

Supporting Information

**Novel 4-Thiophenyl- Pyrazole, Pyridine, and Pyrimidine Derivatives as Potential Antitumor Candidates Targeting Both EGFR and VEGFR-2; Design, Synthesis, Biological Evaluations, and *In Silico* Studies**

Samia M. Al-Muntaser<sup>a,ψ</sup>, Ahmed A. Al-Karmalawy<sup>b,ψ,\*</sup>, Abeer M. El-Naggar<sup>a</sup>, Ali Khalil Ali<sup>a</sup>, Nour E. A. Abd El-Sattar<sup>a</sup>, and Eslam M. Abbass<sup>a,\*</sup>

<sup>a</sup> Department of Chemistry, Faculty of Science, Ain Shams University, Abbassiya 11566, Cairo, Egypt.

<sup>b</sup> Pharmaceutical Chemistry Department, Faculty of Pharmacy, Ahram Canadian University, 6th of October City, Giza 12566, Egypt.

\* Corresponding authors:

**Ahmed A. Al-Karmalawy:** Email: [akarmalawy@acu.edu.eg](mailto:akarmalawy@acu.edu.eg)

**ORCID:** [0000-0002-8173-6073](https://orcid.org/0000-0002-8173-6073)

**Eslam M. Abbass:** Email: [eslammorad@sci.asu.edu.eg](mailto:eslammorad@sci.asu.edu.eg)

**ORCID:** [0000-0002-3245-1653](https://orcid.org/0000-0002-3245-1653)

**ψ:** Equal contribution.

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## Yields and elemental analysis

## Supporting Information

**Table S1.** Yields and elemental analysis of target compounds (**1b-20a**).

Code	Yield (%)	Elemental analysis					
		Calculated			Found		
		C	H	N	C	H	N
<b>1b</b>	55	55.14	2.85		54.89	2.74	
<b>2a</b>	83	65.51	3.78	14.32	65.36	3.70	14.12
<b>2b</b>	63	55.51	2.62	12.14	55.34	3.54	12.21
<b>3a</b>	75	65.58	4.21	10.49	65.45	4.14	4.42
<b>4a</b>	83	63.33	4.43	4.10	63.10	4.32	4.00
<b>5a</b>	67	65.29	3.42	9.52	65.18	3.48	9.60
<b>6a</b>	77	63.32	3.36	15.55	63.09	3.40	15.48
<b>7a</b>	83	63.91	4.95	11.47	63.72	4.84	11.36
<b>8b</b>	75	53.11	3.57	8.26	52.89	3.50	8.35
<b>9b</b>	81	61.13	3.78	7.50	60.87	3.66	7.43
<b>10a</b>	73	55.79	3.68	13.94	55.58	3.72	14.05
<b>10b</b>	65	47.47	2.56	11.86	47.30	2.49	11.76
<b>11a</b>	76	62.44	4.12	15.60	62.23	4.19	15.51
<b>12a</b>	78	61.81	3.07	16.38	61.69	3.00	16.26
<b>12b</b>	63	55.94	3.20	8.90	55.75	3.12	8.79
<b>13a</b>	51	67.54	4.05	11.35	67.39	4.00	11.34
<b>14a</b>	81	63.30	4.52	11.07	63.08	4.59	11.17
<b>15a</b>	75	61.80	5.49	8.48	61.65	5.45	8.57
<b>16a</b>	66	55.25	4.42	12.27	55.09	4.33	12.38
<b>17a</b>	87	53.18	4.46	6.89	53.00	4.38	6.77
<b>18a</b>	83	59.41	3.80	6.60	59.24	3.72	6.71
<b>19a</b>	81	50.78	3.73	7.40	50.39	3.55	7.31
<b>20a</b>	83	48.42	3.30	7.06	48.22	3.22	7.15

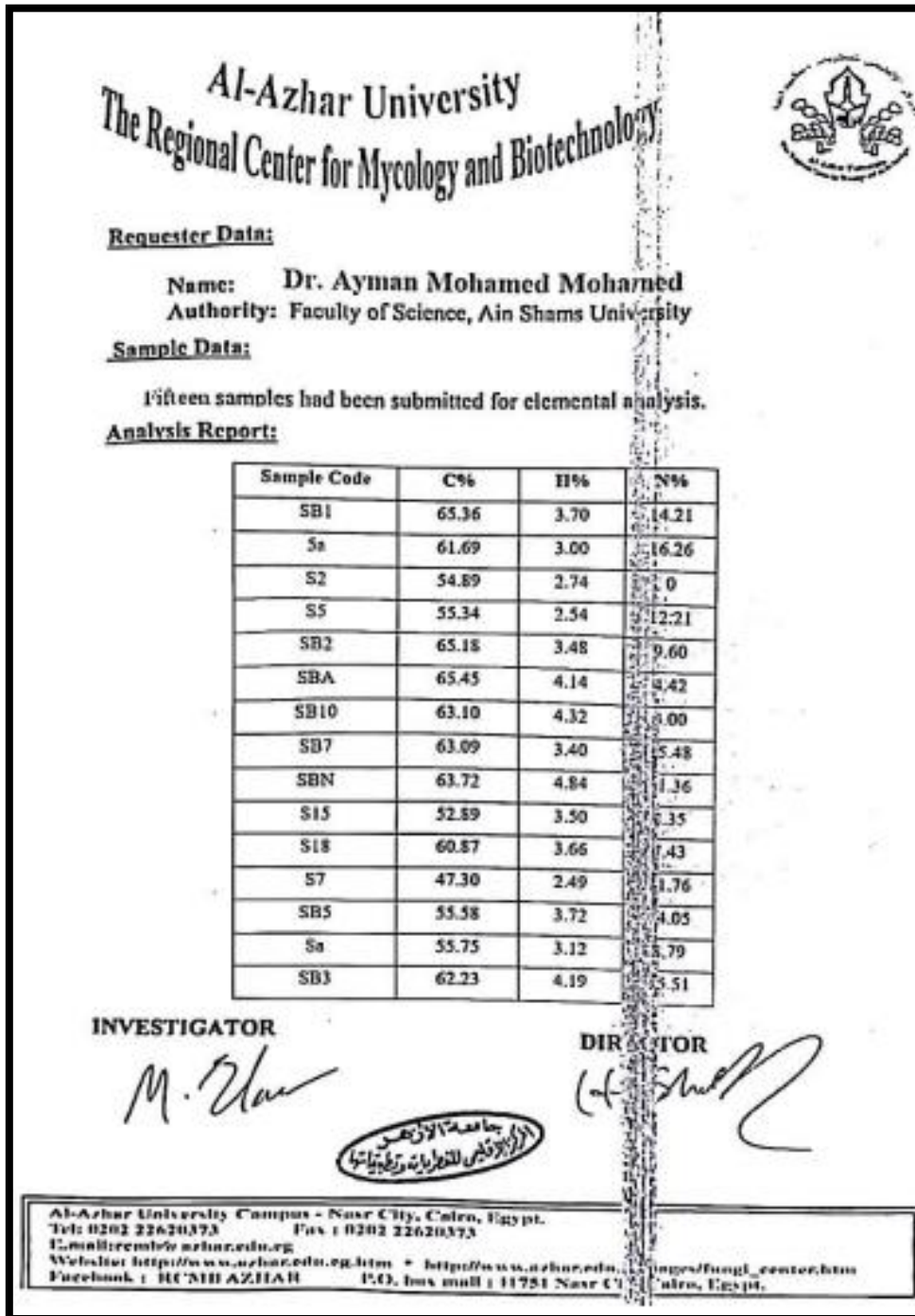


Figure S1. Elemental analysis of fifteen compounds.

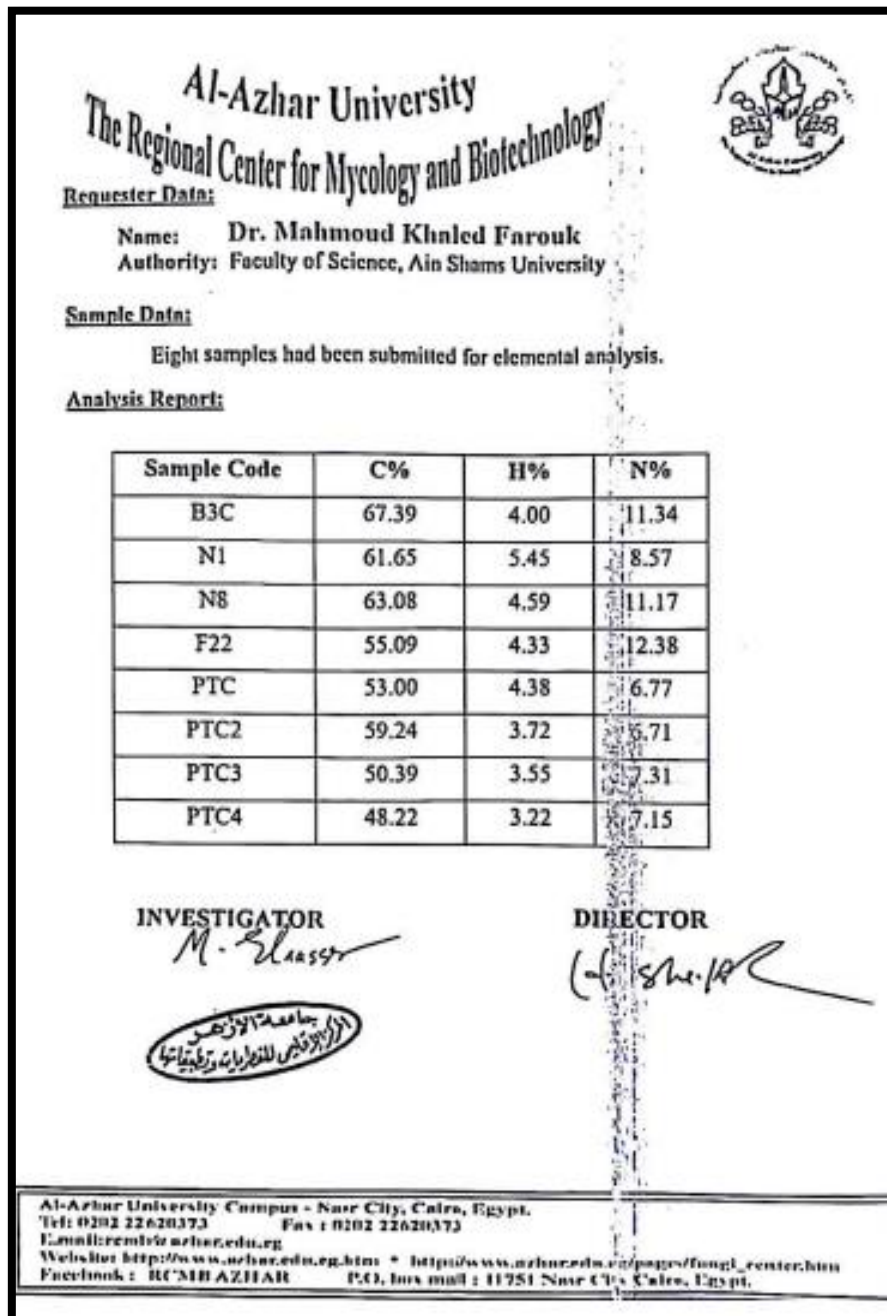


Figure S2. Elemental analysis of eight compounds.

## IR spectral data of the target compounds (1b-20a)

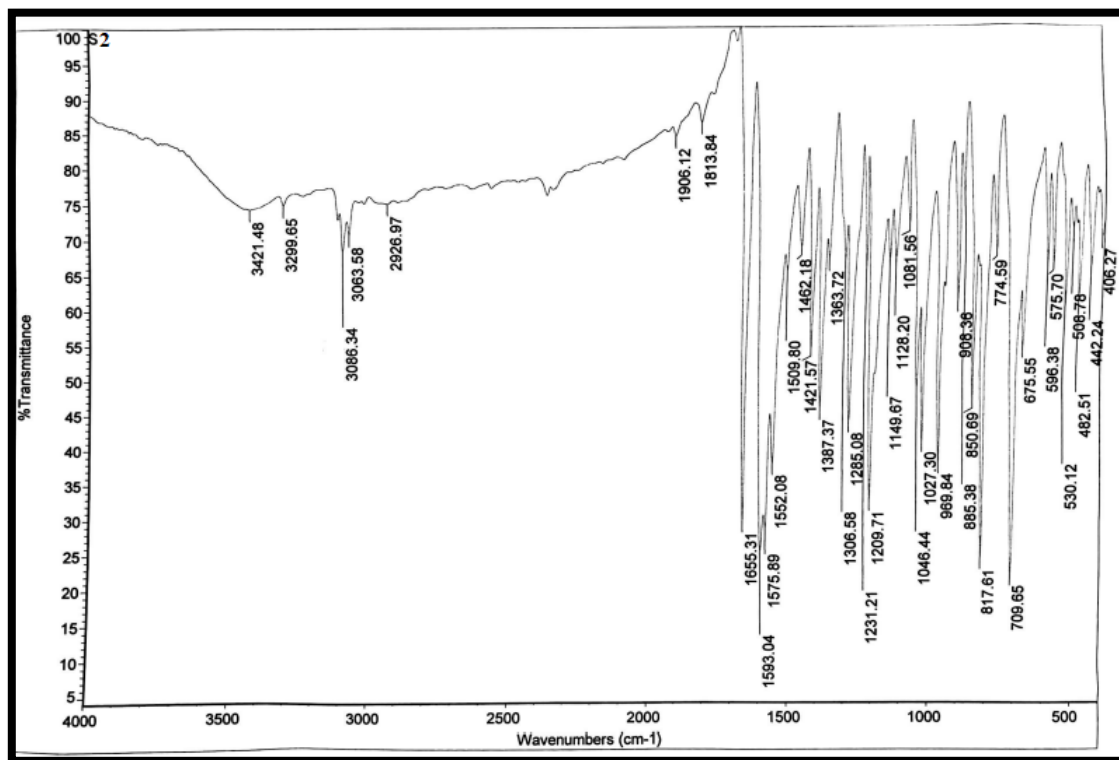


Figure S3. IR spectrum of compound 1b

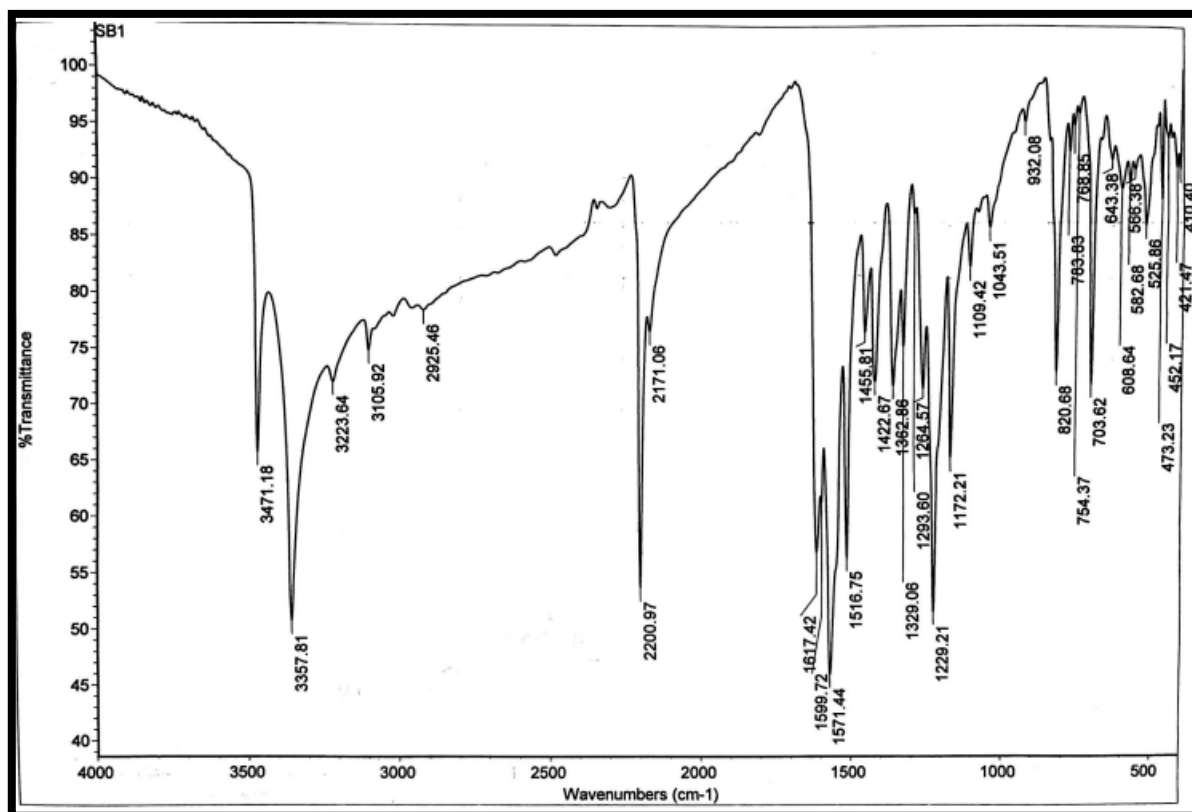


Figure S4. IR spectrum of compound 2a

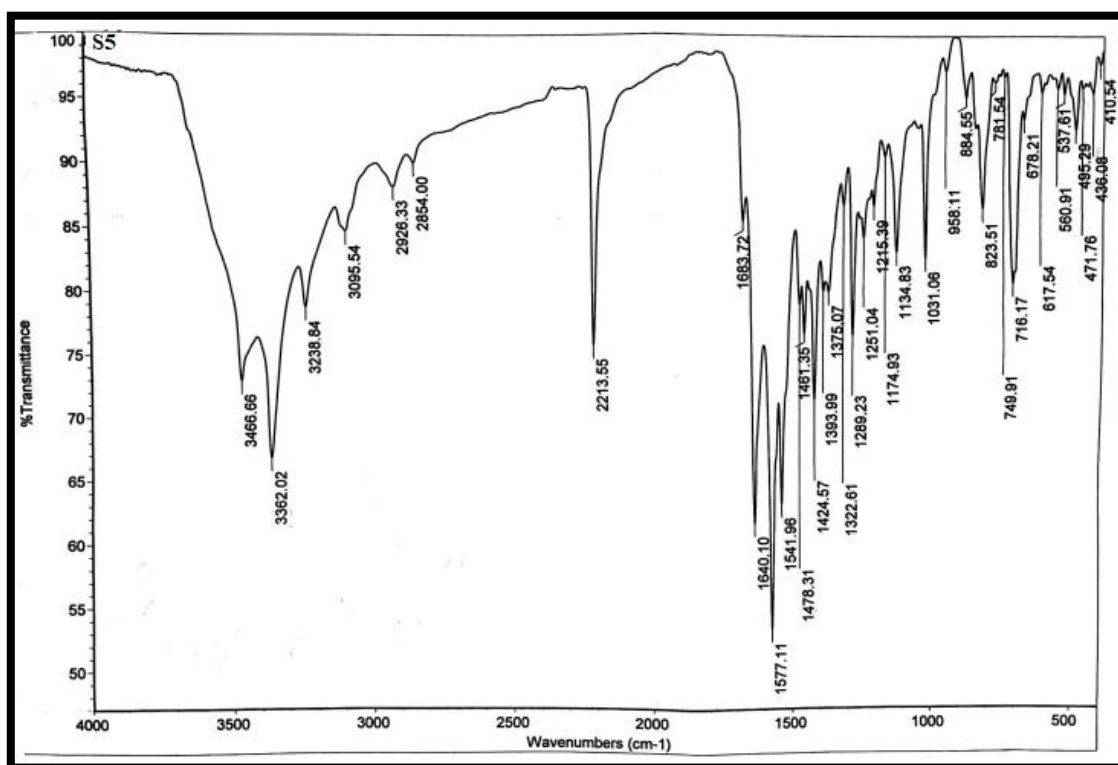


Figure S5. IR spectrum of compound 2b

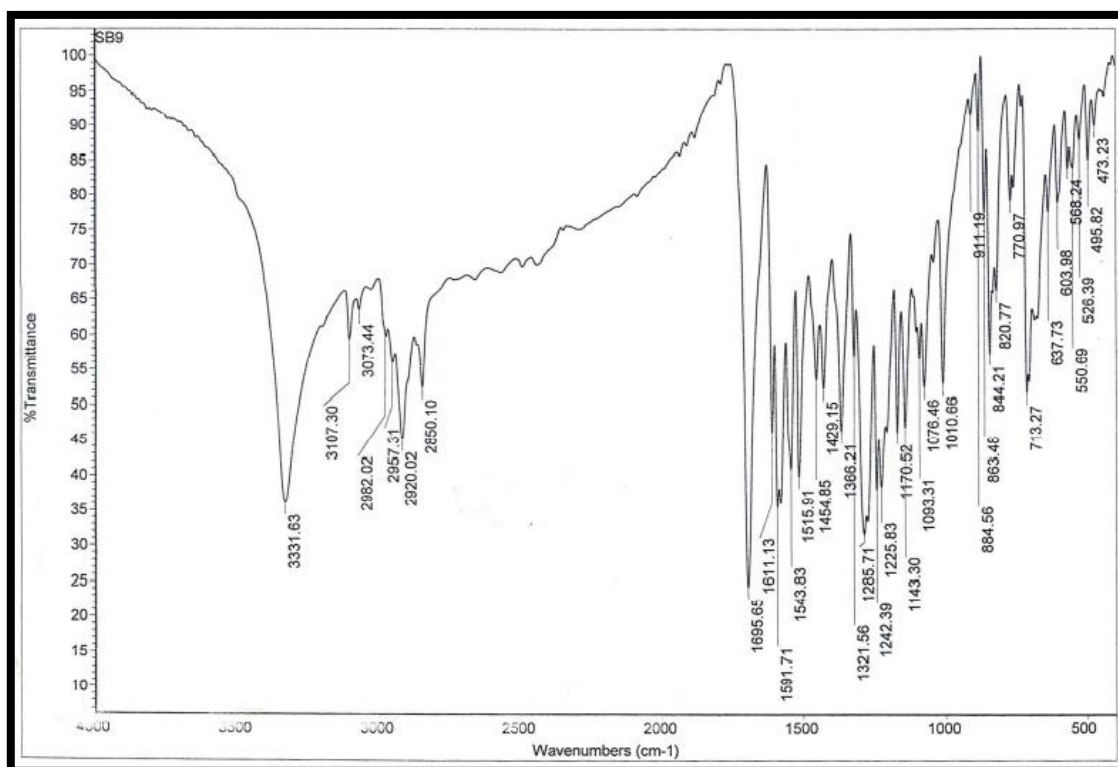


Figure S6. IR spectrum of compound 3a



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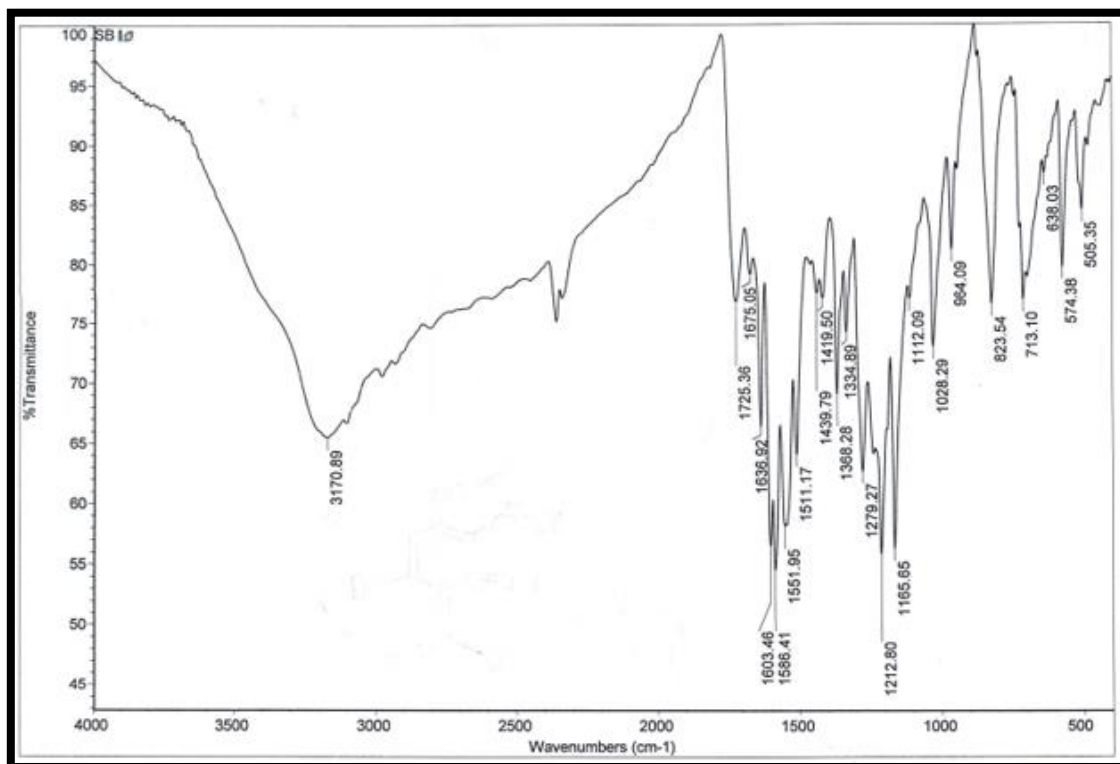


Figure S7. IR spectrum of compound 4a

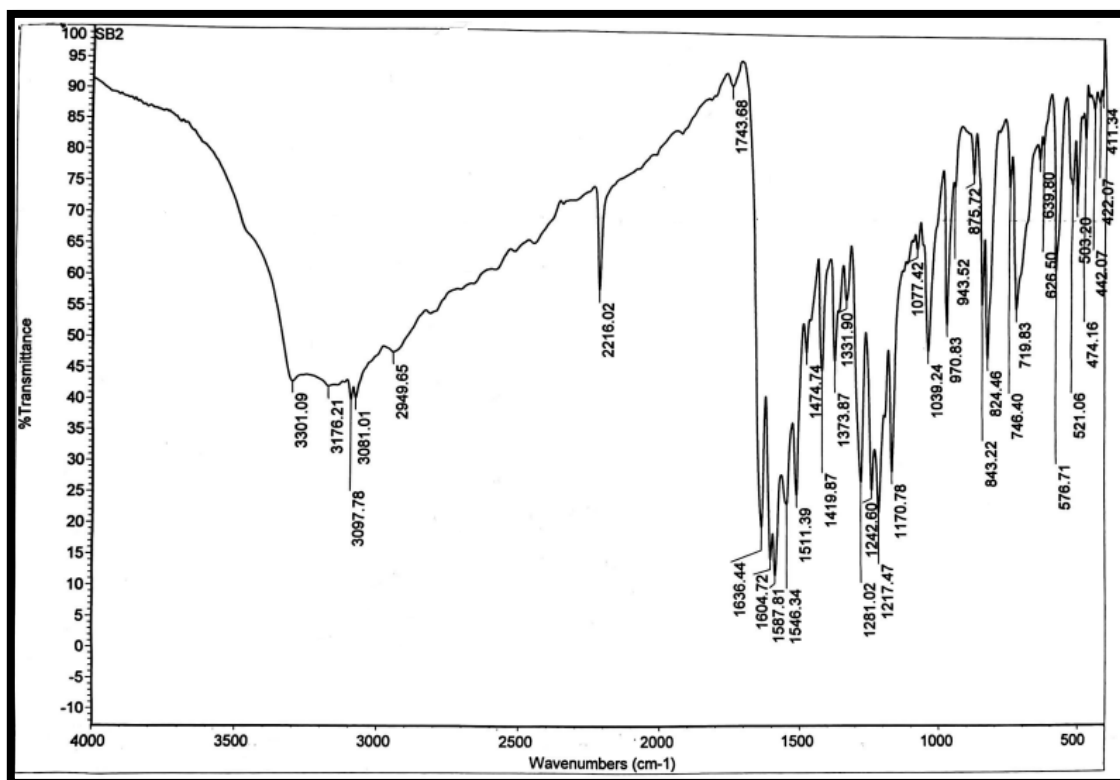


Figure S8. IR spectrum of compound 5a

Supporting Information

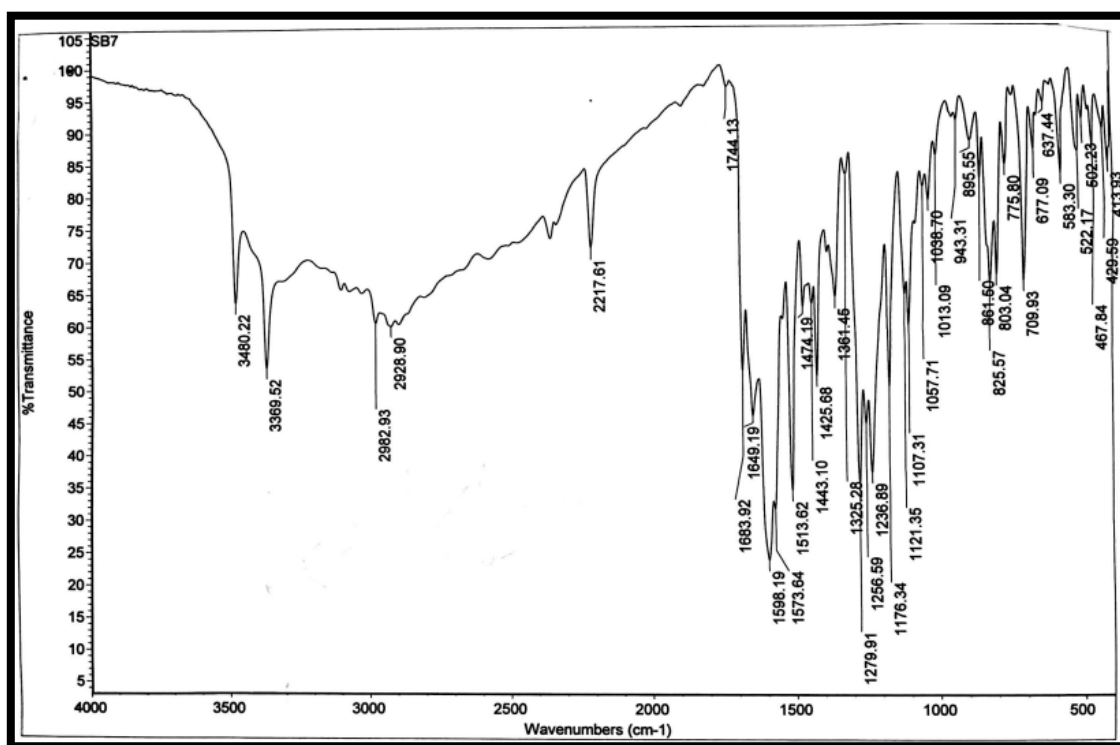


Figure S9. IR spectrum of compound 6a

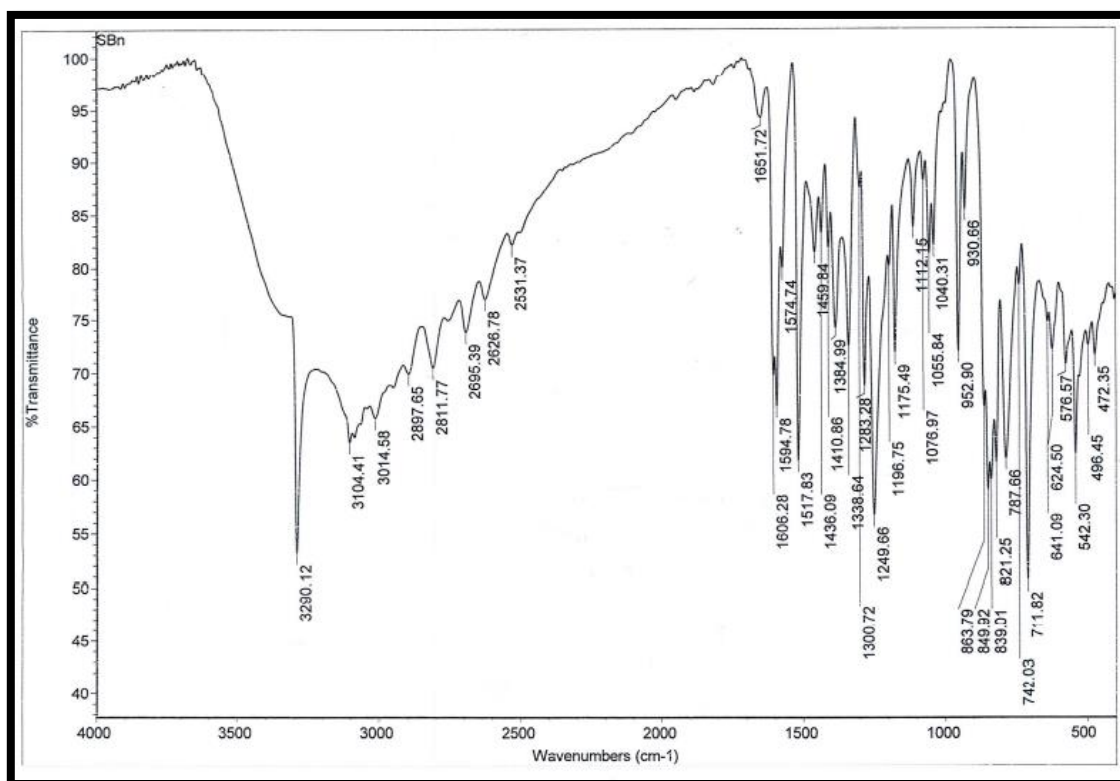


Figure S10. IR spectrum of compound 7a

Supporting Information

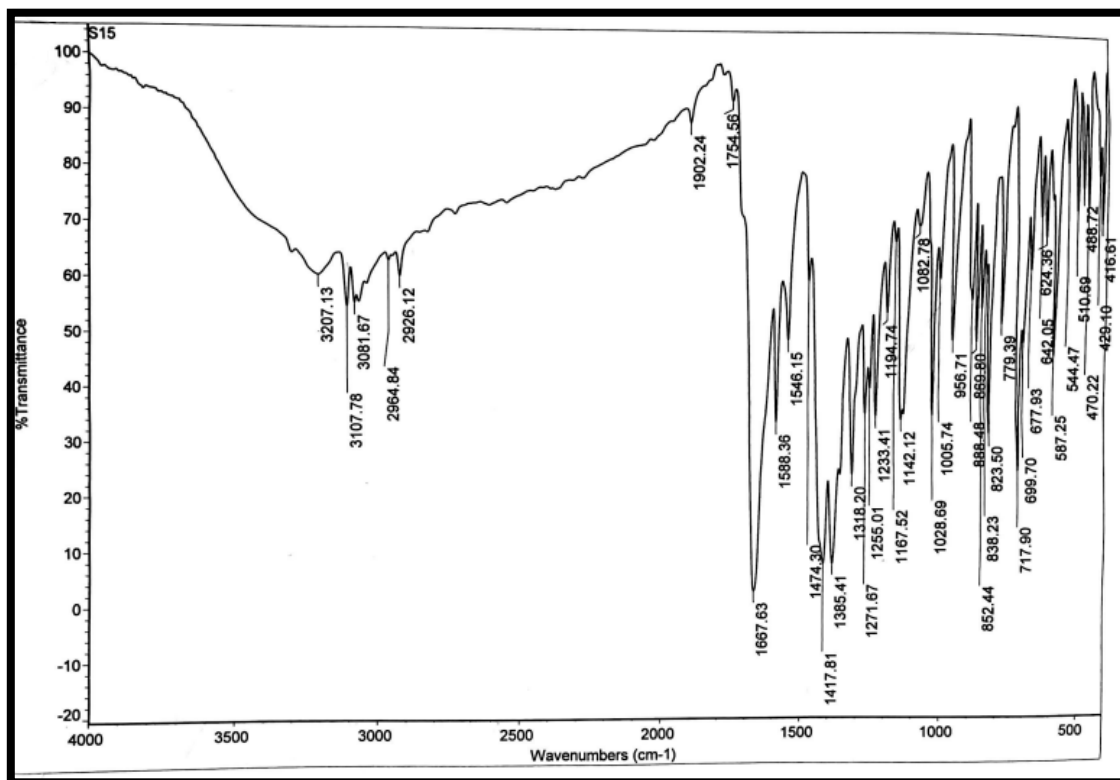


Figure S11. IR spectrum of compound **8b**

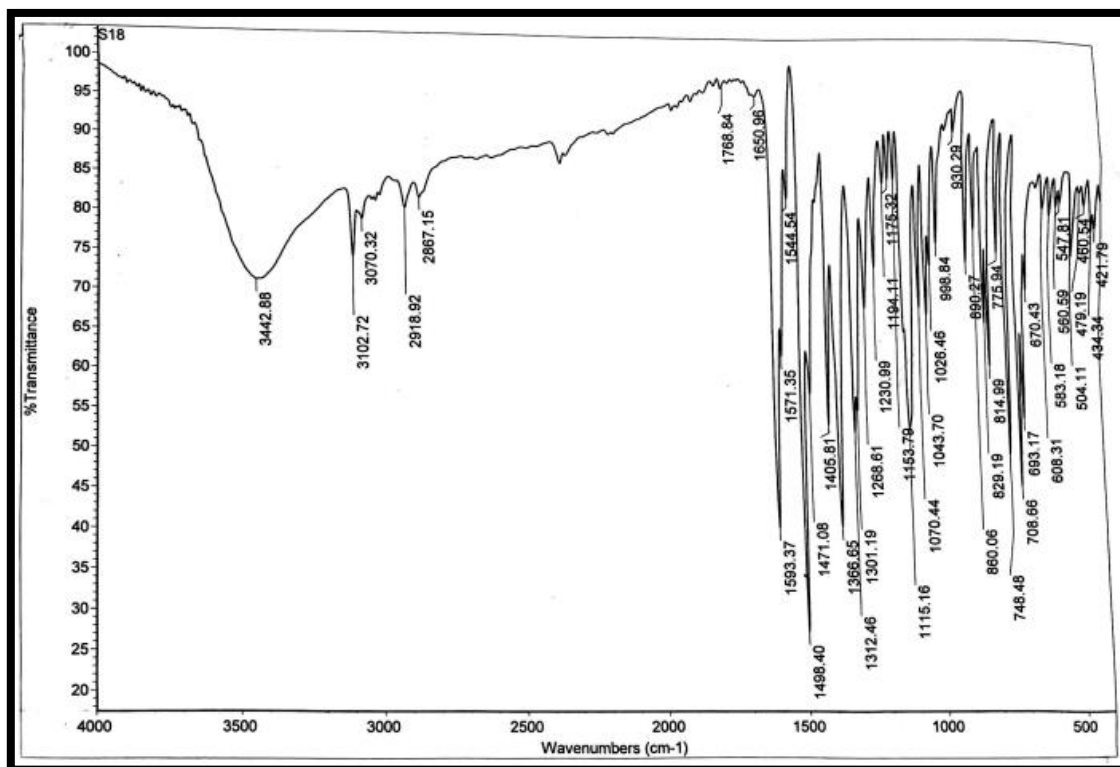


Figure S12. IR spectrum of compound **9b**

## Supporting Information

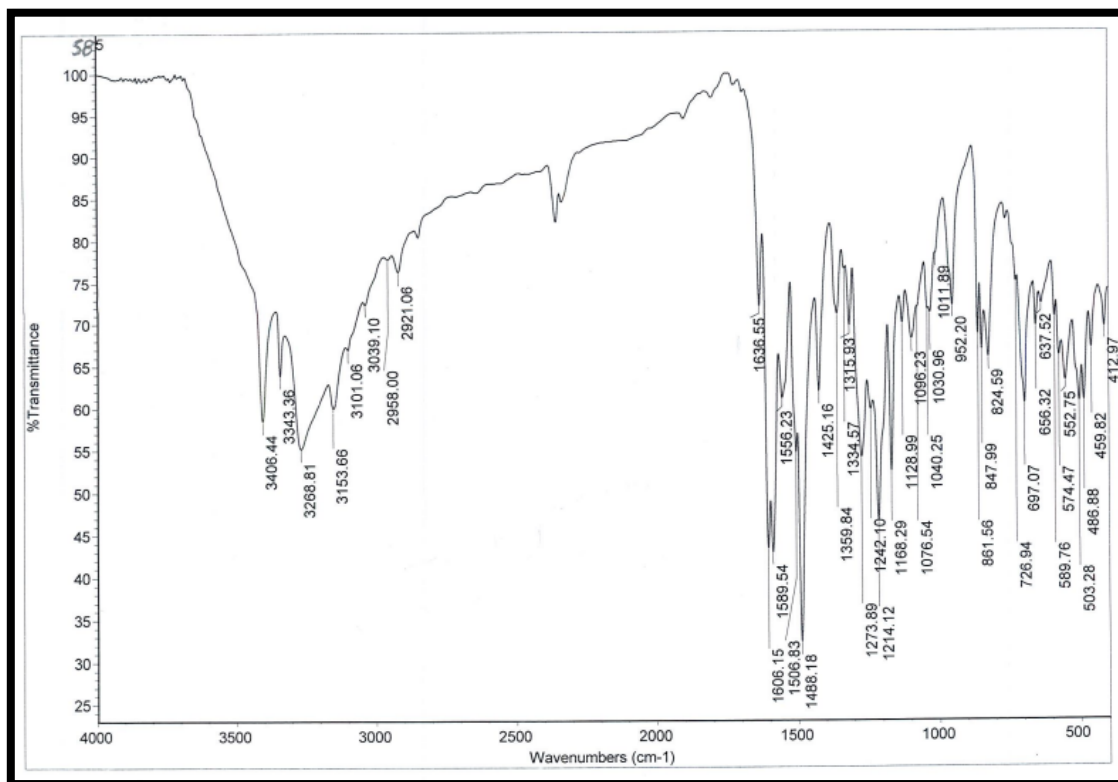


Figure S13. IR spectrum of compound 10a

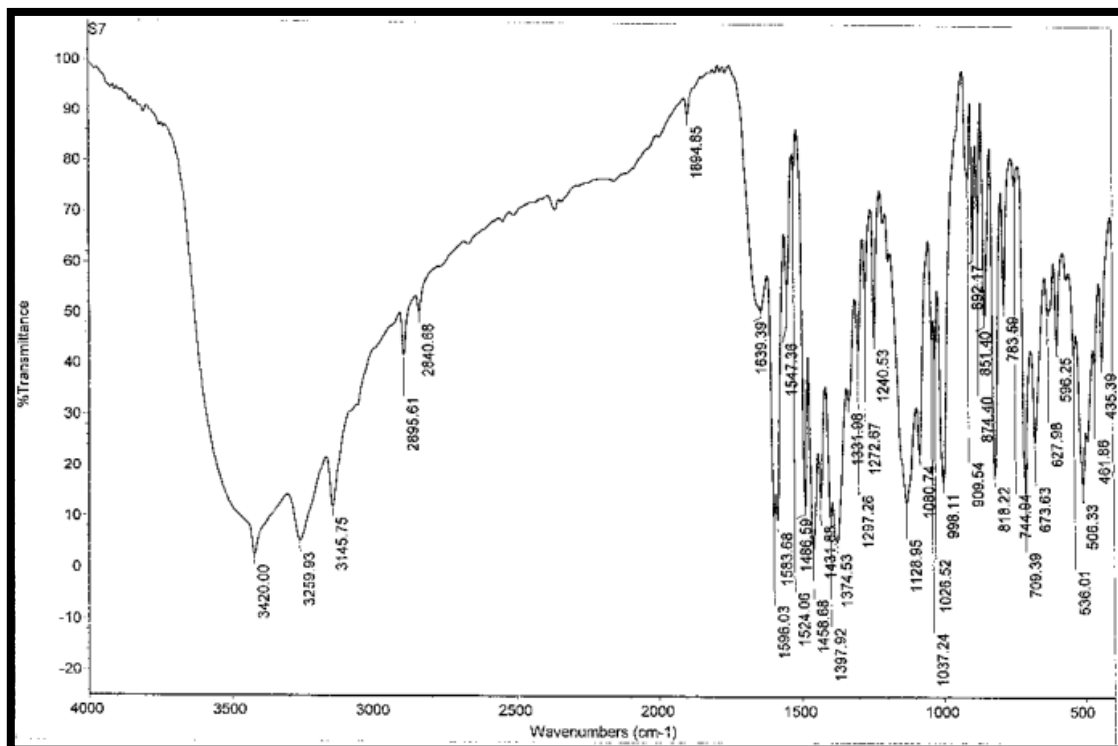


Figure S14. IR spectrum of compound 10b

Supporting Information

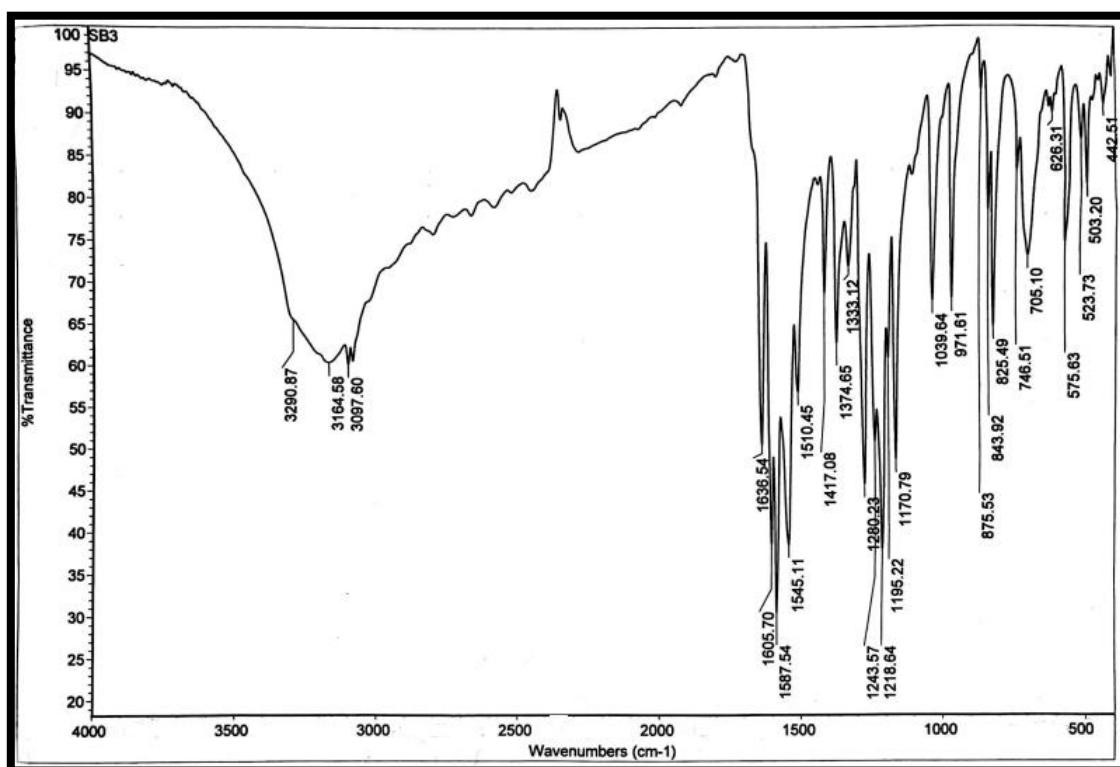


Figure S15. IR spectrum of compound 11a

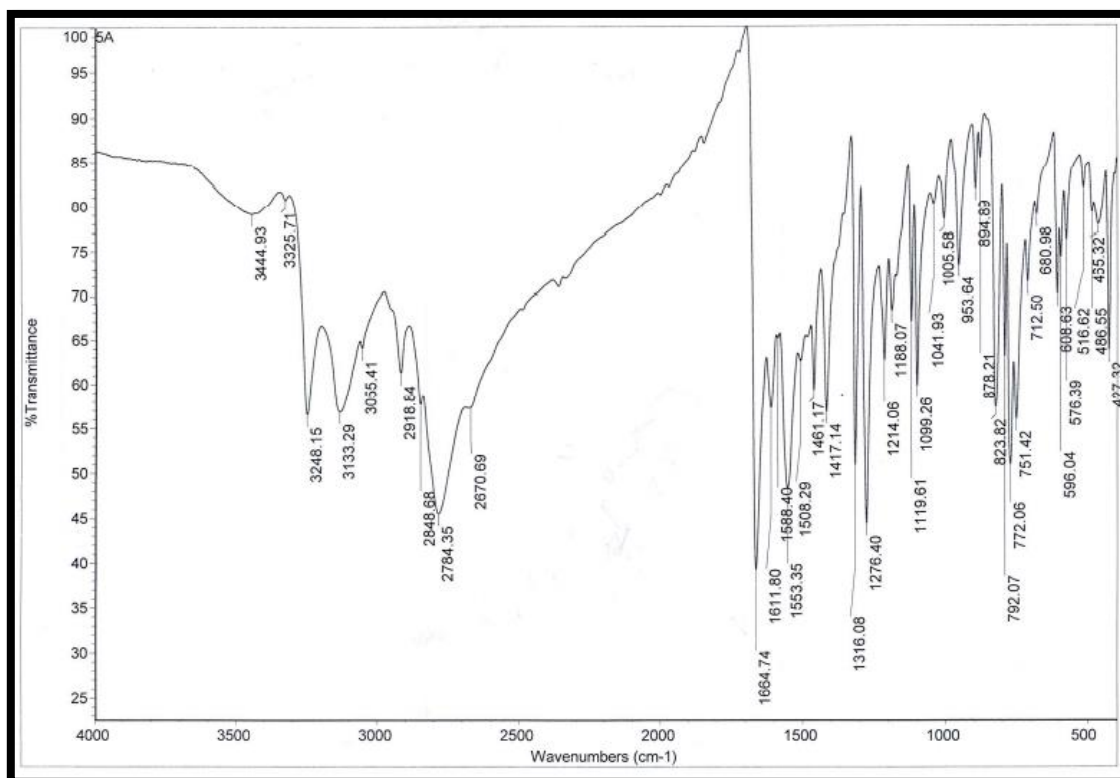


Figure S16. IR spectrum of compound 12a

Supporting Information

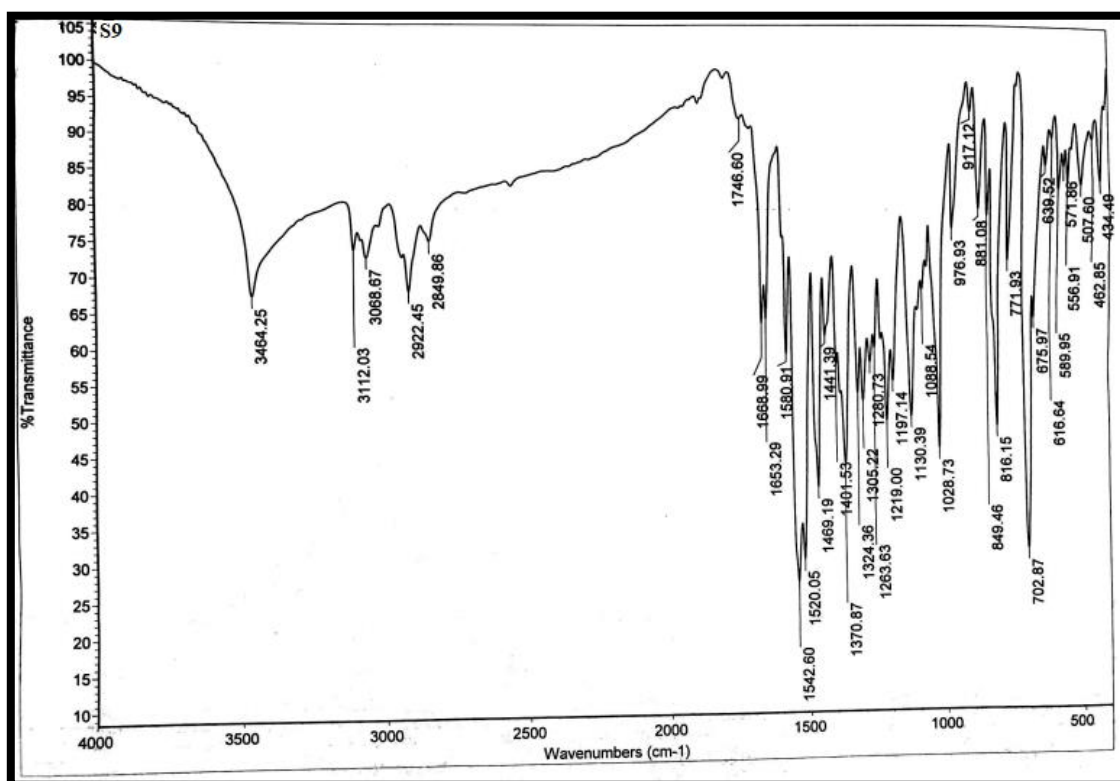


Figure S17. IR spectrum of compound 12b

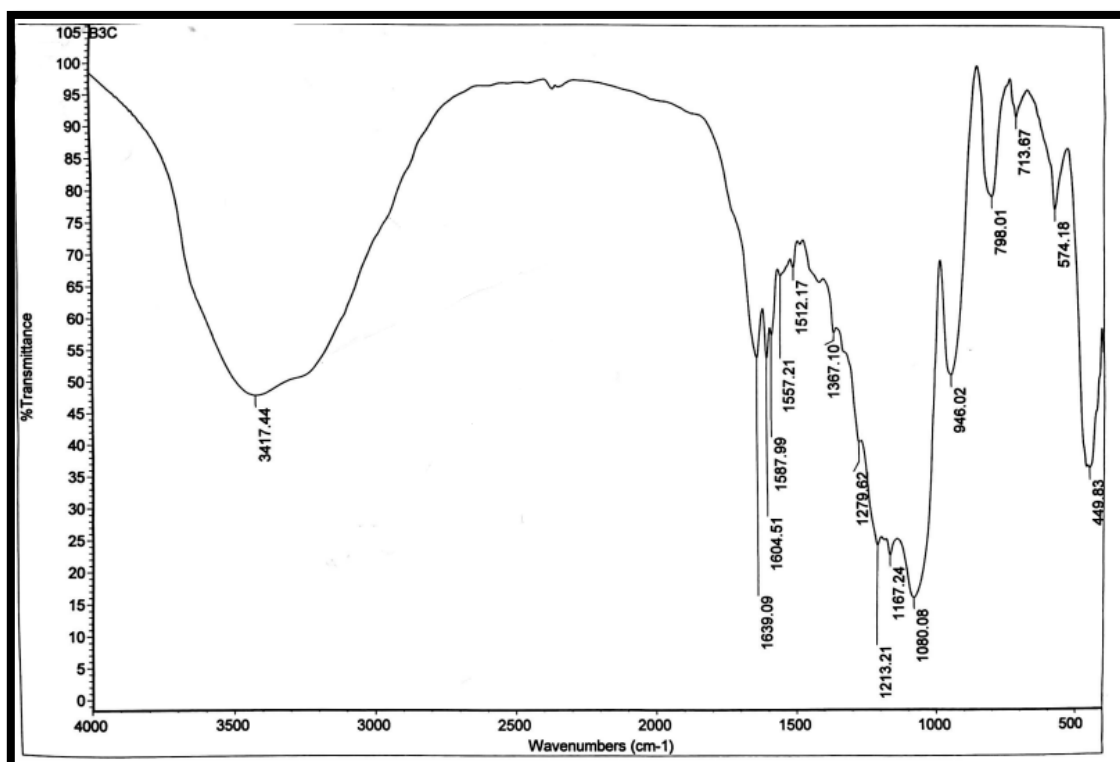


Figure S18. IR spectrum of compound 13a

Supporting Information

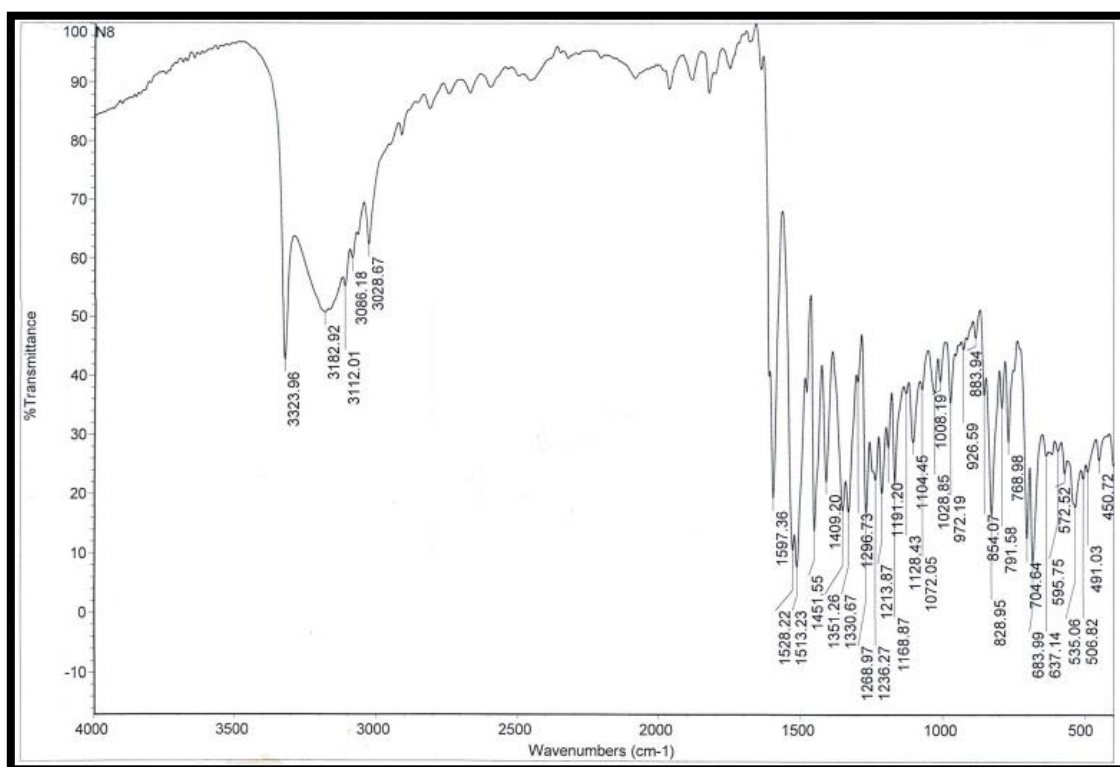


Figure S19. IR spectrum of compound 14a

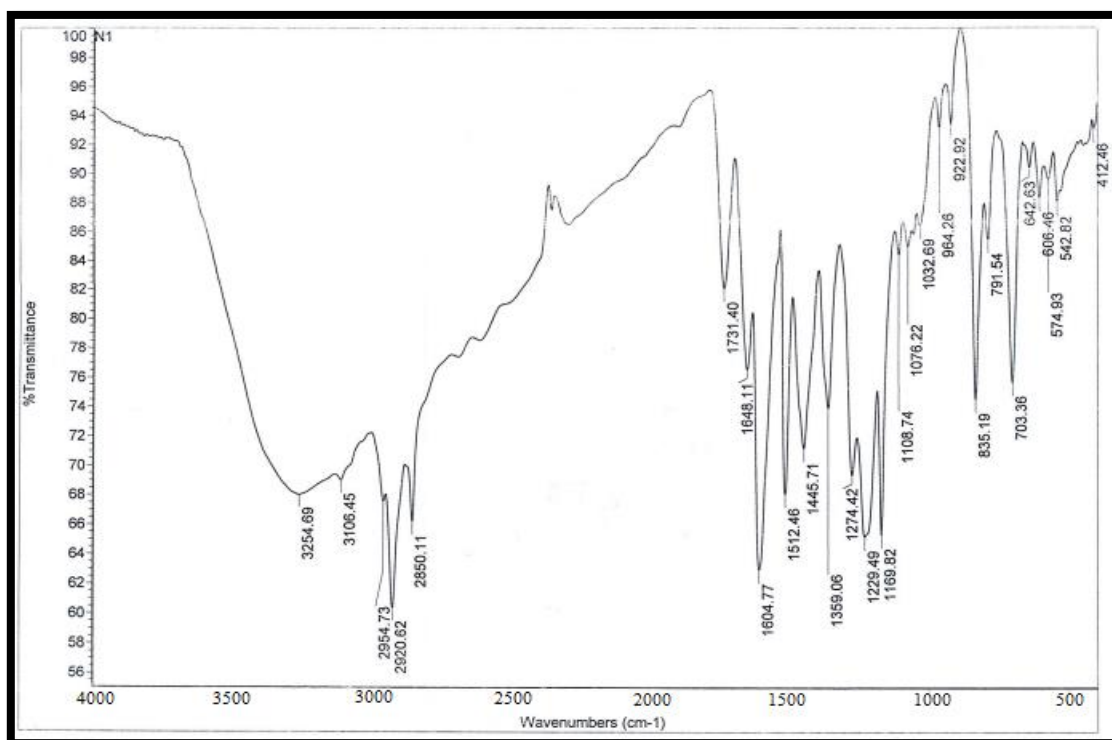


Figure S20. IR spectrum of compound 15a

## Supporting Information

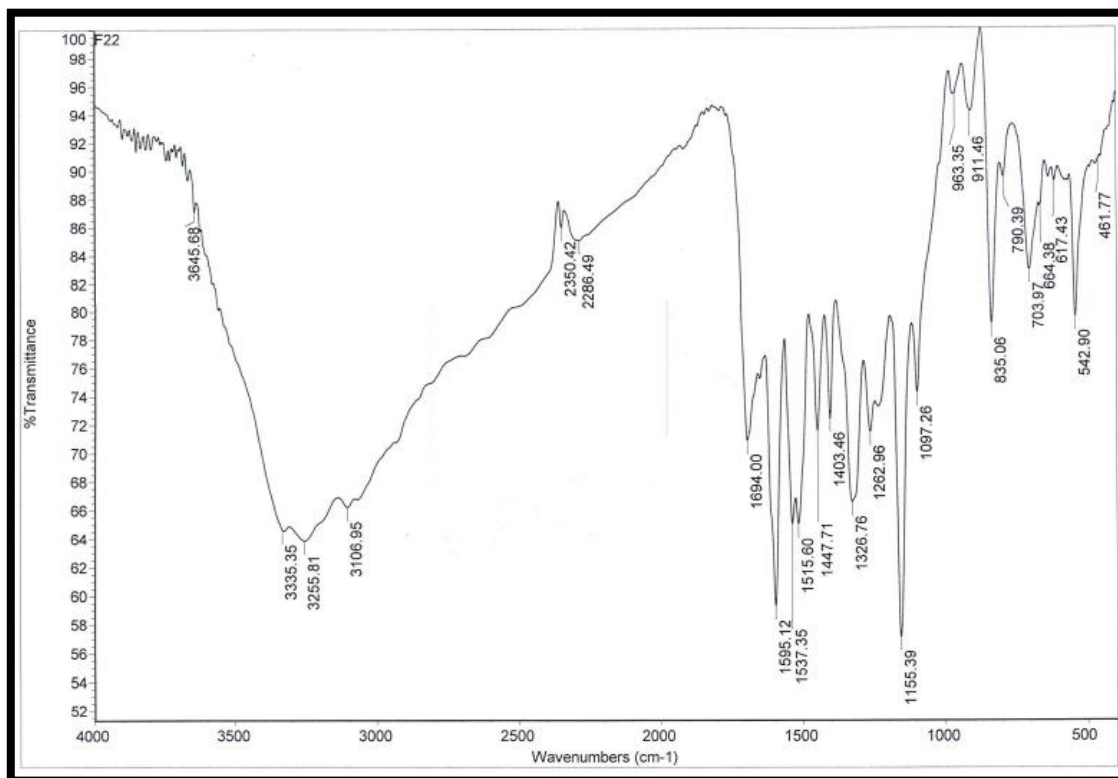


Figure S21. IR spectrum of compound 16a

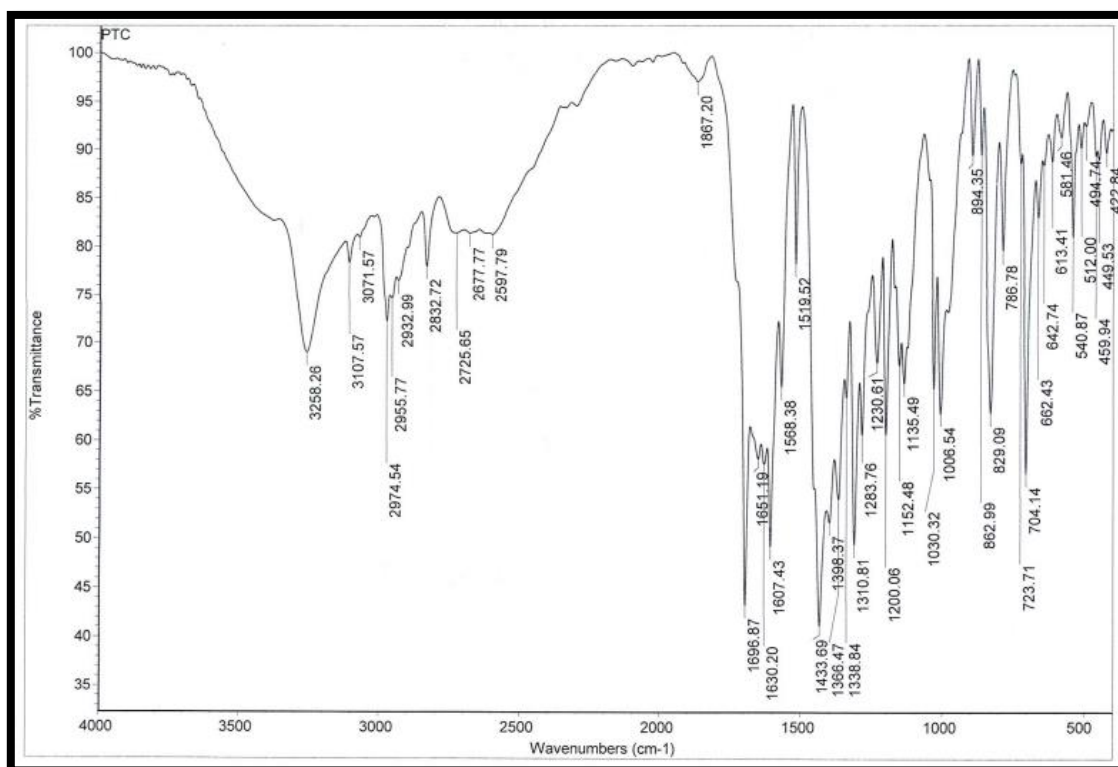


Figure S22. IR spectrum of compound 17a



# Supporting Information

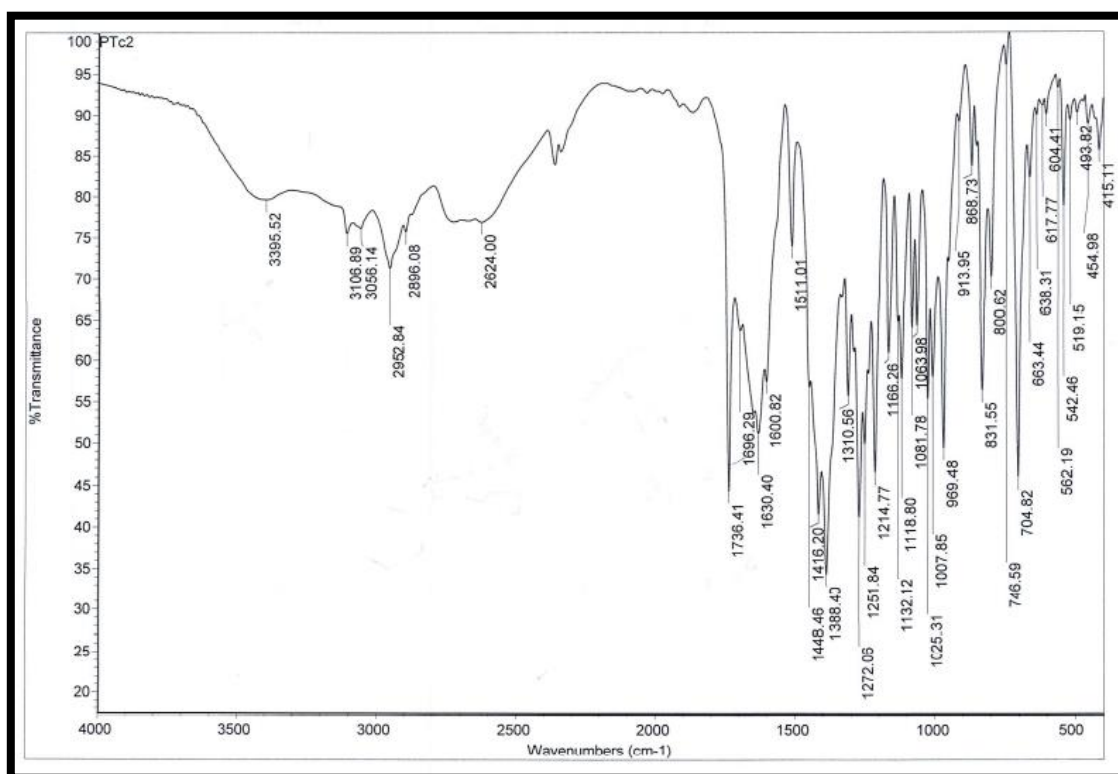


Figure S23. IR spectrum of compound 18a

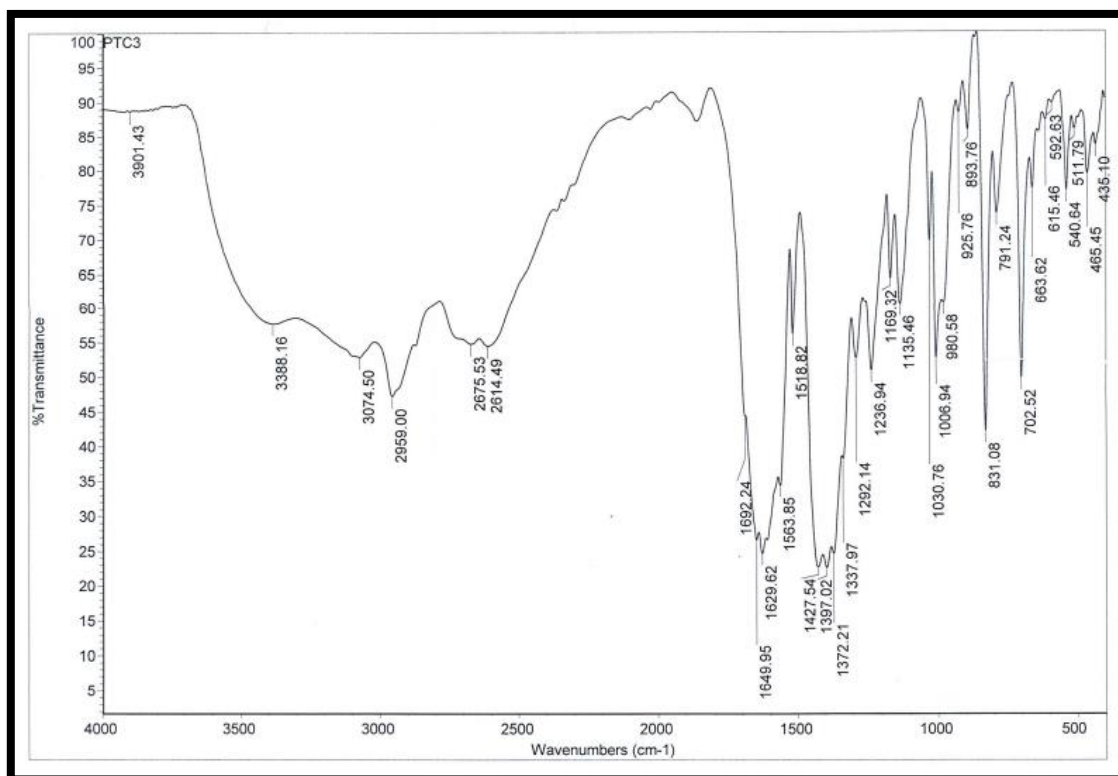


Figure S24. IR spectrum of compound 19a

Supporting Information

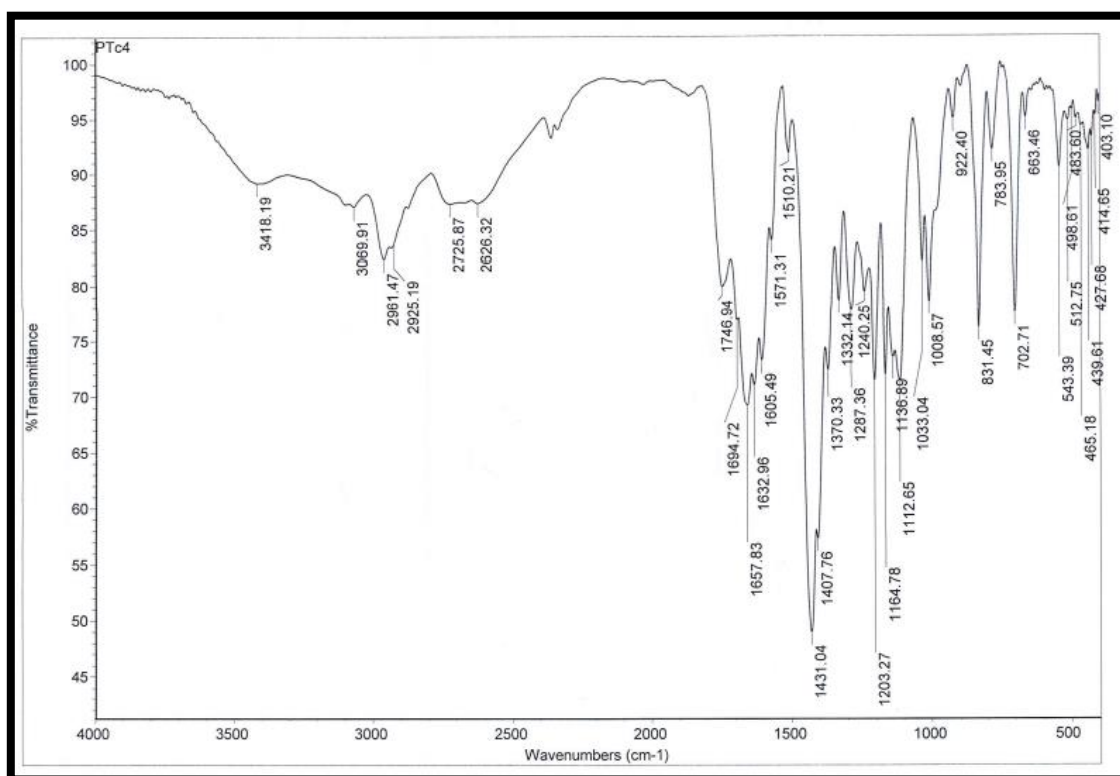
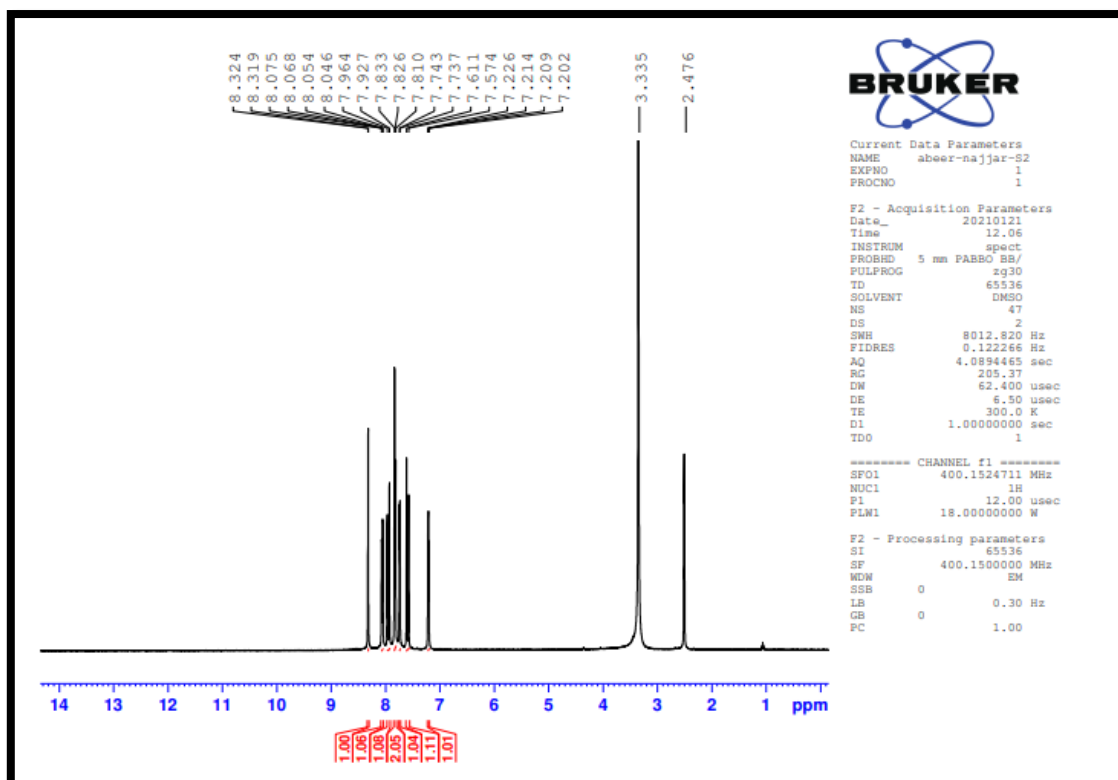
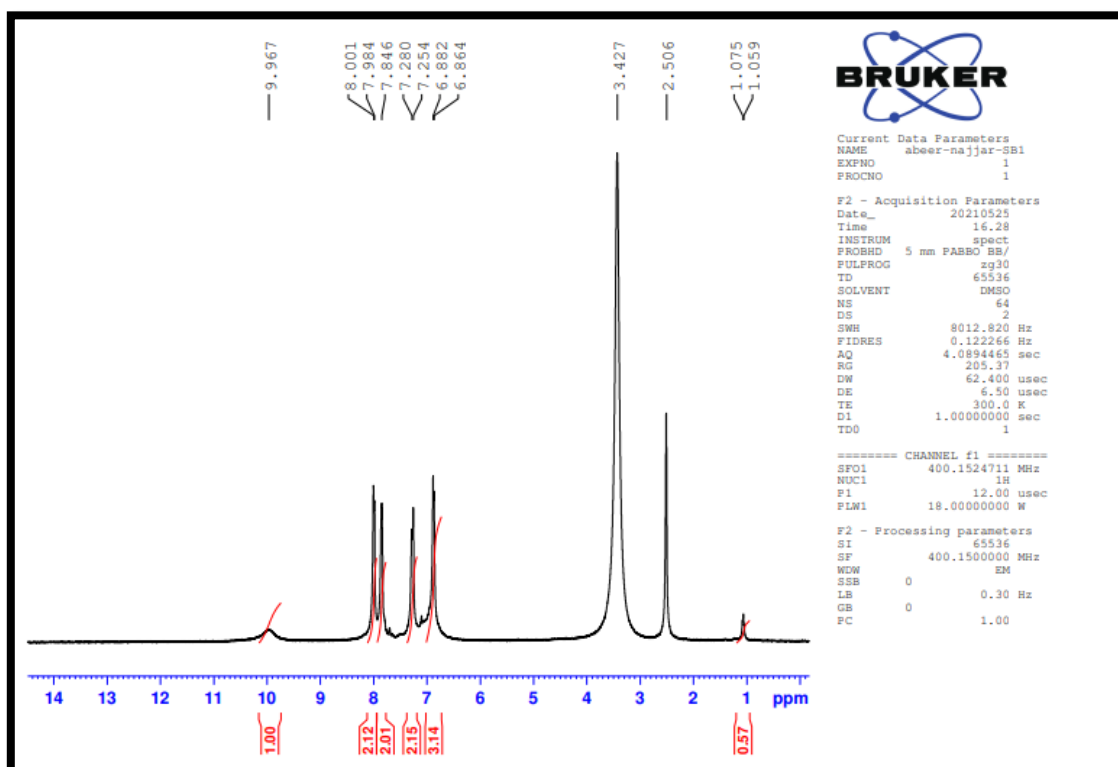
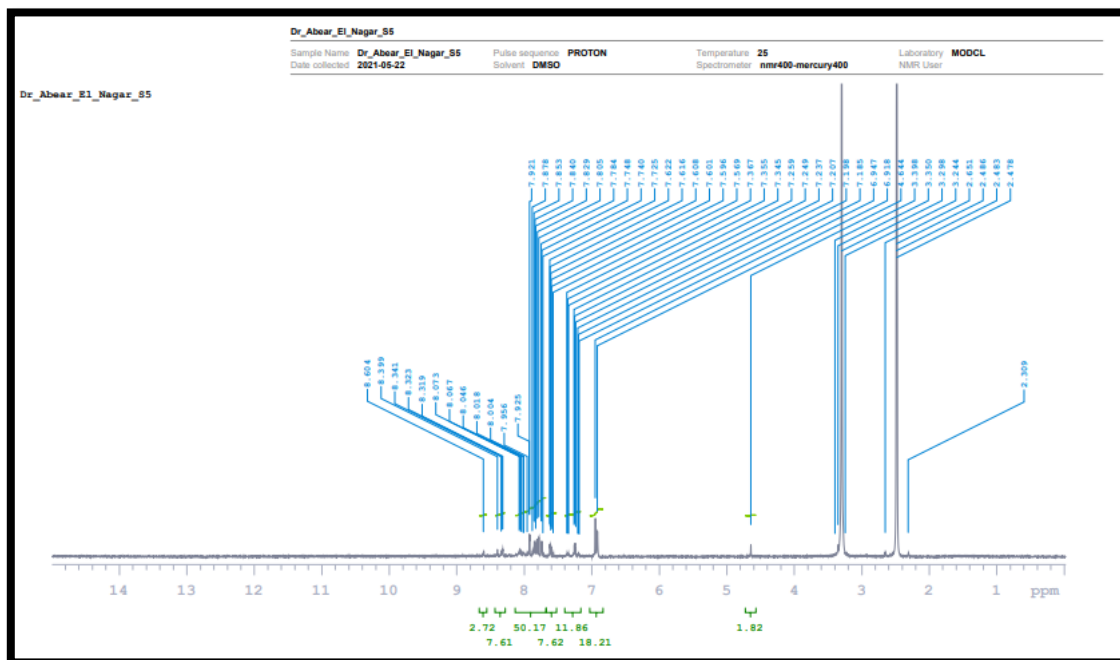


Figure S25. IR spectrum of compound 20a

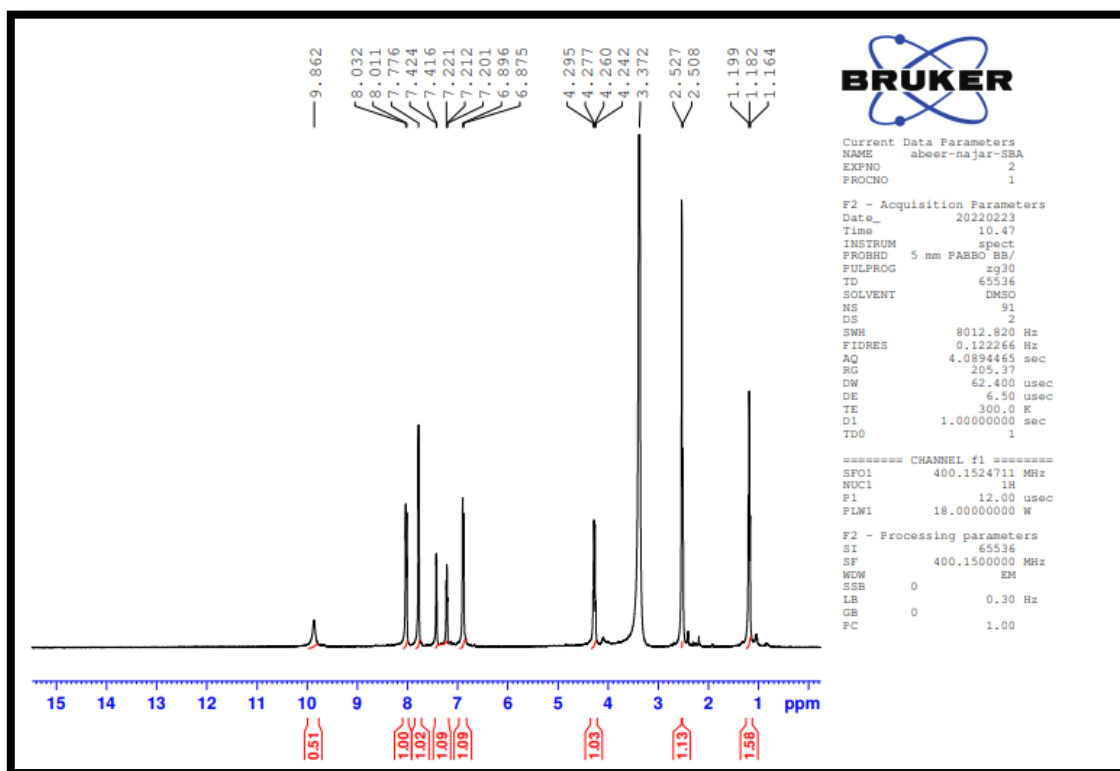
**$^1\text{H}$  NMR spectral data of the target compounds (1b-20a)**Figure S26.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **1b**

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**Figure S27.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **2a**



**Figure S28.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **2b**



**Figure S29.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **3a**

Supporting Information

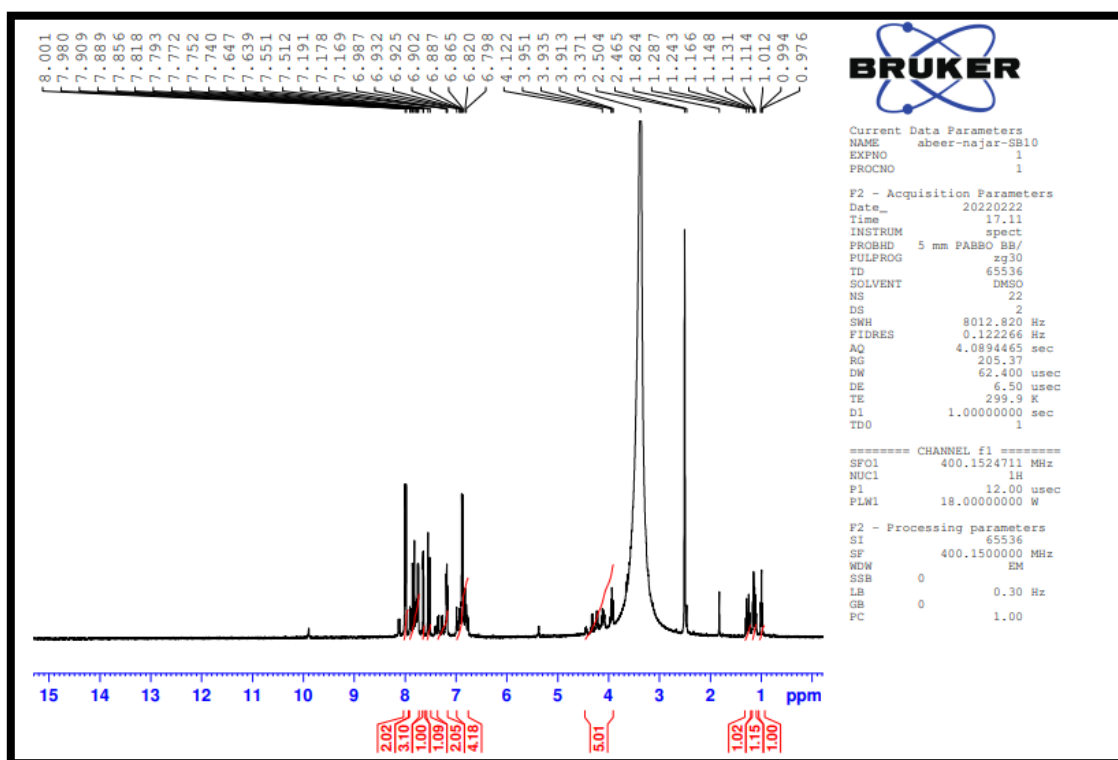


Figure S30.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound 4a

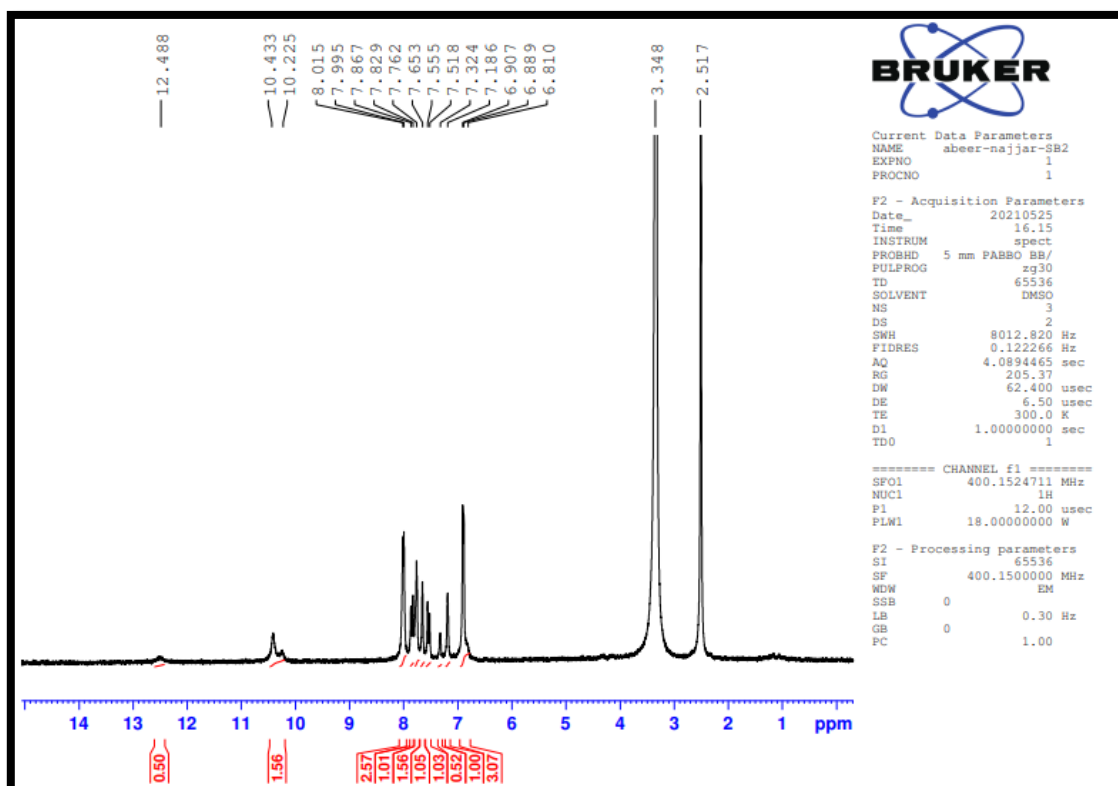
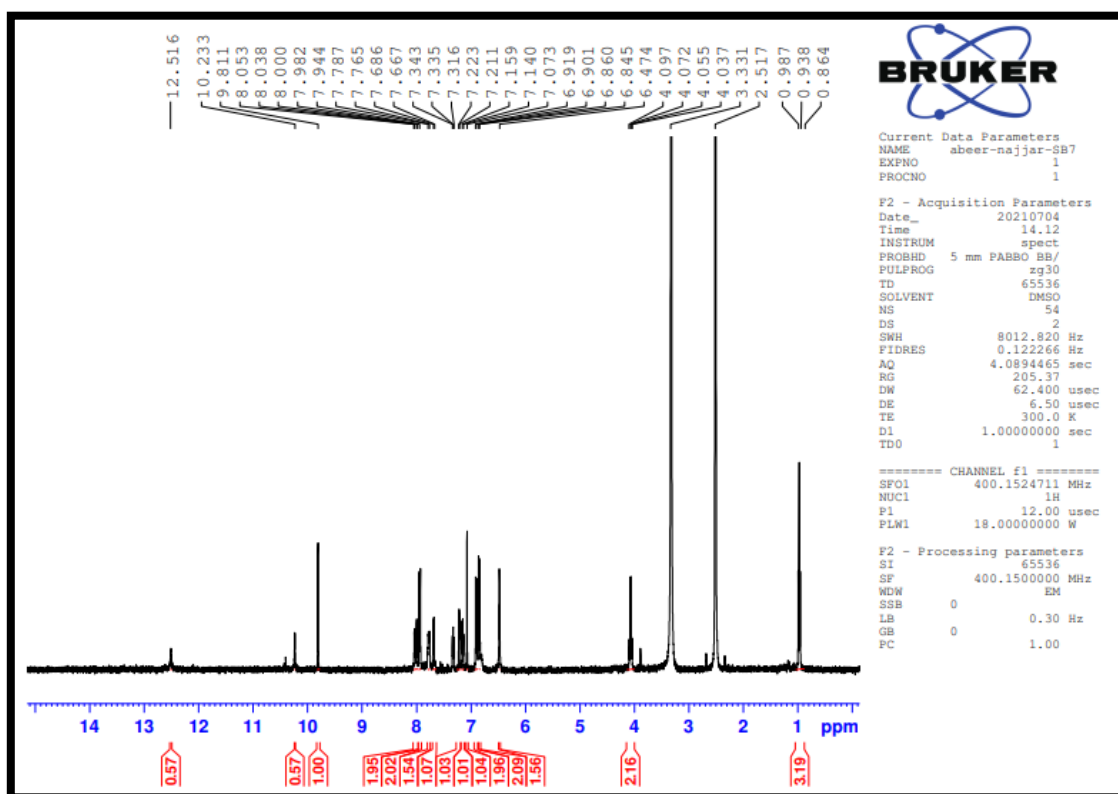
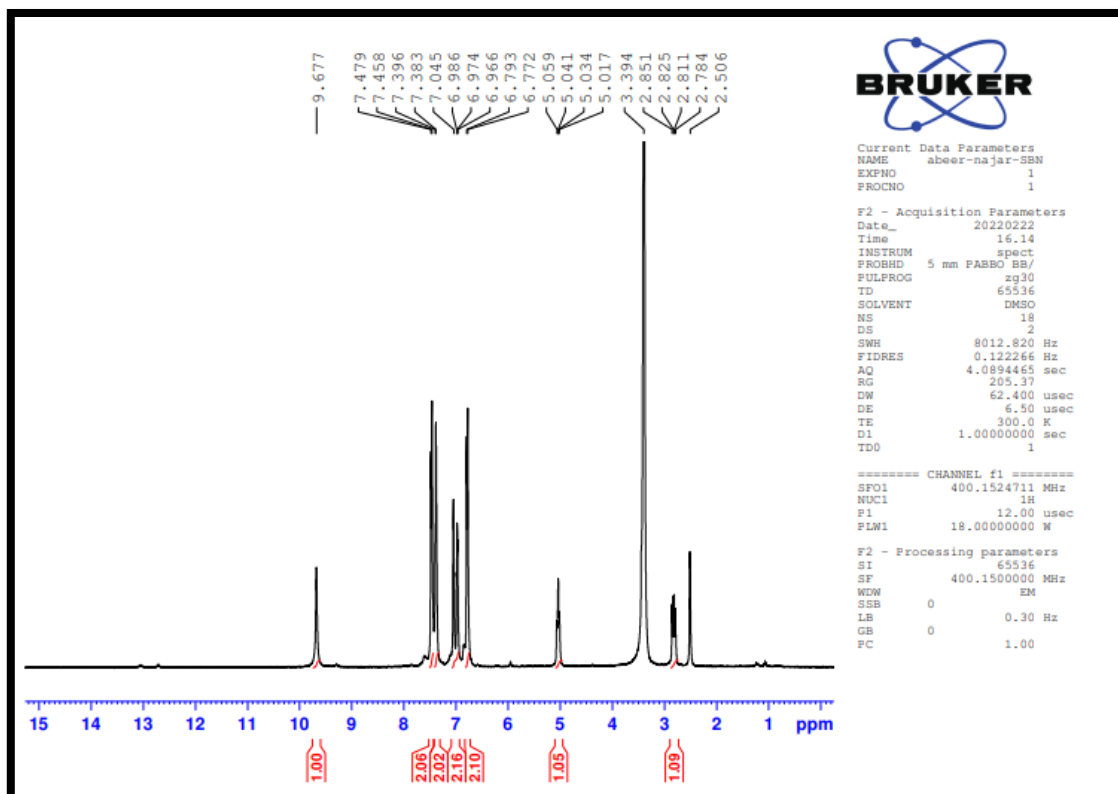


Figure S31.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound 5a

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**Figure S32.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **6a**



**Figure S33.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **7a**

## Supporting Information

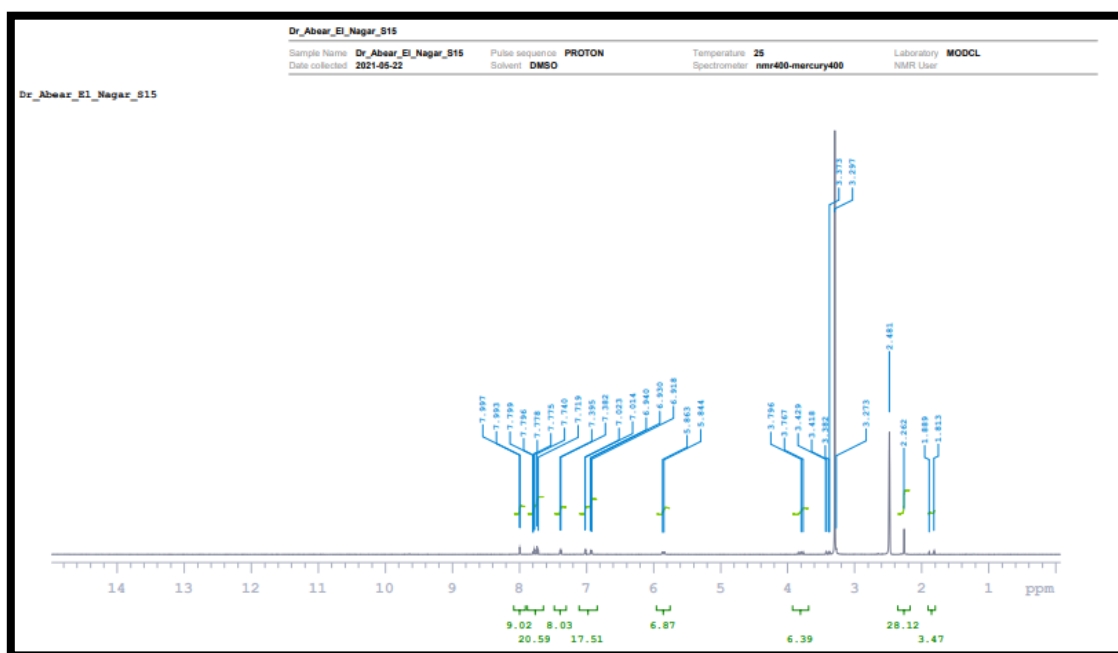


Figure S34.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **8b**

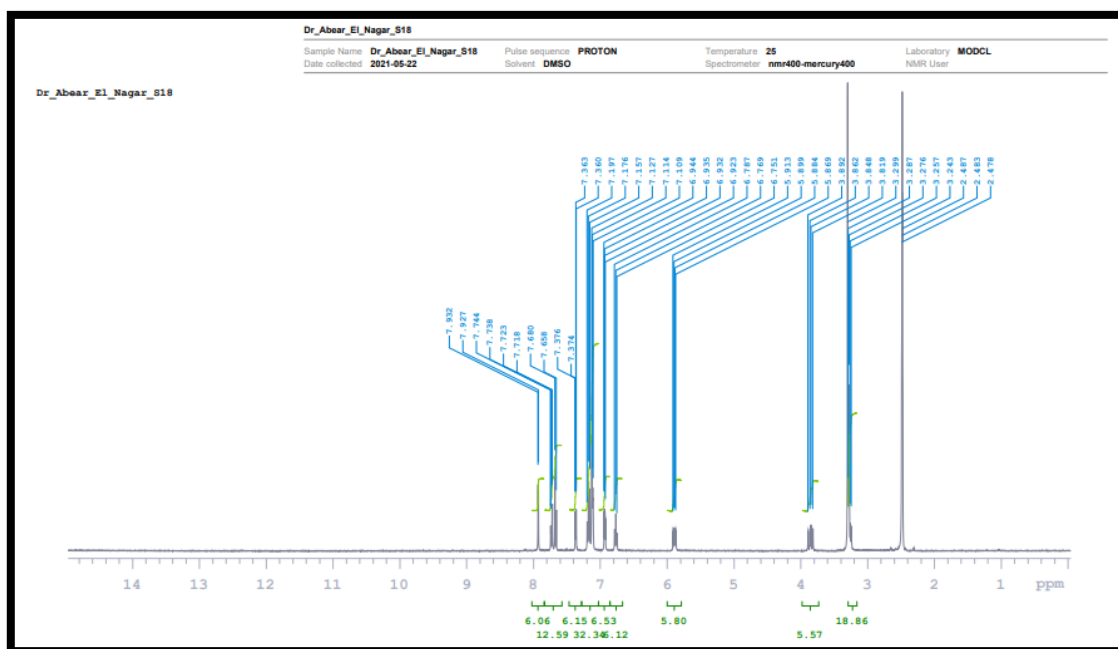
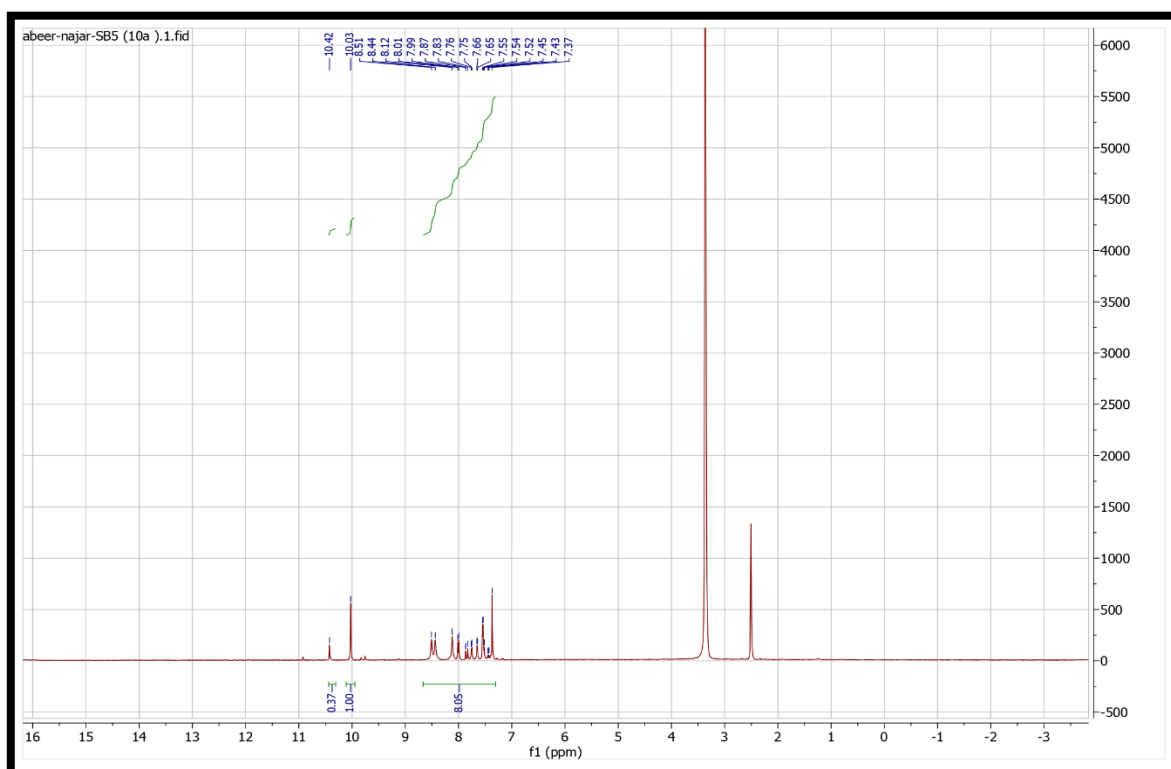
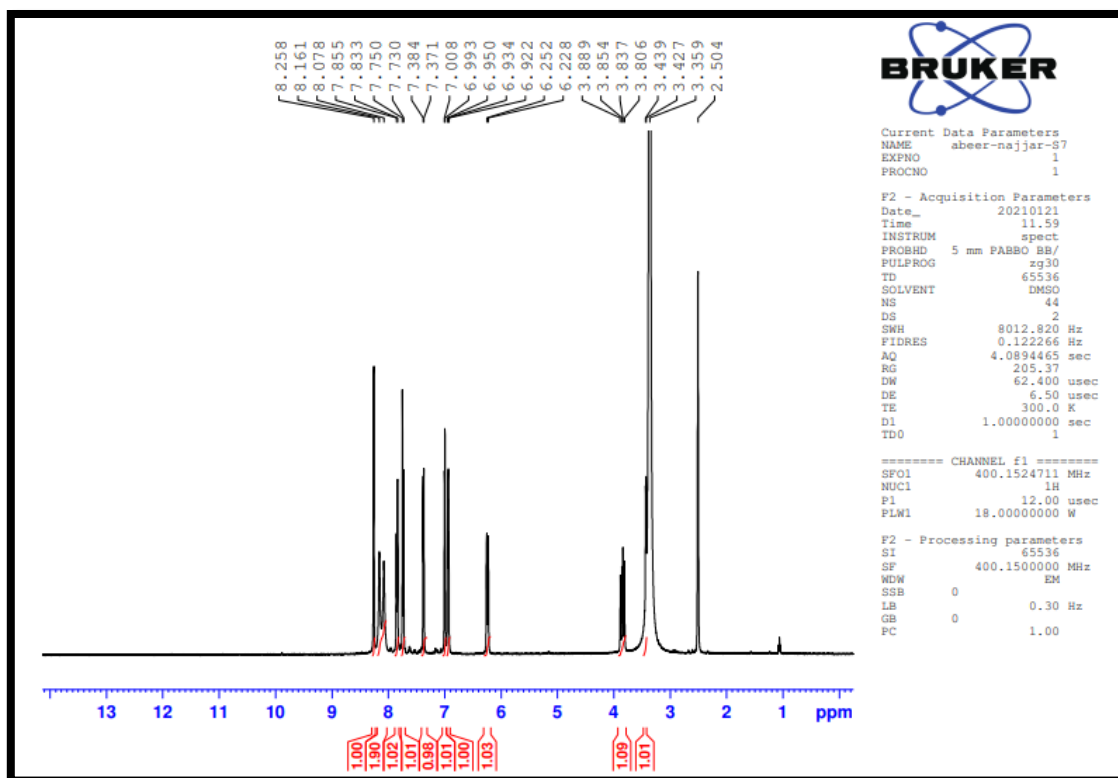


Figure S35.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **9b**

## Supporting Information



**Figure S36.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **10a**



**Figure S37.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **10b**



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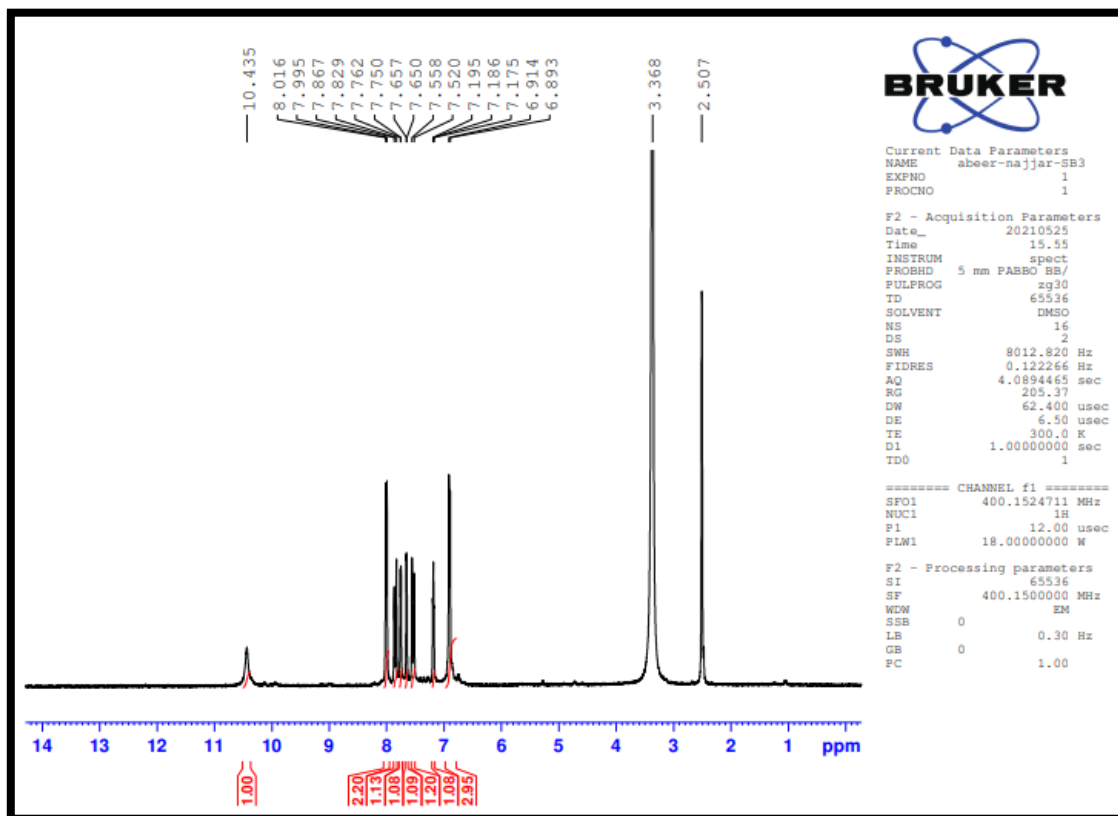


Figure S38.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **11a**

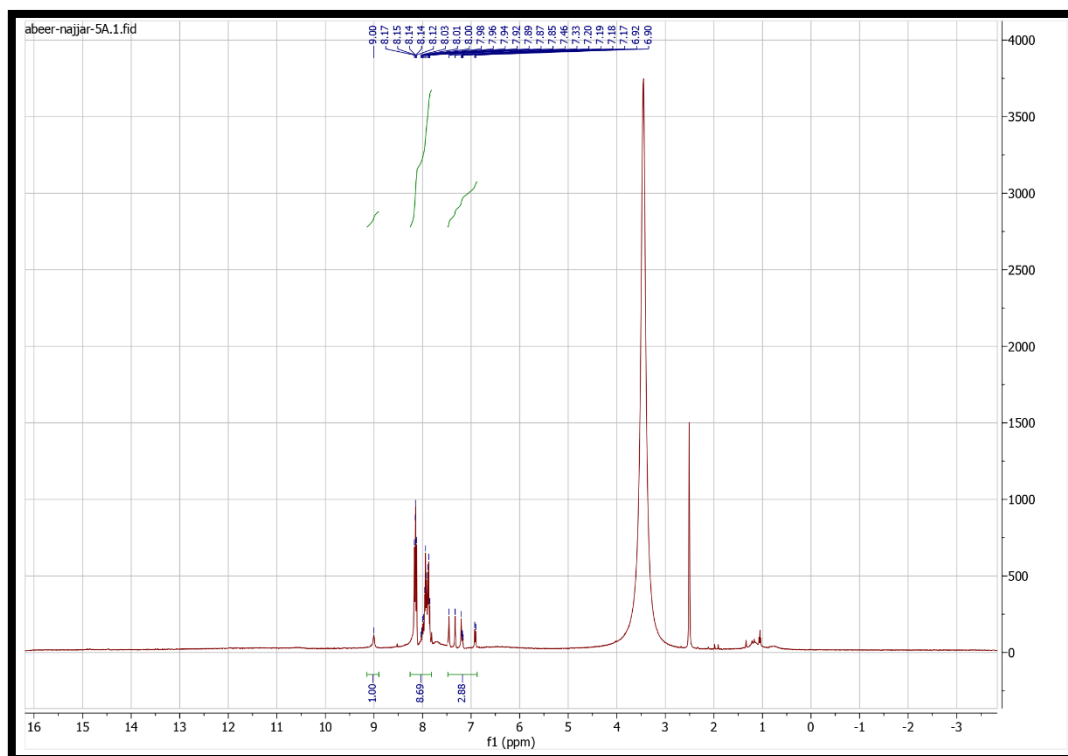


Figure S39.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **12a**

Supporting Information

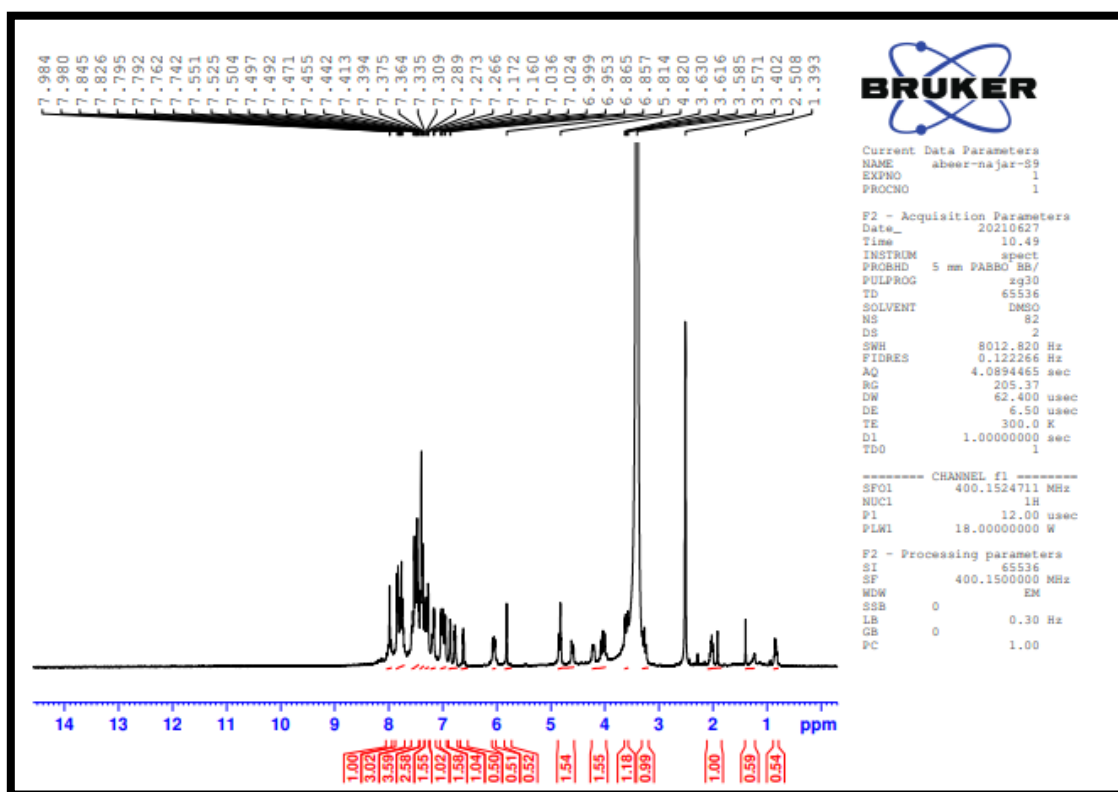


Figure S40.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **12b**

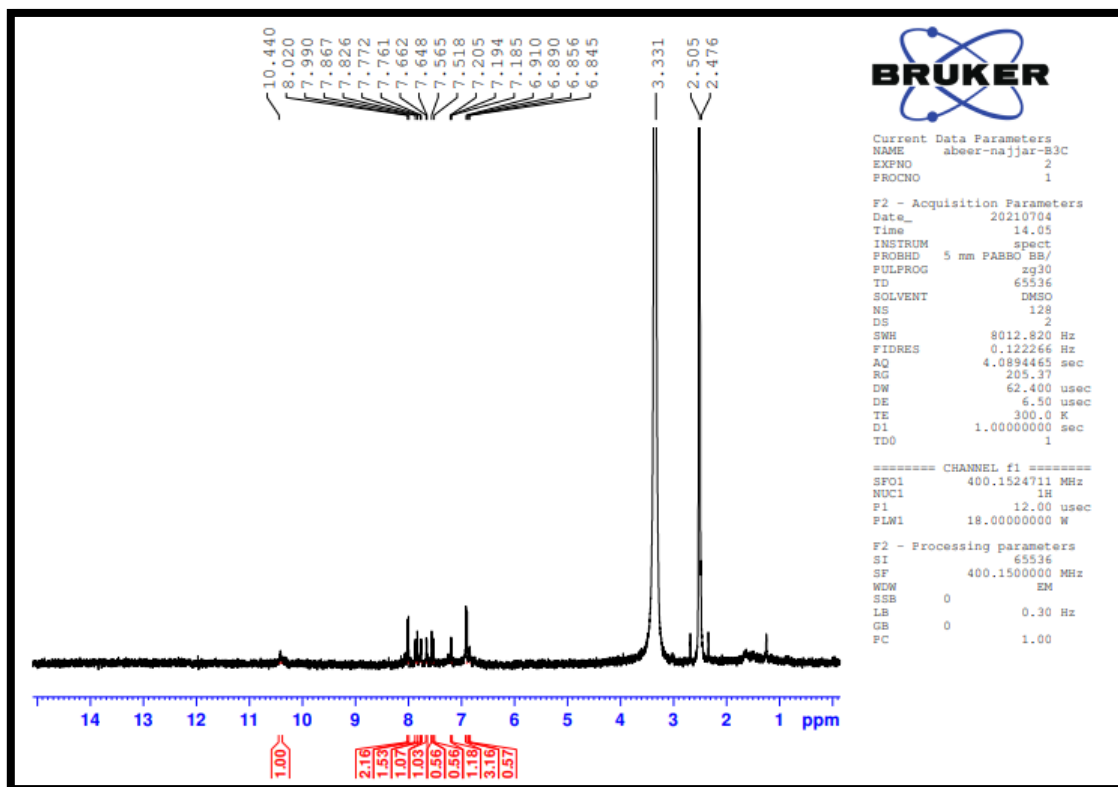


Figure S41.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **13a**

# Supporting Information

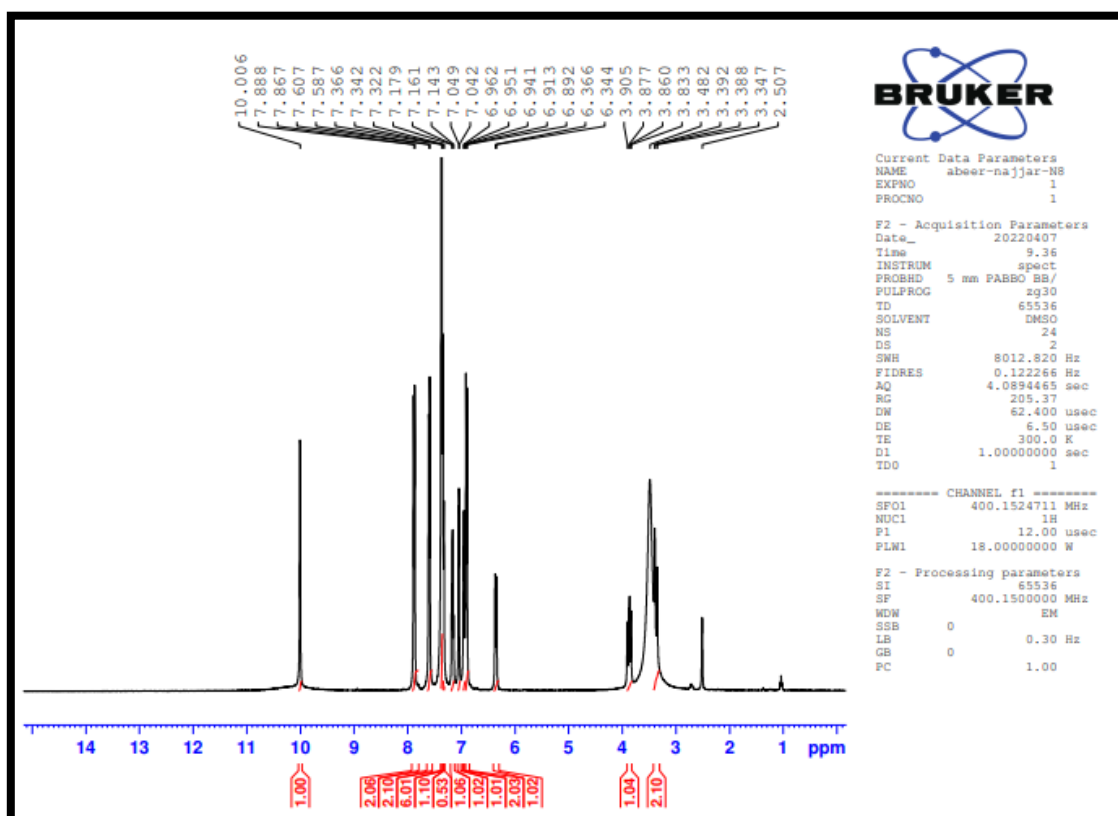


Figure S42. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound 14a

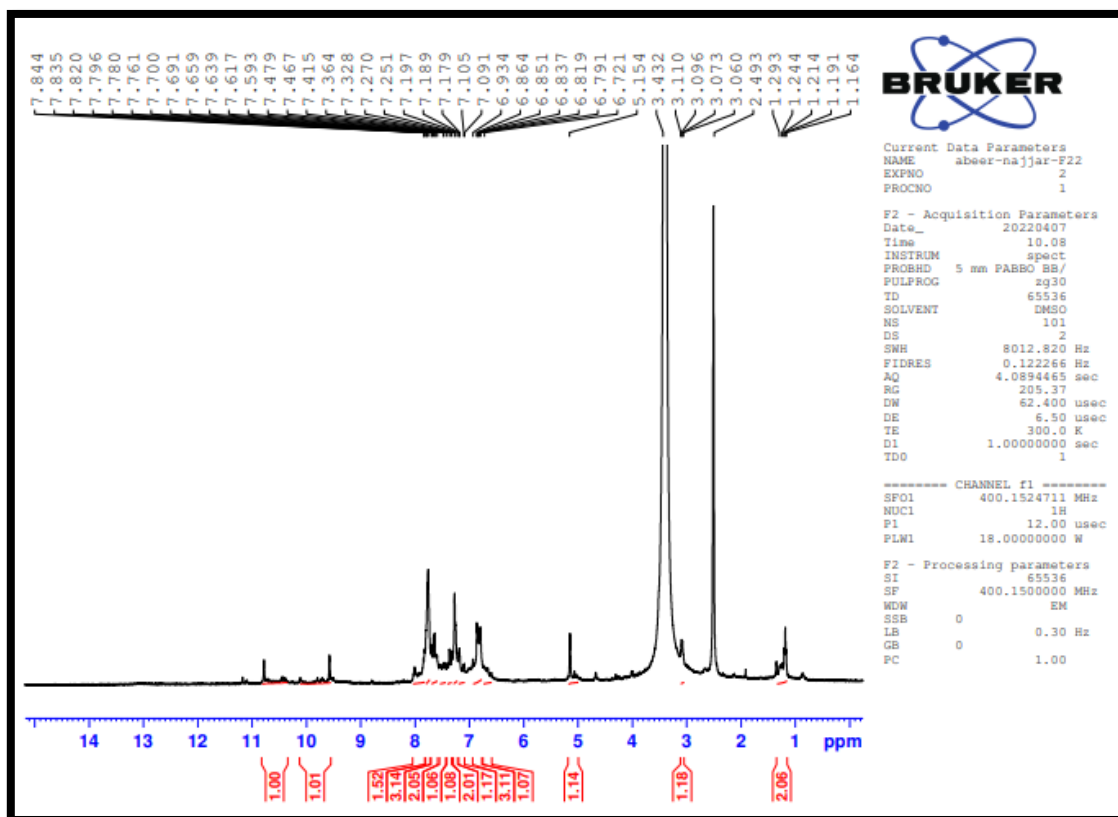


Figure S43. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound 16a

Supporting Information

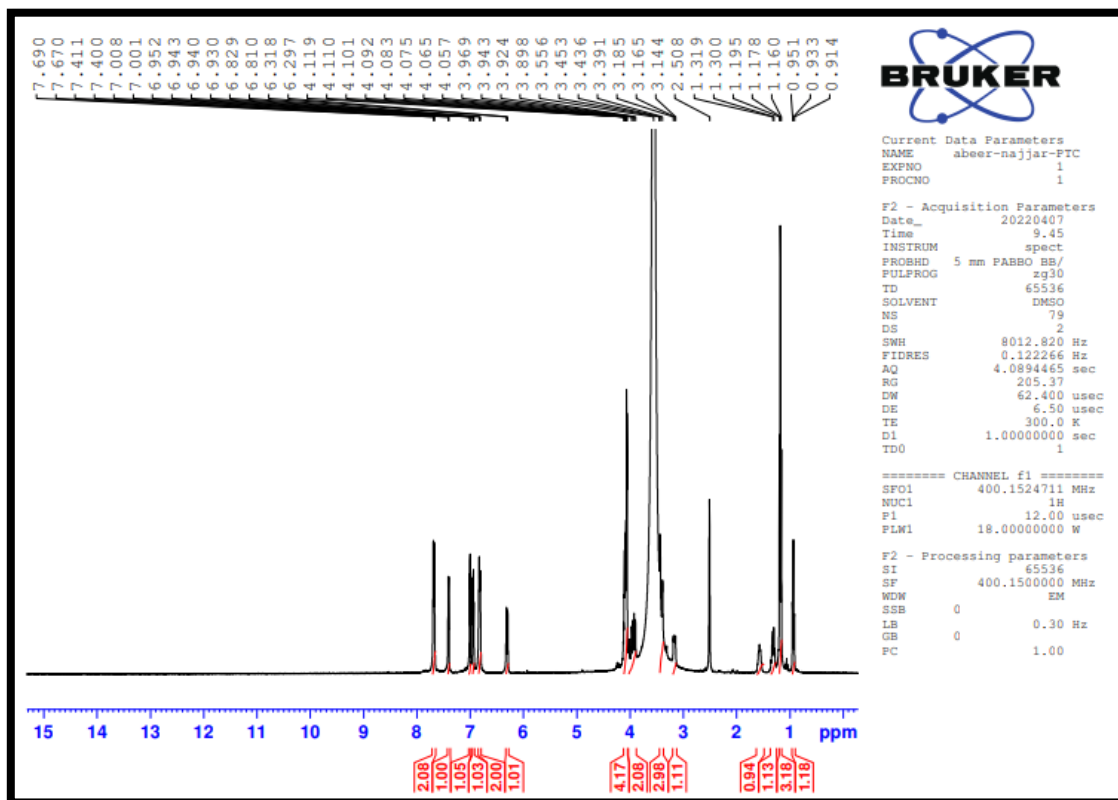


Figure S44. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **17a**

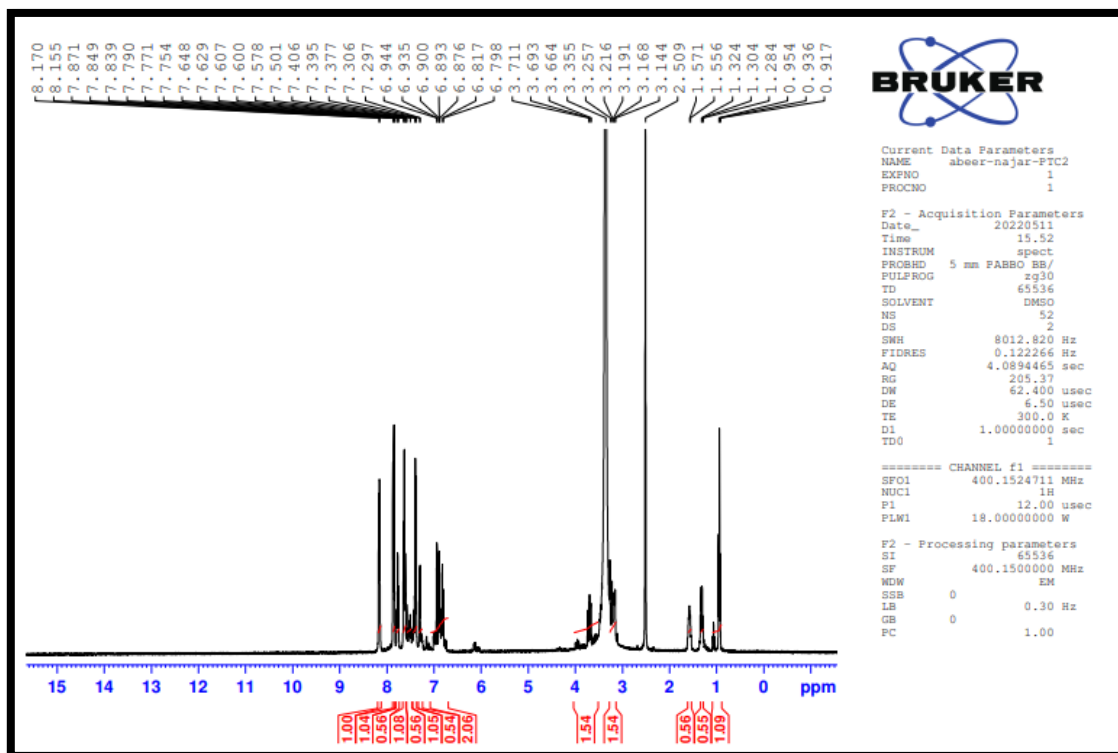
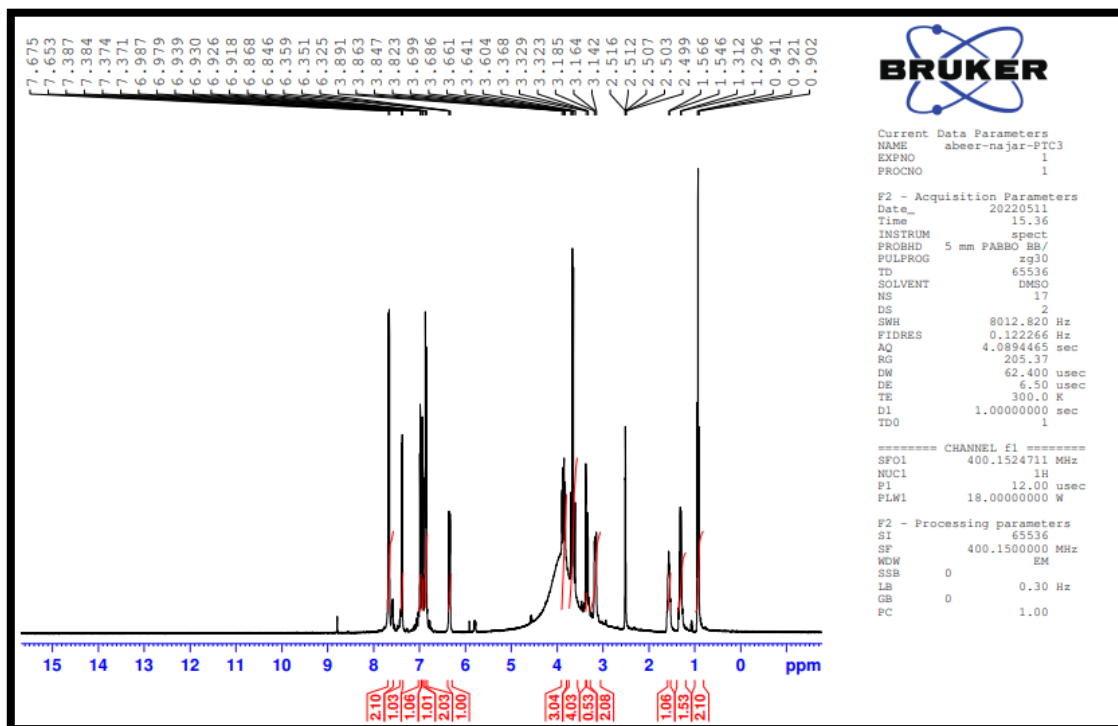
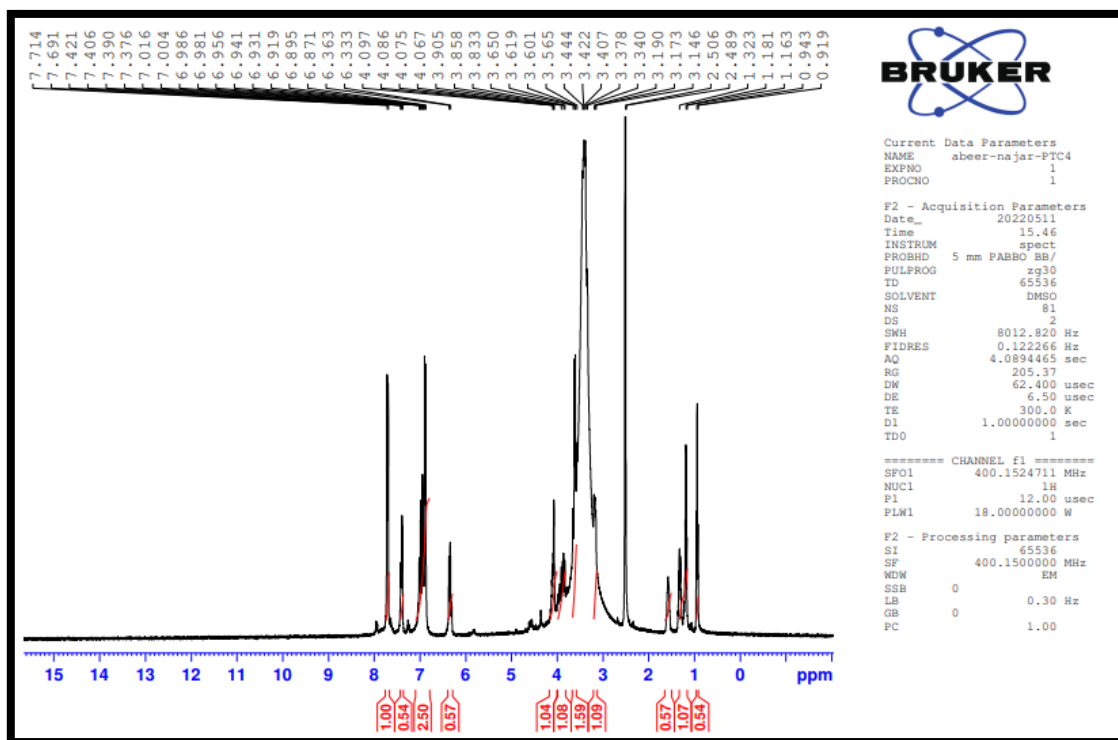


Figure S45. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) spectrum of compound **18a**

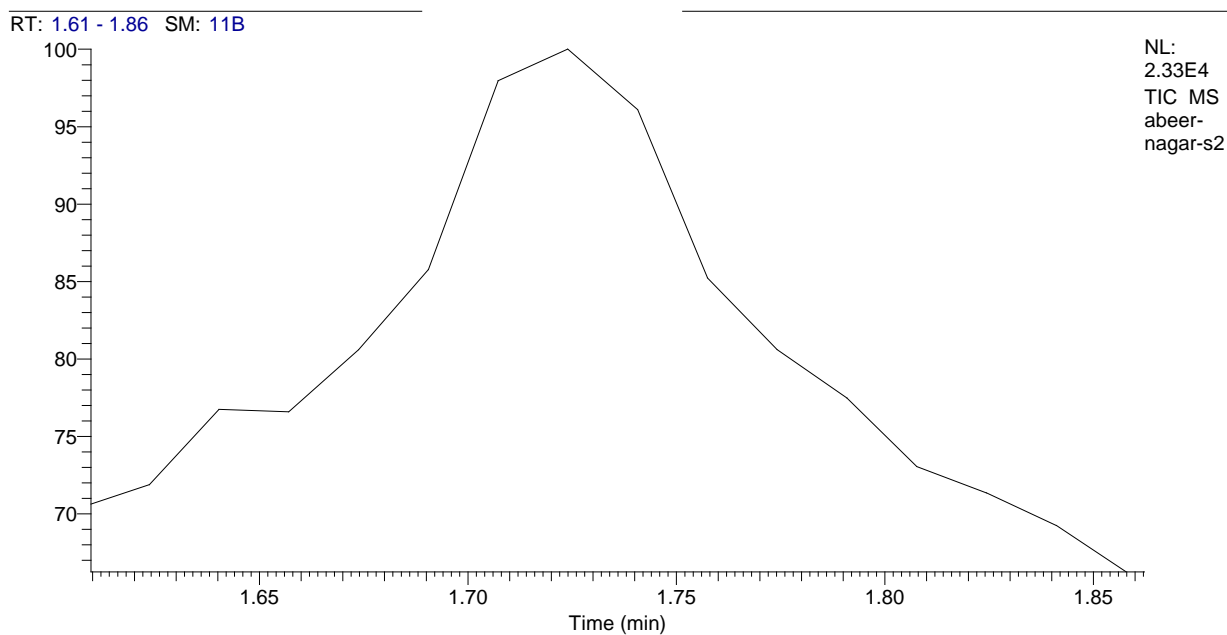
## Supporting Information



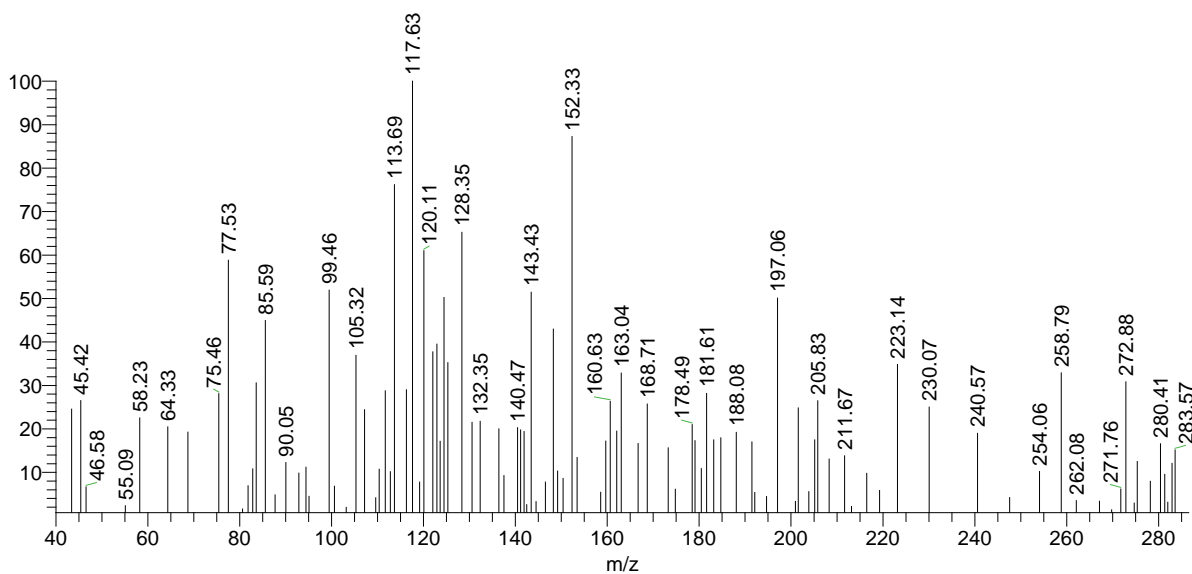
**Figure S46.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **19a**



**Figure S47.**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ) spectrum of compound **20a**

**Mass spectral data of the target compounds (1b,3a,10b,11a, and 18a)**

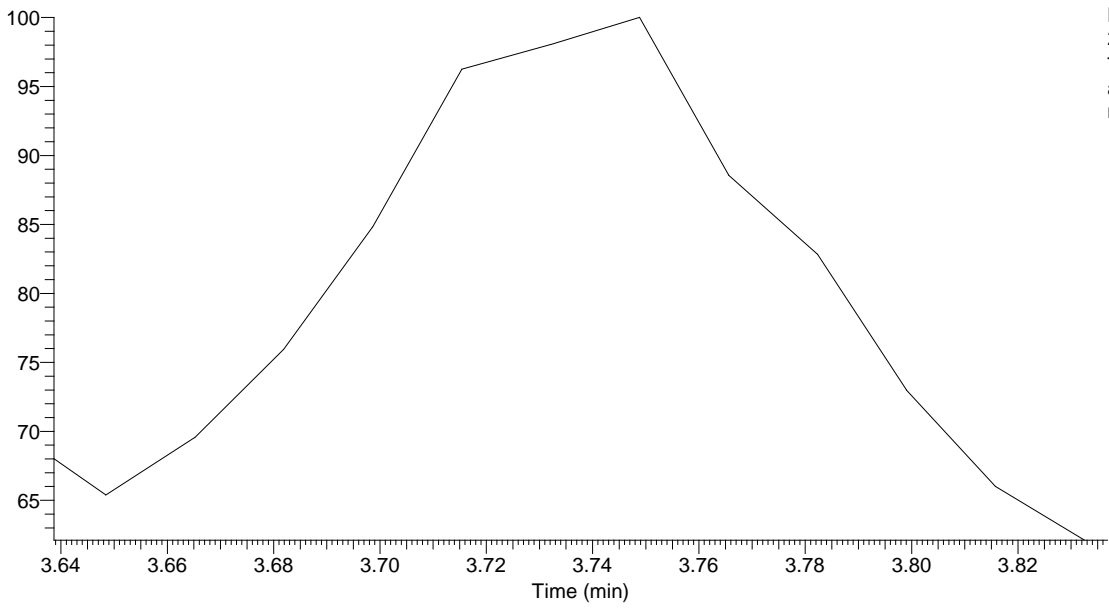
abeer-nagar-s2 #180-183 RT: 3.03-3.08 AV: 4 SB: 26 1.21-1.34 , 0.87-1.14 NL: 1.30E2  
T: + c EI Full ms [40.00-1000.00]



**Figure S49.** Mass spectrum of compound **1b**

# Supporting Information

RT: 3.64 - 3.84 SM: 11B



NL:  
2.82E4  
TIC MS  
abeer-  
nagar-sb9

abeer-nagar-sb9 #110-112 RT: 1.86-1.89 AV: 3 SB: 26 1.21-1.34, 0.87-1.14 NL: 9.85E1  
T: + c EI Full ms [40.00-1000.00]

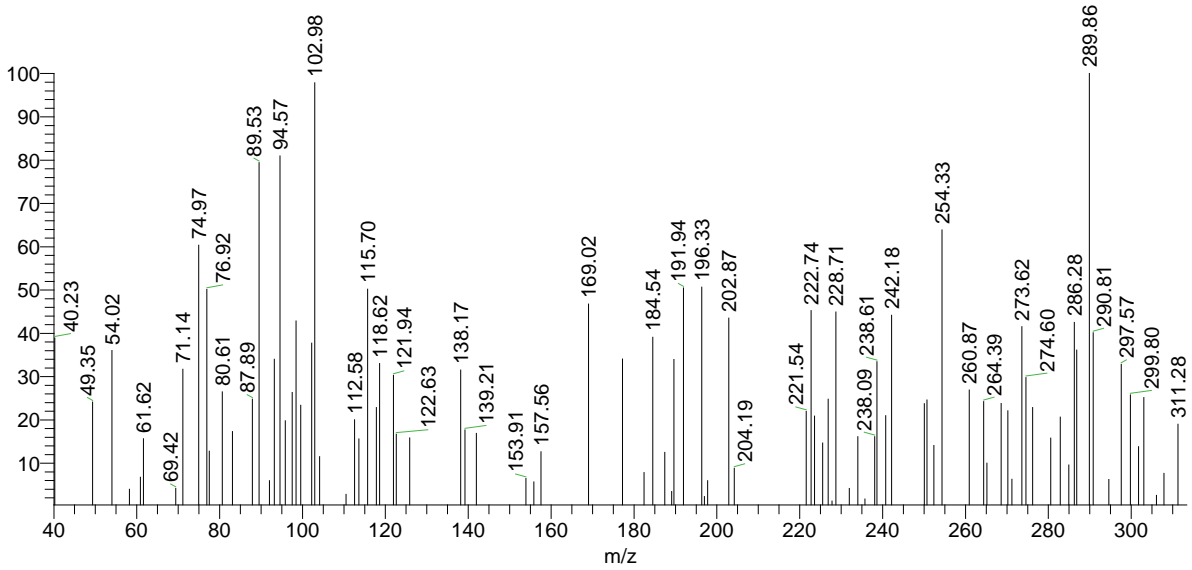
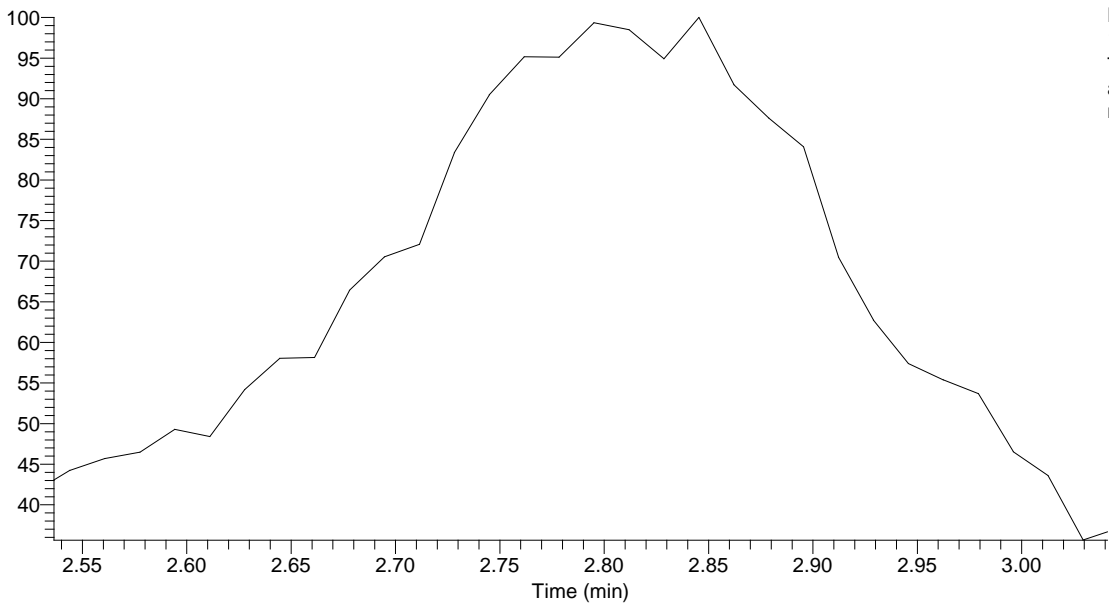


Figure S50. Mass spectrum of compound 3a

# Supporting Information

RT: 2.54 - 3.04 SM: 11B



NL:  
1.54E4  
TIC MS  
abeer-  
nagar-s7

abeer-nagar-s7 #187-189 RT: 3.15-3.18 AV: 3 SB: 26 1.21-1.34, 0.87-1.14 NL: 1.18E2  
T: + c EI Full ms [40.00-1000.00]

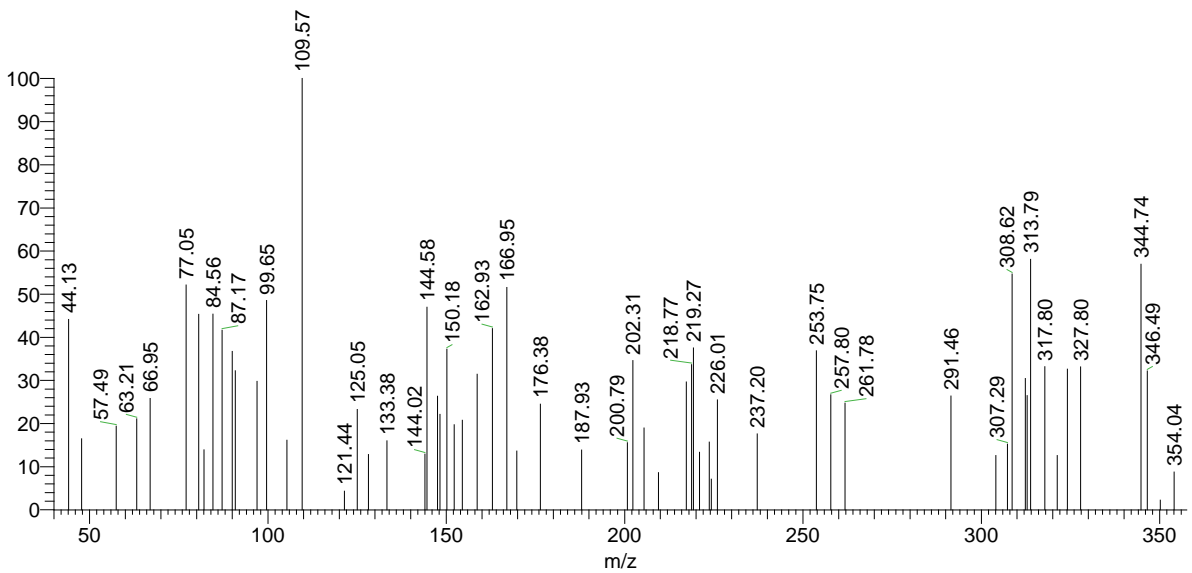
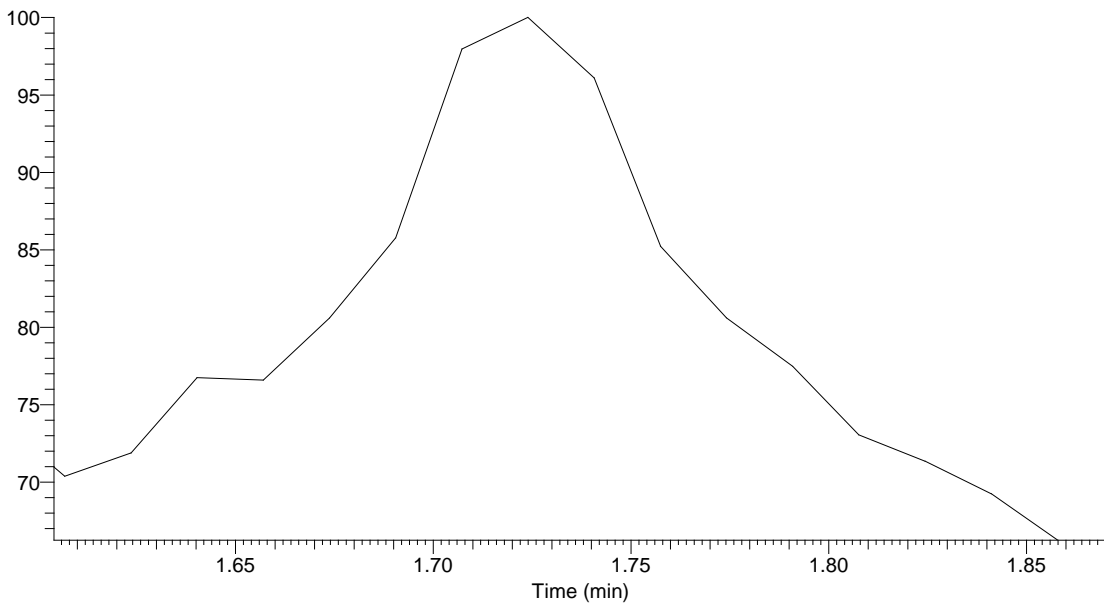


Figure S51. Mass spectrum of compound 10b



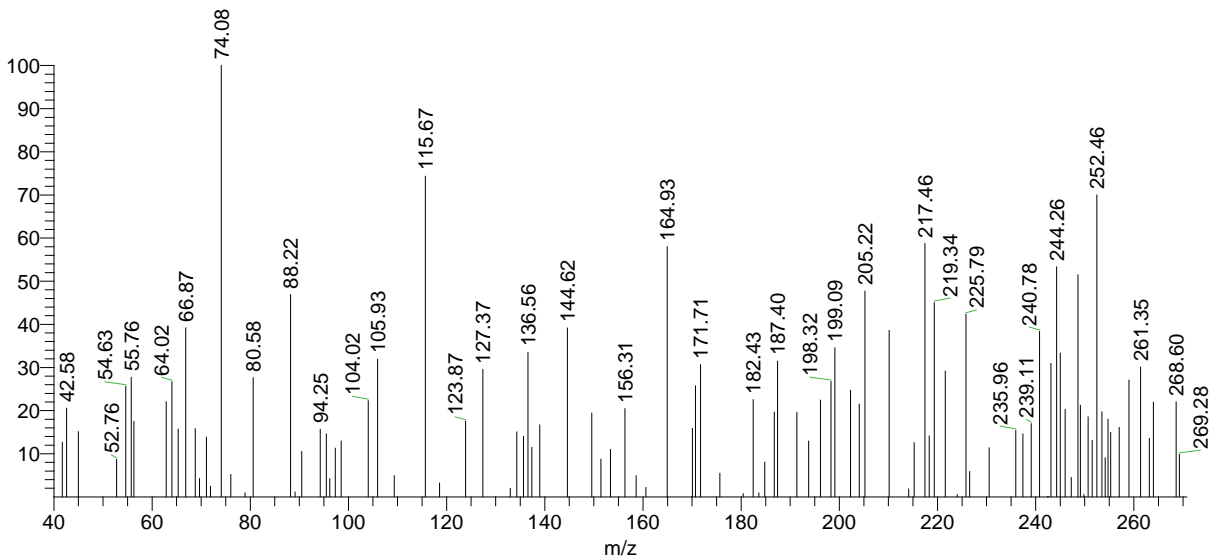
# Supporting Information

RT: 1.60 - 1.87 SM: 11B



NL:  
2.33E4  
TIC MS  
abeer-  
nagar-sB3

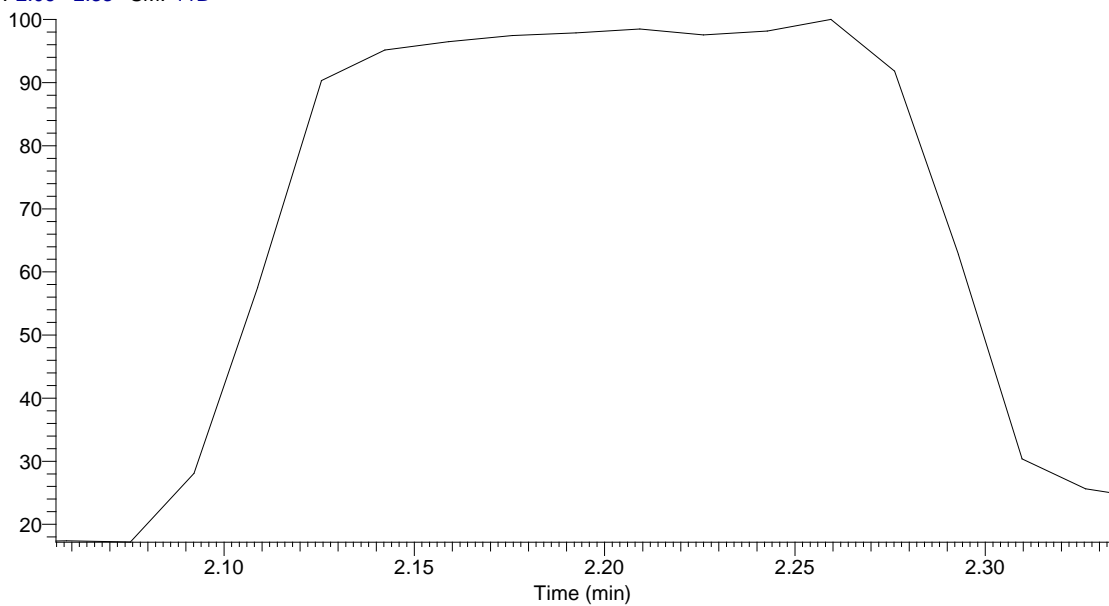
abeer-nagar-sB3 #64-69 RT: 1.09-1.17 AV: 6 SB: 26 1.21-1.34, 0.87-1.14 NL: 8.77E1  
T: + c EI Full ms [40.00-1000.00]



**Figure S52.** Mass spectrum of compound **11a**

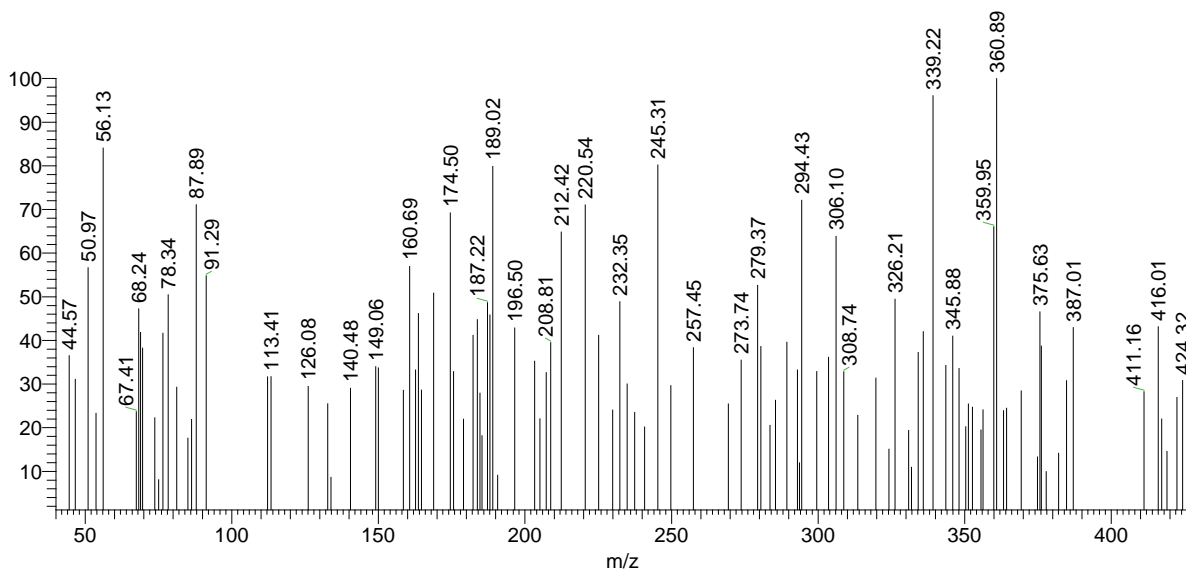
# Supporting Information

RT: 2.06 - 2.33 SM: 11B



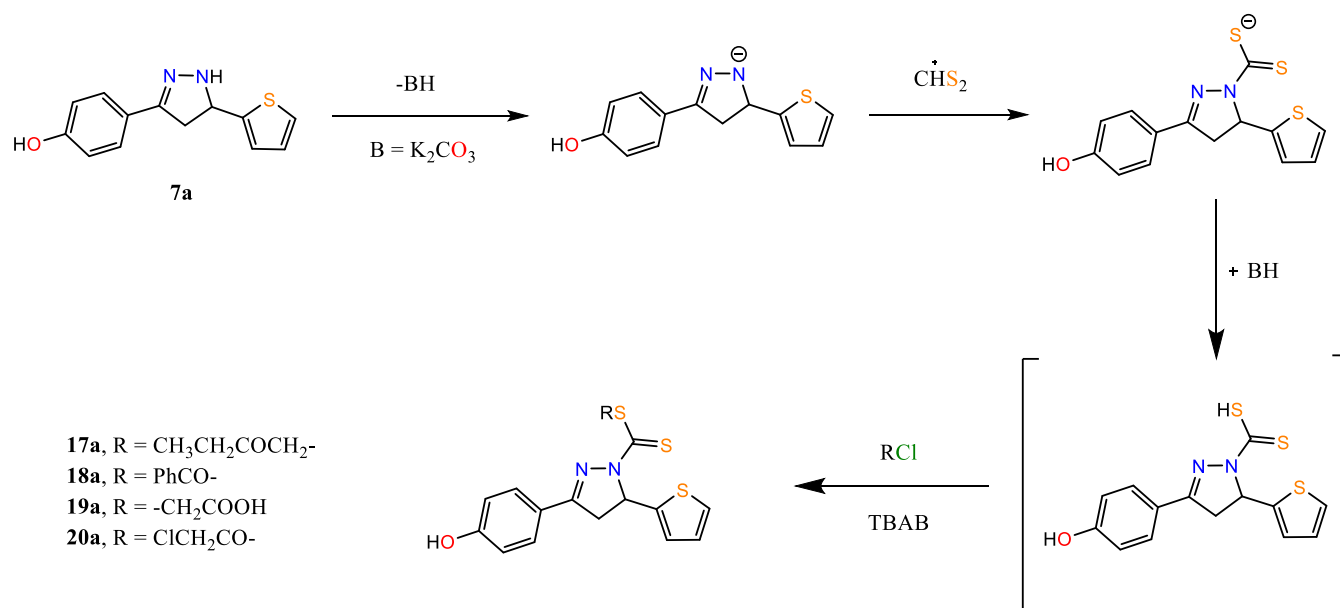
NL:  
8.38E3  
TIC MS  
abeer-  
nagar-ptc2

abeer-nagar-ptc2 #99-100 RT: 1.67-1.69 AV: 2 SB: 26 1.21-1.34, 0.87-1.14 NL: 1.43E2  
T: + c EI Full ms [40.00-1000.00]



**Figure S53.** Mass spectrum of compound **18a**

Supporting Information



**Scheme S1.** Mechanism for the formation of target compounds **17a**, **18a**, **19a**, and **20a**.