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Research Article

Molecular-Docking Study of Thiophene analogues against GABAa Receptor used to design New Antiepileptic agents

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ABSTRACT

Heterocyclic compounds are widely spread in nature and have diversified applications in design of new drug molecules. This approach is used to design new antiepileptic agents. Based on various findings, one of the target proteins for an antiepileptic molecule is selective gamma aminobutyric acid (GABA). Selective GABA is the controller of CNS activity. In this study, thiophene derivatives were used to design the new antiepileptic agents through a selective GABA activation. The probable activity of thiophene derivatives could be increased by substitution in all positions of thiophene except the first position. Molecular docking of selective GABA activation was required to predict their antiepileptic activity. The molecular docking of thiophene analogues was carried out using AutoDock viva Ver.1.1.2. Twenty thiophene analogs were docked into GABAa with protein data bank (PDB) code 4cof. The interaction was assessed based on the docking score. Diazepam was used as the standard for this study. Twenty thiophene analogs showed the approximate docking score -6.3 to -9.6 kcal/mol—thirteen thiophene analogs that value a greater docking score than diazepam used as a standard. Compound T-15 had higher binding energy than other thiophene analogue because it has the lowest docking score. All new thiophene analogs are possible to be synthesize and performed their pre-clinical evaluation.

Introduction

Epilepsy is a chronic non-communicable disease of the brain that affects about 50 million people worldwide. It is characterized by recurrent seizures.[1] For the treatment of epilepsy, the most commonly preferred antiepileptic drugs help to get relief from the associated symptoms but these drugs could not treat epilepsy completely. Antiepileptic drugs mainly act on ion channels, receptors responsible for opening and closing ion channels like GABA, glutamate, and synthesis and function of neurotransmitters. Therapeutic efficacy of the antiepileptic drug is overcome by some unwanted side effects such as gastrointestinal disturbance, gingival, drowsiness, ataxia, megaloblastic anemia, hyperplasia, hirsutism etc.[2] Therefore, it is urgent for researchers to design and discover new drug molecules that possibly offer some of the greatest hopes for success in the present and future era. However, there are still huge numbers of pharmacologically active heterocyclic compounds consistent with clinical use. Heterocyclic compounds are widely distributed in nature and have multipurpose biological activity and synthetic applicability, which implement the new approaches for the researchers to plan and establish towards the discovery of novel drugs.[3] Thiophene is a five-membered heteroaromatic compound containing a sulfur atom at 1 position. Thiophene and its derivatives showed extensive significance in the pharmaceutical area because of its varied biological and clinical applications.[4] Moreover, thiophene derivatives find large application in material science[5-15] and in coordination chemistry[16-17] as well as intermediate in organic synthesis.[18-20]

Literature review revealed that thiophenes and their derivatives have various pharmacological activities such as anti-leishmanial,[21] molluscicidal,[22] anticonvulsant,[23] anti-inflammatory,[24-25] antitumor,[26-27] anticancer,[26-27]

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anti-proliferative,[28] antibacterial,[29] antifungal,[21] antimicrobial,[25] estrogen receptor modulating,[30] kinases inhibiting,[31-32] analgesic,[33] antihypertensive[34] antioxidant and anticorrosion activity.[35]

Although the exact mechanisms of action of thiophene and its derivatives remain unknown, a study in epilepsy indicated that thiophene can enhance GABA action. This study's main objective was to examine the thiophene derivatives and GABA interaction and identify the importance of GABA activation in epilepsy. Docking analysis was also performed to define the residues involved in thiophene binding and down regulatory action on GABA.

Material and Methods

Preparation of Target Protein X-ray Structure

The human gamma-aminobutyric acid receptor's crystal structure, the GABA (A)R-beta3 homopentamer (Protein data bank ID: 4COF) was selected as the target protein and downloaded from the site http://www.pdb.org/.

Design of New Thiophene Derivatives

The role of the new drug development is (i) determining pharmacophore compound, (ii) modifying the substituent of pharmacophore (iii) determine the list of new substituents. In this study, thiophene is a pharmacophore used to design new antiepileptic agents. The substituents are selected for designing new analogs. These substituents are consist of morpholine, pyrrolidine and piperazine ring system as well as -NO_2, -Cl, -Br, -OCH_3. They are substituted in the first position of 2-cyno and 3-amino thiophene ring system.

Ligands Preparation

The structures of thiophene analogs T1-T20 (Figs 1 and 2) were drawn by using Chem Draw Ultra 8.0 (Cambridge Soft). The 2D structures of compounds were converted to the 3D structure utilizing Chem3D Ultra 8.0. The optimization of molecules and minimization geometry of the ligands was performed using MMFF 94 method and saved as PBD format, to be read for the Autodock vina docking program.

Molecular Docking Studies

Molecular docking is an attractive scaffold to understand biomolecular drug interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule into the favored binding site of the target-specific region of the target protein mainly in a non-covalent way to form a stable complex of more specificity and potential efficacy. The study of thiophene analogs and GABA interaction was evaluated using molecular docking techniques on AutoDock vinaVersion 1.1.2. We used the crystal structure of human GABAa (code 4COF, http://www.pdb.org/) as the target protein. Prior to screening the ligands, the docking protocol was validated by re-docking 4COF ligand into its binding pocket within the GABAa crystal to obtain the docked pose and root-mean-square distance (RMSD).

Results and Discussion

Virtual screening experiments are the most convenient way to incorporate protein in the docking process by performing docking using an ensemble of static receptor conformations. Molecular docking is used in modern drug design to help understand the interaction between ligands and target protein. These techniques are supported to the design of novel drug which has specific activity by the mechanism of drug-receptor interaction. Computer-aided drug design (CAAD) helps to identify small molecules by orienting and scoring them in the active binding site a protein. The docking simulation technique was performed using AutoDock vina Version 1.1.2 with quinazolinone derivatives and were docked with GABAa as protein target. This program selected the best docked based on two criteria such as ligand binding position and fitness function scores comparison. The parameter to identify the best ligand binding position was the RMSD.

A docking score is a value that reflects the binding energy required to form a bond between the ligand and receptor, which predicts the activity of compounds. It also causes the bond between the ligand and the receptor to be more stable. The binding energy values of thiophene analogs are shown in Table 1. Twenty Thiophene analogs showed the approximate docking score -6.3 to -9.6 kcal/mol—thirteen thiophene analogs that value a greater docking score than diazepam used as a standard compound. Derivative T-15 had higher binding energy than other thiophene analogs because it has the smallest docking score (-9.6kcal/mol).

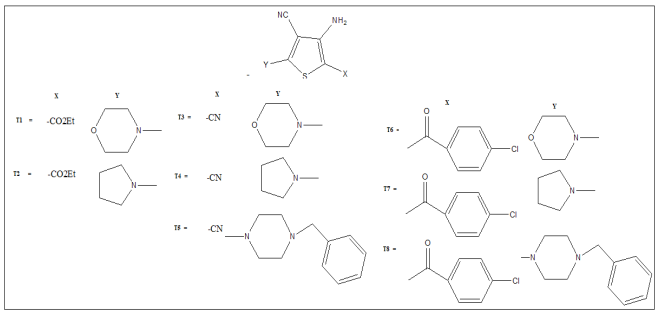

Fig. 1: Structures of thiophene analogs (T1-T8)

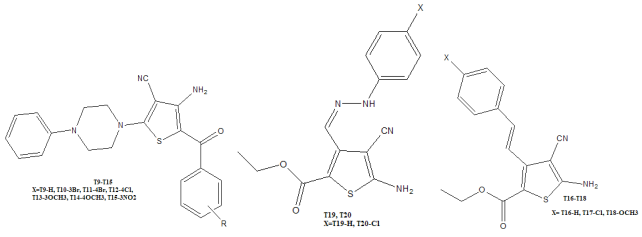

Fig. 2: Structures of thiophene analogs (T9-T20)

Table 1: Docking score of thiophene derivatives(T1-T20) with GABA

Ligand	*Docking Score*	*Ligand*	*Docking Score*
T-1	-6.9	T-11	-8.7
T-2	-6.7	T-12	-9.3
T-3	-6.4	T-13	-8.9
T-4	-6.3	T-14	-8.7
T-5	-7.4	T-15	-9.6
T-6	-8.1	T-16	-7.4
T-7	-7.6	T-17	-7.7
T-8	-8.8	T-18	-7.7
T-9	-8.5	T-19	-7.5
T-10	-9.2	T-20	-7.6
Std (Diazepam)	-7.5		

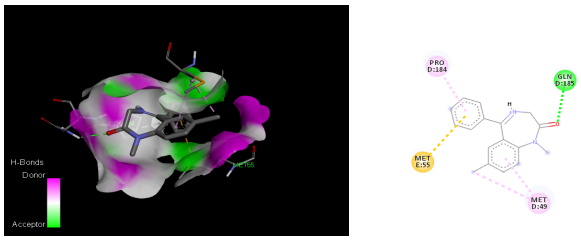

Fig. 3: 3D and 2D structure of diazepam interact with GABA

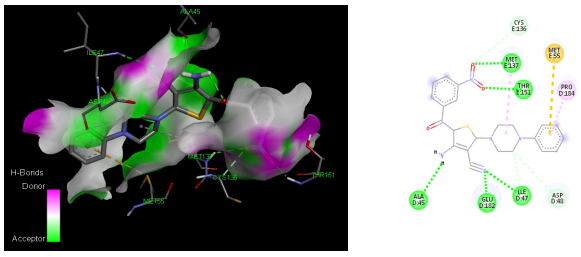

Fig. 4: 3D and 2D structure of T-15 interact with GABA

All thiophene derivatives have hydrogen bond interaction with protein residue. One of them which has a lower docking score is compound T-15. Compound T-15 was substituted at 2nd position with 4-phenylpiperazinyl and 5th position with phenacyl group on 4-amion-3-cyano thiophene ring. This means it has higher binding energy to interact with the target receptor. The interaction of Diazepam in Fig. 3 and compound T-15 with GABA receptor along with hydrogen bonds are shown in Fig. 4.

Conclusion

Twenty molecular structures of Tetrasubstitutted thiophene analogs possess 3-amino, 4-cyno, 4-Phenylpiperidine moiety at 1st position and nitro group phenecarbonitriles side chain attached at 5th position have been docked, and score obtained to identify the ligands that bind to GABAa protein structure. The result shows that thirteen analogs showed a higher docking score than diazepam. It means they have higher binding energy interaction with the target receptor. Therefore, these compounds could be considered potent GABAergic molecules. For further investigation, synthesis and in vitro evaluation are required to get antiepileptic activity.

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