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Short communication

Synthesis and study of 2-aminobenzimidazole arylhydrazones as potential antineoplastic agents with antioxidant action

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Introduction

The administration of antioxidants is a leading strategy in the prevention and treatment of health disorders resulting from decreased antioxidant capacity. The prolonged exposure to oxidative stress is a key factor in cancer development because it damages cellular structures and impairs cellular functions related to DNA mutations, gene instability and cellular proliferation (Heyes et al., 2020). It is known that the reactive oxygen species (ROS) act as a secondary precursor in the intracellular signaling pathway that induces and maintains the oncogenic phenotype of cancer cells. The increased generation of ROS is characteristic for cancer cells where changes in the signal transduction are observed. The oxidative stress induces cellular redox imbalance that can be observed in different types of cancer cells compared to normal cells. The redox imbalance is related to oncogenic stimulation. These are among the reasons why antioxidants are a useful instrument in the fight against cancer.

Many benzimidazoles have found application in the medical treatment of cancer as neoplastic agents such as *Nocodazole, Bendamustine, Dovtinib,* and *Hoechst 33342*. 2-Aminobenzimidazole heterocycle can be seen as a structural fragment in different biologically active molecules and is of main importance as a precursor for the synthesis of novel benzimidazoles with antitumor activity (Dimov et al., 2021). A considerable number of benzimidazole derivatives containing hydrazone fragments have been studied and they have shown high activity against different cell lines: L1210, CEM, HeLa and Mia Paca-2 (Onnis et al., 2016). Additionally, benzimidazole hydrazones show promising properties as inhibitors of tubulin polymerization. The microtubules are protein biopolymers which form as a result of the polymerization of the heterodimers of α- and β-tubulins. Disruption of the microtubules could induce cell cycle arrest which makes them attractive targets in anticancer therapy.

The scientific data demonstrating a connection between oxidative stress and the processes of carcinogenesis directs the design and synthesis of compounds with antioxidant properties as potential antineoplastic agents to be of current scientific priority. Currently, we are presenting the synthesis of a series of 2-aminobenzimidazole-arylhydrazone hybrids as potential drug candidates with antitumor and antioxidant activity. Additional studies beyond this short communication will clarify the capability to affect the tubulin polymerization.

Materials and methods

Chemistry

All synthetic chemicals and reagents were obtained from Sigma-Aldrich (Germany) and Alfa Aesar (Germany). The progress of the reactions was monitored using thin layer chromatography (TLC) on Merck precoated plates (silica gel. 60 F254, 0.25 mm) and visualized by fluorescence quenching under UV light (254 nm). As mobile phase 4:1 benzene/methanol system was used.

General procedure for the synthesis of 3,4-dihydrobenzo(4,5)imidazo(1,2-a)pyrimidin-2(1H)-one (**1**)

To a solution of 2-aminobenzimidazole (0.0038 mol) in dry THF were added anhydrous K_2CO_3 (0.0076 mol) and TBAB (0.0011 mol). Then ethyl 2-bromopropionate (0.0076 mol) was added dropwise and by cooling the reaction mixture. The suspension was vigorously stirred

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for 12 h at room temperature. The reaction completion was evidenced by TLC. The product obtained in its hydrobromide form was converted to the free base by adding water to the mixture and extracting with chloroform. Yield 80%.

General procedure for the synthesis of 3-(2-amino-1H-benzo(d)imidazol-1-yl)propanehydrazide (**2**)

To a suspension of **1** in ethanol an excess of hydrazine hydrate was added and the reaction was refluxed for 2 h. The white precipitate was filtered and washed with ethanol. Yield 90%.

General procedure for the synthesis 3-(2-amino-1H-benzo(d)imidazol-1-yl)-N'-substituted benzylidenepropanehydrazide (**3-8**)

To a solution of the hydrazide 2 (0.1 g, 1.0 equiv) in absolute ethanol the respective substituted aldehyde (1.0 equiv) was added, and the solution was refluxed for 2-6 h. The products were recrystallized from ethanol. Yield 60 – 80%.

Results and Discussion

The cyclic benzimidazole pyrimidinone product **1** was obtained under solid-liquid phase transfer catalysis (PTC) using anhydrous potassium carbonate and tetrabutyl ammonium bromide as a catalyst in a 1:2:2 ratio with a high yield of 80%. The product underwent hydrazinolysis with an excess of hydrazine hydrate. The six target hydrazones were obtained by the condensation of the obtained hydrazide **2** with various aldehydes: 2,3-dihydroxy, 2,4-dihydroxy, 3,4-dihydroxy-, 2-hydroxy-4-methoxy-, 3,4,5-trimetroxybenzaldehyde, and piperonal. The structure and purity of the compounds were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra.

Potential drug-candidates should possess a favorable pharmacokinetic profile, *i.e*. sufficient bioavailability and ability to be transported through different membranes and reach the target receptor binding site, optimal metabolization and elimination profile. A preliminary evaluation of the molecular properties including lipophilicity, molecular size, flexibility and presence of a hydrogen donor and acceptors could provide useful information and such was done using the SwissADME tool (Daina et al., 2017). The data indicated that all of the 2-aminobenzimidazole hydrazones had zero violations of the Lipinski rule. The molecular weights (MW) ranged between 330 and 394 g/mol. Low MW (< 500) signifies that the molecules could easily pass through the cell membranes and such substances favor oral absorption. The parameter LogP (n-octanol/water partition coefficients) has a key role in the oral absorption as well as the drug-target interactions. The values of LogP of compounds **3**-**8** were less than five, in accordance with the Lipinski rule, in the range 1-2 suggesting higher hydrophilicity. The topological polar surface area (TPSA) represents the sum of all polar atoms (oxygen and nitrogen atoms and the hydrogens attached to them). It is another significant physico-chemical parameter important for drug transport and absorption. A high gastrointestinal absorption was predicted, as the TPSA values were in the range 103.76-125.76 Å^2 (lower than 140 Å^2). The flexibility of the molecules is indicated by the number of rotatable bonds. The parameter is related to the oral bioavailability and efficient binding to receptors. The rotatable bonds in all the hydrazones are between 6-9, therefore a good bioavailability is expected.

Conclusion

In conclusion, a small series of new and promising 2-amino benzimidazole arylhydrazones containing substituents of various hydroxy-, methoxybenzaldehydes and piperonal have been synthesized. Next *in vitro* studies of the cytotoxic effects on different cancer cell lines and the ability to modulate the tubulin polymerization will be carried out. Also, their ability to scavenge free radicals will be investigated.

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