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Synthesis of New Coumarin-1,2,3-triazole-oxadiazole Hybrids as Anti-Cancer Agents

Kiana Fahimi [1,*], Tahmine Akbarzadeh [1,2], Maryam Mohammadi-Khanaposhtani [1], Elahe Karimpour-Razkenari [2]

[1] *Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran*

**Corresponding author: Kiana Fahimi, Department of Medicinal Chemistry, Faculty of Pharmacy, Teran University of Medical Sciences, Tehran, Iran. E-mail: kiana.fahimi@gmail.com*

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Abstract

Introduction: Cancer is the second most common cause of death after heart disease. In this respect, chemotherapy which is the use of medicines or drugs to treat cancer has attracted lots of attention. However, reported side effects has encouraged medicinal chemists to design and synthesize new and effective cytotoxic agents. For this purpose, heterocyclic compounds such as coumarins, 1,2,3-triazoles, and oxadiazoles have shown satisfactory cytotoxicity. It seems that hybridization of these skeletons would be more effective agents. In this work, we focused on the design, synthesis, and evaluation of novel coumarin-1,2,3-triazole-oxadiazoles as anticancer agents.

Materials and Methods: Synthesis of the title compounds was performed through three main steps: I) preparation of oxadiazole scaffold by the reaction of benzonitrileand hydroxylamine hydrochloride in presence of NaOH in ethanol; reaction of the latter derivatives with chloroacetyl chloride in presence of K2CO3 in acetone; then, the cyclization reaction of the obtained products in refluxing toluene. II) Reaction of various hydroxycoumarins with propargylbromide in the presence of K2CO3 and KI in acetone. III) Click reaction between derivatives obtained in steps II and III based on the procedure described by Sharpless et al. Next, all compounds were evaluated for their capacity of cytotoxicity against human breast cell lines.

Results: The structure of all derivatives was confirmed by using IR and NMR spectroscopy.All compounds were evaluated for their anticancer activity against three human breast cancer cell lines including MCF-7, T-47D, and MDA-MB-231. They showed moderate activity and among them, 4-((1-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)-2H-chromen-2-one was the most active compound comparing with etoposide as the standard drug.

Conclusions: The results revealed that designed coumarin-1,2,3-triazole-oxadiazole hybrids would be effective anticancer agents and the presence of chlorine on the aromatic ring connected to oxadiazolemoiety plays an important role in the cytotoxicity.