

Discovery of Novel Analgesic Agents Targeting Neuropathic Pain: Computer-Aided Drug Design

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ABSTRACT

Background: Neurotrophin family combines nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (N3) and neurotrophin 4 (N4). p75 receptor is the target for these neurotrophins. They bind to it by tropomyosin related kinase enzyme Trk with different affinity.

Trk enzyme is classified into TrkA, TrkB and TrkC with different selectivity to neurotrophins family. NGF signals preferentially through TrkA, BDNF and N4 through TrkB, and N3 through TrkC. These neurotrophins have been found to be involved in pathophysiology of neuropathic pain.

Material and Method: Molecular docking approach was used to conduct this study. Prior to start docking procedure, some modifications were made including removal of water from the receptor, application of energy minimization and Lipinski rule of five to the ligands.

Toxicity studies, p-glycoprotein and human intestinal absorption were studied for the docked ligands.

Result: 28 ligands of FDA approved drugs and 72 non-FDA approved ligands have shown high affinity to TrkA enzyme with different energies and hence are possible to be active against neuropathic pain. These 28 ligands of FDA approved drugs and 72 ligands of non-FDA approved drugs have declined to 10 ligands and 2 ligands respectively after studying toxicity, p-glycoprotein substrate, human intestinal absorption and hepatotoxicity. The least energy was consumed was -40.8985 by the FDA-approved drug N-Hydroxy-N'-phenyloctanediarnide.

Conclusion: The docked ligands were assumed to possess therapeutic activity against neuropathic pain based on their affinity to TrkA enzyme.

Keywords

Analgesic agents, Neuropathic pain, Computer-aided drug design

Introduction

The International Association for the Study of Pain introduced the term neuropathic pain, defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system.” While this definition has been useful in distinguishing some characteristics of neuropathic and nociceptive types of pain, it lacks defined boundaries [1].

Neuropathic pain caused by trauma e.g. phantom limb, spinal cord injury, peripheral nerve injury and surgery, infection/inflammation e.g. post-herpetic neuralgia and HIV, compression e.g. trigeminal neuralgia and sciatic neuralgia, cancer (due to compression or invasion of nerve tissue by the tumour), ischaemia e.g. post-stroke pain and diabetes, demyelination e.g. multiple sclerosis and drugs e.g. Vinca alkaloid, Taxol, Ethanol and Antibacterial in TB and HIV [2].

Drugs were initiated at first diagnosis record for 46–66% of conditions, usually one item, with antidepressants included in 30% of prescriptions, anticonvulsants in 20% and opioid analgesics in 20%. The most commonly prescribed items were the same across conditions; amitriptyline, carbamazepine, coproxamol, codydramol and codeine + paracetamol. Carbamazepine was prescribed to 58% of the trigeminal neuralgia cohort. In 2600 patients followed to stable therapy, there was a median of one to two drug changes. The primary care managed incidence of four neuropathic pain conditions was provided. For commonly prescribed treatments, changes in therapy are less frequent when initial therapy was with antidepressants or anticonvulsants rather than conventional analgesics [4].

Molecular docking is a powerful technique for structure-based drug discovery. It has been used since the early 1980s. It is used to identify the effect of a molecule on the binding site of target protein and explanation of the fundamental biochemical processes. It involves two steps: prediction of the ligand conformation, position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity.

Knowing the location of the binding site before docking processes significantly increases the docking efficiency [4].

As the structures of more and more proteins and nucleic acids become available, molecular docking is increasingly considered for lead discovery.

Recent studies consider the hit-rate enhancement of docking screens and the accuracy of docking structure predictions. As more structures are determined experimentally, docking against homology-modeled targets also becomes possible for more proteins. With more docking studies being undertaken, the 'drug-likeness' and specificity of docking hits is also being examined [5].

Justification of the Research

Tricyclic antidepressants are considered first-line agents for neuropathic pain, but their use is restricted as they are associated with risks of cardiovascular mortality [7].

A study has revealed that TCAs is also associated with diarrhea and dry mouth while SSRIs are associated with palpitation and nausea [7]. The most serious adverse effects of SSRI during long-term use are sexual dysfunction, weight gain and sleep disturbance [8].

Although Carbamazepine is effective in treatment of neuropathic pain, it causes side effects that are intolerant by patients such as sedation, confusion, disorientation and postural hypotension which make it not preferred. It is also teratogenic and hence should be avoided during first trimester.

Pregabalin is very effective but the generic drugs are not as effective as the innovator (Lyrica). Its problem is that, it is not available in Sudan. Most of these drugs especially pregabalin are associated with withdrawal effect, so they require tapering down.

Local anesthetic lidocaine (xylocaine) can be used for neuropathic pain but can cause seizure and nystagmus if entered blood circulation and reached brain.

This research aims to discover new safe and effective drugs to solve all these problems associated with treatment of neuropathic pain.

Literature Review

McKelvey, L and his group said that, nerve growth factor (NGF) is the founding member of the neurotrophins family of proteins. It was discovered more than half a century ago through its ability to promote sensory and sympathetic neuronal survival and axonal growth during the development of the peripheral nervous system, and is the paradigmatic target-derived neurotrophic factor on which the neurotrophic hypothesis is based. Since that time, NGF has also been shown to play a key role in the generation of acute and chronic pain and in hyperalgesia in diverse pain states. NGF is expressed at high levels in damaged or inflamed tissues and facilitates pain transmission by nociceptive neurons through a variety of mechanisms. Genetic mutations in NGF or its tyrosine kinase receptor TrkA, lead to a congenital insensitivity or a decreased ability of humans to perceive pain [9].

Since their discovery in the 1950s, neurotrophic factors have raised expectations that their clinical application to neurodegenerative diseases might provide an effective therapy for what are now untreatable conditions. Nerve growth factor (NGF) was the first neurotrophic factor to be discovered and was one of the earliest to proceed to clinical trials. NGF, which is selectively trophic for small fiber sensory and sympathetic neurons, was selected as a potential therapy for diabetic polyneuropathy because of the serious consequences associated with degeneration of those neuronal populations in this condition. In addition, evidence shows that reduced availability of NGF may contribute to the pathogenesis of diabetic neuropathy, and animal models of neuropathy respond to the exogenous administration of NGF [10].

Ugolini G, et al. [11], stated that nerve growth factor (NGF) is involved in pain transduction mechanisms and plays a key role in many persistent pain states, notably those associated with inflammation. On this basis, both the NGF ligand and its receptor TrkA (tyrosine kinase A) represent an eligible target for pain therapy. Although the direct involvement of NGF in pain modulation is well established, the effect of a direct functional block of the TrkA receptor is still unknown [11].

A study conducted by Watson JJ, Allen SJ, Dawbarn D. has shown that nerve growth factor (NGF) is a major mediator of inflammatory and neuropathic pain, providing a new therapeutic target. Although originally discovered as a trophic factor for sympathetic and sensory neurons during development, it now appears that in adults, levels of NGF are elevated in many acute and chronic pain conditions. Furthermore, preclinical animal models of inflammatory and neuropathic pain also show increased NGF levels, while the sequestration of NGF alleviates the associated hyperalgesia. The molecular mechanisms involved are being elucidated.

This review briefly examines pain signaling pathways and describes currently available analgesics. It then investigates the approaches taken in targeting NGF-mediated pain. Current options being explored include the development of humanized monoclonal antibodies to NGF or its tyrosine kinase receptor TrkA (also known as neurotrophic tyrosine kinase receptor, type 1 [NTRK1]), and the sequestration of NGF using TrkA domain 5 (TrkAd5), a soluble receptor protein that binds NGF with picomolar affinity. Administration of either antibodies or TrkAd5 has been shown to be effective in a number of preclinical models of pain, including cystitis, osteoarthritis, UV irradiation (sunburn), and skeletal bone pain due to fracture or cancer. Other possible future therapies examined in this review include small-molecule TrkA antagonists, which target either the extracellular NGF binding domain of TrkA or its intracellular tyrosine kinase domain [12].

In The systemic administration of anti-nerve growth factor (NGF) antibodies can prevent local sensory hypersensitivity and block nociceptive fibers from sprouting into denervated adult rat skin. However, in the case of chronic constriction injury (CCI) in a rat, there is evidence that NGF reverses some effects of axotomy and alleviates thermal hyperalgesia. It is with this in mind that we investigated the influence of local anti-NGF and NGF on neuropathic pain and collateral sprouting caused by CCI. In our study, we looked at the effects to the ligated nerves after 30 consecutive days of local injections of anti-NGF and NGF. A high-dose of anti-NGF (1800 ng) was found to eradicate heat and cold hyperalgesia during postoperative days 16–28 and from days 8 to 34 after CCI, respectively. Our results show that a low-dose anti-NGF (18 ng) only mildly alleviates heat hyperalgesia but not cold hyperalgesia. There is evidence that a rebound phenomenon occurs for a short period of time after the anti-NGF injections cease. Results show that anti-NGF injections, whether in a high or low dose, significantly reduce the severity of autotomy or prevents the spread of collateral sprouting from the saphenous nerve into the sciatic innervation territory. In contrast, when a NGF (0.75 ng/g body weight) was applied to the ligated nerve immediately after the ligation, heat and cold hyperalgesia were eradicated during postoperative days 4–68 and from days 4 to 28, respectively. The results show that the effect of anti-NGF is delayed at the onset, is short in duration, and is dependent on the dosage. However, anti-NGF but not NGF blocked collateral sprouting and decreased the severity of autotomy, suggesting that anti-NGF may be a better potential alternative analgesic for the treatment of neuropathic pain in humans. The different initiation times to abolish thermal hyperalgesia by anti-NGF (delayed onset) and NGF (early onset) suggests that alterations in neurotrophic factors contribute to the development of behavioral hyperalgesia via a complex mechanism in CCI rats [13].

Material and Methods

Pre-docking procedures

Preparation and optimization of Ligands

Ligands for the study were unapproved FDA Building blocks and approved FDA Building blocks which were collected from ZINC database [14] in SDF format. In order to enhance the probability

of successful docking, ligands were filtered according to Lipinski rule of 5 [15] using Open babel [16] only those structures that strictly followed the Lipinski's rule were selected for docking.

Preparation and optimization of Protein

The crystallographic structure of human TrkA receptor was retrieved from protein data bank with a resolution [Å]:2.33 [17].

Interactive visualization and analysis of molecular structures were done using MOE [18] for better understanding of active site.

Energy minimization

In order to prepare the selected compounds for docking, hydrogens and Gasteiger charges were added and all the hetero-atoms and water molecules were removed from protein structure. The protonated protein initially optimized in order to remove all the bad steric clashes using AMBER 99 force field [19], while MMFF94s force field parameters [20,21] were performed for small molecules. All the minimizations were performed with MOE (grad <0.001). The protonated and optimized structures were saved for further preparation and analysis.

Docking Approach and operation:

Docking studies were performed by MOE for each ligand (other parameters were kept default) as described in diagram (1).

- (1) The co-crystallized protein with its inhibitor compound was identified; therefore, the binding site was identified with its residues.
- (2) Ligand interactions were computed for the X-ray co-crystallized protein to reveal the different types of interaction as a validation for the coming docking procedure.
- (3) The inhibitor compound is then removed and the selected compounds are used instead.
- (4) The docking was done with the default settings of the MOE–DOCK as following:
 - a) The scoring function was London dG.
 - b) 10 conformers of the ligand were retained with highest and best score by default.
 - c) The virtual dock of standard allosteric agonist after re-docked into the active site pocket was used as a minimum score for novel binders and then demonstrated by 2D ligand-receptor interactions.

The scoring configuration of the ligand–Target complexes was selected on energetic grounds (MM/GBVI); best poses with the lowest binding energy was chosen for each compound. The docking scores, docking binding energy, and chemical structures of selected ligands were then presented.

Post-docking procedures

Prediction of toxicity profile

Carcinogenicity, mutagenicity

admetSAR was used to predict the carcinogenicity and mutagenicity, online server (<http://lmmd.ecust.edu.cn/admetSar1/>).

Acute Oral Toxicity Prediction

ProTox was used for the prediction of acute oral toxicity depending on chemical similarities between compounds with known toxic effects and the presence of toxic fragments.

Toxic doses are often given as LD₅₀ values in mg/kg body weight, whereas toxicity classes are defined according to the globally harmonized system of classification of labelling of chemicals (GHS):

- Class I: fatal if swallowed (LD₅₀ ≤ 5 mg/kg)
- Class II: fatal if swallowed (5 < LD₅₀ ≤ 50 mg/kg)
- Class III: toxic if swallowed (50 < LD₅₀ ≤ 300 mg/kg)
- Class IV: harmful if swallowed (300 < LD₅₀ ≤ 2000 mg/kg)
- Class V: may be harmful if swallowed (2000 < LD₅₀ ≤ 5000 mg/kg)
- Class VI: non-toxic (LD₅₀ > 5000 mg/kg)

Prediction of toxicity profile

P-glycoprotein substrate

By the use of ADMETsar, ligands were identified as P-glycoprotein substrate or not, only those which are not P-glycoprotein substrate were included in the study.

Human intestinal absorption

By the use of ADMETsar, HIA were determined for all ligands, and only those which are absorbed by human intestine were included in the study.

Hepatotoxicity

By the use of Protox, hepatotoxicity was determined for the docked ligands. Ligands marketed as hepatotoxic are excluded and those marketed as non-hepatotoxic or have low tendency are involved in the study.

Discussion

Compounds used for docking are synthetic and were obtained specifically from zinc database for several reasons: it is free, large as it contains 727 842 molecules, each with 3D structure and available in several common file formats including SMILES, mol2, 3D SDF, and DOCK flexibase format.

ZINC database is an open-access database of commercially available small organic molecules for drug discovery and currently contains more than 13 million unique compounds, which were processed in SMILES format and annotated with its molecular formula [22].

FDA- approved drugs are also docked as it is safe and were obtained from zinc database too [14]. Lipinski's rule of five, also known as Pfizer's rule of five or rule of five (RO5) was applied to these compounds before docking. It is a rule of thumb that assess if a drug can be orally active by detecting the presence of physical and chemical properties.

According to observation done by Christopher A. Lipinski in 1997 that orally active drugs are small in size and lipophilic, then the rule of five was applied to predict if the drug is orally active [21,23]. The prediction is based on criteria, they are:

- 1-No more than 5 hydrogen bond donors (the total number of nitrogen-hydrogen and oxygen-hydrogen bonds),
- 2-No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms),
- 3-A molecular mass less than 500 daltons, and

4-An octanol-water partition coefficient log *P* not greater than 5. It is noticed that all numbers are multiples of five, which is the source of the rule's name.

Receptor optimization

Neurotrophin (NT) family of growth factor consists of nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) and neurotrophin 4 (NT4). These neurotrophins bind to p75 receptor that belongs to the TNFR superfamily through tropomyosin related kinase Trk enzyme with different affinity, NGF signals preferentially through TrkA, BDNF and N4 through TrkB, and N3 through TrkC [24].

NTs are involved in the pathophysiology of neuropathic pain [25]. Energy minimization is a process in which the energy of protein and ligands is reduced or minimized to render them in the stable state by relaxing bond length, angles and non-bonded interactions.

Partial charge is the net or actual charge of an atom of the molecule. It is determined by electronegativity of the atom as it evaluates the electron withdrawing power of an atom. Gasteiger charge was used and the only problem of this method is that it assumes an overall net neutral state for the respective molecular system. Thus, protonation states of the amino acids of the receptor were checked.

Protein resolution is the measurement of quality of data obtained from protein structure. It is important feature in docking because the placement of side chain depends on resolution. It should be above 2 angstrom. High-resolution structures, with resolution values of 1 Å, are highly ordered and it is easy to see every atom in the electron density map. Lower resolution structures, with resolution of 3 Å or higher, show only the basic contours of the protein chain, and the atomic structure must be inferred.

Most crystallographic-defined structures of proteins fall in between these two extremes. Another parameter should be taken into consideration is water molecules, water molecule is present in the protein structure as loosely bound to protein and hence readily displaced by ligand and sometimes completely artificial.

Depending on the target, water molecules can be deleted or preserved. In most cases, water molecule should be deleted before docking for several reasons:

- 1-To ease the process of computation,
- 2-To clear the binding pocket of possible water molecules that would distort the pose search, and
- 3-To prevent wrong conformation resulting from formation of water mediated hydrogen bonds with ligand

Water molecules should be reserved if they are required for binding of ligand to target and its activity.

Toxicity profile

AdmetSAR server is a comprehensive free tool that predict the ADMET properties of drug that play key roles in the discovery and development of drugs, pesticides, food additives, consumer

products and industrial chemicals as well as to conduct environmental and human hazard assessment.

In admetSAR, above 210,000 ADMET annotated data points for more than 96,000 unique molecules with 45 kinds of ADMET-associated properties, proteins, species, or organisms have been carefully curated from a large number of diverse literatures [26]. It allows searching for molecules by CASRN (chemical abstract service number), common name and smile.

Toxicity was studied by the aid of use of a free web server for the *in-silico* prediction of rodent oral toxicity called Protox. Toxic effects of drugs are determined usually by animal trials which use About 100 million rodents. Protox is considered an alternative approach as it consumes less time, cost and animal experiments.

The prediction upon the analysis of similar compounds with known median lethal doses (LD_{50}) and incorporation of the identification of toxic fragments, therefore representing a novel approach in toxicity prediction [27].

Because drug-induced hepatotoxicity is the most common reason for withdrawal of approved drugs, hepatotoxicity was studied for these ligands. Hepatotoxicity can be dose-related or not dose-related. Hepatotoxicity result in moderate-to-severe damage to hepatocytes with a clinical image that resembles viral hepatitis, characterized by a rapid onset of malaise and jaundice in association with increased aminotransferase levels [28].

P-glycoprotein is a product of the *ABCB1* [also known as multidrug resistance 1 (*MDR1*)] gene. It acts as efflux transporter that excretes most of xenobiotics out of cells. This function results in the following effects including: 1-limitation of absorption of orally administered drugs, 2-promotion of drug elimination into bile and urine, 3-protection of various tissues (e.g. brain, testis and fetus) from potentially toxic xenobiotics.

P-glycoprotein is also detected in a broad variety of normal tissues with excretory function (small intestine, liver and kidney) and at blood–tissue barriers (blood–brain barrier, blood–testis barrier and placenta), [29].

To be specific for orally active drugs, human intestinal absorption was applied for the docked ligand, prediction of HIA has helped in accelerating the process of finding compounds with improved properties, eventually making the entire drug discovery process shorter and more cost efficient [30].

Conclusion and Recommendation

Conclusion

This study aims to discover new chemical entities for treatment of neuropathic pain by the use of molecular docking approach. The docked ligands were assumed to have affinity based on the energies they have consumed to bind to receptor TrkA (table 1 and table 2) which was found out to be related to neuropathic pain. Although the affinity of these ligands to the enzyme is greater than

the affinity of endogenous ligand in the body, it is not necessary to have great efficacy as binding is not a measure of efficacy.

Name	Energy
ZINC000044154868	-27.2864
ZINC000003818726	-24.2885

Table 1: Non-FDA approved ligands.

Name	Energy
N-Hydroxy-N'-phenyloctanediamide	-40.8985
3, 3-dimethyl-6-(5-methyl-3-phenyl-1, 2-oxazole-4-amido)-7-Oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid	-38.8878
1-[4-Hydroxy-5-(hydroxymethyl) oxolan-2-yl]-5-(trifluoromethyl)-(1 <i>H</i> , 3 <i>H</i>)-pyrimidine-2, 4-dione	-36.2872
3-Benzyl-1,1-dioxo-6-(trifluoromethyl)-3,4-dihydro-2 <i>H</i> -1,2,4-benzothiadiazine-7-sulfonamide	-36.1464
9-[(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6,9-dihydro-1 <i>H</i> -purin-6-one	-32.4745
4-amino-N-(3,4-dimethyl-1,2-oxazol-5-yl)benzenesulfonamide	-30.9816
2-amino-3-(1 <i>H</i> -indol-3-yl)propanoic acid	-30.1545
1-[4-hydroxy-5-(hydroxymethyl) oxolan-2-yl]-5-methyl-1, 2, 3, 4-tetrahydropyrimidine-2, 4-dione	-30.0327
5-chloro-6-[(2-iminopyrrolidin-1-yl) methyl]-1, 2, 3, 4-tetrahydropyrimidine-2,4-dione hydrochloride	-27.504
Trans-4-(aminomethyl)cyclohexanecarboxylic acid	-22.44

Table 2: FDA approved ligands.

Regarding the docked ligands, a hypothesis of being active against neuropathic pain cannot be emphasized because molecular docking approach does not differ between inducer and inhibitor, therefore, animal experiments is the only approach for prediction of efficacy but unfortunately, it was not conducted in this study.

To ensure safe and effective drugs, some tests were conducted for these ligands, they are p-glycoprotein substrate, human intestinal absorption and hepatotoxicity, only those which are non p-glycoprotein substrate, absorbed by human intestine and non-hepatotoxic were selected.

According to the conducted tests, these ligands might solve many patients and drugs problems such as cost, adherence to medication, side effects, frequency of doses and safe for patients with hepatic disorder.

Recommendation

For the ligands to be active against neuropathic pain, they should be efficient in inhibiting TrkA enzyme and this can be determined by experimenting these ligands in experimental animals and then to prepare them for clinical trials, as a consequence, ending up with formulating effective drugs.

Unfortunately, this step was not applied for the ligands because ligands were found to be unaffordable as well as difficulty in finding rats. Advance, this project can be expanded to involve studying the pharmacological effects of these ligands on TrkA enzyme and accordingly evaluating their therapeutic effects on neuropathic pain.

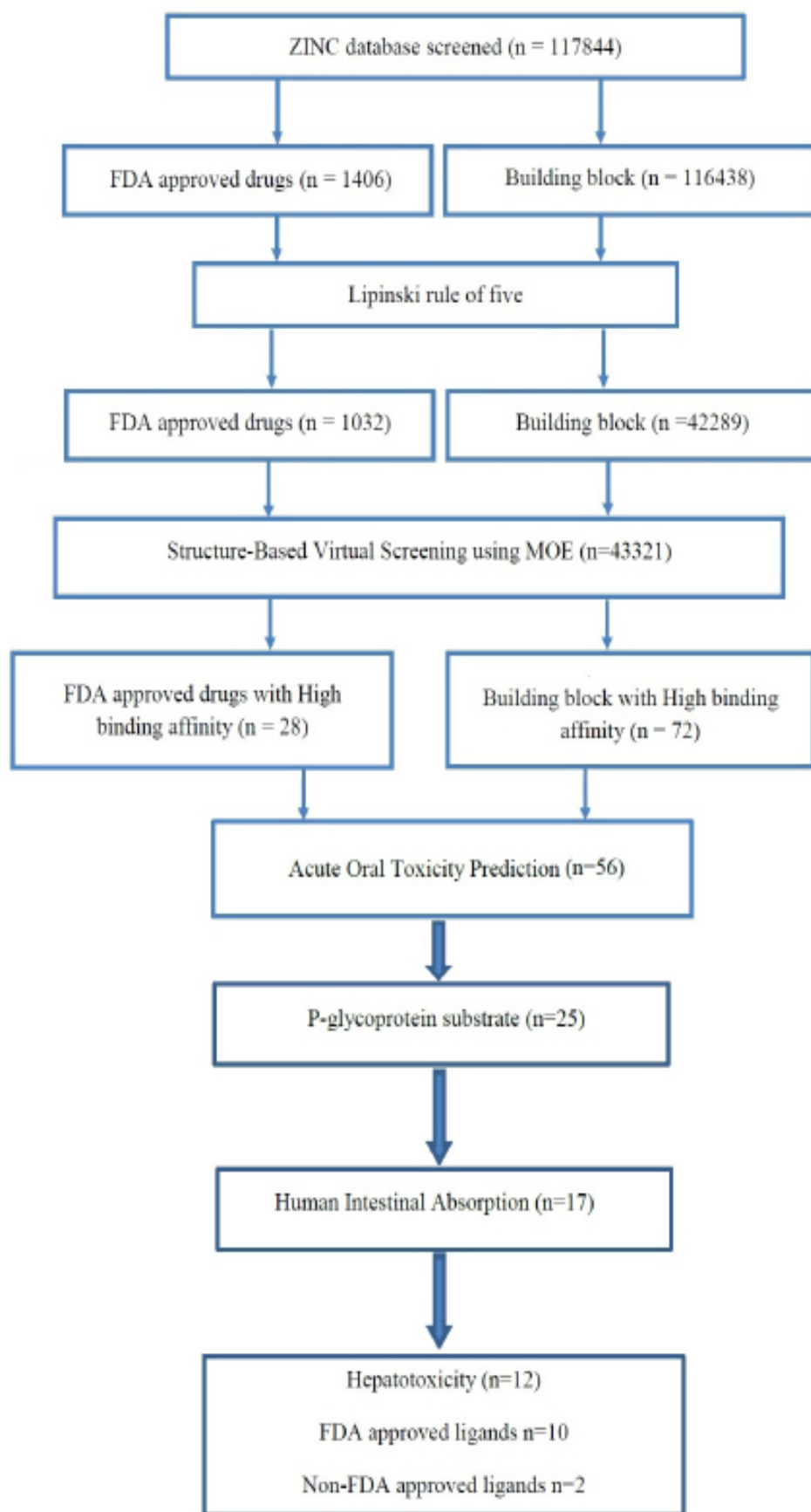


Figure 1: Flow chart of docking studies were performed for each ligand.

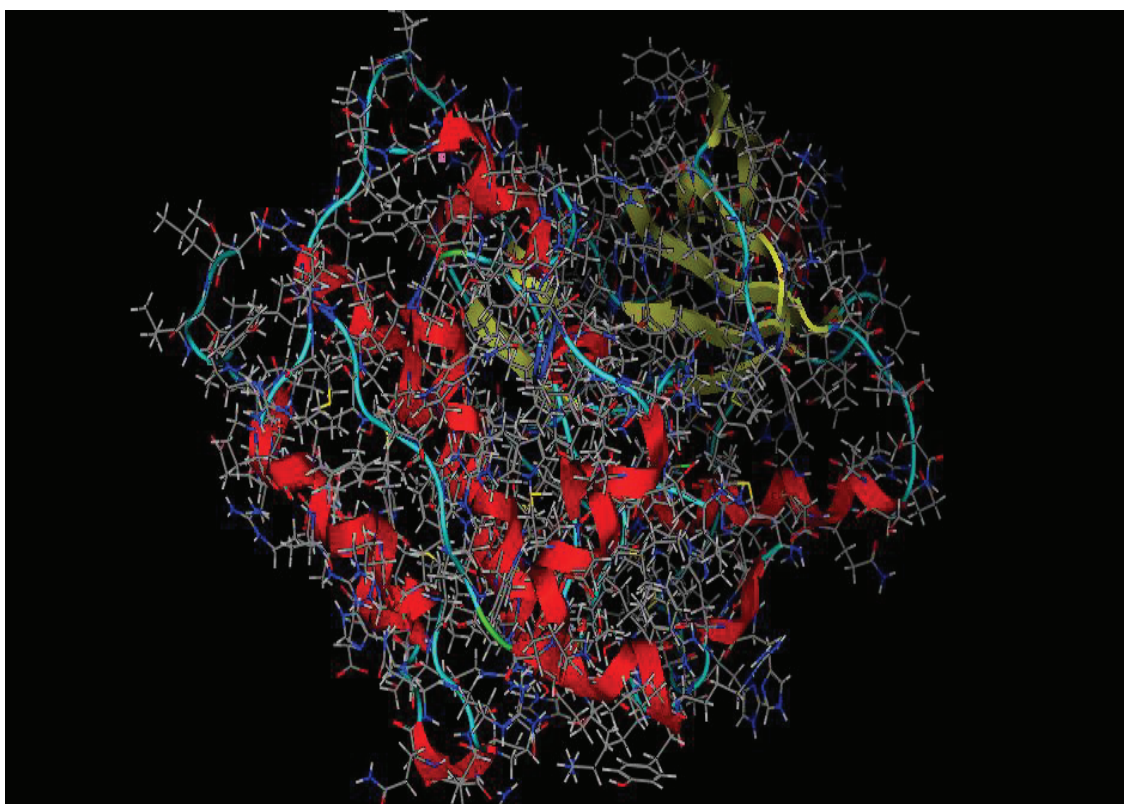
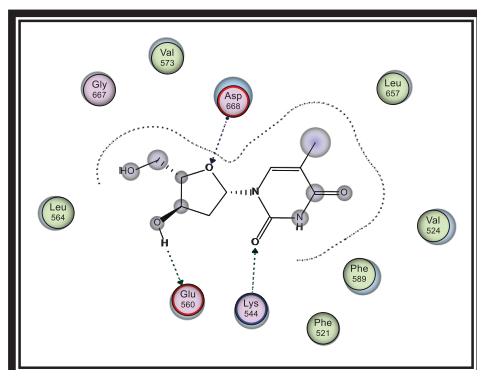
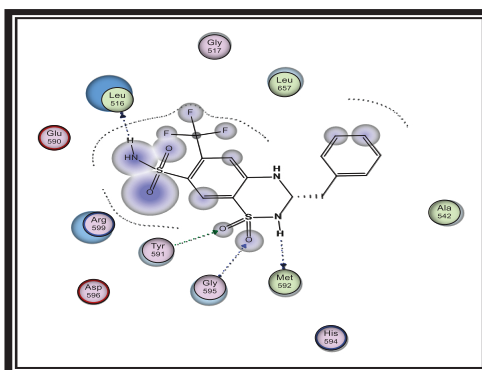


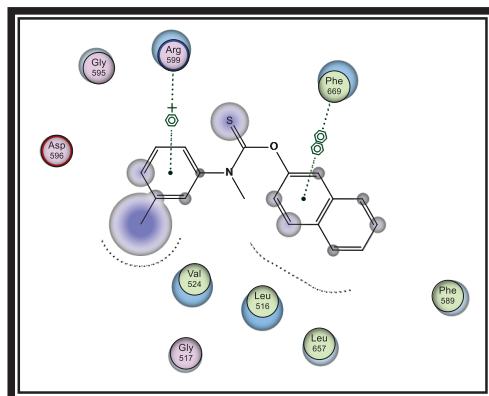
Figure 2: An inside view of molecular surface representation of binding pocket residues of human TrkA receptor.



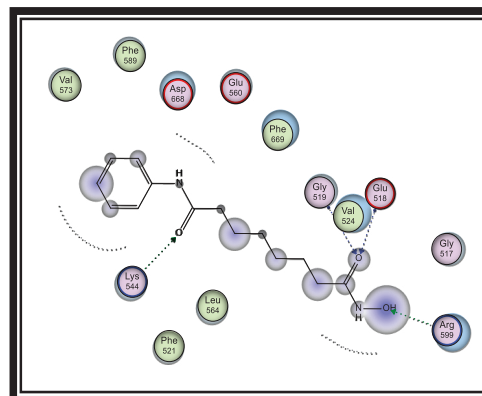
N-Hydroxy-N'-phenyloctanediamide



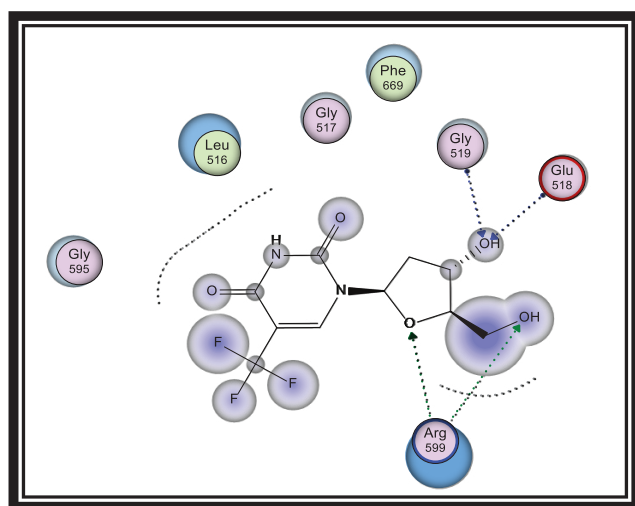
3,3-dimethyl-6-(5-methyl-3-phenyl-1,2-oxazole-4-amido)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid



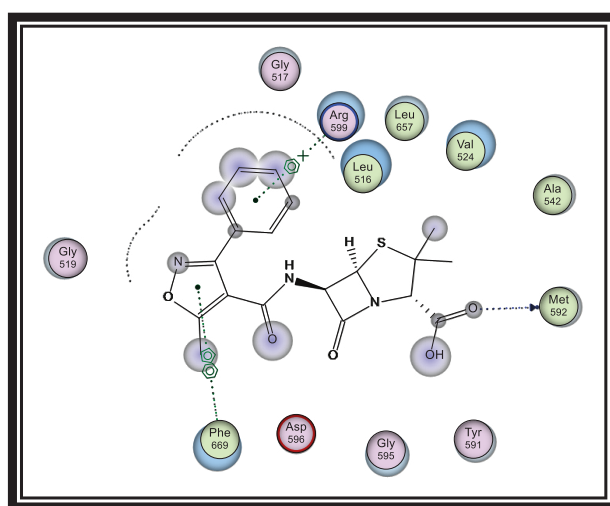
1-[4-Hydroxy-5-(hydroxymethyl) oxolan-2-yl]-5-(trifluoromethyl)-1H,3H-pyrimidine-2,4-dione



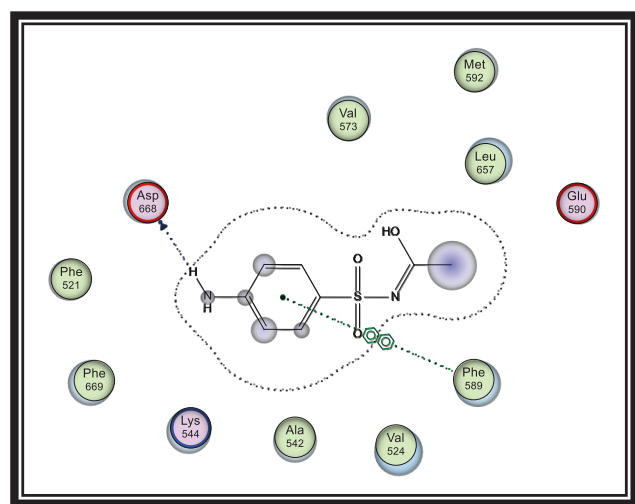
3-Benzyl-1,1-dioxo-6-(trifluoromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide



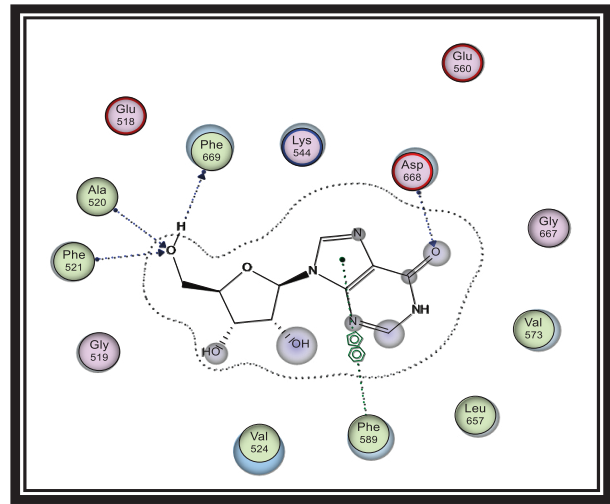
9-[(2R, 3R, 4S, 5R)-3, 4-dihydroxy-5-(hydroxymethyl) oxolan-2-yl]-6, 9-dihydro-1H-purin-6-one



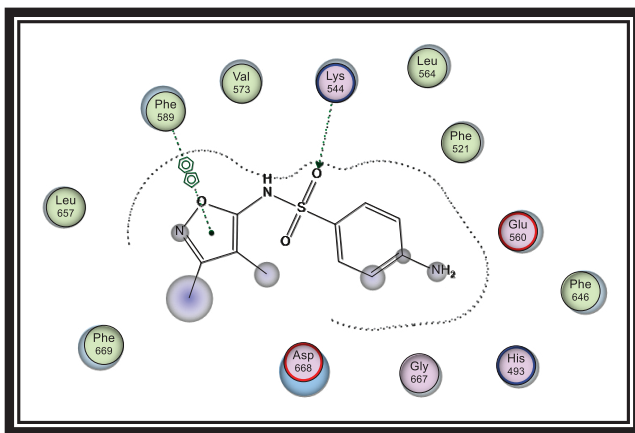
4-amino-N-(3, 4-dimethyl-1, 2-oxazol-5-yl) benzenesulfonamide



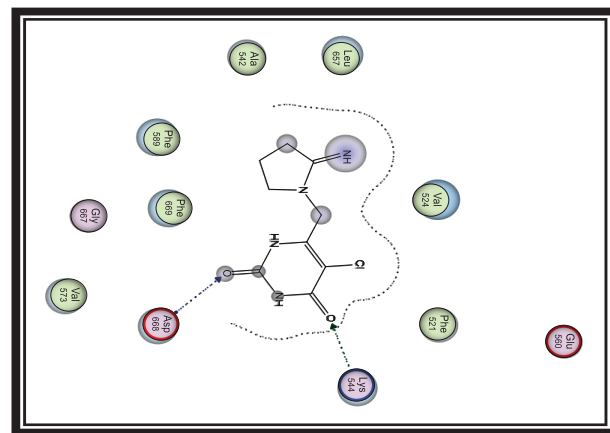
2-amino-3-(1H-indol-3-yl)propanoic acid



1-[4-hydroxy-5-(hydroxymethyl) oxolan-2-yl]-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione



5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione hydrochloride



Trans-4-(aminomethyl)cyclohexanecarboxylic acid

Figure 3: A representation of intermolecular interaction of best ligand targeting human TrkA receptor.

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