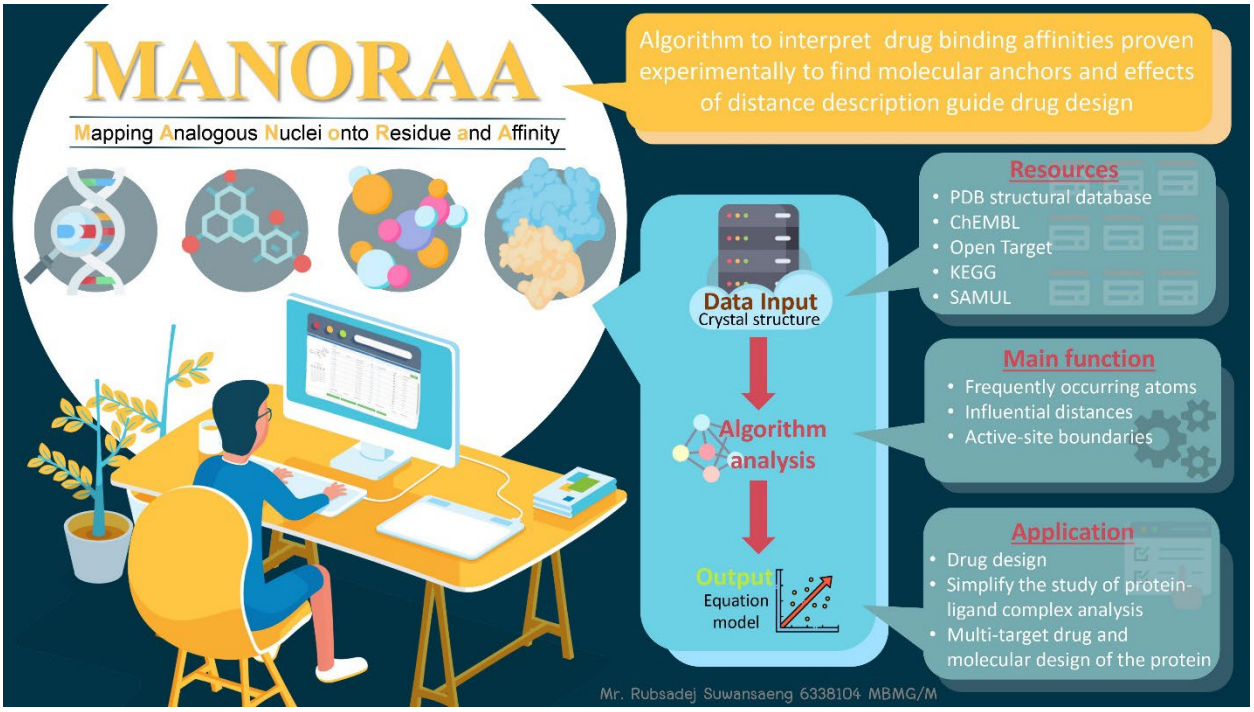
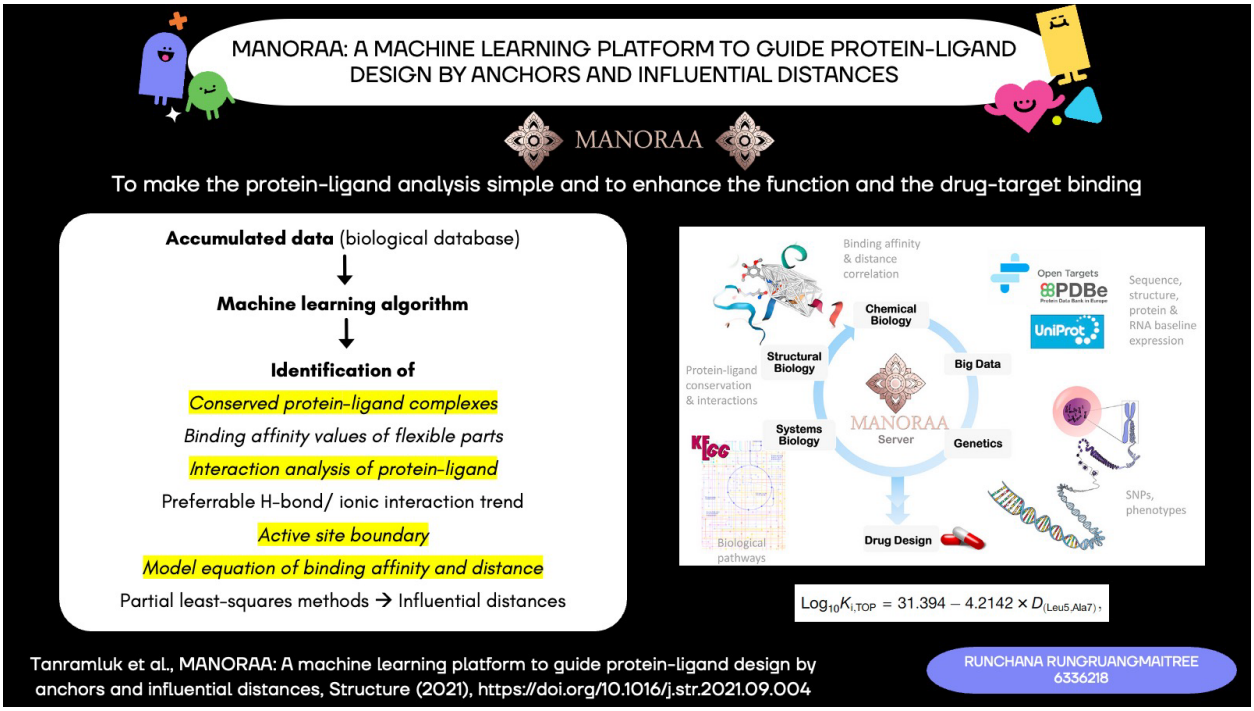
MANORAA functions and example of drug research done using AI-driven Drug Discovery Platforms

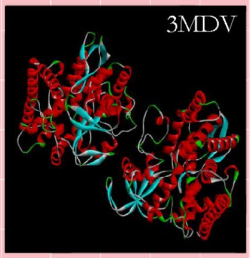




Isara Nachampa 6137814 MBMG/M

Clotrimazole

Target protein



Clotrimazole complex of Cytochrome P450 46A1

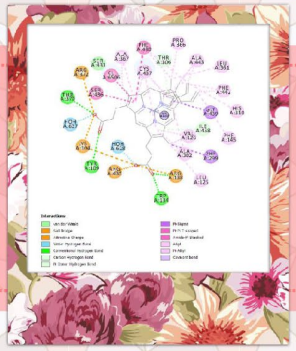
Clotrimazole, an imidazole derivative with a broad spectrum of antimycotic activity, inhibits biosynthesis of the sterol ergostol, an important component of fungal cell membranes. Clotrimazole inhibits ergosterol synthesis, and inhibit the transformation of yeasts to mycelial forms and the uptake of purine. Clotrimazole is used to treat yeast infections of the vagina, mouth, and skin such as athlete's foot, and body ringworm. It can also be used to prevent oral thrush in certain patients.

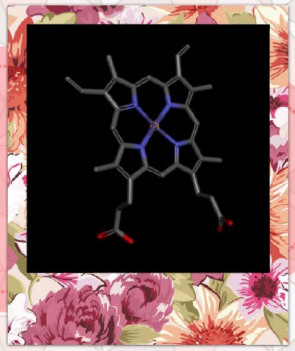
Symptoms of overdose include erythema, stinging, blistering, peeling, edema, pruritus, urticaria, and general irritation of the skin, and cramps.

STRUCTURE STUDIES

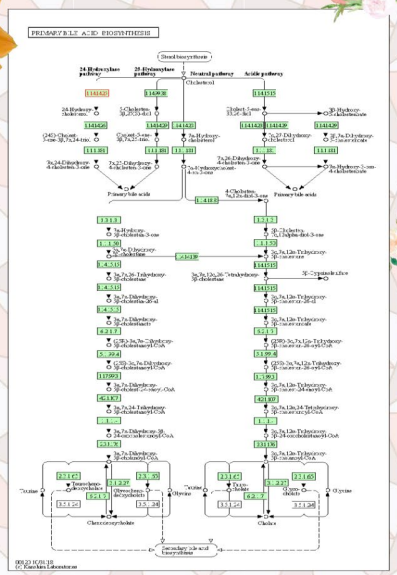
CONSERVED INTERACTION

PROTEIN-LIGAND INTERACTION





PATHWAY



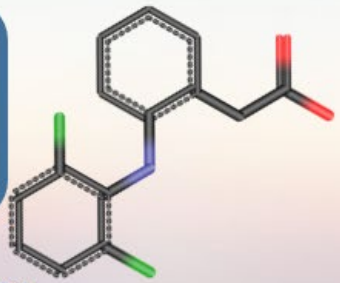
PROTEIN/RNA EXPRESSION

Conclusion

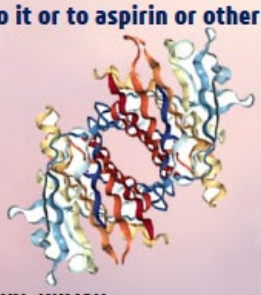
The information from studying Clotrimazole and target protein show the structural studies, pathway, protein/RNA expression, and target protein of Clotrimazole. The advantages of using the MANORAA program, it can decrease time-consuming and costs to develop the efficiency of the drug and reduce the side effects

Reference: www.MANORAA.org

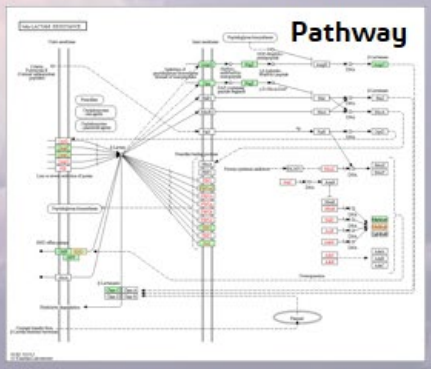
DICLOFENAC

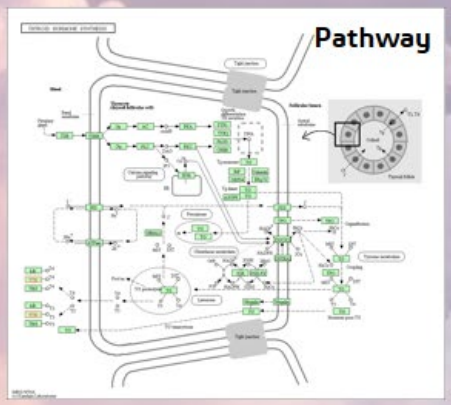


Diclofenac is a potent non-steroidal anti-inflammatory drugs (NSAIDs) taken or applied to reduce inflammation and as an analgesic reducing pain in certain conditions. It is supplied as or contained in medications under a variety of trade names, so it has side effect include Upset stomach, Nausea, Heartburn, Diarrhea, Constipation, Gas, Headache, Drowsiness, Dizziness and before taking diclofenac should be concern about allergic to it or to aspirin or other NSAIDs may occur.

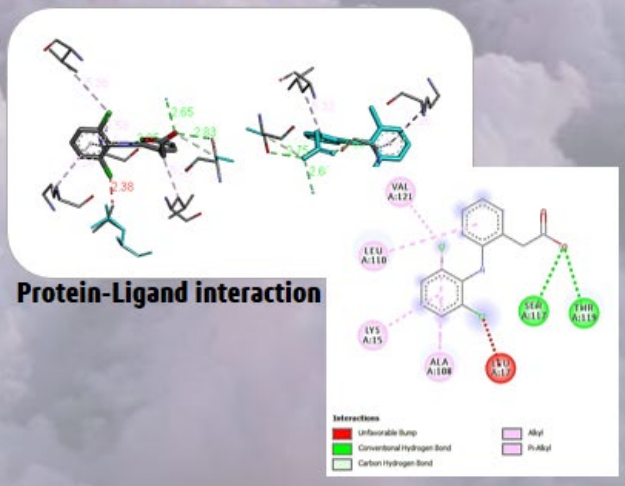


Target protein TTHY_HUMAN
HUMAN TRANSTHYRETIN IN COMPLEX WITH DICLOFENAC

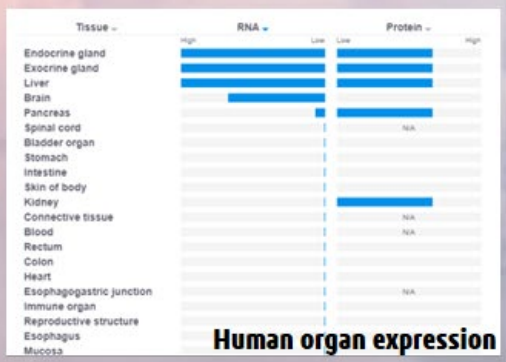




Diclofenac (Voltaren®) targets COX1 and COX2. It is also prescribed for numerous inflammatory pains, in particular joint pains such as in arthrosis or sciatica. It is used in the composition of creams and plasters used for sprains. Diclofenac is also prescribed in pediatrics because it is very effective against ear infections for example. It was discovered in the 1970s and is now in the public domain.



Protein-Ligand interaction



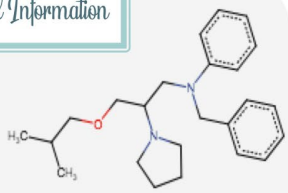
Human organ expression

Iyacoob Khunsri 6137816

Bepridil

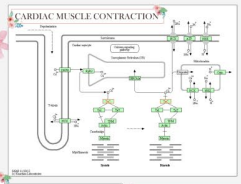
By: Patcharaporn Ruamwong
Institute of Molecular Biosciences Mahidol University

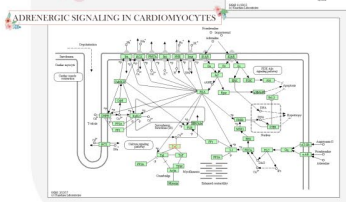
Bepridil Information

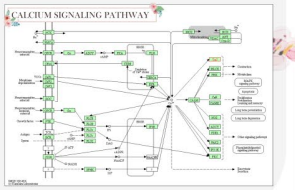


Bepridil is a long-acting calcium-blocking agent with significant anti-anginal activity. The drug produces significant coronary vasodilation and modest peripheral effects.
It has antihypertensive and selective anti-arrhythmia activities and acts as a calmodulin antagonist. Bepridil is a long-acting calcium-blocking agent with significant anti-anginal activity. The drug produces significant coronary vasodilation and modest peripheral effects. It has antihypertensive and selective anti-arrhythmia activities and acts as a calmodulin antagonist.

Pathway

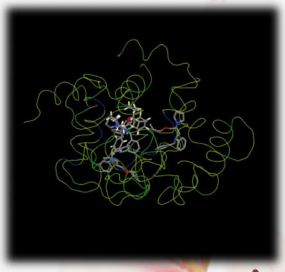




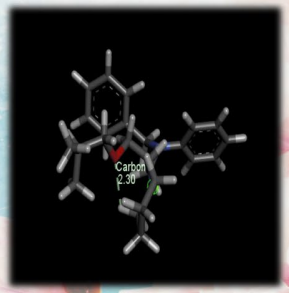


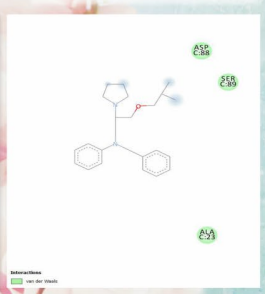
Structural Studies

Conserved Interaction

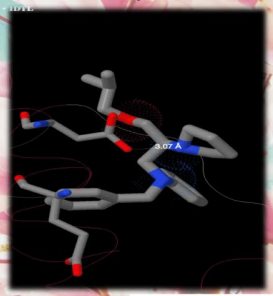


Conserved Interaction

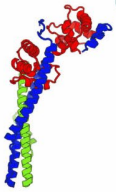




Protein-Ligand Interaction



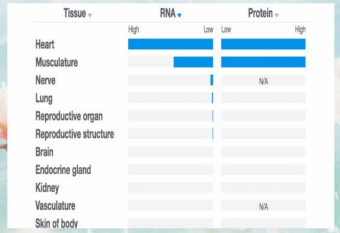
Target Protein



1LXF

Structure of the Regulatory N-domain of Human Cardiac Troponin C in Complex with Human Cardiac Troponin-I(147-163) and Bepridil

Protein/RNA Expression



Tissue	RNA	Protein
	High Low	Low High
Heart		
Musculature		
Nerve		N/A
Lung		
Reproductive organ		
Reproductive structure		
Brain		
Endocrine gland		
Kidney		
Vasculature		N/A
Skin of body		

Conclusion

Bepridil's information from MANORAA website show the structural studies, pathways, target protein and protein/RNA expression of bespridil. These informations make practical use for drug design. In addition, it can safe the time and decrease the cost to improve the efficiency of the drug and reduce the side effects of any factors for biochemical and medical research.

References: www.manoraa.org

Irosustat : Pharmacological treatment of hormone-sensitive cancers and endometrial cancer

Author: Natthakorn Ardyotha
Advisor: Dr. Duangrudee Tanramluk

Abstract

Cancer is a killer disease in Thailand. More than 122,000 new patients are diagnosed with cancer each year. This report focused on a drug in clinical trials called Irosustat. It has been used as a pharmacological treatment for hormone-sensitive cancers, i.e., breast, prostate, and endometrial cancers. The study shows that irosustat is an orally active, irreversible, nonsteroidal inhibitor for steroid sulfatase (STS), so it prevents the body from producing estrogen and androgen. In addition, the drug can bind to carbonic anhydrase II (CA II), thereby affecting various pathways in the body, which may lead to several side effects.

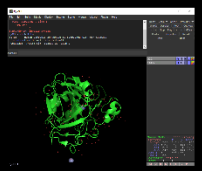
Methodology

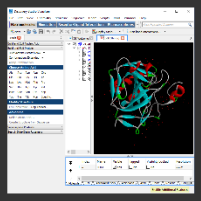
Search for Irosustat at Manoraa database

Investigate the information of irosustat, which contains of:

- UniProt
- KEGG Pathway
- Target protein
- PDB file
- etc.

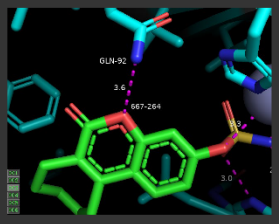
Analyzing and visualizing the protein by download PDB file, using bioinformatics tools, i.e., PyMOL and Biovia: Discover Studio Visualizer .

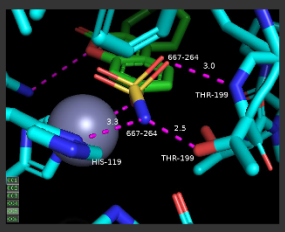


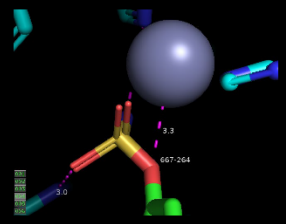


Result

Irosustat is an orally active, irreversible, nonsteroidal inhibitor for steroid sulfatase (STS). It is under clinical trials. It prevents the body from producing estrogen and androgen by preventing the conversion of hormonally inactive steroid sulfates such as dehydroepiandrosterone sulfate (DHEA-S) and estrone sulfate (EIS) by STS into their respective active forms, i.e. DHEA and estrone. These precursor compounds can be transformed into more potent androgens and estrogens, respectively.







The drug can bind to carbonic anhydrase II (CA II). thereby affecting various pathways in the body as follows: nitrogen metabolism, proximal tubule bicarbonate reclamation, collecting duct acid secretion, gastric acid secretion, pancreatic secretion, and bile secretion pathways.

Discussion

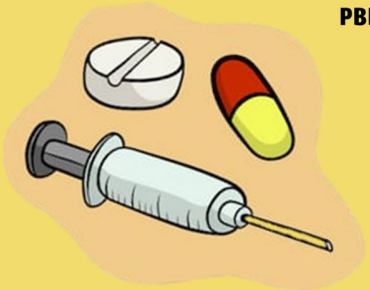
Irosustat has a function as a nonsteroidal inhibitor of steroid sulfatase (STS). Inhibiting STS prevents the body from producing estrogen and androgen by preventing the conversion of hormonally inactive steroid sulfates. The drug has been beneficial since it is irreversible, so the patients can be treated their hormone-sensitive tumor. The study shows that the drug can bind to carbonic anhydrase II (CA II). CAII is critical for acid-base homeostasis and bone remodeling. So inhibition may cause alkalinization of urine resulting from increased bicarbonate excretion which may promote development of oxalate kidney stones. Furthermore, by using this technique, it may help researchers discover the affected pathways by any kind of drug or may help pioneer any target in biological pathways with a low scientific trial cost.

References: 1.https://manoraa.icbs.mahidol.ac.th/Manoraa/ssta/ligandquery.php?queryby=lig&lignum=667&drugname=Irosustat 2.https://pubchem.ncbi.nlm.nih.gov/compound/Irosustat 3.https://pubmed.ncbi.nlm.nih.gov/21342037/ 4.https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/irosustat

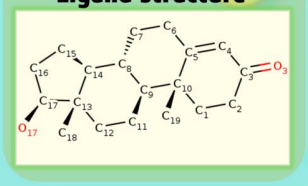
Contact: Department of Biochemistry, Faculty of Science, Khon Kaen University, Email: natthakorn.a@kkumail.com

TESTOSTERONE

PBD code: 1J96

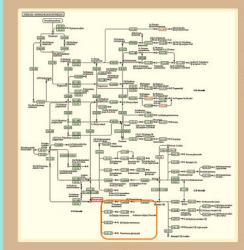


Ligand structure



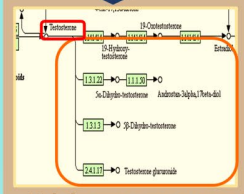
Pathway

Steroid Hormone Biosynthesis



Steroid hormone biosynthesis - Homo sapiens (human)

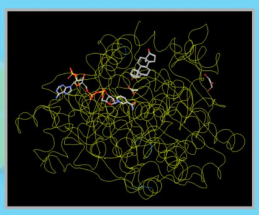
- Steroid hormones derived from cholesterol are a class of biologically active compounds in vertebrates.
- Pregnenolone and progesterone are the starting materials for the three groups of steroids: C21 steroids of glucocorticoids and mineralocorticoids, C19 steroids of androgens, and C18 steroids of estrogens.



- Male hormone testosterone is formed from pregnenolone by two pathways, delta5 pathway via dehydroepiandrosterone and delta4 pathway via androstenedione.
- Female hormones estrone and estradiol are formed from testosterone and 4-androstene-3,17-dione by oxidative removal of the C19 methyl group and subsequent aromatization of ring A.

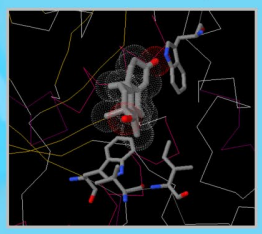
Structural studies

Conserved Interaction



Position-specific interaction by highlighting the active site based on the percent conservation of the atomic position surrounding the ligand substructure for TES superposed complexes.

Protein-Ligand Interaction



Interaction of Ligand: TES by **HYDROPHOBIC** interaction

RNA and Protein Expression Target

RNA and protein expression are mostly found in endocrine gland, exocrine gland and liver.

Human 3alpha-HSD type 3 in Ternary Complex with NADP and Testosterone

Drug Information

- Testosterone is a steroid sex hormone indicated to treat primary hypogonadism and hypogonadotropic hypogonadism.
- Testosterone antagonizes the androgen receptor to induce gene expression that causes the growth and development of masculine sex organs and secondary sexual characteristics.

Mechanism of action

Testosterone and its active metabolite dihydrotestosterone (DHT) antagonize the androgen receptor to develop masculine sex organs including the prostate, seminal vesicles, penis, and scrotum.

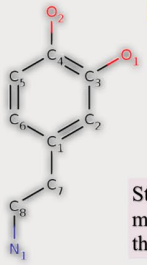
MANORAA

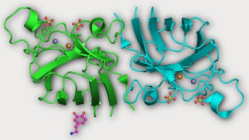
MBMG/M 6236160 Kotchaporn Thongmak

Mahidol University
Institute of Molecular Biosciences

Mr.Nitipon Srionrod 6237630 MBSB/D

Dopamine



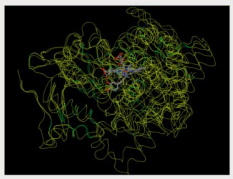


Structure of human I113T SOD1 mutant complexed with dopamine in the p21 space group

Drug Information

Dopamine was synthesized in our body as a nervous tissue and adrenal glands. There is a member of the catecholamine family of neurotransmitters in the brain and is a precursor to epinephrine (adrenaline) and norepinephrine (noradrenaline). Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. The dopamine receptors mediates its action, which plays a major role in reward-motivated behavior.

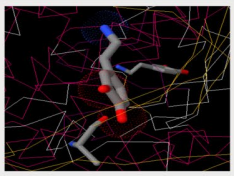
Structural Conservation



Position-specific interaction by highlighting the active site based on the percent conservation of the atomic position surrounding the ligand substructure for LDP superposed complexes.

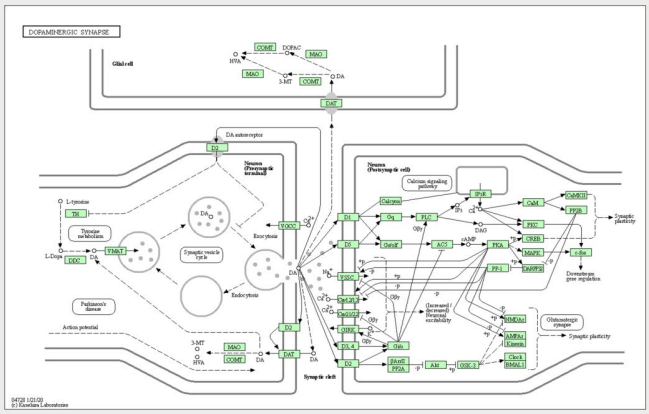
Binding-Distance Correlation

Protein-Ligand Interaction



The interaction of Cytochrome p450 bm3h-9d7 mri sensor bound to dopamine. Affinity=1.3μM

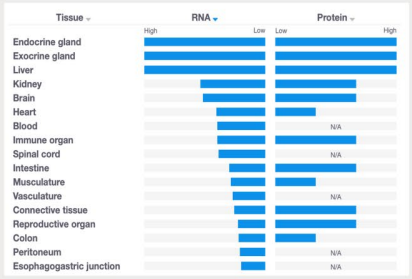
The pathway of Dopaminergic synapse Homo sapiens (human)



Dopamine interacts with at least five receptor subtypes in the central nervous system (CNS), which have been divided into two groups: the D1-like receptors (D1Rs), comprising D1 and D5 receptors, both positively coupled to adenylyl cyclase and cAMP production, and the D2-like receptors (D2Rs), comprising D2, D3, and D4 receptors, whose activation results in inhibition of adenylyl cyclase and suppression of cAMP production.

Presynaptically localized D2Rs regulate synthesis and release of dopamine as the main autoreceptor of the dopaminergic system.

RNA and protein base line expression are mostly found in endocrine gland, exocrine gland, and liver.



Conclusion

The dopamine drug information from MANORAA.org, structural bioinformatics, including structural conservation, protein-ligand interaction, binding-distance correlation, pathway, and expression of RNA/protein in different organs, that can help to design drug discovery with less side effect and time-consuming.

http://manoraa.icbs.mahidol.ac.th
https://pubchem.ncbi.nlm.nih.gov
https://www.genome.jp