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Drug repositioning for CD73 using a ligand-based virtual screening method

Gustavo Machado das Neves *[a]; Adriano Ronchi Spillere [b]; Luciano Porto Kagami [a]; Itamar Luis Gonçalves [a]; Ana Maria Oliveira Battastini [b]; Fabrício Figueiró [b,c]; Vera Lucia Eifler-Lima[a]

[a] Laboratório de Síntese Orgânica Medicinal/LaSOM, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [b] Programa de Pós-Graduação em Ciências Biológicas: Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [c]Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
**Doctoral student since 2018*

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Introduction

The ecto-5'-nucleotidase (CD73) converts AMP into adenosine, it is a promising anticancer target (1,2). The drug repositioning (DR) is a strategy to find new uses for drugs and it may help to overcome the challenges on finding new anticancer compounds. One of the DR methods relies on the chemical information of the compounds, which include similarity metrics and Ligand-Based Virtual Screening (LBVS). This work aims to identify several potential inhibitors of CD73 contained in DrugBank dataset through LBVS.

Experimental section

The LBVS was performed by the software SHAFTS (3). The compound AB680 was used as reference and the DrugBank dataset was used as query. The top 10 compounds had the score evaluated and one of them was chosen for testing on recombinant CD73 enzyme by malachite green-based assay. The compound was tested in 50, 75, 100 and 200 µM and compared to the standard inhibitor (AMPCP) at 1.25, 2.5, 5, 10 and 25 µM.

Results and Discussion

The LBVS performed by SHAFTS using AB680 revealed two purine analogs, two sulfonamides and some anti-inflammatories with high similarity to the reference compound (**Table 1**). Naproxen was chosen to be screened against CD73. Although the hybrid score showed a higher value than AMPCP, the compound did not show remarkable inhibitory activity on the tested concentrations (**Figure 1**). This may be related to the possible difficulty of naproxen to interact with important residues of CD73, which were not considered in the screening. Furthermore, the compound did not alter the expression of CD73 in glioma and in peripheral lymphocites (4).

Table 1 - SHAFTS results using AB680 as reference compound.

Rank	Name	HybScore	ShapeScore	FeatureScore
1	Cladribine	1.026	0.7133	0.3128
2	Sulfacytine	0.9948	0.7337	0.261
3	Clofarabine	0.9785	0.7231	0.2555
4	Suprofen	0.9687	0.6927	0.2761
5	**Naproxen**	**0.9684**	**0.6727**	**0.2956**
6	Parecoxib	0.9647	0.7082	0.2566
7	Sulfamethazine	0.9647	0.7226	0.2421
8	Clomifene	0.963	0.7066	0.2565
9	Erlotinib	0.9557	0.6783	0.2774
10	**AMPCP**	**0.9551**	**0.7148**	**0.2403**

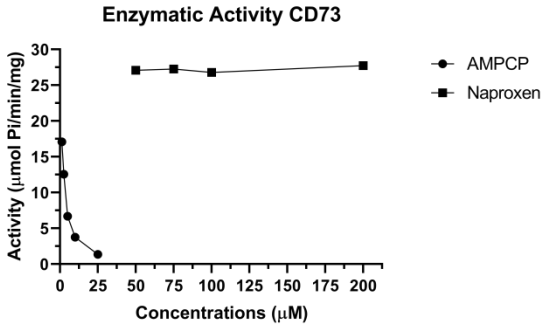

Figure SEQ Figura * ARABIC 1 - Enzymatic activity assay of naproxen in CD73

Conclusions

Although LBVS conducted by SHAFTS revealed RSK2 inhibitors (3), the screened compound naproxen did not show activity compared to AMPCP on the tested concentrations. These analyses may be considered exploratory, since they were based only on compounds' similarities and did not include target information (structural approach). Therefore, more studies and assays will be performed with other compounds and different approaches.

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