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Molecular Modeling Study of PDE4 Inhibitors Based on Discovery Studio

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Abstract: A series of novel aryl amide analogues as PDE4 inhibitors were designed. Based on the crystal structure of phosphodiesterase IV subtype (PDE4) (PDB: 1XOQ), the Discovery Studio 4.5 software was used to screen the compounds by discovery studio docking. The result indicated that the 15 of the newly designed inhibitors have the most prospect and desired to be synthesized.

Keywords: PDE4 Inhibitors, Discovery studio, Molecular Docking

INTRODUCTION

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are second messengers in cells and have important implications in cell life activities[1-2]. The regulation of intracellular cAMP levels is mainly achieved by the synthesis of adenylate cyclase and the hydrolysis of phosphodiesterases (PDEs)[3]. PDEs can catalyze the hydrolysis of 3′, 5′-phosphodiester bonds of adenosine, causing cAMP levels to decline, thereby affecting the body's physiological activities. PDEs are a large multi-gene family, with more specificity for substrates, inhibitor sensitivity, and calcium/calmodulin dependence, which can be divided into 11 subtypes[4], in which phosphodiesterase IV subtype (PDE4) specifically hydrolyzed cAMP[5-6]. PDE4 can be divided into 4 subtypes: PDE4A, PDE4B, PDE4C and

PDE4D. PDE4 mainly exists in inflammatory cells. By interacting with other proteins such as inhibitory protein, a kinase anchored protein, and activated C kinase 1 receptor, the cAMP concentration is decreased, and various cellular functions are selectively regulated. PDE4 inhibitors can be used for the treatment of diseases caused by inflammation, such as asthma, chronic obstructive pulmonary diseases, etc., and diseases of the central nervous system caused by neuronal damage caused by potential inflammation, such as Alzheimer's disease, Parkinson's disease, and A stroke[6-15]. Therefore, as a drug target, the research and development of PDE4 inhibitors is of great significance.

With the rapid development of proteomics, more and more protein structures have been resolved. Drug development based on protein structure analysis of specific drug targets has received extensive attention. Virtual drug screening technology is a technique that uses a computer to chemically evaluate the binding between small molecule compounds and target sites. Due to its great advantages in reducing the range of compounds and experiments in the drug development process, shortening research and development cycles, and reducing experimental costs, virtual screening is currently a standard approach to designing new drugs[16]. Discovery Studio (DS) [17] is a large-scale comprehensive simulation software developed by Accelrys for the life science field and mainly used for the study of protein structure and function. The flow of different functions in the DS software is modularized and highly integrated, which provides researchers with great convenience. It is a protein structural analysis software that researchers are currently optimistic about. This article uses the Discovery Studio 4.5 Molecular Simulation Software Package (Beijing Chuang Teng Technology Co., Ltd.). The PDE4 protein 1XOQ was used as a target and docking was performed from the designed compounds. The screening results were compared and analyzed. The structure of protein ligand 1XOQ is shown in Figure 1 (Figure 1).

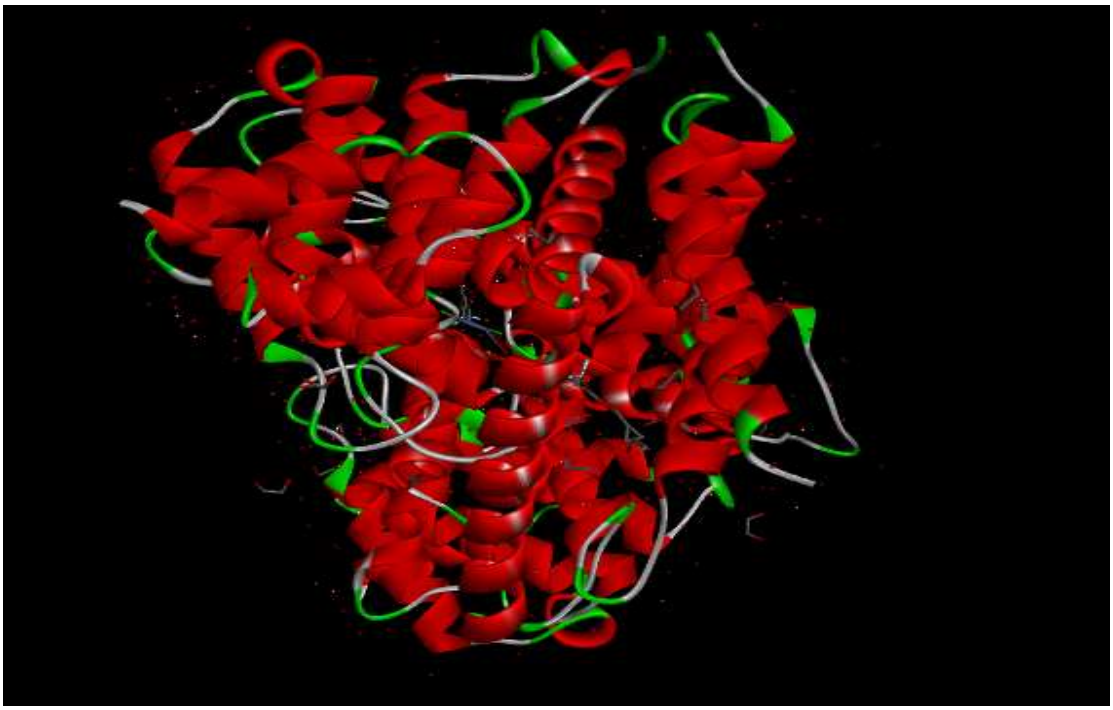
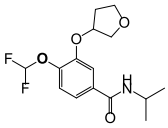
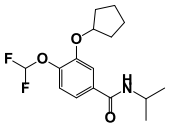
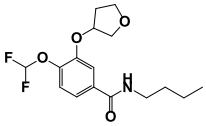
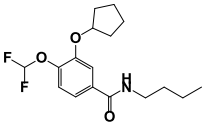
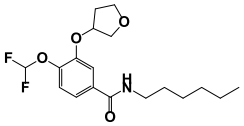
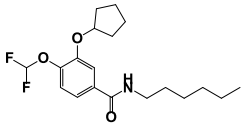
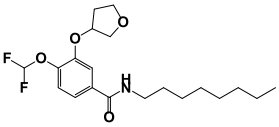
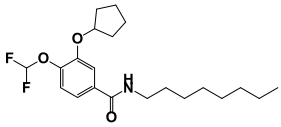
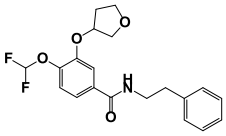
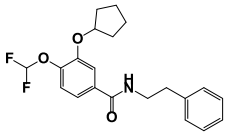
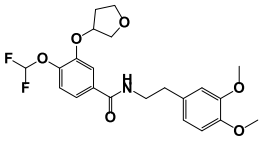
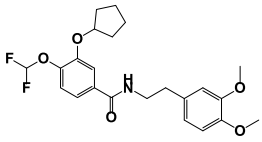
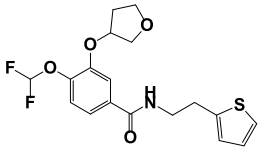
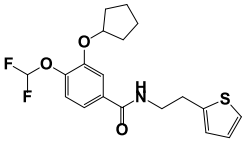


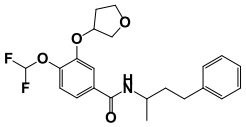
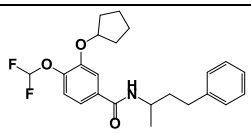
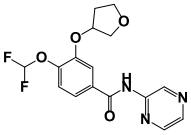
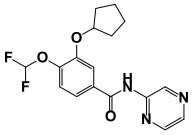
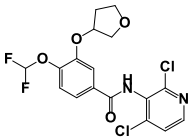
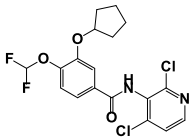
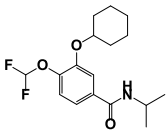
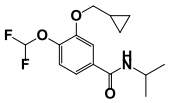
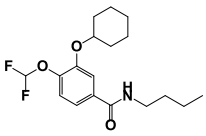
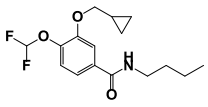
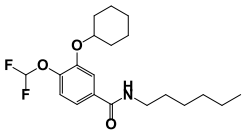
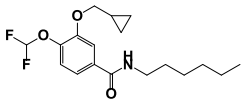
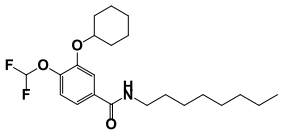
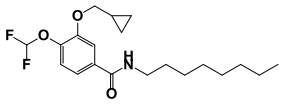
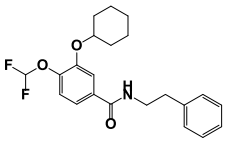
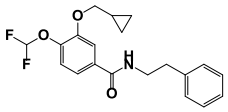
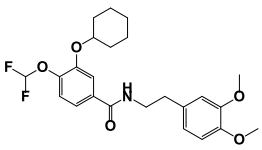
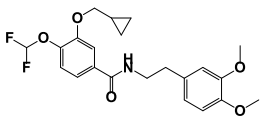
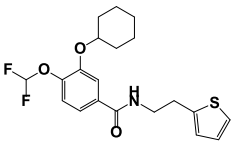
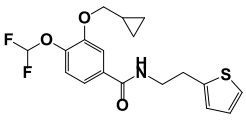
Figure 1 : Crystal Structure of Phosphodiesterase4D (1XOQ)

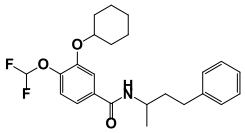
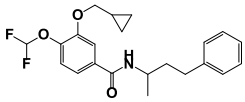
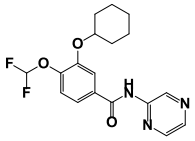
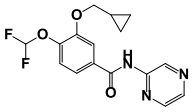
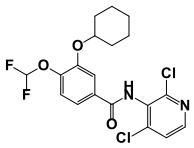
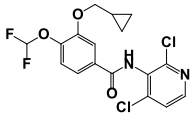
MATERIAL AND METHODS

Preparation of ligand: The structure of the designed compound was plotted using ChemDraw software. The commercially available PDE4 inhibitor Roflumilast (No. RO10) was used as a template to design 39 different compound structures as docking ligands. The protonation state was determined and the excess structure removed by the pH-based method (pH range set to 7.5) in the Prepare Ligand module in Discovery Studio. The structure of the compound is shown in Table 1 (Table 1).

Table 1: Structure of the Designed Compounds

No.	Structure	No.	Structure
CY01		CY21	
CY02		CY22	
CY03		CY23	
CY04		CY24	
CY05		CY25	
CY06		CY26	
CY07		CY27	

CY08		CY28	
CY09		CY29	
CY10		CY30	
CY11		CY31	
CY12		CY32	
CY13		CY33	
CY14		CY34	
CY15		CY35	
CY16		CY36	
CY17		CY37	

CY18		CY38	
CY19		CY39	
CY20		CY40	

Preparation of receptor: From the PDB (Program Database File) 1XOQ as the structure of the receptor PDE4, the protonation mode of the residue was determined by the default parameter of the Prepare Protein module in the Discovery Studio and the distance from the center of the receptor to the center of the original ligand molecule was less than 11.0 Å. The area serves as a docking site. The docking site area is shown in Figure 2 (Figure 2).

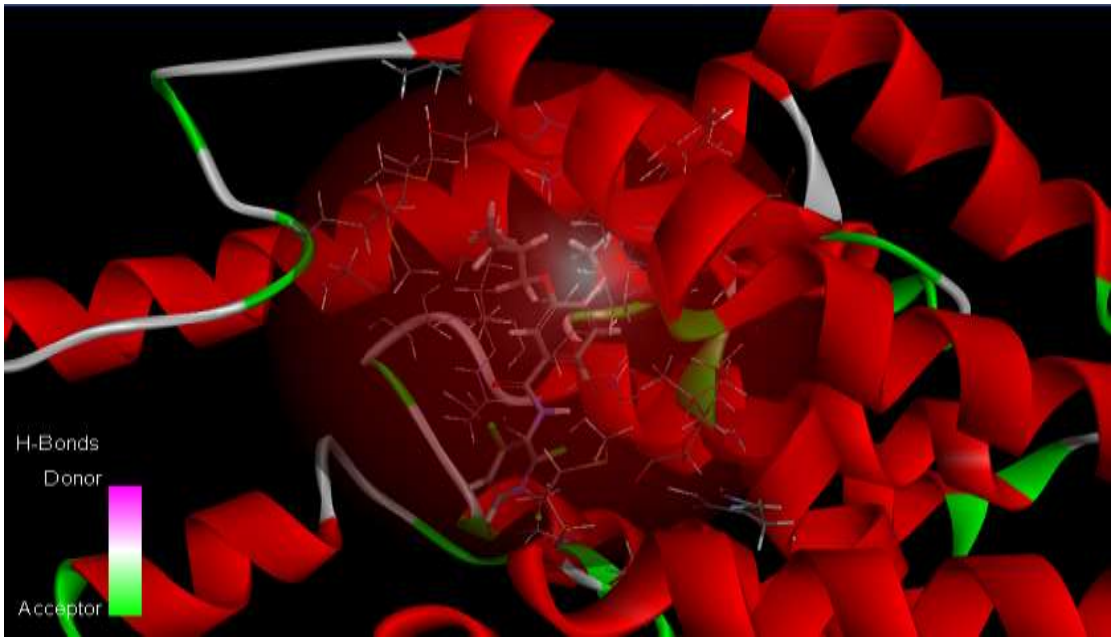


Figure 2: The docking site area of 1XOQ

Virtual Screening: DS integrates a large number of modules such as protein characterization, homology modeling, molecular mechanics calculations and molecular dynamics simulation, structural drug design tools, and small molecule-based drug design tools. Users can select the appropriate module according to

their task. CDOCKER, a structural drug design tool, is suitable for highly accurate virtual screening. CDOCKER is a molecular docking method based on the CHARMM force field. This method can produce highly accurate docking results. Set the prepared 1XOQ receptor molecule and ligand file in the CDOCKER graphic options box, select the appropriate parameters, and click the Run button to start the screening. Each molecule docking result retains the highest score of the CODCKER INTERACTION_ENERGY item. The results are shown in Table 2 (Table 2).

Table 2: The COCKER scores (kcal/mol) from of compounds

NAME	-CODCKER INTERACTION_ENERGY	NAME	-CODCKER INTERACTION_ENERGY
CY01	44.6474	CY21	47.4094
CY02	47.8067	CY22	54.1996
CY03	51.9598	CY23	51.2157
CY04	60.0284	CY24	54.4065
CY05	49.6155	CY25	51.2968
CY06	61.02	CY26	60.8014
CY07	48.5064	CY27	52.208
CY08	54.1017	CY28	55.1259
CY09	49.9855	CY29	50.2487
CY10	53.1796	CY30	54.422
CY11	49.1829	CY31	44.1666
CY12	49.394	CY32	46.9565
CY13	55.1509	CY33	50.7861
CY14	57.7172	CY34	56.6755
CY15	53.0328	CY35	49.7085
CY16	56.7572	CY36	60.0106
CY17	51.556	CY37	46.3101
CY18	55.6397	CY38	53.2589
CY19	54.6181	CY39	50.6985
CY20	55.7331	CY40	53.5897

RESULTS AND DISCUSSION

According to the reports of the existing literature and the analysis of residues in this paper, we found that the interaction between Roflumilast and PDE4D protein is mainly the two hydrogen bonding forces between GLN369 and π-π conjugated with PHE372. The binding mode results are shown in Figure 3 (Figure 3) based on this condition, the binding patterns of the 16 compound CDOCKER results were analyzed and a hit small molecule that met this condition was obtained. The CDOCKER scoring results and protein crystal binding conditions are shown in Table 3 (Table 3).

Sixteen small molecules were screened out from the designed compounds, and they all showed better prediction activity for PDE4D compared with Roflumilast, and the binding pattern with PDE4D was in line with the existing prediction model (the -CODCKER INTERACTION_ENERGY was The ideal interval is 53.589-61.02kcal/mol). Among them, there was a compound with a docking score higher than 53.5897, which was larger than the -CODCKER INTERACTION_ENERGY score of the listed drug Roflumilast, and the binding mode showed better results. Therefore, the predicted activity of some small molecules in this part was higher or higher than the existing marketed drugs.

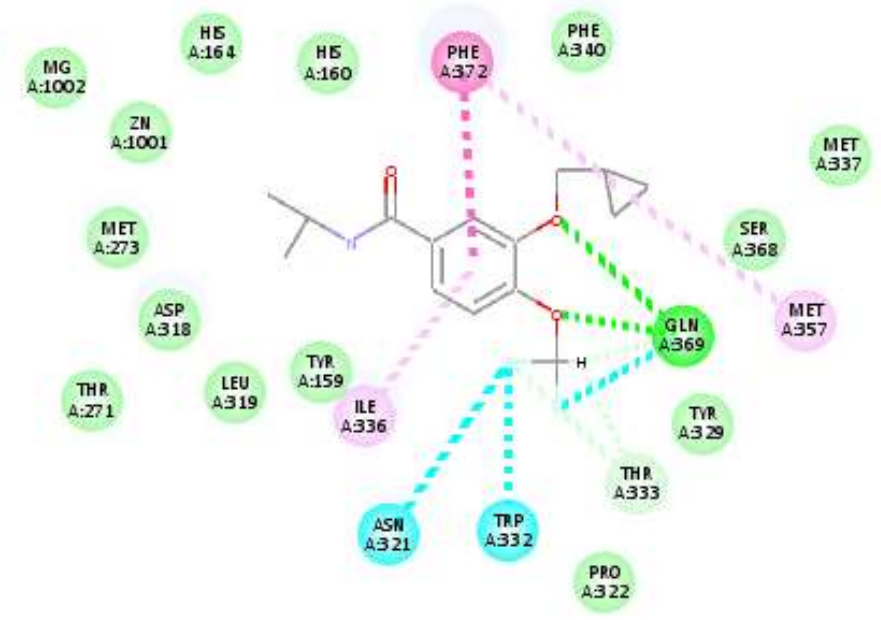


Figure 3: The binding mode results of Roflumilast

Table 3: CDOCKER scoring results (kcal/mol) and protein crystal binding

Number	-CODCKER INTERACTION_ENERGY	Hydrogen Bonding Force	π-π Conjugated
CY04	60.0284	2	1
CY06	61.02	2	1
CY08	54.1017	1	1
CY13	55.1509	2	1
CY14	57.7172	2	1
CY16	56.7572	2	0
CY18	55.6397	2	1
CY19	54.6181	2	1
CY20	55.7331	2	1
CY34	56.6755	2	1
CY36	60.0106	2	1
CY22	54.1996	0	1
CY24	54.4065	2	1
CY26	60.8014	2	1

CY28	55.1259	2	1
CY40	54.422	1	1

CONCLUSION

We used Discovery Studio on a computer to simulate the most realistic ligand-receptor binding, using different docking methods and different scoring functions to screen ligand molecules. From the 40 small molecular structures, 15 molecules with relatively good predictive activity were screened. Next, we look forward to further bioactivity studies to verify the validation of compound screening results. The use of virtual screening technology has greatly improved the efficiency of finding PDE4D inhibitors, saving a lot of manpower and material costs. However, in Discovery Studio 4.5, the program can only display a part of the hydrophobic effect, which is only a part of the van der Waals function. This makes the level of the scoring function not completely determine the level of a molecular activity, so the virtual screening also needs to be different. The screening methods are mutually supportive. It is believed that with the in-depth study of PDE4D inhibitors, computer virtual screening will play a greater role. Through computer-assisted drug design, fragment-based drug design, etc., more potential inhibitors can be designed based on a number of reported compounds with better inhibitory activity, and the activity verification in vitro and in vivo can be carried out.

REFERENCES

1. F. A. Antoni. Molecular diversity of cyclic AMP signaling. *Front Neuroendocrinol*, 2000, 21 (2): 103.

2. J. A. Beavo, L. L. Brunt. Cyclic nucleolide research still expanding after half a century. Nat Rev Mol Cell Biol, 2002, 3 (9): 710.

3. M. D. Houslay. Adaption in cAMP signaling processes: a central role in cyclic AMP phosphodiesterases. *Sem Cell Dew Biol*, 1998, 9 (2): 161.

4. C. I. Crocker, R. G. Townley. Therapeutic potential of phosphodiesterase 4 inhibitiors in allergic diseases. *Drugs Today*, 1999, 35 (7): 519.

5. M. M. Teixeira, R. W. Gristwood. Phosphodiesterase (PDE) inhibitors : antiflammatory drugs of the future. *Trends Pharmacol Sci*, 1997, 18 (5): 167.

6. A. Castro, M. J. Jerez, C. Gil, et al. Cyclic nucleotide phosphodiesterases and their role in immunomodulatory responses: advances in the development of specific phosphodiesterase inhibitiors. *Med Res Rev*, 2005, 25 (2): 229.

7. R. Duggirala, D. H. O'Leary, et al. Genetic basis of variation in carotid artery wal lthickness. *Sroke*. 1996, 5 (5): 833.

8. H. Lin, Y. C. Liao, C. W. Liou, et al. The phosphodiesterase 4D gene for early onset ischemic stroke among normotensive patients. *BioMed Research International*. 2007, 2 (2): 436.

9. C. Wang, X. M. Yang, Y. Y. Zhuo, et al. The phosphodiesterase-4 inhibitor rolipram reverses Aβ-induced cognitive impairment and neuroinflammatory and apoptotic responses in rats . *Int J Neuropsychopharmacol*. 2012, 6 (6):749.

10. N. Li, Z. H, Xu. Association of PDE4D and IL-1 gene polymorphism with ischemic stroke in a Han Chinese population. *Brain Research Bulletin*. 2010, 1 (1):38.

11. H. G. Kim, M. Moon, J. G. Choi, et al. Donepezil inhibits the amyloid-beta oligomer-induced microglial activation in vitro and in vivo. *Neurotoxicology*. 2014, 23.

12. S. Kotani, T. Yamauchi, T. Teramoto, et al. Donepezil, an acetylcholinesterase inhibitor, enhances adult hippocampal neurogenesis. *Chem Biol Interact* . 2008, 1/3 (1/3): 227.

13. A. T. Bender, J. A. Beavo. Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. *Pharmacological reviews*. 2006, 3 (3): 488.

14. D. Dlaboga, H. Hajjhussein, J. M. O'donnell. Regulation of phosphodiesterase-4 (PDE4) expression in mouse brain by repeated antidepressant treatment: comparison with rolipram. *Brain Research*. 2006, 1 (1): 104.

15. A. Kojima, S. Takita, T. Sumiya, et al. Phosphodiesterase inhibitors. Part 6: Design, synthesis, and structure-activity relationships of PDE4-inhibitory pyrazolo[1, 5- a] pyridines with anti-inflammatory activity. *Bioorganic & Medicinal Chemistry Letters*. 2013, 19 (19): 5311.

16. W. P. Walters, M. P. Stahl and M. A. Mureko. Virtual screening-an overview. *Drug Discovery Today*, 1998, 3 (4): 160.

17. Y. D. GAO, J. F. HUANG. An extension strategy of Discovery Studio 2.0 for non-bonded interaction energy automatic calculation at the residue level. *Zoological Research*, 2011, 32 (03): 262.

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