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Synthesis and anticancer evaluation of new heterocyclic compounds designed as phenstatin analogues

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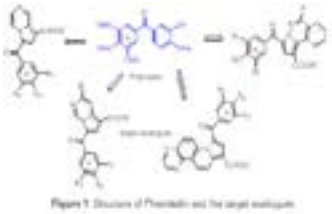
In the past decades, considerable efforts and research have been focused on the design and development of new anticancer drugs with improved efficiency, limited toxicity and less susceptibility to develop multidrug (MDR) resistance. Among the huge variety of structures synthesized and tested as anticancer agents in the last years, phenstatin stands as one of the most potent tubulin polymerization inhibitors binding to the colchicine site of the tubulin and thus, interfering with the equilibrium dynamics associated with the cell division process. Because of the structural simplicity of this compound, it continues to be a target for the design in anticancer therapy, the recent literature being rich in pharmacomodulators of Phenstatin. Inspired by a recent report in which by the replacement of 3-hydroxy-4-methoxyphenyl ring of Phenstatin with indolizine derivatives, the authors obtained compounds showing an interesting cytotoxic activity, we decided to synthesize new analogues containing different fused heterocycles in substitution of the 3-hydroxy-4-methoxyphenyl ring of Phenstatin (ring A), in order to evaluate their anticancer properties. Pyrrole is a therapeutically active moiety exploited in recent years for the synthesis of diverse derivatives with various biological activities (antimalarial, antitubercular, antitumor, antioxidant, enzyme inhibiting properties). Pyrrole derivatives are also found in a variety of biological contexts as part of co-factors and natural products. The fusion of two or more heterocycle rings result in different classes of compound, and fused heterocycles containing a pyrrole ring showing a broad range of properties including biological activity. Considering all these above data we describe here the synthesis and evaluation of the cytotoxicity of new analogues of phenstatin, bearing different fused pyrrolo-heterocycle systems (in substitution of 3-hydroxy-4-methoxyphenyl ring) combined with either a 3,4,5-trimethoxyphenyl ring, 3,5-dihydroxyphenyl or a 3,4-dihydroxyphenyl ring. The new phenstatin analogues were tested for their anticancer activity at the National Cancer Institute (NCI) by screening against 60 human tumor cell lines panel.



Recent Publications

1. Gholap S S (2016) Pyrrole: an emerging scaffold for construction of valuable therapeutic agents. European Journal of Medicinal Chemistry 110:13-31.
2. Ghinet A, Abuhaie CM, Gautret P, Rigo B, Dubois J et al. (2015) Studies on indolizines: Evaluation of their biological properties as microtubule-interacting agents and as melanoma targeting compounds. European Journal of Medicinal Chemistry 89:115-127.
3. Jahnz-Wechmann Z, Framski G, Januszczyk P and Boryski J (2015) Bioactive fused heterocycles: Nucleoside analogs with an additional ring. European Journal of Medicinal Chemistry 97:388-396.
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Biography

Ramona Danac obtained her PhD in Organic Chemistry from the Alexandru Ioan Cuza University of Iasi, Romania, working in the field of N-heterocycles (especially in field of 1,10-phenanthroline) compounds with bioactive, electrical or optical properties. Her research career continued with a Postdoctoral Marie Curie Intraeuropean Fellowship at University of Oxford, UK, working in the field of Sugar Chemistry. In 2001, she joined the Department of Chemistry, Faculty of Chemistry from at Alexandru Ioan Cuza University of Iasi, as a Teaching Assistant. In 2013 she occupied the position of Associate Professor at the same department. Her research is focused on the synthesis and structural and functional analysis of heterocyclic compounds, medicinal chemistry and supramolecular chemistry.

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