# Supplementary Information

**Table S1.** Original parameter of docking data for the compounds from training set.

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Androstenedione** | | | | | | | |
| 1 | 2.04 | − | − | − | −31.4616 | 3 | 6-Hydroxylation |
| 2 | 6.67 | $H_2O$619 Ser119 | + | + | −30.8448 | 6 | |
| 3 | 2.45 | − | + | + | −29.0663 | 16 | |
| 4 | 9.03 | − | − | − | −28.568 | 7 | |
| 5 | 2.71 | − | + | + | −28.321 | 16 | |
| 6 | 8.83 | − | − | − | −27.9362 | 7 | |
| 7 | 8.96 | − | − | − | −27.3553 | 10-Methyl | |
| 8 | 9.52 | − | − | − | −27.0542 | 10-Methyl | |
| 9 | 4.07 | − | + | − | −26.5437 | 16 | |
| 10 | 9.32 | − | − | − | −25.3265 | 7 | |
| **Boldenone** | | | | | | | |
| 1 | 3.66 | $H_2$0637 | − | − | −31.5316 | 3 | 6-Hydroxylation |
| 2 | 9.65 | − | − | − | −31.2291 | 10-Methyl | |
| 3 | 2.75 | − | + | − | −28.3998 | 2 | |
| 4 | 5.76 | − | − | + | −28.3105 | 15 | |
| 5 | 4.34 | Arg105 Ala305 Ile301 | + | − | −25.634 | 12 | |
| 6 | 3.89 | $H_2$0637 | − | − | −25.5377 | 3 | |
| 7 | 10.32 | − | − | − | −24.353 | 7 | |
| 8 | 6.76 | − | − | − | −23.5347 | 16 | |
| 9 | 3.04 | − | + | + | −22.6789 | 6 | |
| 10 | 10.56 | − | − | − | −21.8564 | 7 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Budesonide** | | | | | | | |
| 1 | 2.18 | $H_2O$623 | − | + | −37.2385 | 27 | 6-Hydroxylation |
| 2 | 2.96 | − | − | − | −36.8346 | 25 | |
| 3 | 3.89 | Arg105 GLu374 | + | − | −36.538 | 3 | |
| 4 | 3.08 | − | − | − | −36.4359 | 25 | |
| 5 | 3.54 | Arg105 | + | − | −36.394 | 3 | |
| 6 | 3.59 | Arg105 GLu374 | + | − | −36.3256 | 3 | |
| 7 | 3.95 | − | − | − | −36.2559 | 3 | |
| 8 | 2.32 | $H_2O$623 | − | + | −36.163 | 27 | |
| 9 | 4.28 | $H_2$0637 | + | + | −36.1132 | 6 | |
| 10 | 4.23 | Arg105 GLu374 | + | − | −36.0791 | 3 | |
| **Cholesterol** | | | | | | | |
| 1 | 2.3 | $H_2O$637 $H_2O$619 Arg372 | − | + | −39.8893 | 23 | 4-Hydroxylation |
| 2 | 2.35 | $H_2O$619 Arg372 heme | − | − | −39.4872 | 26 | |
| 3 | 3.77 | − | − | − | −39.3215 | 23 | |
| 4 | 2.38 | − | − | − | −39.3057 | 26 | |
| 5 | 3.12 | $H_2O$619 Arg372 | − | + | −39.1173 | 24 | |
| 6 | 9.38 | − | − | − | −39.0149 | 7 | |
| 7 | 3.91 | − | − | − | −38.8462 | 23 | |
| 8 | 3.04 | − | + | + | −38.7725 | 4 | |
| 9 | 4.6 | − | − | − | −38.5956 | 23 | |
| 10 | 10.08 | − | − | − | −38.5865 | 7 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Cinobufagin** | | | | | | | |
| 1 | 6.32 | Glu308 | − | + | −33.4728 | 5 | 1,5-Hydroxylation |
| 2 | 5.7 | − | − | + | −33.2657 | 5 | |
| 3 | 3.96 | Heme | − | − | −33.0704 | 3 | |
| 4 | 3.07 | − | + | − | −32.7474 | 16-Benzene ring | |
| 5 | 8.25 | − | − | − | −32.7373 | 10-Methyl | |
| 6 | 4.21 | Heme | − | − | −32.5876 | 3 | |
| 7 | 3.53 | − | + | − | −32.4844 | 16-Benzene ring | |
| 8 | 8.76 | − | − | − | −32.4595 | 13-Methyl | |
| 9 | 4.65 | − | − | − | −32.2311 | 3 | |
| 10 | 9.25 | − | − | − | −32.1357 | 10-Methyl | |
| **Corticosterone** | | | | | | | |
| 1 | 1.99 | Leu210 | − | − | −38.8151 | 3 | 6-Hydroxylation |
| 2 | 3.9 | Leu210 | − | − | −37.6235 | 3 | |
| 3 | 3.91 | − | − | − | −36.2652 | 3 | |
| 4 | 2.18 | $H_2$0637 heme | − | − | −34.7941 | 20 | |
| 5 | 3.94 | Leu210 | − | − | −34.6832 | 3 | |
| 6 | 3.21 | $H_2$0637 heme | − | − | −34.2786 | 20 | |
| 7 | 5.62 | Arg105 Glu308 Gln484 | − | − | −34.1306 | 6 | |
| 8 | 5.18 | $H_2$0637 | − | − | −33.7562 | 20 | |
| 9 | 7.25 | Heme | − | − | −33.4578 | 20 | |
| 10 | 7.64 | $H_2$0637 heme | − | − | −33.1325 | 20 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Cortisol** | | | | | | | |
| 1 | 6.46 | − | + | − | −33.9684 | 17 | 6-Hydroxylation |
| 2 | 6.49 | − | + | − | −33.2572 | 17 | |
| 3 | 6.85 | − | − | − | −32.5628 | 17 | |
| 4 | 8.23 | − | − | − | −31.7041 | 7 | |
| 5 | 6.79 | − | + | − | −31.3267 | 17 | |
| 6 | 4.09 | − | − | + | −31.0709 | 6 | |
| 7 | 4.23 | − | − | + | −30.8649 | 6 | |
| 8 | 7.23 | − | − | − | −30.695 | 18 | |
| 9 | 7.24 | − | − | − | −30.3425 | 18 | |
| 10 | 8.03 | − | − | − | −30.125 | 18 | |
| **Cyproterone Acetate** | | | | | | | |
| 1 | 6.87 | − | + | + | −35.968 | 15 | 15-Hydroxylation |
| 2 | 9.51 | − | − | − | −35.6617 | 10-Methyl | |
| 3 | 5.11 | $H_2O637$ | − | − | −35.4992 | 3 | |
| 4 | 928 | − | − | − | −35.1236 | 7 | |
| 5 | 5.24 | − | + | + | −34.9375 | 3 | |
| 6 | 10.25 | − | − | − | −34.6228 | 10-Methyl | |
| 7 | 9.87 | − | − | − | −33.8329 | 10-Methyl | |
| 8 | 10.63 | − | − | − | −33.1345 | 10-Methyl | |
| 9 | 10.08 | − | − | − | −32.6743 | 7 | |
| 10 | 10.35 | − | − | − | −32.4228 | 7 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Dexamethasone** | | | | | | | |
| 1 | 5.28 | Arg105 | − | + | −30.6036 | 6 | 6-Hydroxylation |
| 2 | 5.63 | Arg105 | − | + | −30.5376 | 6 | |
| 3 | 4.43 | $H_2O$637 Glu74 | − | + | −30.4537 | 4 | |
| 4 | 5.54 | Arg105 | − | − | −30.2758 | 6 | |
| 5 | 4.54 | $H_2O$637 Glu74 | − | + | −30.1045 | 4 | |
| 6 | 3.68 | $H_2O$637 | − | − | −29.9487 | 2 | |
| 7 | 5.94 | − | − | + | −29.753 | 6 | |
| 8 | 6.09 | Arg105 | − | + | −29.6432 | 6 | |
| 9 | 5.83 | − | − | − | −29.5415 | 4 | |
| 10 | 2.48 | − | − | − | −29.4292 | 22 | |
| **DHEA** | | | | | | | |
| 1 | 7.79 | Ser119 Val240 | − | − | −38.1107 | 10-Methyl | 7-Hydroxylation |
| 2 | 5.53 | Ser119 | − | − | −36.3542 | 10-Methyl | |
| 3 | 7.92 | Ser119 Val240 | − | − | −34.9812 | 10-Methyl | |
| 4 | 8.05 | Ser119 Glu308 | + | + | −33.1552 | 7 | |
| 5 | 7.98 | − | − | − | −31.8528 | 3 | |
| 6 | 8 | Ser119 Val 240 | − | − | −30.4589 | 10-Methyl | |
| 7 | 8.12 | − | − | − | −29.6338 | 3 | |
| 8 | 4.81 | Arg372 | − | + | −28.8657 | 13 | |
| 9 | 3.04 | Arg106 Glu374 | + | + | −28.7962 | 16 | |
| 10 | 8.23 | − | − | − | −27.8442 | 3 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Dihydrotestosterone** | | | | | | | |
| 1 | 8.94 | − | − | − | −28.671 | 10-Methyl | 5-Hydroxylation |
| 2 | 8.85 | − | − | − | −27.4635 | 10-Methyl | |
| 3 | 4.21 | − | + | − | −26.3921 | 3 | |
| 4 | 2.6 | − | + | − | −26.0321 | 13-Methyl | |
| 5 | 8.29 | − | + | − | −25.5539 | 3 | |
| 6 | 8.65 | − | − | − | −24.963 | 7 | |
| 7 | 9.21 | − | − | − | −24.1265 | 7 | |
| 8 | 9.44 | − | − | − | −23.568 | 10-Methyl | |
| 9 | 6.78 | Arg372 | + | − | −23.1156 | 5 | |
| 10 | 9.78 | − | − | − | −22.2897 | 10-Methyl | |
| **Epitesterone** | | | | | | | |
| 1 | 7.3 | Leu210 | + | + | −33.0614 | 6 | 6-Hydroxylation |
| 2 | 3.46 | − | − | − | −32.8545 | 3 | |
| 3 | 4.39 | − | − | − | −32.4326 | 3 | |
| 4 | 4.39 | heme | + | − | −31.9293 | 17 | |
| 5 | 7.5 | − | − | − | −31.5436 | 6 | |
| 6 | 4.89 | − | − | − | −30.6887 | 3 | |
| 7 | 4.92 | heme | + | − | −29.7235 | 17 | |
| 8 | 8.52 | Ile369 Leu483 | − | − | −28.7048 | 10-Methyl | |
| 9 | 5.04 | − | − | − | −28.3235 | 3 | |
| 10 | 5.88 | − | − | − | −27.6542 | 3 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Eplerenone** | | | | | | | |
| 1 | 1.85 | Thr309 | − | − | −35.7939 | 2 | 6,21-Hydroxylation |
| 2 | 1.92 | Thr309 | − | − | −35.3216 | 2 | |
| 3 | 2.32 | − | − | − | −34.6532 | 2 | |
| 4 | 2.05 | Thr309 | − | − | −34.1503 | 2 | |
| 5 | 3.75 | − | − | − | −33.4281 | 2 | |
| 6 | 3.87 | Ser119 | + | − | −32.7908 | 3 | |
| 7 | 3.85 | − | − | + | −32.597 | 21 | |
| 8 | 4.03 | − | − | − | −32.4978 | 21 | |
| 9 | 4.36 | − | − | + | −31.9885 | 21 | |
| 10 | 4.72 | $H_2$0637 Thr637 | − | − | −31.5642 | 6 | |
| **Finasteride** | | | | | | | |
| 1 | 4.72 | Arg372 | − | − | −34.3664 | T-Butyl | T-Butyl-Oxidation |
| 2 | 2.55 | − | − | − | −33.5396 | 19 | |
| 3 | 2.01 | − | + | − | −32.7063 | 3 | |
| 4 | 4.7 | − | − | − | −32.6547 | T-Butyl | |
| 5 | 8.36 | Arg105 | − | − | −32.6214 | 13-Methyl | |
| 6 | 4.01 | − | − | − | −32.6018 | 4 | |
| 7 | 4.72 | Arg105 | − | − | −32.4325 | T-Butyl | |
| 8 | 4.93 | − | − | − | −32.123 | T-Butyl | |
| 9 | 2.87 | − | + | − | −31.8776 | 3 | |
| 10 | 4.47 | − | − | − | −31.6314 | 19 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Medroxyprogesterone** | | | | | | | |
| 1 | 8.32 | − | − | − | −30.3548 | 10-Methyl | 1,2,6-Hydroxylation |
| 2 | 3.25 | $H_2O$623 Arg105 | − | + | −29.7153 | 6 | |
| 3 | 9.23 | − | − | − | −28.6432 | 13-Methyl | |
| 4 | 9.76 | − | − | − | −27.7032 | 10-Methyl | |
| 5 | 9.56 | − | − | − | −26.3215 | 10-Methyl | |
| 6 | 4.04 | − | + | − | −25.892 | 2 | |
| 7 | 3.97 | − | + | − | −25.1325 | 2 | |
| 8 | 5.65 | − | − | − | −24.3216 | 19 | |
| 9 | 4.32 | − | − | − | −23.6879 | 23 | |
| 10 | 4.79 | − | − | − | −22.3216 | 23 | |
| **Metandienone** | | | | | | | |
| 1 | 4.43 | Arg372 | + | − | −34.0604 | 3 | 6-Hydroxylation |
| 2 | 9.32 | − | − | − | −33.7855 | 7 | |
| 3 | 3.09 | $H_2$0637 | − | + | −32.4879 | 13-Methyl | |
| 4 | 3.38 | $H_2$0637 | − | + | −32.0393 | 13-Methyl | |
| 5 | 9.79 | − | − | − | −31.6541 | 10-Methyl | |
| 6 | 9.68 | − | − | − | −30.9864 | 10-Methyl | |
| 7 | 3.33 | − | + | − | −30.2339 | 17-Methyl | |
| 8 | 3.86 | − | − | + | −30.1732 | 6 | |
| 9 | 10.23 | − | − | − | −29.654 | 7 | |
| 10 | 5.19 | − | + | − | −28.8697 | 17-Methyl | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Methyltesterone** | | | | | | | |
| 1 | 9.24 | − | − | − | −35.3666 | 3 | 6-Hydroxylation |
| 2 | 9.38 | − | − | − | −33.3371 | 10-Methyl | |
| 3 | 3.85 | − | + | + | −32.7932 | 6 | |
| 4 | 9.79 | − | − | − | −32.1546 | 13-Methyl | |
| 5 | 4.18 | − | + | + | −30.4565 | 6 | |
| 6 | 10.23 | − | − | − | −29.7834 | 13-Methyl | |
| 7 | 6.99 | Arg372 | + | − | −29.3065 | 2 | |
| 8 | 10.85 | − | − | − | −28.8945 | 13-Methyl | |
| 9 | 10.97 | − | − | − | −28.2346 | 10-Methyl | |
| 10 | 11.05 | − | − | − | −27.5648 | 10-Methyl | |
| **Pregnenolone** | | | | | | | |
| 1 | 1.98 | Leu210 | − | − | −35.0142 | 20 | 16-Hydroxylation |
| 2 | 4.19 | − | − | − | −34.7378 | 20 | |
| 3 | 3.03 | $H_2$0637 Glu374 | + | − | −34.4651 | 16 | |
| 4 | 9.85 | − | − | − | −32.2739 | 13-Methyl | |
| 5 | 4.69 | Leu210 | − | − | −30.8978 | 20 | |
| 6 | 8.79 | − | − | − | −30.2537 | 13-Methyl | |
| 7 | 8.35 | − | − | − | −29.7865 | 10-Methyl | |
| 8 | 9.36 | − | − | − | −29.3425 | 10-Methyl | |
| 9 | 10.03 | − | − | − | −28.6545 | 7 | |
| 10 | 9.98 | − | − | − | −27.8556 | 13-Methyl | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Progesterone** | | | | | | | |
| 1 | 2.68 | $H_2$0637 | + | − | −37.0959 | 6 | 6,16-Hydroxylation |
| 2 | 3.03 | − | − | − | −36.9991 | 2 | |
| 3 | 3.59 | − | − | − | −34.8775 | 3 | |
| 4 | 3.25 | − | − | − | −33.7225 | 2 | |
| 5 | 3.29 | − | − | − | −32.3576 | 3 | |
| 6 | 3.45 | − | − | − | −30.9865 | 2 | |
| 7 | 3.65 | − | − | − | −29.7685 | 2 | |
| 8 | 4.05 | − | − | − | −28.6534 | 2 | |
| 9 | 3.86 | − | − | − | −27.3456 | 2 | |
| 10 | 4.13 | − | − | − | −26.4561 | 2 | |
| **Resibufagenin** | | | | | | | |
| 1 | 3.71 | Glu374 | − | + | −35.2461 | 11 | 5-Hydroxylation |
| 2 | 4.17 | Arg105 Arg106 | + | + | −34.0458 | 5 | |
| 3 | 4.35 | Arg106 | + | + | −33.7865 | 5 | |
| 4 | 5.04 | Ser19 | + | − | −33.485 | 3 | |
| 5 | 4.13 | − | − | − | −33.3622 | 3 | |
| 6 | 5.21 | Ser19 | + | − | −33.2542 | 3 | |
| 7 | 5.95 | Ser19 Arg105 | + | − | −33.1563 | 3 | |
| 8 | 7.09 | − | + | − | −33.0235 | 3 | |
| 9 | 2.62 | − | − | − | −32.9837 | 19 | |
| 10 | 9.63 | − | − | − | −32.4635 | 13-Methyl | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Stanazole** | | | | | | | |
| 1 | 3.4 | − | − | − | −28.0198 | 3 | 6-Hydroxylation |
| 2 | 3.59 | − | − | − | −27.6352 | 3 | |
| 3 | 7.62 | − | − | − | −26.14738 | 10-Methyl | |
| 4 | 7.95 | − | − | − | −25.2125 | 10-Methyl | |
| 5 | 4.1 | − | + | + | −24.2746 | 6 | |
| 6 | 4.58 | − | + | + | −23.565 | 6 | |
| 7 | 4.62 | Ile301 | + | + | −22.8542 | 6 | |
| 8 | 3.9 | Arg373 | + | − | −22.40254 | 2 | |
| 9 | 3.72 | Arg373 | + | − | −22.0412 | 2 | |
| 10 | 8.64 | − | − | − | −21.2345 | 10-Methyl | |
| **Taurochenodeoxycholic Acid** | | | | | | | |
| 1 | 4.53 | − | + | − | −36.4201 | 24 | 6-Hydroxylation |
| 2 | 8.79 | − | − | − | −35.3709 | 13-Methyl | |
| 3 | 4.54 | − | + | − | −34.9812 | 24 | |
| 4 | 4.85 | − | + | − | −34.2304 | 24 | |
| 5 | 4.97 | − | + | − | −33.9324 | 24 | |
| 6 | 4.25 | Gl+481 heme | + | − | −32.9213 | 3 | |
| 7 | 3.73 | Arg106 $H_2O$623 heme | + | + | −32.9118 | 6 | |
| 8 | 5.03 | − | + | − | −32.3412 | 24 | |
| 9 | 5.08 | − | + | − | −32.0265 | 24 | |
| 10 | 9.78 | − | − | − | −31.7845 | 13-Methyl | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Testosterone** | | | | | | | |
| 1 | 2.74 | heme | + | + | −31.4668 | 17 | 6-Hydroxylation |
| 2 | 3.35 | $H_2O623$ | − | − | −31.419 | 6 | |
| 3 | | $H_2O623$,ser119 | − | − | −31.1069 | 12 | |
| 4 | 4.41 | $H_2O623$ | − | − | −30.8546 | 6 | |
| 5 | 4.48 | $H_2O623$,ser119 | − | − | −30.4225 | 6 | |
| 6 | 3.25 | − | + | + | −30.1354 | 17 | |
| 7 | 4.87 | − | + | + | −29.9865 | 17 | |
| 8 | 5.6 | $H_2O623$,ser119 | − | − | −29.6526 | 12 | |
| 9 | 7.75 | Leu 210 | + | − | −28.7545 | 13-Methyl | |
| 10 | 7.85 | − | + | − | −28.2384 | 13-Methyl | |
| **4-ChlorodehydroMethyltesterone** | | | | | | | |
| 1 | 1.95 | − | + | − | −33.7054 | 3 | 6-Hydroxylation |
| 2 | 2.02 | − | + | − | −32.053 | 3 | |
| 3 | 2.51 | − | + | − | −30.987 | 3 | |
| 4 | 2.47 | Thr309 | + | + | −29.3985 | 4 | |
| 5 | 8.36 | − | − | − | −28.7045 | 7 | |
| 6 | 3.41 | − | + | − | −27.697 | 2 | |
| 7 | 3.88 | − | + | − | −25.8245 | 6 | |
| 8 | 4.22 | Leu483 | − | + | −25.7083 | 1 | |
| 9 | 3.07 | − | + | − | −24.6328 | 4 | |
| 10 | 4.09 | − | + | − | −24.0354 | 3 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **5β-Cholestone-3α-7α-12α-triol** | | | | | | | |
| 1 | 2.3 | $H_2O637$ $H_2O619$ Arg372 | + | − | −31.2291 | 23 | 23,24,25-Hydroxylation |
| 2 | 2.35 | $H_2O619$ Arg372 heme | − | − | −31.2249 | 26 | |
| 3 | 2.35 | $H_2O619$ Arg372 | − | − | −28.7235 | 26 | |
| 4 | 3.77 | H2O637 Arg372 | + | − | −26.3245 | 23 | |
| 5 | 3.12 | $H_2O619$ Arg372 | − | − | −24.7414 | 24 | |
| 6 | 4.6 | $H_2O619$ Arg372 | − | + | −22.31 | 6 | |
| 7 | 4.98 | $H_2O619$ | − | + | −20.4653 | 6 | |
| 8 | 3.77 | $H_2O619$ Arg372 | − | − | −19.8546 | 25 | |
| 9 | 3.91 | $H_2O619$ Arg372 | + | − | −18.4625 | 23 | |
| 10 | 3.85 | $H_2O619$ Arg372 | + | − | −18.2354 | 23 | |
| **Lilopristone** | | | | | | | |
| 1 | 4.23 | − | + | − | −44.2677 | 15 | 11-*N*-Demethylation |
| 2 | 4.65 | − | + | − | −44.1235 | 14 | |
| 3 | 4.82 | − | + | − | −44.0582 | 16 | |
| 4 | 3.78 | − | − | − | −43.911 | 17 | |
| 5 | 3.97 | − | + | − | −43.6212 | 18 | |
| 6 | 4.25 | − | + | − | −43.5963 | 11-N | |
| 7 | 4.36 | − | + | − | −43.2345 | 14 | |
| 8 | 4.48 | − | + | − | −43.0872 | 14 | |
| 9 | 4.97 | − | + | − | −42.8532 | 15 | |
| 10 | 5.32 | − | + | − | −42.4637 | 15 | |

**Table S1.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Mestranol** | | | | | | | |
| 1 | 2.09 | − | + | − | −33.733 | 3-Methyl | 3-Demethylation |
| 2 | 2.35 | − | + | − | −33.6543 | 3-Methyl | |
| 3 | 2.26 | − | − | − | −33.5205 | 18 | |
| 4 | 2.67 | − | − | − | −33.154 | 18 | |
| 5 | 2.96 | − | + | − | −32.745 | 3-Methyl | |
| 6 | 8.67 | − | − | − | −32.1497 | 13-Methyl | |
| 7 | 2.44 | − | $H_2O637$ | − | −31.6227 | 15 | |
| 8 | 3.22 | − | + | − | −31.054 | 3-Methyl | |
| 9 | 3.68 | − | + | − | −30.685 | 3-Methyl | |
| 10 | 4.55 | − | − | − | −30.1225 | 13-Methyl | |
| **Mifepristone** | | | | | | | |
| 1 | 3.57 | − | + | − | −38.6142 | 16 | 11-*N*-Demethylation |
| 2 | 3.76 | − | + | − | −38.0564 | 16 | |
| 3 | 3.17 | − | + | − | −37.6844 | 11-N | |
| 4 | 4.04 | − | + | − | −36.4583 | 16 | |
| 5 | 2.3 | − | + | − | −35.3137 | 2 | |
| 6 | 8.98 | − | − | − | −33.9396 | 13-Methyl | |
| 7 | 9.35 | − | − | − | −33.7345 | 13-Methyl | |
| 8 | 3.68 | Leu210 | + | − | −33.5876 | 3 | |
| 9 | 4.57 | − | + | − | −32.9875 | 16 | |
| 10 | 4.97 | − | + | − | −32.2564 | 16 | |

**Table S2.** Original parameter of docking data for the compounds from test set.

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| | | | | **Bufalin** | | | |
| 1 | 2.02 | Val240 | − | − | −38.9729 | 24 | 3-Keto 5-Hydroxylation |
| 2 | 4.05 | $H_2$0619 Arg106 Ala305 Ile301 | + | + | −35.4563 | 5 | |
| 3 | 4.54 | $H_2$0619 Arg106 Ile301 | + | + | −34.9685 | 5 | |
| 4 | 9.63 | − | − | − | −34.2356 | 13-Methyl | |
| 5 | 2.13 | Val240 | − | − | −33.6542 | 24 | |
| 6 | 2.24 | − | − | − | −33.023 | 24 | |
| 7 | 2.88 | − | − | − | −32.6452 | 24 | |
| 8 | 4.59 | Arg372 | − | + | −31.7943 | 14 | |
| 9 | 2.76 | − | − | − | −30.6398 | 24 | |
| 10 | 3.59 | Val240 | − | − | −30.2567 | 24 | |
| | | | | **Bufotalin** | | | |
| 1 | 4.49 | $H_2$0637 Arg106 | + | + | −29.1787 | 5 | 1,5-Hydroxylation |
| 2 | 5.46 | heme | − | − | −28.6532 | 3 | |
| 3 | 3.38 | Thr309 $H_2$O619 | + | − | −28.2145 | 17 | |
| 4 | 3.32 | Thr309 | + | − | −27.5704 | 17 | |
| 5 | 3.45 | Thr309 $H_2$O619 | + | − | −26.9864 | 17 | |
| 6 | 8.95 | − | − | − | −26.3265 | 13-Methyl | |
| 7 | 3.69 | Thr309 $H_2$O619 | + | − | −25.6397 | 17 | |
| 8 | 8.78 | − | − | − | −25.0231 | 13-Methyl | |
| 9 | 9.65 | − | − | − | −24.6897 | 7 | |
| 10 | 9.78 | − | − | − | −23.864 | 13-Methyl | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Cortisone** | | | | | | | |
| 1 | 3.22 | heme | − | − | −33.5642 | 21 | 6-Hydroxylation |
| 2 | 3.44 | heme | − | − | −33.5324 | 21 | |
| 3 | 9.89 | − | − | − | −33.5162 | 10-Methyl | |
| 4 | 3.35 | − | − | − | −32.6373 | 21 | |
| 5 | 3.46 | heme | − | − | −31.7865 | 21 | |
| 6 | 4.65 | − | − | − | −31.1996 | 16 | |
| 7 | 5.63 | − | − | − | −30.4117 | 20-O | |
| 8 | 4.72 | − | − | − | −29.9865 | 16 | |
| 9 | 4.12 | − | − | + | −29.4542 | 6 | |
| 10 | 4.96 | heme | − | − | −28.63 | 21 | |
| **Epiandrosterone** | | | | | | | |
| 1 | 9.83 | − | − | − | −30.6879 | 10-Methyl | 16-Hydroxylation |
| 2 | 9.92 | − | − | − | −29.9875 | 10-Methyl | |
| 3 | 10.23 | − | − | − | −29.3524 | 10-Methyl | |
| 4 | 3.79 | Ser119 | + | − | −28.633 | 16 | |
| 5 | 4 | Ser119 | + | − | −28.265 | 16 | |
| 6 | 7.33 | Ser119 | + | + | −27.9834 | 6 | |
| 7 | 10.56 | − | − | − | −27.6375 | 7 | |
| 8 | 10.58 | − | − | − | −27.3425 | 7 | |
| 9 | 4.78 | Arg372 | − | + | −27.0084 | 13-Methyl | |
| 10 | 10.65 | − | − | − | −26.6425 | 10-Methyl | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Fluticasone** | | | | | | | |
| 1 | 2.31 | − | − | + | −35.0291 | 17 | 17-Carboxylic acid formation |
| 2 | 2.57 | − | − | + | −34.6532 | 17 | |
| 3 | 3.22 | − | − | + | −34.0261 | 17 | |
| 4 | 4.41 | − | − | − | −33.8653 | 17 | |
| 5 | 4.57 | − | − | + | −32.453 | 17 | |
| 6 | 4.35 | − | − | − | −31.6789 | 17 | |
| 7 | 1.95 | − | + | − | −30.2586 | 3 | |
| 8 | 4.21 | − | − | − | −29.3524 | 3 | |
| 9 | 3.36 | − | − | + | −28.7645 | 17 | |
| 10 | 4.22 | − | + | − | −28.0362 | 3 | |
| **Lithcholic Acid** | | | | | | | |
| 1 | 5.43 | Leu210 | + | − | −32.6542 | 24 | 6-Hydroxylation |
| 2 | 5.36 | Leu210 | + | − | −31.4532 | 24 | |
| 3 | 5.65 | Ile301 | − | − | −30.6523 | 24 | |
| 4 | 6.35 | Ile301 Glu308 | + | − | −30.0214 | 23 | |
| 5 | 6.62 | Ile301 Glu308 | − | − | −29.6532 | 23 | |
| 6 | 8.96 | − | − | − | −28.3214 | 13-Methyl | |
| 7 | 9.02 | − | − | − | −27.9856 | 13-Methyl | |
| 8 | 9.1 | − | − | − | −27.2415 | 13-Methyl | |
| 9 | 6.35 | $H_2O$637 Gln484 Ser312 | + | + | −26.654 | 19-Methyl | |
| 10 | 7.23 | Glu374 Arg105 | + | + | −26.0355 | 6 | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Methylpredisolone** | | | | | | | |
| 1 | 3.82 | − | + | + | −30.1996 | 10-Methyl | 6-Hydroxylation |
| 2 | 3.46 | − | + | + | −29.3672 | 10-Methyl | |
| 3 | 5.42 | − | − | − | −28.4329 | 1 | |
| 4 | 5.63 | − | − | − | −27.8635 | 1 | |
| 5 | 4.63 | Ile301 Glu308 | + | + | −27.1689 | 6 | |
| 6 | 5.63 | − | − | − | −26.7256 | 4 | |
| 7 | 4.87 | Ile301 Glu308 | − | + | −26.3985 | 6 | |
| 8 | 3.98 | − | + | + | −25.4692 | 10-Methyl | |
| 9 | 4 | − | − | − | −23.8534 | 10-Methyl | |
| 10 | 3.98 | − | − | + | −23.233 | 10-Methyl | |
| **Prednisolone** | | | | | | | |
| 1 | 1.98 | Leu210 | − | − | −35.0142 | 20-O | 16-Hydroxylation |
| 2 | 2.19 | − | − | − | −34.8564 | 20-O | |
| 3 | 3.03 | $H_2$0637 Glu374 | + | − | −34.4651 | 16 | |
| 4 | 8.69 | − | − | − | −32.2739 | 13-Methyl | |
| 5 | 8.74 | − | − | − | −31.5642 | 13-Methyl | |
| 6 | 3.03 | Leu210 | − | − | −30.7854 | 20-O | |
| 7 | 8.96 | − | − | − | −30.125 | 10-Methyl | |
| 8 | 9.05 | − | − | − | −29.6874 | 10-Methyl | |
| 9 | 9.04 | − | − | − | −28.6325 | 13-Methyl | |
| 10 | 9.23 | − | − | − | −28.3624 | 10-Methyl | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Onapristone** | | | | | | | |
| 1 | 5.38 | Leu210 | − | + | −42.8212 | 11-N | 11-*N*-Demethylation |
| 2 | 5.6 | Ala370 | − | − | −40.2616 | 15 | |
| 3 | 9.23 | − | − | − | −40.137 | 10-Methyl | |
| 4 | 5.65 | − | − | + | −39.8452 | 11-N | |
| 5 | 5.65 | − | − | + | −39.2332 | 11-N | |
| 6 | 5.9 | Glu308 | − | − | −39.6532 | 11-N | |
| 7 | 4.19 | Arg105 Glu374 | − | + | −38.4142 | 6 | |
| 8 | 4.9 | Arg105 Glu374 | − | + | −38.0235 | 6 | |
| 9 | 9.78 | − | − | − | −37.6524 | 10-Methyl | |
| 10 | 4.83 | Arg105 | − | + | −36.632 | 6 | |
| **Tirilazad** | | | | | | | |
| 1 | 5.48 | − | + | − | −53.0624 | 6 | 6-Hydroxylation |
| 2 | 5.42 | Ile301 | + | − | −52.321 | 6 | |
| 3 | 4.14 | − | − | − | −50.0319 | 16-Methyl | |
| 4 | 2.97 | − | + | − | −49.9946 | 4 | |
| 5 | 1.92 | − | − | − | −49.917 | 3 | |
| 6 | 2.29 | − | − | − | −49.6564 | 2 | |
| 7 | 3.58 | − | − | − | −49.3625 | 3 | |
| 8 | 4.49 | Arg372 | + | − | −49.1728 | 12 | |
| 9 | 3.9 | − | − | − | −48.6324 | 3 | |
| 10 | 5.49 | − | + | − | −48.0234 | 4 | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Other Structure Alprazolam** | | | | | | | |
| 1 | 2.84 | Arg105 | − | + | −33.2899 | 6 | 1,4-Hydroxylation |
| 2 | 3.17 | Arg105 | − | + | −31.2568 | 6 | |
| 3 | 3.27 | Ser119 | + | − | −29.1964 | 1 | |
| 4 | 3.25 | − | + | − | −28.6335 | 1 | |
| 5 | 3.38 | − | + | − | −27.8324 | 1 | |
| 6 | 4.26 | − | − | − | −27.1235 | 1 | |
| 7 | 3.42 | Ser119 | + | − | −26.3563 | 1 | |
| 8 | 4.86 | Ser119 | + | − | −25.9836 | 1 | |
| 9 | 4.75 | − | − | − | −25.6321 | 1 | |
| 10 | 3.97 | − | + | − | −24.5642 | 1 | |
| **Clozapine** | | | | | | | |
| 1 | 2.34 | − | − | + | −26.5332 | 4 | *N*-Oxidation |
| 2 | 8.65 | − | − | − | −26.0737 | N | |
| 3 | 2.28 | − | − | + | −25.9836 | 4 | |
| 4 | 2.35 | − | − | + | −25.9326 | 4 | |
| 5 | 3.25 | − | − | + | −25.7325 | 4 | |
| 6 | 9.68 | − | − | + | −25.2381 | 4 | |
| 7 | 9.75 | − | − | − | −25.0317 | N | |
| 8 | 8.96 | − | − | − | −24.9368 | N | |
| 9 | 9.48 | − | − | − | −24.7328 | N | |
| 10 | 2.37 | − | + | − | −24.6407 | N | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Flunitrazepam** | | | | | | | |
| 1 | 5.73 | Arg105 | − | − | −26.1514 | 1 | 3-Hydroxylation *N*-Demethylation |
| 2 | 5.73 | Arg105 | − | − | −25.3212 | 1 | |
| 3 | 3.54 | Arg105 | + | − | −24.8818 | 3 | |
| 4 | 3.46 | Arg105 | + | − | −24.2356 | 3 | |
| 5 | 5.72 | Arg105 | − | − | −23.6547 | 1 | |
| 6 | 5.95 | − | + | − | −23.0615 | 1 | |
| 7 | 5.78 | Arg105 | − | − | −22.3214 | 1 | |
| 8 | 8.65 | − | − | − | −21.9874 | 3 | |
| 9 | 5.83 | − | + | − | −21.5632 | 3 | |
| 10 | 8.79 | − | − | − | −20.3654 | 3 | |
| **Ketamine** | | | | | | | |
| 1 | 7.96 | − | − | − | −27.4334 | 2 | *N*-Demethylation |
| 2 | 2.48 | − | + | − | −27.0365 | N | |
| 3 | 2.33 | − | + | − | −26.6897 | 2 | |
| 4 | 3.21 | − | + | − | −26.3214 | 2 | |
| 5 | 8.06 | − | − | − | −25.4368 | 2 | |
| 6 | 8.63 | − | − | − | −24.7635 | 2 | |
| 7 | 8.45 | − | − | − | −24.0321 | 2 | |
| 8 | 8.98 | − | − | − | −23.306 | N | |
| 9 | 9.02 | − | − | − | −23.2605 | N | |
| 10 | 5.69 | − | − | + | −22.5102 | 2 | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **LAAM** | | | | | | | |
| 1 | 5.35 | − | + | − | −32.8456 | 6 | *N*-Demethylation |
| 2 | 5.42 | − | + | − | −31.4532 | 6 | |
| 3 | 5.38 | − | − | − | −30.265 | 6 | |
| 4 | 2.82 | − | − | + | −29.0164 | 3 | |
| 5 | 3.78 | Ser19 | − | + | −28.5253 | 3 | |
| 6 | 4.23 | − | − | − | −28.1325 | 4 | |
| 7 | 3.93 | − | − | − | −27.8652 | 4 | |
| 8 | 5.07 | − | + | − | −27.6637 | 4 | |
| 9 | 5.36 | − | − | − | −26.9836 | 4 | |
| 10 | 5.67 | − | − | − | −26.3256 | 6 | |
| **Midazolam** | | | | | | | |
| 1 | 3.27 | − | + | − | −26.6934 | 3 | 1,4-Hydroxylation |
| 2 | 2.75 | − | − | + | −26.3068 | 6 | |
| 3 | 2.88 | − | − | + | −25.5423 | 6 | |
| 4 | 5.78 | − | − | + | −24.8249 | 8−Chloro | |
| 5 | 3.46 | − | − | + | −24.503 | 3 | |
| 6 | 2.72 | − | + | − | −24.0718 | 1 | |
| 7 | 2.97 | − | + | − | −23.6423 | 1 | |
| 8 | 3.73 | − | − | + | −23.1254 | 3 | |
| 9 | 3.56 | − | + | − | −22.645 | 1 | |
| 10 | 4.18 | − | + | − | −21.9863 | 1 | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Quinidine** | | | | | | | |
| 1 | 5.55 | Ile301 | − | + | −34.6414 | 3 | 3-Hydroxylation |
| 2 | 5.54 | Ile301 | − | + | −33.2563 | 3 | |
| 3 | 5.65 | Ile301 | − | + | −32.6534 | 3 | |
| 4 | 5.72 | Ile301 | − | + | −31.2357 | 3 | |
| 5 | 3.86 | − | + | − | −30.6583 | N | |
| 6 | 3.93 | − | + | − | −30.1031 | C | |
| 7 | 4.59 | − | + | − | −29.6875 | N | |
| 8 | 4.02 | − | + | − | −29.3214 | N | |
| 9 | 4.23 | − | + | − | −28.6573 | N | |
| 10 | 4.22 | − | + | − | −27.3321 | N | |
| **Schizandrin A** | | | | | | | |
| 1 | 5.36 | Ser119 | + | − | −34.3394 | 1 | 7-Hydroxylation |
| 2 | 5.65 | Ser119 | + | − | −33.6345 | 1 | |
| 3 | 5.58 | Ser119 | − | − | −32.9785 | 1 | |
| 4 | 5.05 | $H_2O$623 | − | + | −32.1586 | 7 | |
| 5 | 5.55 | $H_2O$623 | − | + | −31.6325 | 7 | |
| 6 | 7.93 | − | − | − | −30.7835 | 2 | |
| 7 | 8.32 | − | − | − | −30.0244 | 2 | |
| 8 | 6.36 | − | + | − | −29.6345 | 1 | |
| 9 | 8.49 | − | − | − | −28.6378 | 2 | |
| 10 | 6.47 | − | + | − | −28.4237 | 1 | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Schizandrin B** | | | | | | | |
| 1 | 2.12 | − | + | − | −26.5975 | 1 | 7-Hydroxylation |
| 2 | 3.18 | $H_2$0623 Ile 369 | − | − | −25.1363 | 12 | |
| 3 | 3.09 | $H_2$0623 | − | − | −24.6358 | 12 | |
| 4 | 8.05 | − | − | − | −24.1121 | 2 | |
| 5 | 7.98 | − | − | − | −23.9874 | 2 | |
| 6 | 3.89 | $H_2$0637 | − | + | −23.4794 | 7 | |
| 7 | 4.7 | − | + | − | −22.7865 | 1 | |
| 8 | 3.85 | − | + | − | −22.5632 | 1 | |
| 9 | 4.23 | − | | − | −22.2341 | 1 | |
| 10 | 4.08 | − | + | − | −21.745 | 1 | |
| **Toremifene** | | | | | | | |
| 1 | 4.71 | − | − | + | −42.1659 | 4-Chloro | 2-Hydroxylation *N*-Demethylation |
| 2 | 8.4 | − | − | − | −41.5638 | 2-Phenoxy | |
| 3 | 4.92 | − | − | + | −40.7652 | 4-Chloro | |
| 4 | 4.89 | − | − | + | −40.6321 | 4-Chloro | |
| 5 | 8.23 | − | − | − | −40.0325 | 2-Phenoxy | |
| 6 | 8.56 | − | − | − | −39.6985 | 2-Phenoxy | |
| 7 | 8.98 | − | − | − | −39.2312 | 2-Phenoxy | |
| 8 | 4.68 | − | + | − | −38.4699 | 2-Phenoxy | |
| 9 | 4.61 | − | + | − | −38.35 | N | |
| 10 | 6.4 | − | − | + | −37.9865 | 4-Chloro | |

**Table S2.** *Cont.*

| Rank | Distance | Key Interaction Features | | | Chemscore | Predicted Metabolic Sites | Actual Metabolic Sites |
|---|---|---|---|---|---|---|---|
| | | Hydrogen Bond Interaction | Lilophilic Interaction toward Heme | Lilophilic Interaction with Phe−Cluster | | | |
| **Triazolam** | | | | | | | |
| 1 | 10.32 | − | − | − | −26.3366 | 4 | 1,4-Hydroxylation |
| 2 | 4.49 | − | + | − | −24.1722 | 3 | |
| 3 | 4.72 | − | + | − | −24.1308 | 3 | |
| 4 | 3.01 | − | + | − | −24.0811 | 1 | |
| 5 | 10.18 | − | − | − | −23.6324 | 4 | |
| 6 | 10.65 | − | − | − | −22.987 | 4 | |
| 7 | 4.68 | − | + | − | −22.2654 | 3 | |
| 8 | 4.93 | − | + | − | −21.5665 | 3 | |
| 9 | 3.2 | − | + | − | −21.0235 | 1 | |
| 10 | 5.15 | − | − | − | −20.6452 | 3 | |
| **Zotepine** | | | | | | | |
| 1 | 3.45 | − | − | − | −37.1058 | 2 | S-Oxidation *N*-Demethylation |
| 2 | 7.93 | − | − | − | −36.5328 | 2 | |
| 3 | 3.49 | − | − | − | −35.7356 | 2 | |
| 4 | 3.36 | Arg372 | − | + | −35.1572 | S | |
| 5 | 8.15 | − | − | − | −34.2315 | S | |
| 6 | 8.09 | − | − | − | −33.0238 | 2 | |
| 7 | 8.23 | − | − | − | −31.5192 | 2 | |
| 8 | 3.78 | − | − | + | −31.2638 | S | |
| 9 | 3.82 | Arg372 | − | + | −31.0872 | S | |
| 10 | 4.01 | − | + | − | −30.9275 | N | |

Distance, the distances (*r*) between the heme iron of CYP3A4 and the atoms of the substrates; +, The lilophilic interaction (toward heme or with phe−cluster) was formed in the prediction of substrate-enzyme interaction; −, No hydrogen bond interaction or lilophilic interaction was formed in the prediction of substrate-enzyme interaction.