

# **Molecular-level understanding of the Somatostatin receptor 1 (SSTR1)-ligand binding: a structural biology study based on computational methods**

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**Table S1:** Model validation statistics for the predicted SSTR1 homology models.

| Model                | Template PDB ID | RMSD         | Ramachandran plot        |                        |                | QMEAN DisCO  | ProSA        | ERRAT        |
|----------------------|-----------------|--------------|--------------------------|------------------------|----------------|--------------|--------------|--------------|
|                      |                 |              | Number of residues in    |                        |                |              |              |              |
|                      |                 |              | favoured region (~98.0%) | allowed region (~2.0%) | outlier region |              |              |              |
| 1                    | 5C1M            | 0.123        | 94.60                    | 3.10                   | 2.30           | -5.10        | -2.59        | 62.22        |
| 2                    |                 | 0.168        | 96.70                    | 2.30                   | 1.00           | -4.36        | -2.19        | 67.22        |
| 3                    |                 | 0.174        | 94.60                    | 4.40                   | 1.00           | -3.99        | -2.71        | 74.79        |
| 4                    |                 | 0.125        | 95.40                    | 2.80                   | 1.80           | -4.62        | -2.88        | 75.98        |
| 5                    |                 | 0.159        | 96.10                    | 2.10                   | 1.80           | -4.35        | -2.30        | 75.75        |
| 6                    | 4RWA            | 0.184        | 95.10                    | 3.30                   | 1.50           | -4.51        | -2.18        | 73.86        |
| 7                    |                 | 0.163        | 94.30                    | 4.90                   | 0.80           | -4.75        | -2.32        | 81.50        |
| <b>8<sup>#</sup></b> |                 | <b>0.149</b> | <b>94.10</b>             | <b>3.30</b>            | <b>2.60</b>    | <b>-4.96</b> | <b>-2.60</b> | <b>81.90</b> |
| 9                    |                 | 0.163        | 95.10                    | 3.60                   | 1.30           | -4.52        | -2.64        | 74.24        |
| 10                   |                 | 0.117        | 94.90                    | 3.10                   | 2.10           | -4.94        | -1.81        | 75.32        |
| 11                   | 4N6H            | 0.107        | 93.60                    | 4.60                   | 1.80           | -5.12        | -3.39        | 71.35        |
| 12                   |                 | 0.108        | 93.60                    | 4.10                   | 2.30           | -5.05        | -3.34        | 65.62        |
| 13                   |                 | 0.135        | 93.60                    | 4.40                   | 2.10           | -5.84        | -2.90        | 70.22        |
| 14                   |                 | 0.123        | 93.60                    | 3.90                   | 2.60           | -5.35        | -3.18        | 71.30        |
| 15                   |                 | 0.116        | 91.50                    | 5.90                   | 2.60           | -5.61        | -3.28        | 73.39        |
| 16                   | 5DHG            | 0.182        | 93.10                    | 3.90                   | 3.10           | -6.59        | -1.66        | 70.66        |
| 17                   |                 | 0.275        | 92.80                    | 4.40                   | 2.80           | -6.84        | -1.96        | 66.77        |
| 18                   |                 | 0.127        | 95.10                    | 3.10                   | 1.80           | -5.67        | -2.46        | 75.32        |
| 19                   |                 | 0.132        | 94.60                    | 3.60                   | 1.80           | -5.67        | -2.26        | 74.28        |
| 20                   |                 | 0.139        | 94.90                    | 3.10                   | 2.10           | -6.42        | -2.46        | 72.50        |

|  |         |       |       |       |      |        |       |       |
|--|---------|-------|-------|-------|------|--------|-------|-------|
| 21   | 4EA3    | 0.171 | 94.10 | 3.30  | 2.60 | -6.64  | -2.46 | 66.56 |
| 22   |         | 0.188 | 93.30 | 4.60  | 2.10 | -6.23  | -2.29 | 71.18 |
| 23   |         | 0.168 | 93.30 | 2.80  | 3.90 | -7.35  | -2.08 | 67.07 |
| 24   |         | 0.148 | 91.30 | 4.40  | 4.40 | -7.16  | -2.14 | 63.64 |
| 25   |         | 0.200 | 92.80 | 3.90  | 3.30 | -7.21  | -2.08 | 64.24 |
| 26   | 4DJH    | 0.263 | 95.60 | 2.80  | 1.50 | -6.25  | -1.90 | 74.79 |
| 27   |         | 0.214 | 93.10 | 5.40  | 1.50 | -4.88  | -1.87 | 69.79 |
| 28   |         | 0.268 | 95.40 | 3.90  | 0.80 | -5.19  | -1.78 | 70.84 |
| 29   |         | 0.214 | 93.30 | 4.90  | 1.80 | -6.05  | -2.28 | 66.09 |
| 30   |         | 0.245 | 94.90 | 3.60  | 1.50 | -5.49  | -2.24 | 72.70 |
| 31   | 4EJ4    | 0.106 | 96.70 | 2.60  | 0.80 | -5.48  | -2.15 | 72.42 |
| 32   |         | 0.118 | 96.90 | 1.80  | 1.30 | -5.18  | -1.80 | 64.93 |
| 33   |         | 0.149 | 97.20 | 1.80  | 1.00 | -4.74  | -1.76 | 74.16 |
| 34   |         | 0.165 | 95.60 | 3.60  | 0.80 | -5.53  | -2.05 | 84.71 |
| 35   |         | 0.157 | 96.10 | 2.80  | 1.00 | -4.99  | -1.97 | 78.29 |
| 36   | 4DKL    | 0.170 | 94.10 | 4.10  | 1.80 | -5.80  | -2.26 | 66.56 |
| 37   |         | 0.139 | 94.60 | 4.10  | 1.30 | -4.66  | -2.47 | 72.81 |
| 38   |         | 0.216 | 95.60 | 2.60  | 1.80 | -4.12  | -2.31 | 72.98 |
| 39   |         | 0.134 | 94.10 | 4.90  | 1.00 | -4.69  | -1.89 | 64.69 |
| 40   |         | 0.209 | 95.60 | 2.60  | 1.80 | -4.82  | -2.51 | 69.46 |
| 41   | ITasser | -     | 81.50 | 10.80 | 7.70 | -9.74  | -1.43 | 84.86 |
| 42   |         | -     | 83.30 | 10.30 | 6.40 | -10.03 | -1.81 | 95.82 |
| 43   |         | -     | 85.90 | 8.00  | 6.20 | -8.64  | -3.00 | 97.13 |
| 44   |         | -     | 84.80 | 8.70  | 6.40 | -8.34  | -2.60 | 89.82 |
| 45   |         | -     | 78.40 | 14.90 | 6.70 | -9.44  | -2.09 | 90.60 |
| # Selected model based on the validation scores. |         |       |       |       |      |        |       |       |

**Table S2.** Model validation statistics for the predicted homology models of Cortistatin-14 and SRIF-28

| Protein        | Model    | Ramachandran plot             |                              |                   | QMEAN<br>DisCO | ProSA        | ERRAT         |
|----------------|----------|-------------------------------|------------------------------|-------------------|----------------|--------------|---------------|
|                |          | Number of residues in         |                              |                   |                |              |               |
|                |          | favored<br>region<br>(~98.0%) | allowed<br>region<br>(~2.0%) | outlier<br>region |                |              |               |
| Cortistatin-14 | 1        | 100.00                        | 0.00                         | 0.00              | -1.57          | 0.90         | 83.33         |
|                | <b>2</b> | <b>100.00</b>                 | <b>0.00</b>                  | <b>0.00</b>       | <b>-1.49</b>   | <b>1.08</b>  | <b>83.33</b>  |
|                | 3        | 100.00                        | 0.00                         | 0.00              | -1.66          | 0.52         | 83.33         |
| SRIF-28        | <b>1</b> | <b>88.00</b>                  | <b>8.00</b>                  | <b>4.00</b>       | <b>-1.61</b>   | <b>-1.75</b> | <b>100.00</b> |
|                | 2        | 68.00                         | 20.00                        | 12.00             | -1.06          | -1.85        | 100.00        |
|                | 3        | 84.00                         | 8.00                         | 8.00              | -2.07          | -1.83        | 100.00        |
|                | 4        | 64.00                         | 28.00                        | 8.00              | -2.14          | -0.74        | 100.00        |
|                | 5        | 76.00                         | 20.00                        | 4.00              | -1.38          | -0.73        | 93.75         |

**Table S3:** Docking results of the antagonists with selected model (model **08**). Binding site residues are represented in bold font.

| <b>Compound</b> | <b>Total Surflex dock score</b> | <b>No. of H bonds</b> | <b>Residues and its atom type involved in H-bonding with antagonist molecule</b> |
|-----------------|---------------------------------|-----------------------|--|
| 01              | 4.83                            | -                     | -  |
| 02              | 4.87                            | 2                     | <b>Y1.39, C208</b>   |
| 03              | 2.67                            | 1                     | <b>Y1.39</b>   |
| 04              | 4.03                            | -                     | -  |
| 05              | 4.05                            | 2                     | <b>Y1.39, T5.43</b>  |
| 06              | 3.70                            | 1                     | <b>Y1.39</b>   |
| 07              | 5.89                            | 1                     | <b>Y1.39</b>   |
| 08              | 5.29                            | -                     | -  |
| 09              | 3.50                            | -                     | -  |
| 10              | 5.20                            | 2                     | <b>S7.37, V7.38</b>  |
| 11              | 3.90                            | -                     | -  |
| 12              | -1.84                           | 2                     | <b>Y1.39, A3.33</b>  |
| 13              | 3.34                            | -                     | -  |
| 14              | 4.59                            | -                     | -  |
| 15              | 5.08                            | 1                     | <b>Y1.39</b>   |
| 16              | 4.74                            | -                     | -  |
| 17              | 3.46                            | -                     | -  |
| 18              | 4.69                            | 2                     | <b>R121, V206</b>  |
| 19              | 3.85                            | 2                     | <b>S1.31</b>   |
| 20              | 3.94                            | -                     | -  |
| 21              | 3.17                            | -                     | -  |
| 22              | 3.27                            | -                     | -  |
| 23              | 4.37                            | 4                     | <b>R121</b>  |
| 24              | 3.76                            | 1                     | <b>Y1.39</b>   |

|    |      |   |                            |
|----|------|---|----------------------------|
| 25 | 4.32 | 1 | <b>Y1.39</b>               |
| 26 | 3.76 | 3 | <b>Y1.39, R121</b>         |
| 27 | 4.26 | - | -                          |
| 28 | 4.24 | - | -                          |
| 29 | 3.60 | 2 | <b>C208, S7.37</b>         |
| 30 | 4.45 | 4 | <b>Y1.39, T5.43, Q6.55</b> |
| 31 | 3.74 | 1 | <b>Y1.39</b>               |
| 32 | 4.85 | - | -                          |
| 33 | 4.06 | - | -                          |
| 34 | 4.55 | 1 | <b>S7.34</b>               |
| 35 | 4.05 | - | -                          |
| 36 | 3.30 | - | -                          |
| 37 | 3.21 | 2 | <b>V206, C208</b>          |
| 38 | 5.82 | 1 | <b>Y1.39</b>               |
| 39 | 5.42 | 1 | <b>Y1.39</b>               |
| 40 | 4.97 | 1 | <b>Y1.39</b>               |
| 41 | 2.78 | 2 | P41, T50                   |
| 42 | 3.77 | 1 | <b>Y1.39</b>               |
| 43 | 4.81 | 1 | <b>Y1.39</b>               |
| 44 | 3.48 | 4 | <b>Y1.39, T5.43, Q6.55</b> |
| 45 | 4.41 | 6 | <b>Y1.39, R121, C208</b>   |
| 46 | 2.60 | 3 | <b>N6.58, S7.37, V7.38</b> |
| 47 | 4.25 | - | -                          |
| 48 | 3.98 | 1 | <b>Y1.39</b>               |
| 49 | 5.12 | 1 | <b>Y1.39</b>               |
| 50 | 3.87 | 1 | <b>Y1.39</b>               |
| 51 | 3.22 | - | -                          |
| 52 | 3.40 | 1 | <b>C208</b>                |

|    |      |   |                            |
|----|------|---|----------------------------|
| 53 | 4.47 | 1 | <b>Y1.39</b>               |
| 54 | 3.97 | - | -                          |
| 55 | 4.77 | 1 | D3.32                      |
| 56 | 3.78 | 1 | <b>Y1.39</b>               |
| 57 | 4.42 | 1 | <b>Y1.39</b>               |
| 58 | 5.53 | 2 | <b>Y1.39, C208</b>         |
| 59 | 2.96 | 1 | <b>S7.37</b>               |
| 60 | 2.67 | 2 | <b>S1.31, V206</b>         |
| 61 | 5.42 | 1 | <b>Y1.39</b>               |
| 62 | 6.11 | - | -                          |
| 63 | 4.26 | 1 | <b>Y1.39</b>               |
| 64 | 3.36 | 1 | <b>C208</b>                |
| 65 | 5.21 | 1 | <b>Y1.39</b>               |
| 66 | 3.12 | 1 | <b>Y1.39</b>               |
| 67 | 3.80 | 1 | <b>S1.31</b>               |
| 68 | 3.90 | 1 | <b>R121</b>                |
| 69 | 4.30 | - | -                          |
| 70 | 4.41 | 2 | <b>C208, Y1.39</b>         |
| 71 | 5.05 | 4 | <b>Y1.39, R121, N6.58</b>  |
| 72 | 4.96 | 6 | <b>Y1.39, T5.43, Q6.55</b> |
| 73 | 4.57 | 5 | <b>Y1.39, T5.43, Q6.55</b> |
| 74 | 3.43 | 2 | <b>R121</b>                |
| 75 | 3.50 | - | -                          |
| 76 | 3.33 | - | -                          |
| 77 | 3.45 | - | -                          |
| 78 | 4.82 | 5 | <b>Y1.39, T5.43, Q6.55</b> |
| 79 | 3.59 | 2 | <b>Y1.39, Q7.35</b>        |
| 80 | 2.72 | 1 | <b>S1.31</b>               |



|     |      |   |                           |
|-----|------|---|---------------------------|
| 81  | 3.42 | - | -                         |
| 82  | 3.96 | 1 | <b>Y1.39</b>              |
| 83  | 4.53 | 2 | <b>T5.43, Q6.55</b>       |
| 84  | 3.34 | - | -                         |
| 85  | 5.34 | - | -                         |
| 86  | 4.29 | - | -                         |
| 87  | 3.57 | 2 | <b>R121, Y7.42</b>        |
| 88  | 4.20 | 2 | <b>N201, Y7.42</b>        |
| 89  | 5.02 | - | -                         |
| 90  | 6.60 | 2 | <b>Y1.39, Q6.55</b>       |
| 91  | 7.06 | 1 | <b>Y1.39</b>              |
| 92  | 4.24 | 3 | <b>R121, Y7.42</b>        |
| 93  | 3.96 | 3 | <b>Y1.39, H122, Q7.35</b> |
| 94  | 6.28 | 2 | <b>Y1.39, C208</b>        |
| 95  | 4.90 | 2 | <b>Y1.39, C208</b>        |
| 96  | 4.88 | 1 | <b>Y7.42</b>              |
| 97  | 3.65 | 1 | S2.63                     |
| 98  | 4.37 | - | -                         |
| 99  | 5.55 | - | -                         |
| 100 | 3.81 | 1 | <b>Y1.39</b>              |
| 101 | 3.99 | - | -                         |
| 102 | 5.42 | - | -                         |
| 103 | 3.07 | 4 | <b>T5.43, Q6.55</b>       |
| 104 | 4.29 | - | -                         |
| 105 | 4.90 | 1 | <b>Y1.39</b>              |
| 106 | 5.08 | 4 | <b>Y1.39, R121, V206</b>  |
| 107 | 4.14 | 1 | <b>Y1.39</b>              |
| 108 | 5.94 | - | -                         |

|     |      |   |                            |
|-----|------|---|----------------------------|
| 109 | 4.89 | 2 | <b>Y1.39, V206</b>         |
| 110 | 4.65 | 2 | <b>Y1.39, V206</b>         |
| 111 | 7.43 | 1 | <b>Y1.39</b>               |
| 112 | 7.32 | 3 | <b>T5.43, Q6.55</b>        |
| 113 | 6.58 | 1 | <b>T2.64</b>               |
| 114 | 5.22 | 2 | <b>Y1.39, S7.34</b>        |
| 115 | 7.26 | 1 | <b>Y1.39</b>               |
| 116 | 6.74 | 3 | N48, <b>Y1.39</b>          |
| 117 | 6.73 | 4 | <b>T5.43, Q6.55</b>        |
| 118 | 8.55 | 1 | <b>T2.64</b>               |
| 119 | 6.85 | 1 | <b>Y1.39</b>               |
| 120 | 6.64 | 1 | <b>T2.64</b>               |
| 121 | 5.04 | 4 | <b>S1.31, Y1.39, S7.34</b> |
| 122 | 6.68 | 5 | <b>T5.43, Q6.55</b>        |
| 123 | 7.04 | 2 | <b>T5.43, Q6.55</b>        |
| 124 | 6.41 | 2 | <b>T5.43, Q6.55</b>        |
| 125 | 6.01 | 1 | <b>Y1.39</b>               |
| 126 | 5.69 | - | -                          |
| 127 | 5.40 | 1 | <b>Y1.39</b>               |
| 128 | 4.71 | 1 | <b>T2.64</b>               |
| 129 | 5.46 | - | -                          |
| 130 | 5.49 | 1 | <b>Y1.39</b>               |
| 131 | 6.54 | - | -                          |
| 132 | 6.09 | - | -                          |
| 133 | 6.89 | - | -                          |
| 134 | 6.01 | 1 | <b>C208</b>                |
| 135 | 6.84 | 1 | <b>T2.64</b>               |
| 136 | 6.89 | - | -                          |

|     |      |   |                     |
|-----|------|---|---------------------|
| 137 | 6.81 | - | -                   |
| 138 | 6.40 | 1 | <b>S1.31</b>        |
| 139 | 5.47 | 2 | <b>T2.64, S7.34</b> |
| 140 | 7.63 | 1 | <b>T2.64</b>        |
| 141 | 5.35 | 1 | <b>Y1.39</b>        |
| 142 | 5.12 | 1 | <b>Y1.39</b>        |
| 143 | 6.09 | 2 | <b>Y1.39, A3.33</b> |
| 144 | 6.77 | 1 | <b>Y1.39</b>        |

**Table S4.** Protein-protein docking scores of model **08** with peptides SRIF28 and Cortistatin-14.

| Compound       | Weighted Score |               | No. of H bonds | Residues and its atom type involved in H-bonding with antagonist molecule |
|----------------|----------------|---------------|----------------|---|
|                | Center         | Lowest Energy |                |   |
| SRIF-28        | -977.6         | -1108.5       | 25             | S202, D203, T205, E298, A7.31, <b>S7.34, Y7.42</b>                        |
| Cortistatin-14 | -975.0         | -975.0        | 8              | <b>S1.31</b> , L2.65, D3.32, D300, <b>S7.34, Y7.42</b>                    |

**Table S5:** Actual and predicted activity values ( $pK_d$ ) values obtained from CoMFA and CoMSIA models

| Compound | Actual $pK_d$ | CoMFA            |          | CoMSIA           |          |
|----------|---------------|------------------|----------|------------------|----------|
|          |               | Predicted $pK_d$ | Residual | Predicted $pK_d$ | Residual |
| 1        | 7.76          | 6.81             | 0.9500   | 7.45             | 0.3070   |
| 3        | 7.28          | 7.96             | -0.6840  | 7.72             | -0.4410  |
| 4        | 6.33          | 7.20             | -0.8680  | 7.16             | -0.8300  |
| 5        | 8.45          | 7.56             | 0.8910   | 7.93             | 0.5190   |
| 6        | 6.98          | 7.05             | -0.0660  | 7.91             | -0.9300  |
| 9        | 8.12          | 7.79             | 0.3320   | 8.12             | -0.0020  |
| 11       | 7.06          | 7.24             | -0.1780  | 7.11             | -0.0500  |
| 12       | 8.06          | 8.19             | -0.1260  | 7.35             | 0.7110   |
| 14       | 7.58          | 8.06             | -0.4790  | 7.73             | -0.1450  |
| 15       | 6.54          | 7.30             | -0.7640  | 7.11             | -0.5650  |
| 16       | 8.24          | 7.73             | 0.5080   | 7.67             | 0.5670   |
| 17       | 6.45          | 7.03             | -0.5820  | 7.04             | -0.5910  |
| 18       | 8.44          | 7.95             | 0.4860   | 7.73             | 0.7140   |
| 21       | 7.97          | 7.96             | 0.0130   | 8.47             | -0.5030  |
| 22       | 8.91          | 8.23             | 0.6830   | 8.56             | 0.3510   |
| 23       | 7.06          | 7.50             | -0.4420  | 7.77             | -0.7070  |
| 24       | 7.75          | 7.68             | 0.0680   | 7.76             | -0.0070  |
| 27       | 8.70          | 8.71             | -0.0140  | 8.14             | 0.5590   |
| 28       | 8.09          | 7.25             | 0.8370   | 7.72             | 0.3670   |
| 30       | 8.88          | 8.14             | 0.7420   | 8.20             | 0.6850   |
| 33       | 6.56          | 7.20             | -0.6400  | 7.15             | -0.5860  |
| 35       | 6.82          | 6.59             | 0.2310   | 6.70             | 0.1170   |
| 36       | 6.79          | 6.63             | 0.1580   | 7.13             | -0.3430  |
| 37       | 5.82          | 6.80             | -0.9840  | 5.56             | 0.2640   |
| 38       | 5.77          | 5.74             | 0.0300   | 5.97             | -0.2040  |
| 39       | 4.09          | 5.09             | -0.9980  | 3.92             | 0.1700   |
| 40       | 6.20          | 6.22             | -0.0200  | 5.97             | 0.2320   |
| 41       | 6.23          | 6.40             | -0.1650  | 5.92             | 0.3090   |

|    |      |      |         |       |         |
|----|------|------|---------|-------|---------|
| 42 | 9.13 | 8.67 | 0.4560  | 8.73  | 0.3990  |
| 43 | 8.55 | 8.88 | -0.3280 | 8.17  | 0.3780  |
| 44 | 8.49 | 8.58 | -0.0860 | 8.89  | -0.3950 |
| 45 | 6.96 | 7.53 | -0.5660 | 7.69  | -0.7330 |
| 46 | 8.76 | 7.96 | 0.7980  | 8.85  | -0.0880 |
| 47 | 6.68 | 7.06 | -0.3790 | 6.93  | -0.2470 |
| 48 | 6.58 | 7.08 | -0.4980 | 6.52  | 0.0620  |
| 49 | 7.09 | 7.25 | -0.1560 | 7.09  | -0.0010 |
| 51 | 6.31 | 6.57 | -0.2610 | 6.67  | -0.3600 |
| 52 | 6.31 | 6.28 | 0.0330  | 6.61  | -0.2960 |
| 53 | 7.15 | 6.65 | 0.5050  | 7.29  | -0.1420 |
| 54 | 6.34 | 6.89 | -0.5470 | 7.03  | -0.6940 |
| 55 | 4.98 | 5.91 | -0.9340 | 5.52  | -0.5360 |
| 56 | 8.85 | 8.48 | 0.3750  | 9.00  | -0.1480 |
| 57 | 6.80 | 7.76 | -0.9550 | 7.03  | -0.2280 |
| 58 | 9.15 | 8.74 | 0.4070  | 8.31  | 0.8360  |
| 59 | 9.09 | 8.41 | 0.6850  | 8.67  | 0.4230  |
| 60 | 7.73 | 8.20 | -0.4650 | 8.13  | -0.4010 |
| 61 | 7.60 | 8.38 | -0.7830 | 7.87  | -0.2650 |
| 62 | 8.32 | 8.52 | -0.1950 | 8.57  | -0.2540 |
| 63 | 9.39 | 9.35 | 0.0440  | 9.55  | -0.1620 |
| 64 | 8.81 | 9.07 | -0.2630 | 9.80  | -0.9880 |
| 65 | 7.80 | 8.36 | -0.5550 | 8.04  | -0.2370 |
| 66 | 8.22 | 8.18 | 0.0370  | 8.30  | -0.0830 |
| 67 | 8.91 | 8.30 | 0.6110  | 8.02  | 0.8860  |
| 68 | 8.92 | 8.76 | 0.1590  | 8.58  | 0.3430  |
| 69 | 9.67 | 9.48 | 0.1900  | 9.68  | -0.0130 |
| 70 | 9.24 | 9.80 | -0.5590 | 9.81  | -0.5690 |
| 71 | 9.40 | 9.39 | 0.0070  | 10.06 | -0.6630 |
| 72 | 8.45 | 8.68 | -0.2290 | 8.60  | -0.1510 |
| 73 | 8.34 | 8.71 | -0.3720 | 8.63  | -0.2920 |
| 74 | 8.10 | 8.55 | -0.4540 | 8.35  | -0.2480 |

|     |      |      |         |      |         |
|-----|------|------|---------|------|---------|
| 75  | 8.92 | 8.70 | 0.2160  | 8.36 | 0.5620  |
| 76  | 9.08 | 8.51 | 0.5660  | 8.09 | 0.9890  |
| 77  | 7.46 | 8.34 | -0.8820 | 8.09 | -0.6280 |
| 79  | 7.85 | 7.24 | 0.6120  | 7.76 | 0.0920  |
| 80  | 7.89 | 7.23 | 0.6560  | 7.95 | -0.0560 |
| 82  | 7.78 | 7.16 | 0.6240  | 8.02 | -0.2420 |
| 83  | 6.62 | 7.28 | -0.6620 | 7.44 | -0.8220 |
| 86  | 6.51 | 6.61 | -0.1000 | 7.02 | -0.5050 |
| 87  | 6.77 | 7.47 | -0.7020 | 6.21 | 0.5600  |
| 88  | 5.94 | 5.25 | 0.6890  | 6.47 | -0.5310 |
| 89  | 5.76 | 5.44 | 0.3200  | 6.70 | -0.9360 |
| 90  | 5.83 | 5.66 | 0.1670  | 6.48 | -0.6480 |
| 91  | 5.63 | 6.04 | -0.4140 | 6.09 | -0.4580 |
| 92  | 9.31 | 9.30 | 0.0140  | 9.17 | 0.1400  |
| 93  | 9.01 | 8.59 | 0.4230  | 8.94 | 0.0720  |
| 94  | 9.12 | 9.38 | -0.2630 | 8.65 | 0.4690  |
| 95  | 9.41 | 9.41 | 0.0010  | 9.11 | 0.3010  |
| 96  | 9.69 | 9.82 | -0.1270 | 9.37 | 0.3210  |
| 97  | 9.42 | 9.32 | 0.0990  | 9.28 | 0.1360  |
| 98  | 9.55 | 9.68 | -0.1320 | 9.30 | 0.2470  |
| 99  | 7.71 | 7.89 | -0.1810 | 6.98 | 0.7300  |
| 100 | 8.38 | 8.75 | -0.3710 | 8.13 | 0.2480  |
| 101 | 8.26 | 8.83 | -0.5650 | 8.32 | -0.0560 |
| 102 | 8.41 | 8.83 | -0.4210 | 8.87 | -0.4580 |
| 103 | 8.90 | 8.85 | 0.0480  | 9.06 | -0.1550 |
| 104 | 8.87 | 8.78 | 0.0870  | 9.09 | -0.2190 |
| 105 | 9.22 | 9.10 | 0.1170  | 8.82 | 0.3970  |
| 106 | 9.41 | 9.32 | 0.0920  | 8.94 | 0.4730  |
| 107 | 9.43 | 9.06 | 0.3720  | 9.23 | 0.2000  |
| 108 | 8.99 | 8.63 | 0.3590  | 8.99 | -0.0010 |
| 109 | 9.62 | 8.71 | 0.9060  | 9.10 | 0.5210  |
| 110 | 9.43 | 8.73 | 0.6970  | 9.15 | 0.2770  |

|     |      |      |         |       |         |
|-----|------|------|---------|-------|---------|
| 111 | 7.74 | 7.85 | -0.1100 | 7.808 | -0.0680 |
| 112 | 7.94 | 7.76 | 0.1800  | 7.76  | 0.1810  |
| 113 | 7.53 | 8.02 | -0.4900 | 7.92  | -0.3880 |
| 114 | 7.90 | 8.28 | -0.3810 | 8.00  | -0.1030 |
| 115 | 9.05 | 8.56 | 0.4940  | 8.08  | 0.9700  |
| 116 | 9.15 | 8.23 | 0.9170  | 8.17  | 0.9790  |
| 117 | 6.48 | 7.20 | -0.7200 | 7.02  | -0.5420 |
| 118 | 7.11 | 6.78 | 0.3320  | 6.86  | 0.2470  |
| 119 | 6.56 | 6.66 | -0.1040 | 6.88  | -0.3190 |
| 120 | 7.86 | 8.46 | -0.6020 | 8.22  | -0.3570 |
| 121 | 9.02 | 8.31 | 0.7150  | 8.59  | 0.4350  |
| 122 | 8.33 | 8.10 | 0.2300  | 7.94  | 0.3890  |
| 123 | 8.15 | 8.28 | -0.1300 | 8.04  | 0.1060  |
| 124 | 7.34 | 7.40 | -0.0580 | 7.89  | -0.5460 |
| 125 | 8.77 | 8.32 | 0.4490  | 8.59  | 0.1810  |
| 126 | 7.75 | 7.92 | -0.1680 | 7.88  | -0.1320 |
| 127 | 7.62 | 8.33 | -0.7050 | 8.04  | -0.4170 |
| 128 | 8.72 | 8.25 | 0.4720  | 8.02  | 0.7010  |
| 129 | 8.44 | 7.66 | 0.7830  | 7.92  | 0.5250  |
| 130 | 8.48 | 8.50 | -0.0170 | 8.20  | 0.2780  |
| 131 | 9.24 | 8.44 | 0.8050  | 8.56  | 0.6770  |
| 132 | 7.50 | 8.38 | -0.8790 | 8.11  | -0.6060 |
| 133 | 7.21 | 7.05 | 0.1630  | 7.69  | -0.4770 |
| 134 | 8.71 | 8.67 | 0.0400  | 7.94  | 0.7680  |
| 135 | 8.34 | 8.97 | -0.6270 | 8.23  | 0.1140  |
| 137 | 8.67 | 8.66 | 0.0070  | 7.90  | 0.7660  |
| 138 | 8.18 | 8.86 | -0.6800 | 8.40  | -0.2170 |
| 139 | 7.67 | 7.93 | -0.2570 | 7.82  | -0.1530 |
| 140 | 9.13 | 8.43 | 0.7000  | 8.89  | 0.2390  |
| 141 | 8.90 | 8.70 | 0.2010  | 8.06  | 0.8420  |
| 142 | 8.34 | 8.11 | 0.2330  | 8.02  | 0.3230  |
| 143 | 9.11 | 9.13 | -0.0180 | 8.58  | 0.5330  |

|     |      |      |        |      |         |
|-----|------|------|--------|------|---------|
| 144 | 9.49 | 8.79 | 0.6970 | 9.89 | -0.3980 |
|-----|------|------|--------|------|---------|

**Table S6:** DFT statistics of SST1 ligands

| Compound | Total Energy (eV) | Molecular dipole moment (Debye) | $E_{HOMO}$ (eV) | $E_{LUMO}$ (eV) | HOMO/LUMO Gap | Absolute hardness ( $\eta$ ) | Global softness ( $\sigma$ ) | Electro-negativity ( $\chi$ ) | Chemical potential ( $\mu$ ) | Electro-philicity index ( $\omega$ ) |
|----------|-------------------|---------------------------------|-----------------|-----------------|---------------|------------------------------|------------------------------|-------------------------------|------------------------------|--------------------------------------|
| 1        | -36501.08         | 4.28                            | -5.42           | -0.34           | 5.08          | 2.54                         | 0.20                         | -2.88                         | 2.88                         | 1.64                                 |
| 2        | -36500.89         | 3.27                            | -5.75           | -0.04           | 5.71          | 2.86                         | 0.18                         | -2.90                         | 2.90                         | 1.47                                 |
| 3        | -36936.57         | 2.01                            | -5.69           | -1.11           | 4.58          | 2.29                         | 0.22                         | -3.40                         | 3.40                         | 2.52                                 |
| 4        | -37427.61         | 3.40                            | -5.64           | -0.83           | 4.80          | 2.40                         | 0.21                         | -3.24                         | 3.24                         | 2.18                                 |
| 5        | -39011.26         | 3.92                            | -5.79           | -1.12           | 4.67          | 2.34                         | 0.21                         | -3.45                         | 3.45                         | 2.55                                 |
| 6        | -45672.41         | 1.55                            | -5.73           | -0.82           | 4.91          | 2.46                         | 0.20                         | -3.28                         | 3.28                         | 2.19                                 |
| 7        | -62646.10         | 4.60                            | -5.72           | -1.69           | 4.03          | 2.01                         | 0.25                         | -3.70                         | 3.70                         | 3.41                                 |
| 8        | -45904.66         | 1.75                            | -5.26           | -0.12           | 5.14          | 2.57                         | 0.19                         | -2.69                         | 2.69                         | 1.41                                 |
| 9        | -38530.64         | 3.50                            | -5.74           | -0.53           | 5.20          | 2.60                         | 0.19                         | -3.13                         | 3.13                         | 1.89                                 |
| 10       | -39617.52         | 4.61                            | -5.41           | -0.77           | 4.65          | 2.32                         | 0.22                         | -3.09                         | 3.09                         | 2.05                                 |
| 11       | -40245.05         | 3.44                            | -5.20           | -0.87           | 4.33          | 2.17                         | 0.23                         | -3.04                         | 3.04                         | 2.13                                 |
| 12       | -42755.16         | 6.99                            | -5.62           | -1.67           | 3.94          | 1.97                         | 0.25                         | -3.64                         | 3.64                         | 3.37                                 |
| 13       | -41751.57         | 2.87                            | -5.57           | -1.00           | 4.57          | 2.29                         | 0.22                         | -3.28                         | 3.28                         | 2.36                                 |
| 14       | -40682.07         | 1.86                            | -5.38           | -1.11           | 4.27          | 2.13                         | 0.23                         | -3.25                         | 3.25                         | 2.47                                 |
| 15       | -40681.92         | 4.04                            | -5.15           | -1.19           | 3.96          | 1.98                         | 0.25                         | -3.17                         | 3.17                         | 2.54                                 |
| 16       | -42779.32         | 1.01                            | -5.70           | -1.89           | 3.81          | 1.90                         | 0.26                         | -3.80                         | 3.80                         | 3.79                                 |
| 17       | -41554.64         | 4.07                            | -5.60           | -2.04           | 3.56          | 1.78                         | 0.28                         | -3.82                         | 3.82                         | 4.10                                 |
| 18       | -41524.19         | 5.50                            | -5.59           | -0.57           | 5.02          | 2.51                         | 0.20                         | -3.08                         | 3.08                         | 1.89                                 |
| 19       | -41087.56         | 3.20                            | -5.02           | -0.07           | 4.95          | 2.48                         | 0.20                         | -2.54                         | 2.54                         | 1.31                                 |
| 20       | -50314.73         | 2.35                            | -5.54           | -0.74           | 4.79          | 2.40                         | 0.21                         | -3.14                         | 3.14                         | 2.06                                 |
| 21       | -49878.08         | 0.90                            | -5.11           | -0.31           | 4.80          | 2.40                         | 0.21                         | -2.71                         | 2.71                         | 1.53                                 |
| 22       | -50314.84         | 1.62                            | -5.01           | -0.80           | 4.21          | 2.11                         | 0.24                         | -2.90                         | 2.90                         | 2.00                                 |
| 23       | -40516.90         | 2.32                            | -5.72           | -1.25           | 4.47          | 2.24                         | 0.22                         | -3.48                         | 3.48                         | 2.71                                 |



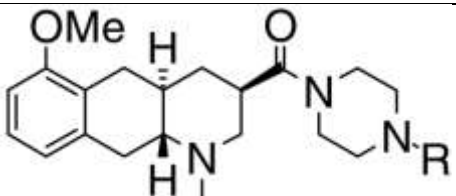
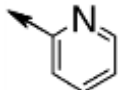
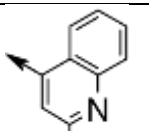
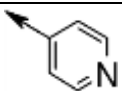
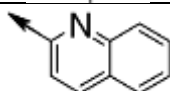
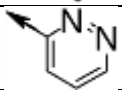
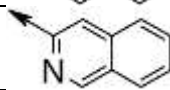
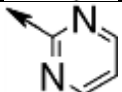
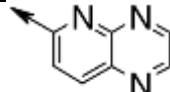
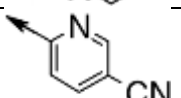
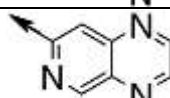
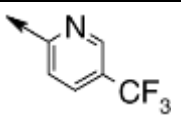
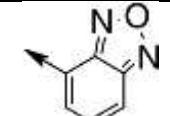
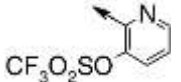
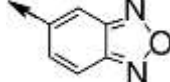
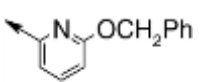
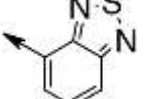
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| 24 | -38764.56 | 3.70 | -5.35 | 0.04  | 5.39 | 2.70 | 0.19 | -2.66 | 2.66 | 1.31 |
| 25 | -38764.69 | 2.17 | -5.38 | 0.06  | 5.44 | 2.72 | 0.18 | -2.66 | 2.66 | 1.30 |
| 26 | -38764.61 | 2.54 | -5.22 | -0.18 | 5.04 | 2.52 | 0.20 | -2.70 | 2.70 | 1.44 |
| 27 | -38574.41 | 5.53 | -5.70 | -1.17 | 4.53 | 2.27 | 0.22 | -3.44 | 3.44 | 2.61 |
| 28 | -38574.55 | 5.86 | -5.75 | -0.84 | 4.90 | 2.45 | 0.20 | -3.29 | 3.29 | 2.21 |
| 29 | -41628.93 | 5.17 | -5.73 | -2.09 | 3.64 | 1.82 | 0.27 | -3.91 | 3.91 | 4.20 |
| 30 | -41629.20 | 4.23 | -5.78 | -2.26 | 3.52 | 1.76 | 0.28 | -4.02 | 4.02 | 4.59 |
| 31 | -41629.30 | 6.32 | -5.84 | -1.95 | 3.90 | 1.95 | 0.26 | -3.90 | 3.90 | 3.89 |
| 32 | -45235.67 | 2.76 | -5.55 | -0.54 | 5.01 | 2.50 | 0.20 | -3.05 | 3.05 | 1.85 |
| 33 | -45235.71 | 3.64 | -4.85 | -0.03 | 4.81 | 2.41 | 0.21 | -2.44 | 2.44 | 1.24 |
| 34 | -38111.02 | 3.32 | -5.62 | -0.28 | 5.34 | 2.67 | 0.19 | -2.95 | 2.95 | 1.63 |
| 35 | -40218.22 | 4.78 | -5.53 | -1.03 | 4.50 | 2.25 | 0.22 | -3.28 | 3.28 | 2.39 |
| 36 | -42253.47 | 4.42 | -5.49 | -0.94 | 4.55 | 2.27 | 0.22 | -3.21 | 3.21 | 2.27 |
| 37 | -40655.07 | 5.63 | -5.46 | -0.59 | 4.88 | 2.44 | 0.21 | -3.03 | 3.03 | 1.88 |
| 38 | -44933.88 | 3.28 | -5.32 | -0.30 | 5.02 | 2.51 | 0.20 | -2.81 | 2.81 | 1.57 |
| 39 | -43536.68 | 5.34 | -3.72 | -1.47 | 2.25 | 1.13 | 0.44 | -2.60 | 2.60 | 3.00 |
| 40 | -53113.48 | 4.25 | -4.73 | -0.36 | 4.37 | 2.19 | 0.23 | -2.54 | 2.54 | 1.48 |
| 41 | -53549.93 | 3.99 | -5.75 | -0.32 | 5.43 | 2.71 | 0.18 | -3.04 | 3.04 | 1.70 |
| 42 | -41464.72 | 2.75 | -5.39 | -0.22 | 5.17 | 2.59 | 0.19 | -2.80 | 2.80 | 1.52 |
| 43 | -41274.64 | 5.93 | -5.74 | -1.28 | 4.45 | 2.23 | 0.22 | -3.51 | 3.51 | 2.77 |
| 44 | -44139.19 | 6.12 | -5.87 | -2.44 | 3.43 | 1.71 | 0.29 | -4.15 | 4.15 | 5.04 |
| 45 | -50800.17 | 4.78 | -5.81 | -2.38 | 3.43 | 1.71 | 0.29 | -4.10 | 4.10 | 4.90 |
| 46 | -57626.10 | 1.90 | -5.77 | -2.45 | 3.33 | 1.66 | 0.30 | -4.11 | 4.11 | 5.08 |
| 47 | -37570.88 | 4.33 | -5.39 | -0.37 | 5.03 | 2.51 | 0.20 | -2.88 | 2.88 | 1.65 |
| 48 | -42699.02 | 5.31 | -5.83 | -1.95 | 3.87 | 1.94 | 0.26 | -3.89 | 3.89 | 3.91 |
| 49 | -48101.36 | 3.47 | -5.68 | -0.96 | 4.71 | 2.36 | 0.21 | -3.32 | 3.32 | 2.34 |
| 50 | -36031.59 | 4.58 | -5.62 | -1.08 | 4.54 | 2.27 | 0.22 | -3.35 | 3.35 | 2.47 |
| 51 | -36468.14 | 4.18 | -5.58 | -1.37 | 4.22 | 2.11 | 0.24 | -3.47 | 3.47 | 2.86 |
| 52 | -41692.79 | 4.60 | -5.53 | -0.27 | 5.26 | 2.63 | 0.19 | -2.90 | 2.90 | 1.60 |
| 53 | -37069.09 | 4.01 | -5.40 | -0.20 | 5.20 | 2.60 | 0.19 | -2.80 | 2.80 | 1.51 |
| 54 | -37133.98 | 3.45 | -5.58 | -0.04 | 5.54 | 2.77 | 0.18 | -2.81 | 2.81 | 1.43 |
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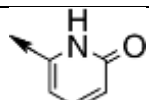
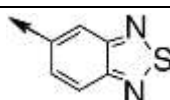
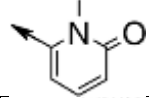
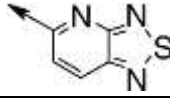
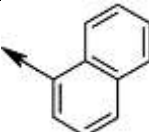
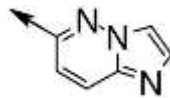
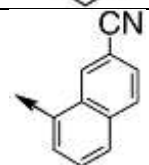
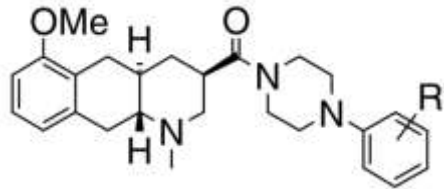
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|----|------------|------|-------|-------|-------|------|------|-------|------|------|
| 56 | -59529.42  | 2.25 | -5.48 | -0.75 | 4.73  | 2.36 | 0.21 | -3.11 | 3.11 | 2.05 |
| 57 | -33384.75  | 3.38 | -5.46 | -0.37 | 5.08  | 2.54 | 0.20 | -2.91 | 2.91 | 1.67 |
| 58 | -41617.18  | 4.80 | -5.52 | -2.74 | 2.78  | 1.39 | 0.36 | -4.13 | 4.13 | 6.13 |
| 59 | -42713.32  | 4.64 | -5.79 | -2.26 | 3.54  | 1.77 | 0.28 | -4.02 | 4.02 | 4.58 |
| 60 | -40559.63  | 4.24 | -5.79 | -2.26 | 3.53  | 1.77 | 0.28 | -4.02 | 4.02 | 4.58 |
| 61 | -50298.12  | 3.78 | -5.65 | -1.50 | 4.15  | 2.07 | 0.24 | -3.58 | 3.58 | 3.09 |
| 62 | -49970.10  | 3.22 | -5.84 | -2.29 | 3.55  | 1.77 | 0.28 | -4.06 | 4.06 | 4.66 |
| 63 | -56556.93  | 4.64 | -5.83 | -2.28 | 3.55  | 1.77 | 0.28 | -4.05 | 4.05 | 4.63 |
| 64 | -64657.54  | 2.79 | -5.86 | -2.30 | 3.56  | 1.78 | 0.28 | -4.08 | 4.08 | 4.68 |
| 65 | -41022.97  | 5.48 | -5.85 | -2.28 | 3.56  | 1.78 | 0.28 | -4.06 | 4.06 | 4.64 |
| 66 | -50298.12  | 3.78 | -5.65 | -1.50 | 4.15  | 2.07 | 0.24 | -3.58 | 3.58 | 3.09 |
| 67 | -50298.12  | 3.78 | -5.65 | -1.50 | 4.15  | 2.07 | 0.24 | -3.58 | 3.58 | 3.09 |
| 68 | -56585.38  | 3.61 | -5.73 | -1.50 | 4.23  | 2.12 | 0.24 | -3.62 | 3.62 | 3.09 |
| 69 | -65225.84  | 2.48 | -5.85 | -1.51 | 4.33  | 2.17 | 0.23 | -3.68 | 3.68 | 3.13 |
| 70 | -71513.08  | 3.84 | -5.79 | -1.51 | 4.29  | 2.14 | 0.23 | -3.65 | 3.65 | 3.11 |
| 71 | -73326.45  | 2.27 | -5.90 | -1.53 | 4.37  | 2.18 | 0.23 | -3.72 | 3.72 | 3.16 |
| 72 | -54135.44  | 4.60 | -5.82 | -2.28 | 3.54  | 1.77 | 0.28 | -4.05 | 4.05 | 4.63 |
| 73 | -111592.59 | 4.55 | -5.82 | -2.28 | 3.54  | 1.77 | 0.28 | -4.05 | 4.05 | 4.63 |
| 74 | -53534.16  | 3.53 | -5.79 | -2.28 | 3.52  | 1.76 | 0.28 | -4.04 | 4.04 | 4.63 |
| 75 | -120261.51 | 4.17 | -5.78 | -1.52 | 4.26  | 2.13 | 0.23 | -3.65 | 3.65 | 3.13 |
| 76 | -53381.86  | 6.31 | -5.68 | -1.51 | 4.16  | 2.08 | 0.24 | -3.60 | 3.60 | 3.11 |
| 77 | -54451.77  | 3.40 | -5.61 | -1.50 | 4.11  | 2.06 | 0.24 | -3.55 | 3.55 | 3.07 |
| 78 | -38355.48  | 4.52 | -5.79 | -2.25 | 3.54  | 1.77 | 0.28 | -4.02 | 4.02 | 4.57 |
| 79 | -35894.93  | 4.48 | -5.25 | -0.33 | 4.92  | 2.46 | 0.20 | -2.79 | 2.79 | 1.59 |
| 80 | -48401.14  | 3.84 | -5.45 | -0.36 | 5.08  | 2.54 | 0.20 | -2.91 | 2.91 | 1.66 |
| 81 | -105858.26 | 3.84 | -5.45 | -0.36 | 5.08  | 2.54 | 0.20 | -2.90 | 2.90 | 1.66 |
| 82 | -46869.73  | 4.98 | -5.44 | -0.54 | -5.44 | 4.90 | 0.20 | -2.99 | 2.45 | 1.83 |
| 83 | -37941.62  | 4.13 | -4.98 | -0.34 | 4.64  | 2.32 | 0.22 | -2.66 | 2.66 | 1.52 |
| 84 | -47800.05  | 5.07 | -5.41 | -0.54 | 4.87  | 2.44 | 0.21 | -2.98 | 2.98 | 1.82 |
| 85 | -49845.56  | 5.20 | -5.48 | -0.67 | 4.82  | 2.41 | 0.21 | -3.08 | 3.08 | 1.96 |
| 86 | -51892.21  | 6.90 | -5.50 | -1.05 | 4.46  | 2.23 | 0.22 | -3.27 | 3.27 | 2.41 |
| 87 | -104788.69 | 3.61 | -5.44 | -0.36 | 5.08  | 2.54 | 0.20 | -2.90 | 2.90 | 1.65 |

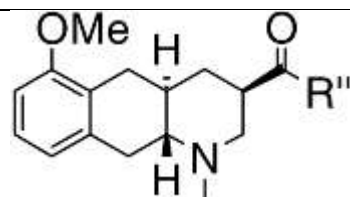
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|-----|------------|------|-------|-------|------|------|------|-------|------|------|
| 88  | -110872.04 | 3.82 | -5.44 | -0.36 | 5.08 | 2.54 | 0.20 | -2.90 | 2.90 | 1.65 |
| 89  | -110137.31 | 3.84 | -5.44 | -0.36 | 5.08 | 2.54 | 0.20 | -2.90 | 2.90 | 1.65 |
| 90  | -110044.05 | 4.49 | -5.46 | -0.38 | 5.08 | 2.54 | 0.20 | -2.92 | 2.92 | 1.68 |
| 91  | -110044.16 | 3.56 | -5.47 | -0.38 | 5.09 | 2.54 | 0.20 | -2.92 | 2.92 | 1.68 |
| 92  | -108746.64 | 2.49 | -5.30 | -0.33 | 4.97 | 2.49 | 0.20 | -2.82 | 2.82 | 1.60 |
| 93  | -109816.38 | 2.57 | -5.30 | -0.33 | 4.97 | 2.49 | 0.20 | -2.81 | 2.81 | 1.59 |
| 94  | -39011.44  | 6.33 | -5.30 | -0.73 | 4.57 | 2.29 | 0.22 | -3.01 | 3.01 | 1.99 |
| 95  | -51517.65  | 4.64 | -5.42 | -0.76 | 4.66 | 2.33 | 0.21 | -3.09 | 3.09 | 2.05 |
| 96  | -108974.77 | 4.78 | -5.42 | -0.76 | 4.66 | 2.33 | 0.21 | -3.09 | 3.09 | 2.05 |
| 97  | -52587.43  | 4.19 | -5.47 | -0.92 | 4.55 | 2.27 | 0.22 | -3.19 | 3.19 | 2.24 |
| 98  | -110044.55 | 4.27 | -5.45 | -0.92 | 4.53 | 2.27 | 0.22 | -3.18 | 3.18 | 2.24 |
| 99  | -47928.20  | 6.75 | -5.34 | -2.24 | 3.09 | 1.55 | 0.32 | -3.79 | 3.79 | 4.65 |
| 100 | -60470.69  | 2.75 | -5.38 | -0.33 | 5.05 | 2.52 | 0.20 | -2.85 | 2.85 | 1.61 |
| 101 | -117927.81 | 2.88 | -5.37 | -0.35 | 5.03 | 2.51 | 0.20 | -2.86 | 2.86 | 1.63 |
| 102 | -41023.15  | 8.17 | -5.35 | -1.93 | 3.42 | 1.71 | 0.29 | -3.64 | 3.64 | 3.88 |
| 103 | -53529.36  | 6.32 | -5.55 | -1.96 | 3.59 | 1.79 | 0.28 | -3.76 | 3.76 | 3.93 |
| 104 | -110986.48 | 6.47 | -5.53 | -1.96 | 3.57 | 1.79 | 0.28 | -3.75 | 3.75 | 3.93 |
| 105 | -53364.78  | 2.45 | -5.42 | -0.33 | 5.08 | 2.54 | 0.20 | -2.87 | 2.87 | 1.62 |
| 106 | -52987.63  | 2.45 | -5.05 | -0.32 | 4.73 | 2.37 | 0.21 | -2.68 | 2.68 | 1.52 |
| 107 | -110444.75 | 5.32 | -5.17 | -0.36 | 4.81 | 2.41 | 0.21 | -2.76 | 2.76 | 1.59 |
| 108 | -49708.66  | 4.54 | -4.98 | -0.77 | 4.21 | 2.11 | 0.24 | -2.87 | 2.87 | 1.96 |
| 109 | -62214.86  | 3.44 | -5.01 | -0.79 | 4.22 | 2.11 | 0.24 | -2.90 | 2.90 | 2.00 |
| 110 | -119671.99 | 3.48 | -5.01 | -0.79 | 4.22 | 2.11 | 0.24 | -2.90 | 2.90 | 2.00 |
| 111 | -44832.50  | 6.78 | -5.91 | -1.96 | 3.96 | 1.98 | 0.25 | -3.94 | 3.94 | 3.92 |
| 112 | -44799.54  | 6.71 | -5.70 | -1.95 | 3.75 | 1.87 | 0.27 | -3.83 | 3.83 | 3.91 |
| 113 | -43751.00  | 7.32 | -5.68 | -2.41 | 3.27 | 1.64 | 0.31 | -4.04 | 4.04 | 4.99 |
| 114 | -53528.48  | 6.00 | -5.70 | -1.97 | 3.73 | 1.87 | 0.27 | -3.83 | 3.83 | 3.94 |
| 115 | -44739.99  | 5.85 | -5.82 | -1.97 | 3.84 | 1.92 | 0.26 | -3.89 | 3.89 | 3.94 |
| 116 | -43130.06  | 5.16 | -5.41 | -2.00 | 3.41 | 1.70 | 0.29 | -3.71 | 3.71 | 4.04 |
| 117 | -43130.06  | 5.16 | -5.41 | -2.00 | 3.41 | 1.70 | 0.29 | -3.71 | 3.71 | 4.04 |
| 118 | -39549.76  | 6.19 | -5.67 | -1.98 | 3.70 | 1.85 | 0.27 | -3.82 | 3.82 | 3.96 |
| 119 | -39549.83  | 6.21 | -5.77 | -1.98 | 3.79 | 1.90 | 0.26 | -3.87 | 3.87 | 3.95 |

|     |           |      |       |       |      |      |      |       |      |      |
|-----|-----------|------|-------|-------|------|------|------|-------|------|------|
| 120 | -42725.73 | 6.52 | -5.95 | -1.96 | 3.99 | 1.99 | 0.25 | -3.96 | 3.96 | 3.92 |
| 121 | -44832.92 | 6.19 | -5.85 | -1.97 | 3.88 | 1.94 | 0.26 | -3.91 | 3.91 | 3.94 |
| 122 | -45902.72 | 6.15 | -5.85 | -1.97 | 3.88 | 1.94 | 0.26 | -3.91 | 3.91 | 3.95 |
| 123 | -45856.49 | 7.12 | -5.74 | -2.42 | 3.33 | 1.66 | 0.30 | -4.08 | 4.08 | 5.00 |
| 124 | -46938.50 | 6.36 | -5.67 | -1.96 | 3.71 | 1.85 | 0.27 | -3.82 | 3.82 | 3.93 |
| 125 | -49634.67 | 2.68 | -5.37 | -0.79 | 4.59 | 2.29 | 0.22 | -3.08 | 3.08 | 2.07 |
| 126 | -49634.85 | 4.01 | -5.73 | -0.74 | 4.99 | 2.50 | 0.20 | -3.24 | 3.24 | 2.10 |
| 127 | -49634.54 | 3.29 | -5.63 | -0.72 | 4.91 | 2.46 | 0.20 | -3.17 | 3.17 | 2.05 |
| 128 | -62140.87 | 2.48 | -5.61 | -0.77 | 4.84 | 2.42 | 0.21 | -3.19 | 3.19 | 2.10 |
| 129 | -39828.75 | 3.28 | -5.39 | -0.86 | 4.53 | 2.27 | 0.22 | -3.13 | 3.13 | 2.15 |
| 130 | -41957.80 | 3.34 | -5.44 | -0.82 | 4.63 | 2.31 | 0.22 | -3.13 | 3.13 | 2.12 |
| 131 | -42528.86 | 3.10 | -5.45 | -0.76 | 4.69 | 2.35 | 0.21 | -3.11 | 3.11 | 2.06 |
| 132 | -46299.90 | 2.95 | -5.78 | -0.76 | 5.01 | 2.51 | 0.20 | -3.27 | 3.27 | 2.13 |
| 133 | -46299.79 | 4.04 | -5.57 | -0.76 | 4.81 | 2.40 | 0.21 | -3.17 | 3.17 | 2.08 |
| 134 | -39828.75 | 1.95 | -5.29 | -0.74 | 4.55 | 2.28 | 0.22 | -3.02 | 3.02 | 2.00 |
| 135 | -39638.50 | 5.30 | -5.74 | -1.21 | 4.53 | 2.26 | 0.22 | -3.47 | 3.47 | 2.66 |
| 136 | -39267.92 | 3.45 | -5.55 | -0.70 | 4.85 | 2.42 | 0.21 | -3.13 | 3.13 | 2.02 |
| 137 | -40681.68 | 3.53 | -5.41 | -0.77 | 4.64 | 2.32 | 0.22 | -3.09 | 3.09 | 2.06 |
| 138 | -41117.74 | 2.36 | -5.43 | -1.50 | 3.93 | 1.96 | 0.25 | -3.46 | 3.46 | 3.06 |
| 139 | -42952.92 | 1.79 | -5.17 | -0.82 | 4.35 | 2.18 | 0.23 | -2.99 | 2.99 | 2.06 |
| 140 | -42151.63 | 1.41 | -4.92 | -0.74 | 4.18 | 2.09 | 0.24 | -2.83 | 2.83 | 1.92 |
| 141 | -41580.99 | 1.78 | -5.75 | -1.28 | 4.47 | 2.24 | 0.22 | -3.51 | 3.51 | 2.76 |
| 142 | -42258.52 | 2.72 | -4.85 | -0.72 | 4.13 | 2.06 | 0.24 | -2.79 | 2.79 | 1.88 |
| 143 | -44575.41 | 1.68 | -5.41 | -0.33 | 5.08 | 2.54 | 0.20 | -2.87 | 2.87 | 1.62 |
| 144 | -44198.22 | 1.35 | -4.91 | -0.31 | 4.60 | 2.30 | 0.22 | -2.61 | 2.61 | 1.48 |

**Table S7:** Chemical structures and biological activities of SSTR1 antagonists selected for the study

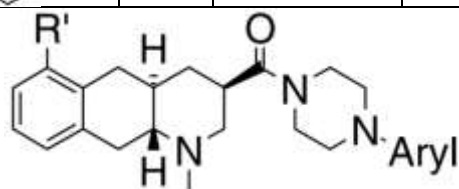
|  |   |        |          |   |        |
|--|---|--------|----------|---|--------|
| Octahydrobenzo[g]quinoline derivatives (arylpiperazines, not phenylpiperazines)    |   |        |          |   |        |
| Compound   | R   | $pK_d$ | Compound | R   | $pK_d$ |
| 1  |    | 7.76   | 13       |    | 6.16   |
| 2  |    | 5.73   | 14       |    | 7.58   |
| 3  |    | 7.28   | 15       |    | 6.54   |
| 4  |    | 6.33   | 16       |    | 8.24   |
| 5  |   | 8.45   | 17       |   | 6.45   |
| 6  |  | 6.98   | 18       |  | 8.44   |
| 7  |  | 6.25   | 19       |  | 8.77   |
| 8  |  | 6.98   | 20       |  | 8.56   |

| 9  |  | 8.12                  | 21       |  | 7.97                  |
|--|---|-----------------------|----------|---|-----------------------|
| 10   |  | 8.74                  | 22       |  | 8.91                  |
| 11   |  | 7.06                  | 23       |  | 7.06                  |
| 12   |  | 8.06                  |          |   |                       |
|  |   |                       |          |   |                       |
| <b>Octahydrobenzo[g]quinoline derivatives (phenylpiperazines)</b>                  |   |                       |          |   |                       |
| Compound   | R'  | <i>pK<sub>d</sub></i> | Compound | R'  | <i>pK<sub>d</sub></i> |
| 24   | 2-F   | 7.75                  | 36       | 4-CO <sub>2</sub> Me  | 6.79                  |
| 25   | 3-F   | 8.48                  | 37       | 4-CONH <sub>2</sub>   | 5.82                  |
| 26   | 4-F   | 8.47                  | 38       | 4-CONEt <sub>2</sub>  | 5.77                  |
| 27   | 2-CN  | 8.70                  | 39       | 4-CO <sub>2</sub> Na  | 4.09                  |
| 28   | 4-CN  | 8.09                  | 40       | 4-SO <sub>2</sub> Me  | 6.20                  |
| 29   | 2-NO <sub>2</sub>   | 8.89                  | 41       | 4-SO <sub>2</sub> NH <sub>2</sub>   | 6.23                  |
| 30   | 3-NO <sub>2</sub>   | 8.88                  | 42       | 3,4-F <sub>2</sub>  | 9.13                  |
| 31   | 4-NO <sub>2</sub>   | 9.15                  | 43       | 2-CN-3-F  | 8.55                  |
| 32   | 3-CF <sub>3</sub>   | 7.63                  | 44       | 2-CN-4-NO <sub>2</sub>  | 8.49                  |
| 33   | 4-CF <sub>3</sub>   | 6.56                  | 45       | 2-NO <sub>2</sub> -4-CF <sub>3</sub>  | 6.96                  |
| 34   | 4-OH  | 6.20                  | 46       | 2-SO <sub>2</sub> Me-4-NO <sub>2</sub>  | 8.76                  |
| 35   | 4-COMe  | 6.82                  |          |   |                       |



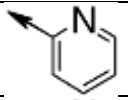
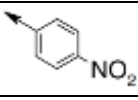
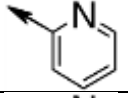
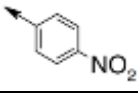
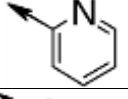
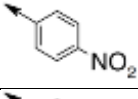
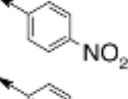
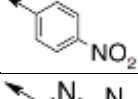
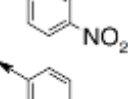
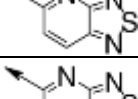
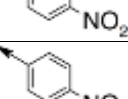
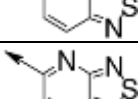
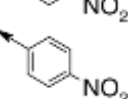
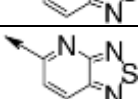
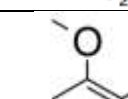
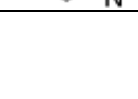
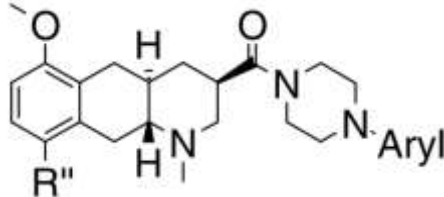
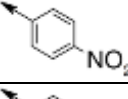
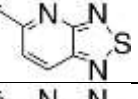
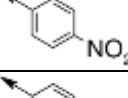
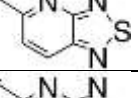
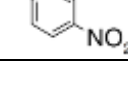
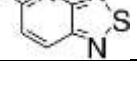
octahydrobenzo[g]quinoline derivatives (cyclic tertiary amides, not piperazines)

| Compound | R'' | $pK_d$ | Compound | R'' | $pK_d$ |
|----------|-----|--------|----------|-----|--------|
| 47       |     | 6.68   | 52       |     | 6.31   |
| 48       |     | 6.58   | 53       |     | 7.15   |
| 49       |     | 7.09   | 54       |     | 6.34   |
| 50       |     | 7.52   | 55       |     | 4.98   |
| 51       |     | 6.31   |          |     |        |

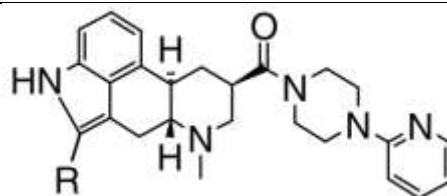


Octahydrobenzo[g]quinoline derivatives having variations at position 6

| Compound | R' | Aryl | $pK_d$ | Compound | R' | Aryl | $pK_d$ |
|----------|----|------|--------|----------|----|------|--------|
|----------|----|------|--------|----------|----|------|--------|

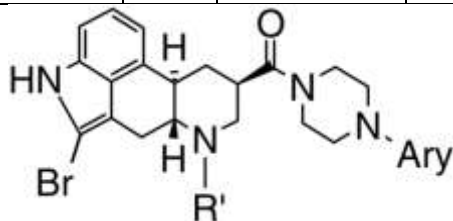
|   |                                   |   |                       |                 |                                   |   |                       |
|---|-----------------------------------|---|-----------------------|-----------------|-----------------------------------|---|-----------------------|
| 56  | -OSO <sub>2</sub> CF <sub>3</sub> |    | 8.85                  | 64              | -OSO <sub>2</sub> CF <sub>3</sub> |    | 8.81                  |
| 57  | -H                                |    | 6.80                  | 65              | -CN                               |    | 7.80                  |
| 58  | -OMe                              |    | 9.15                  | 66              | -COMe                             |    | 8.22                  |
| 59  | -Oi-Pr                            |    | 9.09                  | 67              | -OMe                              |    | 8.91                  |
| 60  | -OH                               |    | 7.73                  | 68              | -OBn                              |    | 8.92                  |
| 61  | -OCOt-Bu                          |    | 7.60                  | 69              | -OSO <sub>2</sub> Me              |    | 9.67                  |
| 62  | -OCO <sub>2</sub> t-Bu            |    | 8.32                  | 70              | -OSO <sub>2</sub> p-Tol           |    | 9.24                  |
| 63  | -OSO <sub>2</sub> Me              |    | 9.39                  | 71              | -OSO <sub>2</sub> CF <sub>3</sub> |    | 9.40                  |
|  |                                   |   |                       |                 |                                   |   |                       |
| <b>Octahydrobenzo[g]quinoline derivatives having variations at position 9</b>       |                                   |   |                       |                 |                                   |   |                       |
| <b>Compound</b>   | <b>R''</b>                        | <b>Aryl</b>   | <b>pK<sub>d</sub></b> | <b>Compound</b> | <b>R''</b>                        | <b>Aryl</b>   | <b>pK<sub>d</sub></b> |
| 72  | -Cl                               |  | 8.45                  | 75              | -Br                               |  | 8.92                  |
| 73  | -Br                               |  | 8.34                  | 76              | -CHO                              |  | 9.08                  |
| 74  | -SMe                              |  | 8.10                  | 77              | -COMe                             |  | 7.46                  |





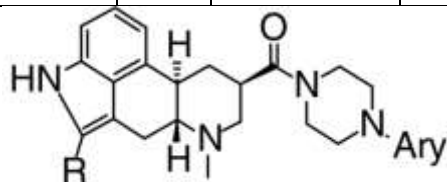
**Ergoline derivatives with variations at position 2**

| Compound | R   | $pK_d$ | Compound | R                   | $pK_d$ |
|----------|-----|--------|----------|---------------------|--------|
| 78       | -H  | 7.85   | 82       | -OH                 | 6.62   |
| 79       | -Cl | 7.89   | 83       | -SMe                | 8.62   |
| 80       | -Br | 8.35   | 84       | -SOMe               | 5.58   |
| 81       | -I  | 7.78   | 85       | -SO <sub>2</sub> Me | 6.51   |



**Ergoline derivatives with variations at position 6**

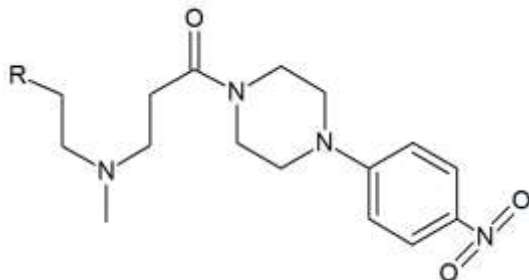
| Compound | R'            | Aryl      | $pK_d$ | Compound | R'  | Aryl            | $pK_d$ |
|----------|---------------|-----------|--------|----------|-----|-----------------|--------|
| 86       | -H            | 2-Pyridyl | 6.77   | 90       |     | 2-Pyridyl       | 5.63   |
| 87       | - <i>n</i> Bu | 2-Pyridyl | 5.94   | 91       | -Me | 3,4-Di-F-phenyl | 9.31   |
| 88       |               | 2-Pyridyl | 5.76   | 92       | -Et | 3,4-Di-F-phenyl | 9.01   |
| 89       |               | 2-Pyridyl | 5.83   |          |     |                 |        |



**Ergoline derivatives with variations of piperazine substituent**

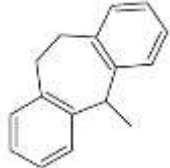
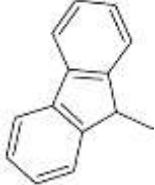
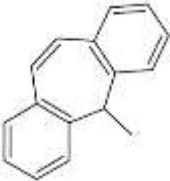
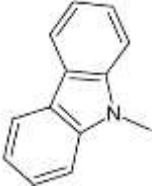
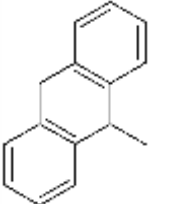
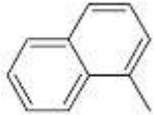
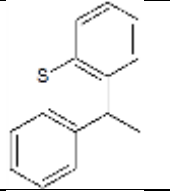
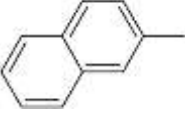
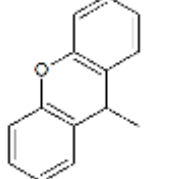
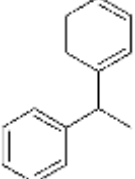
| Compound | R | Aryl | $pK_d$ | Compound | R | Aryl | $pK_d$ |
|----------|---|------|--------|----------|---|------|--------|
|----------|---|------|--------|----------|---|------|--------|

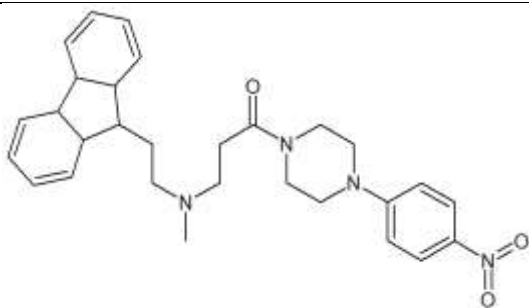
|     |     |  |      |     |     |  |      |
|-----|-----|--|------|-----|-----|--|------|
| 93  | -H  |  | 9.12 | 102 | -Cl |  | 8.90 |
| 94  | -Cl |  | 9.41 | 103 | -Br |  | 8.87 |
| 95  | -Br |  | 9.69 | 104 | -Cl |  | 9.22 |
| 96  | -Cl |  | 9.42 | 105 | -Br |  | 9.31 |
| 97  | -Br |  | 9.55 | 106 | -Cl |  | 9.41 |
| 98  | -H  |  | 7.71 | 107 | -Br |  | 9.43 |
| 99  | -Cl |  | 8.38 | 108 | -H  |  | 8.99 |
| 100 | -Br |  | 8.26 | 109 | -Cl |  | 9.62 |
| 101 | -H  |  | 8.41 | 110 | -Br |  | 9.43 |



**$\beta$ -alanine piperazine amide derivatives with modifications at the polycyclic moiety**

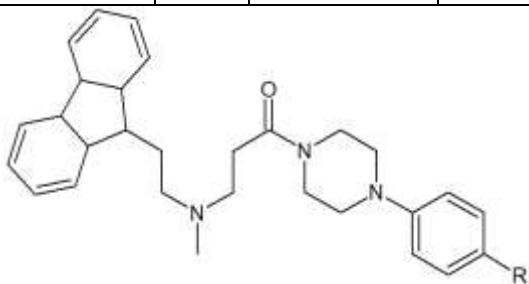
| Compound | R | $pK_d$ | Compound | R | $pK_d$ |
|----------|---|--------|----------|---|--------|
|----------|---|--------|----------|---|--------|

|     |  |      |     |  |      |
|-----|--|------|-----|--|------|
| 111 |   | 7.74 | 116 |   | 9.15 |
| 112 |   | 7.94 | 117 |   | 6.48 |
| 113 |   | 7.53 | 118 |   | 7.11 |
| 114 |   | 7.90 | 119 |   | 6.56 |
| 115 |  | 9.05 | 120 |  | 7.86 |

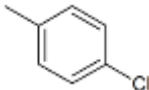
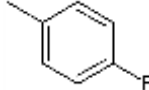
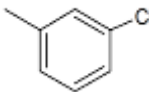
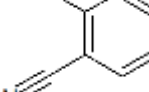
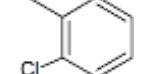
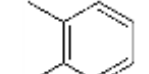


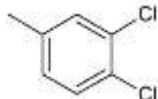
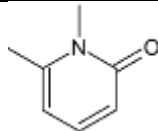
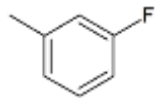
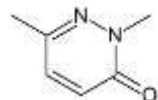
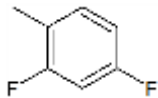
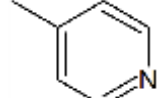
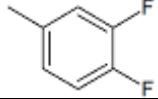
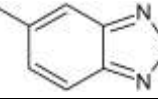
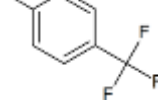
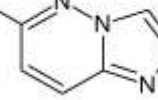
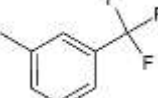
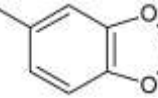
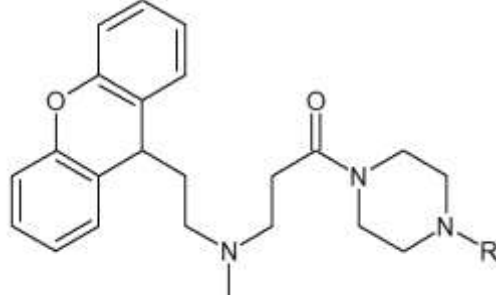
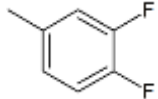
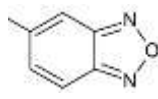
**Fluorene derivatives with modifications at the alkyl moiety**

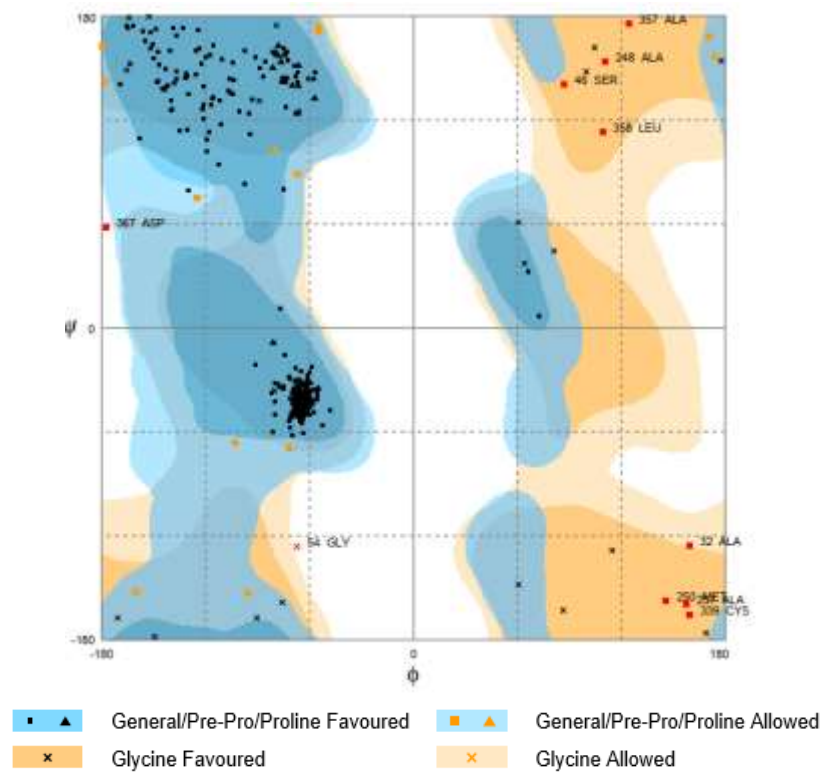
| Compound | R'          | $pK_d$ | Compound | R'                           | $pK_d$ |
|----------|-------------|--------|----------|------------------------------|--------|
| 121      | Et          | 9.02   | 123      | Allyl                        | 8.15   |
| 122      | <i>i</i> Pr | 8.33   | 124      | -CH <sub>2</sub> <i>c</i> Pr | 7.34   |



**Fluorene derivatives with modified arylpiperazine moieties**

| Compound | R   | $pK_d$ | Compound | R   | $pK_d$ |
|----------|---|--------|----------|---|--------|
| 125      |  | 8.77   | 134      |  | 8.71   |
| 126      |  | 7.75   | 135      |  | 8.34   |
| 127      |  | 7.62   | 136      |  | 6.00   |

|   |   |      |     |   |      |
|---|---|------|-----|---|------|
| 128   |    | 8.72 | 137 |    | 8.67 |
| 129   |    | 8.44 | 138 |    | 8.18 |
| 130   |    | 8.48 | 139 |    | 7.67 |
| 131   |    | 9.24 | 140 |    | 9.13 |
| 132   |    | 7.50 | 141 |    | 8.96 |
| 133   |    | 7.21 | 142 |    | 8.34 |
|  |   |      |     |   |      |
| 143   |  | 9.11 | 144 |  | 9.49 |

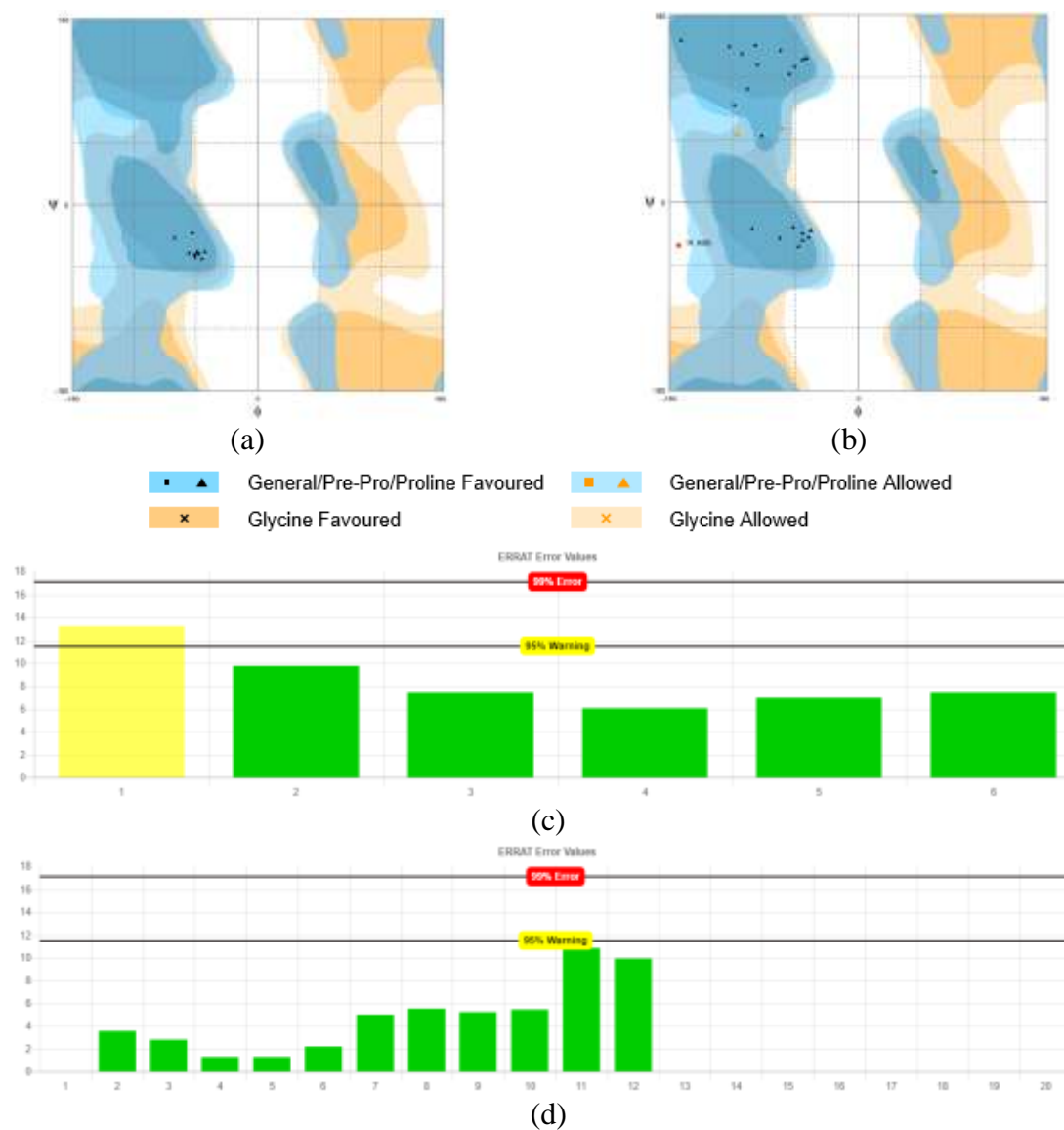


(a)

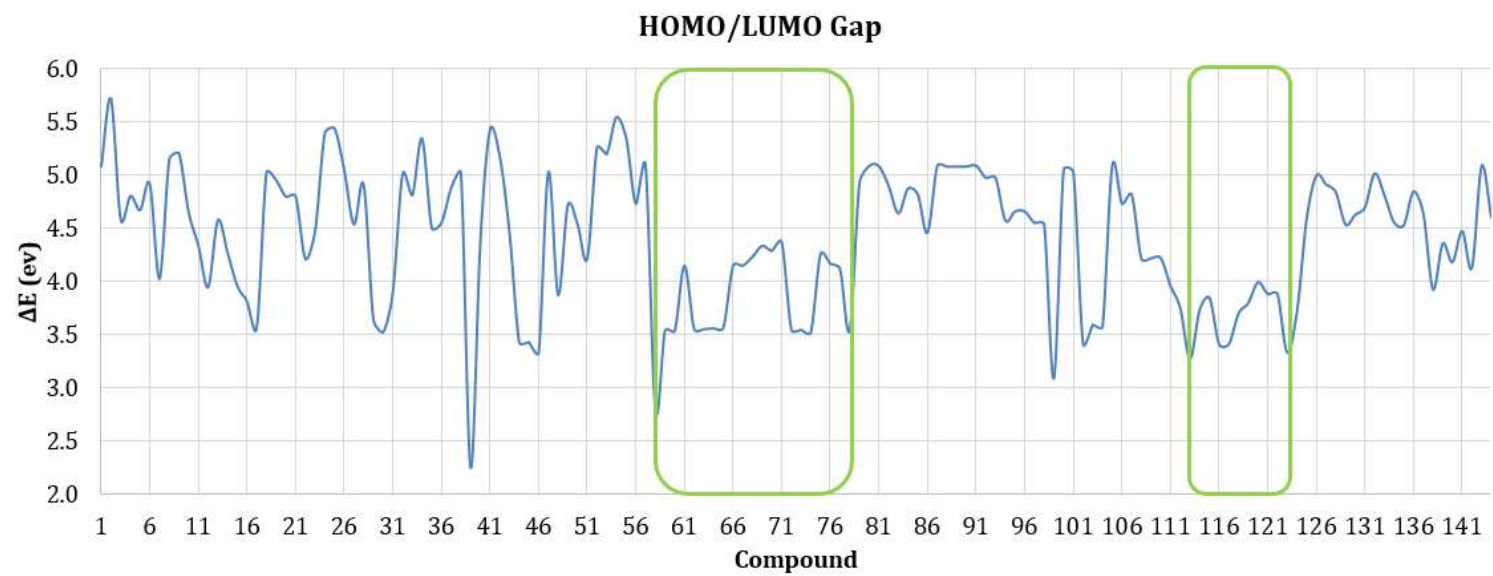


(b)

**Figure S1.** (a) Ramachandran plot of model **08** (b) ERRAT plot of SSTR1 model **08**.

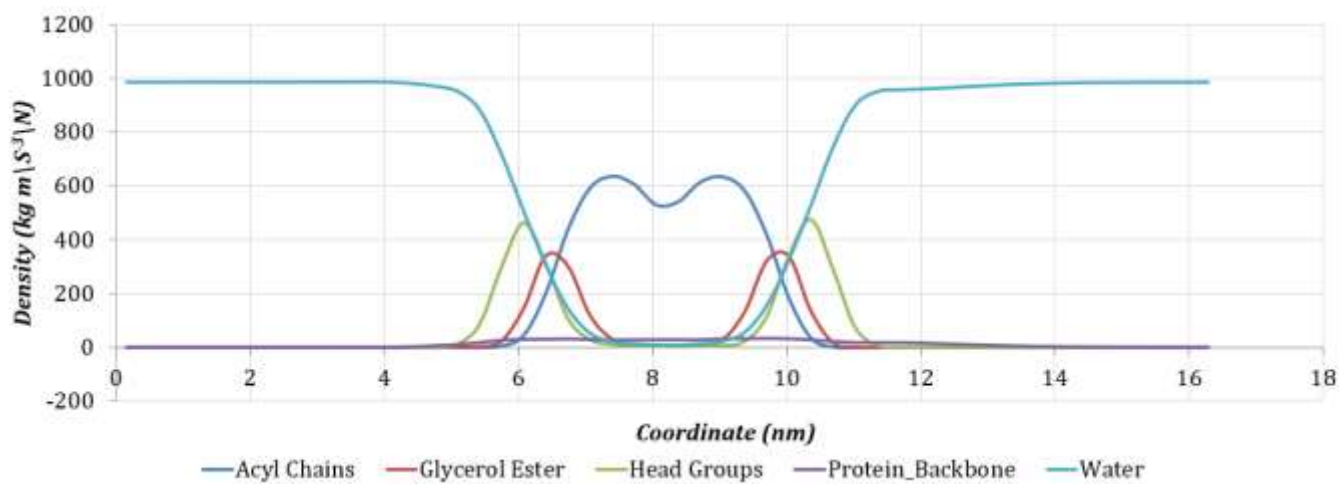


**Figure S2.** (a and b) Ramachandran plot (c and d) ERRAT plot of the selected homology models of Cortistatin-14 and SRIF-28 respectively

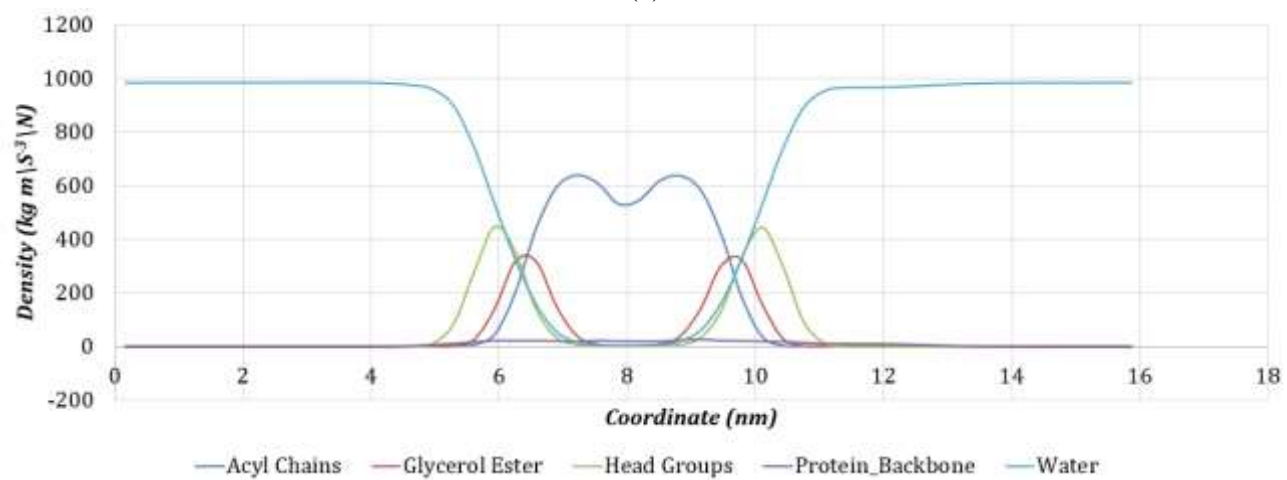


**Figure S3.** Energy gap ( $\Delta E$ ) distribution of molecules

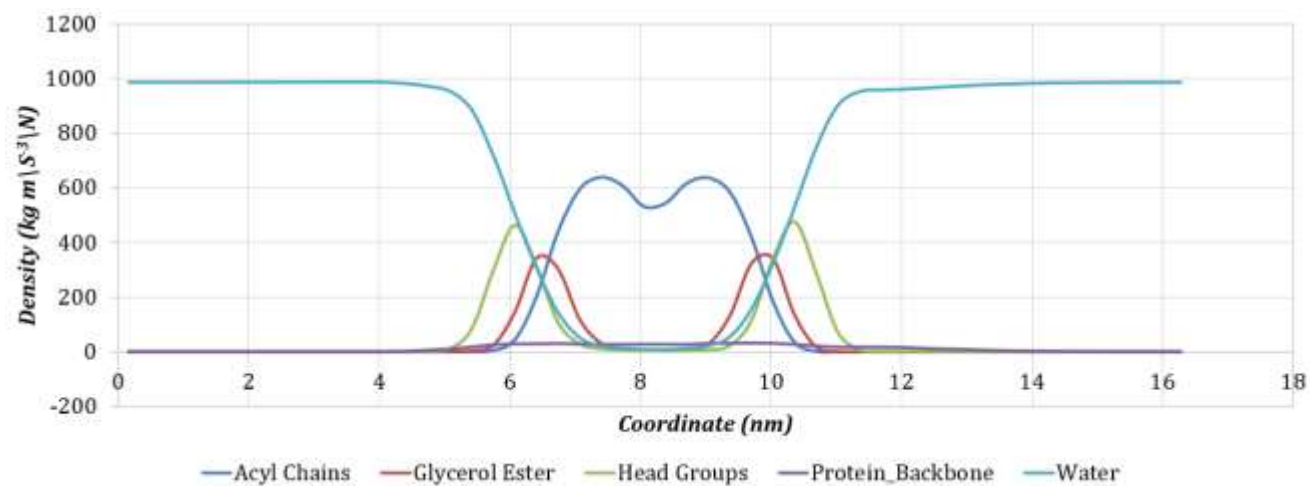




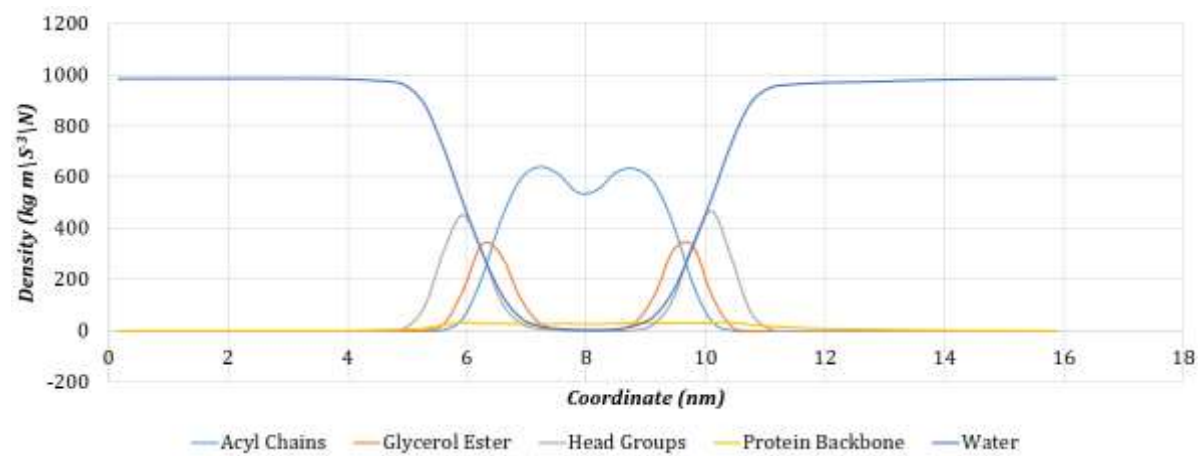
(a)



(b)

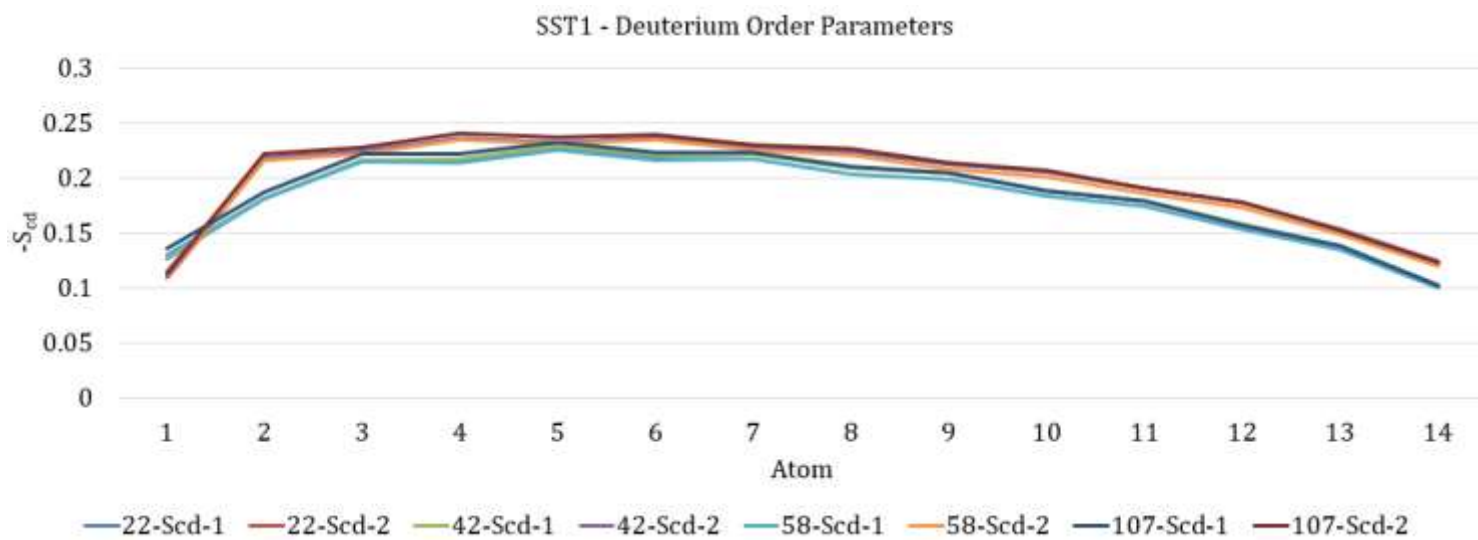


(c)



(d)

**Figure S4.** Average density of different membrane components over the simulation time with (a) compound **22** (b) compound **42** (c) compound **58** (d) compound **107**



**Figure S5.** Comparison of deuterium order parameters of each simulated system.

