

Supplementary Information

Design and development of sulfenylated 5-aminopyrazoles as the inhibitors of acetylcholinesterase and butyrylcholinesterase: Exploring the implication on A β ₁₋₄₂ aggregation inhibition in Alzheimer's disease

Payal Rani,¹ Sandhya Chahal,² Anju Ranolia,¹ Kiran,¹ Devendra Kumar,^{3,9} Ramesh Kataria,⁴ Parvin Kumar,⁵ Devender Singh,⁶ Anil Duhan,¹ Vibhu Jha,⁷ Muhammad Wahajuddin,⁷ Gaurav Joshi,^{7,8}, Jayant Sindhu,^{1*}

¹Department of Chemistry, COBS&H, CCS Haryana Agricultural University, Hisar, India-125004

²Department of Chemistry, Chaudhary Ranbir Singh University, Jind, India-126102

³School of Pharmacy, Narsee Monjee Institute of Management Studies (NMIMS) Dist. Dhule, Maharashtra- 424001

⁴Department of Chemistry at Panjab University, Chandigarh-160014

⁵Department of Chemistry, Kurukshetra University, Kurukshetra-136119

⁶Department of Chemistry, Maharshi Dayanand University, Rohtak-124001

⁷Institute of Cancer Therapeutics School of Pharmacy and Medical Sciences, University of Bradford, United Kingdom

⁸Department of Pharmaceutical Sciences, Chauras Campus, HNB Garhwal University (A Central University), Srinagar, Uttarakhand 246174, India

⁹Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi 221005, India

***Address of correspondence may be addressed to:**

Gaurav Joshi (Email: garvpharma29@gmail.com; gjoshi@bradford.ac.uk); Jayant Sindhu (Email: jayantchem@gmail.com)

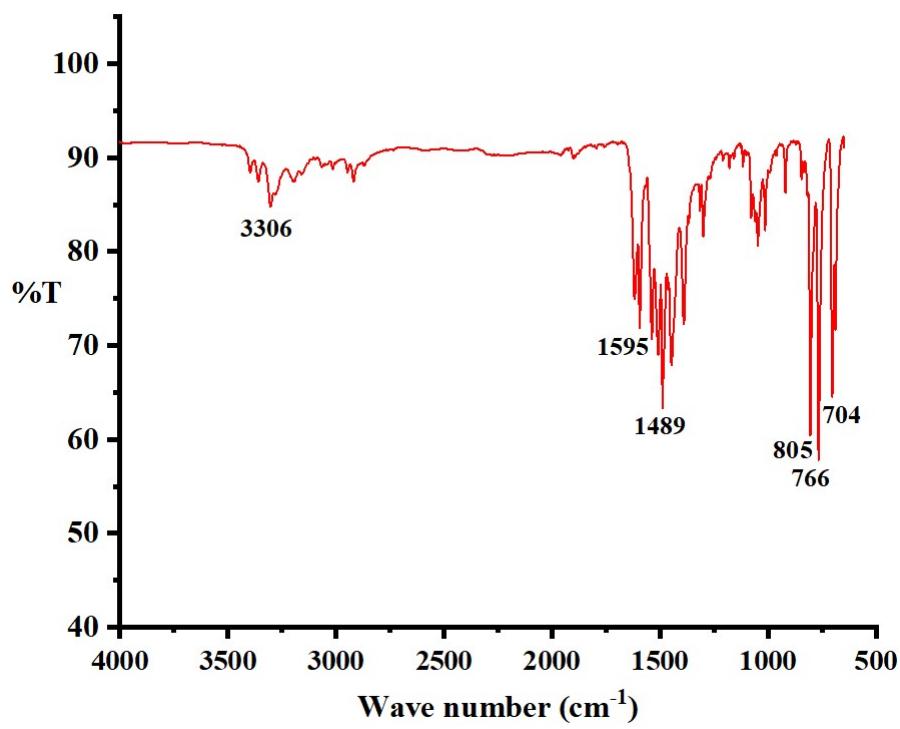


Figure S 1: FT-IR of 3-methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine (**3a**)

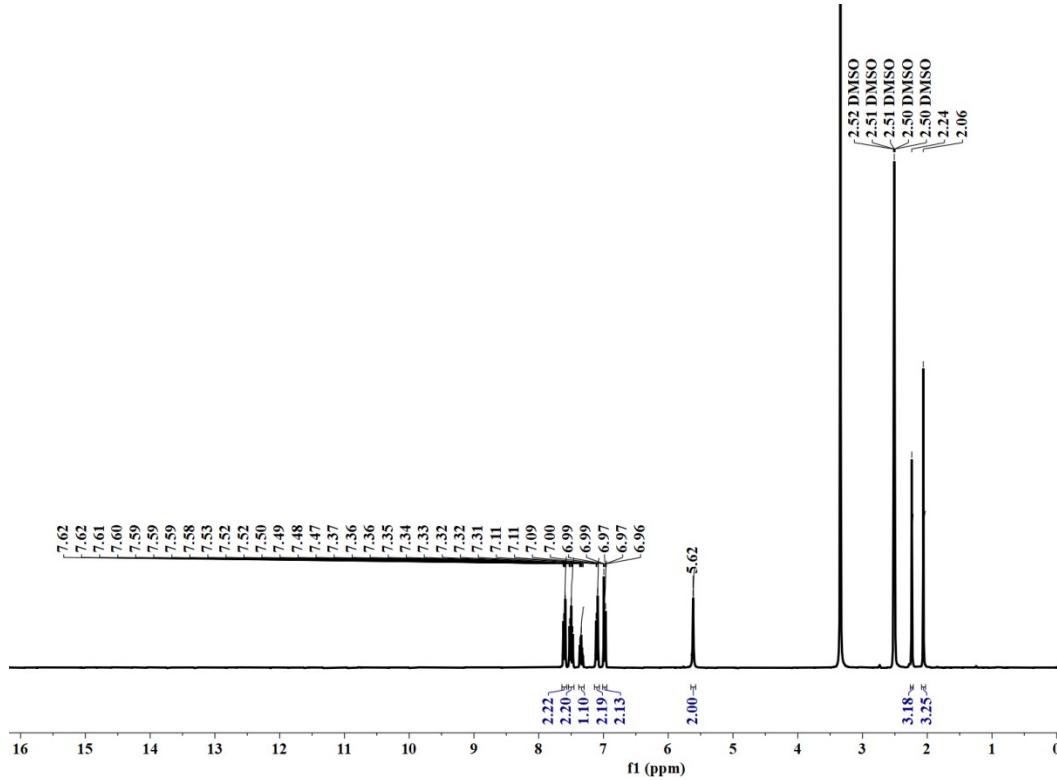


Figure S 2: ¹H NMR of 3-methyl-1-phenyl-4-(*p*-tolylthio)-1*H*-pyrazol-5-amine (**3a**)

Parameter	Value
1 Title	PG-534
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	22.8
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-05T14:24:05
17 Modification Date	2022-12-05T14:45:49
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

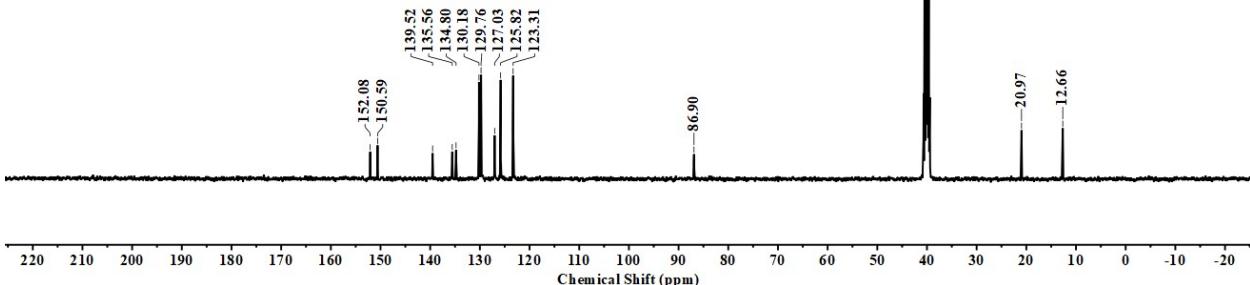
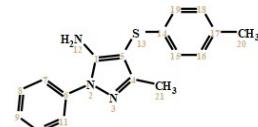


Figure S 3: ¹³C NMR of 3-methyl-1-phenyl-4-(p-tolylthio)-1H-pyrazol-5-amine (3a)

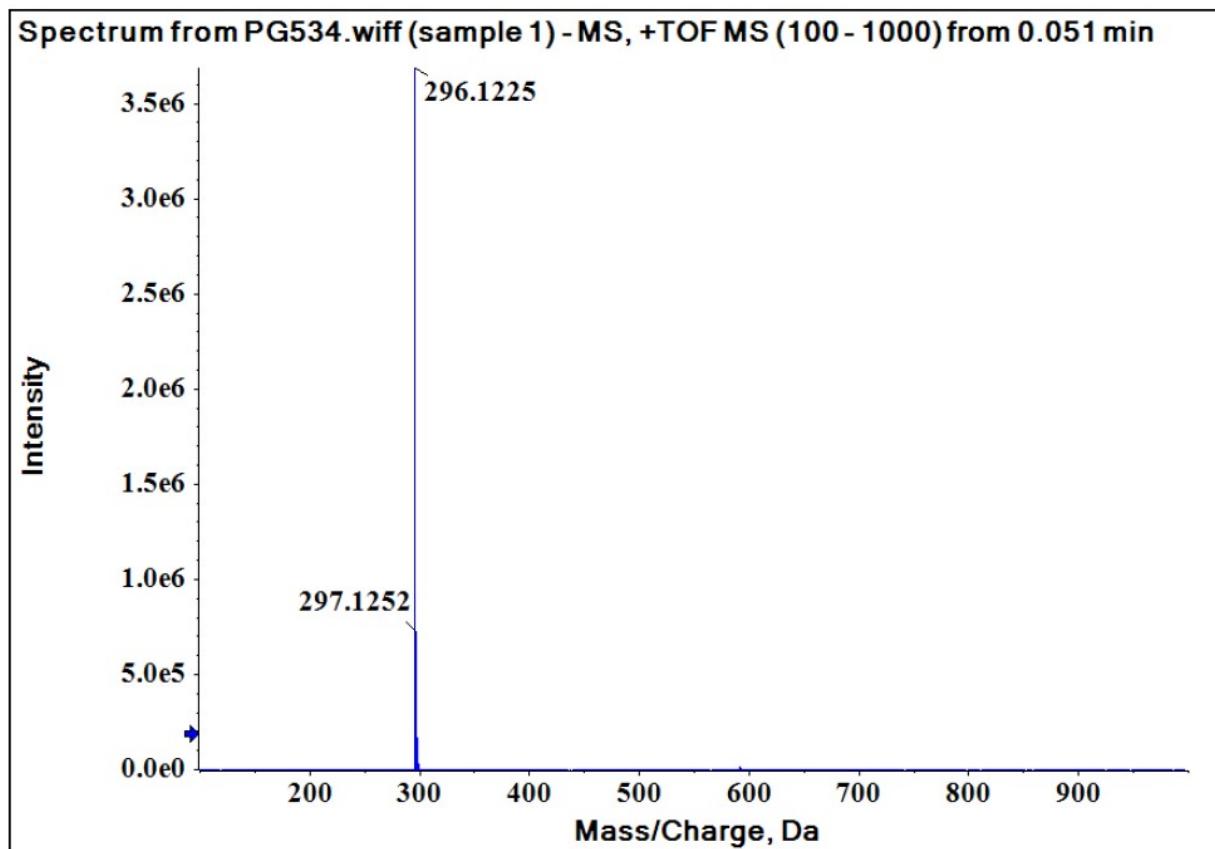


Figure S 4: Mass spectrometry of 3-methyl-1-phenyl-4-(p-tolylthio)-1H-pyrazol-5-amine (3a)

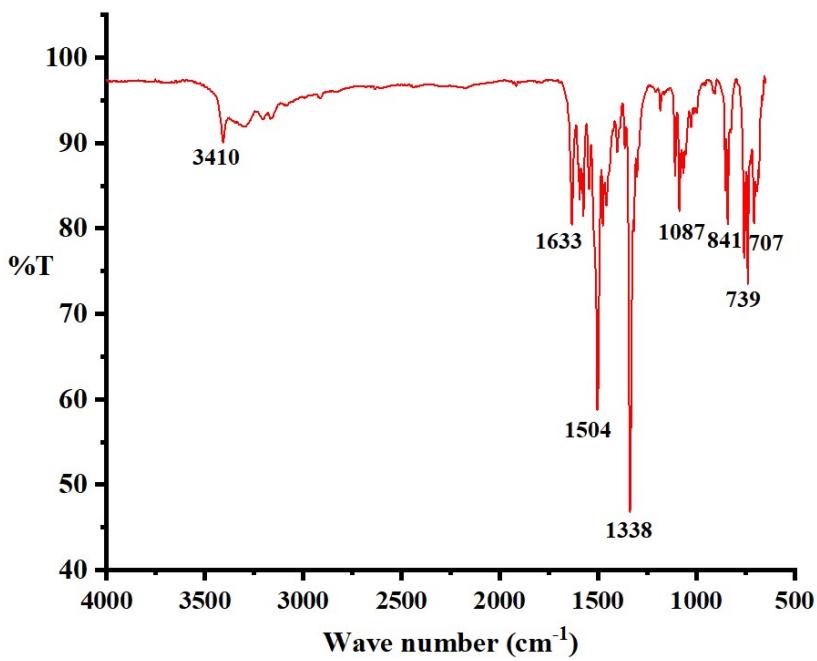


Figure S 5: FT-IR of 3-methyl-4-((4-nitrophenyl)thio)-1-phenyl-1*H*-pyrazol-5-amine (**3b**)

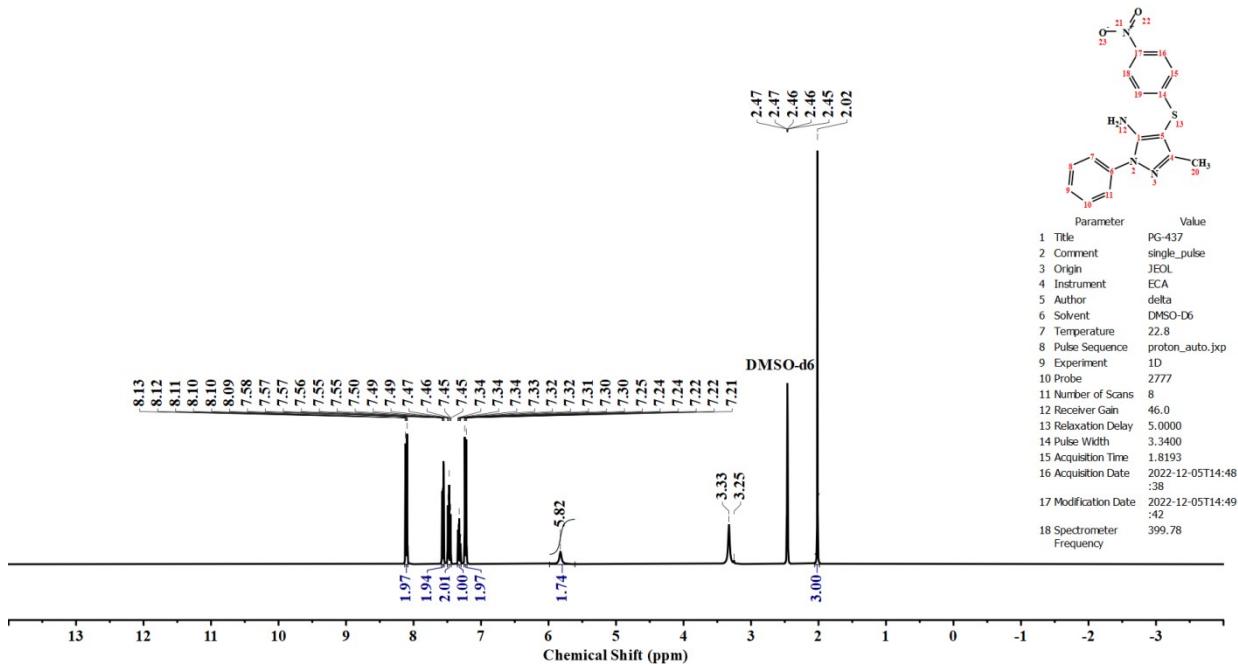


Figure S 6: ^1H NMR of 3-methyl-4-((4-nitrophenyl)thio)-1-phenyl-1*H*-pyrazol-5-amine (**3b**)

Parameter	Value
1 Title	PG-437
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	22.9
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-05T14:50:59
17 Modification Date	2022-12-05T15:12:43
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

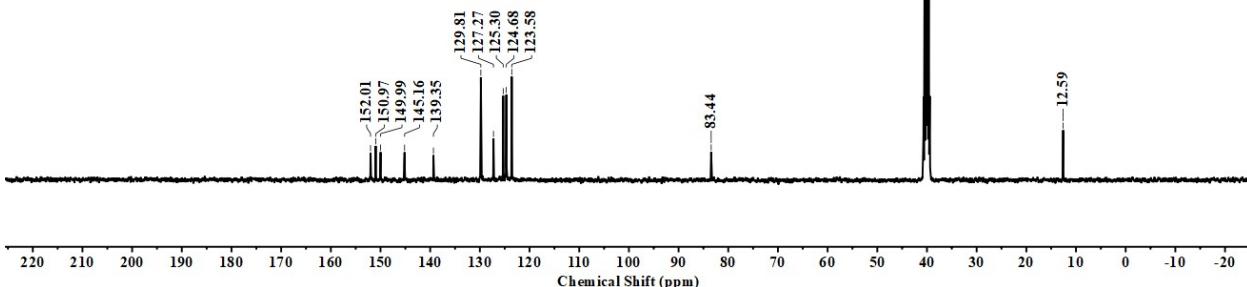
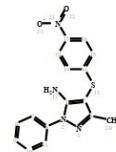


Figure S 7: ¹³C NMR of 3-methyl-4-((4-nitrophenyl)thio)-1-phenyl-1H-pyrazol-5-amine (**3b**)

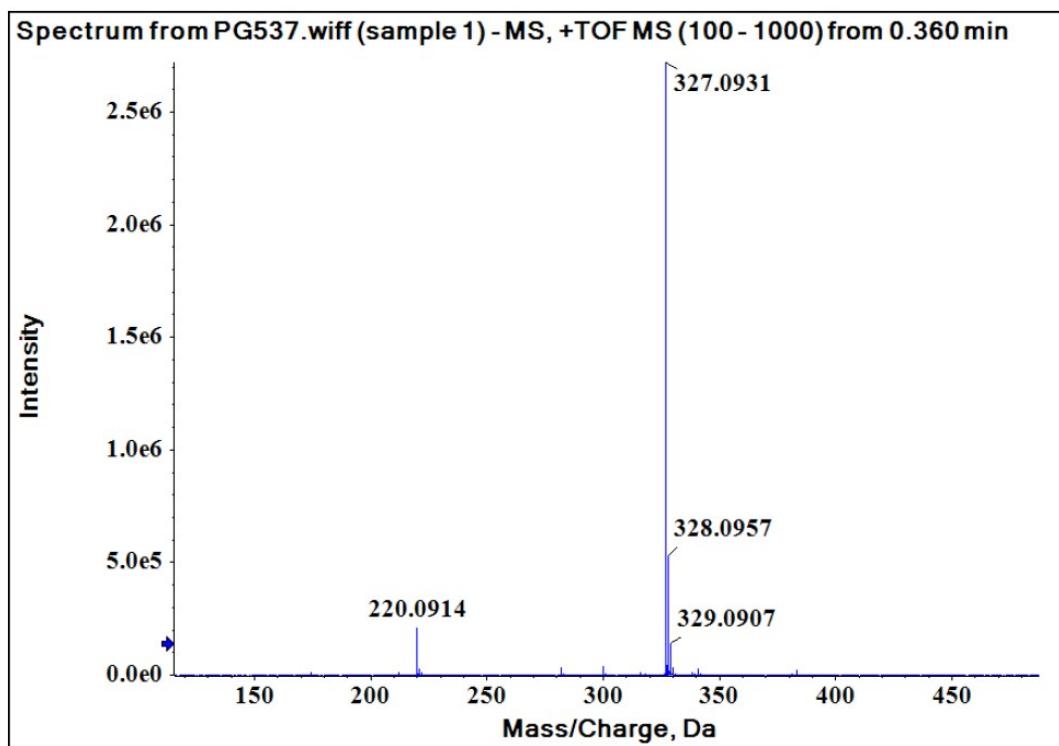
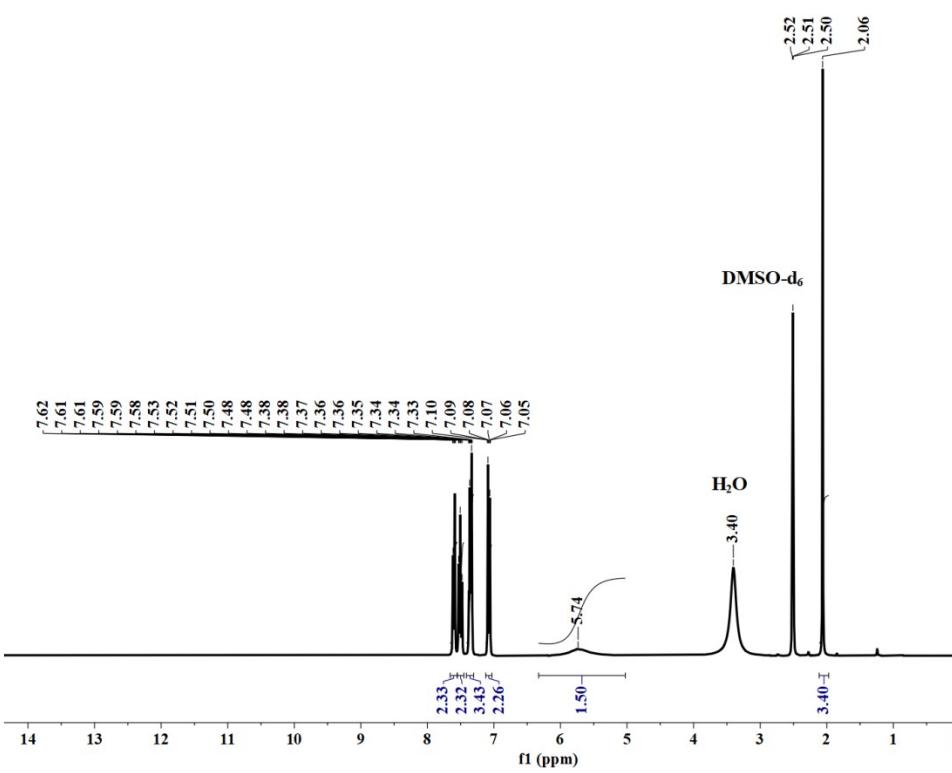
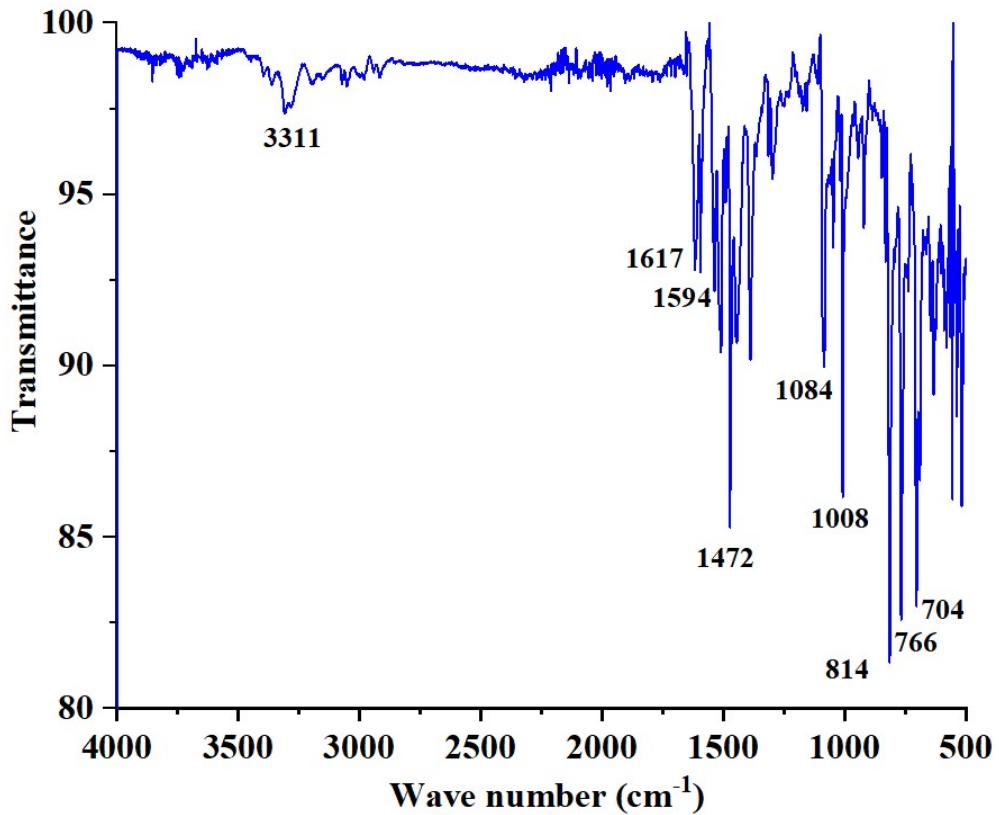


Figure S 8: Mass spectrometry of 3-methyl-4-((4-nitrophenyl)thio)-1-phenyl-1H-pyrazol-5-amine (**3b**)



Parameter	Value
1 Title	PG-439
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	23.0
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-05T15:18:11
17 Modification Date	2022-12-05T15:39:54
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

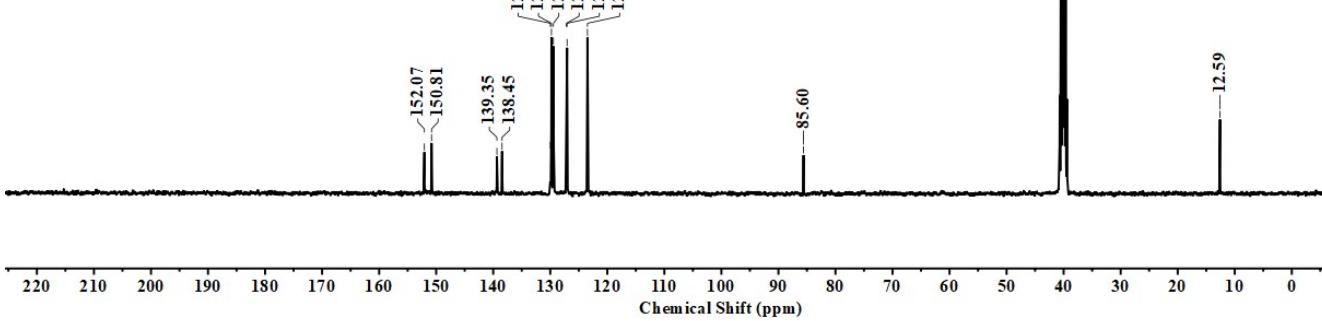
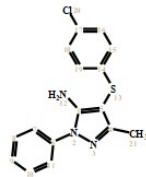


Figure S 11: ¹³C NMR of 4-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3c)

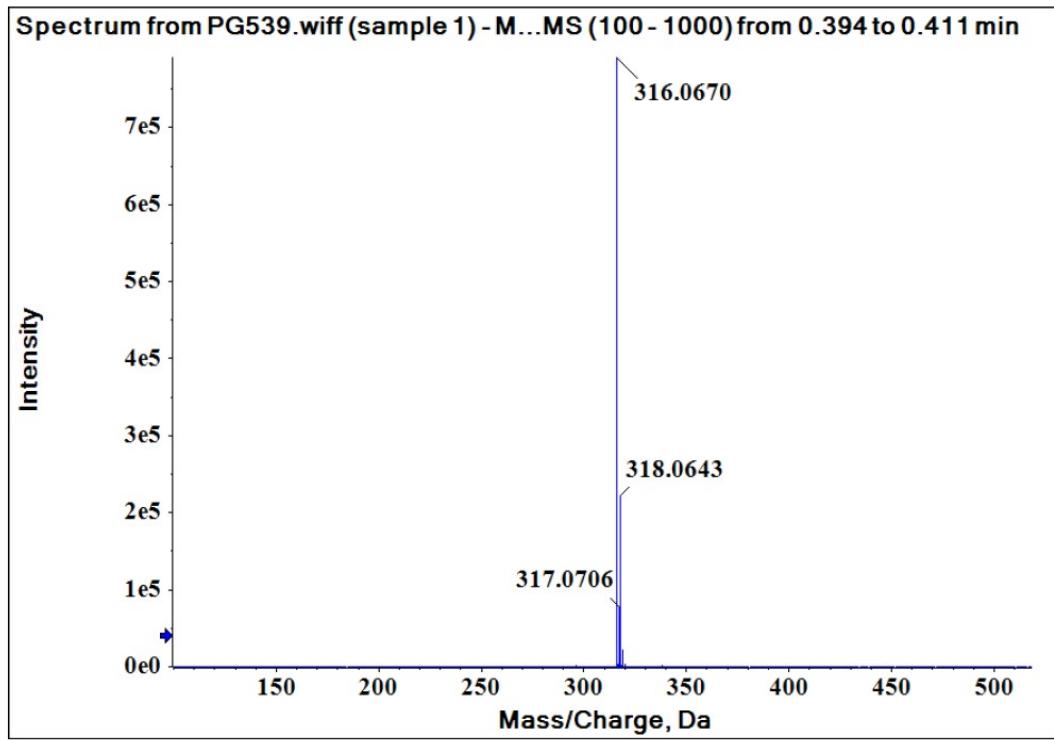


Figure S 12: Mass spectrometry of 4-((4-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3c)

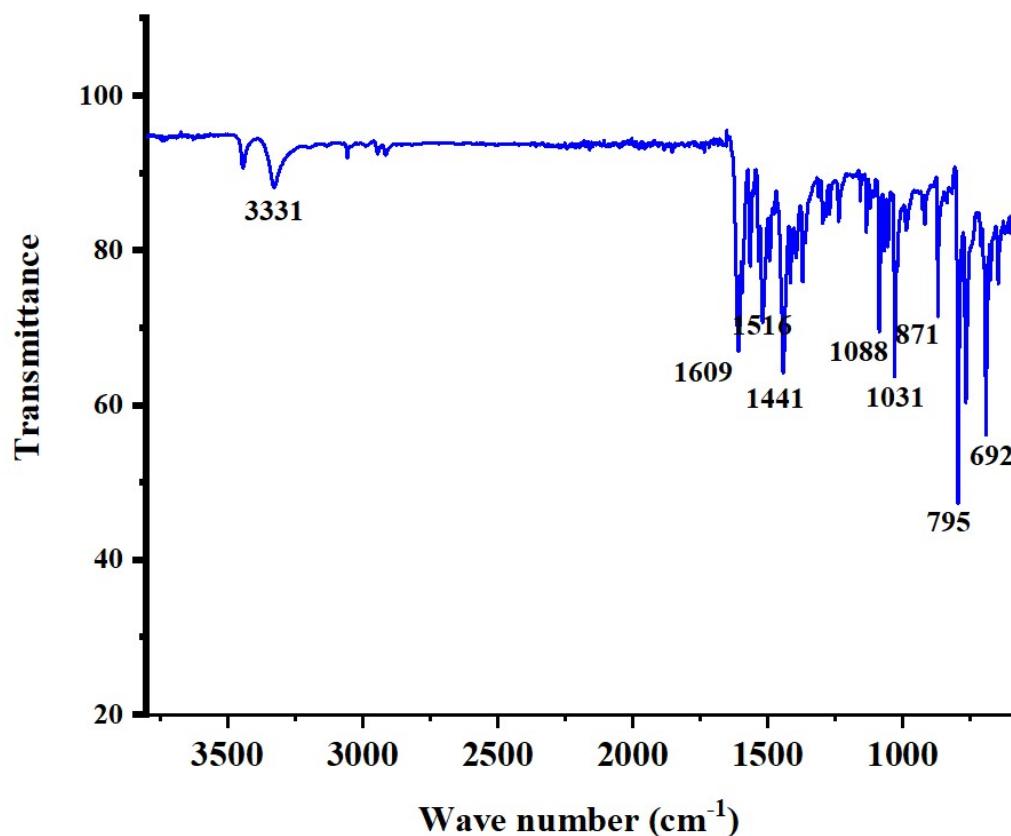


Figure S 13: FT-IR of 4-((2,5-dichlorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3d**)

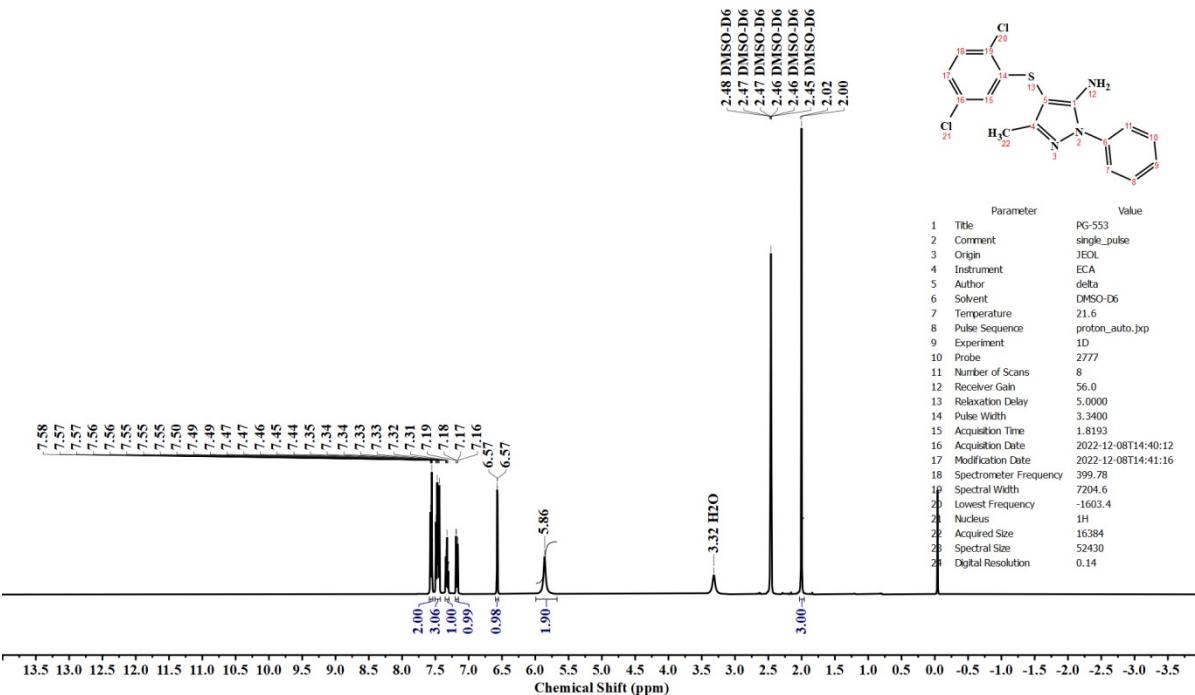


Figure S 14: ¹H NMR of 4-((2,5-dichlorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3d**)

Parameter	Value
1 Title	PG-553
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	21.6
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-08T14:42:25
17 Modification Date	2022-12-08T15:04:07
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

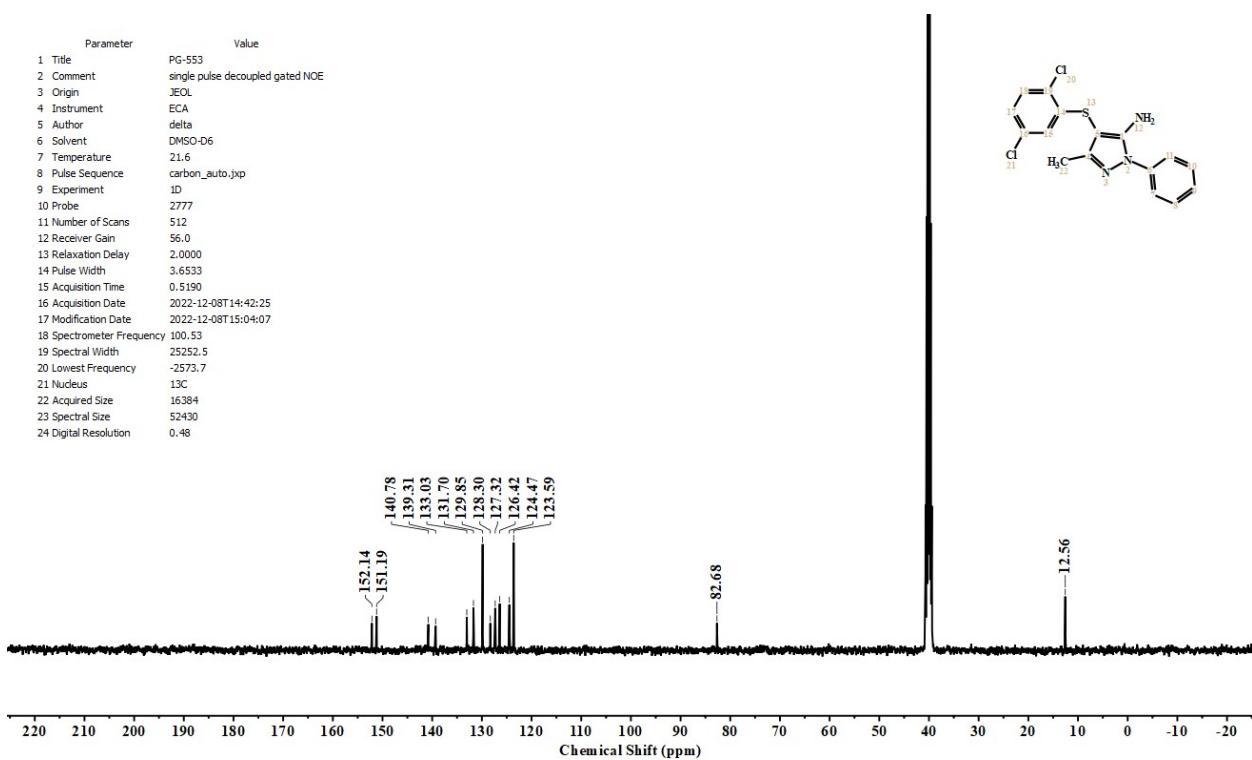
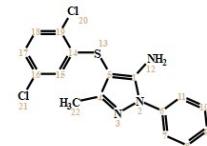


Figure S 15: ¹³C NMR of 4-((2,5-dichlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**3d**)

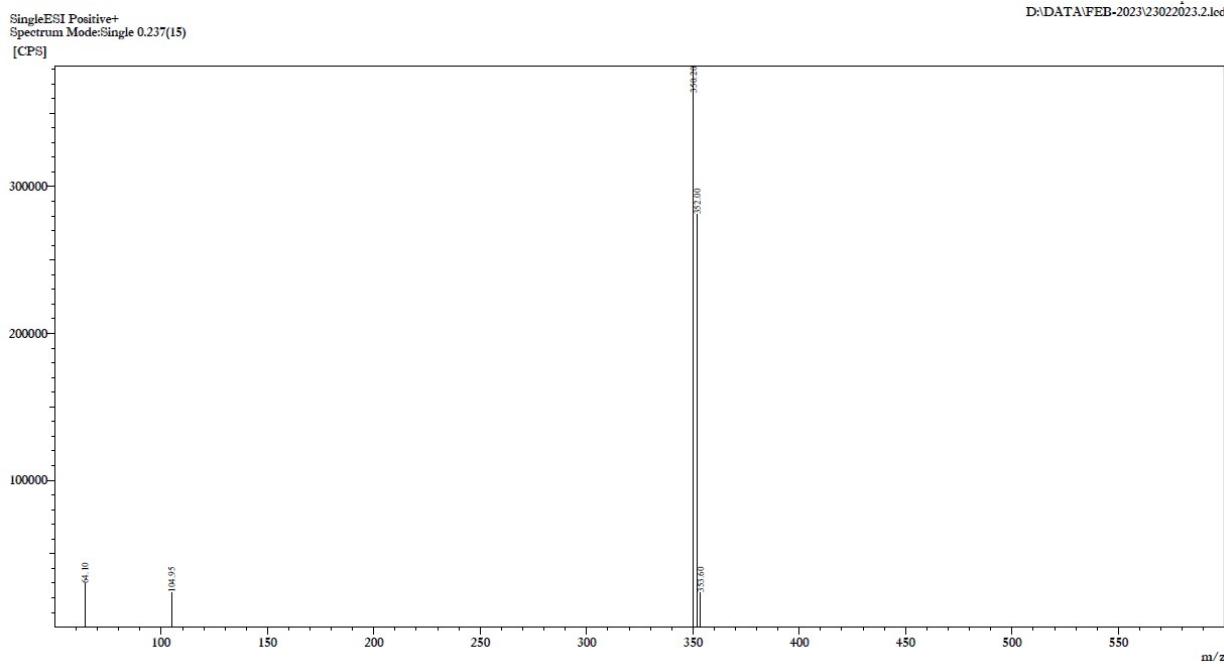


Figure S 16: Mass spectrometry of 4-((2,5-dichlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**3d**)

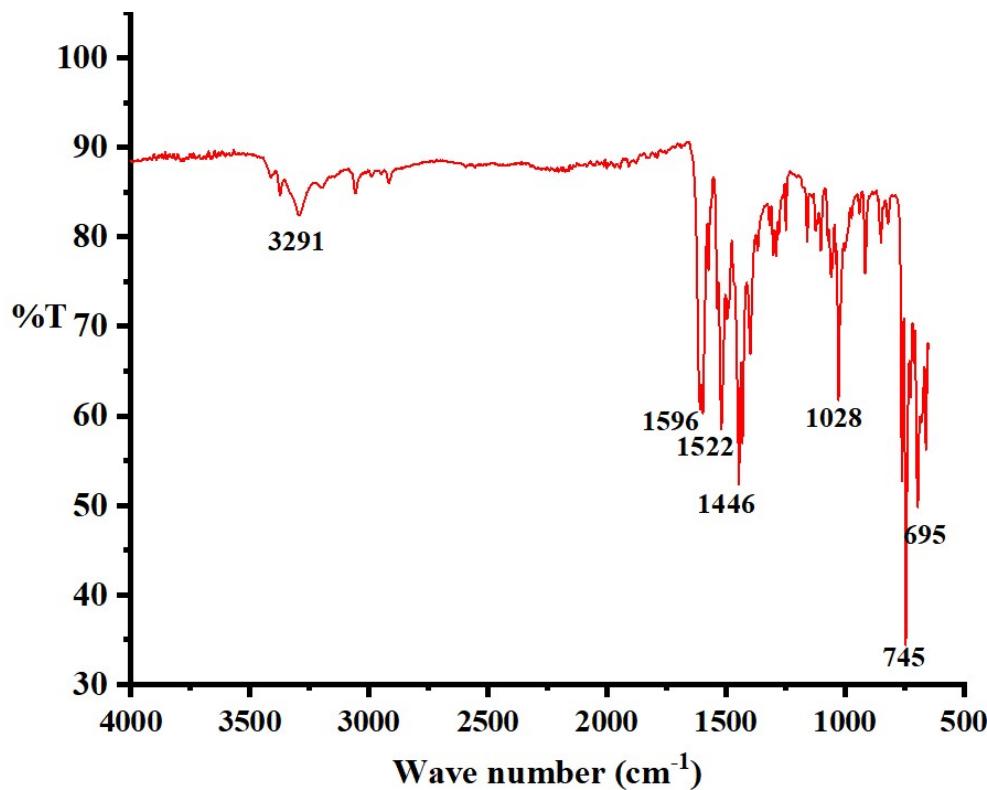


Figure S 17: FT-IR of 4-((2-chlorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3e**)

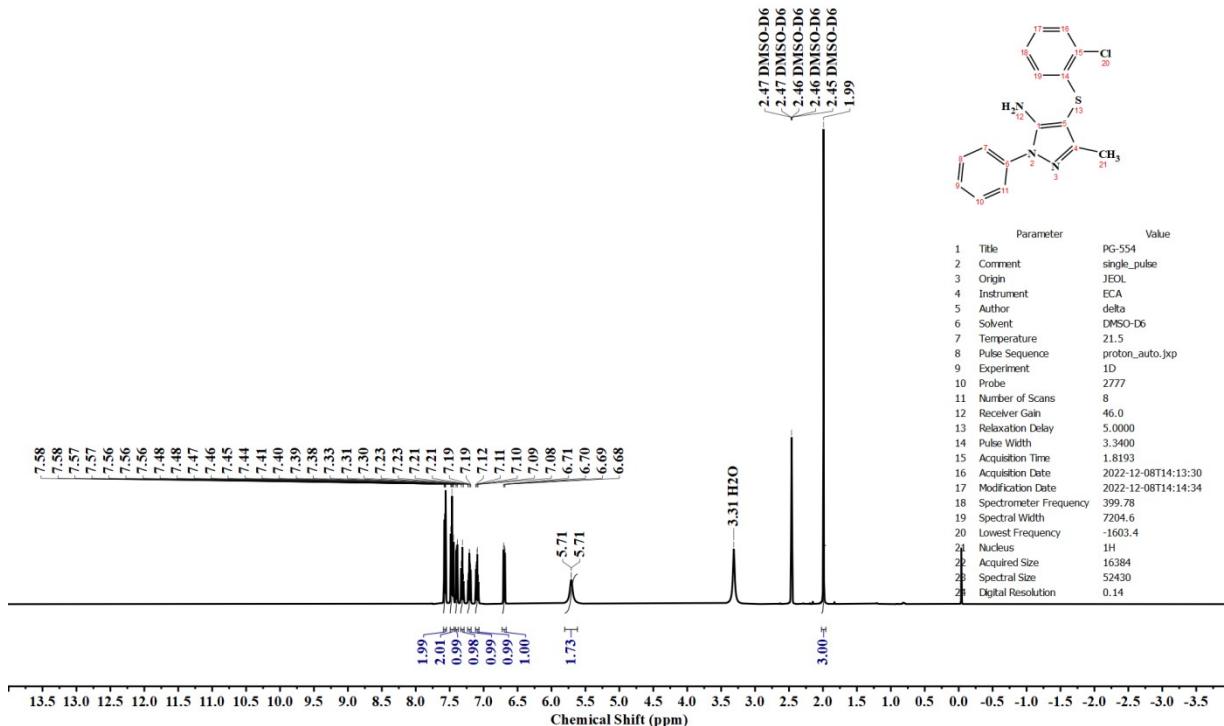


Figure S 18: ¹H NMR of 4-((2-chlorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3e**)

Parameter	Value
1 Title	PG-554
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	21.6
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-08T14:15:50
17 Modification Date	2022-12-08T14:37:32
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

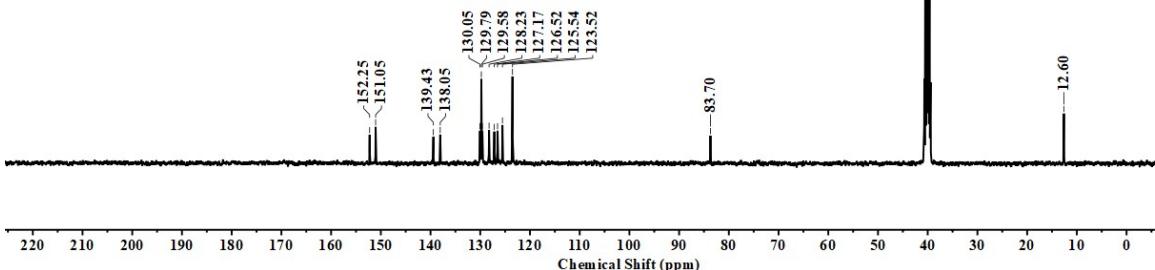
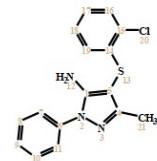


Figure S 19: ¹³C NMR of 4-((2-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3e)

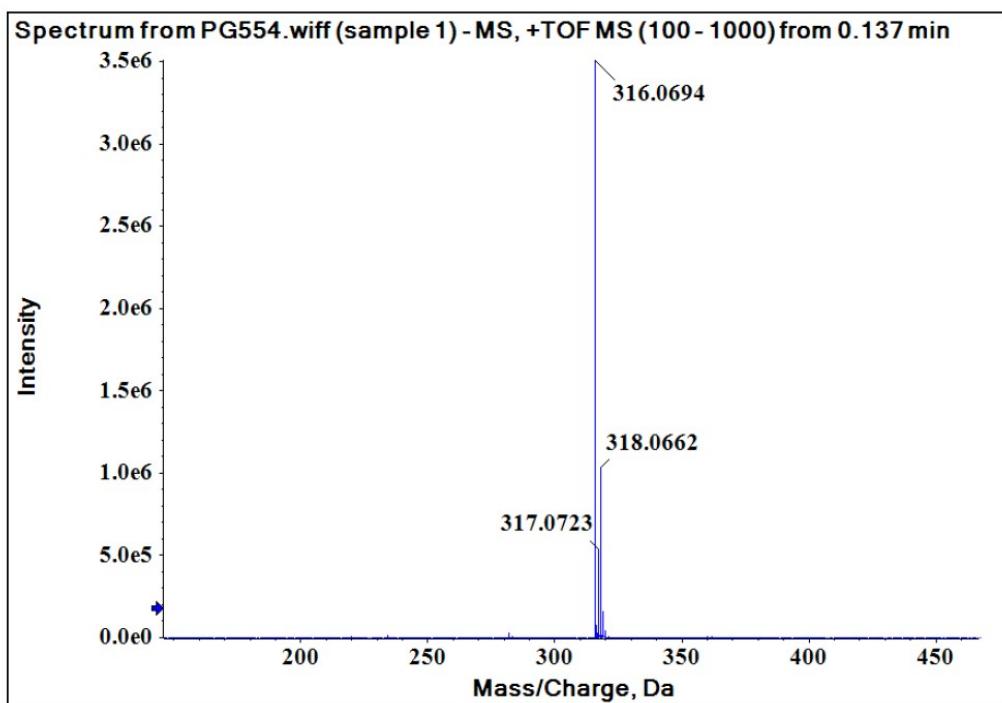


Figure S 20: Mass spectrometry of 4-((2-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3e)

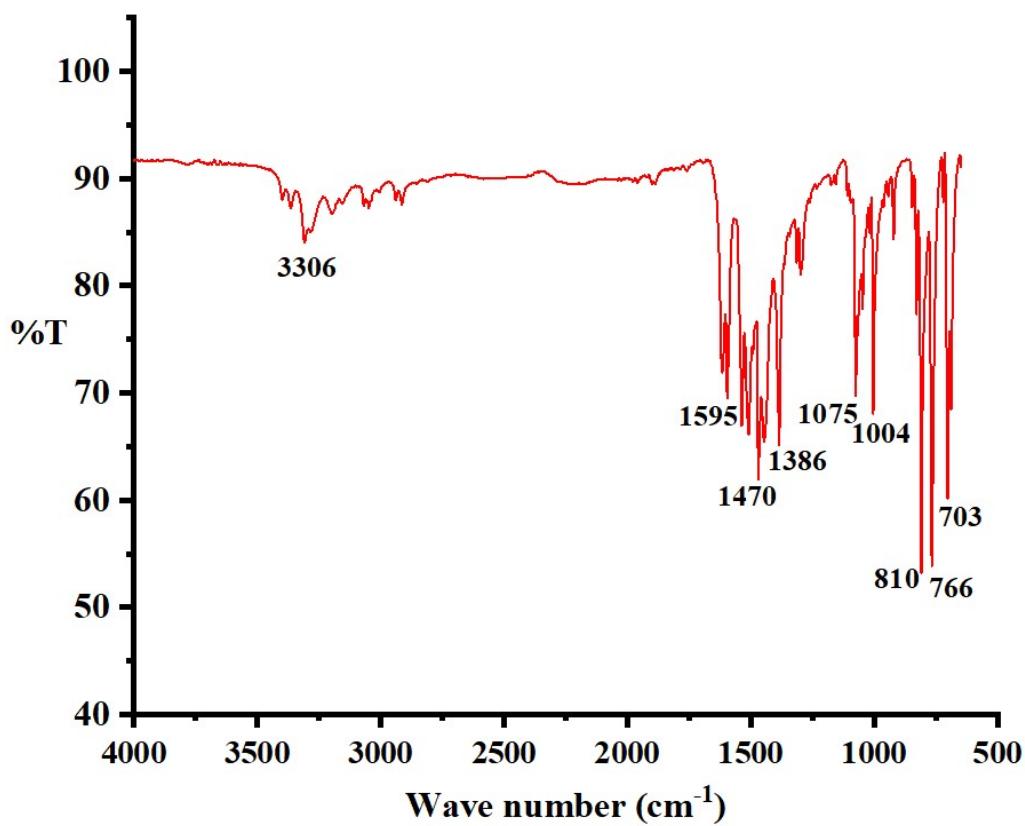
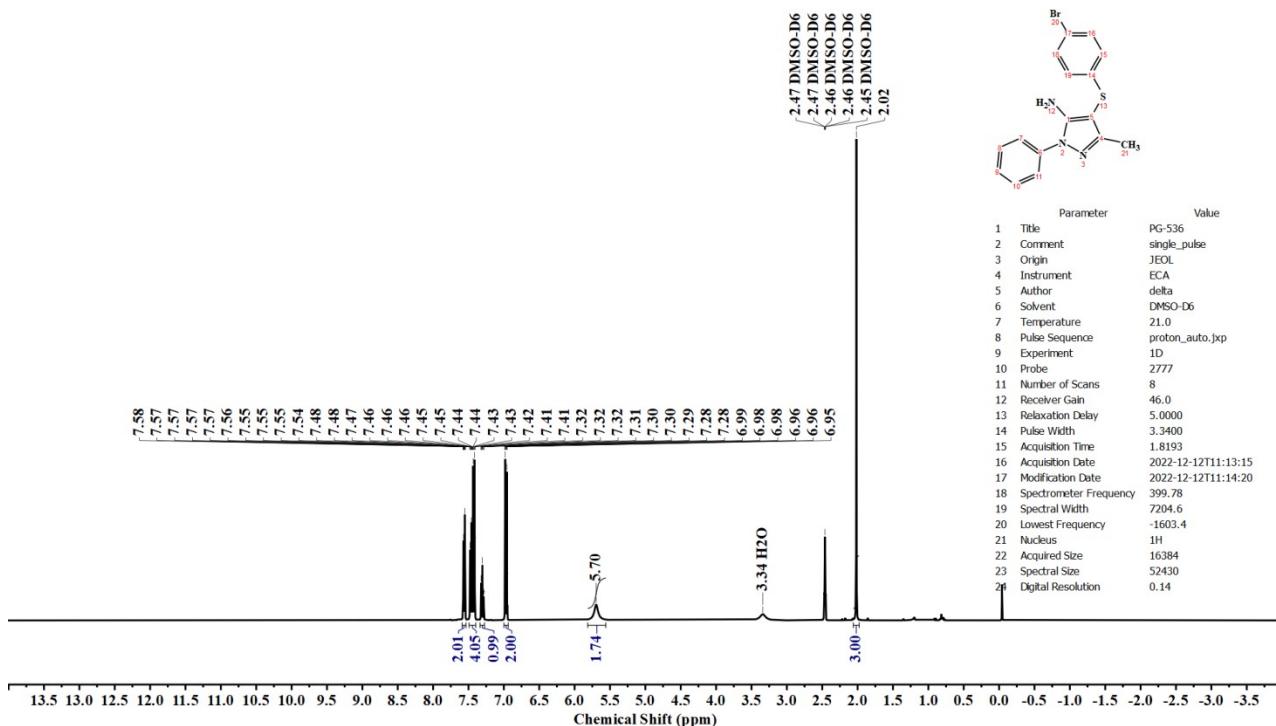


Figure S 21: FT-IR of 4-((4-bromophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3f**)



Parameter	Value
1 Title	PG-536
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	21.3
8 Pulse Sequence	carbon_auto.jpx
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-12T11:16:04
17 Modification Date	2022-12-12T11:37:46
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

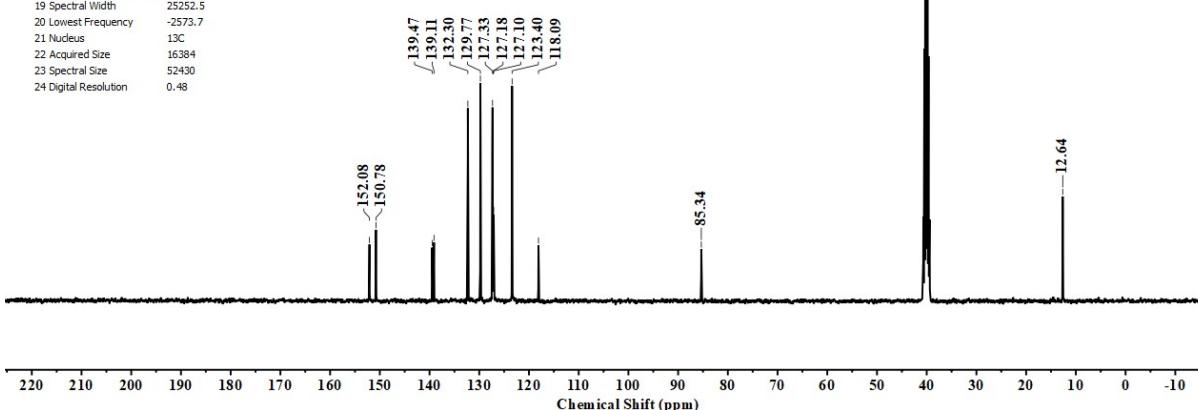
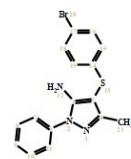


Figure S 23: ¹³C NMR of 4-((4-bromophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3f)

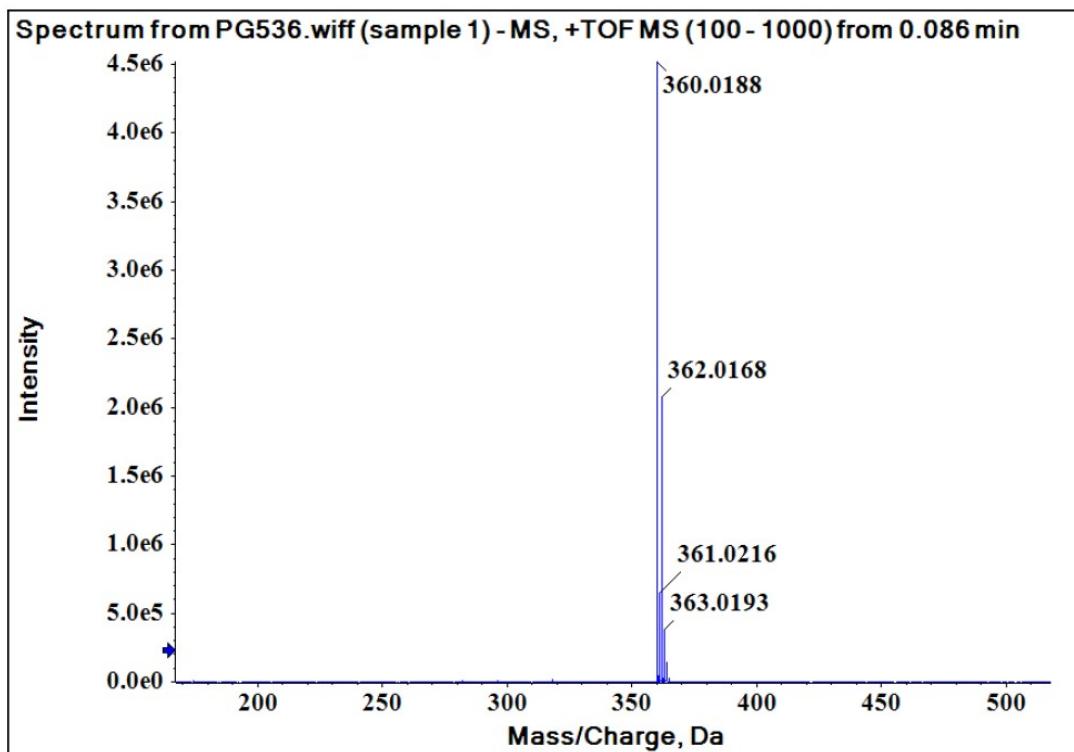


Figure S 24: Mass spectrometry of 4-((4-bromophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3f**)

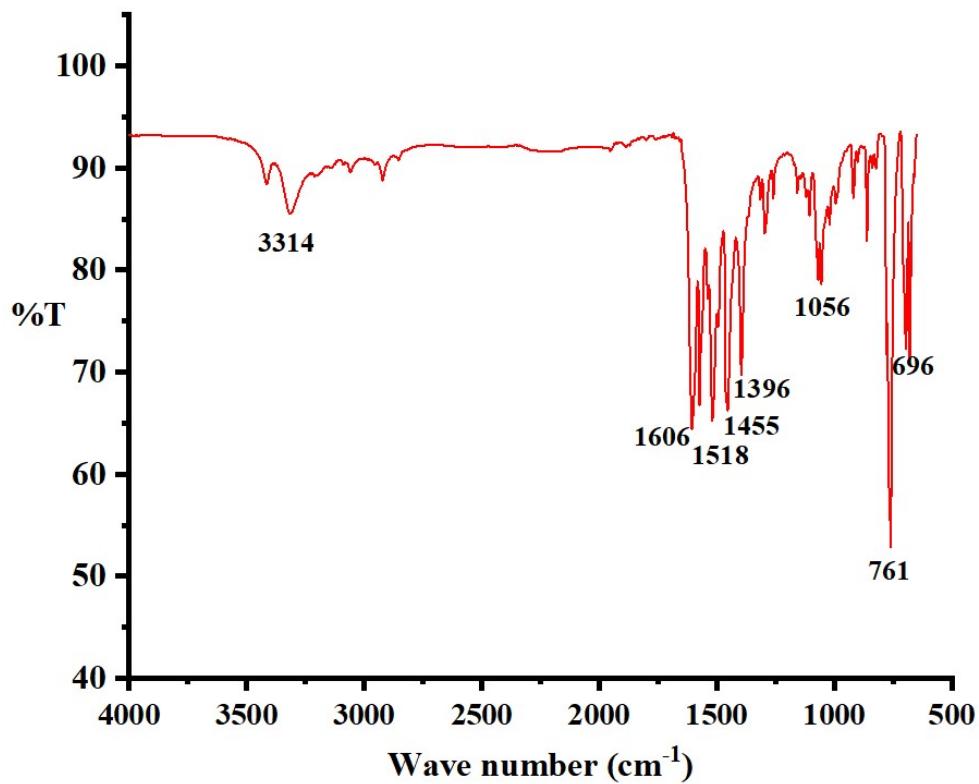


Figure S 25: FT-IR of 4-((3-chlorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3g**)

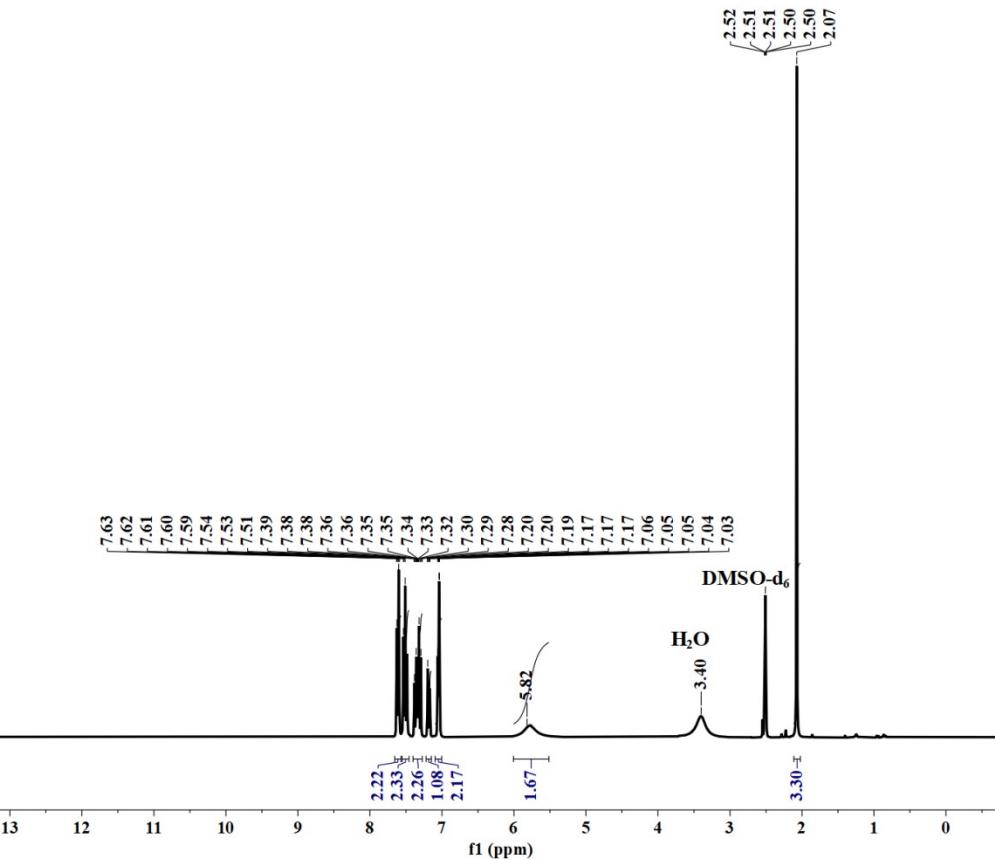


Figure S 26: ¹H NMR of 4-((3-chlorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3g**)

Parameter	Value
1 Title	pg-544
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	19.7
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-12T09:27:18
17 Modification Date	2022-12-12T09:49:00
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

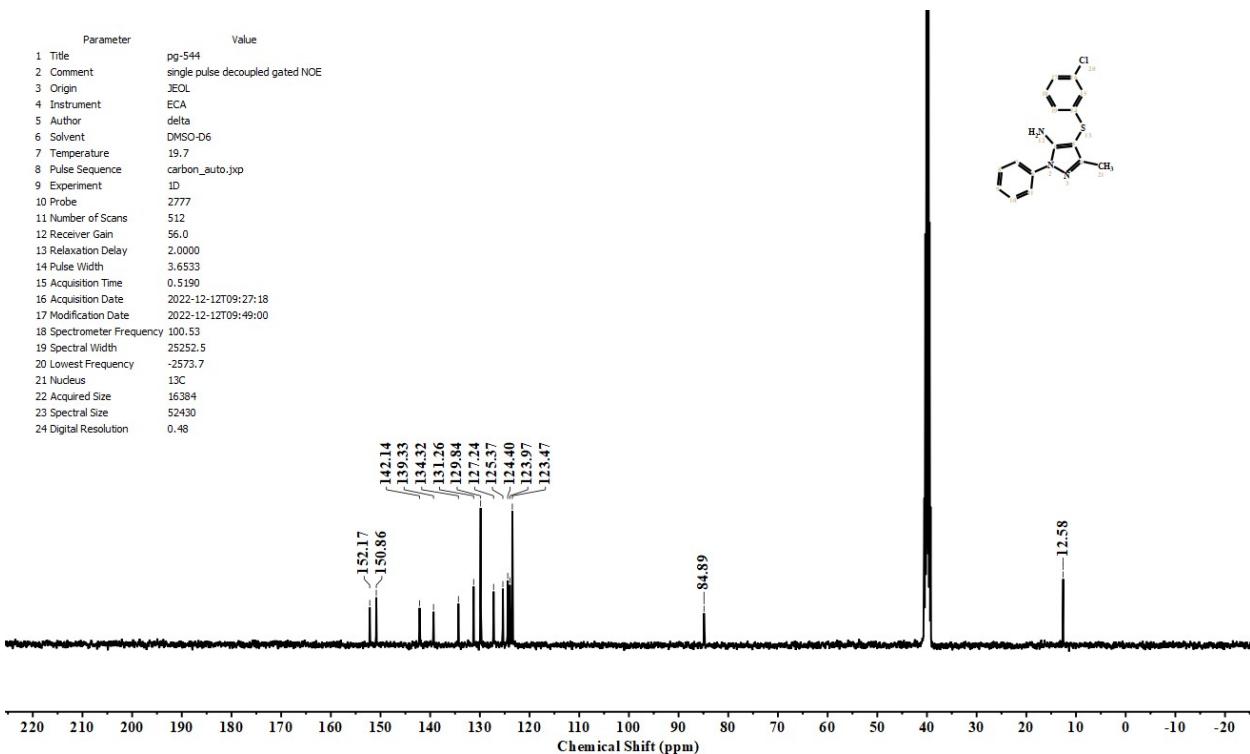
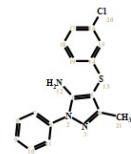


Figure S 27: ¹³C NMR of 4-((3-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3g)

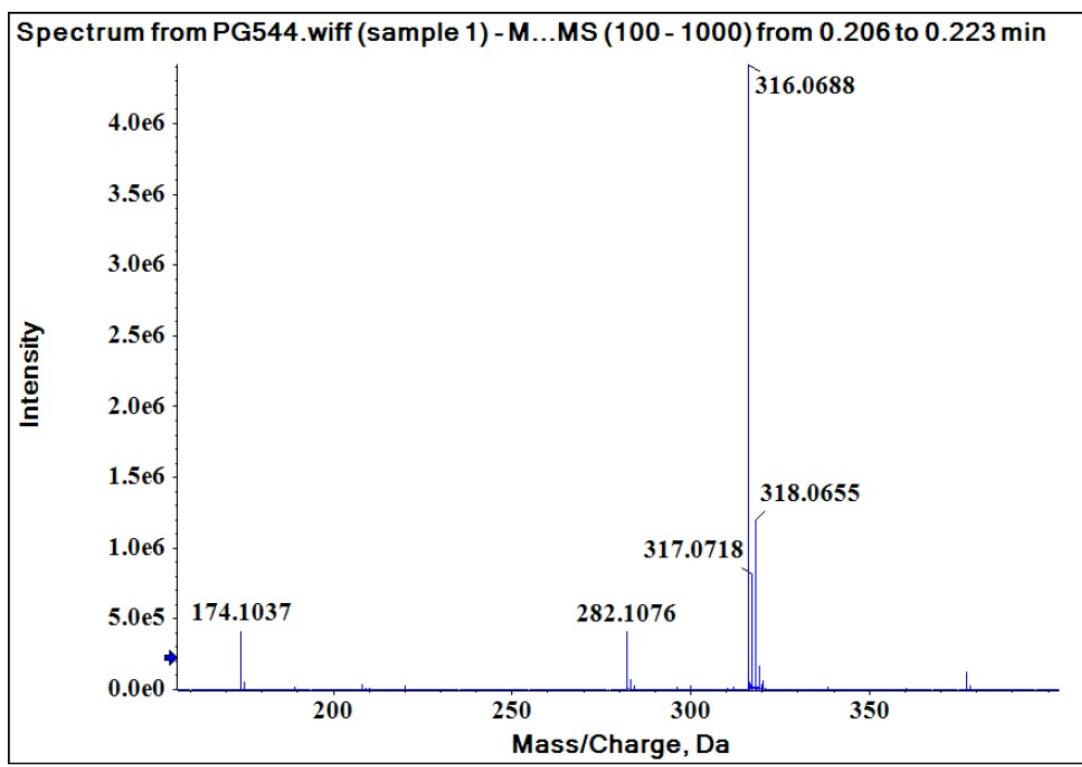


Figure S 28: Mass spectrometry of 4-((3-chlorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3g)

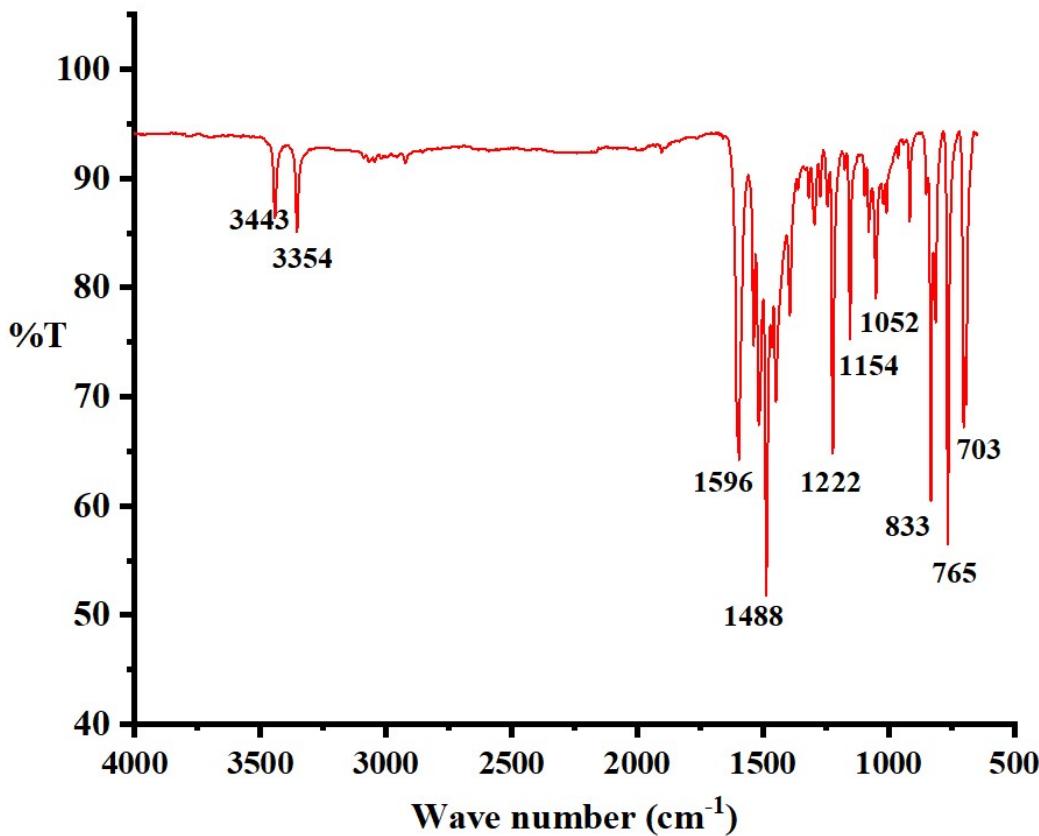


Figure S 29: FT-IR of 4-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3h**)

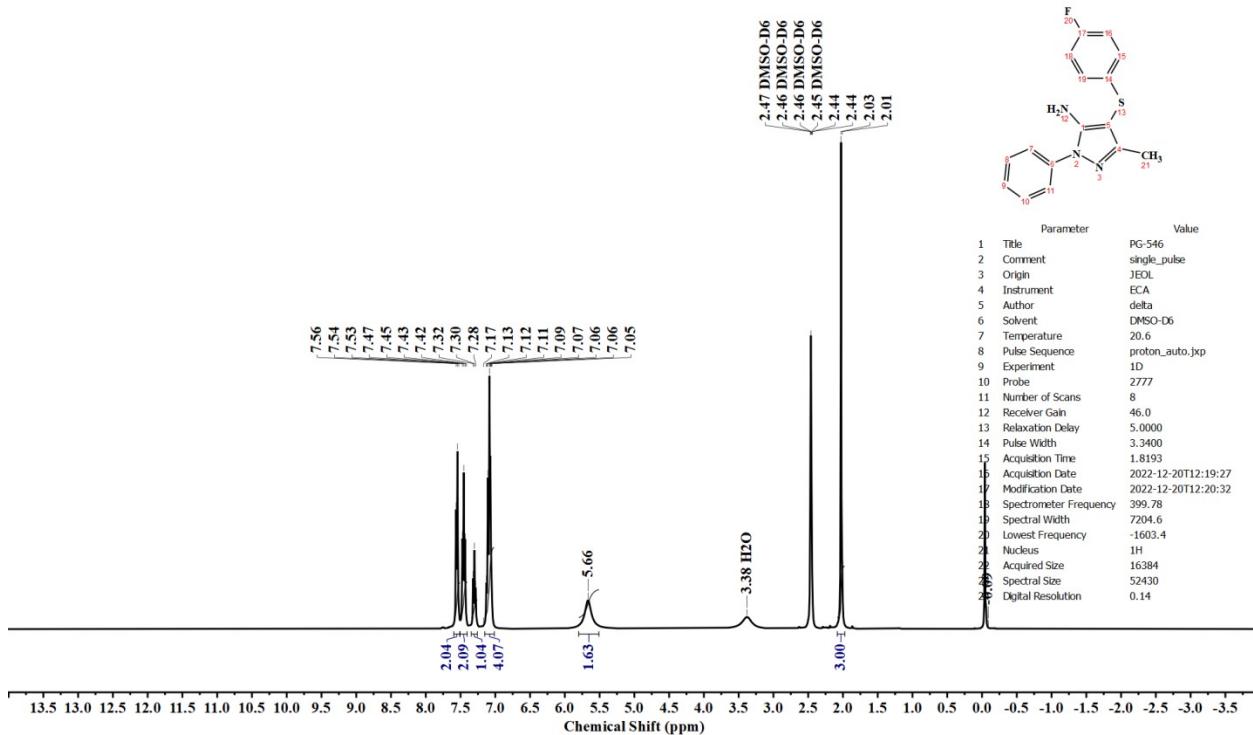


Figure S 30: ¹H NMR of 4-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3h**)

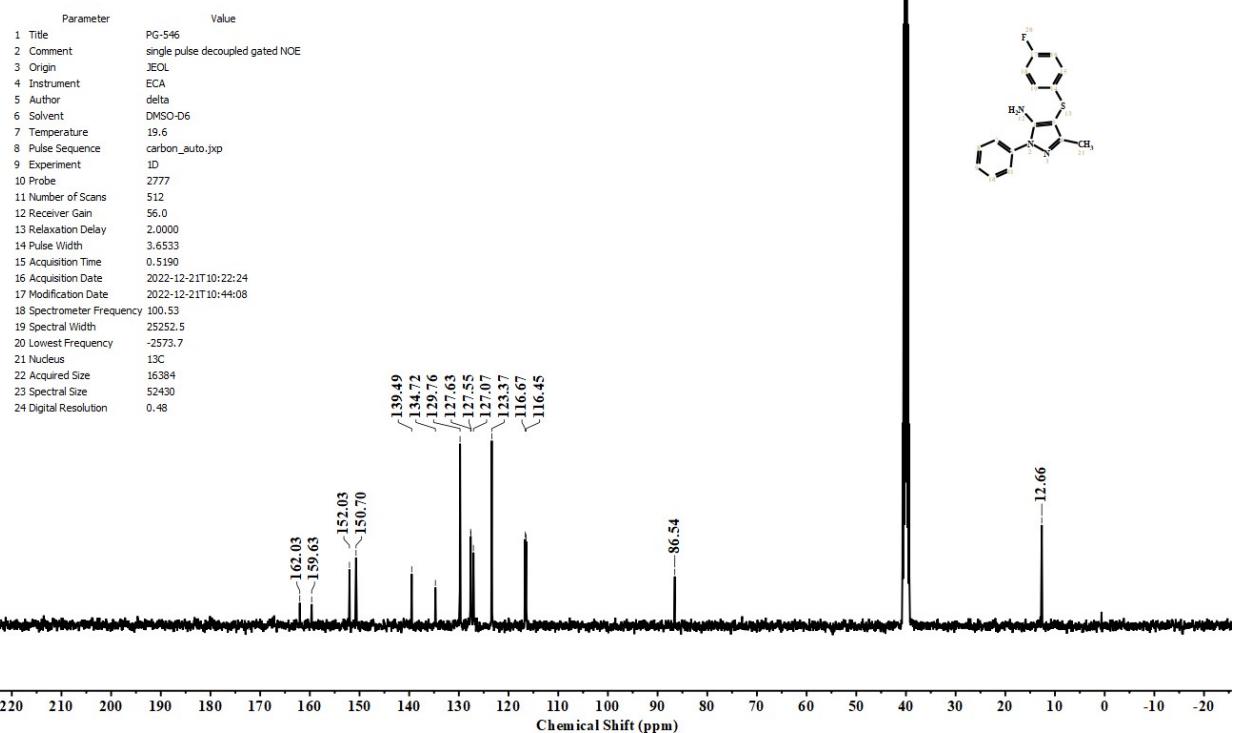


Figure S 31: ^{13}C NMR of 4-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**3h**)

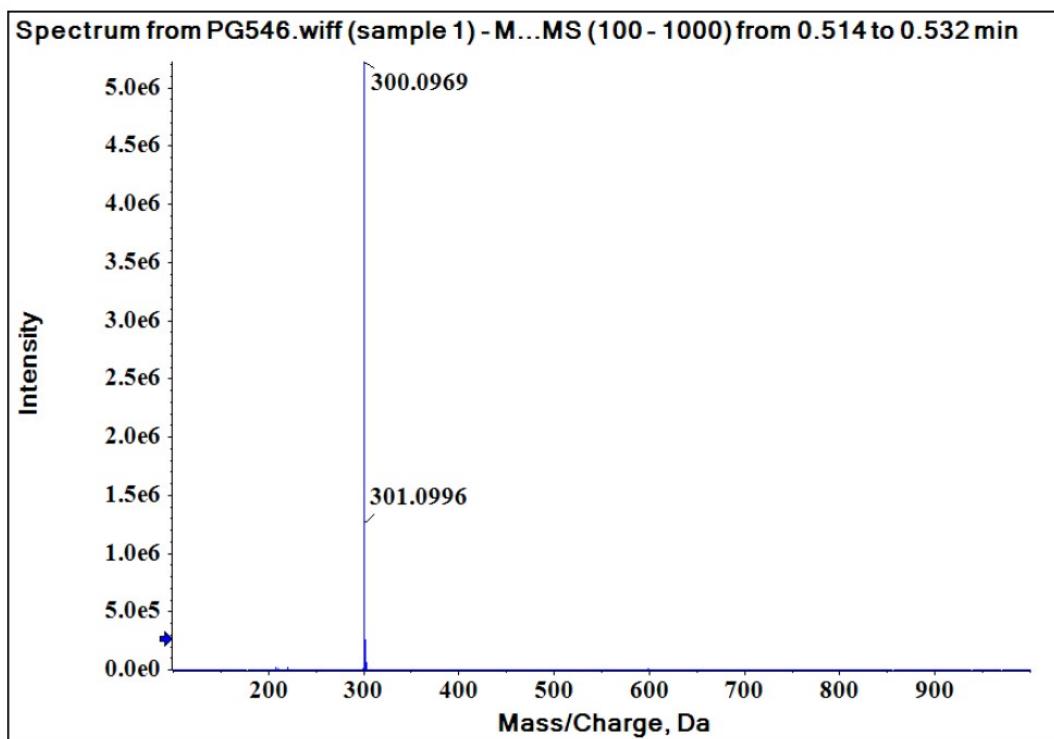


Figure S 32: Mass spectrometry of 4-((4-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**3h**)

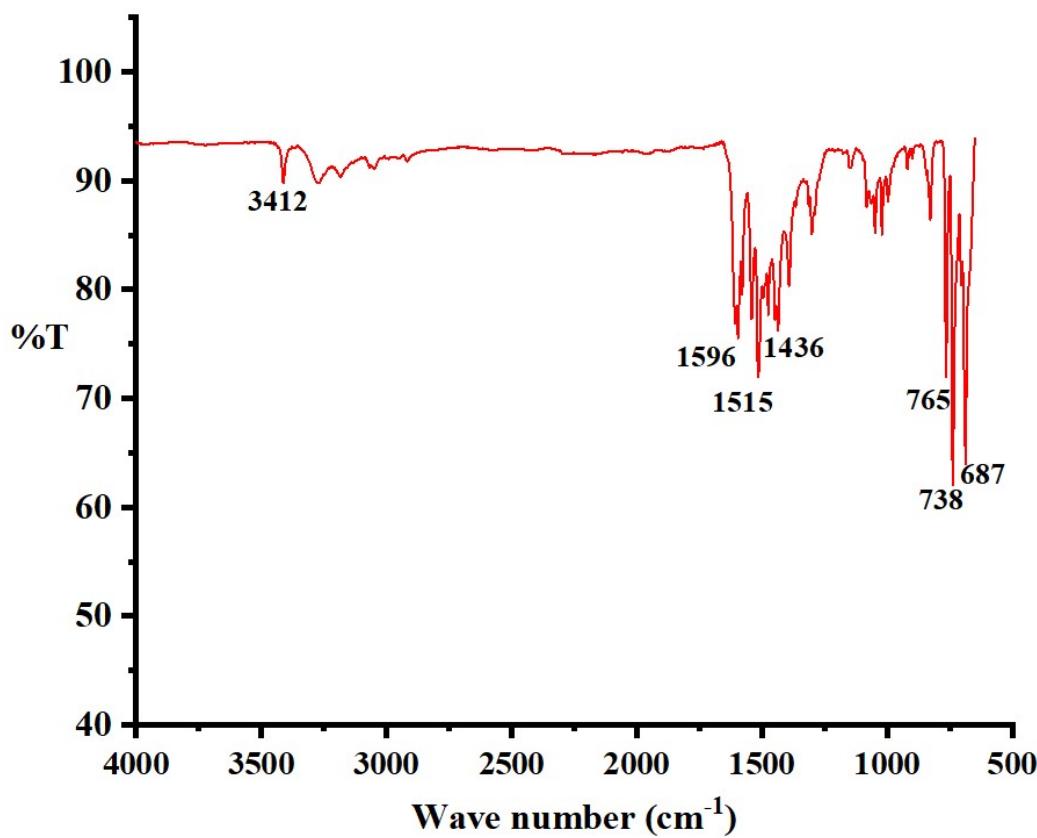


Figure S 33: FT-IR of 3-methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-amine (**3i**)

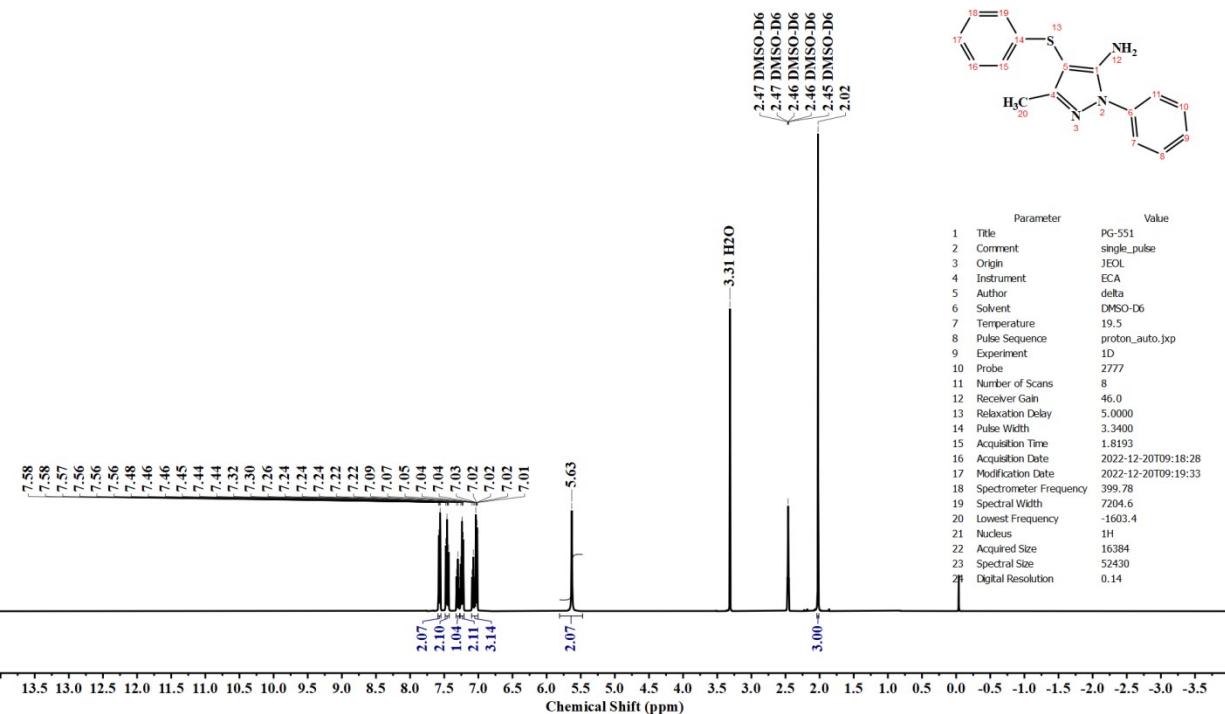


Figure S 34: ¹H NMR of 3-methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-amine (**3i**)

Parameter	Value
1 Title	PG-551
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	19.8
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	ID
10 Probe	277T
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-20T09:20:53
17 Modification Date	2022-12-20T09:42:37
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

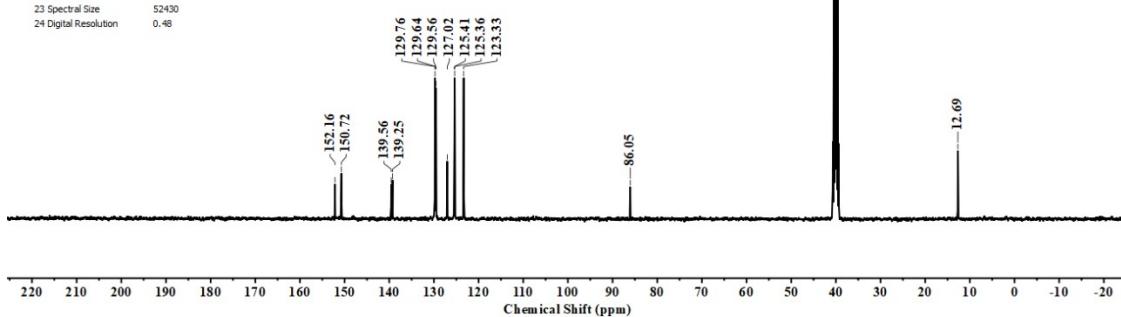
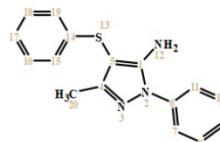


Figure S 35: ¹³C NMR of 3-methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-amine (3i)

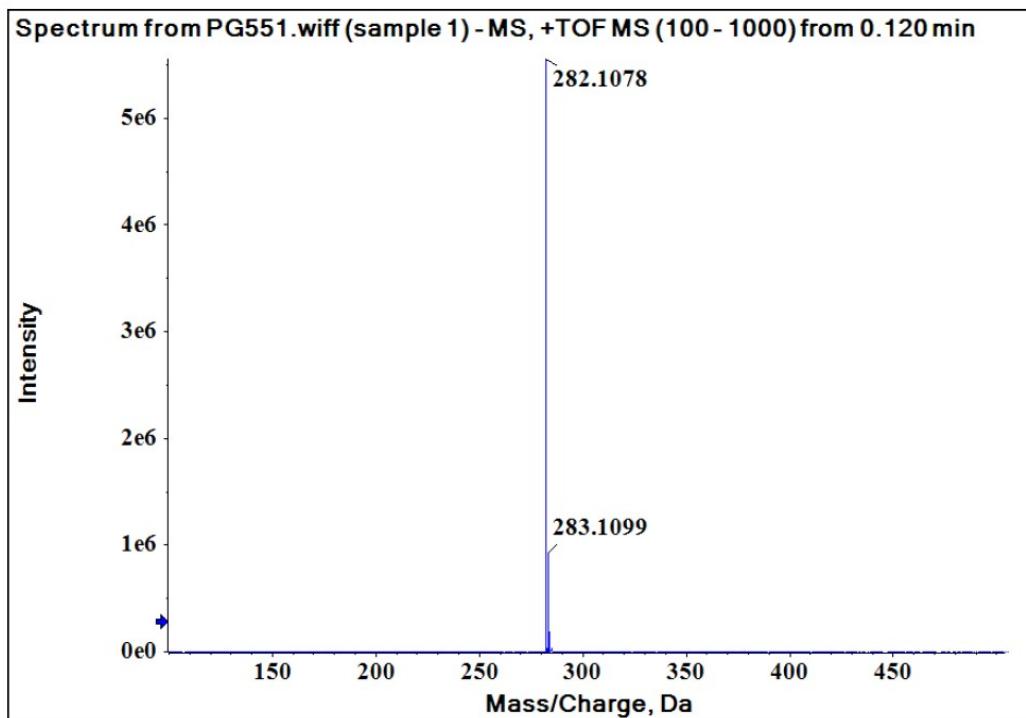


Figure S 36: Mass spectrometry of 3-methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-amine (3i)

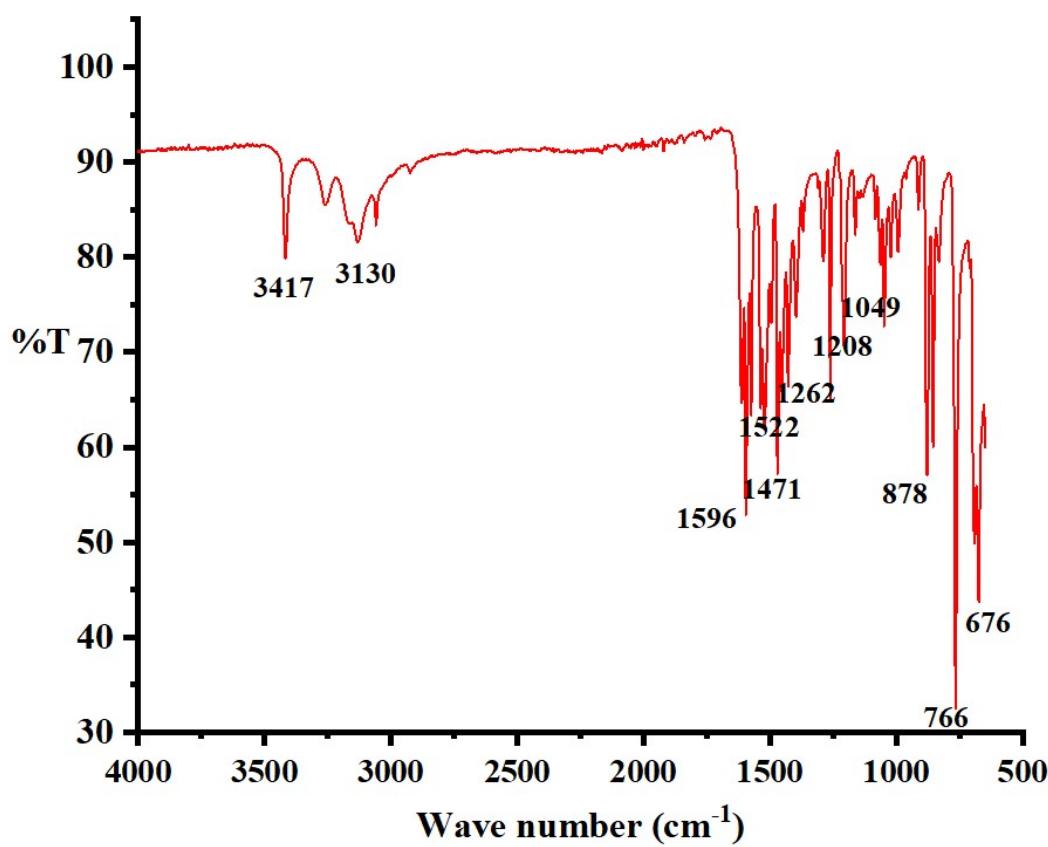


Figure S 37: FT-IR of 4-((3-fluorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3j**)

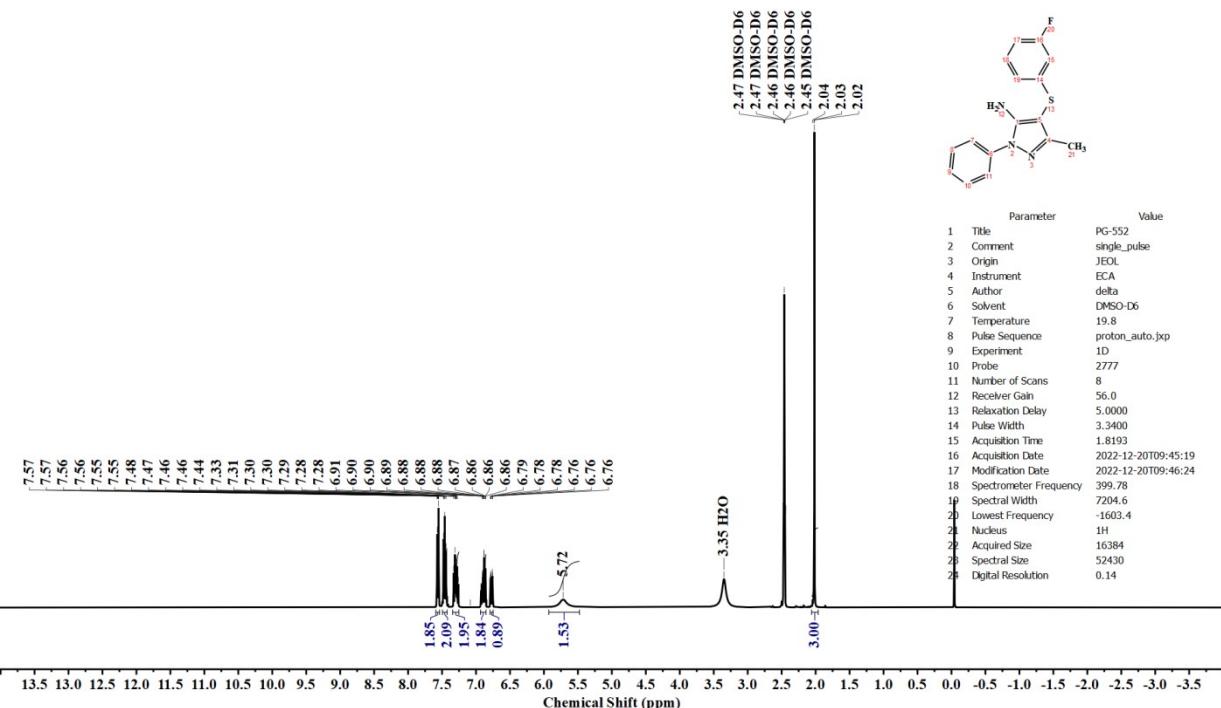


Figure S 38: ¹H NMR of 4-((3-fluorophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3j**)

Parameter	Value
1 Title	PG-552
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	20.0
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2022-12-20T09:47:44
17 Modification Date	2022-12-20T10:09:27
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

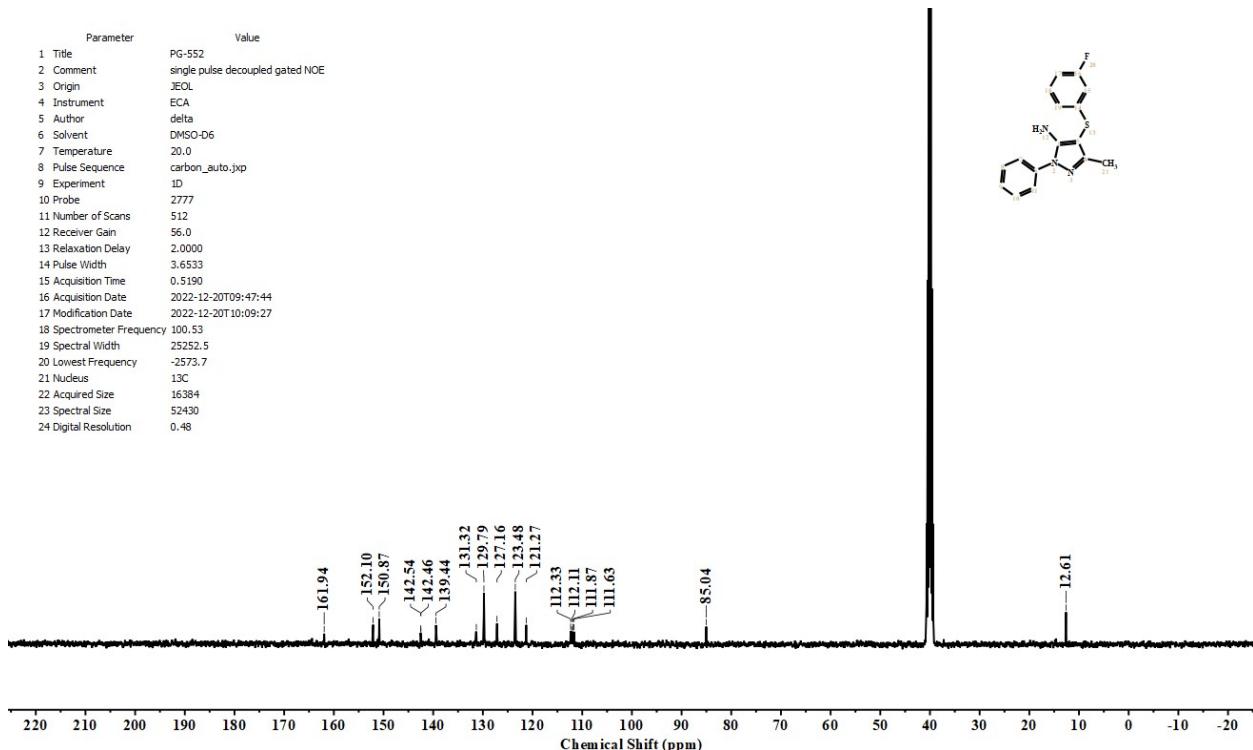
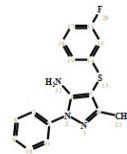


Figure S 39: ^{13}C NMR of 4-((3-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3j)

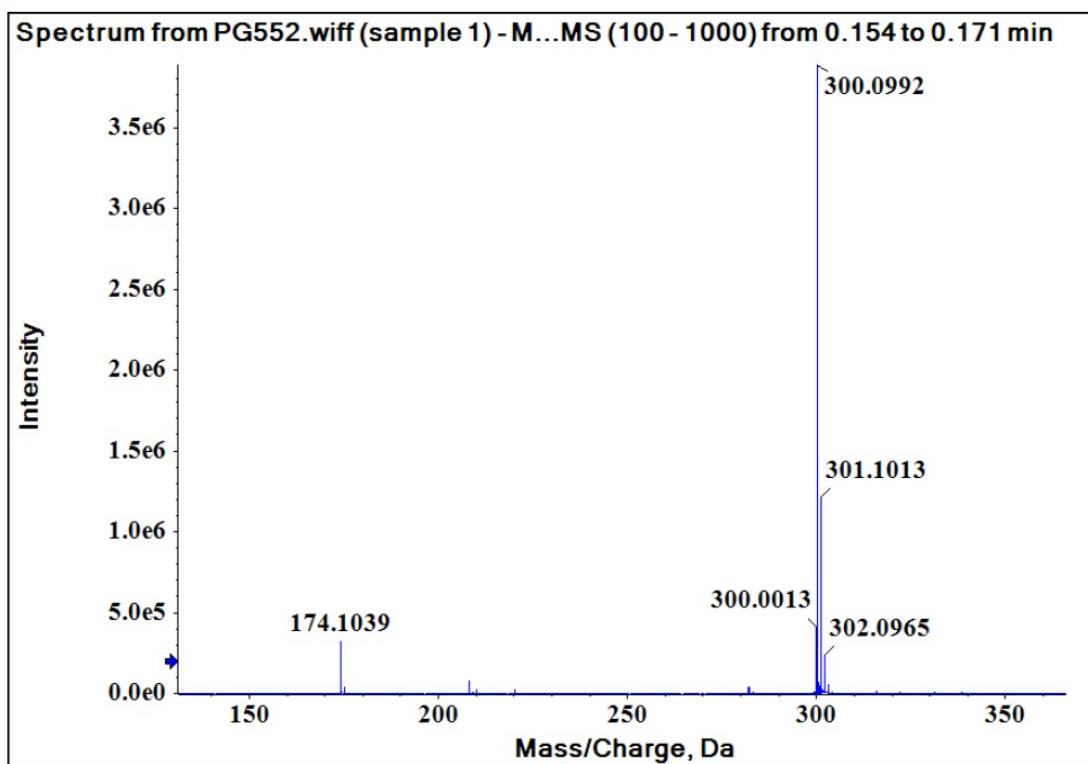


Figure S 40: Mass spectrometry of 4-((3-fluorophenyl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (3j)

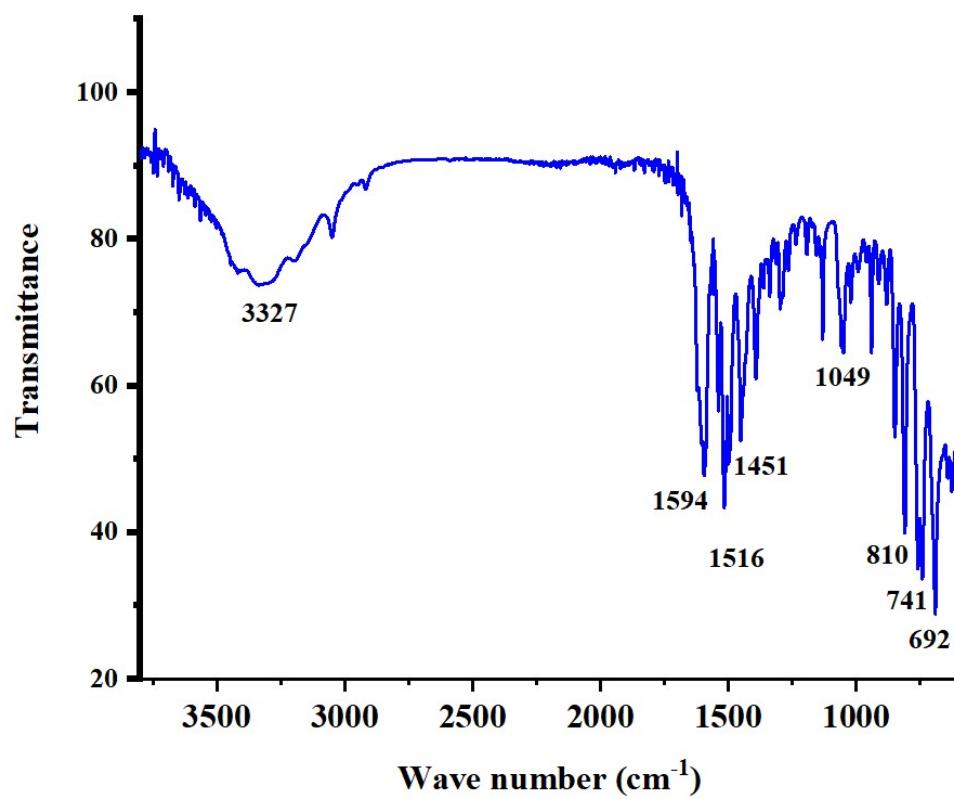


Figure S 41: FT-IR of 3-methyl-4-(naphthalen-2-ylthio)-1-phenyl-1H-pyrazol-5-amine (**3k**)

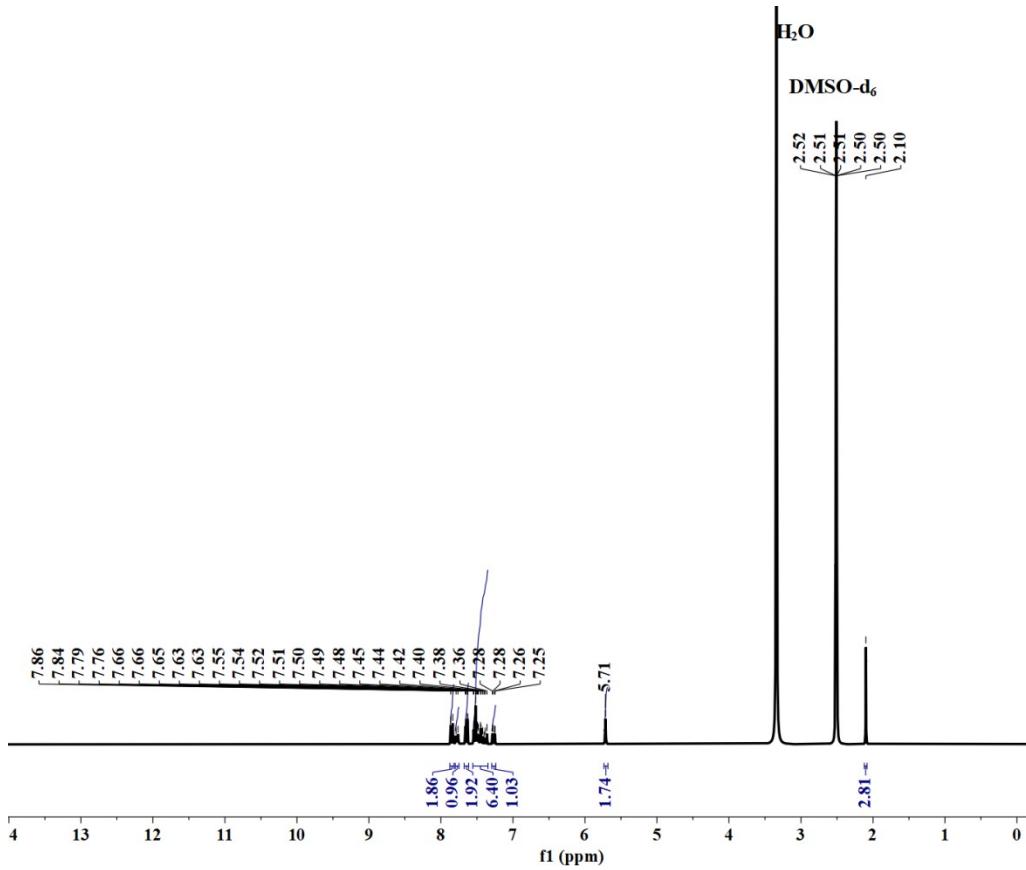


Figure S 42: ¹H NMR of 3-methyl-4-(naphthalen-2-ylthio)-1-phenyl-1H-pyrazol-5-amine (**3k**)

Parameter	Value
1 Title	PG-543
2 Comment	single pulse decoupled gated NOE
3 Origin	JEOL
4 Instrument	ECA
5 Author	delta
6 Solvent	DMSO-D6
7 Temperature	19.2
8 Pulse Sequence	carbon_auto.jxp
9 Experiment	1D
10 Probe	2777
11 Number of Scans	512
12 Receiver Gain	56.0
13 Relaxation Delay	2.0000
14 Pulse Width	3.6533
15 Acquisition Time	0.5190
16 Acquisition Date	2023-01-03T13:34:57
17 Modification Date	2023-01-03T13:56:40
18 Spectrometer Frequency	100.53
19 Spectral Width	25252.5
20 Lowest Frequency	-2573.7
21 Nucleus	¹³ C
22 Acquired Size	16384
23 Spectral Size	52430
24 Digital Resolution	0.48

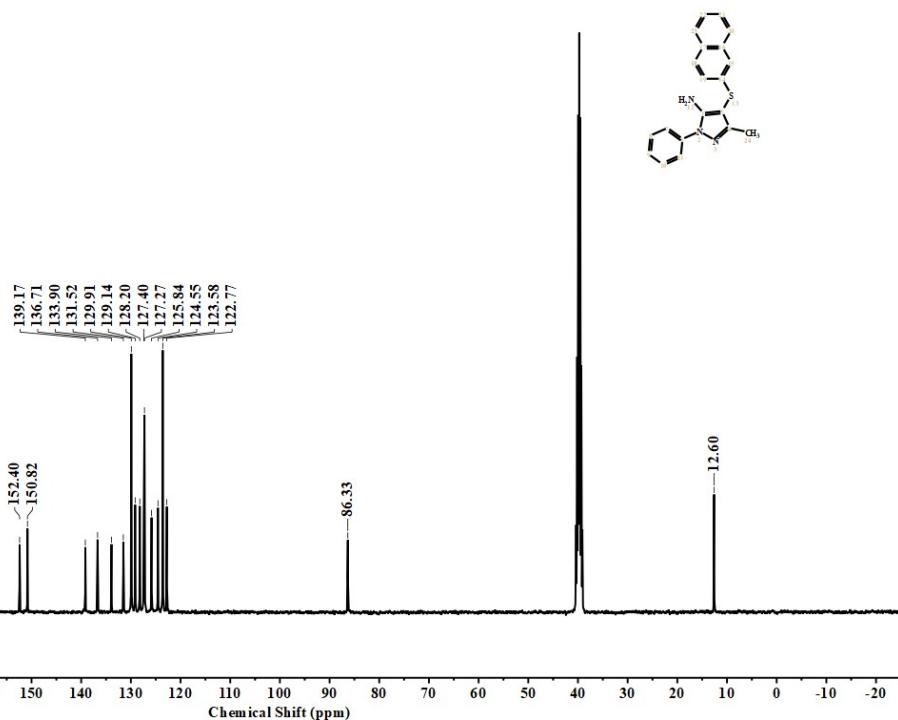


Figure S 43: ^{13}C NMR of 3-methyl-4-(naphthalen-2-ylthio)-1-phenyl-1*H*-pyrazol-5-amine (**3k**)

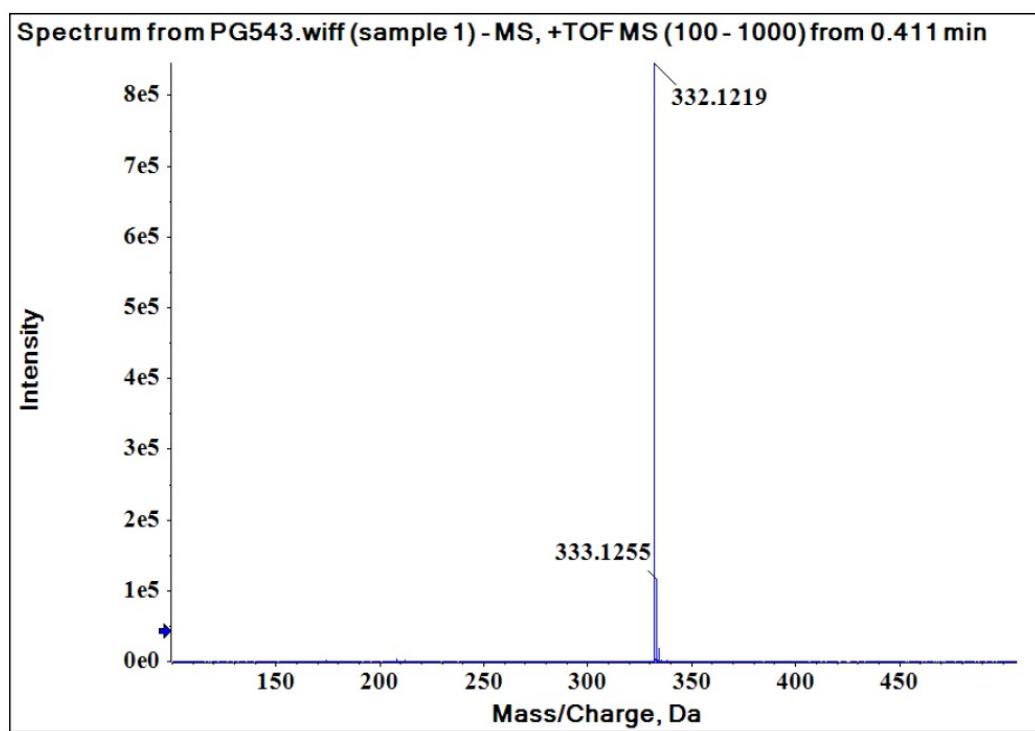


Figure S 44: Mass spectrometry of 3-methyl-4-(naphthalen-2-ylthio)-1-phenyl-1*H*-pyrazol-5-amine (**3k**)

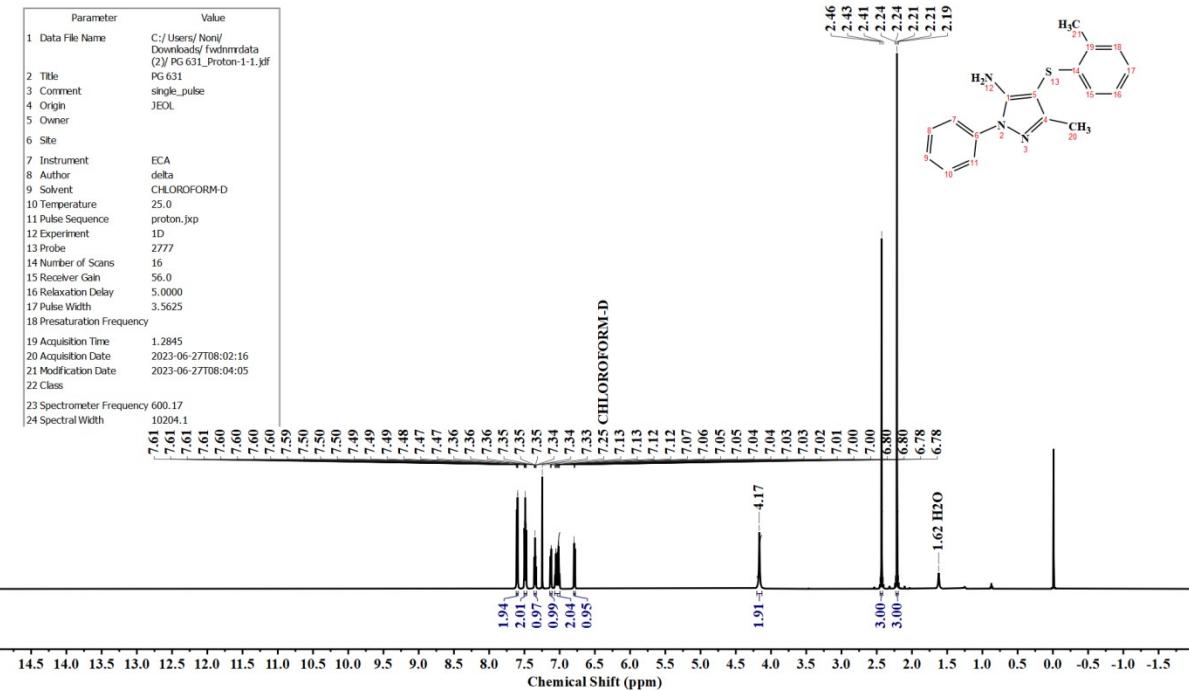


Figure S 45: ¹H NMR of 3-methyl-1-phenyl-4-(*o*-tolylthio)-1*H*-pyrazol-5-amine (**3l**)

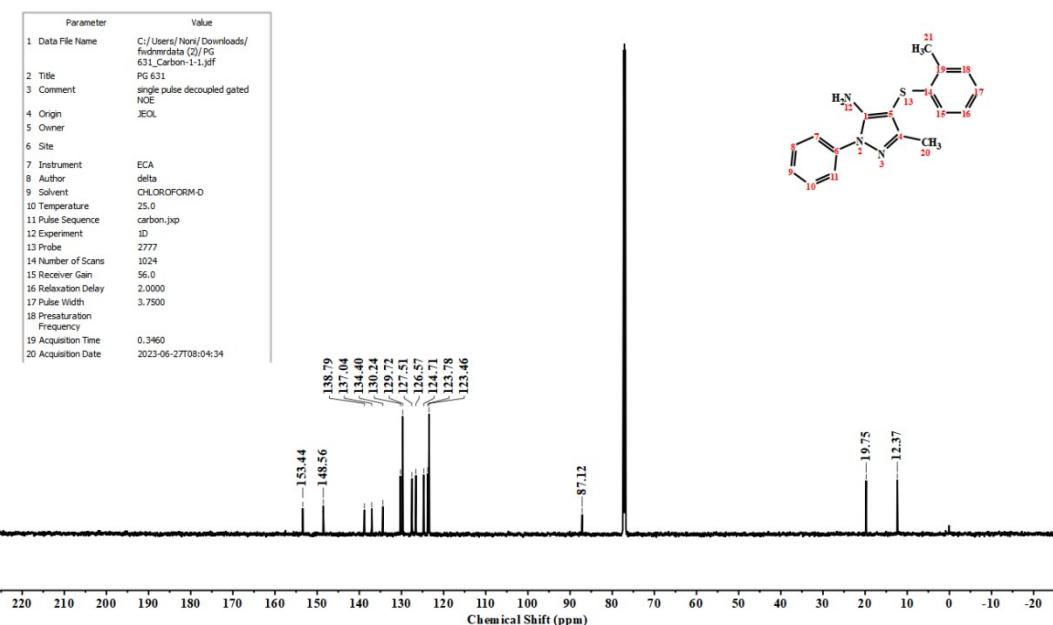


Figure S 46: ¹³C NMR of 3-methyl-1-phenyl-4-(*o*-tolylthio)-1*H*-pyrazol-5-amine (**3l**)

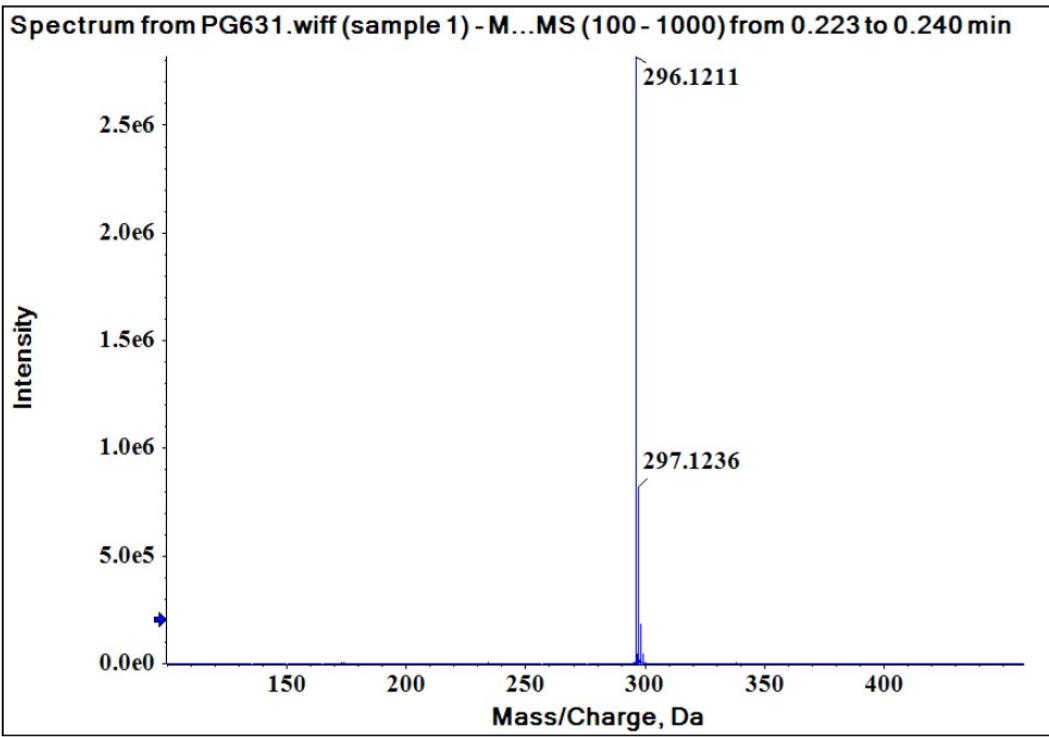


Figure S 47: Mass spectrometry of 3-methyl-1-phenyl-4-(*o*-tolylthio)-1*H*-pyrazol-5-amine (**3l**)

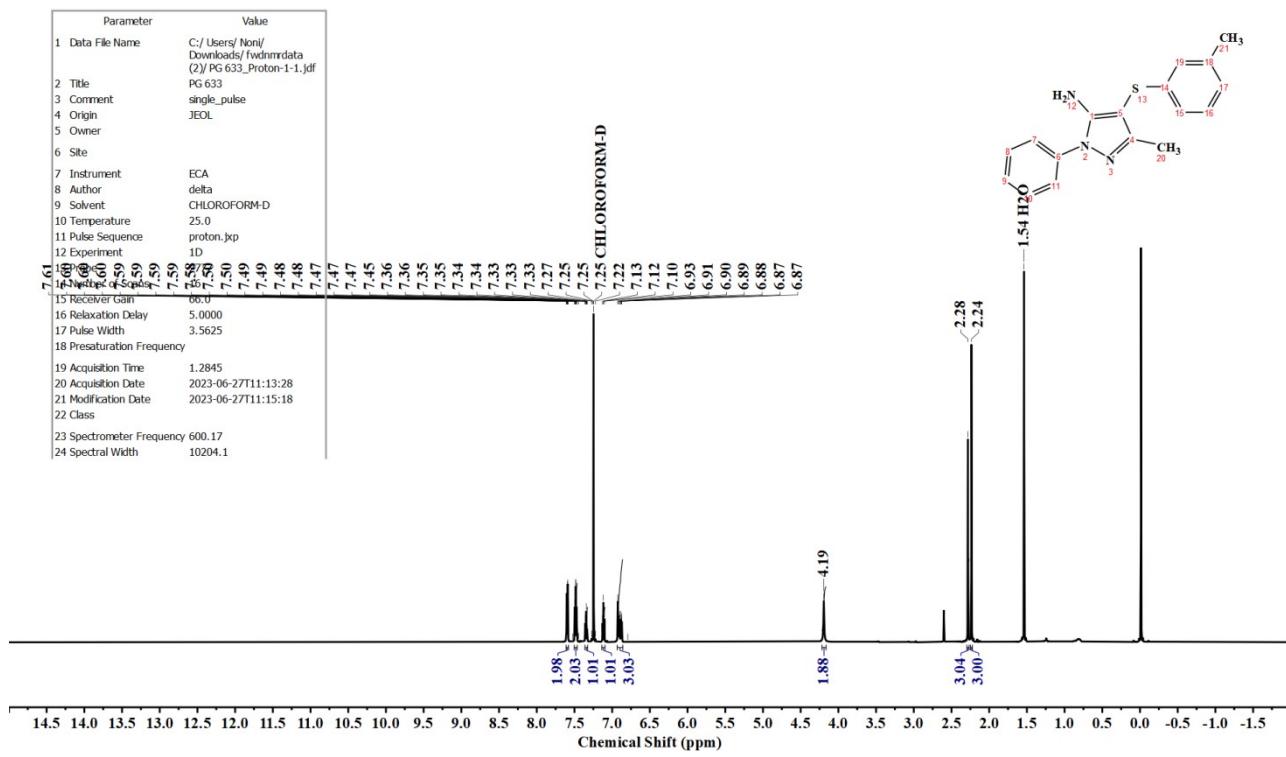


Figure S 48: ¹H NMR of 4-((3-methylphenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3m**)

Parameter	Value
1 Data File Name	C:/Users/Nan/Downloads/fwdmrdata (2)/PG633_Carbon-1-1.jdf
2 Title	PG 633
3 Comment	single pulse decoupled gated NOE
4 Origin	JEOL
5 Owner	
6 Site	
7 Instrument	ECA
8 Author	delta
9 Solvent	CHLOROFORM-D
10 Temperature	25.0
11 Pulse Sequence	carbon.jxp
12 Experiment	1D
13 Probe	2777
14 Number of Scans	1024
15 Receiver Gain	56.0
16 Relaxation Delay	2.0000
17 Pulse Width	3.7500
18 Presaturation Frequency	
19 Acquisition Time	0.3460
20 Acquisition Date	2023-06-27T11:15:48

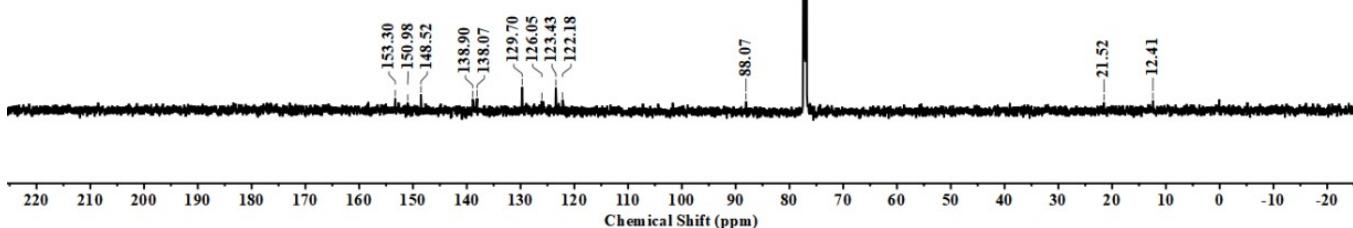
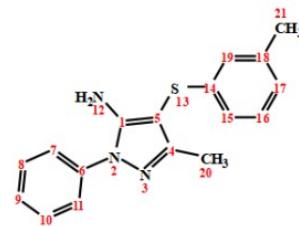


Figure S 49: ¹³C NMR of 4-((3-methylphenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3m**)

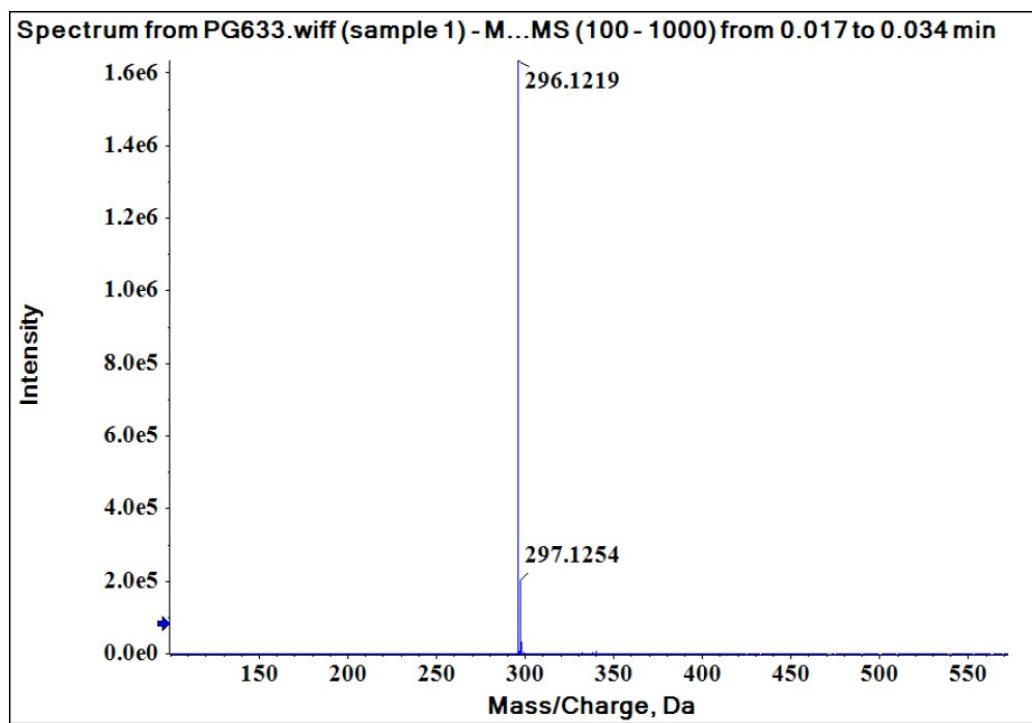


Figure S 50: Mass spectrometry of 4-((3-methylphenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3m**)

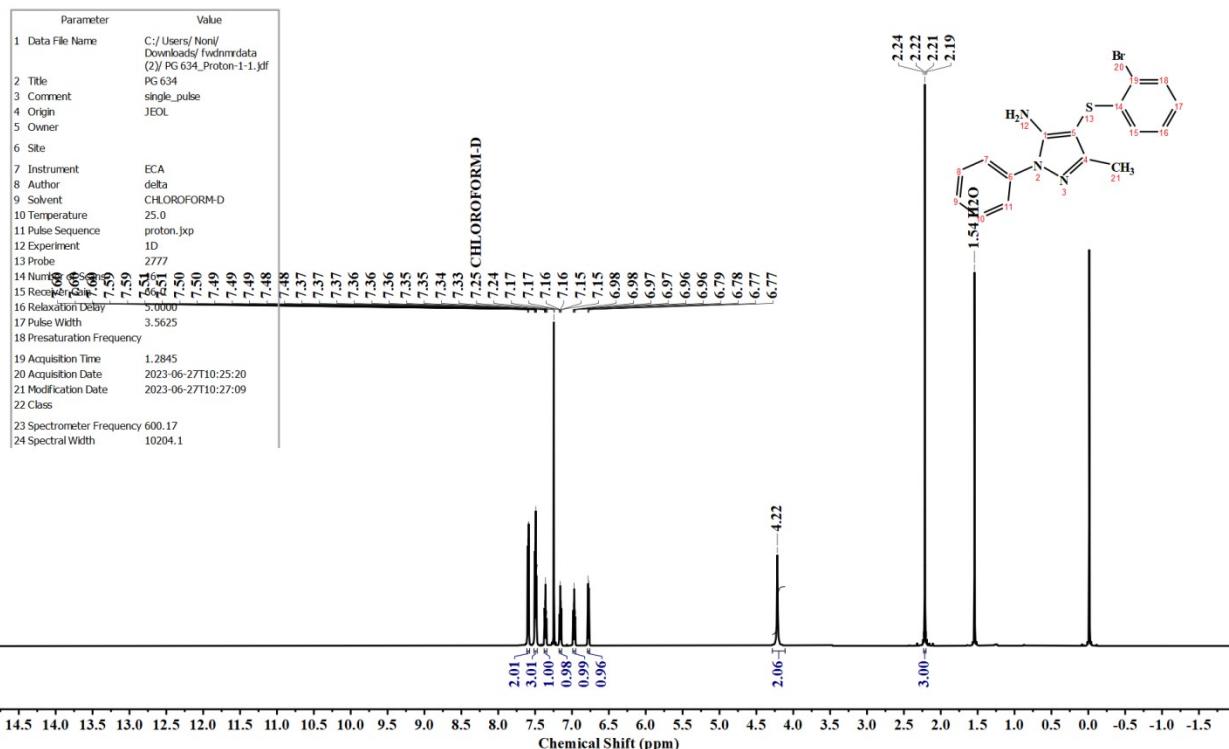


Figure S 51: ¹H NMR of 4-((2-bromophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3n**)

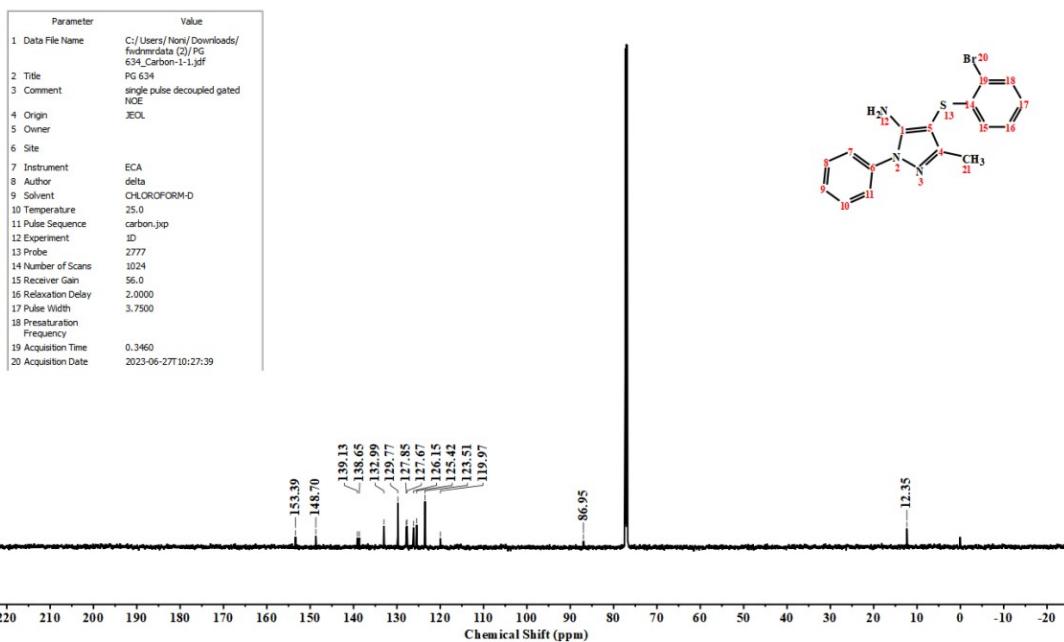


Figure S 52: ¹³C NMR of 4-((2-bromophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3n**)

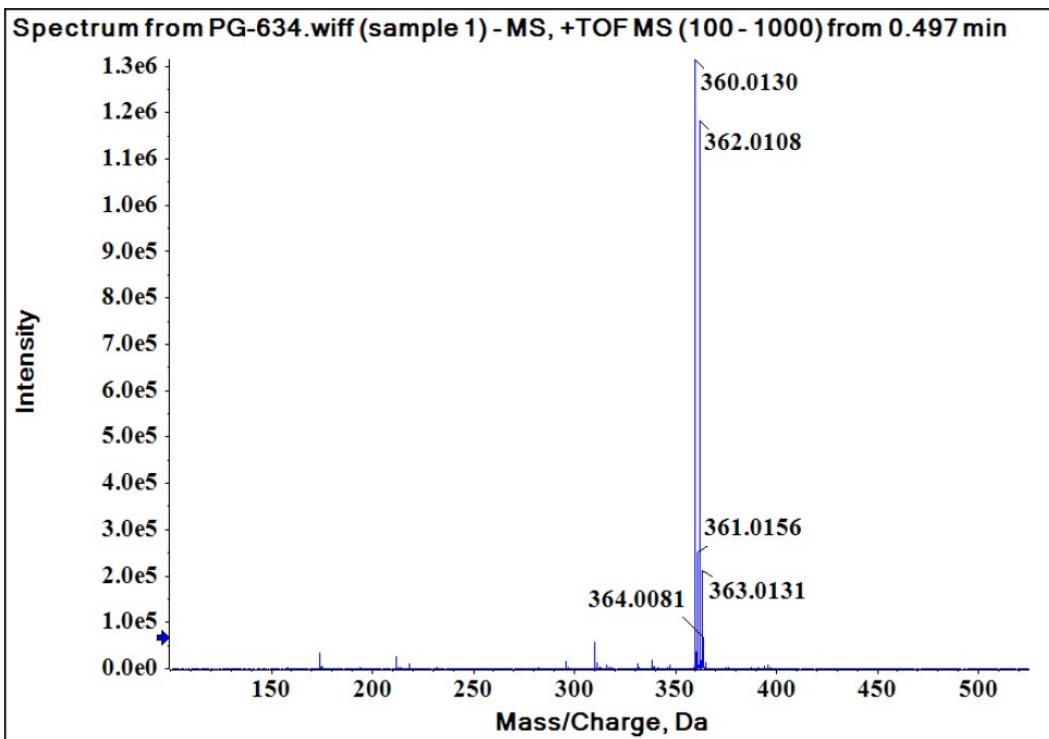


Figure S 53: Mass spectrometry of 4-((2-bromophenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3n**)

Parameter	Value
Title	PG-638
Comment	single_pulse
Origin	JEOL
Instrument	ECA
Author	della
Solvent	CHLOROFORM-D
Temperature	25.0
Pulse Sequence	proton.jpx
Experiment	1D
Probe	2777
Number of Scans	16
Receiver Gain	56.0
Relaxation Delay	5.0000
Pulse Width	3.5625
Acquisition Time	1.2845
Acquisition Date	2023-07-10T07:01:48
Modification Date	2023-07-10T07:03:38
Spectrometer Frequency	600.17
Spectral Width	10204.1
Lowest Frequency	-1200.9
Nucleus	1H
Acquired Size	16384
Spectral Size	104858
Digital Resolution	0.10

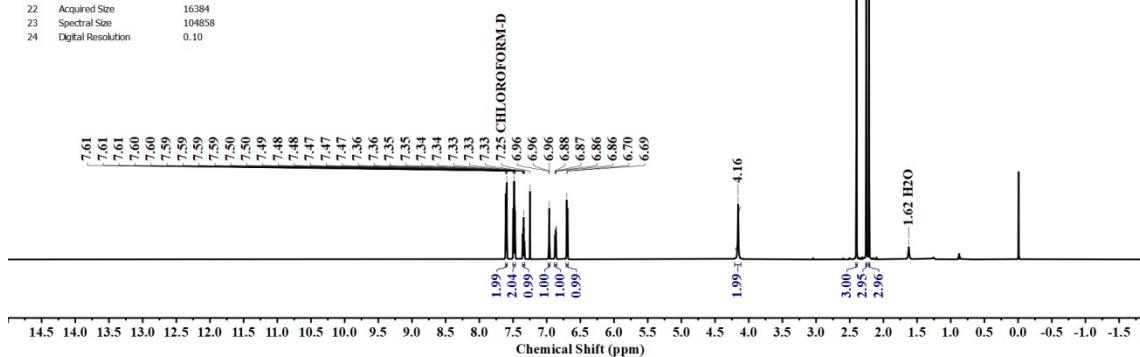
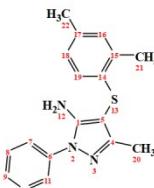


Figure S 54: ¹H NMR of 4-((2,4-dimethylphenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3o**)

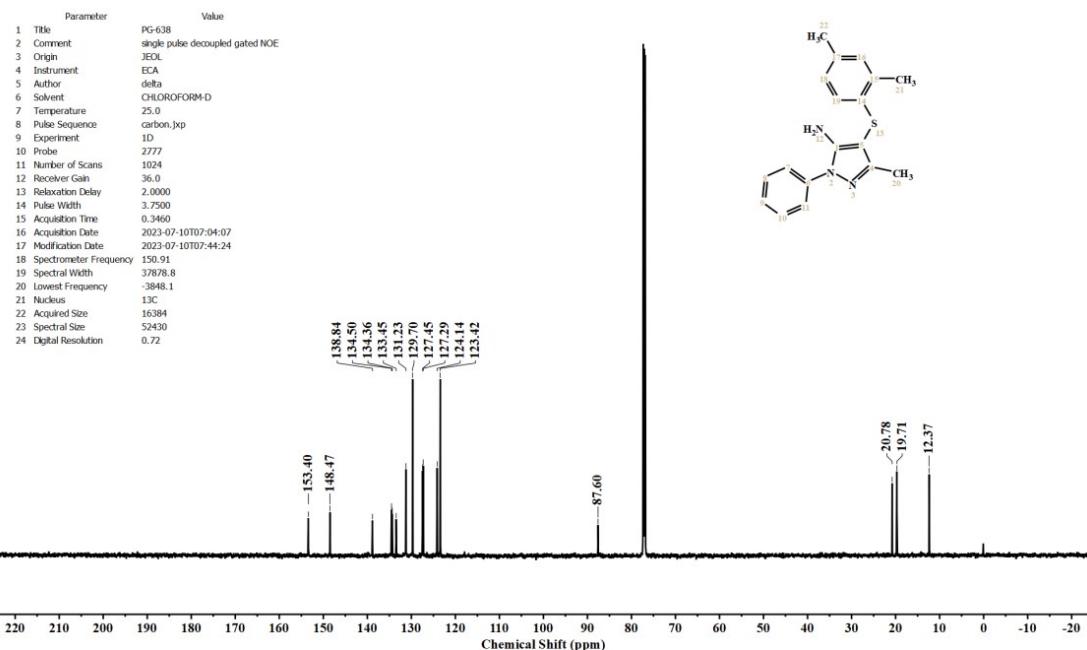


Figure S 55: ¹³C NMR of 4-((2,4-dimethylphenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3o**)

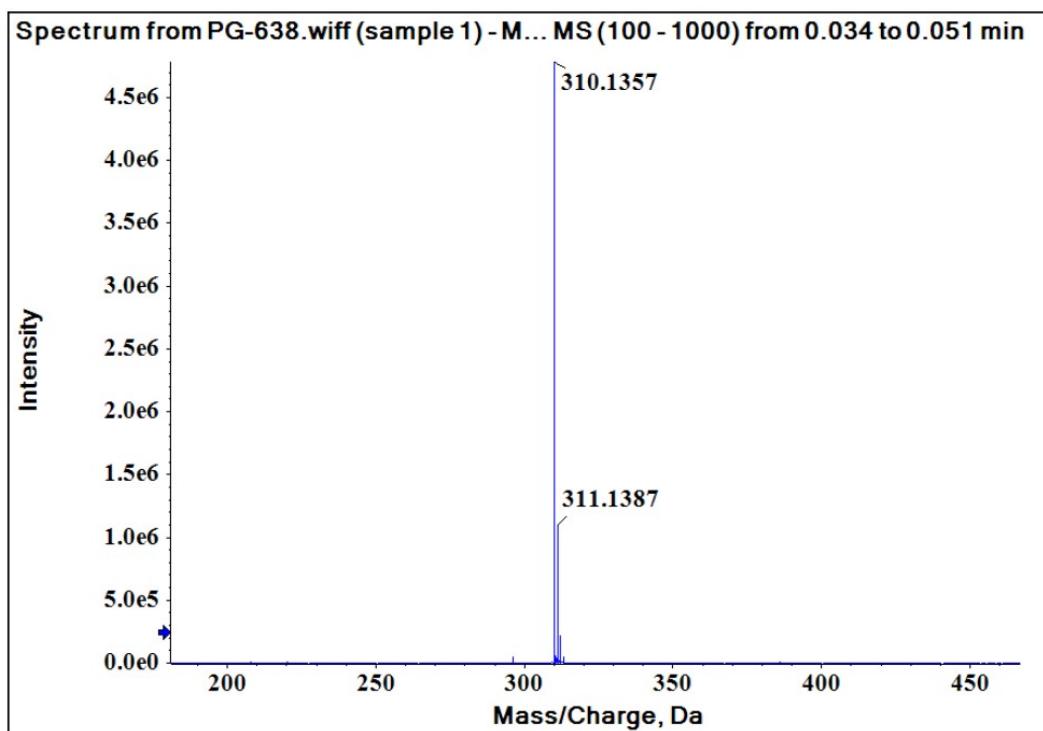


Figure S 56: Mass spectrometry of 4-((2,4-dimethylphenyl)thio)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3o**)

Single crystal X-ray diffraction studies

Suitable single crystals of **3i** were selected for X-ray diffraction studies. A Supernova single source at offset/far, HyPix3000 diffractometer was used for diffraction studies. All the data was collected at 293(2) K. Olex2 program was utilised for solving X-ray structure using Charge Flipping. All the data refinements were performed using the same package by employing the Gauss-Newton minimization. The crystallographic data for structure **3i** have been deposited with the Cambridge Crystallographic Data Centre under CCDC No. 2305521.

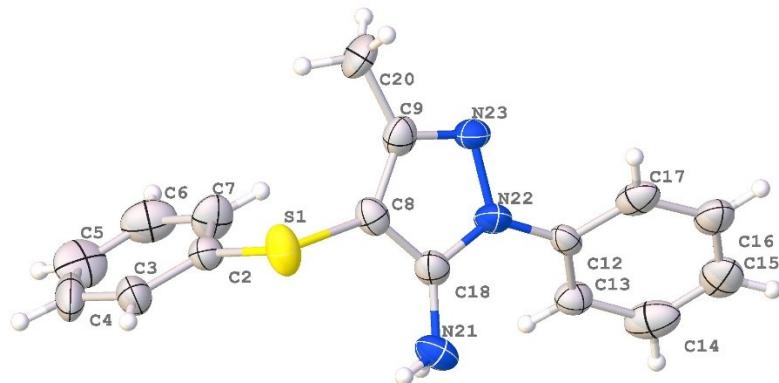
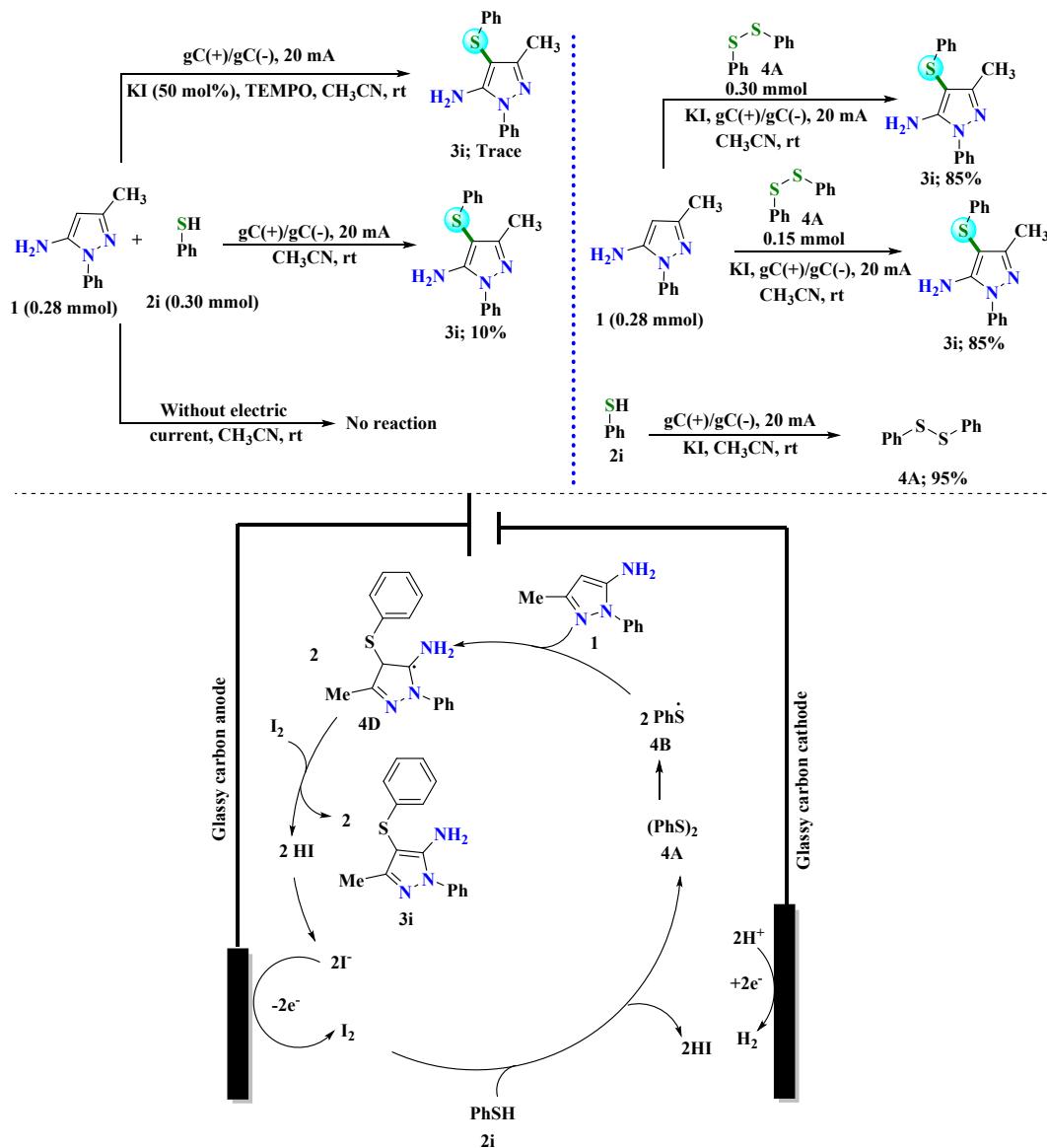


Figure S 57: Ortep diagram of **3i**

Table S1: Crystal data and structure refinement parameters for **3i**

Empirical formula	C ₁₆ H ₁₅ N ₃ S (3i)
Formula weight	281.37
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	Pna ₂ ₁
a/Å	11.7569(10)
b/Å	9.4089(9)
c/Å	26.936(3)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2979.6(5)
Z	8
ρ _{calc} g/cm ³	1.254
μ/mm ⁻¹	0.211
F(000)	1184.0
Crystal size/mm ³	0.16 × 0.14 × 0.12
Radiation	Mo Kα (λ = 0.71073)

2θ range for data collection/°	6.318 to 52.746
Index ranges	-13 ≤ h ≤ 14, -11 ≤ k ≤ 8, -30 ≤ l ≤ 33
Reflections collected	11829
Independent reflections	4866 [R _{int} = 0.2698, R _{sigma} = 0.1505]
Data/restraints/parameters	4866/7/365
Goodness-of-fit on F ²	0.984
Final R indexes [I>=2σ (I)]	R ₁ = 0.0949, wR ₂ = 0.2448
Final R indexes [all data]	R ₁ = 0.1829, wR ₂ = 0.3321
Largest diff. peak/hole / e Å ⁻³	0.41/-0.42



Scheme S1: Controlled experiments and plausible reaction mechanism for the electro-organocatalyzed sulfonylation of aminopyrazole