

De Novo Drug Design for Antipsychotics: A case study with Llama 3.2 1B

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Abstract. The development of antipsychotic drugs poses challenges due to the complex pharmacology of psychiatric drugs and the limited diversity of existing drugs. Recent advances in deep-generative models have enabled the exploration of vast chemical spaces for the design of novel drugs. In this study, we leverage the use of the Llama 3.2 1B model to predict potential antipsychotic drugs. We use the ligands and target information in the BindingDB dataset. The ligands were represented using the SELFIES and Group SELFIES notation. Initially, the model was trained for unconditional generation. We also studied the effect of relative attention on the model performance using both the SELFIES and Group SELFIES representation. Then we use a pre-trained model to fine-tune the ligand-target dataset in order to discover molecules that bind to Dopamine D2 and Serotonin receptors (the primary receptors for antipsychotics). We found 10 potential candidates. We then screen them for drug candidacy. Next, a docking analysis was conducted on the screened drugs to find the binding affinity of the drug to the different proteins within the receptors. Finally, we suggest 4 molecules as potential antipsychotic drugs.

Keywords: Novel Antipsychotics · Unconditional-Conditional Generation · Deep Generative Models

1 Introduction

Antipsychotic drugs remain central to the pharmacotherapy of schizophrenia and other psychotic disorders. Although a variety of compounds have been developed since antipsychotics were first introduced in the 1950s, many patients do not respond sufficiently to existing therapies or experience adverse effects that lead to discontinuation of treatment [9]. It is estimated that 20–50% of individuals with schizophrenia exhibit a poor response to standard antipsychotic drugs and are classified as treatment-resistant [35]. Currently, clozapine remains the most effective option for managing treatment resistant schizophrenia; however, even among these patients, 40–70% do not achieve significant therapeutic benefit [10]. This highlights the pressing need to explore and develop novel antipsychotic agents.

Drug discovery is an inherently time-consuming and resource-intensive process, involving multiple stages such as target identification, molecular ideation,

experimental synthesis, and molecular docking [26]. The need to navigate vast chemical spaces further extends this timeline. Moreover, experimental approaches are often associated with high failure rates and significant resource expenditure. In this context, the application of deep generative models offers a rational and efficient strategy to accelerate de novo drug design and optimize the discovery pipeline.

Text-based deep-generative algorithms have demonstrated remarkable success in a range of applications, including text generation, machine translation, question answering, and text summarization [47]. In this study, we leverage the capabilities of the lightweight LLM, LLaMA 3.2 1B [1], to establish a complete pipeline for the generation of de novo antipsychotic drugs. Through this approach, we successfully identified four potential drug candidates predicted to bind to Dopamine D2 and/or Serotonin receptors (two of the primary receptors of anti-psychotic drugs [9]).

The main contributions of this paper are as follows:

1. We built a complete pipeline for target-specific de novo antipsychotic drug design based on Llama 3.2 1B. Specifically, we studied the ability of generated potential drugs with their ability to bind to Dopamine D2 and Serotonin receptors by docking analyses.
2. Compared relative attention with standard attention with regard to validity, uniqueness, and novelty of generated molecules.
3. Captum-based integrated gradient analysis of token-contribution towards next-token generation.
4. Trained the model first for unconditional generation and fine-tune it for target-based conditional generation.

To the best of our knowledge, this is a novel work in which a Llama-based model has been trained and fine-tuned for the design of de novo target-specific antipsychotic drugs, with specific studies on next-token generation.

2 Related Works

Deep learning algorithms have been at the heart of de novo drug design for quite some time now. Applications of deep learning models for de novo drug design have ranged from RNNs [18, 33, 49], variational autoencoders [36, 42], graph convolution networks [4, 31, 40] and transformer-based approaches [15, 24, 32, 43, 50]. By leveraging attention mechanisms, transformer architectures enable parallel processing and efficient learning of long-range dependencies, which is particularly valuable in drug design for capturing distant interactions between atoms within molecules or between ligands and protein targets. As a result, transformer models have gained prominence as powerful tools for de novo drug generation.

In [15], a transformer-based model has been trained by treating target-specific drug generation as a machine translation task between amino acid sequences and SMILES. Transantivirus [32] leverages the architecture of the T5

model for molecular generation to address the SARS-CoV-2 virus. DrugEx [29] has been used to design ligands for the adenosine A2A receptor. MolGPT [7], SMILESGPT [5], iupacGPT [12], cMolGPT [46] explore the chemical space using SMILES as input; with SMILESGPT and iupacGPT using the GPT-2 architecture. PETrans [45] uses target protein information to generate target-specific drugs. Another paper by Hu et. al. [17], trains GPT-2 to generate anti-SARS-CoV-2 drugs. Inspired by GPT-based studies, we formulate a drug discovery problem statement as a text generation task and employ a decoder-only architecture (Llama 3.2 1B) to achieve our goal. We note that there are alternative generation techniques based on diffusion models [6]; however, they require more compute, longer generation times, and complex training pipelines. LLM-based approach, in contrast, are advantageous for rapid generation and scale.

Many de novo drug design studies have used the SMILES representation of the ligands for training. However, unlike SMILES, which can produce invalid molecular structures due to its context-sensitive grammar, SELF-referencing Embedded Strings (SELFIES) is based on a context-free grammar with self-referencing symbols, ensuring that every SELFIES string corresponds to a valid molecular graph [25]. In fact, there are strong indications that it is easier for machines to “understand” SELFIES (as compared to SMILES and DeepSMILES) [37, 38]. Hence, we use SELFIES as the molecular representation for our work.

3 Methods

3.1 Data

We retrieve the data from BindingDB [14]. BindingDB is a publicly available, curated repository of experimentally measured binding affinities between small molecule ligands and protein targets. We used the full dataset version, uploaded on 29 April 2025 for our study. BindingDB contains 3.0M data for 1.3M Compounds and 9.5K Targets [2]. The database aggregates data from peer-reviewed scientific publications and patents, ensuring reliable high-quality measurements of binding constants such as K_i , K_d , IC_{50} , and EC_{50} values. We filter the data set according to a modified version scheme as described in [15]:

1. The field “Target Source Organism According to Curator or DataSource” equals “Homo sapiens”.
2. The record has an IC_{50} value less than 100 nm; if the IC_{50} is missing, then K_d is less than 100 nm; if both are missing, then EC_{50} is less than 100 nm.
3. The record has a chemical identifier (PubChem CID), a protein identifier (Uniprot ID) and a SMILES representation.
4. The molecular weight is less than 1000 Da.
5. Protein amino acid sequence length is greater than 80 and lower than 2050.

At the end of the filtration, we were left with 451,977 ligands (SMILES). We use this version for unconditional generation. For conditional generation, we add one more filter, *i.e.*, we keep only those records in which the number of protein

chains in the target is 1 (for simplicity). Hence, for conditional generation, we were left with 415,271 ligands (SMILES) and 1424 unique UniProt IDs. The model is trained on a prompt-based dataset which has the UniProt ID with its corresponding binding ligand.

3.2 Data Representation

In addition to conventional SELFIES, we also utilized an enhanced version known as Group SELFIES [11]. Group SELFIES extends the standard SELFIES grammar by incorporating predefined chemical substructures and functional groups as atomic-level tokens. This augmentation allows the language model to capture higher-level chemical semantics and pharmacophoric patterns more efficiently.

3.3 Model

We train our dataset using Llama 3.2 1B (released by Meta on September 25, 2024). It is a lightweight, open-source model, which can be deployed on mobile and edge devices. This is especially true for drug developers, who may want an easy, WebApp module which they can use as a guide for synthesis and may not want to get into complication of model training and inferencing. As previously mentioned, Llama 3.2 1B has a decoder-only, transformer architecture, with context length of 128k tokens, enabling the model to capture long-range dependencies. In addition, Llama 3.2 1B has inbuilt Rotary Position Embedding (RoPE), which has been shown to increase model performance [30].

Relative Attention In conventional transformer models, positional information is typically introduced via absolute positional encodings, which are added to token embeddings before feeding them into the attention mechanism. However, this approach lacks flexibility when dealing with variable-length sequences and struggles to model relative dependencies effectively — a crucial requirement for chemical language modeling where the relative positioning of atoms or functional groups directly impacts molecular validity and properties.

To address this, we incorporated into the Llama 3.2 1B, relative position attention mechanism that models the distance between sequence elements directly within the attention computation. Instead of encoding absolute positions, relative positional biases or embeddings are integrated into the attention score computation, enabling the model to attend based on the relative distance between tokens.

As per Huang et al [19], the relative attention is calculated as follows:

$$\text{RelativeAttention} = \text{softmax}\left(\frac{QK^T + S_{rel}}{\sqrt{d_k}}\right)V$$

where $S_{rel} = QR^T$, being the relative attention term (R is the matrix of relative position embeddings and Q corresponds to query vectors in the transformer model).

With two kinds of representation (SELFIES and Group SELFIES) and two kinds of attention (standard and relative attention), we have four models on which we perform unconditional training - standard attention with SELFIES (Model 1), standard attention with Group SELFIES (Model 2), relative attention with SELFIES (Model 3) and relative attention with Group SELFIES (Model 4).

Tokenizer We had a choice between Atomic Pair Encoding (APE) and Byte Pair Encoding (BPE) tokenizers. According to [27], APE significantly improves the accuracy of molecular classification tasks over BPE. Hence, we use APE tokenizer over BPE for training our model. The choice of using APE tokenizer over BPE tokenizer is also evident from the ablation study reported in the Results and Discussion section. The BindingDB SMILES data was converted to both SELFIES and Group SELFIES representation. For Group SELFIES we use a grammar of ~ 530 fragments, generated after fragmenting the dataset using MMPA fragmentation technique [20]. These fragments were then converted into “groups”, making them the basis of Group SELFIES representation. We generate both SELFIES and Group SELFIES tokens, and train the tokenizers for both the representations. For conditional generation, we add the protein tokens before fine-tuning the model.

3.4 Unconditional and Conditional Generation

In the domain of molecular generative modeling, sequence generation tasks can be broadly categorized into **conditional** and **unconditional generation** strategies.

Unconditional generation involves sampling novel molecular sequences from the model without providing any explicit guiding information or constraints during the generation process. The model, trained on a large corpus of molecular representations, learns the underlying distribution of valid chemical structures and generates new molecules purely based on this learned distribution. This approach is useful for exploring the general chemical space and discovering novel compounds without predefined property constraints.

In contrast, *conditional generation* involves generating molecular sequences conditioned on specific attributes or requirements - here we tune the model for protein targets.

In our pipeline, we first train the model unconditionally and then fine-tune it for conditional generation. The weights obtained after unconditional training give us flexibility regarding the target property (eg - protein target, molecular weights, QED etc) on which we want to fine-tune the conditional generative model. Hence, unconditional training makes the trained model multi-purpose and versatile. Additionally, a pre-trained unconditional model speeds up the conditional fine-tuning.

Model Training For unconditional generation, we fine-tune a pre-trained language model on a causal language modeling task using parameter-efficient fine-tuning (PEFT) techniques [28] implemented via the Hugging Face peft library. Specifically, Low-Rank Adaptation (LoRA) [16] was applied to the query and value projection modules (q_{proj} and v_{proj}) within the transformer layers. The LoRA configuration used a rank of 8, an alpha of 32, and a dropout rate of 0.1 to balance the model capacity and regularization. Training was carried out using the Hugging Face SFTTrainer (from TRL) framework along with the Accelerate library to enable efficient distributed training and mixed precision (fp16) for faster computation and reduced memory usage. The model was trained for 10 epochs with a learning rate of 3×10^{-4} using the AdamW optimizer with a batch size of 16. The LoRA adaptation was targeted exclusively at q_{proj} and v_{proj} layers, significantly reducing the number of trainable parameters and accelerating convergence. Inference was performed using top-k sampling with $k=50$ and nucleus (top-p) sampling with $p=0.95$ to control the diversity of the generated text. A total of 10,000 molecules were generated for the 4 experiments.

For conditional generation, we fine-tune the weights of the corresponding model trained for unconditional generation on the dataset prepared by keeping the target protein (in UniProt ID format) and the binding ligand. Since the model is already pre-trained, we train it for 3 epochs, keeping early stopping criteria in place, with evaluation loss as the stopping criteria. A train-test split of 90%-10% was performed. The tokenizer was updated to include UniProt IDs. We generate 10 molecules for targets with UniProt IDs P14416 (Dopamine D2 receptor) and P28223 (Serotonin receptor).

All training and inferencing was performed on a NVIDIA H100 100 GB GPU. Training and inferencing codes are available at github.com/ysharshit/llama_nw.git.

4 Results and Discussion

4.1 Chemical Feasibility Analysis for Unconditional Generation

We use the following metrics to evaluate the performance of unconditional generation:

1. **Validity** : It refers to the fraction of valid molecules among the generated molecules. It was checked using RDkit [3]. For SELFIES and Group SELFIES, the validity comes out to be 1 by definition.
2. **Uniqueness** : It refers to the fraction of valid molecules that are unique. Low uniqueness denotes that the molecules are repeated.
3. **Novelty** : It refers to the fraction of valid and unique molecules which are novel generated by the model with respect to the training set. Low novelty is an indication of model overfitting.
4. **Average Diversity** : Morgan fingerprints are generated for each of the molecules. Pairwise Tanimoto similarity is computed for each pair of fingerprints. Diversity is computed by how much these similarities diverge from the perfectly similar fingerprints (*i.e.*, similarity score of 1). Averaging over all these divergences gives us the average diversity.

To evaluate the impact of tokenization strategy on molecule generation, we performed an ablation study comparing APE and BPE tokenizers. We found that uniqueness, novelty, average diversity are 0.9707, 0.9465, 0.8794 for APE and 0.9388, 0.9123, 0.8640 for BPE. APE tokenizer shows considerable improvement over BPE tokenizer; hence, we use APE tokenizer for further analyses. Table 1 shows the ablation study in which the temperature parameter was varied from 0.7 to 1.0 in steps of 0.1. We find that uniqueness, novelty and average diversity increase as we move from 0.7 to 1.0, thereby indicating the generation of novel compounds. Hence, we use the temperature parameter of 1.0 for further analyses.

Table 1: Effect of Temperature Parameter Variation

Metric	Model 1				Model 2			
	T=0.7	T=0.8	T=0.9	T=1.0	T=0.7	T=0.8	T=0.9	T=1.0
Uniqueness	0.9114	0.9390	0.9589	0.9707	0.7883	0.8686	0.9195	0.9415
Novelty	0.9031	0.9122	0.9308	0.9465	1	1	1	1
Avg Diversity	0.8592	0.8681	0.8743	0.8795	0.8756	0.8851	0.8918	0.897745

Table 2 shows these results for unconditional generation for all four models. (We do not include validity here because it is 1 by definition for SELFIES and Group SELFIES representations).

Table 2: Evaluation Metrics for 4 different configurations of the model (Std Attn=Standard Attention, Rel Attn=Relative Attention, Grp SELFIES=Group SELFIES)

Metric	Model 1 (Std Attn & SELFIES)	Model 2 (Std Attn & Grp SELFIES)	Model 3 (Rel Attn & SELFIES)	Model 4 (Rel Attn & Grp SELFIES)
Uniqueness	0.9707	0.9415	0.9710	0.9474
Novelty	0.9465	1.0000	0.9465	1.0000
Avg Diversity	0.8795	0.8977	0.8813	0.8915

Addition of relative attention leads to considerable improvements in all parameters.

From the tables, we see that uniqueness increases slightly as we go from standard attention to relative attention (97.07% to 97.10% for SELFIES and 94.15% to 94.74% for GroupSELFIES representation). Uniqueness drops from 97.07% to 94.15% for standard attention and from 97.10% to 94.74% for relative attention as goes from SELFIES to Group SELFIES - this is natural because due to groupings, the number of tokens gets reduced, which implies that randomness is reduced. This further leads to more repetitions and decrease in exploratory diversity; hence, uniqueness value reduces.

Group SELFIES gives more drug-like molecules as compared to SELFIES, as can be inferred from a higher proportion of generated molecules beyond a QED value of 0.6 (Fig 1). SELFIES already guarantee that any string generated decodes to a valid molecule. Group SELFIES further improves this by steering

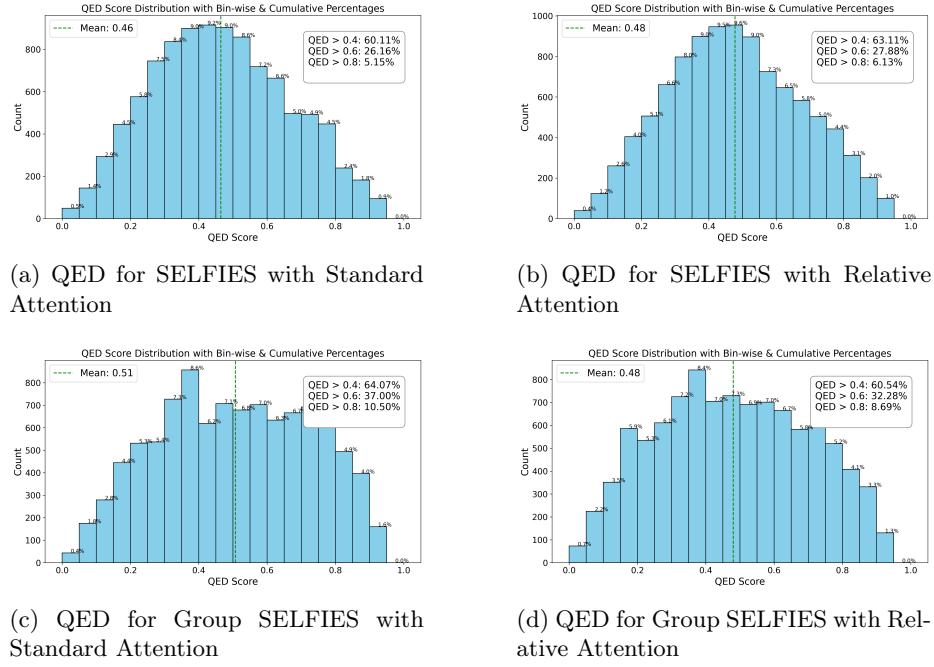


Fig. 1: QED Distribution Plots for the Generated Molecules

generation towards chemically reasonable or drug-like regions of chemical space, leading to more drug-like compounds.

Another interesting feature we observed was that there were lesser number of drug-like molecules in relative attention model for Group SELFIES than in standard attention model (47% molecules above QED of 0.6 in Group SELFIES, mean=0.51 with standard attention in contrast to 40% with relative attention, mean=0.48) (Fig 1). In Group SELFIES, token groups often represent meaningful chemical fragments or substructures. The standard attention model may have implicitly learned positional patterns correlating with good QED molecules. By switching to relative positional encoding, the model focuses on relative distances between tokens rather than absolute sequence positions. If the model doesn't adapt to this new inductive bias, it might disrupt patterns that previously yielded high QED; hence lower proportion of drug-like molecules in Group SELFIES with relative attention framework.

Average diversity increases from as we go from SELFIES to Group SELFIES (Table 2), demonstrating the ability of the model to generate novel structures beyond the training set. A little drop is observed as we go from standard to relative attention for the case of Group SELFIES. The reason may be that the model gets biased towards preserving relative distances between recurring group tokens seen during training, thereby learning fixed group-group adjacency

patterns. As a result, it overfits to a narrower set of known group orderings. This reduces exploration of novel combinations — hence, the diversity drops.

Another interesting aspect of this study is the calculation of position-wise contribution of tokens towards the next token generation. This analysis was performed using the Integrated Gradients method [41] as implemented in the Captum library [23]. We calculate the average position-wise contribution for the first 25 positions. The results are shown in Fig 2. Results show that except for the case of Group SELFIES with standard attention, the 1st token “retards” the generation of further tokens. Explanation for this may require layer-based attention analysis, which is beyond the scope of the present study. We also study the average token contribution of each individual token. The highest contributors for each of the models are ‘[SH1-1]’ for Model 1, ‘[:1frag61]’ for Model 2, ‘[Zn]’ for Model 3 and ‘[:0sulfan_general]’ for Model 4, where frag61 is $O1C2=C(*1)C(*1)=C(*1)C(*1)=C2C(*1)(*1)C(*1)C1(*1)*1$ and sulfan_general is $*x1[S@@](=O)(=*x2)(*x1)$.

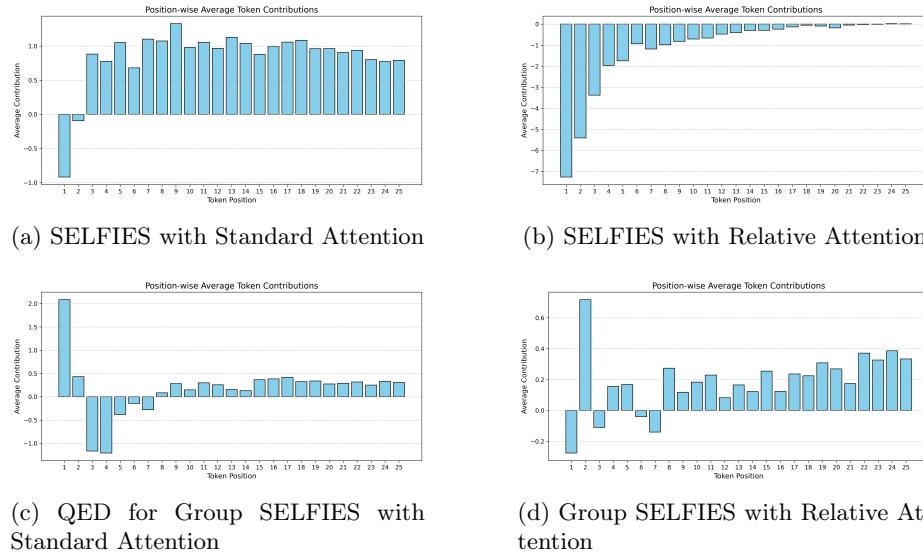


Fig. 2: Average Position-wise contribution of the tokens in the four models

4.2 Conditional Generation

Despite differences in uniqueness, novelty and average QED values of all the 4 configurations, we train the models conditionally on all the four configurations to evaluate possibilities of novel antipsychotic drugs. We obtain a total of 40 possible ligands (10 molecules from each of the 4 configurations) which can bind to Dopamine D2 and Serotonin receptors. We then screened these potential molecules based on the drug-likeness criteria as mentioned in Table 3. To balance drug-likeness with molecular diversity, we applied a threshold of $\text{QED} \geq 0.6$,

consistent with distributions reported for approved drugs in [8]. Note that we have used a criteria of $\text{TPSA} < 90\text{\AA}^2$ (instead of the general criteria of 140\AA^2) because antipsychotics act on the CNS (central nervous system); hence they have to overcome the blood-brain barrier. We also checked for novelty. We use RDkit package for calculating these properties.

Table 3: Drug-Likeness Criteria

Property	Constraints
logP	< 5
Molecular Weight (Da)	< 500
Number of hydrogen Donors	< 5
Number of hydrogen Acceptors	< 10
Number of Rotational Bonds	< 10
Topological Polar Surface Area (\AA^2)	< 90
Quantitative Estimate of Drug-likeness (QED)	≥ 0.6
Synthetic Accessibility Score	< 6

After screening based on the above criteria, we obtain the 4 potential antipsychotic drugs, on which further docking analyses were carried out. Drug 1 was generated using Group SELFIES with relative attention model, Drugs 2 and 3 were generated using SELFIES with standard attention model and Drug 4 was generated using Group SELFIES with relative attention model. These potential drugs are shown in Fig 3. These were then evaluated for protein docking.

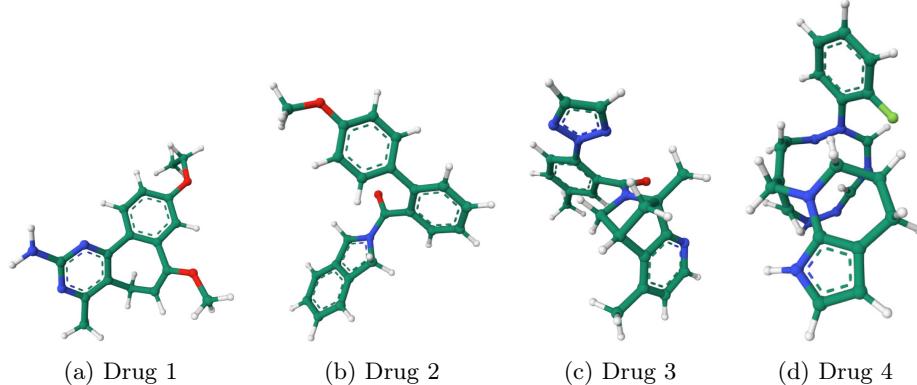


Fig. 3: Four potential anti-psychotic drugs

4.3 Protein Docking

Structural analyses were conducted using available Protein Data Bank (PDB) entries corresponding to the human Dopamine D2 (UniProt ID: P14416) and Serotonin (UniProt ID: P28223) receptors. The following PDBs were utilized for human Dopamine D2: 6CM4, 6LUQ, 6VMS, 7DFP, 7JVR, 8IRS, 8TZQ, and 8U02. The following PDBs were utilized for Serotonin: 6A93, 6A94, 6WGT, 6WH4, 6WHA, 7RAN, 7VOD, 7VOE, 7WC4, 7WC5, 7WC6, 7WC7, 7WC8, 7WC9, 8JT8, 8UWL, 8V6U and 8ZMG. A subset of these PDBs was selected for detailed analysis based on relevance to antagonist-bound or agonist-bound

states, resolution, and structural quality. Specifically, 6CM4, and 6LUQ were used for Dopamine D2 receptor modeling [34, 44], and 6A93, 6A94, 6WH4 and 6WGT for Serotonin 5-HT2A receptor modeling [21, 22].

We follow the following steps to perform docking:

1. We procure the PDB files corresponding to the targets from the PDB database (www.rcsb.org).
2. These were then reduced using the “reduce” [48] tool (part of ADFRsuite).
3. The .pdb file was then converted to .pdbqt file using “prepare_receptor” tool (part of ADFRsuite).
4. All the potential drugs were also converted to .pdbqt format.
5. Docking was performed using AutoDock Vina [13] tool.

We obtain the following binding energies by AutoDock Vina-based docking studies on how the 4 potential anti-psychotics bind to the 6 above-mentioned proteins, *viz.*, 6CM4, 6LUQ, 6A93, 6A94, 6WH4 and 6WGT (Table 4). We used AutoDock Vina primarily because of its faster search algorithm to speed up docking computations.

Table 4: Binding Affinities of the Potential Anti-psychotic Drugs with Proteins (all values in kcal/mol)

Anti-Psychotic Drug	Dopamine D2			Serotonin		
	6CM4	6LUQ	6A93	6A94	6WH4	6WGT
Drug 1 (QED = 0.943)	-6.065	-6.139	-4.415	-5.383	-5.919	-5.47
Drug 2 (QED = 0.707)	-6.229	-6.032	-4.643	-5.474	-6.918	-6.491
Drug 3 (QED = 0.705)	-5.784	-6.392	-4.876	-5.143	-6.515	-6.479
Drug 4 (QED = 0.714)	-6.821	-7.269	-5.06	-5.264	-6.547	-6.91

We select those interactions that are stable and whose binding affinities are less than -6 kcal/mol. We find that drugs 1,2 and 4 bind nicely with the 6CM4 receptor, drugs 1,2,3 and 4 with 6LUQ, drugs 2,3 and 4 with both 6WH4 and 6WGT. These docking poses are shown in the Fig 4 (figures made using PyMol [39]).

Thus we propose drugs 1,2 and 4 as potential binders for Dopamine D2 receptor and drugs 2,3 and 4 as potential binders for Serotonin. Further experimental studies have to be carried out to actually test the efficacy of these drugs.

5 Conclusion

To the best of our knowledge, this is a unique study where we leverage Llama 3.2 1B to give a complete pipeline for the prediction of anti-psychotic drugs. We represented the ligands using SELFIES and Group SELFIES representation and trained them using standard and relative attention. Ablation studies were carried out to see the effects of temperature and tokenzier on molecule generation, following which studies were carried out for these four configurations for unconditional generation. Then we fine-tuned these models for target-specific study. We obtained 40 tentative drug-like molecules, which we filtered based on drug-likeness properties. Integrated gradients-based analysis was carried out to

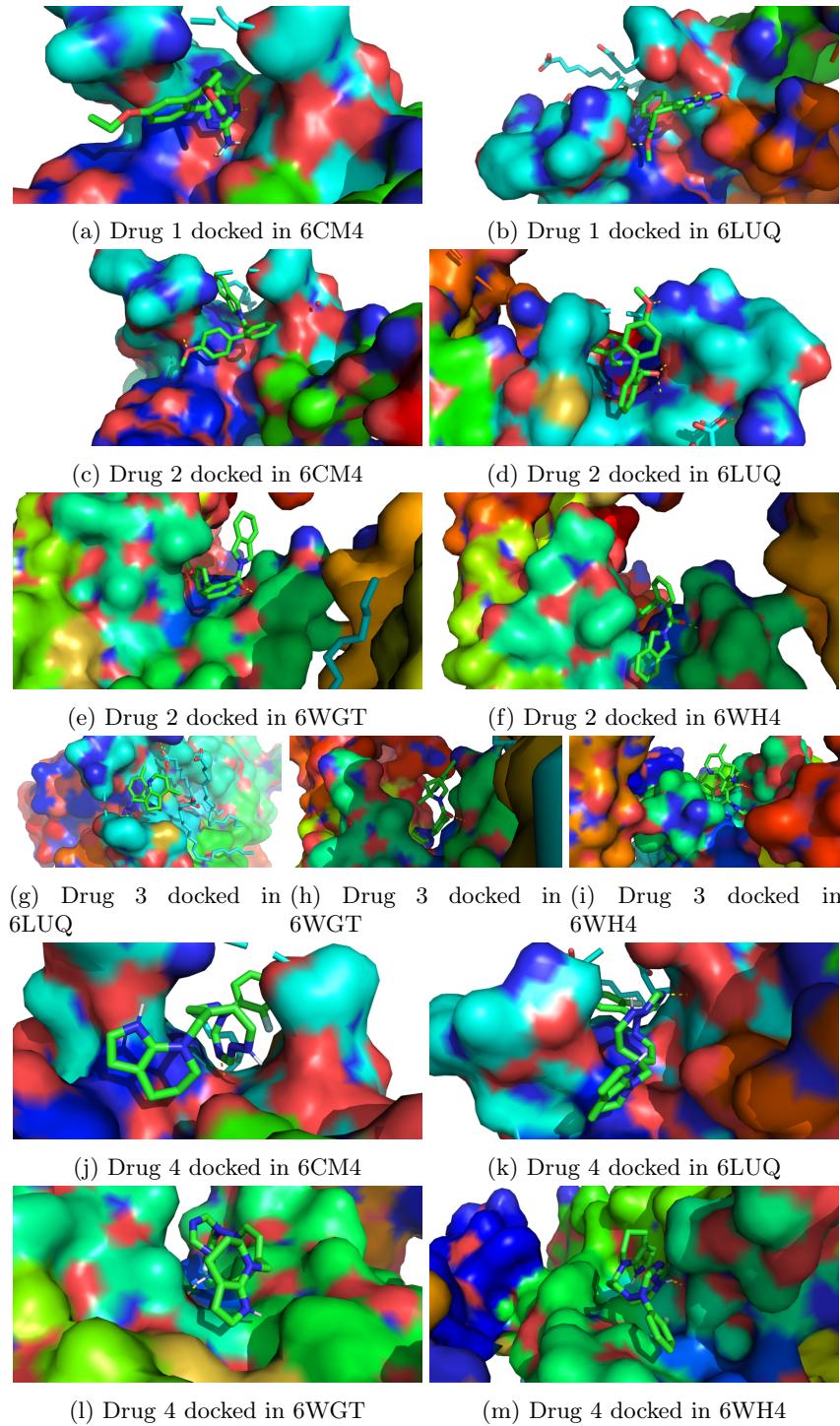


Fig. 4: Docking Analyses on the 4 potential anti-psychotic drugs

understand impact of specific tokens in token generation. After filtering, we were left with 4 such molecules, for which we studied their binding affinities using Vina and PyMol softwares. Thus we proposed 4 molecules as potential anti-psychotic drug. One of them had a QED value of 0.94, which can be checked further by experimental synthesis. This study can further be extended for any other targets also. SMILES and SELFIES overlook crucial graph structures and 3D chemical information. One possible area of improvement is to include graph-based representation to include the 3D aspects of the molecule. In future, we would like to make a detailed comparison of the present approach with diffusion-based approaches. Finally, more visualization tools and model interpretation techniques can be used for further analyses.

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