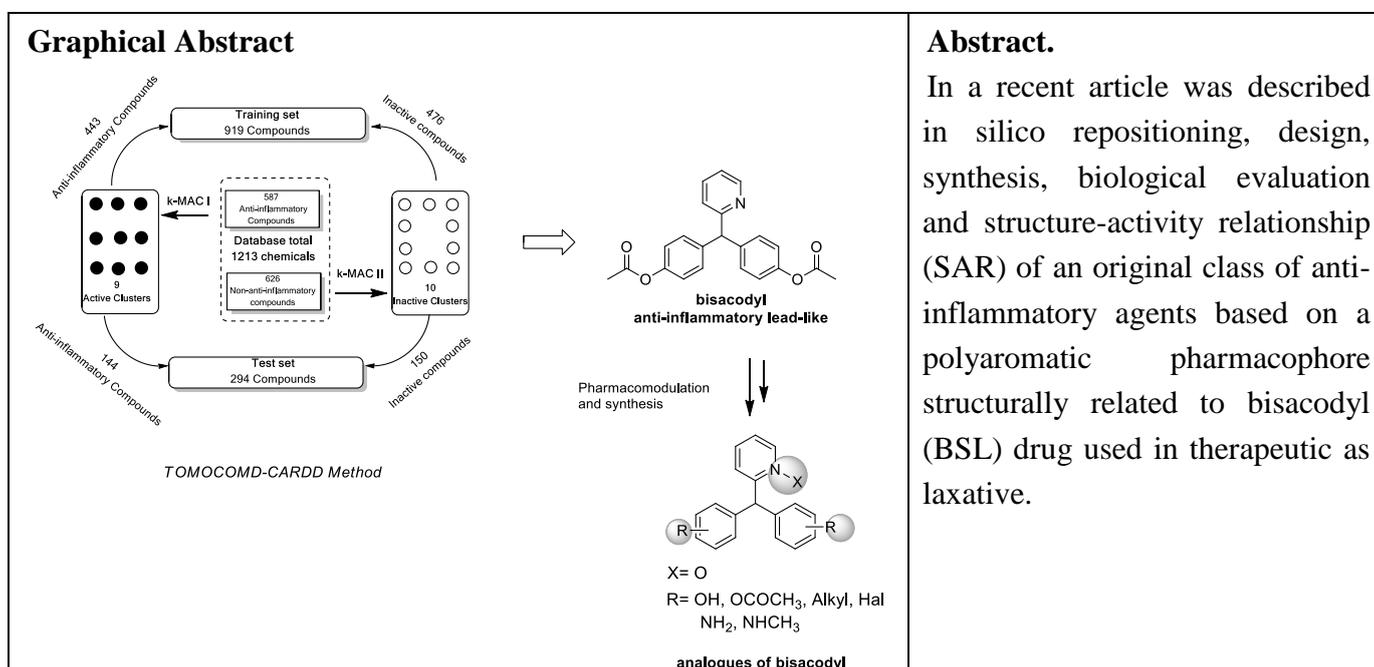


In Silico Repurposing, Design, Synthesis and Biological Evaluation of Bisacodyl Analogues

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Introduction

Drug repositioning allows the development of new indications for existing drugs with identified pharmacokinetic profiles, known safety profile and already resolved manufacturing issues [1]. The aim of this research was to identify new anti-inflammatory drug-like agents using in silico repurposing from a diverse series of known drugs, then design, synthesis and biological evaluation of analogs [2].

Materials and Methods

The potential of TOMOCOMD-CARDD (topological molecular computational design-computer aided rational drug design) methods to find out new anti-inflammatory drug-like agents from a diverse series of compounds using the total and local atom based bilinear indices as molecular descriptors was used [3]. Several biological in vitro (Nitrite and PGE2 production in LPS-stimulated cells, inhibitory effect on TNF- α and IL-6 release in cells) and in vivo (LPS-enhanced leukocyte migration to the injury zone in Zebrafish, TPA-induced mouse ear oedema, carrageenan-induced paw oedema test in rats) assays were performed in order to understand the mechanism of action of the identified known drug. A set of analogues of this drug was prepared using low-cost synthetic procedures and further biologically investigated in zebrafish models using LPS-enhanced leukocyte migration assay.

Results and Discussion

The models obtained with the TOMOCOMD-CARDD suites were validated by biological studies. BSL was identified as the first anti-inflammatory lead-like using in silico repurposing from commercially available drugs. At 30 μ M, BSL showed the best result with an anti-inflammatory activity superior to the value obtained by positive control indomethacin (85%). BSL reduced oedema and inhibited leukocyte infiltration comparable to indomethacin at 0.5 mg/ear. At dose of 20 mg/kg, BSL showed equipotent anti-inflammatory activity in protecting rats from carrageenan-induced inflammation when compared to indomethacin, while the effect was higher at 40 mg/kg. Considering the biological results, it was suggested that anti-inflammatory activity of BSL observed in vivo assays may be related to the release of cytokines, in particular with IL-6.

Diarylmethylpyridines and their corresponding *N*-oxides were synthesized by Friedel-Crafts hydroxylalkylation reaction with no more than two steps from commercially available inexpensive reagents. Among others, eighteen new compounds were synthesized in this work. Best anti-inflammatory activities reached 10 μ M in the pyridyl series and *N*-oxide respectively. The *N*-oxide functionality generally improved the anti-inflammatory activity and decrease toxicity in most series of BSL analogues.

Conclusions

Two compounds exhibited higher anti-inflammatory activities than BSL and represent new promising anti-inflammatory agents for further preclinical development.

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