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In Silico Pharmacological Prediction of Substituted Aminonitriles †

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Abstract: Aminonitriles are heterocyclic compounds commonly used as intermediates in the synthesis of various compounds, but which have versatility in physiological processes, with peculiar characteristics and high biological value that still needs to be investigated with greater avidity. Given this perspective, the present study aimed to determine the probability of substituted aminonitriles interacting with classes of pharmacological targets in the human body. For this, 8 aminonitriles (HAN-1 to HAN-8) were synthesized and used in the in silico prediction of the compounds, using the Molinspiration software, where the potentiality of the substances to act as a G Protein Coupled Receptor (GPCR) ligand was evaluated, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor. Thus, it was observed that the molecules showed moderate bioactivity in 100% for GPCR ligand (−0.27 to −0.5), 87.5% as enzyme inhibitor (−0.33 to −0.49), 75% as a kinase inhibitor (−0.39 to −0.5), 62.5% as an ion channel modulator (−0.3 to −0.47) and as a protease inhibitor (−0.45 to −0.49) and 37.5% as nuclear receptor ligand (−0.43 to −0.46). The computational analysis carried out in this study indicated that the HAN-4 and HAN-6 molecules were the only ones that reached a considerable activity score for all classes of proposed pharmacological targets, thus being the most promising to be possible therapeutic tools, being necessary, yet, advances in studies, such as the performance of pre-clinical and clinical tests to verify its real bioactivity.

Keywords: in silico; aminonitriles; pharmacological targets; computer simulation

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1. Introduction

The in silico study is a revolutionary method of analysis that allows research without the need for an experimental laboratory, which facilitates the process of analyzing natural products and discovering new medicines [1]. In this context, high-performance computing and theoretical improvement have led to science to be investigated by the in silico method to design scenarios before carrying out physical experiments [2].

With regard to natural products, it is well known that such products and their structural analogues have historically made a great contribution to pharmacotherapy, especially for cancer and infectious diseases [3]. However, natural products also present challenges for drug discovery, such as technical barriers to screening, isolation, characterization and optimization [4].

One of the strategies to solve these challenges is through computational analysis, which consists of screening low molecular weight compounds against macromolecular targets, generally proteins, of clinical relevance. In this way, small molecular fragments can bind to one or more sites on the target and act as starting points for the development of lead compounds [5]. Furthermore, in recent years, several technological and scientific developments–including the in silico method–are opening up opportunities for drug analysis and discovery [4].

In this context, the use of aminonitriles, modified natural compounds that represent versatile and valuable building blocks in organic synthesis, stands out, given that they offer many reactivity options [6]. Indeed, natural products continue to be the main sources of bioactive compounds and drug candidates, not only because of their unique chemical structures, but also because of their overall favorable metabolism and pharmacokinetic properties and the number of natural products database accessible to the public has increased significantly in recent years [7].

Therefore, it is considered extremely important to evaluate the in silico bioactivities of natural products in order to improve the administration of these phytoconstituents. Therefore, this study aims to analyze the probability of substituted aminonitriles interacting with classes of pharmacological targets in the human body.

2. Materials and Methods

2.1. Molecules

8 aminonitriles were used: HAN-1 to HAN-8. The molecules were synthesized and provided in collaboration by professor Dr. Helivaldo Diogenes da Silva Souza from the Synthesis Laboratory at the Federal University of Paraíba.

2.2. Preparation of SMILE Codes

For compound analysis, molecule files were inserted in .pdb format and converted to SMILES (Simplified Molecular-Input Line-Entry System) format, which is a way of representing chemical structures using ASCII characters (American Standard Code for Information interchange). The conversion was carried out using the Discovery Studio program [8].

2.3. Analysis of Pharmacokinetic Parameters and Biological Targets

Molinspiration Molecule Viewer software (www.molinspiration.com) enables molecule perception by employing sophisticated Bayesian statistics, which combine the structures and properties of the representative compound active in the specific target with the structures of inactive molecules, to recognize substructure features typical of the active molecules. This program is capable of evaluating the molecule, providing several parameters, including the ability to predict the compound's probability of acting on certain pharmacological targets [9,10].

Furthermore, the software is capable of reporting important physicochemical parameters in predicting the theoretical oral bioavailability of the drug under study. These parameters are: total polar surface area (TPSA), partition coefficient (water/oil)-cLogP, molecular weight, number of hydrogen acceptors-nALH, number of hydrogen donors-nDLH [11,12].

To verify whether the substance can be planned to be administered orally, an analysis will be carried out based on the "Rule of Five", as described by Lipinski (2004). In this rule, if the molecule presents scores of at least 3 parameters meeting the requirements (TPSA < 140 A2; cLogP ≤ 5; molecular weight < 500 daltons; nALH ≤ 10; nDLH ≤ 5), the molecule will possibly present, theoretically, a good oral bioavailability.

3. Results

It has been shown that in silico analysis is an important scientific tool to expand pharmacological and toxicological studies of natural products, as it allows studies to be carried out without the need for a physical laboratory [13,14]

To obtain the molecular parameters TPSA (total polar surface area of the molecule), hydrophobicity (MLogP) and spatial volume (Vol), the Molinspiration software was used. The prediction results for aminonitriles obtained after analyzing the program can be seen in Table 1.

Table 1. Theoretical analysis of the physicochemical properties of aminonitriles using Molispiration software.

Compound	Physicochemical Properties [1]					
	TPSA	**nON**	**MlogP**	**Nv**	**nROTB**	**Vol**
HAN-1	35.82	2	3.16	0	3	201.54
HAN-2	35.82	2	3.61	0	3	218.10
HAN-3	45.05	3	3.22	0	4	227.09
HAN-4	35.82	2	4.67	0	4	251.49
HAN-5	35.82	2	3.84	0	3	215.08
HAN-6	65.28	4	2.50	0	4	235.10
HAN-7	35.82	2	4.06	0	3	234.66
HAN-8	45.05	3	4.04	0	5	260.45

[1] TPSA: área de superfície polar total; nON: Interação O/NH O-HN; nV: número de violação; nROTB: número de rotação; Vol: volume.

The potential similarity with other drugs or drug likeness of aminonitriles was calculated considering the MlogP (partition coefficient), molecular mass, number of heavy atoms, number of hydrogen acceptors, number of hydrogen donors, number of violations, number of bonds rotation and molecular volume. The potential biological targets were evaluated by calculating the activity index of GPCR ligands, ion channel modulator, nuclear receptor ligands, kinase inhibitor and enzyme inhibitor with the help of the software [9].

Regarding the computational analysis carried out with the aminonitrile molecules, Table 2 shows the targets related to the probability of interaction with the pharmacological targets GPCRL (GPCR ligand), ICM (ion channel modulator), KI (kinase inhibitor), NRL (nuclear receptor ligand), PI (protease inhibitor) and EI (enzyme inhibitor) tested in Molispiration.

Table 2. Probability of interaction with pharmacological targets of aminonitriles calculated using Molispiration software.

Compound	"Drug-Likeness" [a]					
	GPCRL	**ICM**	**KI**	**NRL**	**PI**	**EI**
HAN-1	−0.50	−0.48	− 0.54	−0.80	−0.59	−0.49
HAN-2	−0.48	−0.54	−0.51	−0.73	−0.58	−0.52
HAN-3	−0.40	−0.51	−0.42	−0.61	−0.49	−0.45
HAN-4	−0.27	−0.39	−0.35	−0.43	−0.35	−0.33
HAN-5	−0.42	−0.44	−0.47	−0.72	−0.56	−0.48
HAN-6	−0.30	−0.45	−0.30	−0.46	−0.45	−0.34
HAN-7	−0.40	−0.50	−0.42	−0.62	−0.49	−0.45
HAN-8	−0.38	−0.56	−0.41	−0.46	−0.45	−0.48

[a] "*Drug-likeness*": probability of compound interaction with the pharmacological target; GPCRL: GPCR ligand; ICM: ion channel modulator; KI: kinase inhibitor; NRL: nuclear receptor ligand; PI: protease inhibitor; EI: enzyme inhibitor.

Therefore, the probability of aminonitriles binding to certain pharmacological targets was investigated, which can help to understand how the molecule develops its biological activity and its toxic effects. To achieve this, Molinspiration performs calculations to predict possible bioactivities, providing a set of theoretical data that, when evaluated, can indicate some pharmacological targets of the chemical compounds under study.

According to this chemoinformatics platform, a calculated score above 0.00 suggests considerable biological activity for that specific target, while score values between −0.50 and 0.00 indicate moderate biological activity. to the target and, finally, a score below −0.50 suggests inactivity in relation to the pharmacological target considered [15].

It was observed that the molecules showed moderate bioactivity potential in 100% for GPCR ligand (−0.27 to −0.5), 87.5% as enzyme inhibitor (−0.33 to −0.49), 75% as a kinase inhibitor (−0.39 to −0.49), −0.5), 62.5% as an ion channel modulator (−0.3 to −0.47) and as a protease inhibitor (−0.45 to −0.49) and 37.5% as nuclear receptor ligand (−0.43 to −0.46).

In Table 2, it is possible to observe that all aminonitriles presented the targets GPCRL (gPCR ligand), ICM (ion channel modulator), KI (kinase inhibitor), NRL (nuclear receptor ligand), PI (protease inhibitor) and EI (enzyme inhibitor) are negative, that is, it has a low probability of interacting with these biological targets.

Next, the molecular properties of the aminonitriles were calculated according to the molecular descriptors using Lipinski's rule of five, in the Molinspiration software, as seen in Table 3.

Table 3. Theoretical analysis of the physicochemical properties of aminonitriles required for theoretical oral bioavailability compared to Lipinski–Molinspiration "Rule of Five" standards.

Compound	Parameters for Bioavailability Assessment [1]				
	TPSA	**nDLH**	**nALH**	**Da**	**cLogP**
HAN-1	35.82	1	2	208.26	3.16
HAN-2	35.82	1	2	222.29	3.61
HAN-3	45.05	1	3	238.29	3.22
HAN-4	35.82	1	2	250.34	4.67
HAN-5	35.82	1	2	242.71	3.84
HAN-6	65.28	2	4	254.29	2.50
HAN-7	35.82	1	2	236.32	4.06
HAN-8	45.05	1	3	266.34	4.04
Standard of the "Rule of the five" Lipinski	≤140	≤5	≤10	≤500	≤5

[1] nDLH: Number of hydrogen donors; nALH: Number of hydrogen acceptors; Da: Molecular mass; cLogP: Water:oil partition coefficient.

The analysis presents a rationale based on Lipinski's rule of five, whicestablishes structural parameters for predicting the oral bioavailability profile, which is added to the absorption and permeability of possible drugs and depends on five parameters: (1) number of groups hydrogen bond acceptors (nALH) less than or equal to 10; (2) number of hydrogen bond donor groups (nDLH) less than or equal to 5; (3) molecular mass (Da) less than or equal to 500 g/mol; (4) octanol-water partition coefficient (cLogP) less than or equal to 5; (5) total polar surface area (TPSA) less than or equal to 140 Å. Molecules that violate more than one of these rules present problems with bioavailability.

According to the results obtained in Molinspiration using Lipinski's "Rule of Five" (2004), it was possible to infer that all aminonitriles presented good theoretical oral bioavailability, since all physical-chemical parameters evaluated for these molecules presented within the cutoff point established by the Lipinski "Rule of Five" (Table 3).

Furthermore, several approaches have been developed to evaluate drug similarity of bioactive compounds based on topological descriptors, molecular structure fingerprints, or other properties such as molecular weight, water solubility, and cLogP [16].

4. Discussion

The aminonitriles analyzed showed moderate potential for interaction with the biological targets used in the computational analysis. The classes are representatives of different pharmacological targets used in the clinical treatment of different pathologies. The function of G protein-coupled receptors (GPCRs)–which represent the largest class of human membrane proteins and drug targets–depends on their ability to change shape, transitioning between distinct conformations. Determining the structural dynamics of GPCRs is, therefore, essential both for understanding the physiology of these receptors and for the rational design of GPCR-targeted drugs [17].

Regarding kinase inhibition, protein kinases are responsible for regulating a high number of signal transduction pathways in cells, through the phosphorylation of serine, threonine or tyrosine residues. Dysregulation of these enzymes is associated with several diseases, including cancer, diabetes and inflammation. For this reason, specific inhibition of tyrosine or serine/threonine kinases may represent an interesting therapeutic approach [18].

Furthermore, the bioactivity of the molecules through the inhibition of the GPCR enzyme can be used in future studies in an attempt to outline pharmacological strategies through this finding. In relation to kinase inhibition, aminonitrile molecules are strategies for developing drugs associated with diseases generated by the dysregulation of kinases, including cancer, diabetes and inflammation.

Regarding ion channel modulation (ICM), it is known that ion channels are important targets in the treatment of central nervous system pathologies, especially in the study of antiepileptic drugs (AEDs). It is well known that the role of Na+ and Ca+2 channels as targets of new AEDs and the participation of other receptors in this process have been widely discussed over the years and have been the subject of numerous studies [19].

Substituted aminonitriles, which present ion channel modulator (ICM) bioactivity, can be improved and used in future research related to this type of modulation.

Regarding protease inhibitors, it is known that they constitute molecular participants in the biochemical duel against pathogenic microorganisms. In the treatment of patients with HIV (human immunodeficiency virus), the current triple regimen uses reverse transcriptase and protease inhibitors, which have been shown to be effective in reducing the number of circulating viruses (viral load), leading to an increase in CD4 T lymphocytes, improving immunity, with consequent control of associated diseases [20].

Therefore, aminonitrile molecules can be thought of through the inhibition of proteases as possible defense mechanisms to combat pathogens that require proteases for development.

As for Nuclear Receptors (NRs), it is known that they are proteins that regulate gene transcription, being important targets for drug design. NRs are formed by four domains, the most essential of which is the Ligand Binding Domain (LBD), responsible for the selective recognition of ligands and activation of their function. When aminonitriles bind to nuclear receptors, they can be considered for the development of therapeutic strategies that act on these types of receptors [21].

5. Conclusions

The computational analysis carried out in this study indicated that the HAN-4 and HAN-6 molecules were the only ones that reached a moderate activity score for all classes of proposed pharmacological targets, thus being the most promising as possible therapeutic tools, being necessary, even, advances in studies, such as carrying out pre-clinical and clinical tests to verify its real bioactivity.

Therefore, the molecules showed potential to inhibit the GPCR enzyme; kinase inhibition that can be evaluated for the development of drugs associated with diseases generated by the dysregulation of kinases, including cancer, diabetes and inflammation; ionic

modulation; inhibition of proteases to combat pathogens and therapeutic strategies that act on nuclear receptors.

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