Extended Abstract Journal of Clinical Medicine and Therapeutics 2020
Vol.5 No.1

Euro Biopharma 2018: Identifying Novel Anti Osteoporosis leads with a Chemotype-Assembly Approach- Jun Xu- School of Biotechnology and Health Sciences, Wuyi University

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In this paper, we applied a chemotype-assembly approach for ligand-based drug discovery (LBDD) to discover novel anti-osteoporosis leads. With this new approach, we identified 12 chemotypes and derived 18 major chemotype assembly rules from 245 known anti-osteoporosis compounds. Then, we selected 19 compounds from an in-house compound library using chemotype-assembly approach for anti-osteoporosis assays, which resulted in 13 hits. Based on structural features in these 13 compounds, we synthesized 50 possible anti-osteoporosis compounds from the anti-osteoporosis chemotypes by means of click chemistry techniques and discovered a compound (10a, IC50 = 2 nM) with nanomolar activity. Compound 10a was then proved to be an anti-osteoporosis lead since it can prevent bone loss in vivo.

Introduction

Ligand-based drug discovery (LBDD) is an interesting rational drug design method to accelerate the earlier stages of drug discovery.(1) LBDD usually begins with a collection of known molecules that have the same target or treat the same diseases. This collection is then used to perform quantitative structure–activity relationship (QSAR) studies, substructure retrieval, or similarity searches against commercial or in-house databases.(2,3) A key limitation of LBDD is that newly identified molecules are often close analogues of known ligands, and novelty therefore is limited.

Recently, we reported identification of the privileged fragments (substructures of known compounds) and the assembly rules for liver X receptor-β (LXRβ) from known LXRβ agonists.(4) These fragments and rules are then successfully applied to discover new agonists. This approach encourages us to use substructures for LBDD and overcomes the limitations of LBDD. However, a remaining question is whether this approach can be applied to a wider range of diseases. This is an important problem since many diseases lack validated molecular targets.(5) We hypothesize that the active agents related to a disease are constructed from different chemotypes according to some assembly rules. The chemotype is defined as "a chemical structure motif or primary substructure that is common to a group of compounds".(6)

Osteoporosis affects more than 25% of women and more than 10% of men in their lifetimes and is a disease that is characterized by loss of bone mass, leading to increased risk of fractures. It was selected to test our hypothesis.(7−9) Anti-osteoporosis drugs including bisphosphonates,(10) cathepsin K inhibitors,(11) and parathyroid hormone mimetics(12) are available, but challenges in osteoporosis therapy still remain because no drugs have been found that reduce the risk of fractures significantly.(13)

Here, we applied a previously described de novo substructure generation algorithm (DSGA)(4) to extract privileged fragments from a library of known anti-osteoporosis compounds. DSGA allows us to discover frequent substructures or fragments from a chemical structure library. The fragments that remained after "rule of 3"(14) filtering were clustered according to our previously described scaffold-based classification approach (SCA).(15) SCA can provide the scaffold and complexity of a structure. The complexity presents the heavy atom number of substituents on this scaffold. These two parameters are applied to cluster the fragments. One cluster was identified as a chemotype,(6) and then chemotype assembly rules were generated by analysis of the linkages between two neighboring chemotypes. From the chemotypes and their assembly rules, a series of substructures, which are presented by Markush queries, were constructed and used to screen our in-house library. A number of candidate lead compounds were identified according to the bioassay results. Further optimization with click reactions and chemotype assembly rules gave a putative anti-osteoporosis lead compound.

Results

Chemotypes Derived from Known Anti-Osteoporosis Agents

A total of 245 known anti-osteoporosis agents were collected from published sources. These compounds were divided into 28 classes based on their associated targets: 162 compounds have specific protein targets, 19 compounds are involved in signal transduction pathways, 60 compounds are cell-based regulators, and 4 compounds have been tested on animal models but lack target information

Employing DSGA on this library resulted in 502 privileged fragments. According to the "rule of three", fragments were eliminated if (1) they are acyclic; (2) their molecular weight is >300, the number of hydrogen bond donors is >3, the number of hydrogen bond acceptors is >3, and *c*log *P* > 3,(14,16) and (3) the smallest set of smallest rings is >1.(17) This resulted in 54 fragments, which were classified by SCA into 12 chemotypes.

Conclusions and Discussion

The chemotype-assembly approach combines fragments into a ligand-based drug discovery with superior performance. It is divided into three steps: (1) derivation of chemotypes and their assembly rules from a library of known compounds with a common target, a protein or a disease, (2) generation of compounds with affinity for a target or disease based on given chemotype-assembled substructures, and (3) optimization of the

This work is partly presented at 6th European Biopharma Congress September 18-19, 2018 held at Amsterdam, Netherlands

identified leads using click chemistry and in vitro and in vivo testing.

In this way, we successfully assembled 69 anti-osteoporosis candidate compounds, confirmed 52 of these as anti-osteoporosis agents, and discovered 4 lead compounds with new scaffolds and nanomolar activity. The efficacy of the best compound (**10a**) was confirmed by in vivo experiments.
The chemotype-assembly approach allows getting the smallest active substructures for a target or diseases rationally and easily. By assembling the chemotypes through associated rules, the substructures can be easily obtained. These substructures can lead us to discover the hits of variety novel scaffolds with a high hit rate. In this study, we discovered seven novel anti-osteoporosis scaffolds which are never reported before.
Click chemistry is a convenient technology used to quickly generate a compound library. The triazole ring formed by click chemistry belongs to chemotype D; therefore, it can be used to optimize the candidates through the associated assembly rules. In this study, we successfully use click chemistry to optimize thiazole amide to a potent anti-osteoporosis lead compound (**10a**). Click chemistry also can be applied to discover de novo lead compounds according to the chemotype D assembly rules.
Compound **10a** significantly inhibits osteoclastogenesis in vitro and prevents bone loss in vivo. The serum PINP concentration of **10a**-treated osteoporosis rats is closer to normal rats compare to Fosamax-treated ones. This result indicates that compound **10a** may activate new bone formation in vivo since PINP is highly related to this function. Therefore, compound **10a** is a valuable lead for the development of potent anti-osteoporosis drugs that can reduce the risk of fractures.

In conclusion, chemotype assembly-based drug discovery may offer a new approach to ligand-based drug discovery.

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