Oxidative Cyclization Approach to Benzimidazole Libraries

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General Information: All reagents were obtained from commercial suppliers and used without further purification, unless otherwise noted. All solvents used were purchased anhydrous and transferred by nitrogen-purged syringe. Silica gel chromatography was performed using medium pressure Biotage or ISCO systems employing columns pre-packaged by various commercial vendors including Biotage and ISCO. ^{1}H and ^{13}C NMR characterization data were collected at 300 K on a Bruker AS-400 spectrometer operating at 400 and 100 MHz (respectively) with chemical shifts reported in parts per million relative to CD_3OD (^{1}H NMR: 3.31 ppm; ^{13}C NMR: 49.0 ppm). LC-MS were acquired using a Waters Acquity UPLC equipped with a Waters Acquity HSS T3 column, water/MeCN gradient and 0.1% v/v formic acid as modifier.

General Library Procedure A: To a plate of 2-dram vials with septum caps containing the anilines (0.40 mmol, 1.0 equiv) was added THF (2.5 mL, 0.16 M) followed by LiHMDS (0.40 mL, 1 M solution in THF, 1.0 equiv). The resulting solutions were stirred at 23 °C for 20 minutes. Benzonitrile (41 μL, 0.40 mmol, 1.0 equiv) was added via syringe and the reactions were stirred at 23 °C for 17 h. Solvent was then removed via genevac to provide the crude amidine intermediates. DMSO (2.5 mL, 0.16 M) and $Cu(OAc)_2$ (145 mg, 0.80 mmol, 2.0 equiv) were added followed by glacial acetic acid (0.46 mL, 8 mmol, 20 equiv). Without capping the vials, they were placed in a preheated 110 °C plate and stirred for 17 h open to the atmosphere. The vials were cooled and poured into Na_2CO_3 (20 mL, saturated aqueous solution). The mixtures were extracted with EtOAc (2 X 5 mL) and filtered through Na_2SO_4 plugs. Solvent was removed via genevac. The resulting crude benzimidazoles were dissolved in 1 mL DMSO and submitted for high-throughput purification (column: Waters Sunfire C18 19x100, 5μ; Mobile phase A: 0.05% TFA in water (v/v); Mobile phase B: 0.05% TFA in acetonitrile (v/v).

General Library Procedure B:

Imidoyl triflate stock solution: To a dry flask under N2 atmosphere was added N-methyl benzamide (1.0 equiv per reaction) followed by CH_2Cl_2 (0.4 M) and 2,6-lutidine (2.2 equiv). The flask was cooled to 0 °C and triflic anhydride (1.1 equiv per reaction) was added dropwise. The solution was allowed to warm to 23 °C over 2.5 h.

Amidine formation / oxidative cyclization: To a plate of 2-dram vials with septum caps containing the anilines (1.2 equiv) was added CH_2Cl_2 (0.8 M) followed by the imidoyl triflate solution (1.0 equiv per vial). Vials were stirred at 23 °C for 15 h. Reaction mixtures were concentrated under a stream of N_2, then partitioned between water and EtOAc (1:1). The organic phases were separated and the aqueous phases were re-extracted with EtOAc. The combined organic phases were filtered through Na_2SO_4 plugs into 2 dram vials and concentrated under a stream of N_2. To the resulting crude amidines was added MeCN (0.25 M) and $PhI(OAc)_2$ (2.0 equiv per vial). The vials were sealed with pressure-release caps and heated to 100 °C for 2 h. The vials were cooled and concentrated under a stream of N_2. The resulting residues were diluted with H_2O, extracted with EtOAc (2x), and filtered through Na_2SO_4 plugs. Solvent was removed under a stream of N_2. The resulting crude benzimidazoles were dissolved in 1 mL DMSO and submitted for high-throughput purification (column: Waters Sunfire C18 19x100, 5μ; Mobile phase A: 0.05% TFA in water (v/v); Mobile phase B: 0.05% TFA in acetonitrile (v/v).

Spectroscopic Data for Scheme 2

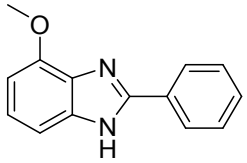
Compounds were prepared in parallel format via General Library Procedure A.

Compound **2f** and **2i** has been fully characterized previously and NMR spectra were matched to reported values:

2f) Huang, J.; He, Y.; Wang, Y.; Zhu, Q. *Chem. Eur. J.* **2012**, *18*, 13964-13967.

2i) Kim, J.; Kim J.; Lee, H.; Lee, B. M.; Kim, B. H. *Tetrahedron* **2011**, *67*, 8027-8033.

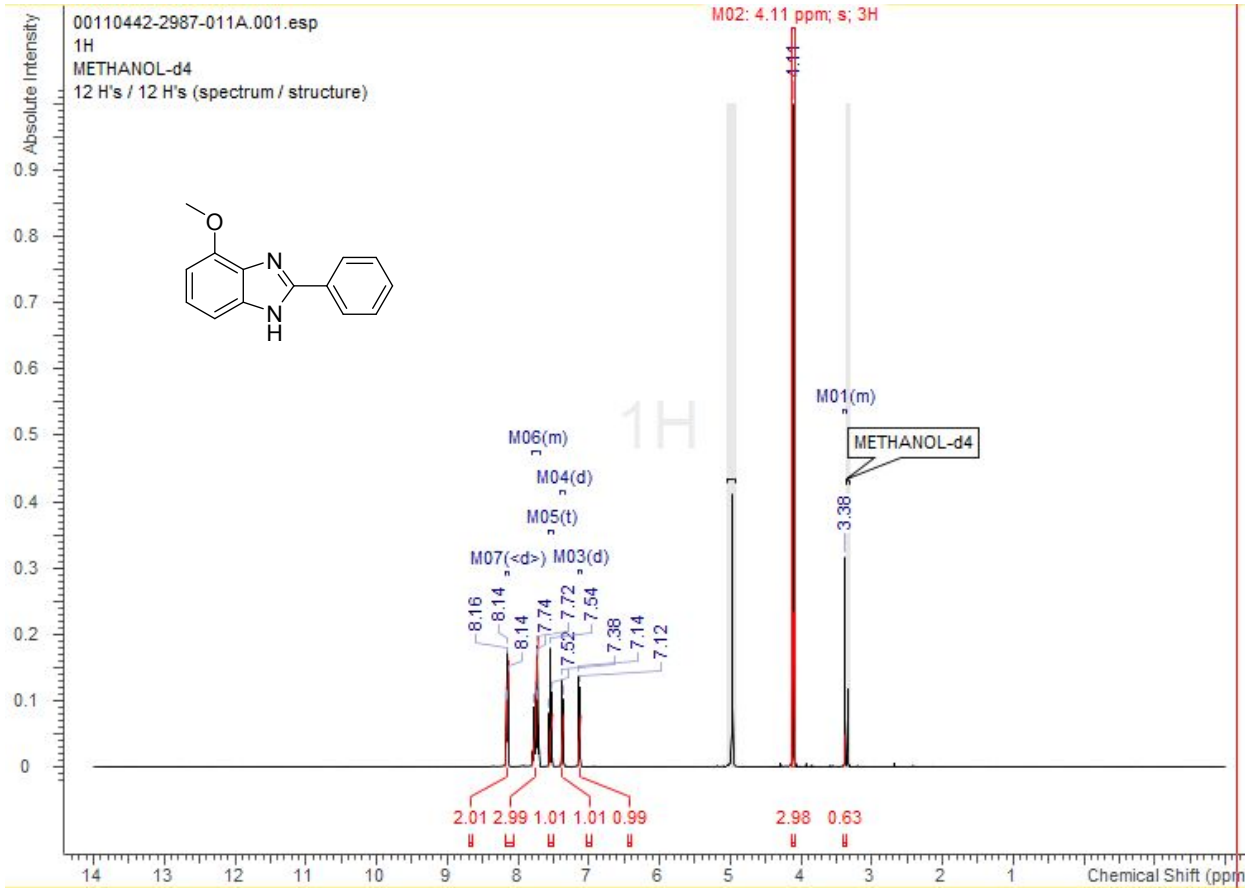
4-methoxy-2-phenyl-1H-benzo[d]imidazole (2a)

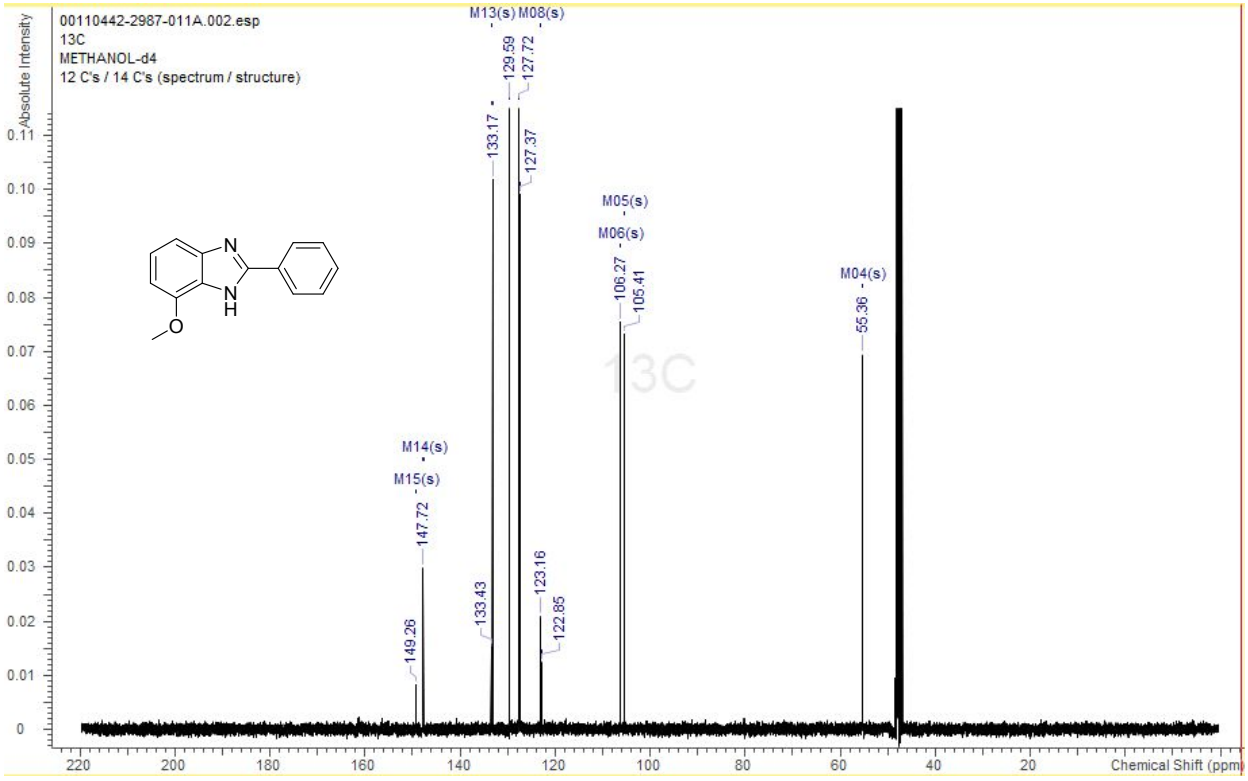


^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.15 (d, *J*=7.3 Hz, 2H), 7.69 - 7.80 (m, 3H), 7.54 (t, *J*=8.2 Hz, 1H), 7.37 (d, *J*=7.8 Hz, 1H), 7.13 (d, *J*=7.8 Hz, 1H), 4.11 (s, 3H) ppm.

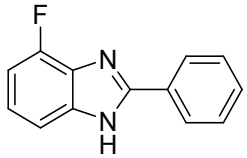
^{13}C NMR (101 MHz, METHANOL-d_4) δ 149.26, 147.72, 133.43, 133.17, 129.59, 129.55, 127.72, 127.37, 123.16, 106.27, 105.41, 55.36 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{12}N_2O$ (M+H): 225.1, Found: 225.3


00110442-2987-011A.001.esp
1H
METHANOL-d4
12 H's / 12 H's (spectrum / structure)
Absolute Intensity
M02: 4.11 ppm; s; 3H
4.11
M01(m)
METHANOL-d4
3.38
M06(m)
M04(d)
M05(t)
M07(<d>)
M03(d)
8.16
8.14
8.14
7.74
7.72
7.54
7.52
7.38
7.14
7.12
2.01 2.99 1.01 1.01 0.99
2.98 0.63
Chemical Shift (ppm)


00110442-2987-011A.002.esp
13C
METHANOL-d4
12 C's / 14 C's (spectrum / structure)
Absolute Intensity
M13(s)
M08(s)
129.59
127.72
133.17
127.37
M05(s)
M06(s)
106.27
105.41
M04(s)
55.36
M14(s)
M15(s)
147.72
149.26
133.43
123.16
122.85
Chemical Shift (ppm)

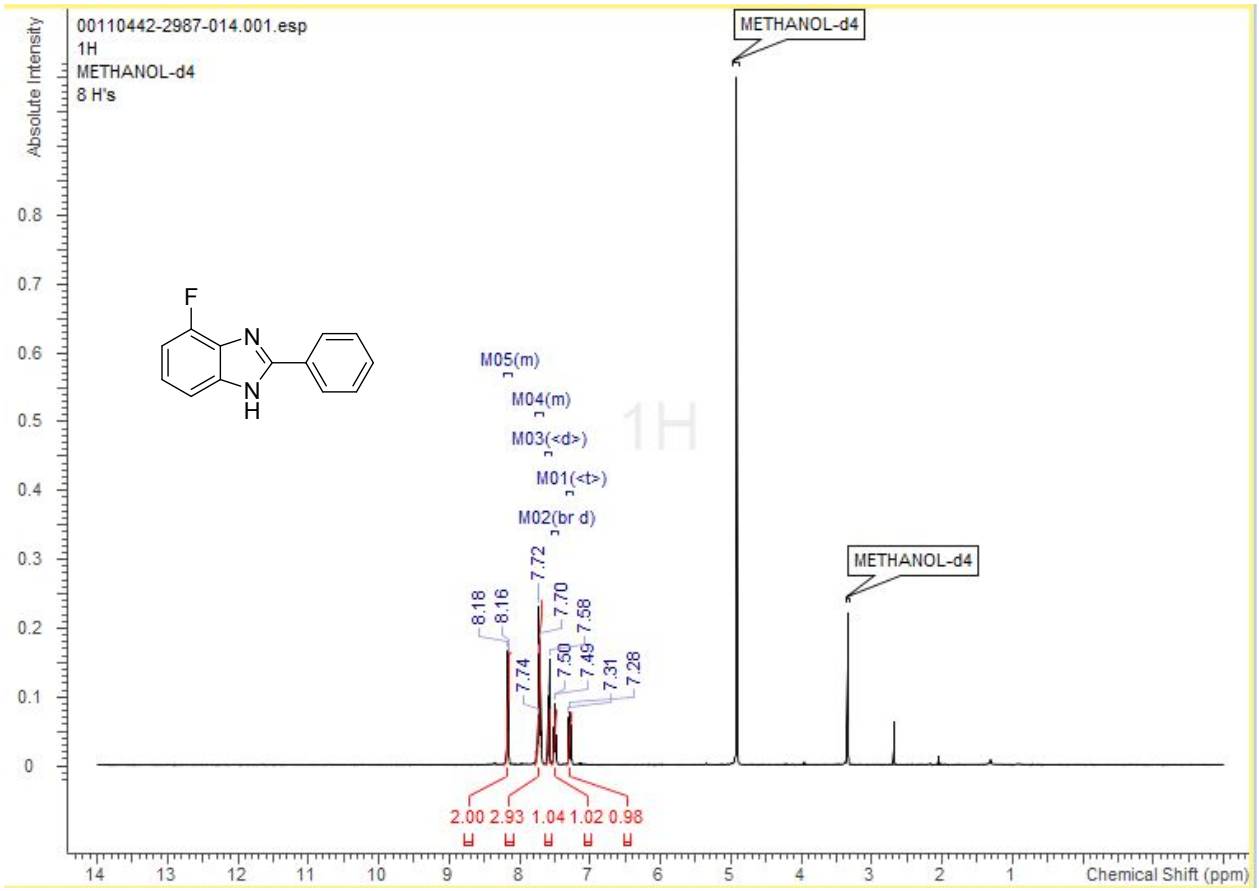
4-fluoro-2-phenyl-1H-benzo[d]imidazole (2b)



^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.12 - 8.22 (m, 2H), 7.66 - 7.78 (m, 3H), 7.59 (d, *J*=7.9 Hz, 1H), 7.50 (br d, *J*=4.7 Hz, 1H), 7.30 (t, *J*=9.2 Hz, 1H) ppm.

^{13}C NMR (101 MHz, METHANOL-d_4) δ 151.70, 149.21, 136.36, 132.60, 129.43, 127.53, 125.79, 124.13, 110.18, 110.01, 109.47 ppm.

LC-MS (ESI) Calcd. for $C_{13}H_9FN_2$ (M+H): 213.1, Found: 213.2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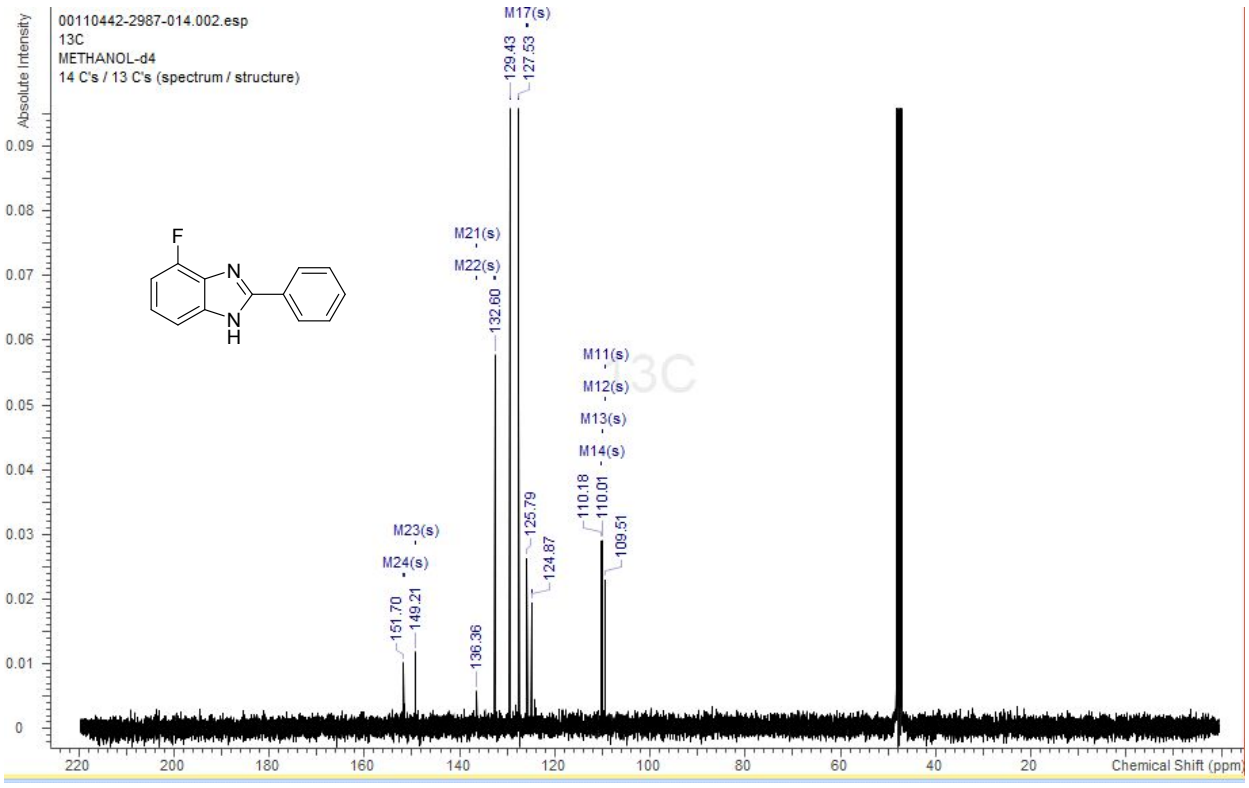
1H
METHANOL-d4
8 H's
Absolute Intensity
METHANOL-d4
METHANOL-d4
M05(m)
M04(m)
M03(<d>)
M01(<t>)
M02(br d)
8.18
8.16
7.74
7.72
7.70
7.58
7.50
7.49
7.31
7.28
2.00 2.93 1.04 1.02 0.98
Chemical Shift (ppm)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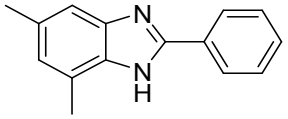
13C
METHANOL-d4
14 C's / 13 C's (spectrum / structure)
Absolute Intensity
M17(s)
129.43
127.53
M21(s)
M22(s)
132.60
M11(s)
M12(s)
M13(s)
M14(s)
110.18
110.01
109.51
125.79
124.87
M23(s)
M24(s)
151.70
149.21
136.36
Chemical Shift (ppm)

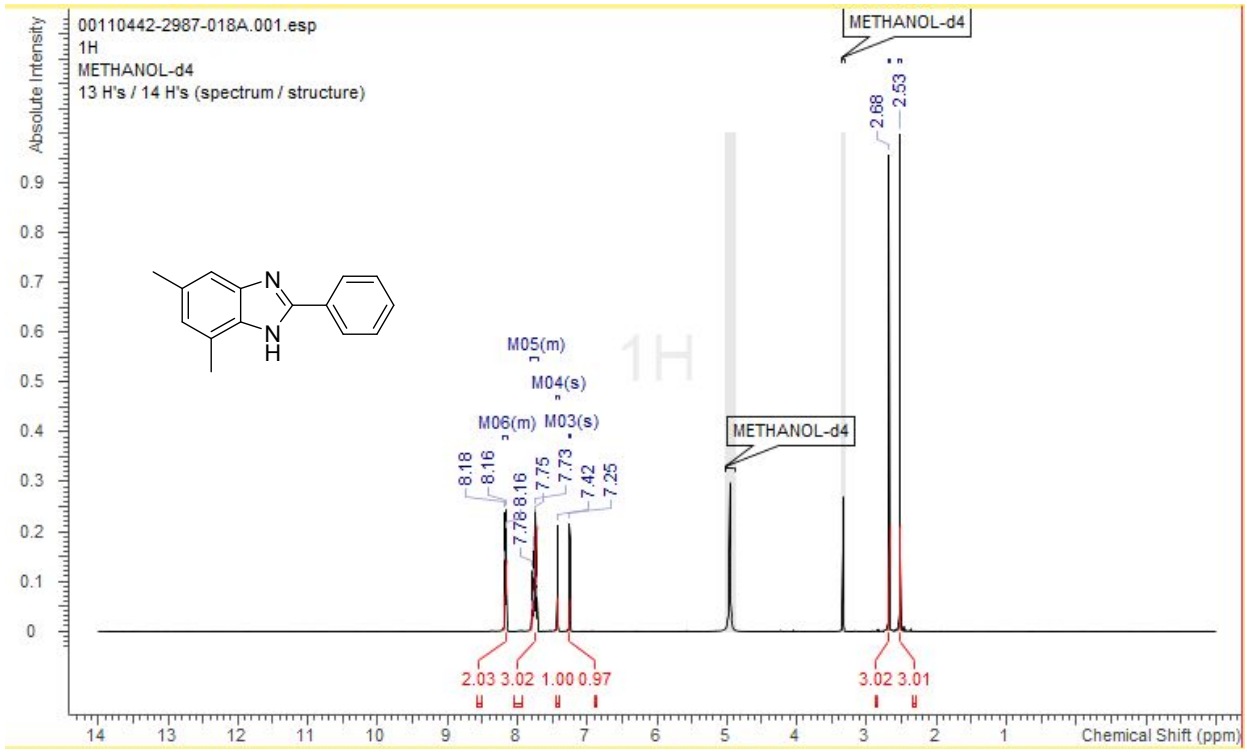
5,7-dimethyl-2-phenyl-1H-benzo[d]imidazole (2e)

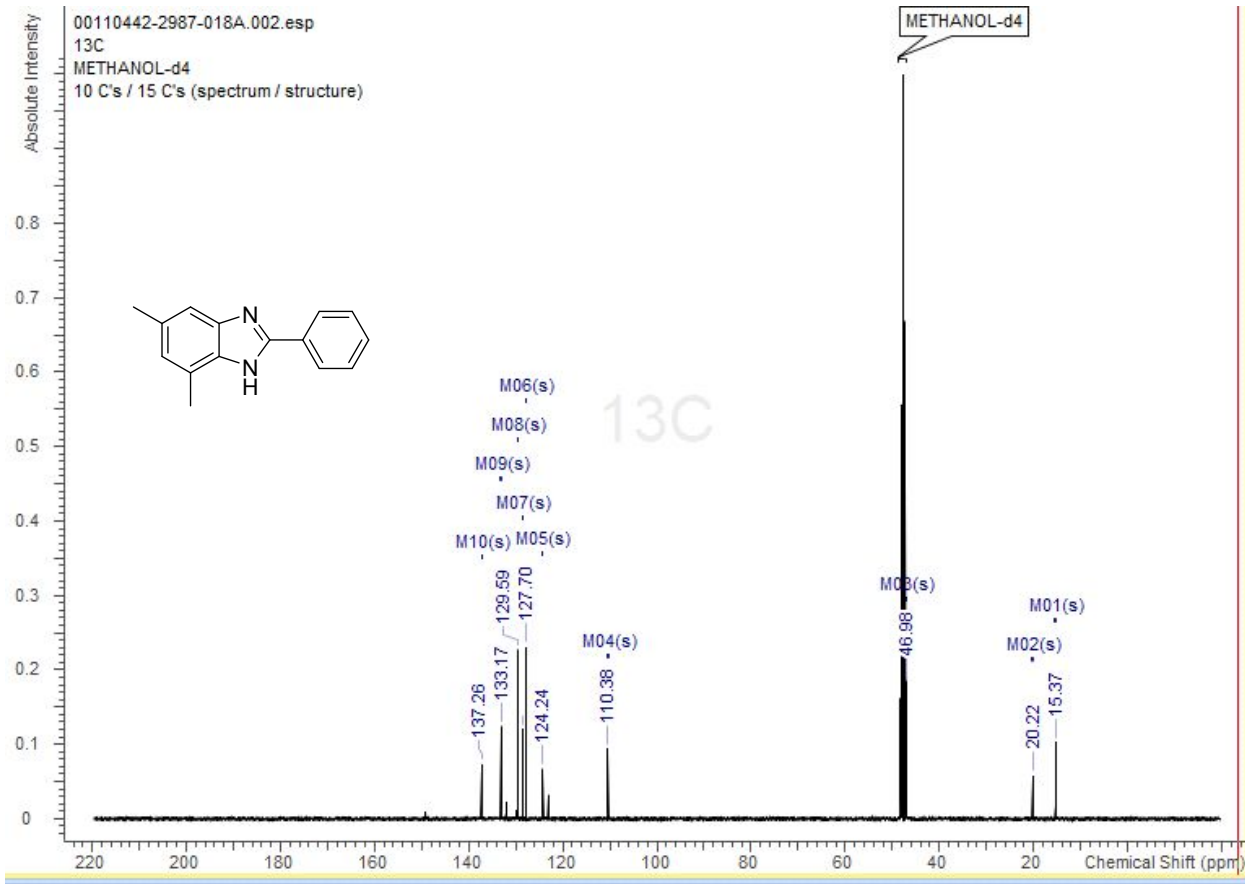


^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.14 - 8.20 (m, 2H), 7.70 - 7.81 (m, 3H), 7.42 (s, 1H), 7.25 (s, 1H), 2.68 (s, 3H), 2.53 (s, 3H) ppm.

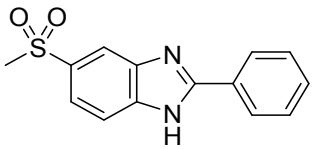
^{13}C NMR (126 MHz, METHANOL-d_4) δ 149.25, 136.82, 132.86, 132.62, 130.26, 129.50, 128.16, 127.55, 124.24, 123.67, 110.48, 20.24, 15.44 ppm.

LC-MS (ESI) Calcd. for $C_{15}H_{14}N_2$ (M+H): 223.1, Found: 223.2


00110442-2987-018A.001.esp
1H
METHANOL-d4
13 H's / 14 H's (spectrum / structure)
Absolute Intensity
Chemical Shift (ppm)
METHANOL-d4
METHANOL-d4
2.68
2.53
M05(m)
M04(s)
M06(m)
M03(s)
8.18
8.16
8.16
7.78
7.75
7.73
7.42
7.25
2.03
3.02
1.00
0.97
3.02
3.01


00110442-2987-018A.002.esp
13C
METHANOL-d4
10 C's / 15 C's (spectrum / structure)
Absolute Intensity
Chemical Shift (ppm)
METHANOL-d4
M06(s)
M08(s)
M09(s)
M07(s)
M10(s)
M05(s)
M03(s)
M01(s)
M02(s)
M04(s)
129.59
127.70
133.17
137.26
124.24
110.38
46.98
20.22
15.37

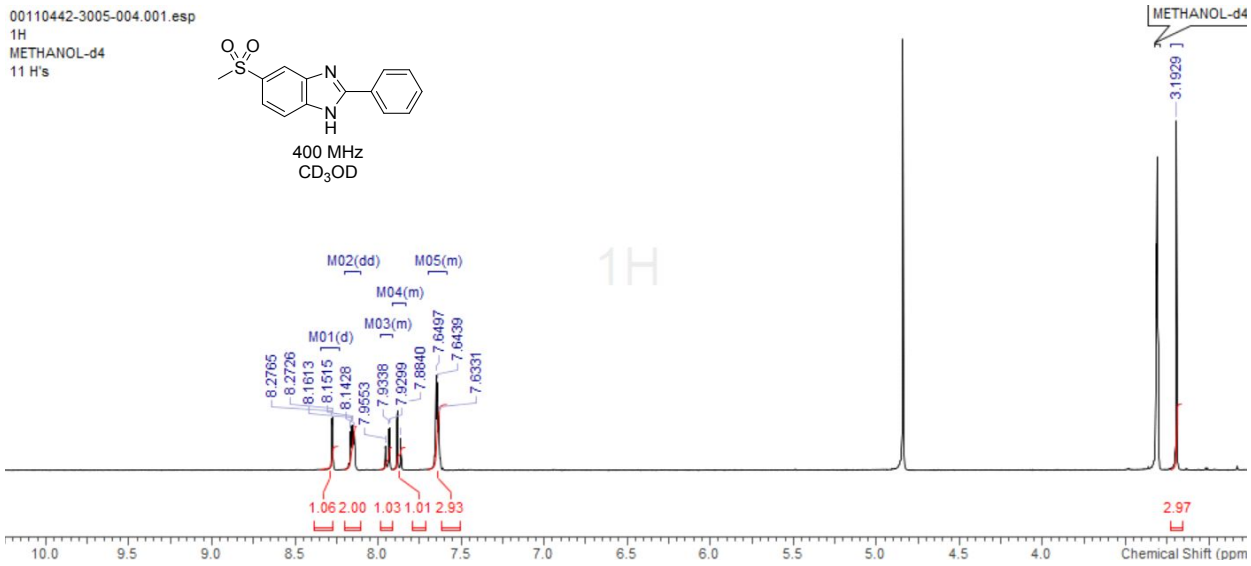
5-(methylsulfonyl)-2-phenyl-1H-benzo[d]imidazole (2g)

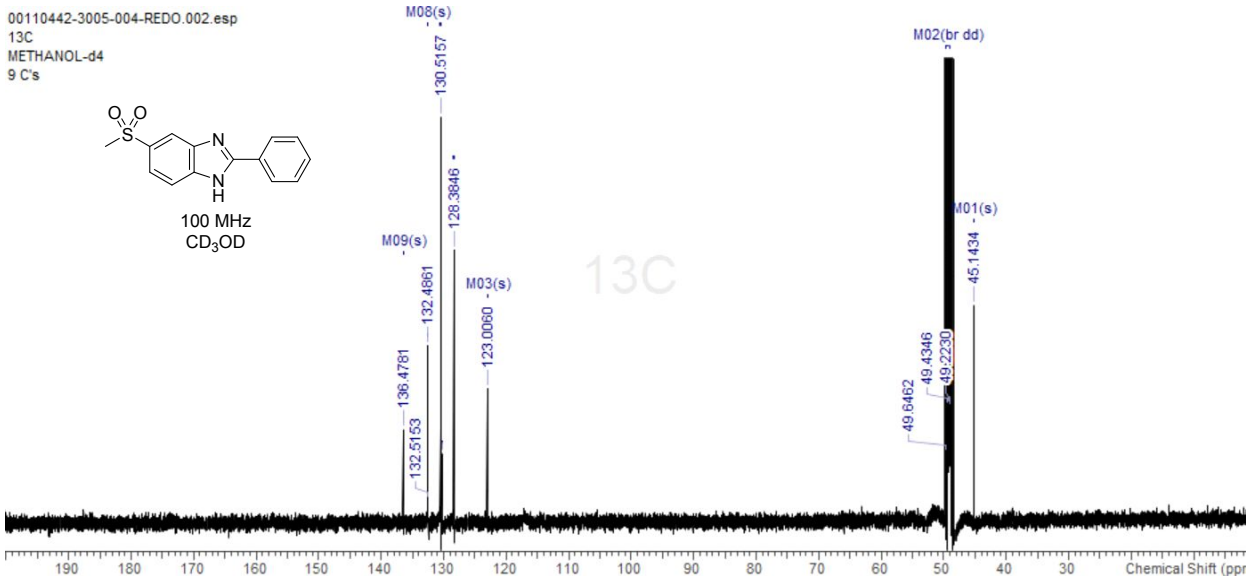


^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.27 (d, J = 1.6 Hz, 1H), 8.16-8.14 (m, 2H), 7.94 (dd, J = 1.6 Hz, 8.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.65-7.63 (m, 3H), 3.19 (s, 3H) ppm.

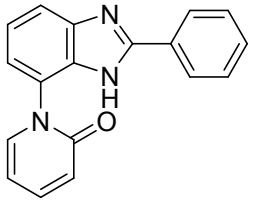
^{13}C NMR (101 MHz, METHANOL-d_4) δ 152.6, 150.5, 141.9, 137.4, 133.2, 130.7, 129.0, 128.6, 123.8, 116.6, 116.4, 45.1 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{12}N_2O_2S$ (M+H): 273.1, Found: 273.3.


00110442-3005-004.001.esp
1H
METHANOL-d4
11 H's
400 MHz
CD3OD
METHANOL-d4
3.1929
M02(dd)
M05(m)
M04(m)
M03(m)
M01(d)
8.2765
8.2726
8.1613
8.1515
8.1428
7.9553
7.9338
7.9299
7.8840
7.6497
7.6439
7.6331
1.06 2.00 1.03 1.01 2.93
2.97
Chemical Shift (ppm


00110442-3005-004-REDO.002.esp
13C
METHANOL-d4
9 C's
100 MHz
CD3OD
M08(s)
130.5157
128.3646
M09(s)
132.4861
136.4781
132.5153
M03(s)
123.0060
M02(br dd)
M01(s)
45.1434
49.6462
49.4346
49.2230
Chemical Shift (ppr

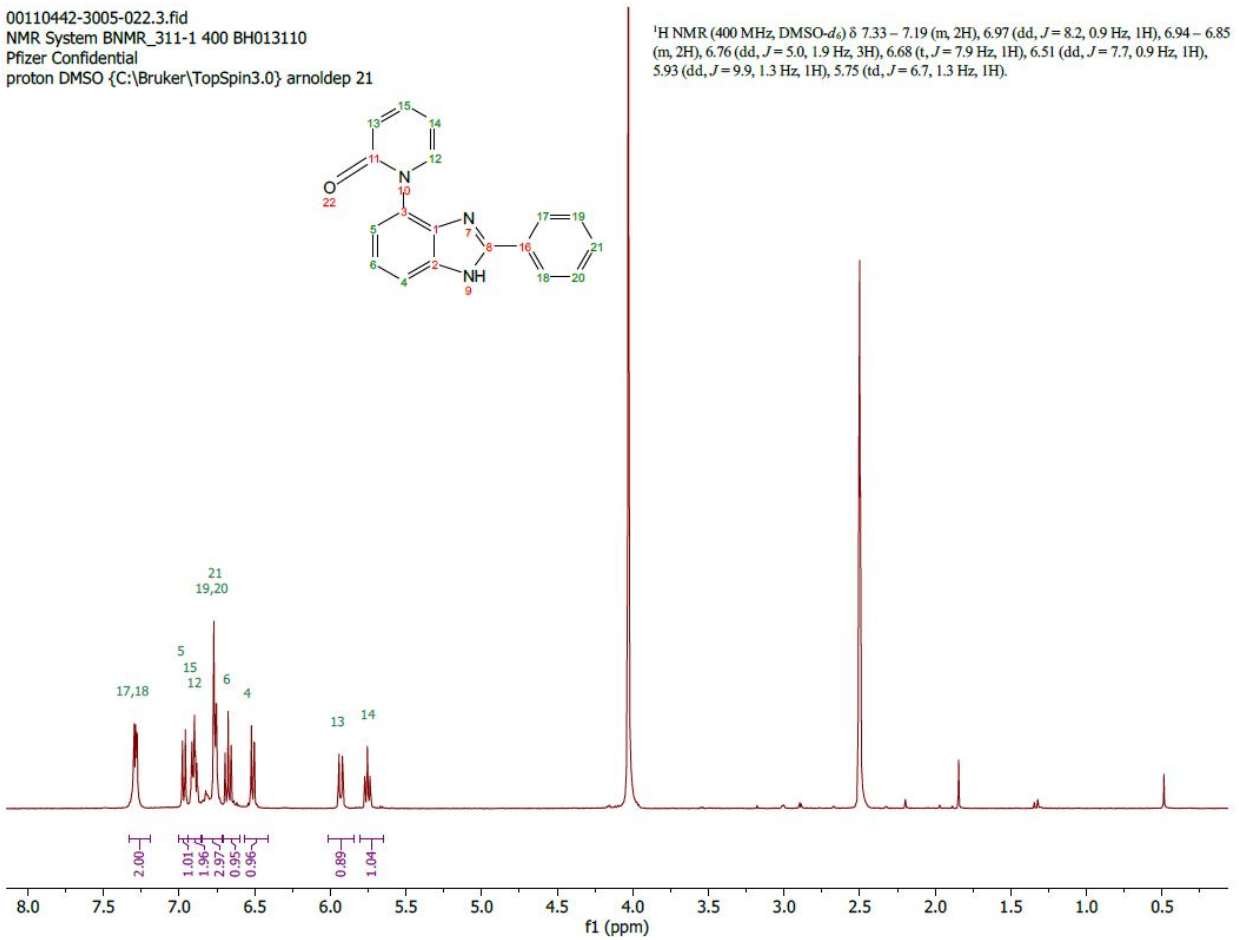
1-(2-phenyl-1H-benzo[d]imidazol-7-yl)pyridin-2(1H)-one (2h)



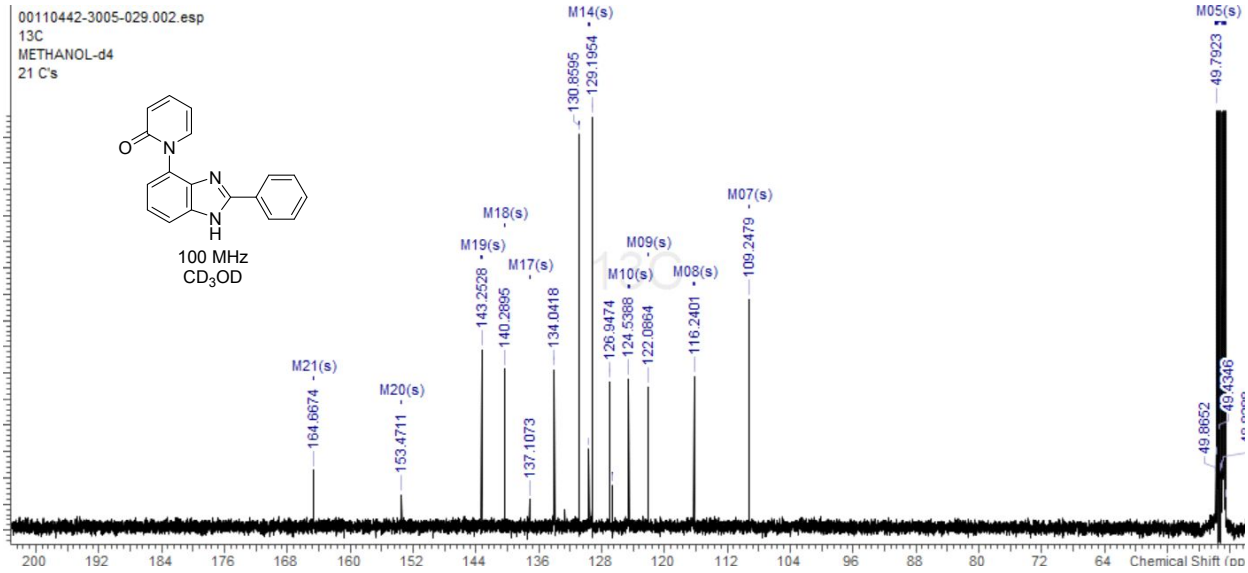
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.06 - 8.17 (m, 2H), 7.87 (d, *J*=8.20 Hz, 1H), 7.60 - 7.77 (m, 5H), 7.47 (d, *J*=7.02 Hz, 1H), 6.75 (d, *J*=9.28 Hz, 1H), 6.61 - 6.59 (m, 1H) ppm.

^{13}C NMR (101 MHz, METHANOL-d_4) δ 164.7, 153.5, 143.3, 140.3, 137.1, 134.0, 132.7, 130.9, 129.6, 129.2, 126.9, 126.7, 124.5, 122.1, 116.2, 109.2 ppm.

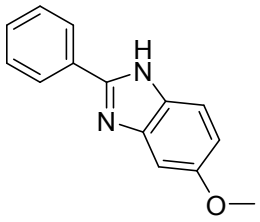
LC-MS (ESI) Calcd. for $C_{18}H_{14}N_3O$ (M+H): 288.3, Found: 288.4



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 – 7.19 (m, 2H), 6.97 (dd, J = 8.2, 0.9 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.76 (dd, J = 5.0, 1.9 Hz, 3H), 6.68 (t, J = 7.9 Hz, 1H), 6.51 (dd, J = 7.7, 0.9 Hz, 1H), 5.93 (dd, J = 9.9, 1.3 Hz, 1H), 5.75 (td, J = 6.7, 1.3 Hz, 1H).



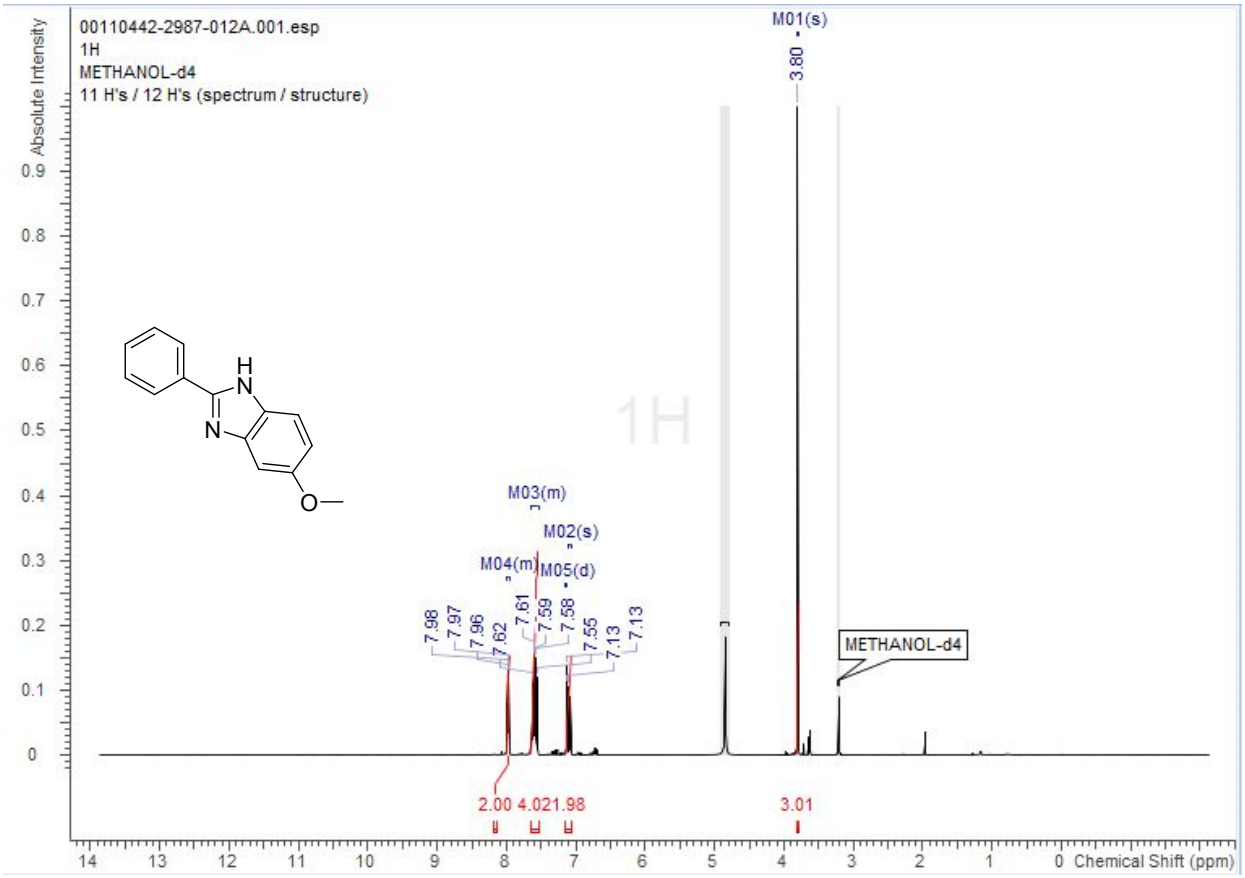
6-methoxy-2-phenyl-1H-benzo[d]imidazole (2j)

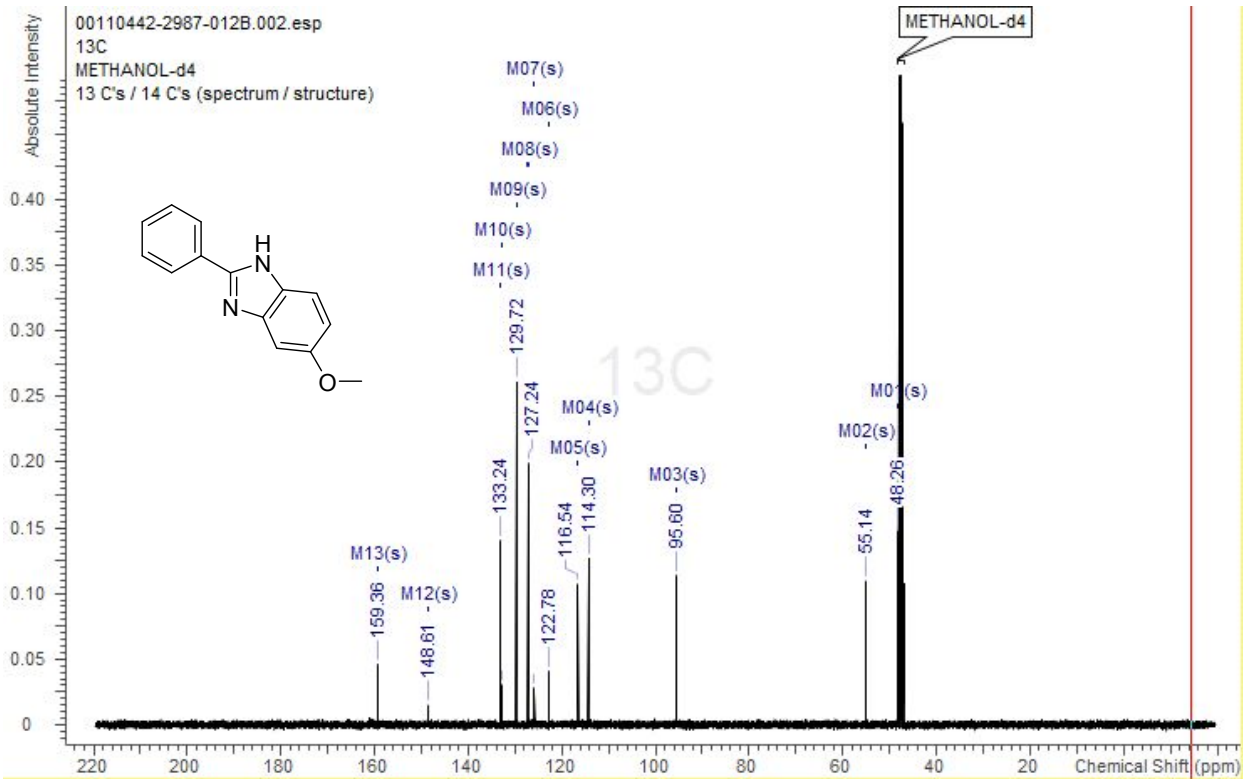


^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.95 - 8.00 (m, 2H), 7.54 - 7.66 (m, 4H), 7.13 (d, *J*=2.3 Hz, 1H), 7.10 (s, 1H), 3.80 (s, 3H) ppm.

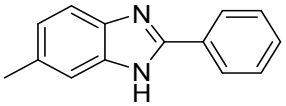
^{13}C NMR (101 MHz, METHANOL-d_4) δ 159.36, 148.61, 133.24, 132.79, 129.72, 127.24, 125.88, 122.78, 116.54, 114.30, 95.60, 55.14 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{12}N_2O$ (M+H): 224.09, Found: 224.3


00110442-2987-012A.001.esp
1H
METHANOL-d4
11 H's / 12 H's (spectrum / structure)
Absolute Intensity
M01(s)
3.80
M03(m)
M02(s)
M04(m)
M05(d)
7.98
7.97
7.96
7.62
7.61
7.59
7.58
7.55
7.13
7.13
METHANOL-d4
2.00
4.02
1.98
3.01
Chemical Shift (ppm)


00110442-2987-012B.002.esp
13C
METHANOL-d4
13 C's / 14 C's (spectrum / structure)
Absolute Intensity
METHANOL-d4
M07(s)
M06(s)
M08(s)
M09(s)
M10(s)
M11(s)
129.72
127.24
133.24
M04(s)
M05(s)
116.54
114.30
122.78
M03(s)
95.60
M13(s)
159.36
M12(s)
148.61
M01(s)
M02(s)
48.26
55.14
Chemical Shift (ppm)

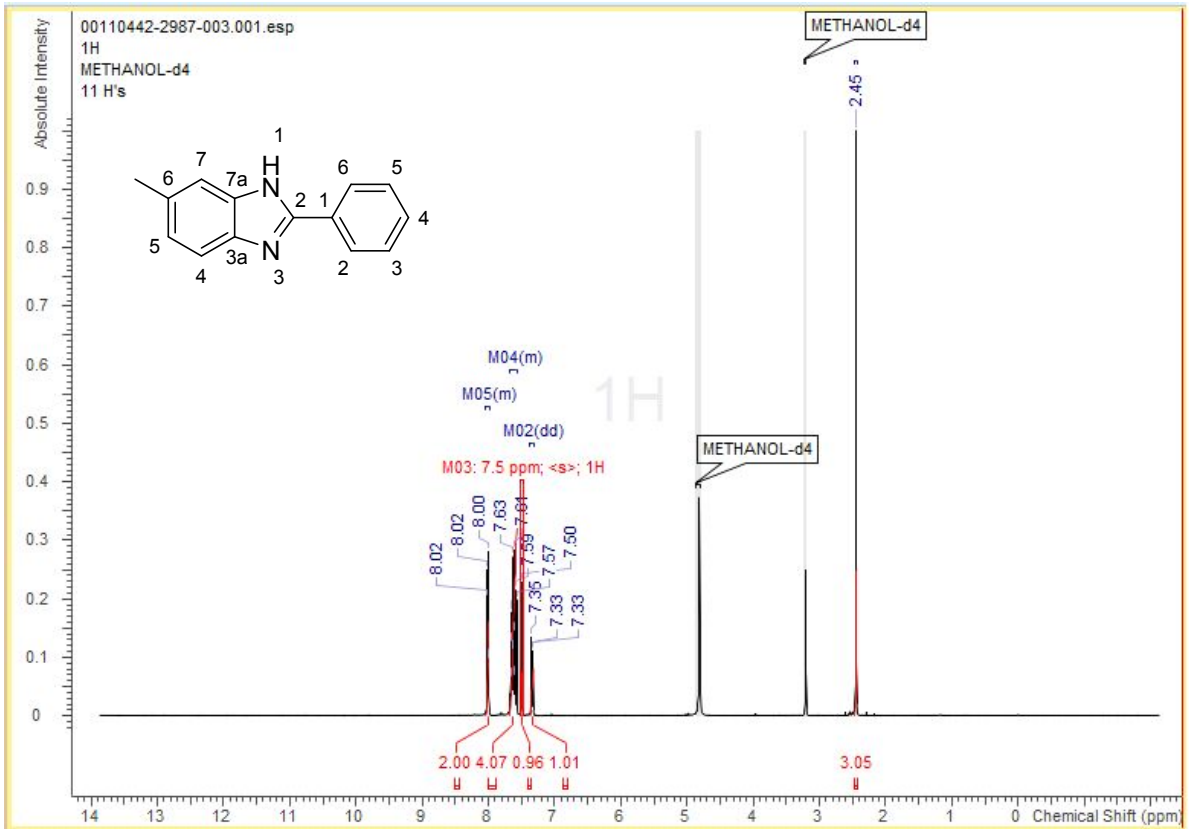
6-methyl-2-phenyl-1H-benzo[d]imidazole (2k)

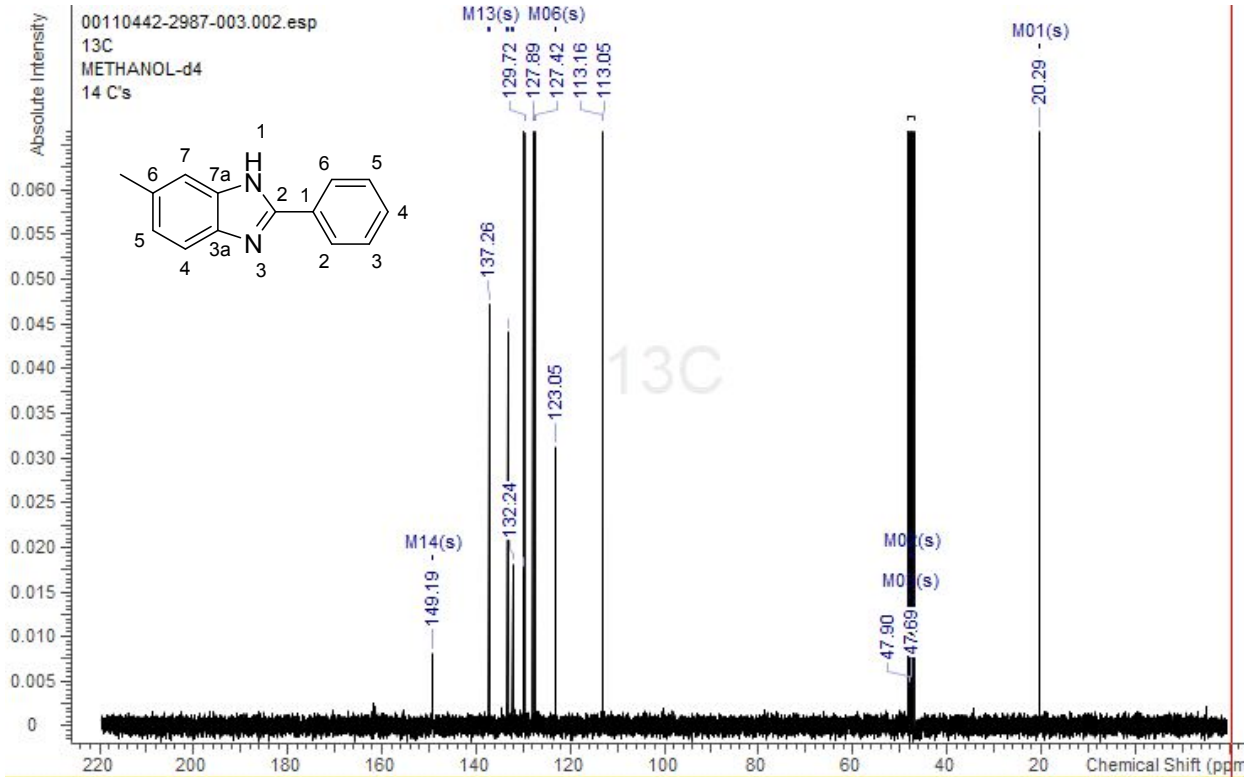


^{1}H NMR (400 MHz, METHANOL-d_4): δ 8.04 – 7.98 (m, 2H), 7.68 – 7.56 (m, 4H), 7.50 (s, 1H), 7.34 (dd, *J* =8.6, 0.8 Hz, 1H), 2.45 (s, 3H) ppm.

^{13}C NMR (101 MHz, METHANOL-d_4) δ 149.19, 137.26, 133.32, 132.24, 130.07, 129.72, 127.89, 127.42, 123.05, 113.16, 113.05, 20.29 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{12}N_2$ (M+H): 209.1, Found: 209.2


00110442-2987-003.001.esp
1H
METHANOL-d4
11 H's
Absolute Intensity
METHANOL-d4
2.45
M04(m)
M05(m)
M02(dd)
M03: 7.5 ppm; <s>; 1H
8.02
8.00
7.63
7.61
7.59
7.57
7.50
7.35
7.33
7.33
METHANOL-d4
2.00 4.07 0.96 1.01
3.05
Chemical Shift (ppm)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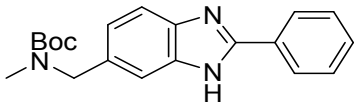
13C
METHANOL-d4
14 C's
Absolute Intensity
M13(s)
M06(s)
129.72
127.89
127.42
113.16
113.05
M01(s)
20.29
137.26
123.05
132.24
M14(s)
149.19
47.90
47.69
Chemical Shift (ppm)

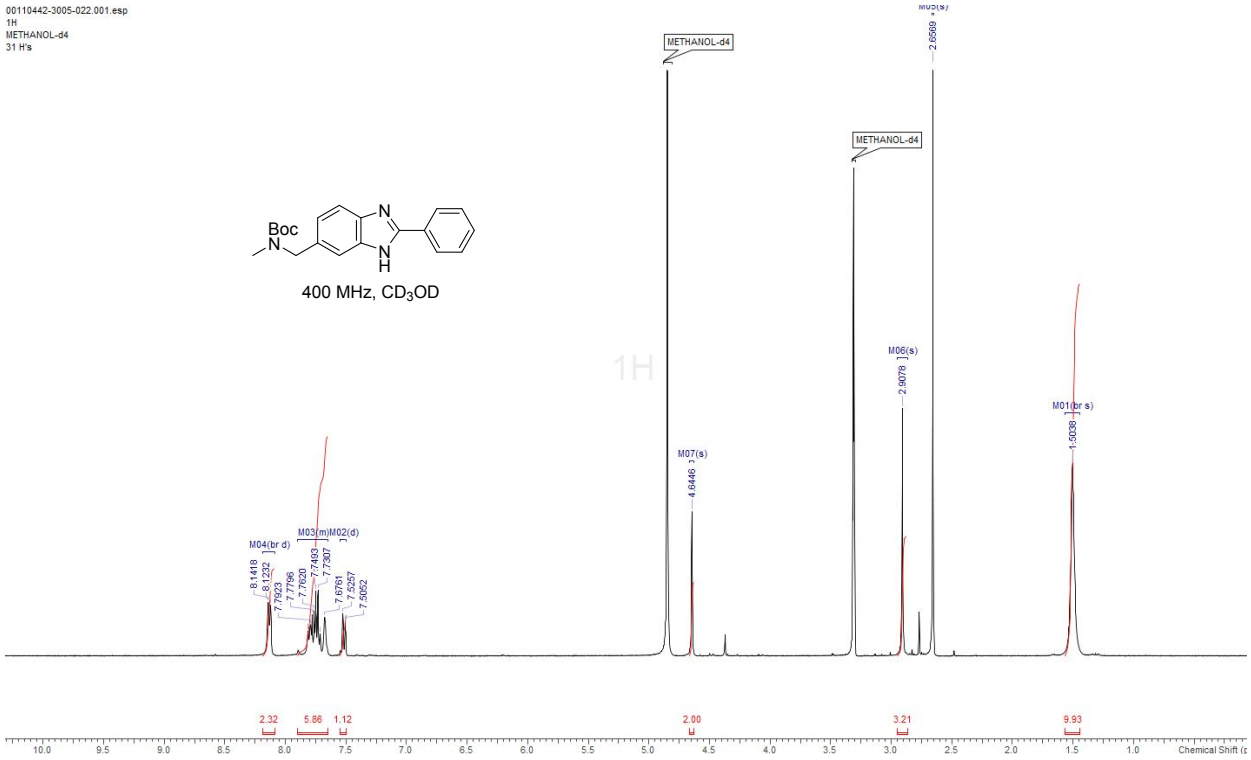
tert-butyl methyl((2-phenyl-1H-benzo[d]imidazol-6-yl)methyl)carbamate (2l)

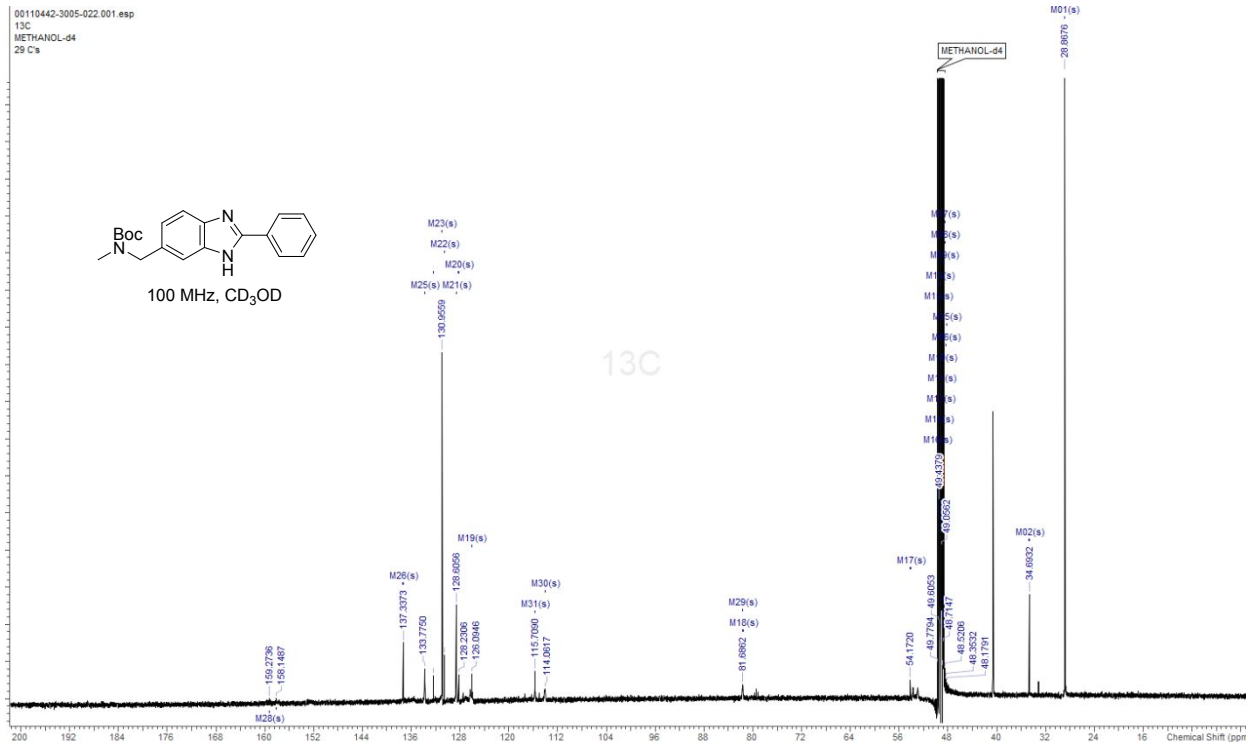


^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.13 (br d, *J*=7.41 Hz, 2 H), 7.70 - 7.90 (m, 4 H), 7.68 (br s, 1 H), 7.52 (d, *J*=8.20 Hz, 1 H), 4.64 (s, 2 H), 2.91 (s, 3 H), 1.50 (s, 9 H) ppm.

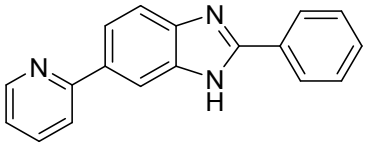
^{13}C NMR (101 MHz, METHANOL-d_4) δ 159.3, 158.1, 137.3, 133.8, 132.4, 131.0, 130.5, 128.6, 128.2, 126.1, 115.7, 114.1, 81.6, 54.2, 34.7, 28.9 ppm.

LC-MS (ESI) Calcd. for $C_{20}H_{24}N_3O_2$ (M+H): 338.4, Found: 338.4


00110442-3005-022.001.esp
1H
METHANOL-d4
31 H's
Boc
N
N
H
400 MHz, CD3OD
METHANOL-d4
METHANOL-d4
M04(br d)
M03(m)M02(d)
M07(s)
M06(s)
M01(br s)
8.1418
8.1232
7.7923
7.7796
7.7620
7.7493
7.7307
7.6761
7.5257
7.5052
4.6446
2.9078
1.5038
2.32
5.86
1.12
2.00
3.21
9.93
Chemical Shift (


00110442-3005-022.001.esp
13C
METHANOL-d4
29 C's
Boc
N
N
H
100 MHz, CD3OD
METHANOL-d4
M01(s)
M23(s)
M22(s)
M20(s)
M25(s) M21(s)
M19(s)
M26(s)
M30(s)
M31(s)
M29(s)
M18(s)
M17(s)
M02(s)
M28(s)
130.9559
128.6056
137.3373
133.7750
129.2306
129.0946
115.7090
114.0617
81.6862
159.2736
158.1487
54.1720
49.7794
49.6063
49.7147
49.0562
48.5206
48.3532
48.1791
34.6932
Chemical Shift (ppm

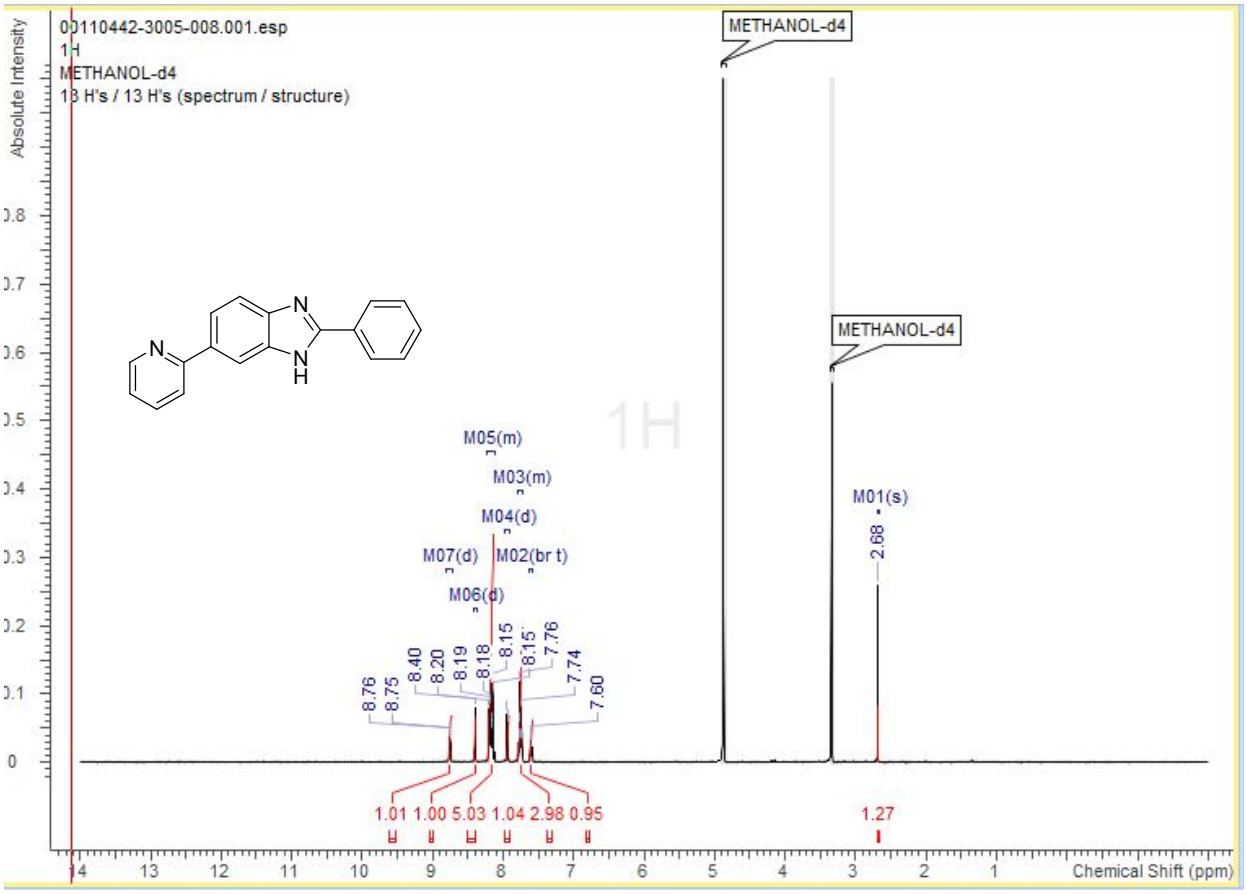
2-phenyl-6-(pyridin-2-yl)-1H-benzo[d]imidazole (2m)

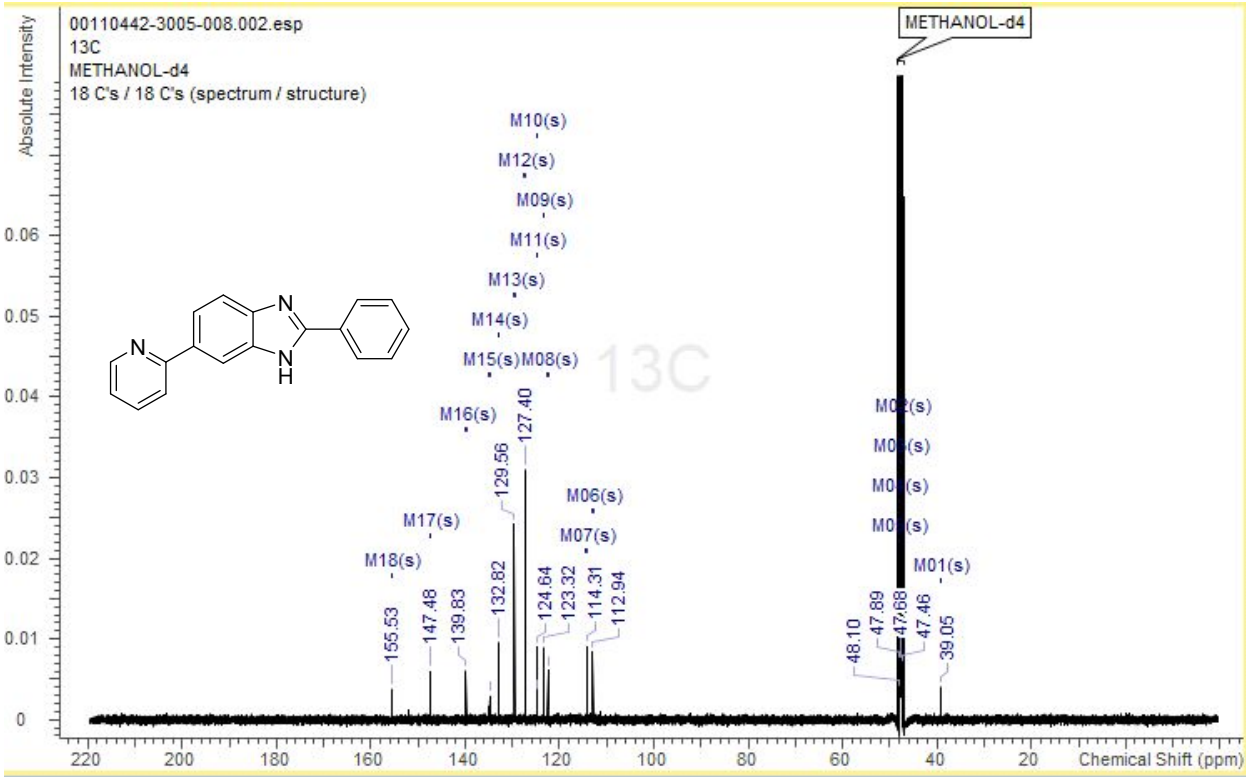


^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.76 (d, *J*=4.7 Hz, 1 H) 8.40 (d, *J*=1.2 Hz, 1 H) 8.12 - 8.22 (m, 5 H) 7.93 (d, *J*=8.6 Hz, 1 H) 7.71 - 7.80 (m, 3 H) 7.60 (br t, *J*=1.8 Hz, 1 H) ppm.

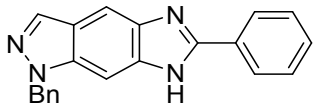
^{13}C NMR (101 MHz, METHANOL-d_4) δ ppm 155.53, 151.96, 147.48, 139.83, 135.00, 134.85, 132.82, 129.56, 127.40, 124.72, 124.64, 123.32, 122.47, 114.31, 112.94, 111.38 ppm.

LC-MS (ESI) Calcd. for $C_{18}H_{13}N_3$ (M+H): 272.1, Found: 272.1


00110442-3005-008.001.esp
1H
METHANOL-d4
13 H's / 13 H's (spectrum / structure)
Absolute Intensity
METHANOL-d4
METHANOL-d4
M05(m)
M03(m)
M04(d)
M07(d)
M02(br t)
M06(d)
M01(s)
2.68
8.76
8.75
8.40
8.20
8.19
8.18
8.15
8.15
7.76
7.74
7.60
1.01 1.00 5.03 1.04 2.98 0.95
1.27
Chemical Shift (ppm)


00110442-3005-008.002.esp
13C
METHANOL-d4
18 C's / 18 C's (spectrum / structure)
Absolute Intensity
METHANOL-d4
M10(s)
M12(s)
M09(s)
M11(s)
M13(s)
M14(s)
M15(s)
M08(s)
M16(s)
127.40
129.56
M06(s)
M17(s)
M07(s)
M18(s)
M01(s)
155.53
147.48
139.83
132.82
124.64
123.32
114.31
112.94
48.10
47.89
47.68
47.46
39.05
Chemical Shift (ppm)

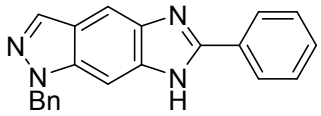
1-benzyl-6-phenyl-1,7-dihydroimidazo[4,5-f]indazole (2n)



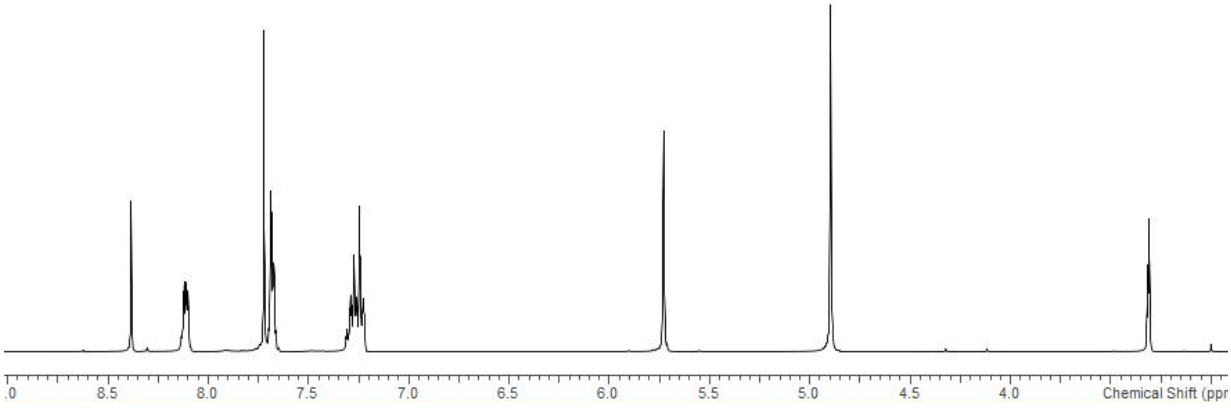
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.38 (s, 1H), 8.11 (m, 2H), 7.65 - 7.75 (m, 5H), 7.21 - 7.31 (m, 5H), 5.73 (s, 2H) ppm.

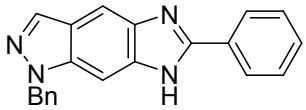
^{13}C NMR (101 MHz, METHANOL-d_4) δ 149.2, 140.5, 138.3, 134.2, 131.4, 131.3, 130.1, 129.3, 129.2, 128.7, 128.6, 127.1, 125.8, 114.5, 112.5, 110.9, 54.5 ppm.

LC-MS (ESI) Calcd. for $C_{21}H_{17}N_4$ (M+H): 325.4, Found: 325.4


N
N
Bn
N
H

1H

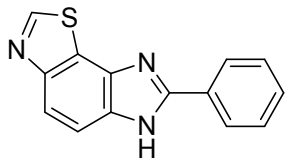

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
Chemical Shift (ppr


N
N
Bn
N
H

13C

150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45

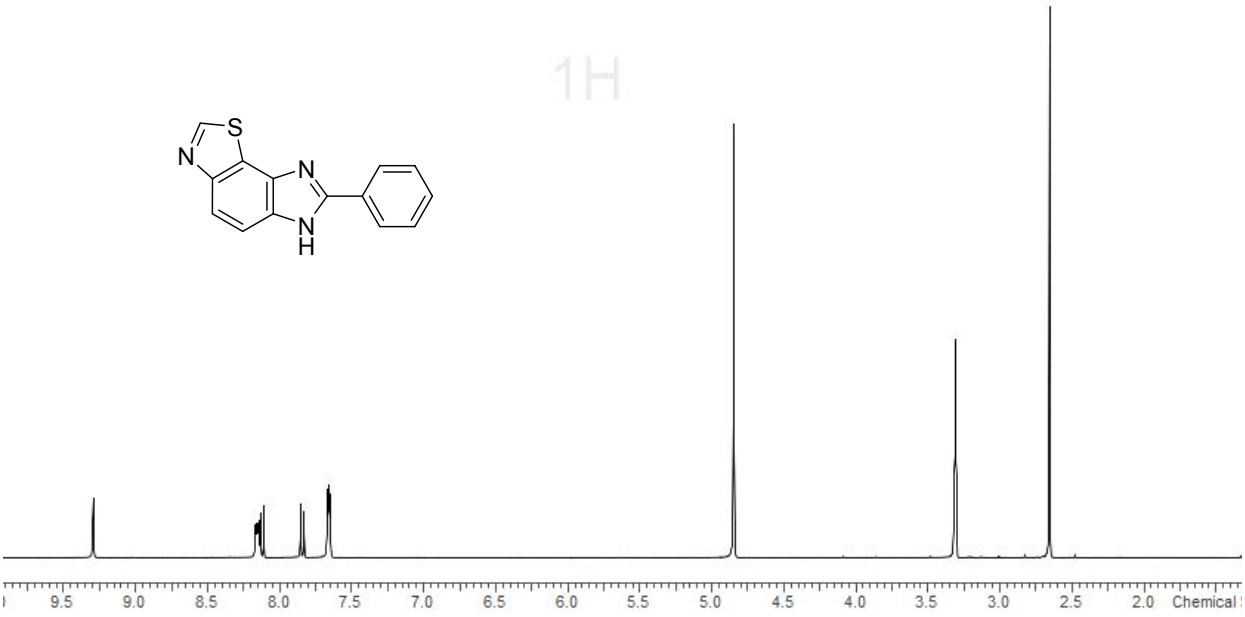
7-phenyl-6H-imidazo[4',5':3,4]benzo[1,2-d]thiazole (2o)

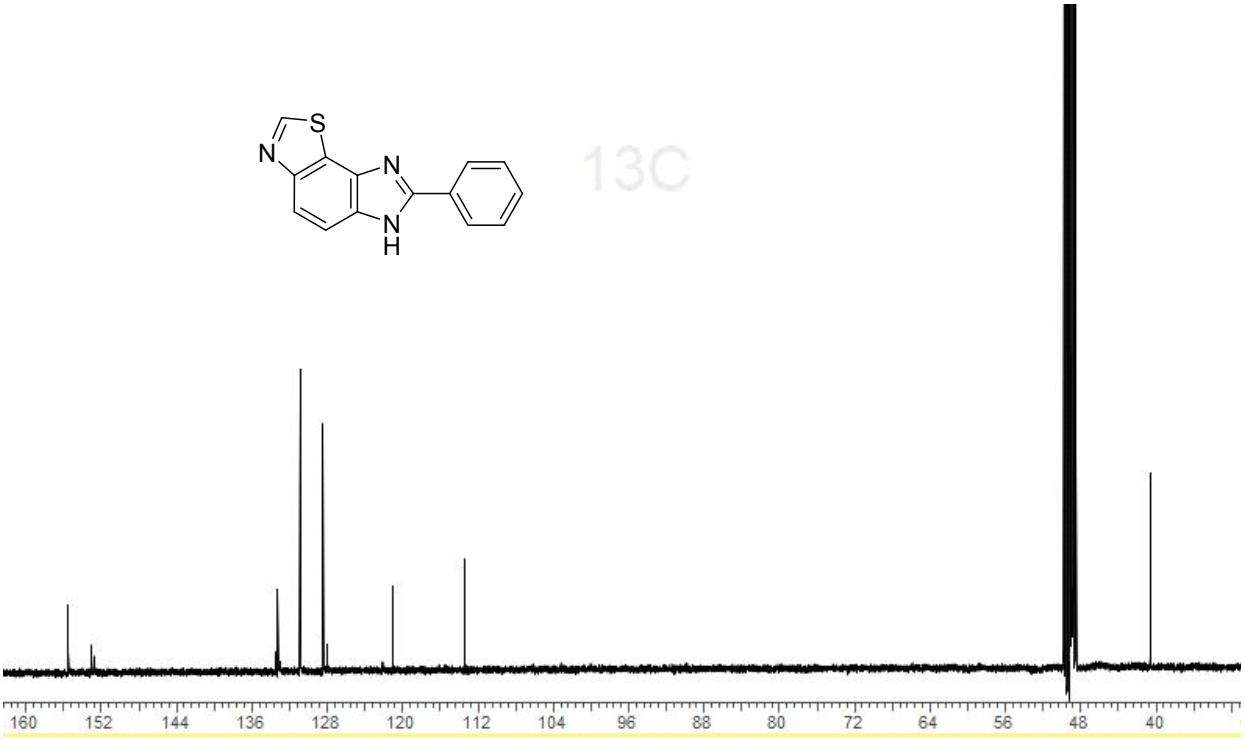


^{1}H NMR (400 MHz, METHANOL-d_4) δ 9.29 (s, 1 H), 8.10 - 8.20 (m, 3 H), 7.84 (d, *J*=8.98 Hz, 1 H), 7.62 - 7.70 (m, 3 H) ppm.

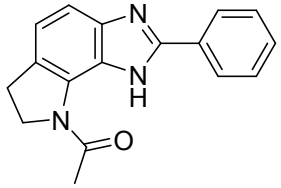
^{13}C NMR ^{13}C NMR (101 MHz, METHANOL-d_4) δ 155.5, 153.1, 152.8, 133.5, 133.2, 133.0, 130.8, 128.5, 128.0, 122.1, 121.1, 113.4 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{10}N_3S$ (M+H): 252.3, Found: 252.3


1H
S
N
N
N
H
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical


13C
S
N
N
N
H
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40

1-(2-phenyl-6,7-dihydroimidazo[4,5-g]indol-8(1H)-yl)ethan-1-one (2p)

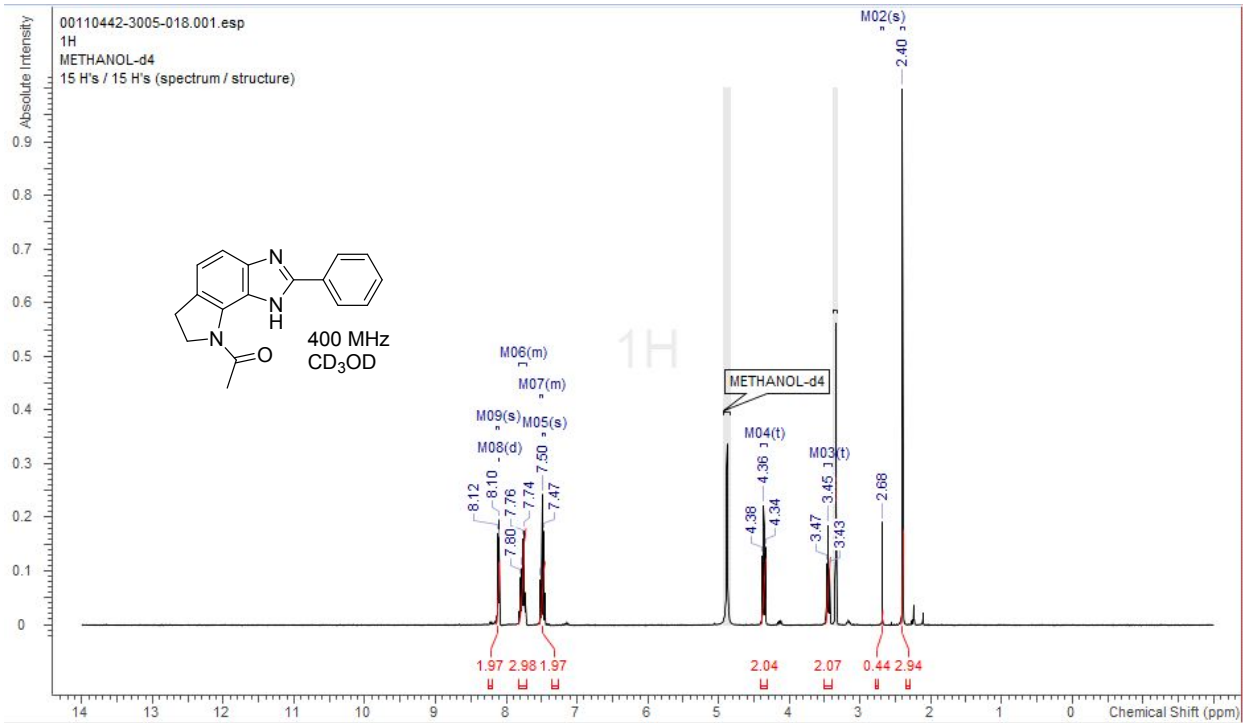


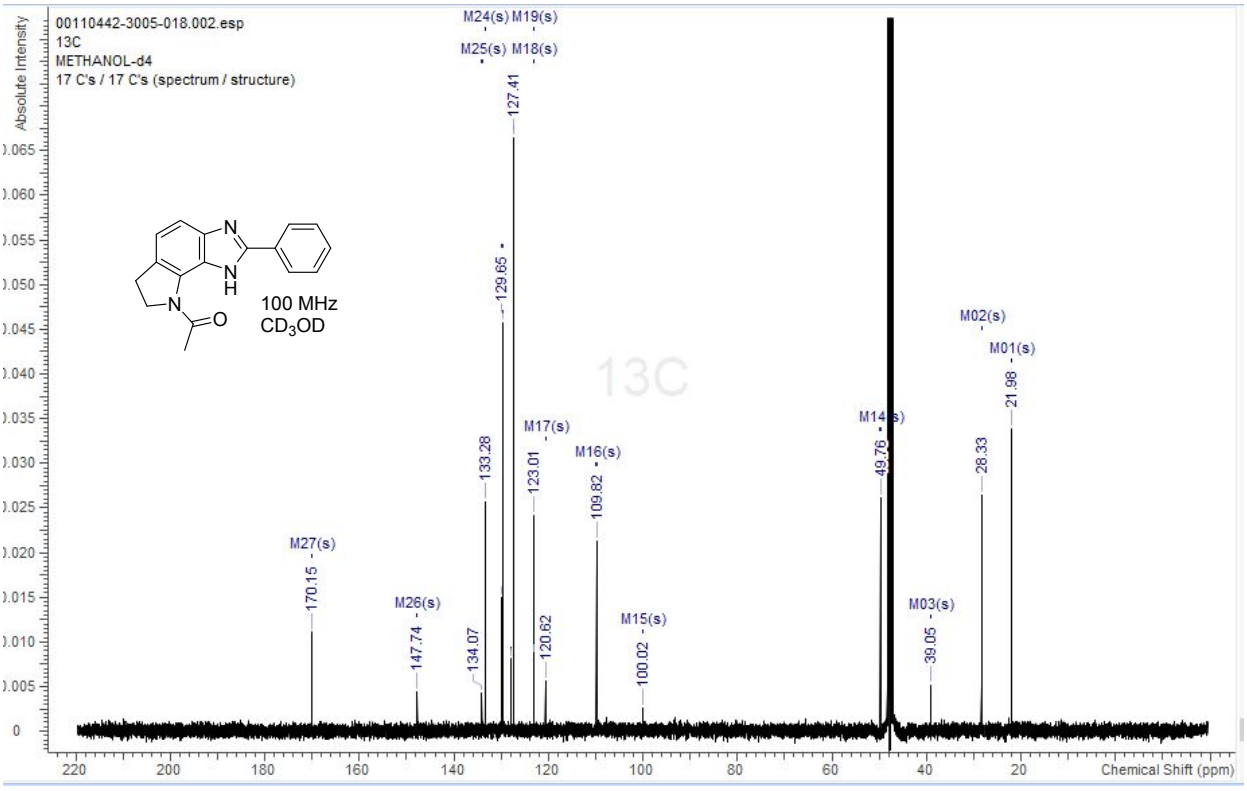
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.12 (s, 1H) 8.10 (d, *J*=1.56 Hz, 1H) 7.71 - 7.82 (m, 3H) 7.49 - 7.52 (m, 1H) 7.47 (s, 1H) 4.36 (t, *J*=8.78 Hz, 2H) 3.45 (t, *J*=8.59 Hz, H) 2.40 (s, 3H) ppm.

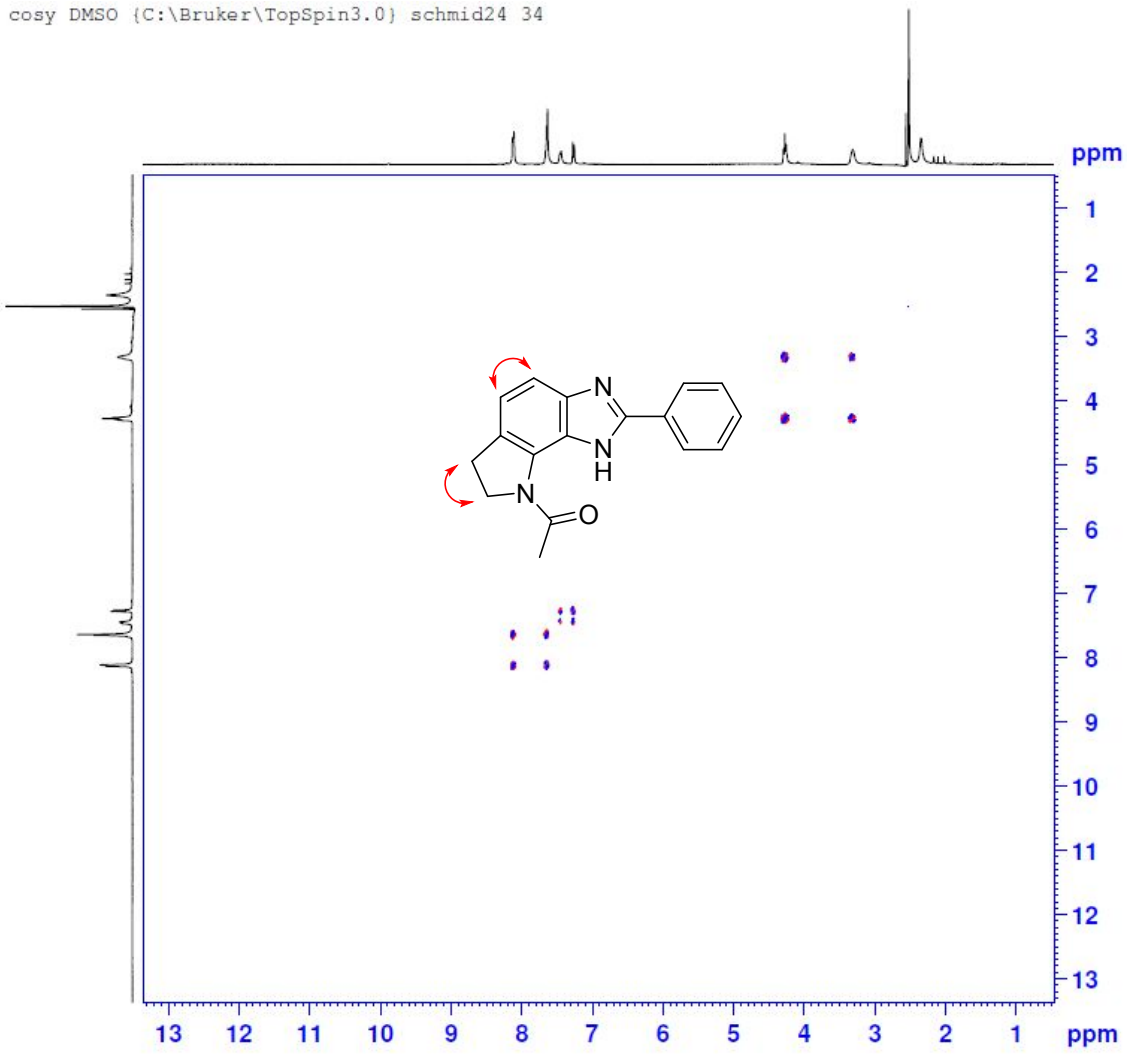
^{13}C NMR (101 MHz, METHANOL-d_4) δ 170.2, 147.7, 134.1, 133.3, 129.8, 129.7, 128.0, 127.4, 123.0, 120.6, 109.8, 100.0, 49.8, 28.3, 22.0 ppm.

LC-MS (ESI) Calcd. for $C_{17}H_{15}N_3O$ (M+H): 278.1, Found: 278.5

Regioselectivity >20:1 - Assigned by COSY


00110442-3005-018.001.esp
1H
METHANOL-d4
15 H's / 15 H's (spectrum / structure)
400 MHz
CD3OD
1H
METHANOL-d4
M02(s)
2.40
M06(m)
M07(m)
M09(s)
M05(s)
M08(d)
M04(t)
M03(t)
8.12
8.10
7.80
7.76
7.74
7.50
7.47
4.38
4.36
4.34
3.47
3.45
3.43
2.68
1.97 2.98 1.97
2.04
2.07
0.44 2.94
Absolute Intensity
Chemical Shift (ppm)

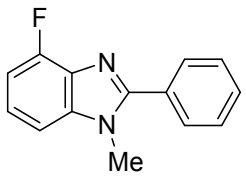

00110442-3005-018.002.esp
13C
METHANOL-d4
17 C's / 17 C's (spectrum / structure)
100 MHz
CD3OD
13C
M24(s) M19(s)
M25(s) M18(s)
127.41
129.65
133.28
123.01
M17(s)
M16(s)
109.82
M27(s)
170.15
M26(s)
147.74
134.07
120.62
M15(s)
100.02
M14(s)
49.76
M03(s)
39.05
M02(s)
28.33
M01(s)
21.98
Absolute Intensity
Chemical Shift (ppm)


cosy DMSO {C:\Bruker\TopSpin3.0} schmid24 34
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
N
N
H
N
O
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Spectroscopic Data for Scheme 3

Compounds were prepared in parallel format via General Library Procedure B.

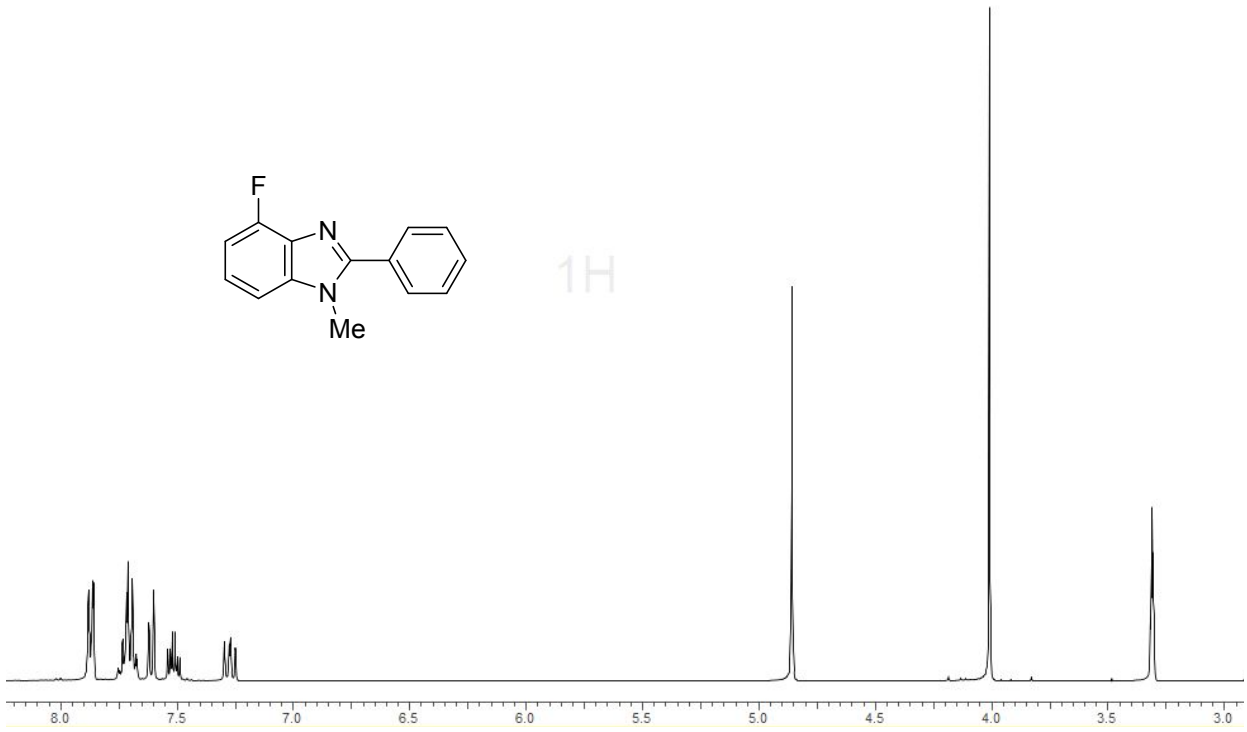
5-fluoro-1-methyl-2-phenyl-1H-benzo[d]imidazole (4a)

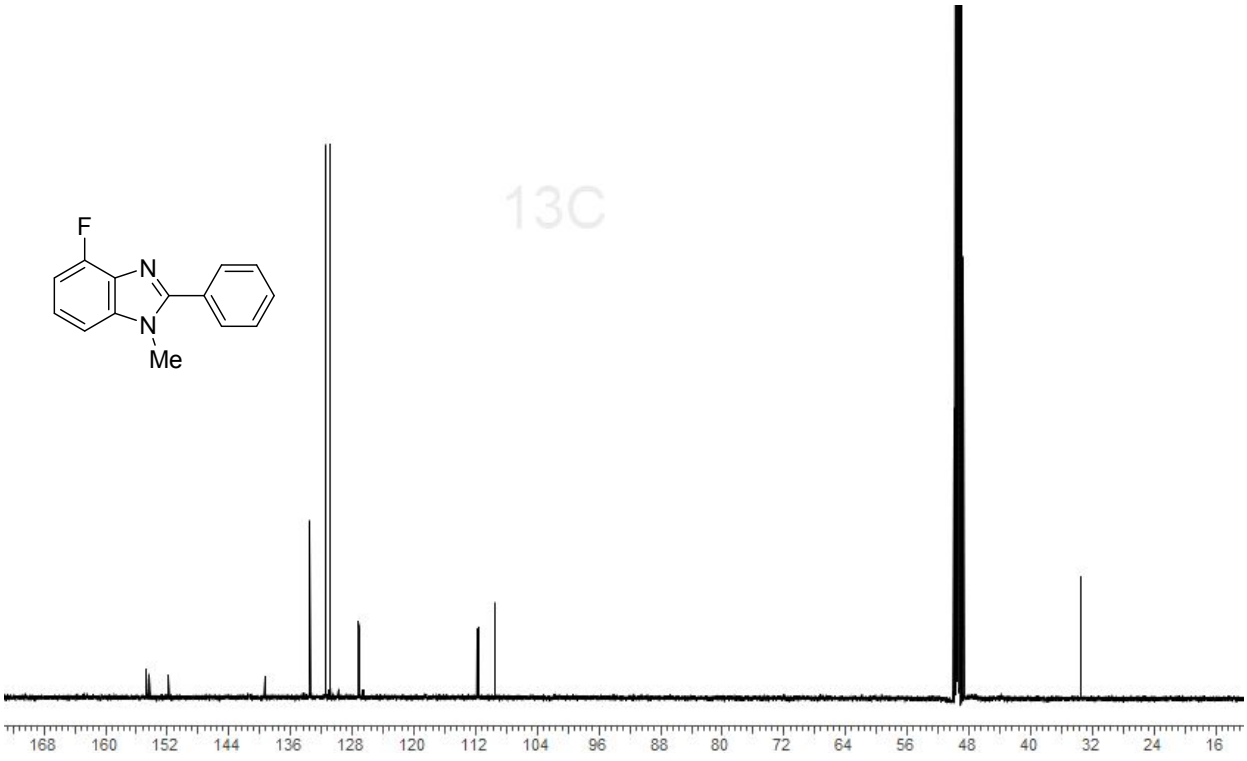


^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.81 - 7.95 (m, 2 H) 7.59 - 7.76 (m, 4 H) 7.51 (td, *J*=8.20, 4.68 Hz, 1 H) 7.28 (t, *J*=9.26 Hz, 1 H) 4.01 (s, 3 H) ppm.

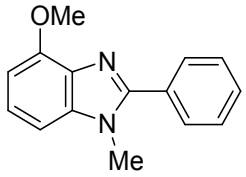
^{13}C NMR (101 MHz, METHANOL-d_4) (C-F coupling observed) δ 154.7, 154.3, 151.8, 139.4, 139.3, 133.6, 131.4, 130.8, 127.2, 127.1, 127.1, 111.8, 111.6, 109.5, 109.4, 33.5 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{12}FN_2$ (M+H): 227.3, Found: 227.3


F
N
N
Me
1H
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0


F
N
N
Me
13C
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16

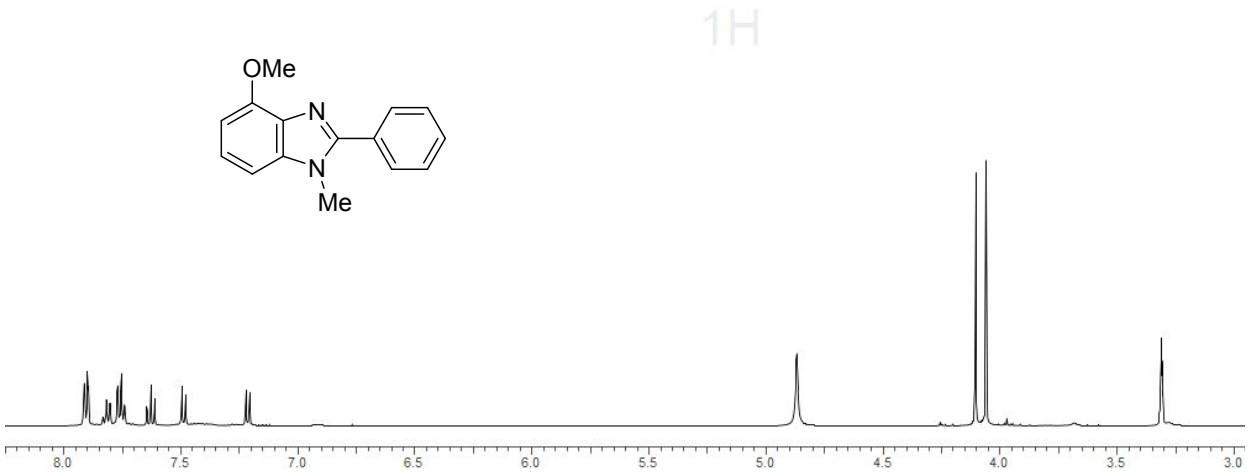
4-methoxy-1-methyl-2-phenyl-1H-benzo[d]imidazole (4b)

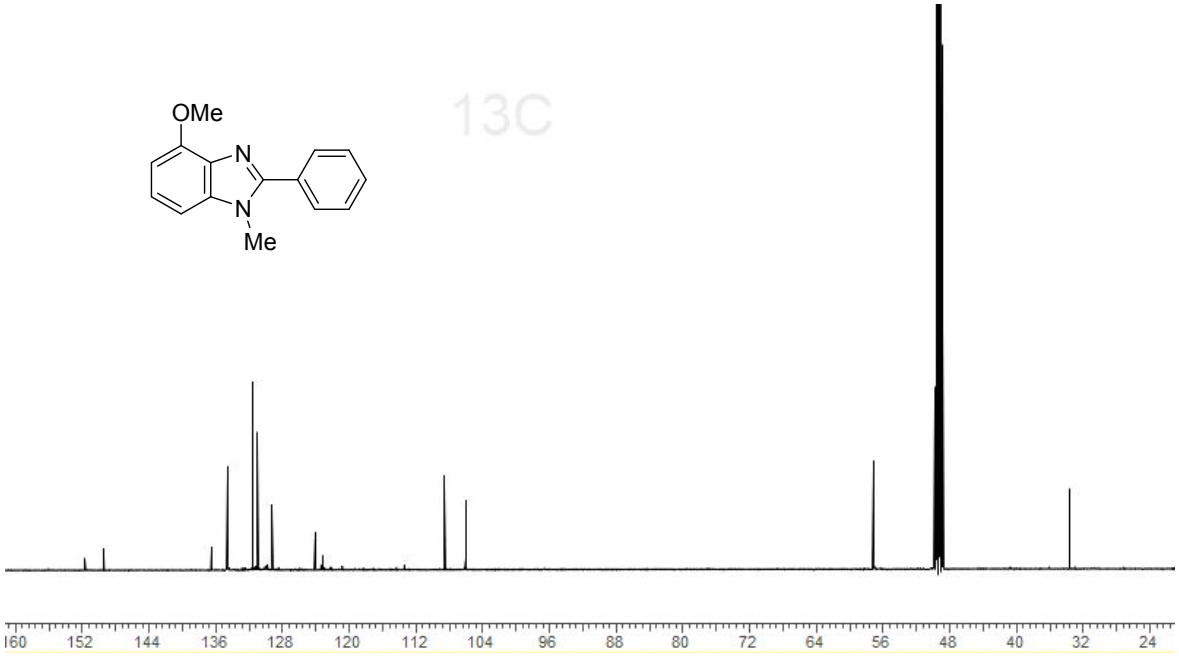


^{1}H NMR (500 MHz, METHANOL-d_4) δ 7.86 - 7.95 (m, 2 H), 7.70 - 7.85 (m, 3 H), 7.63 (t, *J*=8.19 Hz, 1 H), 7.49 (d, *J*=8.07 Hz, 1 H), 7.21 (d, *J*=8.07 Hz, 1 H), 4.10 (s, 3 H), 4.06 (s, 3 H) ppm.

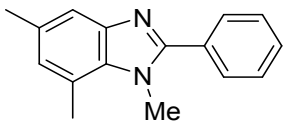
^{13}C NMR (126 MHz, METHANOL-d_4) δ 151.6, 149.4, 136.5, 134.6, 131.5, 131.1, 129.2, 124.1, 123.1, 108.6, 106.1, 57.2, 33.6 ppm.

LC-MS (ESI) Calcd. for $C_{15}H_{15}N_{2O}$ (M+H): 239.3, Found: 239.4


OMe
N
N
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0


OMe
N
N
Me
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24

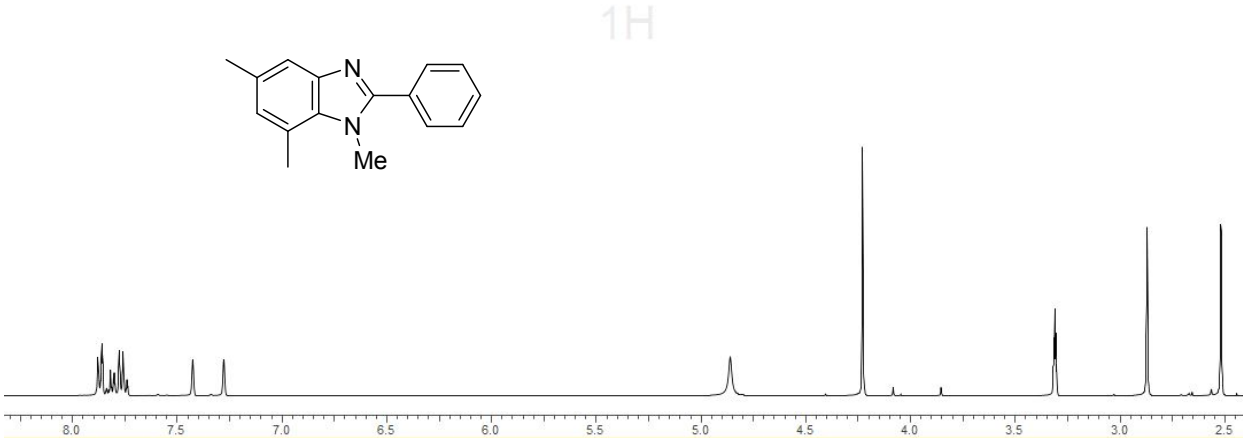
1,5,7-trimethyl-2-phenyl-1H-benzo[d]imidazole (4c)

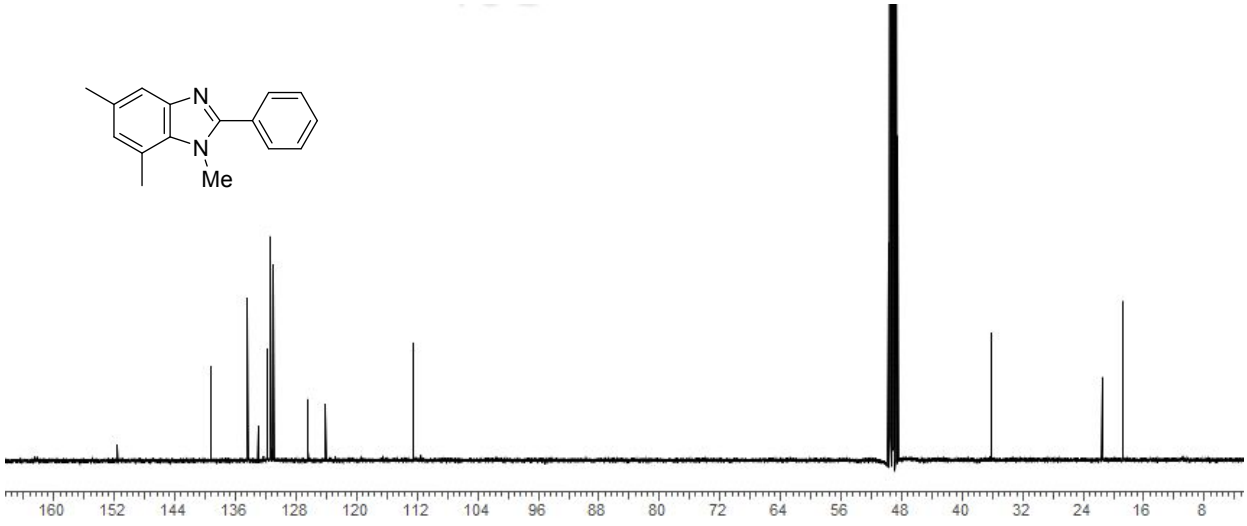


^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.72 - 7.91 (m, 5 H), 7.45 (s, 1 H), 7.31 (s, 1 H), 4.22 (s, 3 H), 2.91 (s, 3 H), 2.57 (s, 3 H) ppm.

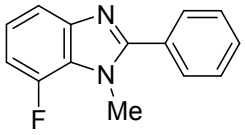
^{13}C NMR (101 MHz, METHANOL-d_4) δ 151.7, 139.3, 134.4, 133.0, 131.8, 131.4, 131.9, 131.0, 126.4, 124.1, 112.5, 36.2, 21.5, 18.8 ppm.

LC-MS (ESI) Calcd. for $C_{16}H_{17}N_2$ (M+H): 237.1, Found: 237.4


N
N
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5


N
N
Me
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

7-fluoro-1-methyl-2-phenyl-1H-benzo[d]imidazole (4d)

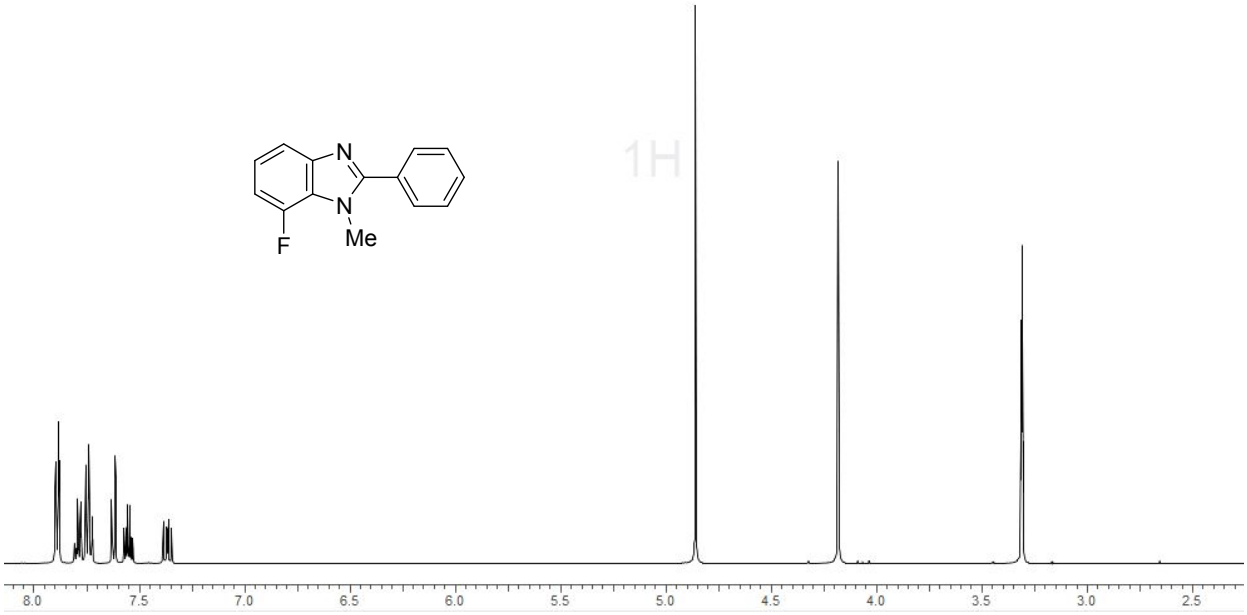


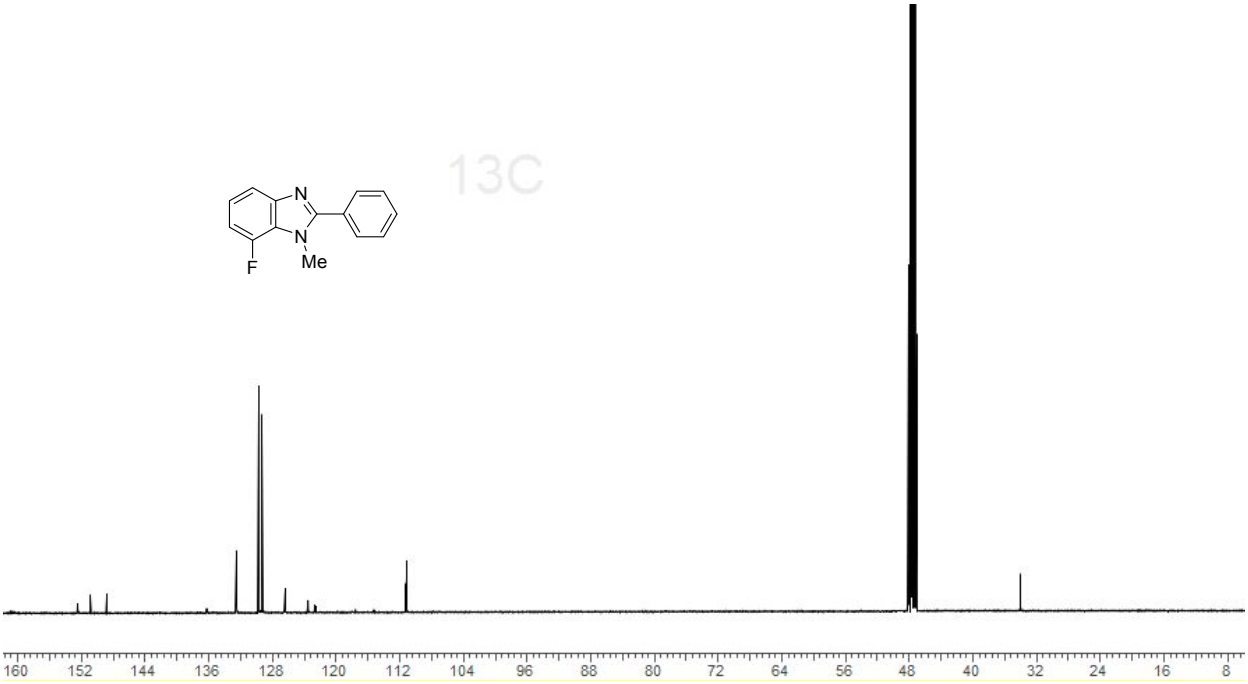
^{1}H NMR (500 MHz, METHANOL-d_4) δ 7.89 (d, *J*=7.18 Hz, 2 H) 7.71 - 7.81 (m, 3 H) 7.59 - 7.65 (m, 1 H) 7.51 - 7.59 (m, 1 H) 7.37 (ddd, *J*=11.74, 8.07, 0.73 Hz, 1 H) 4.18 (d, *J*=1.47 Hz, 3 H) ppm.

^{13}C NMR (126 MHz, METHANOL-d_4) (C-F coupling observed) δ 154.0, 152.4, 150.4, 137.8, 134.1, 131.3, 130.8, 128.0, 127.9, 125.1, 124.2, 124.1, 112.9, 112.8, 35.6 (2 peaks) ppm.

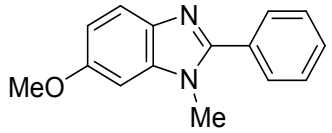
LC-MS (ESI) Calcd. for $C_{14}H_{11}FN_2$ (M+H): 227.3, Found: 227.3

Regioselectivity Assigned by 13C NMR (N1-CH_3 couples to F)


1H
N
N
Me
F
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5


13C
N
N
Me
F
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

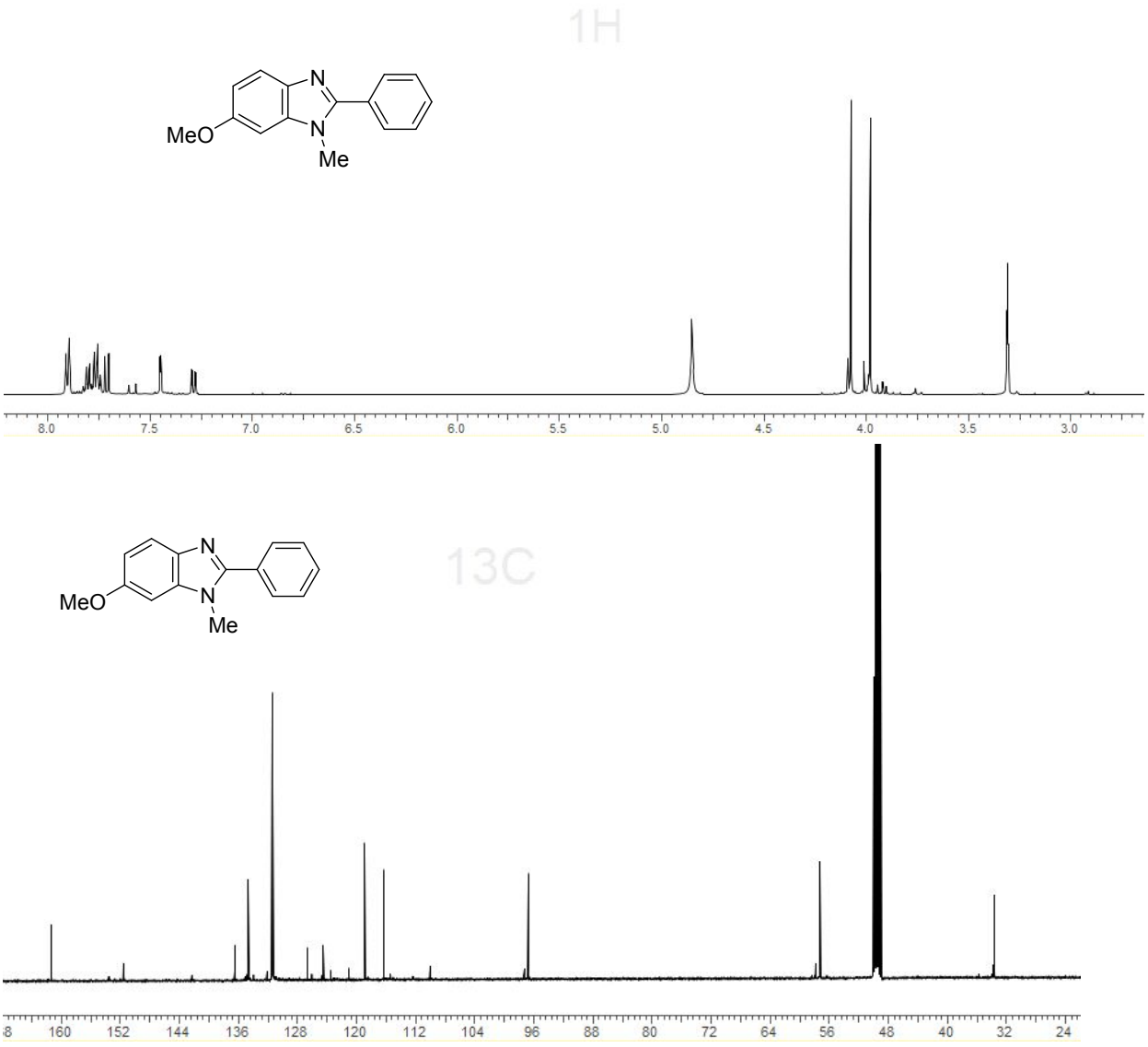
6-methoxy-1-methyl-2-phenyl-1H-benzo[d]imidazole (4e)



^{1}H NMR (500 MHz, METHANOL-d_4) δ 7.93 (d, *J*=6.83 Hz, 2 H), 7.75 - 7.98 (m, 4 H), 7.41 (d, *J*=2.45 Hz, 1 H), 7.36 (m, 1 H), 4.1 (s, 3 H), 3.98 (s, 3 H) ppm.

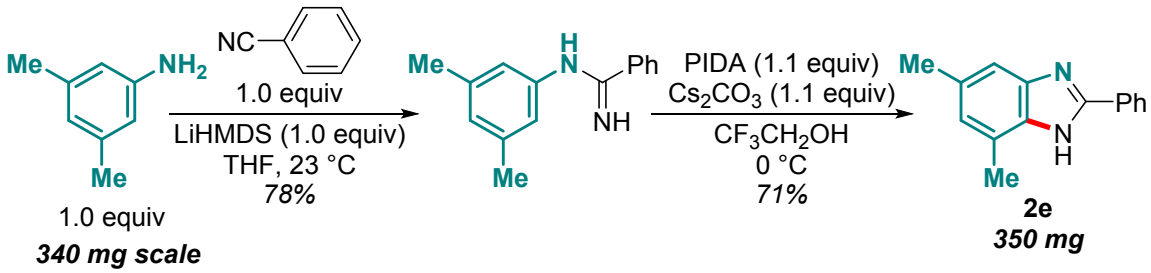
^{13}C NMR (126 MHz, METHANOL-d_4) δ 161.0 151.2, 136.2, 134.4, 131.1, 131.0, 124.2, 118.6, 116.0, 96.5, 56.9, 33.3 ppm.

LC-MS (ESI) Calcd. for $C_{15}H_{15}N_{2O}$ (M+H): 239.3, Found: 239.3


1H
MeO
N
N
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
13C
MeO
N
N
Me
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24

Preparative scale sequences (Scheme 4) – experimental procedures

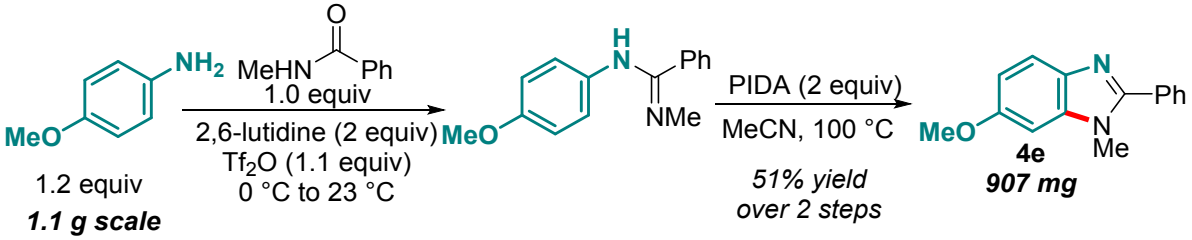
Preparative scale synthesis of compound **2e**



Amidine formation – To 3,5-dimethylaniline (340 mg, 2.81 mmol, 1.0 equiv) in a 3-neck round bottom flask fitted with an addition funnel was added THF (17 mL). The flask was cooled to 0 °C in an ice bath and LiHMDS (1 M in THF, 2.81 mL, 2.81 mmol, 1.0 equiv) was added dropwise via addition funnel. The reaction was stirred for 20 min at 0 °C, then benzonitrile (286 mg, 2.81 mmol, 1.0 equiv) was added. The reaction was warmed to 23 °C and stirred for 17 h. Water (30 mL) was added and the mixture was extracted 2X with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to provide crude amidine intermediate (492 mg, 2.20 mmol, 78% yield) that was used in the subsequent step without purification.

Oxidative cyclization - To the 2-dram vial containing amidine intermediate (2.20 mmol) under air atmosphere was added Cs_2CO_3 (792 mg, 2.43 mmol, 1.1 equiv) and 2,2,2-trifluoroethanol (2.0 mL). Cooled to 0 °C and added PIDA (783 mg, 2.43 mmol, 1.1 equiv). After stirring for 1.5 h, solvent was removed *in vacuo*. The crude mixture was diluted with EtOAc and water; the organic phase was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed (20% EtOAc/heptanes to 50% EtOAc/heptanes) to provide **2e** (350 mg, 1.58 mmol, 71% yield).

Preparative scale synthesis of compound **4e**:



Amidine formation - N-methylbenzamide (1.01 g, 7.5 mmol, 1.0 equiv) was dissolved in 20 mL dry dichloromethane in a 125 mL round-bottom flask. 2,6-lutidine (1.9 mL, 16.5 mmol, 2.2 equiv) was then added drop-wise at 23 °C, under nitrogen. Reaction flask was then cooled in an ice-water bath, and trifluoromethanesulfonic anhydride (1.76 mL, 8.3 mmol, 1.1 equiv) was added drop-wise. The dark-pink/wine color solution generated was stirred under nitrogen, and gradually warmed to 23 °C over 2.5 h. A solution of 4-methoxyaniline (1.1 g, 9.0 mmol, 1.2 eq.) in 5 mL dry dichloromethane was then added to the reaction flask, and contents were stirred overnight at 23 °C. Reaction was quenched by adding 10 mL of water. Organic layer was separated, and aqueous layer was extracted with 2x15 mL of ethyl acetate. Combined organic layers were then dried over sodium sulfate, concentrated and purified using silica gel ISCO Combiflash chromatography (0 to 100% ethyl acetate in heptane). Partially pure amidine (1.8 g, 100%) was obtained, which was used as is in the subsequent step.

Oxidative cyclization – amidine intermediate was dissolved in dry acetonitrile (38 mL, c=0.20 M), and transferred to a sealable tube. Diacetoxyiodobenzene (4.80 g, 14.9 mmol, 2.0 equiv) was added in one

portion. The reaction vessel was sealed and heated at 100 °C for 2 h. After cooling to 23 °C, the mixture was diluted with 40 mL EtOAc and washed with 40 mL water. The aqueous layer was extracted with 2 x 30 mL ethyl acetate. Combined organics were dried, concentrated and purified using ISCO (0 to 100% ethyl acetate in heptane) to give 6-methoxy-1-methyl-2-phenyl-1H-benzo[d]imidazole (907 mg, 51% yield over 2 steps).

Spectroscopic Data for Scheme 5

Compounds were prepared in parallel format via General Library Procedure A.

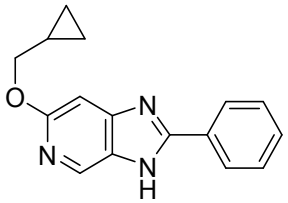
Compounds **6a**, **6b**, and **6e** have been fully characterized previously and NMR spectra were matched to reported values:

6a) Dubey, P. K.; Chowdary, K. S.; Ramesh, B.; Prasada Reddy, P. V. V. *Synth. Commun.* **2010**, *40*, 697-708.

6b) Mishra, A.; Sahu, S.; Dash, N.; Behera, S. K.; Krishnamoorthy, G. *J. Phys Chem. B.* **2013**, *117*, 9469-9477.

6e) Kulkami, S. S.; Newman, A. H. *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 2987-2991.

6-(cyclopropylmethoxy)-2-phenyl-3H-imidazo[4,5-c]pyridine (6d)

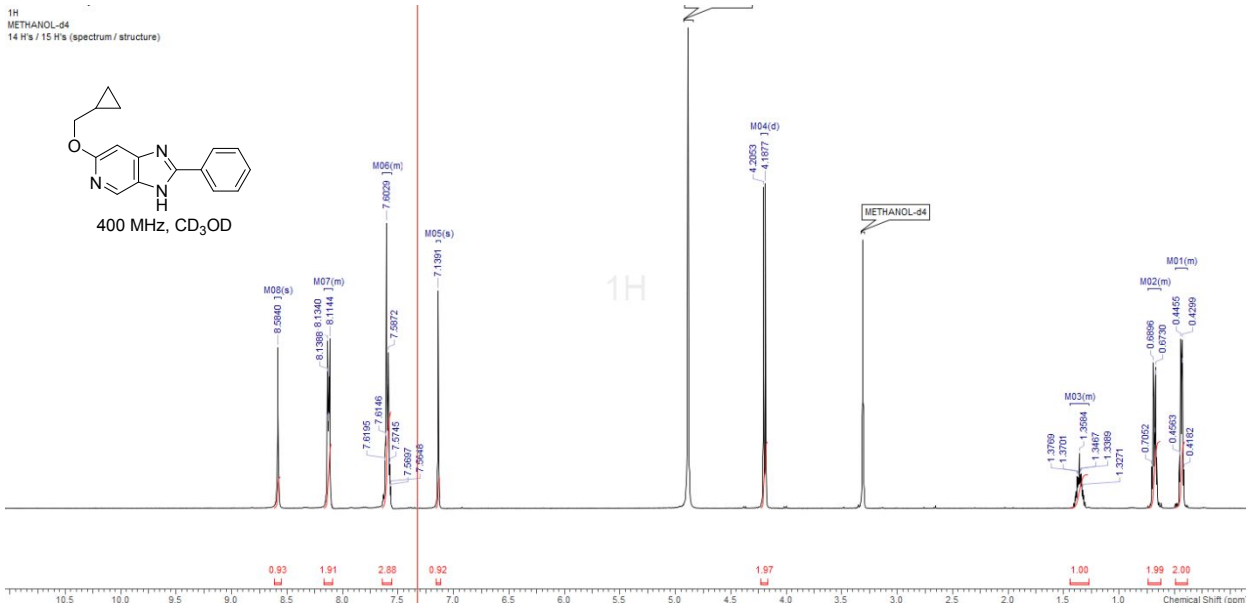


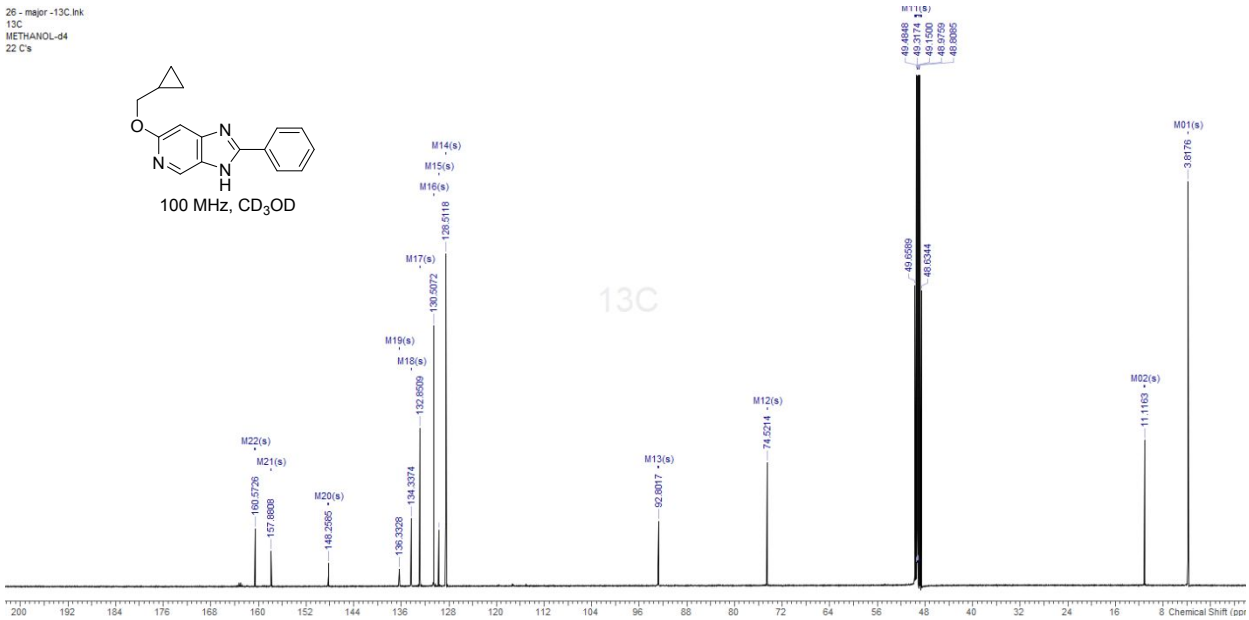
^{1}H NMR (400 MHz, CD_3OD): δ 8.58 (s, 1H), 8.15-8.10 (m, 2H), 7.62-7.57 (m, 3H), 7.14 (s, 1H), 4.19 (d, *J* = 7.0 Hz, 2H), 1.38-1.33 (m, 1H), 0.70-0.66 (m, 2H), 0.46-0.42 (m, 2H) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ 160.6, 157.9, 148.3, 136.3, 134.3, 132.9, 130.5, 128.5, 92.8, 74.5, 11.1, 3.8 ppm.

LC-MS (ESI) Calcd. for $C_{16}H_{15}N_3O$ (M+H): 266.1, Found: 266.3.

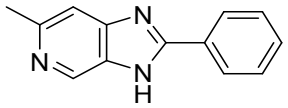
Regioselectivity 2:1 **-** Assigned by ^{1}HNMR.


1H
METHANOL-d4
14 H's / 15 H's (spectrum / structure)
400 MHz, CD3OD
M08(s)
M07(m)
M06(m)
M05(s)
M04(d)
METHANOL-d4
M03(m)
M02(m)
M01(m)
0.93
1.91
2.88
0.92
1.97
1.00
1.99
2.00
Chemical Shift (ppm)


26 - major -13C.lnk
13C
METHANOL-d4
22 C's
100 MHz, CD3OD
M14(s)
M15(s)
M16(s)
M17(s)
M19(s)
M18(s)
M22(s)
M21(s)
M20(s)
M13(s)
M12(s)
M02(s)
M01(s)
Chemical Shift (ppm)

6-methyl-2-phenyl-3H-imidazo[4,5-c]pyridine (6f)

(from 2-methylpyridin-4-amine)

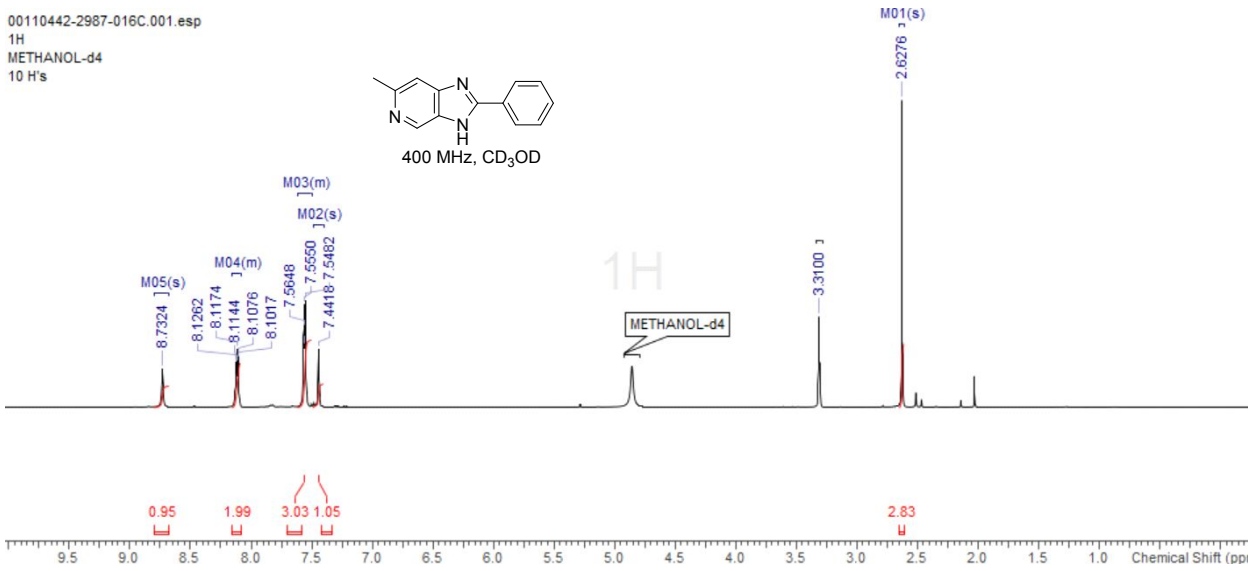


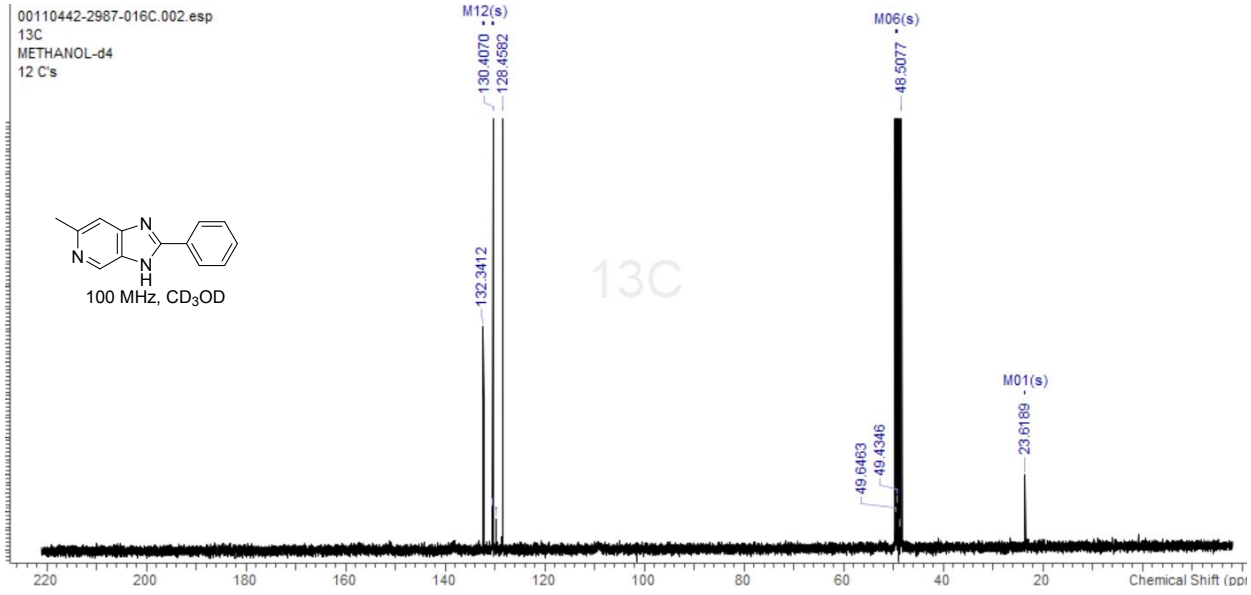
^{1}H NMR (400 MHz, CD_3OD): δ 8.73 (s, 1H), 8.13-8.10 (m, 2H), 7.56-7.55 (m, 3H), 7.44 (s, 1H), 2.63 (s, 3H) ppm.

^{13}C NMR (100 MHz, CD_3OD): (tautomeric mix) δ 157.4, 151.2, 140.7, 133.2, 132.4 (2 peaks), 130.6, 130.5, 130.4, 129.8, 129.7, 128.5, 23.6 ppm.

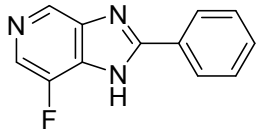
LC-MS (ESI) Calcd. for $C_{13}H_{11}N_3$ (M+H): 210.1, Found: 210.1.

Regioselectivity >20:1 **-** Assigned by ^{1}HNMR.


00110442-2987-016C.001.esp
1H
METHANOL-d4
10 H's
400 MHz, CD3OD
M01(s)
2.6276
M03(m)
M02(s)
M04(m)
M05(s)
8.7324
8.1262
8.1174
8.1144
8.1076
8.1017
7.5648
7.5550
7.5482
7.4418
METHANOL-d4
3.3100
0.95
1.99
3.03
1.05
2.83
Chemical Shift (ppm)


00110442-2987-016C.002.esp
13C
METHANOL-d4
12 C's
100 MHz, CD3OD
M12(s)
130.4070
128.4582
132.3412
M06(s)
48.5077
M01(s)
23.6189
49.6463
49.4346
Chemical Shift (ppm)

7-fluoro-2-phenyl-1H-imidazo[4,5-c]pyridine (6g)

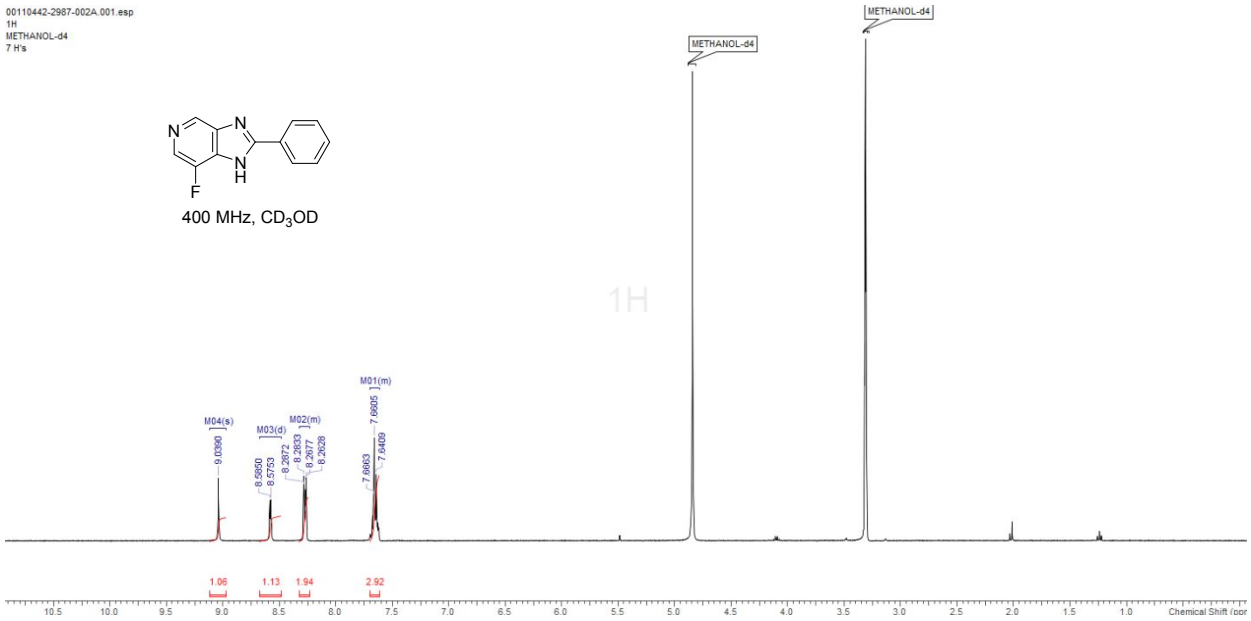


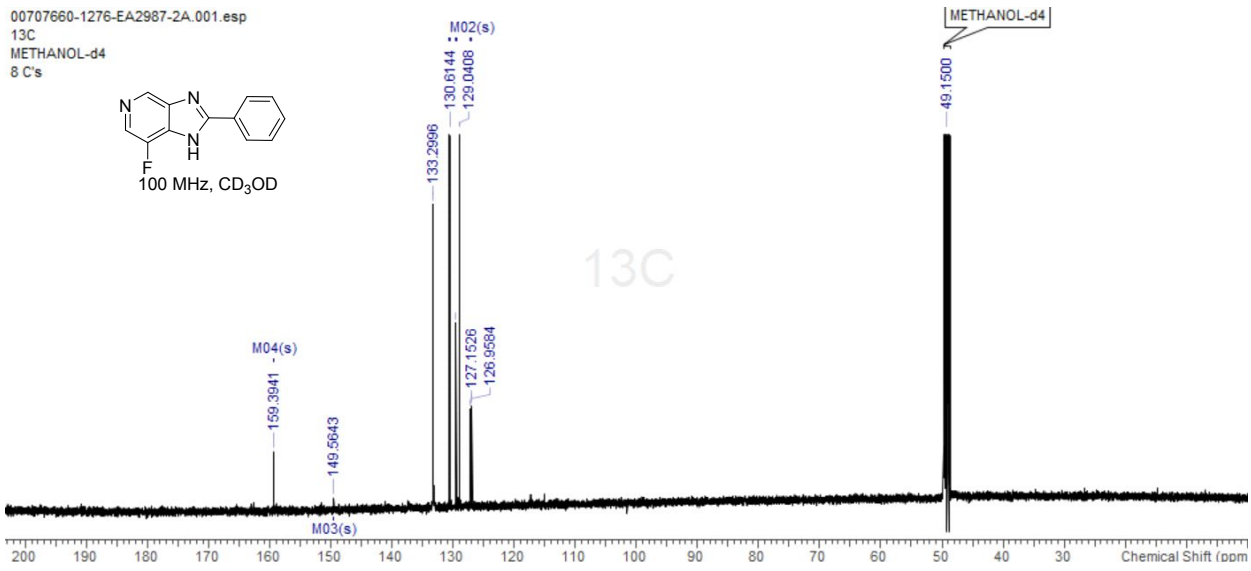
^{1}H NMR (400 MHz, CD_3OD): δ 9.04 (s, 1H), 8.58 (d, *J* = 3.9 Hz, 1H), 8.29-8.26 (m, 2H), 7.68-7.63 (m, 3H) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ 162.8, 159.4, 149.6, 133.3, 133.2, 130.6, 129.5, 129.0, 127.2, 127.0 ppm.

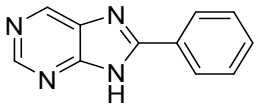
LC-MS (ESI) Calcd. for $C_{12}H_8FN_3$ (M+H): 214.1, Found: 214.3.

Regioselectivity 4:1 - Assigned by ^{1}HNMR.





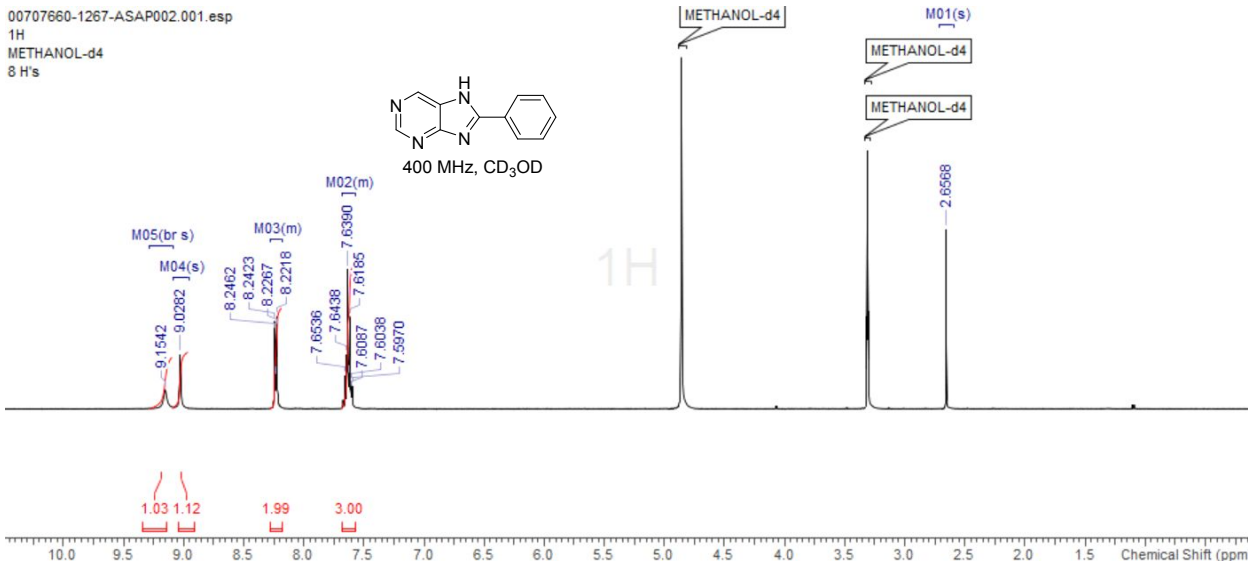
8-phenyl-9H-purine (6h)

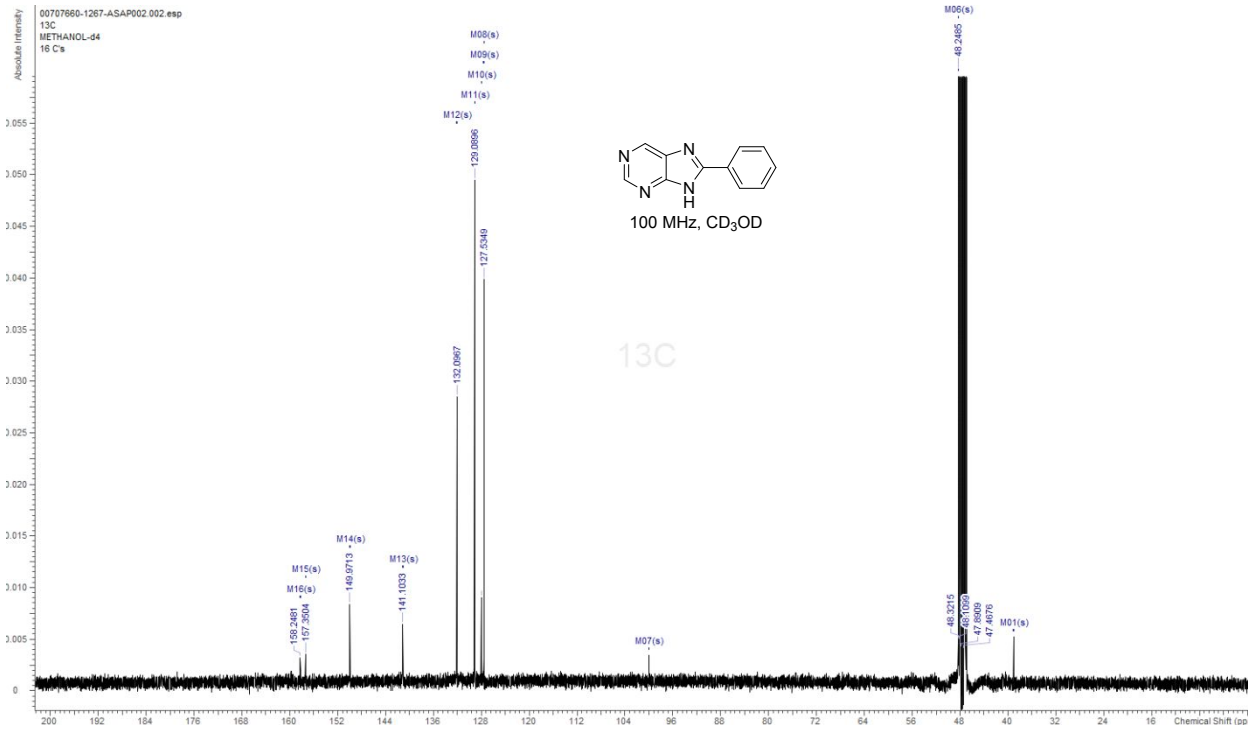


^{1}H NMR (400 MHz, CD_3OD): δ 9.15 (br s, 1H), 9.03 (s, 1H), 8.25-8.22 (m, 2H), 7.66-7.60 (m, 3H) ppm.

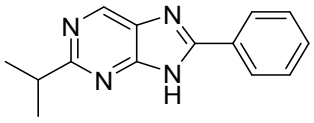
^{13}C NMR (100 MHz, CD_3OD): δ 158.2, 157.4, 150.0, 141.1, 132.1, 129.1, 128.0, 127.6, 127.5 ppm.

LC-MS (ESI) Calcd. for $C_{11}H_8N_4$ (M+H): 197.1, Found: 197.3.





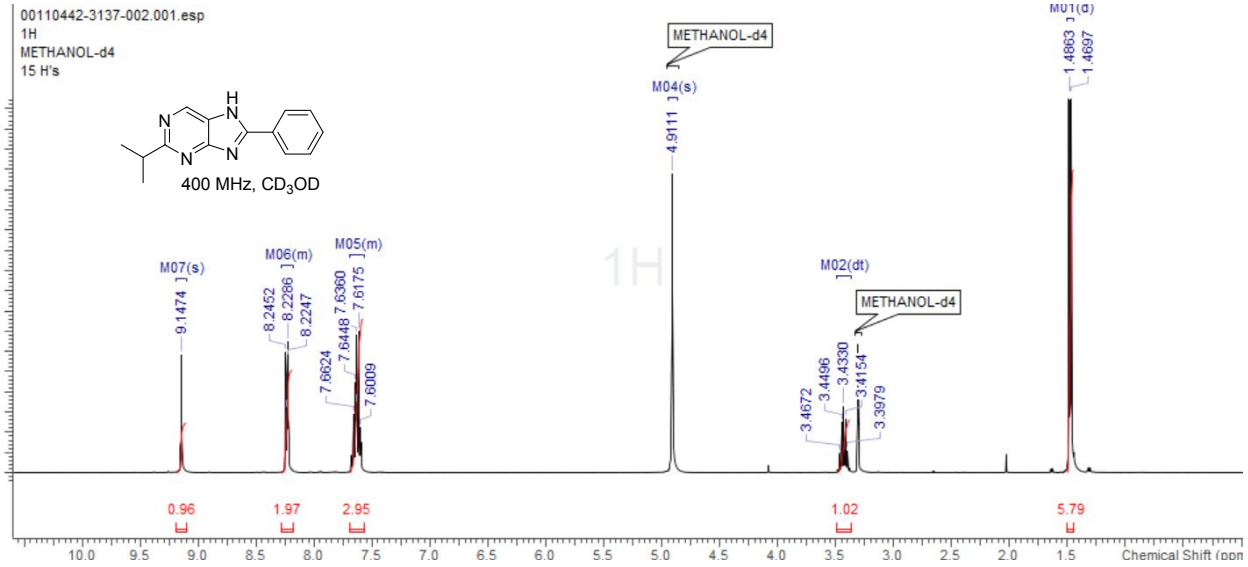
2-isopropyl-8-phenyl-9H-purine (6i)

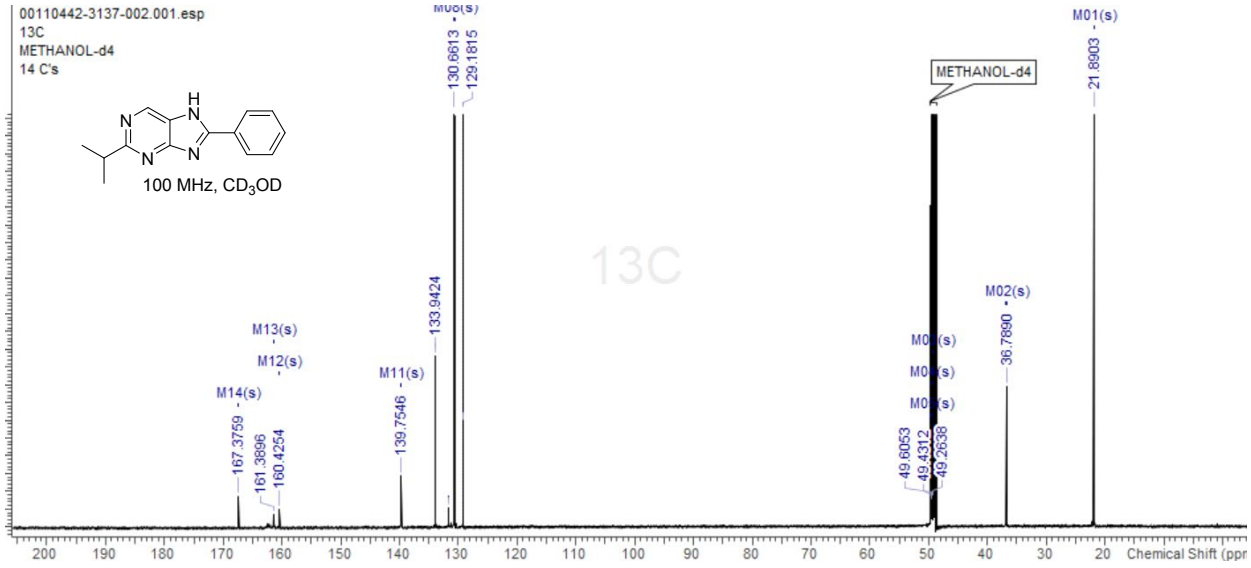


[1]H NMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.24-8.22 (m, 2H), 7.66-7.61 (m, 3H), 3.46--3.40 (m, 1H), 1.47 (d, J = 5.9 Hz, 6H) ppm.

[13]C NMR (100 MHz, CD_3OD): 167.4, 162.5, 161.4, 160.4, 139.8, 133.9, 131.7, 130.7, 129.2, 36.8, 21.9 ppm.

LC-MS (ESI) Calcd. for $C_{14}H_{14}N_4$ (M+H): 239.1, Found: 239.2.


00110442-3137-002.001.esp
1H
METHANOL-d4
15 H's
400 MHz, CD3OD
METHANOL-d4
METHANOL-d4
M07(s)
M06(m)
M05(m)
M04(s)
M02(dt)
M01(d)
9.1474
8.2452
8.2286
8.2247
7.6624
7.6448
7.6360
7.6175
7.6009
4.9111
3.4672
3.4496
3.4330
3.4154
3.3979
1.4863
1.4697
0.96
1.97
2.95
1.02
5.79
Chemical Shift (ppm)


00110442-3137-002.001.esp
13C
METHANOL-d4
14 C's
100 MHz, CD3OD
13C
METHANOL-d4
M01(s)
21.8903
M02(s)
36.7890
M06(s)
130.6613
129.1815
M11(s)
133.9424
139.7546
M12(s)
M13(s)
M14(s)
167.3759
161.3896
160.4254
49.6053
49.4312
49.2638
Chemical Shift (ppm)