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Interactions About Tetra Hydro Carbazole: A View

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INTRODUCTION

The key differences between traditional and rational drug discovery methods. Rational drug design focuses on identifying and modulating specific biological targets involved in disease. A crucial criterion for target selection, ensuring the target can be effectively modulated by small molecules. Establishing the link between target modulation and disease modification is essential. Creating a screening assay using purified target protein is a critical step in the drug discovery process. Expanding on Rational Drug Design To delve deeper into this topic, we could explore Utilizing protein structures to design drug molecules. Its role in predicting drug-target interactions. Overcoming hurdles like target validation and draggability issues. The synergy between these approaches in modern drug discovery.

Computer-aided Drug Design

Predicting binding affinity is indeed a cornerstone of drug design. Understanding the interaction between a small molecule and its target is crucial for developing potent and selective drugs. The primary goal in drug design is to estimate how strongly a molecule will bind to its target. Molecular mechanics and molecular dynamics are commonly used to simulate molecular interactions and predict binding conformations. Methods for predicting the binding pose and affinity of a molecule to a target. More accurate but computationally expensive methods for estimating binding affinity. Its role in understanding electronic interactions between molecules. Limitations of current methods and strategies to improve accuracy. Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. Hit identification using virtual screening (structure- or ligand-based design)
2. Hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
3. Lead optimization of other pharmaceutical properties while maintaining affinity
4. Advanced analysis techniques are being developed to improve the accuracy of binding affinity predictions.

Different types of Interactions

The limitations of molecular docking as a drug discovery tool. hale molecular docking is a powerful technique, it has several inherent limitations: Predicting accurate binding affinities remains a challenge, as scoring functions often overestimate or underestimate binding energies. Most docking tools treat the protein as a rigid structure, which can limit the accuracy of predictions, as proteins are dynamic molecules. Accounting for conformational changes in both the protein and ligand upon binding is still a complex problem. The role of water molecules in protein-ligand interactions is often neglected, which can affect binding affinity and specificity. While docking can efficiently screen large compound libraries, the hit rate for identifying true drug candidates is often low. Despite these limitations, molecular docking remains a valuable tool in drug discovery when used in conjunction with other computational and experimental methods.

Types of Docking -The following are types of docking used often.

Lock and Key or Rigid Docking – In rigid docking, both the internal geometry of the receptor and ligand is kept fixed during docking.

Induced fit or Flexible Docking - In this model, both the ligand and side chain of the protein is kept flexible and the energy for different conformations of the ligand fitting into the protein is calculated. For induced fit docking, the main chain is also moved to incorporate the conformational changes of the protein upon ligand binding. Though it is time consuming and expensive, yet this method can evaluate many different possible conformations which make it more exhaustive and possibly simulate real life phenomenon and hence trustworthy. The error includes model error (bias) and observational variability, that is, the variability in observations even on a correct model.

LITERATURE REVIEW

The provided text discusses a series of compounds derived from tetrahydrocarbazole, specifically focusing on their antidepressant properties. Synthesized compounds structurally similar to the antidepressant tandamine. These compounds, 1-alkyl-1,2,3,4-tetrahydrocarbazole-1-ethanamines, primarily inhibit the reuptake of noradrenaline with minimal impact on serotonin reuptake Reported that the most effective compound, 9-ethyl-N,N-trimethyl-1,2,3,4-tetrahydrocarbazole, exhibited potency similar to desipramine, a well-known antidepressant. Tetrahydrocarbazole derivatives have potential as antidepressants. Selective inhibition of noradrenaline reuptake is a key feature of these compounds. The most potent compound shows promise for treating endogenous depression. Further exploration of the structure-activity relationships within this class of compounds to identify even more potent and selective inhibitors of noradrenaline reuptake. Preclinical and clinical studies to evaluate the efficacy and safety of these compounds in treating depression. Investigation of the potential mechanisms of action underlying the antidepressant effects of these compounds.

In-depth studies on the mechanisms of action for the observed phospholipase A2 and lipoxygenase inhibitory activities. Optimization of the structure of these compounds to improve potency, selectivity, and pharmacokinetic properties. Preclinical and clinical evaluation of promising compounds for the treatment of inflammatory diseases. Exploration of the potential synergistic effects of combining different pharmacological activities within a single tetra hydro carbazole molecule. The provided information highlights the diverse pharmacological potential of tetra hydro carbazole derivatives. Derivatives such as 1-chloro-2-formyl carbazole and pyrazole [3,4-a] carbazole derivatives exhibit antimalarial properties. Tetra hydro carbazole derivative flutroline has demonstrated antipsychotic potential. Some tetra hydro carbazoles have been linked to carcinogenic effects, emphasizing the need for careful evaluation. Carbazoles as a class exhibit a wide range of pharmacological activities, underscoring their potential for drug discovery. Efficient synthetic methods for tetra hydro carbazoles are being developed, facilitating further research. Tetra hydro carbazoles represent a promising scaffold for drug discovery due to their versatility. However, the presence of carcinogenic activity within this class highlights the importance of rigorous safety evaluation during drug development.

RESEARCH METHODOLOGY

Pharmacological properties, specifically focusing on analgesic, anti-inflammatory, antihistaminic, and antimicrobial activities. A comprehensive literature review has revealed the potential of 1,2,3,4-tetrahydrocarbazole derivatives to exhibit a wide range of biological activities, motivating the current research endeavor. Target Molecule Selection: Based on the literature review, identify specific structural modifications to the tetra hydro carbazole scaffold that are likely to enhance the desired biological activities. **Synthesis Planning:** Develop efficient synthetic routes to access the target compounds. Consider factors such as yield, scalability, and cost-effectiveness.

AIM AND OBJECTIVE

- Evaluate these compounds for a range of pharmacological activities, including analgesic, anti-inflammatory, antihistaminic, and antimicrobial properties.
- Conduct QSAR studies to correlate the structure of the compounds with their biological activities.
- Ultimately, identify potent tetrahydrocarbazole-based drug candidates.
- Synthesis of Tetrahydrocarbazoles: Developing new derivatives with potential therapeutic benefits.

PLAN OF WORK

Computational methods were used to predict the interaction between the synthesized compounds and potential biological targets, aiding in compound selection. Based on the docking results, specific compounds from Schemes I, II, III, and IV were chosen for further evaluation. The selected compounds were tested for their analgesic properties using Eddy's hot

plate method. A series of tetra hydro carbazole derivatives were prepared. Computational analysis to predict compound-target interactions. Identification of promising compounds based on docking results. Evaluation of selected compounds using the Eddy's hot plate method.

Molecular docking for kappa receptor (4EJ4) and substituted tetra hydro carbazoles

Biopredicta module of Vlife software. Genetic Algorithm (GA)-based search for optimal ligand pose. Various factors like cycle count, rotation limits, translation, convergence, and molecular flexibility influence docking scores. The docking score reflects the overall binding affinity of the ligand to the receptor. Compounds with favorable docking scores and specific interactions (hydrophobic, charged, van der Waals) were selected for further study. A subset of 20 compounds with promising docking profiles was chosen for pharmacological evaluation.

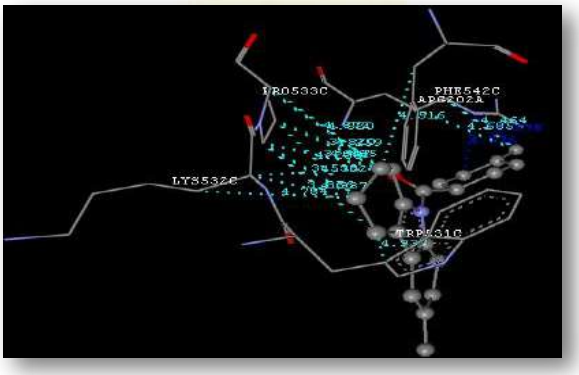


Fig: Hydrophobic interactions between TH27 and LNH1

Molecular docking for Histamine receptor (3RZE) for substituted tetra hydro carbazoles

Your description outlines a standard molecular docking workflow: Biopredicta module of Vlife software. Genetic algorithm (GA) based. The dock score, influenced by parameters like number of cycles, rotation limits, translation, convergence, and flexibility settings. Compounds were selected based on dock score and interaction types (hydrophobic, charged, and vdW). The choice of docking parameters can significantly impact the docking results. Careful optimization is essential. Dock scores are often empirical and may not accurately predict binding affinity. Multiple docking poses are often generated for each ligand. Selecting the most relevant pose is crucial.

The process of filtering compounds based on docking scores and interaction patterns is a common approach in virtual screening. How were the docking parameters optimized for your system? What criteria were used to select the best pose for each ligand? Was the docking score validated against experimental data (e.g., binding affinities)? Were specific interactions (e.g., hydrogen bonds, aromatic interactions) considered in addition to the mentioned ones? Based on the docking results, you've selected 14 compounds for further pharmacological evaluation. It would be interesting to discuss the criteria used for this selection and the potential experimental assays planned. I can provide further insights or suggestions based on your specific research goals.

Table 14. Interactions between proposed Molcules and Receptor

S.No	Ligands	Docking Scores	Hydrogen Bonds	Hydrophobic interactions	Charge	Vdw
1	TH1	-3.5134	1	28	2	24
2	TH2	-4.3231	1	26	1	25
3	TH3	-4.3984	1	41	2	25
4	TH4	-4.2786	1	29	1	36
5	TH5	-2.6483	1	26	2	41
6	TH6	-2.3225	1	45	2	26
7	**TH7**	**-3.1509**	**1**	**36**	**1**	**35**
8	TH8	-2.6656	1	30	2	27
9	TH9	-1.3059	1	22	1	28
10	**TH10**	**-3.5642**	**1**	**39**	**2**	**36**
11	**TH11**	**-4.6058**	**1**	**34**	**2**	**32**
12	**TH12**	**-2.8014**	**1**	**32**	**1**	**33**

13	TH13	-3.1144	1	31	1	261
14	TH14	-4.7222	1	21	2	27
15	TH15	-2.1527	1	29	2	31
16	TH16	-2.6821	1	29	1	32
17	TH17	-4.6372	1	45	1	38
18	TH18	-2.4932	1	34	1	35
19	TH19	-4.2212	1	34	1	28
20	TH20	-2.0117	1	32	1	35
21	TH21	-1.2526	1	31	1	32
22	TH22	-2.1189	1	35	2	31
23	TH23	-2.8861	1	32	1	29
24	TH24	-3.0268	1	32	1	31
25	TH25	-4.0599	1	26	2	43
26	TH26	-1.8061	1	28	1	37
27	TH28	-4.5100	1	57	2	42
29	TH29	-4.2278	1	35	1	37
30	TH30	-4.2278	1	40	2	31
31	TH31	-4.6778	1	25	1	24
32	TH32	-2.8589	1	23		26
33	TH33	-4.2093	1	32	1	32
34	TH34	-4.2093	1	48	1	35
35	TH35	-3.0093	1	38	2	21
36	TH36	-2.2997	1	34	1	32
37	TH37	-2.7753	1	32	1	29
38	TH38	0.1733	1	26	1	28
39	TH39	-0.9475	1	32	1	29
40	TH40	-3.4794	1	34	1	32
41	Chloro pheniramine	-4.0147	1	69	2	48

Fig.: Charge interactions between T38 and 3RZE(Docking Score:0.1790)

SUMMARY, DISCUSSION AND CONCLUSION

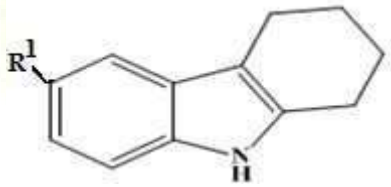
The primary objective of the study is to explore the potential of N-substituted 1,2,3,4-tetrahydrocarbazoles as therapeutic agents. Literature Review: A comprehensive analysis of existing research on N-substituted 1,2,3,4-tetrahydrocarbazoles and their biological activities. The creation of novel N-substituted 1,2,3,4-tetrahydrocarbazole derivatives based on the insights gained from the literature. The chemical preparation of the designed compounds. Theoretical analysis of the compounds' properties and potential interactions with biological targets. Experimental assessment of the synthesized compounds for analgesic, anti-inflammatory, antihistaminic, and antimicrobial activities.

The decision to focus on N-substituted 1,2,3,4-tetrahydrocarbazoles is driven by their demonstrated versatility in exhibiting a wide range of pharmacological properties. Detailed Literature Review: A comprehensive examination of synthetic routes, structure-activity relationships, and biological evaluations of N-substituted 1,2,3,4-tetrahydrocarbazoles.

Molecular Design Strategy: Development of a systematic approach for designing new derivatives based on desired properties and potential mechanisms of action. Synthetic Planning: Outline of the synthetic pathways for the target compounds, considering efficiency, scalability, and purity. Selection of appropriate computational tools and techniques for molecular modeling, docking, and property prediction. Establishment of robust experimental protocols for evaluating analgesic, anti-inflammatory, antihistaminic, and antimicrobial activities.

Scheme-1:

In the first scheme four molecules of 6- substituted tetrahydrocarbazoles were synthesised by refluxing the 4-substituted phyenylhydrazine and cyclohexanone in glacial acetic acid .



R^1= -H, -Cl, -F, $-CH_3$

6-substituted tetra hydro carbazoles (TH1-TH4)

Analgesic activity

This section describes the in-silico and in-vivo studies performed on the synthesized compounds. The kappa opioid receptor was chosen for docking simulations using V life MDS software. The second cavity of the receptor was identified as the most active binding site. Compounds TH3, TH10, TH4, TH8, TH11, TH12, TH16, TH17, TH22, TH27, and TH29 showed good docking scores (ranging from -4.1896 to -4.5763), indicating favorable interactions with the receptor. These compounds exhibited hydrogen bonding with amino acids Gly61 and Try97. Additionally, they displayed hydrophobic, charge, and van der Waals interactions with various other amino acids, visualized in Figures 6 to 16. Substitutions at the sixth position of the THC group with chlorine or fluorine and a methyl group at the para position of the benzoyl ring were associated with good docking scores. The Eddy's hot plate method was used to assess the analgesic activity of the compounds. TH3, TH10, TH11, TH12, TH17, TH22, TH27, and TH29 demonstrated significant analgesic activity.

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