# Supplementary Information for:

# Fragment-centric Topographic Mapping Method Guides the Understanding of ABCG2-inhibitors Interaction

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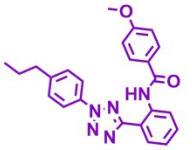

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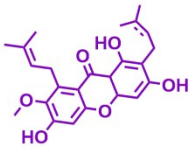

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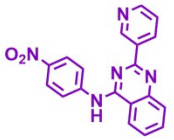

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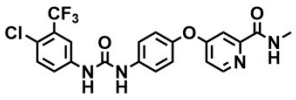

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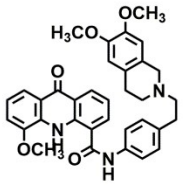

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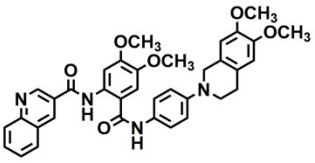

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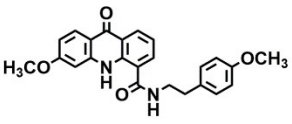

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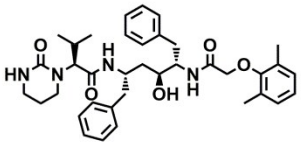

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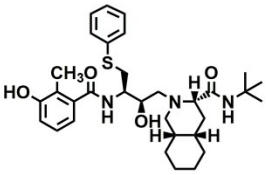

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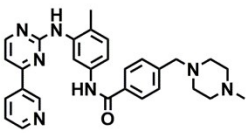

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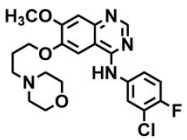

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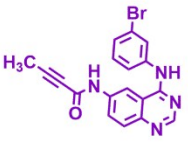

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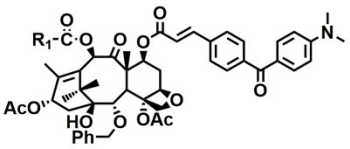

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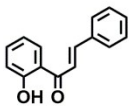

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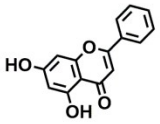

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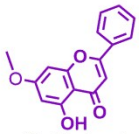

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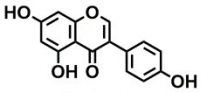

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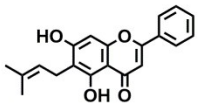

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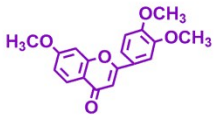

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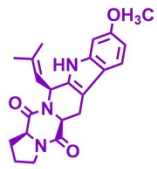

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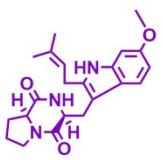

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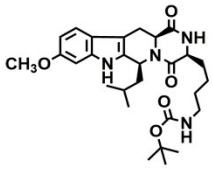

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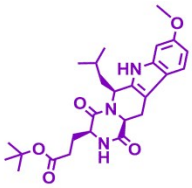

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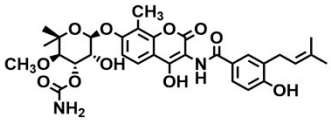

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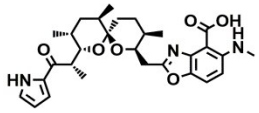

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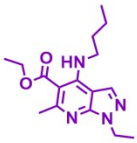

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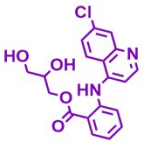

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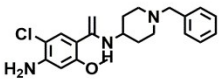

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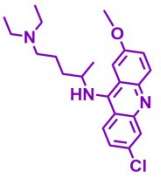

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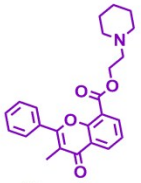

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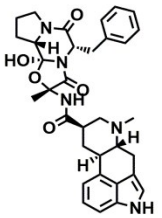

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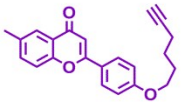

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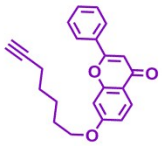

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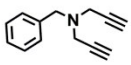

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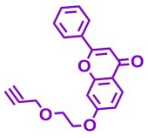

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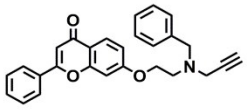

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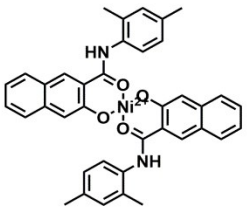

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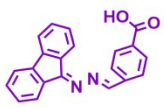

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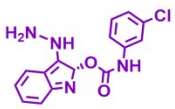

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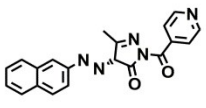

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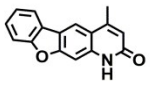

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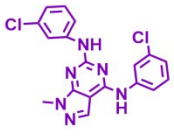

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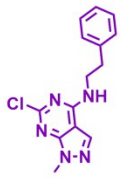

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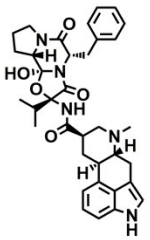

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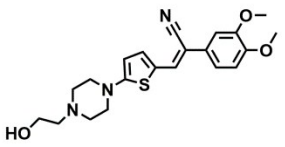

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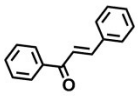

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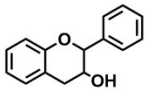

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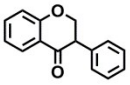

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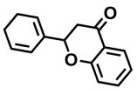

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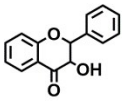

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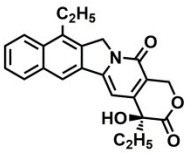

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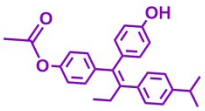

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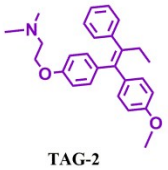

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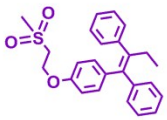

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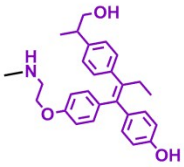

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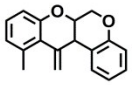
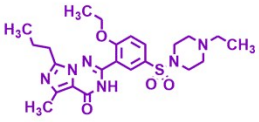
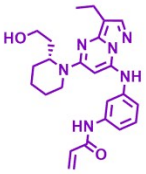


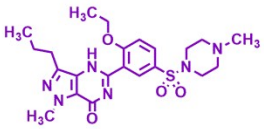
Rotenoid derivatives



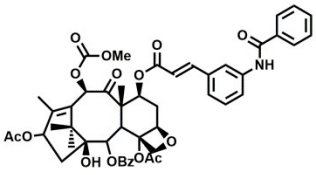
Vardenafil



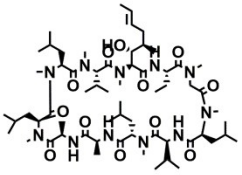
E9



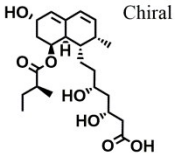
Sildenafil



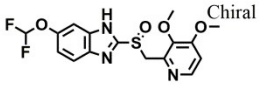
Paclitaxel analogues



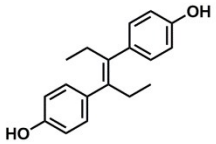
Ciclosporin



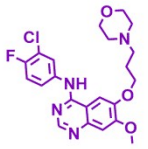

Pravastatin



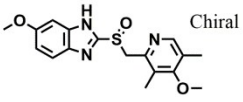

Pantoprazole



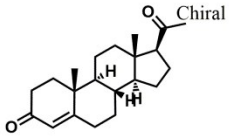
Diethylstilbestrol



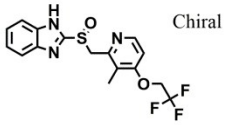
Gefitinib



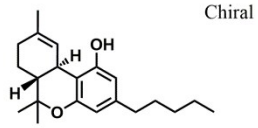

Omeprazole



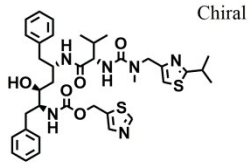

Progesterone



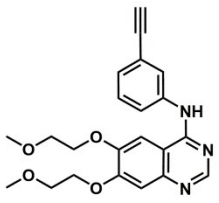

Lansoprazole



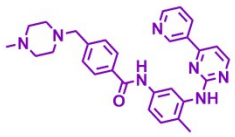

Dronabinol



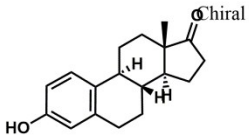

Ritonavir



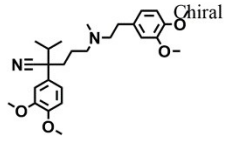
Erlotinib



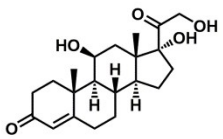
Imatinib



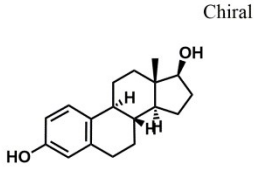

Estrone



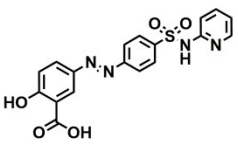

Verapamil



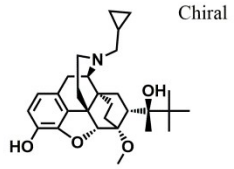
Hydrocortisone



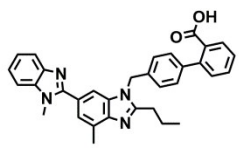

Estradiol



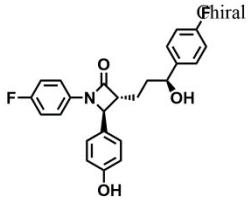
Sulfasalazine



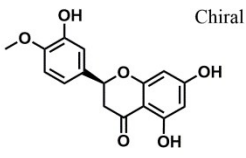

Buprenorphine



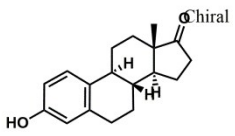
Telmisartan




Ezetimibe




Hesperetin

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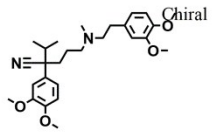
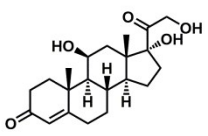
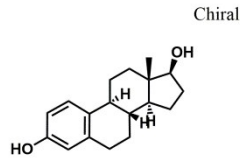



Verapamil



Hydrocortisone

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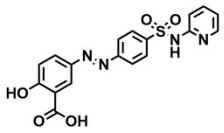
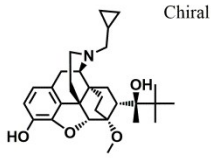
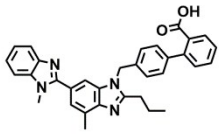


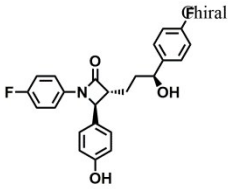
Sulfasalazine




Buprenorphine



Telmisartan

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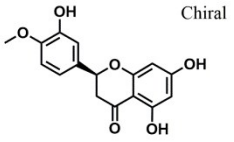
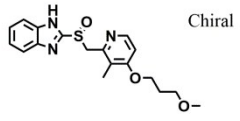
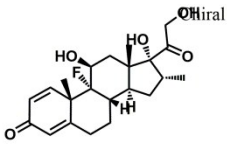



Hesperetin

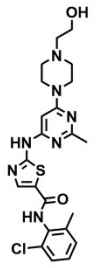



Rabeprazole

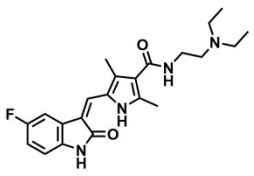

Saquinavir




Dexamethasone



Dasatinib



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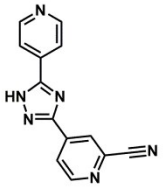
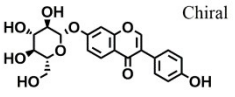


Topiroxostat

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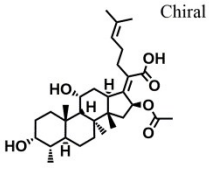
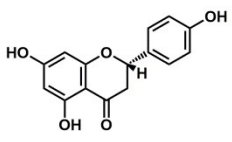
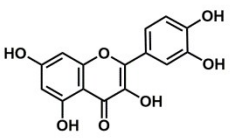


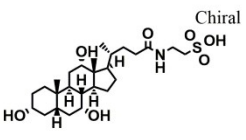

Fusidic Acid



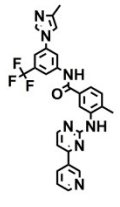
Naringenin



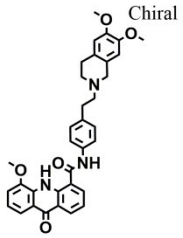
Quercetin



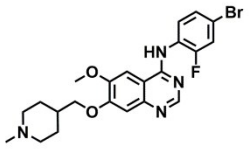

Taurocholic Acid



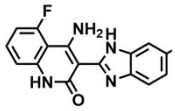
Nilotinib



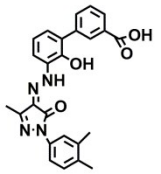

Elacridar



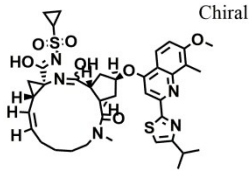
Vandetanib



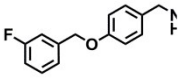
Dovitinib



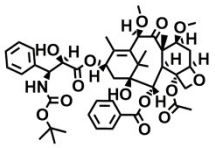
Eltrombopag



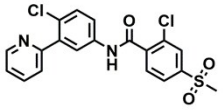

Simeprevir



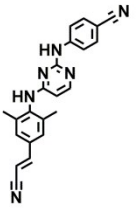
Safinamide



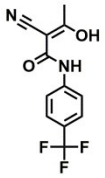
Cabazitaxel



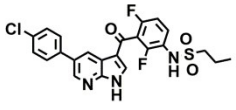
Vismodegib



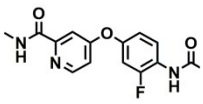
Rilpivirine



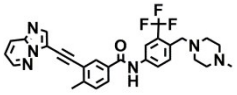
Teriflunomide



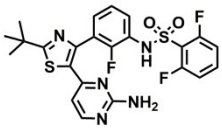
Vemurafenib



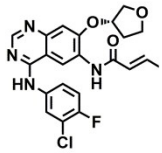
Regorafenil



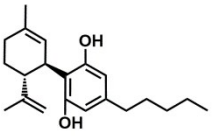
Ponatinib



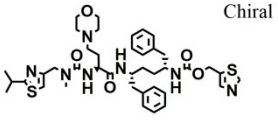
Dabrafenib



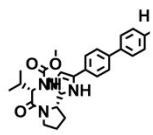
Afatinib



Cannabidiol




Cobicistat



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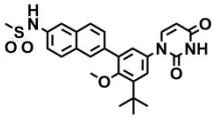
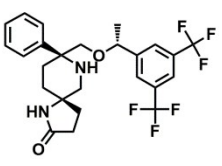
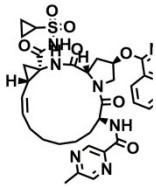


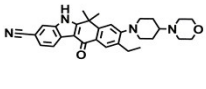
Dasabuvir



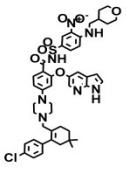
Rolapitant



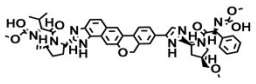
Paritaprevir



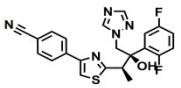
Alectinib



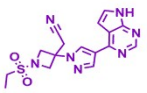
Venetoclax



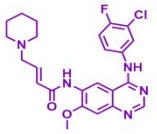
Velpatasvir



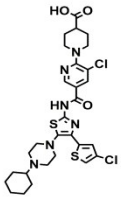
Isavuconazole



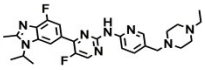
Baricitinib



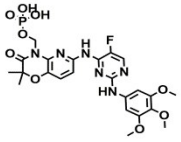
Dacomitinib



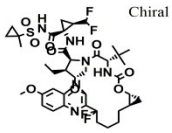
Avatrombopag



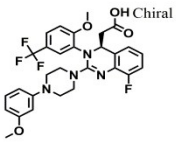
Abemaciclib



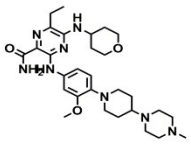
Fostamatinib



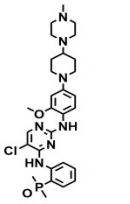
Voxilaprevir



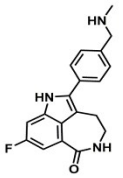
Letermovir



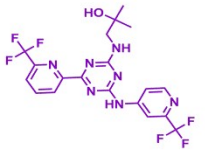
Gilteritinib



Brigatinib



Rucaparib



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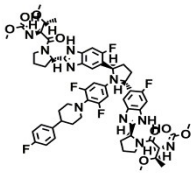
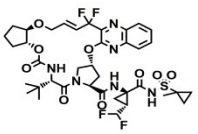
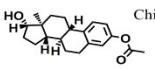


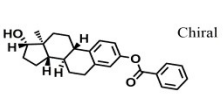
Pibrentasvir



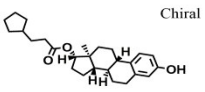
Glecaprevir



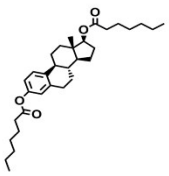
Estradiol acetate



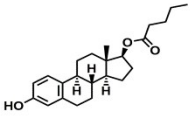
Estradiol benzoate



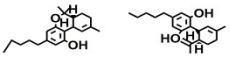
Estradiol cypionate



Estradiol dienanthate



Estradiol valerate



Nabiximols

| Inhibitor name | Reference |
|---|---|
| HM30181 derivatives | [1] |
| Alpha-Mangostin | [2] |
| 4-Anilino-2-pyridylquinazoline | [3] |
| Sorafenib | [4] |
| GF120918 | [5] |
| Tariquidar | [5] |
| analogue of GF 120918 | [5] |
| Lopinavir | [6] |
| Nelfinavir | [6] |
| Gleevec | [7] |
| ZD1839 | [7] |
| EKI-785 | [7] |
| tRA98006 | [8] |
| 2'-Hydroxychalcone | [9-11] |
| Chrysin | [9-11] |
| Techtochrysin | [9-11] |
| Genistein | [9-11] |
| 6-Prenylchrysin | [9-11] |
| 3',4',7-Trimethoxyflavone | [9-11] |
| Fumitremorgin C | [12] |
| Tryprostatin A | [12] |
| Ko132 | [12] |
| Ko134 | [12] |
| Novobiocin | [13] |
| Calcimycin | [14] |
| Tracazolate | [14] |
| Glafenine | [14] |
| Clebopride | [14] |
| Mepacrine | [14] |
| Flavoxate | [14] |
| Dihydroergotamine | [14] |
| Ac5 | [15] |
| Ac12 | [15] |
| Ac15 | [15] |
| Ac13 | [15] |
| Ac13 | [15] |
| NSC306698 | [16] |
| NSC120668 | [16] |
| NSC320582 | [16] |
| NSC303769 | [16] |
| NSC375985 | [16] |
| NSC11668 | [16] |

| | |
|---|---|
| NSC19139 | 16 |
| NSC409663 | 16 |
| EAC 14 | 17 |
| Chalcones | 18 |
| Flavanols | 18 |
| Isoflavones | 18 |
| Flavanones | 18 |
| Flavonols | 18 |
| SN-38 analogues | 15 |
| TAG-1 | 19 |
| TAG-2 | 19 |
| TAG-3 | 19 |
| TAG-7 | 19 |
| Rotenoid derivatives | 20 |
| Vardenafil | 21 |
| E9 | 22 |
| Sildenafil | 23 |
| Paclitaxel analogues | 24 |

**Fig. S1** Small molecules library of ABCG2 inhibitors. The inhibitors marked purple are found to meet the criteria. And inhibitors are from DrugBank ( from Ciclosporin to Nabiximols)

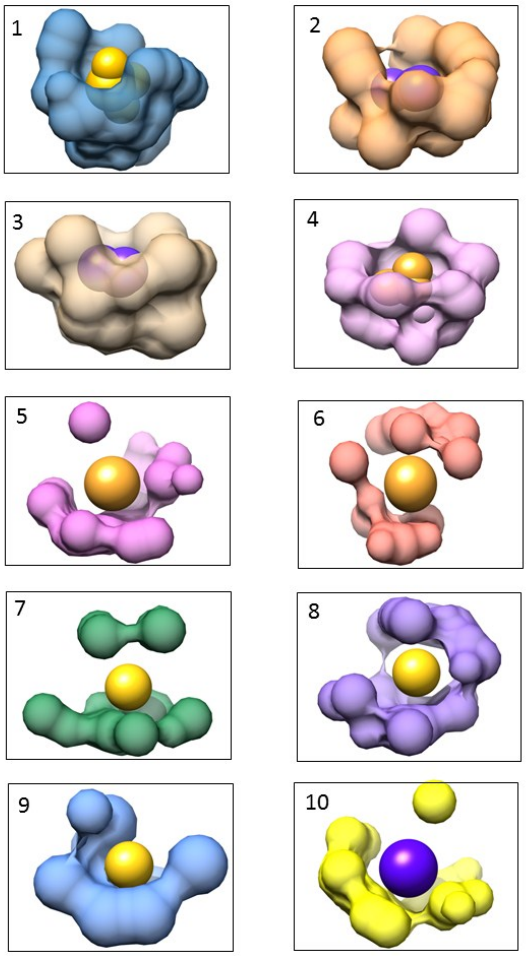



**Fig. S2** The shape of ten pockets of central cavity are shown by AlphaSpace. According to the results, the pockets are divided into categories, we can observe that pockets NO.1, NO.2, NO.3, NO.4 belong to deep pocket, which can firmly wrap the atomic group, and compared with these cavities, the others have more planar structure.

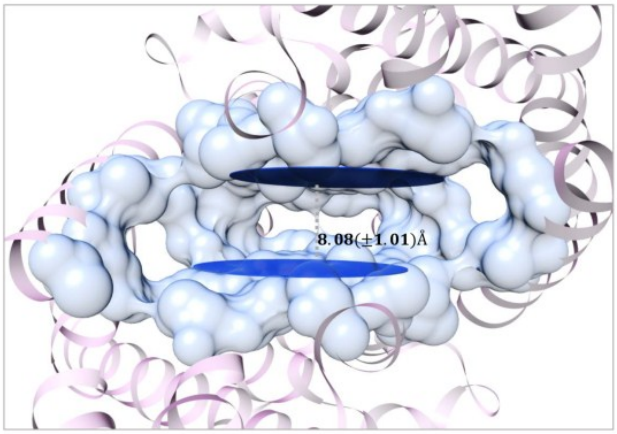



**Fig. S3** The height of cavity is 8.08 $\pm$ 1.01 Å.

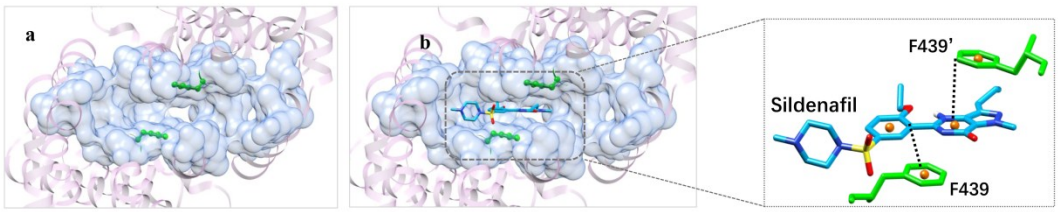



**Fig. S4** (a & b) The inhibitor and the residues ( F439, F439′ ) located in the upper and lower plane of cavity form $\pi$-$\pi$ staking.

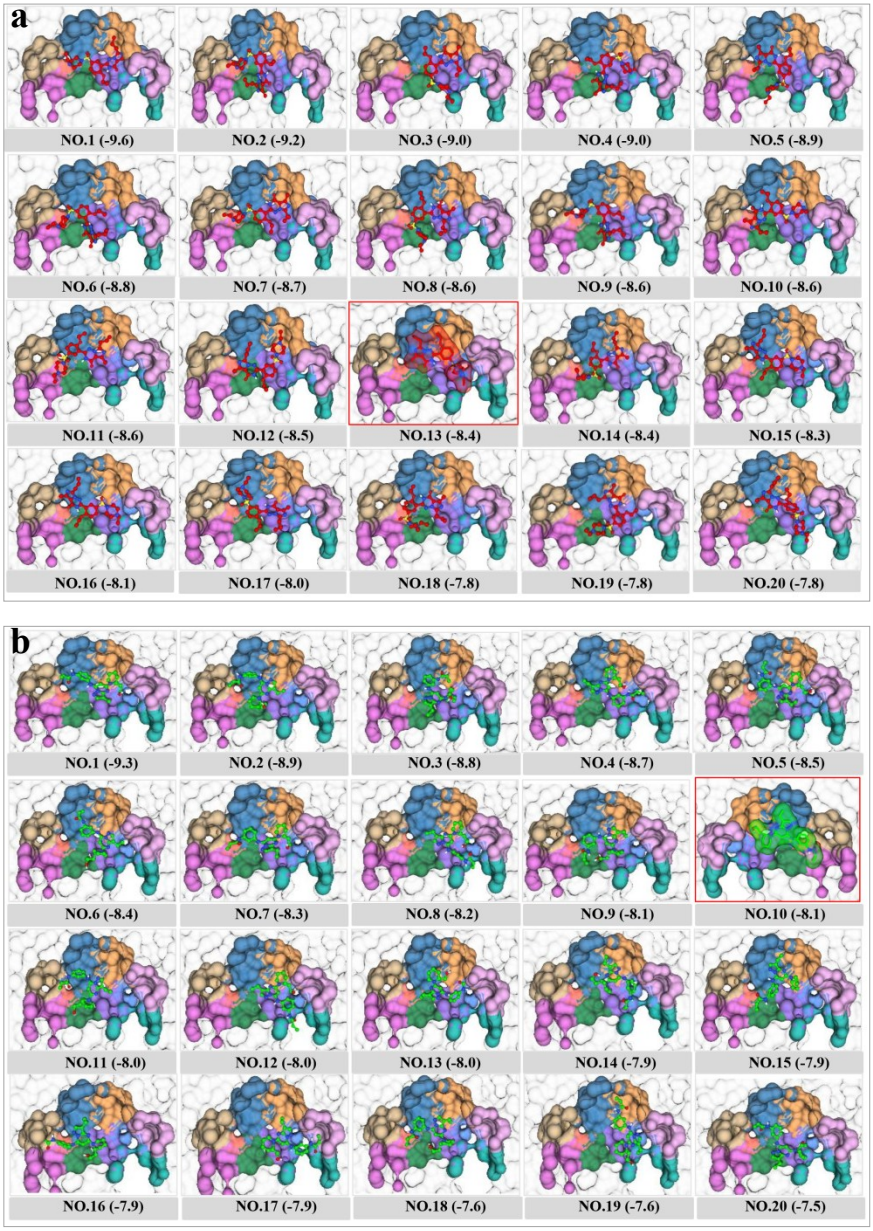



**Fig. S5** The docking poses of vardenafil (a) and E9 (b) in pocket-centric topographical map calculated by *AlphaSpace.* And Auto dock scoring parameters are listed.

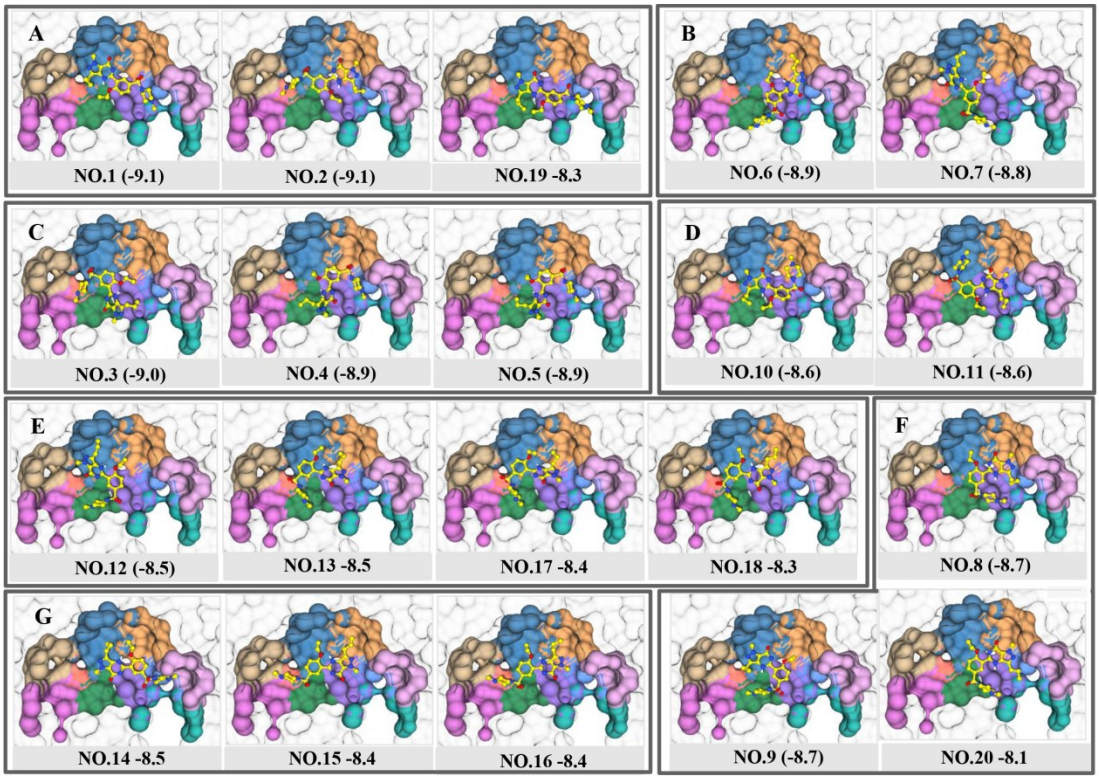



**Fig. S6** 20 docking poses of sildenafil are divided into 7 categories. And Auto dock scoring parameters are listed.

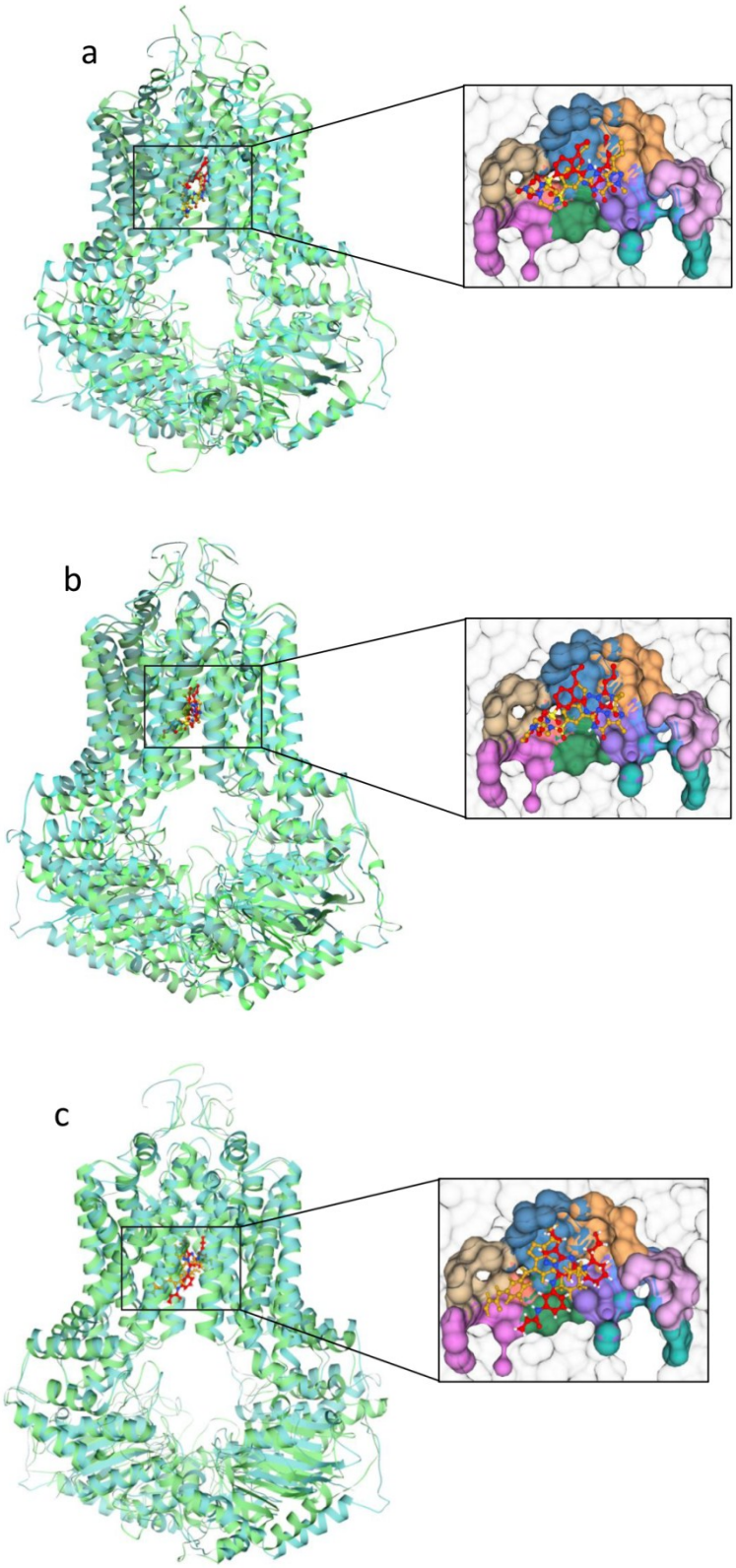



**Fig. S7** Docking (protein light sea green, ligand orange) and after MD simulated (protein lime green, ligand red) superpose structures of all the simulated ligands (a Sildenafil, b Vardenafil, and c E9) inside binding pocket.

**Table S1** Auto dock energy scoring parameters.

| | Sildenafil | Vardenafil | E9 |
|---|---|---|---|
| **NO.1** | -9.1 | -9.6 | -9.3 |
| **NO.2** | -9.1 | -9.2 | -8.9 |
| **NO.3** | -9.0 | -9.0 | -8.8 |
| **NO.4** | -8.9 | -9.0 | -8.7 |
| **NO.5** | -8.9 | -8.9 | -8.5 |
| **NO.6** | -8.9 | -8.8 | -8.4 |
| **NO.7** | -8.8 | -8.7 | -8.3 |
| **NO.8** | -8.7 | -8.6 | -8.2 |
| **NO.9** | -8.7 | -8.6 | -8.1 |
| **NO.10** | -8.6 | -8.6 | -8.1 |
| **NO.11** | -8.6 | -8.6 | -8.0 |
| **NO.12** | -8.5 | -8.5 | -8.0 |
| **NO.13** | -8.5 | -8.4 | -8.0 |
| **NO.14** | -8.5 | -8.4 | -7.9 |
| **NO.15** | -8.4 | -8.3 | -7.9 |
| **NO.16** | -8.4 | -8.1 | -7.9 |
| **NO.17** | -8.4 | -8.0 | -7.9 |
| **NO.18** | -8.3 | -7.8 | -7.6 |
| **NO.19** | -8.3 | -7.8 | -7.6 |
| **NO.20** | -8.1 | -7.8 | -7.5 |

**Table S2** Binding interaction of inhibitors to ABCG2 obtained by MM-PBSA method.

| Energy component | Sildenafil (KJ/mol) | Vardenafil (KJ/mol) | E9 (KJ/mol) |
|---|---|---|---|
| $\Delta E_{ele}$ | **-10.74 ± 3.59** | **-9.21 ± 1.97** | **-18.99 ± 3.60** |
| $\Delta E_{vdw}$ | **-69.70 ± 2.27** | **-71.93 ± 2.46** | **-64.46 ± 2.75** |
| $\Delta G_{pol}$ | **47.94 ± 6.14** | **50.90 ± 5.68** | **43.43 ± 6.67** |
| $\Delta G_{nopol}$ | **-7.20 ± 0.10** | **-7.39 ± 0.11** | **-6.93 ± 0.10** |
| **ΔH** | **-39.70 ± 6.06** | **-37.63 ± 6.40** | **-46.96 ± 6.72** |

**Table S3 The high-scoring amino acid residues in each pocket of the three complexes. (The depth of the color depending on the frequency of amino acid appearance)**

| Pocket | Sildenafil | Vardenafil | E9 |
|---|---|---|---|
| Pocket 1 | F431 | F431 | F431 |
| | T435 | T435 | T435 |
| | M549 | M549 | M549 |
| | M549′ | M549′ | F432 |
| | - | L555 | - |
| | L555′ | L555′ | L555′ |
| Pocket 2 | F431′ | F431′ | F431′ |
| | F432′ | F432′ | F432′ |
| | T435′ | T435′ | T435′ |
| | V546 | V546 | V546 |
| | - | - | N436′ |
| | - | - | M549′ |
| | - | - | L555 |
| Pocket 4 | A397′ | N436′ | Q398′ |
| | V401′ | S440′ | V401′ |
| | L405′ | S443′ | S440′ |
| | S408′ | - | - |
| | N436′ | - | - |
| | L539 | - | - |
| | I543 | - | - |
| Pocket 7 | F439 | F439 | N436 |
| | F439′ | F439′ | F439 |
| | T542 | F545′ | F439′ |
| | T542′ | V546′ | V546′ |
| Pocket 8 | - | L539 | T542 |
| | - | - | T542′ |
| Pocket 9 | F432 | V401′ | - |
| | V546′ | T402′ | - |
| | - | L405′ | - |
| | - | I543 | - |

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