Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Pd-Catalyzed Coupling Reaction of Fluorinated Propargyl Amidines with Aryl Iodides

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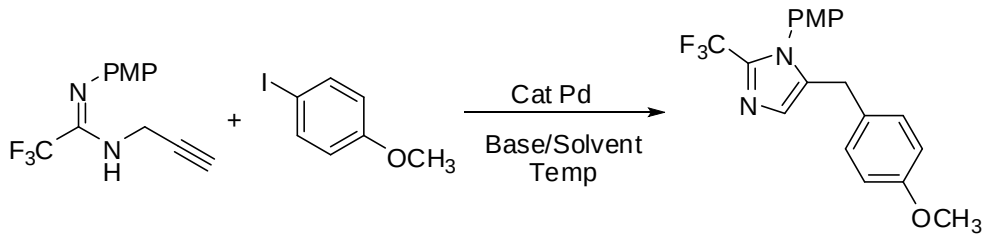
I. General Information

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300(282 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR spectra were taken a Bruker AM-400(100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra and elemental analyses were recorded in this institute. Solvents were purchased form commercial sources and purified before used by standard procedures. Unless otherwise specified, all reactions were carried out under a nitrogen atmosphere in a Schlenk tube and magnetic stirring. TLC analysis was performed on silica gel plates, column chromatography over silica gel (mesh 300-400) and petroleum ethyl acetate combination was used as the eluent.

II. Optimized for the Synthesis of 3aaa.



1aa **2a** **3aaa**

Entry	Catalyst	Solvent	Base	Temp/℃	Yield/%[b]
1	$Pd(OAc)_2$	CH_3CN	K_2CO_3	r. t.	26
2	$Pd(OAc)_2$	CH_3CN	K_2CO_3	50	31
3	$Pd(OAc)_2$	CH_3CN	K_2CO_3	80	45
4	$Pd(OAc)_2$	CH_3CN	K_2CO_3	100	17
5	$Pd(OAc)_2$	CH_3CN	K_3PO_4	80	55[c]
6	$Pd(OAc)_2$	CH_3CN	Na_2CO_3	80	37
7	$Pd(OAc)_2$	CH_3CN	Et_3N	80	42
8	$Pd(OAc)_2$	CH_3CN	Py	80	49[c]
9	$Pd(OAc)_2$	DMF	K_3PO_4	80	47[c]

10	$Pd(OAc)_2$	toluene	K_3PO_4	80	22
11	$Pd(OAc)_2$	THF	K_3PO_4	80	30[d]
12	$Pd(OAc)_2$	DMA	K_3PO_4	80	25
13	$Pd(OAc)_2$	DMF/toluene	K_3PO_4	80	50[c]
14	$Pd(OAc)_2$	DMF/THF	K_3PO_4	80	52[c]
15	$Pd(OAc)_2$	NMP	K_3PO_4	80	41
16	$PdCl_2$	CH_3CN	K_3PO_4	80	33
17	$Pd(PPh_3)_2Cl_2$	CH_3CN	K_3PO_4	80	52[c]
18	$Pd_2(dba)_3 \cdot HCCl_3$	CH_3CN	K_3PO_4	80	17
19	$Pd(biPy)Cl_2$	CH_3CN	K_3PO_4	80	23

a The molar ratio of **1aa**:**2a**:**base** = 1.0:1.2:1.5. b Calculated by ^{19}F NMR. c Isolated yield. d With byproduct of 5-methyl imidazole in 45% yield.

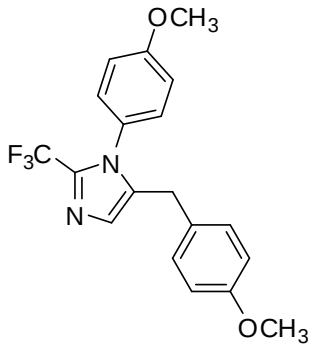
III. General Process for the Synthesis of 5-Benzyl Imidazoles

To a mixture of $Pd(OAc)_2$ (22.4 mg, 10%), fluorinated proprgyl amidines (1.0 mmol), iodoarene (0.7 mmol), K_2CO_3 (166 mg, 1.2 mmol) in a Schlenk tube was added anhydrous DMF (4.0 mL) under N_2 atmosphere., then the reaction system was placed in oil bath (80 ^oC) to the end. The reaction mixture was diluted with water, extracted by ethyl acetate (10 ml x 4), washed with brine (15 mL), dried with anhydrous $MgSO_4$, filtered finally. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel to give the desirable product.

IV. Characterization for the 5-Benzyl Imidazoles (3aaa-3aaba)

3aaa

5-(4-methoxybenzyl)-1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole

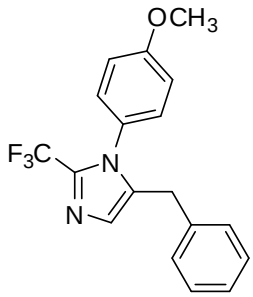


Yellow oil. ^1H NMR (300 Hz, $CDCl_3$): δ 7.00 (m, 2H), 6.90 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H),

3.86 (s, 3H), 3.77 (s, 3H), 3.63 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.02 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 158.3, 155.2, 136.8, 136.4 (q, *J* = 43.0 Hz), 131.4, 129.7, 129.3, 126.6, 122.0 (q, *J* = 249.4 Hz), 120.4, 113.7, 111.8, 55.5, 55.3, 29.7. MS (EI), m/e (%): 362 (M^+, 100), 108 (60), 347 (43). HRMS (EI), Calcd. for $C_{19}H_{17}F_3N_2O_2$: 362.1242, Found: 362.1240. IR (neat): ν 1611, 1515, 1493, 1452, 1253, 1185, 1124, 1037, 970, 837 cm^{-1}.

3aab

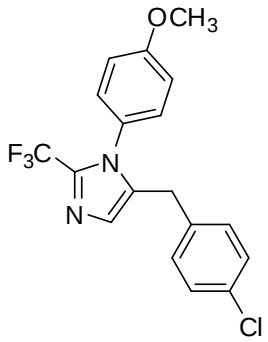
5-benzyl-1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.18 (d, *J* = 8.7 Hz, 2H), 7.98 (m, 3H), 6.92 (m, 2H), 6.86 (m, 3H), 3.86 (s, 3H), 3.67 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.23 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.5, 136.9 (q, *J* = 38.7 Hz), 135.9, 135.6, 132.6, 130.0, 128.9, 128.6, 126.9, 118.7 (q, *J* = 268.3 Hz), 114.4, 55.6, 29.9. MS (EI), m/e (%): 332 (M^+, 45), 108 (100). HRMS (EI), Calcd. for $C_{18}H_{15}F_3N_2O$: 332.1136, Found: 332.1140. IR (neat): ν 1609, 1515, 1492, 1452, 1299, 1254, 1186, 1126, 1038, 970, 837 cm^{-1}.

3aac

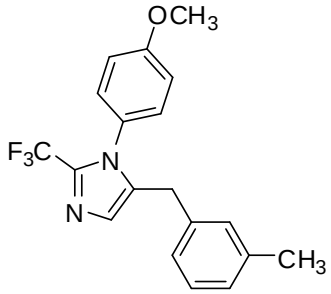
5-(4-chlorobenzyl)-1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.21 (d, *J* = 6.3 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.92 (m, 5H), 3.85 (s, 3H), 3.69 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.18 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.4, 137.1 (q, *J* = 8.2 Hz), 136.6 (q, *J* = 38.4 Hz), 136.5 (q, *J* = 1.7 Hz), 128.9, 128.5, 128.4, 126.8, 126.7, 126.6, 118.3 (q, *J* = 271.5 Hz), 114.3, 55.5, 30.5. MS (EI), m/e (%): 366 (M^+, 23), 108 (100), 256 (82). HRMS (EI), Calcd. for $C_{18}H_{14}ClF_3N_2O$: 366.0747, Found: 366.0750. IR (neat): ν 1606, 1515, 1493, 1253, 1185, 1125, 970, 838, 712 cm^{-1}.

3aad

1-(4-methoxyphenyl)-5-(3-methylbenzyl)-2-(trifluoromethyl)-1H-imidazole

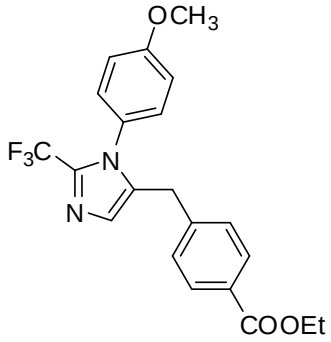


Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.10 (t, *J* = 7.7 Hz, 1H), 6.99 (m, 4H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.73 (m, 2H), 3.85 (s, 3H), 3.65 (s, 2H), 2.26 (s, 3H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 59.92 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.4, 138.1, 137.0, 136.7, 136.6 (q, *J* = 37.9 Hz), 129.4, 129.0, 128.4, 127.4, 126.9, 126.7, 125.6, 118.3 (q, *J* = 268.3 Hz), 114.3, 55.5, 30.5, 21.2. MS (EI), m/e (%): 346 (M^+, 42), 108 (100). HRMS (EI), Calcd. for $C_{19}H_{17}F_3N_2O$: 346.1293, Found: 346.1291. IR (neat): ν 1602, 1515, 1493, 1464, 1299, 1251, 1184, 1124, 1036, 970, 838, 754 cm^{-1}.

3aae

Ethyl

4-((1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl)methyl)benzoate

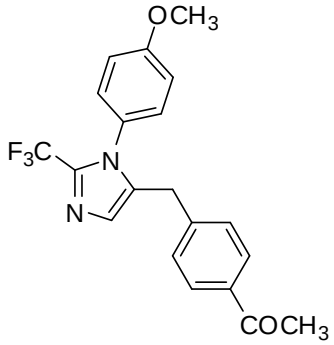


Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.89 (d, *J* = 8.1 Hz, 2H), 6.99 (m, 5H), 6.88 (d, *J* = 8.1 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 2H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.24 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 166.3, 160.5, 142.3, 136.9 (q, *J* = 38.7 Hz), 135.6, 129.8, 129.1, 128.9, 128.5, 127.0, 118.2 (q, *J* = 274.2 Hz), 114.4, 61.0, 55.5, 30.5, 14.3. MS (EI), m/e (%): 404 (M^+, 47), 108 (100). HRMS (EI), Calcd. for $C_{21}H_{19}F_3N_2O_3$: 404.1348, Found: 404.1350. IR (neat): ν 1604, 1515, 1494, 1254, 1185, 1124, 1038, 970, 807 cm^{-1}.

3aaf

1-(4-((1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl)methyl)phenyl)

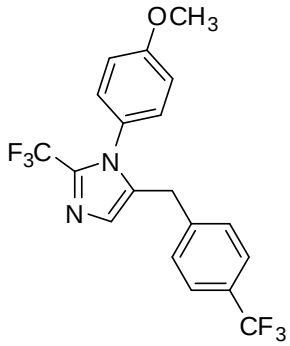
ethanone



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.01 (m, 5H), 6.89 (d, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 2H), 2.57 (s, 3H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.08 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 197.6, 160.5, 142.6, 136.8 (q, *J* = 46.2 Hz), 135.7, 135.4, 128.8, 128.7, 128.6, 127.0, 126.5, 118.6 (q, *J* = 273.2 Hz), 114.4, 55.5, 30.5, 26.6. MS (EI), m/e (%): 374 (M^+, 78), 108 (100), 359 (55). HRMS (EI), Calcd. for $C_{20}H_{17}F_3N_2O_2$: 374.1242, Found: 374.1241. IR (neat): ν 1716, 1610, 1515, 1493, 1278, 1253, 1185, 1108, 970, 838 cm^{-1}.

3aag

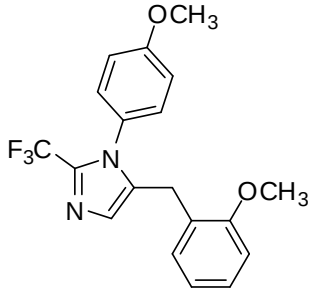
1-(4-methoxyphenyl)-2-(trifluoromethyl)-5-(4-(trifluoromethyl)benzyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.00 (m, 5H), 6.89 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.27 (s, 3F), - 60.22 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.5, 141.2, 137.0 (q, *J* = 40.4 Hz), 135.4, 128.8, 128.7, 127.1 (q, *J* = 202.5 Hz), 126.9, 125.4, 122.7, 118.5 (q, *J* = 271.6 Hz), 114.4, 55.5, 30.4. MS (EI), m/e (%): 400 (M^+, 15), 256 (100). HRMS (EI), Calcd. for $C_{19}H_{14}F_6N_2O$: 400.1010, Found: 400.1007. IR (neat): ν 1515, 1494, 1326, 1254, 1186, 1124, 1067, 970, 838 cm^{-1}.

3aah

5-(2-methoxybenzyl)-1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole

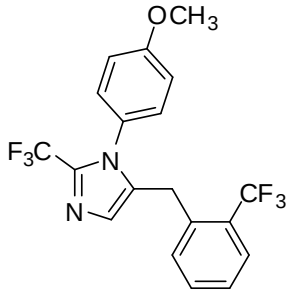


Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.19 (d, *J* = 8.4 Hz,

1H), 7.01 (m, 2H), 6.91 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.63 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 61.48 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.4, 158.5, 137.0, 136.6 (q, *J* = 37.9 Hz), 129.5, 129.1, 128.9, 128.6, 126.6, 126.0, 118.8 (q, *J* = 272.7 Hz), 114.6, 114.3, 113.9, 55.5, 55.2, 29.7. MS (EI), m/e (%): 362 (M^+, 57), 108 (100), 187 (89), 256 (88), 293 (54). HRMS (EI), Calcd. for $C_{19}H_{17}F_3N_2O_2$: 362.1242, Found: 362.1245. IR (neat): ν 1602, 1509, 1494, 1467, 1283, 1246, 1185, 1123, 1027, 909, 755 cm^{-1}.

3aai

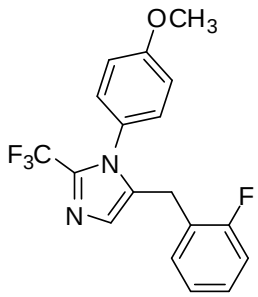
1-(4-methoxyphenyl)-2-(trifluoromethyl)-5-(2-(trifluoromethyl)benzyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.16 (m, 2H), 7.01 (m, 1H), 6.91 (m, 4H), 3.84 (s, 3H), 3.78 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.25 (s, 3F), - 62.38 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.5, 138.1, 137.0 (q, *J* = 38.3 Hz), 135.5, 131.9, 130.7 (q, *J* = 32.2 Hz), 129.0, 128.7, 128.6, 126.9, 126.5, 125.9, 124.3 (q, *J* = 170.2 Hz), 118.6 (q, *J* = 268.8 Hz), 114.4, 55.4, 30.4. MS (EI), m/e (%): 400 (M^+, 9), 256 (100). HRMS (EI), Calcd. for $C_{19}H_{14}F_6N_2O$: 400.1010, Found: 400.1014. IR (neat): ν 1683, 1608, 1515, 1492, 1253, 1185, 1126, 970, 838 cm^{-1}.

3aaj

5-(2-fluorobenzyl)-1-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole

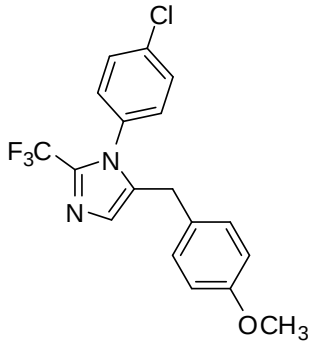


Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.18 (d, *J* = 9.0 Hz, 1H), 7.99 (m, 2H), 6.90 (m, 6H), 3.85 (s, 3H), 3.67 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.23 (s, 3F), - 115.85 (m, 1F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 162.9, 160.4 (d, *J* = 7.4 Hz), 136.8 (q,

J = 38.4 Hz), 136.3, 132.8, 130.0 (d, *J* = 8.2 Hz), 128.8, 128.5, 126.8, 125.9, 118.7 (q, *J* = 268.7 Hz), 115.3 (d, *J* = 21.5 Hz), 114.5, 114.3, 55.5, 29.8. MS (EI), m/e (%): 350 (M^+, 10), 256 (100), 108 (46). HRMS (EI), Calcd. for $C_{18}H_{14}F_4N_2O$: 350.1042, Found: 350.1041. IR (neat): ν 1596, 1528, 1492, 1427, 1345, 1184, 1131, 970, 878, 701 cm^{-1}.

3aba

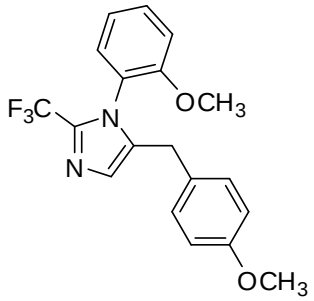
1-(4-chlorophenyl)-5-(4-methoxybenzyl)-2-(trifluoromethyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.95 (s, 1H), 6.75 (m, 4H), 3.74 (s, 3H), 3.62 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.68 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 158.5, 136.6, 136.1, 135.8 (q, *J* = 51.8 Hz), 133.0, 129.9, 129.5, 129.1, 128.8, 127.1, 118.6 (q, *J* = 268.3 Hz), 114.0, 55.3, 29.7. MS (ESI): 367.0 (M + H^+). HRMS (ESI), Calcd. for $C_{18}H_{15}ClF_3N_2O$: 367.08195, Found: 367.08065. IR (film): ν 1691, 1609, 1514, 1496, 1250, 1185, 1128, 1039, 970, 838 cm^{-1}.

3aca

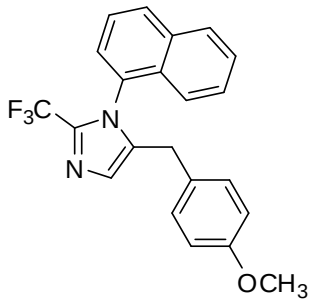
5-(4-methoxybenzyl)-1-(2-methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.45 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.98 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 3.59 (m, 5H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.09 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.3, 157.0, 136.6, 136.1 (q, *J* = 31.8 Hz), 130.0, 129.0, 128.1, 127.0, 126.8, 125.6, 120.3, 118.8 (q, *J* = 273.2), 114.2, 110.3, 55.5, 55.1, 24.5. MS (EI), m/e (%): 362 (M^+, 2.3), 256 (100). HRMS (EI), Calcd. for $C_{19}H_{17}F_3N_2O_2$: 362.1242, Found: 362.1239. IR (neat): ν 1612, 1512, 1494, 1442, 1246, 1190, 1128, 985, 805, 770 cm^{-1}.

3ada

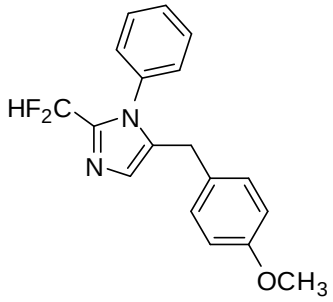
5-(4-methoxybenzyl)-1-(naphthalen-1-yl)-2-(trifluoromethyl)-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 8.01 (m, 2H), 7.51 (m, 4H), 7.08 (m, 3H), 6.65 (m, 4H), 3.73 (s, 3H), 3.47 (q, *J* = 31.8 Hz, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 60.28 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 158.4, 137.7, 137.1 (q, *J* = 43.0 Hz), 133.9, 130.9, 130.5, 129.5, 128.7, 128.3, 127.9, 127.0, 126.9, 126.4, 126.0, 124.9, 121.8, 118.4 (q, *J* = 268.3 Hz), 113.8, 55.2, 29.8. MS (EI), m/e (%): 382 (M^+, 30), 128 (100), 276 (81). HRMS (EI), Calcd. for $C_{22}H_{17}F_3N_2O$: 382.1293, Found: 382.1298. IR (neat): ν 1609, 1515, 1492, 1253, 1188, 1126, 1038, 970, 838 cm^{-1}.

3cea

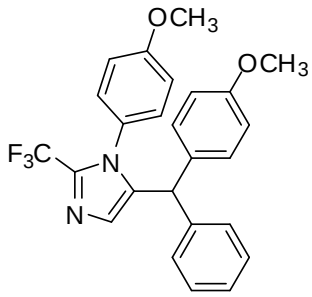
2-(difluoromethyl)-5-(4-methoxybenzyl)-1-phenyl-1H-imidazole



Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.49 (m, 3H), 7.16 (d, *J* = 5.7 Hz, 2H), 6.94 (s, 1H), 6.86 (d, *J* = 6.6 Hz, 2H), 6.76 (d, *J* = 6.6 Hz, 2H), 6.56 (t, *J* = 39.6 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 2H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 110.79 (d, *J* = 52.5 Hz, 2F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 158.4, 140.4 (t, *J* = 26.6 Hz), 135.9, 134.7, 129.6, 129.3, 129.2, 127.9, 127.0, 113.9, 109.6 (t, *J* = 234.8 Hz), 55.2, 29.7. MS (ESI): 315.1 (M + H^+). HRMS (ESI), Calcd. for $C_{18}H_{17}F_2N_2O$: 315.13035, Found: 315.13100. IR (film): ν 1693, 1515, 1356, 1255, 1186, 1138, 1039, 840 cm^{-1}.

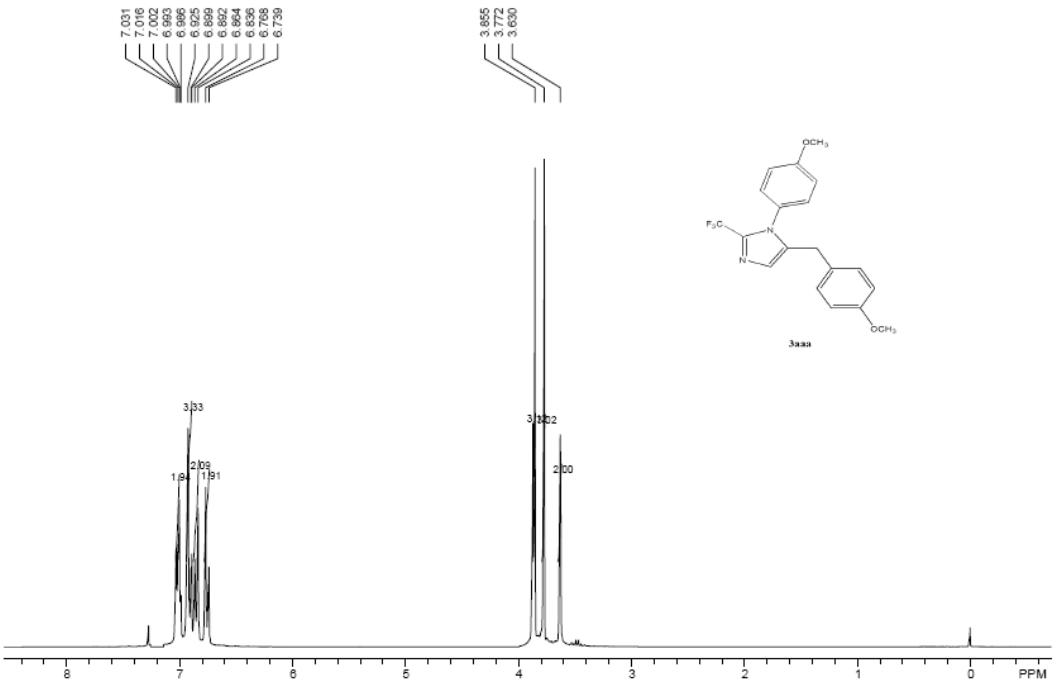
3aaba

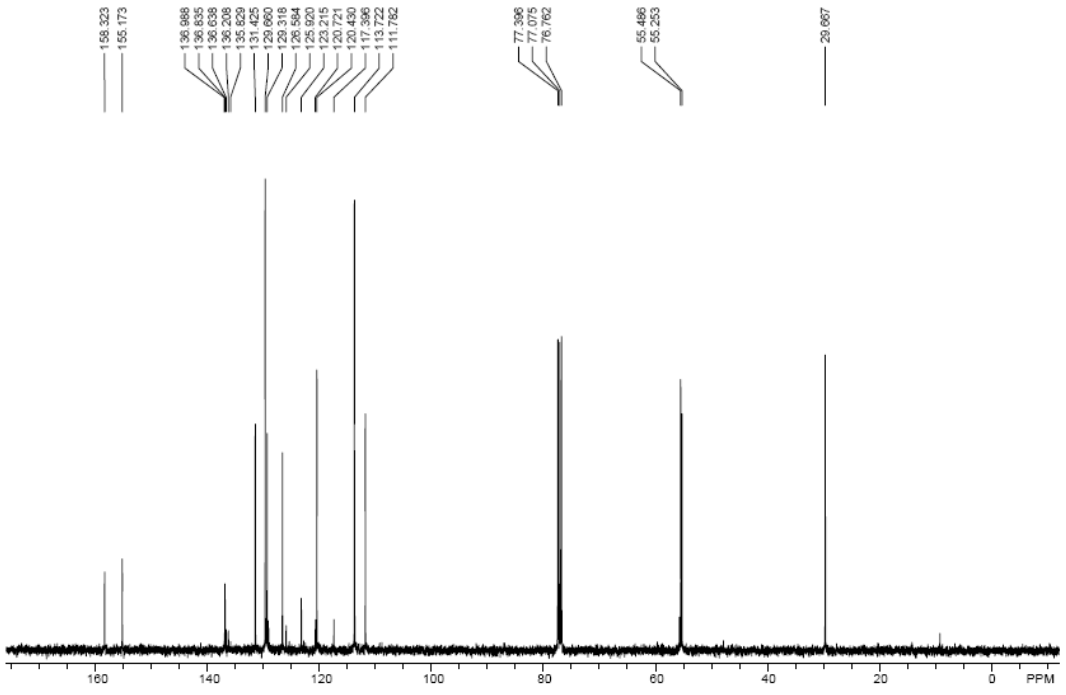
1-(4-methoxyphenyl)-5-((4-methoxyphenyl)(phenyl)methyl)-2-(trifluoromethyl)-1 H-imidazole

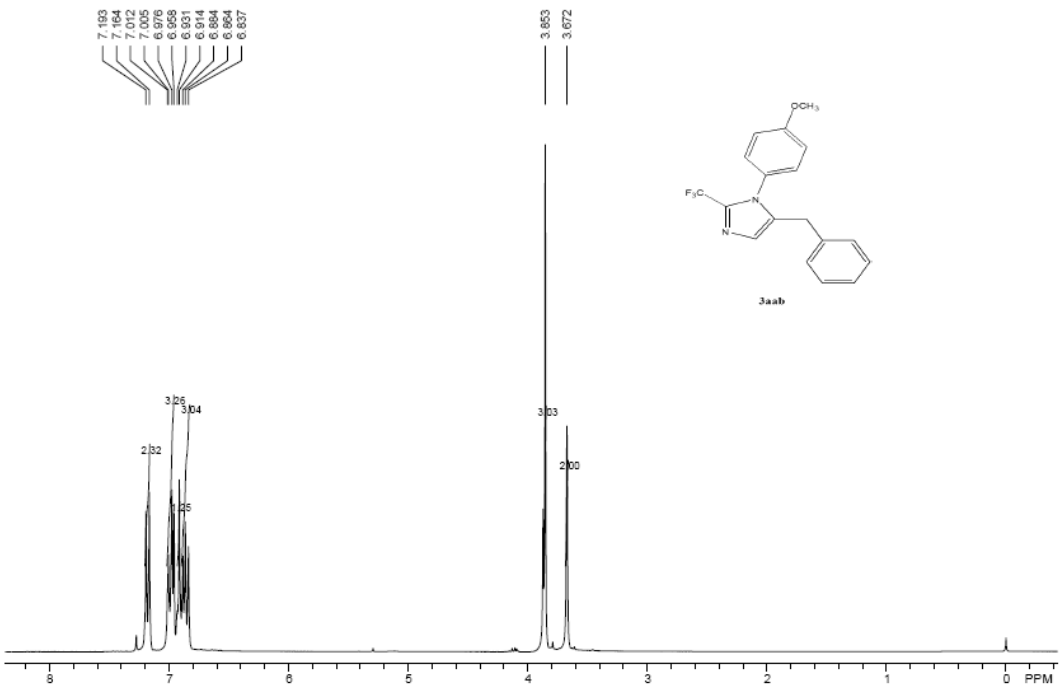


Yellow oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ 7.25 (m, 3H), 7.04 (m, 3H), 6.95 (m, 5H), 6.82 (m, 2H), 6.76 (s, 1H), 4.97 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H). ^{19}F NMR (282 Hz, $CDCl_3$): δ - 59.92 (s, 3F). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.31, 158.6, 141.1, 140.4, 137.1, 136.8 (q, *J* = 38.0 Hz), 132.8, 129.7, 128.9, 128.5 (q, *J* = 2.2 Hz), 127.9, 126.8 (q, *J* = 11.7 Hz), 18.8 (q, *J* = 268.3 Hz), 114.3, 113.9, 55.6, 55.3, 30.4. MS (ESI): 439.1 ($M + H^+$). HRMS (ESI), Calcd. for $C_{25}H_{22}F_3N_2O_2$: 439.16279, Found: 439.16382. IR (film): ν 1609, 1514, 1492, 1456, 1297, 1253, 1185, 1128, 1037, 971, 837 cm^{-1}.

V. NMR spectra for the 5-Benzyl Imidazole







3aab