

## Supplementary Materials

### Synthesis and evaluation of novel nitric oxide-donating ligustrazine derivatives as potent antiplatelet aggregation agents

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**Table S1.** The IC<sub>50</sub> values of target compounds against platelet aggregation in vitro induced by ADP or AA. (Mean  $\pm$  SD, n = 5)

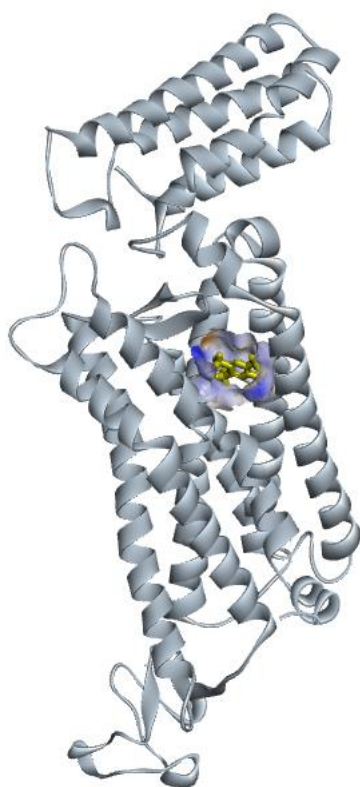
Compound	IC <sub>50</sub> (mM)	
	ADP (10 $\mu$ M)	AA (1mM)
TMP	1.1100 $\pm$ 0.07	0.8155 $\pm$ 0.08
<b>13</b>	2.0810 $\pm$ 0.09	1.7120 $\pm$ 0.21
<b>14a</b>	0.7736 $\pm$ 0.08	0.6232 $\pm$ 0.05
<b>14b</b>	1.7830 $\pm$ 0.15	1.2390 $\pm$ 0.15
<b>14c</b>	2.2970 $\pm$ 0.20	1.8830 $\pm$ 0.14
<b>14d</b>	1.4380 $\pm$ 0.18	1.0400 $\pm$ 0.08
<b>14e</b>	2.5180 $\pm$ 0.26	2.3080 $\pm$ 0.30
<b>15a</b>	1.1710 $\pm$ 0.09	1.6270 $\pm$ 0.16
<b>15b</b>	0.7854 $\pm$ 0.06	0.8505 $\pm$ 0.03
<b>15c</b>	0.9230 $\pm$ 0.08	0.9658 $\pm$ 0.09
<b>15d</b>	0.7347 $\pm$ 0.07	0.5565 $\pm$ 0.03
<b>15e</b>	1.2060 $\pm$ 0.08	0.9412 $\pm$ 0.07

**Table S2:** Docking energies of ligustrazine (TMP) and all new compounds (**13**, **14a-14e**, **15a-15e**) with TBXA2R

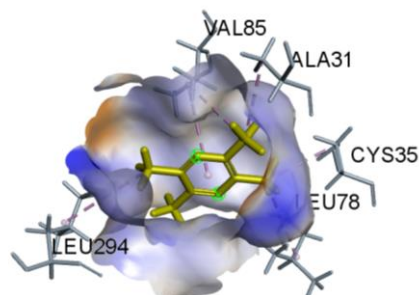
Compound	-CDOCKER_INTERACTION_ENERGY,	-CDOCKER_ENERGY,
	kcal/mol	kcal/mol
TMP	22.6805	15.7133
<b>13</b>	43.7139	26.4085
<b>14a</b>	57.2490	30.5841
<b>14b</b>	56.3094	38.3704
<b>14c</b>	57.3570	38.5336
<b>14d</b>	60.4573	28.8552
<b>14e</b>	56.2685	25.4620
<b>15a</b>	52.6835	27.3096
<b>15b</b>	54.9192	35.3326
<b>15c</b>	53.8605	29.0482
<b>15d</b>	61.9653	42.8464
<b>15e</b>	62.0654	38.7112

## Binding modes of all the compounds at active site of TBXA2R

A



B



C

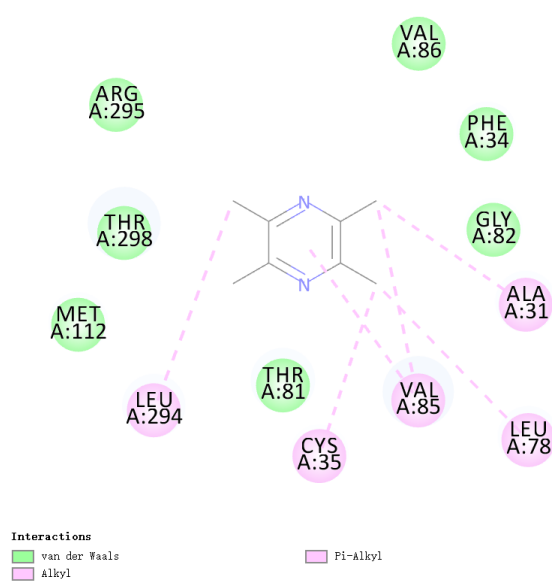
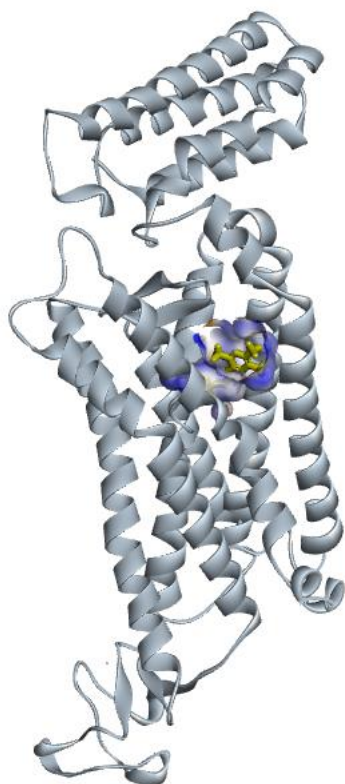
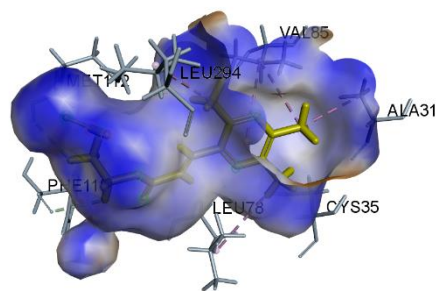


Figure S1. Possible binding mode of TMP at active site of TBXA2R.

A



B



C

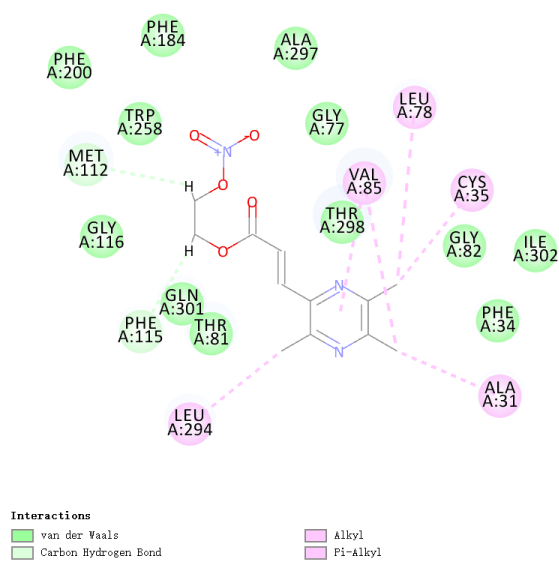
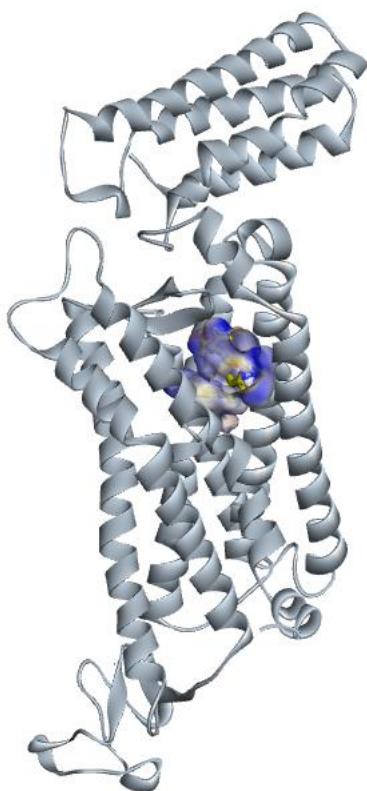
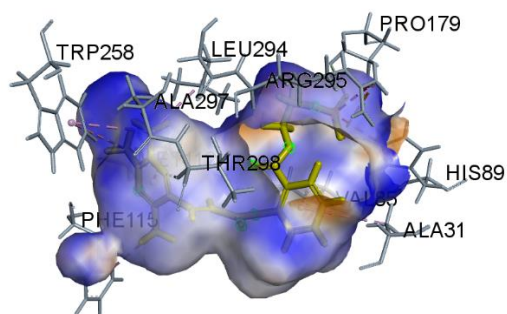


Figure S2. Possible binding mode of **13** at active site of TBXA2R.

A



B



C

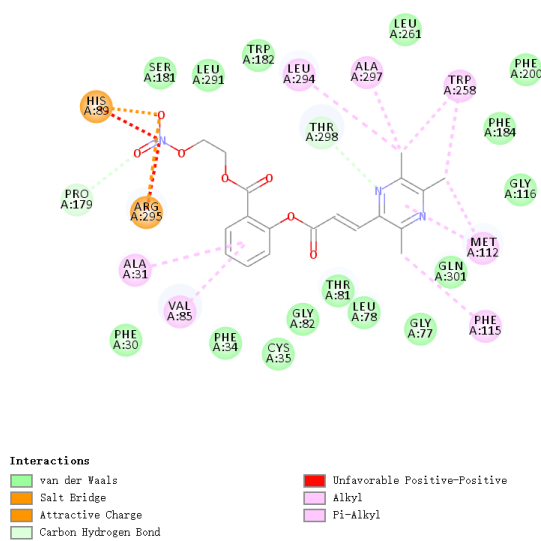


Figure S3. Possible binding mode of **14a** at active site of TBXA2R.

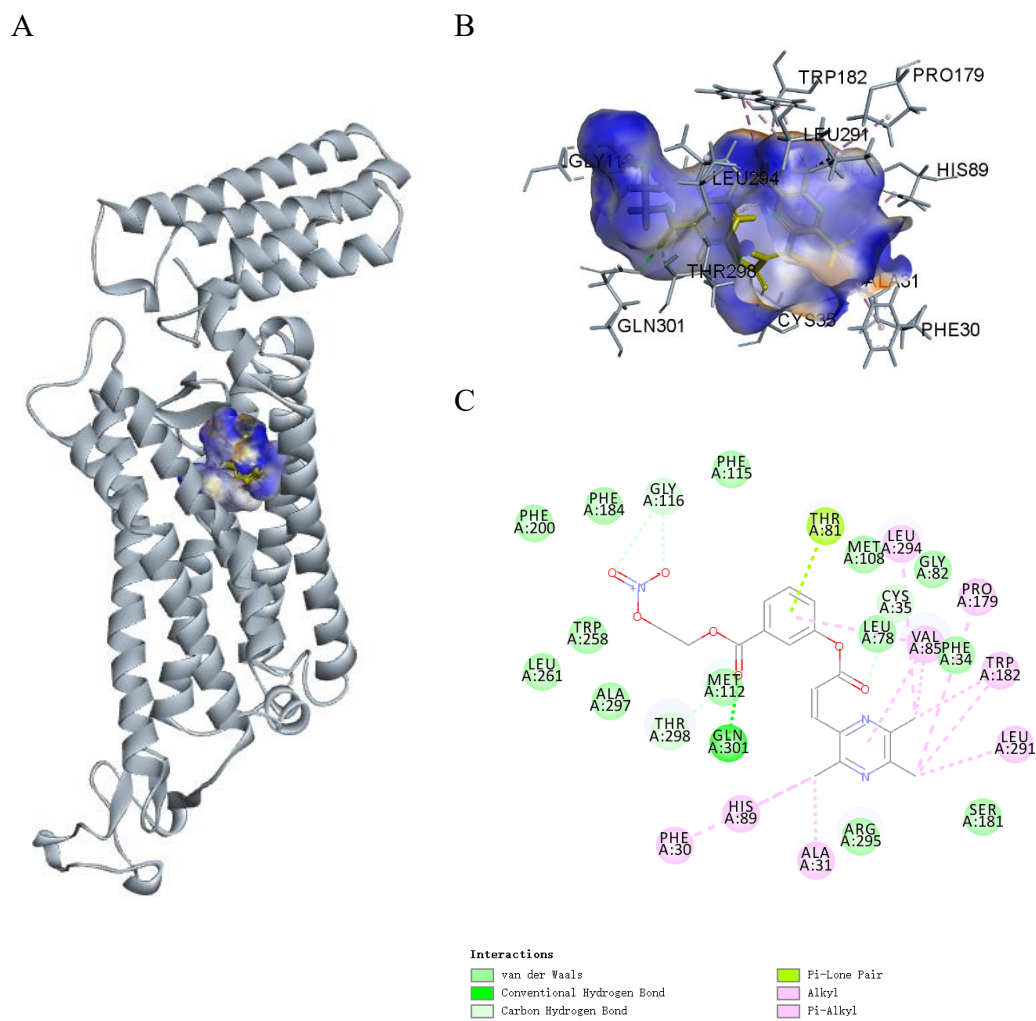
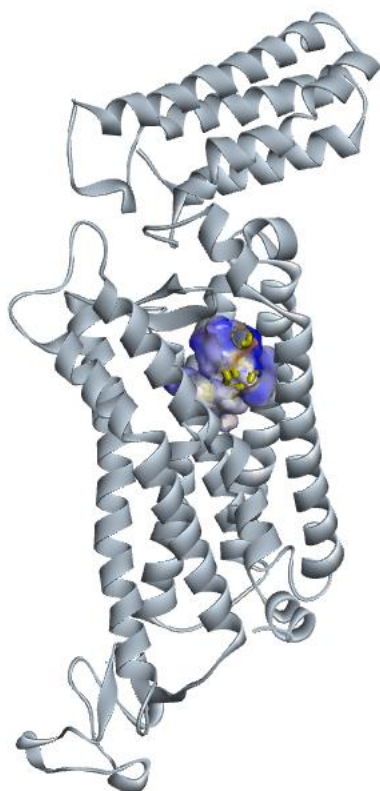


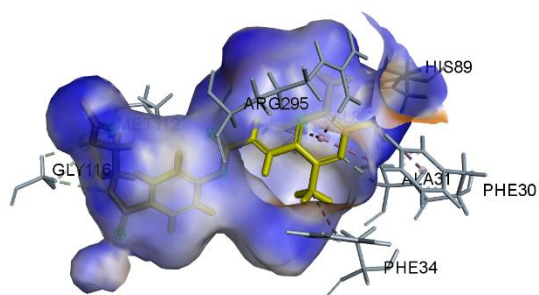
Figure S4. Possible binding mode of **14b** at active site of TBXA2R.



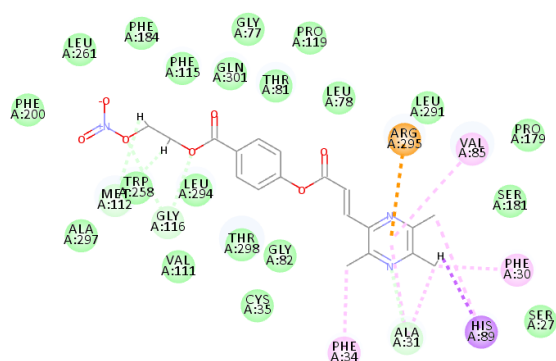
A



B



C

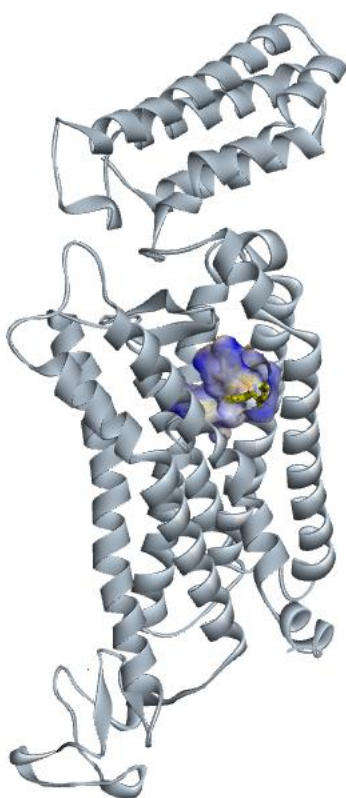


## Interactions

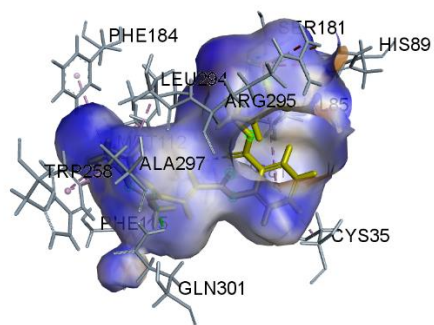
- |                      |          |
|----------------------|----------|
| van der Waals        | Pi-Sigma |
| Carbon Hydrogen Bond | alkyl    |
| Pi-Cation            | Pi-Alkyl |

Figure S5. Possible binding mode of **14c** at active site of TBXA2R.

A



B



C

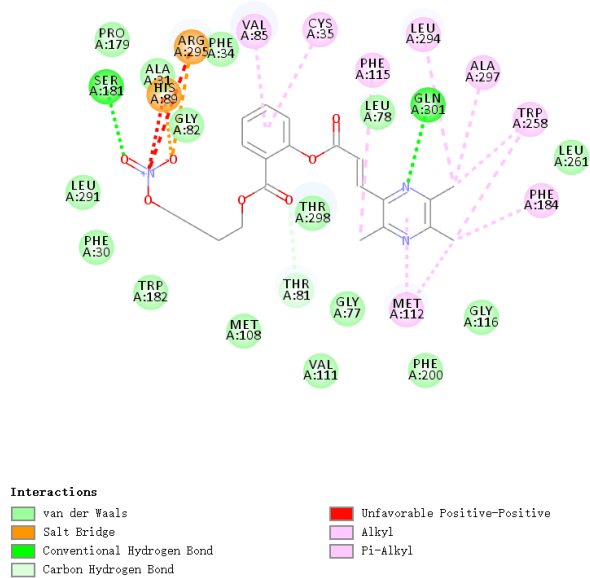


Figure S6. Possible binding mode of **14d** at active site of TBXA2R.

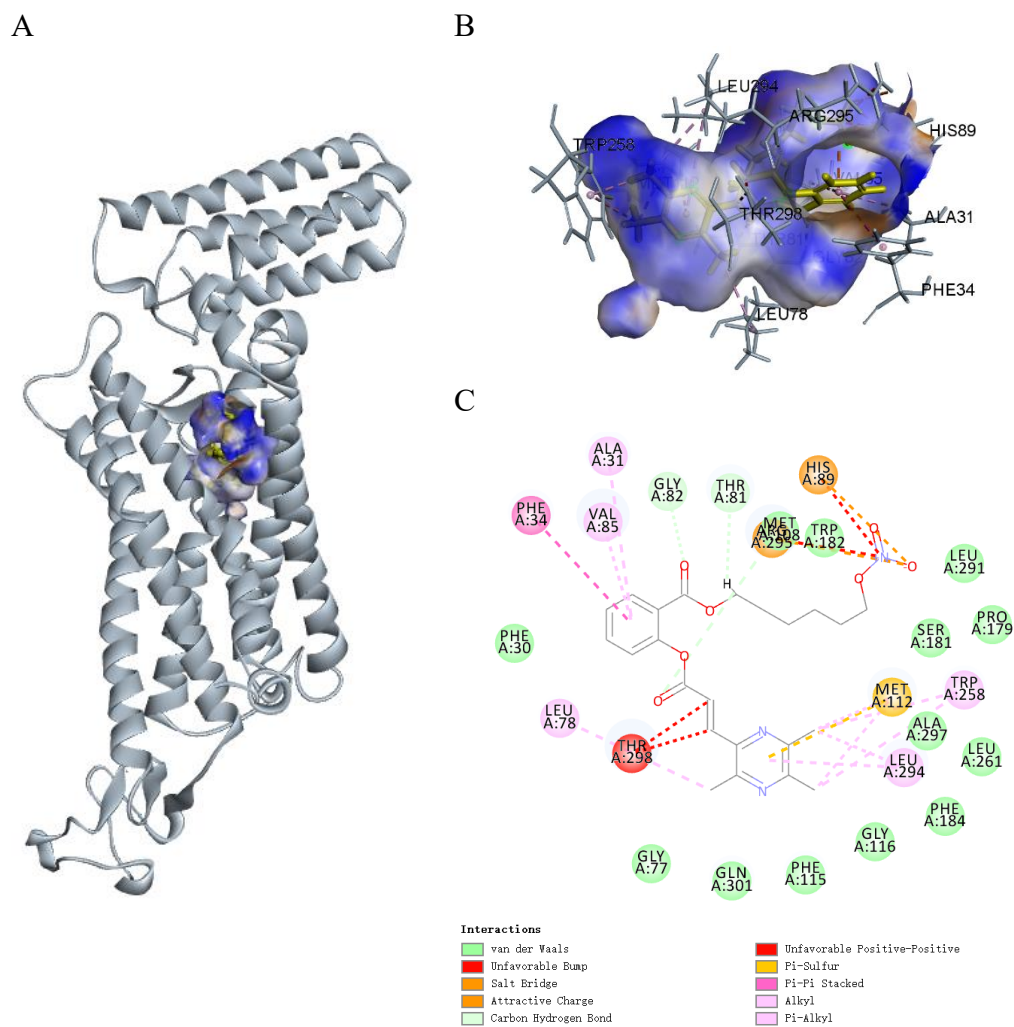


Figure S7. Possible binding mode of **14e** at active site of TBXA2R.

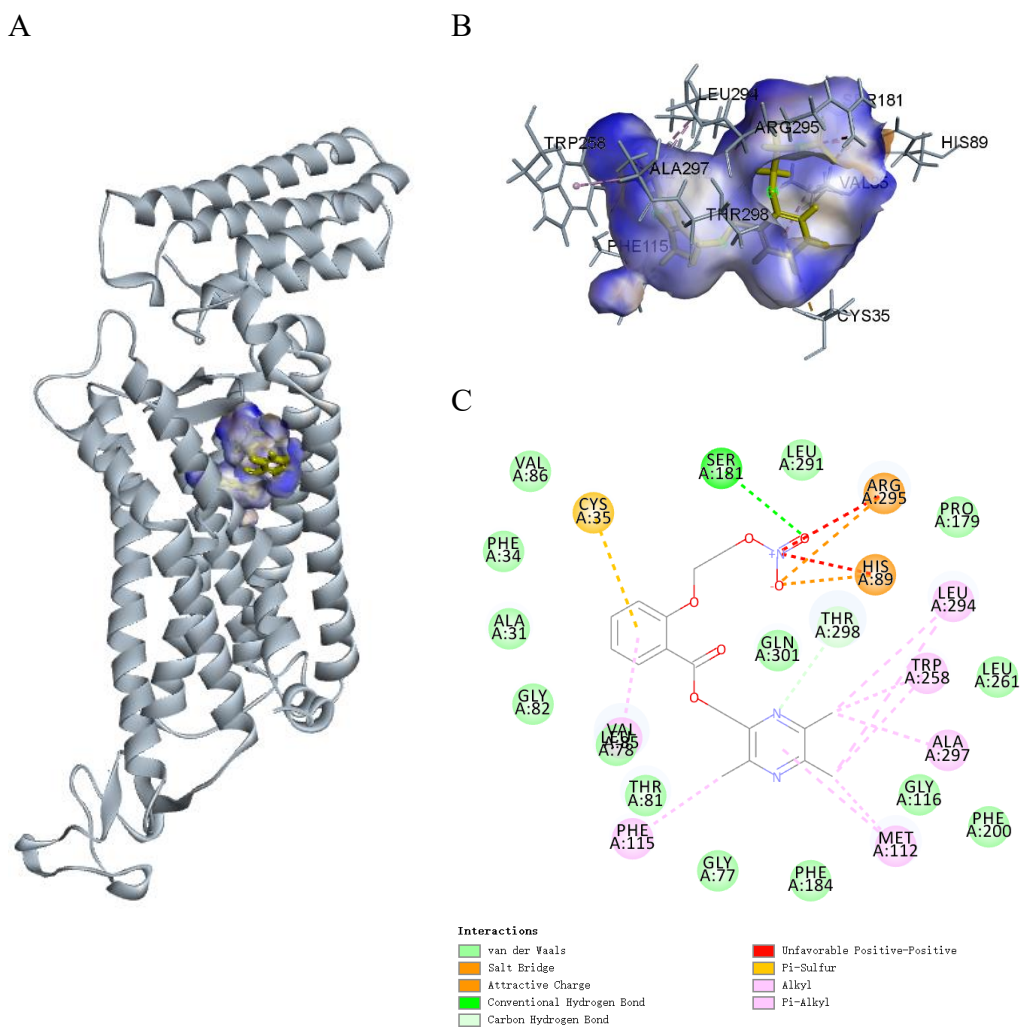


Figure S8. Possible binding mode of **15a** at active site of TBXA2R.

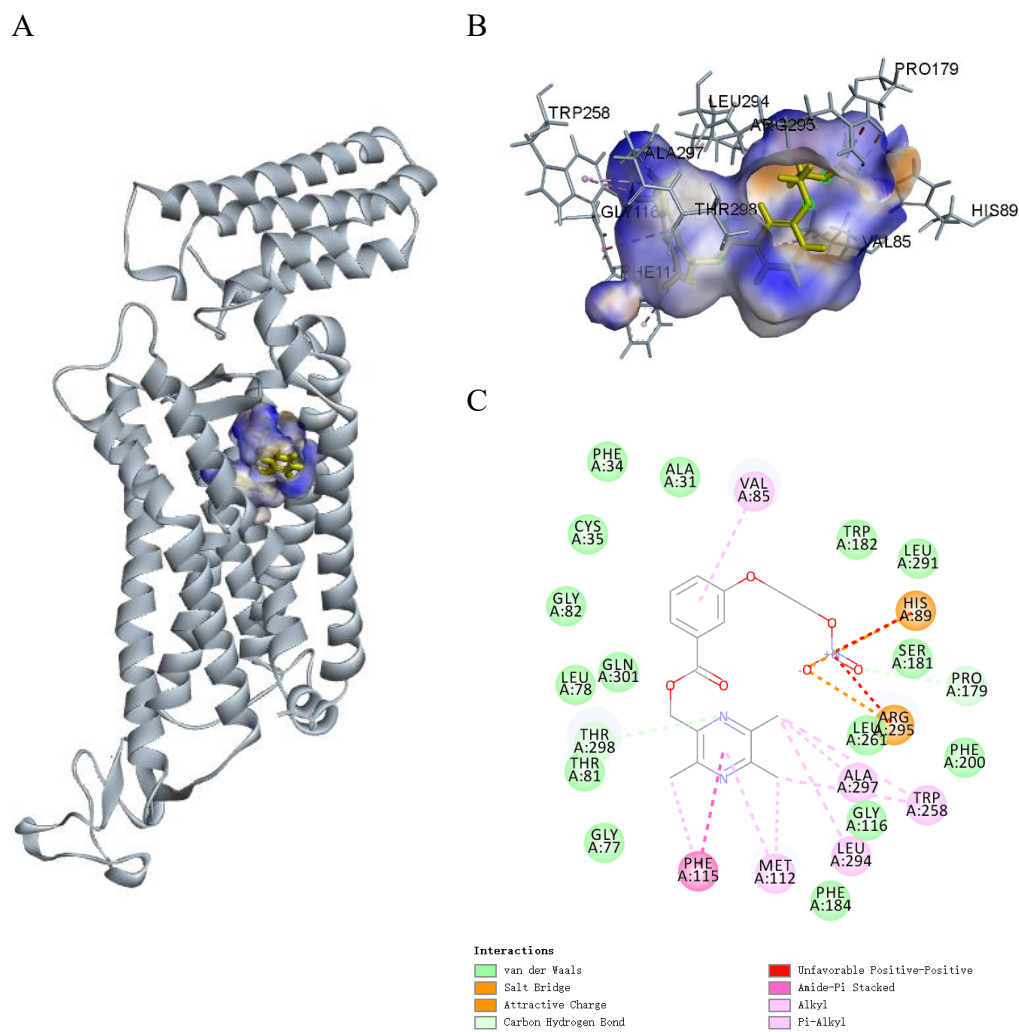


Figure S9. Possible binding mode of **15b** at active site of TBXA2R.

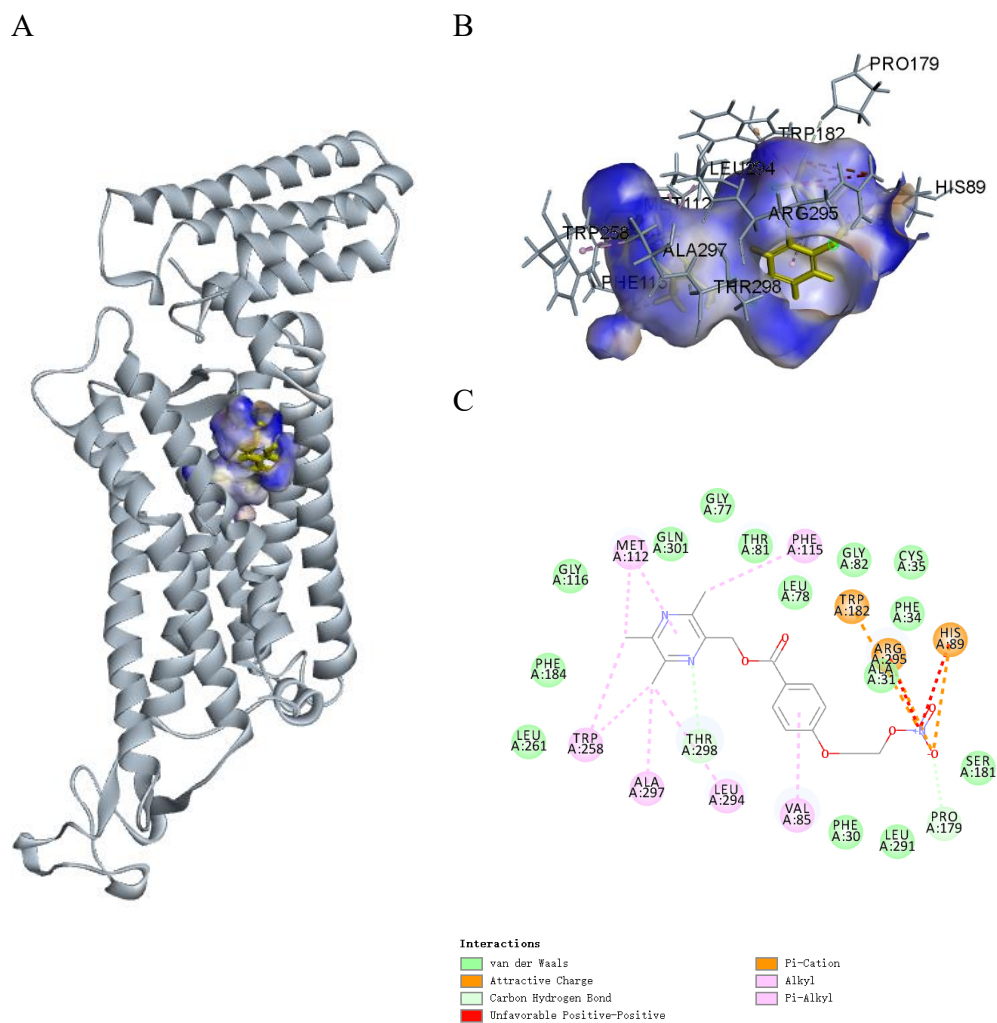
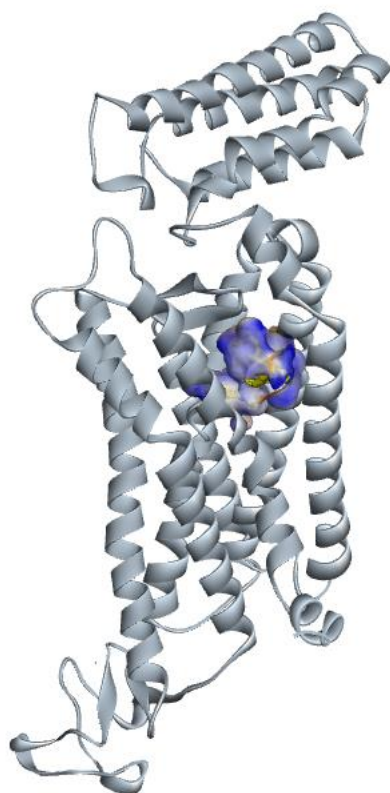


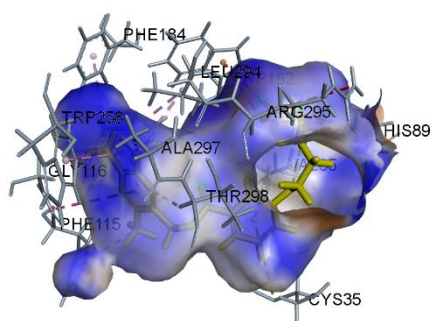
Figure S10. Possible binding mode of **15c** at active site of TBXA2R.



A



B



C

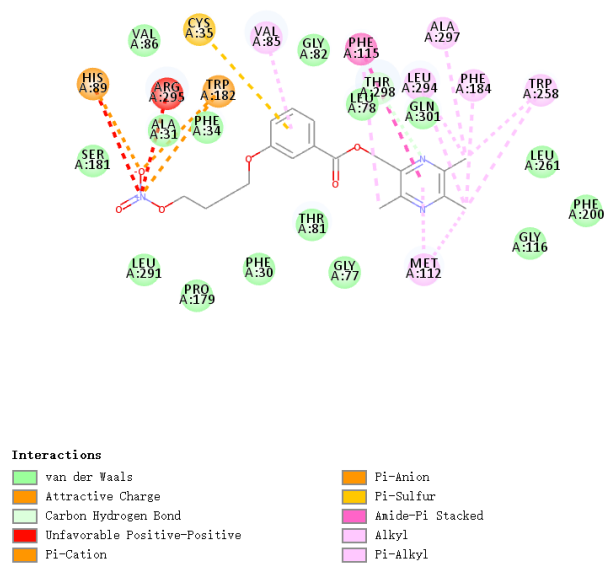
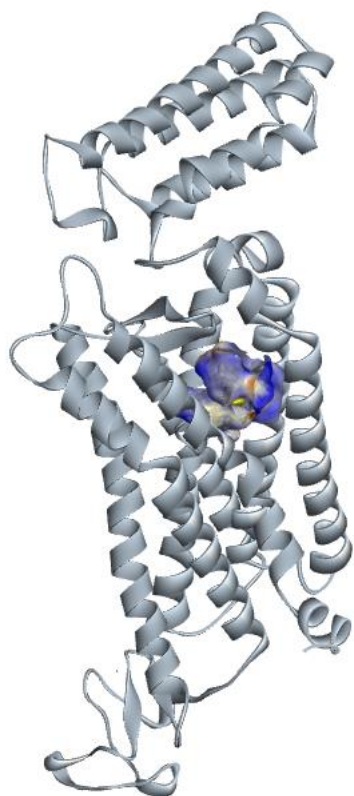
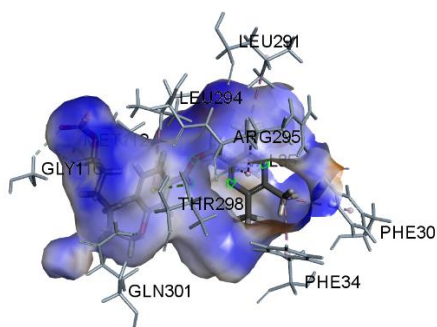


Figure S11. Possible binding mode of **15d** at active site of TBXA2R.

A



B



C

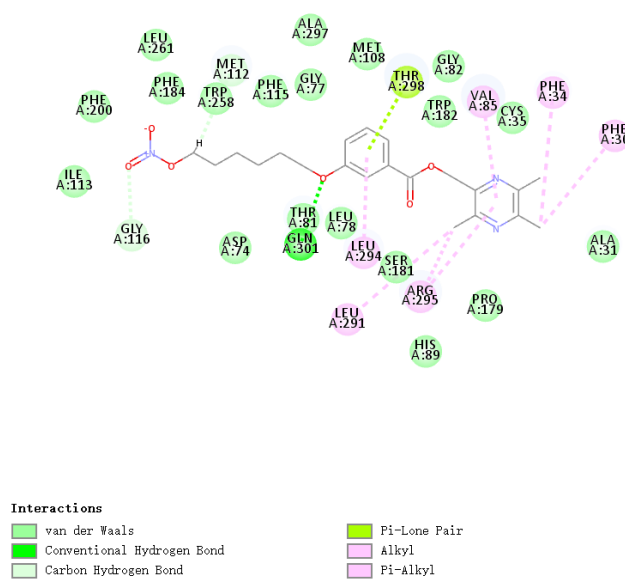


Figure S12. Possible binding mode of **15e** at active site of TBXA2R.



## NMR spectra of all new compounds

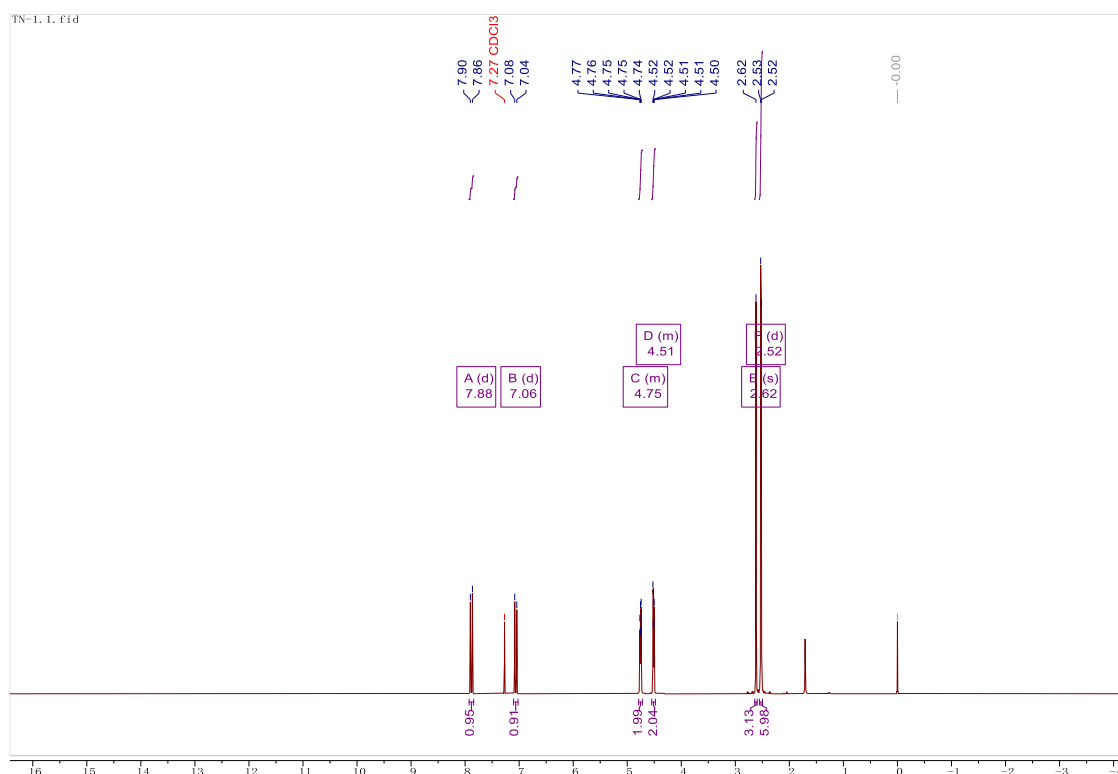


Figure S13.  $^1\text{H}$  NMR spectrum of 2-(nitrooxy)ethyl (E)-3-(3,5,6-trimethylpyrazin-2-yl)acrylate (**13**)

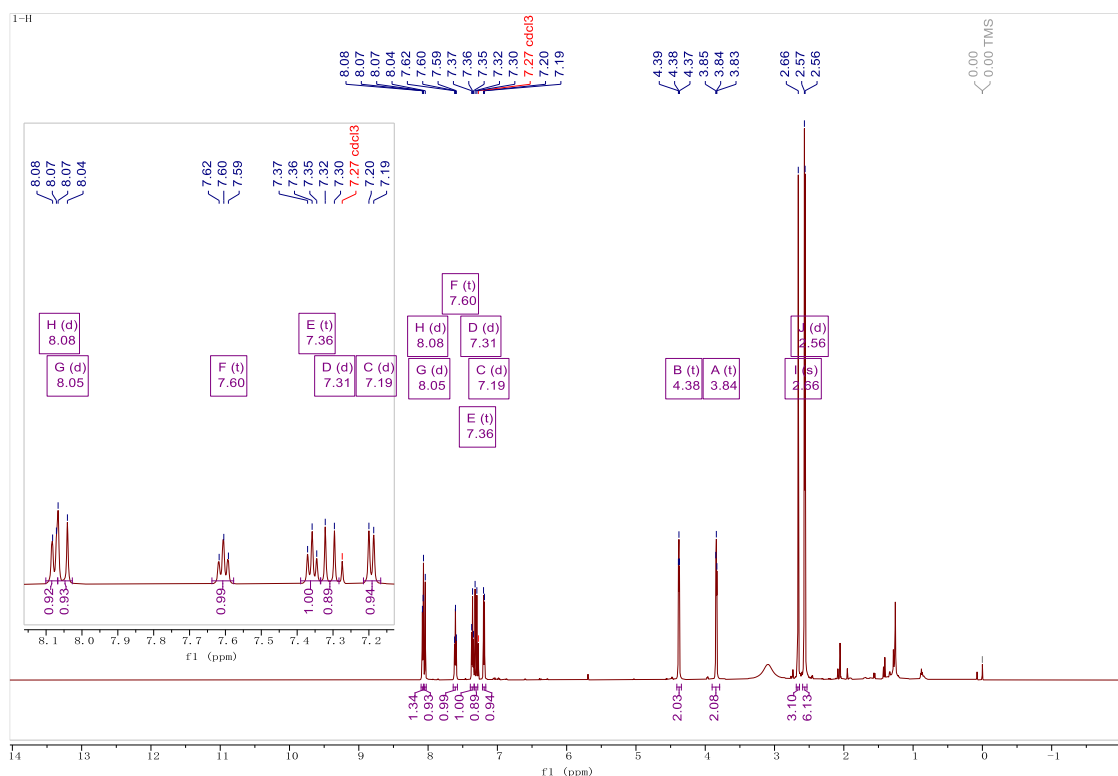


Figure S14.  $^1\text{H}$  NMR spectrum of 2-(nitrooxy)ethyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14a**)

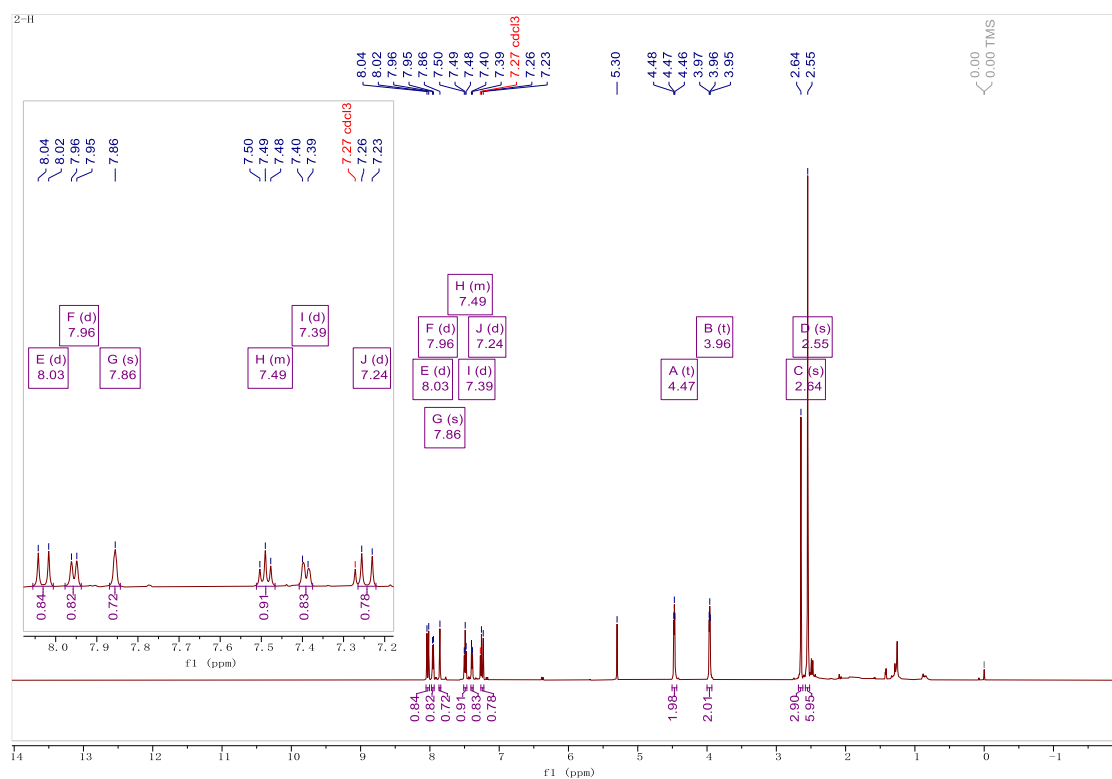


Figure S15.  $^1\text{H}$  NMR spectrum of 2-(nitrooxy)ethyl (E)-3-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14b**)

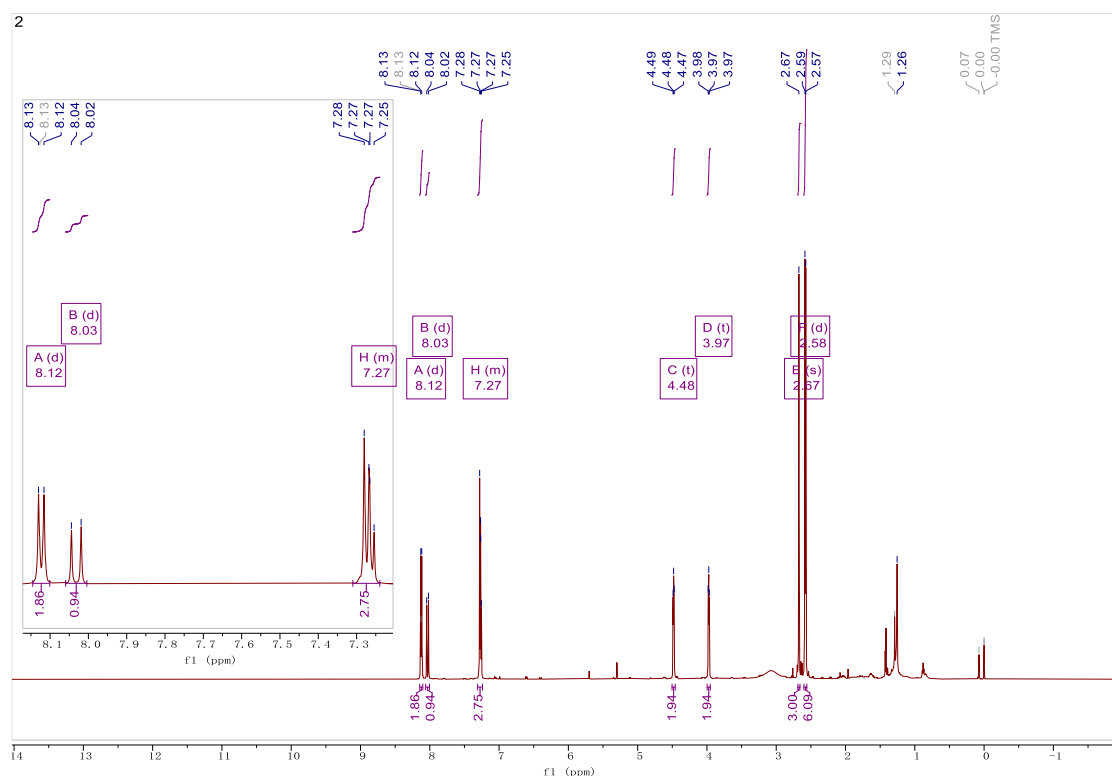


Figure S16.  $^1\text{H}$  NMR spectrum of 2-(nitrooxy)ethyl (E)-4-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14c**)

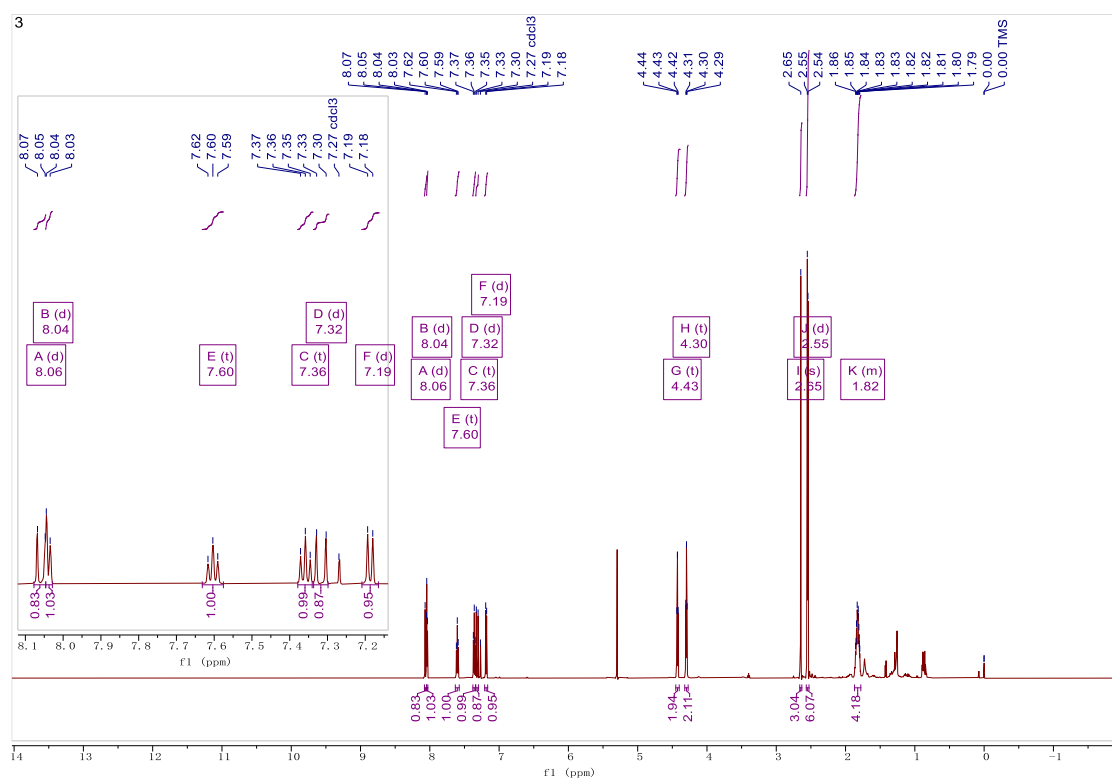


Figure S17. <sup>1</sup>H NMR spectrum of 4-(nitrooxy)butyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (14d)

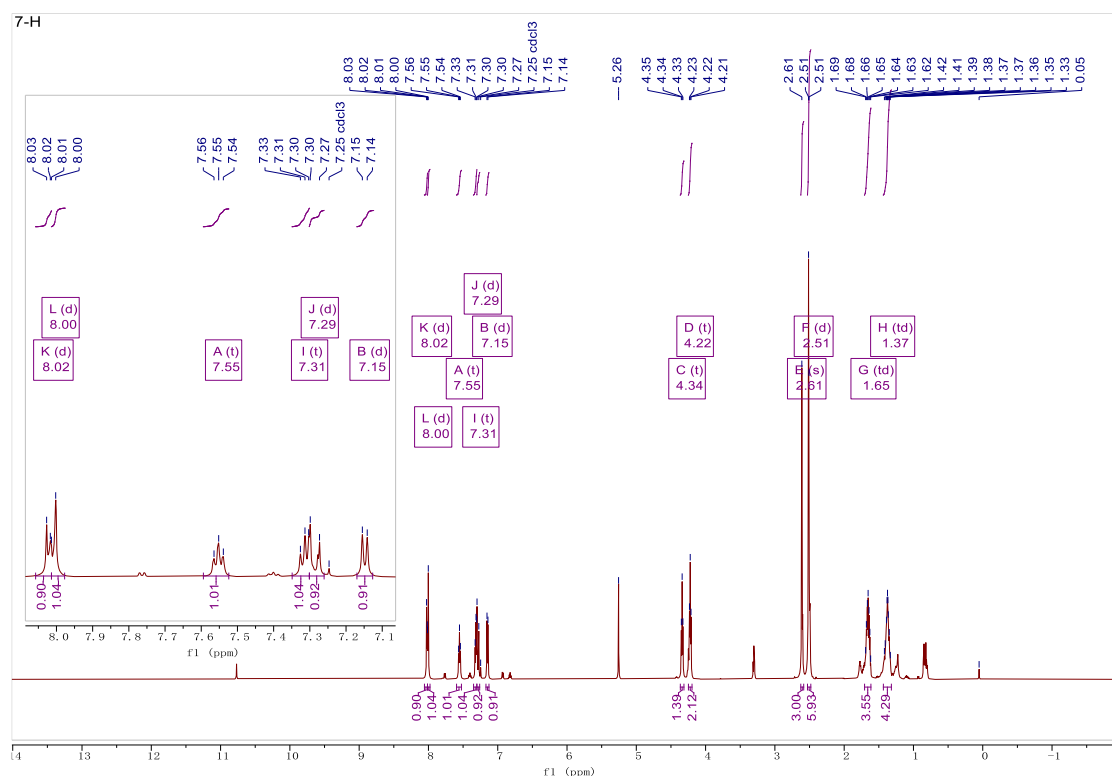


Figure S18. <sup>1</sup>H NMR spectrum of 6-(nitrooxy)hexyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (14e)

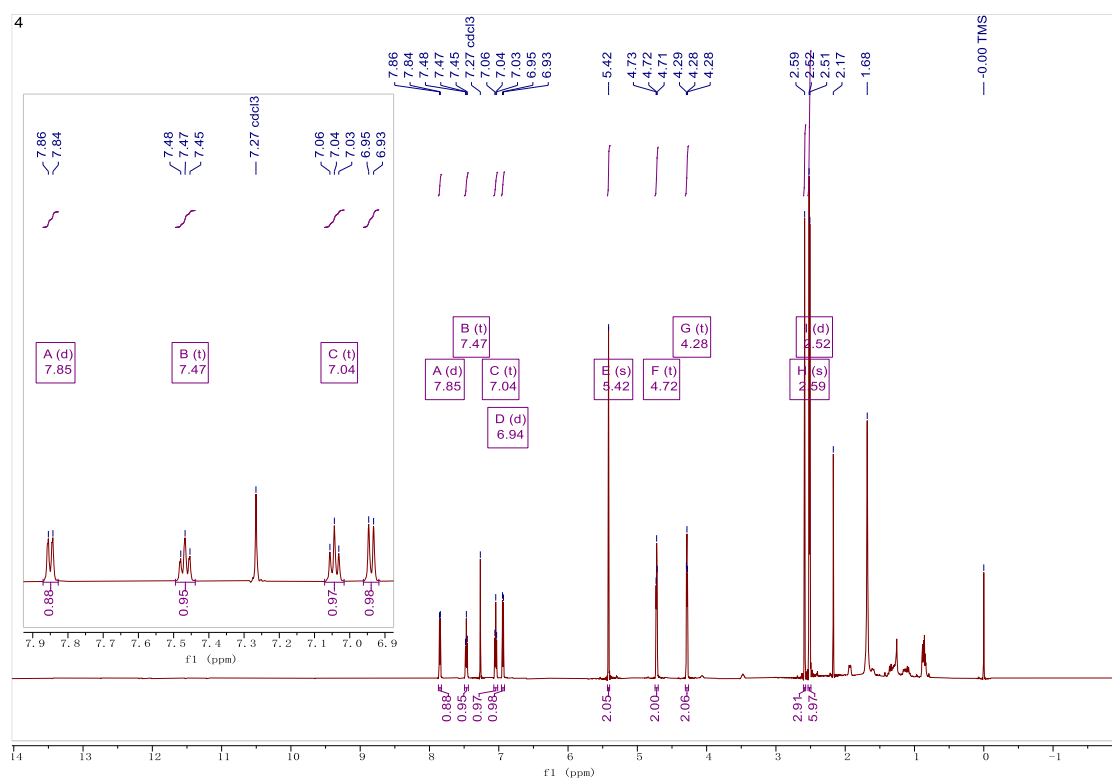


Figure S19.  $^1\text{H}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 2-(2-nitrooxy)ethoxybenzoate (**15a**)

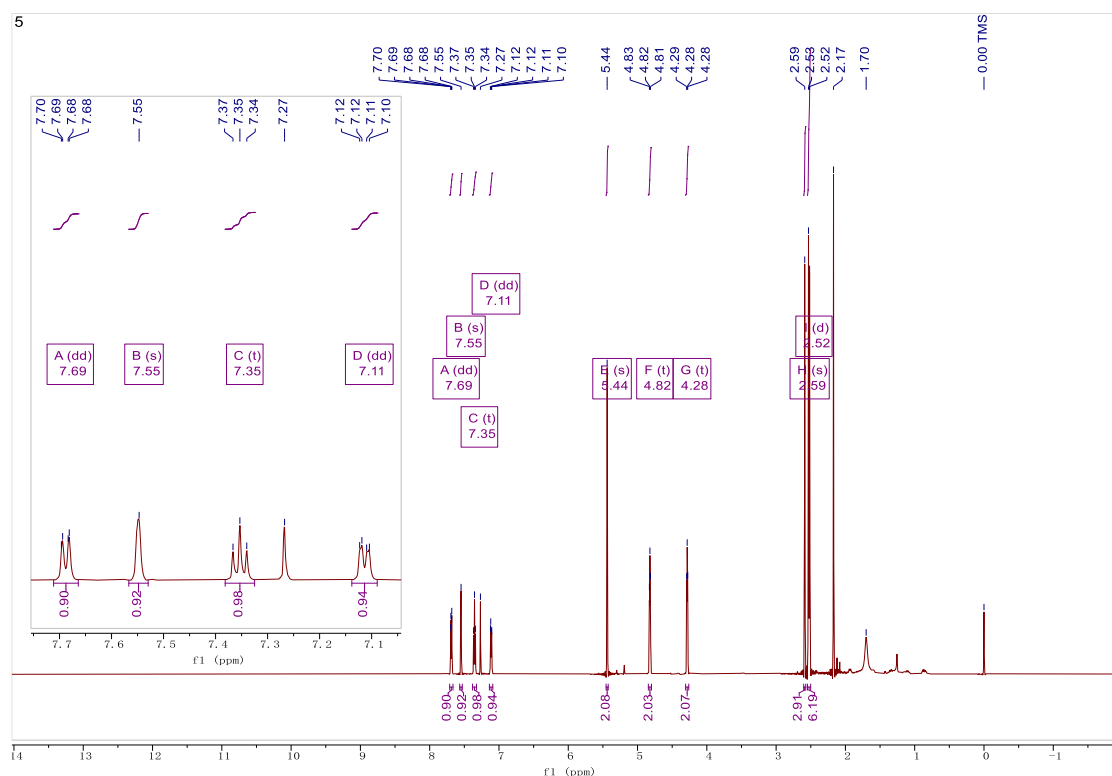


Figure S20.  $^1\text{H}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-(2-nitrooxy)ethoxybenzoate (**15b**)

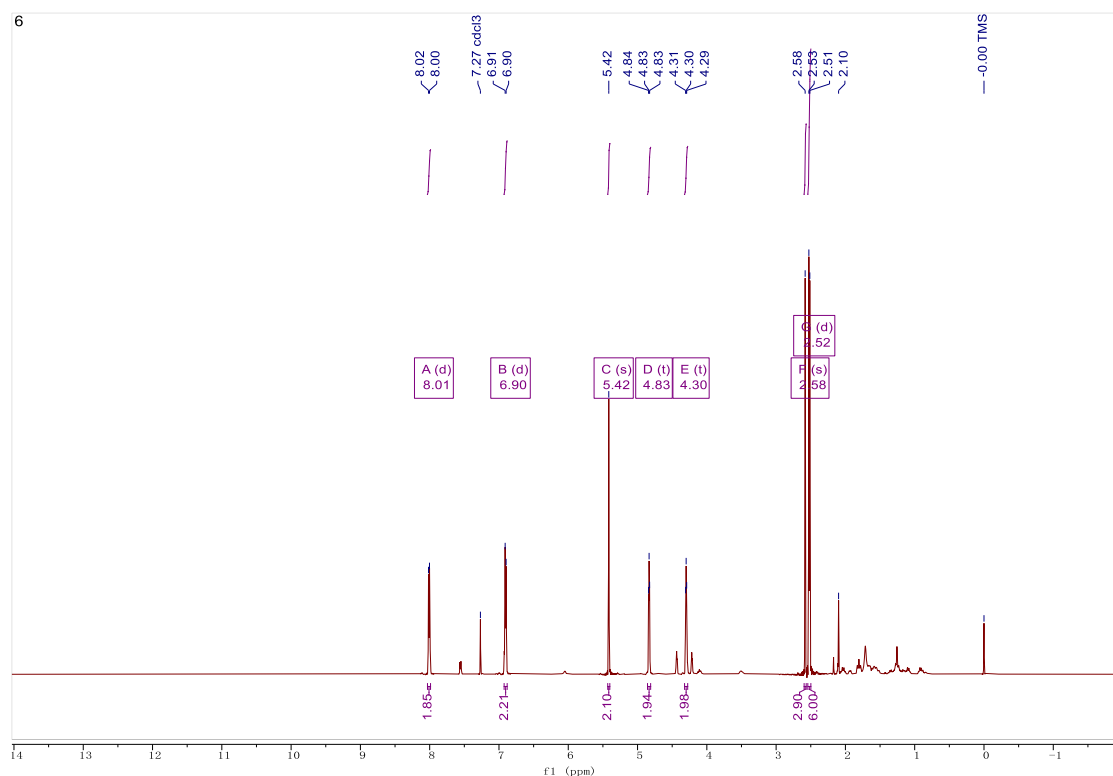


Figure S21.  $^1\text{H}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 4-(2-nitrooxy)ethoxybenzoate (**15c**)

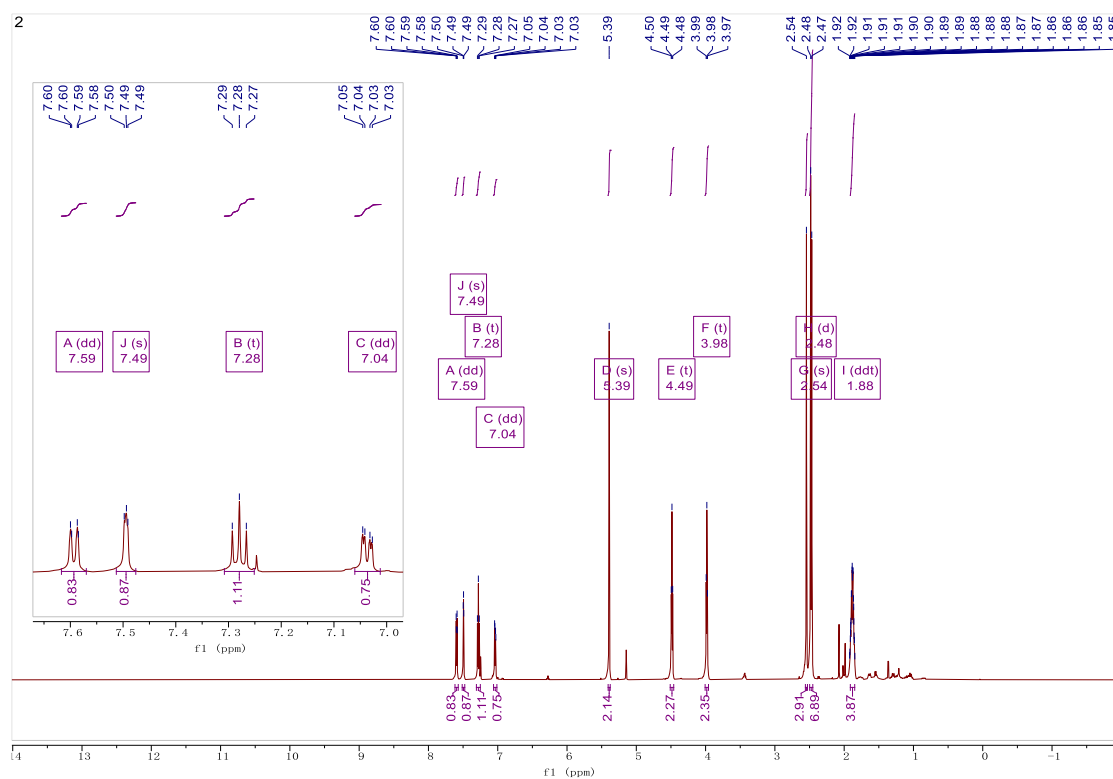


Figure S22.  $^1\text{H}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-(4-nitrooxy)butoxybenzoate (**15d**)

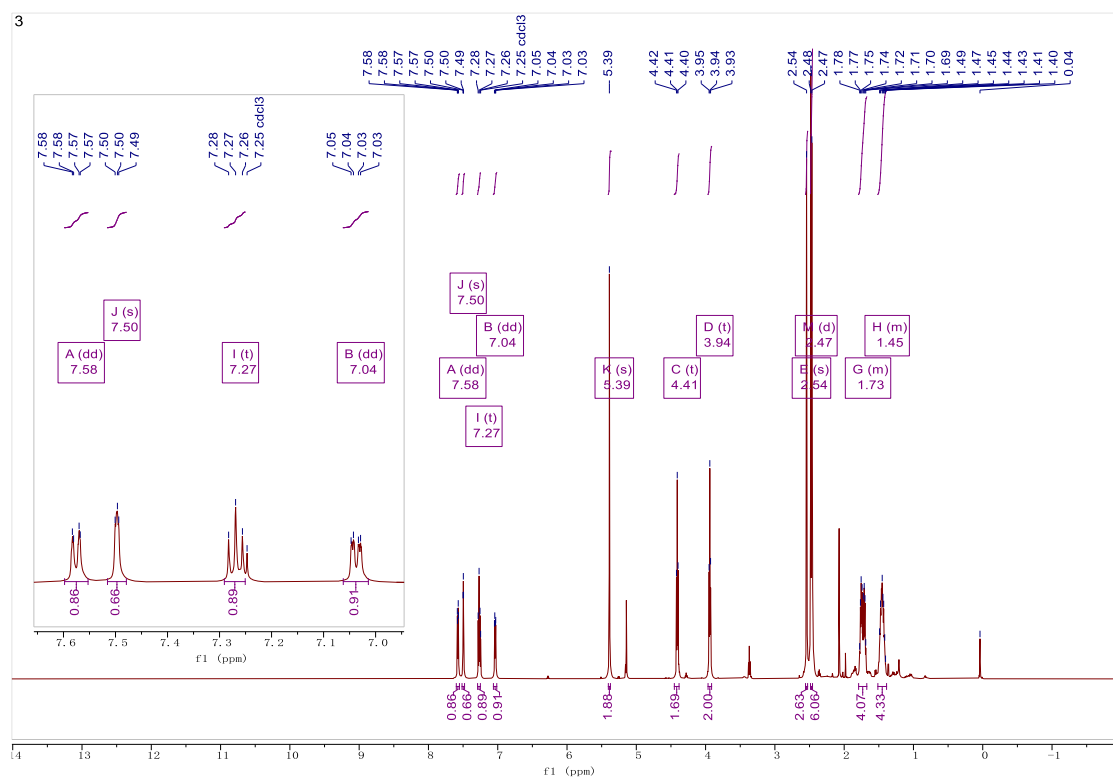


Figure S23. <sup>1</sup>H NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-((6-(nitroxy)hexyl)oxy)benzoate (**15e**)

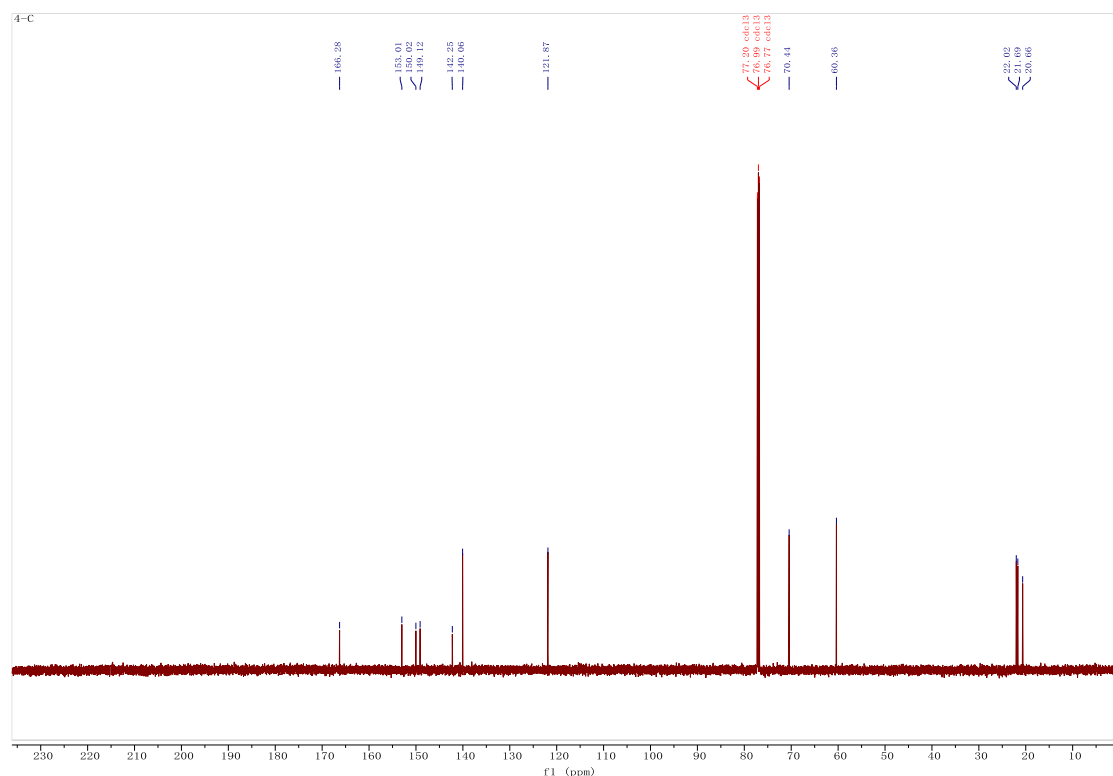


Figure S24. <sup>13</sup>C NMR spectrum of 2-(nitrooxy)ethyl (E)-3-(3,5,6-trimethylpyrazin-2-yl)acrylate (**13**)

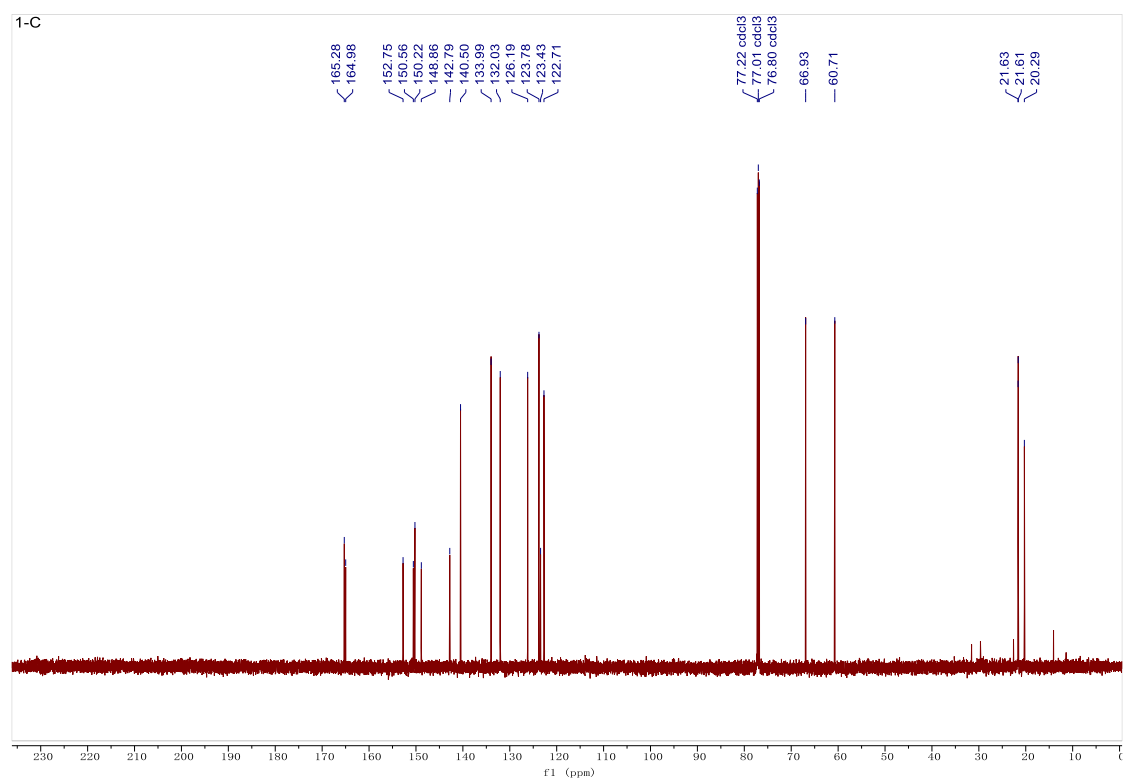


Figure S25.  $^{13}\text{C}$  NMR spectrum of 2-(nitroxy)ethyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14a**)

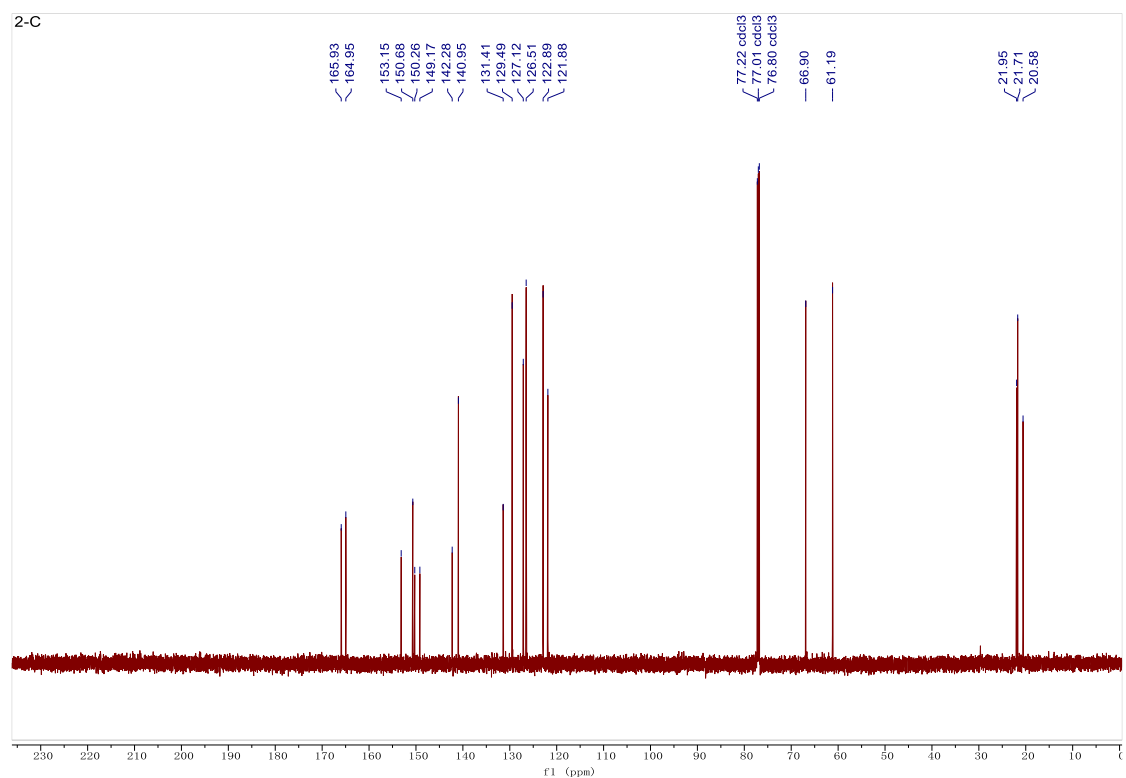


Figure S26.  $^{13}\text{C}$  NMR spectrum of 2-(nitroxy)ethyl (E)-3-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14b**)

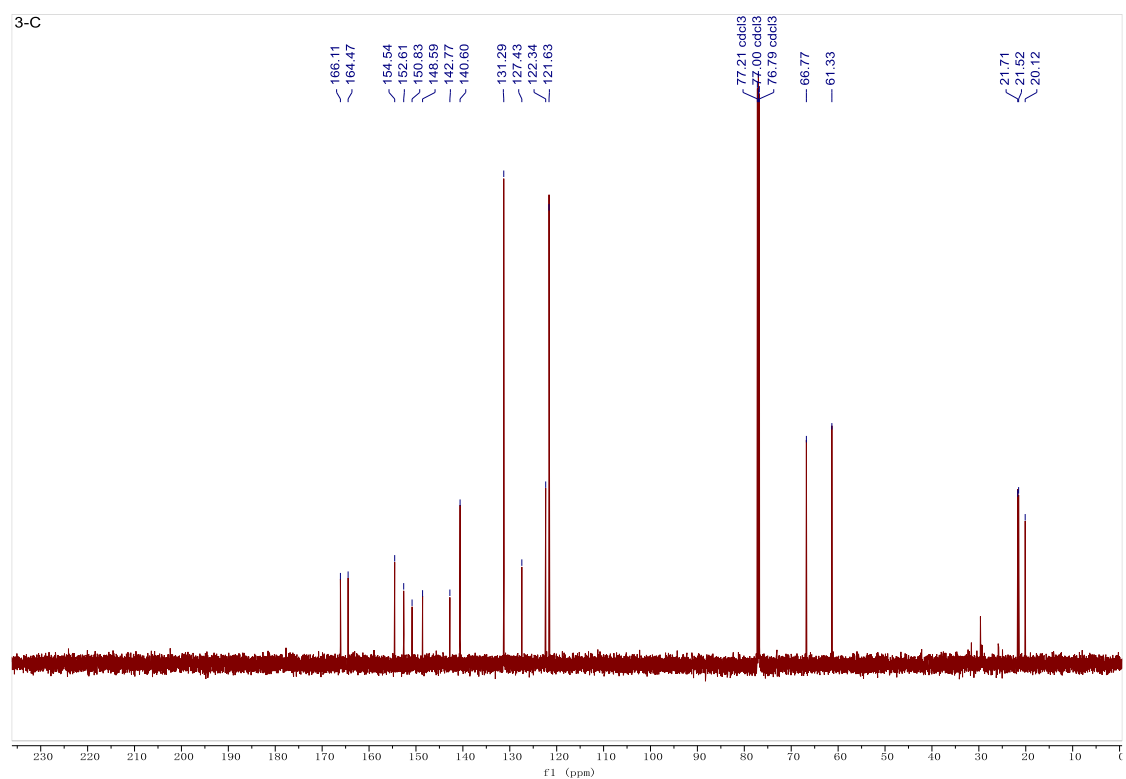


Figure S27.  $^{13}\text{C}$  NMR spectrum of 2-(nitrooxy)ethyl (E)-4-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14c**)

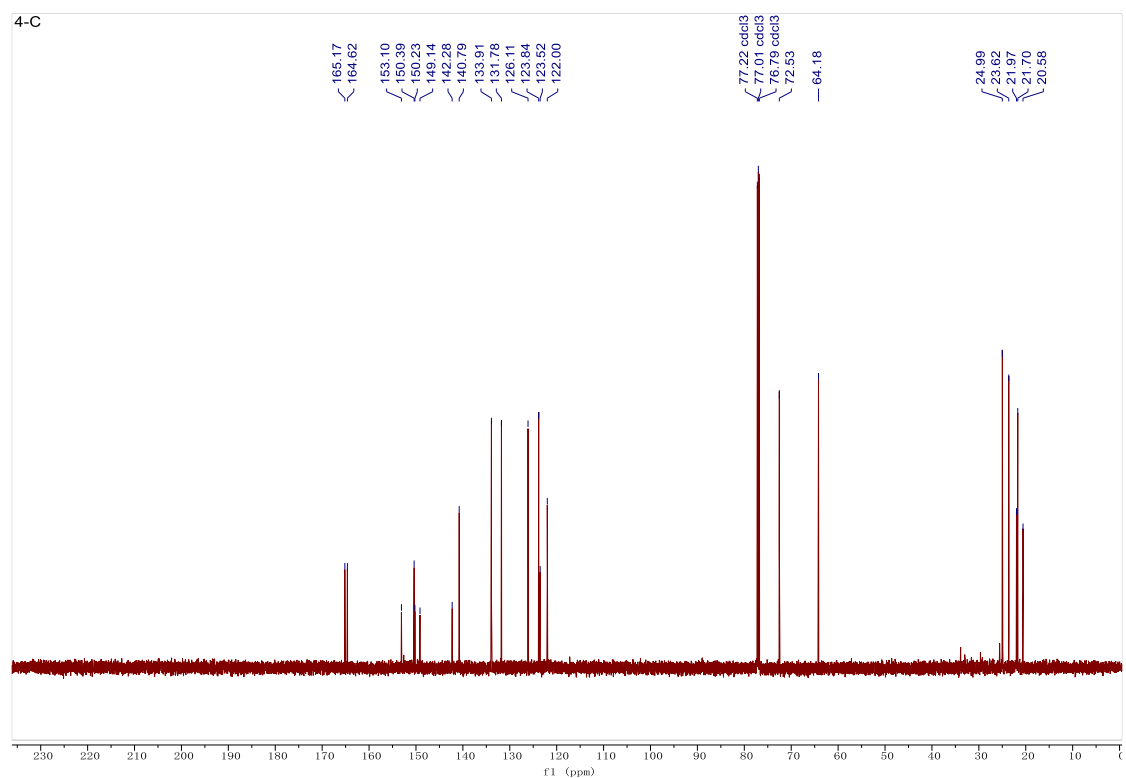


Figure S28.  $^{13}\text{C}$  NMR spectrum of 4-(nitrooxy)butyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14d**)



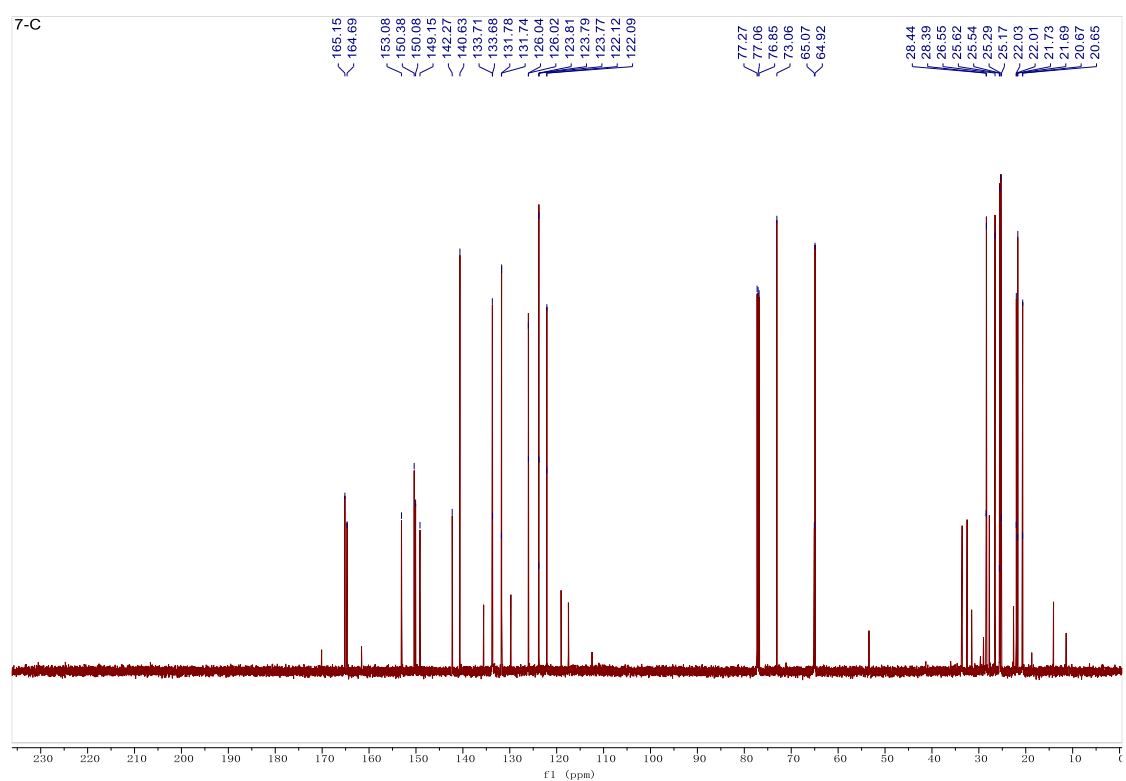


Figure S29.  $^{13}\text{C}$  NMR spectrum of 6-(nitrooxy)hexyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14e**)

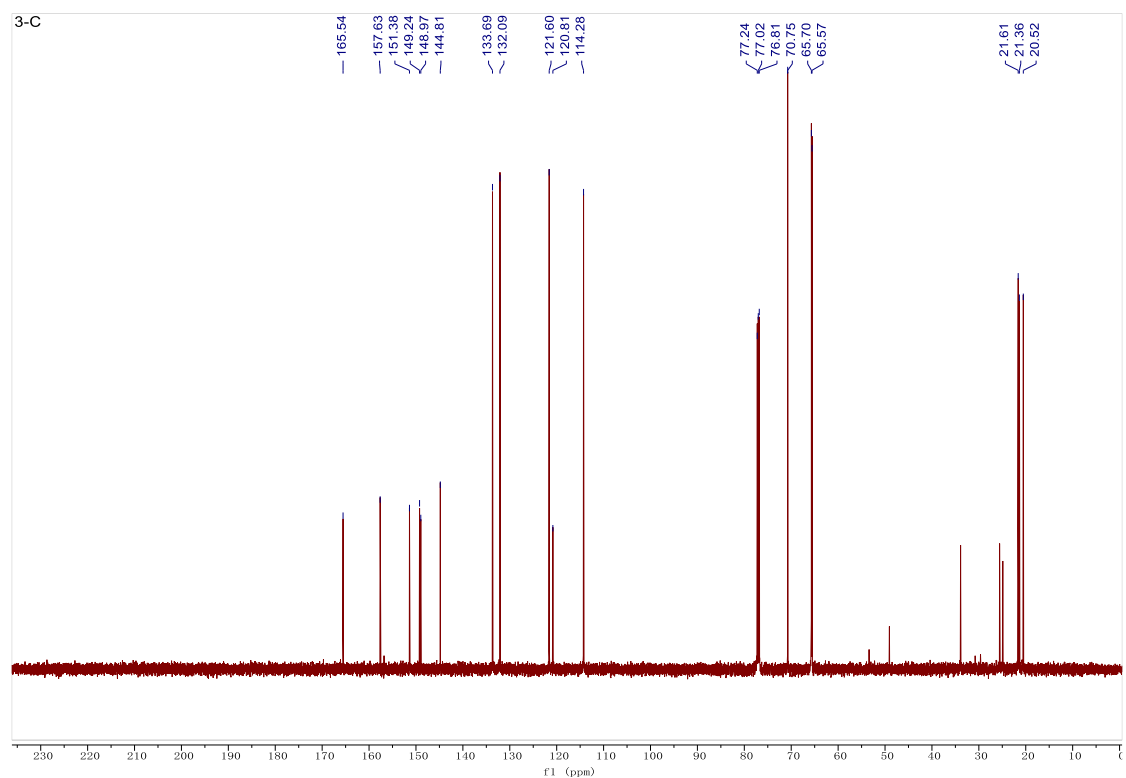


Figure S30.  $^{13}\text{C}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 2-(2-(nitrooxy)ethoxy)benzoate (**15a**)

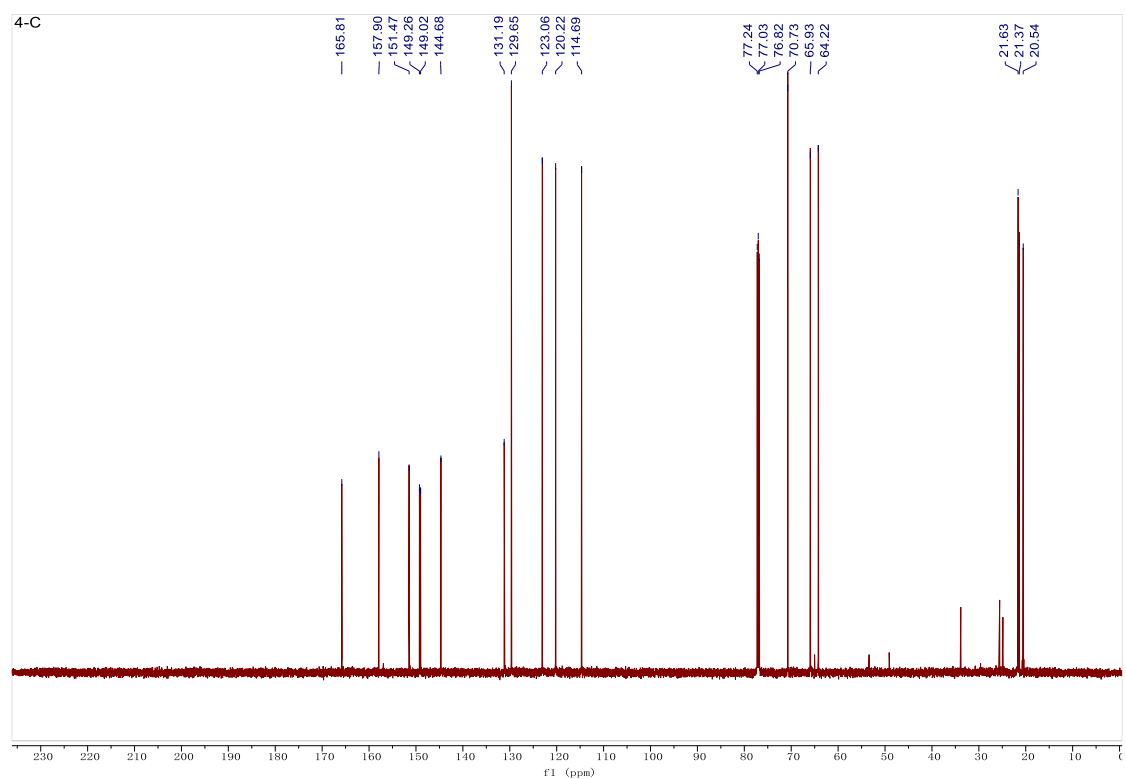


Figure S31.  $^{13}\text{C}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-(2-(nitrooxy)ethoxy)benzoate (**15b**)

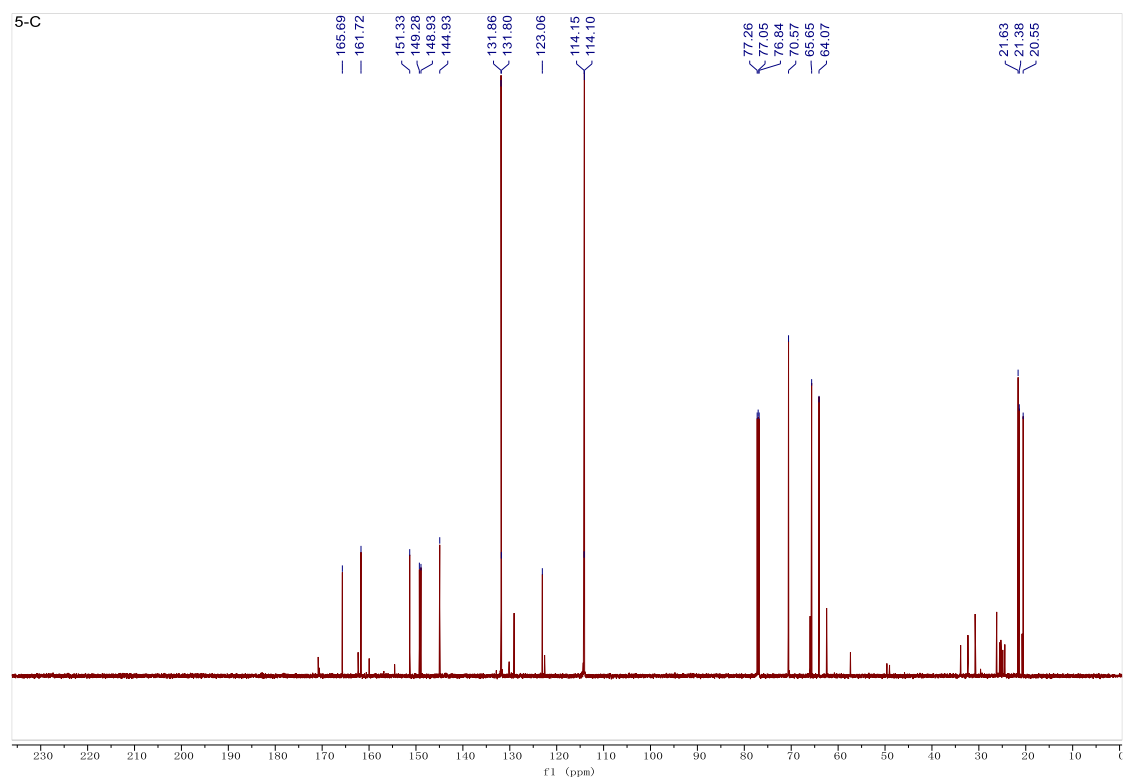


Figure S32.  $^{13}\text{C}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 4-(2-(nitrooxy)ethoxy)benzoate (**15c**)

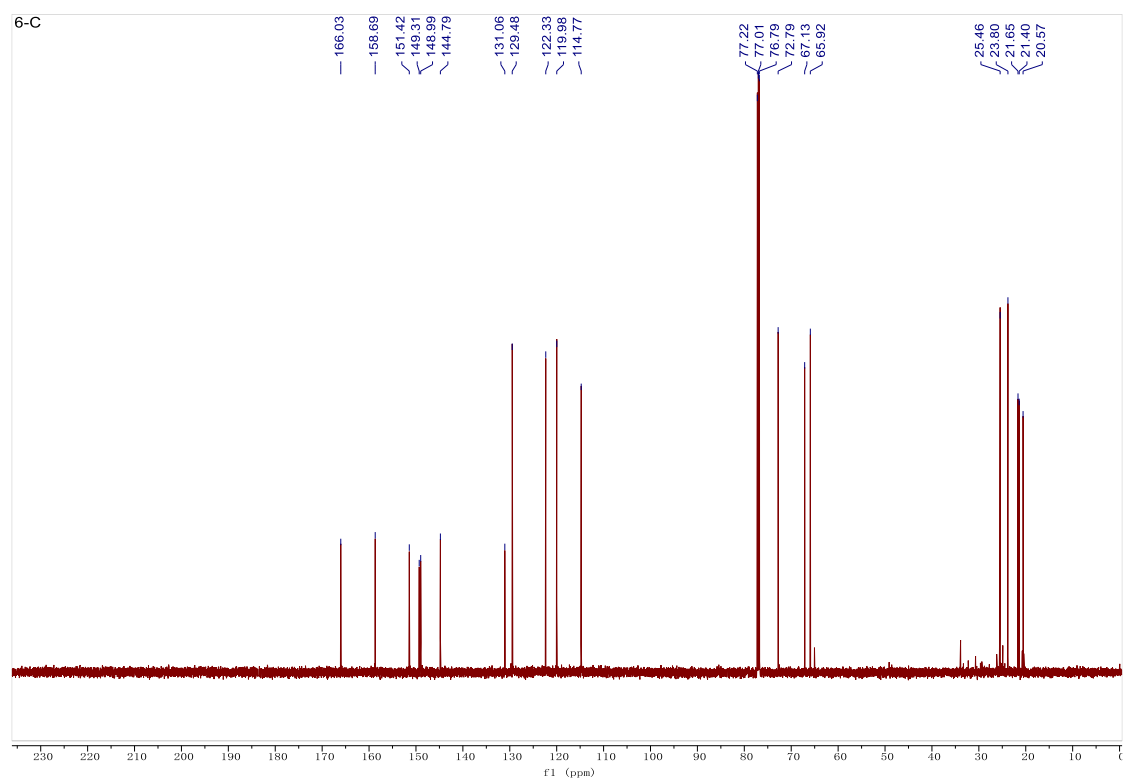


Figure S33.  $^{13}\text{C}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-(4-(nitrooxy)butoxy)benzoate (**15d**)

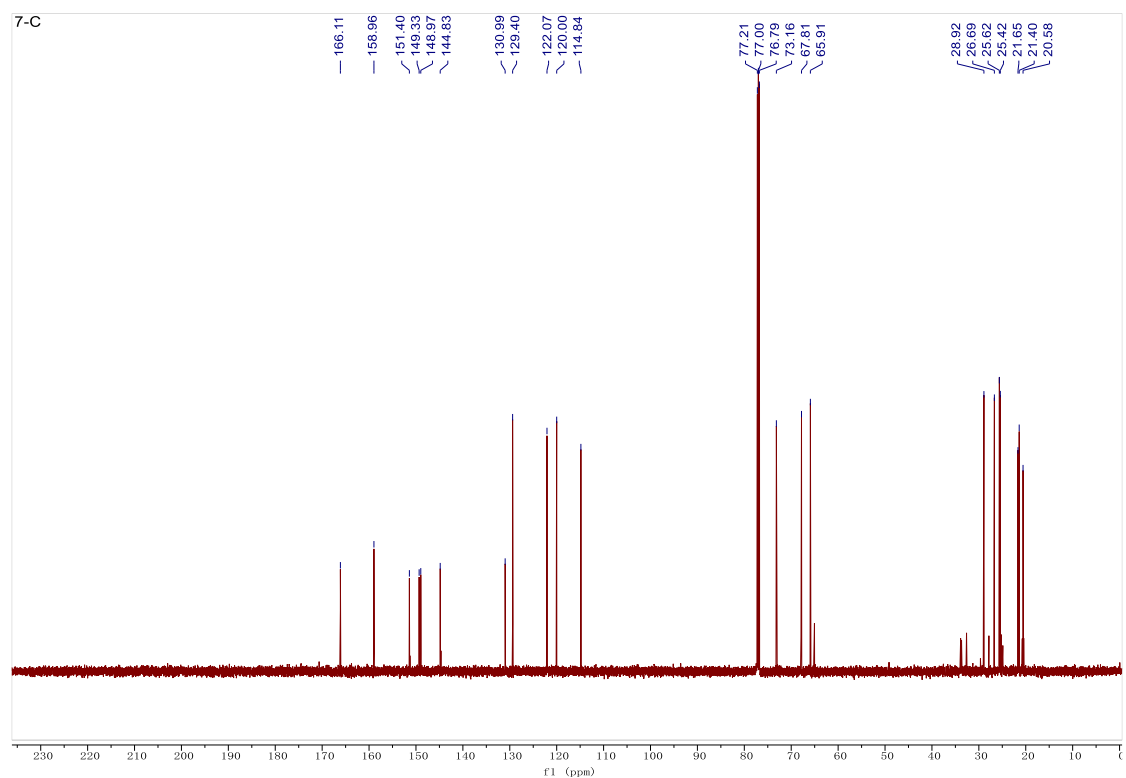


Figure S34.  $^{13}\text{C}$  NMR spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-((6-(nitrooxy)hexyl)oxy)benzoate (**15e**)

## HRMS spectra of all new compounds.

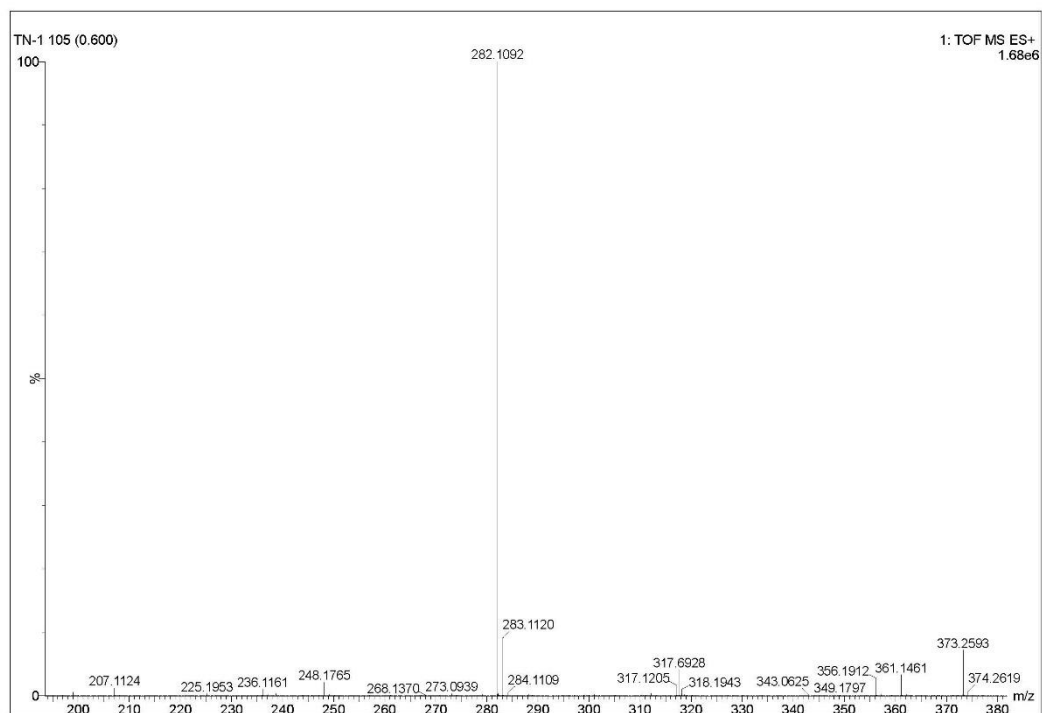


Figure S35. HRMS spectrum of 2-(nitrooxy)ethyl (E)-3-(3,5,6-trimethylpyrazin-2-yl)acrylate (**13**)

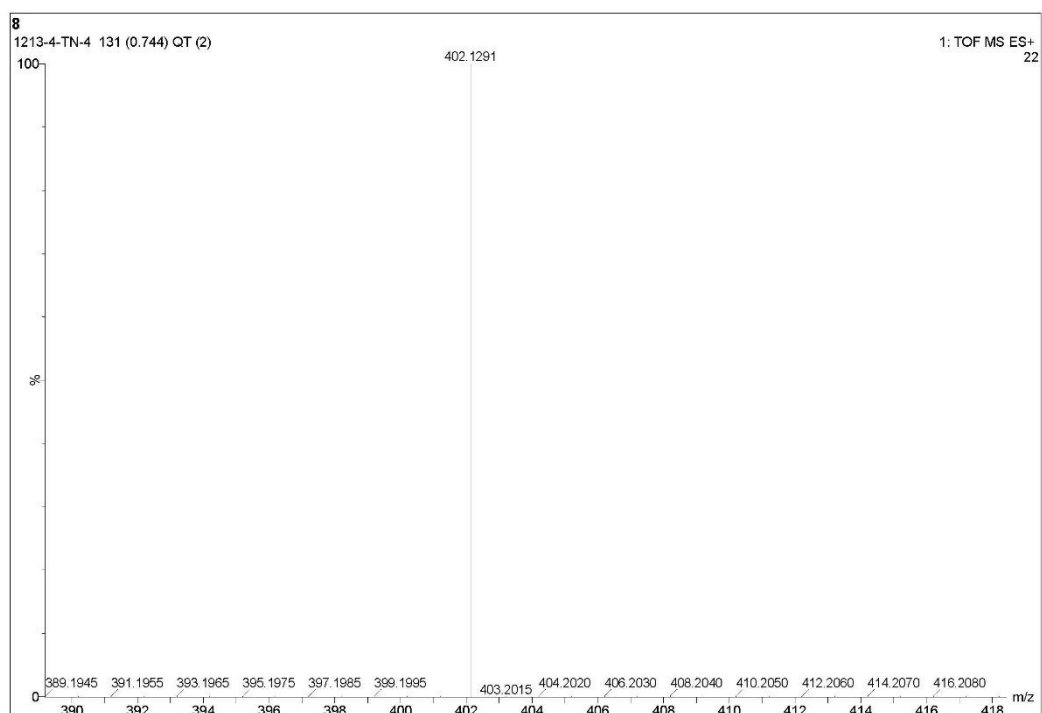


Figure S36. HRMS spectrum of 2-(nitrooxy)ethyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14a**)

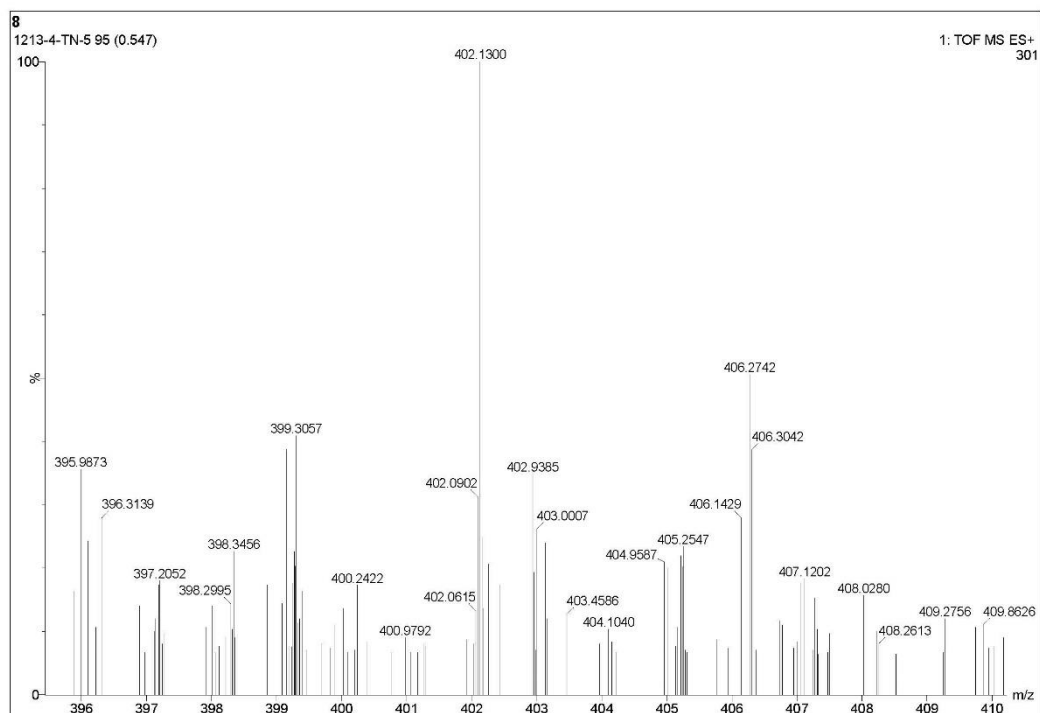


Figure S37. HRMS spectrum of 2-(nitrooxy)ethyl (E)-3-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14b**)

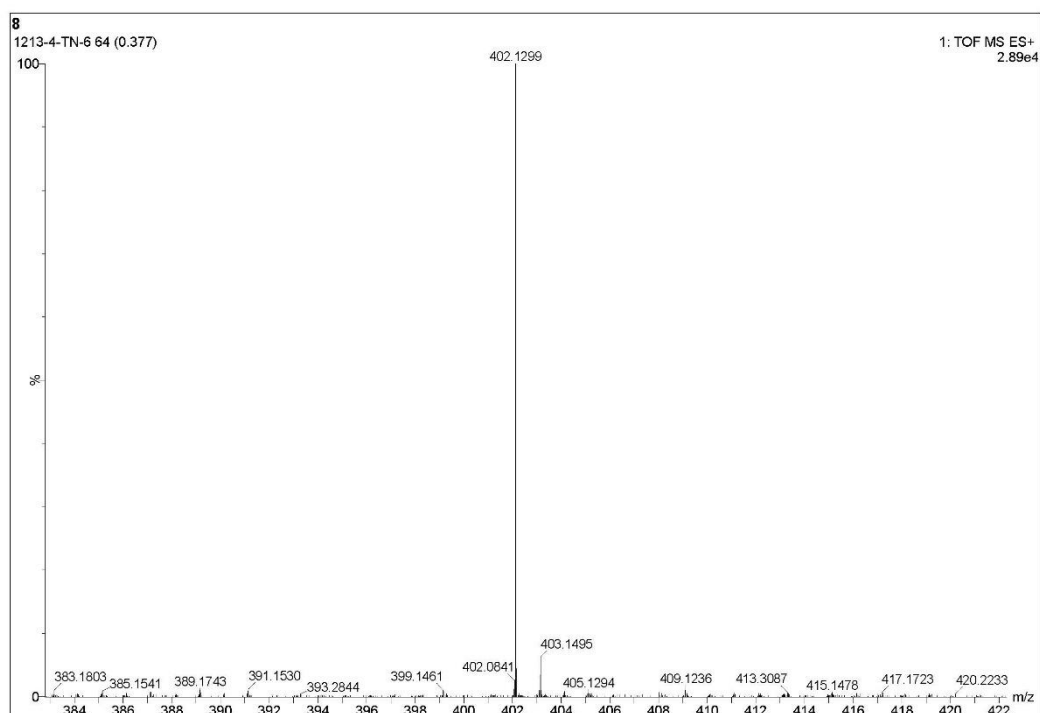


Figure S38. HRMS spectrum of 2-(nitrooxy)ethyl (E)-4-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14c**)

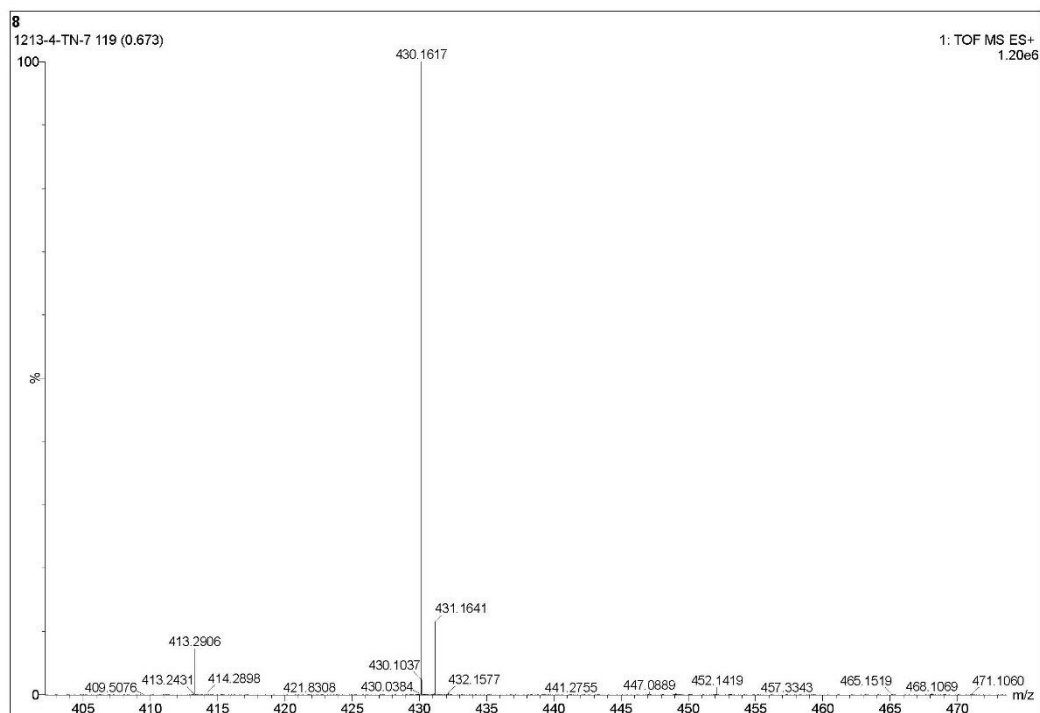


Figure S39. HRMS spectrum of 4-(nitrooxy)butyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14d**)

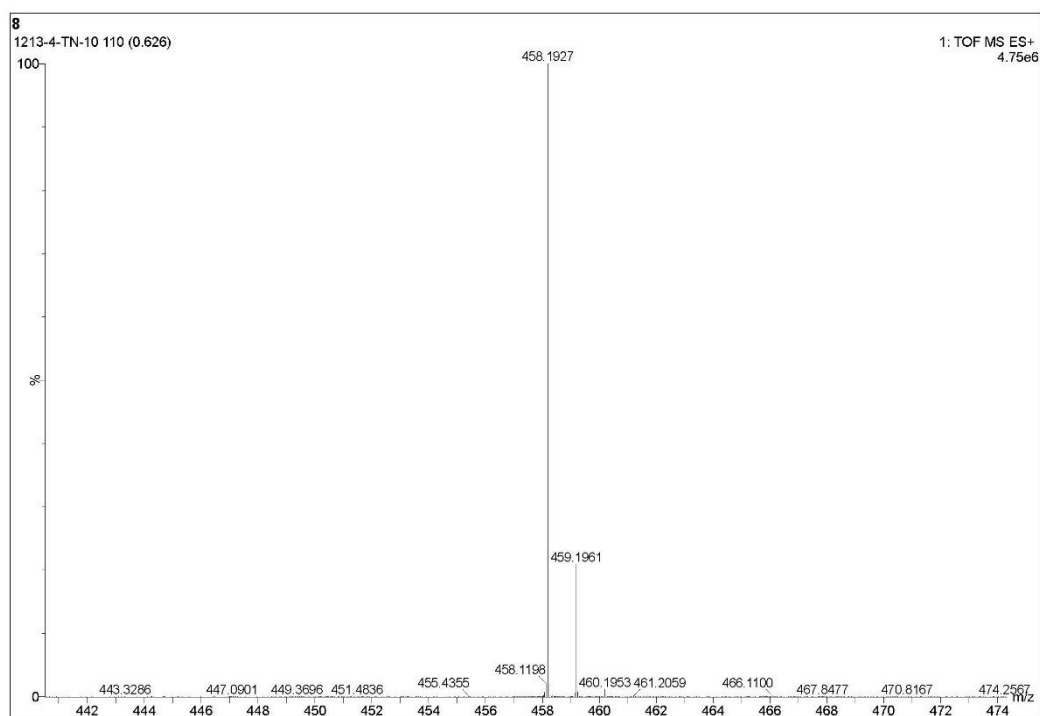


Figure S40. HRMS spectrum of 6-(nitrooxy)hexyl (E)-2-((3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)oxy)benzoate (**14e**)

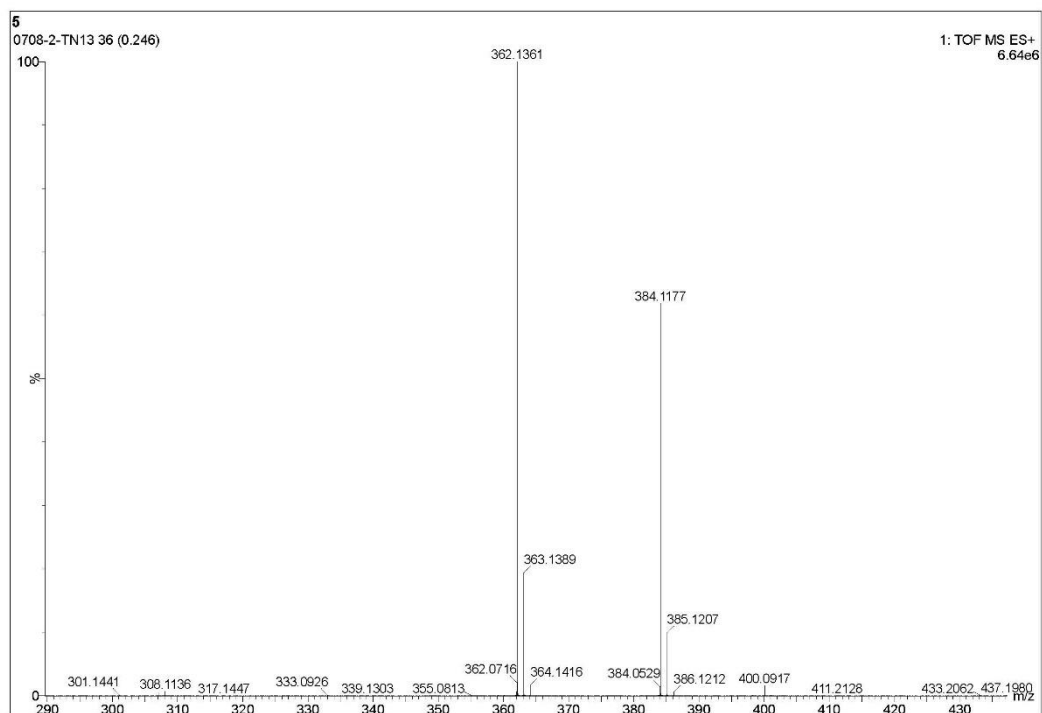


Figure S41. HRMS spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 2-(2-(nitrooxy)ethoxy)benzoate (**15a**)

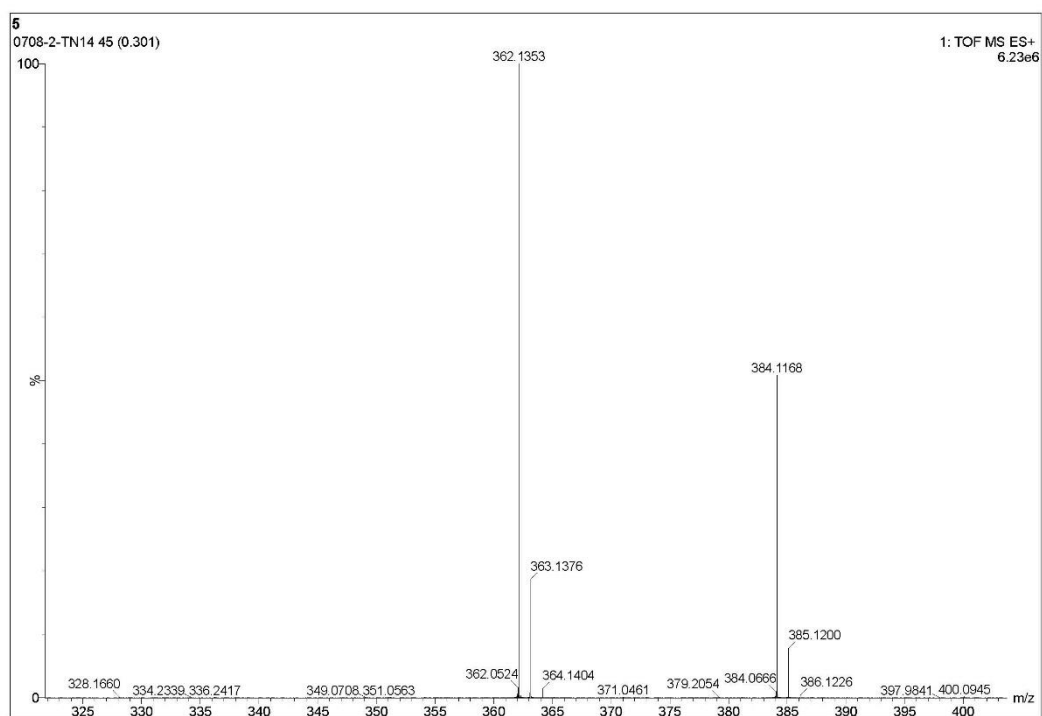


Figure S42. HRMS spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-(2-(nitrooxy)ethoxy)benzoate (**15b**)

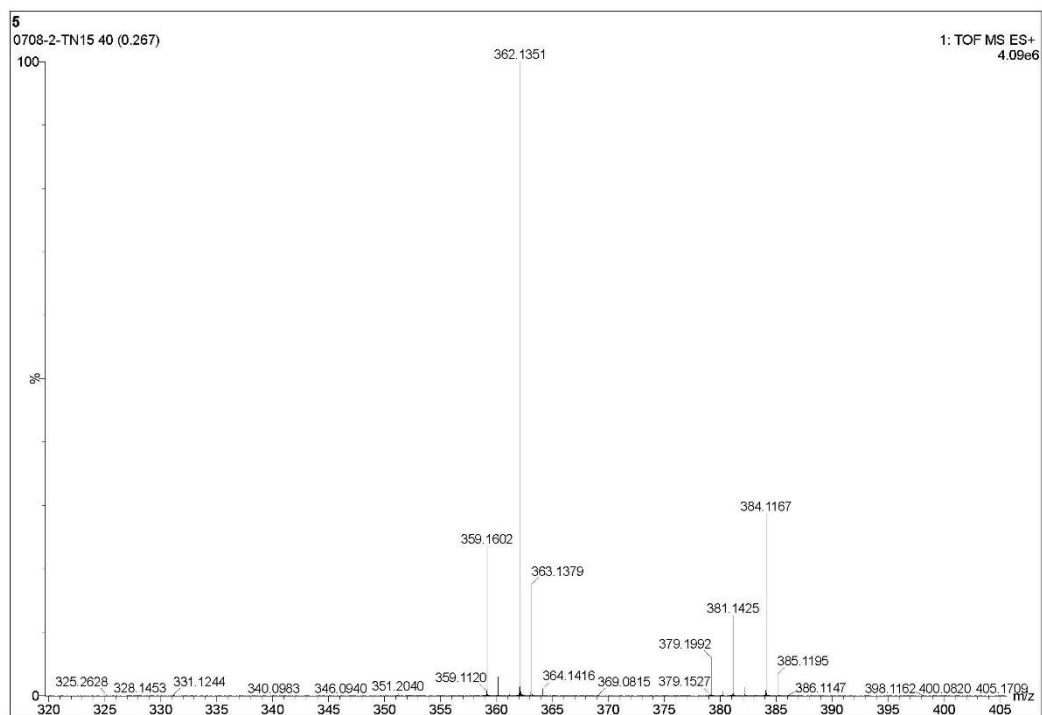


Figure S43. HRMS spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 4-(2-(nitrooxy)ethoxy)benzoate (**15c**)

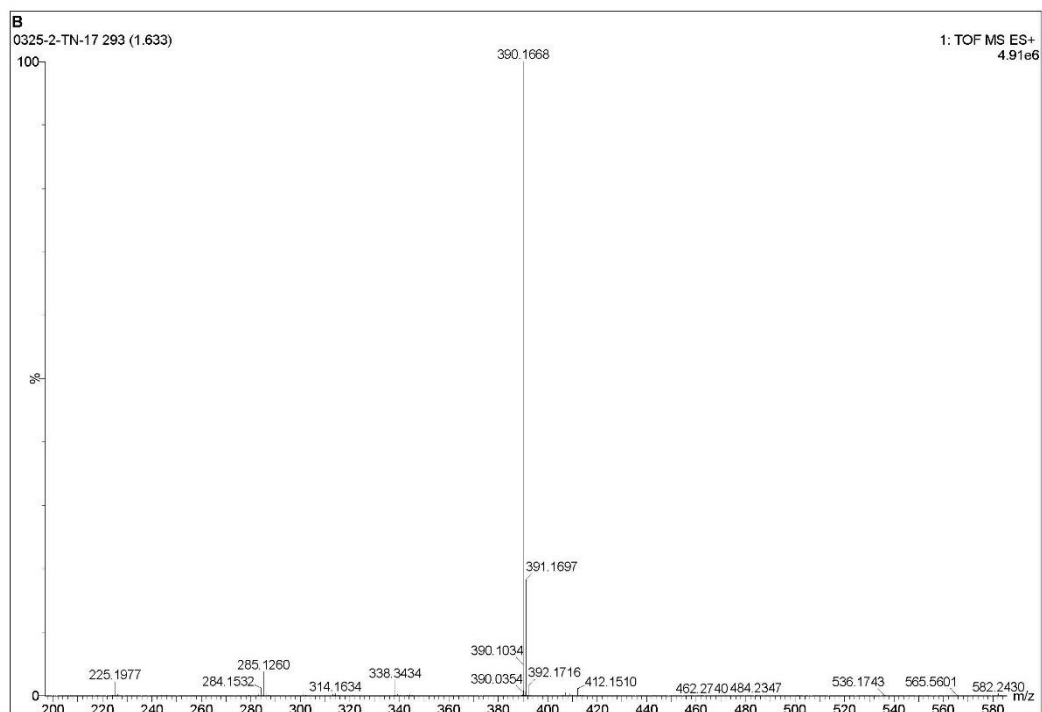


Figure S44. HRMS spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-(4-(nitrooxy)butoxy)benzoate (**15d**)



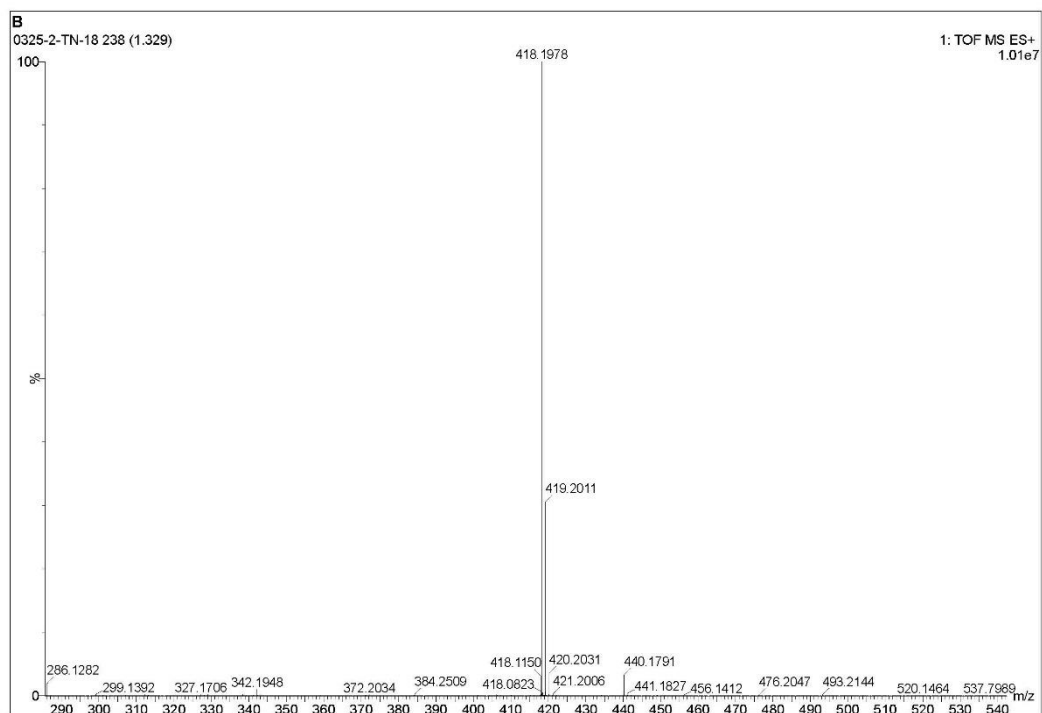


Figure S45. HRMS spectrum of (3,5,6-trimethylpyrazin-2-yl)methyl 3-((6-(nitrooxy)hexyl)oxy)benzoate (**15e**)