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Abstract

Microwave Assisted Synthesis of Pyridophenoxazinones, a class of Powerful Antiproliferative Compounds

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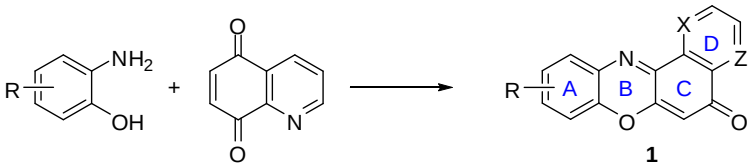
Chemotherapy is the most common treatment of cancer that consists of the use of antineoplastic drugs to destroy cancerous cells. Traditional drugs used in chemotherapy act especially on the cell duplication processes. They are non-specific and cause many undesired concurrent effects on the healthy cells. For this reason, during the last decade, the oncological research has focused on the multimodal therapy, a combination of anticancer treatments acting simultaneously on different biological domains, able to inhibit proliferation of tumor cells present in different phases of the cell cycle(1)**.** In order to obtain new antiproliferative compounds good for acting through the forementioned mechanisms, including DNA intercalation and topoisomerase inhibition, our attention was focused on the derivatives of pyridophenoxazinone (PPH, **1** R=H) system, an iminoquinone containing a planar tetracyclic system suitable for intercalating DNA G-C base pairs in a site specific mode(2).
Namely, we designed, after molecular modeling calculations, PPH carboxyamide derivatives holding at C-9 and C-10 positions an amino acidic chain or a sugar.
Unfortunately, the real obstacle to the availability of such molecule was represented by their synthesis. Therefore, in our opinion it seems to be worthwhile to report a new microwave (μW) assisted synthetic procedure to prepare PPH carboxyamides. In order to assess the validity of our method, we applied the procedure to the synthesis of variously substituted PPHs **1** and received evidence that microwave irradiation enables the preparation of those compounds in high yields and short reaction times.



1

X = N, Z = CH or X = CH, Z = N
R = H, CH_3, CO_2H, NO_2, Cl, Br, F

(1) Hardman, J.G.; Limbird, L.E.; Molinoff, P.B.; Ruddon, R.W. Gilman, A.G. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th ed. 1225-1278, McGraw-Hill, New York.
(2) Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Mazzoni, O.; Novellino, E.; Barone, V.; Pani, A.; Tramontano, E.; La Colla, P.; Murgioni, C.; Serra, I.; Setzu, G.; Loddo, R. *J.Med. Chem.* **2002**, *45*, 5205-5216.