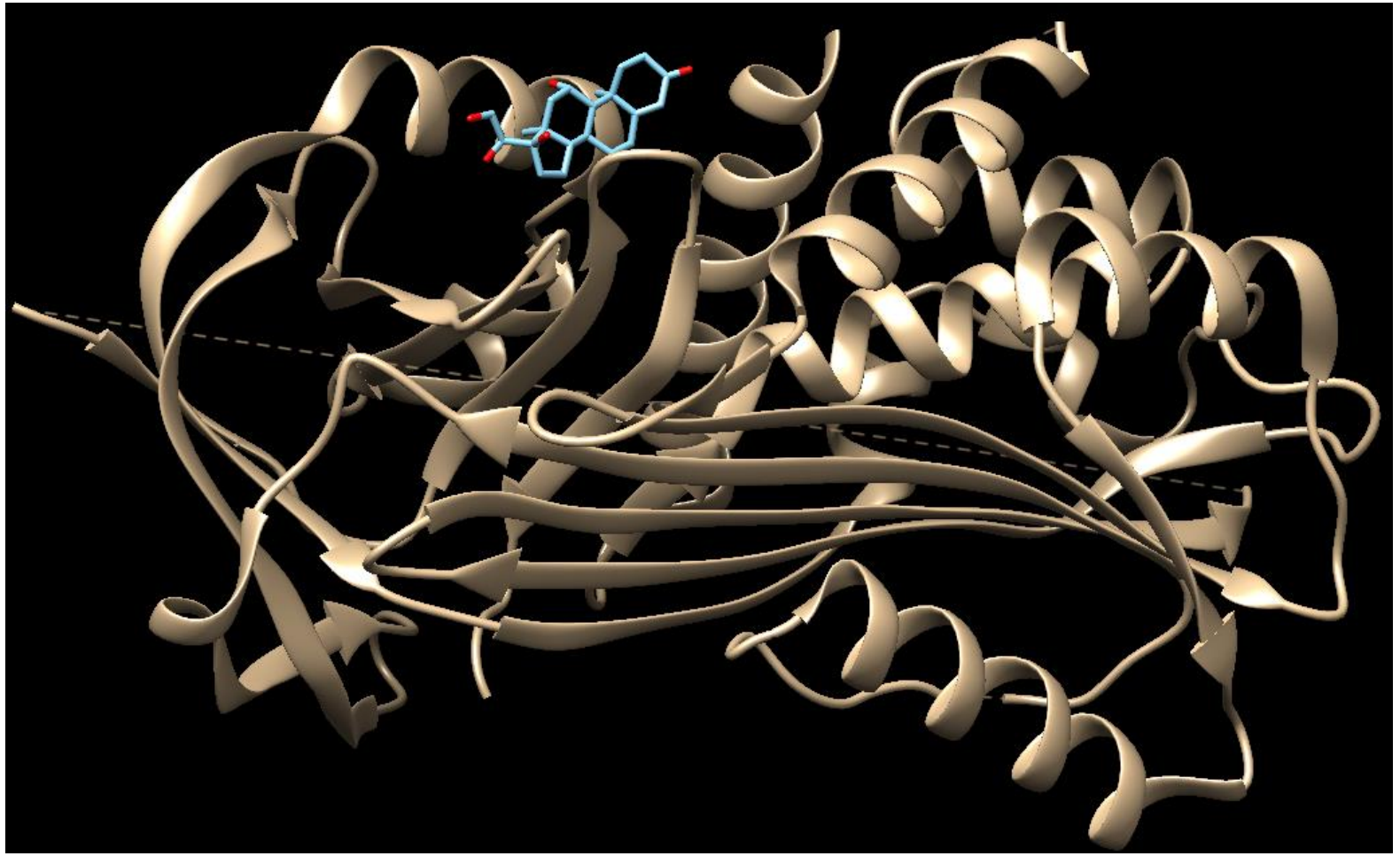
Discovering Novel ligand for CBG (Corticosteroid Binding Globulin) using Smina Docking

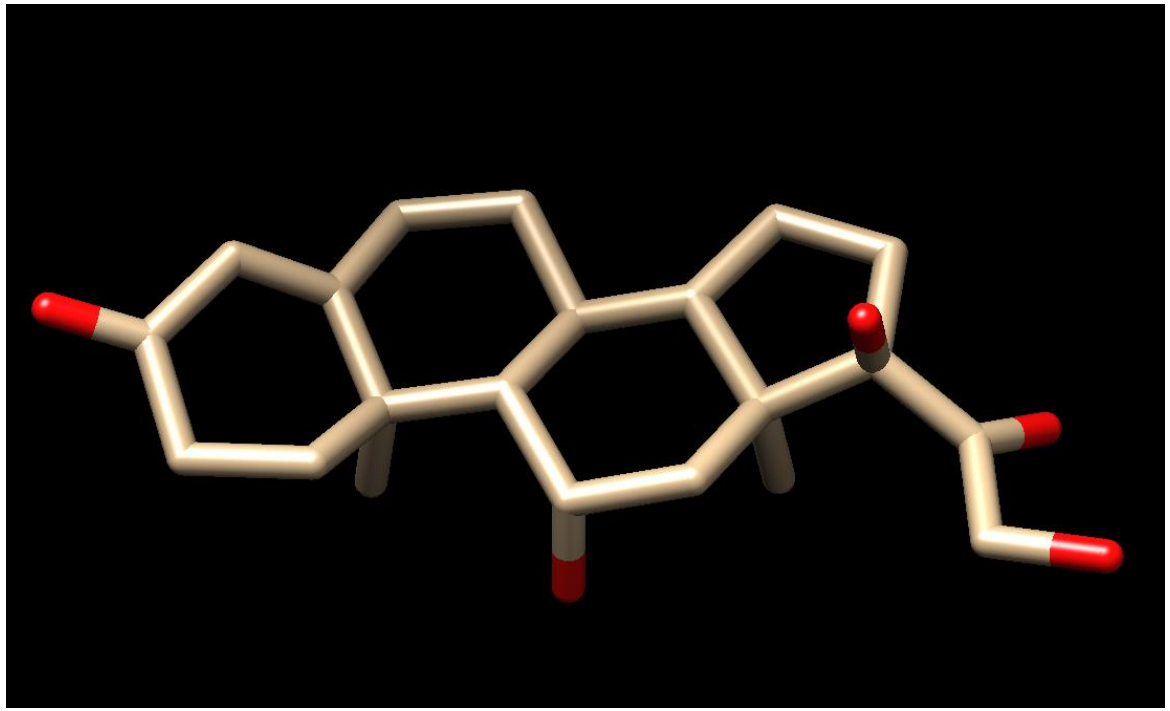
20182818 박주영

2VDY

Crystal structure of the reactive loop cleaved Corticosteroid Binding Globulin complexed with Cortisol



Cortisol

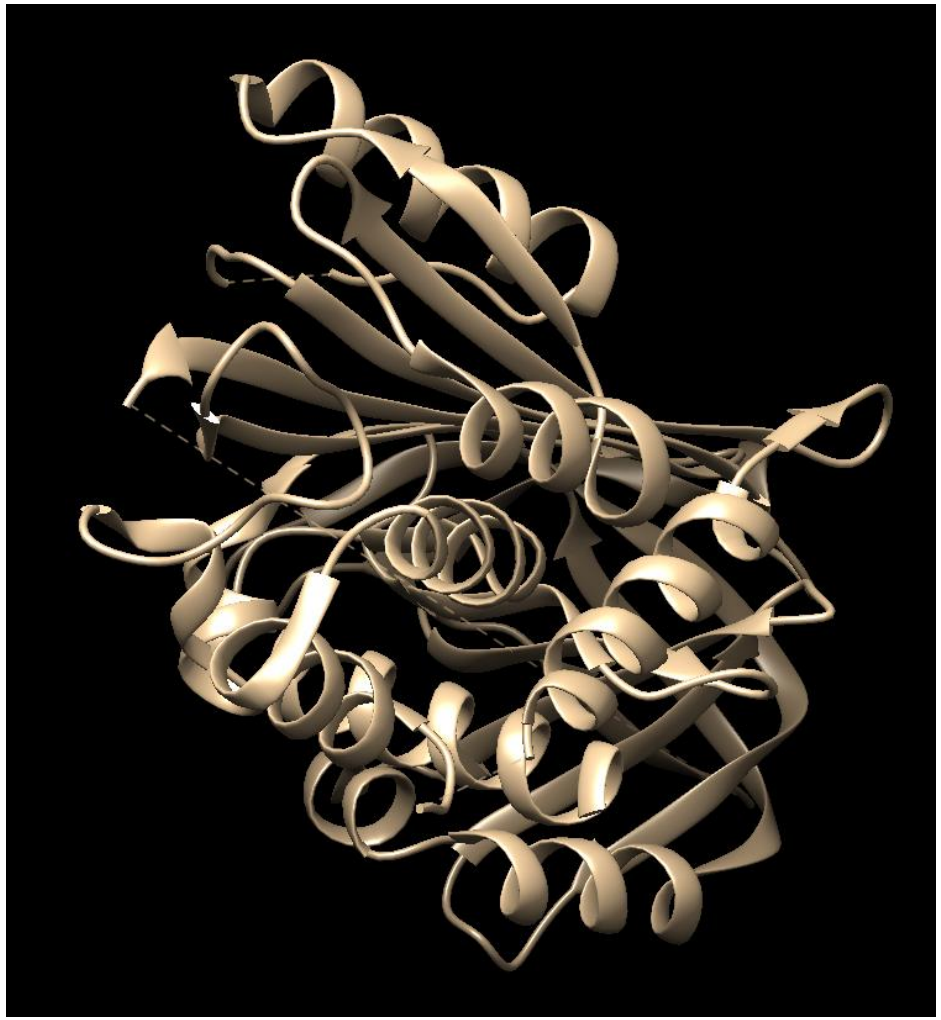


steroid 계 호르몬

혈당 상승
면역 억제 작용
탄수화물, 단백질, 지방의 대사 촉진

과한 염증 반응과 알러지 반응이 일어나지 않도록 조절해주는 역할

Corticosteroid Binding Globulin (Transcortin)



혈액에서 돌아다님

혈액에 있는 free cortisol과 binding 하여
cortisol이 cell로 이동하여 작용하는 것을 억제

free cortisol의 혈중 농도 조절

Corticoid Binding Globulin and Novel Ligand

Corticoid binding globulin에 대한 새로운 ligand는 cortisol에 경쟁적 저해제로써 작용
→ 체내 free cortisol의 농도 증가

기존 steroid 약물들은 Hydrocortisone (인공적으로 만들어진 cortisol) 을 단기간에 체내에 다량 투여
→ 즉각적으로 알러지 반응, 염증 반응 억제
→ 장기 복용할 경우 부작용 심함 (higher risk of infection, gastrointestinal bleeding …)

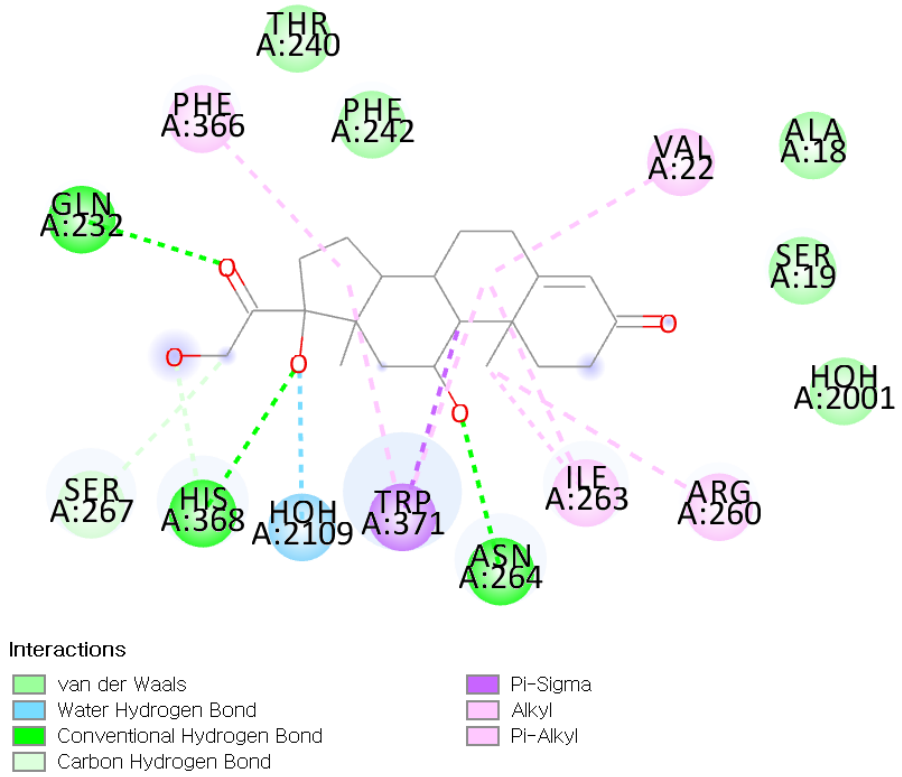
체내에서 자연적으로 생성된 cortisol을 최대한으로 사용하여 부족했던 cortisol 양을 늘리는 방법 고안
→ 우리 몸에서 나온 것인만큼 무리가 없을 것이다.
→ 장기적으로 적용하여도 부작용 덜 할 것이다.

보다 부담없는 약 개발의 후보로 CBG와 affinity가 좋은 ligand를 찾고자 하였다.

Checking missing residue at the active site

```
bee07@Dasan:~/Svina$ pdbCM 2vdy.pdb
['A', 'B']
[373, 373]
 *** Center of Mass Calculation(2020.01.28) ***
Protein Chain :   A (373 : SEQRES)
Protein Chain :   A (350 : 16 ~ 372)
Missing : 22 residues numbers
[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]
[76, 77, 78]
[165, 166, 167]
[350]
COM :    -18.3    16.7   -39.1
Min :    -42.1    -9.7   -73.1
Max :      5.5    44.6    -5.7

Ligand : HCY (      405.5 A^3)
COM :     -8.7     2.9   -39.5
Min :    -11.8     0.5   -44.0
Max :     -3.9     5.5   -33.7
Ma1 :      3.1     2.4     4.5
Ma2 :      4.8     2.6     5.8
```



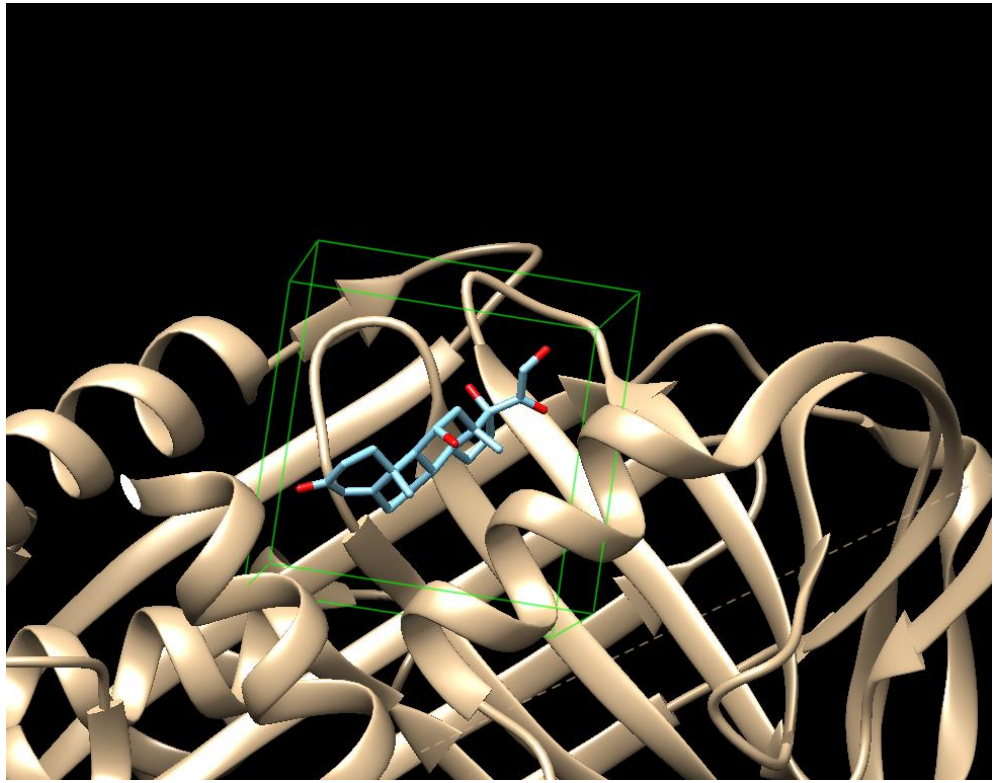
Chimera로 2VDY에 대한 pdb file을 생성한 후 pdbCM으로 missing residue number를 구했다.

BioVia를 통해 interaction을 시각화하여 missing residue가 active site에 포함되었는지 확인하였다.

Checking box for docking with AutoDock Vina

```
Ligand : HCY (     405.5 A^3)
COM :    -8.7    2.9   -39.5
Min :   -11.8    0.5   -44.0
Max :    -3.9    5.5   -33.7
Ma1 :     3.1    2.4     4.5
Ma2 :     4.8    2.6     5.8
```

```
conf='''
receptor = Receptor.pdbqt
center_x = -8.0
center_y = 2.9
center_z = -39.5
size_x = 14
size_y = 14
size_z = 14
```



pdbCM으로 ligand의 center 좌표를 구하고, ma1+ma2 값으로 box size를 먼저 지정해주었다.

Box 안에 ligand가 다 들어가는지 확인하고 튀어 나온 경우 box size를 늘리면서 조정하였다.

SGE docking Tools

Python coding : make configure file / pick 1000 molecules from EDB randomly

Open Babel (obabel) : pbd → pqdqt / sdf → pdbqt

Rdconf.py : smiles code → sdf

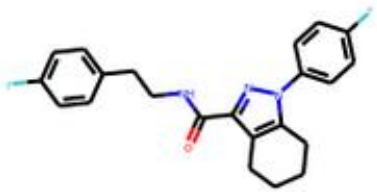
Smina : dock receptor and ligand

Rdkit : sdf → png

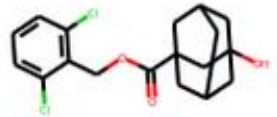
Top 10 ligands with high affinity (=low score)

Z31198425_1
score : -9.4

Z91651150_1
score : -9.4

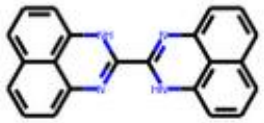


Z224561190_1
score : -9.3



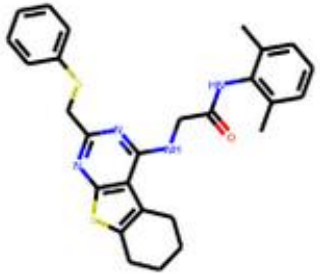
Z25060464_1
score : -9.2

Z26394060_1
score : -9.1



Z56782973_1

Z136992094_1



Z31177230_1

Z2453042365_1

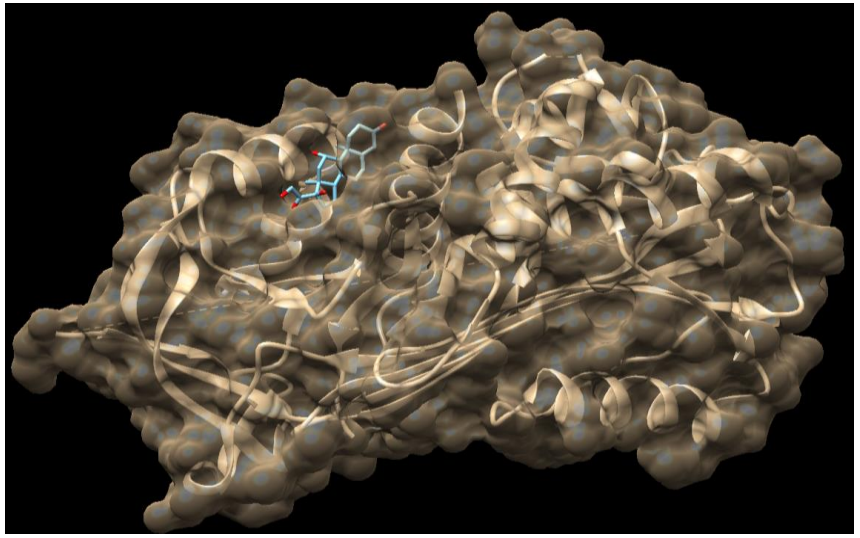
Z87666151_1

EDB에서 random하게 1000개의 molecul을 뽑아 Smina를 이용해 transcortin과 docking을 하여 각 molecule마다 score를 얻었다.

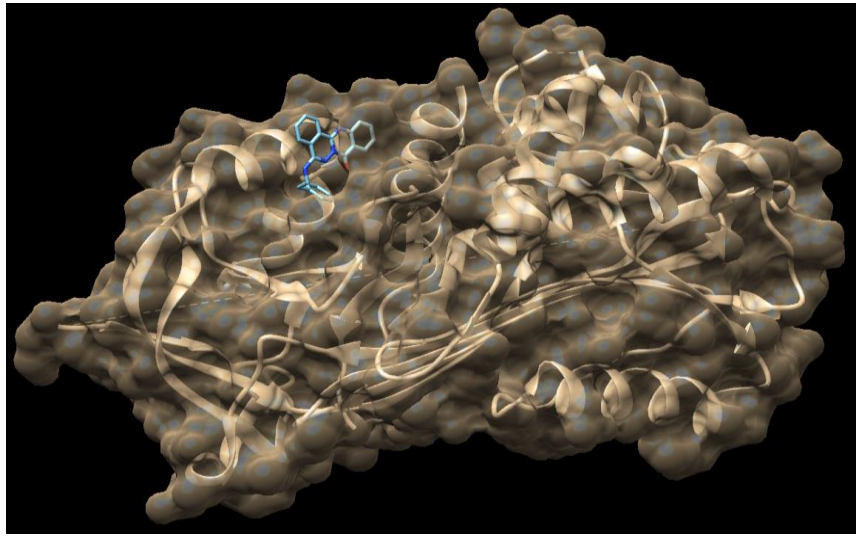
Affinity가 가장 좋은 (=score가 가장 낮은) 20개의 molecule에 대해 그림을 그려 보았다.

Cortisol & Z31198425

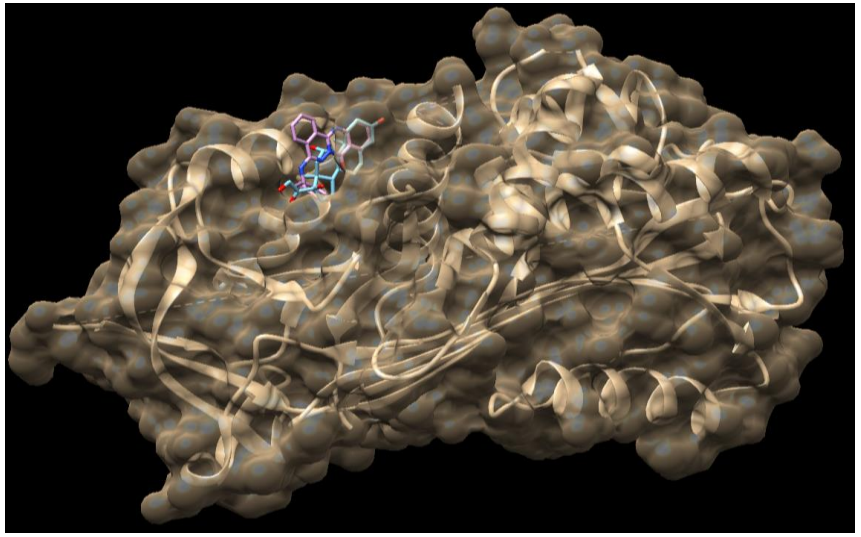
LIGAND



Z31198425



BOTH



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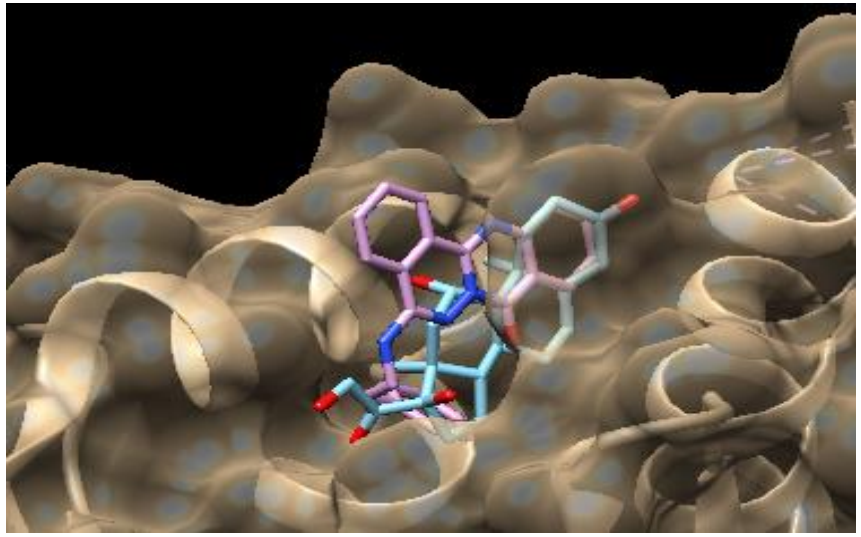
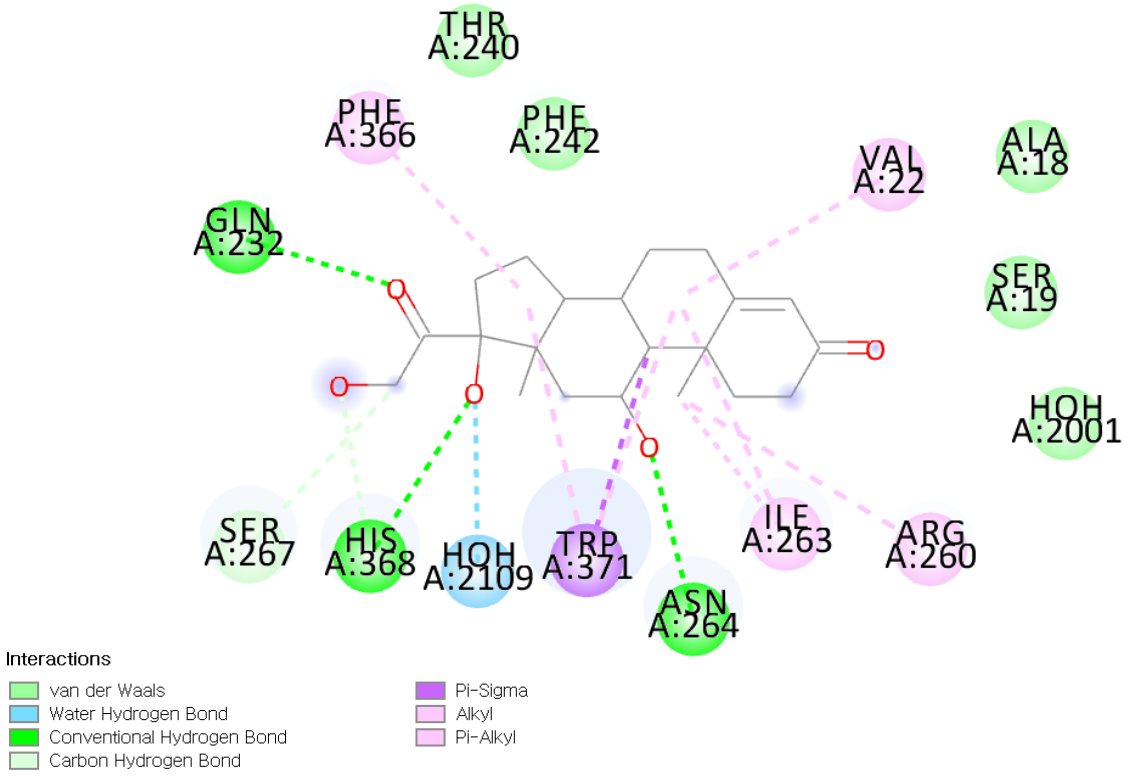
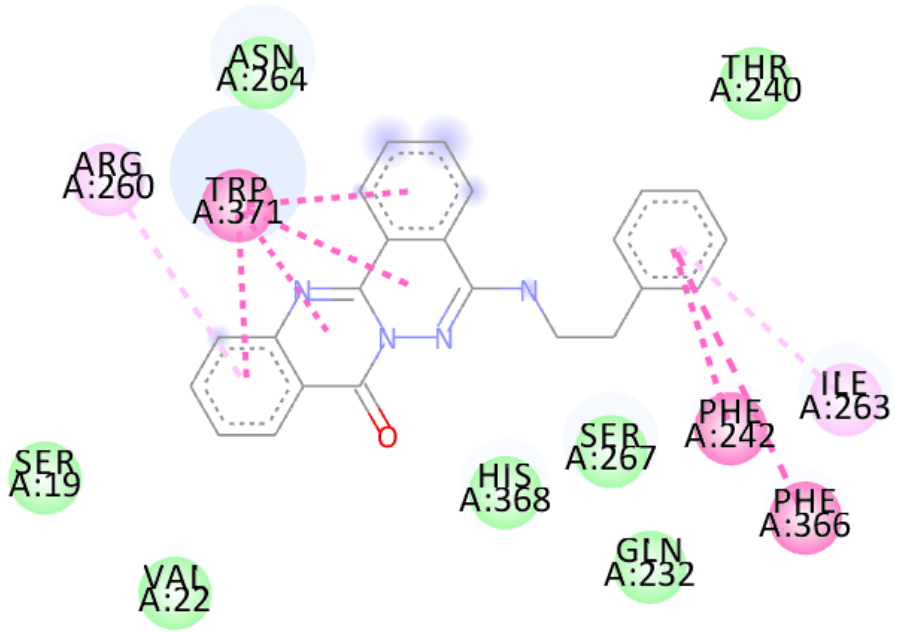


Cortisol & Z31198425

LIGAND



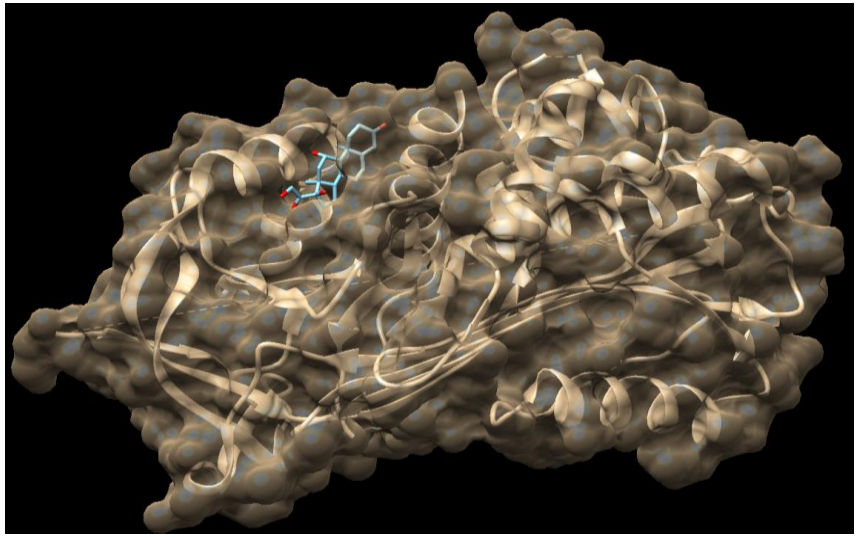
Z31198425



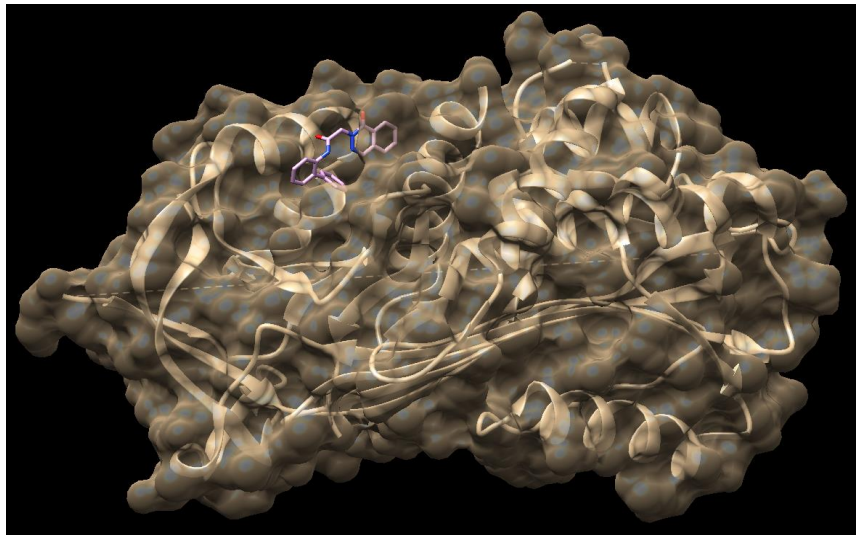
Receptor의 residue 18 이 ligand와 interaction을 하지 않게 되었고, 19 240 263 제외하고는 interaction 종류가 바뀌었다.

Cortisol & Z91651150

LIGAND



Z91651150



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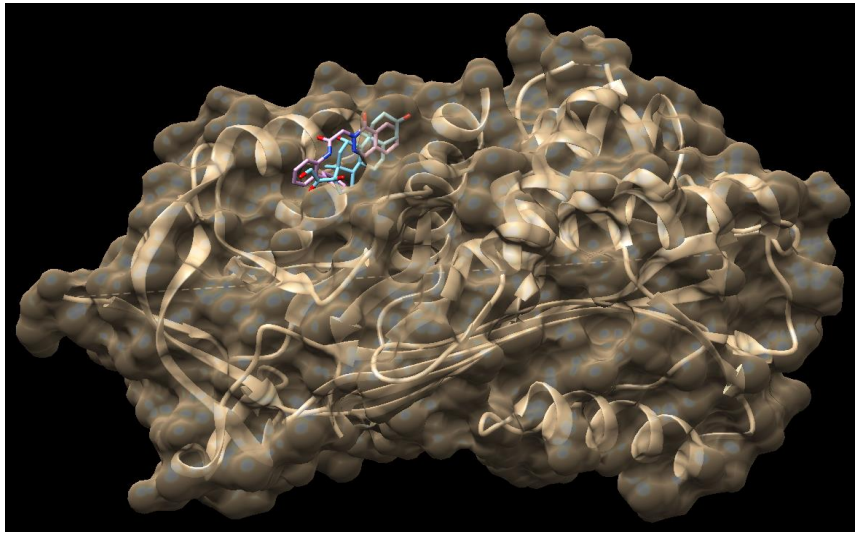

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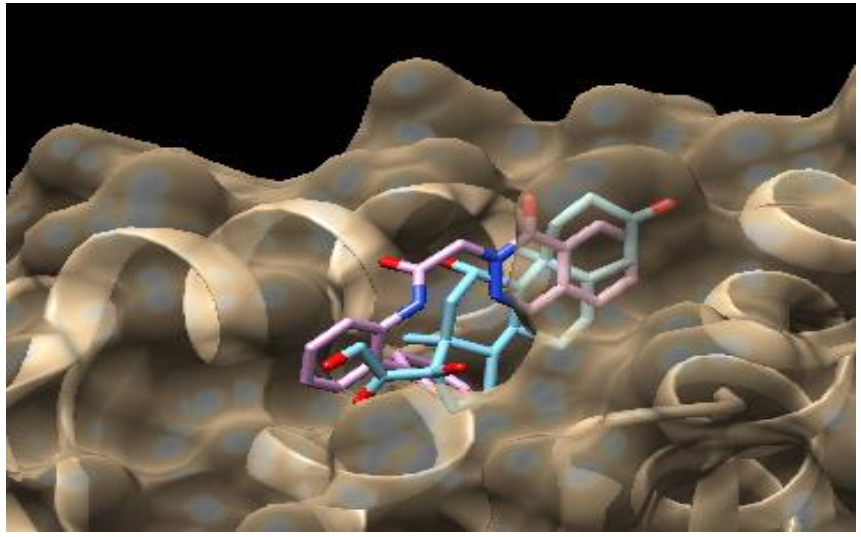
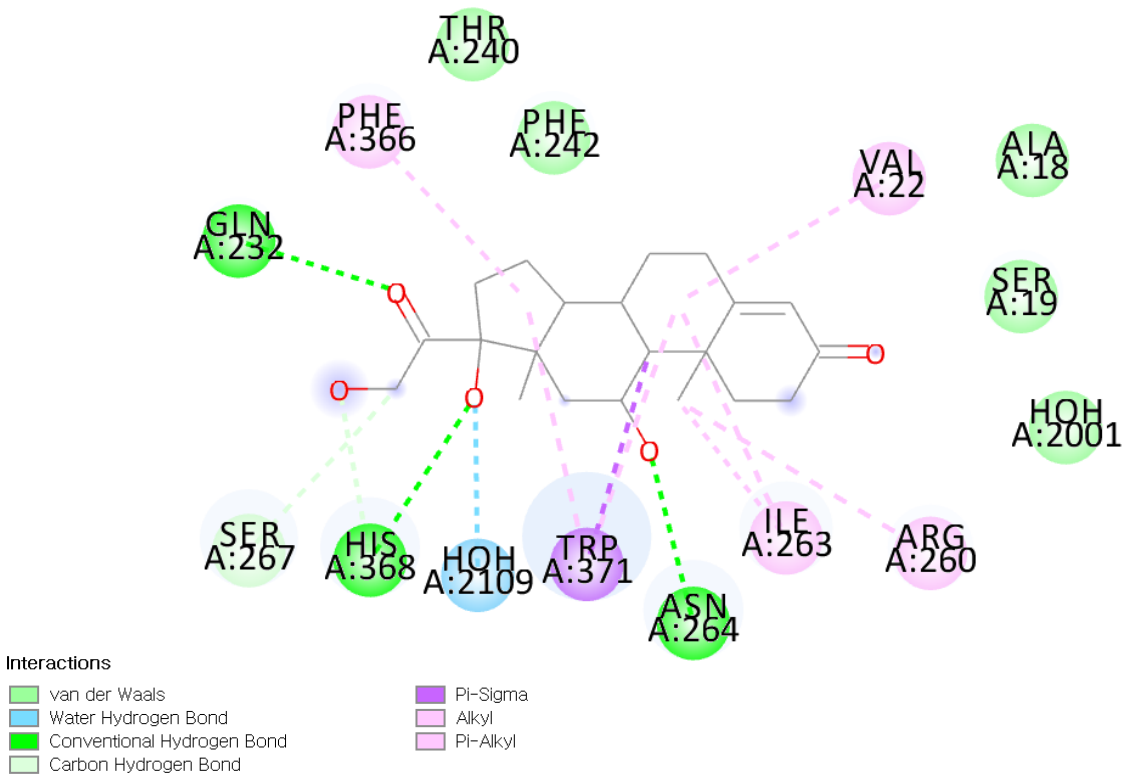
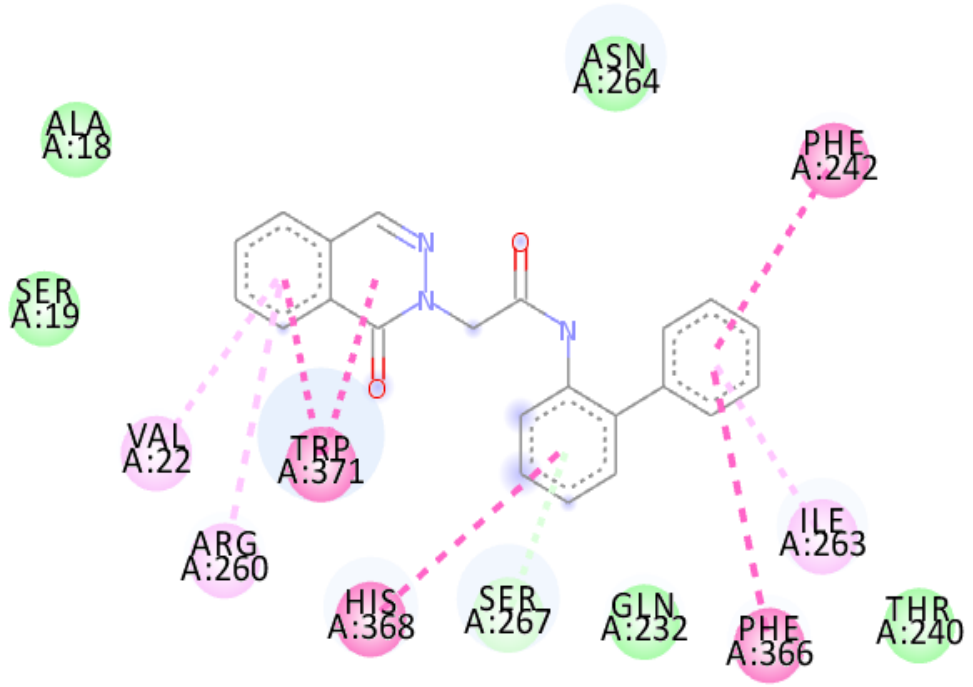


Cortisol & Z91651150

LIGAND



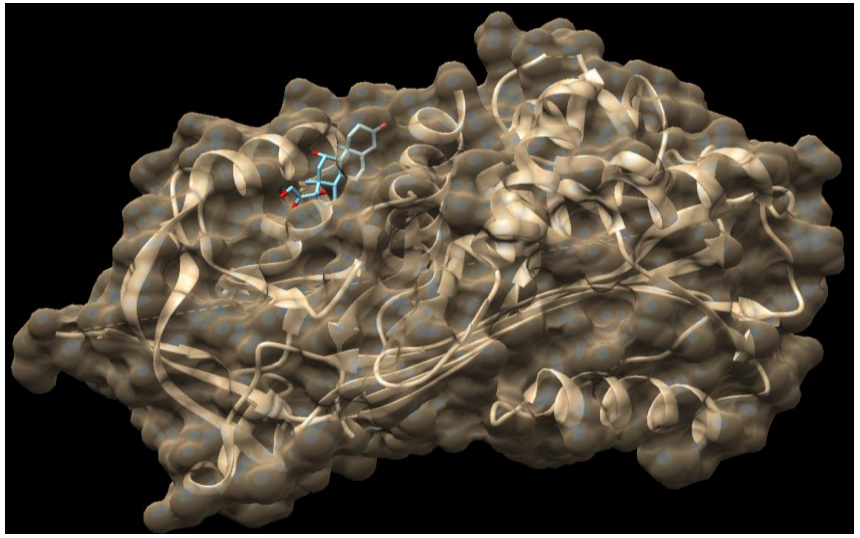
Z91651150



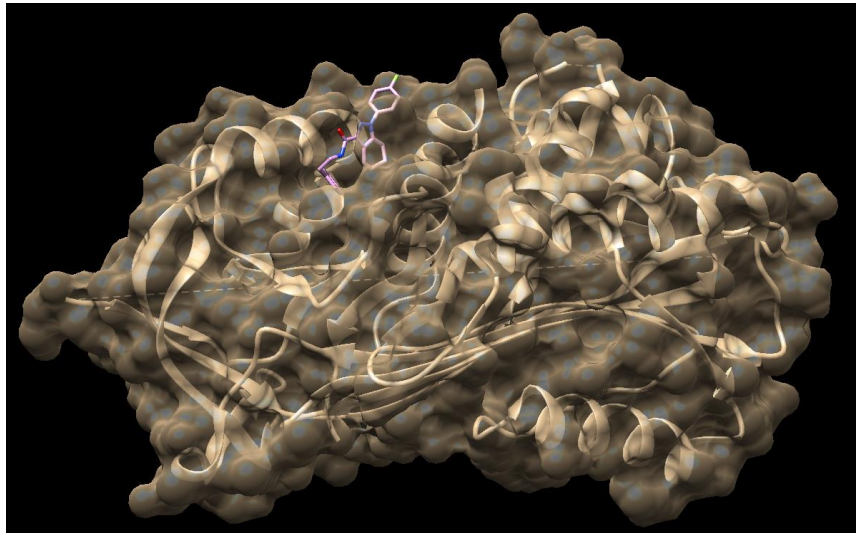
Ligand와 interaction하는 receptor의 residue에는 변화가 없으나 interaction 종류가 residue 18 19 22 267 240 빼고 다 바뀌었다.

Cortisol & Z224561190

LIGAND



Z224561190



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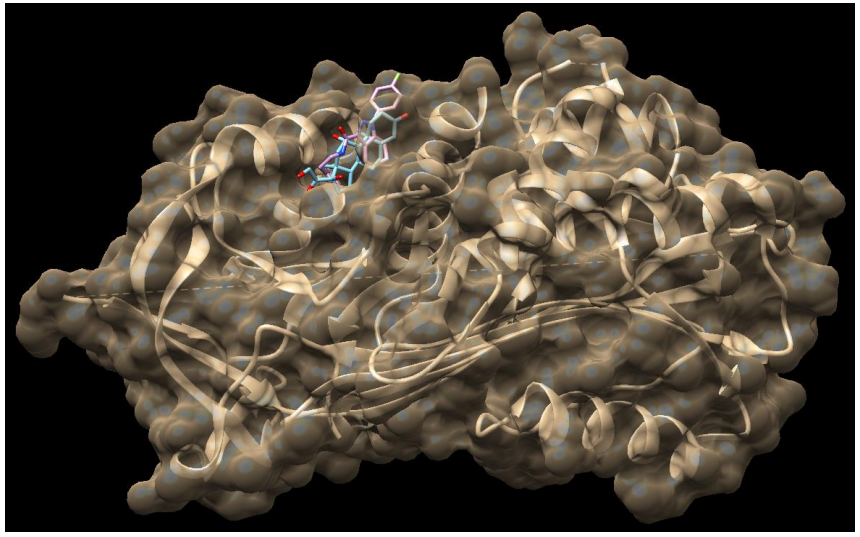
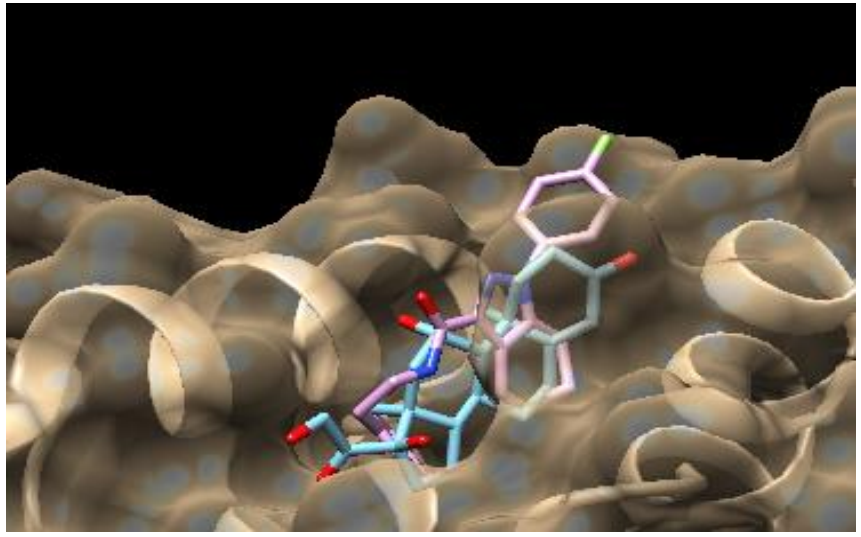
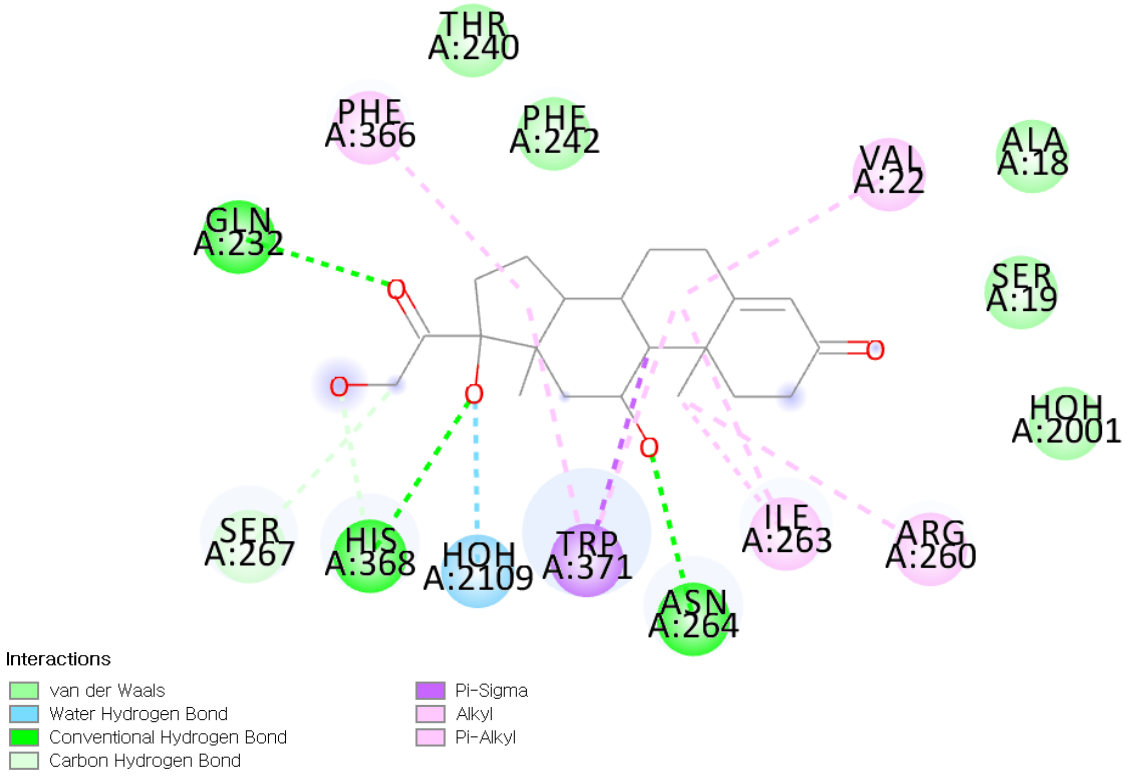


BOTH

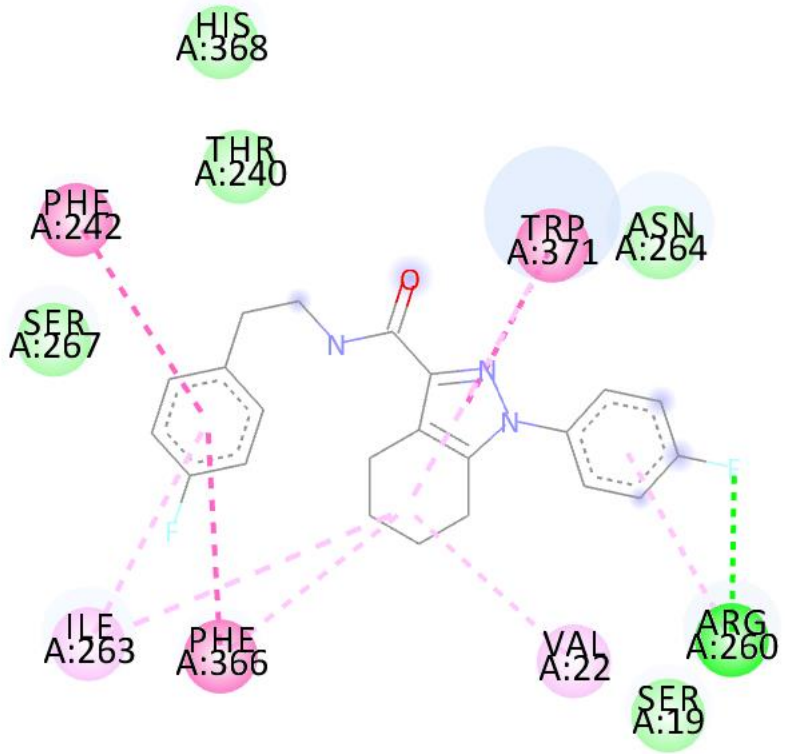


Cortisol & Z224561190

LIGAND



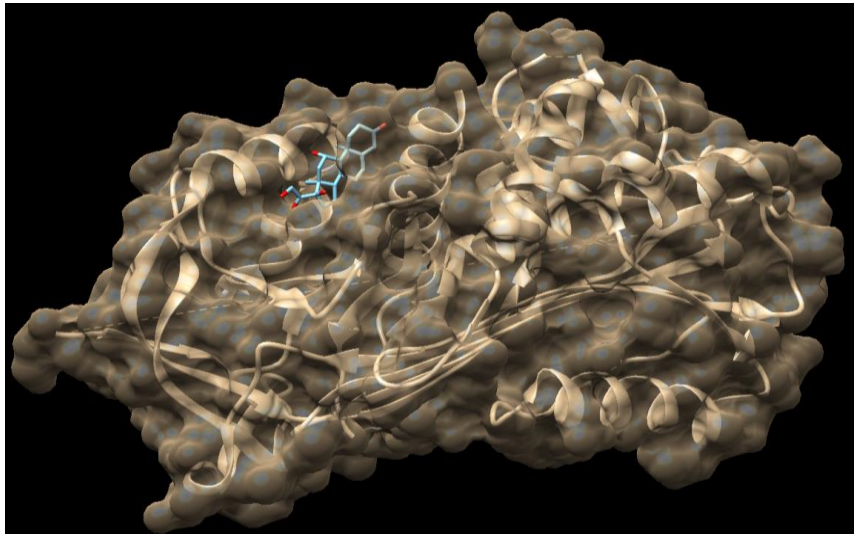
Z224561190



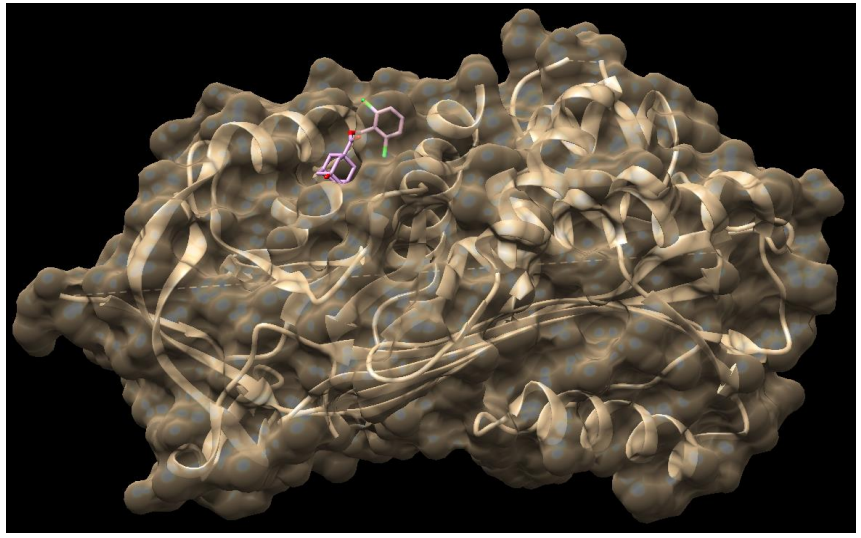
Receptor의 residue 242 232 18 이 ligand와 interaction을 하지 않게 되었고, 263 22 19 240 제외하고는 interaction 종류가 바뀌었다.

Cortisol & Z25060464

LIGAND



Z25060464



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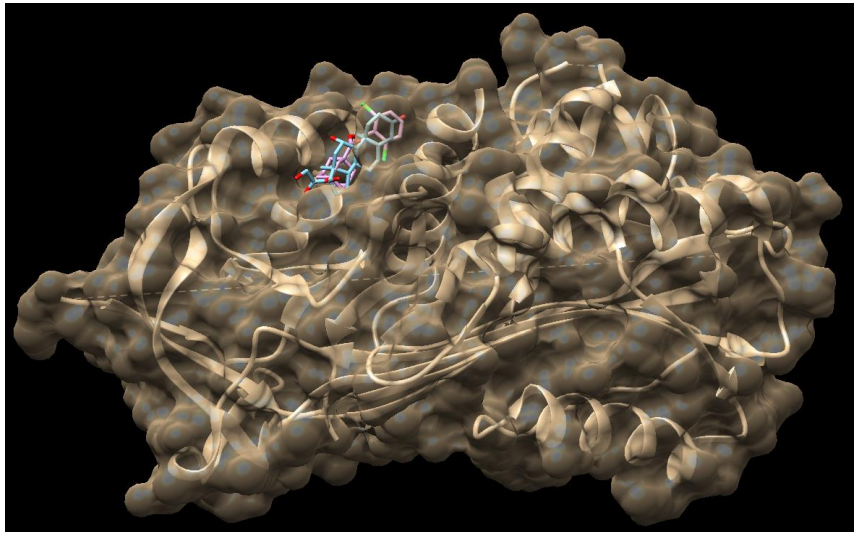

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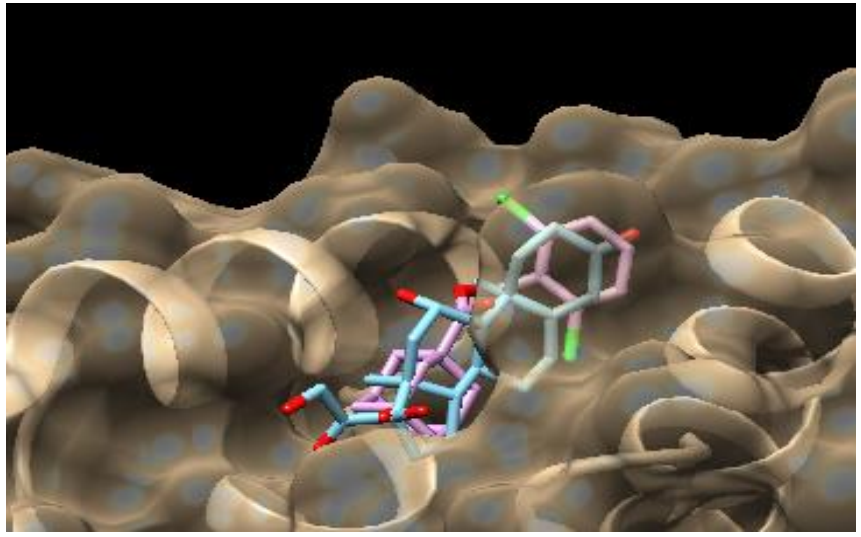
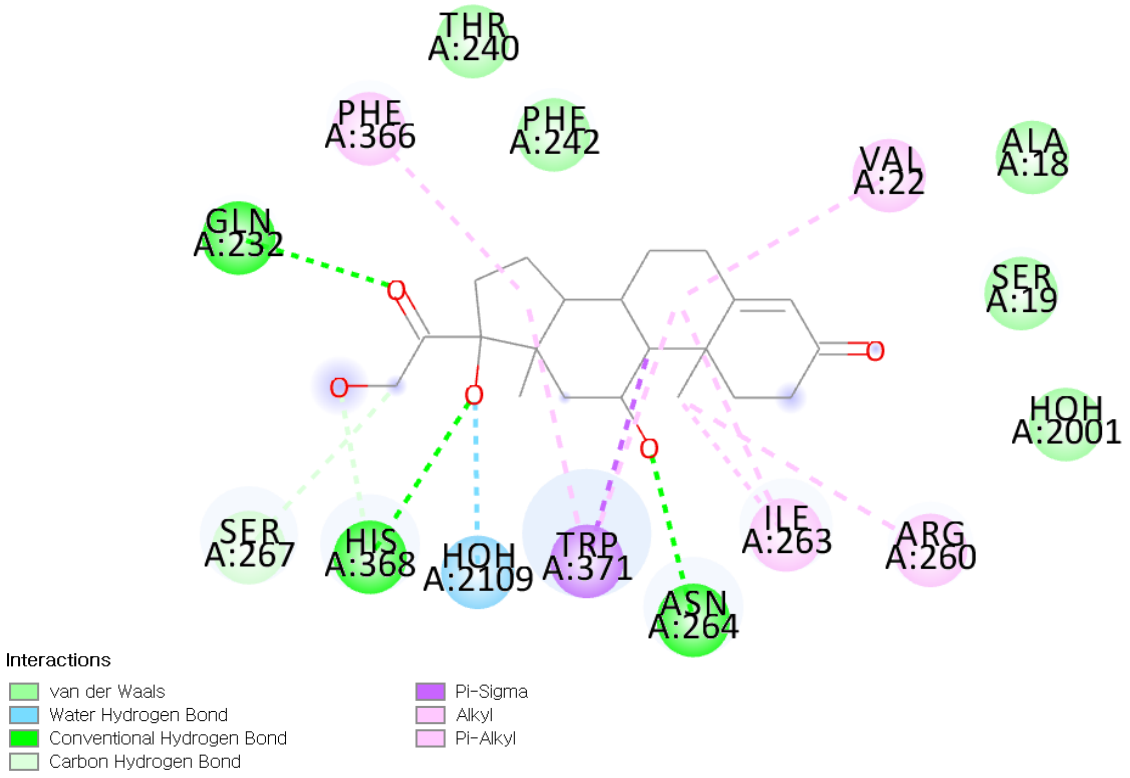
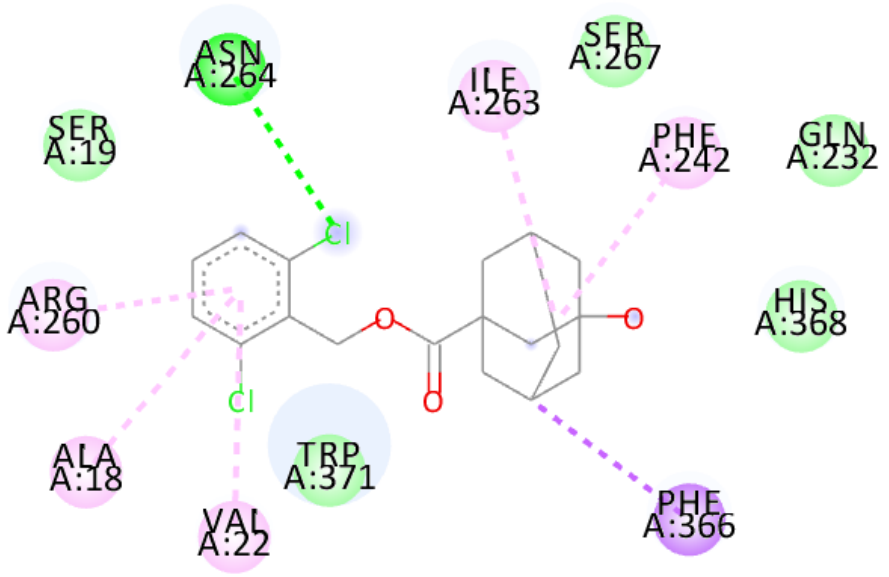


Cortisol & Z25060464

LIGAND



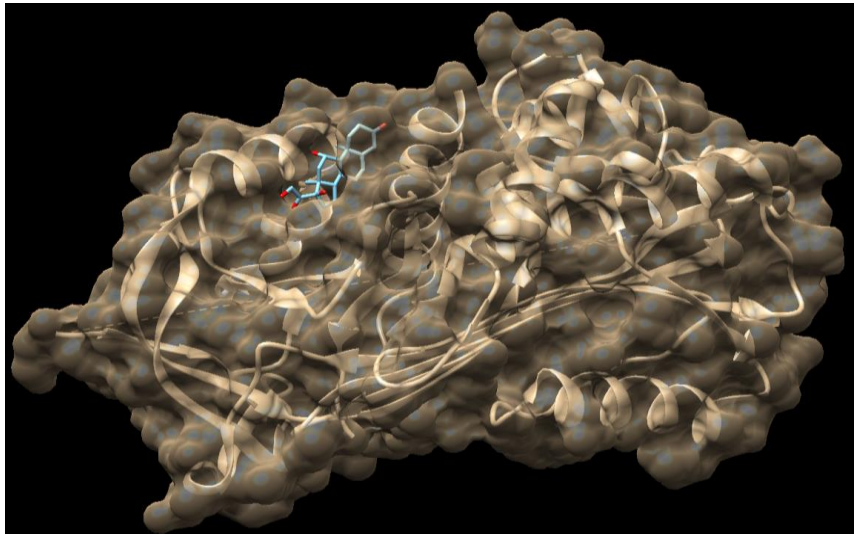
Z25060464



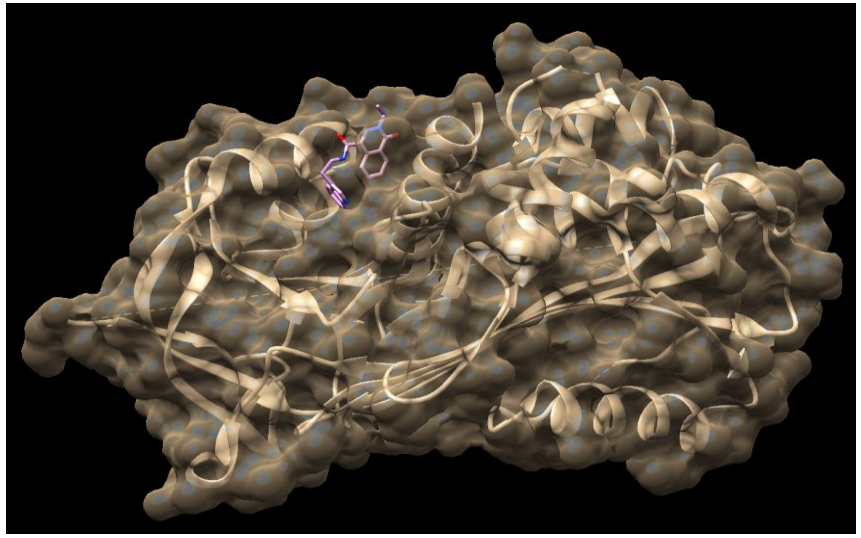
Receptor의 residue 240 이 ligand와 interaction을 하지 않게 되었고, 22 19 264 263 제외하고는 interaction 종류가 바뀌었다.

Cortisol & Z26394060

LIGAND



Z26394060



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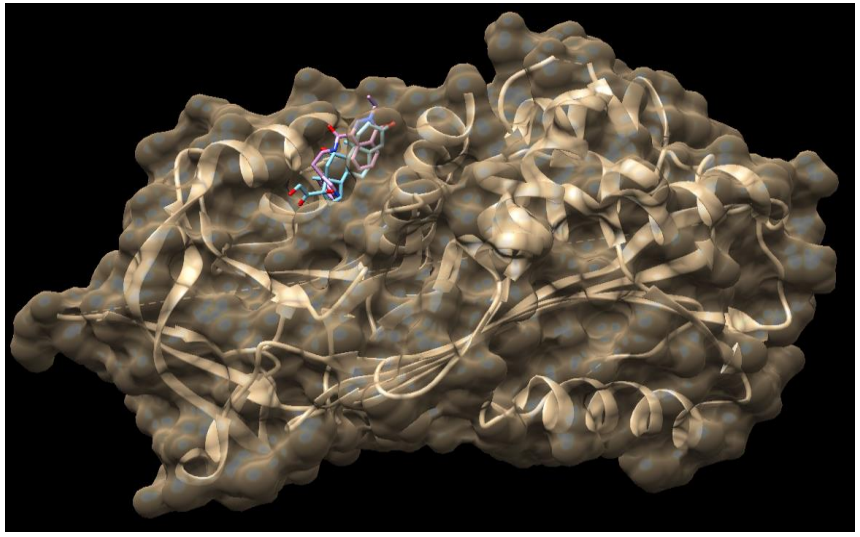

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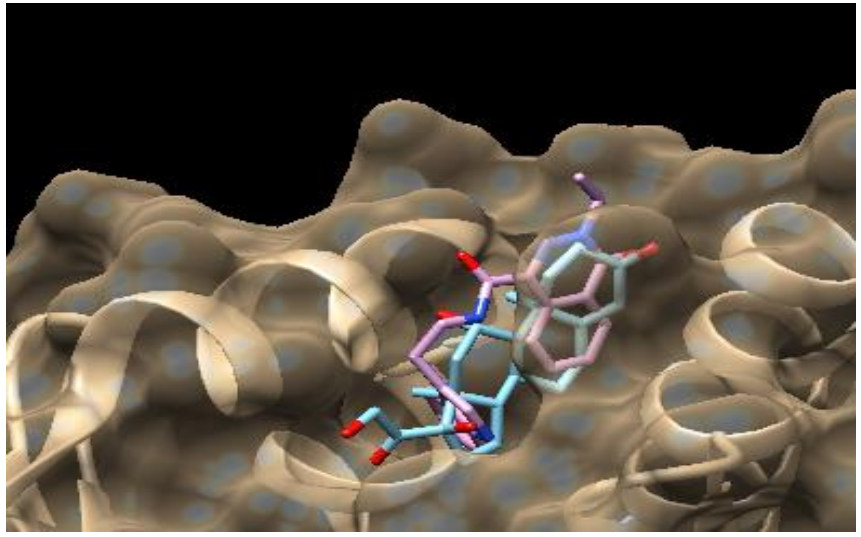
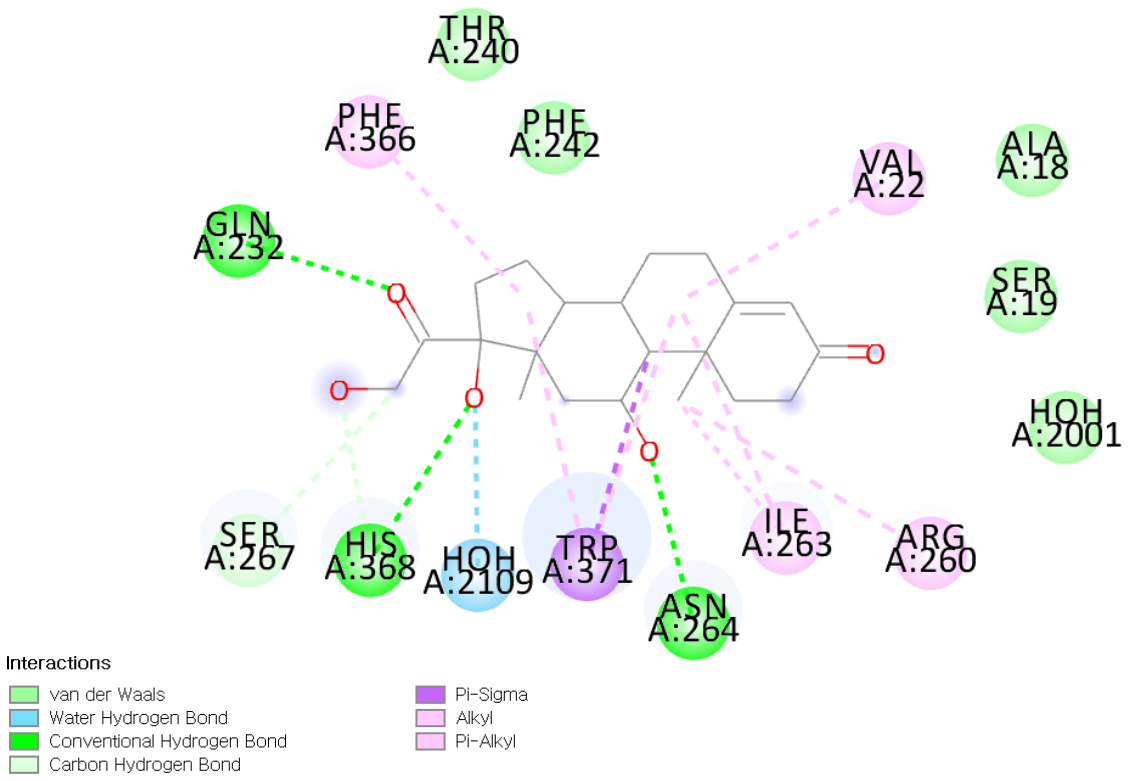
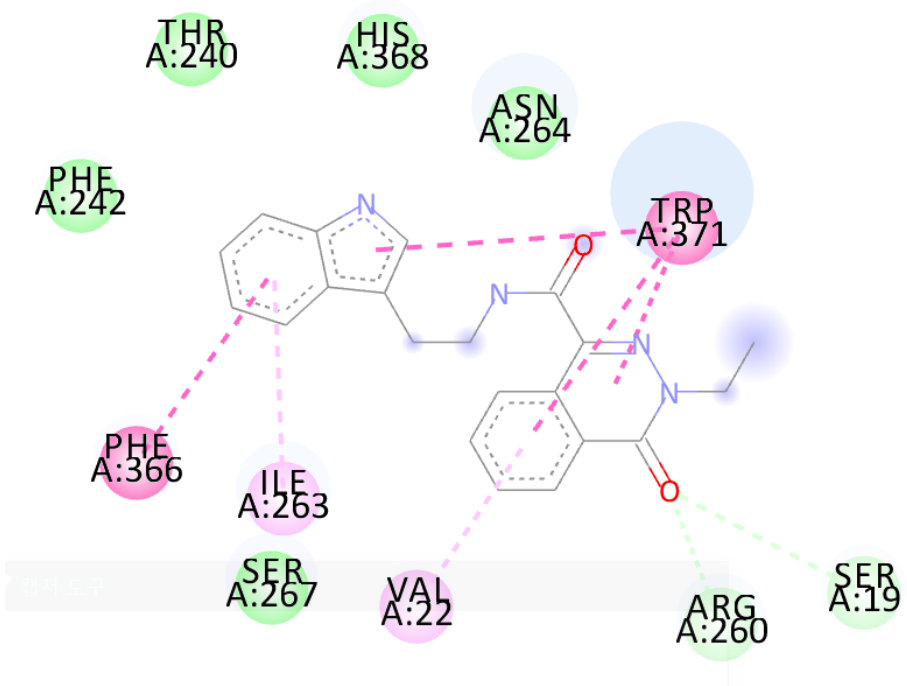


Cortisol & Z26394060

LIGAND

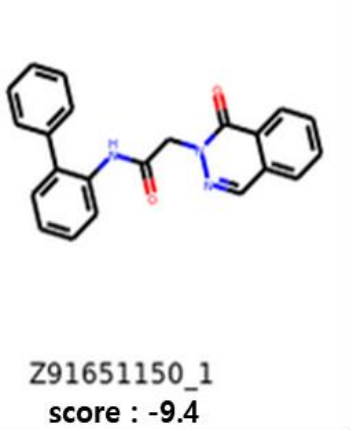


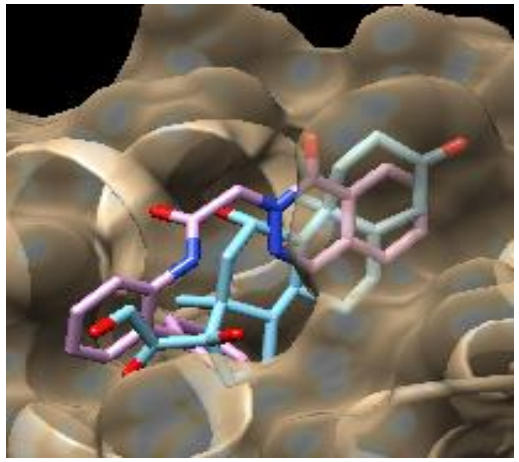
Z26394060



Receptor의 residue 18 232 이 ligand와 interaction을 하지 않게 되었고, 22 263 242 240 제외하고는 interaction 종류가 바뀌었다.

Discussion & Conclusion





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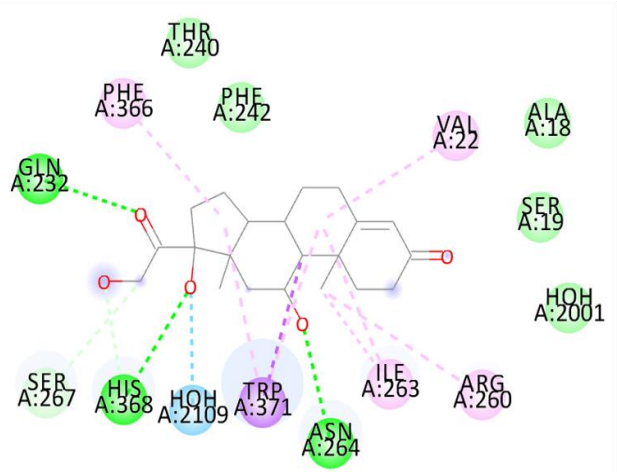
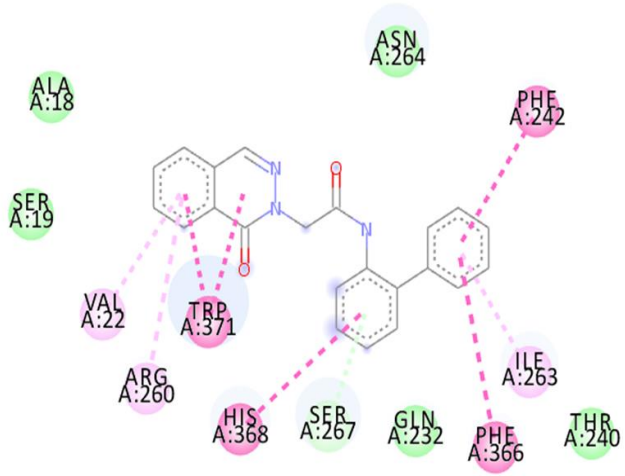


Z91651150



Z91651150_1은 5개의 후보 ligand들 중에서 score가 -9.4로 가장 낮다.
Chimera로 cortisol과 동시에 불러왔을 때도 두 ligand의 많은 부분이 포개져 있음을 볼 수 있었다.
이를 통해 둘의 binding 성격이 비슷함을 예측할 수 있었다.
BioVia를 통해 receptor-ligand interaction을 봤을 때도 interaction 종류는 조금 다르긴 하나 interaction하는 residue에는 차이가 없음을 알 수 있었다.

이 때문에 cortisol과 가장 비슷하다고 보이는 ligand는 Z91651150_1이라고 생각하여
좋은 신약 후보가 될 수 있을 것이라고 판단하였고,
실제 상용화를 위해서는 실험적인 연구 (독성테스트, 실제 효과) 가 더해져야 한다고 결론내었다.

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