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Review article

An insight into the biological activities of heterocyclic–fatty acid hybrid molecules

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ABSTRACT

Heterocyclic compounds are the interesting core structures for the development of new bioactive compounds. Fatty acids are derived from renewable raw materials and exhibit various biological activities. Several researchers are amalgamating these two bioactive components to yield bioactive hybrid molecules with some desirable features. Heterocyclic–fatty acid hybrid derivatives are a new class of heterocyclic compounds with a broad range of biological activities and significance in the field of medicinal chemistry. Over the last few years, many research articles emphasized the significance of heterocyclic–fatty acid hybrid derivatives. The present review article focuses the developments in designing and biological evaluation of heterocyclic-fatty acid hybrid molecules.

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1. Introduction

Heterocyclic compounds are the cyclic compounds in which one or more ring carbon atoms are replaced by non-carbon atom. The non-carbon atoms in such rings are referred to as hetero atoms. Nitrogen, oxygen and sulfur are the most common heteroatoms, however, heterocyclic rings containing other hetero atoms are also known. These are the important class of organic compounds that have been used for many important medicinal and synthetic chemistry applications. Heterocycles are present in variety of drugs, vitamins, natural products, biomolecules and biologically active compounds, including antibacterial [1,2], antifungal [3], antiviral [4], antiinflammatory [5], and antitumor drugs [6–8]. Also, they have been frequently found as a key structural motif in pharmaceuticals and agrochemicals. Heterocyclic structures having the ability to synthesize various compounds based on core structure and screen against a variety of biological activities which provide several active compound leads. Therefore, more combinations of heterocyclic structures can be designed, resulting in new structures

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with expected biological properties.

Fatty acids are the carboxylic acids formed from the cleavage of fats and oils derived from natural sources. Fatty acid is a long chain aliphatic carboxylic acid, which is in general either saturated or unsaturated. Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from 4 to 28. Fatty acids are usually derived from triacylglycerols or phospholipids. These fatty acids have been used to produce pharmacologically interesting compounds through simple transformations. However, there are some literature reports about the presence of cyclopropene, cyclopentene-based unusual fatty acids and also long chain fatty acids and their derivatives are known for their antimicrobial [[9a-c] and [10]], antifungal [11], and pesticidal [12] activities. Literature reports revealed that a variety of modified fatty acids are promising molecules in the treatment of cancers [13–15]. Fatty acid analogues have been found to be associated with diverse biological activities such as antiinflammatory [16], antioxidant [17], antifeedant [18], antiparasitic [19], antimicrobial [20] and neuroprotective [21]. These fatty acid derivatives were chosen as they are more environmentally benign, less toxic, and more cost effective.

It is a well known strategy that molecular combinations derived from two biologically active molecules can result in novel hybrid molecules with enhanced biological activities. Keeping in view the biological activities of heterocycles and fatty acids, the combination of these two molecules could result in potential novel heterocyclic–fatty acid hybrid derivatives with improved biological activities. This review deals with the biomedical importance of synthetic heterocyclic–fatty acid hybrid derivatives in order to enlarge the variety of interesting compounds and to open up a new potential for renewable raw materials. The different types of interesting heterocycles are presented below. (see Figs. 1–80).

2. Biological activities of heterocyclic–fatty acid hybrid derivatives

2.1. Anticancer activity

Ahmad et al. [22] synthesized a long chain substituted 1, 3, 4-oxadiazol-2-thione, 1, 2, 4-triazol-3-thione and 1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazine derivatives and reported their *in vitro* antitumor activity against three human cancer cells such as human hepatocellular carcinoma (Hep3 B), human breast adenocarcinoma (MCF 7) and human cervical carcinoma (HeLa) and PBMCs by MTT assay. All the tested compounds showed moderate to good cytotoxicity against different human cancer cell lines and particularly C_{10} terminal alkenyl fatty acid chain containing compounds, **1a** (IC_{50} value = 8.94 μM against Hep3 B cells), **2a** (IC_{50} value = 9.2 μM against Hep3 B cells) exhibited potent activity against human hepatocellular carcinoma cell. In this study, integration of the 1, 3, 4-thiadiazine ring with the 1, 2, 4-triazole ring having C_{10} terminal alkenyl fatty acid chain derivative **3a** (IC_{50} values = 7.4 μM against Hep3 B cells), 10.3 μM against MCF 7 cells, 8.01 μM against HeLa cells showed an increase in cytotoxicity against all the cancer cell lines. The derivatives **3b** (IC_{50} values of 6.5 μM against Hep3 B cells, 8.59 μM against MCF 7 cells, 8.83 μM against HeLa cells), **3c** (IC_{50} values of 7.36 μM against Hep3 B cells, 8.8 μM against MCF 7 cells, 6 μM against HeLa cells) exhibited antiproliferative activity due to the presence of fused ring system and hydroxyl group on the alkenyl fatty acid substituent. Anticancer activity results of this study revealed that the synthesized compounds are non-toxic to the normal human cells and can be used safely for the treatment of cancer without damaging normal cells. The structural activity study also showed that anticancer activity is also dependent on the nature of fatty acid chain and the heterocyclic ring system.

Yang et al. [23] reported the synthesis of novel aliphatic amido-quaternary ammonium salts based on the structural characteristics of lead compound (NSC126188) and evaluated for their biological activities. Structure activity relationship (SAR) study of these derivatives was carried out based on their Ras homolog gene family, member B, (RhoB) activation using promoter assays and *via* assessment of antiproliferative activities in several human cancer cell types. In this investigation, compounds **4a** [GI_{50} = 0.29 μM against PC-3 (prostate cancer)], **4b** [GI_{50} = 0.31 μM against PC-3 (prostate cancer) and 0.42 μM against NUGC- 3 (gastric cancer)] and **4c** [GI_{50} = 0.48 μM against PC-3 (prostate cancer) and 0.29 μM against NUGC- 3 (gastric cancer)] exhibited potent antiproliferative activity and showed the ability to induce reporter expression in the RhoB promoter-based assay. Among all the compounds, **4d** [GI_{50} = 0.37 μM against PC-3 (prostate cancer) and 0.27 μM against NUGC- 3 (gastric cancer)] emerged as the most promising anticancer agent, exhibiting potent inhibition of cancer cell growth and stimulation of apoptosis. Compounds having a carbon chain length in the range of 14–18 generally exhibited a more robust effect than perifosine on growth inhibition against PC-3 (prostate cancer), NUGC- 3 (gastric cancer) cell types. Results suggest that these novel aliphatic amido-quaternary ammonium salts may be promising chemotherapeutic anticancer agents.

Jubie et al. [24] synthesized and evaluate the anticancer activity

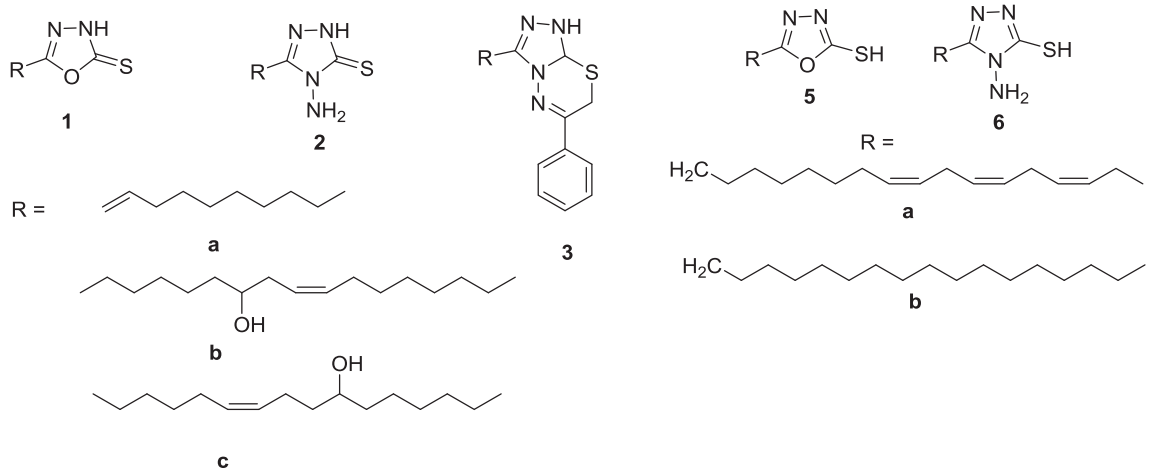

Fig. 1. Chemical structures of oxadiazole, triazole and triazolothiadiazine-based anticancer agents [22,24].

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