C-H-Activation approach in the synthesis of palonosetron core: A 5-HT3 receptor antagonist

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Abstract
Intramolecular rhodium (III) catalyzed annulation of benzamide 8 has been described in the efficient synthesis of palonosetron core, 5-HT3 receptor antagonists. C–H-activation enabled the simultaneous generation of rings B and C, which can further be functionalized to access a series alkaloid.

Keywords: C–H-activation, intramolecular, aloxi, palonosetron

Introduction
Palonosetron, a drug used in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), inhibits 5-HT (3) receptors present in gastrointestinal tract. It has a unique tricyclic core structure of a hydroisoquinoline fused with another ring c at 4 and 5 positions analogous to phenanthridines, which are abundant Amaryllidaceae alkaloids. In modern medicine, alkaloids having phenanthidine nucleus have been screened against various complications. Dinapsoline (1, Figure 1), a drug used for the treatment of Parkinson’s disease whereas, an aromatic derivative (2) has a reasonably good receptor affinity towards 5-HT2A. Many traditional methods have been developed in the past to synthesize these important building blocks. MGI Pharma and Helsinn Healthcare companies of Switzerland have developed Palonosetron, approved by Food and Drug Administration in July 2003 and marketed under the trade name Aloxi. Since then various improved synthesis along the total synthesis of palonosetron have been described, wherein Clark et al. annexed ring C to the piperidine in the final step by N-formylation following benzylic alkylation from derivatives of 6. An improved synthesis of palonosetron was demonstrated by Kowalczyk et al., which utilizes amination of anhydride 7 (Scheme 1).

![Fig 1: Phenanthridine alkaloids](image)

After the successful annulation of Rh (III)-mediated N-hydroxybenzamide derivatives and alkenes in alkaloid synthesis, we planned to extend intramolecular alkene annulation in the synthesis of pharmaceuticals, and found the palonosetron skeleton (4) best fit for the purposeful implementation of the approach.
The C–H-activation strategies are superior to traditional synthetic approaches due to the obviation of prefunctionalization[12]. In an alternative plan, palonosetron could be fragmented into β-lactam 4 and halide 5. Intramolecular C–H-activation could generate β-lactam 4, which after N-alkylation with 3-chloroquinuclidine would produce palonosetron.

Scheme 2: Fragmentation of palonosetron

Results and discussion

With a view towards the synthesis of palonosetron building block using intramolecular C–H-activation technique, 3,4-dialkoxy-substituted N-(pivaloyloxy)-3-alkyl benzamide 8 was prepared. Our synthesis of amide 8 from 3-bromobenzoate 9 with ethyl pivalate 10 provided an approach to amide 8 and its conversion to 4 was presented by F. Glorious group[13].

Scheme 3: Synthesis of Palonosetron Core

A Heck coupling of 3-butenol 9 with ethyl-3-bromobenzoate 10 provided E-alkene 11. A poor conversion was observed while using triethylamine as a base at room temperature. However, the yield was drastically improved by using an excess of triethylamine and elevating the reaction temperature (75 °C). The styrene ester 11 was subjected to reduction of the alkene moiety using hydrogen with palladium on charcoal as catalyst. In order to achieve the desired palonosetron core, the compound needs an extension of one carbon unit. Therefore, the alcohol 12 was oxidized to aldehyde using PCC loaded on silica oxidation, which yielded 77%. The methylene unit was annexed over aldehyde by the use of CH3PPh2Br. The next, N-OPiv benzamide 9 was achieved from benzoic acid ester 14 using our previously optimized reaction conditions[10]. The intramolecular alkene annulation of 9 yielded benzamide 4 in 76% within 8 h. The cross-peaks between 3a-H and 4-H in the COSY spectrum confirm the formation of the palonosetron core.

Experimental section

Ethyl (E)-3-(4-hydroxybutyl-1-en-1-yl)benzoate (11)

To a stirred solution of the aryl bromide 9 (3.00 g, 13.1 mmol) in EtN (3.7 mL, 25.6 mmol, 2.0 equiv) were successively added 3-buten-1-ol 10 (1.9 mL, 22.9 mmol, 1.8 equiv), Pd(OAc)2 (295 mg, 1.37 mmol, 0.1 equiv), and P(o-tol)2 (0.834 g, 2.74 mmol, 0.2 equiv), and the mixture was stirred at 75 °C for 21 h, cooled, and concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and H2O (20 mL). The organic layers were separated, and the aqueous was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated solution of NaCl (2 × 20 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:2) afforded pure ester 11 (2.515 g, 87%) as colorless oil. Rf = 0.5 (EtOAc/petroleum ether, 1:1); 1H NMR (400 MHz, CDCl3): δ = 1.34 (t, J = 7.1 Hz, 3H, OCH2CH3), 2.27 (br, 1H, OH), 2.46 (qd, J = 1.3, 6.6 Hz, 2H, 2-H), 3.73 (t, J = 6.3 Hz, 2H, 1-H), 4.34 (q, J = 7.1, Hz, 2H, OCH2CH3), 6.27 (dt, J = 7.1, 16.0 Hz, 1H, 3-H), 6.47 (d, J = 16.0 Hz, 1H, 4-H), 7.31 (t, J = 7.6 Hz, 1H, Ar), 7.47 (dt, J = 1.3, 7.6 Hz, 1H, Ar), 7.84 (dt, J = 1.3, 7.8 Hz, 1H, Ar), 7.99 (t, J = 2.0 Hz, 1H, Ar); 13C NMR (100 MHz, CDCl3): δ = 14.2 (OCH2CH3), 36.2 (C-2), 60.9 (OCH2CH3), 61.8 (C-1), 126.9, 127.9, 128.0, 128.4, 130.2, 130.6, 131.4, 137.5, 166.6 (CO); HRMS (ESI): calcd for C13H16O3 [M+Na] 243.09917, found 243.09911.

Ethyl 3-(4-hydroxybutyl) benzoate (12)

To a gently stirred solution of styrene derivative 11 (1.211 g, 5.5 mmol) in MeOH/hexane (60 mL, 1:1) was added Pd/C (10%, 267 mg), then the septum having N2 (5.5 mmol) in MeOH/hexane (60 mL, 1:1) was added Pd/C (295 mg, 1.37 mmol, 0.1 equiv), and P(o-tol)2 (0.834 g, 2.74 mmol, 0.2 equiv), and the mixture was stirred at 75 °C for 21 h, cooled, and concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and H2O (20 mL). The organic layers were separated, and the aqueous was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated solution of NaCl (2 × 20 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:2) afforded pure ester 11 (2.515 g, 87%) as colorless oil. Rf = 0.5 (EtOAc/petroleum ether, 1:1); 1H NMR (400 MHz, CDCl3): δ = 1.34 (t, J = 7.1 Hz, 3H, OCH2CH3), 2.27 (br, 1H, OH), 2.46 (qd, J = 1.3, 6.6 Hz, 2H, 2-H), 3.73 (t, J = 6.3 Hz, 2H, 1-H), 4.34 (q, J = 7.1, Hz, 2H, OCH2CH3), 6.27 (dt, J = 7.1, 16.0 Hz, 1H, 3-H), 6.47 (d, J = 16.0 Hz, 1H, 4-H), 7.31 (t, J = 7.6 Hz, 1H, Ar), 7.47 (dt, J = 1.3, 7.6 Hz, 1H, Ar), 7.84 (dt, J = 1.3, 7.8 Hz, 1H, Ar), 7.99 (t, J = 2.0 Hz, 1H, Ar); 13C NMR (100 MHz, CDCl3): δ = 14.2 (OCH2CH3), 36.2 (C-2), 60.9 (OCH2CH3), 61.8 (C-1), 126.9, 127.9, 128.0, 128.4, 130.2, 130.6, 131.4, 137.5, 166.6 (CO); HRMS (ESI): calcd for C13H16O3 [M+Na] 243.09917, found 243.09911.
Ethyl 3-(4-oxobutyl) benzoate (12)
To a flask (100 mL) CH3PPhBr (3.243 g, 9.0 mmol, 2.0 equiv) was taken and THF (40 mL) was added followed by the addition NaH (0.194 g, 8.1 mmol, 1.8 equiv) at 0 °C. The reaction mixture was allowed to react to rt within 2 h. Thereafter, the reaction mixture was re-cooled to 0 °C and before aldehyde 13 (1.00 g, 4.5 mmol) in THF (10 mL) was added dropwise. After complete addition, the reaction mixture was stirred for 2 h, quenched with water (1 mL) at 0 °C, then excess water (10 mL) was added, and the mixture extracted with Et2O (3 × 10 mL). The combined organic layers washed with saturated solution of NaCl (20 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:20) afforded aldehyde 13 (0.50 g, 0.45 mmol) in CH2Cl2/petroleum ether, 1:20; 2.09 (q, J = 7.6 Hz, 2H, 3-H), 2.67 (t, J = 7.6 Hz, 5H), 4.37 (q, J = 7.1 Hz, 2H, CH2), 4.92-5.08 (m, 2H, 1-H), 5.63-5.89 (m, 1H, 2-H), 7.30-7.43 (m, 2H, Ar), 7.83-7.94 (m, 2H, Ar); 13C NMR (100 MHz, CDCl3): δ = 14.3 (OCH2CH3), 23.5 (C(CH3)3), 34.7 (C-C3), 43.0 (C-C2), 60.9 (OCH2CH3), 127.4, 128.4, 129.4, 130.6, 132.9, 141.5, 166.7 (CO2Et), 202.0 (C-1); HRMS (ESI): calcd for C12H14O3 (dimer, 2 × C6H16O3)[M+Na]+ 463.20911, found 463.20927.

Ethyl 3-(pent-4-en-1-yl) benzoate (14)
To a flask (100 mL) CH3PPhBr (3.423 g, 9.0 mmol, 2.0 equiv) was taken and THF (40 mL) was added followed by the addition NaH (0.194 g, 8.1 mmol, 1.8 equiv) at 0 °C. The reaction mixture was allowed to react to rt within 2 h. Thereafter, the reaction mixture was re-cooled to 0 °C and before aldehyde 13 (1.00 g, 4.5 mmol) in THF (10 mL) was added dropwise. After complete addition, the reaction mixture was stirred for 2 h, quenched with water (1 mL) at 0 °C, then excess water (10 mL) was added, and the mixture extracted with Et2O (3 × 10 mL). The combined organic layers washed with saturated solution of NaCl (20 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:20) afforded aldehyde 13 (0.50 g, 0.45 mmol) in CH2Cl2/petroleum ether, 1:20; 2.09 (q, J = 7.6 Hz, 2H, 3-H), 2.67 (t, J = 7.6 Hz, 5H), 4.37 (q, J = 7.1 Hz, 2H, CH2), 4.92-5.08 (m, 2H, 1-H), 5.63-5.89 (m, 1H, 2-H), 7.30-7.43 (m, 2H, Ar), 7.83-7.94 (m, 2H, Ar); 13C NMR (100 MHz, CDCl3): δ = 14.3 (OCH2CH3), 23.5 (C(CH3)3), 34.7 (C-C3), 43.0 (C-C2), 60.9 (OCH2CH3), 127.4, 128.4, 129.4, 130.6, 132.9, 141.5, 166.7 (CO2Et), 202.0 (C-1); HRMS (ESI): calcd for C12H14O3 (dimer, 2 × C6H16O3)[M+Na]+ 463.20911, found 463.20927.

N-Hydroxy-3-(pent-4-en-1-yl) benzamide (15)
To a flask (100 mL) CH3PPhBr (3.423 g, 9.0 mmol, 2.0 equiv) was taken and MeOH (3 mL) was added. The mixture was stirred for 5 min, then methanolic KOH solution (1M in methanol, 7 mL, 5.0 equiv) was added dropwise. The mixture was stirred 48 h at rt. Thereafter most of the MeOH was distilled out in vacuo and the solid residue was dissolved in a mixture of acetic acid/water (1/1, 5 mL), extracted with EtOAc (3 × 7 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuo to provide the crude hydroxamic acid which was washed with diethyl ether (7 mL) to afford the pure hydroxamic acid 15 as transparent solid (0.24 g, 89%); 13C NMR (100 MHz, CDCl3): δ = 30.3 (C-4), 32.9 (C-3), 34.7 (C-4), 115.3 (C-1), 124.6, 127.1, 128.6, 131.5, 132.9, 137.1, 138.6, 142.6, 164.7 (CONH).

2,3,3a,4,5,6-Hexahydror-1H-benzo[d]isoquinolin-1-one (4)
To a flame dried Schlenk tube under N2, was taken n-H-(pivaloyloxy) benzamide 9 (20 mg, 0.07 mmol), [Cp*RhCl2(pivaloyl)] (2 mg, 2.5 mol%), CsOAc (32 mg, 0.17 mmol, 2.5 equiv). Dry EtOH (0.1 mL) was added. The screw cap was closed tightly under positive pressure of N2 followed by stirring of the reaction mixture at room temperature for 8 h (TLC control). The mixture was concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to afford the pure annulation product 4 (10 mg, 76%). 1H NMR (400 MHz, CDCl3): δ = 1.31-1.45 (m, 1H, 4-H), 1.68-1.83 (m, 1H, 5-H), 1.96-2.11 (m, 2H, 4-H, 5-H), 2.47-2.55 (m, 2H, 6-H), 3.05-3.17 (m, 1H, 3a-H), 3.24 (dd, J = 11.6, 13.1 Hz, 1H, 3-H), 3.41 (dd, J = 6.1, 11.6 Hz, 1H, 3-H), 6.07 (br, 1H, NH), 7.26 (d, J = 4.6 Hz, 2H, 7-H, 9-H), 7.88 (t, J = 4.6 Hz, 8-H); HRMS m/z (ESI): calcd for C12H13NO (M+H)+ 188.10699, found 188.10692.

Conclusion
In this paper, we have shown a new approach to the core structure of the palonosetron. The synthetic intermediates have been characterized using 1H NMR, 13C NMR, and high-resolution mass spectra. The final compound structure was established using 2D NMR (COSY). The approach is synthetically important because it does not require pre-functionalization and could be further extended to the synthesis of other phenanthridine alkaloids.

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