Catalyst- and solvent-free synthesis of 2-fluoro-*N*-(3-(methylthio)-1*H*-1,2,4-triazol-5-yl)benzamide through a microwave-assisted Fries rearrangement: X-ray structural and theoretical studies

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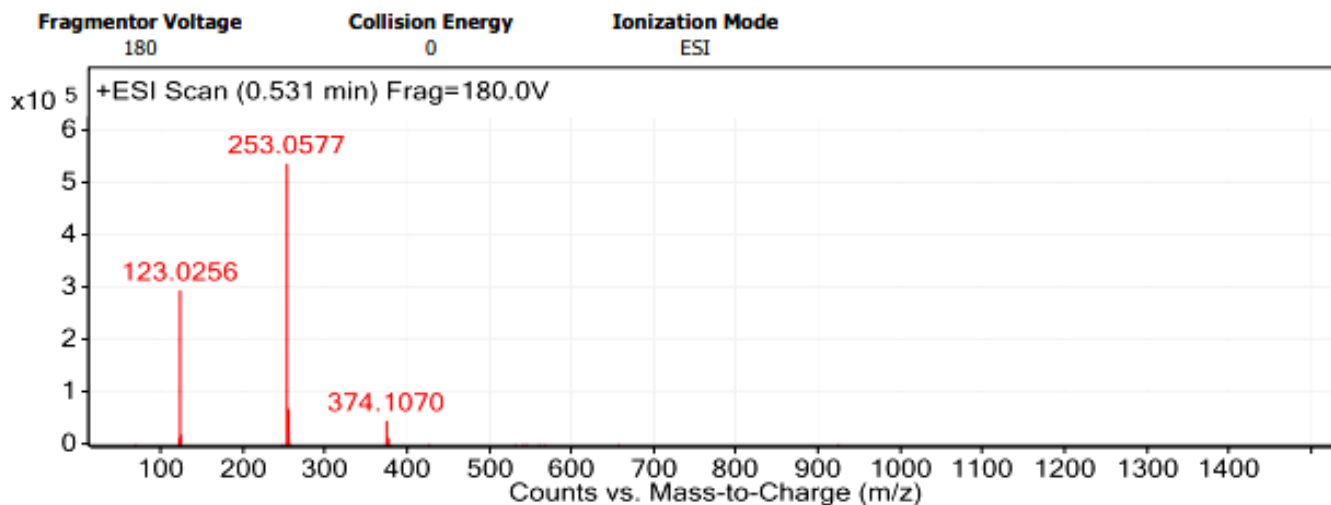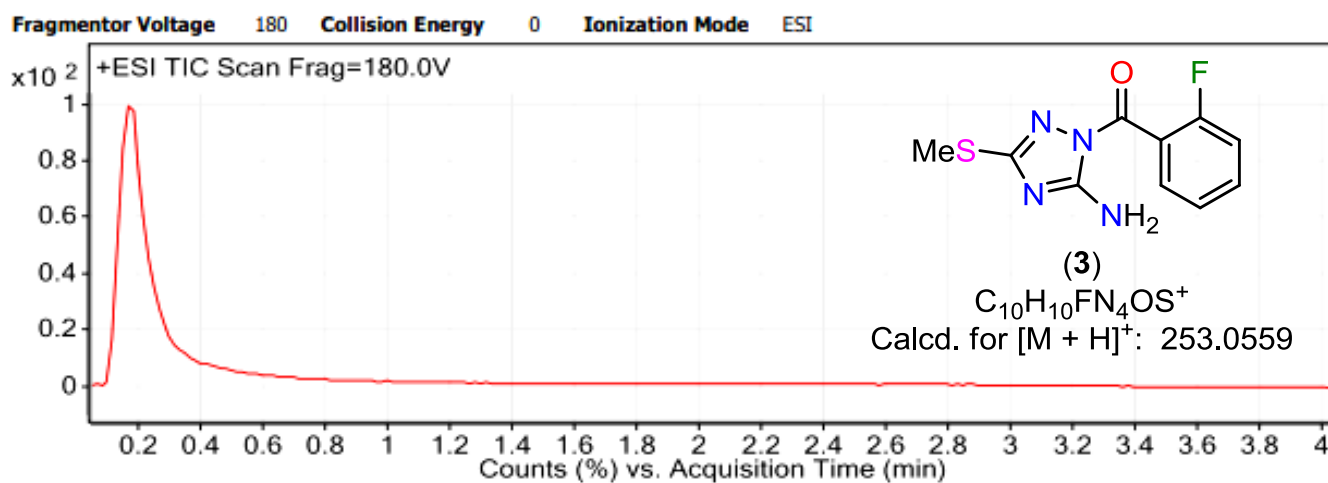
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SUPPORTING INFORMATION

Content:

1. Copy of the HRMS spectrum of compound (3)

Fragmentor Voltage   180   Collision Energy   0   Ionization Mode   ESI

+ESI TIC Scan Frag=180.0V

(3)
$C_{10}H_{10}FN_4OS^+$
Calcd. for $[M + H]^+$: 253.0559

Counts (%) vs. Acquisition Time (min)

Fragmentor Voltage   Collision Energy   Ionization Mode
180   0   ESI

+ESI Scan (0.531 min) Frag=180.0V

253.0577

123.0256

374.1070

Counts vs. Mass-to-Charge (m/z)

Peak List

m/z	z	Abund
123.0256		296426.1
253.0577		539248.6
374.107		46850.6

Figure S1. HRMS spectrum of compound (**3**).

2. Copies of ^{1}H, ^{13}C, DEPT-135 and ^{19}F NMR spectra of compound (3)
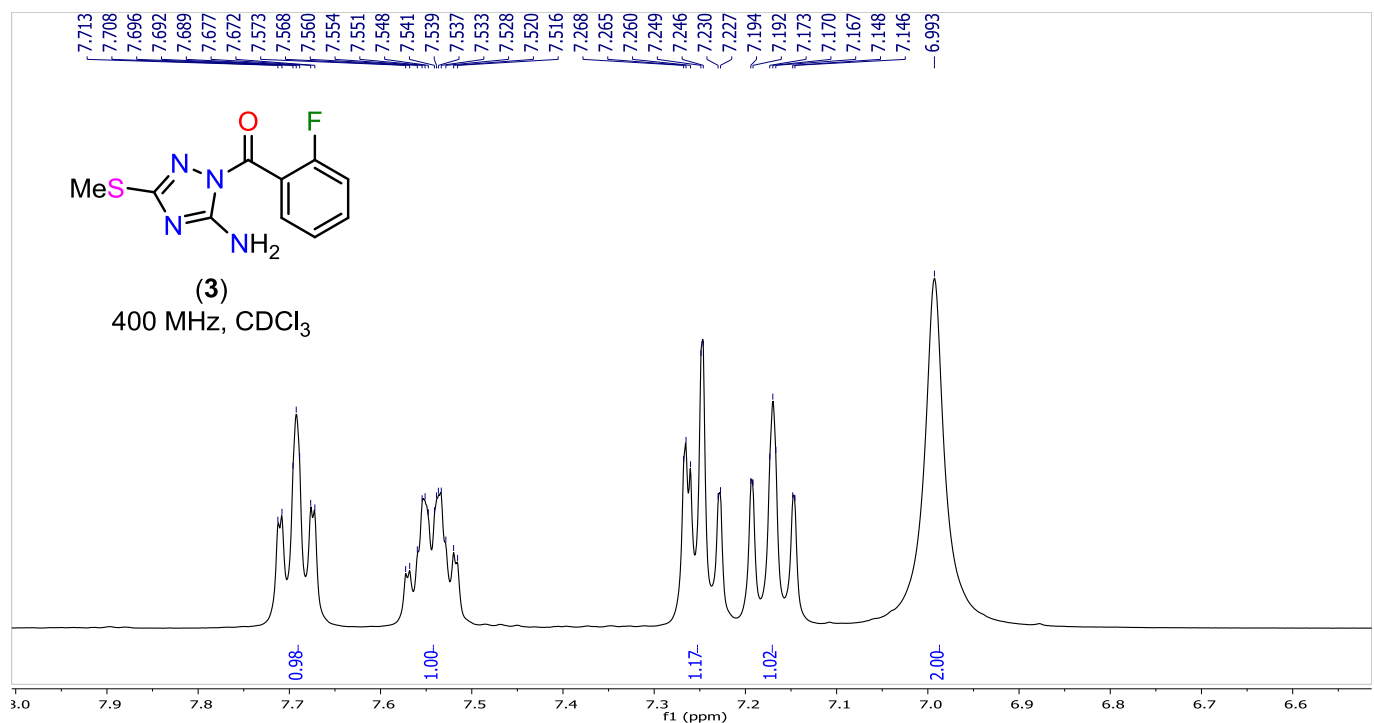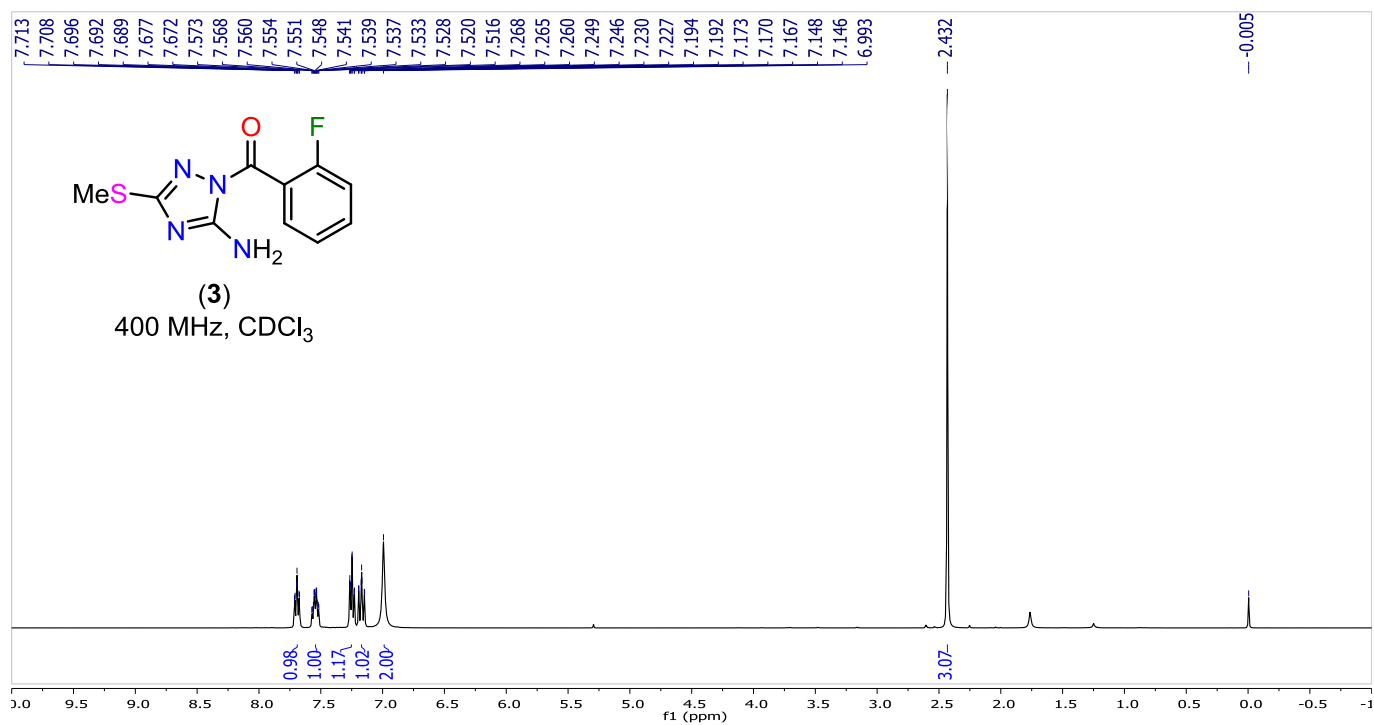
Figure S2. ^{1}H NMR spectrum of compound (**3**).

2. Copies of ^{1}H, ^{13}C, DEPT-135 and ^{19}F NMR spectra of compound (3)
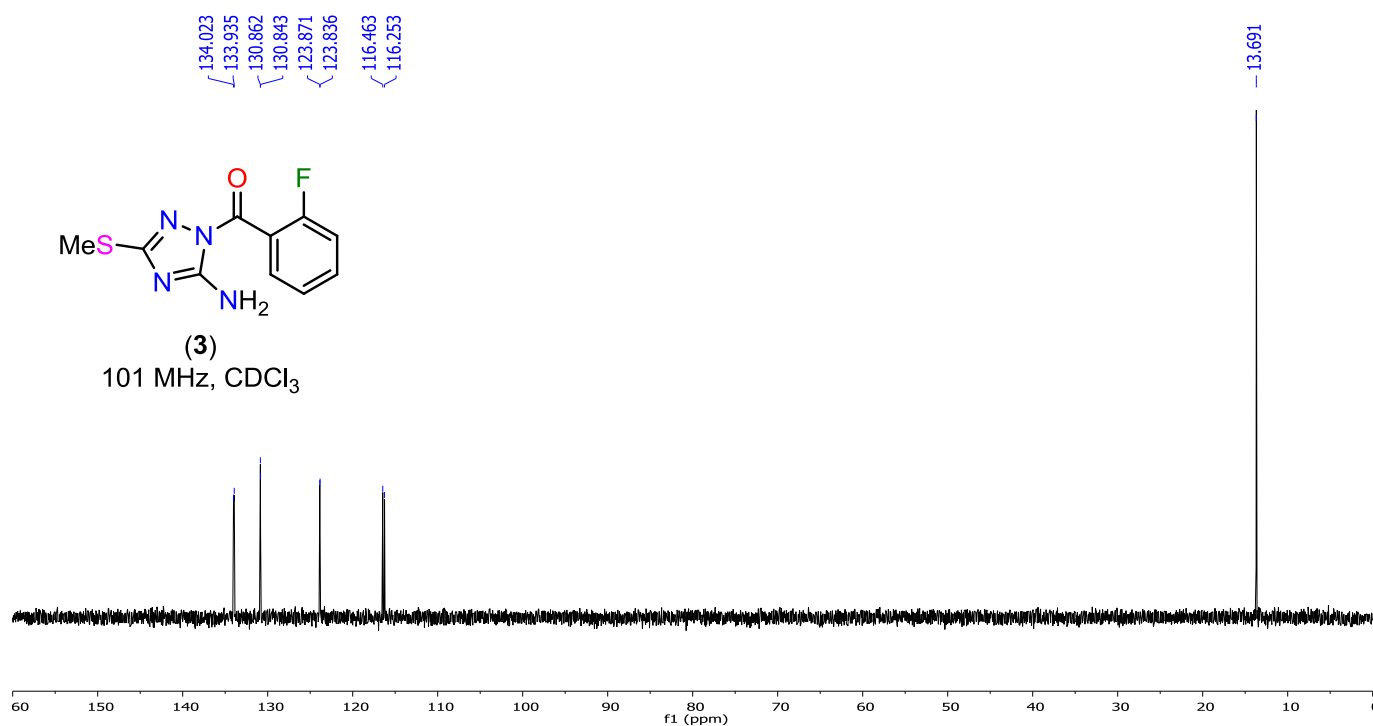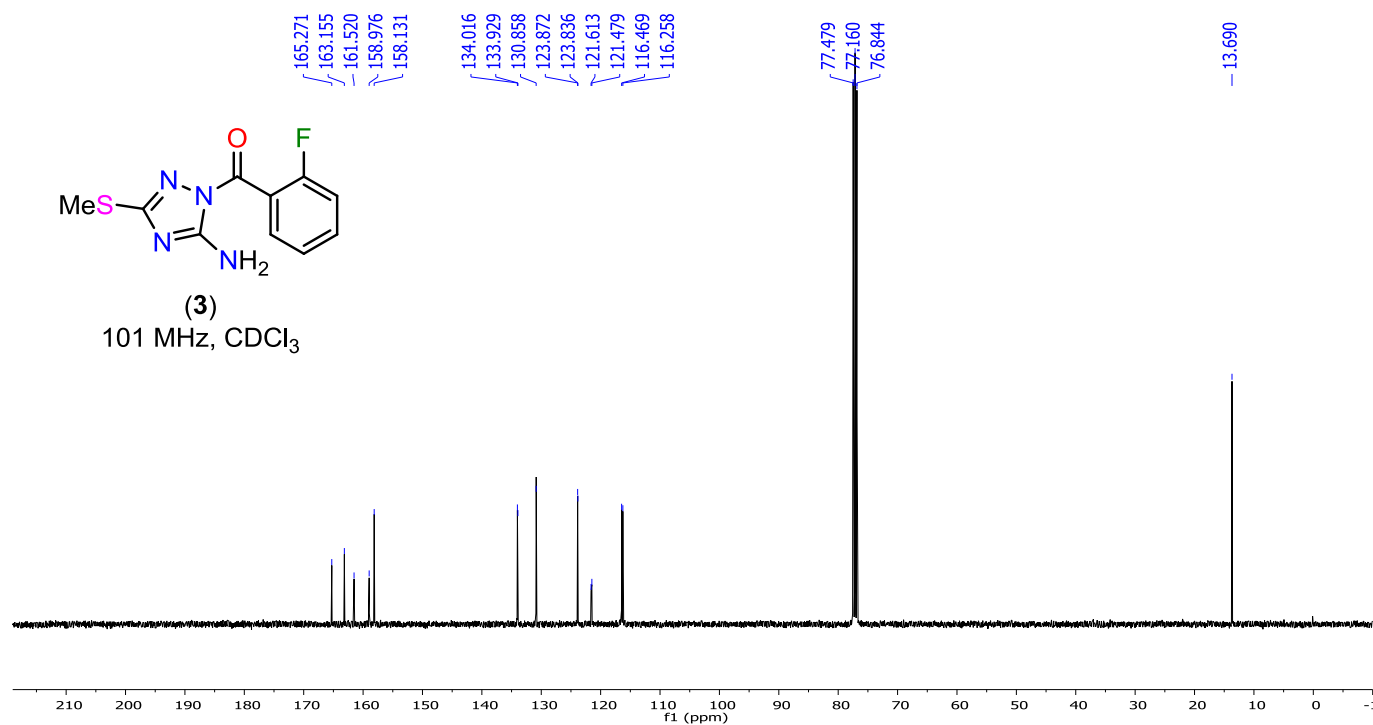
Figure S3. ^{13}C NMR and DEPT-135 spectra of compound (**3**).

2. Copies of ^{1}H, ^{13}C, DEPT-135 and ^{19}F NMR spectra of compound (3)

Figure S4. ^{19}F NMR spectrum of compound (**3**).

3. Copy of the IR spectrum of compound (3)

Figure S5. IR spectrum of compound (**3**).

4. Copy of the HRMS spectrum of compound (4)

Fragmentor Voltage   180   Collision Energy   0   Ionization Mode   ESI

+ESI TIC Scan Frag=180.0V

(4)
$C_{10}H_{10}FN_4OS^+$
Calcd. for $[M + H]^+$: 253.0559

Counts (%) vs. Acquisition Time (min)

Fragmentor Voltage   Collision Energy   Ionization Mode
       180   0   ESI

+ESI Scan (0.531 min) Frag=180.0V

253.0577

123.0256

374.1070

Counts vs. Mass-to-Charge (m/z)
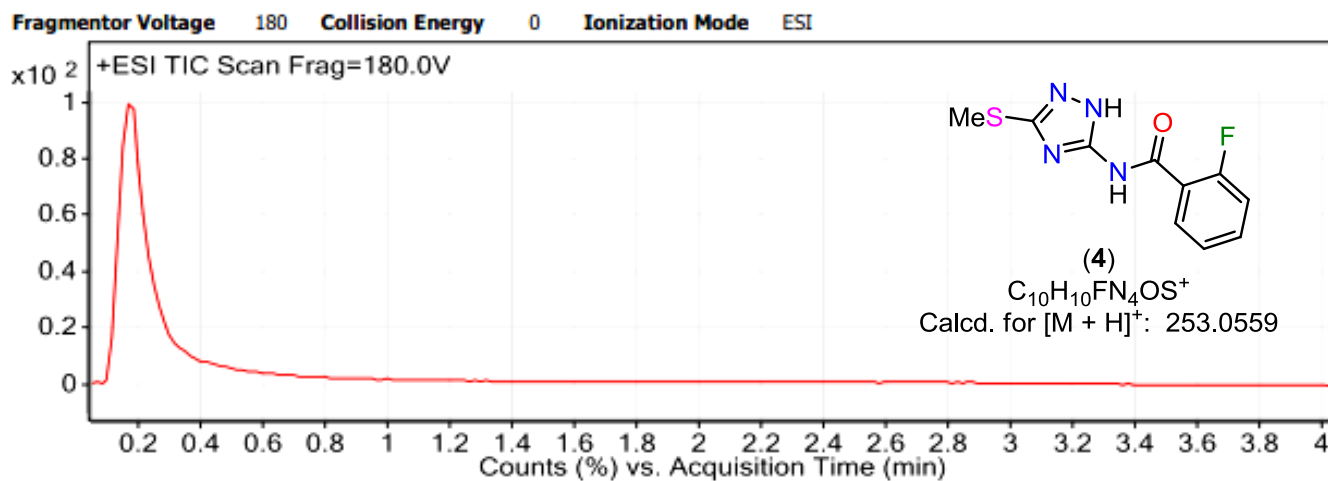
Peak List

m/z	z	Abund
123.0256		296426.1
253.0577		539248.6
374.107		46850.6

Figure S6. HRMS spectrum of compound (**4**).

5. Copies of ^{1}H, ^{13}C, DEPT-135 and ^{19}F NMR spectra for compound (4)
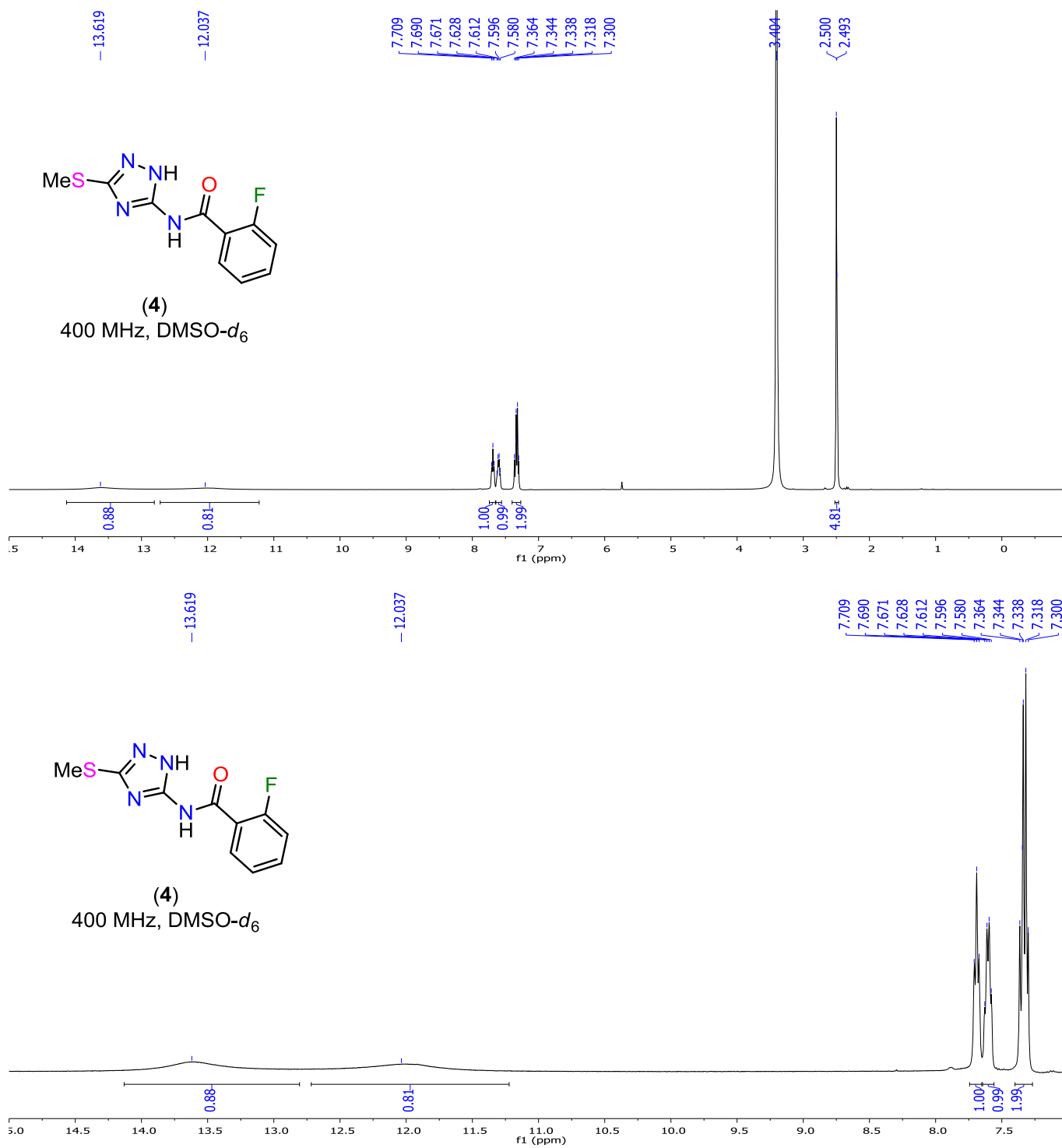
Figure S7. ^{1}H NMR spectrum of compound (**4**).

5. Copies of ¹H, ¹³C, DEPT-135 and ¹⁹F NMR spectra of compound (4)
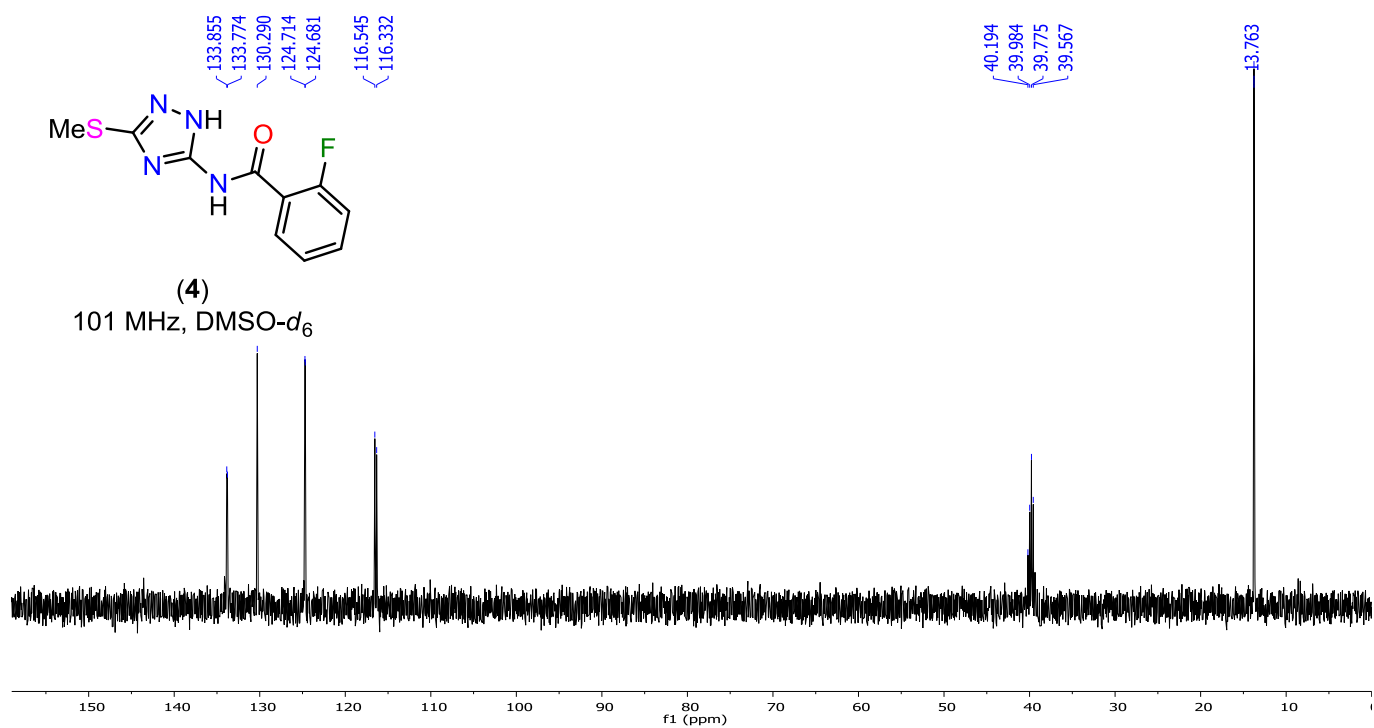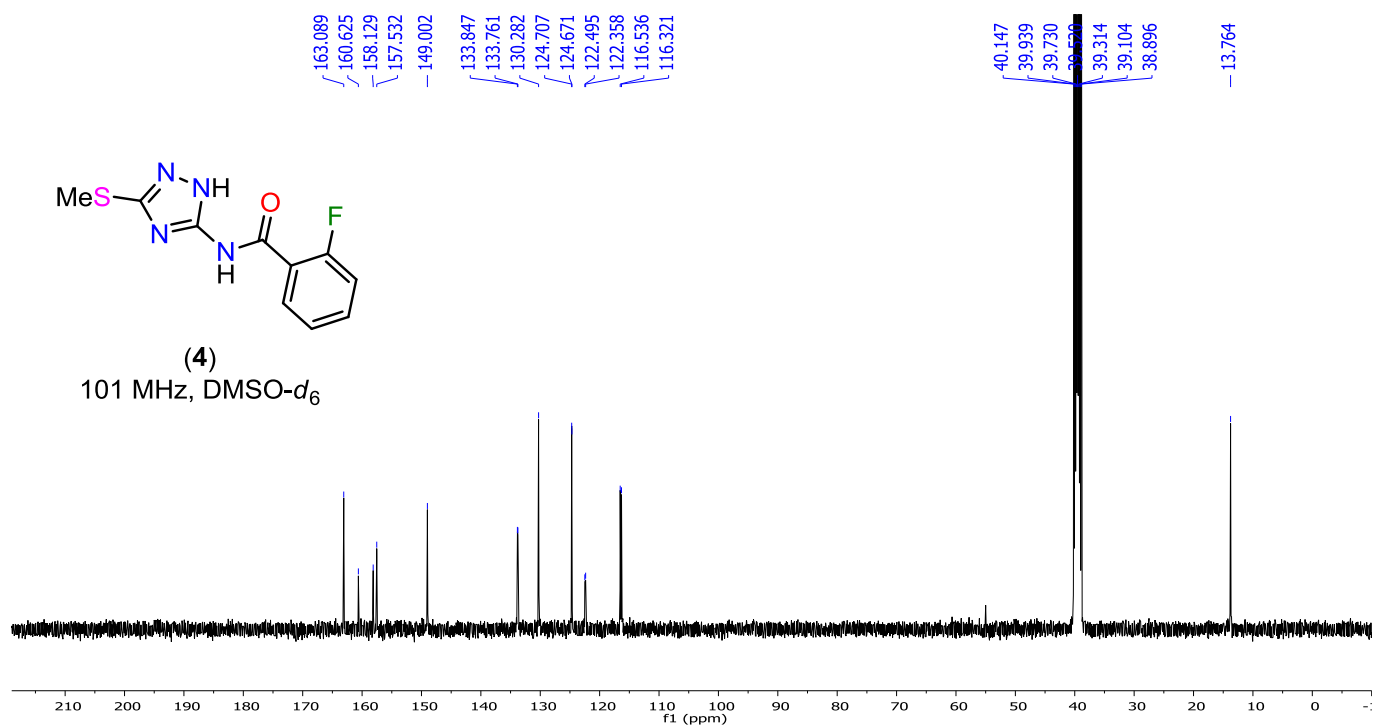
Figure S8. ¹³C NMR and DEPT-135 spectra of compound (**4**).

5. Copies of ^{1}H, ^{13}C, DEPT-135 and ^{19}F NMR spectra of compound (4)
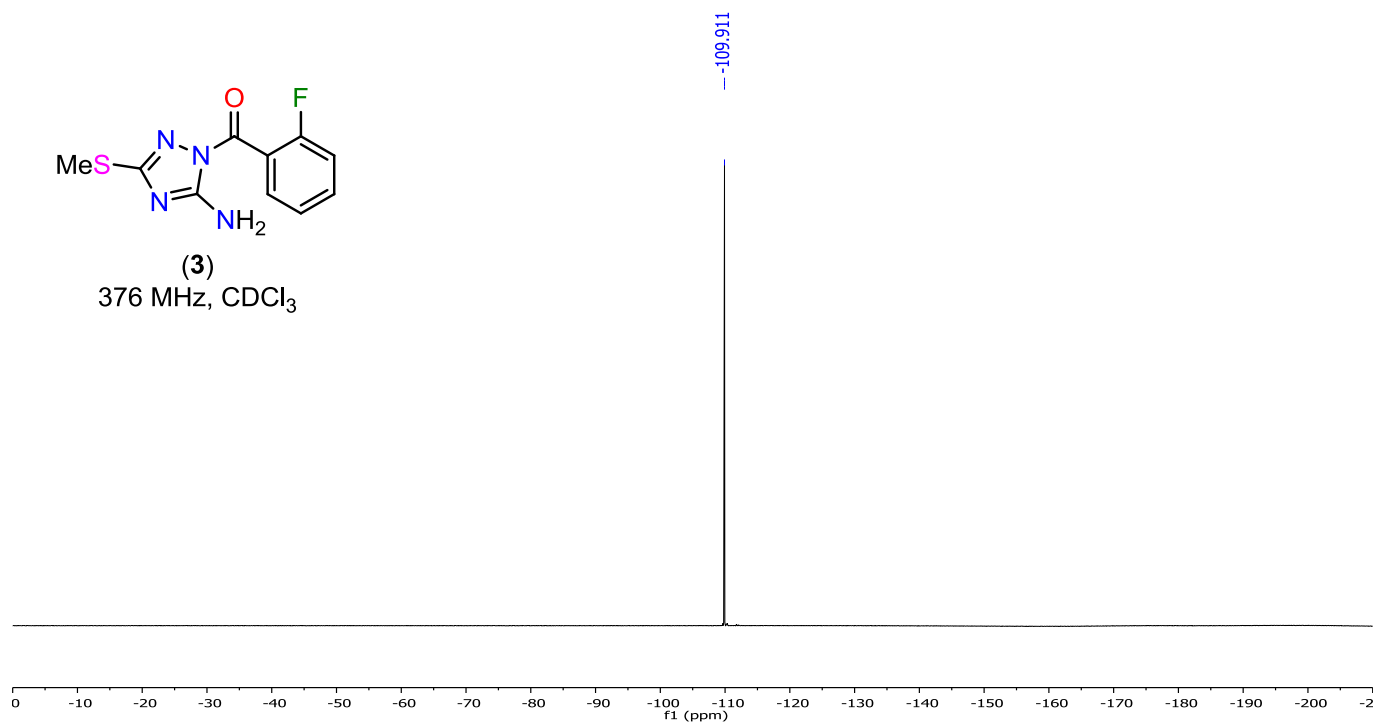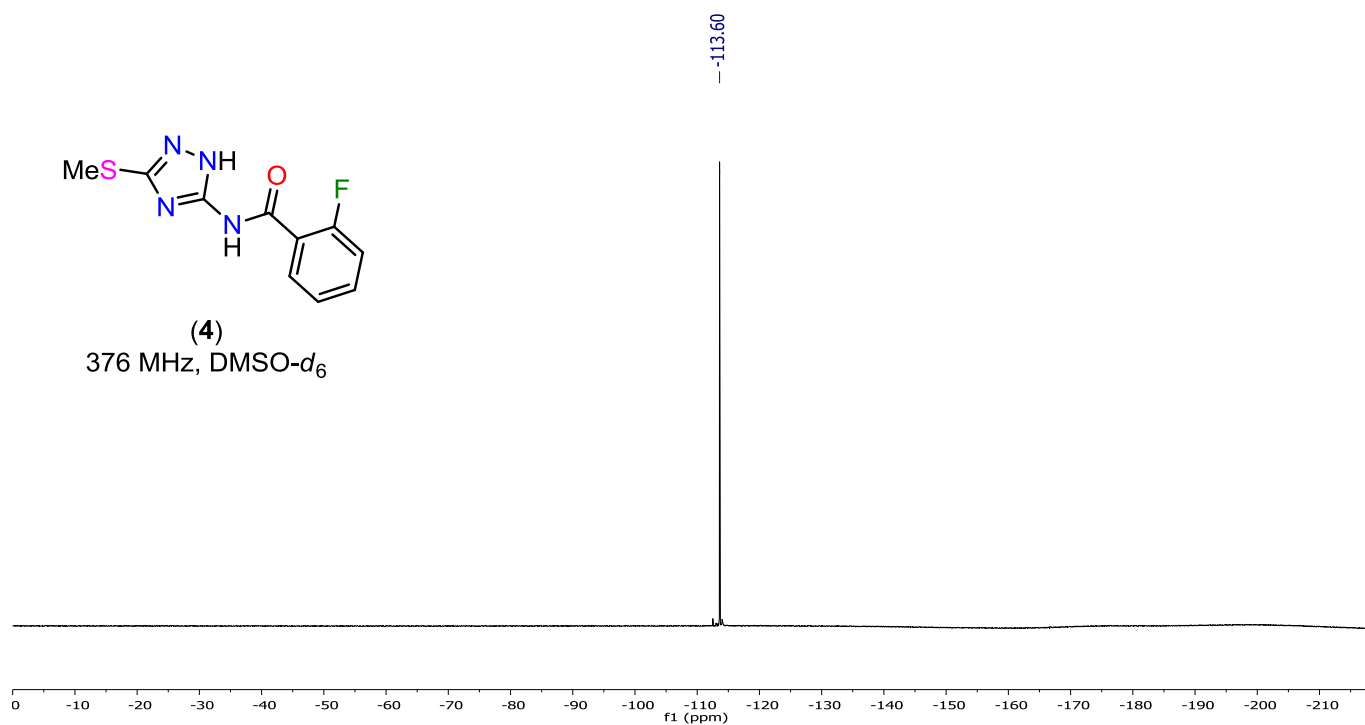

Figure S9. ^{19}F NMR spectrum of compound (**4**).
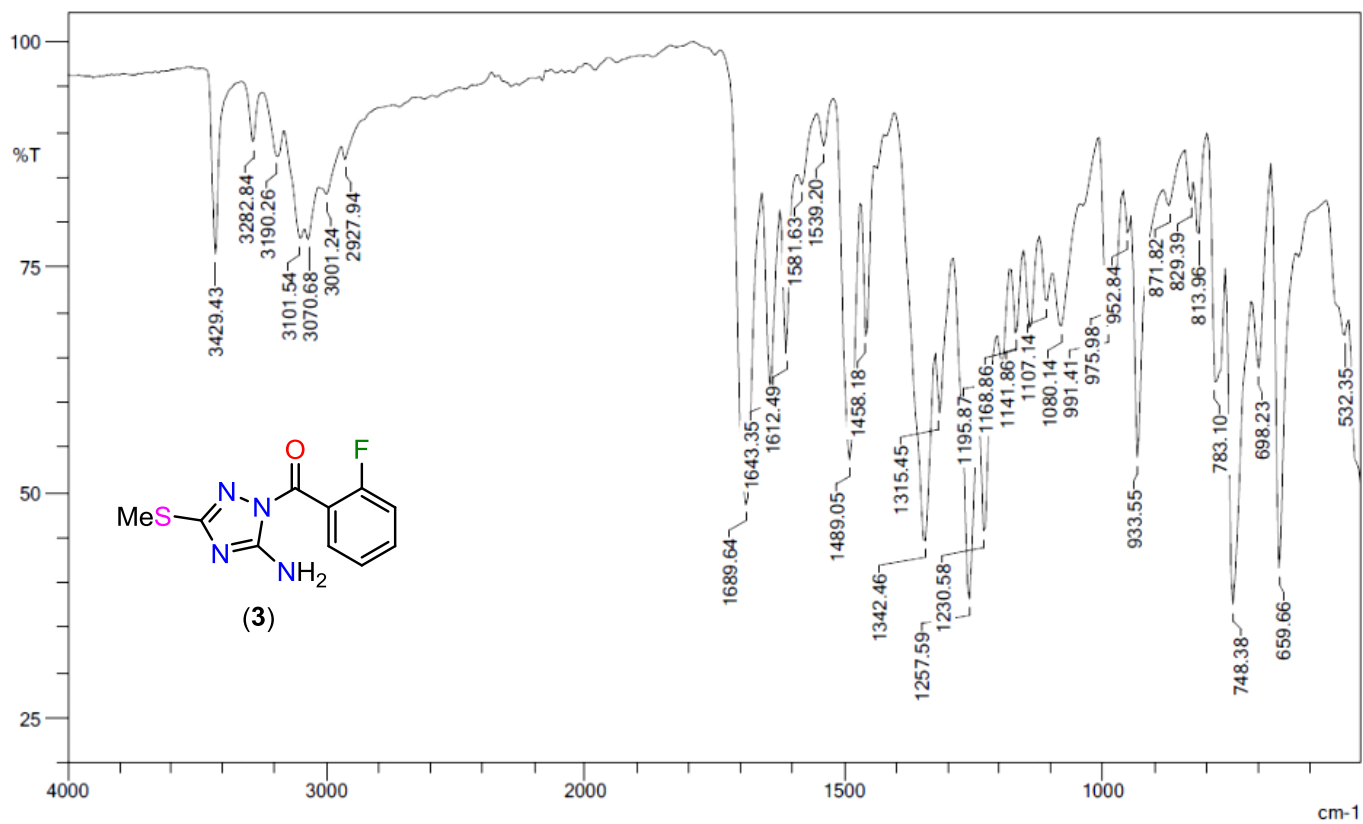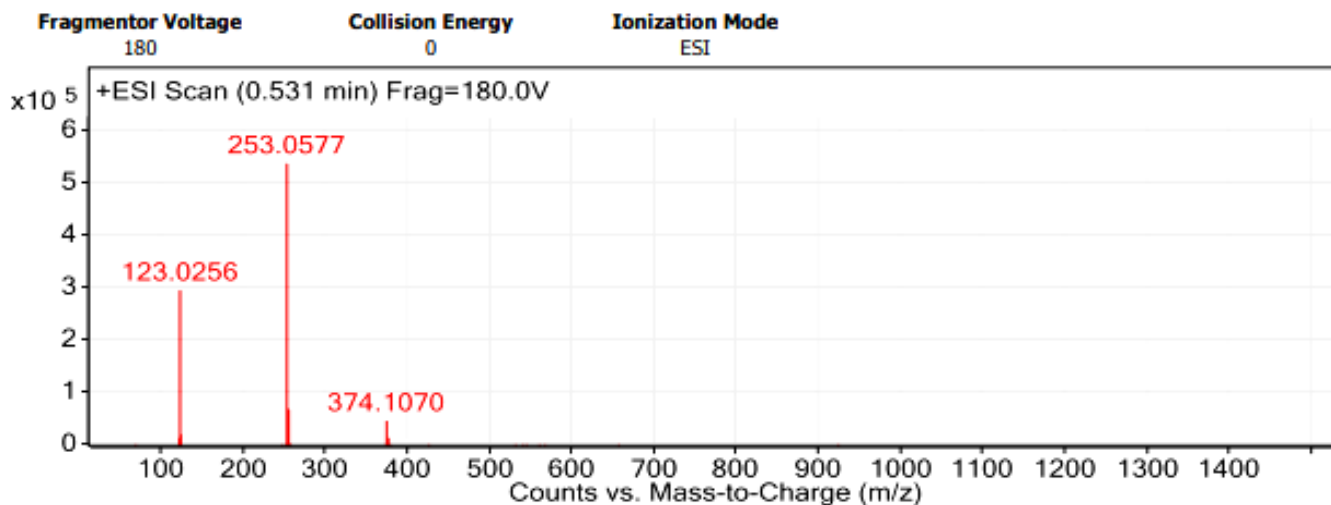
6. Copy of the IR spectrum of compound (4)
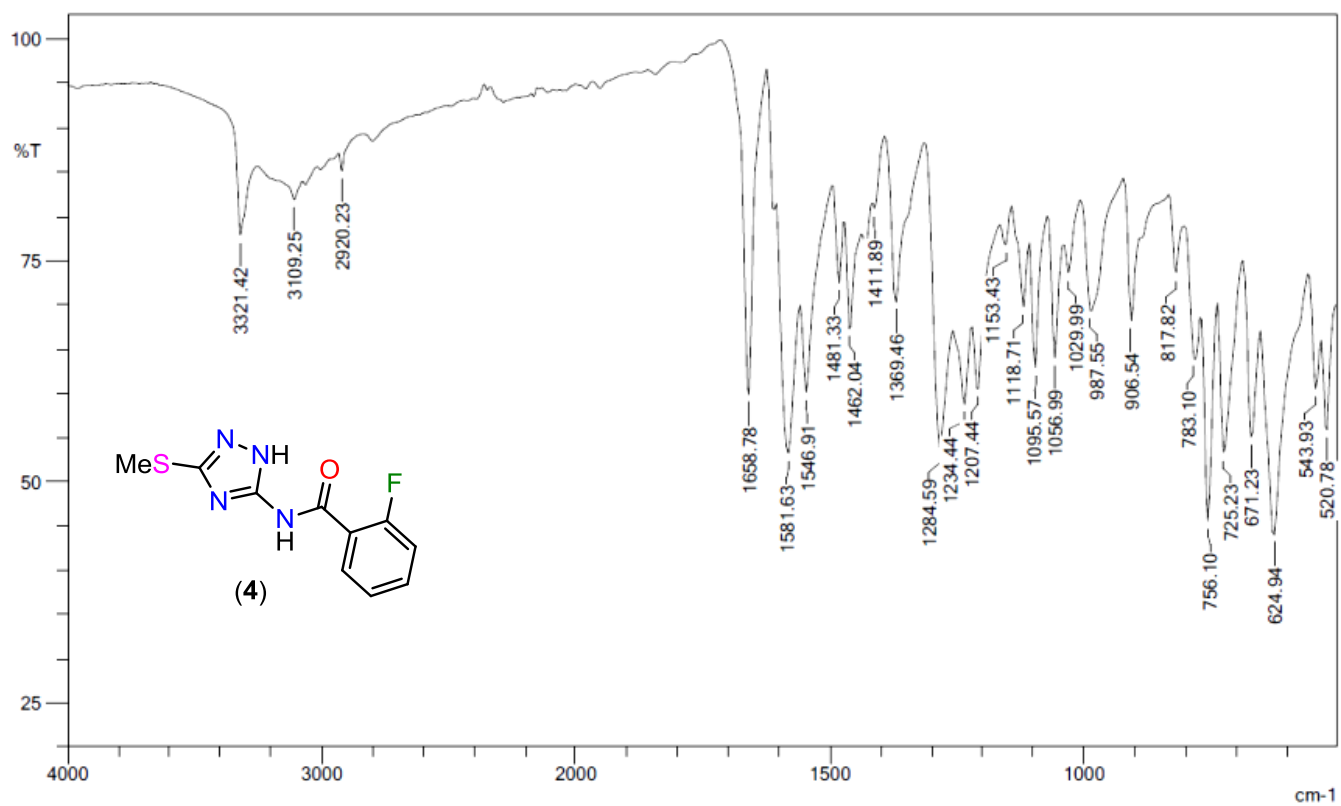
Figure S10. IR spectrum of compound (**4**).

7. Copy of the UV-Vis absorption spectra of compounds (3) and (4)
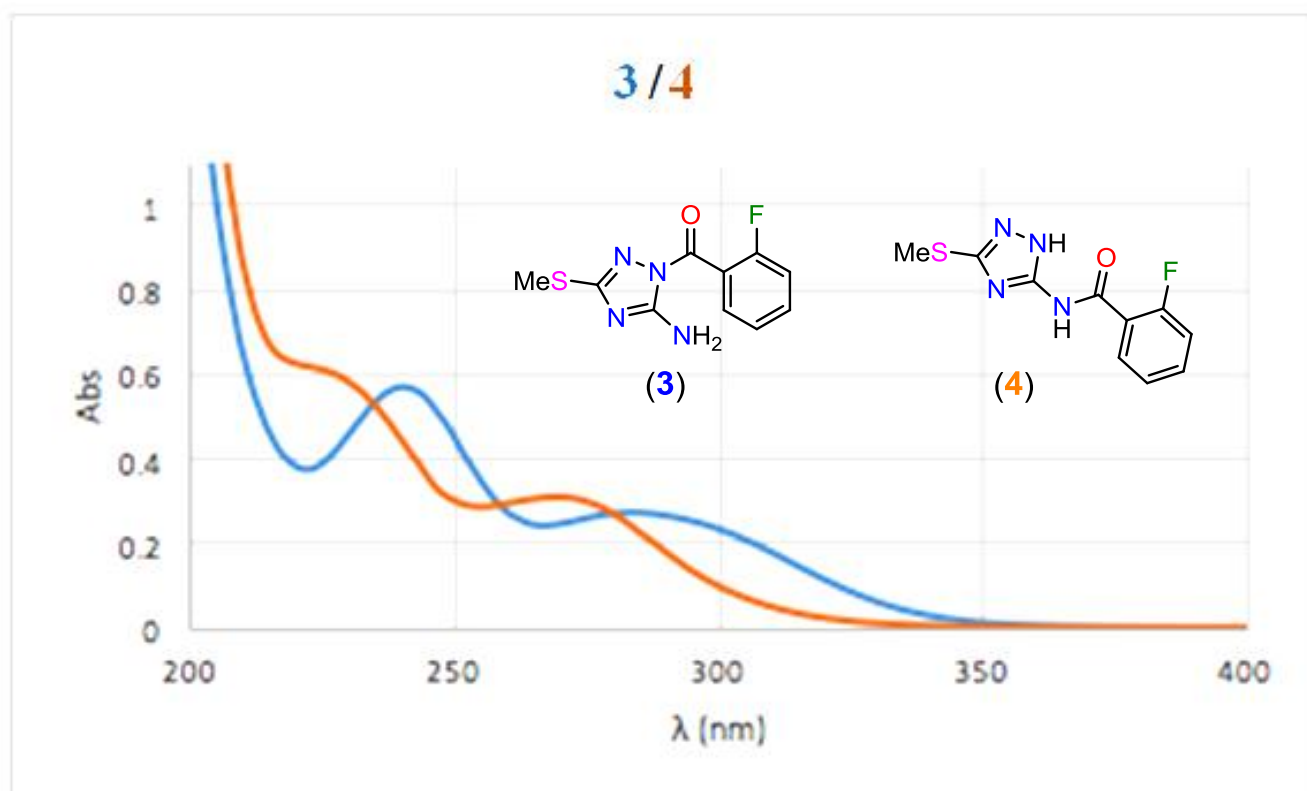
Figure S11. UV-Vis absorption spectra of compounds (**3**) and (**4**).

8. Theoretical computational study and selected computed structural parameters

The relative energy of tautomers **T1**, **T2**, **T3** and **T4**, and transition states **TS₁₂**, **TS₂₃** and **TS₃₄** were computed at the B3LYP/6-311++G(d, p) in gas phase.
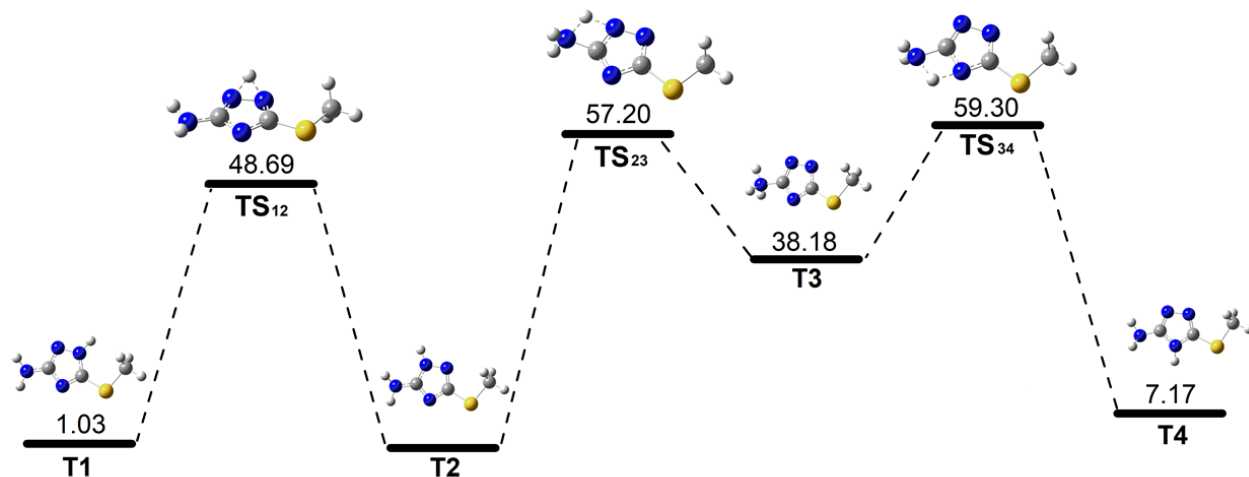
Figure S12. Theoretical study of the prototropy process in amino-1,2,4-triazole (**1**). Energy profile computed at the B3LYP/6-311++G(d,p). Energy values are in $Kcal \cdot mol^{-1}$.

Tautomer T1

```
#   opt   freq   ub3lyp/6-311++g(d,p)   nosymm
geom=connectivity

 ------------------------------------------
 Charge =  0 Multiplicity = 1
 N                    -4.9254    0.66695    0.39869
 C                    -4.97712  -0.64496   -0.05419
 N                    -3.66793  -1.17611   -0.29017
 C                    -2.84176  -0.14406    0.01987
 N                    -3.61941   0.94434    0.46597
 N                    -6.15512  -1.34609   -0.35084
 S                    -1.15383  -0.21945   -0.05373
 C                    -0.66025   1.42574    0.25705
 H                    -3.31982   1.88018    0.60853
 H                    -6.92532  -1.07491    0.22406
 H                    -6.02057  -2.33546   -0.37839
 H                    -0.92049   1.7746     1.28188
 H                     0.45356   1.41378    0.16197
 H                    -1.06773   2.15348   -0.48044


 Sum of electronic and zero point energies= -735.24032434
 0 imaginary frequency
```
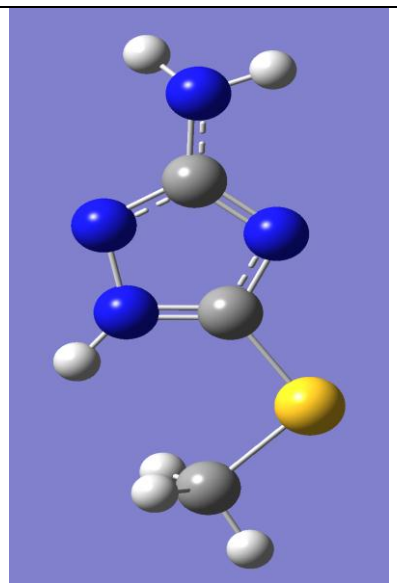
Tautomer T2

```
#  opt  freq  ub3lyp/6-311++g(d,p)  nosymm
geom=connectivity
 ------------------------------------------
 Charge =  0 Multiplicity = 1
 N                     1.97399   0.72636   0.64389
 C                     1.85088  -0.6592    0.3451
 N                     3.06955  -1.11431  -0.09618
 C                     3.88683   0.03485  -0.06287
 N                     3.21419   1.14427   0.39122
 N                     0.6261   -1.35245   0.42751
 S                     5.50659  -0.039    -0.53588
 C                     6.07439   1.6032   -0.3436
 H                     1.26634   1.3589    0.93131
 H                     0.268    -1.35929   1.3625
 H                     0.70855  -2.28131   0.06084
 H                     5.52328   2.3265   -0.98548
 H                     6.01439   1.95829   0.70955
 H                     7.14464   1.57782  -0.65922

 Sum of electronic and zero point energies= -735.24195916
 0 imaginary frequency
```
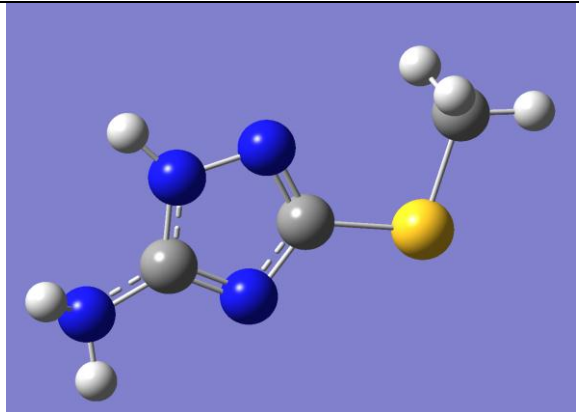

Tautomer T3

```
#  opt  freq  ub3lyp/6-311++g(d,p)  nosymm
geom=connectivity
 ------------------------------------------
 Charge =  0 Multiplicity = 1
 N                     1.79156   0.63357   0.27586
 C                     1.8557   -0.70215   0.17977
 N                     3.06     -1.07741  -0.24144
 C                     3.71945   0.06698  -0.3965
 N                     2.93271   1.1045   -0.07698
 N                     0.75226  -1.62082   0.49501
 S                     5.40601   0.20199  -0.9494
 C                     6.15192   1.6496   -0.23076
 H                    -0.12065  -1.16818   0.31298
 H                     0.79895  -1.87915   1.45994
 H                     5.60673   2.51921  -0.53318
 H                     6.13166   1.56903   0.83601
 H                     7.16575   1.73076  -0.56312
 H                     0.82786  -2.44006  -0.07343

 Sum of electronic and zero point energies= -735.18201706
 0 imaginary frequency
```
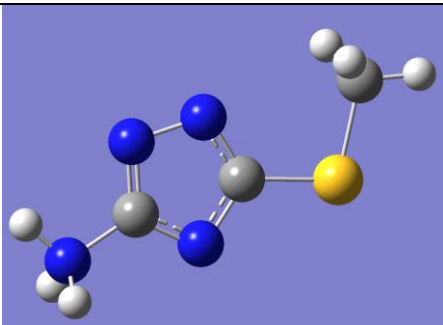
Tautomer T4

```
#  opt  freq  ub3lyp/6-311++g(d,p)  nosymm
geom=connectivity
 ------------------------------------------
 Charge =  0 Multiplicity = 1

 N                    1.76643    0.5379     0.43526
 C                    1.81775   -0.75869    0.38546
 N                    3.2039    -1.20643    0.32612
 C                    3.84492    0.03709   -0.08397
 N                    3.05479    1.04365    0.13688
 N                    0.64621   -1.64658    0.3785
 S                    5.4711     0.15722   -0.79777
 C                    6.19349    1.72613   -0.36754
 H                    3.3573    -1.96838   -0.30309
 H                   -0.12414   -1.1786    -0.05458
 H                    0.40445   -1.88681    1.31863
 H                    5.5792     2.51699   -0.74448
 H                    6.26449    1.80615    0.6971
 H                    7.17102    1.79835   -0.79662


Sum of electronic and zero point energies= -735.23014853
0 imaginary frequency
```
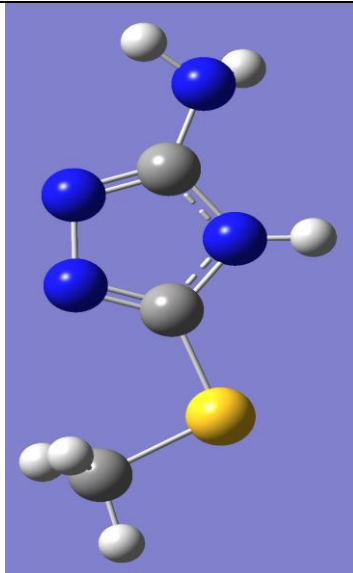
Transition State TS$_{12}$

```
#   opt   freq   ub3lyp/6-311++g(d,p)   nosymm
geom=connectivity
 ------------------------------------------
 Charge =  0 Multiplicity = 1

 N                   -4.96396    0.64343    0.32416
 C                   -4.94975   -0.62155   -0.06546
 N                   -3.71107   -1.14638   -0.30742
 C                   -2.90409   -0.13076   -0.05605
 N                   -3.62202    0.94904    0.31845
 N                   -6.09613   -1.35842   -0.27181
 S                   -1.15639   -0.2422    -0.2101
 C                   -0.65253    1.43758    0.30043
 H                   -3.32048    1.87242    0.57868
 H                   -6.91218   -1.01914    0.21521
 H                   -5.96149   -2.35619   -0.20648
 H                   -0.94002    1.6457     1.33212
 H                    0.43525    1.44727    0.23511
 H                   -1.04634    2.19724   -0.37659


Sum of electronic and zero point energies= -735.15920702
 0 imaginary frequency
```
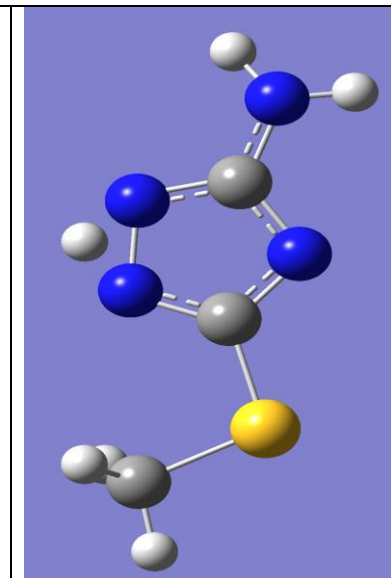
Transition State TS23

```
#   opt   freq   ub3lyp/6-311++g(d,p)   nosymm
geom=connectivity
------------------------------------------
 Charge =  0 Multiplicity = 1

 N                     2.00271    0.66966    0.6674
 C                     1.88338   -0.63355    0.32737
 N                     3.02793   -1.08649   -0.14672
 C                     3.83827    0.01627   -0.08989
 N                     3.2813     1.10997    0.39315
 N                     0.70824   -1.34906    0.41237
 S                     5.51018   -0.09583   -0.62748
 C                     6.05524    1.62073   -0.33239
 H                     1.29869    1.32707    0.96085
 H                     0.13298   -1.16746    1.22265
 H                     0.8473    -2.33631    0.24741
 H                     5.4733     2.31837   -0.93282
 H                     5.96621    1.87709    0.72218
 H                     7.10197    1.65418   -0.63539


Sum of electronic and zero point energies= -735.14613672
 0 imaginary frequency
```
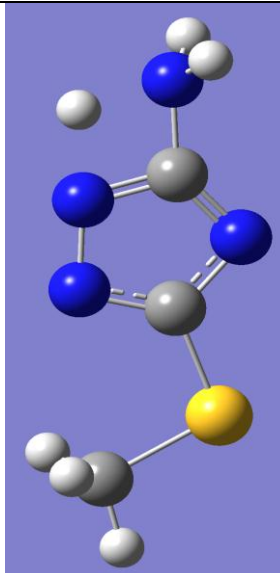
Transition State TS34

```
#   opt   freq   ub3lyp/6-311++g(d,p)   nosymm
geom=connectivity
------------------------------------------
 Charge =  0 Multiplicity = 1

 N                     1.88809    0.65713    0.45554
 C                     1.8446    -0.63332    0.27901
 N                     3.08945   -1.11897   -0.0463
 C                     3.89525    0.00091   -0.07151
 N                     3.20328    1.0653     0.22073
 N                     0.71658   -1.44183    0.31863
 S                     5.61628   -0.10059   -0.4277
 C                     6.02901    1.67678   -0.33843
 H                     3.31773   -2.04806   -0.36388
 H                    -0.10797   -0.88935    0.51984
 H                     0.78479   -2.22311    0.96027
 H                     5.45795    2.233     -1.07894
 H                     5.82064    2.06103    0.65782
 H                     7.09524    1.73906   -0.55519


Sum of electronic and zero point energies= -735.14247997
 0 imaginary frequency
```
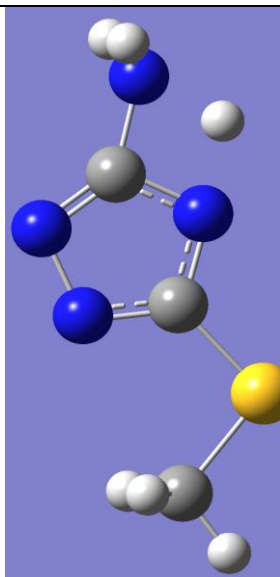
The calculations of the Fries rearrangement of (**3**) to afford (**4**) were computed at the B3LYP/6-31G in gas phase.
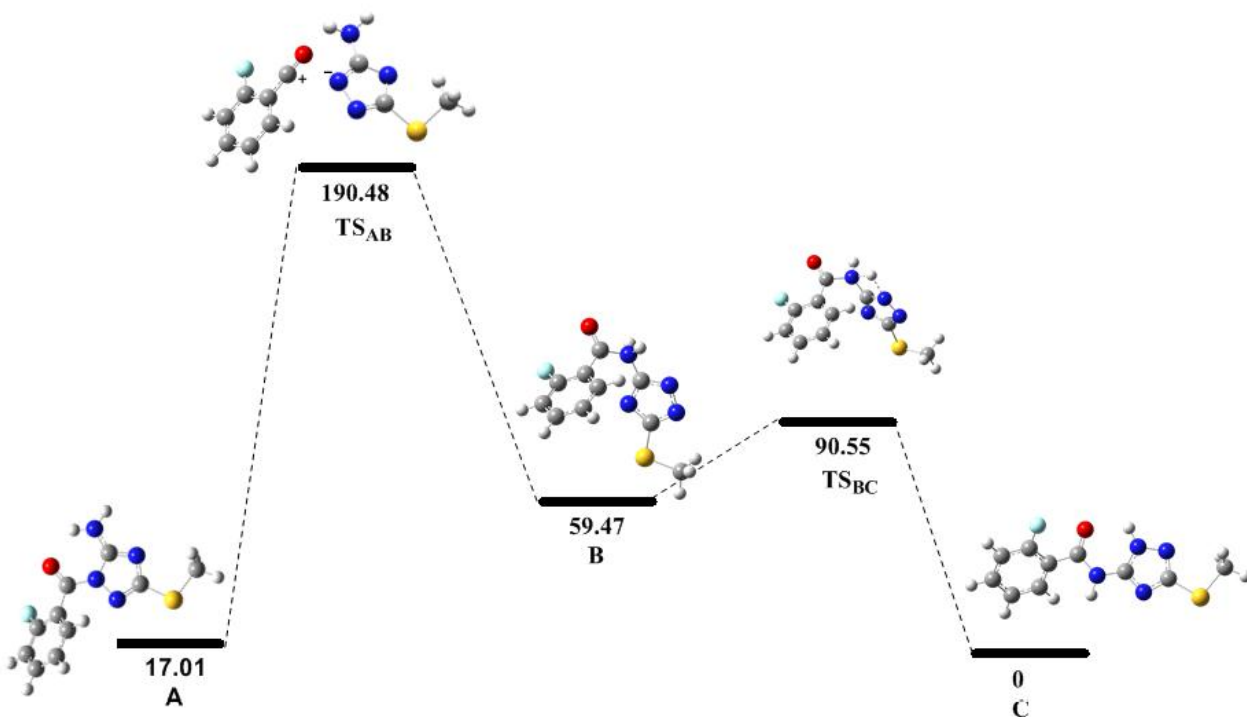
Figure S13. Theoretical study of the Fries rearrangement of (**3**) to afford (**4**) through the formation of an ion-pair as the key step. Energy profile computed at the B3LYP/6-31G in gas phase. Energy values are in Kcal·mol^{-1}.

Tertiary amide A (3)

```
#     opt     freq     ub3lyp/6-31g     nosymm
geom=connectivity
------------------------------------------
 Charge =   0 Multiplicity = 1

 C                    -2.84459    0.24598    0.49837

 C                    -0.83155   -0.54347    0.22812

 N                    -0.77296    0.64821    1.08867

 N                    -2.07722    1.16909    0.99128

 N                     0.34245   -1.24218   -0.31449

 N                    -2.05193   -0.88306    0.00667

 S                    -4.62012    0.34413    0.41918

 C                    -5.2024    -0.5688    -0.99359

 H                    -6.26971   -0.5098    -1.04119

 H                    -4.78206   -0.15256   -1.88519

 H                    -4.90546   -1.59283   -0.90362

 H                     0.12811   -2.21175   -0.43277

 H                     1.11019   -1.14538    0.31892

 C                     0.2584     1.60256    0.65689

 O                     1.3147     1.18508    0.11512

 C                     0.04619    3.11325    0.86757

 C                    -1.13014    3.57816    1.4709

 C                     1.02942    4.02306    0.45594

 C                    -1.32325    4.95289    1.66262

 C                     0.83631    5.39779    0.64765

 H                     1.92757    3.66809   -0.00472

 C                    -0.34003    5.8627     1.25099

 H                    -2.22141    5.30787    2.12328

 H                     1.58702    6.09245    0.33337

 H                    -0.48747    6.91234    1.39737

 F                    -2.0773     2.70172    1.86743
```
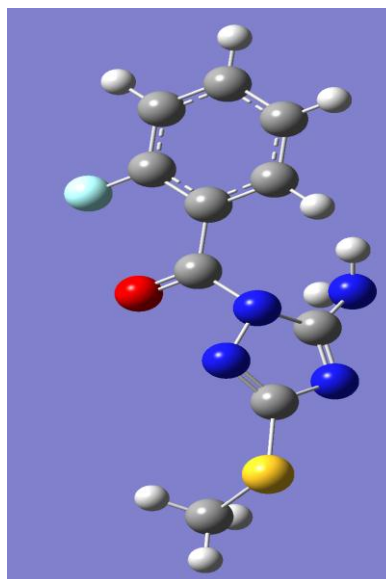
Sum of electronic and zero point energies= -1178.45522907 0 imaginary frequency	

Acylium carbocation

`#    opt    freq    ub3lyp/6-31g    nosymm geom=connectivity`
`----------------------------------------`
` Charge =  1 Multiplicity = 1`
 	
` C                   0.22288  -0.64636   0.`
 	
` C                   1.61804  -0.64636   0.`
 	
` C                   2.31558   0.56139   0.`
 	
` C                   1.61793   1.7699   -0.0012`
 	
` C                   0.2231    1.76982  -0.00168`
 	
` C                  -0.4745    0.56162  -0.00068`
 	
` H                  -0.32688  -1.59868   0.00045`
 	
` H                   2.16755  -1.59887   0.00132`
 	
` H                  -0.32702   2.7221   -0.00263`
 	
` H                  -1.5741    0.5618   -0.00086`
 	
` C                   3.85558   0.5615    0.00089`
 	
` F                   2.29337   2.93878  -0.00127`
 	
` O                   4.33177   1.72076   0.68956`
 	
`Sum of electronic and zero point energies= -443.79425784`
 	
`0 imaginary frequency`	
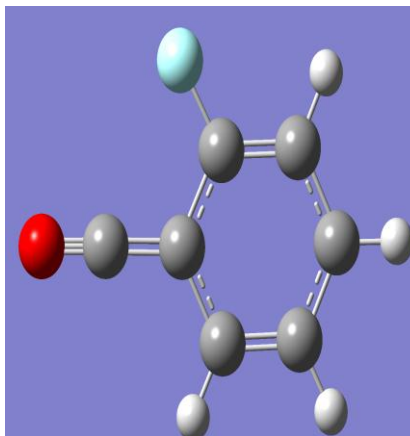
1,2,4-Triazole anion

```
#      opt     freq    ub3lyp/6-31g    nosymm
geom=connectivity
-------------------------------------------
 Charge =  -1 Multiplicity = 1

 C                   1.58742  -1.16343  -0.00166

 C                   0.73994   0.81182   0.33069

 N                  -0.27461  -0.22494   0.41524

 N                   0.30689  -1.30988  -0.23196

 N                   0.50058   2.25204   0.15926

 H                   1.24378   2.76668   0.5868

 H                   0.4623    2.46982  -0.81599

 N                   1.88896   0.23598   0.40074

 S                   2.80188  -2.45399  -0.16885

 C                   2.97717  -3.30841   1.38281

 H                   2.0374   -3.73702   1.66211

 H                   3.70721  -4.08419   1.2823

 H                   3.29229  -2.61762   2.13674

Sum of electronic and zero point energies= -734.38452441

0 imaginary frequency
```
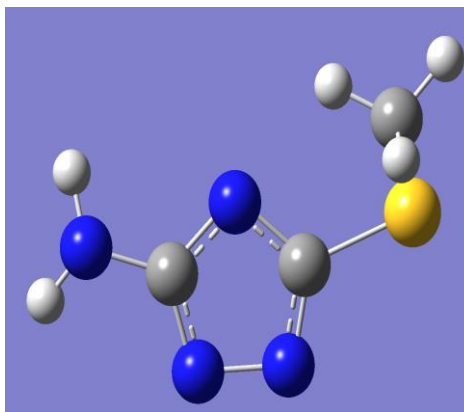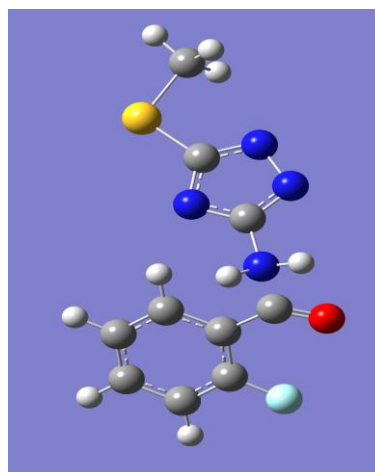
Transition State TS_AB

```
#      opt     freq     ub3lyp/6-31g     nosymm
geom=connectivity
-------------------------------------------
 Charge =   0 Multiplicity = 1

 C                  -0.22537  -0.25171   0.27088

 C                   1.11671  -0.56638   0.52337

 C                   2.12009   0.37291   0.24974

 C                   1.7814    1.62687  -0.27638

 C                   0.43933   1.94154  -0.52887

 C                  -0.56405   1.00224  -0.25524
```
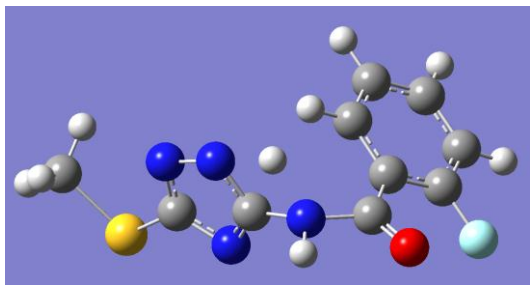
H	-0.99147	-0.96888	0.47981
H	1.3753	-1.52381	0.92507
H	0.18074	2.89896	-0.93057
H	-1.58875	1.2425	-0.44802
C	3.5949	0.02712	0.52719
F	2.74799	2.5317	-0.53998
O	4.16964	0.31843	1.80379
N	4.41184	-0.60242	-0.52027
H	4.85527	0.10673	-1.06843
H	3.82709	-1.16131	-1.10824
C	6.33577	-2.88595	1.46904
C	5.43654	-1.45284	0.10237
N	6.76732	-1.037	0.51154
N	5.30629	-2.6951	0.41311
N	7.00511	-1.77775	1.66429
S	6.60517	-4.40356	2.35938
C	8.31631	-4.5157	2.83669
H	8.56699	-3.6853	3.46319
H	8.47825	-5.42796	3.37189
H	8.93229	-4.50123	1.9619

Sum of electronic and zero point energies= -1178.38730290

0 imaginary frequency

Transition State TS_BC

```
#     opt    freq    ub3lyp/6-31g    nosymm
geom=connectivity
------------------------------------------
 Charge =  0 Multiplicity = 1

 C                 -2.51601  -0.21992  -0.23569
 C                 -0.81106  -1.27844   0.27994
 N                 -1.44976  -1.05237   1.47288
 N                 -2.5989   -0.33247   1.10492
 N                 -1.40315  -0.80089  -0.80882
 N                  0.40196  -2.01859   0.45876
```

```
S              -3.75269    0.63688   -1.24216
C              -4.97872    1.09478    0.12173
H              -5.7909     1.61951   -0.38252
H              -5.33986    0.1889     0.60652
H              -4.49076    1.73837    0.85215
H               0.35938   -3.01004    0.20738
C               1.75537   -1.5425     0.11715
O               2.5522    -2.42504   -0.21058
C               2.04904   -0.10489    0.21206
C               3.09692    0.44691   -0.55065
C               1.35768    0.76548    1.08341
C               3.45179    1.78726   -0.47299
C               1.71032    2.11061    1.1824
H               0.54269    0.39089    1.68846
C               2.7552     2.62363    0.403
H               4.25804    2.15298   -1.09604
H               1.16746    2.75683    1.86201
H               3.0257     3.67138    0.47306
F               3.79608   -0.34398   -1.44207
H              -0.14517   -1.87003    1.8906

Sum  of  electronic  and  zero  point  energies=  -
1178.33802688
0 imaginary frequency
```

Secondary amide C (4)

```
#     opt     freq     ub3lyp/6-31g     nosymm
geom=connectivity
------------------------------------------
 Charge =  0 Multiplicity = 1

 C              -0.15508   -0.54483   -0.77796
 C               1.22258   -0.73487   -0.6052
 C               2.01085    0.29503   -0.0743
 C               1.42145    1.51497    0.28385
 C               0.04379    1.70501    0.11109
 C              -0.74448    0.67511   -0.41981
 H              -0.75694   -1.33119   -1.18332
 H               1.6726    -1.66633   -0.87866
 H              -0.40623    2.63647    0.38455
 H              -1.79636    0.82021   -0.55172
 C               3.52477    0.08619    0.11554
 F               2.1808     2.5071     0.79529
 O               4.2326     1.011      0.59227
 N               4.14302   -1.19347   -0.26013
 H               3.47735   -1.93113   -0.14724
 C               6.66667   -2.33154    2.05557
 C               5.30651   -1.44724    0.60171
 N               6.68178   -1.02116    0.29797
 N               5.26378   -2.08201    1.71917
 N               7.45356   -1.8301     1.154
 S               7.21771   -3.21434    3.49967
 C               8.75426   -4.03823    3.14103
 H               9.49103   -3.31376    2.86314
 H               9.08551   -4.5689     4.00911
 H               8.6099    -4.72728    2.33526
 H               6.91451   -1.14326   -0.66687

Sum of electronic and zero point energies= -1178.48233990,
 Imaginary Freq 0
```
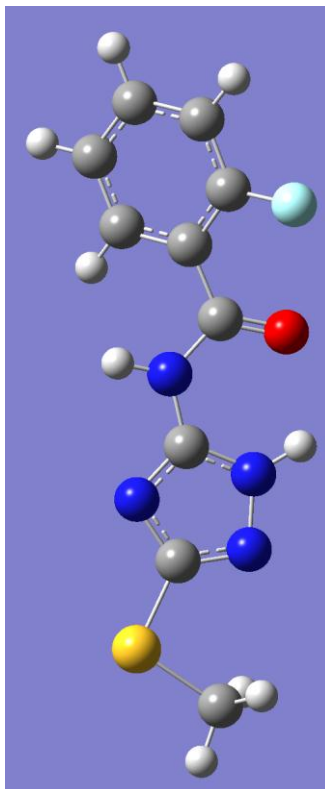
9. Two-dimensional fingerprints plots of compounds (3) and (4) showing contributions from different contacts
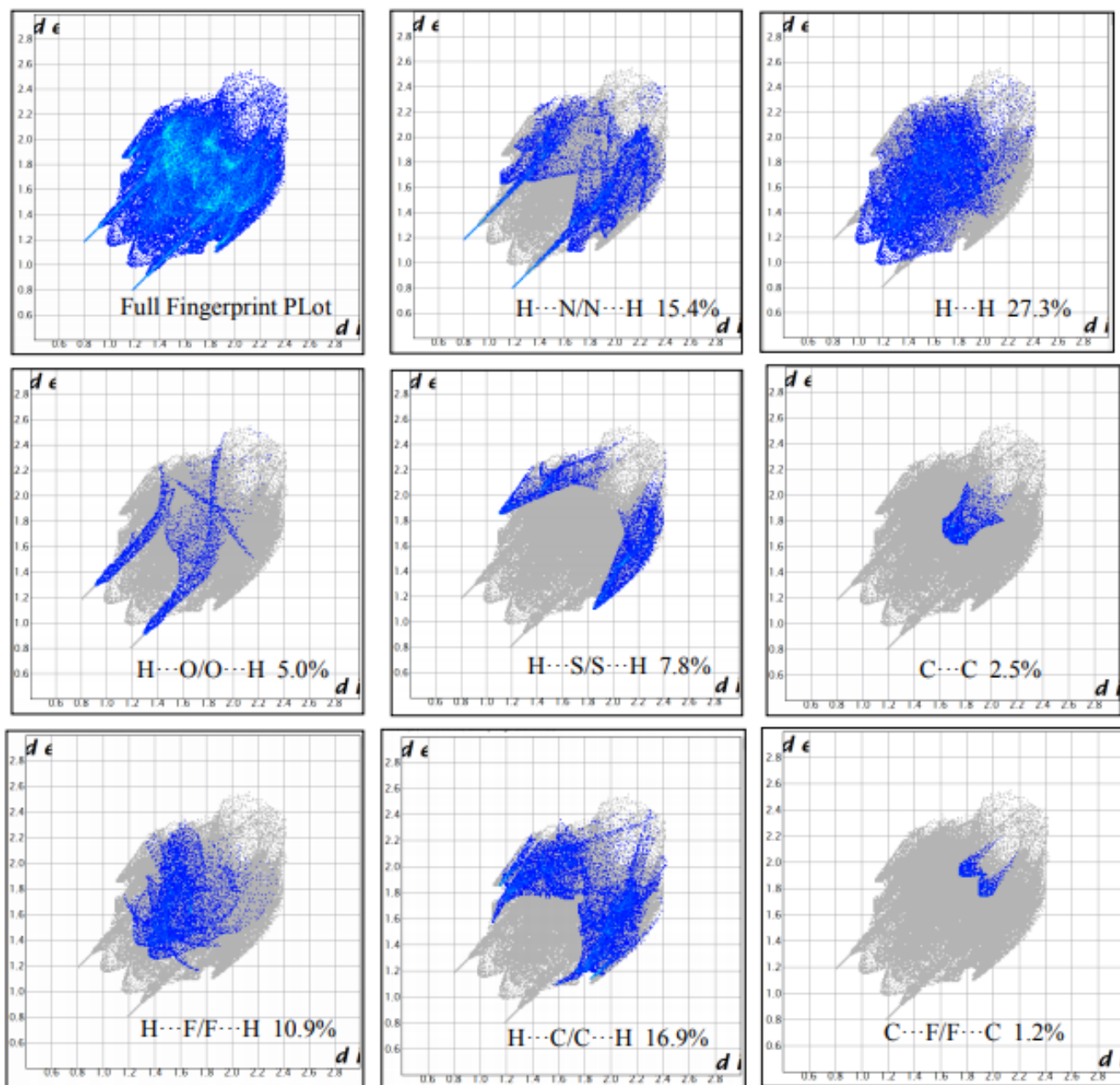

Figure S14. Two-dimensional fingerprints plots for the tertiary amide (**3**) showing contributions from different contacts.
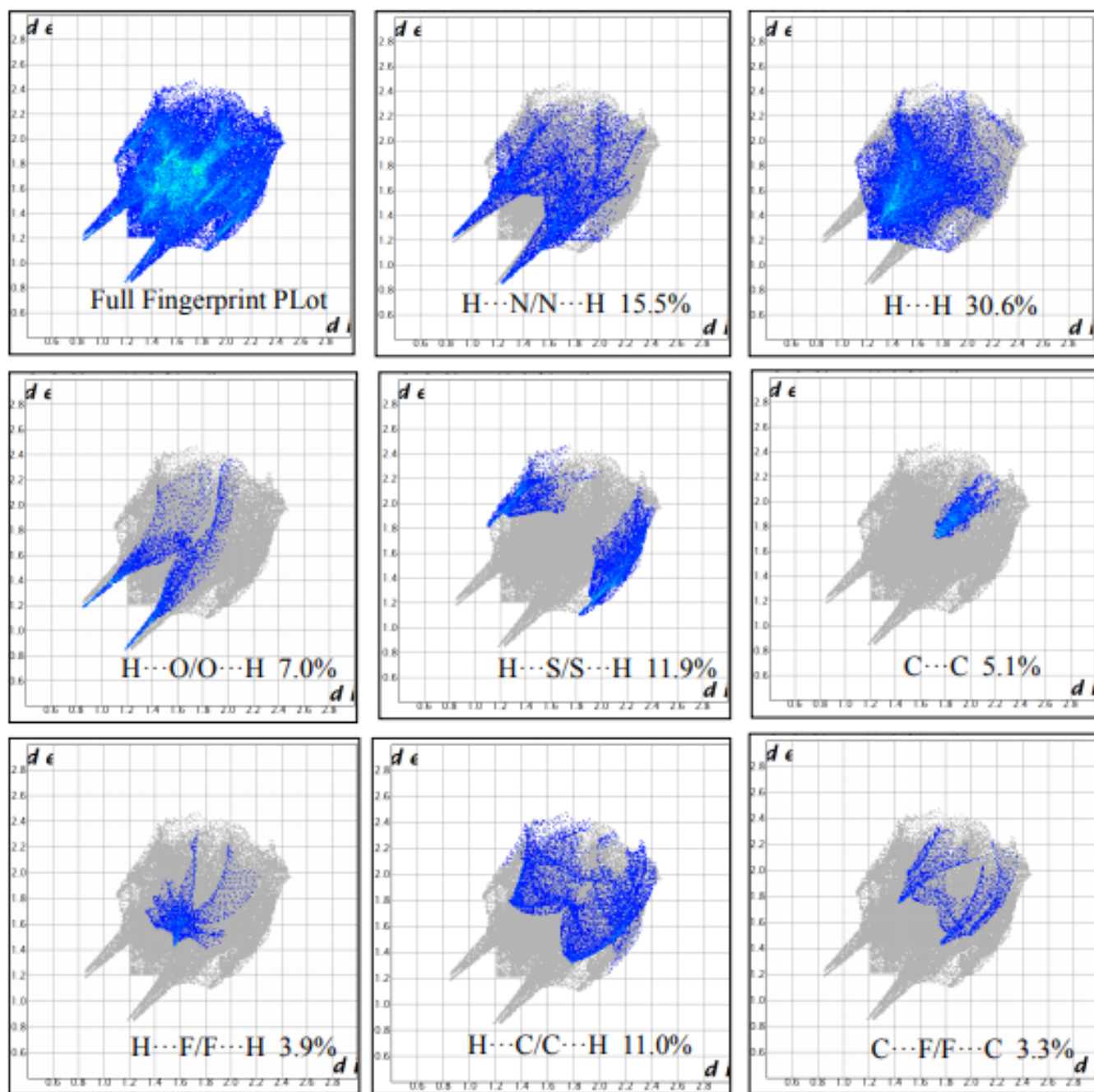
Figure S15. Two-dimensional fingerprints plots for the secondary amide (**4**) showing contributions from different contacts.