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Asymmetric synthesis of *N*-3 substituted phenoxypropyl piperidine benzimidazol-2-one derivatives, potent and selective NOP agonists

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Abstract

The asymmetric synthesis of the potent selective NOP agonist 2-(3-{1-[3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-2-oxo-2,3-dihydro-benzimidazol-1-yl)-*N*-methyl-acetamide and analogues was developed. The key step, chiral reduction of methyl isobutyryl acetate, was achieved using a mild Noyori-type asymmetric hydrogenation.

Keywords: NOP/ORL1 agonist; Chiral reduction; Asymmetric hydrogenation; Noyori catalyst

1. Introduction

In 1994, the fourth member of the opioid receptor family, opioid receptor-like receptor (NOP, ORL1), was identified[1] and has led to extensive research into its physiological role. This G-protein coupled receptor mediates the inhibition of adenylate cyclase and shares a high degree of sequence homology with other opioid receptors. The 17 amino acid peptide nociceptin is an endogenous ligand for the NOP receptor[1] and the receptor is localised in various regions of the central nervous system, which are associated with nociception. Nociceptin binds to the receptor with very high affinity although activation of NOP receptors is functionally complex.[2] For example, depending on its site of activation in the pain pathway, NOP can have opposing actions; it appears to have potent anti-analgesic actions supraspinally[1] and analgesic actions spinally.[3] The use of this peptide has plagued the interpretation of these complex results because of the intrinsic limitations with regard to metabolic stability. However, it is clear that this new member of the opioid receptor family plays an important role in pathways of pain, anxiety, learning and memory.[2]

Postoperative pain is currently served with opiate based products such as morphine. Morphine, an MOP agonist, is still regarded as the 'gold standard' treatment for moderate to severe pain,[4] however, some patients either do not achieve adequate analgesia or suffer opioid related side effects such as respiratory depression,[5] constipation, nausea and vomiting, thus leading to non-patient compliance.[6] Our primary interest has been to develop small molecules with high selectivity and potency for NOP that would be useful for the management of pain without the detrimental side effects observed with MOP agonists.

Many small-molecule NOP ligands have now been reported in the literature.[7] Several of these ligands have high selectivity and potency for the NOP receptor versus the other opioid receptors. The NOP antagonist, J-113397 (Fig. 1), has been well described and pharmacologically characterised.[8] Roche[9] (e.g., Ro 64-6198) and Novo Nordisk[10] (NNC 63-0532) have also described NOP agonists, with Ro 64-6198 showing >100-fold selectivity for the NOP receptor and displaying anxiolytic-like activity without causing tolerance in vivo.[11] Although this compound may mediate its effects through the NOP receptor, it shows moderate affinity towards MOP and KOP receptors as well as other receptor sites.

We have recently published our efforts towards developing potent and selective NOP agonists based on the benzimidazol-

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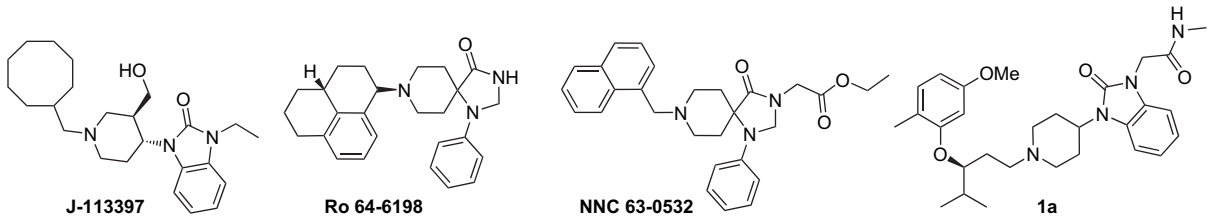


Figure 1. A selection of NOP receptor ligands.

2-one heterocycle.[12] Compound **1a** was identified with an NOP K_i of 0.5 nM, and excellent selectivity over other opioid receptors (NOP/MOP=108, NOP/DOP=6822, NOP/KOP=1068). Furthermore, **1a** was shown to be selective over a further 55 unrelated molecular targets at 10^{-7} M. In a functional cAMP assay **1a** behaved as a full agonist with excellent potency and good efficacy with respect to the nociceptin response (IC_{50}=4 nM, 120% nociceptin response). Given intravenously, **1a** produced antinociceptive effects comparable to morphine in the formalin paw test (FPT).[12b]

The data suggest that **1a** needed to be profiled further in order to determine the potential for development as an analgesic. It was clearly seen that the (+)-enantiomer in this series was the eutomer in all compounds investigated.[12b] We had previously prepared **1a–c** in a racemic fashion and performed optical resolution using chiral column Chiralpak AD (isohexane/isopropanol/diisopropylethylamine 80/20/0.1) to give the enantiomers.[12b] This allowed X-ray crystallography of the HCl salt (Fig. 2) to determine the absolute configuration of the active enantiomer **1c** as (*S*). However, given the limitations of scale with chiral HPLC it was important to develop a facile asymmetric route that was generally applicable and suitable for production of multigram quantities. Herein, we report a general route to **1a–c** that should be applicable to generate further derivatives, utilising the Noyori type asymmetric hydrogenation.

2. Results and discussion

Retrosynthetic analysis (Scheme 1) indicated that the key chiral building block towards **1a** would be the chiral alcohol

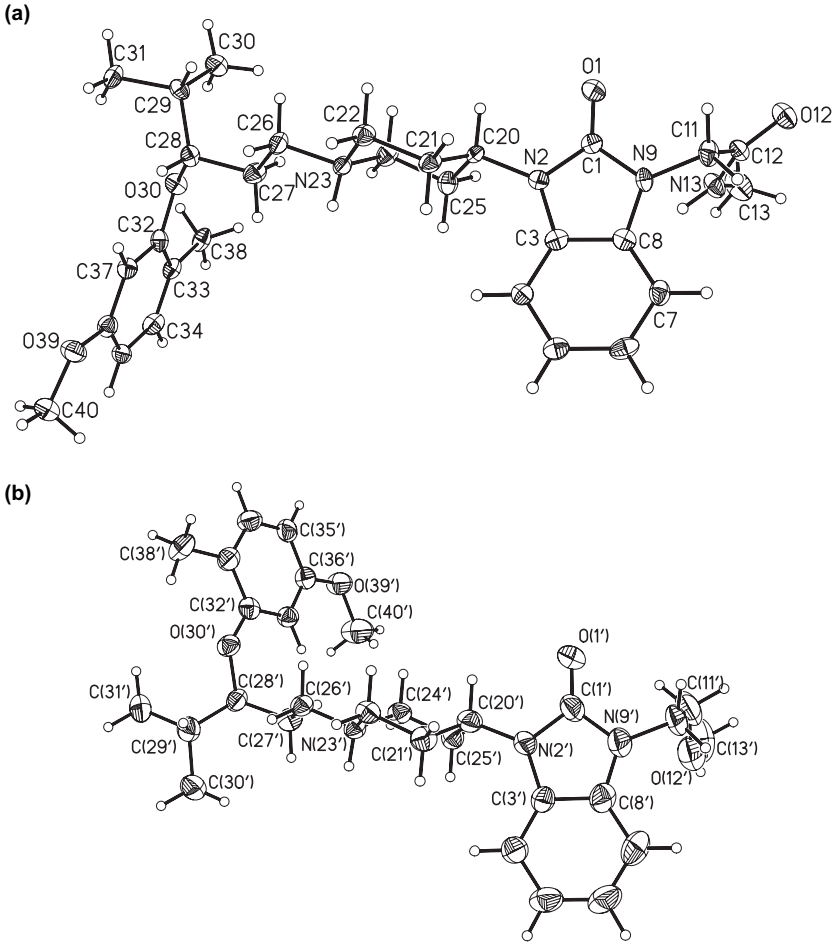
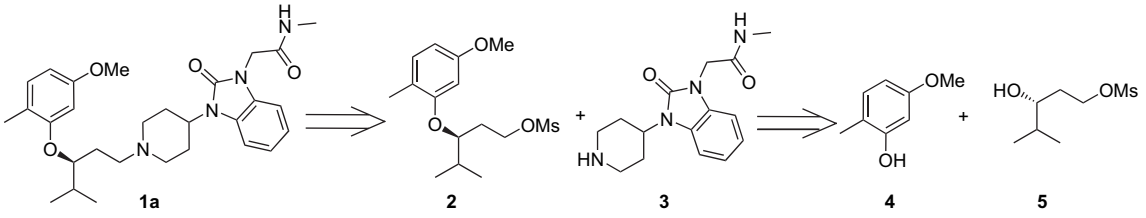


Figure 2. ORTEP drawing of (a) (*S*)-**1a** and (b) (*S*)-**1c** as hydrochloride salts.

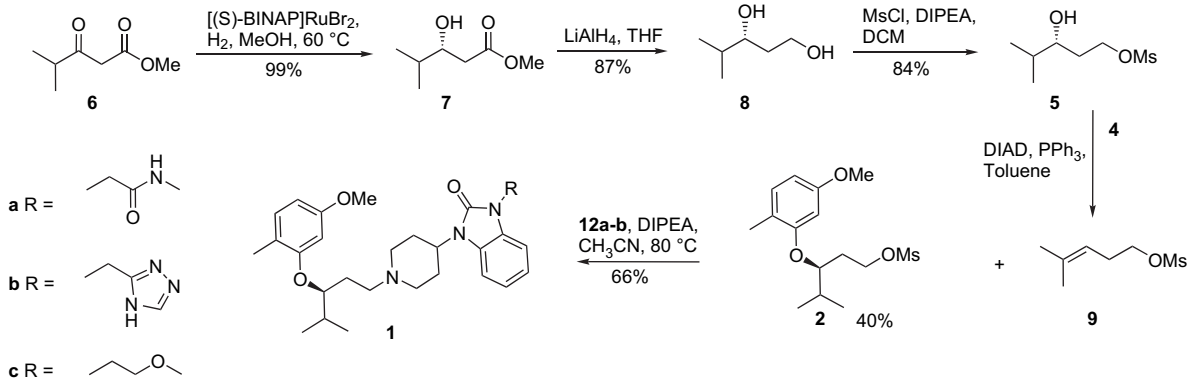


Scheme 1.

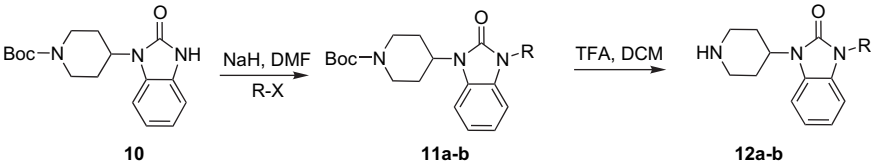
5. This would allow Mitsunobu coupling[13] involving inversion of the stereocentre to give the desired (*S*) stereochemistry found in **1a**. The route to the key chiral intermediate **2** was carried out as shown in Scheme 2. Genet and co-workers[14] have shown that reduction of methyl isobutyryl acetate **6** can be effected under atmospheric pressure at 60 °C for 18 h to obtain **7** in excess of 97% ee in quantitative yield, compared to the extended reaction time utilised by Kitamura and co-workers[15] of 86 atms for 51 h. Following the literature protocol, the Noyori catalyst[16] with the desired absolute configuration was prepared in situ in acetone from (*S*)-BINAP and bis-(2-methylallyl)cycloocta-1,5-diene ruthenium,[17] followed by addition of HBr in methanol. Acetone was removed and replaced with methanol and the hydrogenation of methyl isobutyryl acetate **6** was carried out by following the literature protocol.[14] The enantiomeric ratio for **7**[18] was >98:2 as judged by chiral GC. Standard lithium aluminium hydride reduction to **8**[19] was followed by mono-mesylation of the primary alcohol to give **5** in good yield. Mitsunobu coupling[13] involving S_N2 inversion of the stereocentre of the alcohol **5** with 5-methoxy-2-methylphenol[20] **4** gave only 40% of the desired phenyl ether **2** together with the isopropenyl by-product **9**. The low yield for this step is probably due to the formation of the volatile 4-methyl-1,3-pentadiene that can be formed from elimination of the mesylate before nucleophilic substitution can occur. Limited attempts to optimise this step failed to substantially increase the yield or reduce the proportion of isopropenyl impurity.[21] At this stage, the first purification step was required with partial removal of **9** by silica gel chromatography. Furthermore, since all of **9** could not be removed the enantiomeric excess could not be determined.

Piperidinyl-benzimidazolones **12a**,**b** were prepared as previously published[12b] by Boc protection of the commercially available 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimadazol-2-one to give **10**. N-Alkylation with the appropriate reagent and then deprotection of the Boc group with TFA were achieved to give the desired amine for coupling (Scheme 3). The unsubstituted triazole derivative **12b** was constructed according to the methods of Ladduwahetty and co-workers[22] by preparation of the alkylating reagent from chloroacetonitrile and formylhydrazide to give *N*-formyl-2-chloroacetamidrazone. After alkylation, heating to 140 °C effected cyclisation to the desired triazole **11b**, which was de-protected as previously described to afford **12b**.

The final coupling of the chiral intermediate **2** with the piperidinyl-benzimidazolones **12a**,**b** was carried out in acetonitrile/diisopropylethylamine at 80 °C. Compound **1c** was prepared by direct alkylation of racemic **1d** (**1d**, R=H) with



Scheme 2.



Scheme 3.

2-bromoethyl methyl ether rather than going via **12c**. The single enantiomer was then isolated by chiral HPLC. The product **1a** (13.0 g of a viscous gum) was obtained in 65% yield after purification on silica gel, with an enantiomeric purity of 100% as judged by chiral HPLC, confirming complete inversion during the Mitsunobu coupling. For **1a**, the material was identical to that initially obtained by preparative chiral HPLC. The overall yield was 19% for the five steps compared to 5.6% for the racemate described previously.[12b] The water soluble methanesulfonate salt of **1a** was prepared and crystallised from acetone to give 12.8 g of white solid. A sample of the more crystalline hydrochloride salt of **1a** was prepared and crystallised from isopropanol as fine needles. Subsequent recrystallisation from isopropanol resulted in rosettes from a relatively concentrated solution, while slow crystallisation from more dilute solutions gave small prisms suitable for X-ray crystallography as a hydrate of the hydrochloride salt. The hydrochloride salt of **1c** crystallised as the ether solvate.

There are two crystallographically independent molecules in the crystal structures of both **1a** and **1c** but only one of each is shown for clarity (Fig. 2). The two independent molecules have very different conformations in both structures. They differ significantly in the relative orientations of the phenoxypropyl groups at C23 with respect to *N*-methyl acetamidide (**1a**) and ethylmethoxy (**1c**) substituents on N1. Refinement of both (*R*) and (*S*) forms was carried out and the absolute structural parameter, *R*-factor and standard uncertainties on the bond lengths were best for the (*S*) form. Therefore, the stereochemistry was determined to be (*S*) at C28 and C28′ for **1a** and **1c** (Fig. 2).

The benzimidazolone group is approximately perpendicular to the mean plane of the piperidine ring and both substituents on the piperidine ring are in equatorial positions.

3. Conclusion

We have developed an asymmetric synthetic route towards a potential development candidate acting at the NOP receptor. The route utilises a Noyori asymmetric reduction to chiral alcohol **5** followed by inversion of the stereocentre by means of Mitsunobu coupling to give excellent enantiomeric purity. The methodology was applied to a series of piperidinyl-benzimidazolones suitable for medium scale production to support early development studies. The desired (*S*) configuration was confirmed by X-ray crystallography.

4. Experimental section

4.1. Materials and methods

NMR spectra were recorded using a Bruker DPX 400 or DRX 400 instrument with tetramethylsilane as an internal standard. The chemical shifts are reported in δ values (parts per million). The following notations are used for ^{1}H NMR signal patterns: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a Perkin Elmer Spectrum 1000 FT-IR spectrometer. Optical rotations were recorded on an Optical Activity AA-1000 polarimeter. High resolution mass spectra (HRMS) were recorded on an Applied Biosystems Inc Mariner (TOF) instrument, error limit <5 ppm. HPLC analyses were recorded on a Perkin Elmer Integral 4000 Quaternary HPLC system with UV detection or a Perkin Elmer Series 200 HPLC system with 200 Diode Array detectors. Chiralpak AD or Chiracel OD (Daical) columns (250×4.6 mm) were used for enantiomeric ratio determinations and Max RP C12 (Phenomenex) columns (150×4.6 mm, 4 μm) or Xterra RP C18 (Waters) columns (100×4.6 mm, 5 μm) for purity determinations. The (*S*) enantiomers were eluted first on the Chiralpak AD column (isohexane/isopropanol/diisopropylethyalamine 80/20/0.1), but the order of elution was reversed on the Chiracel OD columns. Gas chromatographic (GC) analysis was carried out using a β-cyclodextrin dimethyl column (30×0.32 mm, oven temperature 75 °C) on a Agilent GC 6890 instrument with FID detector and ChemStation software. Thin layer chromatography (TLC) was carried out using Kieselgel 60 F_{254} aluminium backed plates (Merck). Matrix silica gel, particle size 0.040–0.063 mm, was used for column chromatography. Solvents used were of commercial grades from either Aldrich or BDH and used without further purification. Petrol refers to petroleum ether 40–60 °C fraction.

4.2. (R)-3-Hydroxy-4-methyl-methylpentanoate (7)[18]

(*S*)-BINAP (2.5 g, 4.02 mmol) and bis-(2-methylallyl)cycloocta-1,5-diene ruthenium (1.25 g, 3.91 mmol) were suspended in de-gassed acetone (1 L). After stirring for 5 min, 0.29 M HBr in methanol (34.4 mL, 8.44 mmol) was added and the mixture stirred at room temperature for 1 h to give a dark brown solution. Acetone was removed under reduced pressure and a de-gassed solution of methyl isobutyrylacetate **6** (60.0 g, 0.42 mol) in methanol (800 mL) was added. This mixture was heated at 60 °C under hydrogen (1 atm) for 18 h. Methanol was removed under reduced pressure and the residue digested with a mixture of petrol/ethyl acetate (200 mL, 1/1). After filtering off the catalyst residue, the filtrate was concentrated and then filtered through silica gel (1 kg), eluting with petrol/ethyl acetate (1/1) to give (*R*)-3-hydroxy-4-methyl-methylpentanoate **7**, as an orange liquid, (65.1 g, 99%). Enantiomeric ratio by chiral GC >98:2. Lit.[18] $[\alpha]_D$ −43.9 (*c* 1.00, $CHCl_3$) for other enantiomer; $[\alpha]_D$ +37.1 ($CHCl_3$). IR (thin film) 3472, 2961, 1736, 1439, 1369, 1279, 1171, 1055, 996, 880, 847 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, d, *J*=6.5 Hz), 0.96 (3H, d, *J*=6.5 Hz), 1.71 (1H, m), 2.41 (2H, dd, *J*=9.5 and 16.5 Hz), 2.51 (2H, dd, *J*=4.0 and 16.5 Hz), 2.80 (1H, d, *J*=4.0 Hz), 3.72 (3H, s), 3.78 (1H, m). ^{13}C NMR ($CDCl_3$): δ 17.7, 18.4, 33.2, 38.3, 51.8, 72.7, 173.9. HRMS (TOF) $(M+H)^+$ calculated for $C_7H_{15}O_3$: 147.1016, found: 147.1013.

4.3. (R)-4-Methylpentan-1,3-diol (8)[19]

A 1 M solution of lithium aluminium hydride in THF (445 mL, 0.45 mol) was added over 40 min to a solution of (*R*)-3-hydroxy-4-methyl-methylpentanoate **7** (65.0 g, 0.44 mol) in THF (600 mL) cooled with an ice/methanol bath. The

mixture was stirred at room temperature for 30 min and then for 20 min at 40 °C. Cautious addition of water (17 mL) to the cooled reaction mixture was followed by the addition of 4 N NaOH (17 mL) and then further by water (51 mL). The inorganic precipitate was filtered off through Celite and further extracted with warm ethyl acetate/dichloromethane mixture (600 mL, 2/1). Solvents were removed from the combined extracts and the residue dissolved in dichloromethane and dried over sodium sulfate. Removal of solvents at reduced pressure gave (*R*)-4-methylpentan-1,3-diol **8** as a clear liquid (46.0 g, 87%). $[\alpha]_D$ +13.5 ($CHCl_3$). IR (thin film) 3306, 2959, 1469, 1386, 1368, 1139, 1053, 973, 958, 891, 843 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (3H, d, J=7.0 Hz), 0.94 (3H, d, J=7.0 Hz), 1.65–1.71 (3H, br m), 2.42 (1H, br s), 2.57 (1H, br s), 3.61 (1H, br s), 3.80–3.92 (2H, br m). ^{13}C NMR ($CDCl_3$): δ 17.6, 18.4, 34.0, 35.0, 62.3. HRMS (TOF) $(M+H)^+$ calculated for $C_6H_{15}O_2$: 119.1067, found: 119.1073 (error 5.5 ppm, due to poor ionisation).

4.4. (R)-Methanesulfonic acid 3-hydroxy-4-methyl-pentyl ester (5)[12c]

(*R*)-4-Methylpentan-1,3-diol **8** (46.0 g, 0.39 mol) was dissolved in dichloromethane (400 mL), cooled with an ice/methanol bath and diisopropylethylamine (68.0 mL, 0.39 mol) added. A solution of methanesulfonyl chloride (30.0 mL, 0.39 mol) in dichloromethane (200 mL) was added over 1 h. The reaction mixture was then poured into ice cold water (300 mL), the layers separated and the organic layer washed with chilled water and then with brine. Removal of solvent after drying with sodium sulfate gave the crude product, which was filtered through a silica gel column (450 g), eluting with petrol/ethyl acetate 3/2. (*R*)-Methanesulfonic acid 3-hydroxy-4-methyl-pentyl ester **5** was obtained as a pale yellow oil (64.4 g, 84%). $[\alpha]_D$ +41.4 ($CHCl_3$). IR (thin film) 3544, 3025, 2964, 2877, 1470, 1351, 1174, 1144, 1094, 1057, 953, 914, 850, 813 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (6H, d, J=7.0 Hz), 1.62–1.78 (3H, m), 1.91–2.0 (1H, m), 3.02 (3H, s), 3.52–3.59 (1H, m), 4.35–4.40 (1H, s), 4.43–4.49 (1H, m). ^{13}C NMR ($CDCl_3$): δ 17.3, 18.5, 33.3, 33.9, 37.2, 68.0, 72.3. HRMS (TOF) $(M+H)^+$ calculated for $C_7H_{17}O_4S$: 197.0842, found: 197.0842.

4.5. (S)-Methanesulfonic acid 3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl ester (2)

Triphenylphosphine (39.3 g, 0.15 mol), 5-methoxy-2-methylphenol[20] **4** (20.7 g, 0.15 mol) and (*R*)-1-methanesulfonyloxy-4-methyl-pentan-3-ol **5** (29.4 g, 0.15 mol) were added to dry toluene (250 mL) and the solution cooled to 5 °C. A solution of diisopropyl azodicarboxylate (DIAD) (30.3 g, 0.15 mol) in toluene was added over 90 min, maintaining the temperature below 10 °C. The solution was then left at room temperature overnight. The precipitated triphenylphosphine oxide was filtered off and the filtrate washed with water, dilute sodium hydroxide solution, water and finally brine. Toluene was removed under reduced pressure and replaced with diethyl ether/heptane to precipitate further triphenylphosphine oxide on cooling. The crude residue from the filtrate was then chromatographed on silica gel (720 g), eluting with a gradient of petrol/ethyl acetate 6/1 to 3/1. (*S*)-Methanesulfonic acid 3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl ester **2** was obtained as a yellow liquid (23.3 g, 40%). (It was found to contain 15% 4-methyl-pent-3-en-1-ol 1-methanesulfonate **9**.) $[\alpha]_D$ −24.6 ($CHCl_3$, impure). IR (thin film) 2965, 2838, 1698, 1613, 1589, 1506, 1468, 1421, 1355, 1284, 1260, 1197, 1176, 1129, 1112, 1041, 973, 817 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (3H, d, J=7.0 Hz), 0.97 (3H, d, J=7.0 Hz), 2.03–2.11 (3H, m), 2.14 (3H, s), 2.86, (3H, s), 3.77 (3H, s), 4.22–4.33 (2H, m), 4.36–4.42 (1H, m), 6.38 (1H, dd, J=2.5 and 8.0 Hz), 6.44 (1H, d, J=2.5 Hz), 7.02 (1H, d, J=2.5 Hz). ^{13}C NMR ($CDCl_3$): δ 15.7, 17.3, 18.0, 30.1, 30.6, 37.0, 55.4, 67.3, 80.4, 100.1, 103.9, 119.5, 131.0, 157.0, 158.4. HRMS (TOF) $(M+H)^+$ calculated for $C_{15}H_{25}O_5S$: 317.1417, found: 317.1411.

4.6. 2-(3-{1-[3-(5-Methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-2-oxo-2,3-dihydro-benzimidazol-1-yl)-N-methyl-acetamide methanesulfonate (1a)

A mixture of (*S*)-methanesulfonic acid 3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl ester **2** (17.2 g, 54.4 mmol, purity ~85%), *N*-methyl-2-(2-oxo-3-piperidin-4-yl-2,3-dihydro-benzimidazol-1-yl)-acetamide **12a**[12b] (16.5 g, 57.2 mmol), diisopropylethylamine (12.5 mL, 71.7 mmol) and sodium iodide (0.5 g, 3.33 mmol) was heated at reflux in acetonitrile (350 mL) for 10 h. After filtering off a small quantity of insoluble material, acetonitrile was removed under reduced pressure and the residue partitioned between water and dichloromethane. The organic layer was washed with water and then with brine and dried over sodium sulfate. The crude product (32.0 g) was chromatographed on silica gel (1.0 kg), eluting with dichloromethane and then a gradient of 2% ethanol increasing to 5%. 2-(3-{1-[3-(5-Methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-2-oxo-2,3-dihydro-benzimidazol-1-yl)-*N*-methyl-acetamide **1a** was obtained as viscous gum (13.0 g, 66 %). Purity 97.7% by HPLC (Phenomenex RP18 column, 15 cm×0.46 cm, 5 μm, 230 nm, flow 1 mL/min, 30 °C; mobile phase: A=water+0.1% formic acid, B=acetonitrile+0.1% formic acid; gradient of A/B 95/5 for 5 min then increased to 10/90 over 8 min followed by 5 min at 10/90); enantiomeric ratio 100:0 by chiral HPLC (Chiralpak AD column, 25 cm×0.46 cm, flow 1 mL/min, 30 °C; mobile phase: isohexane/isopropanol/diethylamine 80/20/0.1). $[\alpha]_D$ −6.3 (methanol), $[\alpha]_D$ −41.3 ($CHCl_3$). IR (CH_2Cl_2) 3684, 3601, 3445, 3356, 2962, 2812, 1698, 1613, 1588, 1536, 1504, 1492, 1468, 1340, 1318, 1196, 1163, 1228, 1112, 1016, 997, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.97 (3H, d, J=7.0 Hz), 1.00 (3H, d, J=7.0 Hz), 1.75–1.87 (4H, m), 1.96–2.05 (1H, m), 2.05–2.17 (2H, m), 2.16 (3H, s), 2.38–2.54 (4H, m), 2.79 (3H, d, J=5.0 Hz), 2.98 (1H, br d, J=12.0 Hz), 3.10 (1H, br d, J=12.0 Hz), 3.76 (3H, s), 4.25 (1H, dd, J=5.0 and 11.5 Hz), 4.33–4.42 (1H, m), 4.50 (2H, s), 6.13 (1H, br s), 6.36 (1H, dd, J=2.5 and 8.0 Hz), 6.63

(1H, d, J=2.5 Hz), 7.02 (1H, d, J=8.0 Hz), 7.04–7.14 (3H, m), 7.35 (1H, m). ^{13}C NMR ($CDCl_3$): δ 15.8, 17.9, 18.0, 26.3, 28.0, 29.2, 29.4, 31.2, 45.3, 51.6, 52.8, 53.7, 54.8, 55.3, 80.3, 100.8, 102.9, 108.3, 110.3, 119.7, 121.5, 122.0, 128.3, 129.0, 130.6, 153.9, 157.9, 158.8, 167.9. HRMS (TOF) $(M+H)^+$ calculated for $C_{29}H_{41}N_4O_4$: 509.3122, found: 509.3107.

The above free base **1a** (13.0 g, 25.5 mmol) was converted to the methanesulfonate salt by treatment with methanesulfonic acid (2.45 g, 25.5 mmol) in dichloromethane. The solvent was removed under reduced pressure, replaced with acetone, taken to low volume and a small volume of diethyl ether added to give a crystalline solid. A second crystallisation from acetone gave 2-(3-{1-[3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-2-oxo-2,3-dihydro-benzimidazol-1-yl)-*N*-methyl-acetamide methanesulfonate as a white solid (12.8 g, 83%). Purity by HPLC 99.5%, enantiomeric ratio by chiral HPLC 100:0. $[\alpha]_D$ +27.8 (methanol), $[\alpha]_D$ +7.0 ($CHCl_3$). IR (KBr) 3286, 2964, 2687, 1704, 1613, 1588, 1496, 1467, 1412, 1284, 1260, 1196, 1162, 1128, 1040, 999, 956, 926, 835, 772, 751, 737, 700, 656, 613, 553, 526 cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.01 (3H, d, J=6.5 Hz), 1.05 (3H, d, J=6.5 Hz), 2.02–2.19 (6H, m), 2.16 (3H, s), 2.70 (3H, s), 2.76 (3H, s), 2.73–2.84 (2H, m), 3.18–3.32 (4H, m), 3.69–3.78 (2H, m), 3.76 (3H, s), 4.26 (1H, dd, J=6.0 and 11.0 Hz), 4.54 (2H, s), 4.53–4.61 (1H, m), 6.43 (1H, dd, J=2.5 and 8.0 Hz), 6.52 (1H, d, J=2.5 Hz), 7.04 (2H, m), 7.09 (2H, m), 7.32 (1H, d, J=8.0 Hz), 12.5 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 15.4, 17.3, 17.5, 24.7, 25.4, 25.8, 30.0, 39.8, 43.0, 47.2, 51.3, 53.1, 55.0, 78.4, 100.1, 104.3, 108.4, 108.5, 118.3, 120.8, 120.8, 127.6, 129.6, 130.7, 152.8, 156.4, 158.6, 166.9.

*4.7. 4-[2-Oxo-3-(4H-[1,2,4]triazol-3-ylmethyl)-2,3-dihydro-benzimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**11b**)*

A magnetically stirred solution of **10** (4.99 g, 15.7 mmol) in anhydrous *N*,*N*-dimethylformamide (50 mL) was treated with sodium hydride (60% dispersion in mineral oil, 0.63 g, 15.7 mmol) added portion-wise under a nitrogen atmosphere. The reaction mixture was stirred for 1 h to give a colourless solution. *N*-Formyl-2-chloroacetamidrazone[22] (1.78 g, 15.7 mmol) in anhydrous *N*,*N*-dimethylformamide (5.0 mL) was added dropwise with cooling to maintain ambient temperature and the resultant mixture stirred overnight. The intermediate product was not isolated, but ring closure was effected by heating the reaction mixture in *N*,*N*-dimethylformamide at 140 °C for 1 h. The resulting mixture was chromatographed on silica gel with a gradient elution with dichloromethane/ethanol 98/2 to 94/6 to give the title compound as a yellow gum in 27% yield. ESI m/z=399.3 $[M+H]^+$. IR (KBr) 3366, 3070, 2978, 2934, 2852, 1689, 1618, 1606, 1493, 1438, 1414, 1367, 1345,1315, 1274, 1240, 1192, 1160, 1137, 1076, 1064, 1048, 1018, 998, 985, 944, 870, 858, 830, 808, 754, 736, 687, 661, 641, 604 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.50 (9H, s), 1.78 (2H, d, J=12.5 Hz), 2.31 (2H, dq, J=12.5 and 4.2 Hz), 2.84 (2H, t, J=12.2 Hz), 4.29 (2H, m), 4.47 (1H, tt, J=4.1 and 12.3 Hz), 5.21 (2H, s), 7.05–7.14 (3H, m), 7.19–7.24 (1H, m), 8.06 (1H, br s), 12.5 (1H, br s). ^{13}C NMR (CD_3OD): δ 28.7 (3C), 30.1 (2C), 38.7, 43.8–45.3 (br, 2C), 52.9, 81.3, 109.7, 110.1, 122.5, 122.8, 129.7, 130.3, 146.0–147.5 (br, 2C), 155.1, 156.4. (Note: in this CD_3OD spectrum, the triazole carbons are weak and broad, while in a $CDCl_3$ spectrum they are not detected. In both solvents, the ^{13}C peaks for the carbons *ortho* to the piperidine nitrogen are broad due to restricted rotation of the carbamate group.) HRMS (TOF) $(M+H)^+$ calculated for $C_{20}H_{27}N_6O_3$: 399.21236, found: 399.21391.

The above Boc protected product (**11b**) was deprotected with TFA treatment and evaporated to dryness to give **12b**. This crude bis-TFA salt was reacted directly with the mesylate **5**. Attempted isolation of the free base resulted in negligible recovery due to high water solubility.

*4.8. 1-{1-[(S)-3-(5-Methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-3-(4H-1,2,4-triazol-3-ylmethyl)-1,3-dihydro-benzimidazol-2-one methanesulfonate (**1b**)*

Prepared in a similar manner to **1a** using **12b** in place of **12a**, but using 3 equiv of diisopropylamine: purity by HPLC 98.68%, enantiomeric ratio 100:0. $[\alpha]_D$ +26.7 (methanol). IR (KBr) 3407, 2962, 2644, 1694, 1612, 1589, 1506, 1493, 1409, 1320, 1283, 1259, 1196, 1162, 1128, 1111, 1040, 1000, 978, 955, 834, 795, 752, 700, 635, 600 cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.02 (3H, d, J=6.5 Hz), 1.05 (3H, d, J=6.5 Hz), 2.02–2.24 (5H, m), 2.16 (3H, s), 2.89 (2H, dq, J=3.5 and 13.0 Hz), 3.25 (2H, br t, J=13.0 Hz), 3.26–3.34 (2H, m), 3.72–3.81 (2H, m), 3.76 (3H, s), 4.37 (1H, q, J=5.5 Hz), 4.64 (1H, tt, J=4.0 and 12.5 Hz), 5.32 (2H, s), 6.42 (1H, dd, J=2.5 and 8.0 Hz), 6.53 (1H, d, J=2.0 Hz), 7.02 (1H, d, J=9.0 Hz), 7.08–7.13 (2H, m), 7.13–7.18 (1H, m), 7.44 (1H, d, J=7.5 Hz), 8.92 (1H, s). ^{13}C NMR (D_2O): δ 14.7, 16.5, 17.2, 24.9, 26.1 (2C), 30.3, 37.5, 48.4, 52.1, 52.3, 54.2, 55.5 (2C), 80.3, 101.0, 105.6, 108.8, 109.3, 120.3, 122.11, 122.2, 127.6, 128.5, 131.4, 145.4, 154.1, 156.4, 156.9, 158.1. HRMS (TOF) $(M+H)^+$ calculated for $C_{29}H_{39}N_6O_3$: 519.3078, found: 519.3061.

*4.9. 1-(2-Methoxy-ethyl)-3-{1-[(S)-3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-1,3-dihydro-benzimidazol-2-one methanesulfonate (**1c**)*

The *N*-methoxyethyl derivative **1c** was prepared prior to the development of the described chiral synthetic route and the racemate obtained by direct alkylation of the coupled benzimidazole (**1d**) with 2-bromoethyl methyl ether as the final step.[12b] Separation of enantiomers was achieved by chiral HPLC. Thus 6.5 g of racemic material was separated over several runs on a Chiralpak AD (250×20 mm) column, eluting with isohexane/isopropanol 9/1, 2.63 g, 5.31 mmol of the first eluting (*S*)-enantiomer was obtained and converted to the methanesulfonate salt by treatment with methanesulfonic acid (510 mg, 5.31 mmol). Crystallisation from acetone/ether

gave 1-(2-methoxy-ethyl)-3-{1-[(*S*)-3-(5-methoxy-2-methyl-phenoxy)-4-methyl-pentyl]-piperidin-4-yl}-1,3-dihydro-benzimidazol-2-one methanesulfonate **1c** as a white solid (2.51 g, 4.24 mmol) in 79.8% yield. Purity by HPLC 99.03%, enantiomeric ratio by chiral HPLC 100:0. $[\alpha]_D$ +6.4 ($CHCl_3$). IR (KBr) 3449, 2964, 2938, 2900, 2835, 2677, 2582, 1692, 1614, 1589, 1505, 1496, 1428, 1405, 1368, 1327, 1280, 1257, 1234, 1197, 1130, 1073, 1059, 1032, 993, 976, 960, 930, 896, 844, 804, 768, 743, 700, 645, 591,572, 553, 535, 523, 507 cm^{-1}. ^1H NMR (CD_3OD): δ 1.02 (3H, d, J=7.0 Hz), 1.06 (3H, d, J=7.0 Hz), 2.05–2.20 (5H, m), 2.16 (3H, s), 2.71 (3H, s), 2.74–2.89 (2H, dq, J=2.5 and 13.0 Hz), 3.23 (2H, t, J=17.8 Hz), 3.30 (3H, s), 3.30–3.32 (3H, m), 3.67 (2H, t, J=5.2 Hz), 3.76 (3H, s), 4.06 (2H, t, J=5.2 Hz), 4.35 (1H, q, J=5.5 Hz), 4.58 (1H, tt, J=4.2 and 12.0 Hz), 6.42 (1H, dd, J=2.3 and 8.0 Hz), 6.52 (1H, br s), 7.04 (1H, d, J=8.0 Hz), 7.10–7.15 (2H, m), 7.20–7.24 (1H, m), 7.31 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 15.8, 17.1, 18.3, 24.9, 26.0, 26.1, 30.5, 39.4, 41.4, 47.4, 52.2, 53.6, 55.2, 55.4, 59.0, 70.4, 79.1, 100.0, 104.3, 108.6, 110.4, 119.2, 121.6, 122.0, 126.9, 129.7, 131.2, 153.6, 156.3, 158.9. HRMS (TOF) $(M+H)^+$ calculated for $C_{29}H_{41}N_3O_4$: 496.3151, found: 496.3169.

*4.10. X-ray structural determination of **1a** and **1c***

Compound **1a** was dissolved in methanol and 1 M HCl in diethyl ether added to cause precipitation of a white solid. The solid was filtered and washed with diethyl ether. The solid was then dissolved in hot isopropanol and left to stand to give fine colourless needles. A colourless crystal of **1a**$Cl\cdot 2(H_2O)$, space group $P2_1$, a=9.608(2) Å, b=30.059(5) Å, c=10.868(2) Å, β=100.970(10)°, V=3081.4(10) $Å^3$, was coated in Nujol and vacuum grease and then mounted on glass fibres. Final R indices [$I>2\sigma(I)$, 4920 data] $R1$=0.0473, $wR2$=0.1191; R indices (all data, 5760) $R1$=0.0621, $wR2$=0.1319; absolute structural parameter −0.03(9); largest diff. peak and hole 0.272 and −0.348 e $Å^{-3}$.

Compound **1c** was dissolved in methanol and 1 M HCl in diethyl ether added to cause precipitation of a white solid. The solid was filtered and washed with diethyl ether. The solid was then dissolved in acetone and diethyl ether added giving fine colourless needles on standing. A colourless crystal of **1c**$Cl\cdot 0.5(C_4H_{10}O)$, space group $P2_1$, a=8.401(5) Å, b=31.656(5) Å, c=11.955(5) Å, β=98.756(5)°, V=3142(2) $Å^3$, was coated in Nujol and vacuum grease and then mounted on glass fibres. Final R indices [$I>2\sigma(I)$, 4530 data] $R1$=0.0539, $wR2$=0.1368; R indices (all data, 5854) $R1$=0.0762, $wR2$=0.1547; absolute structural parameter −0.10(9); largest diff. peak and hole 0.381 and −0.302 e $Å^{-3}$.

Diffraction data were measured at 160(2) K on a Bruker AXS P4 four-circle diffractometer[23] fitted with graphite-monochromated Mo Kα radiation, 0.71073 Å. Semiempirical absorption corrections by ϕ-scans were applied. Structural solution and refinements (full-matrix least-squares on F^2) were performed using the SHELXTL 5.1 suite of programs.[24] All hydrogen atoms except aqua were constrained to idealised positions and refined using a riding model with riding isotropic displacement parameters. Aqua hydrogen atoms for **1a** were found in the difference Fourier map and during refinement, the O–H distance was restrained to 0.9(5) Å. Crystallographic data for **1a** and **1c** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK as CCDC reference numbers 658438 and 658439, respectively.

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