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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 need 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, eight 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, an ion channel modulator, a kinase inhibitor, a nuclear receptor ligand, a protease inhibitor and an enzyme inhibitor was evaluated. Thus, it was observed that the molecules showed moderate bioactivity in 100% of cases as a GPCR ligand (−0.27 to −0.5), 87.5% as an 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 molecules that reached a considerable activity score for all classes of proposed pharmacological targets, thus being the most promising as possible therapeutic tools, with further advances in studies on the performance of pre-clinical and clinical tests to verify their real bioactivity still being necessary.

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

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1. Introduction

In silico studies represent 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 the use of in silico methods 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 in silico methods—have opened 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 in databases 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

Eight 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, accessed on 28 August 2023) 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 the total polar surface area (TPSA), the partition coefficient (water/oil) (cLogP), the molecular weight, the number of hydrogen acceptors (nALH), and the number of hydrogen donors (nDLH) [11,12].

To verify whether the substance can be planned to be administered orally, an analysis was carried out based on the "Rule of Five", as described by Lipinski (2004). According to this rule, if the molecule presents scores of at least 3 parameters meeting the requirements (TPSA < 140 A2; cLogP $\leq$ 5; molecular weight < 500 daltons; nALH $\leq$ 10; nDLH $\leq$ 5), the molecule possibly presents, 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: total polar surface area; nON: O/NH O-HN Interaction; nV: violation number; nROTB: rotation number; Vol: volume.

The potential similarity to other drugs or the 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 rotations and molecular volume. The potential biological targets were evaluated by calculating the activity index of GPCR ligands, ion channel modulators, nuclear receptor ligands, kinase inhibitor sand enzyme inhibitors 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.

Therefore, the probability of aminonitriles binding to certain pharmacological targets was investigated, which can help us 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 in relation 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% of cases as a GPCR ligand (−0.27 to −0.5), 87.5% as an enzyme inhibitor (−0.33 to −0.49), 75% as an 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).

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.

In Table 2, it is possible to observe that all aminonitriles representing 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, demonstrating that the compounds have 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 Cheminformatics 2023 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, which establishes 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) the number of groups hydrogen bond acceptors (nALH) being less than or equal to 10; (2) the number of hydrogen bond donor groups (nDLH) being less than or equal to 5; (3) the molecular mass (Da) being less than or equal to 500 g/mol; (4) the octanol–water partition coefficient (cLogP) being less than or equal to 5; and (5) the total polar surface area (TPSA)

being 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 were below the cutoff point established by the Lipinski "Rule of Five" (Table 3).

Furthermore, several approaches have been developed to evaluate the 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, the 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 with 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 the number of CD4 T lymphocytes, improving immunity, with the 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 the 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, with further advances in studies, such as carrying out pre-clinical and clinical tests to verify their real bioactivity, still being necessary.

Therefore, the molecules showed potential to act in the inhibition of the GPCR enzyme; in kinase inhibition, which that can be evaluated for the development of drugs associated with diseases generated by the dysregulation of kinases, including cancer, diabetes and inflammation; in ionic modulation; in the inhibition of proteases to combat pathogens; and in therapeutic strategies that act on nuclear receptors.

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