



Synthesis of 1-[3-(Cyclopentyloxy)-4-methoxyphenyl]cyclopentanol as Potential Phosphodiesterase-4 Inhibitor

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The enzyme phosphodiesterase-4 (PDE4) plays a key role in many physiological or pathological processes in mammalian organs, where its inhibition increases cyclic adenosine monophosphate (cAMP) causing benefits in many diseases or conditions. The aim of this study is to synthesize 1-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclopentanol (**6**) as potential phosphodiesterase-4 inhibitor. Starting from 2-methoxy phenol (**1**), 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene (**5**) was synthesized in good yields. 1-[3-(Cyclopentyloxy)-4-methoxyphenyl]cyclopentanol (**6**) was prepared from **5** using two different methods.

Key Words: Phosphodiesterase, Cyclic adenosine monophosphate, Mammalian organs.

INTRODUCTION

Cyclic nucleotide phosphodiesterases (PDEs), are the enzymes responsible for the hydrolysis of second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and are classified into at least 11 major families regarding their substrate specificity, sequence similarity and sensitivity to inhibitory drugs^{1,2}. Inhibitors of phosphodiesterases (PDEIs) have demonstrated various pharmacological properties including cardiogenic, vasodilator, smooth muscle relaxant, antidepressant, antithrombotic, bronchodilator, antiinflammatory, antioxidant³⁻⁷, increasing salivary flow rate and secretion of epidermal growth factor⁸ and enhancer of cognitive function such as learning and memory based on type of PDE inhibiting⁹⁻¹². PDE-4 is a cAMP-specific enzyme, separated in four human isoforms (PDE-4 A, B, C and D)¹³ and represents a capable potential molecular target for the development of new antiasthmatic, antiinflammatory, autoimmune diseases and various gastrointestinal and neurological diseases^{1,14-18}. Moreover than synthetic PDE-4 inhibitors, several natural ones derived from medicinal plants have been distinguished such as 3-O-methylquercetin from *Rhamnus nakaharai* and naringenin from citrus fruits¹⁹. Unfortunately, the development of PDE-4 inhibitors, such as rolipram and structurally-related compounds has been so far limited by several side effects, such as nausea, emesis, gastric acid secretion or central nervous system activation^{1,17,18,20}. Thus, the design of novel, potent and

selective second generation of PDE-4 inhibitors with reduced side effects represent a critical need in the pharmaceutical industry^{15,18,21}. One way to increase both the potency and the selectivity of PDE-4 inhibitors and thus improving the therapeutic index, is to develop new compounds featuring original chemical structures, different than those of the known PDE-4 inhibitors²², if the side effects are not mechanism-based.

The present study extends our work on addition reaction of organolithium (*n*-butyllithium) with a ketone (cyclopentanone). Present study describes the preparation of 1-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclopentanol (**6**) as potential phosphodiesterase-4 inhibitor from two methods (A, B).

EXPERIMENTAL

All chemicals and reagents were obtained from Merck Chemical Company (Darmstadt, Germany). Melting points were determined using Kofler hot stage apparatus and are uncorrected. The IR spectra were taken using a Shimadzu 470 spectrophotometer (potassium bromide disks). The mass spectra were run on a GC-Mass model: 5973 network mass selective detector, Gc 6890 Agilent. ¹H NMR spectra were recorded using a Varian 400 spectrometer and chemical shifts are expressed as δ (ppm) with tetramethyl silane (TMS) as internal standard. The purity of the synthesized compounds was confirmed by thin layer chromatography (TLC) using various solvents of different polarities. Merck silica gel 60 F₂₅₄ plates

were applied for analytical TLC. Column chromatography was performed on Merck silica gel (70-230 mesh) for purification of compounds.

Preparation of 2-methoxyphenyl acetate²³ (2): To a mixture of 2-methoxy phenol (**1**) (1.24 g, 10 mmol) and acetic anhydride (20 mL) was added two drops of conc. H₂SO₄ with vigorous stirring. The reaction mixture was heated at 100 °C for 7 h and then allowed to cool to 25 °C and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (3 × 15 mL). The combined ethereal extracts were washed with water (15 mL) followed by brine (15 mL) and concentrated under reduced pressure to give crude product, which was further purified by vacuum distillation to afford acetate **2** (1.60 g). Yield: 96 %; colourless liquid; ¹H NMR (400 MHz, CDCl₃): δ 2.3 (s, 3H), 3.8 (s, 3H), 6.91-7.25 (m, 4H); MS (m/z, % rel intensity): (M⁺ 166), 124, 109, 95, 91, 81, 77, 64; IR (KBr, ν_{max}, cm⁻¹): 3070, 3010, 2944, 2841, 1770.

Preparation of 5-bromo-2-methoxyphenyl acetate²³ (3): A solution of 2-methoxyphenyl acetate (**2**) (1.29 g, 7.81 mmol) and NBS (1.41 g, 8.6 mmol) in dry CH₃CN (18 mL) was heated at 60 °C under argon atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with a saturated solution of sodium sulfite (15 mL), water (15 mL) followed by brine (15 mL) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford pure 1.7 g of pale yellow colour gum, bromoester **3**. Yield: 95 %; pale yellow colour gum; ¹H NMR (400 MHz, CDCl₃): δ 2.3 (s, 3H), 3.8 (s, 3H), 6.85 (d, *J* = 9.2 Hz, 1H), 7.2 (d, *J* = 2.4 Hz, 1H), 7.32-7.34 (d, *J* = 2.4 Hz, 1H); MS (m/z, % rel intensity): (M⁺ 244, 11), 204 (100), 187 (55), 173(3), 161 (11), 143 (3), 123 (5), 108 (5), 94 (7), 79 (20), 63 (7), 43 (12); IR (KBr, ν_{max}, cm⁻¹): 3107, 3015, 2971, 2941, 2904, 1764.

Preparation of 5-bromo-2-methoxyphenol²³ (4): A 25 mL flask was charged with ester **3** (1.83 g, 7.5 mmol), 10 % NaHCO₃ (1.25 g, 11 mmol) and MeOH (7 mL) under argon atmosphere. The solution was allowed to reflux for 3 h. Then EtOAc (25 mL) was added to reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (15 mL) followed by brine (15 mL) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (8:2) as eluent to phenol **4** (1.40 g). Yield: 93 %; yellow solid; m.p. 102-105 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.86 (s, 3H), 6.70 (d, *J* = 8 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 7.06 (d, *J* = 1.6 Hz, 1H); MS (m/z, % rel intensity): (M⁺ 204, 100), 202 (100), 189 (89), 160 (39), 131 (5), 107 (8), 91 (4), 79 (11), 62 (11), 51(22); IR (KBr, ν_{max}, cm⁻¹): 3478, 3407, 2971, 2938.

Preparation of 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene²³ (5): To a mixture of bromo phenol **4** (1.02 g, 5 mmol) and K₂CO₃ (0.6 g, 4.3 mmol) in DMF (20 mL) was added cyclopentyl bromide through a syringe at 50 °C with vigorous stirring for 12 h. After completion of the reaction

(monitored by TLC), the reaction mixture was allowed to cool to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with water (15 mL) followed by brine (15 mL) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to afford bromo ether **5** (1.20 g). Yield: 88 %; yellowish liquid; ¹H NMR (400 MHz, CDCl₃): 1.6-2.0 (m, 8H), 3.8 (s, 3H), 4.73 (m, 1H), 6.71 (d, *J* = 8 Hz, 1H), 6.97 (s, 1H), 6.98-7.1 (m, 1H); MS (m/z, % rel intensity): (M⁺ 272, 17), 270 (17), 202 (100), 187 (44), 173 (4), 159 (8), 142 (4), 123 (5), 108 (5), 94 (7), 79 (10), 63 (7); IR (KBr, ν_{max}, cm⁻¹): 2959, 2871, 2838, 1586, 1505.

Preparation of 1-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclopentanol (**6**)

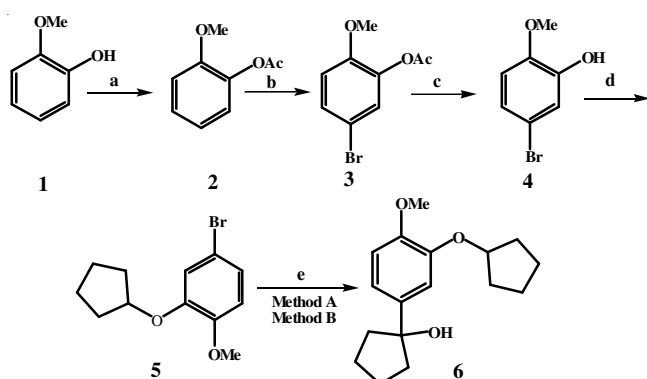
Method A: A mixture of magnesium splinters (0.05 g, 2.08 mmol) and 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene **5** (0.5 g, 1.85 mmol) in dry THF (10 mL) was stirred under argon atmosphere. The mixture was stirred gently and heated until the reaction started. The reaction had been maintained until all magnesium was disappeared. The mixture was cooled to room temperature and cyclopentanone (0.17 g, 2.06 mmol) in 10 mL of dry THF was added dropwise and the resulting solution was refluxed for 2 h. The reaction was stopped by adding 20 mL of saturated NH₄Cl and extracted three times with 10 mL portions of ether. The organic layer was separated, washed with NaOH solution (10 %, 10 mL) followed by water (10 mL). The organic layer was dried over sodium sulfate and the solvent was evaporated. The resulting product was purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) to give 1-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclopentanol (**6**) as yellowish liquid. Yield: 11 %; ¹H NMR (400 MHz, CDCl₃): 1.2-2.1 (m, 16H), 1.95 (s, 1H), 3.81 (s, 3H), 4.78 (m, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H); MS (m/z, % rel intensity): (M⁺ 276, 6), 258 (33), 208 (6), 190 (100), 175 (22), 159 (22), 143 (4), 129 (11), 115 (9), 91 (9), 77 (6), 67 (9); IR (KBr, ν_{max}, cm⁻¹): 3427, 2958, 2870.

Method B: A solution of 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene **5** (0.5 g, 1.85 mmol) in dry THF (10 mL) was cooled to -78 °C and *n*-butyl lithium (1.5 M, 1.2 mL) was added slowly by syringe (0.5 h) at the same temperature. Then a solution of cyclopentanone (0.14 g, 1.7 mmol) in dry THF (3 mL) was added dropwise and the mixture was stirred at -78 °C for additional 0.5 h. The mixture was reached to room temperature and stirred for 2 h. The reaction was quenched by adding saturated NH₄Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (15 mL) followed by brine (15 mL) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to give 1-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclopentanol (**6**). Yield: 16 %; yellowish liquid; ¹H NMR (400 MHz, CDCl₃): δ 1.2-2.1 (m, 16H), 1.95 (s, 1H), 3.81 (s, 3H), 4.78 (m, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H); MS (m/z, % rel intensity):

(M⁺ 276, 6), 258 (33), 208 (6), 190 (100), 175 (22), 159 (22), 143 (4), 129 (11), 115 (9), 91 (9), 77 (6), 67 (9); IR (KBr, ν_{\max} , cm⁻¹): 3452, 2958, 2871.

RESULTS AND DISCUSSION

Reaction sequence employed for the synthesis of 1-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclopentanol (**6**) is shown in **Scheme-I**. Starting material 2-methoxy phenol (**1**) was converted into 2-methoxyphenyl acetate (**2**). Compound **2** on reaction with NBS in dry CH₃CN yielded 5-bromo-2-methoxyphenyl acetate (**3**) in good yield. 5-bromo-2-methoxyphenol (**4**) was obtained by refluxing **3** with 10 % NaHCO₃ in methanol under argon atmosphere. Similarly, 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene (**5**) was synthesized by heating compound **4** with cyclopentyl bromide in DMF at 50 °C. The synthesis of **6** from method A: compound **5** was reacted with magnesium splinters in dry THF. After heating the solution, cyclopentanone was added dropwise under argon atmosphere to give compound **6**. The synthesis of **6** from method B: the reaction of compound **5** with *n*-butyl lithium in dry THF at -78 °C gave aryllithium. Then a solution of cyclopentanone in dry THF was added dropwise (**Scheme-I**). Both of the method (A and B) gave 1-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclopentanol (**6**) in low yield.



Scheme-I: Synthesis of 1-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclopentanol from 2-methoxy phenol. Conditions: (a) Ac₂O, conc. H₂SO₄, 100 °C, 7 h, 96 %; (b) NBS, CH₃CN, 60 °C, 10 h, 95 %; (c) aq. 10 % NaHCO₃, MeOH, reflux, 3 h, 93 %; (d) cyclopentyl bromide, K₂CO₃, DMF, 50 °C, 12 h, 88 %; (e) Method A: Mg, cyclopentanone, THF (dry), reflux, 2 h, 11 %; Method B: BuLi, cyclopentanone, THF (dry), -78 °C, 0.5 h, 16 %

Conclusion

1-[3-(Cyclopentyloxy)-4-methoxy-phenyl]cyclopentanol (**6**) has been synthesized as potential phosphodiesterase-4 inhibitor.

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