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Ligand-based virtual screening of a benzylisoquinoline alkaloids dataset with anti-inflammatory potential activity.

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Abstract:

Inhibitor of nuclear factor kappa B kinase beta subunit (IKK-B) and extracellular signal-regulated kinase 1 (ERK1) are two proteins involved in cytokine intracellular signaling pathways, which have a great importance due to their anti-inflammatory role. In this work, from the ChemBL database were obtained 775 and 48 structures with activity against IKK-B (CHEMBL1991) and ERK1 (CHEMBL3385) respectively. The compounds were classified using values of $pIC_{50,}$ presenting a range of 4.29 (from 5.01 to 9.30) for IKK-B and 3.10 (From 5.05 to 8.15) for ERK-1. From SMILES codes, two-dimensional (2D) structures were generated in Standardizer and after calculated 1064 two-dimensional molecular descriptors in Dragon 7 software. Obtained results were imported to Knime 3.1.0 software. All variables were submitted to autoscaling and after were partitioned to generate two groups, a training group composed by the 80% of the whole molecules set and a test group composed by the remaining 20%. (Q)SAR models was performed using a Random Forest (RF) algorithm. Models were evaluated through cross validation (leave-one-out), Q^2_{LOO} = 0.69 and 0.66 as well as external test, Q^2_{ext} = 0.74 and 0.58 for IKK-B and ERK1 respectively. Finally, pIC50 value of 179 benzylisoquinoline alkaloids were predicted in the (Q)SAR models found 4 compound with the highest activity for each one protein studied.

Keywords: benzylisoquinoline alkaloids, IKK-B, ERK1, anti-inflammatory activity, Virtual screening

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1. Introduction

The inflammatory process is a nonspecific complex, stereotype, coordinated response of tissues to injury [1]. Several proteins with specific roles are present in the signaling pathways involved in these processes.

Nuclear factor-κB (NF-κB), is a transcriptional factor, which plays a key role in numerous physiological, these include inflammatory processes [2]. NF-κB activation is stimulated by a kinase complex, IκB kinase (IKK), which is composed of three core proteins: IKK1/ IKK-α, IKK2/IKK-β and NEMO/IKK-γ [2,3], being IKK-α and IKK-β two catalytic subunits which are structurally related kinases.

IKK-β, is an interesting target due to its role in the inflammation-induced tumour growth and progression, as well as an important modulator of tumour surveillance and rejection [4].

In turn, extracellular signal-regulated kinase 1 (ERK1) being one of the two isoforms of ERK described. It is present in the Ras/Raf/MEK/ERK signaling pathway, which has vital importance, since many essential cell processes are involved. In ~30 % of cancers and cognitive disorders, exists an abnormally activation [5].

ERK1 is a serine/threonine kinase of the GMGC group that plays a critical role in the regulation of cell growth and differentiation [6].

Benzylisoquinoline alkaloids (BIA) are metabolites which present a great diversity (~2,500 BIAs are known today) and several pharmacological activities such as antimicrobial agent, muscle relaxant, and potential anticancer drug, among others [7,8].

In this work, through of a random forest model using 2D molecular descriptors was performed to in order to predict the anti-inflammatory activity 179 BIAs structures.

2. Results and Discussion

Ligand-based virtual screening

(Q)SAR models was performed using a Random Forest algorithm. Models were evaluated through cross validation (leave-one-out), $Q^2_{LOO} = 0.69$ and 0.66 as well as external test, $Q^2_{ext} = 0.74$ and 0.58 for IKK-B and ERK1 respectively (see Figure 1 and 2)

After, pIC50 value of 179 benzylisoquinoline alkaloids were predicted in the (Q)SAR models. For IKK-B and ERK1, four structures presented the highest anti-inflammatory activity for each target (Table 2).

The two BIAs with highest anti-inflammatory activity for IKK-B present a structural similarity regarding to the presence of methoxyl and hydroxyl groups at the positions 9 and 10 respectively (Table 2a).

Meanwhile for ERK1, protoberberine skeleton presents the highest predicted value of pIC50, therefore, none structural modification regarding the core of this structure present in our database seem to increase the activity (Table 2b).

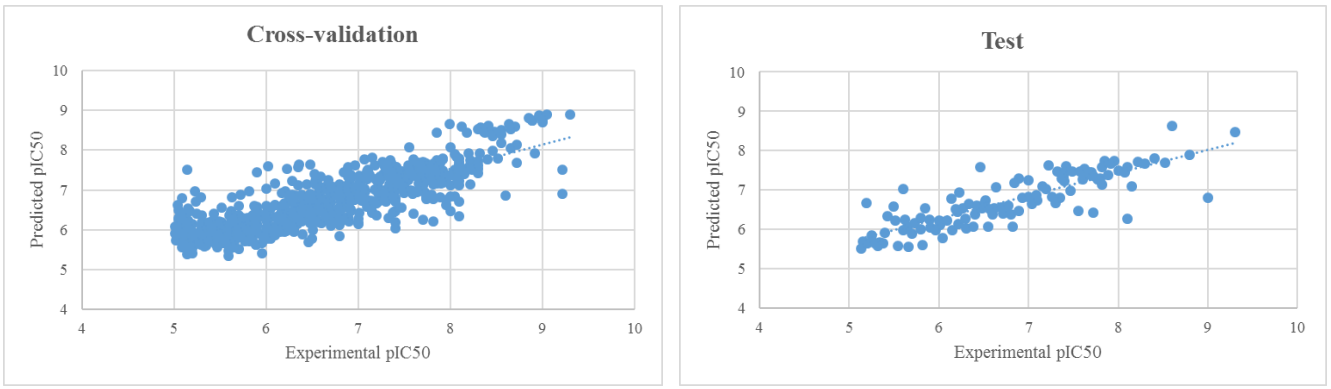


Figure 1. Plot of experimental vs predicted values of pIC50 for cross-validation and test set generated by IKK-B QSAR model

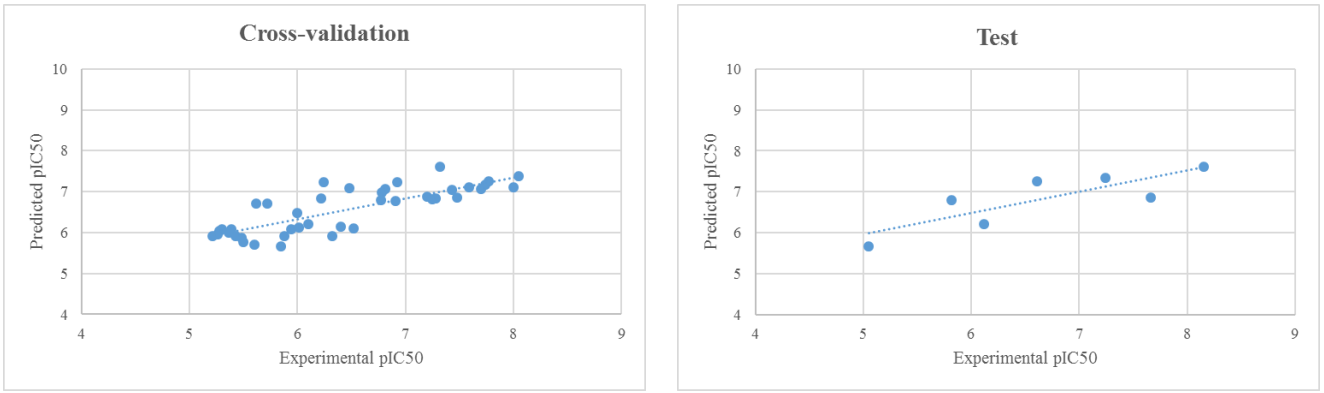
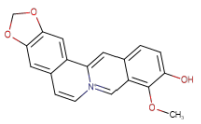
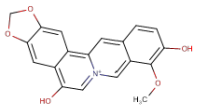
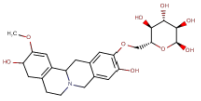
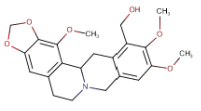
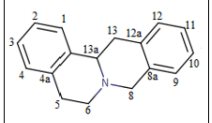
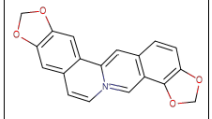
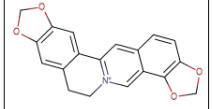
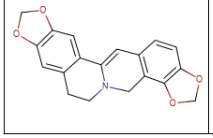


Figure 2. Plot of experimental vs predicted values of pIC50 for cross-validation and test set generated by ERK1 QSAR model

Table 1. benzylisoquinoline alkaloids with the highest anti-inflammatory activities for a) IKK-B and b) ERK1

Structure	Predicted pIC50
	6.39
	6.38
	6.36
	6.33

a)

Structure	Predicted pIC50
	6.17
	6.13
	6.12
	6.11

b)

3. Materials and Methods

From the ChemBL database were obtained 775 and 48 structures with activity against IKK-B (CHEMBL1991) and ERK1 (CHEMBL3385) respectively (https://www.ebi.ac.uk/chembl/). The compounds were classified using values of pIC_{50} (-log IC_{50}), presenting a range of 4.29 (from 5.01 to 9.30) for IKK-B and 3.10 (From 5.05 to 8.15) for ERK1. In this case, IC_{50} represents the concentration required for 50% inhibition of enzymatic activity. From SMILES codes, two-dimensional (2D) structures were generated in Standardizer software that canonized structures, added hydrogens, performed aromatic form conversions [JChem 14.9.1.0, 2014; ChemAxon (http://www.chemaxon.com)]. After were calculated 1064 two-dimensional molecular descriptors in Dragon 7 software. Obtained results were imported to Knime 3.1.0 software (www.knime.org). All variables were submitted to autoscaling and after were partitioned to generate two groups, a training group composed by the 80% of the whole molecules set and a test group composed by the remaining 20%. (Q)SAR models was performed using a Random Forest algorithm. Models were evaluated through cross validation (leave-one-out), $Q^2_{LOO,}$ as well as external test, Q^2_{ext}

4. Conclusions

The Ligand-based model using Random Forest and 2D molecular descriptors selected protoberberine skeleton with methoxyl and hydroxyl groups at the positions 9 and 10 as the most potential activity structures against IKK-B from an in-house database of benzylisoquinoline alkaloids. For ERK1 the RF model selected the same core without any substitution as the most potential active compound.

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Author Contributions

LS, MFA built database; CHA performed all calculus; and CHA, MTS and MFFMD wrote the paper. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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