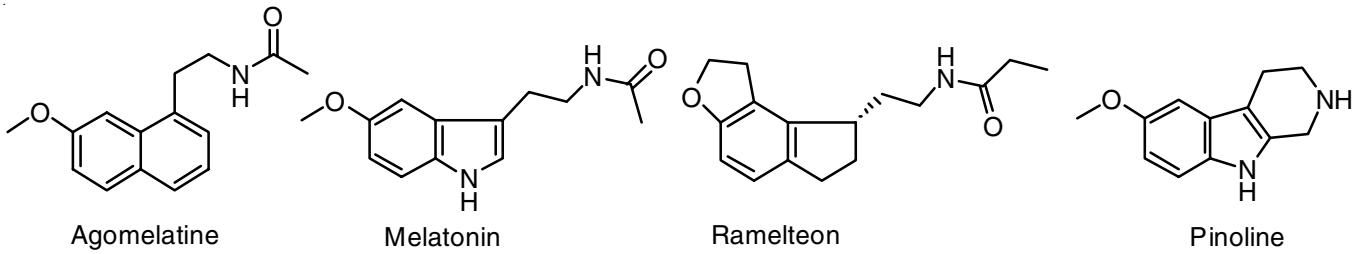


Fig. 1. Chemical structures of representative antidepressants

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without further purification. The reactions were monitored by TLC plates Merck silica gel 60, F254 and visualization with UV light (254 and 365 nm). ^{1}H NMR spectra were recorded on Bruker-400 spectrometer in $CDCl_3$ using TMS as internal reference. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer using KBr discs. The Mass spectrum (70 eV) was recorded on an HP 5989 A LC-MS spectrometer. Melting points were recorded on Buchi R-535 apparatus and are uncorrected.

Step-1: Synthesis of [(*E*)-2-cyano-2-(2,3-dihydro-6-methoxy naphthalen-4(1*H*)-ylidene) acetic acid] (2a): This Knoevenagel reaction was initiated. It was noticed that less product formation and incompleteness of reaction even after heating reaction at 100-110 °C for 24 h. Better conversion and product formation observed in using ammonium acetate and acetic acid as dehydrating agent. Reactions were screened using different bases and solvents, KO^{t}Bu, NaH, TEA, piperidine and NaOMe without encouraging results as shown in the below table (entry 1-10, Table-1).

A mixture of the 7-methoxy-1-tetralone (10.0 g, 56.7 mmol), ethyl cyanoacetate (7.7 g, 68.1 mmol), then added ammonium acetate (1.09 g, 14.1 mmol) followed by added glacial acetic acid (5 mL, 2.0 vol) in toluene (100 mL, 10 vol) the mixture warmed to reflux with a Dien stark water trap for 24 h. The reaction mixture was cooled and diluted with toluene (100 mL, 10 vol) washed with water (2 × 100 mL) and the washed aqeous layer were extracted with toluene (2 × 100 mL), the combined organic layer was over under Na_2SO_4, the solvent was evoparated and the resulting oil distilled under vacuum to get a clear oil consisting of a mixture of **2** and its geometrical isomers (12.67 g, 82.3 % yield). b.p.: 164-168 °C (0.3 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 2.0 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.99 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 4.33 (q, 7.2 Hz, 2H), 3.85 (s, 3H), 3.25 (t, *J* = 6.4 Hz, 2H), 2.7 (t, *J* = 6.0 Hz, 2H), 1.83 (qt, *J* = 6.0 Hz, 2H), 1.38 (*J* = 7.2 Hz, 3H); EI-MS *m/z* (%): 244 (M + 1, 26), 177 (98), 164 (20).

Step-2a: 2-(1,2-Dihydro-6-methoxynaphthalen-4-yl)acetic acid (3): To a solution of step-1 (mixture of exo and endo) (6 g, 22.1 mmol), in ethanol (60.0 mL, 10 vol) at 25-30 °C, was added 50 % NaOH (8.84 g, 221.1 mmol) solution drop wise in to reaction mass at 0-5 °C. After addition, the mixture was stirred for overnight at 25-30 °C. Reaction mass was concentrated completely under reduced pressure and obtained crude was purified by column chromatography on 100-200 silica gel by eluting 50 % ethyl acetate in *n*-hexane, to get off-white solid (3.45 g, 71.6 % yield).

IR (KBr, ν_{max}, cm^{-1}): 3017, 2927, 2842, 2731, 2642, 2533, 2362, 2338, 2082, 1876, 1712, 1492, 1461, 1698, 1566, 1407, 1444, 1298, 1373, 1335, 1251, 1220, 1197, 1170, 1080, 1042, 392, 889, 812, 754, 731, 656; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.8 (dd, J_1 = 2.8 Hz, J_2 = 8.0 Hz, 1H), 6.02 (t, *J* = 4.4 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.41 (s, 1H), 3.40 (s, 1H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.23-2.32 (m, 2H), 1.24 (t, *J* = 7.4 Hz, 3H); EI-MS *m/z* (272.21 %, M + 1).

Step-2b: 2-(2,3-Dihydro-6-methoxynaphthalen-4(1H)-ylidene)malononitrile: To a solution of 7-methoxy-3,4-dihydro-naphthalen-1(2H)-one (10 g, 56.7 mmol,) and malononitrile (4.07 mL, 64.7 mmol) in toluene (40.0 mL, 4 vol) was added ammonium acetate (0.938 g, 13.1 mmol) and acetic acid (3.90 mL, 68.1 mmol). The mixture was refluxed vigorously for 17 h and water was removed by using a Dien stark trap under the reflux condenser. The resulting mixture was concentrated and purified by silica gel column chromatography to give (9.32 g, 73.2 % yield).

IR (KBr, ν_{max}, cm^{-1}): 2939, 2838, 2216, 1724, 1608, 1493, 1251, 1223, 1032; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.84 (s, 3H), 3.00 (t, *J* = 6.5 Hz, 2H), 2.83 (t, *J* = 6.2 Hz, 2H), 1.99-1.96 (m, 2H), ^{13}C NMR (75MHz, $CDCl_3$): δ 172.6, 157.9, 134.5, 130.5, 130.4, 121.9, 114.2, 110.9, 79.6, 55.7, 33.1, 28.9, 22.5; EI-MS *m/z*: 225.25 (M + H).

Step-3: Ethyl 2-(1,2-dihydro-6-methoxynaphthalen-4-yl)acetate (4): 2-(1,2-Dihydro-6-methoxynaphthalen-4-yl) acetic acid (3 g, 13.7 mmol) was dissolved in ethanol (15 mL, 5 vol) and H_2SO_4 (0.134 g, 1.3 mmol) was added drop wise to the reaction mass, stir for 12 h at 100-102 °C. Ethanol was evaporated under reduced pressure, obtained mass (crude) was dissolved in ethyl acetate (30 mL, 10 vol) washed successively with water (15 mL, 3 × 5 vol) and followed by brine (15 mL, 3 × 5 vol), dried over with Na_2SO_4. The solvent was evaporated under reduced pressure to afford brown coloured compound, crude was purified by column chromatography on 100-200 silica gel by eluting with 50 % ethyl acetate in *n*-hexane, obtained colourless oily liquid (2.82 g, 83.4 % yield).

b.p.: 60-90 °C; IR (KBr, ν_{max}, cm^{-1}): 2980, 28336, 2833, 2360, 1996, 1736, 1605, 1572, 1492, 1278, 1155, 1043; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.69 (dd, J_1 = 2.4 Hz, J_2 = 8.0, 1H), 6.01 (t,

TABLE-1
DIFFERENT BASES AND SOLVENT SCREENING

S. No.	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	TEA (2.0 eq)	Toluene (10 vol)	100-110	24	No conversion
2	NaH (1.5 eq)	THF (10 vol)	60-65	24	12.0
3	Piperidine (1.2 eq)	Acetic acid (1 vol)	110-115	24	24.5
4	Piperidine (1.2 eq)	Ethanol (10 vol)	80-85	24	No conversion
5	NaOMe (1.5 eq)	THF (10 vol)	60-65	24	No conversion
6	KO^{t}Bu (1.5 eq)	THF (10 vol)	60-65	24	5.0
7	KO^{t}Bu (1.5 eq)	Toluene (10 vol)	100-110	24	No conversion
8	Benzyl amine (0.3 eq)	Toluene (10 vol)	100-110	24	25.2
9	NH_4OAc (2 eq)	Toluene (10 vol)	100-110	24	56.8
10	NH_4OAc (0.25 eq)	Toluene (10 vol)	100-110	24	82.3

4.4 Hz, 1H), 4.1 (q, *J* = 14 Hz, 2H), 3.78 (s, 3H), 3.40 (s, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.32-2.21 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); EI-MS, *m/z* (%): 247 (M + 1, 100), 177 (17), 132 (46), 118 (40).

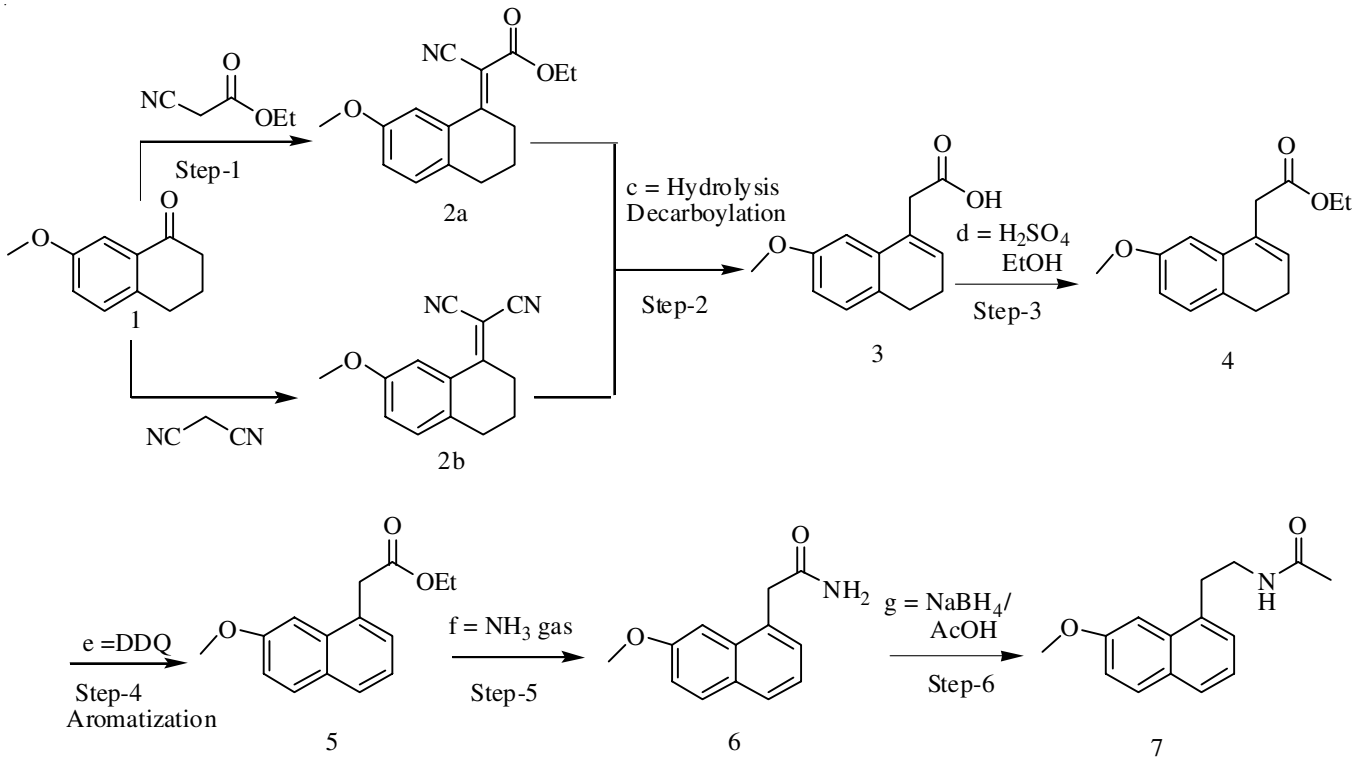
Step-4: 1-(7-Methoxynaphthalen-1-yl)butan-2-one (5): To a solution of ethyl-2-(2-methoxynaphthalen-8-yl) acetate (3 g, 12.1 mmol) in anhydrous dichloromethane (45 mL, 15 vol) and added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 4.15 g, 18.2 mmol) at 15 °C. After addition, the mixture was stirred at 25-30 °C for 12 h. The mixture was filtered and the precipitate solid was washed with CH_2Cl_2 (30 mL, 10 vol), the combined organic phase was washed successively with saturated $NaHCO_3$ solution (15 mL, 3 × 5 vol), water (15 mL, 3 × 5 vol) and followed by brine (15 mL, 3 × 5 vol), organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to afford brown coloured compound, crude was purified by column chromatography on 100-200 silica gel using 20 % ethyl acetate in *n*-hexane, to obtain colourless oil (2.59 g, 87.3 % yield).

IR (KBr, ν_{max}, cm^{-1}): 2981, 2937, 2834, 1733, 1627, 1601, 1511, 1469, 1450, 1260, 1213, 1159, 133, 832; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H) 7.38 (d, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.16 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.0 (s, 2H), 3.93 (s, 3H), 1.2 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100Hz, DMSO-d_6): δ 171.1, 157.46, 132.99, 130.01, 129.79, 128.74, 128.37, 127.25, 123.02, 117.88, 117.88, 102.76, 60.23, 54.94, 14.0; EI-MS, *m/z* (%)**:** 245 (M + 1, 100), 171 (17).

Step-5: 2-(2-Methoxynaphthalen-8-yl)acetamide (6): Ethyl 2-(2-methoxy naphthalen-8-yl)acetate (2.0 g, 8.1 mmol) was dissolved in ethanol (40 mL, 20 vol) and cooled to -78 to -74 °C, ammonia gas was purged to reaction mass for 30 min at -78 to -74 °C, after purging slowly allowed to 25-30 °C and stir for 2 h. The reaction mass stored for 48 h at 25-30 °C, then mass was concentrated completely under reduced pressure to obtained crude material which was triturated in toluene (20 mL, 10 vol) for 1 h and filtered the solid, then washed with toluene (10 mL, 5 vol) suck dried the compound to get pale yellow coloured solid (1. 5 g, 87.6 % yield).

IR (KBr, ν_{max}, cm^{-1}): 3395, 3203, 2939, 2831, 1643, 1401, 1259, 1203, 1024, 827 ; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.61 (brs, 1H), 7.4 (t, *J* = 6.8 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.19 (dd, J_1 = 2.0 Hz, J_2 = 9.2 Hz, 1H), 7.02 (brs, 1H), 3.87 (s, 3H), 3.81 (s, 2H); ^{13}C NMR (100Hz, DMSO-d_6): δ 172.14, 157.22, 133.14, 131.67, 129.87, 128.65, 128.20, 126.62, 123.01, 117.58, 103.37, 55.11; EI-MS *m/z* (%): 216 (M + 1, 84), 199 (27), 171 (100).

Step-6: *N*-[2-(2-Methoxynaphthalen-8-yl)ethyl]acetamide (agomelaine): To a solution of 2-(2-methoxynaphthalen-8-yl)acetamide (1.2 g, 5.57 mmol) in 1,4-dioxane (24 mL, 20 vol), cooled to 5-10 °C, added acetic acid lot-I (2.0 g, 29.4 mmol) drop wise to reaction mass and added lot wise $NaBH_4$ (1.14 g, 29.4 mmol) at 5-10 °C with for the period of 30 min. The reaction mass allowed to room temperature 25-30 °C and then, warm to 95-98 °C, maintained for 5-6 h at same temperature. The reaction mixtre was cooled to 30-32 °C and added acetic acid lot-II drop wise (highly exothermic) at same temperature, after added again warm to 95-98 °C and maintained for 16 h at 95-98 °C. The starting material was disappeared in TLC. 1,4-Dioxane was removed from reaction mass under pressure, obtained mass was dissloved in ethyl acetate (24 mL, 20 vol) washed with water (12 mL, 10 vol) and followed by brine (12 mL, 10 vol), organic layer was dried Na_2SO_4, concentrated solvent completly under reduced pressure, obtained crude was purified by column chromatography on 100-200 silica gel by



Scheme-I

using 20 % ethyl acetate in *n*-hexane to get desired compound (1.03 g, 76.3 % yield).

m.p.: 107-108 °C; IR (KBr, ν_{max}, cm^{-1}): 3243, 3073, 2965, 2941, 1640, 1543, 1434, 1412, 1252, 1202, 1183, 1030, 867; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 9.2 Hz, 1H), 7.69 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 5. 57 (br, 1H), 3.99 (s, 3H), 3.62 (q, J = 13.Hz, 2H), 3.25 (t, J = 7.2 Hz, 2H), 1.95 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): δ 171.30, 158.02, 133.24, 133.12, 130.28, 129.29, 127.15, 123.13, 118.30, 102.35, 55.56, 40.48, 32.96, 22.73; EI-MS *m/z* (%): 244.1 (M + 1, 100).

RESULTS AND DISCUSSION

As a part of our ongoing program on the identification of scalable and cost-effective processes for active pharmaceutical ingredients, we were interested in identifying readily available chemicals which would serve as the starting material for the synthesis. In this regard, we report a route for agomelatine, as the key intermediate which is derived from 7-methoxy-1-tetralone, as the starting material (**Scheme-I**). Knoevenagel condensation, cyano conversion of acid followed by decarboxylation, esterification, aromatization, amide formation and the reaction sequence includes a novel one pot conversion of reductive acetylation by using low cost chemicals and reagents.

Conclusion

In conclusion, a simple and scalable process for the high yielding synthesis of agomelatine has been discussed. The important features of this procedure are control of the impurities in Knoevenagel condensation, minimization of impurities in the hydrolysis step and *in situ* acetylation leading to isolation of agomelatine in good yields.

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