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Research Article

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Establishment of a virtual molecule fragment library for non-steroidal aromatase inhibitors

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ABSTRACT

Breast cancer is a common and frequently-occurring disease which has serious impact on women's health and life. Aromatase inhibitors play an important role in endocrine treatment of breast cancer. It is necessary to find new aromatase inhibitors for the improvement of the treatment efficacy and the reduction of drug resistance and side effects. In this paper,490 molecules in Binding DB with the top aromatase activities (the lowest IC_{50} for aromatase inhibition) were disassembled into a few basic pieces to build molecular common structural fragment libraries of aromatase inhibitors using the RECAP analysis function module in MOE 2013 software. This library can provide basic molecular structural source materials for the new drug design of aromatase inhibitors.

Keywords: Aromatase inhibitors, virtual molecule fragment library, RECAP analysis,MOE software,IC_{50}

INTRODUCTION

Breast cancer is one of the most common malignant tumors of women around the world. There are about 1000000 new female breast cancer patients each year[1,2].While in China, in recent years, breast cancer patients is increasing year by year and it has become the second leading cause of death in female malignant tumors. There are about 2/3 of the patients which are estrogen dependent. In the body, estrogen can be formed from androgen by multistep reactions participated with aromatase (CYP19). Therefore, aromatase is an ideal target for treatment of breast cancer.

Aromatase is a member of the cytochrome P450 family of enzymes. In vivo it transfers testosterone, androstene and 16-α-hydroxy androstene to oestrone and estradiol through aromatic reaction[3]. The peripheral circulating estrogen level is significantly decreased for postmenopausal women, however, it is 10 times higher in breast tissue with high expression of aromatase and the substrate, androstenedione is 8 times higher than the peripheral. It can be said that the high estrogenic environment in breast tissue promotes breast cancer's recurrence and transfe[r[4]. Therefore, inhibiting the activity of aromatase and reducing the secretion of estrogen level have become the important means in the treatment of breast cancer.

Aromatase inhibitors have been developed by the three generations[5]. They can be divided into two classes, the steroidal and the non-steroidal. Although these drugs showed a good therapeutic effect, but the side effects such as drug resistance and osteoporosis may resulted from the long-term use of them, therefore, it is necessary for the further development of new aromatase inhibitors with higher activity and little side effects. At present, the new drug discovery has turned from the universal screening to the period of rational drug design and computer aided drug design has become an indispensable tool in drug research and development.

Recently, the idea of reverse synthesis (retrosynthesis) is introduced into the molecular fragments mosaicing method for new drug design. It includes the process that the structure of a molecule in molecular database is fragmented according to the principle of reverse synthesis (i.e. the bond is split apart only when a corresponding classical connecting chemical reaction is existed between the two atoms bonded). Some simple molecular fragments were generated to form a fragment library and the atoms and chemical bonds at the broken positions were labeled. Two arbitrarily chosen fragments can be linked when a classical connecting chemical reaction existed between their labeled atoms and thus a new molecule formed. Therefore, the majority of the novel compounds generated with this method can be synthesized and the generation of a large number of unwanted compounds without practical synthesis reactions can be avoided. With this process, most of new compounds generated not only has the structure novelty and diversity, but also can be the synthesized practically.

In this study, 490 molecules in Binding DB(http://www.bindingdb.org/) with the top aromatase activities (the lowest IC_{50} for aromatase inhibition) were split into a few basic pieces to build molecular common structural fragment libraries of non-steroidal aromatase inhibitors using the RECAP analysis function module in MOE 2013 software [6]. This library can provide basic molecular structural source materials for the new drug design of aromatase inhibitors.

EXPERIMENTAL SECTION

The non-steroidal compounds with the aromatase inhibitory activities were obtained by searching the compounds targeting on CYP19 in Binding DB database. These compounds were sorted by IC_{50} values are 490 non-steroidal compounds with the top activities were selected as the source molecules to be fragmented.

The RECAP analysis module in Chemical Computing Group company's MOE software (the version No. is 2013.08)[6] was used for the fragmentation of the source molecules and a small fragment library formed from the resulted fragments.

RESULTS AND DISCUSSION

The small fragment library generated by MOE software includes the structures of 127 fragments and their frequencies appeared in 490 non-steroidal compounds of aromatase inhibitors. The top ten typical functional groups with the highest frequencies are listed in table 1.

As can be seen from table 1, imidazole and triazole (fragment No. 1 and 2) are the fragments with the highest frequencies appeared in the non-steroidal aromatase inhibitors, and there is only one of them appeared in an aromatase inhibitor. In addition, triazole often appeared in the molecules with the top aromatase inhibitory activity.The new generation aromatase inhibitor, letrozole (Fig.1) , is a combination of triazole with 4-cyanophenyl groups. It has the high selectivity and activity[7] and it has no effect on the functions of glucocorticoids, mineralocorticoids and thyroid. It doesn't influence the secretion of corticosteroid substances with a high dose situation. The clinical studies have demonstrated that letrozole has less toxicity to the body and the target organ, and has none of mutagenic and carcinogenic effects. Compared with other aromatase inhibitors and anti-estrogen drugs, it has stronger anti-tumor effect and suitable for early breast cancer treatment and the case of breast cancer patients in postmenopausal insensitive to anti-estrogen therapy.

Another example drug is anastrozole (IC_{50}=15nM, Fig.2), which contains a triazole group and the fragment No. 6 in table 1, it belongs to the third generation aromatase inhibitors. Anastrozole is a potent non-steroidal aromatase inhibitor, applicable to the postmenopausal women with advanced breast cancer which can't be controlled with tamoxifen and other anti-estrogen drugs.

Table 1. The top ten typical fragments with the highest occurrence frequencies in the small fragment library

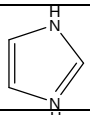
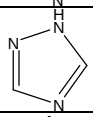
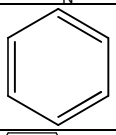
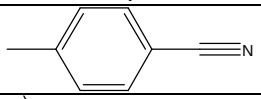
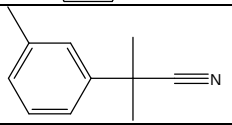
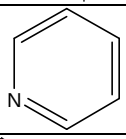
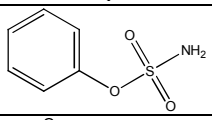
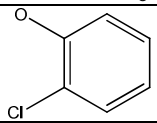
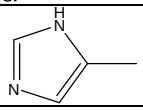
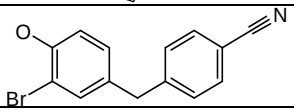
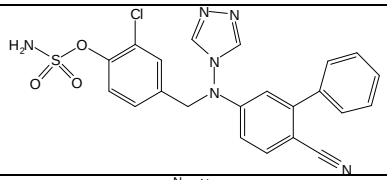
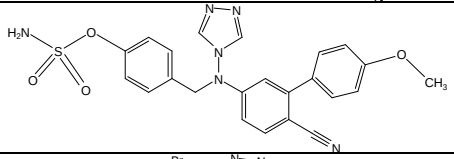
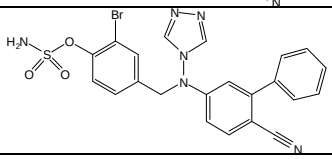
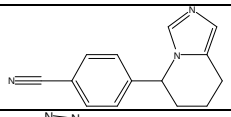
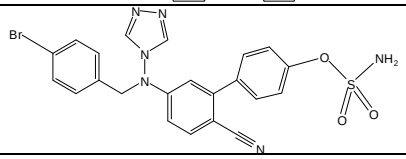
Fragment No.	Structure	Occurrence
1		128
2		118
3		30
4		24
5		20
6		12
7		10
8		8
9		8
10		6

Table 2. The aromatase inhibitors with lowest IC_{50} values in Binding DB

Compound No.	Structure	IC_{50}（nM）
I		0.015
II		0.015
III		0.018

IV		0.03
V		0.05

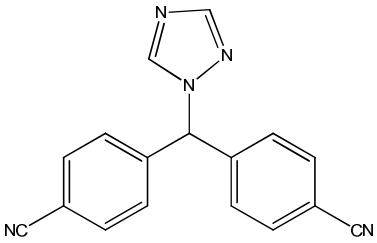


Fig. 1 Letrozole

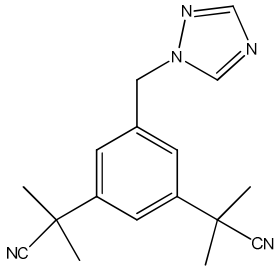


Fig. 2 Anastrozole

The structures and activities of the compounds with the lowest IC_{50} values for CYP19 in Binding DB are listed in table 2. It can be seen that the fragments 1, 2, 4 and 7 are the main fragments appeared in these compounds with top aromatase inhibitory activities.

From the structure and occurrence analysis of these fragments obtained from the known compounds with high aromatase inhibitory activities, we can obtain the knowledge about the contribution of different fragments to the aromatase inhibitory activities. The recombination and re arrangement of these fragments may generate new potent aromatase inhibitors with higher activities and lower side effects, thus, a fragment library generated from the structure of known aromatase inhibitors will help the discovery of new aromatase inhibitors.

Acknowledgments
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