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Synthesis, Characterization of Ibuprofen N-Acyl-1,3,4-Oxadiazole Derivatives and Anticancer Activity against MCF-7 Cell Line

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ABSTRACT
Purpose: To synthesis and investigate the anti- cancer activity of some ibuprofen-oxadiazole derivatives as a molecular hybrid model.
Method: Five derivatives of Ibuprofen-Oxadiazole have been synthesized from ibuprofen through several steps to obtained and identified the final derivatives by analytical techniques, FTIR, 1HNMR and elemental analysis. All the derivatives were evaluated for their anticancer activity by MTT assay. The possibility to improve the physical properties of ibuprofen and also give an additional biological activity, so our research was an application of this idea. The synthesized derivatives were studied theoretically, and some chemical parameters were calculated using the PM3 method to study the stability of derivatives IV (a-e).
Results: showed that the synthesized derivatives revealed promising in vitro cytotoxicity.
Conclusion: The molecular hybrid system of ibuprofen-oxadizole has demonstrated additional biological effectiveness for ibuprofen.
Keywords: Oxadiazole, Ibuprofen, Hybrid molecule, anticancer, Ibuprofen-1,3,4-oxadiazole.
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INTRODUCTION

Over the last few years, the molecular hybridization technique has emerged as a novel approach involving the confluence of two or more pharmacophores in a single molecular scaffold for the creation of multifunctional hybrid molecules[1].

These molecules may be further modified to demonstrate beneficial pharmacokinetics and bioavailability for oral use. Several research groups invented and synthesized multiple synthetic molecules using this approach[2]. Although, Ibuprofen (IBU) is the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects [3, 4]. The frequent medication of IBU, however, is well known to cause serious gastrointestinal damage, like other NSAIDs[5]. A possible way to solve this problem is to derivatize the carboxylic functional group of the IBU to a combination or hybrid with another molecule, heterocyclic moiety such as oxadiazole ring.

Oxadiazole is Heterocyclic ring containing one oxygen and two nitrogen atoms in a five-member ring have been investigated for a long time because of their important medicinal properties [6]. In the last few decades, the chemistry of five-membered heterocyclic rings has received considerable attention owing to their synthetic and effective biological importance, therefore derivatives of 1,3,4–oxadiazole have been found to possess a wide spectrum of biological activities[7-10]. They are also useful intermediates in organic synthesis [11-14] and widely employed as electron-transporting and hole-blocking materials [15]. Further, 1,3,4-oxadiazole heterocycles are very good bioisosteres of amides and esters, which can contribute substantially to increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors [16].

Given the great medicinal significance and material applications, several synthetic routes have been developed for oxadiazole conjugated with another biological molecule, so ibuprofen conjugated with oxadiazole to investigate the possible biological activity. The majority of them are based on the preparation acid hydrazide from aromatic acid and converted to hydrazone derivative, followed by direct cyclization by acetic anhydride as dehydration agent. The antiproliferative effect of ibuprofen on different cancer cell line was studied [17].

MATERIALS AND METHODS

Materials

All chemicals were of commercial-grade, used without further purification and were obtained from Sigma-Aldrich Chemical Co. (Germany). Melting points were carried out by the open capillary tube method using an Electrical melting point-Stuart the SMP30 United Kingdom, and they are uncorrected. Elemental Microanalyses were recorded using C.H.N. analyzers Eager 300 for EA 1112, Tehran University. Infrared Spectra were recorded on FT-IR spectrophotometer SHIMADZU 8100s Japan, and expressed in wavenumber (cm^{-1}), using potassium bromide discs, Basrah University, Pharmaceutical Department.^{1}H NMR spectra were carried out using a Varian Inova (USA)500 MHz spectrophotometer, Tehran University. The chemical shifts were expressed in δ ppm units using tetramethylsilane as the internal standard. The exchangeable protons were exchanged by D_2O. All reactions were monitored by thin-layer chromatography Silica gel/TLC with fluorescent indicator 254 nm; layer thickness 0.2 mm; 20 × 20 cm aluminium cards were used. Ethyl acetate: n-hexane (3:7), ethanol: dioxane (1:1) and methanol: chloroform (1:9) was the adopted solvent system.