LIGAND-BASED VIRTUAL SCREENING FOR NEW ANTAGONISTS OF DOPAMINE RECEPTOR D2/D3

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Contents

ABSTRACT

Dopamine is an important neurotransmitter plays a number of important physiological roles in the bodies of animals, modulating movement, cognitive, and emotional functions of the brain through activation of dopamine receptors. More and more studies focus on finding antagonists of dopamine receptor and design relevant drug for a variety of neuropsychiatric disorders. In this study we mainly tried to use virtual screening to find possible antagonists candidates of human dopamine receptor D2/D3. Molecular finger prints are analyzed to cluster the data sets of known antagonists. Finger prints of one of the clusters, which contain Eticlopride, are used for 2D similarity analysis and 23 candidates are extracted from 1/5 of "lead-like" datasets from ZINC database. Then we constructed the pharmacophore model on the basis of flexible alignments of this cluster, and further optimized it by reference to ligand-protein interaction and shape of the pocket. We utilized the pharmacophore query to extract another 26 candidates. All the candidates are further analyzed by docking. The placement method (Alpha PMI) and docking scoring function (ASE) are validated by complex of D2/D3 receptor and Eticopride. The correlation between docking scores and inhibition activities of antagonists are validated by biochemistry experiment data from PubChem (BioAssay 625253 and 625254). Finally we found three prominent candidate molecules that are very likely to bind D2/D3 dopamine receptor. The results can be further validated by molecular dynamics simulation in future.

Key Words: Dopamine, Dopamine Receptor, Ligand-based virtual screening, Structure-based virtual screening, lead-like, Zinc, molecule finger prints, flexible alignment, pharmacophore model, docking, MOE, Eticopride, PubChem

1 INTRODUCTION

1.1 VIRTUAL SCREENING

Virtual screening is a computational technique that has become an integral part of drug discovery process. It deals with quick search of large libraries of chemical structures to identify the structures which are most likely to bind to a drug target, typically a protein receptor or enzyme[1][2]. VS has largely been focusing on questions like how can we filter down the enormous number of chemical conceivable compounds to a manageable number that can be synthesized, purchased, and tested[3]. Thus, success of a virtual screen is defined in terms of finding interesting new scaffolds rather than many of these hits. Interpretations of virtual screening accuracy should therefore be considered with caution. Low hit rates of interesting scaffolds are clearly preferable over high hit rates of already known scaffolds.

There are broadly two categories of screening techniques: ligand-based and structure-based[4]. One way of implementing a ligand-based virtual screening demands pharmacophore models, which can be constructed from precise extraction of useful information from a set of structurally diverse ligands that bind to the target of interest. So that candidate ligands can be compared to the model and determine whether it is likely to bind[5]. Another way to do ligand-based virtual screening is to utilize chemical similarity analysis to scan a database against one or more active ligand structure which only take 2D information of ligands into consideration[6]. Different from ligand-based virtual screening mentioned above, structure-based virtual screening also involves docking of candidate ligands into a protein target by applying a scoring function to estimate the likelihood that the ligand would bind to the receptor or enzyme with high affinity[7][8]. A number of prospective applications of both techniques have come into existence[9]. In this study, we combined both ligand-based and structure-based virtual screening to scan the database efficiently and estimate the bind affinity of the candidate ligands.

1.2 DOPAMINE

Dopamine is a simple organic chemical in the catecholamine family, is a monoamine neurotransmitter which plays a number of important physiological roles in the bodies of animals. In addition to being a catecholamine and a monoamine, dopamine may be classified as a substituted phenethylamine. Fig.1 is dopamine’s molecular formula and structure.

In the brain, dopamine functions as a neurotransmitter—a chemical released by nerve cells to send signals to other nerve cells. The human brain uses five known types of dopamine receptors, labeled D1, D2, D3, D4, and D5. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.

Dopamine plays a major role in the brain system that is responsible for reward-driven learning. Every type of reward that has been studied increases the level of dopamine transmission in the brain, and a variety of highly addictive drugs, including stimulants such as cocaine and methamphetamine, act directly on the dopamine system. There is evidence that people with extraverted (reward-seeking) personality types tend to show higher levels of dopamine activity than people with introverted personalities. Several important diseases of the nervous system are associated with dysfunctions of the dopamine system. Parkinson's disease, an age-related degenerative condition causing tremor and motor impairment, is caused by loss of dopamine-secreting neurons in the substantia nigra. Schizophrenia has been shown to involve elevated levels of dopamine activity in the mesolimbic pathway and decreased levels of dopamine in the prefrontal cortex. Attention deficit hyperactivity disorder (ADHD) and restless legs syndrome (RLS) are also believed to be associated with decreased dopamine activity.

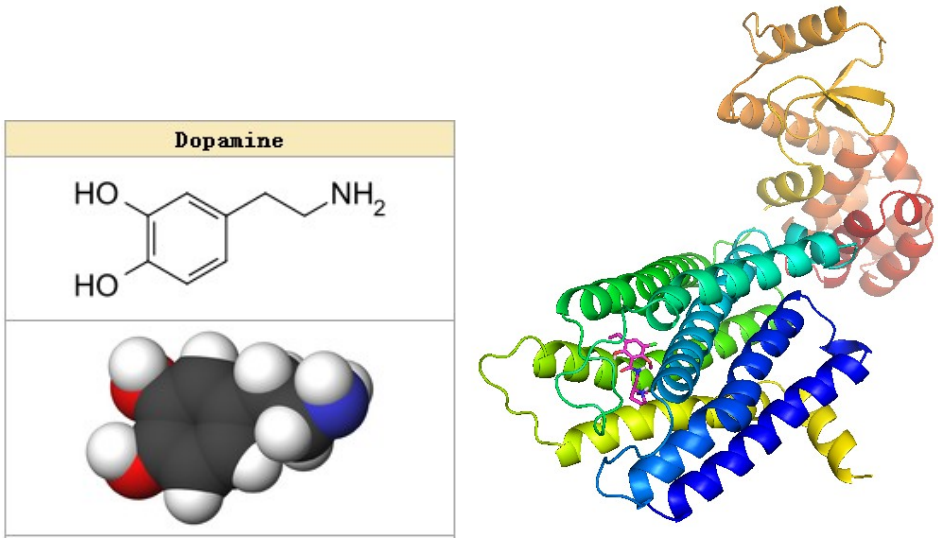

Fig.1 Left: Molecular formula and structure of dopamine; Right: Complex of human D3 dopamine receptor and Eticlopride(PDB code: 3PBL)

1.3 DOPAMINE RECEPTOR

Dopamine receptors are a class of G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS). The neurotransmitter dopamine is the primary endogenous ligand for dopamine receptors.

Dopamine receptors are implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, as well as modulation of neuroendocrine signaling. Abnormal dopamine receptor signaling and dopaminergic nerve function is implicated in several neuropsychiatric disorders. Thus, dopamine receptors are common neurologic drug targets; antipsychotics are often dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors. So finding new antagonists of dopamine receptor has important significance in treating diseases of the nervous system.

There are at least five subtypes of dopamine receptors, D1, D2, D3, D4, and D5. The D1 and D5 receptors are members of the D1-like family of dopamine receptors, whereas the D2, D3 and D4 receptors are members of the D2-like family. There is also some evidence that suggests the existence of possible D6 and D7 dopamine receptors, but such receptors have not been conclusively identified. At a global level, D1 receptors have widespread expression throughout the brain. Furthermore, D1-2 receptor subtypes are found at 10-100 times the levels of the D3-5 subtypes. Table.1 shows differences of the two families of dopamine receptors.

Family	Receptor	Gene	Type	Mechanism
D1-like	D1	DRD1	G_s-coupled	Increasing intracellular levels of cAMP by activating adenylate cyclase.
	D5	DRD5		
D2-like	D2	DRD2	G_i/G_o-coupled	Decreasing intracellular levels of cAMP by inhibiting adenylate cyclase
	D3	DRD3		
	D4	DRD4		

Table.1 Differences of the two families of dopamine receptors.

Dopamine receptors control neuronal signaling that modulates many important behaviors, such as spatial working memory. Although dopamine receptors are widely distributed in the brain, different areas have different receptor types densities, presumably reflecting different functional roles.

1.4 DOPAMINE OR DOPAMINE RECEPTOR RELATED DISEASE

Dysfunction of dopaminergic neurotransmission in the CNS has been implicated in a variety of neuropsychiatric disorders, including social phobia, Tourette's syndrome, Parkinson's disease, schizophrenia, neuroleptic malignant syndrome, attention-deficit hyperactivity disorder (ADHD), and drug and alcohol dependence. Dopamine receptors are common neurologic drug targets; antipsychotics are often dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors. So finding new antagonists of dopamine receptor has important significance in treating diseases of the nervous system.

1.5 MECHANISM AND SIDE EFFECTS OF DRUGS

This kind of drug binds to but do not activate dopamine receptors, thereby blocking the actions of dopamine or exogenous agonists. Many drugs used in the treatment of psychotic disorders (ANTIPSYCHOTIC AGENTS) are dopamine antagonists, although their therapeutic effects may be due to long-term adjustments of the brain rather than to the acute effects of blocking dopamine receptors. Dopamine antagonists have been used for several other clinical purposes including as ANTIEMETICS, in the treatment of Tourette syndrome, and for hiccup.

Dopamine receptor antagonists are used for some diseases such as Schizophrenia, Bipolar disorder, nausea and vomiting. It can also control the symptoms of hypersexuality and increased orgasmic activity. Antidopaminergics such as haloperidol can be an antidote for poisoning with cocaine, amphetamines and dopamine agonists such as Bromocriptine and/or Ropinirole.

However, this kind of drugs have varieties of side effects, following is typical side effects of them: Dysphoria, Parkinsonism (due to effects on the nigrostriatal pathway), Hyperprolactinaemia (due to effects on the tuberoinfundibular

pathway),Tardive dyskinesia (long term use), galactorrhea (due to removal of dopamine-mediated inhibition of prolactin release from lactotroph cells in the anterior pituitary), sexual dysfunction and impotence (due to blockage of the pleasure center), Sedation, Irritability, Narcolepsy, Symptoms similar to ADHD, Increased risk of severe depression, Anxiety disorders (such as Social Phobia), Increased appetite, Increased risk of obesity, Paranoia, Aggression, Psychomotor agitation, Increased risk of Type 2 Diabetes mellitus, Akathisia, Extrapyramidal symptoms, Clinical depression. Other side effects may include menstrual dysfunction, low libido, and impotence.

1.6 "LEAD-LIKE" SUBSETS OF ZINC DATABASE

ZINC is a free public resource for ligand discovery. The database contains over twenty million commercially available molecules in biologically relevant representations that may be downloaded in popular ready-to-dock formats and subsets. The Web site also enables searches by structure, biological activity, physical property, vendor, catalog number, name, and CAS number[10]. Among Lipinski compliant[11], 202134 are "lead-like" molecules[12][13][14], which we define here as having molecular weight between 150 and 350, calculated LogP less than four, number of hydrogen-bond donors less than or equal to three, and number of hydrogen-bond acceptors less than or equal to six.

Current opinion favors general purpose screening libraries that are filtered by physicochemical properties, particularly for molecules that have low complexity[15]. A popular choice is subset "lead-like"[14], for assays and techniques where binding is not observed directly and requires higher affinities and therefore more mass. Limited by the storage capacity of disk, we only downloaded one fifth of "lead-like" for scanning, which contains 143604 different molecules.

2 MATERIALS & METHODS

2.1 MATERIALS

2.1.1 ANTAGONISTS OF HUMAN DOPAMINE D2/D3 ANTAGONIST

We collected 49 known human dopamine D2/D3 antagonists' molecular structures as the training set in following studies.

Amisulpride	Clomipramine	Fluspirilene	Mesoridazine
Amoxapine	Domperidone	Haloperidol	Metoclopramide
Bromopride	Droperidol	Hydroxyzine	Perazine
Chlorpromazine	Fluphenazine	Loxapine	Perphenazine
Prochlorperazine	Tiapride	Remoxipride	Remoxipride
Promazine	Trifluoperazine	Eticlopride	Eticlopride
Risperidone	Trifluperidol	Ziprasidone	Ziprasidone
Spiperone	Triflupromazine	Tetrahydropalmatine	Tetrahydropalmatine
Spiroxatrine	Acepromazine	Iodobenzamide	Iodobenzamide
Sulpiride	Azaperone	Nemonapride	
Sultopride	Pimozide	Raclopride	
Thiethylperazine	Benperidol	Nafadotride	
Thioridazine	Penfluridol	Butaclamol	

Table.2 Known human Dopamine D2/D3 antagonists

2.1.2 PUBCHEM

Part of the known antagonists we have collected have biochemistry activity records in PubChem database. Compounds with activity <= 50uM or explicitly reported as active by ChEMBL are flagged as active in these PubChem assay presentation. Systematic error can be diminished due to the fact that experiments are conducted on the same conditions.

Mol	IC50 D2 (BioAssay:625253)/uM	IC50 D3 (BioAssay: 625254)/uM
Fluphenazine	0.001616	0.000594
Risperidone	0.02	0.024
Droperidol	0.002407	0.002765
Domperidone	0.002647	0.018
Haloperidol	0.006592	0.02
Prochlorperazine	0.011	0.013
Thioridazine	0.035	0.009892
Tiapride	1.232	1.149
Sulpiride	0.205	0.169
Clomipramine	0.413	0.139
Promazine	0.505	0.205
Chlorpromazine	0.054	0.012
Amoxapine	0.2	0.134
Metoclopramide	0.127	0.2

2.1.3 MACROMOLECULE STRUCTURE

In this study, we used the crystal structure of the human dopamine D3 receptor in complex with Eticlopride[16](PDB code: 3PBL) as the structure of receptor. Docking, ligand-receptor interactions analyses are all conducted on the basis of this structure.

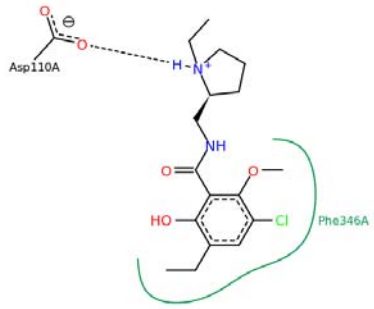

Fig 2. Ligand-receptor interaction of Eticlopride. From PDB website.

2.2 MOLECULAR FINGER PRINT

A molecular "fingerprint" is a widely used concept in chemical informatics[6]. Comparing molecules is hard. Comparing bitstrings is easy. Many people turn a molecule into a bitstring under the assumption that comparing the bitstring gives insight to how to compare molecules.

There are many kinds of fingerprint, in this study, we mainly used MACCS. MDL MACCS keys were originally developed for the purpose of database substructure searching. Each "key" describes a small substructure consisting of about one to ten non-hydrogen atoms. These substructures can be used to characterize molecules. In MOE, a MACCS fingerprint consists of a set of indicators showing whether each of the 166 MACCS keys was found to be present in a given molecule. The fingerprint is stored internally as a vector of indices, where the presence of an index in the vector indicates the presence of the corresponding substructure (key) in the molecule.

All fingerprint types in MOE 2009.10 (Chemical Computing Group, Montreal, Quebec, Canada) support two Tanimoto similarity metrics. These metrics measure the similarity between two fingerprints A and B by comparing the number of common features to the total number of features in each.

2.3 PHARMACOPHORE

MOE's pharmacophore modeling tools determine the chemical features and their spatial arrangement in 3D that are essential to the binding of a ligand to its receptor and thus to the ligand's drug activity. Pharmacophore models can be generated from the structural data of protein-ligand complexes as well as from ligands when no receptor information is available and from the receptor structure when no ligands are available. The generated models can be used to screen virtual compound libraries for potentially active molecules.

In MOE, the computerized representation of a hypothesized pharmacophore is called a pharmacophore query. A MOE pharmacophore query is a set of query features that are typically created from ligand annotation points. Annotation points (automatically detected in MOE) are markers in space that show the location and type of biologically important atoms and groups, such as hydrogen donors and acceptors, aromatic centers, projected positions of possible interaction partners or R-groups, charged groups, and bio-isosteres. The annotation points on a ligand are the potential locations of the features that will constitute the pharmacophore query. Annotation points relevant to the pharmacophore are converted into query features with the addition of an extra parameter: a non-zero radius that encodes the permissible variation in the pharmacophore query's geometry.

Once generated, a pharmacophore query can be used to screen virtual compound libraries for novel ligands. Pharmacophore queries can also be used to filter conformer databases, e.g. output from molecular docking runs, for biologically active conformations.

2.4 DOCK

The purpose of the Dock application is to search for favorable binding configurations between small to medium-sized ligands and a not-too-flexible macromolecular target, which is usually a protein. For each ligand, a number of configurations called poses are generated and scored in an effort to determine favorable binding modes. Optionally, poses can be constrained to fit a pharmacophore query. The top scoring poses are written out to a database for further analysis.

The search for binding modes is usually constrained to a specific, small region of the receptor called the site. As one would expect, the predictive power of Dock correlates with the degrees of freedom of the system. Docking results are expected to be reliable when the ligands are molecules with limited flexibility, and the site is not significantly larger than the ligand. Ligands having up to 10 rotatable bonds can be handled reasonably. However, if there is extra pharmacophore information, docking more flexible ligands may still produce reasonable results.

The Dock workflow is divided into stages. For each stage, multiple methods are available, and new methods can easily be integrated. The stages are:

1. Conformational Analysis. If ligand conformations are not supplied via a conformation database, Dock can be used to generate conformations from a single 3D conformer by applying a collection of preferred torsion angles to the rotatable bonds. Bond lengths and bond angles will not be altered. Rings will not be flexed.

2. Placement. A collection of poses is generated from the pool of ligand conformations using one of the placement methods.

3. Rescoring. Poses generated by the placement methodology can be rescored using one of the available methods. Typically, scoring functions emphasize favorable hydrophobic, ionic and hydrogen bond contacts. For the Dock framework to work properly, all new scoring methods should assign low scores to good poses.

4. Refinement. Poses resulting from the placement stage can be refined using either the explicit molecular mechanics forcefield method or the grid-based energetics method.

5. Rescoring. Poses resulting from the refinement stage can be rescored using one of the scoring schemes.

6. Pharmacophore Constraint. The user may provide a pharmacophore to constrain the final poses. If a pharmacophore constraint is provided, the Pharmacophore placement method is recommended as the other methods do not make direct use of the pharmacophore information. (However, the Pharmacophore placement method does not work if there is no pharmacophore.) Volume pharmacophore constraints are applied only at the filtering stage. Note that if volume pharmacophore constraints have been specified, they will always be applied. The top scoring poses are output, subject to optional duplication removal.

It is possible to perform rescoring or further refinement of existing docking results by using the output database from the earlier Dock Run as the source for the input ligands, and setting the placement step to None. Note that in such a case, the database columns should not have been rearranged since the first column of type 'molecule' will be used as the input ligand poses. Also any refinement would use the receptor defined in the Dock panel rather than any stored in the database.

3 RESULT & DISCUSSION

3.1 CLUSTER ANALYSIS OF COLLECTED ANTAGONISTS

We clustered the collected antagonists based on their molecular fingerprints MACCS keys (computed by MOE). The similarity and overlap was measured by Tanimoto Coefficient Matrix[6][17][18]. The thresholds of similarity and overlap were set to 59% and 61%, respectively. 49 structures were clustered into 13 clusters,

and mainly 7 skeletons were presented.

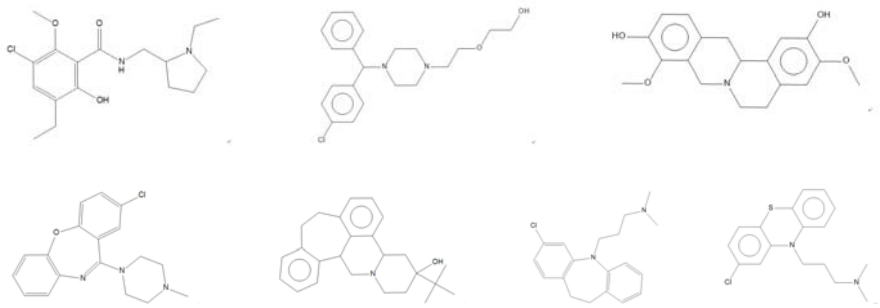

Fig 3. Seven typical molecules structures of each cluster. The first molecule is Eticlopride, of which cluster would be further studied.

Then we used the MACCS keys of Eticlopride to search for similar molecules in one fifth of "lead-like". The threshold was set to 70%, and we got 23 candidates.

3.2 RAISING A REASONABLE PHARMACOPHORE QUERY

The searching based on fingerprints involves only 2D information of molecules. To raise a more reasonable query based on the 3D structure of ligand and considering candidate molecules that can have different structures from known antagonists, we had to construct the pharmacophore model. However, we only had very limited knowledge about the collected antagonists and we had no idea what their conformations and pharmacophores exactly were when binding receptor. It was unrealistic to superpose every molecule we had collected. So we chose the cluster of 12 effective antagonists, including Eticlopride, and used "flexible alignment" to superpose them.

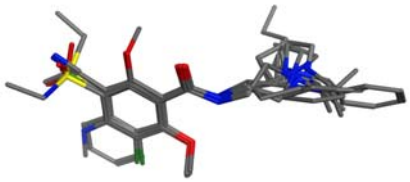

Fig 4. Results of "flexible alignment".

Then we extracted possible pharmacophores from each molecule, and used the "consensus" module to find the common features of this cluster. The tolerence radius was set to 0.7 Å, and consensus threshold was set to 50%. Other parameters were set as default.

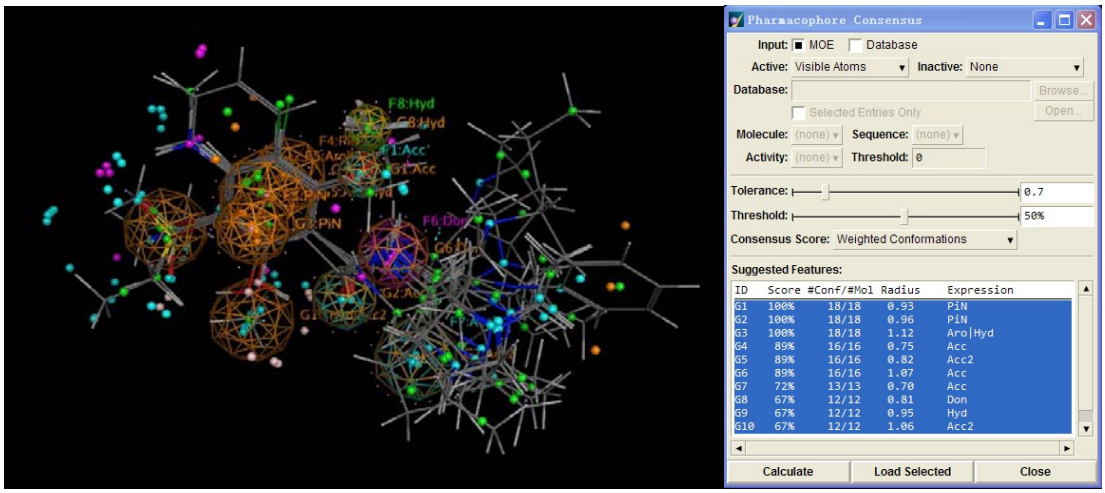

Fig 5.Common features extracted from pharmacophore analyses of molecules in the same cluster. Radius and expression of each pharmacophore feature is shown in the right picture. PiN=>Aromatic or Pi ring; Aro:Aromatic center; Acc:H-bond acceptor; Don: H-bond donor; Acc2: H-bond acceptor projection; Don2: H-bond donor projection; Hyd: Hydrophobic centroid.

We used the features of above pharmacophore model as query to scan the one fifth "lead-like" database we had downloaded. However, the results were not good. Only one molecule was selected out. A more reasonable pharmacophore query was needed.

To construct a better pharmacophore model, we compared the molecular structures of different clusters. We found that the pharmacophores of antagonists were highly diversified. It seemed that there were not obvious necessary chemical features, or substituents, that can determine the effectivity of molecules. So we inferred that the geometric features might be the critical point. We analysized the geometric features from two perspectives.

First we analysized the ligand-receptor interactions of the complex (3PBL), namely the interactions between Eticlopride and D3 receptor. The result showed also that there were few obvious specific interactions formed. Another evidence was that most dopamine receptor antagonists were not very specific, and they could also inhibit other receptors, such as 5-HT receptor. This may be one of the reasons why these drugs cause considerable side effects. The only hydrogen bond was formed between Asp110 and nitrogen atom at the pyrrole. However, the exposure part of ligand is very small, indicating that the geometric shape of the ligand perfectly matched the pocket. This further proved our assumption.

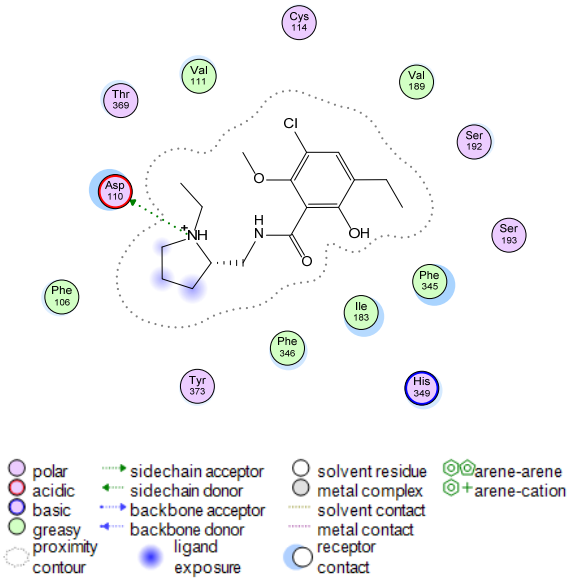

Fig 6. Ligand-receptor interactions between Eticlopride and human D3 dopamine receptor. Structure used from PDB database, PDB code(3PBL).

We also analyzed the shape of pocket, by utilizing the "sitefinder" tool and computed the molecular surface around the pocket. The purpose of Site Finder was to calculate possible active sites in a receptor from the 3D atomic coordinates of the receptor. Alpha spheres[19] were calculated and classified into hydrophobic and hydrophilic. From these spheres we could find the position into which bulky hydrophobic or hydrophilic fragments were supposed to be docked. So at these positions were more likely to be effective pharmacophores. Furthermore, the arrangement of spheres can indicate the shape of pocket. There was a bump on the surface inside the pocket, which allows no molecular fragments entering into it.

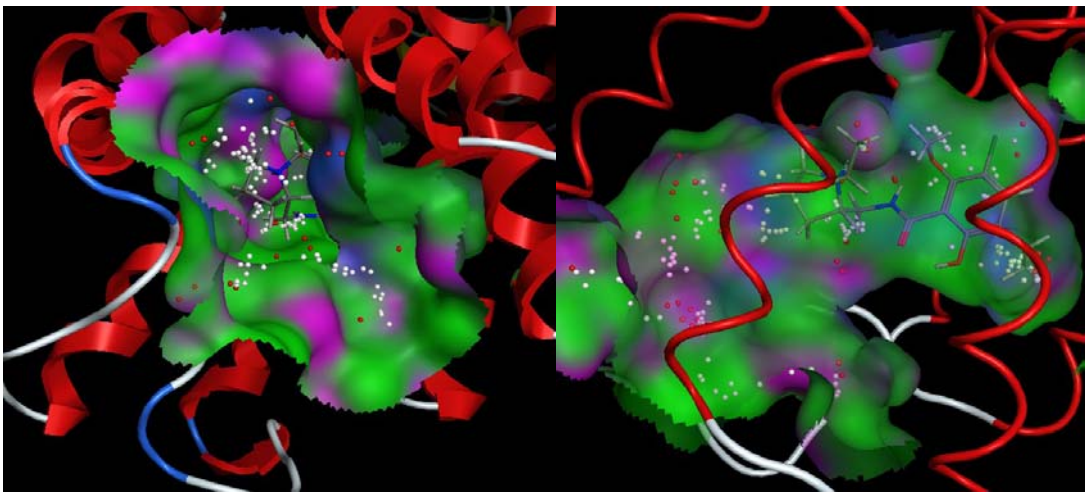

Fig 7. Pocket shape analysis by using "site finder". Left and right pictures are mutually perpendicular views. Red: hydrophilic; White: hydrophobic.

Considering the results of analyses above, we constructed another pharmacophore query. This query(see Fig 7) simply included two hydrophobic/Aromatic centroid(F2, F3), one hydrogen donor(F1) and one important volume indicator(V1) where the bump of pocket was. Other features were just trying to fill in the space. They were set as optional during the search process. We got another 25 candidates by running this query.

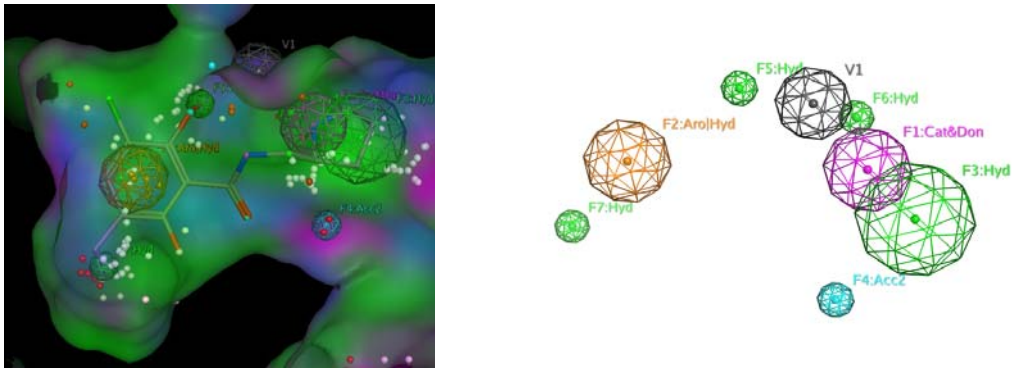

Fig 8. New pharmacophore query. F1, F2, F3 are necessary part, other features are mainly for filling the space, namely forming a shape as similar to the pocket as possible.

3.3 BINDING AFFINITY ANALYSIS BY DOCKING

3.3.1 DOCKING PARAMETERS INITIALIZATION AND DOCKING OF ANTAGONISTS COLLECTED

MOE offered several different built-in methods for ligand placement in docking process: Alpha Triangle, Alpha PMI, Proxy Triangle and Triangle Matcher. Several different scoring functions were also available: ASE, Affinity dG, Alpha HB and London dG. To find out the scoring function and method of placement that best suit this system, we docked Eticlopride into the pocket using different combinations of methods and scoring funcion. It turned out that best suitable method and scoring function were Alpha PMI and ASE, respectively. All conformations generated were refined by AMBER99 force field[20]. The result of this combination varied little from the original position(see Fig 8), with its RMSD equal to 0.89Å.

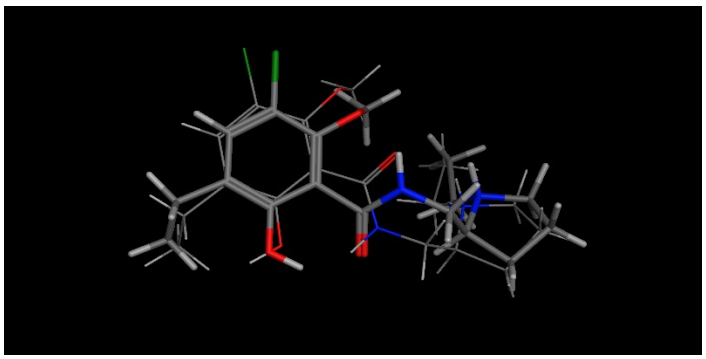

Fig 9. Results of docking, using Alpha PMI as placement method, and ASE scoring function, with original ligand shown as tube model, docking result shown as stick model. Notice that the conformations are very similar.Only the peptide bond utilizes different directions.

Then we docked the antagonists we have collected using Alpha PMI and ASE scoring function. The docking scores ranged from -21 to -31 kJ(Table S1).

3.3.2 CORRELATION BETWEEN DOCKING SCORES AND BIOACTIVITIES

In general, molecules that have higher scores, to be exact, lower energy, in docking are supposed to be more likely to bind the receptor. However, the likelihood varies with different scoring function. For example, there are no reliable correlation between the docking scores of Autodock and IC50. It was necessary to explore the correlation between docking function(ASE) we used and bioactivities.

MOE would generate a series of conformations for the ligand during docking process. If the conformation is acceptable, it would be retained and refined, and finally recorded with a docking score(binding energy). We took scores of all possible conformations, and calculated the average score of each molecule.

IC50 of part of the antagonists we had collected were tested and recorded in PubChem. We calculated log(IC50) as well as the average score of each molecule. The correlation between them were valiated by linear regression. The correlation coefficent was about 0.67(see Fig 9).

mol	Average Score/kJ	Log(IC50)
Amoxapine	-21.0652	-0.8729
Chlorpromazine	-21.1306	-1.92082
Clomipramine	-22.1849	-0.85699
Domperidone	-25.0928	-1.74473
Droperidol	-25.4104	-2.5583
Fluphenazine	-28.5565	-3.22621
Haloperidol	-24.8813	-1.69897

mol	Average Score/kJ	Log(IC50)
Metoclopramide	-21.0172	-0.69897
Prochlorperazine	-24.694	-1.88606
Promazine	-21.6143	-0.68825
Risperidone	-27.1934	-1.61979
Sulpiride	-22.7249	-0.77211
Thioridazine	-24.4344	-2.00472
Tiapride	-23.8443	0.06032

Table 2 Average score (docking energy) and log(IC_{50}) of part of antagonists we had collected.

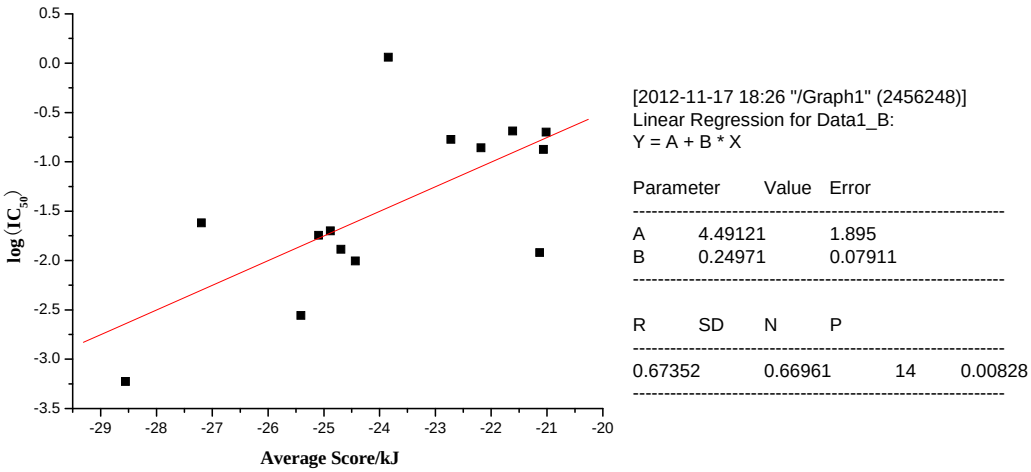

Fig 10. Correlation between log(IC_{50}) and docking scores.

3.3.3 DOCKING STUDY OF CANDIDATE LIGANDS

We collected all the candidate ligands from virtual screening based on MACCS and pharmacophore query, 49 molecules in total, and docked them into the pocket. The results shown in Table S2(数据量太大，暂未整理). Among the results, three molecules (ZINC73612128, ZINC72956930, ZINC73437371) exibited remarkable docking scores, namely very low average binding energy. The average energy from docking were -28.44kJ, -26.71kJ, -28.24kJ, respectively. We chosed the conformation of each molecule with lowest binding energy and analysized the ligand-receptor interactions.

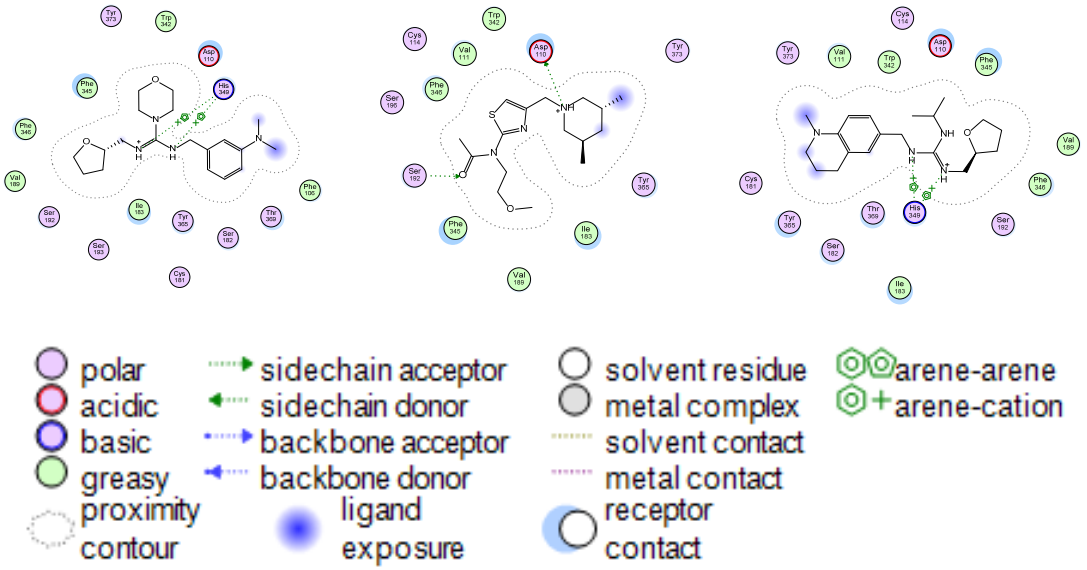

Fig 11. Ligand-receptor interactions of three remarkable candidate molecules. Left: ZINC73612128, Middle: ZINC72956930, Right: ZINC73437371.

These molecules all formed close contacts with pocket, with very small exposure. In addition, more hydrogen bonds and arene-arene interactions were formed than original ligand, Eticloprode. They presented great potential value for drug discovery and design.

3.4 DISCUSSION

In this study, we found that there were few specific interactions between human dopamine D3 receptor and ligand, Eticlopride. The geometric features of the ligand seemed more important than its chemical features. We used both ligand-based and structure-based virtual screening on one fifth "lead-like" subset from ZINC database, and obtained three promising candidate molecules. All of them were among the results of searching based on pharmacophores. The correlation between docking scores and bioactivity was validated by biochemistry test of part of collected antagonists.

We did not have enough time to rebuild the "lead-like" database with every molecule's different conformations generated. We just kept the original conformation of molecules and simply minimized the potential energy, using MMFF94x force field[21]. This defect can lead to considerable loss of valuable candidate.

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Table S1 Docking results of antagonists collected

mol	mseq	S
Acepromazine	1	-25.46
Acepromazine	1	-25.1989
Acepromazine	1	-24.9076
Acepromazine	1	-24.838
Acepromazine	1	-24.3732
Acepromazine	1	-24.1662
Acepromazine	1	-24.0692
Acepromazine	1	-23.8524

mol	mseq	S
Acepromazine	1	-23.851
Acepromazine	1	-23.5874
Acepromazine	1	-23.5734
Acepromazine	1	-23.5431
Acepromazine	1	-23.2457
Acepromazine	1	-23.1888
Acepromazine	1	-23.0049
Acepromazine	1	-22.7217
Acepromazine	1	-22.5252
Acepromazine	1	-21.8277
Acepromazine	1	-21.4834
Acepromazine	1	-21.4673
Acepromazine	1	-21.3393
Acepromazine	1	-20.7078
Acepromazine	1	-20.62
Acepromazine	1	-20.5809
Acepromazine	1	-20.5408
Acepromazine	1	-20.5163
Acepromazine	1	-20.2928
Acepromazine	1	-19.7922
Acepromazine	1	-19.1493
Acepromazine	1	-18.9988
Acepromazine	1	-14.186
Acepromazine	1	-11.9404
Chlorpromazine	2	-22.6187
Chlorpromazine	2	-22.4075
Chlorpromazine	2	-22.357
Chlorpromazine	2	-22.3506
Chlorpromazine	2	-22.1852
Chlorpromazine	2	-22.0633
Chlorpromazine	2	-21.8361
Chlorpromazine	2	-21.6955
Chlorpromazine	2	-21.6815
Chlorpromazine	2	-21.4652
Chlorpromazine	2	-21.0573
Chlorpromazine	2	-21.0006
Chlorpromazine	2	-20.257
Chlorpromazine	2	-17.2089
Chlorpromazine	2	-16.774
Clomipramine	3	-25.1454
Clomipramine	3	-24.7721
Clomipramine	3	-24.4596

mol	mseq	S
Clomipramine	3	-23.9926
Clomipramine	3	-23.4381
Clomipramine	3	-23.171
Clomipramine	3	-23.0457
Clomipramine	3	-22.8198
Clomipramine	3	-22.6927
Clomipramine	3	-22.3998
Clomipramine	3	-22.2821
Clomipramine	3	-19.3401
Clomipramine	3	-18.7093
Clomipramine	3	-14.321
Mesoridazine	4	-27.4973
Mesoridazine	4	-27.3878
Mesoridazine	4	-26.8423
Mesoridazine	4	-26.8378
Mesoridazine	4	-26.8198
Mesoridazine	4	-26.7058
Mesoridazine	4	-26.6676
Mesoridazine	4	-26.6034
Mesoridazine	4	-26.5502
Mesoridazine	4	-26.5345
Mesoridazine	4	-26.5197
Mesoridazine	4	-26.5017
Mesoridazine	4	-26.4588
Mesoridazine	4	-26.2775
Mesoridazine	4	-26.1335
Mesoridazine	4	-26.0766
Mesoridazine	4	-25.6675
Mesoridazine	4	-25.3892
Mesoridazine	4	-25.2355
Mesoridazine	4	-24.8801
Mesoridazine	4	-24.7089
Mesoridazine	4	-24.2882
Mesoridazine	4	-23.787
Mesoridazine	4	-23.6311
Mesoridazine	4	-23.2634
Mesoridazine	4	-23.0974
Mesoridazine	4	-21.7474
Mesoridazine	4	-21.1161
Mesoridazine	4	-20.3324
Methotrimeprazine	5	-26.9638
Methotrimeprazine	5	-25.9211

mol	mseq	S
Methotrimeprazine	5	-25.847
Methotrimeprazine	5	-25.4917
Methotrimeprazine	5	-25.3619
Methotrimeprazine	5	-25.3475
Methotrimeprazine	5	-25.139
Methotrimeprazine	5	-24.9048
Methotrimeprazine	5	-24.4809
Methotrimeprazine	5	-24.4743
Methotrimeprazine	5	-24.4629
Methotrimeprazine	5	-24.4439
Methotrimeprazine	5	-24.1232
Methotrimeprazine	5	-24.1056
Methotrimeprazine	5	-23.9504
Methotrimeprazine	5	-23.9335
Methotrimeprazine	5	-23.9249
Methotrimeprazine	5	-23.3291
Methotrimeprazine	5	-23.2718
Methotrimeprazine	5	-23.0869
Methotrimeprazine	5	-22.2162
Methotrimeprazine	5	-21.9655
Methotrimeprazine	5	-21.694
Methotrimeprazine	5	-21.0237
Methotrimeprazine	5	-21.0191
Methotrimeprazine	5	-20.8617
Perazine	6	-26.3873
Perazine	6	-26.1414
Perazine	6	-25.992
Perazine	6	-25.8118
Perazine	6	-24.9984
Perazine	6	-24.8446
Perazine	6	-24.7994
Perazine	6	-24.7216
Perazine	6	-24.7173
Perazine	6	-23.5642
Perazine	6	-23.3859
Perazine	6	-23.1999
Perazine	6	-22.8155
Perazine	6	-22.7666
Perazine	6	-22.4308
Prochlorperazine	7	-26.339
Prochlorperazine	7	-26.3354
Prochlorperazine	7	-25.6441

mol	mseq	S
Prochlorperazine	7	-25.4696
Prochlorperazine	7	-25.2319
Prochlorperazine	7	-25.1957
Prochlorperazine	7	-25.1746
Prochlorperazine	7	-25.1012
Prochlorperazine	7	-23.9185
Prochlorperazine	7	-23.6642
Prochlorperazine	7	-23.639
Prochlorperazine	7	-23.0163
Prochlorperazine	7	-22.2919
Promazine	8	-22.8461
Promazine	8	-22.6859
Promazine	8	-22.6261
Promazine	8	-22.407
Promazine	8	-22.4002
Promazine	8	-22.371
Promazine	8	-22.2725
Promazine	8	-22.0657
Promazine	8	-21.9385
Promazine	8	-21.8885
Promazine	8	-21.7405
Promazine	8	-20.0898
Promazine	8	-19.7169
Promazine	8	-17.5508
Thiethylperazine	9	-29.0343
Thiethylperazine	9	-28.9482
Thiethylperazine	9	-28.7076
Thiethylperazine	9	-28.5541
Thiethylperazine	9	-28.4928
Thiethylperazine	9	-28.3895
Thiethylperazine	9	-28.3067
Thiethylperazine	9	-28.1437
Thiethylperazine	9	-28.1102
Thiethylperazine	9	-28.0487
Thiethylperazine	9	-27.0802
Thiethylperazine	9	-26.6077
Thiethylperazine	9	-26.0083
Thiethylperazine	9	-25.922
Thiethylperazine	9	-25.0996
Thiethylperazine	9	-25.0631
Thiethylperazine	9	-24.6996
Thiethylperazine	9	-24.2915

mol	mseq	S
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Thiethylperazine	9	-23.888
Thiethylperazine	9	-23.2419
Thioridazine	10	-28.4885
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Thioridazine	10	-27.7028
Thioridazine	10	-27.6416
Thioridazine	10	-27.1216
Thioridazine	10	-26.9903
Thioridazine	10	-26.7943
Thioridazine	10	-26.5928
Thioridazine	10	-26.4885
Thioridazine	10	-26.232
Thioridazine	10	-25.9881
Thioridazine	10	-25.6263
Thioridazine	10	-25.3018
Thioridazine	10	-25.2891
Thioridazine	10	-25.1893
Thioridazine	10	-24.4747
Thioridazine	10	-24.28
Thioridazine	10	-24.1111
Thioridazine	10	-24.0816
Thioridazine	10	-23.9471
Thioridazine	10	-23.422
Thioridazine	10	-23.2149
Thioridazine	10	-23.1014
Thioridazine	10	-22.9285
Thioridazine	10	-22.5706
Thioridazine	10	-22.4821
Thioridazine	10	-22.2464
Thioridazine	10	-22.1047
Thioridazine	10	-21.8096
Thioridazine	10	-21.8089
Thioridazine	10	-20.5967
Thioridazine	10	-20.5176
Thioridazine	10	-19.4573
Trifluoperazine	11	-28.0349
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Trifluoperazine	11	-27.8608
Trifluoperazine	11	-26.1975
Trifluoperazine	11	-25.1412

mol	mseq	S
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Triflupromazine	12	-23.7399
Triflupromazine	12	-23.3179
Triflupromazine	12	-23.2549
Triflupromazine	12	-22.7271
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Triflupromazine	12	-20.3306
Triflupromazine	12	-20.068
Triflupromazine	12	-19.9131
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Amisulpride	13	-28.1159
Amisulpride	13	-27.9343
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Amisulpride	13	-27.226
Amisulpride	13	-27.2023
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Amisulpride	13	-26.8611
Amisulpride	13	-26.7999
Amisulpride	13	-26.7575
Amisulpride	13	-26.7066
Amisulpride	13	-26.6441
Amisulpride	13	-26.4729
Amisulpride	13	-26.3665
Amisulpride	13	-26.3588
Amisulpride	13	-26.2763
Amisulpride	13	-25.9521
Amisulpride	13	-25.7553
Amisulpride	13	-25.7044
Amisulpride	13	-25.5567
Amisulpride	13	-25.494
Amisulpride	13	-25.3314
Amisulpride	13	-25.3195
Amisulpride	13	-25.1649
Amisulpride	13	-25.1485
Amisulpride	13	-24.8633
Bromopride	14	-23.8167
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Bromopride	14	-22.7325
Bromopride	14	-22.6472

mol	mseq	S
Bromopride	14	-22.5542
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Bromopride	14	-22.2267
Bromopride	14	-22.1019
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Bromopride	14	-22.0124
Bromopride	14	-21.994
Bromopride	14	-21.923
Bromopride	14	-21.7385
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Bromopride	14	-21.3376
Bromopride	14	-21.3246
Bromopride	14	-21.2836
Bromopride	14	-21.2685
Bromopride	14	-21.2393
Bromopride	14	-21.199
Bromopride	14	-21.1118
Bromopride	14	-20.9888
Bromopride	14	-20.9238
Bromopride	14	-20.9176
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Bromopride	14	-19.0216
Bromopride	14	-18.805
Eticlopride	15	-27.8826
Eticlopride	15	-27.6857
Eticlopride	15	-27.5988
Eticlopride	15	-27.5278
Eticlopride	15	-27.4943
Eticlopride	15	-27.1467
Eticlopride	15	-27.135
Eticlopride	15	-27.103
Eticlopride	15	-27.0815

mol	mseq	S
Eticlopride	15	-26.7527
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Eticlopride	15	-26.4226
Eticlopride	15	-26.3966
Eticlopride	15	-26.3265
Eticlopride	15	-26.1471
Eticlopride	15	-26.143
Eticlopride	15	-26.1332
Eticlopride	15	-26.1319
Eticlopride	15	-26.0878
Eticlopride	15	-26.0342
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Eticlopride	15	-25.568
Eticlopride	15	-25.5341
Eticlopride	15	-25.3067
Eticlopride	15	-25.2832
Eticlopride	15	-25.2769
Eticlopride	15	-24.9243
Eticlopride	15	-24.658
Eticlopride	15	-24.0891
Iodobenzamide	16	-24.1385
Iodobenzamide	16	-22.6562
Iodobenzamide	16	-22.6367
Iodobenzamide	16	-22.4746
Iodobenzamide	16	-22.2717
Iodobenzamide	16	-22.2658
Iodobenzamide	16	-21.91
Iodobenzamide	16	-21.8842
Iodobenzamide	16	-21.5672
Iodobenzamide	16	-21.5502
Iodobenzamide	16	-21.544
Iodobenzamide	16	-21.4806
Iodobenzamide	16	-21.2648
Iodobenzamide	16	-21.1424
Iodobenzamide	16	-21.0919
Iodobenzamide	16	-20.4083
Iodobenzamide	16	-20.0706
Iodobenzamide	16	-20.0528
Iodobenzamide	16	-19.9677
Iodobenzamide	16	-19.9557
Iodobenzamide	16	-19.0791
Iodobenzamide	16	-19.0528

mol	mseq	S
Metoclopramide	17	-23.0926
Metoclopramide	17	-22.7264
Metoclopramide	17	-22.6713
Metoclopramide	17	-22.6384
Metoclopramide	17	-22.5583
Metoclopramide	17	-22.4901
Metoclopramide	17	-22.0735
Metoclopramide	17	-21.9768
Metoclopramide	17	-21.726
Metoclopramide	17	-21.6994
Metoclopramide	17	-21.6225
Metoclopramide	17	-21.4126
Metoclopramide	17	-21.4026
Metoclopramide	17	-21.3527
Metoclopramide	17	-21.2512
Metoclopramide	17	-21.2253
Metoclopramide	17	-21.0228
Metoclopramide	17	-20.9818
Metoclopramide	17	-20.9654
Metoclopramide	17	-20.8515
Metoclopramide	17	-20.7966
Metoclopramide	17	-20.6218
Metoclopramide	17	-20.3863
Metoclopramide	17	-20.3747
Metoclopramide	17	-20.0831
Metoclopramide	17	-19.9628
Metoclopramide	17	-19.9289
Metoclopramide	17	-19.8835
Metoclopramide	17	-19.8812
Metoclopramide	17	-19.8521
Metoclopramide	17	-19.2679
Metoclopramide	17	-18.7259
Metoclopramide	17	-18.0613
Nafadotride	18	-30.5216
Nafadotride	18	-30.2941
Nafadotride	18	-30.2867
Nafadotride	18	-30.1283
Nafadotride	18	-30.0863
Nafadotride	18	-29.9383
Nafadotride	18	-29.8696
Nafadotride	18	-29.4795
Nafadotride	18	-29.3169

mol	mseq	S
Nafadotride	18	-29.2606
Nafadotride	18	-28.6381
Nafadotride	18	-28.4535
Nafadotride	18	-28.0389
Nafadotride	18	-27.9523
Nafadotride	18	-27.7155
Nafadotride	18	-27.4371
Nafadotride	18	-27.3518
Nafadotride	18	-27.2694
Nafadotride	18	-26.171
Nafadotride	18	-26.1212
Nafadotride	18	-24.2655
Nemonapride	19	-25.6093
Nemonapride	19	-25.2734
Nemonapride	19	-25.223
Nemonapride	19	-24.9643
Nemonapride	19	-24.2918
Nemonapride	19	-24.279
Nemonapride	19	-23.4902
Nemonapride	19	-22.4879
Raclopride	20	-24.2927
Raclopride	20	-22.548
Raclopride	20	-22.0619
Raclopride	20	-22.0544
Raclopride	20	-21.9719
Raclopride	20	-21.9679
Raclopride	20	-21.7423
Raclopride	20	-21.4319
Raclopride	20	-21.2914
Raclopride	20	-21.0943
Raclopride	20	-21.0433
Raclopride	20	-20.8841
Raclopride	20	-20.8584
Raclopride	20	-20.7651
Raclopride	20	-20.649
Raclopride	20	-20.3158
Raclopride	20	-20.2914
Raclopride	20	-20.2577
Raclopride	20	-20.2342
Raclopride	20	-20.2311
Raclopride	20	-20.1458
Raclopride	20	-20.0147

mol	mseq	S
Raclopride	20	-19.9721
Raclopride	20	-19.89
Raclopride	20	-19.8686
Raclopride	20	-19.8096
Raclopride	20	-19.678
Raclopride	20	-19.3919
Raclopride	20	-19.2943
Raclopride	20	-19.2511
Raclopride	20	-18.7194
Remoxipride	21	-25.2474
Remoxipride	21	-25.0499
Remoxipride	21	-24.8309
Remoxipride	21	-24.7853
Remoxipride	21	-24.65
Remoxipride	21	-24.1382
Remoxipride	21	-24.0955
Remoxipride	21	-24.0749
Remoxipride	21	-23.9338
Remoxipride	21	-23.8622
Remoxipride	21	-23.6496
Remoxipride	21	-23.6102
Remoxipride	21	-23.6034
Remoxipride	21	-23.5683
Remoxipride	21	-23.4905
Remoxipride	21	-23.3755
Remoxipride	21	-23.2808
Remoxipride	21	-22.8705
Remoxipride	21	-22.8609
Remoxipride	21	-22.7828
Remoxipride	21	-22.6158
Remoxipride	21	-22.5001
Remoxipride	21	-22.4091
Remoxipride	21	-22.4071
Remoxipride	21	-22.33
Remoxipride	21	-22.2528
Remoxipride	21	-21.9126
Remoxipride	21	-21.8549
Remoxipride	21	-21.7773
Remoxipride	21	-21.5983
Remoxipride	21	-21.5577
Remoxipride	21	-21.1255
Remoxipride	21	-20.8961

mol	mseq	S
Remoxipride	21	-20.1673
Remoxipride	21	-19.8101
Sulpiride	22	-25.1209
Sulpiride	22	-25.0253
Sulpiride	22	-24.6334
Sulpiride	22	-24.3124
Sulpiride	22	-24.2686
Sulpiride	22	-24.2389
Sulpiride	22	-24.1431
Sulpiride	22	-23.8031
Sulpiride	22	-23.5202
Sulpiride	22	-23.2462
Sulpiride	22	-23.1558
Sulpiride	22	-23.1326
Sulpiride	22	-23.1132
Sulpiride	22	-23.0362
Sulpiride	22	-22.9134
Sulpiride	22	-22.6458
Sulpiride	22	-22.5268
Sulpiride	22	-22.1679
Sulpiride	22	-22.1227
Sulpiride	22	-21.9434
Sulpiride	22	-21.9217
Sulpiride	22	-21.8279
Sulpiride	22	-21.5563
Sulpiride	22	-21.4815
Sulpiride	22	-21.2443
Sulpiride	22	-21.1487
Sulpiride	22	-20.7697
Sulpiride	22	-20.0224
Sulpiride	22	-19.9797
Sultopride	23	-28.6764
Sultopride	23	-28.5406
Sultopride	23	-28.5206
Sultopride	23	-28.4785
Sultopride	23	-28.4746
Sultopride	23	-28.4442
Sultopride	23	-28.438
Sultopride	23	-28.3309
Sultopride	23	-28.251
Sultopride	23	-27.8203
Sultopride	23	-27.7155

mol	mseq	S
Sultopride	23	-27.3019
Sultopride	23	-27.2628
Sultopride	23	-27.2197
Sultopride	23	-27.2084
Sultopride	23	-27.1664
Sultopride	23	-27.131
Sultopride	23	-27.0228
Sultopride	23	-26.8565
Sultopride	23	-26.8421
Sultopride	23	-26.3892
Sultopride	23	-25.7944
Sultopride	23	-25.5444
Sultopride	23	-25.5168
Sultopride	23	-24.6478
Sultopride	23	-24.4782
Sultopride	23	-23.8638
Sultopride	23	-23.2122
Sultopride	23	-23.2084
Tiapride	24	-25.8535
Tiapride	24	-25.4618
Tiapride	24	-25.2915
Tiapride	24	-25.2695
Tiapride	24	-25.1984
Tiapride	24	-25.0402
Tiapride	24	-24.9425
Tiapride	24	-24.9383
Tiapride	24	-24.8391
Tiapride	24	-24.7729
Tiapride	24	-24.4629
Tiapride	24	-24.388
Tiapride	24	-24.3785
Tiapride	24	-24.3677
Tiapride	24	-24.3115
Tiapride	24	-24.2818
Tiapride	24	-24.2687
Tiapride	24	-24.1762
Tiapride	24	-24.1594
Tiapride	24	-24.096
Tiapride	24	-23.8065
Tiapride	24	-23.7672
Tiapride	24	-23.7446
Tiapride	24	-23.6272

mol	mseq	S
Tiapride	24	-23.6199
Tiapride	24	-23.5337
Tiapride	24	-23.5256
Tiapride	24	-23.4726
Tiapride	24	-23.4325
Tiapride	24	-23.3661
Tiapride	24	-23.3446
Tiapride	24	-23.3307
Tiapride	24	-23.2653
Tiapride	24	-23.2192
Tiapride	24	-23.0049
Tiapride	24	-22.9192
Tiapride	24	-22.8108
Tiapride	24	-22.5845
Tiapride	24	-22.5533
Tiapride	24	-22.275
Tiapride	24	-22.1059
Tiapride	24	-21.9306
Tiapride	24	-21.5651
Amoxapine	25	-21.1891
Amoxapine	25	-21.0843
Amoxapine	25	-21.0178
Amoxapine	25	-20.9695
Azaperone	26	-25.782
Azaperone	26	-25.1459
Azaperone	26	-25.1035
Azaperone	26	-25.0024
Azaperone	26	-24.7455
Azaperone	26	-24.7057
Azaperone	26	-24.6506
Azaperone	26	-24.5733
Azaperone	26	-24.4607
Azaperone	26	-24.2667
Azaperone	26	-23.9803
Azaperone	26	-23.9784
Azaperone	26	-23.9396
Azaperone	26	-23.7983
Azaperone	26	-23.7175
Azaperone	26	-23.6022
Azaperone	26	-23.3951
Azaperone	26	-22.9077
Azaperone	26	-22.8635

mol	mseq	S
Azaperone	26	-22.5874
Azaperone	26	-22.4369
Azaperone	26	-22.1831
Azaperone	26	-22.1021
Azaperone	26	-21.2104
Azaperone	26	-20.9497
Azaperone	26	-19.5251
Azaperone	26	-18.6649
Benperidol	27	-27.2548
Benperidol	27	-27.2393
Benperidol	27	-26.9977
Benperidol	27	-26.8154
Benperidol	27	-26.79
Benperidol	27	-26.7665
Benperidol	27	-26.3575
Benperidol	27	-26.3354
Benperidol	27	-26.3312
Benperidol	27	-26.1314
Benperidol	27	-26.0434
Benperidol	27	-26.0395
Benperidol	27	-25.8747
Benperidol	27	-25.8115
Benperidol	27	-25.7353
Benperidol	27	-25.6903
Benperidol	27	-25.6493
Benperidol	27	-24.9618
Benperidol	27	-24.9105
Benperidol	27	-24.6885
Benperidol	27	-24.6542
Benperidol	27	-24.5695
Benperidol	27	-24.4851
Benperidol	27	-24.0765
Benperidol	27	-23.4968
Benperidol	27	-23.3793
Benperidol	27	-23.2172
Benperidol	27	-23.0899
Benperidol	27	-23.002
Benperidol	27	-22.4184
Benperidol	27	-22.2516
Benperidol	27	-22.1358
Benperidol	27	-21.3695
Domperidone	28	-27.5977

mol	mseq	S
Domperidone	28	-26.9628
Domperidone	28	-26.7665
Domperidone	28	-26.7046
Domperidone	28	-26.572
Domperidone	28	-26.5226
Domperidone	28	-26.3151
Domperidone	28	-26.3128
Domperidone	28	-26.1958
Domperidone	28	-26.1615
Domperidone	28	-26.1552
Domperidone	28	-26.155
Domperidone	28	-25.0964
Domperidone	28	-24.9876
Domperidone	28	-24.8281
Domperidone	28	-24.8031
Domperidone	28	-24.7552
Domperidone	28	-24.6454
Domperidone	28	-24.4717
Domperidone	28	-24.3075
Domperidone	28	-24.1418
Domperidone	28	-23.9842
Domperidone	28	-23.9581
Domperidone	28	-23.6596
Domperidone	28	-23.5912
Domperidone	28	-23.5577
Domperidone	28	-23.1348
Domperidone	28	-23.0935
Domperidone	28	-22.252
Droperidol	29	-26.887
Droperidol	29	-26.8789
Droperidol	29	-26.762
Droperidol	29	-26.4704
Droperidol	29	-26.4378
Droperidol	29	-26.4291
Droperidol	29	-26.1431
Droperidol	29	-26.0346
Droperidol	29	-26.0248
Droperidol	29	-25.9897
Droperidol	29	-25.9822
Droperidol	29	-25.9369
Droperidol	29	-25.9265
Droperidol	29	-25.9203

mol	mseq	S
Droperidol	29	-25.8952
Droperidol	29	-25.6936
Droperidol	29	-25.5734
Droperidol	29	-25.4766
Droperidol	29	-25.4455
Droperidol	29	-25.1036
Droperidol	29	-25.058
Droperidol	29	-25.0521
Droperidol	29	-24.8033
Droperidol	29	-24.5325
Droperidol	29	-24.5066
Droperidol	29	-24.3065
Droperidol	29	-24.1537
Droperidol	29	-24.0976
Droperidol	29	-22.7278
Droperidol	29	-22.0636
Fluspirilene	30	-31.1104
Fluspirilene	30	-30.4544
Fluspirilene	30	-30.3909
Fluspirilene	30	-30.3338
Fluspirilene	30	-29.7446
Fluspirilene	30	-29.6797
Fluspirilene	30	-29.1565
Fluspirilene	30	-28.7605
Fluspirilene	30	-28.743
Fluspirilene	30	-28.1118
Fluspirilene	30	-27.6177
Fluspirilene	30	-27.4891
Fluspirilene	30	-27.488
Fluspirilene	30	-27.348
Fluspirilene	30	-27.3215
Pimozide	31	-29.3385
Pimozide	31	-28.5684
Pimozide	31	-27.9554
Pimozide	31	-27.3458
Pimozide	31	-27.3133
Pimozide	31	-26.3715
Pimozide	31	-26.2553
Risperidone	32	-30.1878
Risperidone	32	-30.0153
Risperidone	32	-29.6399
Risperidone	32	-29.639

mol	mseq	S
Risperidone	32	-29.1398
Risperidone	32	-28.9512
Risperidone	32	-28.8067
Risperidone	32	-28.7659
Risperidone	32	-28.6631
Risperidone	32	-28.6342
Risperidone	32	-28.6185
Risperidone	32	-28.4216
Risperidone	32	-28.1972
Risperidone	32	-28.161
Risperidone	32	-28.0372
Risperidone	32	-27.9387
Risperidone	32	-27.4304
Risperidone	32	-27.3008
Risperidone	32	-27.1219
Risperidone	32	-27.0013
Risperidone	32	-26.9482
Risperidone	32	-26.9403
Risperidone	32	-26.8978
Risperidone	32	-26.8713
Risperidone	32	-26.2278
Risperidone	32	-25.9932
Risperidone	32	-25.8065
Risperidone	32	-25.541
Risperidone	32	-24.5657
Risperidone	32	-24.4867
Risperidone	32	-23.9782
Risperidone	32	-23.4335
Risperidone	32	-23.282
Risperidone	32	-22.9309
Spiperone	33	-27.5372
Spiperone	33	-27.4473
Spiperone	33	-27.3776
Spiperone	33	-27.1824
Spiperone	33	-27.1236
Spiperone	33	-26.8703
Spiperone	33	-26.8286
Spiperone	33	-26.8258
Spiperone	33	-26.7527
Spiperone	33	-26.5463
Spiperone	33	-26.4551
Spiperone	33	-26.2429

mol	mseq	S
Spiperone	33	-25.6692
Spiperone	33	-25.4909
Spiperone	33	-25.4715
Spiperone	33	-25.4318
Spiperone	33	-24.8515
Spiperone	33	-24.8114
Spiperone	33	-24.5511
Spiperone	33	-23.798
Spiperone	33	-23.3794
Spiperone	33	-20.7474
Spiroxatrine	34	-26.9615
Spiroxatrine	34	-26.6435
Spiroxatrine	34	-26.5761
Spiroxatrine	34	-26.1958
Spiroxatrine	34	-26.0607
Spiroxatrine	34	-25.9063
Spiroxatrine	34	-25.8534
Spiroxatrine	34	-25.8513
Spiroxatrine	34	-25.5273
Spiroxatrine	34	-25.1311
Spiroxatrine	34	-25.0439
Spiroxatrine	34	-24.8229
Spiroxatrine	34	-24.7807
Spiroxatrine	34	-24.4952
Spiroxatrine	34	-24.4296
Spiroxatrine	34	-24.3058
Spiroxatrine	34	-24.215
Spiroxatrine	34	-23.8716
Spiroxatrine	34	-23.7538
Spiroxatrine	34	-23.5645
Spiroxatrine	34	-23.4987
Spiroxatrine	34	-23.3589
Spiroxatrine	34	-22.9899
Spiroxatrine	34	-22.5699
Spiroxatrine	34	-21.8532
Spiroxatrine	34	-20.2302
Spiroxatrine	34	-20.0699
Spiroxatrine	34	-18.8345
Ziprasidone	35	-26.5681
Ziprasidone	35	-26.0904
Ziprasidone	35	-26.0414
Ziprasidone	35	-25.6624

mol	mseq	S
Ziprasidone	35	-25.4728
Ziprasidone	35	-25.4022
Ziprasidone	35	-25.3833
Ziprasidone	35	-24.7924
Ziprasidone	35	-24.7654
Ziprasidone	35	-24.5331
Ziprasidone	35	-24.5235
Ziprasidone	35	-24.5073
Ziprasidone	35	-23.9406
Ziprasidone	35	-23.923
Ziprasidone	35	-23.907
Ziprasidone	35	-23.4762
Ziprasidone	35	-23.4289
Ziprasidone	35	-23.39
Ziprasidone	35	-23.2993
Ziprasidone	35	-23.0043
Ziprasidone	35	-22.9279
Ziprasidone	35	-21.1038
Ziprasidone	35	-20.9379
Ziprasidone	35	-20.7511
Butaclamol	36	-27.1128
Butaclamol	36	-26.5141
Butaclamol	36	-26.1388
Butaclamol	36	-20.9977
Chlorprothixene	37	-22.4095
Chlorprothixene	37	-21.9914
Chlorprothixene	37	-21.9853
Chlorprothixene	37	-21.7912
Chlorprothixene	37	-20.9631
Chlorprothixene	37	-20.4495
Chlorprothixene	37	-19.3828
Chlorprothixene	37	-19.2454
Chlorprothixene	37	-18.8532
Chlorprothixene	37	-18.8317
Chlorprothixene	37	-18.6909
Chlorprothixene	37	-18.6339
Chlorprothixene	37	-18.6121
Chlorprothixene	37	-18.3179
Chlorprothixene	37	-18.2926
Chlorprothixene	37	-18.2867
Chlorprothixene	37	-18.1929
Chlorprothixene	37	-17.8851

mol	mseq	S
Chlorprothixene	37	-17.7265
Chlorprothixene	37	-17.6769
Chlorprothixene	37	-17.3168
Chlorprothixene	37	-17.259
Chlorprothixene	37	-17.248
Chlorprothixene	37	-16.9974
Chlorprothixene	37	-16.9928
Chlorprothixene	37	-16.968
Chlorprothixene	37	-15.3853
Chlorprothixene	37	-15.126
Chlorprothixene	37	-14.5646
Chlorprothixene	37	-13.3646
Chlorprothixene	37	-7.53833
Clopenthixol	38	-27.8776
Clopenthixol	38	-26.036
Clopenthixol	38	-25.8891
Clopenthixol	38	-24.9308
Flupentixol	39	-28.9272
Flupentixol	39	-28.0498
Fluphenazine	40	-29.7055
Fluphenazine	40	-29.4156
Fluphenazine	40	-29.0781
Fluphenazine	40	-28.9261
Fluphenazine	40	-28.7468
Fluphenazine	40	-28.4113
Fluphenazine	40	-28.3034
Fluphenazine	40	-27.6369
Fluphenazine	40	-26.7845
Haloperidol	41	-26.467
Haloperidol	41	-26.2059
Haloperidol	41	-26.1981
Haloperidol	41	-25.9586
Haloperidol	41	-25.8095
Haloperidol	41	-25.6398
Haloperidol	41	-25.5017
Haloperidol	41	-25.4176
Haloperidol	41	-25.123
Haloperidol	41	-25.0902
Haloperidol	41	-25.0297
Haloperidol	41	-24.9722
Haloperidol	41	-24.8804
Haloperidol	41	-24.7101

mol	mseq	S
Haloperidol	41	-24.0197
Haloperidol	41	-23.5671
Haloperidol	41	-22.9961
Haloperidol	41	-22.6504
Haloperidol	41	-22.5073
Hydroxyzine	42	-26.6188
Hydroxyzine	42	-26.6072
Hydroxyzine	42	-26.489
Hydroxyzine	42	-26.186
Hydroxyzine	42	-26.0753
Hydroxyzine	42	-25.9252
Hydroxyzine	42	-25.8233
Hydroxyzine	42	-25.5387
Hydroxyzine	42	-25.4333
Hydroxyzine	42	-25.3907
Hydroxyzine	42	-25.3099
Hydroxyzine	42	-25.3074
Hydroxyzine	42	-24.655
Hydroxyzine	42	-24.4937
Hydroxyzine	42	-24.4651
Penfluridol	43	-30.4107
Penfluridol	43	-30.3647
Penfluridol	43	-29.6233
Penfluridol	43	-29.3916
Penfluridol	43	-29.2996
Penfluridol	43	-29.1788
Penfluridol	43	-29.0013
Penfluridol	43	-28.7796
Penfluridol	43	-27.962
Penfluridol	43	-26.9768
Penfluridol	43	-26.05
Penfluridol	43	-25.7335
Penfluridol	43	-24.8285
Penfluridol	43	-24.6297
Trifluperidol	44	-25.8585
Trifluperidol	44	-25.3565
Trifluperidol	44	-25.2841
Trifluperidol	44	-25.1835
Trifluperidol	44	-25.1371
Trifluperidol	44	-25.008
Trifluperidol	44	-24.9905
Trifluperidol	44	-24.6284

mol	mseq	S
Trifluperidol	44	-24.591
Trifluperidol	44	-24.39
Trifluperidol	44	-24.347
Trifluperidol	44	-24.3337
Trifluperidol	44	-24.302
Trifluperidol	44	-24.0797
Trifluperidol	44	-23.6546
Trifluperidol	44	-23.6177
Trifluperidol	44	-23.4821
Trifluperidol	44	-23.4709
Trifluperidol	44	-22.4597
Loxapine	45	-23.8801
Loxapine	45	-22.3996
Loxapine	45	-21.7489
Perphenazine	46	-27.5777
Perphenazine	46	-27.3743
Perphenazine	46	-26.5153
Perphenazine	46	-26.0867
Perphenazine	46	-25.9183
Perphenazine	46	-25.6026
Perphenazine	46	-25.4258
Perphenazine	46	-24.6923
Perphenazine	46	-22.3602
Perphenazine	46	-22.1903
Stepholidine	47	-23.9634
Stepholidine	47	-23.931
Stepholidine	47	-23.864
Stepholidine	47	-23.1516
Stepholidine	47	-22.8836
Stepholidine	47	-22.7864
Stepholidine	47	-22.7
Stepholidine	47	-22.5885
Tetrahydropalmatine	48	-27.9578
Tetrahydropalmatine	48	-26.4309
Tetrahydropalmatine	48	-26.3655
Tetrahydropalmatine	48	-26.0822
Tetrahydropalmatine	48	-25.7037
Tetrahydropalmatine	48	-25.633
Tetrahydropalmatine	48	-25.2599
Tetrahydropalmatine	48	-24.5369
Tetrahydropalmatine	48	-24.4271
Thiothixene	49	-30.4769

mol	mseq	S
Thiothixene	49	-29.4883
Thiothixene	49	-26.4992