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Electronic Supporting Information (ESI)

Discovery of 4-acetyl-3-(4-fluorophenyl)-1-(p-tolyl)-5-methylpyrrole as a dual inhibitor of human P-glycoprotein and *Staphylococcus aureus* Nor A efflux pump¤

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S1. General procedure for synthesis of pyrroles 5a-q.

To the stirred solution of aniline (**2a**, 0.132 g, 1.42 mmol), benzaldehyde (**3a**, 0.1 g, 0.94 mmol), and acetylacetone (**4a**, 0.094 g, 0.94 mmol) in nitromethane (**5a**, 1.1 ml, 20 mmol) was added 10 mol% montmorillonite clay K10 or clay KSF catalyst. The mixture was refluxed for 5-8 h and then cooled to room temperature. The excess solvent was removed under vacuum, and the residue was purified by silica gel (#100-200) column chromatography using EtOAc: n-hexane (95:5) to get pyrroles **7a-q** in 68-88% yield. Pyrroles **1a-1d** and **1m** were characterized by comparison of their spectral data with literature values.[1]

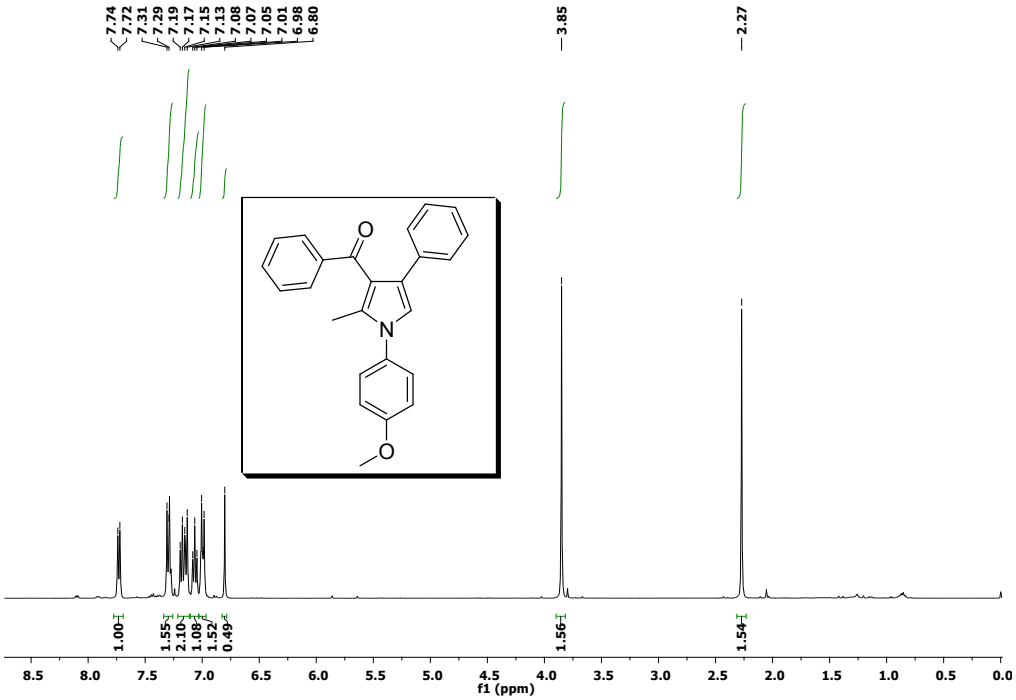
S2. Spectral data of representative compounds:

1-(4-(4-Fluorophenyl)-2-methyl-1-p-tolyl-1H-pyrrol-3-yl)ethanone (5i): Yellow Solid; m.p. 109-110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.06 (t, J = 8.0 Hz, 2H), 6.61 (s, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.2, 163.1 (d, $^{1}J_{CF}$ = 230 Hz), 138.2, 136.1, 135.6, 132.1, 130.8, 130.0, 126.1, 125.1, 122.4, 120.8, 115.3 (d, $^{2}J_{CF}$ = 53.8 Hz), 31.1, 21.1, 13.0; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -116.0, -116.0 (m, 1F); IR ($CHCl_3$): ν_{max} 2918, 1650, 1553, 1418, 1384, 1275, 1220, 1041 cm^{-1}; ESI-MS: *m/z* 308.00 $[M+H]^+$; HR-ESIMS: *m/z* 308.1449 calcd for $C_{20}H_{18}FNO+H^+$ (308.1445).

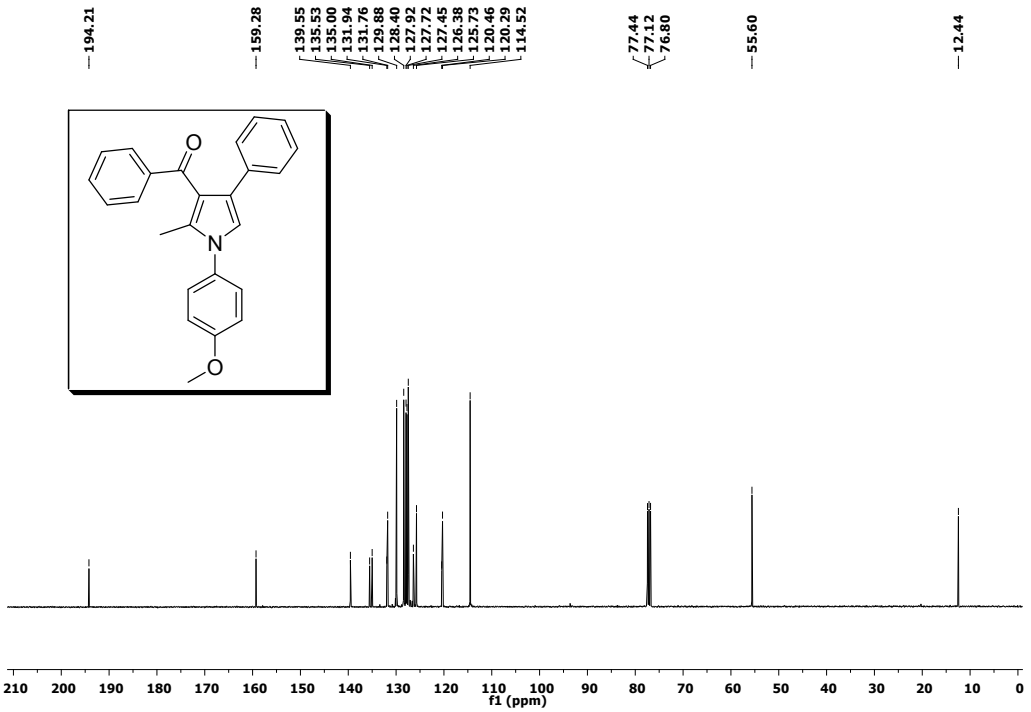
(1-(4-Methoxyphenyl)-2-methyl-4-phenyl-1H-pyrrol-3-yl)(phenyl)methanone (5q): Brown sticky solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 3H), 7.19-7.13 (m, 4H), 7.07 (t, J = 8.0 Hz, 2H), 7.01 (d, J = 12.0 Hz, 3H), 6.80 (s, 1H), 3.85 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 194.2, 159.3, 157.9, 139.6, 135.5, 135.0, 131.9, 131.8, 129.9, 128.4, 127.9, 127.7, 127.5, 126.4, 125.7, 120.5, 120.3, 114.5, 55.6, 12.5; IR ($CHCl_3$): ν_{max} 2905, 1720, 1616, 1601, 1574, 1320, 1251 cm^{-1}; ESI-MS: *m/z* 368.00 $[M+H]^+$; HR-ESIMS: *m/z* 368.1648 calcd for $C_{25}H_{21}NO_2+H^+$ (368.1645).

S3. ^{1}H, ^{13}C, DEPT135 and HMBC NMR spectra scans of compound 5q

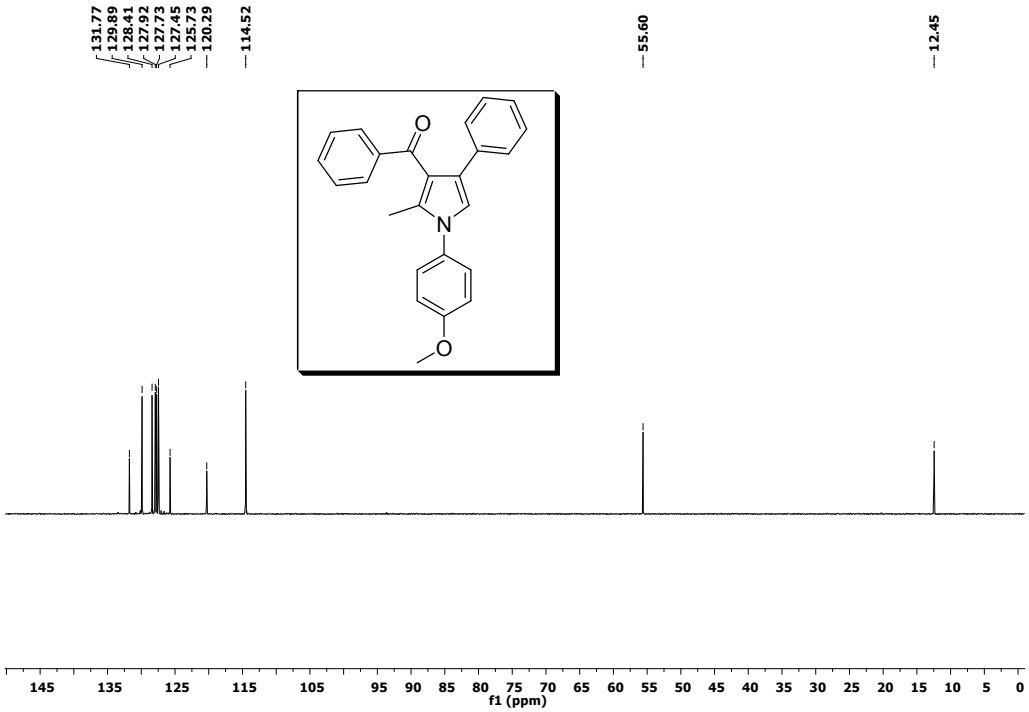
^{1}H NMR



^{13}C NMR



DEPT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128.41
127.92
127.73
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55.60
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O
N
O
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
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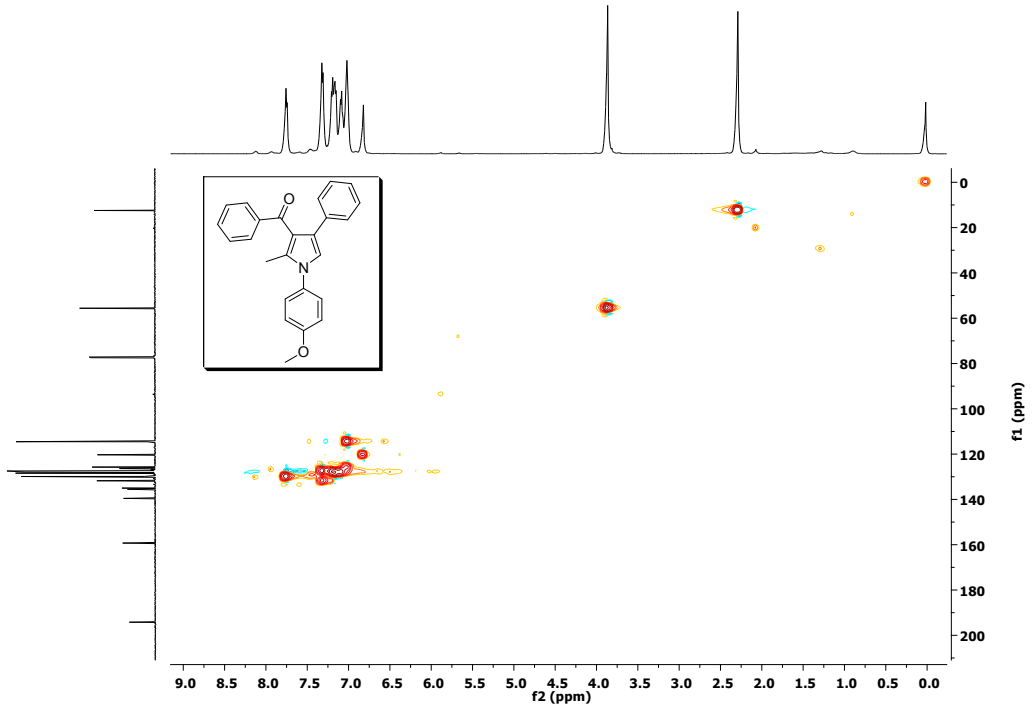
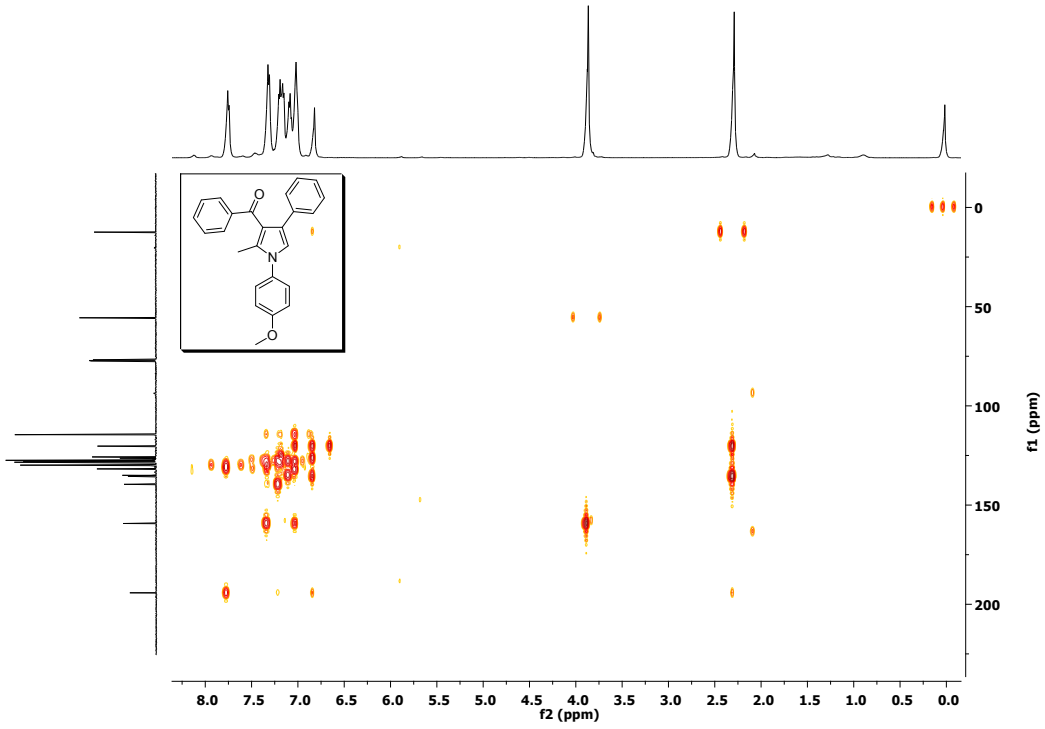
35
30
25
20
15
10
5
0
f1 (ppm)

HSQC

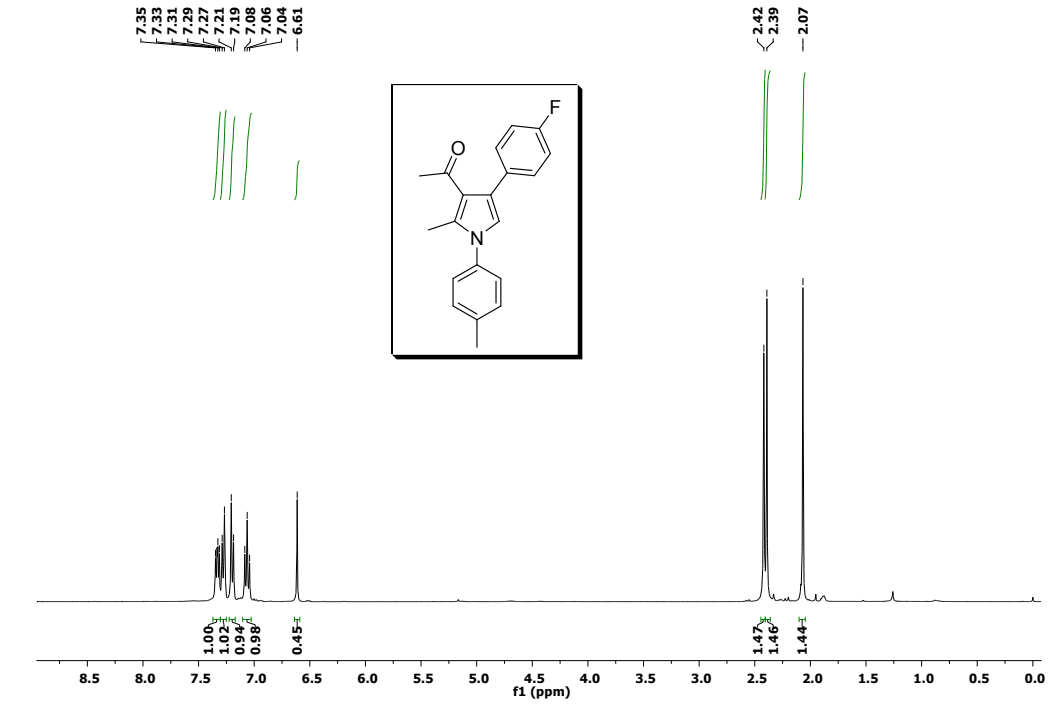


HMBC

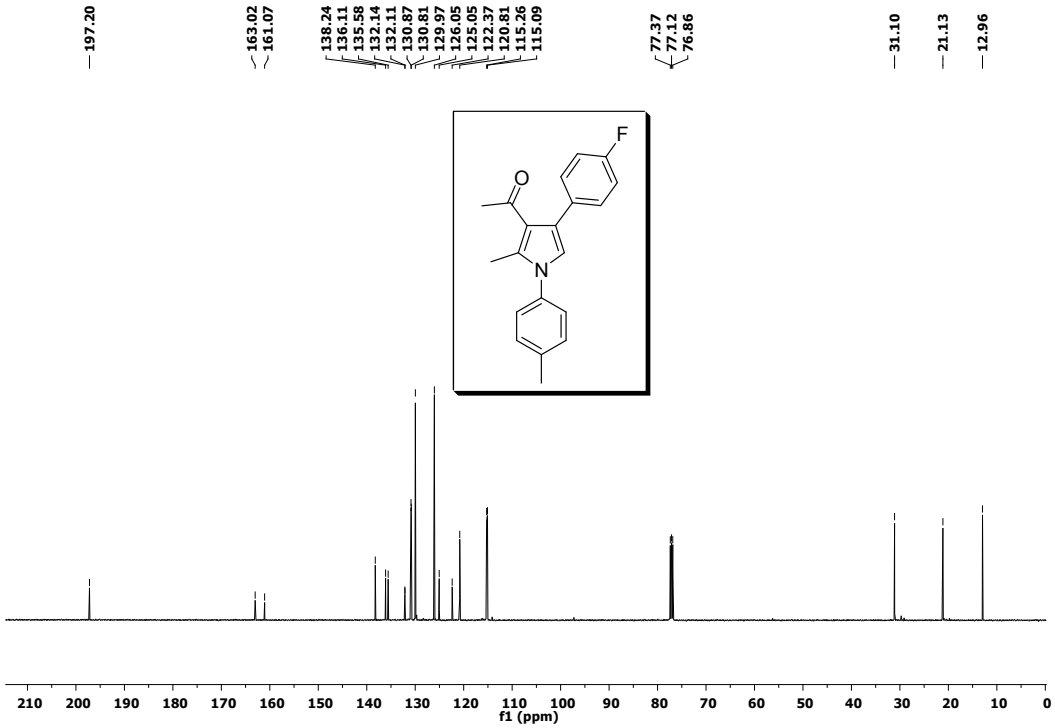


S4. ^{1}H, ^{13}C, DEPT135 and HMBC NMR spectra scans of compound 5i

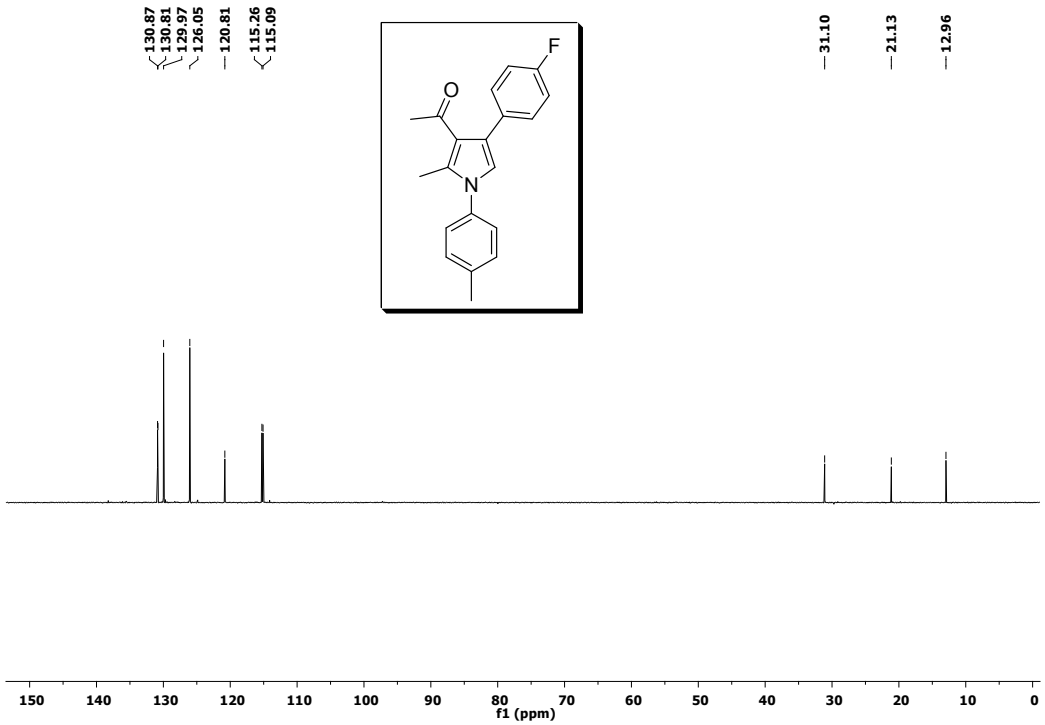
^{1}H NMR



^{13}C NMR



DEPT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130.81
129.97
126.05
120.81
115.26
115.09
31.10
21.13
12.96
F
O
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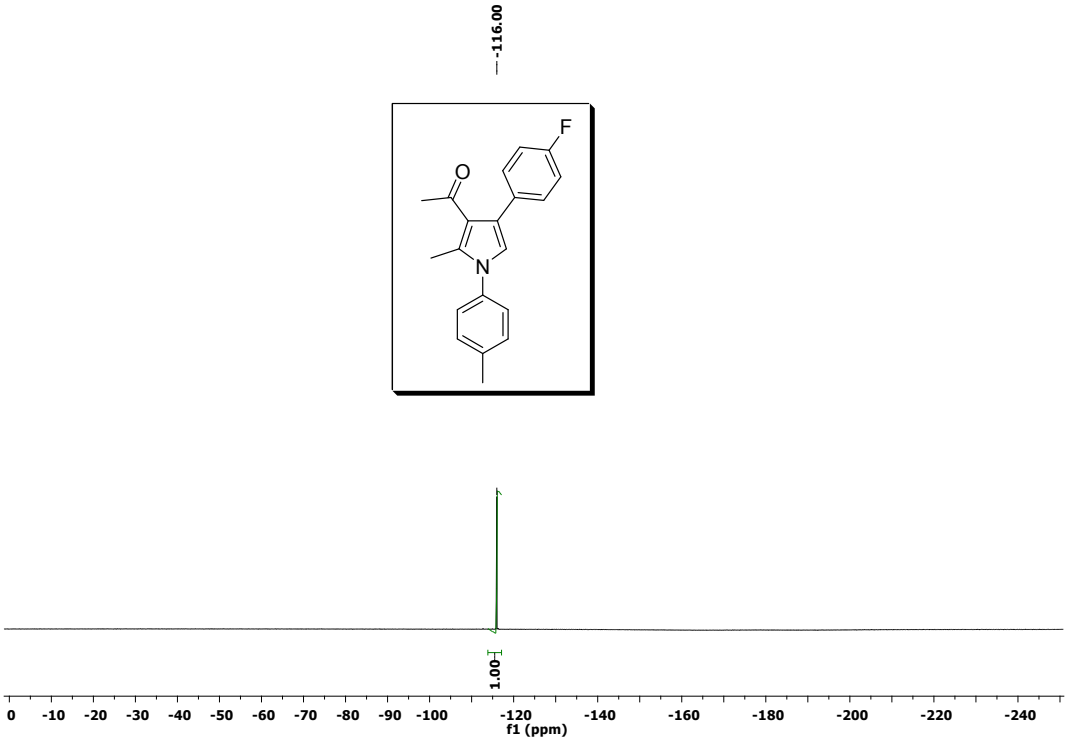
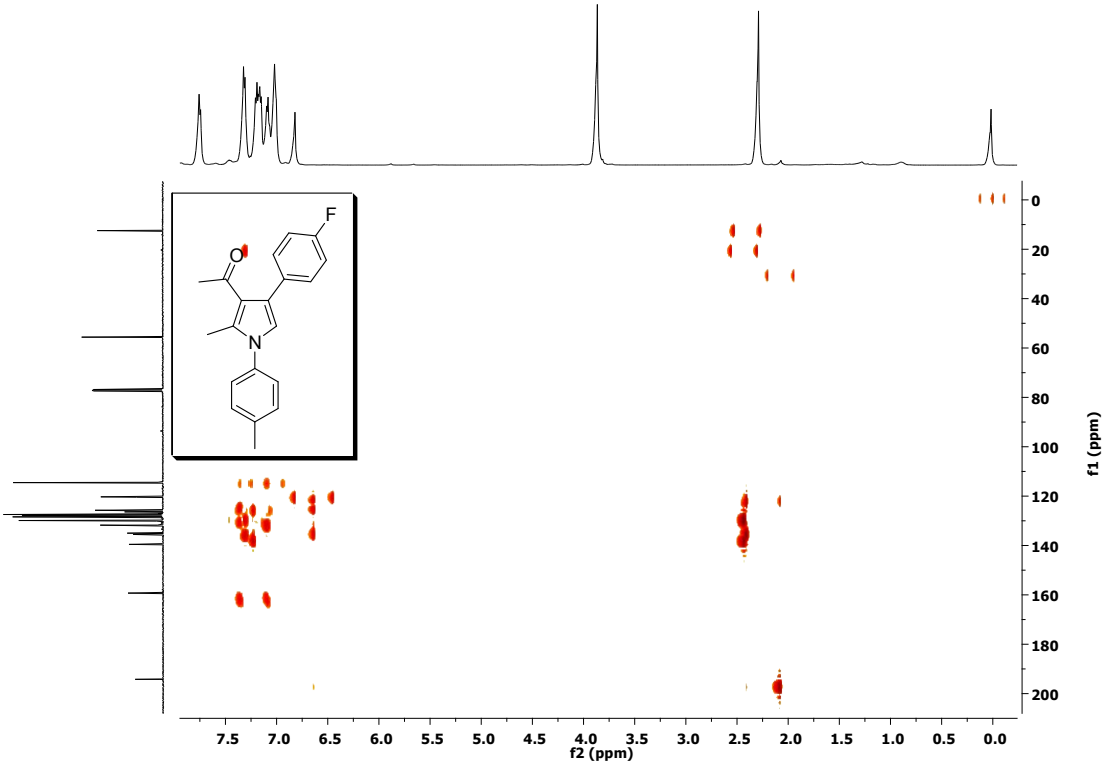
f1 (ppm)

^{19}F NMR

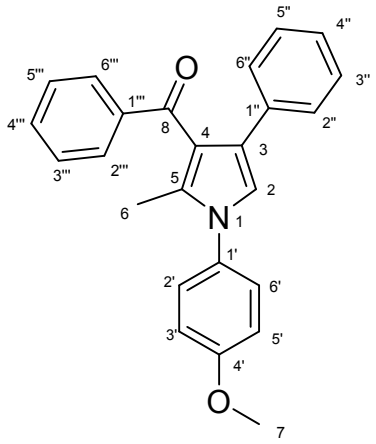

-116.00
F
O
N
1.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

HMBC

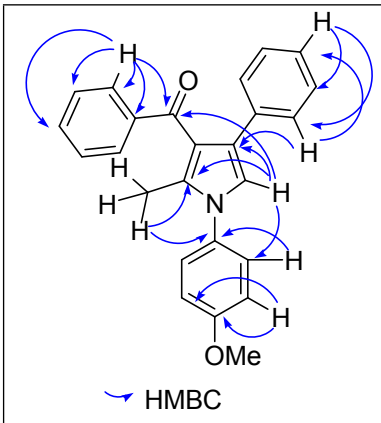
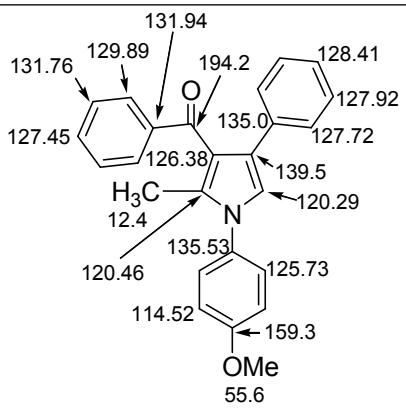
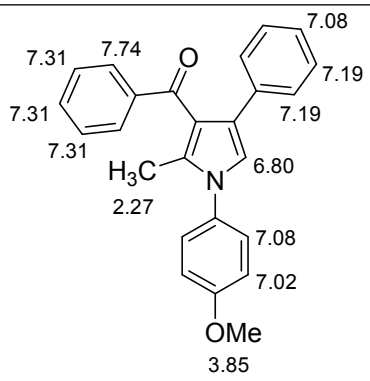

F
O
N
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)

S5. HMBC correlations and structure assignments for compound 5q

Compound numbering:



Key correlations and assignments:

		
Key HMBC correlations	**^{13}C NMR assignments**	**^{1}H NMR assignments**

Assignment table:

position	**5q**		
	δ_C	δ_H (J)	Key HMBC correlations
2	120.3, CH	6.80, s	C_3 (139.5), C_5 (120.46), C_8 (194.2), C_6' (125.73)
3	139.5, C		
4	126.4, C		
5	120.5, C		
6	12.4, CH_3	2.27, s	C_5 (120.46), C_1' (135.53)

7	55.6, CH_3	3.85 s	
8	194.2, CO		
1′	135.5, C		
2′, 6′	125.7, CH	7.10-7.08, m	C_1' (135.53)
3′, 5′	114.5, CH	7.02, d (12)	C_4' (159.3), C_3' (114.52)
4′	159.3, C		
1′′	135.0, C		
2′′, 6′′	127.7, CH	7.19-7.13, m	C_3 (139.5), C_4'' (128.41)
3′′, 5′′	127.9, CH	7.19-7.13, m	
4′′	128.4, CH	7.08, t, (12)	C_3'' (127.92), C_2'' (127.72)
1′′′	131.9, C		
2′′′, 6′′′	129.9, CH	7.74, d, (8)	C_6''' (129.89), C_1''' (131.94), C_8 (194.2), C_5''' (131.76), C_4''' (127.45)
3′′′, 5′′′	131.8, CH	7.31, d, (8)	
4′′′	127.5, CH	7.31, d, (8)	

S6. Pharmacokinetic parameters of compound 5i. The pharmacokinetic study of compound **5i** was carried out in BALB/c male mice of age 4-6 weeks, by administering compound orally and IV formulation at dose of 10 and 1 mg/kg, respectively. Plasma samples were collected at appropriate time points between the range of 0 hours to 24 hours (0.25, 0.5, 1, 2, 4, 8, 10 and 24 h time intervals) and analyzed by LC-MS-MS. Mean plasma concentration was calculated and data was further analyzed for PK parameters evaluation using WinNonlin 5.3 software package.

The pharmacokinetic parameters are listed in Table S1.

Table S1. Pharmacokinetic parameters of compound **5i** in BALB/c mice

Parameter	Unit	IV (1 mg/kg)	PO (10 mg/kg)
$t_{1/2, ß}$	(h)	1.31	0.82
C_{max}	(ng/mL)	158	15.9
C_0	(ng/mL)	216	nd
AUC_{0-t}	(ng·h/mL)	75.4	14.1
$AUC_{0-\infty}$	(ng·h/mL)	79.5	17.8
CL	(mL/min/kg)	210	nd
V_d	(L/kg)	23.8	nd
V_{dss}	(L/kg)	11.4	nd
T_{last}	(h)	4.00	nd
Time points considered for $t_{1/2,\beta}$ calculation		1-4 h	0.5-2 h
Bioavailability	F (%)	-	2.25

References

1. S. Maiti, S. Biswas and U. Jana, *J. Org. Chem.*, 2010, **75**, 1674-1683.