Synthesis of novel fluorophenylaryl / heteroaryl ether derivatives

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Abstract
A detailed syntheses of some fluorophenylaryl / heteroaryl ether derivatives **1a, b–4a, b** have been described which was accomplished by using a variety of convenient phenolic coupling methods and subsequent Pd-C catalyzed hydrogenation of the coupled intermediates. The compounds synthesized are structurally similar to a number of anti-inflammatory agents.

Keywords: Synthesis, flurophenylaryl / heteroaryl, ether derivatives, phenolic coupling, hydrogenation

Introduction

Earlier we published a research article where we described briefly the existence of intramolecular C-F---H-N hydrogen bonding using compounds **1-4**, which were designed as covalently-linked base pair models of **F** (difluorotoluene deoxynucleoside) and **A** (adenine deoxynucleoside) (Figure 1).[1,2] Although our study failed to find any C-F---H-N intramolecular hydrogen bonding and supported Kool's theory that shape complementarities between the base pairs play the major role in DNA replication fidelity,[3] several papers have been published subsequently showing intramolecular C-F--H-N interactions and the role of organic fluorine in hydrogen bonding by means of density functional theory, *ab initio* and MMFF force field calculations.[4] We couldn't explain definitely the reason of not finding intramolecular C-F---H-N hydrogen bonding and it was assumed that the problem might be the design of the compounds. Therefore we didn't proceed for further investigation. Later on we found that our compounds are structurally similar to a number of biologically interesting fluorophenylaryl ether type compounds (Figure 2).[5,6,7] The most promising compounds belonging this class is Flosulide (**I**) and its sulfone analogue (**II**), which have already been proven as selective cyclo-oxygenase-2

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(COX-2) inhibitors[6,7]. Besides these, 5'-cyano-2'(2,4-difluorophenoxy)-biphenyl-4-sulfonamide (**III**), 2-benzyl-6-cyclohexylsulfanyl-5-(3-fluoro-phenoxy)-1H-benzimidazole (**IV**) have anti-inflammatory properties[8,9] and 4-(biphenyl-4-yloxy)-3-fluorobenzoic acid (**V**) is a potent human prostatic 5-α-reductase inhibitor.[10] Therefore these compounds are therapeutically important as analgesic, antipyretic, antiarthritic (especially rheumatoid arthritis) and anticancer agents. The compounds **1-4** are expected to have similar biological activities due to their structural similarities with these compounds (Figure 2). In this paper we disclose the detailed synthetic procedures with characterization of these compounds. These compounds can be utilized as the lead compound for the design of some biologically active compounds.

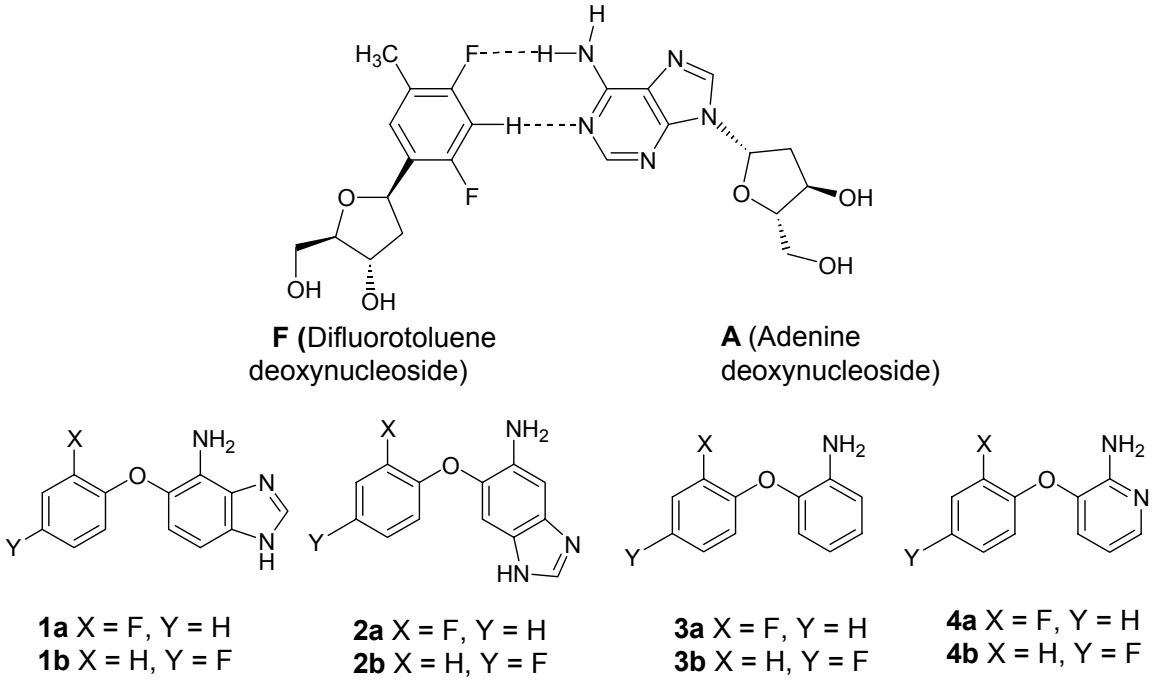


Figure 1

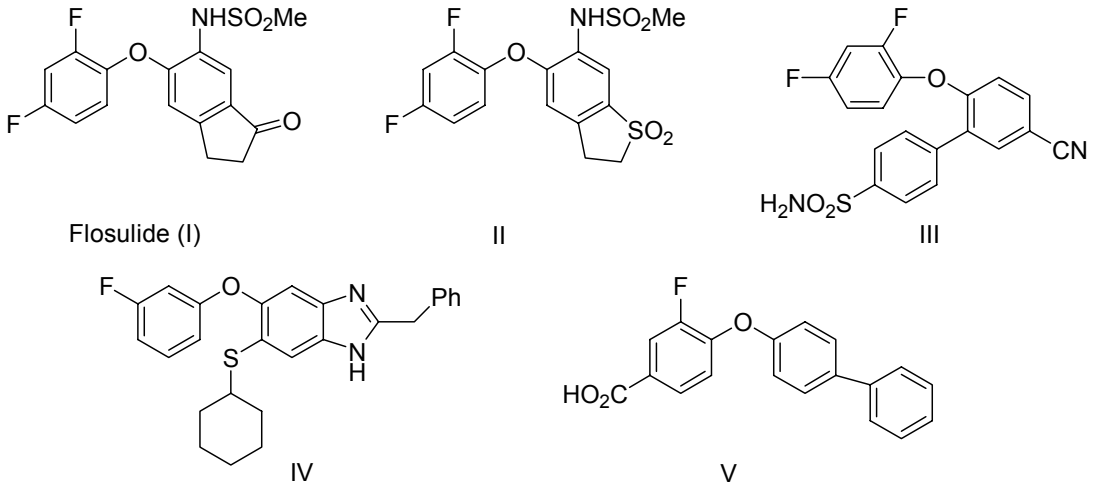
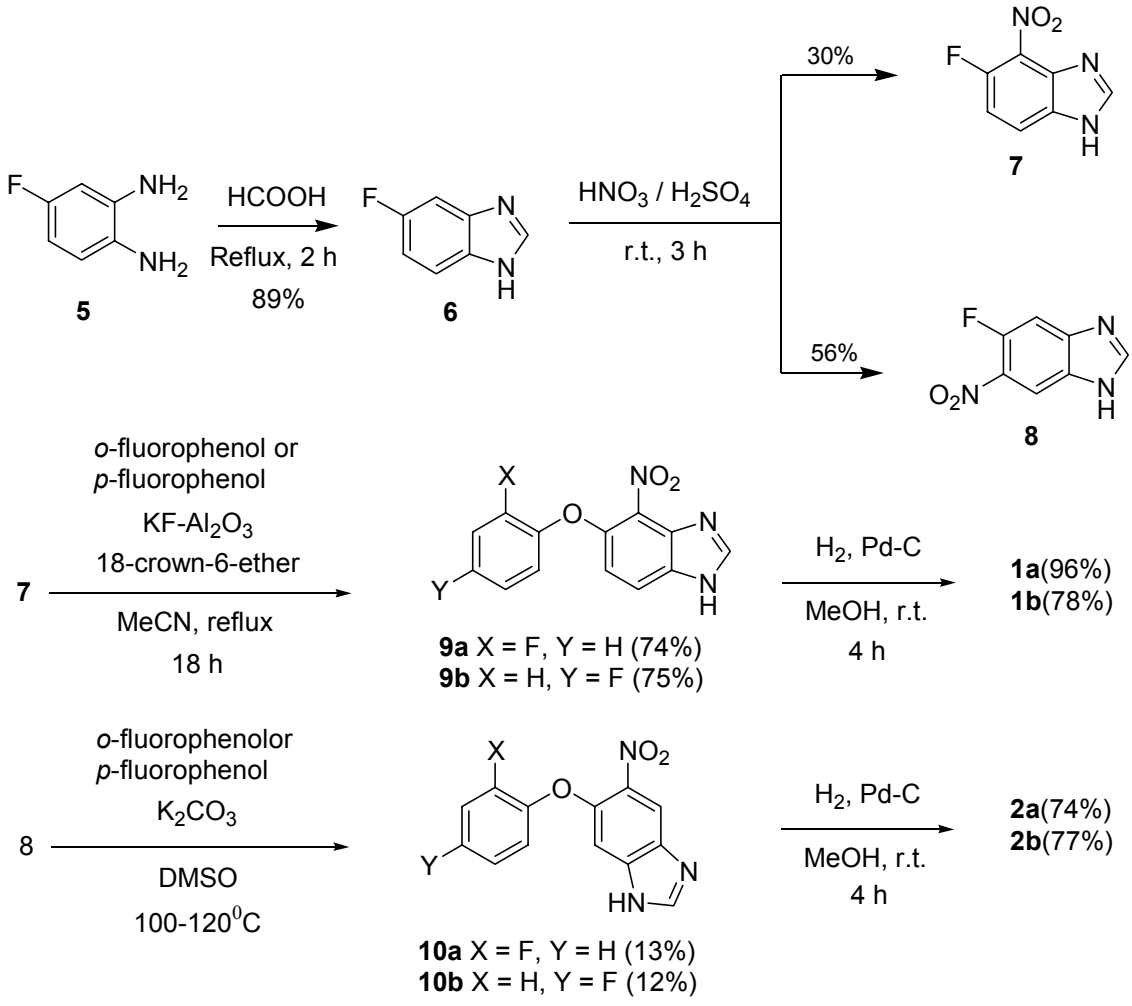


Figure 2. Some reported biologically active fluorophenylaryl / heteroaryl ether compounds.

Results and Discussion

The synthesis of compounds **1**–**4** was accomplished by using a variety of phenol coupling methods as key steps (Scheme 1 and 2). 4-Fluoro-1,2-phenylenediamine **5**[11] was first converted into 5-fluorobenzimidazole **6** by heating in formic acid solution. Nitration of **6** under relatively mild conditions gave a mixture of two regioisomers 5-fluoro-4-nitrobenzimidazole **7** and 5-fluoro-6-nitrobenzimidazole **8**. The 4-nitro compound **7** was subjected to KF-Al_2O_3[12] mediated coupling with *o*-fluorophenol and *p*-fluorophenol in the presence of catalytic amount of 18-crown-6-ether[13] in MeCN to give fluorophenyl benzimidazole (heteroaryl) ethers **9a**–**9b**. Pd-C catalyzed hydrogenation of **9a**–**9b** at atmospheric pressure afforded compounds **1a**–**1b**, respectively in excellent yields.

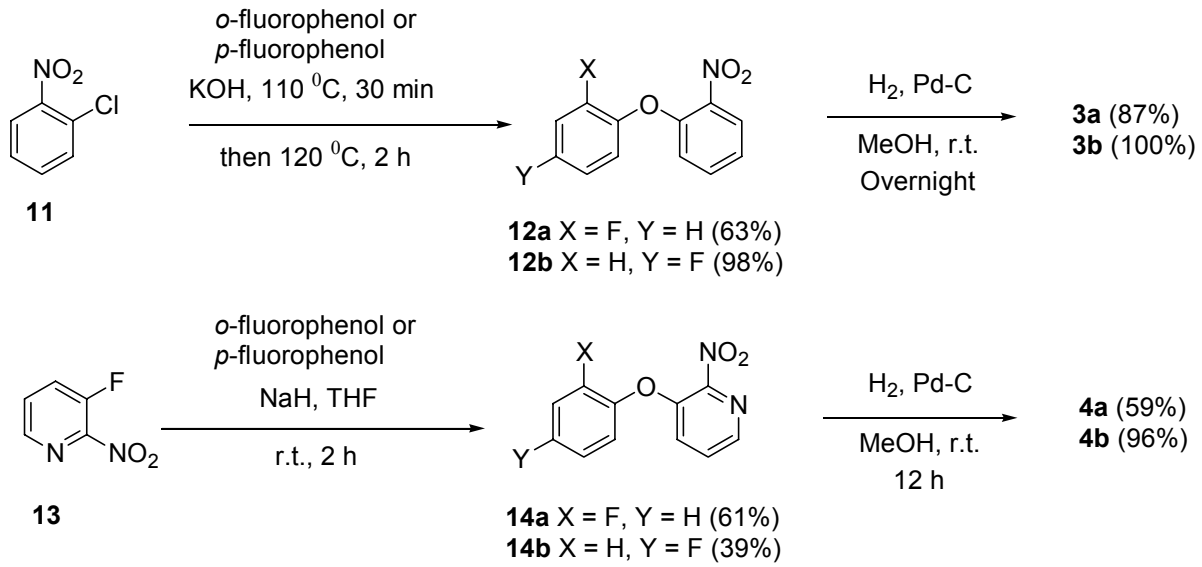


Scheme 1

However, KF-Al_2O_3 mediated coupling reaction[12,13] of 6-nitro compound **8** with fluorophenols failed unexpectedly. We then investigated an alternative procedure. The coupling

reaction of **8** with *o*-fluorophenol and *p*-fluorophenol was performed in the presence of K_2CO_3 in DMSO at 100–120 °C[10a] affording the fluorophenyl benzimidazole (heteroaryl) ethers **10a**–**10b**, which on hydrogenation gave the desired compounds **2a**–**2b**, respectively in good yields.

Preparation of the model compounds **3** and **4** required different phenolic coupling conditions. Coupling of commercially available 2-chloronitrobenzene **11** with the potassium salt of *o*-fluorophenol at 110–120 °C[5b] yielded the fluorophenylaryl ether compound **12a** which on Pd-C catalyzed hydrogenation gave **3a**. The compound **4a** was prepared from NaH based coupling[14] of **13**[15] with *o*-fluorophenol to afford the fluorophenyl phenyl pyridyl (heteroaryl) ether **14a** with subsequent Pd/C catalyzed hydrogenation. *p*-Fluorinated compounds **3b** and **4b** were prepared in similar sequences from **12** and **14**, respectively in good yields (Scheme 2).



Scheme 2

In summary, we have demonstrated the detailed syntheses of some novel fluorophenylaryl / heteroaryl ether derivatives which are structurally similar to some potent anti-inflammatory agents like Flosulide. The synthetic procedures are more straightforward and convenient than the traditional multi-step syntheses. These synthetic studies are expected to be helpful to generate some highly potent compounds of similar biological activities. The biological activity studies of the synthesized compounds are in progress.

Experimental Section

General Procedures. All melting points were determined with a Yanagimoto Micro Melting Point apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 1600 spectrometer. ^{1}H-NMR spectra were measured as solutions in $CDCl_3$, CD_3OD, D_2O or DMSO-d_6

and chemical shifts are expressed in ppm relative to internal Me_4Si (0.00 ppm) and were recorded on a JEOL GX-270 (270 MHz) spectrometer. ^{19}F- NMR spectra were measured with $CFCl_3$ as an internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts were quoted as negative δ values. ^{13}C NMR spectra were recorded at 125.76, 75.46 and 68 MHz using Unity plus 500, Varian Gemini 300 and JEOL GX-270 instruments. Chemical shifts are quoted in ppm and are referenced to $CDCl_3$. Electron ionization (EI) mass spectra were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative TLC were performed on BW-200 (Fuji Silysia) and Kieselgel 60 (Merck, art. 7748), respectively. All reactions were carried out under a dry N_2 atmosphere. Unless otherwise noted, reagents were added by syringe. MeOH was distilled from CaO and DMF was distilled over CaH_2 immediately prior to use. Commercially available dehydrated THF [stabilized with butylated hydroxytoluene (BHT)] was used for reaction.

5-Fluorobenzimidazole (6). A solution of 4-fluoro-1, 2-phenylenediamine **5** (3.5 g, 27.7 mmol) in 90% formic acid (50 ml) was heated at reflux for 2 h. Following removal of the solvent, the residue was chromatographed on silica gel [chloroform- methanol (9:1)] to yield **7** as a yellowish solid (3.36 g, 89%) which was recrystallized from chloroform; mp 87–88 °C; IR (KBr, cm^{-1}) 3108, 3062, 1597, 1335; ^1H-NMR ($CDCl_3$) 7.04–7.62 (3H, m, ArH), 8.22 (1H, br s, N=C*H*–NH); ^{19}F-NMR ($CDCl_3$) –118.9 (m); MS *m/z* (EI) 136 (M^+), 135 ($M^+ - 1$); HRMS Calcd. $C_7H_5N_2F$: 136.0437, Found: 136.0440.

5-Fluoro-4-nitrobenzimidazole (7) and 5-Fluoro-6-nitrobenzimidazole (8). To a solution of **6** (5.5 g, 40.4 mmol) in concentrated sulphuric acid (6.4 ml, 120 mmol) was added concentrated nitric acid (5.1 ml, 120 mmol) slowly and the whole mixture was stirred at room temperature for 3h. The solution was poured into ice-water. A solid was formed which was filtered and subsequently washed with water and saturated sodium bicarbonate solution. The liquid portion was neutralized by adding KOH pellets. The solid still present was filtered off and the mother liquid was extracted with ethyl acetate (100 ml x 2). The total solids were taken and the organic portion was concentrated *in vacuo*. The residue was chromatographed on silica gel (3–5% methanol in dichloromethane) to give **7** (2.2 g, 30%) and **8** (4.07 g, 56%), both as a yellowish solid. Data for **7**: mp 191–192 °C (from dichloromethane); ^1H-NMR (5% CD_3OD in $CDCl_3$) 7.25 (1H, dd, *J* = 2.7, 8.1 Hz, ArH), 8.09 (1H, dd, *J* = 3.7, 8.7 Hz, ArH), 8.50 (1H, br s, N=C*H*–NH); ^{19}F-NMR (5% CD_3OD in $CDCl_3$) –120.5 (m); MS *m/z* (EI) 181 (M^+), 135 ($M^+ - NO_2$); HRMS Calcd. $C_7H_4O_2N_3F$: 181.0296, Found: 181.0297. Data for **8**: mp 189–190 °C (from dichloromethane); IR (KBr, cm^{-1}) 3601, 3107, 2981, 1532, 1423, 1304; ^1H-NMR (5% CD_3OD in $CDCl_3$) 7.50 (1H, d, *J* = 10.9 Hz, ArH), 8.35 (1H, br s, N=C*H*–NH), 8.45 (1H, d, *J* = 6.3 Hz, ArH); ^{19}F-NMR (5% CD_3OD in $CDCl_3$) –124.0 (m); MS *m/z* (EI) 181 (M^+), 182 ($M^+ + 1$), 135 ($M^+ - NO_2$); HRMS Calcd. $C_7H_4O_2N_3F$: 181.0305, Found: 181.0307.

5-(2-Fluorophenyl)-4-nitrobenzimidazole ether (9a). To a stirred solution of **7** (150 mg, 0.83 mmol) in a mixture of acetonitrile (10 ml) and DMSO (0.5 ml) were added 18-crown-6-ether (219 mg, 0.25 mmol), KF-Al_2O_3 (700 mg), *o*-fluorophenol (78.0 mg, 0.69 mmol) and refluxed at 100 °C for 18 h. The reaction mixture was first filtered and to the filtrate 0.5 M KOH (10 ml) and ethyl acetate (100 ml) were added. The layers were separated and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (dichloromethane-methanol 9:1) to yield the product **9a** (166 mg, 74%) as a brown crystalline solid; mp 162–163 °C (from dichloromethane); *Anal.* Calcd. $C_{13}H_8N_3O_3F$: C, 57.15; N, 15.38, H, 2.95, Found: C, 56.90; N, 15.37; H, 2.99; IR (KBr, cm^{-1}) 2992, 1580, 1538, 1341, 1033, 765; ^{1}H-NMR ($CDCl_3$) 6.91–7.26 (5H, m, ArH + benzimidazole 6-*H*), 8.01 (1H, d, *J* = 8.7 Hz, benzimidazole 7-*H*), 8.24 (1H, br s, N=C*H*-NH); ^{19}F-NMR ($CDCl_3$) –130.5 (m); MS *m/z* (EI) 273 (M^+), 274 (M^+ + 1); HRMS Calcd. $C_{13}H_8N_3O_3F$: 273.0550, Found: 273.0571.

5-(4-Fluorophenyl)-4-nitrobenzimidazole ether (9b). Compound **9b** (223 mg, 75%) was prepared from the coupling of *p*-fluorophenol (123 mg, 1.10 mmol) with **8** (200 mg, 1.10 mmol) by the procedure analogous to **9a** as a brown solid; mp 198–200 °C (from dichloromethane); *Anal*. Calcd. $C_{13}H_8N_3O_3F$: C, 57.15; N, 15.38, H, 2.95, Found: C, 57.12; N, 15.44; H, 2.84; IR (KBr, cm^{-1}) 2998, 1579, 1539, 1343, 1091, 782; ^{1}H-NMR ($CDCl_3$) 6.94–7.24 (5H, m, ArH + benzimidazole 6-*H*), 8.03 (1H, m, benzimidazole 7-*H*), 8.22 (1H, d, *J* = 8.9 Hz, N=C*H*–NH); ^{19}F-NMR ($CDCl_3$) –118.9 (m); MS *m/z* (EI) 273 (M^+), 274 (M^+ + 1), 227 ($M^+ - NO_2$); HRMS Calcd. $C_{13}H_8N_3O_3F$: 273.0550, Found: 273.0531.

5-(2-Fluorophenyl)-4-aminobenzimidazole ether (1a). To a solution of **9a** (107 mg, 0.391 mmol) in MeOH (10 ml) under N_2 was added Pd/C (20 mg) and H_2 gas was allowed to pass through the solution with stirring for 4 h until completion of the reaction by TLC. The reaction mixture was filtered off through a plug of celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform-methanol 9:1) to yield **1a** (91 mg, 96%) as a grey crystalline solid; mp 127–128 °C (from dichloromethane); *Anal.* Calcd. $C_{13}H_{10}N_3OF$: C, 64.19; N, 17.28, H, 4.14, Found: C, 63.98; N, 17.42; H, 4.15; IR (KBr, cm^{-1}) 3439, 3358 (NH_2), 3156, 3055, 1500, 1368, 1252, 797; ^{1}H-NMR (DMSO-d_6) 5.08 (2H, br s, NH_2), 6.65–7.29 (6H, m, ArH + benzimidazole-*H*), 8.10 (1H, br s, N=C*H*–NH); ^{13}C-NMR (CD_3OD) 102.74, 117.57, 118.82, 123.71, 123.80, 125.47, 125.53, 130.63, 134.02, 137.25, 141.63, 147.61, 154.27; ^{19}F-NMR (DMSO-d_6) –133.9 (m); MS *m/z* (EI) 243 (M^+), 223 (M^+ – HF); HRMS Calcd. $C_{13}H_{10}N_3OF$: 243.0808, Found: 243.0782.

5-(4-Fluorophenyl)-4-aminobenzimidazole ether (1b). Compound **1b** (76.0 mg, 78%) was prepared by Pd/C (30.0 mg) catalyzed reduction of **1a** (109 mg, 0.399 mmol) as a grey crystalline solid; mp 186–188 °C (from dichloromethane); *Anal*. Calcd. $C_{13}H_{10}N_3OF$: C, 64.19; N, 17.28, H, 4.14, Found: C, 64.12; N, 17.30; H, 4.12; IR (KBr, cm^{-1}) 3386 (NH_2), 3156, 2912, 1628, 1503, 964; ^{1}H-NMR (DMSO-d_6) 4.99 (2H, br s, NH_2), 6.75–7.15 (6H, m, ArH + benzimidazole-*H*), 8.09 (1H, br s, N=C*H*–NH); ^{19}F-NMR(DMSO-d_6) –122.5 (m); MS *m/z* (EI) 243 (M^+), 244 (M^+ + 1), 242 (M^+ – 1); HRMS Calcd. $C_{13}H_{10}N_3OF$: 243.0808, Found: 243.0785.

5-(2-Fluorophenyl)-6-nitrobenzimidazole ether (10a). To a stirred solution of **8** (200 mg, 1.10 mmol) in DMSO (5 ml) were added *o*-fluorophenol (0.147 ml, 1.10 mmol) and anhydrous K_2CO_3 (334 mg, 2.20 mmol) and the mixture was heated at 100 °C for one week. The reaction mixture was diluted with ethyl acetate (100 ml) and was washed successively with 1M KOH (10 ml), water (20 ml), and brine (20 ml). The organic layer dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (chloroform-methanol 9:1) to yield the product **10a** (38.0 mg, 13%) as a brown crystalline solid; mp 216–217 °C (from chloroform); IR (KBr, cm^{-1}) 3100, 2963, 1588, 1530, 1333, 740; ^{1}H-NMR (CD_3OD) 7.03–7.30 (5H, m, ArH + benzimidazole 4-*H*), 8.33 (1H, br s, N=C*H*–NH), 8.39 (1H, br s, benzimidazole 7-*H*); ^{19}F-NMR (CD_3OD) –131.9 (m); MS *m/z* (EI) 273 (M^+), 272 ($M^+ - 1$); HRMS Calcd. $C_{13}H_8N_3O_3F$: 273.0559, Found: 273.0549

5-(4-Fluorophenyl)-6-nitrobenzimidazole ether (10b). Compound **10b** (35.0 mg, 12%) was prepared from the coupling of *p*-fluorophenol (134 mg, 1.10 mmol) with **8** (200 mg, 1.10 mmol) by the procedure analogous to **10a** as a brown crystalline solid; mp 181–185 °C (from chloroform); *Anal.* Calcd. $C_{13}H_8N_3O_3F$: C, 57.15; N, 15.38, H, 2.95, Found: C, 57.06; N, 15.41; H, 3.04.); IR (KBr, cm^{-1}) 3102, 1533, 1500, 1336, 1278, 755; 1H-NMR (CD_3OD) 6.99–7.15 (4H, m, ArH), 7.27 (1H, br s, benzimidazole 4-*H*), 8.31 (1H, br s, N=C*H*–NH), 8.38 (1H, br s, benzimidazole 7-*H*); ^{19}F-NMR (CD_3OD) –120.2 (m); MS *m/z* (EI) 273 (M^+), 272 ($M^+ - 1$); HRMS Calcd. $C_{13}H_8N_3O_3F$: 273.0550, Found: 273.0558.

5-(2-Fluorophenyl)-6-aminobenzimidazole ether (2a). To the solution of **10a** (20.0 mg, 0.073 mmol) in dry methanol (10 ml) was added Pd/C (10 mg) and H_2 gas was allowed to pass for 4 h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated *in vacuo* to give the residue which was purified by preparative TLC (chloroform-methanol 9:1) to yield **2a** (13.0 mg, 74%) as a grey crystalline solid; mp 99–100 °C (from chloroform-methanol); IR (KBr, cm^{-1}) 3374, 3122 (NH_2), 2960, 1500, 1364, 1259, 750; ^{1}H-NMR (DMSO-d_6) 4.79 (2H, br s, NH_2), 6.85–7.34 (6H, m, ArH + benzimidazole-*H*), 8.26 (1H, br s, N=C*H*–NH); ^{19}F-NMR (DMSO-d_6) –132.8 (m); MS *m/z* (EI) 243 (M^+), 244 ($M^+ + 1$), 223 ($M^+ - HF$); HRMS Calcd. $C_{13}H_{10}N_3OF$: 243.0808, Found: 243.0831.

5-(4-Fluorophenyl)-6-aminobenzimidazole ether (2b). Compound **2b** (10.0 mg, 75%) was prepared by Pd-C (10 mg) catalyzed reduction of **10b** (15 mg, 0.054 mmol) as a grey crystalline solid; mp 208–209 °C (from chloroform-methanol); IR (KBr)/cm^{-1} 3787, 3431 (NH_2), 1501, 1416, 1362, 759; ^{1}H-NMR (DMSO-d_6) 4.72 (2H, br s, NH_2), 6.92–7.16 (6H, m, ArH + benzimidazole-*H*), 7.92 (1H, br s, N=C*H*–NH); ^{19}F-NMR (DMSO-d_6) –119.2 (m); MS *m/z* (EI) 243 (M^+), 244 ($M^+ + 1$), 227 ($M^+ - NH_2$); HRMS Calcd. $C_{13}H_{10}N_3OF$: 243.0807, Found M^+ 243.080.

1-(2-Fluorophenyl)-2-nitrobenzene ether (12a). To a stirred mixture of *o*-fluorophenol (1.00 g, 8.92 mmol) and dried powdered KOH (500 mg, 8.92 mmol) heated at 110 °C for 30 minutes was added 2-chloronitrobenzene **11** (1.40 g, 8.92 mmol) in one portion and heated at 120 °C for 2 h. The reaction mixture was diluted with ethyl acetate (100 ml) and brine (20 ml) was added to it. The whole mixture was successively washed with 1 M NaOH (20 ml), 1 M HCl (20 ml) and

brine (20 ml). The organic portion was dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The residue was chromatographed on silica gel (hexane-ethyl acetate 9:1) to give **12a** (1.31 g, 63%) as a yellow oil; IR (neat, cm^{-1}) 3091, 1584, 1529, 1356; ^{1}H-NMR ($CDCl_3$) 6.91–7.23 (6H, m, FAr-H), 7.48–7.52 (1H, m, NO_2-ArH), 7.98 (1H, dd, J = 1.3, 8.3 Hz, NO_2-ArH); ^{19}F-NMR ($CDCl_3$) –130.4 (m); MS *m/z* (EI) 233 (M^+), 234 (M^+ + 1); HRMS Calcd. $C_{12}H_8NO_3F$: 233.0488, Found: 233.050.

1-(4-Fluorophenyl)-2-nitrobenzene ether (12b). Compound **12b** (2.03 g, 98%) was prepared by following the procedure analogous to **12a** using **11** (1.68 g, 10.7 mmol), *p*-fluorophenol (1.0 g, 8.92 mmol) and KOH (600 mg, 10.7 mmol) as a yellow oil; IR (neat, cm^{-1}) 3079, 2871, 1529, 1353; ^{1}H-NMR ($CDCl_3$) 6.95–7.19 (6H, m, Ar*H* + NO_2-ArH), 7.51 (1H, m, NO_2-ArH), 7.94 (1H, dd, J =1.3, 8.3 Hz, NO_2-ArH); ^{19}F-NMR ($CDCl_3$) –118.6 (m); *m/z* (EI) 233 (M^+), 234 (M^+ + 1), 187 ($M^+ - NO_2$); HRMS Calcd. $C_{12}H_8O_3NF$: 233.0472, Found: 233.0434.

2-(2-Fluorophenyl) phenylamine ether (3a). To a solution of **12a** (200 mg, 0.858 mmol) in anhydrous methanol (10 ml) under nitrogen was added Pd/C (50.0 mg). The flask was evacuated and hydrogen gas was allowed to pass through the solution overnight. After being ensured of the completion of the reaction by TLC, the reaction mixture was filtered through a plug of celite to remove Pd/C and the filtrate was concentrated and purified by column chromatography on silica gel (hexane-ethyl acetate 9:1) to give **3a** (151 mg, 87%) as a yellow oil; IR (neat, cm^{-1}) 3364, 3333 (NH_2), 3038, 2868, 1308, 782; ^{1}H-NMR ($CDCl_3$) 3.79 (2H, br s, NH_2), 6.65–6.83 (4H, m, NH_2-ArH), 6.96–7.18 (4H, m, F-ArH); ^{19}F-NMR ($CDCl_3$) –133.2 (m); MS *m/z* (EI) 203 (M^+), 204 (M^+ + 1), 187 ($M^+ - NH_2$); HRMS Calcd. $C_{12}H_{10}ONF$: 203.0746, Found: 203.0721.

2-(4-Fluorophenyl) phenylamine ether (3b). Compound **3b** (355 mg, 100%) was prepared by the Pd/C (100 mg) catalyzed reduction of **12b** (400 mg, 1.72 mmol) as a yellow oil; IR (neat, cm^{-1}) 3471, 3383 (NH_2), 3002, 1269, 1201, 703; ^{1}H-NMR ($CDCl_3$) 3.79 (2H, br s, NH_2), 6.66–6.89 (4H, m, NH_2-ArH), 6.94–7.02 (4H, m, F-ArH); ^{19}F-NMR ($CDCl_3$) –121.7 (m); MS *m/z* (EI) 203 (M^+), 204 (M^+ + 1), 187 ($M^+ - NH_2$); HRMS Calcd. $C_{12}H_{10}ONF$: 203.0768, Found: 203.0746.

3-(2-Fluorophenyl)-2-nitropyridyl ether (14a). To a stirred dispersion of *o*-fluorophenol (0.32 ml, 3.52 mmol) and NaH (140 mg, 5.83 mmol) in THF (5 ml) was added 3-fluoro-2-nitropyridine **13** (100 mg, 0.703 mmol) and stirred for 2 h. The reaction was quenched by saturated aqueous NH_4Cl (30 ml) solution and extracted with ethyl acetate (250 ml). The organic layer was washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography over silica gel (hexane-dichloromethane 6:4) to give **14a** (101 mg, 61%) as a yellow oil; IR (neat, cm^{-1}) 1545, 1368 (NO_2); ^{1}H-NMR ($CDCl_3$) 6.86 (1H, m, ArH), 6.96–7.09 (3H, m, ArH), 7.20–7.35 (2H, m, Pyridyl-*H*), 8.24 (1H, br d, *J* 4.3, NC*H*=CH); ^{19}F-NMR ($CDCl_3$) –141.5 (m); MS *m/z* (EI) 234 (M^+), 235 (M^+ + 1); HRMS Calcd. $C_{11}H_7N_2O_3F$: 234.0441, Found: 234.0439.

3-(4-Fluorophenyl)-2-nitropyridyl ether (14b). Compound **14b** (128 mg, 39%) was prepared by following the procedure analogous to **14a** using **13** (200 mg, 1.41 mmol), *p*-fluorophenol (789 mg, 7.04 mmol) and NaH (282 mg, 7.04 mmol) as a yellowish solid; mp 61–62 °C (from hexane-

ethyl acetate); *Anal.* Calcd. $C_{11}H_7N_2O_3F$: C, 56.42; N, 11.96; H, 3.01, Found: C, 56.28; N, 11.81; H, 3.31; IR (KBr, cm^{-1}) 1547, 1372 (NO_2); ^{1}H-NMR ($CDCl_3$) 7.07–7.15 (4H, m, F-Ar*H*), 7.37 (1H, m, Pyridyl-*H*), 7.49 (1H, m, Pyridyl-*H*), 8.24 (1H, br d, *J* 3.2, NC*H*=CH); ^{19}F-NMR ($CDCl_3$) –116.9 (m); MS *m/z* (EI) 234 (M^+), 235 ($M^+ + 1$); HRMS Calcd. $C_{11}H_7N_2O_3F$: 234.044, Found: 234.0439.

3-(2-Fluorophenyl)-2-pyridylamine ether (4a). To the solution of **14a** (100 mg, 0.427 mmol) in methanol (5 ml) was added Pd/C (50 mg) and hydrogen gas was passed through the solution for 12 hr. until the completion of the reaction. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated *in vacuo* and purified by preparative TLC (ethyl acetate 100%) to give **4a** (51 mg, 58%) as a yellow oil; IR (neat, cm^{-1}) 3481, 3305 (NH_2), 3146, 2927, 1481, 1251; ^{1}H-NMR (DMSO-d_6) 5.99 (2H, br s, NH_2), 6.49–7.07 (3H, m, Ar*H*), 7.18–7.39 (3H, m, Ar*H* + Pyridyl-*H*), 7.75 (1H, br d, *J* = 4.3 Hz, NH_2C=NC*H*); ^{19}F-NMR ($CDCl_3$) –131.7 (m); MS *m/z* (EI) 204 (M^+), 188 ($M^+ – NH_2$); HRMS Calcd. $C_{11}H_9N_2OF$: 204.0699, Found: 204.0677.

3-(4-Fluorophenyl)-2-pyridylamine ether (4b). Compound **4b** (83.0 mg, 96%)was prepared from Pd-C (100 mg) catalyzed reduction of **14b** (100 mg, 0.427 mmol) according to the procedure analogous to **4a**, as an oil; IR (neat, cm^{-1}) 3471, 3283 (NH_2), 3002, 1508, 1269, 1144, 753; ^{1}H-NMR (DMSO-d_6) 5.89 (2H, br s, NH_2), 6.51–7.01 (4H, m, ArH + Pyridyl-*H*), 7.15–7.22 (2H, m, Pyridyl-*H*), 7.75 (1H, br d, *J* 4.3, NH_2C=NC*H*); ^{19}F-NMR ($CDCl_3$) –119.9 (m); MS *m/z* (EI) 204 (M^+), 188 ($M^+ – NH_2$); HRMS Calcd. $C_{11}H_9N_2OF$: 204.0699, Found: 204.0761.

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