REGIOSELECTIVE SYNTHESIS OF PYRAZOLES AND PYRAZOLO[1,5-*a*]PYRIMIDINES: STRUCTURAL CHARACTERIZATION BY HMBC NMR

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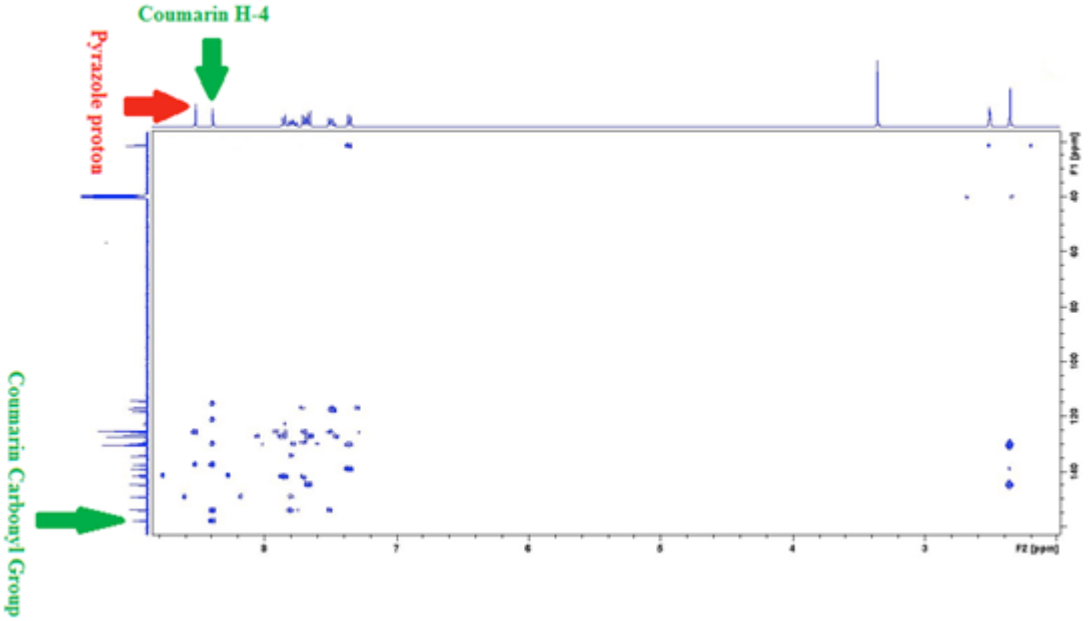
Supporting Information

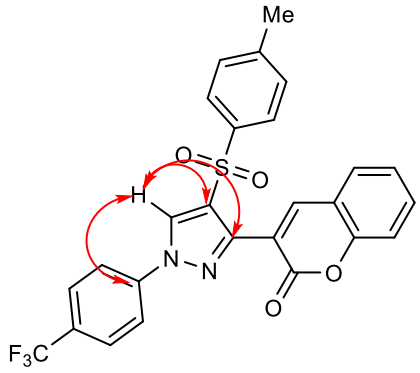
S1: Differentiation between the two possible pyrazole regioisomers 5a-c and 6a-c.

From the full ^{1}H-^{13}C HMBC spectrum of the isolated regioisomer, a signal was observed at δ 158.04 ppm corresponding to the carbonyl carbon of coumarin; it exhibited correlation peak with the singlet signal at δ 8.39 ppm assigned to coumarin H-4. Thus, the singlet signal at δ 8.52 ppm is assigned to the pyrazole proton (Figure S1a). Based on the number of correlations between the pyrazole proton and carbons that are two and three bonds away we can easily determine which isomer formed (Figure S1b). The presence of two correlations in the ^{1}H-^{13}C HMBC spectrum of the isolated product is conclusive evidence for the proposed structure of **5c** (Figure S1c).

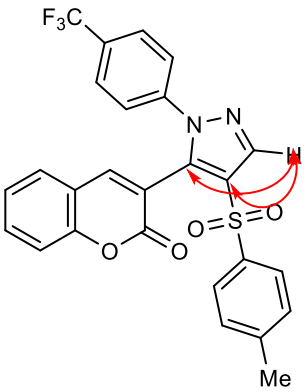
(a)



(b)



6a-c



5a-c

(C)

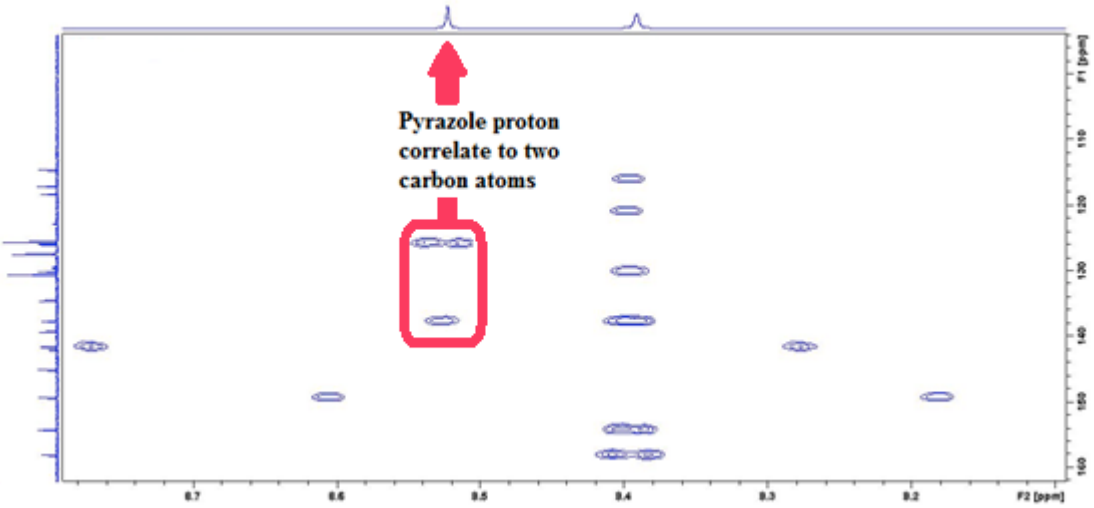
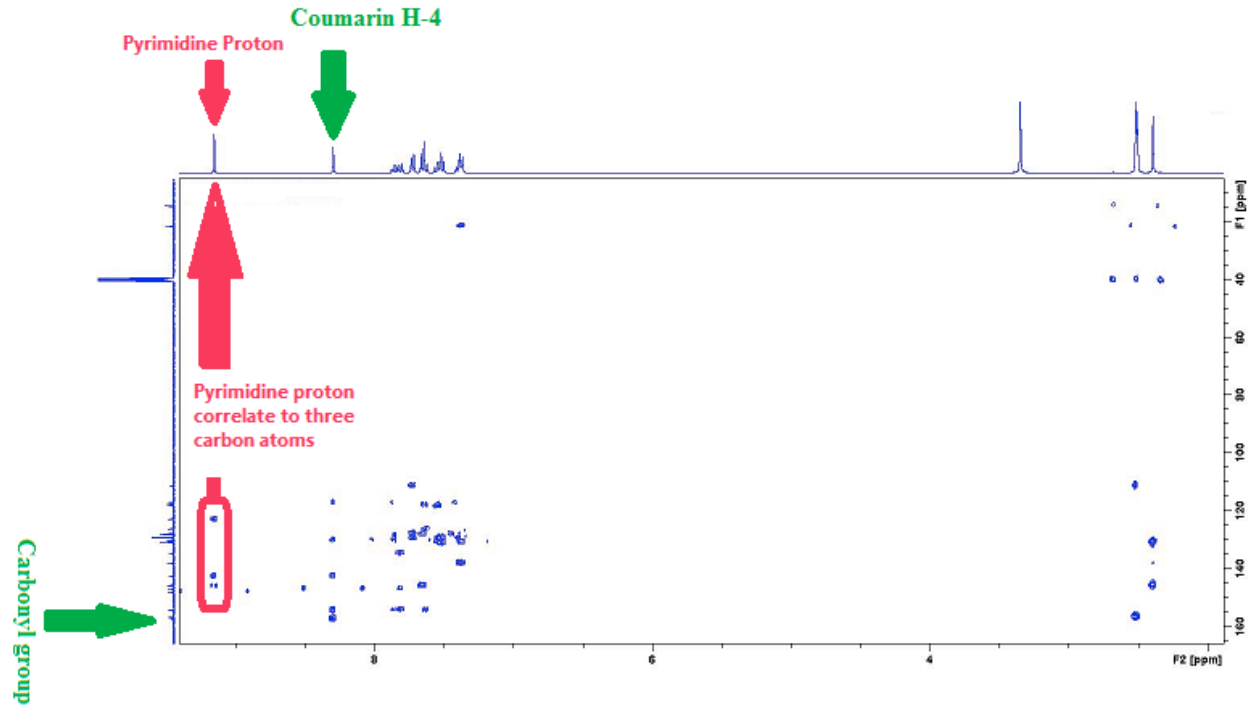


Figure S1. (a) Full ^{1}H-^{13}C HMBC spectrum of the isolated compound **5c** and assignment of the pyrazole proton and coumarin H-4; (b) Number of correlations between the pyrazole proton toward carbons in the possible regioselective isomers **5c** and **6c**; (c) number of correlation between the pyrazole proton and carbon atoms.

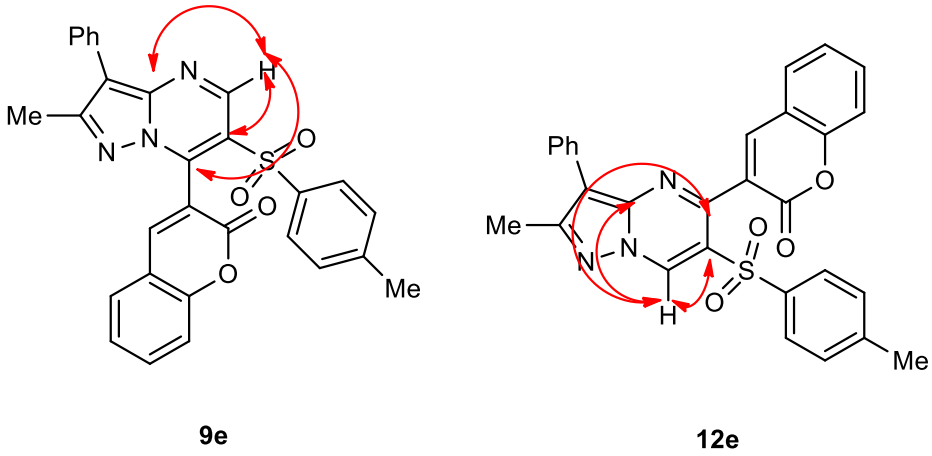
S2: ^{1}H-^{13}C HMBC of pyrazolo[1,5-*a*]pyrimidine derivatives.

The positions of coumarin H-4 and the pyrimidine proton were supported by ^{1}H-^{13}C HMBC. Figure S2a shows the full ^{1}H-^{13}C HMBC spectrum of regioisomer **9e** or **12e**. A signal was observed at δ 157.19 ppm, which corresponds to the carbonyl carbon of coumarin; it exhibited correlation peak with a singlet signal at δ 8.30 ppm, assigned to coumarin H-4. Thus, the singlet signal at δ 9.16 ppm is assigned to the pyrimidine proton. Correlations were also observed between the pyrimidine proton and carbons that were two and three bonds away (three correlations were observed, as shown in Figure S2a and S2b). However, even with these results, we could not differentiate between the two possible structure of isomers **9e** and **12e**. More information is necessary to solve this discrepancy reported in literature as to whether the pyrazolo[1,5-*a*]pyrimidine derivatives form *via* (i) addition of the exocyclic amino group to the activated double bond of the enaminone) or *via* (ii) addition of the endocyclic nitrogen to the activated double bond of the enaminone).

(a)



(b)



9e **12e**

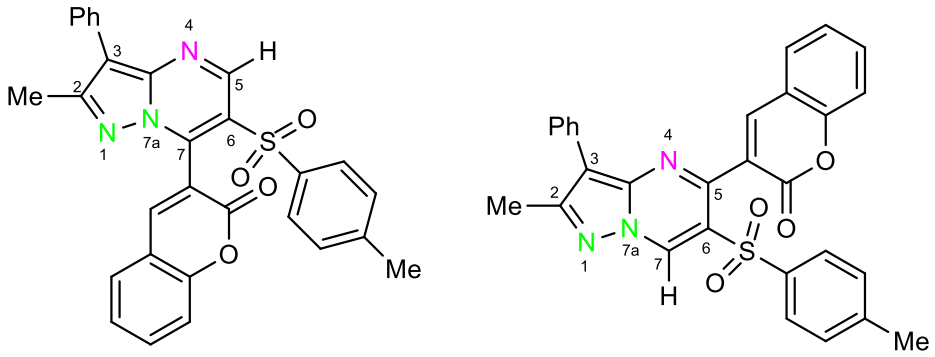
Figure S2 (a) Full ^{1}H-^{13}C HMBC spectrum of the isolated regioisomer **9e** and assignment for pyrimidine proton and coumarin H-4; (b) Number of correlations between the pyrimidine proton and carbons in the possible regioisomers **9e** and **12e**.

S3: Differentiation between the possible two regioisomers 9a-e and 12a-e

The structures of the obtained regioisomers were unambiguously elucidate by advanced ^{1}H-^{15}N HMBC techniques, where all connectivities were observed for the assignment the nitrogen chemical shifts. Using the product obtained from the reaction of **2** with the aminopyrazole derivative **7e** as representative examples (Figure S3a), the chemical shifts of the nitrogen atoms are N-4 (280.40 ppm), N-1 (275.45 ppm) and N-7a (216.12 ppm), consistent with those reported in literature. [4,5]

Figure S3b shows the ^{1}H–^{15}N HMBC spectrum of the obtained product (may be **9e** or **12e**). It was found that pyrimidine nitrogen atom 4 (indicated by purple) was key in differentiating between the two possible isomers. Connectivity was observed between the pyrimidine proton and N-4 ($^{2}J_{H3\text{-}N4}$) (Figure 6b). Therefore, the results confirmed the existence of isomer **9e** over the alternative structure **12e.**

(a)



9e **12e**

(b)

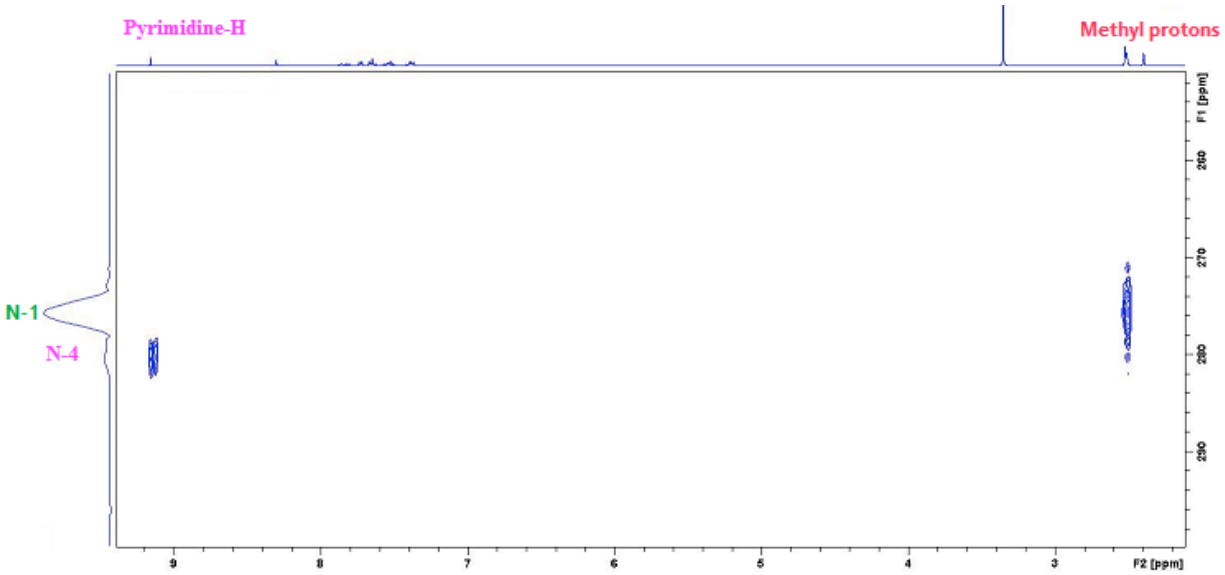
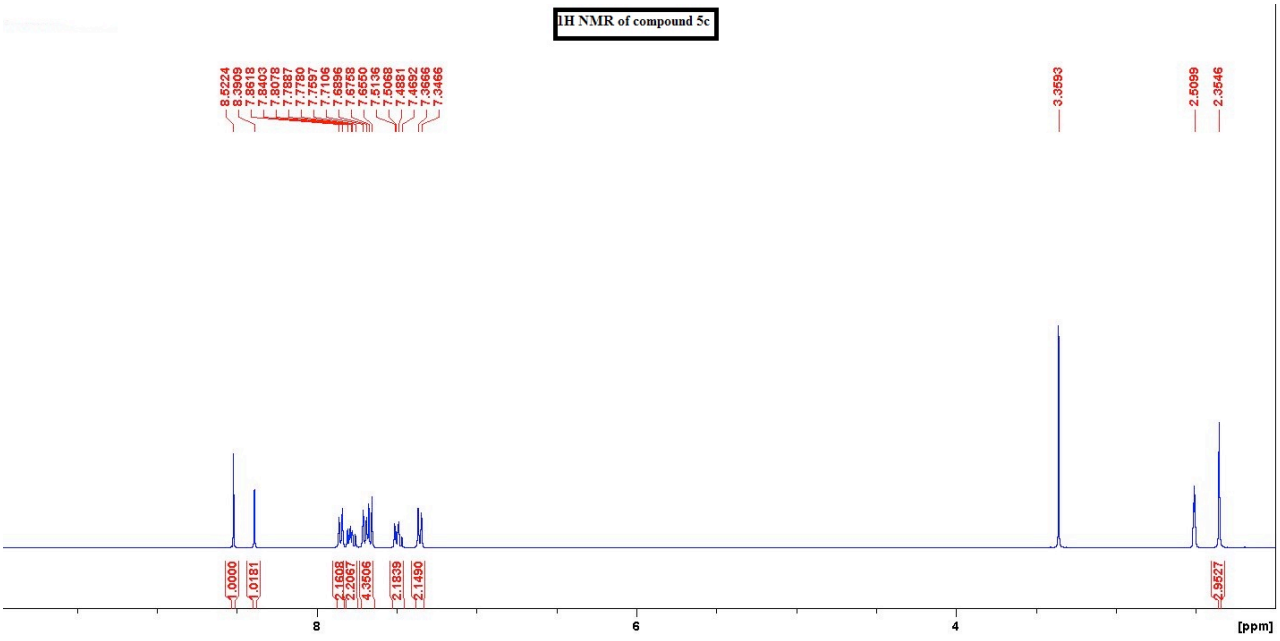
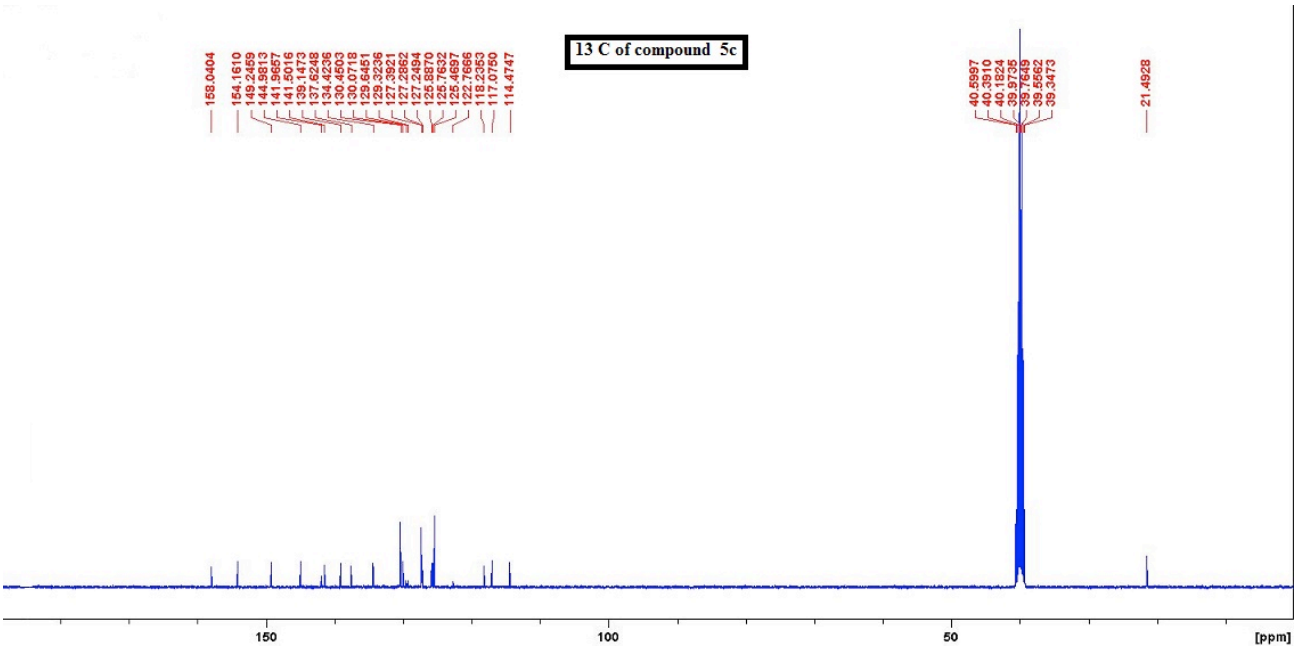


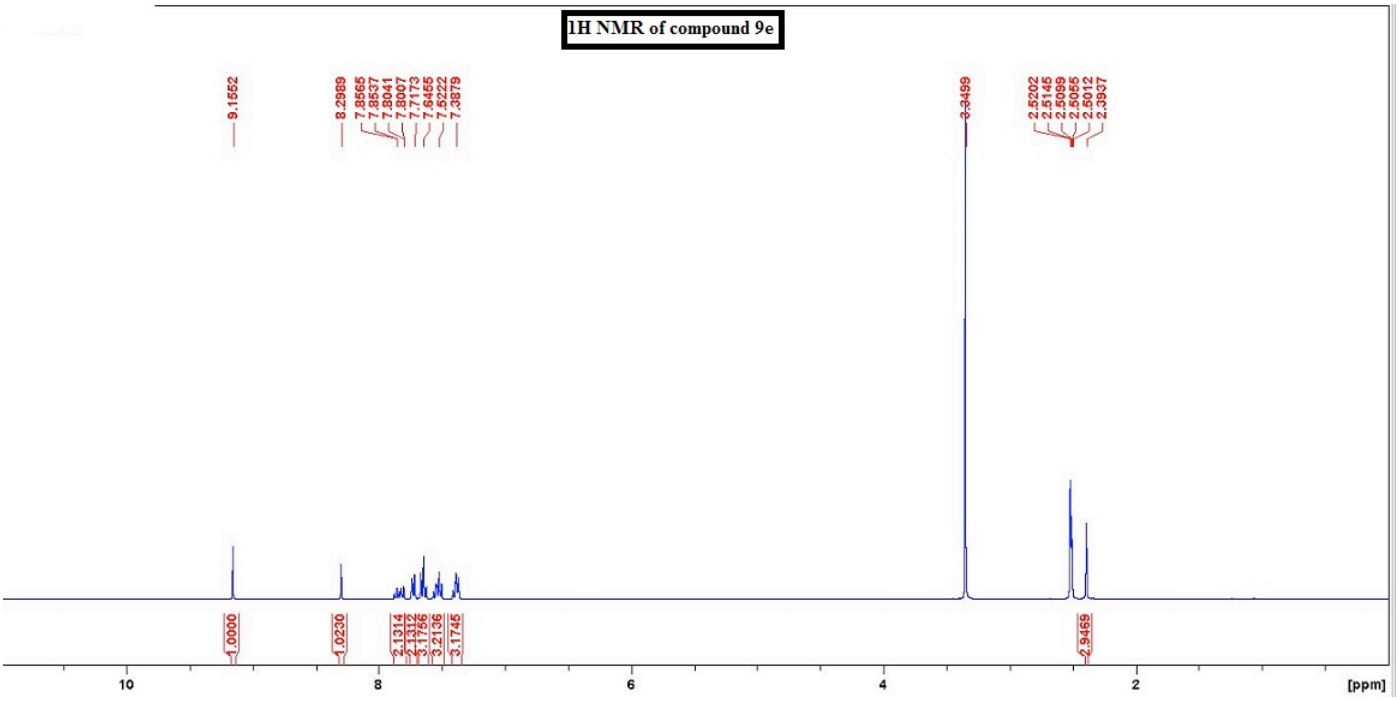
Figure S3. (a) Diagnostic correlations in the ^{1}H-^{15}N HMBC spectrum for two isomers 9e and 12e (b) ^{1}H-^{15}N HMBC spectrum of the isolated product 9e.

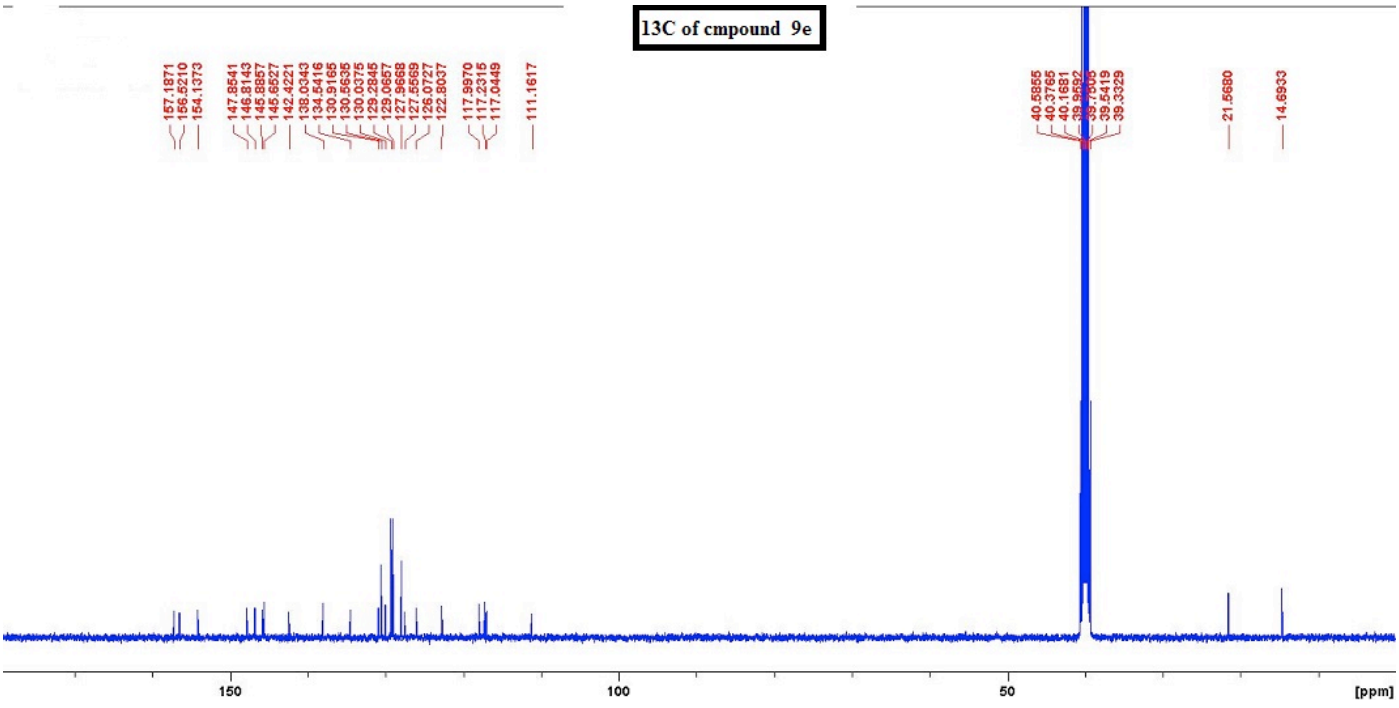
In addition to the other observed connectivities in the ^{1}H–^{15}N HMBC spectrum, connectivity was observed between the methyl proton (position 2) and N-1 (Figure S3b). Furthermore, N-7a can be used to differentiate between the two isomers, however, no connectivity was observed between pyrimidine-H and N-7a. Therefore, this lack of connectivity served as additional evidence for the selective formation of **9e.**

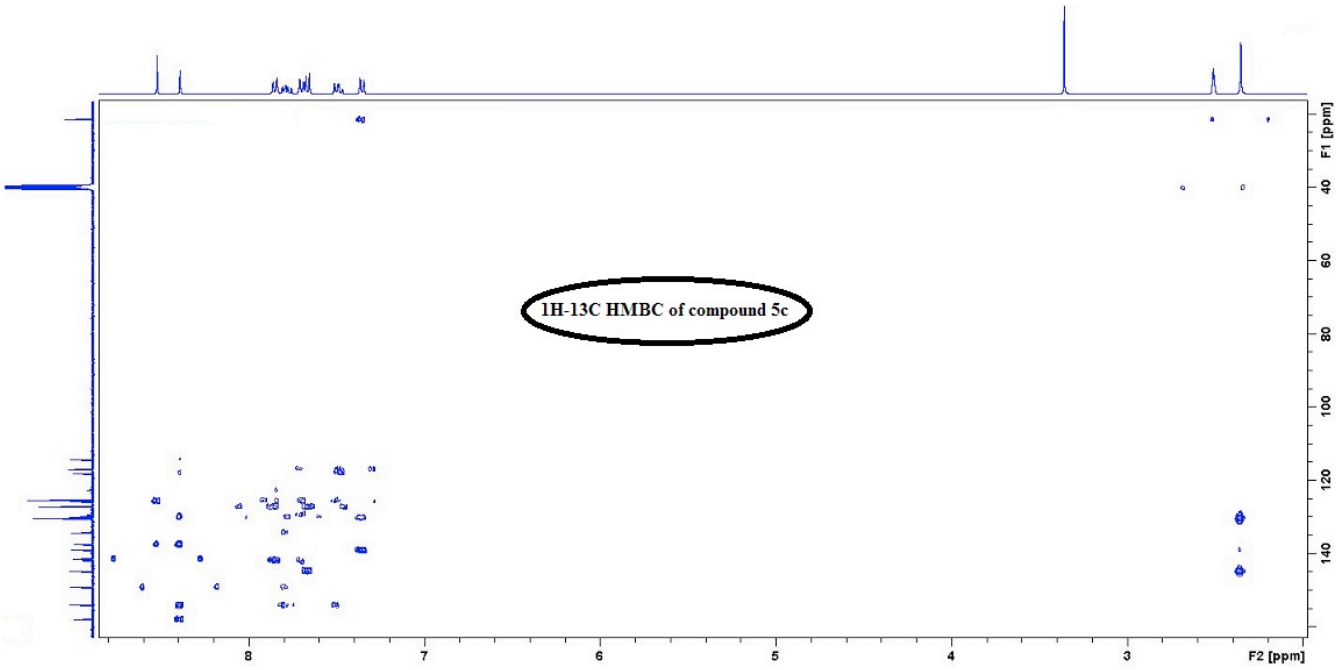
S4: Some NMR Data

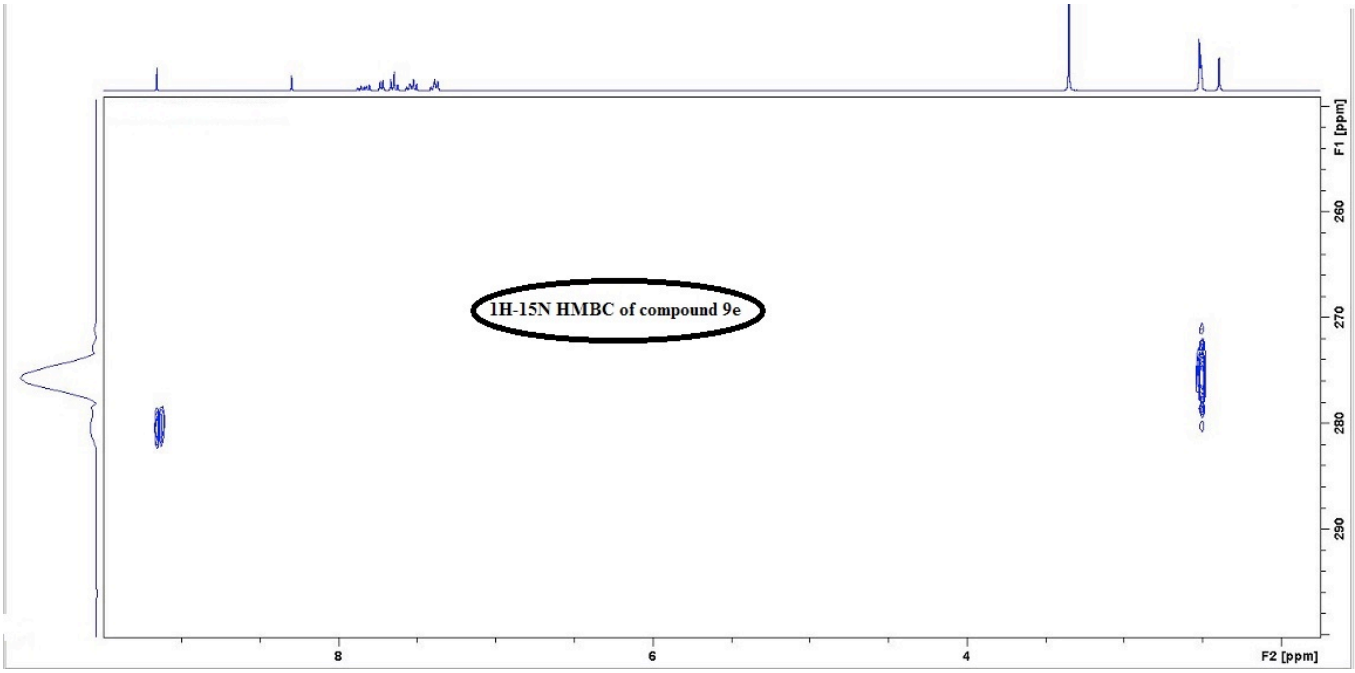


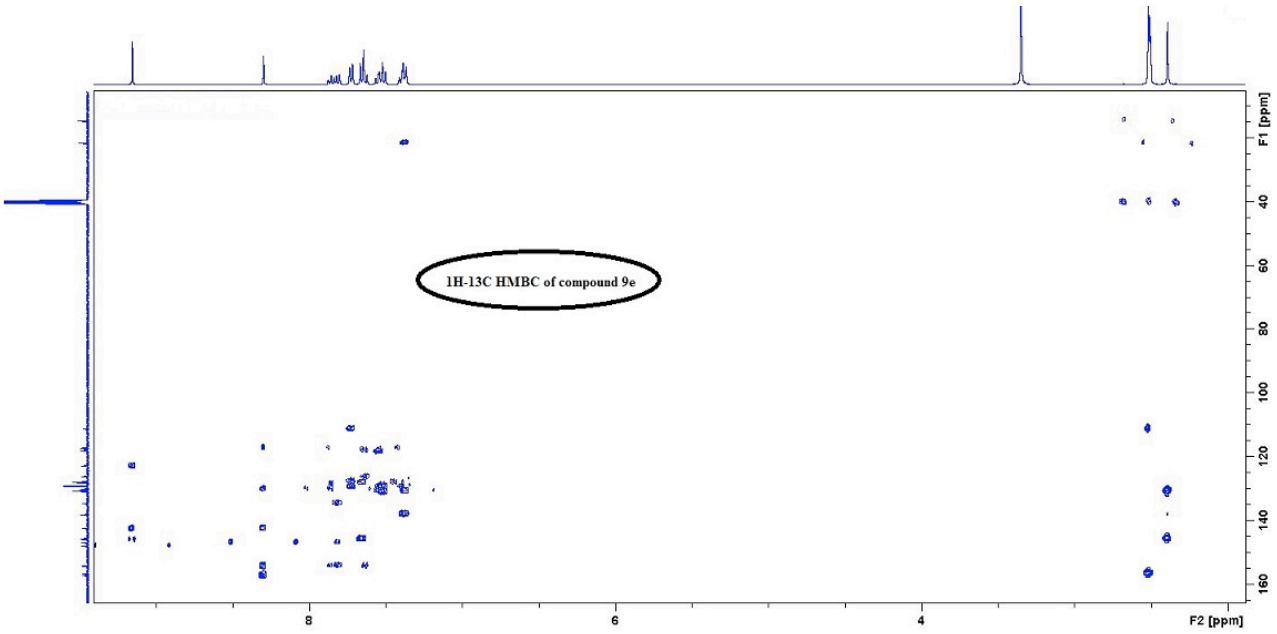


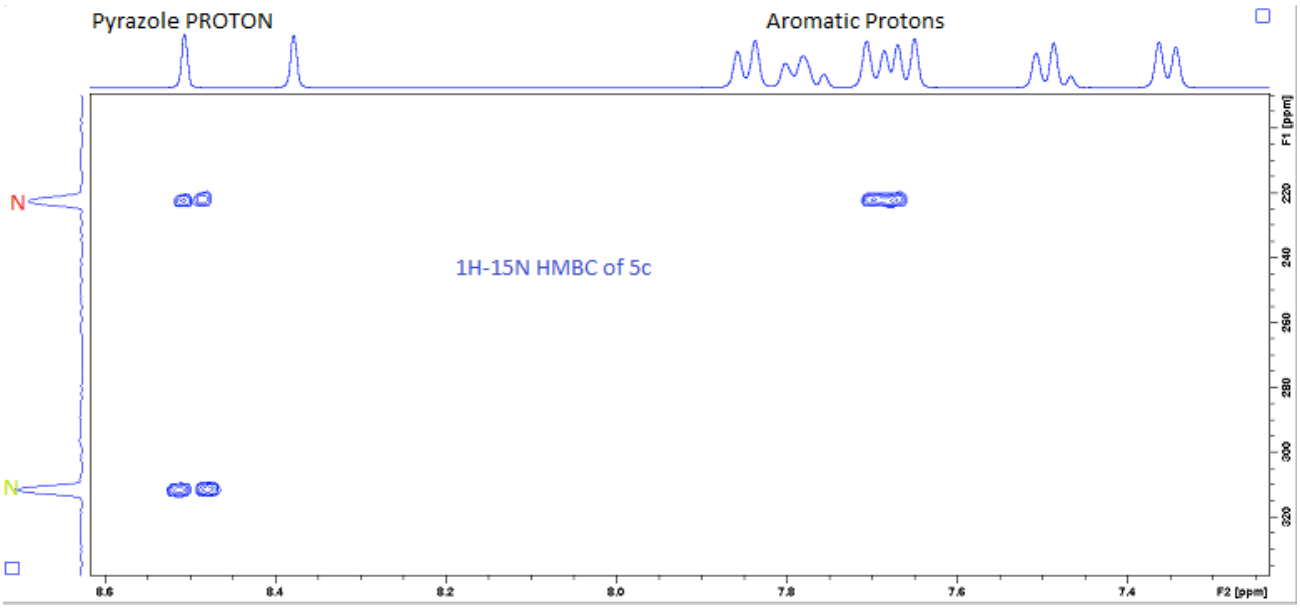

1H NMR of compound 9e
9.1552
8.2989
7.8565
7.8537
7.8041
7.8007
7.7173
7.6485
7.5222
7.3879
3.3499
2.5202
2.5145
2.5099
2.5065
2.5012
2.3937
1.0000
1.0230
2.1314
2.1312
3.1756
3.2136
3.1745
2.9469
10
8
6
4
2
[ppm]


13C of cmpound 9e
157.1871
156.6210
154.1373
147.8541
146.8143
145.8857
145.6527
142.4221
138.0343
134.5416
130.9165
130.5638
130.0375
129.2845
129.0657
127.9688
127.5569
126.0727
122.8037
117.9970
117.2315
117.0449
111.1617
40.5855
40.3765
40.1681
39.9592
39.7505
39.5419
39.3329
21.5680
14.6933
150
100
50
[ppm]


1H-13C HMBC of compound 5c
F1 [ppm]
F2 [ppm]


1H-15N HMBC of compound 9e
F1 [ppm]
F2 [ppm]


1H-13C HMBC of compound 9e
F1 [ppm]
F2 [ppm]


Pyrazole PROTON
Aromatic Protons
1H-15N HMBC of 5c
N
N
F1 [ppm]
F2 [ppm]