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REPURPOSING CINACALCET, A CALCIMIMETIC AGENT, FOR DEPRESSION TREATMENT: A LIGAND-BASED APPROACH UTILIZING MORGAN FINGERPRINTS

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Keywords:

Cinacalcet, Depression, Drug Repurposing, Fluoxetine, Binding Affinity, Calcium Signaling, Neuroplasticity, Molecular Docking, Structural Validation, Antidepressants

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ABSTRACT

The present study aims to analyze the relevance of cinacalcet as a therapeutic agent for depression rather than its original indication in chronic kidney disease as was intended. A ligand-based drug repurposing mechanism was utilized to perform screening and docking studies on the representative compounds including fluoxetine and its derivatives. Out of all the ligands identified, fluoxetine was the best anchoring ligand due to its efficiency and safety as well as the structural information which allows it to be modeled as a pharmacophore for the design of new antidepressants which target multiple pathways including neuro-inflammation. While performing DrugRep platform screening, the different compounds demonstrated various levels of binding affinity, with fluoxetine attaining the top score of 1.000 and cinacalcet, 0.316 which is moderate affinity. With regards to the PDB-REDO validation, it has performed remarkably well and improved the structural accuracy of the docking model considerably as shown by the bond length and angle RMZ Z-scores, which were lower and ipso, and Ramachandran plot normality which was enhanced. Also, cinacalcet is distinctly able to interact with critical binding residues related to calcium signaling pathways, which may in turn be responsible for mood changes. In particular, those studies allow us to propose for further investigation the role of cinacalcet and fluoxetine derivatives in the treatment of depression.

1. INTRODUCTION

Repositioning also refers to drug repurposing which is a drug strategy that involves developing a new therapeutic use for a drug which has already been approved[1]. This approach is being widely practiced in the recent past and is one of the practices that can help screen candidate drugs faster and bring drugs to the market at a lower cost[2]. It is estimated that the process of designing and developing a new drug from scratch can take at least more than ten years and the drug in question may pass through various phases of preclinical and clinical testing stages many of which may fail[3]. On the other hand, to repurpose a drug that is already widely used and established means that data on the safety and efficacy and some clinical practice are already available, making it possible to use the drug for a different indication in a shorter time frame[4]. Such a change in view offers more drug new uses but also help in measuring the impacts of drug development strategy – especially in times of new health challenges [5].

It is interesting to note that the ligand-based drug discovery methods knew no bounds in modern day medical research activity since 70 % of the drugs fall under the repurposed therapy[6]. It principally focuses on the ligand, the active drug molecule, and determines the target systems that provide the activity of the mechanism of action by which the ligand acts[7]. The targets through which the cellular activity transpires, the cellular signaling pathways, the drug metabolizing enzymes, and the nuclear hormone receptors are all assessed and the cellular outputs are determined to be compared with other compounds[8]. These compounds or a library containing a complex mix of molecules will be taken and screened using molecular docking, QSAR modeling, and other drug-like assessments[9]. The aim of this entire process is to dose the target with molecular drugs that share the systems and pathways used by the principal drugs to make the re-discovery more effective and to use drugs currently in use[10].

Fluoxetine or Prozac as it is popularly known, is a selective serotonin reuptake inhibitor (SSRI) that is approved by the FDA and is very popular for the treatment of major depressive disorder, obsessive compulsive disorder and other mood disorders[11]. Fluoxetine has been available since the late 1980s and since then it has been considered to be safe and has become one of the most used antidepressants all around the world[12]. Its action is through the prevention of serotonin reuptake in the brain thus increasing the amount of serotonin present, an area of which is already associated with the mood and the control of emotions[13]. Given the vast clinical experience and the consistent pharmacological profile of Fluoxetine, it is a good patient for ligand-based drug repurposing as this drug's interactions and effects can easily be utilized to search for other therapeutic targets[14].

The general aim of this study is to consider the tool of Morgan fingerprints to identify other potential repurposing candidates for drugs that show some similarity to Fluoxetine[15]. This study wishes to find

novel therapeutic uses for existing drugs within the FDA-approved drug library in a ligand-based screening approach[16]. The systematic study of the molecular features and interactions will highlight these compounds potential efficacy as SSRIs or in related therapeutic areas[17].The approach shall aim not only to expand the depictions of Fluoxetine in pharmacological landscapes but also to contribute to drug repurposing as a field by way of the demonstration of the efficiency of ligand-based methods to identify new drug candidates.Through this study, we hope to hereby garner important clues towards drug-readaptation for existing molecules to their transitioned clinical indications and assist improvements in patient's therapeutic choices[18].

2. MATERIALS AND METHODS

2.1 Data Sources- A collection of FDA approved drug library is used in the present study. It is a database that comprises a well-structured library of compounds with information and data attributed by the latest scientific research. The library is a comprehensive resource for all FDA-approved drugs with medically significant structural and biochemical properties elucidating their potential use in drug repurposing . The source of data is described in Open DrugBindingDatabase ,DrugBank and ChEMBL . The library was collected from the above mentioned open source biological databases. Simulations were performed for computational modeling using various ligand similarity tools . These tools facilitated us to calculate the molecular similarity based on various descriptors which we utilized as starting point for virtual screening of the potential drugs for repurposing.

2.2. Ligand Preparation- The structure of Fluoxetine required for screening was downloaded from PubChem. To convert it into a proper 3-D structure, the 2-D structure obtained from the database PubChem was the appropriate stereo-chemical and protonation state of this hypothetical ligand (Figure 1). Further conformational optimization of the 3-D structure of Fluoxetine was carried out using molecule geometry optimization on molecular mechanic (MM) level of theory in the software package, Chem3D.

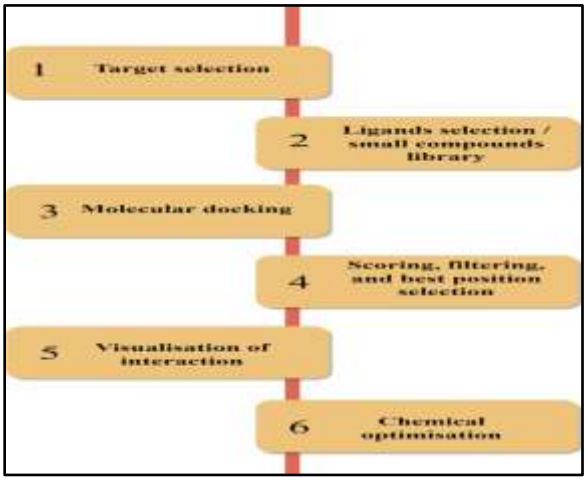

Figure 1: Ligand Based Virtual Screening

2.3 Morgan Fingerprint Generation- Morgan fingerprints were generated as a circular fingerprint for identifying candidates similar to Fluoxetine. This method encodes the molecular structure into fixed-length bit strings. The parameters such as a radius of 2 that captures local atom environments and a bit length of 2048 were used. The chosen bit length could provide a sufficiently expanded representation space to differentiate against compounds. Subsequently, the generated circular finger-prints were used for similarity comparison with the compounds from drugs library.

2.4 Virtual Screening Protocol- Virtual screening performs similarity-based compound screening by different tools. The similarity screening methods involve, the preliminary screening with molecular 3D structures by LigMate, the structural alignment and ligand-based docking by FitDock-align and the structural similarity-based screening by LSAlign. Similarity was quantified as a Tanimoto value, where the value ranges from 0 to 1 with zero indicating no similarity and one indicates identical. For ranking the best compounds, ligands that have maximum Tanimoto coefficient value were considered.

2.5 Docking Studies-Molecular Docking was conducted using CB-Dock to measure the binding affinity and pose of the selected best hit compounds. The following steps were carried out during the docking process. Target Protein: Selection of Target protein was carried based on interaction with Fluoxetine (Table 1). Other neuro receptors that regulate mood and act as SSRIs were screened. Binding Site: The crystal structure of the targets was utilized to understand the binding site. The Protein Data Bank (PDB) was used to determine the crystal structure. Docking Simulation: This step involves the flexible docking input, where the ligands were given conformational flexibility and rotation. A residue of 4 Å was maintained within the bound box which defines the binding site pocket (Table 2). The docking scores of the top ranked candidates were compared to the natural ligand and considered for further validation**.**

3. RESULTS AND DISCUSSION

3.1 Results of Ligand-Based Drug Repurposing

Table 1: Justification for selecting fluoxetine as the primary ligand for designing new agents targeting Depression

Justification	Description
Established Efficacy	Well-studied with strong evidence supporting effectiveness in major depressive disorder and mood disorders.
Mechanism of Action	Inhibits serotonin reuptake, increasing serotonin availability; central to modern antidepressants.
Safety Profile	Favorable safety compared to older antidepressants; fewer side effects and lower toxicity in overdose.
Drug Design Insights	Provides valuable structural insights; informs development of compounds with improved efficacy and safety.

Potential for Novel Derivatives	Serves as a lead compound for creating derivatives targeting additional pathways (e.g., neuroinflammation).
Existing Research Foundation	Extensive research on pharmacodynamics and outcomes supports informed modifications in new designs.
Patient Compliance	Well-known profile aids in developing agents that improve adherence by focusing on dosing and side effects.
Combination Therapies	Studied in combination with other agents, allowing exploration of multimodal therapies targeting depression.

3.2 Results of Ligand –Based Screening using the DrugRep platform:

Table 2: Binding scores and target interaction of various compounds

Rank	Compound	Name	Score	Rank	Compound	Name	Score
1	DB00472	Fluoxetine	1.000	**11**	DB08941	Isoxsuprine	1.000
2	DB00289	Atomoxetine	0.429	**12**	DB00508	Triflupromazine	0.429
3	DB00476	Duloxetine	0.316	**13**	DB00985	Dimenhydrinate	0.316
4	DB01012	Cinacalcet	0.316	**14**	DB01075	Diphenhydramine	0.316
5	DB00600	Monobenzone	0.316	**15**	DB00573	Fenoprofen	0.316
6	DB01237	Bromodiphen hydramine	0.293	**16**	DB01620	Pheniramine	0.293
7	DB02266	Flufenamic acid	0.293	**17**	DB08976	Floctafenine	0.324
8	DB01173	Orphenadrine	0.270	**18**	DB00283	Clemastine	0.323
9	DB06152	Nylidrin	0.250	**19**	DB14195	4-(Isopropylamino)diphenylamine	0.321
10	DB04825	Prenylamine	0.241	**20**	DB14120	Phenylethyl resorcinol	0.321

3.3 Docking studies and Validation process results:

Table 3: Validation metrics from PDB-REDO

Validation Metric	Original	PDB-REDO
Crystallographic Refinement		
R	0.2497	0.2477
R-free	0.2776	0.2860
Bond Length RMS Z-score	0.836	0.220
Bond angle RMS Z- score	0.749	0.407

Model Quality Raw Scores (Percentiles)		
Ramchandran plot normality	6	16
Rotamer normality	19	24
Coarse packing	N/A	97
Fine packing	N/A	90
Bump severity	34	45
Hydrogen bond satisfaction	59	77

The Table 3 shows, a considerable improvement in geometric fidelity is indicated by lower RMS Z-scores of bond length and angle and higher hydrogen bond satisfaction. The increase in R-free should be considered with caution since it might reflect overfitting, but the improvements in packing, along with the high clarity of the Ramachandran plot, indicate the PDB-REDO model is a better option structurally for functional predictions. Performing continuous monitoring of the R-free value is recommended.

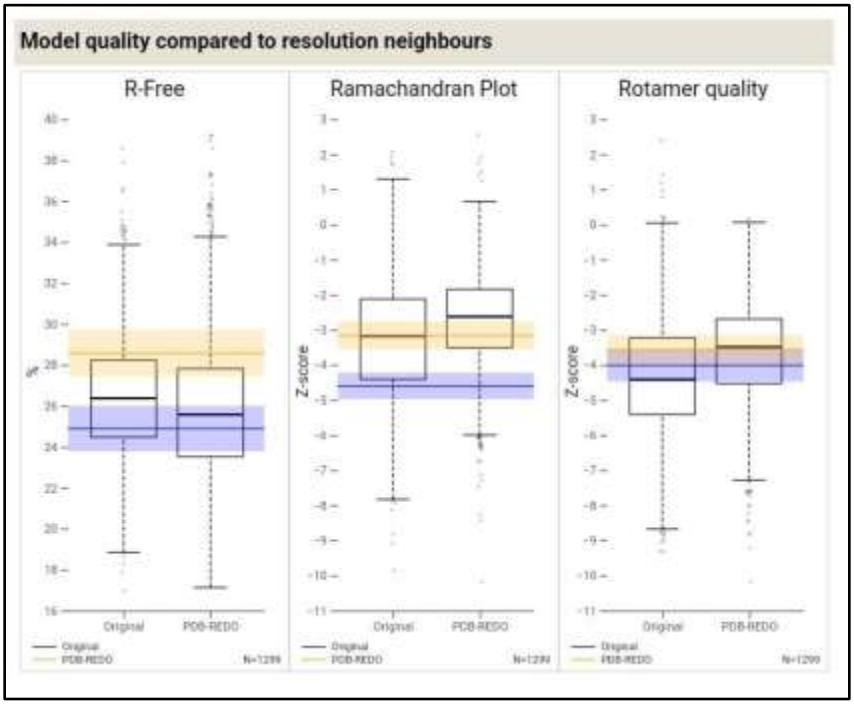

Figure 2: A Study on the Quality Metrics of the Different Models: Original and PDB-REDO Structure.

The Figure 2 shows that the use of PDB-REDO improvements the R-free values obtained, suggesting increased model accuracy, as well as marginally improving the Ramachandran and Rotamer quality Z-scores. Altogether, more complete and polished protein structures are attained upon using PDB-REDO.

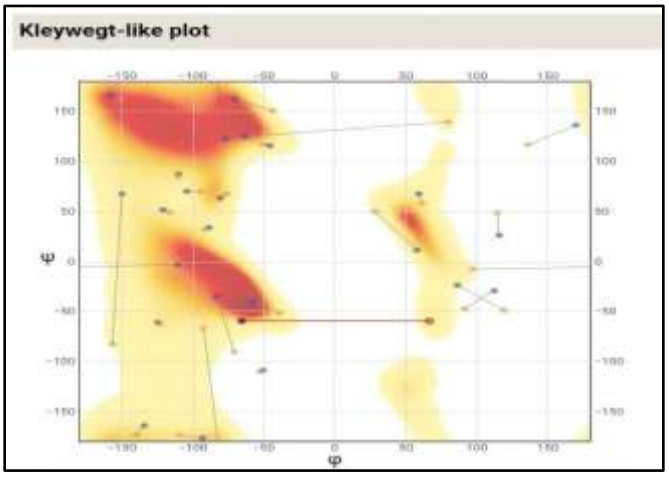

Figure 3: Kleywegt-like plot

The Figure 3 Kleywegt-like plot shows the dihedral backbone angles of the protein which are the φ (phi) and ψ(psi) angles. The areas of density represent the preferred configurations such as the α-helices and β-sheets. Points represent the individual residues while lines portray the structural connections however, some points which fail to conform to the general trend and uncommon lines highlight regions of flexibility or distinctive positions.

3.4 Docking results:

Table 4: Binding Affinity Analysis of Drug Bank Compounds to Target Pockets: Identification of Potential Drug Candidates:

Drug Bank(ID)	Pocket	Score	Chain	Drug Bank (ID)	Pocket	Score	Chain
DB00472	C2	-7.9	Chain A	DB08941	C2	-9.0	Chain A
DB00289	C2	-7.2	Chain A	DB00508	C2	-7.9	Chain A
DB00476	C2	-7.4	Chain A	DB00985	C2	-8.0	Chain A
DB01012	C2	-10.2	Chain A	DB01075	C2	-7.4	Chain A
DB00600	C2	-7.9	Chain A	DB00573	C2	-8.0	Chain A
DB01237	C2	-7.5	Chain A	DB01620	C2	-7.3	Chain A
DB02266	C2	-9.4	Chain A	DB08976	C2	-8.8	Chain A
DB01173	C2	-7.6	Chain A	DB00283	C2	-8.6	Chain A
DB06152	C2	-8.8	Chain A	DB14195	C2	-7.9	Chain A
DB04825	C2	-9.5	Chain A	DB14120	C2	-8.7	Chain A

The Table 4 shows the range of binding energies of Drug Bank compounds targeting Chain A, pocket C2 as illustrated a range between -7.2 to -10.2. Among top candidates DB01012, DB04825, DB02266, and DB08941 have the best binding affinities and are expected to be the most potent. Moderate-affinity compounds (like DB00985, DB00573) should be useful too, but low-affinity ones tend to be suboptimal. High-affinity compounds would be useful for drug development process but would require additional experimental validation.

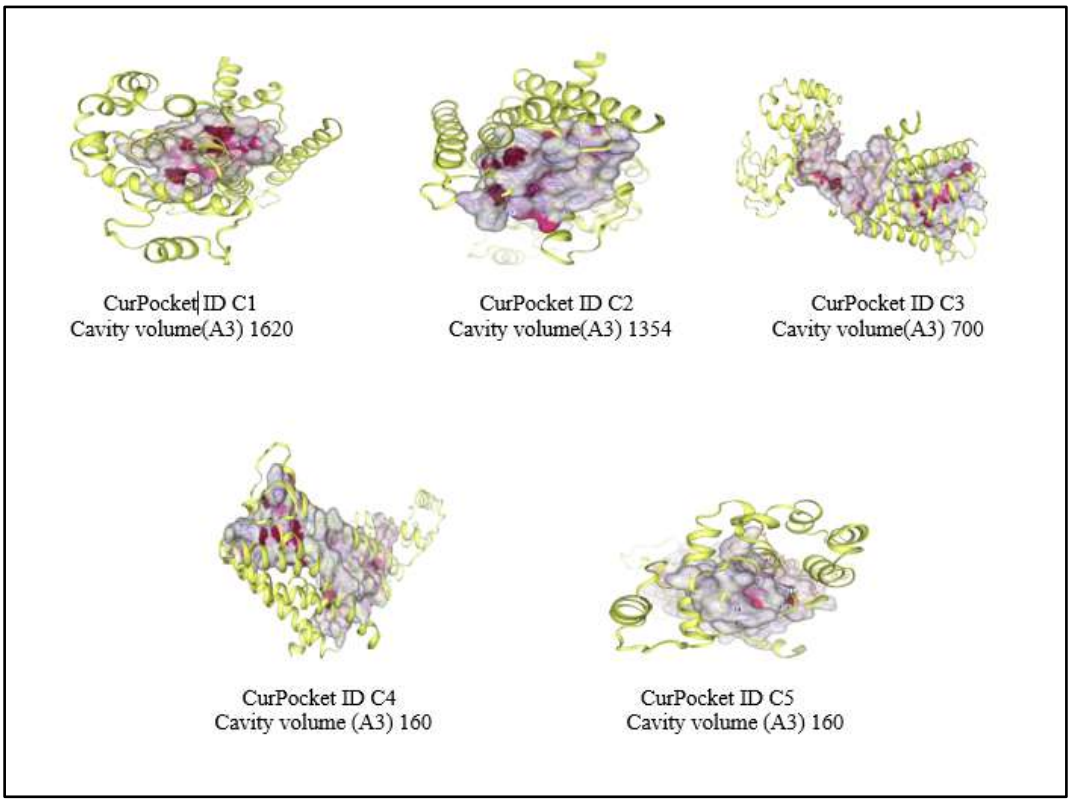

Figure 4: Illustration of the target protein's several binding pockets (CurPocket IDs C1–C5)

Five unique binding pockets (CurPocket IDs C1–C5) with varying volumes that are present on the target protein are shown in Figure 4. Among these are C1, the largest binding pocket, with a volume of 1620 Å³; C2, with a volume of 1354 Å³; and C3, with a volume of 700 Å³. The lower binding cavity volumes of 160 Å³ for the other two binding sites, C4 and C5, may offer some insight into the ligand and ion populations of binding affinity and accessibility potential, respectively.

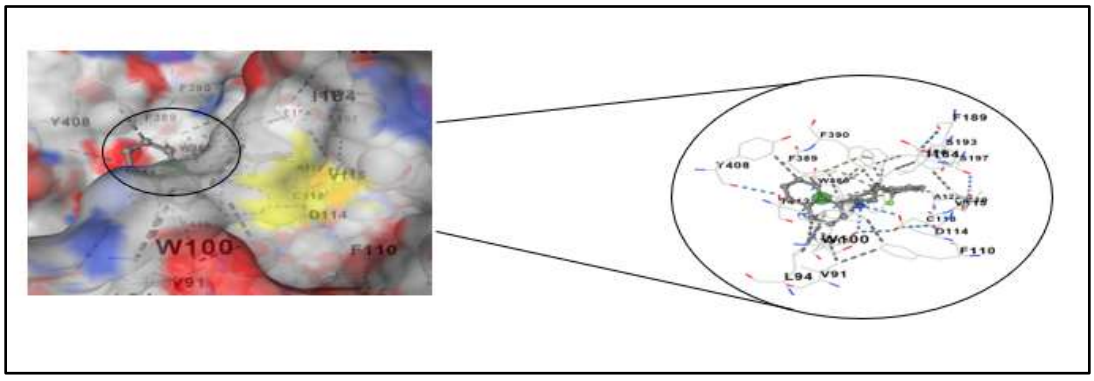

Figure 5: Molecular docking of Cinacalcet: Key binding interactions for Treatment of Depression

The Prozac and manic-depression, previously unassociated conditions, may have found a remedy. This drug acts on calcium-sensing receptors which have also

been used to explain calcium signaling pathways that are responsible for neurotransmission. The findings of the molecular docking study demonstrated that cinacalcet entrenched to the target protein through a network of hydrophobic, hydrogen bonding and aromatic stacking interactions involving W100, Y408, F389, and D114 residues. The results also suggest that cinacalcet's interaction with this receptor could affect pathways regulating mood (Figure 5), which begs further investigation of its potential use in combination with other mood disorder treatments particularly, depression, as a treatment for its off-target or adjunctive effects.

4. CONCLUSION

This study provides convincing evidence that depression as an indication may be included in the label of Cinacalcet Heart, a repurposed drug from its initial pharmacologic indication of being a calcimimetic in chronic renal disease. This research presents a ligand-based approach for drug repurposing followed by screening and docking process to determine candidates resulting in a fluoxetine scaffold, analogs of cinacalcet for depression therapeutics. The significant perspectives comprise:

In the current scenario, fluoxetine was mainly taken as a lead ligand owing to a fair degree of efficacy, high degree of safety, availability of adequate information and its scope that makes it a good possibility in the preparation of newer antidepressants.

It is, therefore, believed that this is the base for the other derivates that are meant to improve impairing neuroinflammation signaling pathways, thus widening its pharmacological action.

The DrugRep interface identified fluoxetine and several other compounds (such as atomoxetine, duloxetine, and cinacalcet) that displayed different binding scores, which indicated their varying affinities towards the target protein. On the other hand, cinacalcet is a well-known calcimimeticexhibiting interesting binding affinity and is also promising to be repurposed as an antidepressant via calcium signaling and neuroplasticity enhancement.

Binding scores of candidate compounds: drug rep platform screening showed fluoxetine (DB00472) to have the highest rank with a binding score of 1,000, thus serving as benchmark to other drugs. Cinacalcet (DB01012) demonstrated significant effectiveness, although it had a score of 0.316 suggesting moderate level of the estimation. Other scores have included, though there appears to be no such context within this study, isoxsuprine (DB08941) and duloxetine (DB00476) which are therefore likely to be included in further repudeau– repodings and craniu similar to these scores.

Potential Role of Cinacalcet in Depression: Docking studies of cinacalcet provided evidence for strong binding interactions with residues W100, Y408, F389, and D114, effects of which were thought to be governed by hydrophobic, hydrogen-bonding, and aromatic-stacking interactions. These interactions provide evidence for cinacalcet's remedial role for modulating calcium signaling pathways in those involved in the mood regulation

process. Hence, cinacalcet is a candidate for possible adjunctive therapy in depression.

Binding Pocket Analysis: Visualization of the five binding pockets (CurPocket IDs C1-C5) presented diverse cavity volumes, with pocket C1 (1620 Å^3) and pocket C2 (1354 Å^3) being the most accessible.The ability of cinacalcet to fit snugly in the C2 pocket indicates that high affinity ligands are also likely to occupy this much bigger space and hence there are stronger interaction possibilities with the target protein.

In summary, the repositioning strategy and subsequent structural modifications and binding affinities have proven the success of fluoxetine derivatives and cinacalcet in the treatment of depression. Compounds with a much higher binding affinity directed against active pockets with the most encouraging binding scores should be sought in order designed experimental studies of their efficacy in treating affective disorders.

5. REFERENCES

1. Hua Y, Dai X, Xu Y, Xing G, Liu H, Lu T, Chen Y, Zhang Y. Drug repositioning: Progress and challenges in drug discovery for various diseases. European journal of medicinal chemistry. 2022 Apr 15;234:114239. https://doi.org/10.1016/j.ejmech.2022.114239
2. Bender A, Cortés-Ciriano I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 1: Ways to make an impact, and why we are not there yet. Drug discovery today. 2021 Feb 1;26(2):511-24. https://doi.org/10.1016/j.drudis.2020.12.009
3. Milliken RL, Quinten T, Andersen SK, Lamprou DA. Application of 3D printing in early phase development of pharmaceutical solid dosage forms. International journal of pharmaceutics. 2024 Mar 25;653:123902.https://doi.org/10.1111/cts.12582
4. Roy S, Dhaneshwar S, Bhasin B. Drug repurposing: an emerging tool for drug reuse, recycling and discovery. Current Drug Research Reviews Formerly: Current Drug Abuse Reviews. 2021 Jul 1;13(2):101-19.https://doi.org/10.2174/2589977513666210211163711
5. Esmaeilzadeh P. Challenges and strategies for wide-scale artificial intelligence (AI) deployment in healthcare practices: A perspective for healthcare organizations. Artificial Intelligence in Medicine. 2024 May 1;151:102861https://doi.org/10.1016/j.artmed.2024.102861
6. Siddiqui B, Yadav CS, Akil M, Faiyyaz M, Khan AR, Ahmad N, Hassan F, Azad MI, Owais M, Nasibullah M, Azad I. Artificial Intelligence in Computer-Aided Drug Design (CADD) Tools for the Finding of Potent Biologically Active Small Molecules: Traditional to Modern Approach. Combinatorial Chemistry & High Throughput Screening. 2025 Jan 15.https://doi.org/10.2174/0113862073334062241015043343
7. Zięba A, Stępnicki P, Matosiuk D, Kaczor AA. What are the challenges with multi-targeted drug design for complex diseases?. Expert Opinion on Drug Discovery. 2022 Jul 3;17(7):673-

83.https://doi.org/10.1080/17460441.2022.2072827

8. Sharma A, Anand SK, Singh N, Dwivedi UN, Kakkar P. AMP-activated protein kinase: An energy sensor and survival mechanism in the reinstatement of metabolic homeostasis. Experimental cell research. 2023 Jul 1;428(1):113614.https://doi.org/10.1016/j.yexcr.2023.113614
9. Mouhsin M, Abchir O, El Otmani FS, Oumghar AA, Oubenali M, Chtita S, Mbarki M, Gamouh A. Identification of novel NLRP3 inhibitors: A comprehensive approach using 2D-QSAR, molecular docking, molecular dynamics simulation and drug-likeness evaluation. Chemical Papers. 2024 Jan;78(2):1193-204.https://doi.org/10.3390/molecules26185593
10. Talevi A, Bellera C. An update on the novel methods for the discovery of antiseizure and antiepileptogenic medications: where are we in 2024?. Expert Opinion on Drug Discovery. 2024 Aug 2;19(8):975-90. https://doi.org/10.1080/17460441.2024.2373165
11. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA, Kaye AD, Viswanath O, Urits I, Boyer AG, Cornett EM. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. Neurology international. 2021 Aug 5;13(3):387-401. https://doi.org/10.3390/neurolint13030038
12. Montano CB, Jackson WC, Vanacore D, Weisler R. Considerations when selecting an antidepressant: a narrative review for primary care providers treating adults with depression. Postgraduate Medicine. 2023 Jul 4;135(5):449-65https://doi.org/10.1080/00325481.2023.2189868
13. Azizi SA. Monoamines: dopamine, norepinephrine, and serotonin, beyond modulation,"switches" that alter the state of target networks. The neuroscientist. 2022 Apr;28(2):121-43.https://doi.org/10.1177/1073858420974336
14. Meenakshi DU, Nandakumar S, Francis AP, Sweety P, Fuloria S, Fuloria NK, Subramaniyan V, Khan SA. Deep Learning and Site-Specific Drug Delivery: The Future and Intelligent Decision Support for Pharmaceutical Manufacturing Science. Deep Learning for Targeted Treatments: Transformation in Healthcare. 2022 Sep 16:1-38. https://doi.org/10.1002/9781119857983.ch1
15. Kumar A, Qian M, Xu Y, Benz A, Covey DF, Zorumski CF, Mennerick S. Multifaceted Actions of Neurosteroids. bioRxiv. 2025 Jan 24:2025-01. https://doi.org/10.1101/2025.01.22.634297
16. BelenahalliShekarappa S, Kandagalla S, Lee J. Development of machine learning models based on molecular fingerprints for selection of small molecule inhibitors against JAK2 protein. Journal of Computational Chemistry. 2023 Jun 15;44(16):1493-504. https://doi.org/10.1002/jcc.27103

17. Halder AK, Mitra S, Cordeiro MN. Designing multi-target drugs for the treatment of major depressive disorder. Expert Opinion on Drug Discovery. 2023 Jun 3;18(6):643-58. https://doi.org/10.1080/17460441.2023.2214361

18. Paliwal A, Jain S, Kumar S, Wal P, Khandai M. Predictive Modelling in pharmacokinetics: from in-silico simulations to personalized medicine. Expert Opinion on Drug Metabolism & Toxicology. 2024 Apr 2;20(4):181-95. https://doi.org/10.1080/17425255.2024.2330666

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