Synthesis and spectroscopic characterisation of novel roflumilast analogues

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A series of new N-heterocyclic or phenoxy substituted roflumilast analogues have been designed and synthesised. N-heterocyclic or phenoxy substituted benzaldehydes were first prepared from 3-hydroxy-4-methoxybenzaldehbyde and 1-bromo-3-chloropropane by an alkylation reaction. The roflumilast analogues were then obtained by oxidation, acylation, amidation and alkylation reactions. These compounds were characterised by ^{1}H NMR, IR, ESI-MS and elemental analyses.

Keywords: roflumilast analogue, 3-hydroxy-4-methoxybenzaldehyde

Roflumilast is a phosphodiesterase 4 (PDE4) inhibitor which was marketed in the European Union for the treatment of chronic bronchitis in 2009, and in the USA in 2012, for the treatment of chronic obstructive pulmonary disease (COPD).[1,2] In addition to the treatment of COPD, it is used to treat many inflammation related diseases[2] including emphysema,[3] asthma,[4] diabetes mellitus[5] and allergic rhinitis.[6] However, it still has some slight side effects, such as gastrointestinal upsets, headache, and weight loss,[7] which limit its therapeutic potential. It is therefore important to discover novel PDE4 inhibitors with a better therapeutic index.

The pharmacophores of roflumilast were a catechol ring, pyridine group and two chlorine atoms (Fig. 1). In docking with the PDE4 enzymes, the catechol ring is placed at the hydrophobic clamp and the 3, 5-dichloropyridine group extends to the divalent metal–ion site and forms a hydrogen bond to a water molecule that is coordinated to Mg^{2+}. The two chlorine atoms also form additional hydrophobic interactions with residues in the metal binding pocket.[2] Research with PDE4 inhibitors, including the chemical structures within the pharmacophore models, showed that some heterocyclic groups, such as morpholine, pyridine, piperidine, and piperazine could play a major role in their biological activity.[8–11]

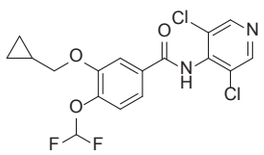


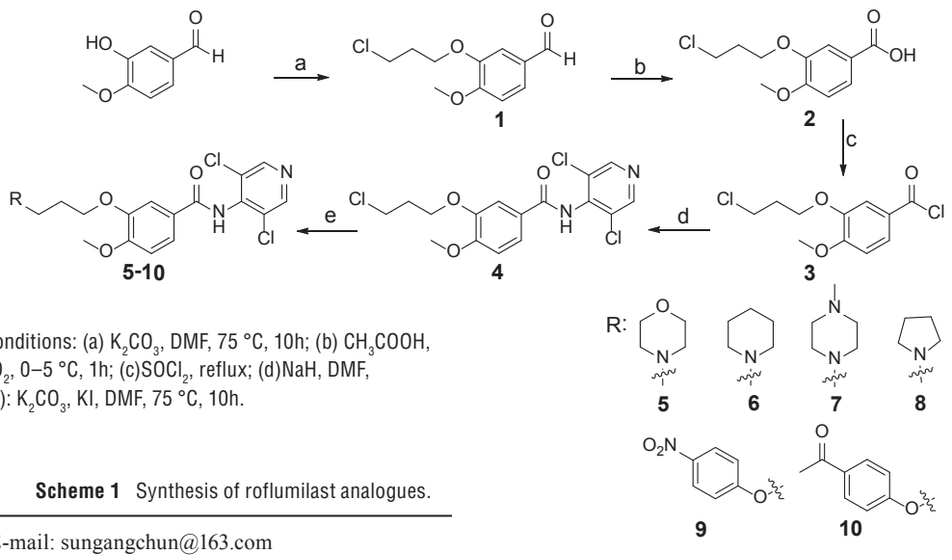
Fig. 1 Structure of roflumilast.

In this study, we have synthesised a series of benzamide compounds mostly starting from the archetypical inhibitor roflumilast by introducing N-heterocyclic or substituted phenoxy groups. We found that these compounds were a good match with the PDE4 enzymes by using the drug design software Autodock Vina.[12] We expect that these novel roflumilast analogues will exhibit biological activity and this study is ongoing. The structure of target molecules was confirmed by IR and ^{1}H NMR spectroscopy, mass spectrometry and element analyses.

Results and discussion

The synthetic strategies used for the preparation of the "N-heterocyclic" type roflumilast analogues are illustrated in Scheme 1. As shown in this Scheme, **1** was obtained from 1-bromo-3-chloropropane and with 3-hydroxy-4-methoxybenzaldehyde by an alkylation reaction. Then after oxidation and acylation, **3** reacted with 3,5-dichloropyridin-4-amine to give the key intermediate **4.** Reaction with either an N-heterocyclic or substituted phenol gave the products **5–10**.

The conditions for the preparation of the key intermediate **4** was investigated using several methods. When we used DCC as the dehydrating agent, the reaction was not successful. When **3** reacted with 3,5-dichloropyridin-4-amine, three conditions were examined. The key intermediate **4** was obtained in high yield when NaH was used as a base in anhydrous THF, but the reaction did not proceed with CaH_2 or without any base. This indicated that the nucleophilic substitution activity of the amine was reduced by the pyridine and by steric hindrance from the two chlorine atoms at the *ortho*-position.



Reagents and conditions: (a) K_2CO_3, DMF, 75 °C, 10h; (b) CH_3COOH, HSO_3NH_2, $NaClO_2$, 0–5 °C, 1h; (c)$SOCl_2$, reflux; (d)NaH, DMF, 15–25 °C, 5h; (e): K_2CO_3, KI, DMF, 75 °C, 10h.

Scheme 1 Synthesis of roflumilast analogues.

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The reactions of **4** with piperidine, pyrrolidine were relatively easy, but difficult with N-methyl piperazine or morpholine, and when reacted with 2,6-dimethylpiperidine the corresponding product could not be obtained. This showed that the activity of heterocyclic ring was reduced by the greater steric hindrance of the methyl groups.

The IR spectra of the products showed the N–H stretching absorption at 3236–3217 cm^{-1}, CH_2 at 2970–2924 cm^{-1}, CO at 1726–1680 cm^{-1}. The ^1H NMR spectra showed the pyridine proton resonance at a chemical shift δ ~8.55 ppm, benzamide NH proton resonance at a chemical shift between δ 7.78–7.61 ppm as a broad singlet, except for **5**. The 2-proton resonance of the benzene ring in most products appeared at δ 7.57–7.54 ppm. This was a doublet signal because of long range coupling. The 6-proton resonance was a doublet–doublet signal at δ 7.55–7.50 ppm, while the 5-proton resonance appeared at δ 7.08–6.93 ppm as a doublet. The methyl proton resonance always appeared at δ 3.94 ppm as a singlet. The structure of the products was further proved by mass spectroscopic data.

Experimental

Melting points were determined by microscope melting point apparatus and were uncorrected. ^1H NMR spectra were recorded on a Bruker-400 spectrometer, using $CDCl_3$ as the solvent and TMS as internal reference, coupling constants *J* are given in Hz. IR spectra were recorded on Prestige-21 Shimadzu IR Spectrophotometer in KBr pellets and reported in cm^{-1}. MS (ESI) spectra were collected using an Agilent LC-MS 6310EV. Elemental analyses were measured with a Flash EA 1112 elemental analyser.

3-(3-Chloropropoxy)-4-methoxybenzaldehyde (**1**): A mixture of 3-hydroxy-4-methoxy benzaldehyde (2.00 g, 13.14 mmol) and potassium carbonate (2.20 g, 15.95 mmol) in DMF 15 mL was stirred at room temperature for 30 min. 1-Bromo-3-chloropropane (1.69 mL, 17.09 mmol) was added dropwise over 5 min. Then the mixture was heated to 75 °C for 10 h. After 3-hydroxy-4-methoxybenzaldehyde has disappeared by analytical TLC (PE-EA, 2:1 in v:v), the reaction mixture was poured onto ice water (50 mL) and extracted with dichloromethane (25 mL × 3). The combined organic layer was washed with sodium hydroxide solution (30 mL, 8%), water (200 mL × 3), then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography using PE-EA (7:1 in v:v) as eluent to afford **1** as a faint yellow solid (2.26 g, 75.3% yield), m.p. 52–54 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.91 (1H, s), 7.54 (1H, dd, *J*=8.1 Hz, 1.8 Hz), 7.49 (1H, d, *J*=1.7 Hz), 7.05 (1H, d, *J*=8.2 Hz), 4.30 (2H, t, *J*=5.9 Hz), 4.00 (3H, s), 3.85 (2H, t, *J*=6.3 Hz), 2.40 (2H, m). IR (KBr) ν (cm^{-1}): 2937 (–CH_3), 1689 (CO), 1593, 1583, 1441 (Ph). MS (*m/z*): 227.8 (M^-). Anal. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73. Found: C, 57.49; H, 5.86%.

3-(3-Chloropropoxy)-4-methoxybenzoic acid (**2**): Compound **1** (2.00 g, 8.75 mmol) was added to a solution of sulfamic acid (1.38 g, 14.21 mmol) in acetic acid (9 mL). A solution of sodium chloride (1.23 g, 13.60 mmol) in 4 mL of water was added slowly to this mixture with vigorous stirring, whilst keeping the temperature in the range of 0–5 °C under ice-bath conditions for 1 h. The reaction mixture was poured on water (100 mL), and a milky precipitate appeared. After vigorous stirring for 5 min, and then boiling for 20 min, the solid precipitate which was obtained was collected by filtration, dried and then recrystallised from acetonitrile and PE (1:1 in v:v) to give **2** as a white solid (1.96 g, 91.6% yield), m.p. 140–143 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (1H, dd, *J*=8.4Hz, 1.8 Hz), 7.63 (1H, d, *J*=1.8 Hz), 6.94 (1H, d, *J*=8.5 Hz), 4.23 (2H, t, *J*=5.4 Hz), 3.94 (3H, s), 3.80 (2H, t, *J*=6.1 Hz), 2.33 (2H, m). IR (KBr) ν (cm^{-1}): 2918 (–CH_3), 1685 (CO), 1597, 1583, 1437 (Ph). MS (*m/z*): 243.7 (M^-). Anal. Calcd for $C_{11}H_{13}ClO_4$: C, 54.00; H, 5.36. Found: C, 53.79; H, 5.51%.

3-(3-Chloropropoxy)-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamine (**4**): Compound **2** (2.00 g, 8.17 mmol) was dissolved in thionyl chloride (15 mL) and the reaction mixture was refluxed for 2 h. Then the excess thionyl chloride was evaporated to dryness under vacuum to give intermediate **3**. This was dissolved in dry tetrahydrofuran (5 mL), and then added dropwise to a magnetically stirred solution of 3,5-dichloropyridin-4-amine (1.46 g, 8.96 mmol) and sodium hydride (4.04 g, 60% suspension) in dry tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was stirred for 5 h at 15–25 °C and acidified to pH 2 with hydrochloric acid (1 mol), and then extracted with ethyl acetate (25 mL × 3). The combined layer was washed with sodium hydroxide solution (20 mL, 5%) and water (10 mL) and then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography using PE-EA (4:1 in v:v) as eluent to afford a white solid (0.81 g, 25% yield), m.p. 143–144 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.57 (1H, s), 7.68 (1H, s), 7.57 (1H, d, *J*=7.3 Hz), 7.54 (1H, s), 6.98 (1H, d, *J*=8.6 Hz), 4.28 (2H, t, *J*=5.4 Hz), 3.96 (3H, s), 3.81 (2H, t, *J*=6.2 Hz), 2.36 (2H, q, *J*=6.1 Hz). IR (KBr) ν (cm^{-1}): 3226 (NH), 2933(–CH_3), 1676 (CO). MS (*m/z*): 388.8 (M^-). Anal. Calcd for $C_{16}H_{15}Cl_3N_2O_3$: C, 49.32; H, 3.88; N, 7.19. Found: C, 49.11; H, 3.86; N, 7.28%.

N-(3,5-Dichloropyridin-4-yl)-4-methoxy-3-(3-morpholinopropoxy) benzamide (**5**): A mixture of **4** (1.25 g, 3.21 mmol), potassium carbonate (0.53 g, 3.85 mmol) and potassium iodide (0.33 g) in DMF (7 mL) was stirred at room temperature for 30 min. Morpholine (0.56 g, 6.42 mmol) was added dropwise over 5 min. Then the mixture was heated to 75 °C for 10 h. The reaction mixture was poured onto ice water (50 mL) and extracted with dichloromethane (20 mL × 2). The combined organic layer was washed with water (50 mL × 2). It was then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography using PE-EA (3:1–1:1) as eluent to afford ***5*** as a yellow solid (0.29 g, 21% yield), m.p. 146–147 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (2H, s), 7.74 (1H,s), 7.55 (1H, d, *J* =1.9 Hz), 7.53 (1H, dd, *J*=8.4 Hz, 1.8 Hz), 6.96 (1H, d, *J*=8.4 Hz), 4.19 (2H, t, *J* =6.6 Hz), 3.94 (3H, s), 3.72 (4H, m), 2.56 (6H, m), 2.07 (2H, m). IR (KBr) ν (cm^{-1}): 3236 (NH), 2933(–CH_3), 1726 (CO). MS (*m/z*): 438.5 (M^-). Anal. Calcd for $C_{20}H_{23}Cl_2N_3O_4$: C, 54.55; H, 5.26; N, 9.54. Found: C, 54.95; H, 5.51; N, 9.38%.

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-(piperidin-1-yl) propoxy)benzamide (**6**): The synthetic method followed that of **5** to give a yellow solid 0.40 g,(yield 51%), m.p. 159–160 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.55 (2H, s), 7.78 (1H, s), 7.53 (1H, s), 7.51 (1H, d, *J*=2.1 Hz), 6.95 (1H, d, *J*=8.0 Hz), 4.16 (2H, t, *J*=6.7 Hz), 3.94 (3H, s), 2.50 (2H, t, *J*=7.3 Hz), 2.39 (4H, s), 2.07 (2H, m), 1.60 (4H, m), 1.43 (2H, m). IR (KBr) ν (cm^{-1}): 3263 (NH), 2933 (–CH_3), 1651 (CO). MS (*m/z*):436.8 (M^-). Anal. Calcd for $C_{21}H_{25}Cl_2N_3O_3$: C, 57.54; H, 5.75; N, 9.59. Found: C, 57.07; H, 5.78; N, 9.72%.

N-(3,5-Dichloropyridin-4-yl)-4-methoxy-3-(3-(4-methylpiperazin-1-yl)propoxy)benzamide (**7**): The synthetic method followed that of **5** to give a yellow solid 0.42 g,(yield 36%), m.p. 162–163 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (2H, s), 8.02 (1H,s), 7.54 (1H, d, *J*=1.8 Hz), 7.53 (1H, dd, *J*=8.2 Hz, 1.8 Hz), 6.95 (1H, d, *J*=8.3 Hz), 4.17 (2H, t, *J*=6.6 Hz), 3.94 (3H, s), 2.57–2.48 (10H, m), 2.28 (3H, s). 2.07–2.03 (2H, m). IR (KBr) ν (cm^{-1}): 3246 (NH), 2937 (–CH_3), 2790 (–CH_2), 1647 (CO). MS (*m/z*): 451.8 (M^-). Anal. Calcd for $C_{21}H_{26}Cl_2N_4O_3$: C, 55.63; H, 5.78; N, 12.36. Found: C, 55.26; H, 5.85; N, 12.49%.

N-(3,5-Dichloropyridin-4-yl)-4-methoxy-3-(3-(pyrrolidin-1-yl) propoxy)benzamide (**8**): The synthetic method followed that of **5** to give a white solid 0.56 g, (yield 36%), m.p. 160–161 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (2H, s), 7.55 (1H, d, *J*=2.0 Hz), 7.54 (1H, dd, *J*=8.7 Hz, 2.5 Hz), 6.95 (1H, d, *J*=8.1 Hz), 4.19 (2H, t, *J*=6.8 Hz), 3.95 (3H, s), 2.65 (2H, t, *J*=7.3 Hz), 2.52 (4H, s), 2.12 (2H, m), 1.81 (4H, m). IR (KBr) ν (cm^{-1}): 3222 (NH), 2954 (–CH_3), 2790 (–CH_2), 1647 (CO). MS (*m/z*): 422.9 (M^-). Anal. Calcd for $C_{20}H_{23}Cl_2N_3O_3$: C, 56.61; H, 5.46; N, 9.90. Found: C, 56.05; H, 5.54; N, 9.97%.

N-(3,5-Dichloropyridin-4-yl)-4-methoxy-3-(3-(4-nitrophenoxy) propoxy)benzamide (**9**): The synthetic method followed that of **5** to give

a faint yellow solid 0.27 g (yield 21%), m.p. 194–195 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (2H, s), 8.30 (1H, d, *J*=1.9 Hz), 8.18 (1H, d, *J*=1.7 Hz), 7.64 (1H, s),7.57 (1H, d, *J*=2.1 Hz), 7.54 (1H, dd, *J*=8.2 Hz, 2.0 Hz), 6.99 (1H, d, *J*=2.1 Hz), 6.97 (1H, d, *J*=1.7 Hz), 6.95 (1H, s), 4.32 (4H, m), 3.94 (3H, s), 2.42 (2H, m). IR (KBr) ν (cm^{-1}): 3176 (NH), 2924 (–CH_3), 1668, 1647 (CO). MS (*m/z*): 490.6 (M^-). Anal. Calcd for $C_{22}H_{19}Cl_2N_3O_6$: C, 53.67; H,3.89; N,8.54. Found: C, 53.12; H, 3.96;N, 8.93%.

3-(3-(4-Acetylphenoxy)propoxy)-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide (**10**): The synthetic method followed that of **5** to give a white solid 0.36 g (yield 28.80%), m.p. 152–153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55 (2H, s),7.92 (1H, s), 7.90 (1H, s), 7.69 (1H, s), 7.57 (1H, d, *J*=2.0 Hz), 7.55 (1H, dd, *J*=8.4 Hz, 1.8 Hz), 6.96 (3H, m), 4.32 (2H, t, *J*=6.1 Hz), 4.27 (2H, t, *J*=6.0 Hz), 3.94 (3H, s), 2.54 (3H, s). 2.40 (2H, m), IR (KBr) ν (cm^{-1}): 3176 (NH), 2924 (–CH_3), 2854 (–CH_3), 1680, 1650 (CO). MS (*m/z*): 488.0 (M^-). Anal. Calcd for $C_{24}H_{22}Cl_2N_2O_5$: C, 58.91; H, 4.53; N, 5.72. Found: C, 58.72; H, 4.6; N, 5.81%.

This work was supported by the Natural Science Foundation of Henan Educational Commission (2010A1500007), Key Scientific and Technological Project of Henan Province (102102210027, 092102210007).

Received 30 May 2013; accepted 1 July 2013
Paper 1301978 doi: 10.3184/174751913X13782291519608
Published online: 7 October 2013

References

1 A. Hatzelmann and C. Schudt, *J. Pharmacol. Exp. Ther.*, 2001, **297**, 267.
2 D.R. Gorja, S. Mukherjee, Ch. L.T. Meda, G.S. Deora, K.L. Kumar, A. Jain, G.H. Chaudhari, K.S. Chennubhotla, R.K. Banote, P. Kulkarni, K.V.L. Parsa, K. Mukkanti and M. Pal, *Org. Biomol. Chem.*, 2013, **11**, 2075.
3 P.A. Martorana, R. Beume, M. Lucattelli, L. Wollin and G. Lungarella, *Am. J. Respir. Crit. Care. Med.*, 2005, **172**, 848.
4 W. Timmer, V. Leclerc, G. Birraux, M. Neuhauser, A. Hatzelmann, T. Bethke and W. Wurst, *J. Clin. Pharmacol.*, 2002, **42**, 3297.
5 E.F.M. Wouters, D. Bredenbröker, P. Teichmann, M. Brose, K.F. Rabe, L.M. Fabbri and B. Göke, *J. Clin. Endocrin. Metab.*, 2012, **97**, 1720.
6 S.T. Holgate and D. Broide, *Nat. Rev. Drug Discov.*, 2003, **2**, 903.
7 K.F. Rabe, E.D. Bateman and D.O. Donnel, *Lancet*, 2005, **366**, 563.
8 K. Kagayama, T. Morimoto, S. Nagata, F. Katoh, X. Zhang, N. Inoue, A. Hashino, K. Kageyama, J. Shikaura and T. Niwa, *Bioorg. Med. Chem.*, 2009, **17**, 6959.
9 J. Taltavull, J. Serrat, J. Gràcia, A. Gavaldà, M. Andrés, M. Córdoba, M. Miralpeix, D. Vilella, J. Beleta, H. Ryder and L. Pagès, *J. Med. Chem.*, 2010, **53**, 6912.
10 R. Adepu, R. Sunke, Ch. L.T. Meda, D. Rambabu, G.R. Krishna, C.M. Reddy, G.S. Deora, K.V.L. Parsa and M. Pal, *Chem. Commun.,* 2013, **49**, 190.
11 R.R. Poondra, R.V. Nallamelli, Ch. L.T. Meda, B.N.V. Srinivas, An. Grover, J. Muttabathula, S.R. Voleti, B. Sridhar, M. Pal and K.V.L. Parsa, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1104.
12 O. Trott and A.J. Olson, *J. Comp. Chem.,* 2010, **31**, 455.