Unusual synthesis of 1-(4-fluorobenzyl)-*N*-(1-(1-(4-fluorobenzyl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-yl)piperidin-4-yl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-amine

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Abstract

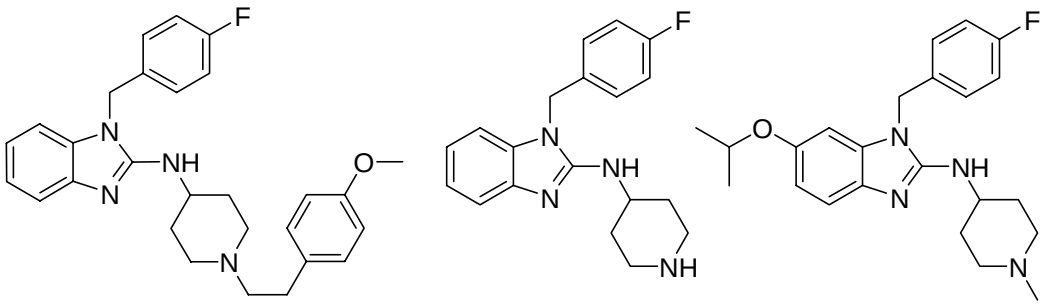
The title compound was formed while attempting the synthesis of 1-(4-fluorobenzyl)-6-isopropoxy-*N*-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-2-amine, a candidate anti-histamine. Its formation involves an unusual mechanism where 1-(4-fluorobenzyl)-2-chloro-6-isopropoxy-1*H*-benzo[*d*]imidazole reacts with 1-methylpiperidinamine presumably through *N*-demethylation followed by self-catalyzed *N*-diarylation. Apparently the formation of the desired 1-(4-fluorobenzyl)-6-isopropoxy-*N*-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-2-amine is rate limiting and, once formed, it reacts faster with 1-methylpiperidinamine to yield the title compound. A plausible explanation for this unusual behavior is proposed.

Keywords: Antihistamine, *N*-arylation, *N*-demethylation, astemizole, coupling

Introduction

Hismanal® (**1**, astemizole) is a histamine H_1-receptor antagonist which was used clinically to alleviate allergy symptoms until 1999 when it was pulled out of market owing to cardiovascular side effects.[1] Norastemizole (**2**) is a metabolite of astemizole and is found to be a more potent histamine H_1-receptor antagonist with lesser side effects.[2]

We had designed several analogs of norastemizole and during the synthesis of one such analog (**3**), an unusual reaction was encountered which is being reported here. While following literature procedures for similar reactions[3,4] S_NAr amination of 1-(4-fluorobenzyl)-2-chloro-6-isopropoxy-1*H*-benzo[*d*]imidazole (**12**) with 1-methylpiperidin-4-amine (**6**) resulted in formation of 1-(4-fluorobenzyl)-*N*-(1-(1-(4-fluorobenzyl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-yl)-piperidin-4-yl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-amine (**4**).



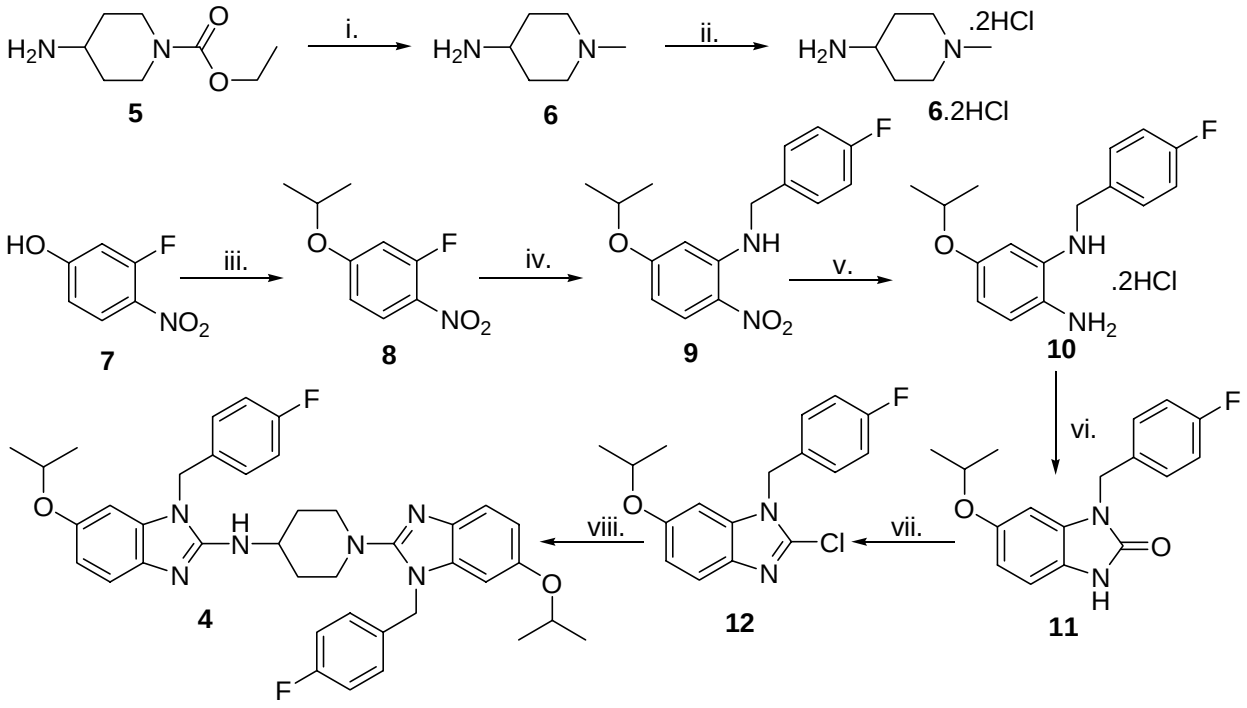
1; Astemizole (Hismanal®) **2 (Norastemizole)** **3**

Figure 1. Molecular structures of astemizole (**1**), norastemizole (**2**) and one of its analogs (**3**).

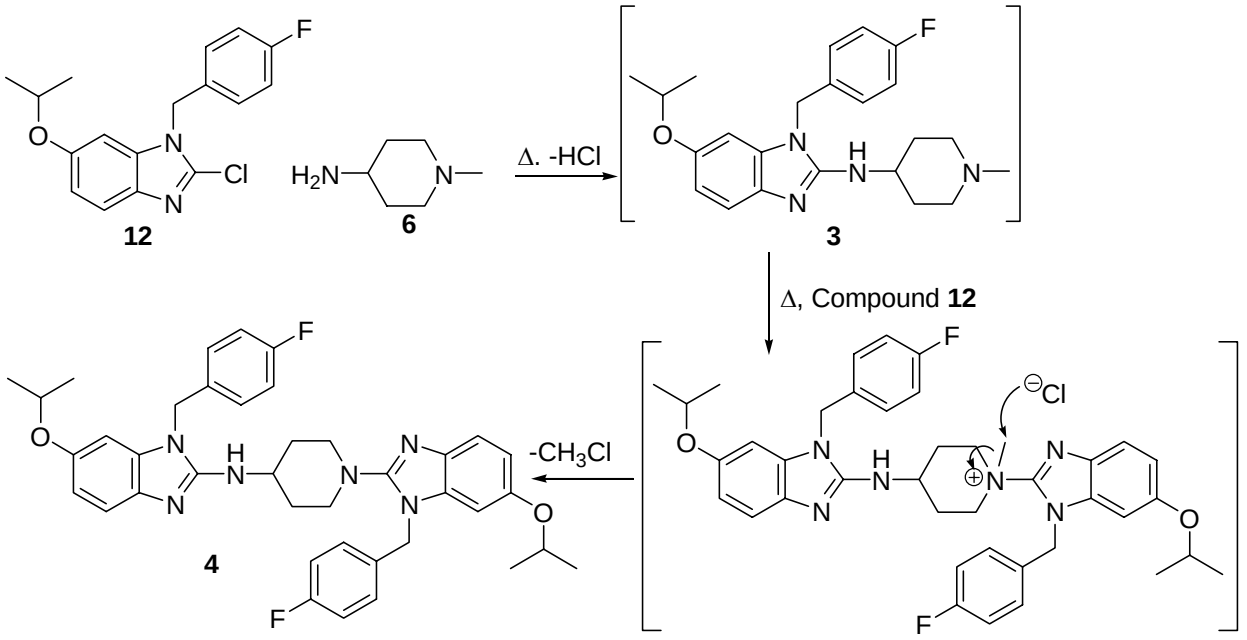
Results and Discussion

Compound **4**, which apparently is easily synthesizable from 2 equivalents of compound **12** and 1 equivalent of 4-piperidinamine, was obtained in a rather unusual fashion while following scheme 1 to prepare compound **3**. Briefly, 1-methylpiperidin-4-amine (**6**) was prepared from commercially available carbamate **5** by $LiAlH_4$ reduction.[5] 3-Fluoro-4-nitrophenol (**7**) was isopropylated under anhydrous basic conditions[6] and aminated[7] by 4-fluorobenzylamine in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce compound **9**. Compound **9** was then reduced by hydrogenation over Raney Ni[8] and isolated as dihydrochloride **10** (free base was found to be air and/or light sensitive). Raney Ni was specifically chosen to avoid *N*-debenzylation. Treatment of compound **10** with 1/3 equivalents of triphosgene under basic conditions[9] resulted in formation of benzimidazolone **11**, which was in turn converted to compound **12** by the action of $POCl_3$.[10] Finally when compound **12** was reacted with two equivalents of compound **6** to obtain compound **3** according to literature reports on similar reactions,[3,4] compound **4** was the only product isolated while substantial amount of compound **12** was recovered. Although synthesis of compound **3** requires one equivalent each of compound **6** and compound **12**, excess of compound **6** was used to trap the released HCl.

Isolation of compound **4** from the final reaction mixture was a surprise since such a reaction is rather atypical if not completely unprecedented.[11] The most plausible mechanism is outlined in Scheme 2. The desired product **3** is probably an intermediate which forms a quaternary salt with another equivalent for 2-chlorobenzimidazole **12** which decomposes to compound **4** after loss of CH_3Cl. Since majority of 2-chlorobenzimidazole **12** was recovered after 72 hr reaction time (*c.f.* Experimental), formation of compound **3** appears to be rate limiting and reaction of compound **3** with compound **6** is much faster than the reaction of compound **12** with compound **6** (Scheme 2).

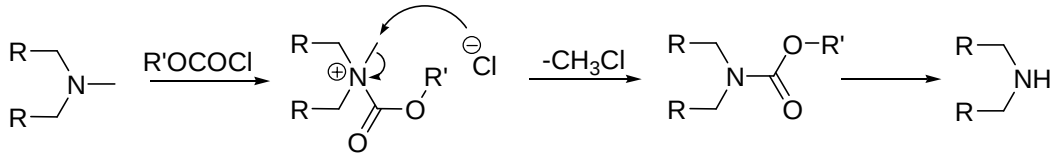


Scheme 1. Synthetic scheme that led to formation of compound **4**. Conditions: i. $LiAlH_4$, Ether, Δ; ii. HCl (g), Ether; iii. Isopropyl iodide, anh. K_2CO_3, 2-butanone, Δ; iv. 4-Fluorobenzylamine, DBU, CH_3CN; v. Raney Ni, H_2, EtOH, and then conc. HCl; vi. Triphosgene, Et_3N, $CHCl_3$; vii. $POCl_3$, viii. Compound **6**, Δ



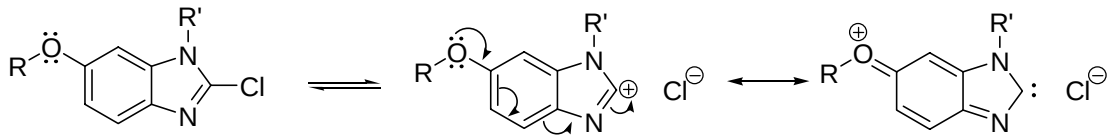
Scheme 2. Proposed mechanism for the formation of compound **4**

A similar mechanism is widely used for N-demethylation using alkyl chloroformates (Scheme 3).[11] Use of simple alkyl chloroformates necessitates an additional carbamate deprotection step but this may be avoided by use of α-chloroethyl chloroformate.[11]



Scheme 3. Mechanism of N-demethylation using alkyl chloroformates

Upon close examination, the apparent feasibility of quaternization of compound **12** may be explained. The cation formed after the ionization of 1-alkyl-2-chloro-6-alkoxy-benzimidazole is resonance stabilized by the lone pair on the O atom (Scheme 4). This also explains why the behavior witnessed during this investigation is not seen earlier in similar situations which were devoid of facilitating alkoxy (or similar group) at the appropriate position.[4]



Scheme 4. Resonance hybrids of 1-alkyl-2-chloro-6-alkoxy-benzimidazole: stabilization of aromatic cation.

In conclusion, a novel mode of amination of 1-(4-fluorobenzyl)-2-chloro-6-isopropyloxy-1*H*-benzo[*d*]imidazole by tertiary amine is reported. The alkoxy group at position 6 appears to play crucial role in this amination process facilitating N-demethylation of the tertiary amine. Although this procedure appears to be applicable to a specific class of compounds, the observation is unprecedented and novel.

Experimental Section

General Procedures. All chemicals and reagents including ethyl 4-aminopiperidine-1-carboxylate (**5**) and 3-fluoro-4-nitrophenol (**7)** were obtained from Aldrich Chemical Co. Column chromatography purifications were undertaken using silica gel (230-400 mesh) obtained from Aldrich Chemical Co. ^{1}H NMR spectra were recorded on a Bruker AMX 500 NMR spectrometer at 500 MHz and mass spectra were obtained on VG-Analytical (Manchester, UK) VG-70 SEQ spectrometer.

1-Methylpiperidin-4-amine (6). A solution of compound **5** (5.16 g, 30 mmol) in dry ether (100 ml) was cooled by an ice-bath to 0-5ºC. Under anhydrous conditions, $LiAlH_4$ (2.84 g, 75 mmol) was added in portions with stirring. After 30 minutes the ice-bath was replaced with an oil-bath and the reaction mixture was slowly heated to reflux (44^{o}C bath temperature). The reaction mixture was refluxed for 17 h. Thin layer chromatography using precoated fluorescent silica gel and a developing solvent of 1:5 MeOH: $CHCl_3$ showed the formation of a slower moving product. After cooling the reaction mixture by an ice-bath, additional amount of ether (100 ml) was added. The unreacted $LiAlH_4$ was quenched by dropwise addition of 10% aq. NaOH solution until the effervescence subsided. The resulting slurry was filtered and the solid cake was washed with ether (100 ml). Combined filtrate was rotary evaporated under vacuum at rt to obtain compound **6** as clear liquid. Yield 76%. R_f= 0.21 (MeOH/$CHCl_3$, 1:5). The product was characterized as dihydrochloride salt which was formed as follows. Under anhydrous conditions, freshly generated dry hydrogen chloride gas (by action of conc. H_2SO_4 on NaCl) was passed briskly for 3 minutes through the solution of compound **6** (100 mg) in ether (5 ml). The white precipitate thus obtained was retained by decanting the majority of the ether and the product was dried under vacuum.

Compound 6. m.p. 237-239^{o}C [Lit.[12] m.p. 242-245^{o}C] ^{1}H NMR (500 MHz, D_2O) δ (ppm): 1.81-1.87 (2H, m, 2x-CH_a), 2.19-2.23 (2H, m, 2x-CH_b), 2.77 (3H, s, N-CH_3), 3.02-3.06 (2H, m, 2x-NCH_a) and 3.41-3.51 (3H, m, 2x-NCH_b; 4-NCH). MS (FAB+), *m/z* (rel. intensity): 115 (100) [$M+H^+$], 98 (22).

2-Fluoro-4-isopropoxynitrobenzene (8). To a solution of compound **7** (4.71 g, 30 mmol) in 2-butanone (100 ml) anh. K_2CO_3 (5.5 g. 40 mmol) was suspended. The mixture was refluxed for 1 h under anhydrous conditions. A solution of isopropyl iodide (6.8 g, 40 mmol) in 2-butanone (50 ml) was introduced in the reaction flask through a dropping funnel over 10 min. The resulting mixture refluxed for 17 h. Thin layer chromatography using precoated fluorescent silica gel and a developing solvent of 1:19 EtOAc: hexanes showed the formation of a faster moving product. The reaction mixture was suction filtered to remove inorganic salts and the filtrate was rotary evaporated to dryness. Aq. NaOH solution (10% w/v) was added to the residue and extracted with ether (100 ml). The dried organic layer (anh. Na_2SO_4) was rotary evaporated to yield crude product which was purified by silica gel column chromatography using $CHCl_3$ as eluent. Fractions containing pure product were pooled and rotary evaporated to get the desired product as thick oil.

Compound 8. Yield: 97%. R_f= 0.87 (EtOAc/ hexanes, 1:19); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.36 (6H, d, J=6.0 Hz, 2x-CH_3), 4.57-4.63 (1H, m, -OCH), 6.64-6.71 (2H, m, -$CH^{3,5}$) and 8.03-8.07 (1H, m, -CH^6). HRMS calculated for $C_9H_{10}FNO_3$: 199.0645, found: 199.0643. MS (EI), 70 eV, *m/z* (rel. intensity): 199 (25) [M^+], 157 (100), 141 (16) and 127 (30).

***N*-(4-Fluorobenzyl)-5-isopropoxy-2-nitrobenzenamine (9).** Compound **8** (5.5 g, 27.6 mmol), 4-fluorobenzylamine (4.15 g, 33.3 mmol) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 5.04 g, 33.2 mmol) was dissolved in CH_3CN (150 ml). The resulting mixture was refluxed (bath temperature 90^{o}C) for 17 h. Thin layer chromatography using precoated fluorescent silica gel

and a developing solvent of 1:9 EtOAc:hexanes showed the formation of a slower moving product. The reaction mixture was rotary evaporated to dryness and the residue was purified by silica gel column chromatography using $CHCl_3$ as eluent. Fractions containing pure product were pooled and rotary evaporated to get the desired product as yellow crystalline solid.

Compound 9. Yield: 76%. R_f= 0.62 (EtOAc/ hexanes, 1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.24 (6H, d, J=6.1 Hz, 2x-CH_3), 4.43-4.48 (3H, m, -OCH, N-CH_2), 6.02 (1H, d, J=2.5 Hz, -CH^6), 6.20 (1H, dd, J=9.5, 2.5 Hz, -CH^4), 7.01-7.06 (2H, m, -$CH^{3',5'}$), 7.29-7.32 (2H, m, -$CH^{2',6'}$), 8.12 (1H, d, J=9.5 Hz, -CH^3) and 8.62 (1H, bs, NH). HRMS calculated for $C_{16}H_{17}FN_2O_3$: 304.1223, found: 304.1229. MS (EI), 70 eV, *m/z* (rel. intensity): 304 (27) [M^+], 244 (18), 123 (68) and 109 (100).

***N*$^{1-}$(4-Fluorobenzyl)-5-isopropoxybenzene-1,2-diamine dihydrochloride (10)**. Compound **9** (5.9 g, 19.4 mmol), Raney Ni (7.0 g) and EtOH (300 ml) were charged in a hydrogenation bottle and the Parr hydrogenation apparatus was set-up with H_2 pressure at 60 psi. The reaction was carried out at rt for 6 h during which time the yellow color of the starting material disappeared. Thin layer chromatography using precoated fluorescent silica gel in $CHCl_3$ showed the formation of a slower moving product (air and/or light sensitive). The reaction mixture was filtered over suction in a flask containing conc. HCl (10 ml). The filtrate was rotary evaporated to dryness to yield the desired product as dihydrochloride salt in pure form.

Compound 10. Yield: 95%). R_f= 0.56 ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.11 (6H, d, J=6.1 Hz, 2x-CH_3), 4.30 (2H, s, N-CH_2), 4.40-4.46 (1H, m, -OCH), 6.01 (2H, bs, NH_2^+), 6.05 (1H, d, J=2.5 Hz, -CH^6), 6.19 (1H, dd, J=8.6, 2.5 Hz, -CH^4), 7.10-7.15 (2H, m, -$CH^{3',5'}$), 7.31 (1H, d, J=8.6 Hz, -CH^3), 7.48-7.52 (2H, m, -$CH^{2',6'}$), and 10.18 (3H, bs, NH_3^+). MS (FAB+), *m/z* (rel. intensity): 274 (100) [M^+], 231 (14), 123 (29) and 109 (34).

1-(4-Fluorobenzyl)-6-isopropoxy-1*H*-benzo[d]imidazol-2(3*H*)-one (11). A mixture of compound **10** (6.0 g, 17.27 mmol) and Et_3N (8.7 g, 86.4 mmol) in $CHCl_3$ (100 ml) was cooled by an ice-bath to 0-5ºC. Under anhydrous conditions, a solution of triphosgene (2.05 g, 7.0 mmol) was added dropwise over 30 min. The ice-bath was removed and the reaction mixture was stirred for 17 h at room temperature. Thin layer chromatography using precoated fluorescent silica gel and a developing solvent of 1:19 MeOH:$CHCl_3$ showed the formation of a slower moving product. The reaction mixture was evaporated to dryness under vacuum. The residue was dissolved in $CHCl_3$ (200 ml) and extracted with water (200 ml). The dried $CHCl_3$ layer (anh. Na_2SO_4) was rotary evaporated and the resulting residue triturated in ether (100 ml). The white precipitate thus obtained was suction filtered, washed with cold ether (2 x 10 ml) and dried.

Compound 11. Yield: 81%. R_f= 0.34 (MeOH/$CHCl_3$, 1:19). m.p. 182-183ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.25 (6H, d, J=6.1 Hz, 2x-CH_3), 4.34-4.39 (1H, m, -OCH), 4.98 (2H, s, N-CH_2), 6.41 (1H, d, J=1.8 Hz, -CH^7), 6.59 (1H, dd, J=8.5, 1.8 Hz, -CH^5), 6.94 (1H, d, J=8.5 Hz, -CH^4), 6.96-7.00 (2H, m, -$CH^{3',5'}$), 7.27-7.30 (2H, m, -$CH^{2',6'}$), and 9.40 (1H, bs, NH). HRMS calculated for $C_{17}H_{17}FN_2O_2$: 300.1274, found: 300.1270. MS (EI), 70 eV, *m/z* (rel. intensity): 300 (28) [M^+], 258 (40), 140 (8) and 109 (100).

1-(4-Fluorobenzyl)-2-chloro-6-isopropoxy-1*H*-benzo[*d*]imidazole (12). A mixture of compound **11** (4.0 g, 13.32 mmol) and $POCl_3$ (5.1 g, 33.3 mmol) was heated by an oil-bath at 110°C with stirring for 21 h. Thin layer chromatography using precoated fluorescent silica gel and a developing solvent of 1:19 MeOH:$CHCl_3$ showed the formation of a faster moving product. The reaction mixture was poured over ice-cold aq. NaOH solution (5% w/v) and extracted with ether (2x50 ml). The dried organic layer (anh. Na_2SO_4) was rotary evaporated to dryness and the residue was purified by silica gel column chromatography using $CHCl_3$ as eluent. Fractions containing pure product were pooled and rotary evaporated to get the desired product as while solid.

Compound 12. Yield: 87%. R_f= 0.77 (MeOH/$CHCl_3$, 1:19). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.28 (6H, d, J=6.1 Hz, 2x-CH_3), 4.43-4.50 (1H, m, -OCH), 5.26 (2H, s, N-CH_2), 6.65 (1H, d, J=2.3 Hz, -CH^7), 6.86 (1H, dd, J=8.8, 2.3 Hz, -CH^5), 6.97-7.01 (2H, m, -$CH^{3',5'}$), 7.12-7.15 (2H, m, -$CH^{2',6'}$) and 7.55 (1H, d, J= 8.8 Hz, -CH^4).

1-(4-Fluorobenzyl)-*N*-(1-(1-(4-fluorobenzyl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-yl)piperidin-4-yl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-amine (4). While maintaining anhydrous conditions, compounds **12** (3.5 g, 11 mmol) and **6** (2.5 g, 22 mmol) were heated together at 120°C by using an oil-bath for 72 h. Thin layer chromatography using precoated fluorescent silica gel and a developing solvent of 1:9 MeOH:$CHCl_3$ revealed formation of a new compound while unreacted starting materials were still prominently visible. The reaction mixture was subjected to silica gel column chromatography with $CHCl_3$ as the eluent and gradually increasing the polarity with MeOH. Fractions obtained from $CHCl_3$ yielded compound **12** (2.9 g). Fractions eluting with 2% MeOH in $CHCl_3$ resulted in isolation of the new product which was characterized as 1-(4-fluorobenzyl)-*N*-(1-(1-(4-fluorobenzyl)-6-isopropoxy-1*H*-benzo[*d*]-imidazol-2-yl)piperidin-4-yl)-6-isopropoxy-1*H*-benzo[*d*]imidazol-2-amine (**4**).

Compound 4. Yield: 65%, based on recovered **12**); m.p. 196-197ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.24 (6H, d, J=6.1 Hz, 2x-CH_3), 1.27 (6H, d, J=6.1 Hz, 2x-CH_3), 1.50-1.58 (2H, m, 2x-CH_a), 2.10-2.14 (2H, m, 2x-CH_b), 3.06-3.12 (2H, m, 2x-NCH_a), 3.32-3.37 (2H, m, 2x-NCH_b), 3.78 (1H, bs, NH), 4.02-4.09 (1H, m, -NHCH), 4.36-4.45 (2H, m, 2x-OCH), 4.96 (2H, s, N-CH_2), 5.06 (2H, s, N-CH_2), 6.48 (1H, d, J=2.3 Hz, -CH^7), 6.59 (1H, d, J=2.2 Hz, -$CH^{7'}$), 6.72 (1H, dd, J=8.6, 2.3 Hz, -CH^5), 6.77 (1H, dd, J=8.5, 2.2 Hz, -$CH^{5'}$), 6.94-7.01 (4H, m, 2x-$CH^{3'',5''}$), 7.05-7.10 (4H, m, 2x-$CH^{2'',6''}$), 7.34 (1H, d, J= 8.6 Hz, -CH^4) and 7.46 (1H, d, J= 8.5 Hz, -$CH^{4'}$). IR, KBr Disc, ν: 3260, 2974, 1717, 1629, 1606, 1509, 1479, 1273, 1224, 970 and 823 cm^{-1}. UV-Vis, MeOH, λ_{max}: 223, 250 and 297 nm. HRMS calculated for $C_{39}H_{42}F_2N_6O_2$: 664.3337, found: 664.3331. MS (EI), 70 eV, *m/z* (rel. intensity): 664 (100), 621 (13), 365 (17), 300 (13), 256 (32), 214 (21) and 109 (63).

Acknowledgements

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