

## Supplementary Material

### 3D-QSAR design of new Bcr-Abl inhibitors based on purine scaffold and cytotoxicity studies on CML cell lines sensitive and resistant to imatinib

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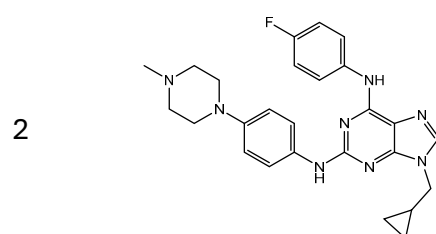
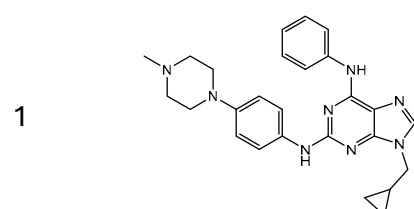
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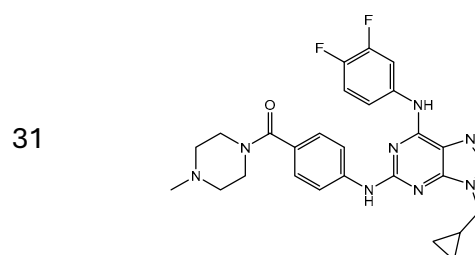
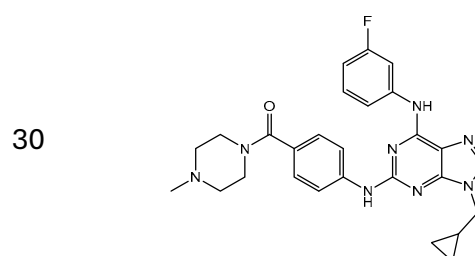
**Figure S3.** Time evolution of the RMSD for the Bcr-Abl protein in complex with different ligands. Six systems were analysed: imatinib-Bcr-Abl<sup>WT</sup> (blue), imatinib-Bcr-Abl<sup>T315I</sup> (red), **7f**-Bcr-Abl<sup>WT</sup> (green), **7f**-Bcr-Abl<sup>T315I</sup> (purple), **7e**-Bcr-Abl<sup>WT</sup> (orange), and **7e**-Bcr-Abl<sup>T315I</sup> (brown).....page 28

**Table S1.** The Chemical structure of the 58 in-house purine compounds.

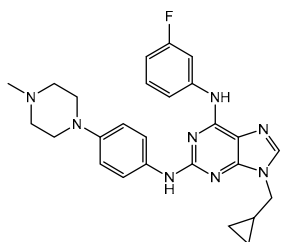
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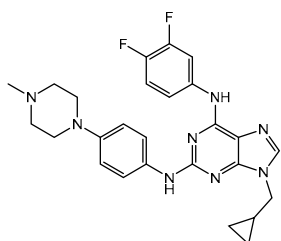
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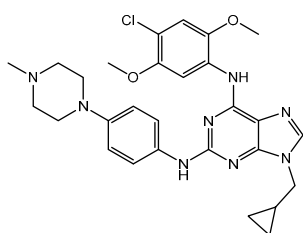
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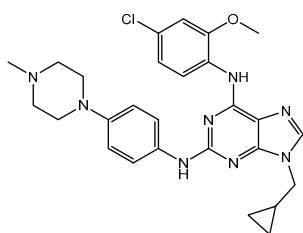
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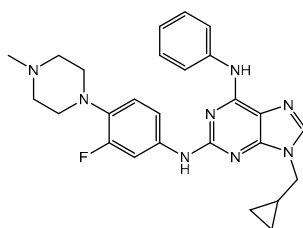
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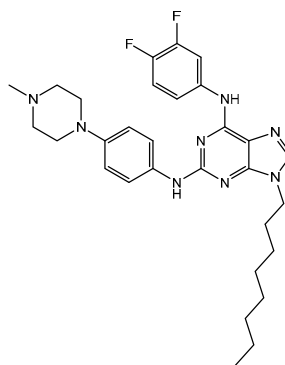


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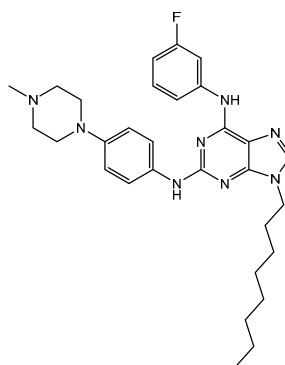


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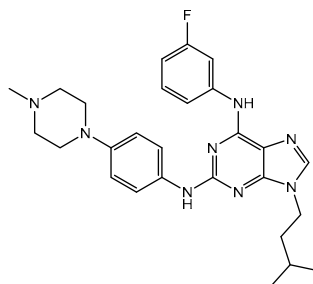
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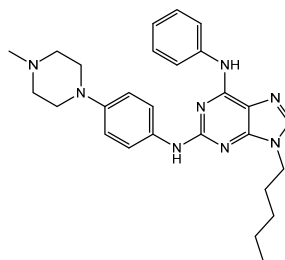
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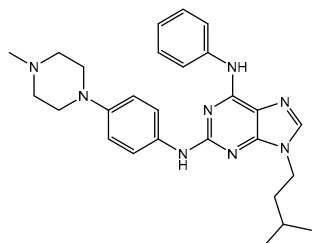
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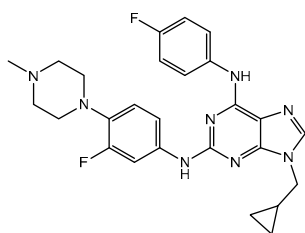
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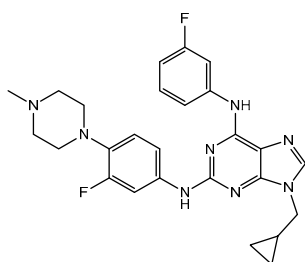
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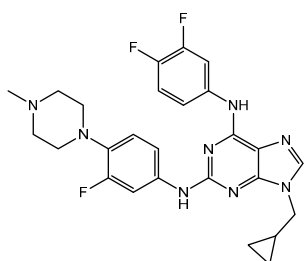
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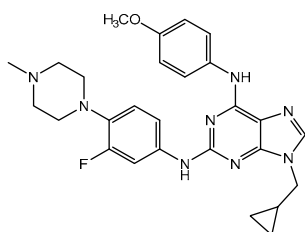
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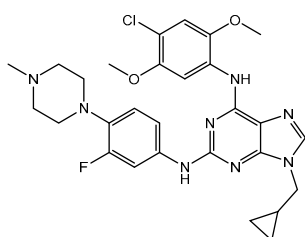
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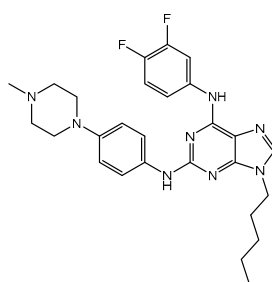
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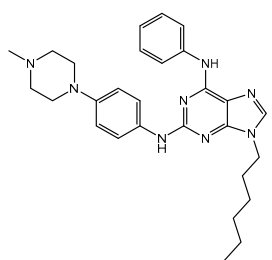
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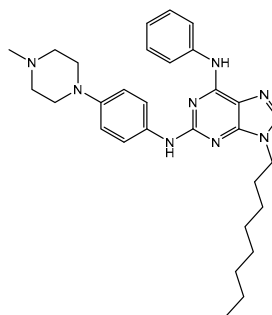
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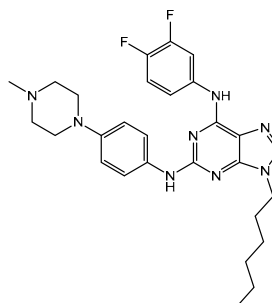
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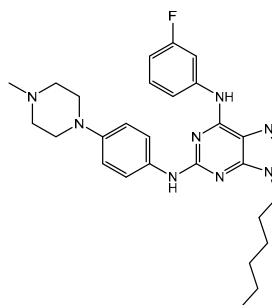
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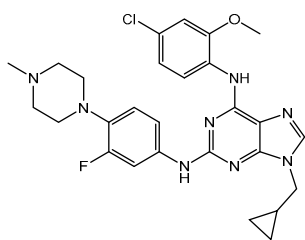


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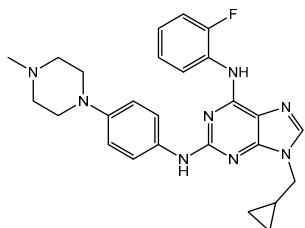


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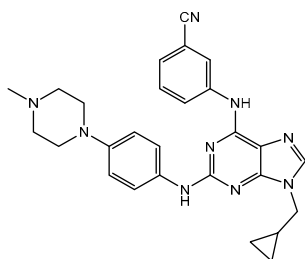
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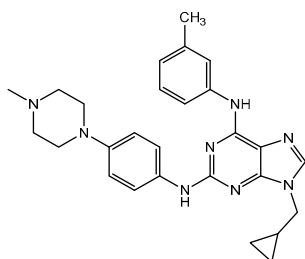
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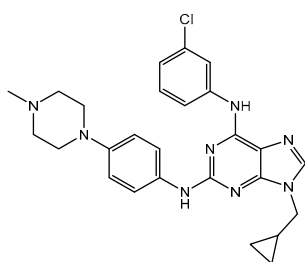
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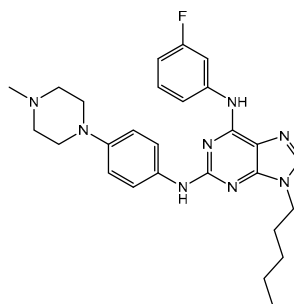
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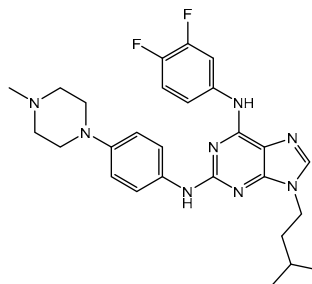
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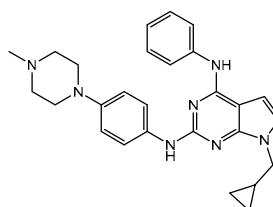
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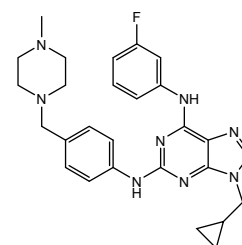
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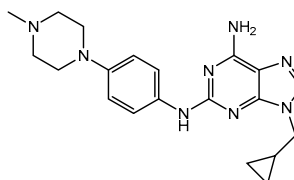
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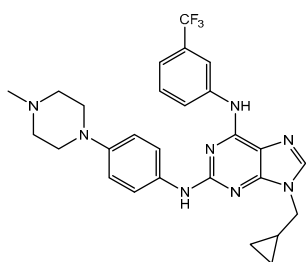
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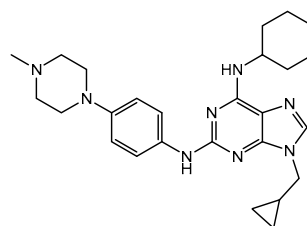
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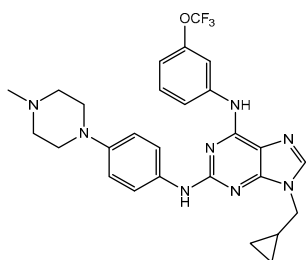
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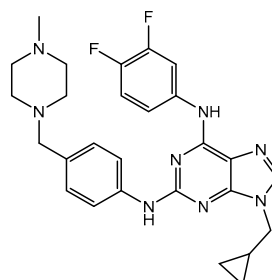
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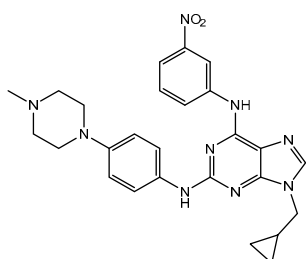
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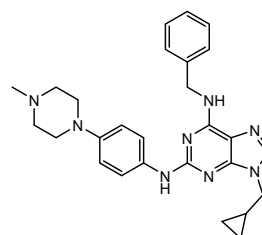
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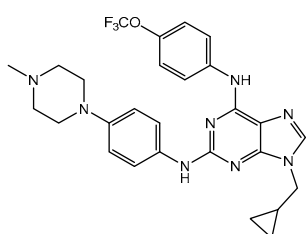
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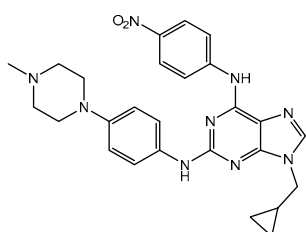


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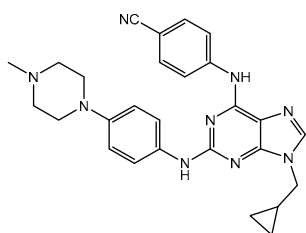
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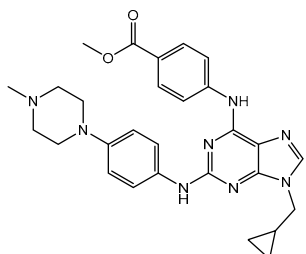


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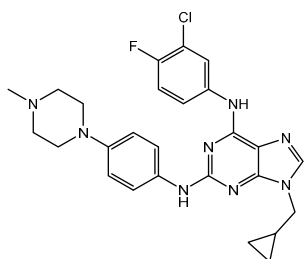
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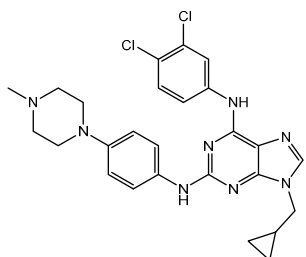
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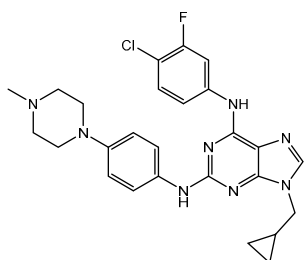
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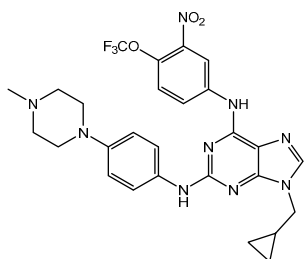
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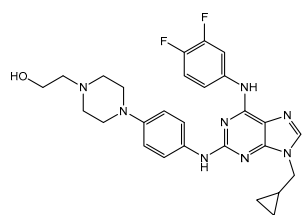
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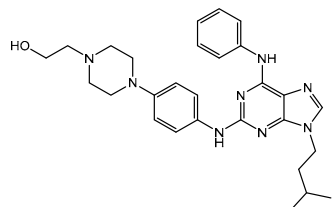
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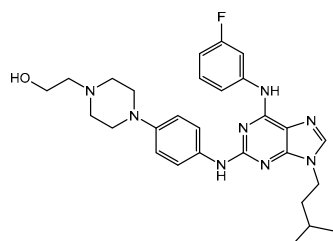
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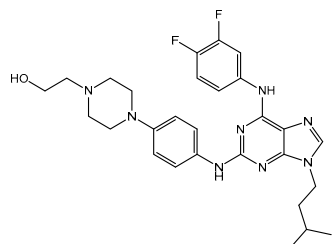
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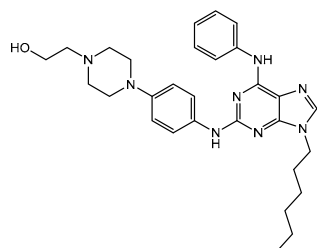
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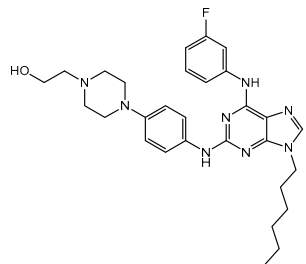
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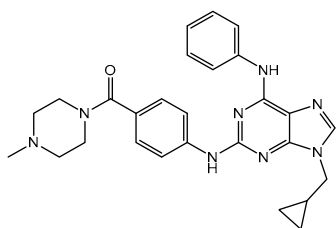
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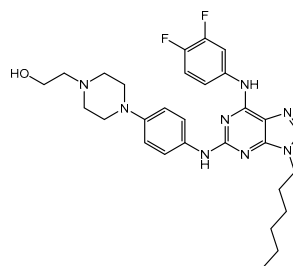
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**Table S2.** Statistical parameters and field combinations for CoMFA and CoMSIA.

| Model       |         | q <sup>2</sup> | N  | SEP   | SEE   | r <sup>2</sup> <sub>Ncv</sub> | F       | Field Contributions |       |       |       |       |
|-------------|---------|----------------|----|-------|-------|-------------------------------|---------|---------------------|-------|-------|-------|-------|
|             |         |                |    |       |       |                               |         | S                   | E     | H     | D     | A     |
| CoMFA-S     |         | 0.477          | 3  | 0.676 | 0.433 | 0.785                         | 42675   | 1                   |       |       |       |       |
| CoMFA-E     |         | 0.327          | 13 | 0.859 | 0.204 | 0.966                         | 54659   |                     | 1     |       |       |       |
| CoMFA-SE    |         | 0.576          | 6  | 0.637 | 0.241 | 0.939                         | 82729   | 0.587               | 0.413 |       |       |       |
| CoMSIA-S    |         | 0.516          | 3  | 0.699 | 0.499 | 0.716                         | 29343   | 1                   |       |       |       |       |
| CoMSIA-E    |         | 0.531          | 8  | 0.692 | 0.439 | 0.811                         | 16100   |                     | 1     |       |       |       |
| CoMSIA-H    |         | 0.44           | 3  | 0.700 | 0.526 | 0.683                         | 25157   |                     |       | 1     |       |       |
| CoMSIA-D    |         | 0.331          | 10 | 0.855 | 0.805 | 0.407                         | 1919.00 |                     |       |       | 1     |       |
| CoMSIA-A    |         | 0.002          | 4  | 0.948 | 0.814 | 0.265                         | 3065.00 |                     |       |       |       | 1     |
| CoMSIA-SE   | 2,3     | 0.571          | 5  | 0.631 | 0.329 | 0.883                         | 50005   | 0.428               | 0.572 |       |       |       |
| CoMSIA-SEH  | 2,3,4   | 0.637          | 6  | 0.589 | 0.252 | 0.934                         | 74988   | 0.249               | 0.472 | 0.279 |       |       |
| CoMSIA-SEHD | 2,3,4,5 | 0.567          | 5  | 0.634 | 0.31  | 0.897                         | 57169   | 0.229               | 0.404 | 0.237 | 0.13  |       |
| CoMSIA-SEHA | 2,3,4,6 | 0.525          | 7  | 0.685 | 0.285 | 0.918                         | 49569   | 0.206               | 0.381 | 0.211 |       | 0.202 |
| CoMSIA-SED  | 2,3,5   | 0.569          | 5  | 0.612 | 0.311 | 0.896                         | 56849   | 0.337               | 0.535 |       | 0.128 |       |
| CoMSIA-SEA  | 2,3,6   | 0.503          | 8  | 0.712 | 0.295 | 0.915                         | 40153   | 0.313               | 0.476 |       |       | 0.211 |
| CoMSIA-SEDA | 2,3,5,6 | 0.514          | 9  | 0.716 | 0.258 | 0.937                         | 47864   | 0.281               | 0.466 |       | 0.047 | 0.206 |
| CoMSIA-SH   | 2,4     | 0.463          | 3  | 0.685 | 0.505 | 0.708                         | 28269   | 0.468               |       | 0.532 |       |       |
| CoMSIA-SD   | 2,5     | 0.481          | 2  | 0.665 | 0.555 | 0.637                         | 31640   | 0.757               |       |       | 0.243 |       |
| CoMSIA-SA   | 2,6     | 0.428          | 6  | 0.74  | 0.506 | 0.732                         | 14574   | 0.58                |       |       |       | 0.42  |
| CoMSIA-SHD  | 2,4,5   | 0.472          | 2  | 0.67  | 0.551 | 0.643                         | 32401   | 0.387               |       | 0.383 | 0.231 |       |

|                    |         |       |    |       |       |       |       |       |       |       |       |       |
|--------------------|---------|-------|----|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| <b>CoMSIA-SHA</b>  | 2,4,6   | 0.424 | 3  | 0.71  | 0.548 | 0.657 | 22363 | 0.305 |       | 0.28  |       | 0.415 |
| <b>CoMSIA-SDA</b>  | 2,5,6   | 0.431 | 6  | 0.738 | 0.494 | 0.745 | 15607 | 0.503 |       |       | 0.093 | 0.404 |
| <b>CoMSIA-SHDA</b> | 2,4,5,6 | 0.425 | 3  | 0.709 | 0.546 | 0.659 | 22577 | 0.292 |       | 0.269 | 0.063 | 0.376 |
| <b>CoMSIA-EH</b>   | 3,4     | 0.583 | 6  | 0.632 | 0.264 | 0.927 | 67984 |       | 0.572 | 0.428 |       |       |
| <b>CoMSIA-ED</b>   | 3,5     | 0.503 | 10 | 0.737 | 0.278 | 0.929 | 36791 |       | 0.835 |       | 0.165 |       |
| <b>CoMSIA-EA</b>   | 3,6     | 0.245 | 6  | 0.87  | 0.497 | 0.742 | 15304 |       | 0.658 |       |       | 0.342 |
| <b>CoMSIA-EHD</b>  | 3,4,5   | 0.608 | 6  | 0.612 | 0.243 | 0.938 | 80960 |       | 0.52  | 0.355 | 0.126 |       |
| <b>CoMSIA-EHA</b>  | 3,4,6   | 0.506 | 8  | 0.71  | 0.263 | 0.932 | 51458 |       | 0.465 | 0.312 |       | 0.223 |
| <b>CoMSIA-EDA</b>  | 3,5,6   | 0.252 | 5  | 0.833 | 0.558 | 0.664 | 13070 |       | 0.551 |       | 0.1   | 0.349 |
| <b>CoMSIA-EHDA</b> | 3,4,5,6 | 0.505 | 8  | 0.711 | 0.258 | 0.935 | 53519 |       | 0.438 | 0.302 | 0.052 | 0.209 |
| <b>CoMSIA-HD</b>   | 4,5     | 0.457 | 2  | 0.68  | 0.574 | 0.613 | 28499 |       |       | 0.74  | 0.26  |       |
| <b>CoMSIA-HA</b>   | 4,6     | 0.398 | 5  | 0.747 | 0.547 | 0.678 | 13883 |       |       | 0.591 |       | 0.409 |
| <b>CoMSIA-HDA</b>  | 4,5,6   | 0.404 | 5  | 0.74  | 0.532 | 0.695 | 15017 |       |       | 0.541 | 0.078 | 0.381 |
| <b>CoMSIA-DA</b>   | 5,6     | 0.084 | 12 | 1.038 | 0.626 | 0.667 | 4333  |       |       |       | 0.193 | 0.807 |
| <b>CoMSIA-ALL</b>  |         | 0.523 | 7  | 0.687 | 0.279 | 0.921 | 51678 | 0.197 | 0.364 | 0.208 | 0.044 | 0.186 |

$q^2$  = the square of the leave-one-out (LOO) cross-validation (CV) coefficient; N = the optimum number of components; SEP = standard error of prediction; SEE is the standard error of estimation of non-CV analysis;  $r^2_{ncv}$  is the square of the non CV coefficient; F is the F-test value; S, E, H, D, and A are the steric, electrostatic, hydrophobic, hydrogen-bond donor, and hydrogen-bond acceptor contributions respectively.

**Table S3.** Experimental and predicted  $pIC_{50}$  and residual values for the studied compounds according to CoMFA and CoMSIA.

| Cmpd.    | $pIC_{50}$ Exp | CoMFA-SE        |       | CoMSIA-SEH      |       | Cmpd.     | $pIC_{50}$ Exp | CoMFA-SE        |       | CoMSIA-SEH      |       |
|----------|----------------|-----------------|-------|-----------------|-------|-----------|----------------|-----------------|-------|-----------------|-------|
|          |                | $pIC_{50}$ Pred | Res   | $pIC_{50}$ Pred | Res   |           |                | $pIC_{50}$ Pred | Res   | $pIC_{50}$ Pred | Res   |
| <b>1</b> | 7.046          | 7.150           | -0.10 | 7.120           | -0.07 | <b>29</b> | 5.917          | 5.748           | 0.17  | 6.066           | -0.15 |
| <b>2</b> | 6.959          | 7.199*          | -0.24 | 7.089*          | -0.13 | <b>30</b> | 6.244          | 6.010           | 0.23  | 6.210           | 0.03  |
| <b>3</b> | 7.398          | 7.464           | -0.07 | 7.509           | -0.11 | <b>31</b> | 6.027          | 5.890           | 0.14  | 6.015           | 0.01  |
| <b>4</b> | 7.398          | 7.214           | 0.18  | 7.072           | 0.33  | <b>32</b> | 4.063          | 3.959           | 0.10  | 3.675           | 0.39  |
| <b>5</b> | 4.444          | 6.227**         | -1.78 | 6.239*          | -1.80 | <b>34</b> | 4.301          | 4.346           | -0.04 | 4.567           | -0.27 |

|           |       |         |       |        |       |           |       |         |       |        |       |
|-----------|-------|---------|-------|--------|-------|-----------|-------|---------|-------|--------|-------|
| <b>6</b>  | 6.097 | 6.029   | 0.07  | 6.259  | -0.16 | <b>35</b> | 5.910 | 5.821   | 0.09  | 5.897  | 0.01  |
| <b>7</b>  | 6.237 | 6.289   | -0.05 | 6.388  | -0.15 | <b>36</b> | 5.750 | 5.533   | 0.22  | 5.372  | 0.38  |
| <b>8</b>  | 5.971 | 6.256*  | -0.29 | 6.047* | -0.08 | <b>37</b> | 5.866 | 6.443*  | -0.58 | 5.962* | -0.10 |
| <b>9</b>  | 6.222 | 6.319   | -0.10 | 6.395  | -0.17 | <b>38</b> | 5.008 | 4.952   | 0.06  | 5.178  | -0.17 |
| <b>10</b> | 6.237 | 6.298*  | -0.06 | 6.092* | 0.14  | <b>40</b> | 4.469 | 4.908   | -0.44 | 4.803  | -0.33 |
| <b>11</b> | 6.469 | 6.476   | -0.01 | 6.331  | 0.14  | <b>42</b> | 6.187 | 6.094   | 0.09  | 6.045  | 0.14  |
| <b>13</b> | 5.074 | 4.828   | 0.25  | 4.850  | 0.22  | <b>43</b> | 5.642 | 5.890   | -0.25 | 5.565  | 0.08  |
| <b>14</b> | 5.378 | 5.934   | -0.56 | 6.155  | -0.78 | <b>44</b> | 4.206 | 7.578** | -3.37 | 7.781* | -3.58 |
| <b>15</b> | 7.155 | 6.754   | 0.40  | 7.116  | 0.04  | <b>45</b> | 6.744 | 6.608   | 0.14  | 6.592  | 0.15  |
| <b>16</b> | 7.000 | 6.654   | 0.35  | 6.852  | 0.15  | <b>46</b> | 5.403 | 7.147** | -1.74 | 7.229* | -1.83 |
| <b>17</b> | 6.921 | 6.915   | 0.01  | 6.931  | -0.01 | <b>47</b> | 4.956 | 7.115** | -2.16 | 6.526* | -1.57 |
| <b>18</b> | 5.75  | 6.460   | -0.71 | 5.948  | -0.20 | <b>48</b> | 6.649 | 6.814*  | -0.17 | 6.531* | 0.12  |
| <b>19</b> | 5.939 | 5.997   | -0.06 | 6.044  | -0.10 | <b>49</b> | 6.076 | 6.194   | -0.12 | 5.929  | 0.15  |
| <b>20</b> | 6.770 | 6.669   | 0.10  | 6.782  | -0.01 | <b>50</b> | 7.432 | 7.419*  | 0.01  | 7.839* | -0.41 |
| <b>21</b> | 6.409 | 7.160** | -0.75 | 7.206* | -0.80 | <b>51</b> | 7.833 | 7.909   | -0.08 | 7.724  | 0.11  |
| <b>22</b> | 6.886 | 6.850   | 0.04  | 6.709  | 0.18  | <b>52</b> | 7.703 | 7.604   | 0.10  | 7.792  | -0.09 |
| <b>23</b> | 7.000 | 6.809*  | 0.19  | 6.626* | 0.37  | <b>53</b> | 5.907 | 5.774   | 0.13  | 6.234  | -0.33 |
| <b>24</b> | 7.398 | 7.418   | -0.02 | 7.360  | 0.04  | <b>54</b> | 6.886 | 6.820   | 0.07  | 6.829  | 0.06  |
| <b>25</b> | 6.569 | 6.839   | -0.27 | 6.663  | -0.09 | <b>55</b> | 5.754 | 5.956*  | -0.20 | 6.079* | -0.32 |
| <b>26</b> | 7.155 | 7.030   | 0.12  | 6.610  | 0.54  | <b>56</b> | 6.081 | 6.404*  | -0.32 | 6.233* | -0.15 |
| <b>27</b> | 6.699 | 6.849   | -0.15 | 6.742  | -0.04 | <b>57</b> | 6.174 | 6.193   | -0.02 | 6.069  | 0.10  |
| <b>28</b> | 6.357 | 6.339*  | 0.02  | 6.571* | -0.21 | <b>58</b> | 5.775 | 5.782   | -0.01 | 5.775  | 0.00  |

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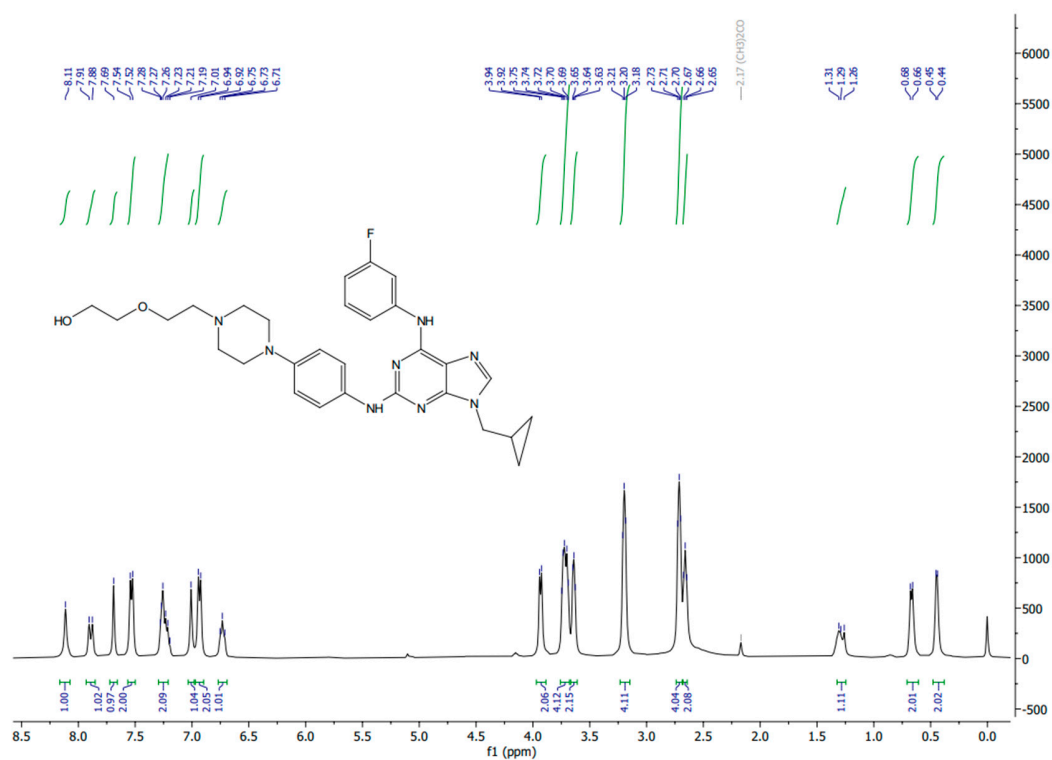
\* Test Set compound

\*\* Outliers.

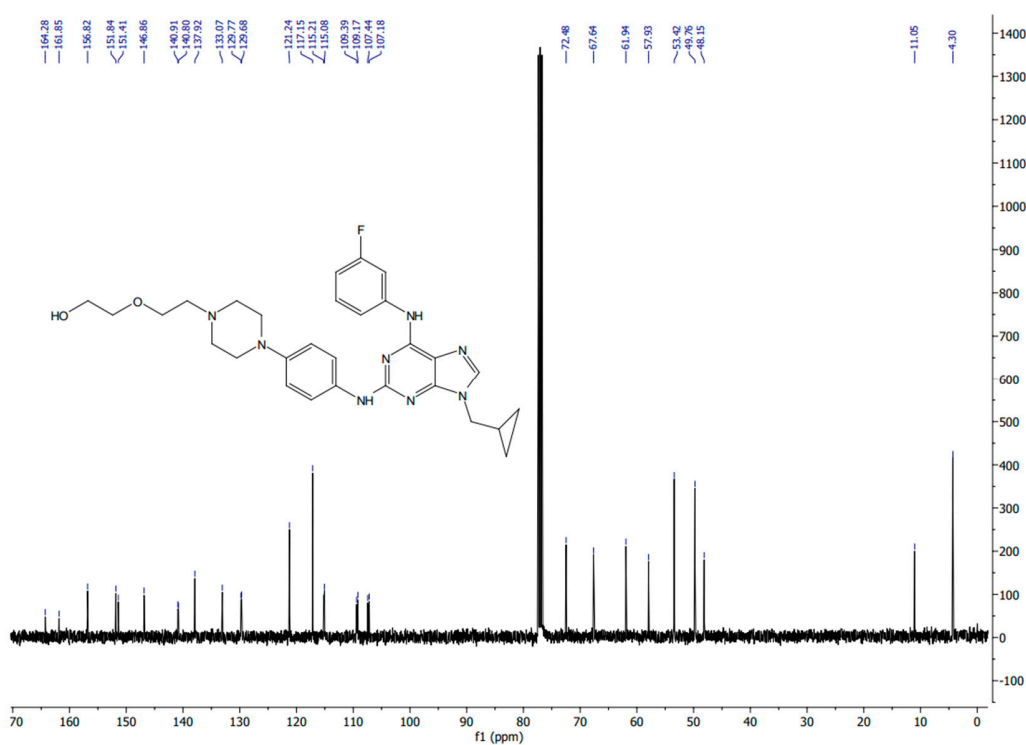
**Table S4.**  $q^2$  and  $r^2_{ncv}$  values after several Y-randomization tests.

|                 | CoMFA-SE |             | COMSIA-SEH |             |
|-----------------|----------|-------------|------------|-------------|
|                 | $q^2$    | $r^2_{ncv}$ | $q^2$      | $r^2_{ncv}$ |
| <b>Random1</b>  | -0.132   | 0.23        | -0.059     | 0.116       |
| <b>Random2</b>  | -0.116   | 0.225       | -0.156     | 0.164       |
| <b>Random3</b>  | -0.25    | 0.276       | -0.2       | 0.101       |
| <b>Random4</b>  | -0.095   | 0.185       | -0.045     | 0.132       |
| <b>Random5</b>  | -0.145   | 0.194       | -0.123     | 0.117       |
| <b>Random6</b>  | 0.027    | 0.261       | 0.087      | 0.148       |
| <b>Random7</b>  | -0.176   | 0.243       | -0.196     | 0.138       |
| <b>Random8</b>  | -0.071   | 0.174       | -0.053     | 0.126       |
| <b>Random9</b>  | -0.034   | 0.19        | -0.065     | 0.119       |
| <b>Random10</b> | -0.299   | 0.184       | -0.215     | 0.134       |

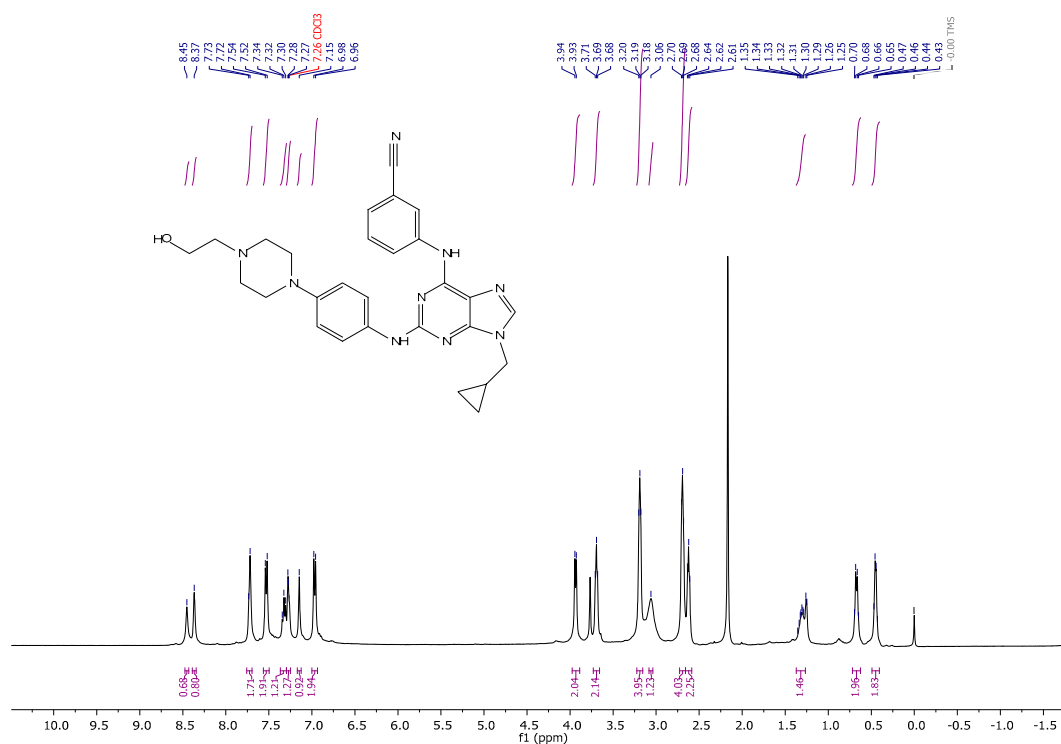
$^1\text{H}$  NMR spectra of compound **7a**.



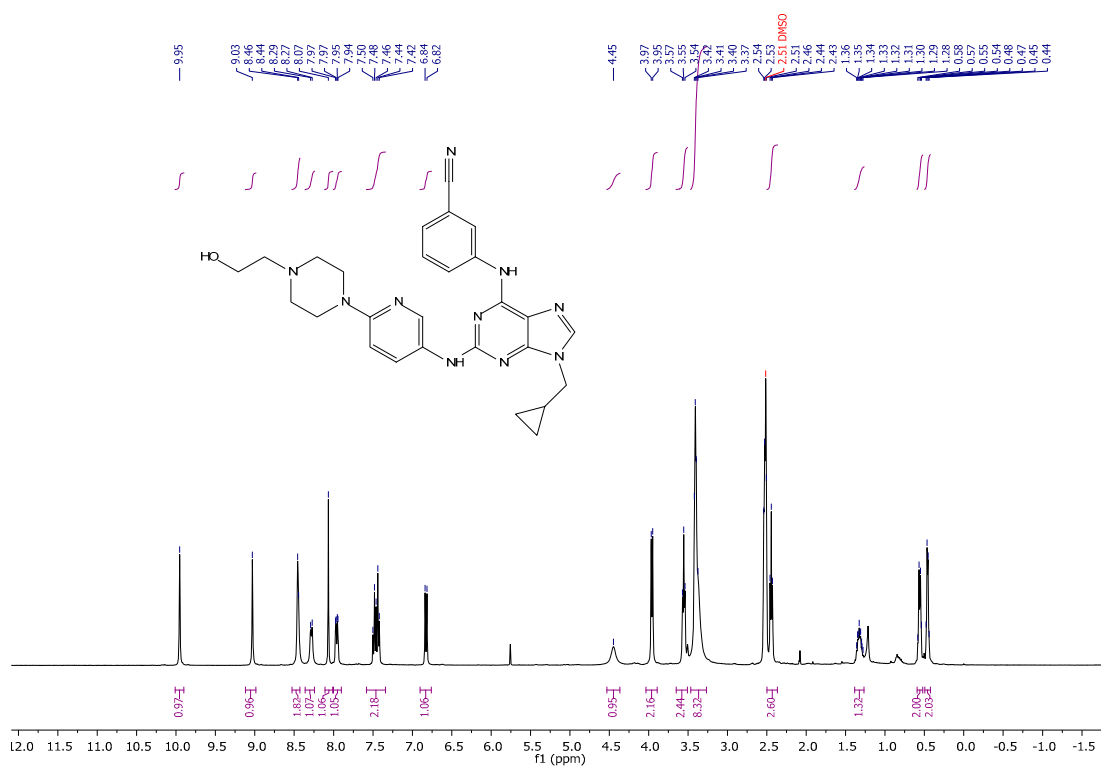
<sup>13</sup>C NMR spectra of compound 7a.



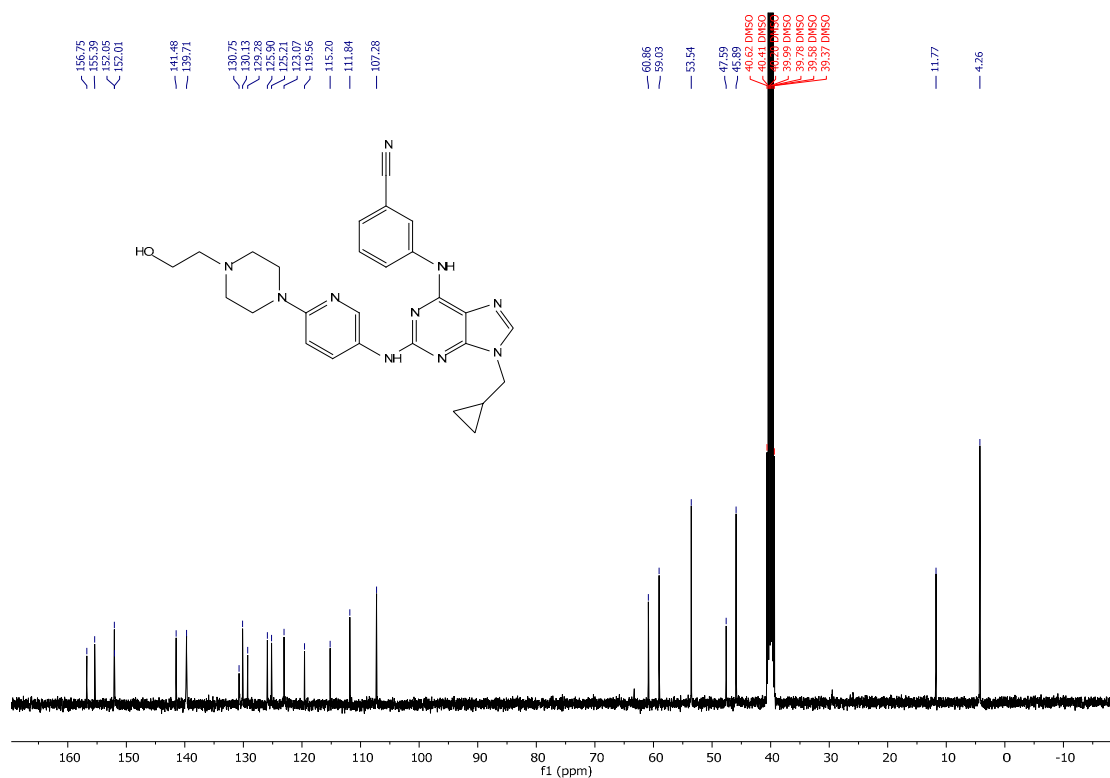
$^1\text{H}$  NMR spectra of compound **7b**.



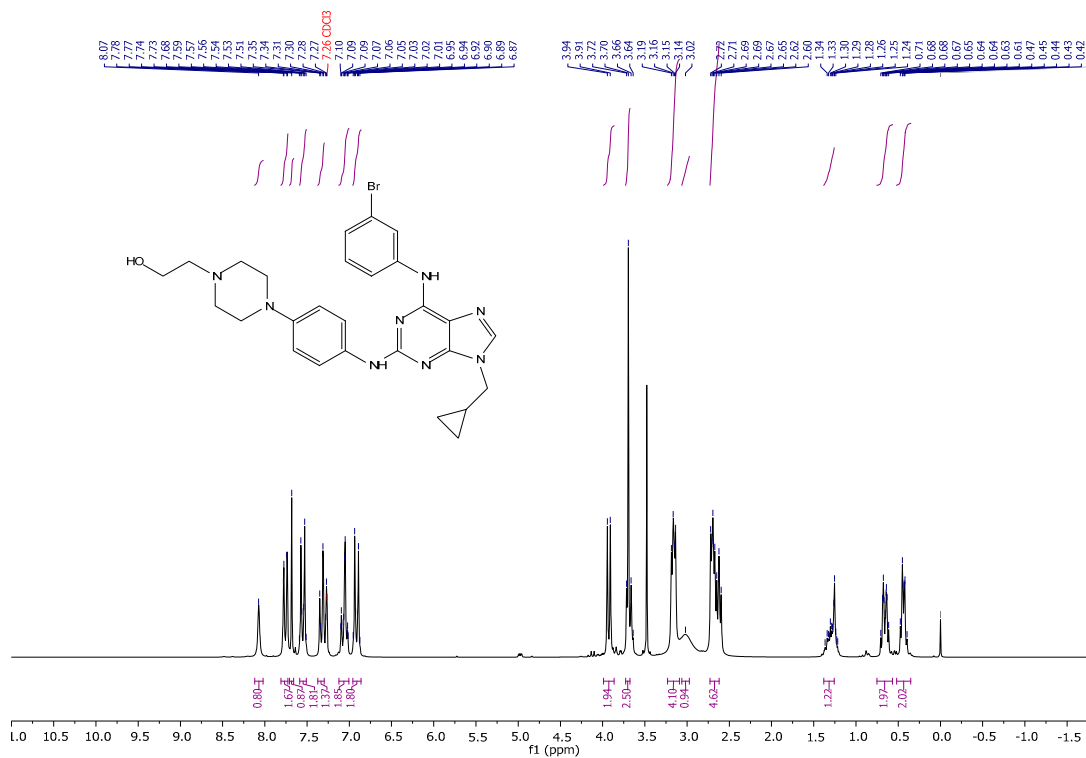
$^1\text{H}$  NMR spectra of compound **7c**.



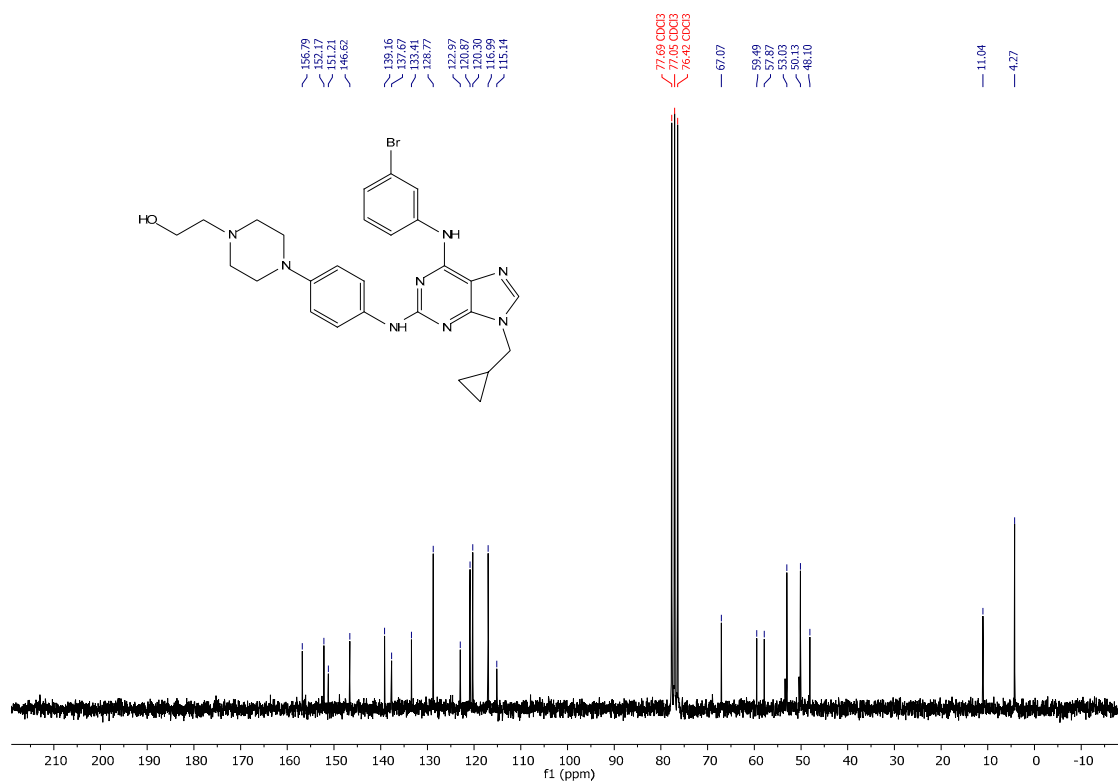
$^{13}\text{C}$  NMR spectra of compound **7c**.



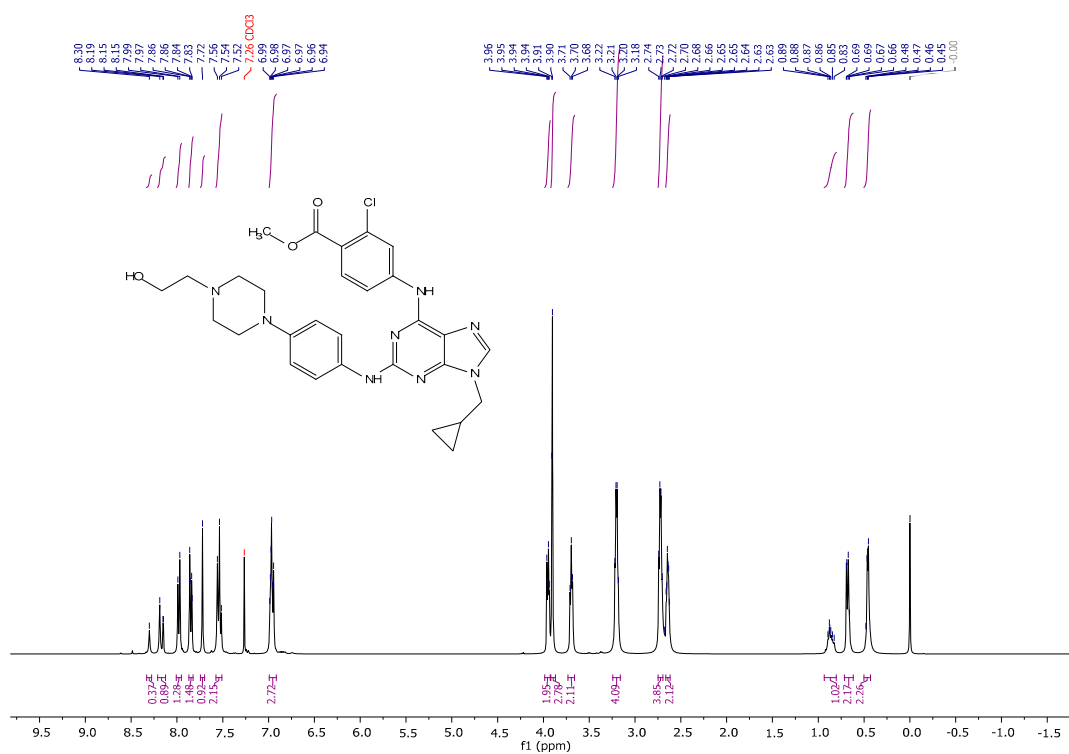
<sup>1</sup>H NMR spectra of compound 7d.



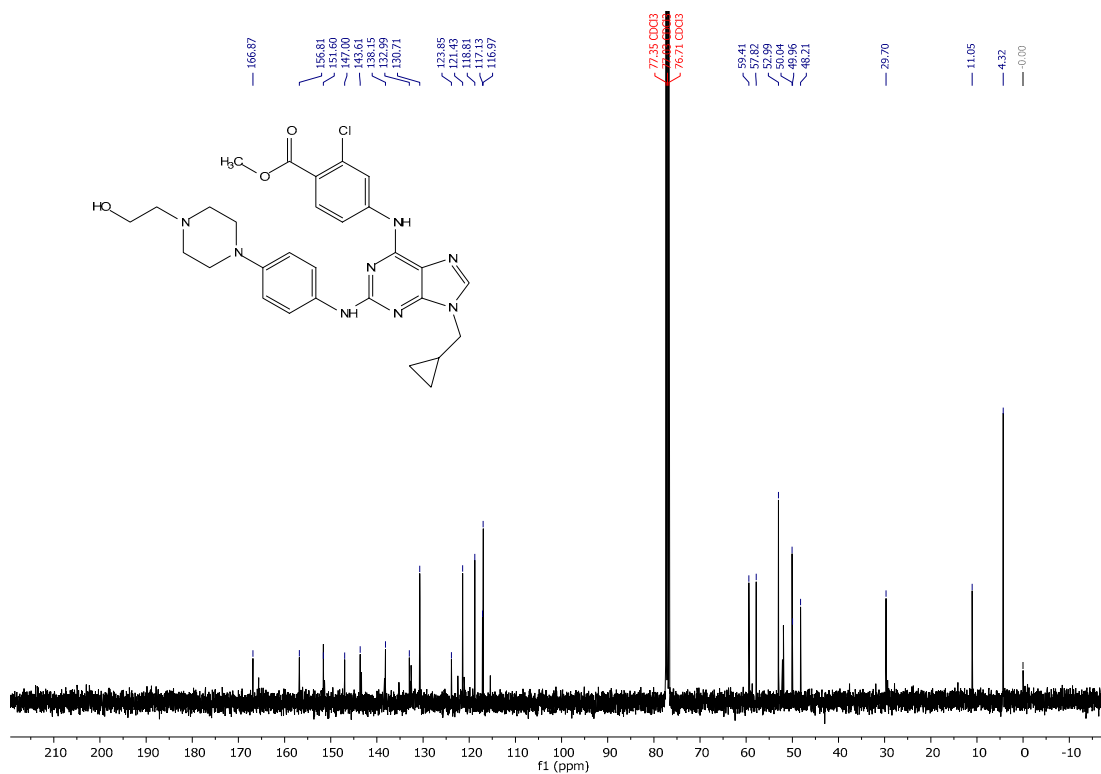
$^{13}\text{C}$  NMR spectra of compound **7d**.



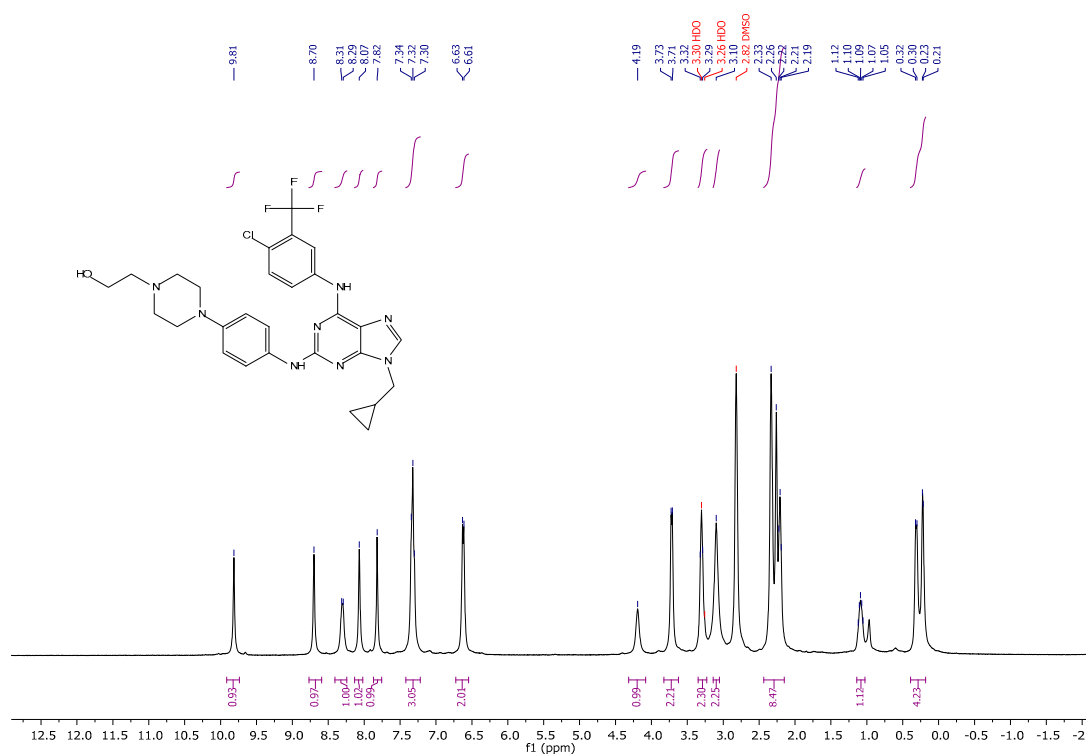
$^1\text{H}$  NMR spectra of compound **7e**.



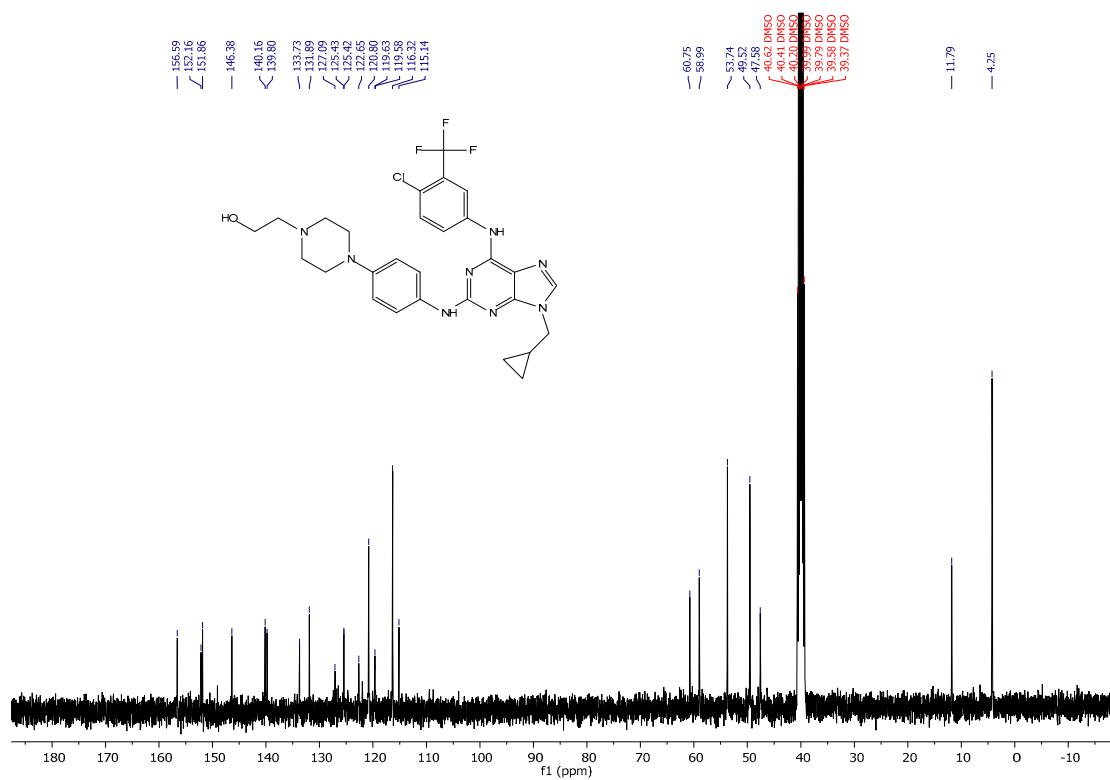
<sup>13</sup>C NMR spectra of compound 7e.



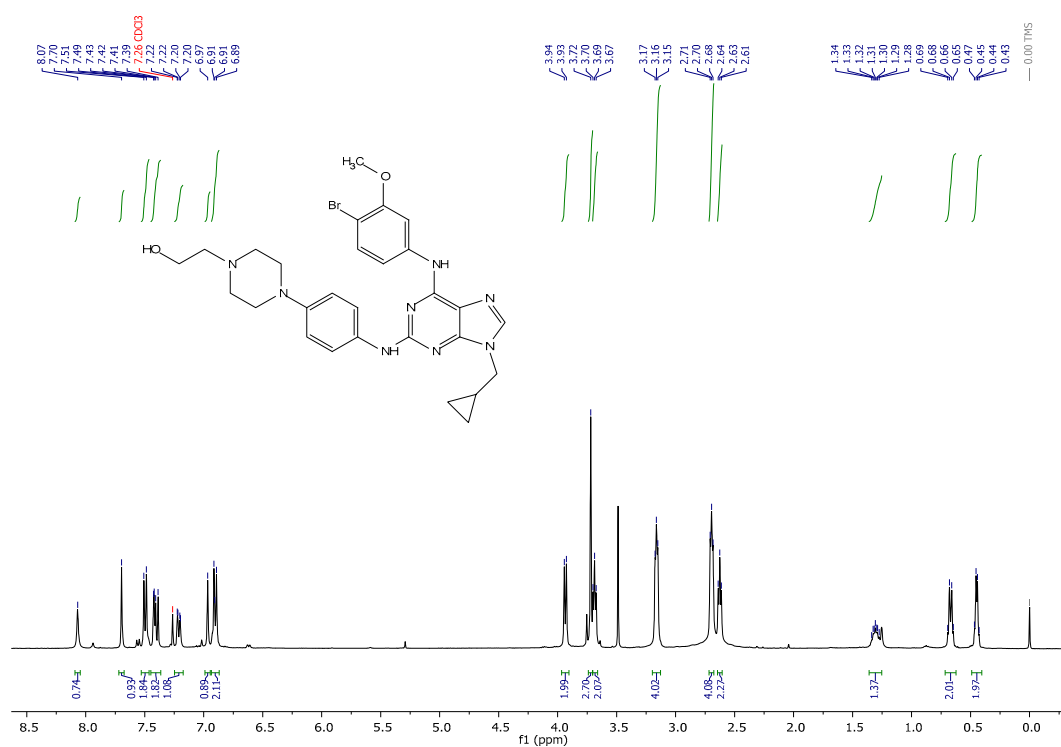
$^1\text{H}$  NMR spectra of compound **7f**.



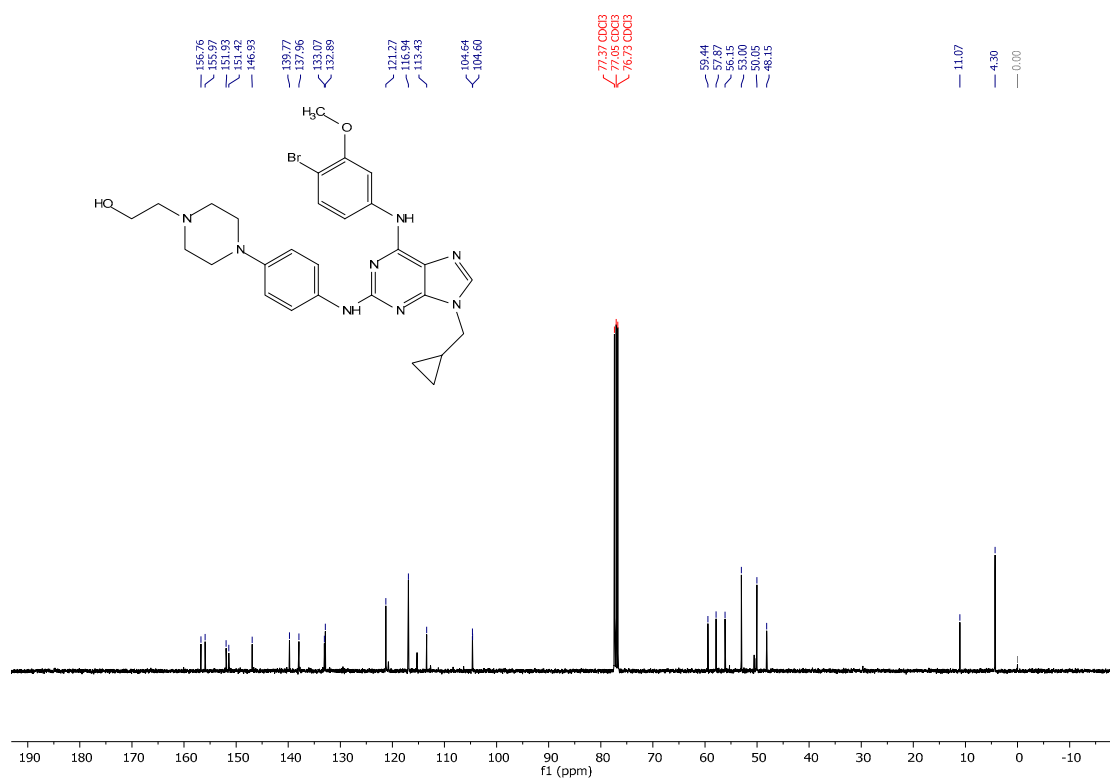
$^{13}\text{C}$  NMR spectra of compound **7f**.



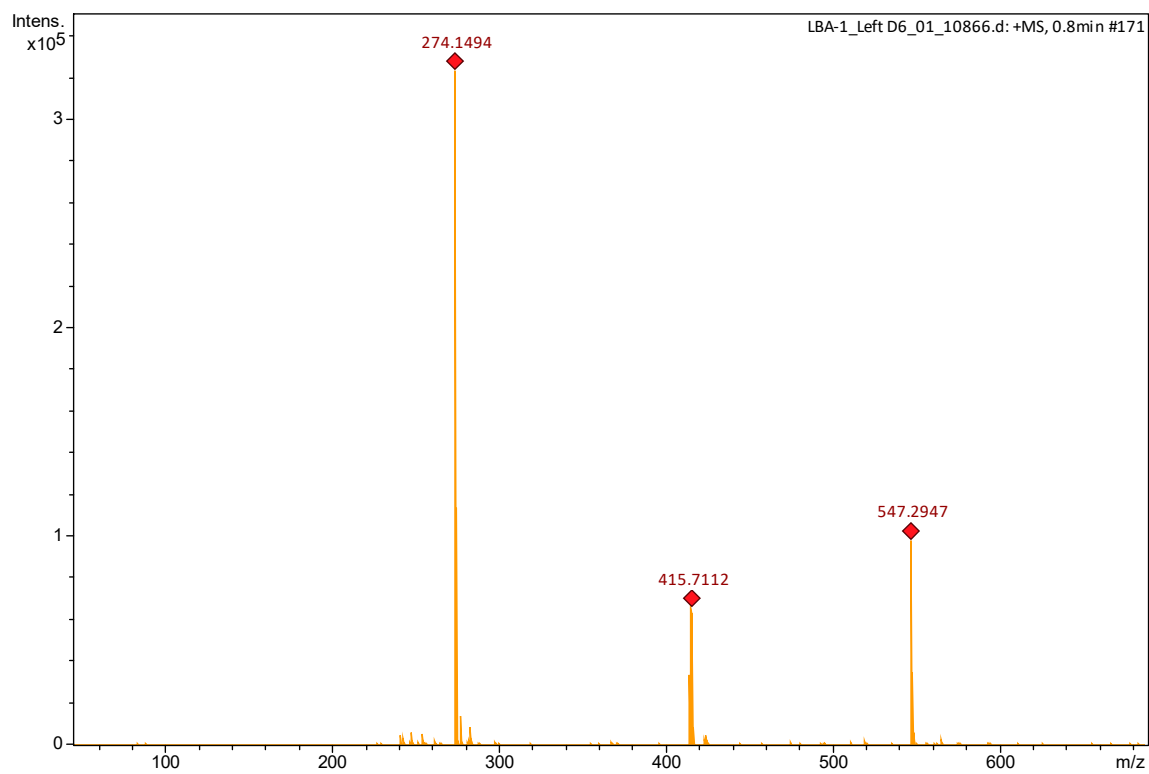
$^1\text{H}$  NMR spectra of compound **7g**.



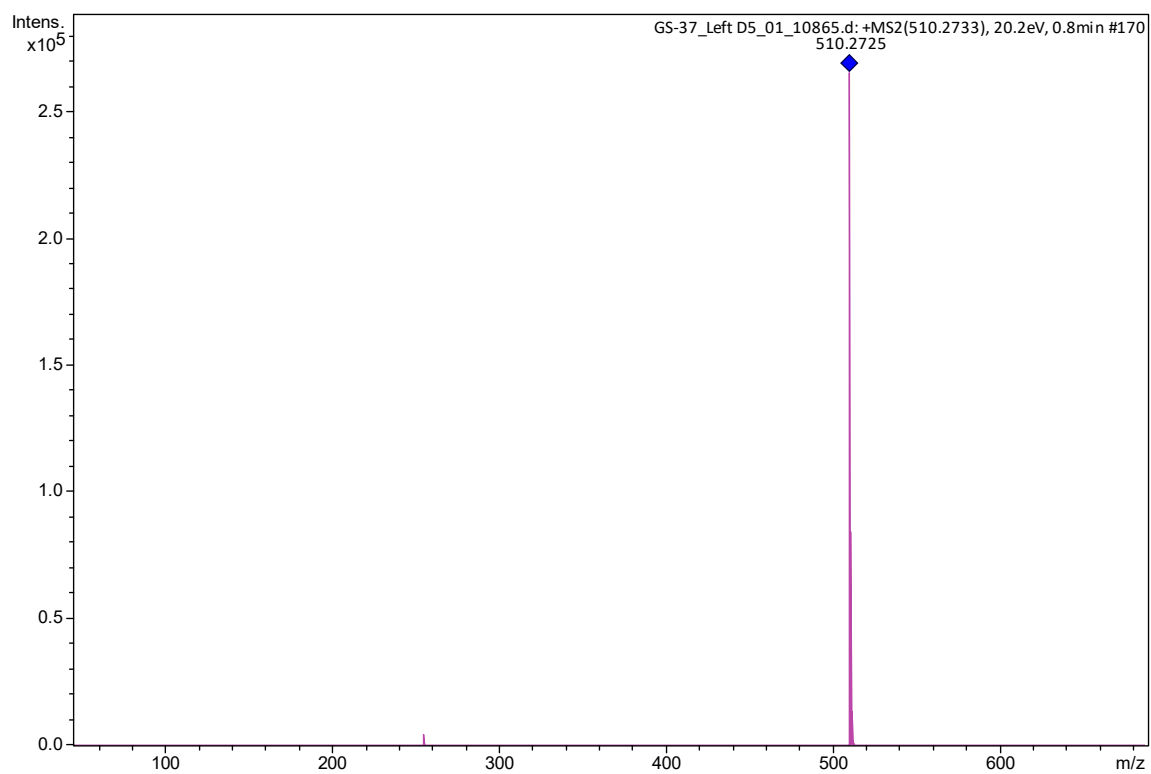
$^{13}\text{C}$  NMR spectra of compound **7g**.



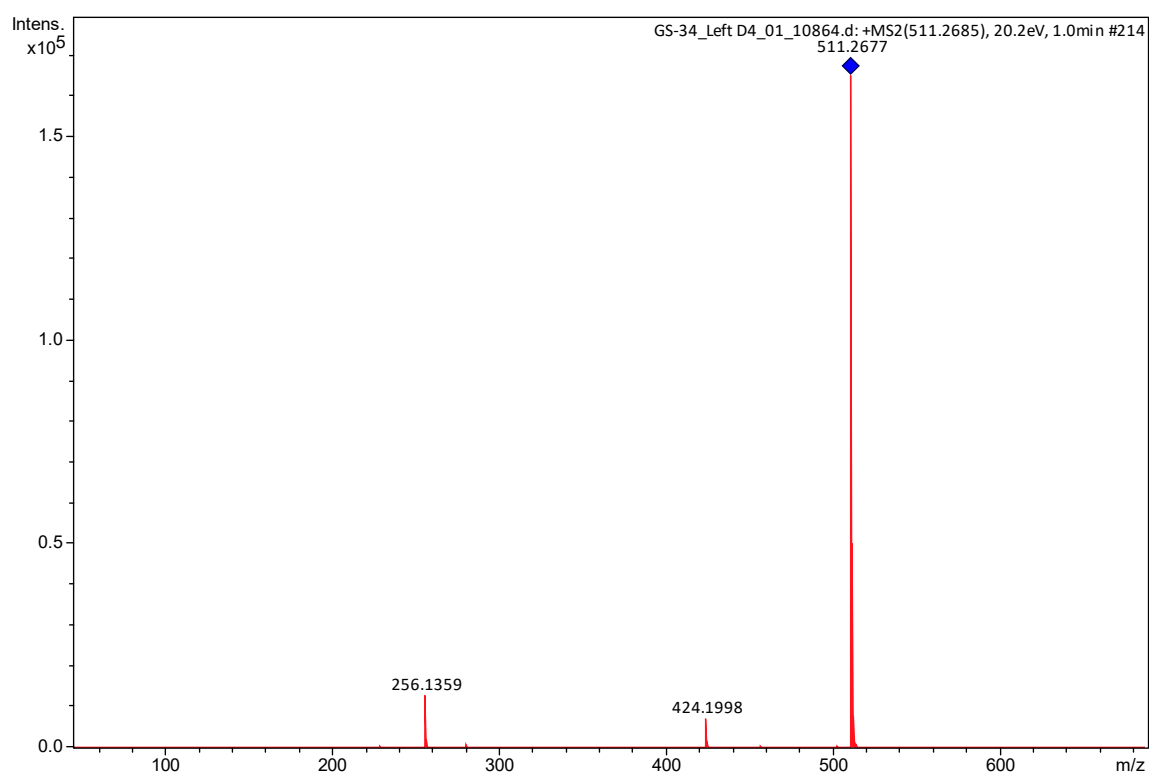
Mass spectra of compound **7a**.



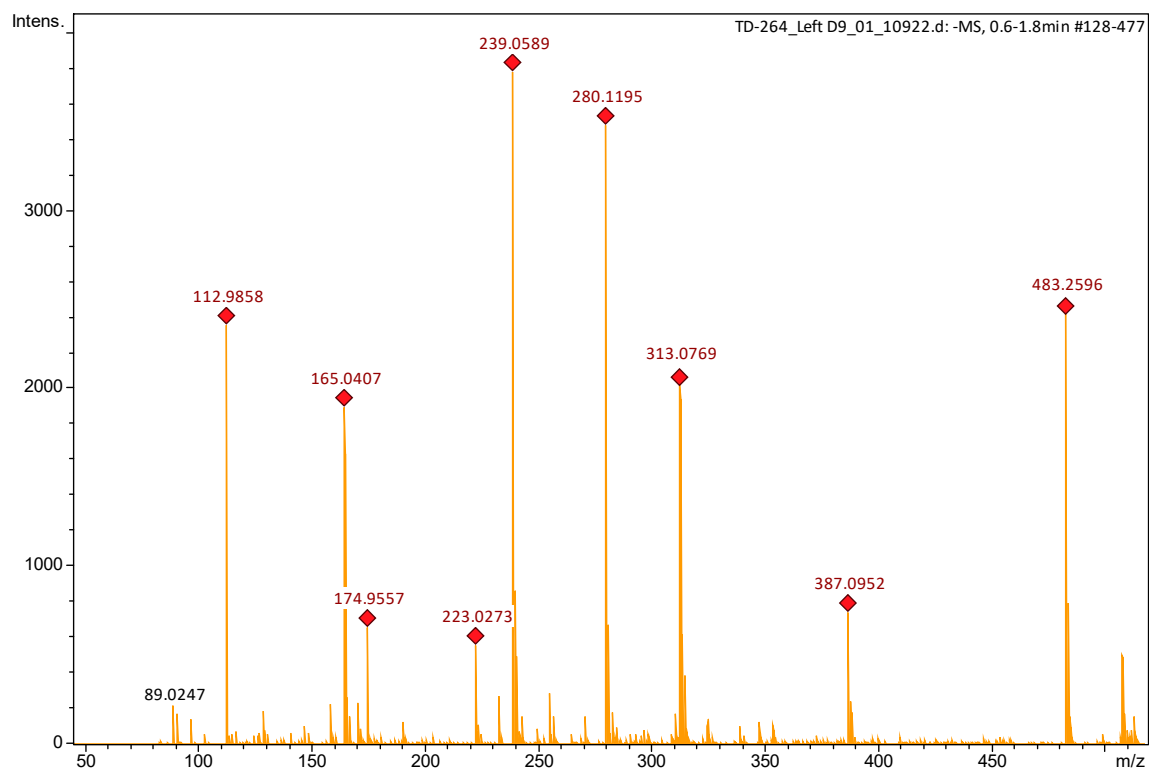
Mass spectra of compound **7b**.



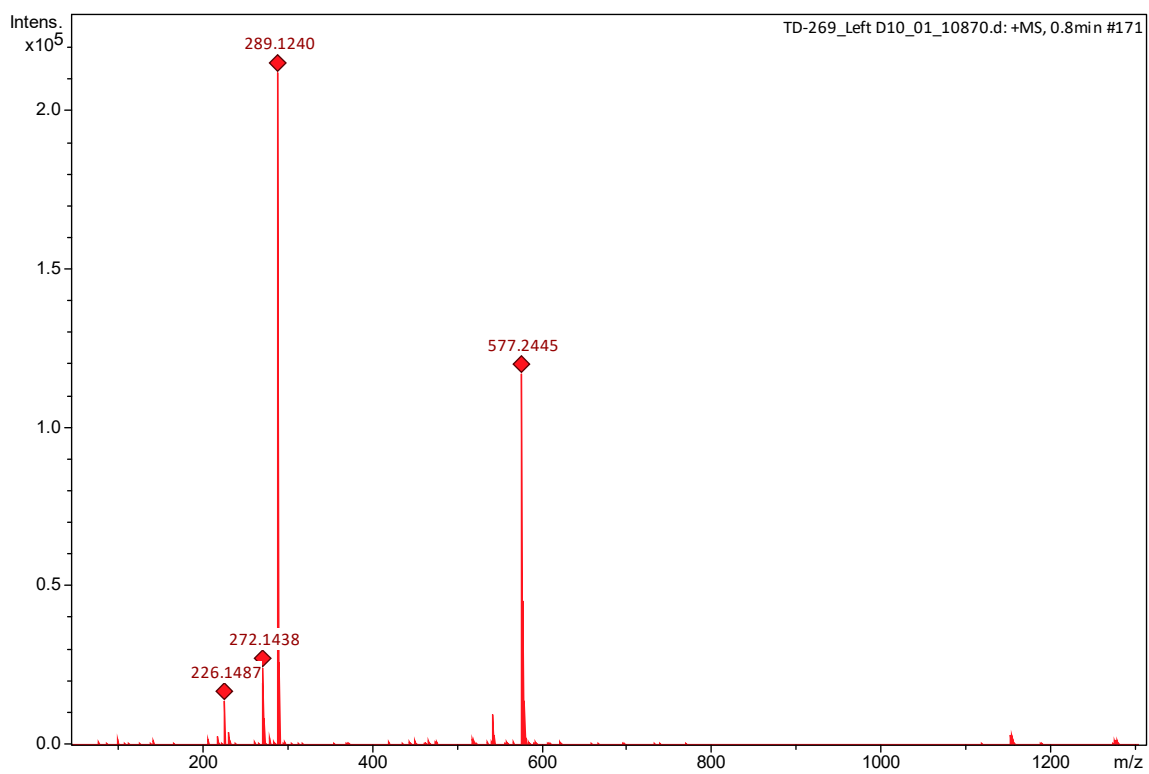
Mass spectra of compound **7c**.



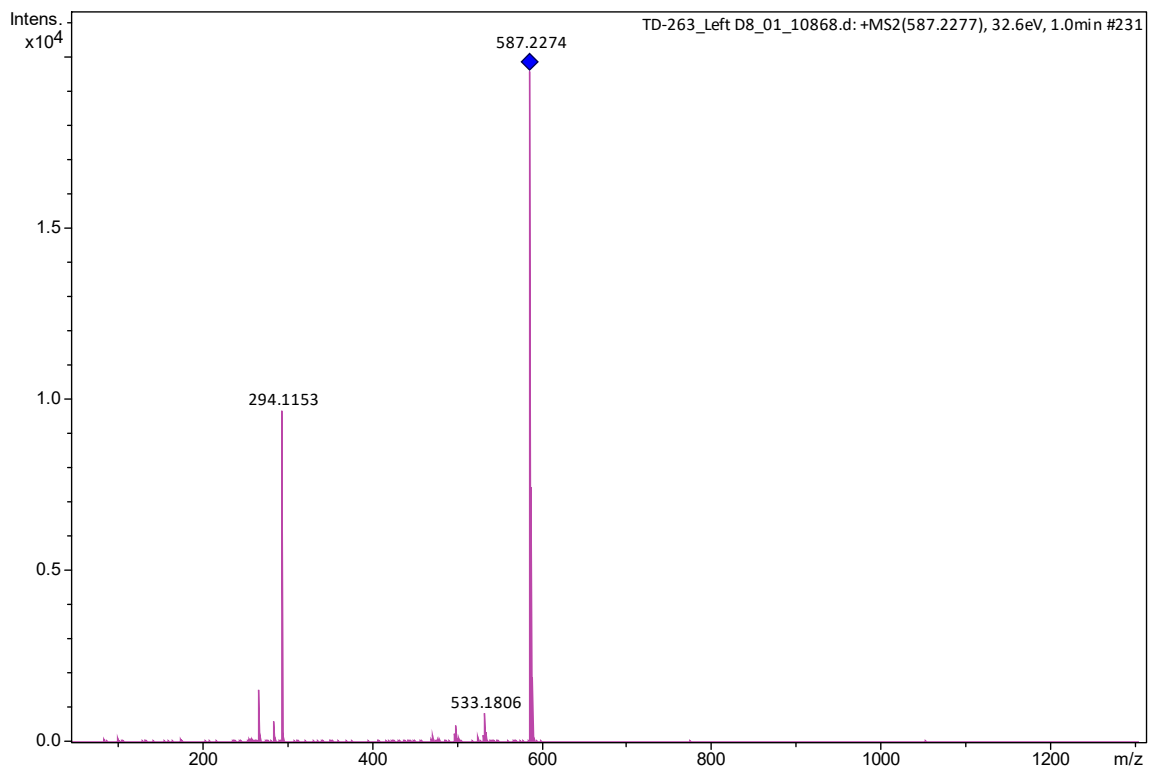
Mass spectra of compound **7d**.



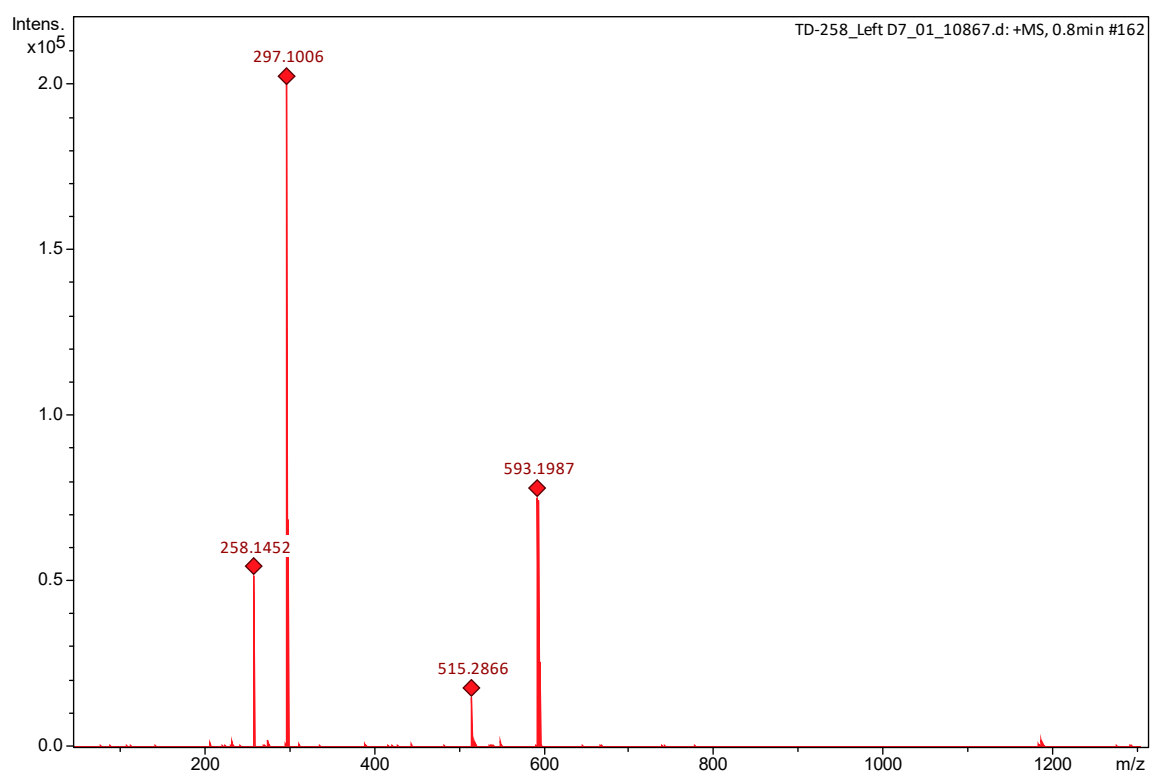
### Mass spectra of compound 7e.



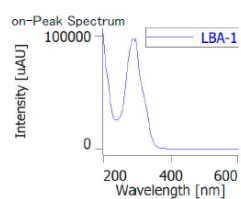
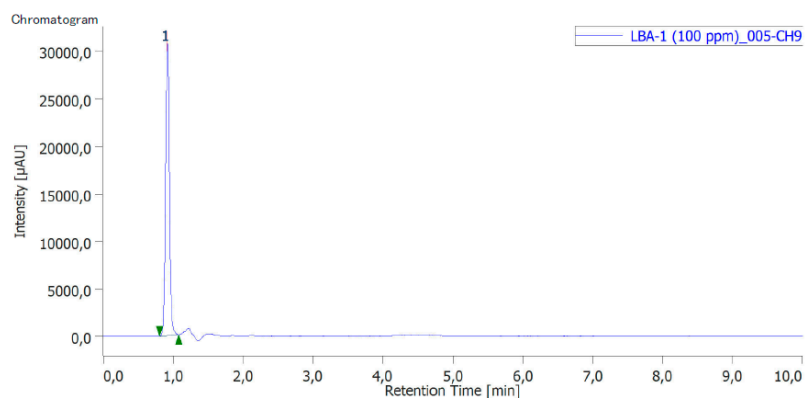
### Mass spectra of compound 7f.



# Mass spectra of compound 7g.



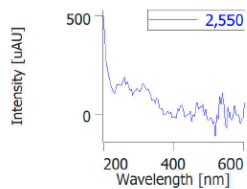
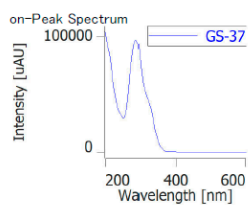
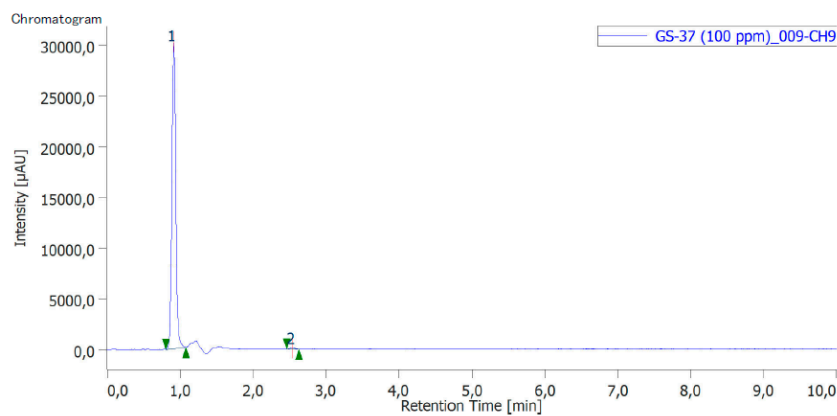
## HPLC analysis of compound **7a**.



Peak Information

| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area%   | Height% | Quantity | Resolution |
|---|-----------|----|----------|---------------|-------------|---------|---------|----------|------------|
| 1 | LBA-1     | 9  | 0.920    | 117920        | 30890       | 100.000 | 100.000 | N/A      | N/A        |

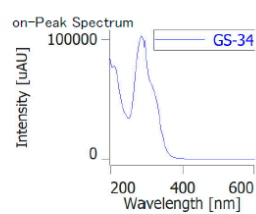
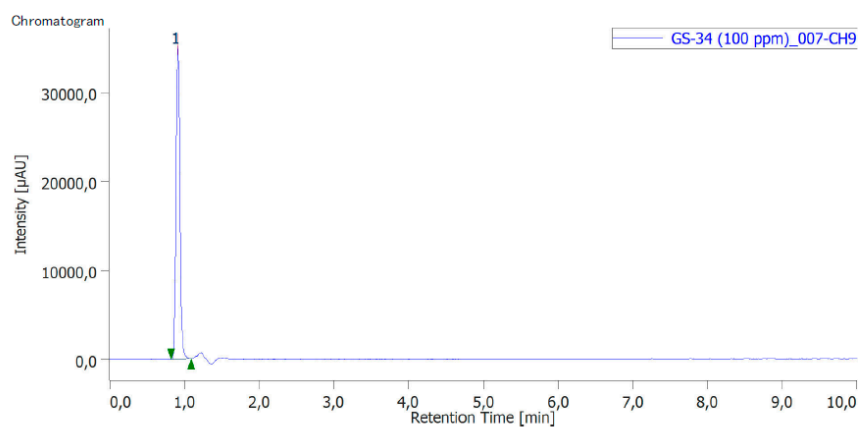
## HPLC analysis of compound **7b**.



Peak Information

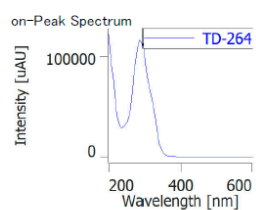
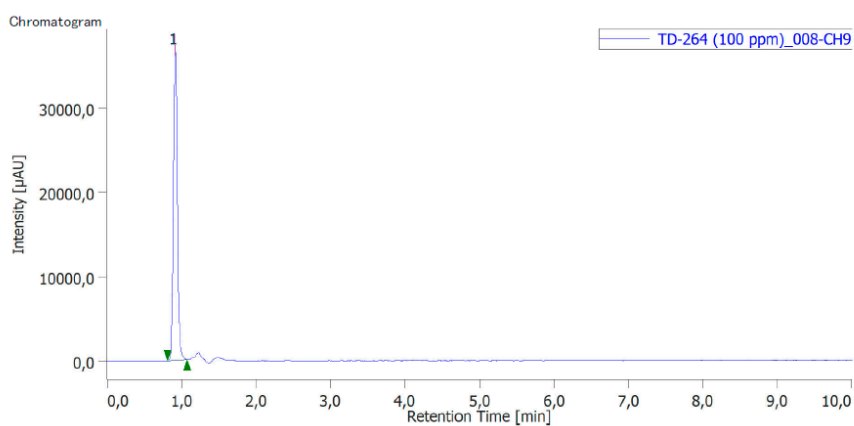
| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area%  | Height% | Quantity | Resolution |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------------|
| 1 | GS-37     | 9  | 0.917    | 114073        | 30218       | 99.445 | 99.562  | N/A      | 14.509     |
| 2 | Unknown   | 9  | 2.550    | 636           | 133         | 0.555  | 0.438   | N/A      | N/A        |

## HPLC analysis of compound **7c**.



| Peak Information |           |    |          |               |             |         |         |
|------------------|-----------|----|----------|---------------|-------------|---------|---------|
| #                | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area%   | Height% |
| 1                | GS-34     | 9  | 0.917    | 129456        | 35338       | 100.000 | 100.000 |

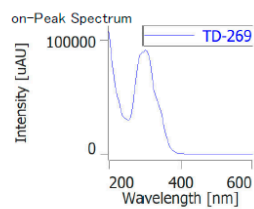
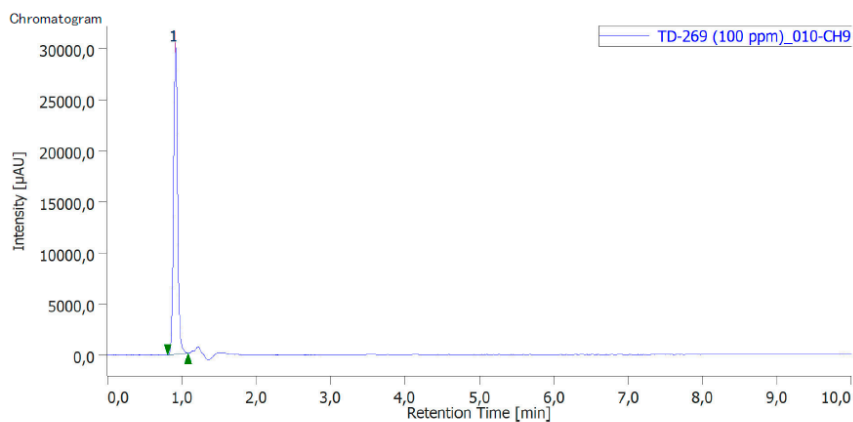
## HPLC analysis of compound **7d**.



Peak Information

| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area%   | Height% | Quantity | Resolution |
|---|-----------|----|----------|---------------|-------------|---------|---------|----------|------------|
| 1 | TD-264    | 9  | 0.920    | 139816        | 37331       | 100,000 | 100,000 | N/A      | N/A        |

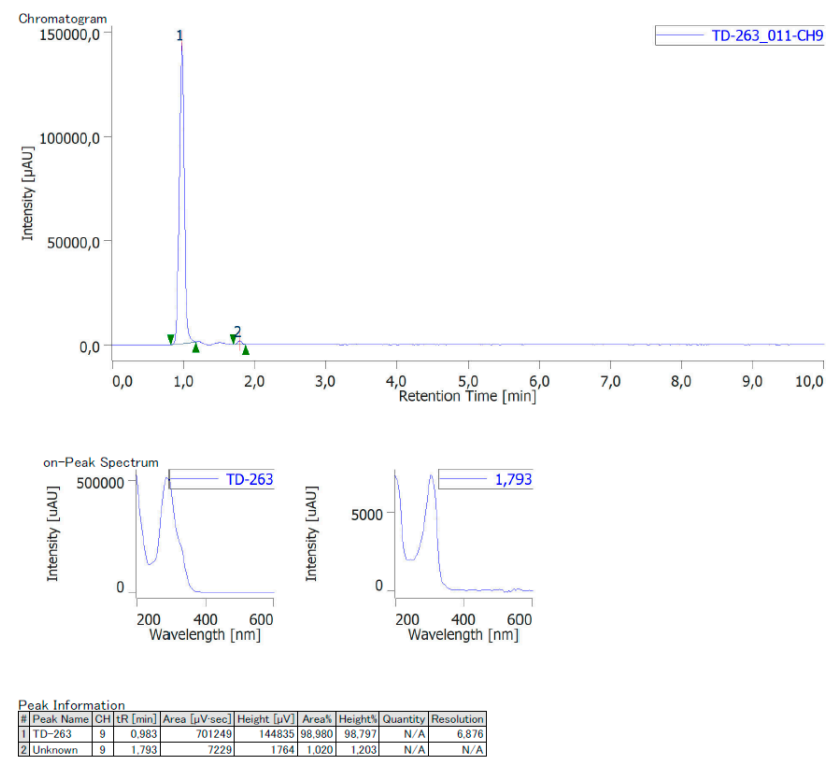
## HPLC analysis of compound **7e**.



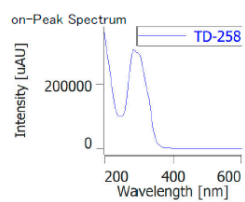
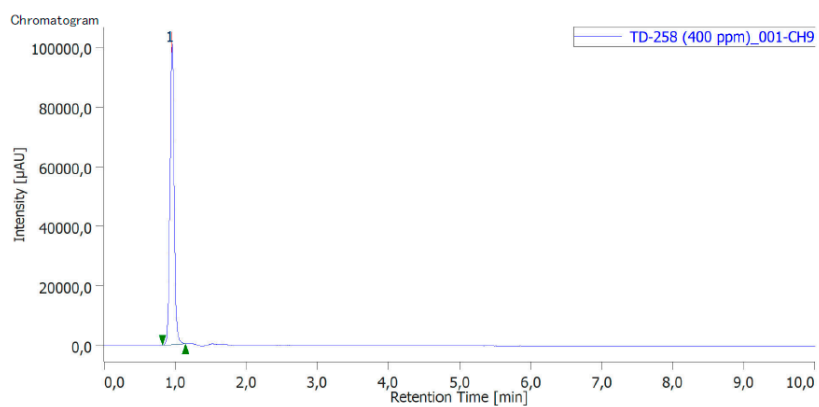
Peak Information

| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area%   | Height% | Quantity | Resolution |
|---|-----------|----|----------|---------------|-------------|---------|---------|----------|------------|
| 1 | TD-269    | 9  | 0.920    | 117494        | 30554       | 100,000 | 100,000 | N/A      | N/A        |

HPLC analysis of compound **7f**.



HPLC analysis of compound **7g**.



| Peak Information |           |    |          |               |             |         |         |          |
|------------------|-----------|----|----------|---------------|-------------|---------|---------|----------|
| #                | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area%   | Height% | Quantity |
| 1                | TD-258    | 9  | 0.960    | 420867        | 101224      | 100.000 | 100.000 | N/A      |

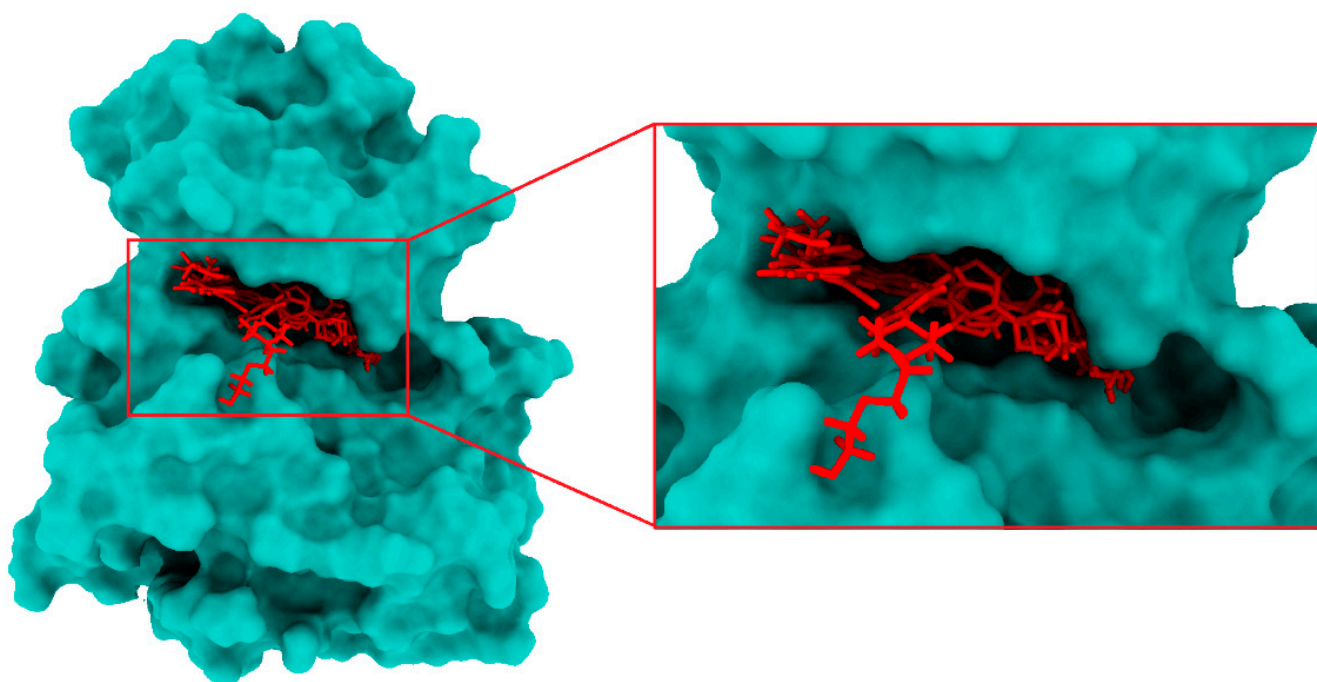


**Figure S1.** Representation of the Bcr-Abl surface, providing an overview of the binding site location and the conformations adopted by the studied molecules during the docking process (PDB = 6BL8).

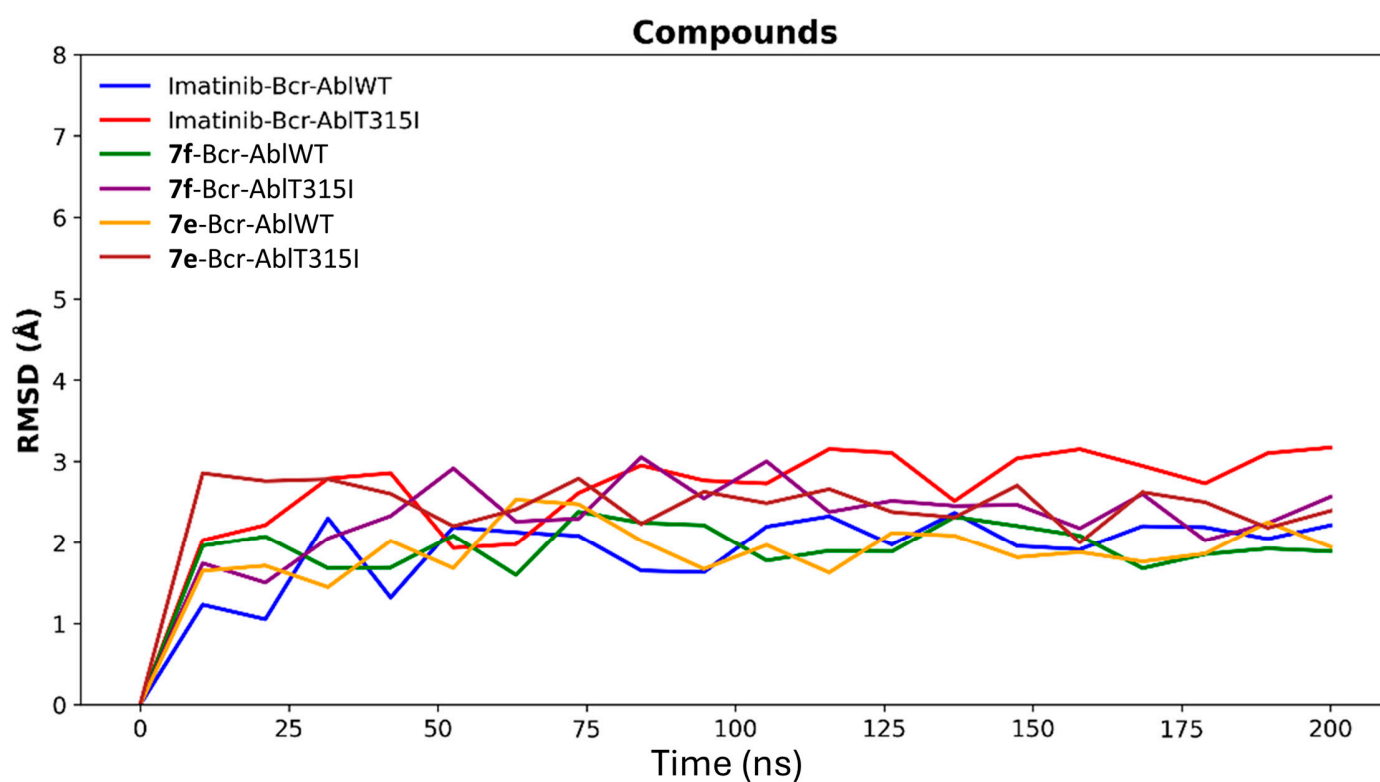


**Figure S2.** Time evolution of the RMSD for Bcr-Abl complexes with different ligands. Six systems were analysed: imatinib-Bcr-Abl<sup>WT</sup> (blue), imatinib-Bcr-Abl<sup>T315I</sup> (red), **7f**-Bcr-Abl<sup>WT</sup> (green), **7f**-Bcr-Abl<sup>T315I</sup> (purple), **7e**-Bcr-Abl<sup>WT</sup> (orange), and **7e**-Bcr-Abl<sup>T315I</sup> (brown).

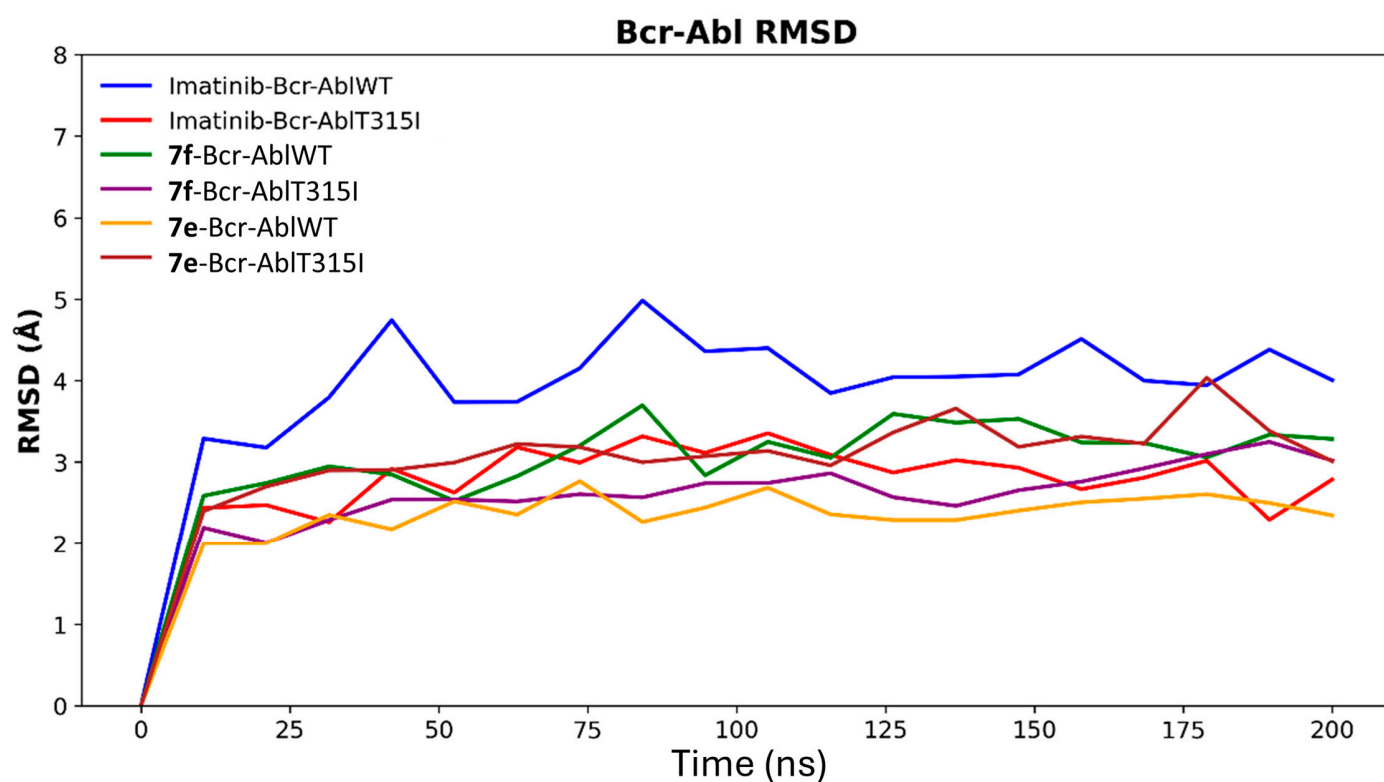


**Figure S3.** Time evolution of the RMSD for the Bcr-Abl protein in complex with different ligands. Six systems were analysed: imatinib-Bcr-Abl<sup>WT</sup> (blue), imatinib-Bcr-Abl<sup>T315I</sup> (red), **7f**-Bcr-Abl<sup>WT</sup> (green), **7f**-Bcr-Abl<sup>T315I</sup> (purple), **7e**-Bcr-Abl<sup>WT</sup> (orange), and **7e**-Bcr-Abl<sup>T315I</sup> (brown).