

Supporting Information

Development of a regioselective N-methylation of (benz)imidazoles providing the more sterically hindered isomer

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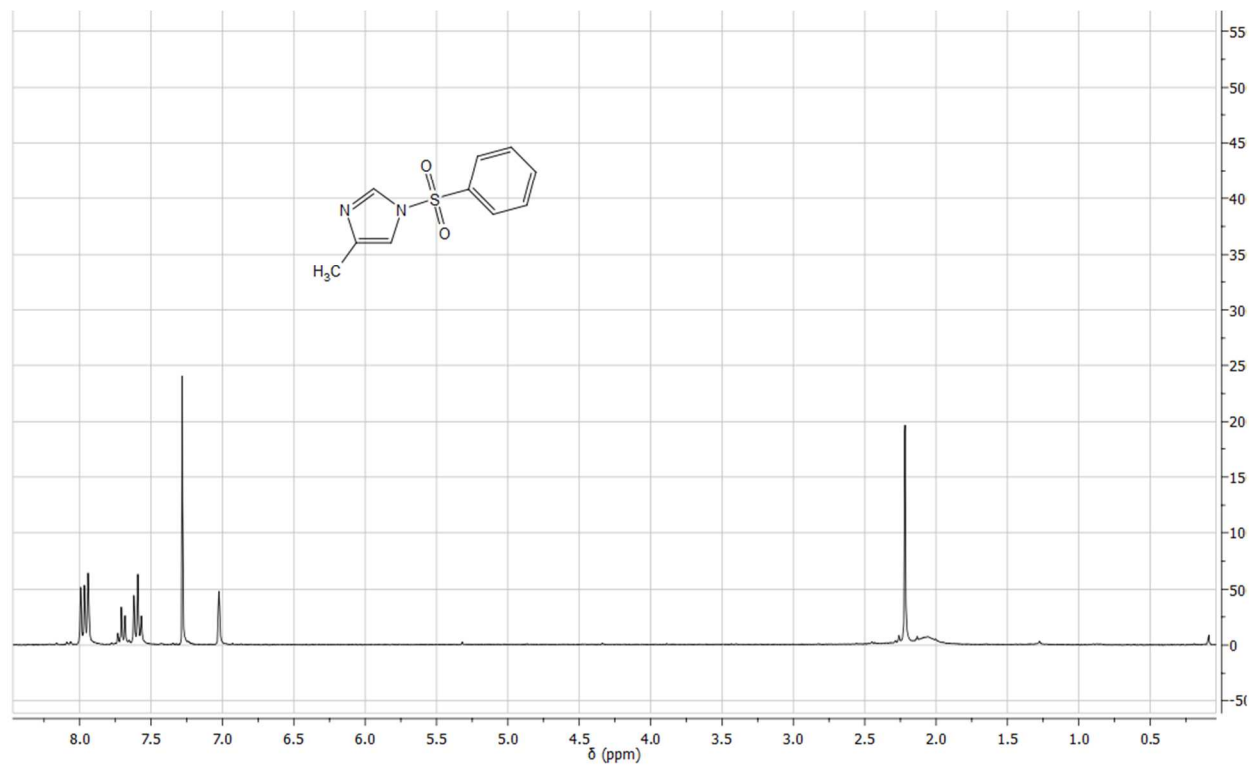
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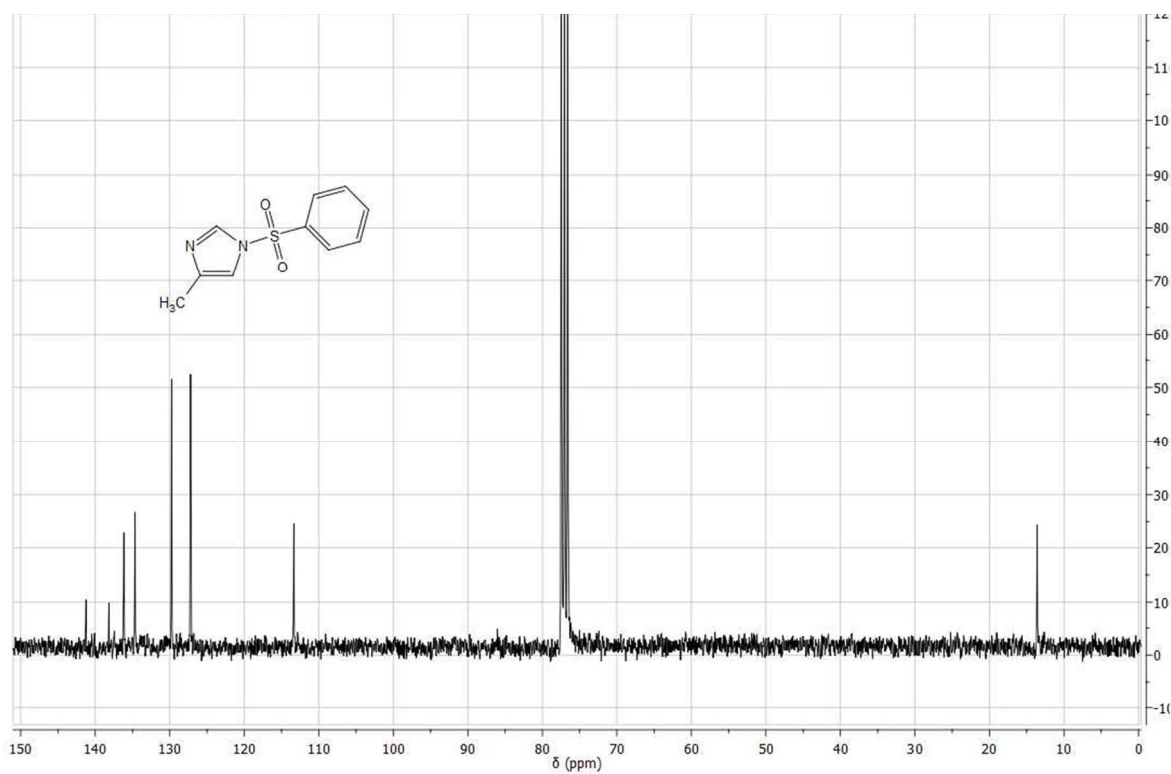
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^1H and ^{13}C NMR spectra

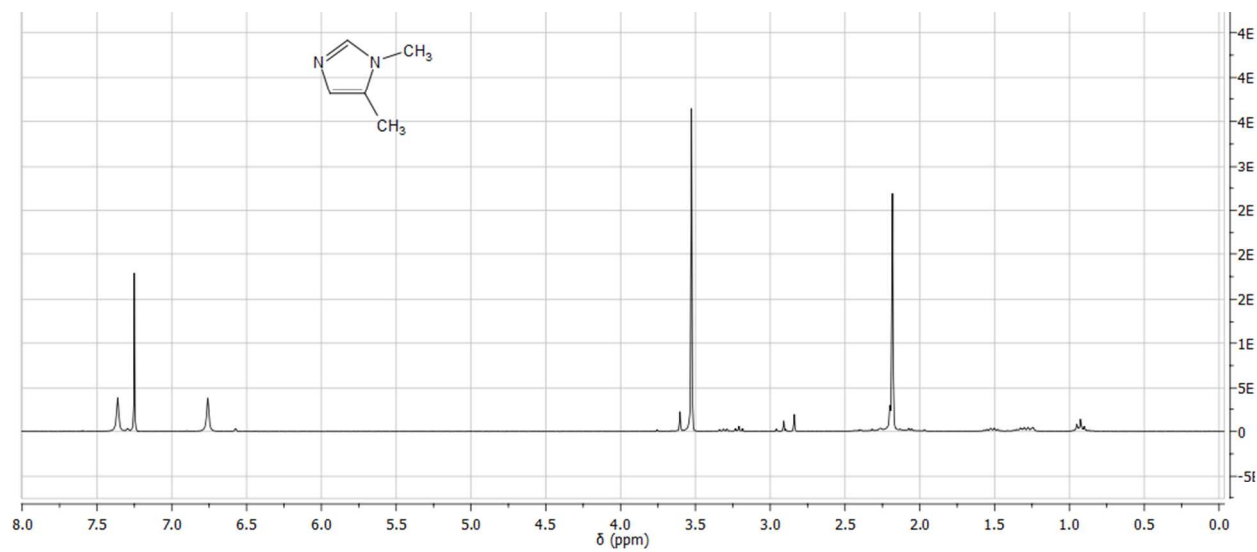
Compound **1d** (^1H NMR, CDCl_3 , 300 MHz):



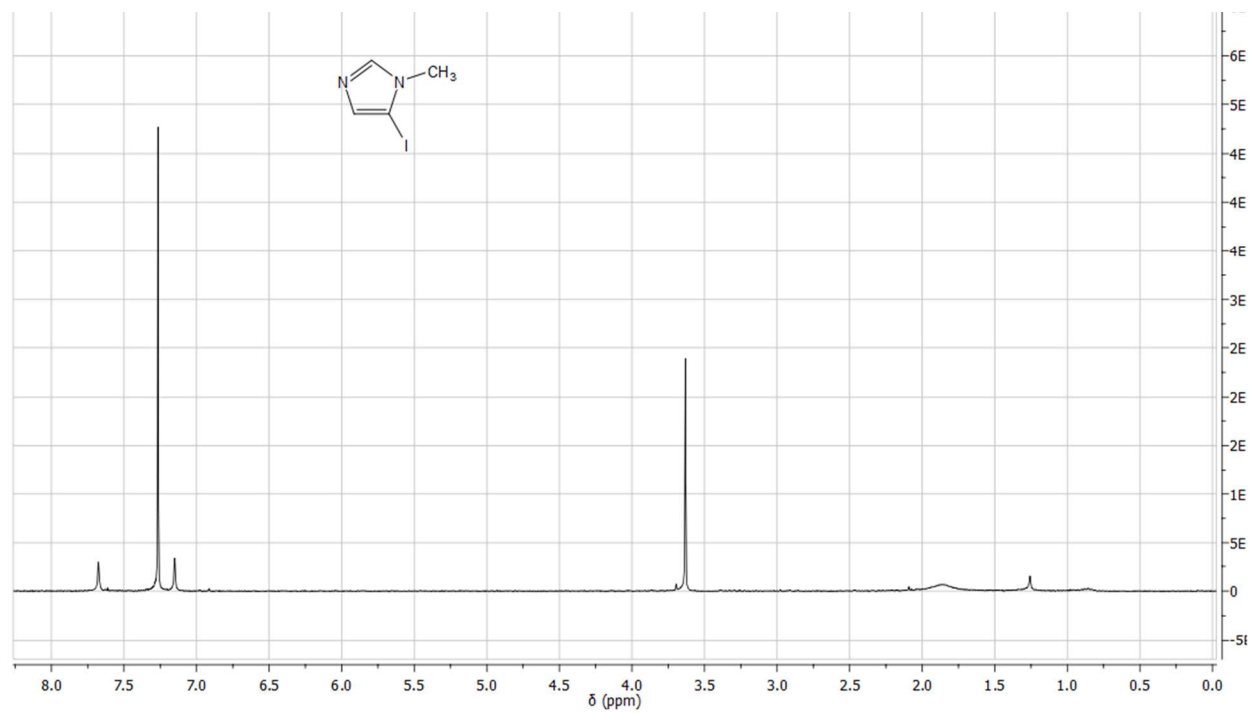
Compound **1d** (^{13}C NMR, CDCl_3 , 125 MHz):



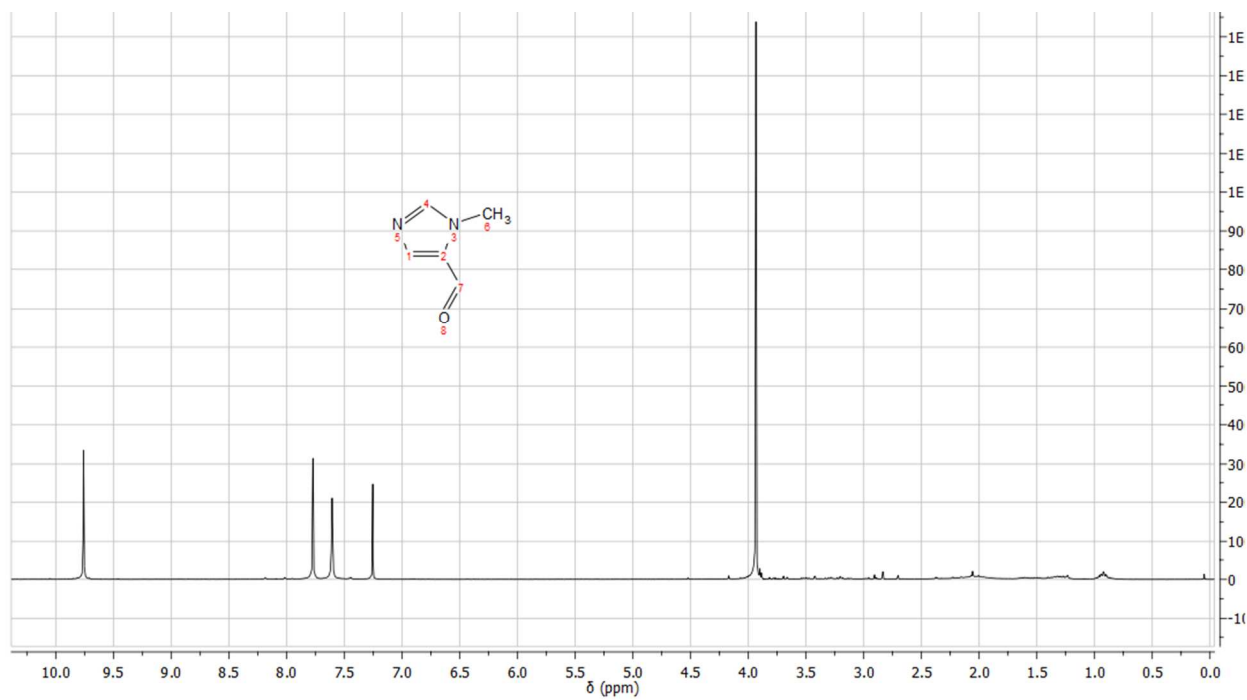
Compound **4** (^1H NMR, CDCl_3 , 300 MHz):



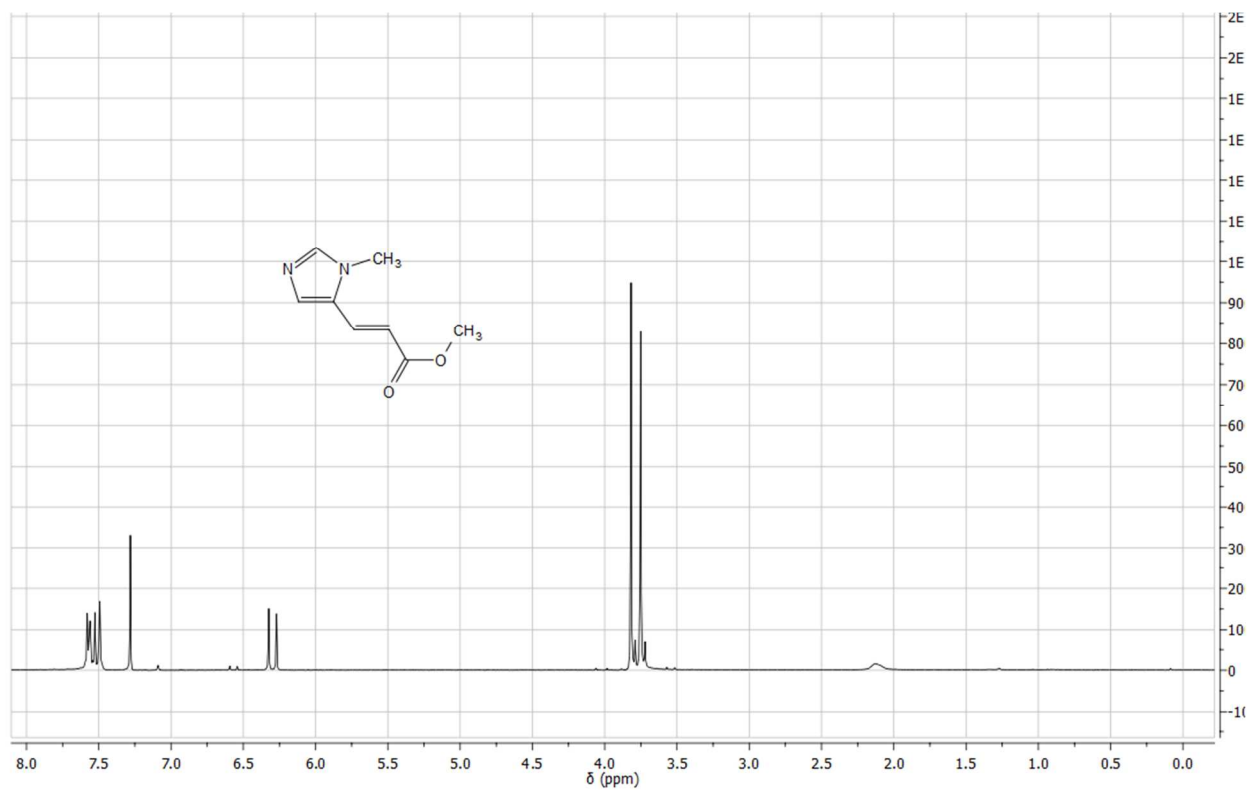
Compound **5** (^1H NMR, CDCl_3 , 300 MHz):



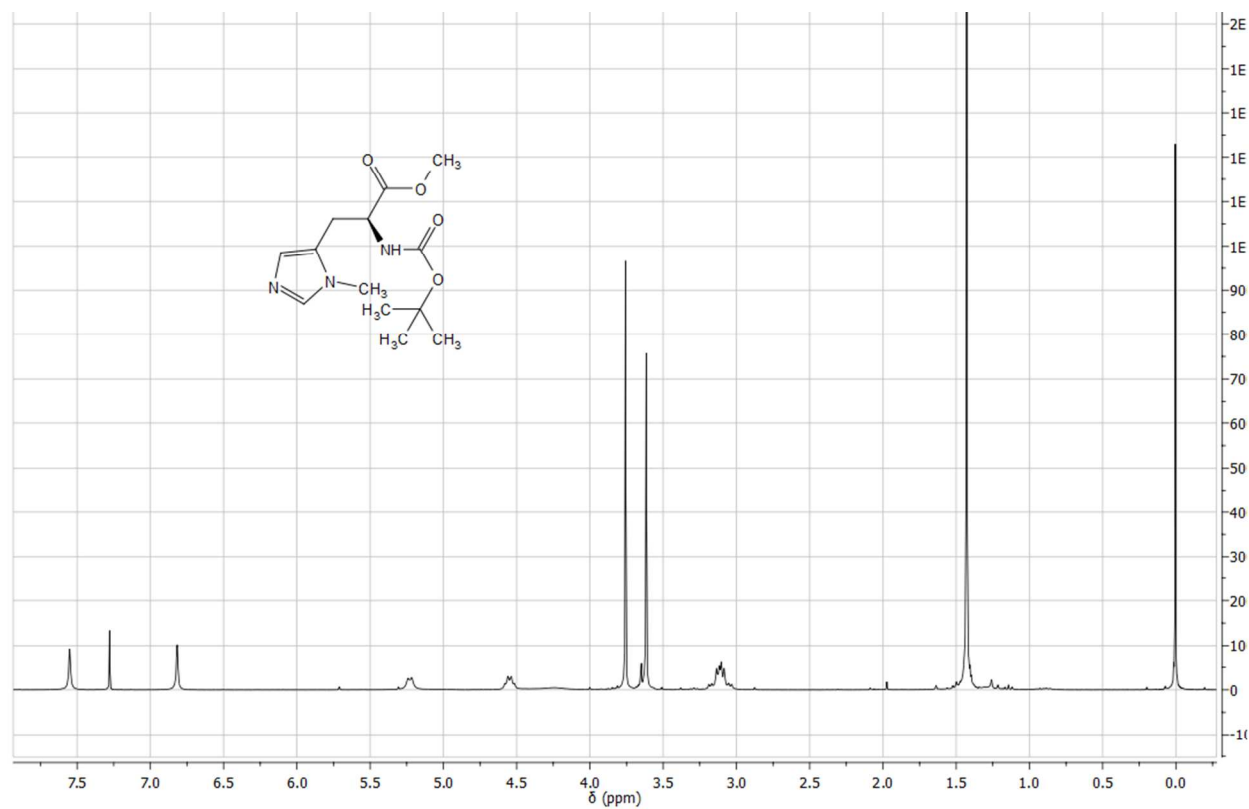
Compound **6** (^1H NMR, CDCl_3 , 300 MHz):



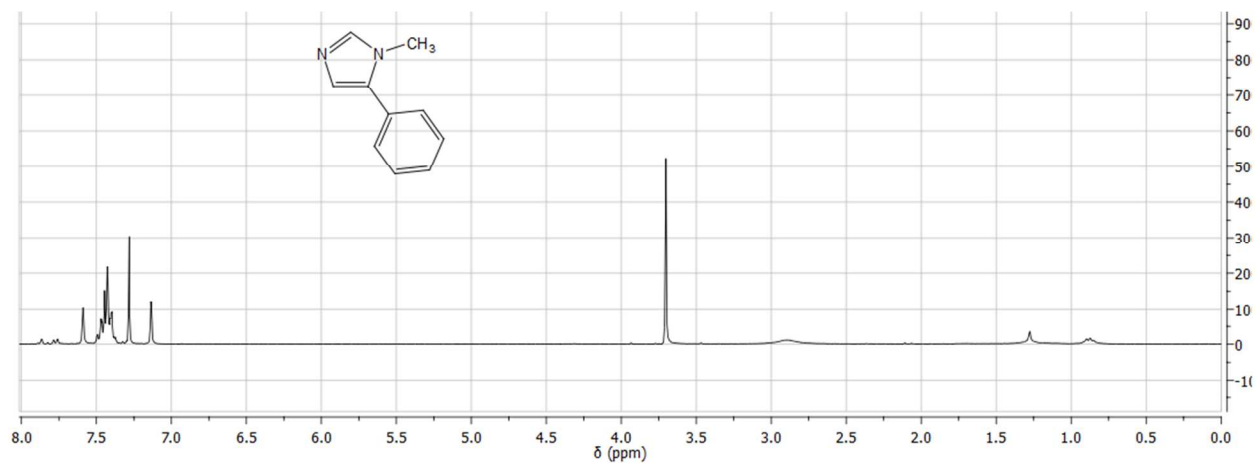
Compound **7** + traces of the other isomer (^1H NMR, CDCl_3 , 300 MHz):



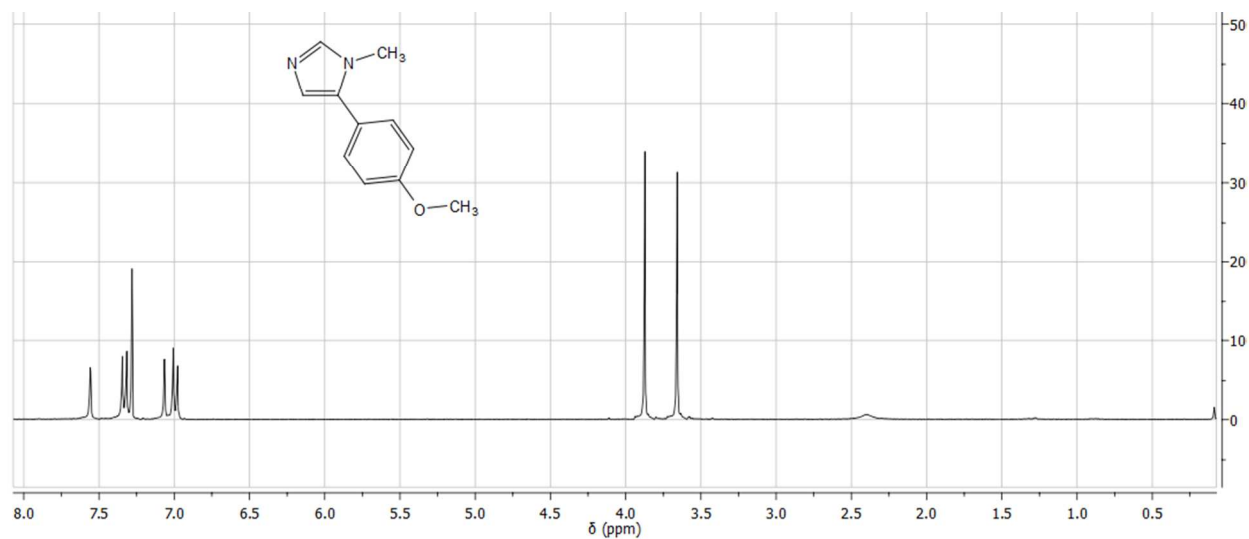
Compound **8** (^1H NMR, CDCl_3 , 300 MHz):



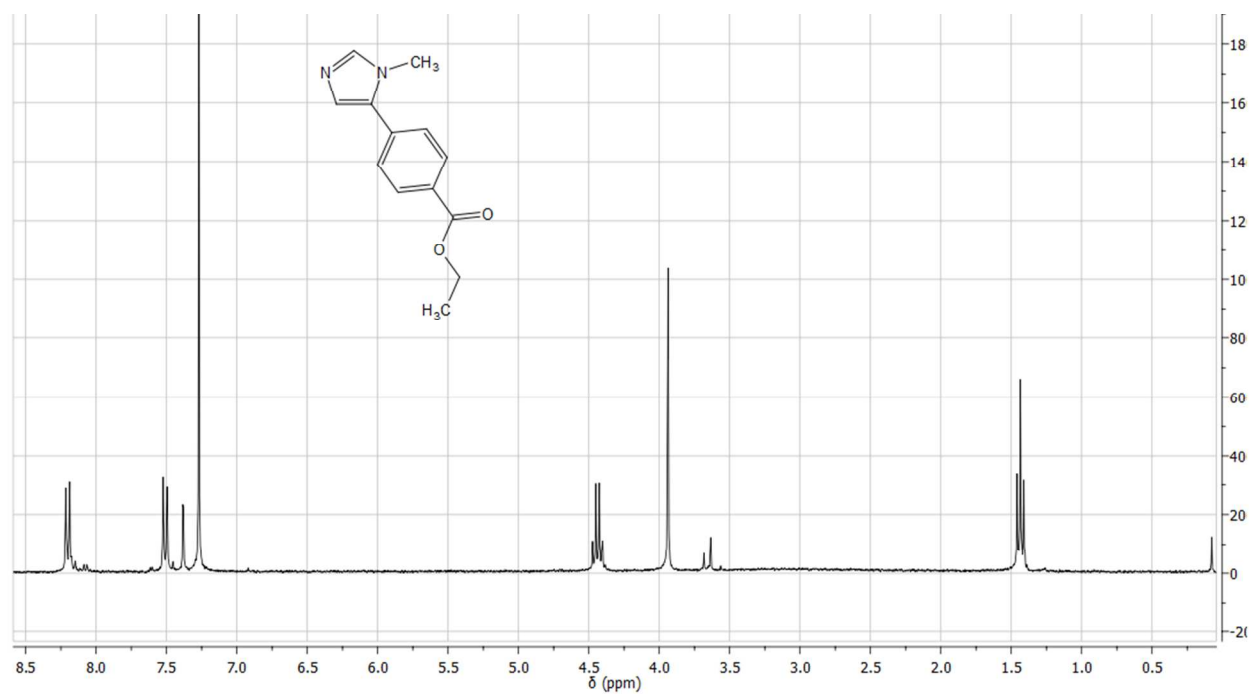
Compound **9** (^1H NMR, CDCl_3 , 300 MHz):



Compound **10** (^1H NMR, CDCl_3 , 300 MHz):



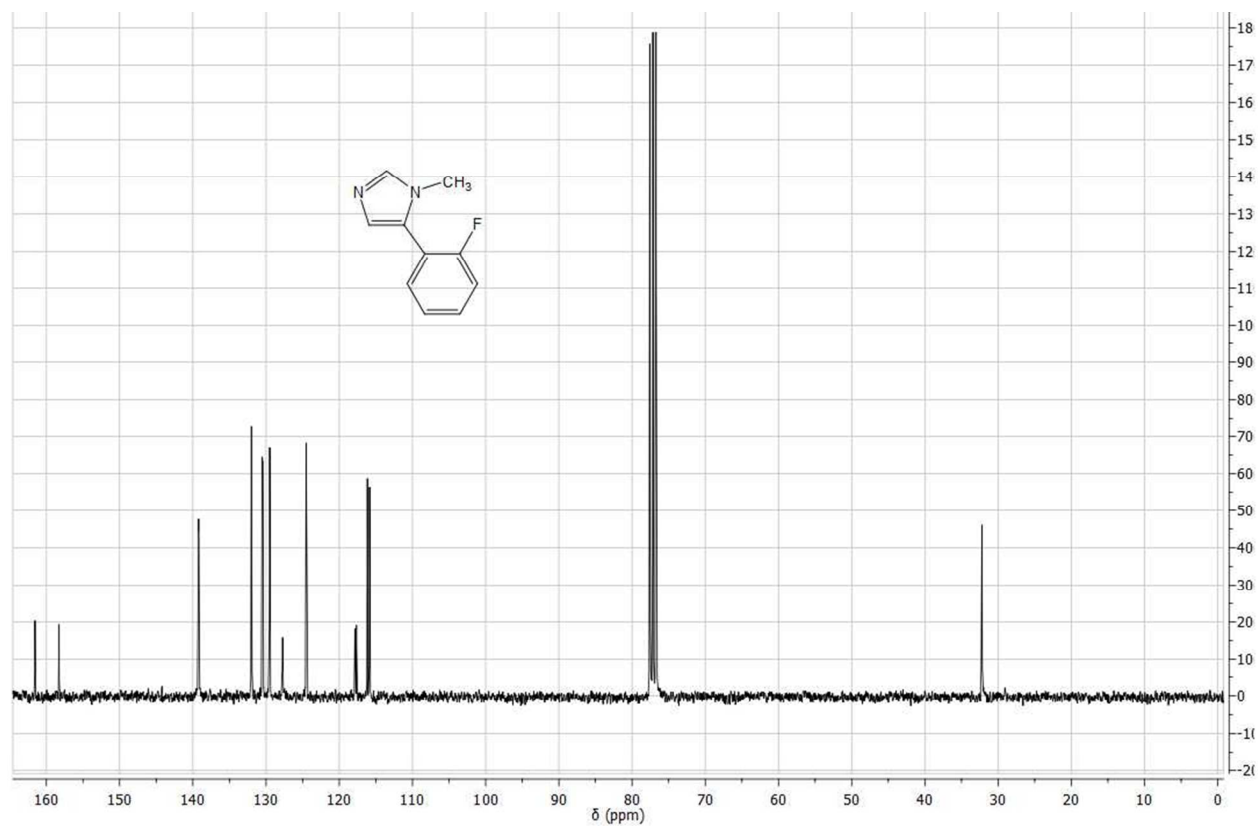
Compound **11** (^1H NMR, CDCl_3 , 300 MHz):



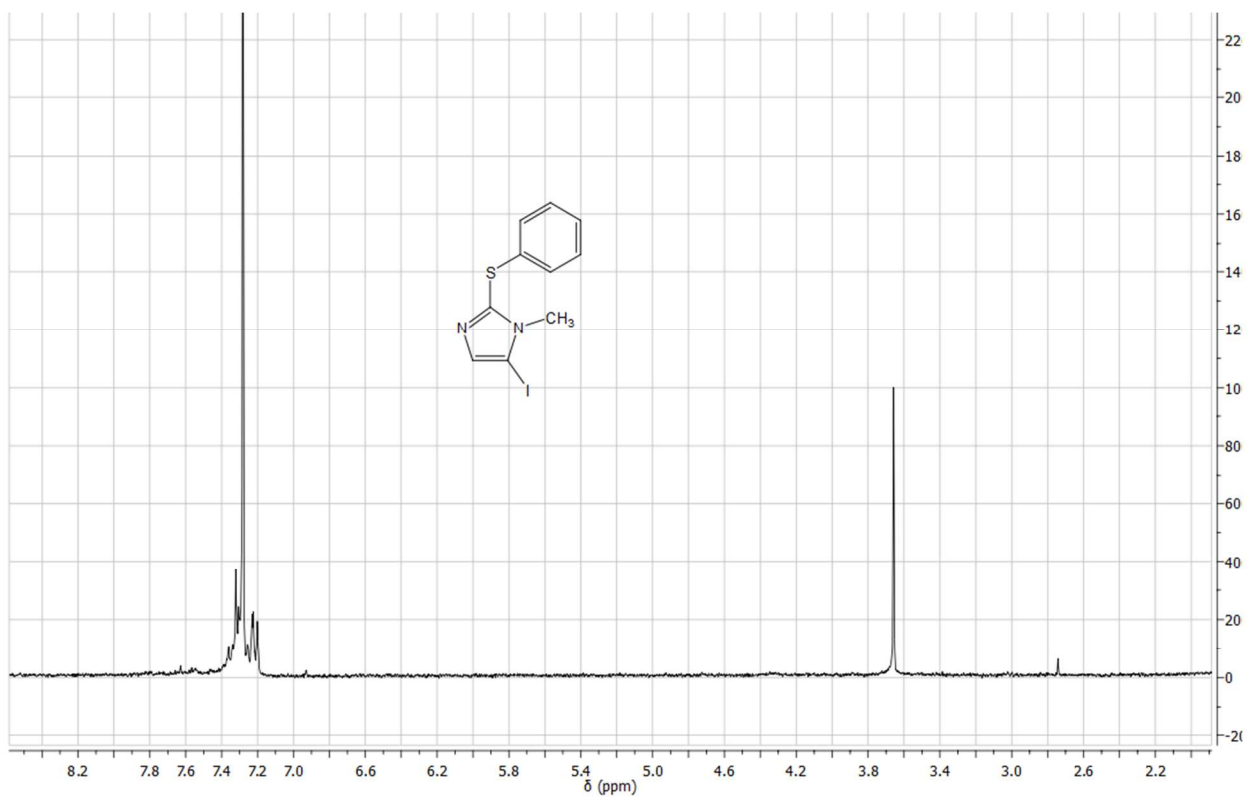
Chemical structure of 1-methyl-2-(2-fluorophenyl)imidazole is shown above the spectrum.

¹H NMR spectrum (400 MHz, CDCl₃) showing peaks in the aromatic region (7.0-7.6 ppm) and a sharp singlet at 3.7 ppm corresponding to the methyl group. The x-axis is labeled δ (ppm) and ranges from 0.0 to 8.0. The y-axis represents intensity, ranging from -10 to 2E+02.

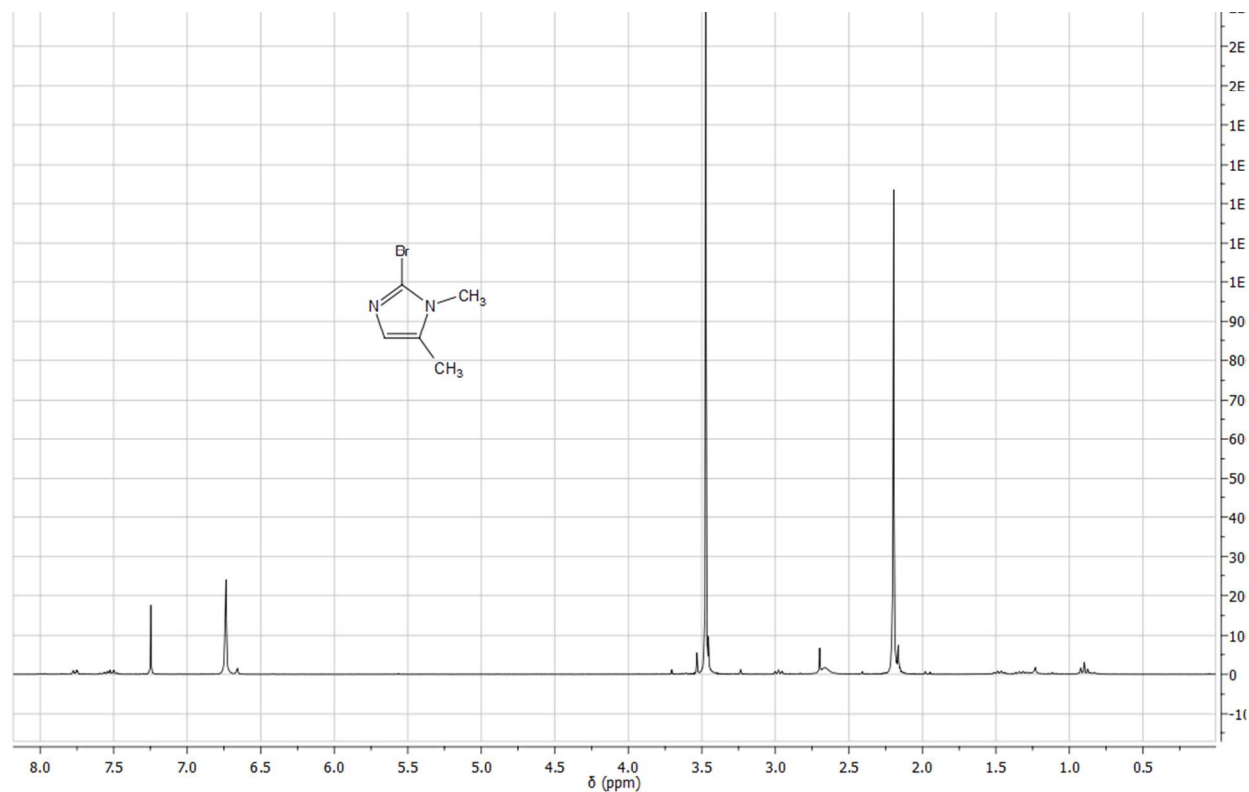
Compound **12** (^{13}C NMR, CDCl_3 , 75 MHz):



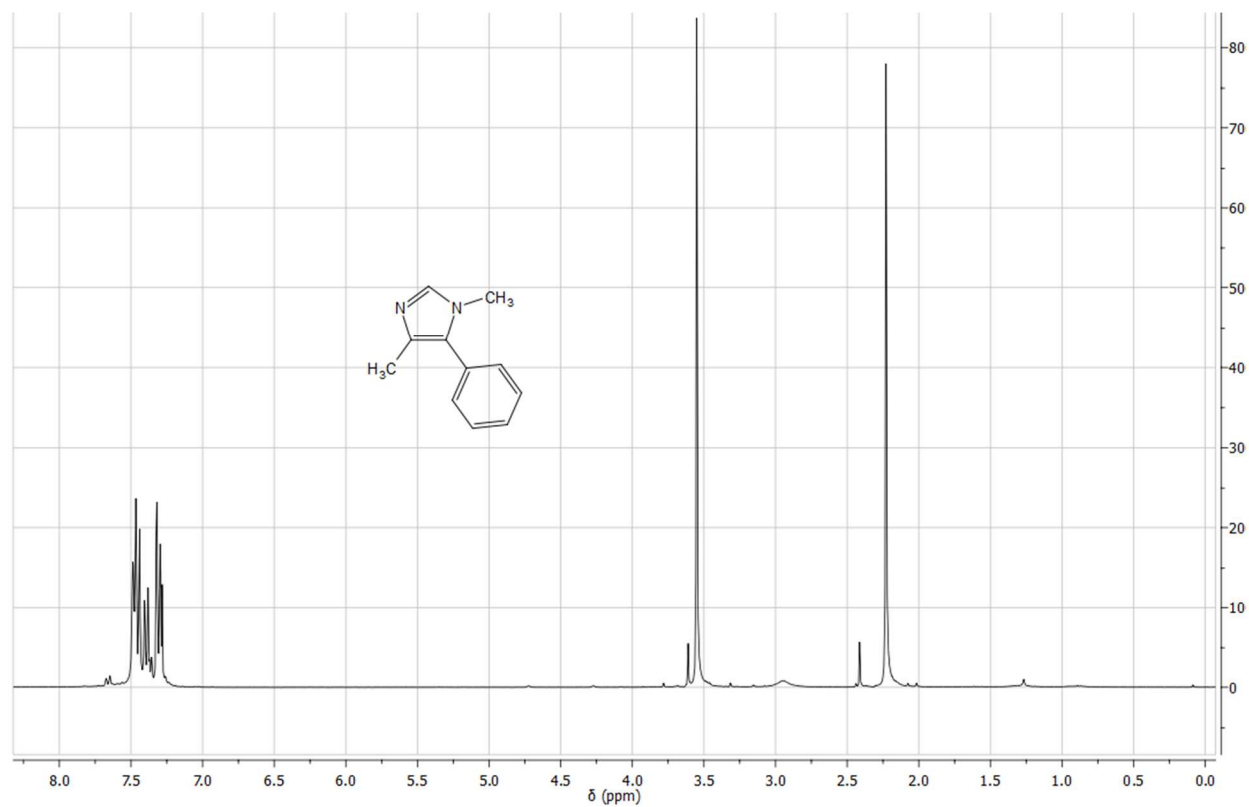
Compound **13** (^1H NMR, CDCl_3 , 300 MHz):



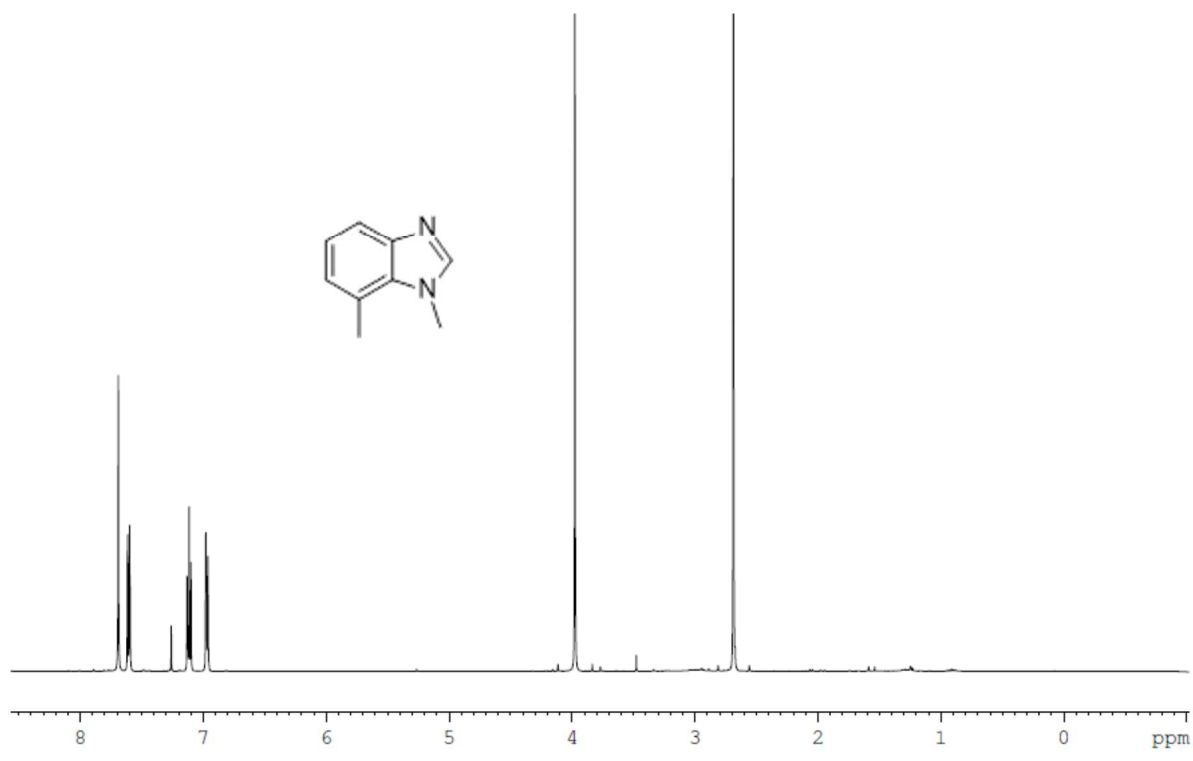
Compound **14** (^1H NMR, CDCl_3 , 300 MHz):



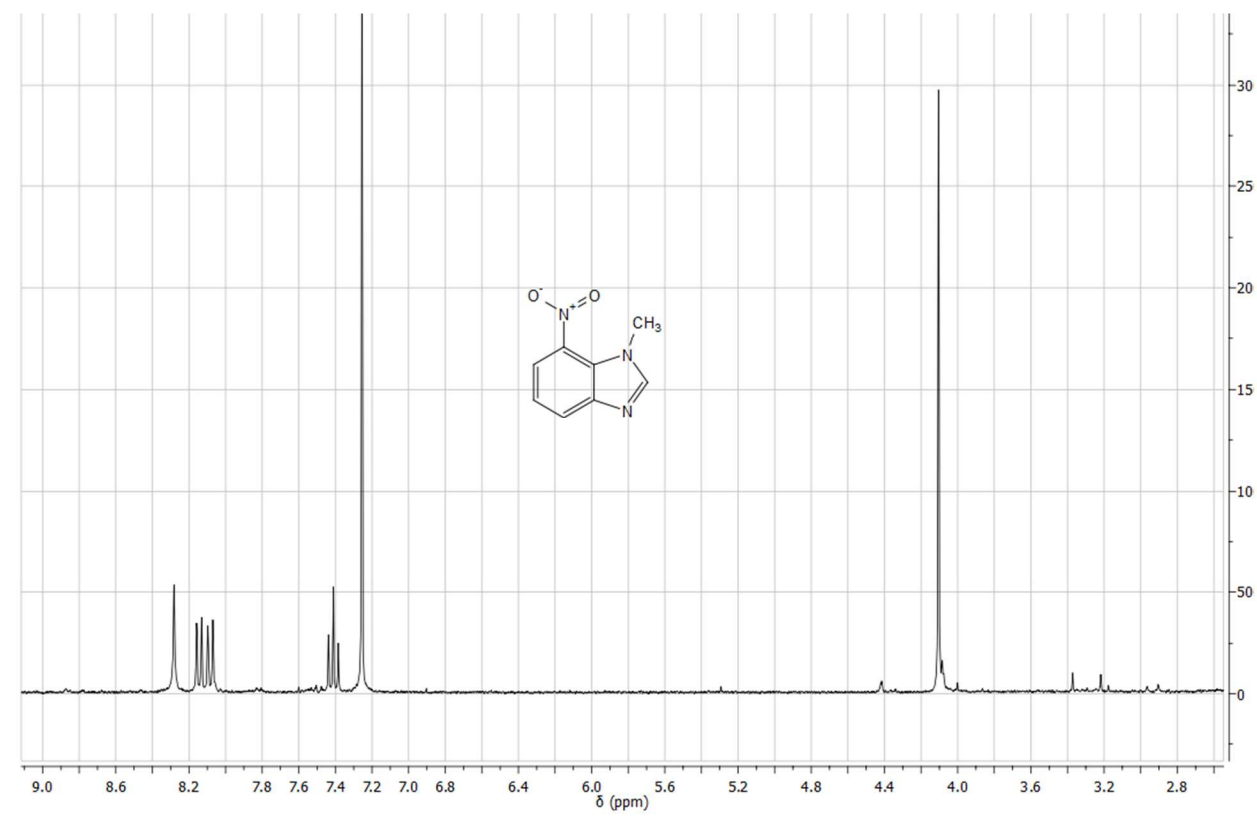
Compound **15** + the other isomer (^1H NMR, CDCl_3 , 300 MHz):



Compound **16** (^1H NMR, CDCl_3 , 500 MHz):



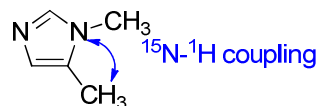
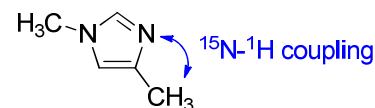
Compound **17** (^1H NMR, CDCl_3 , 300 MHz):



^1H - ^{15}N HMBC

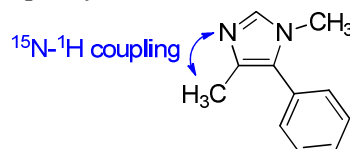
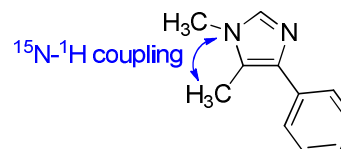
Regiochemistry was determined by ^1H - ^{15}N HMBC for compounds **4**, **15** and **16** whereas for compounds **5-14** and **17** data were compared to the literature (see manuscript for references).

- In the case of **4**, observation of a coupling between N(1) (162.8 ppm) and the ^1H of the methyl group at 2.19 ppm indicates that this latter is in position 5 (and not 4). In the minor isomer (obtained by classical alkylation methods), that is N(3) (at 250.7 ppm) which shows a coupling with the C- CH_3 . These attributions are in perfect agreement with reported ^1H NMR data (see Kashima, I.; Harada, Y.; Hosomi, A. *Heterocycles* **1993**, 35, 433-440).

**4**

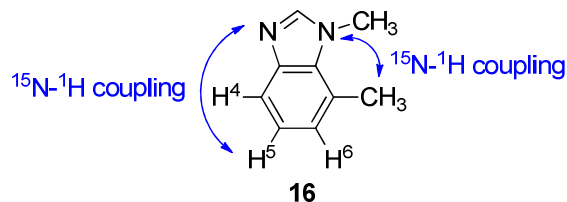
other isomer

- For **15**, the ^1H - ^{15}N HMBC analysis of the major isomer shows a coupling between N(3) (257.6 ppm) and the C- CH_3 (2.23 ppm) allowing to identify it as 1,4-dimethyl-5-phenyl-1H-imidazole. In the minor isomer, that is the N(1) which shows a coupling with C- CH_3 in agreement with the 1,5-dimethyl-4-phenyl-1H-imidazole structure.

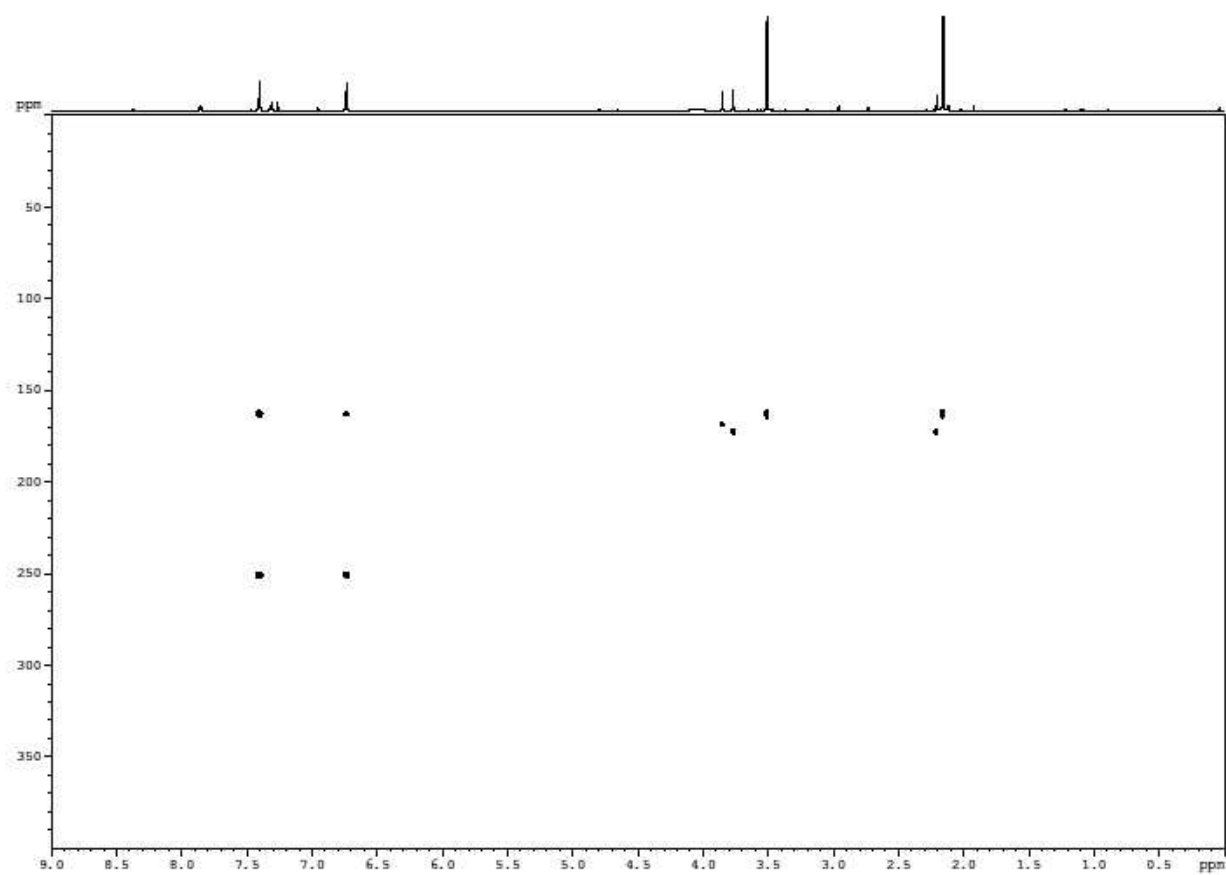
**15**

minor isomer

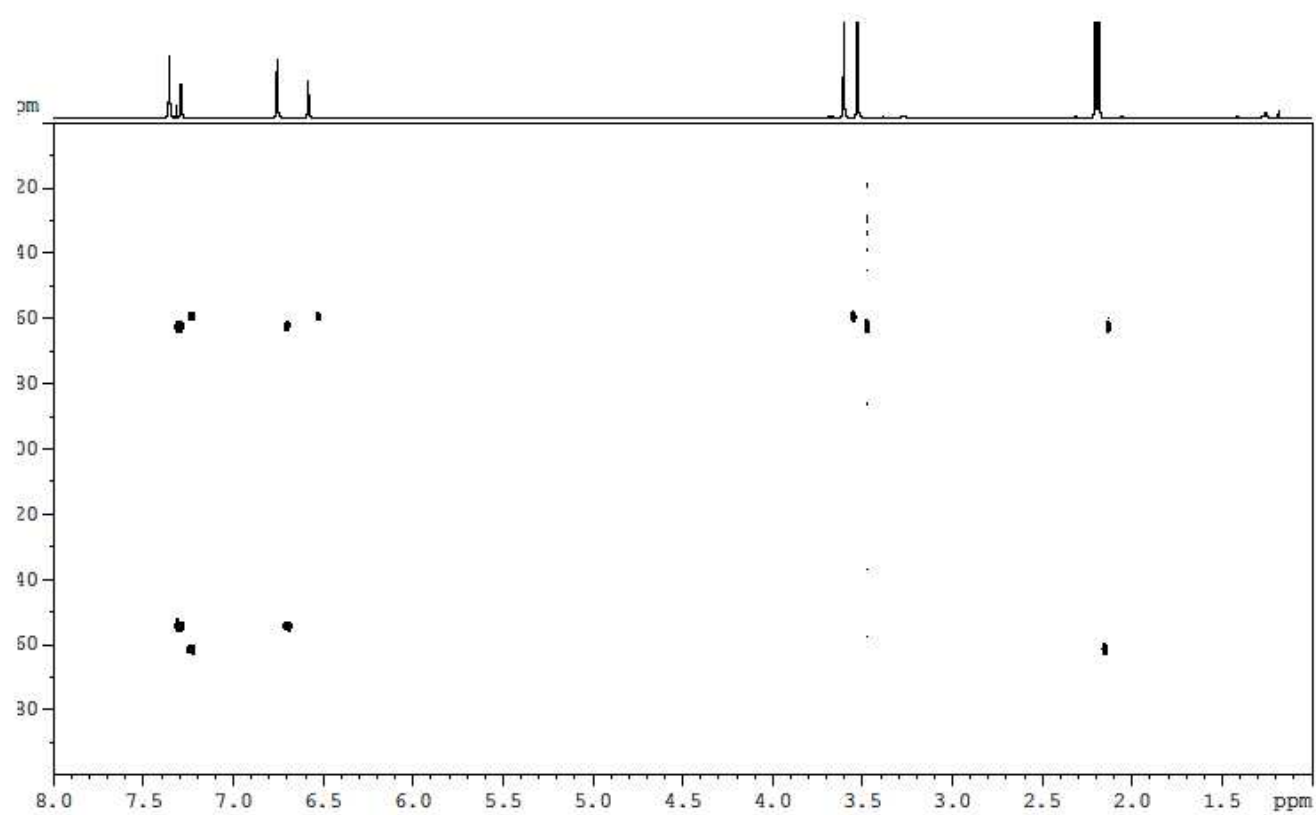
- The ^1H - ^{15}N HMBC analysis of **16** reveals a coupling between H(5) (at 7.15 ppm) and N(3) (at 240.4 ppm) what allows attributing the 1,7-dimethyl-1H-benzo[d]imidazole regiochemistry to **16**. A coupling between C- CH_3 (2.74 ppm) and N(1) (144.0 ppm) is also observed.

**16**

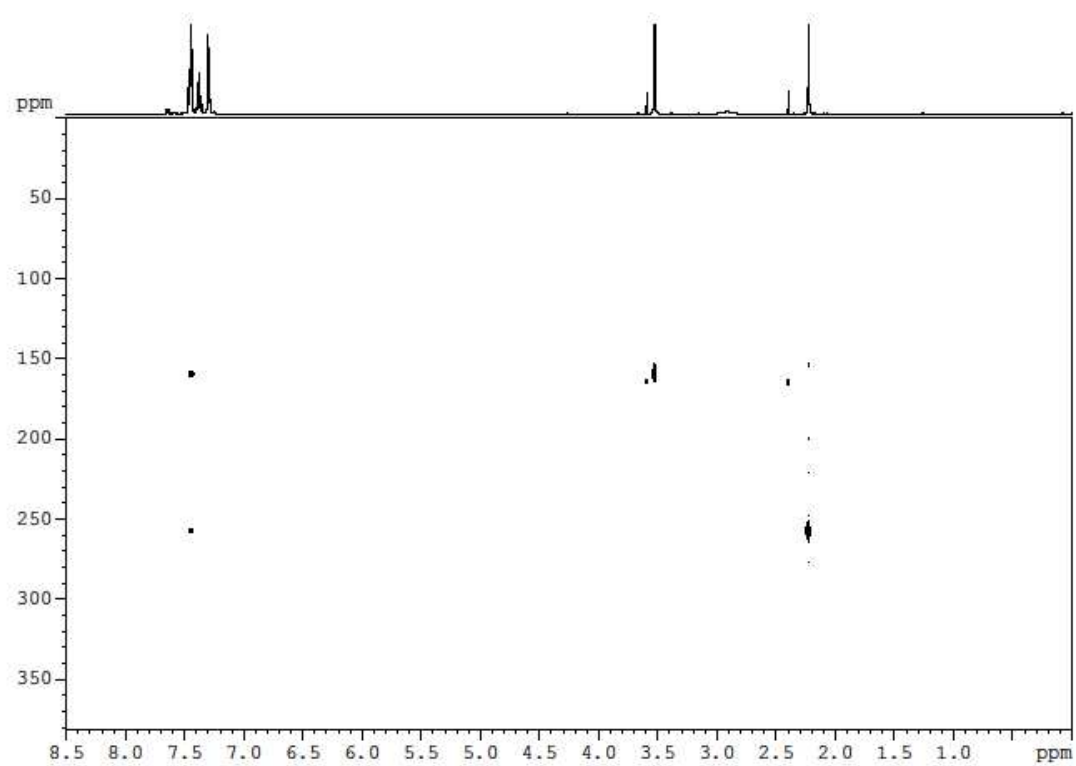
Compound **4** (CDCl₃, 500 MHz)



Compound **4** and the other regioisomer (CDCl₃, 500 MHz)



Compound **15** + traces of the other regioisomer (CDCl₃, 500 MHz)



Compound **16** (CDCl₃, 500 MHz)

