Saudi Pharmaceutical Journal 25 (2017) 873–883

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Synthesis, molecular modeling and anticancer activity of new coumarin containing compounds

Shaimaa A. Morsy, Abdelbasset A. Farahat *, Magda N.A. Nasr, Atif S. Tantawy

Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy Mansoura University, Mansoura 35516, Egypt

ARTICLE INFO

Article history:
Received 3 October 2016
Accepted 8 February 2017
Available online 10 February 2017

Keywords:
Coumarin
Triazole
Oxadiazole
Thiadiazole
Anticancer

ABSTRACT

A series of new coumarin containing compounds were synthesized from 4-bromomethylcoumarin derivatives **2a, b** and different heteroaromatic systems **4a-e, 6a-d, 8, 10** *via* methylene thiolinker. Twenty-four compounds were screened biologically against two human tumor cell lines, breast carcinoma MCF-7 and hepatocellular carcinoma HePG-2, at the national cancer institute, Cairo, Egypt using 5-fluorouracil as standard drug. Compounds **5h, 7d, 7**h, **9a, 13a** and **13d** showed strong activity against both MCF-7 and HepG-2 cell lines with being compound **13a** is the most active with IC_{50} values of 5.5 μg/ml and 6.9 μg/ml respectively. Docking was performed with protein 1KE9 to study the binding mode of the designed compounds.

© 2017 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Uncontrolled cellular proliferation, mediated by dysregulation of the cell-cycle machinery and activation of cyclin-dependent kinases (CDKs) to promote cell-cycle progression, lies at the heart of cancer as a pathological process (O'Leary et al., 2016)

CDKs are key regulatory kinases of the cell cycle (Morgan, 1997). They regulate different phases of cell cycle by binding to distinct regulatory subunit called a cyclin (Abdel Latif et al., 2016). The importance of CDKs in cell division process directed the attention of the medicinal chemists towards the use of them as a potential targets in the treatment of human cancer (Meijer et al., 1999).

Many molecules were found to be CDK specific ATP-competitive inhibitors and few of them have progressed into human clinical trials as flavopiridol compound **I** (Fig. 1) which is a coumarin derivative (Senderowicz et al., 1998 and Sedlacek et al., 1996).

Coumarins are bioactive compounds of both nature and synthetic origin and there has been a growing interest in their synthesis due to their useful and diverse pharmaceutical and biological activities (Salem et al., 2016).

Several heterocyclic compounds containing coumarin ring are associated with diverse pharmacological properties as anti-inflammatory (El-Haggar and Al-Wabli, 2015), antimicrobial (Shi and Zhou, 2011), antiviral (Tsay et al., 2013) and antitumor (Leonetti et al., 2004; Seidel et al., 2014; Jacquot et al., 2007). Moreover, coumarins bearing substitution at 4-position are known to exhibit different biological activities including antiproliferative activity against liver carcinomas ex. compound **II** (Neelgundmath et al., 2015) and compound **III** (Benci et al., 2012) and breast carcinoma as compound **IV** (Bana et al., 2015) and compound **V** (Kini et al., 2012) (Fig. 1). Coumarin itself also exhibited cytotoxic effects against Hep2 cells (human epithelial type 2) in a dose dependent manner and showed some typical characteristics of apoptosis with loss of membrane microvilli, cytoplasmic hypervacualization and nuclear fragmentation (Mirunalini et al., 2014).

Many compounds bearing five-membered heterocyclic rings in their structure have an extensive spectrum of pharmacological activities, among them 1,2,4-triazole,compound **VI** (Park et al., 2009) and **VII** (Reddy et al., 2014),1,3,4-oxadiazole,compound **VIII** (Zhang et al., 2011) and 1,3,4-thiadiazole,compound **IX** (Rashid et al., 2015) have attracted considerable interest as they all showed anticancer activity against various cancer cell lines (Fig. 1).

Based on the previous information we designed and synthesized a series of new coumarin containing compounds where the coumarin ring is substituted at position 4 with different five and

* Corresponding author.
E-mail address: abdelbastahmed@yahoo.com (A.A. Farahat)
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2017.02.003
1319-0164/© 2017 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

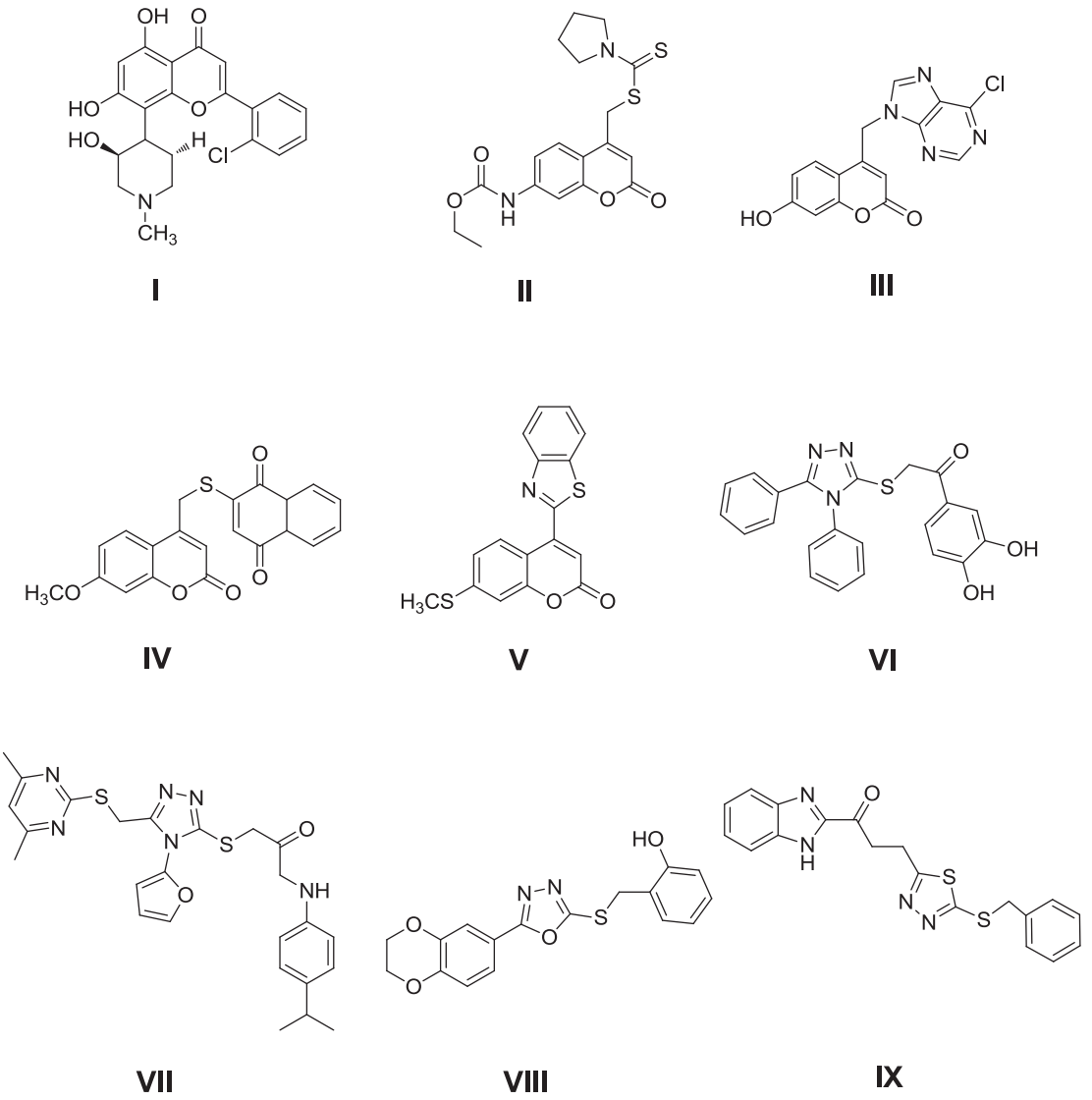

Fig. 1. Structures of anticancer active agents (**I-IX**).

six member heterocycles *via* a methylene thiolinker to test the anticancer effect of these new structure combinations against MCF-7 and HepG-2 cell lines (Fig. 2).

2. Results and discussion

2.1. Chemistry

Scheme 1 illustrates the synthesis of the final compounds **5a-j, 7a-h, 9a, b**. Ethyl 4-bromoacetoacetate **1** was obtained *via* bromination of ethyl acetoacetate using molecular bromine in ether at room temperature (Sousa et al., 2012). This bromo compound was allowed to go through Pechmann condensation with the phenol derivatives **2a, b** in concentrated sulfuric acid to afford the intermediates 4-bromomethylcoumarin derivatives **3a, b** (Khan et al., 2012 and Basanagouda et al., 2014). The triazole derivatives **4a-e** (Kusmeierza et al., 2014; Malbec et al., 1984; Sandstrom and Wennerbeck, 1966) and oxadiazole derivatives **6a-d** (Charistos et al., 1994) were synthesized using the appropriate substituted phenyl hydrazide and phenylisothiocyanate or carbon disulfide, respectively while compound **8** (Kashtoh et al., 2014) was prepared applying the same procedure using hydrazine hydrate and carbon disulfide. The final compounds **5a-j**, **7a-h**, **9a, b** were obtained in good yield after the reaction of the 4-bromomethylcoumarin derivatives **3a, b** with various thiol containing heteroaromatics **4a-e, 6a-d** and **8** in acetone utilizing potassium carbonate as a base

The synthesis of different pyrimidine-5-carbonitril derivatives **13a-d** was described in Scheme 2. The first part of this scheme involved the preparation of the pyrimidine thiol **10** through condensation of benzaldehyde with thiourea and ethyl cyanoacetate according to the reported procedure (Shaquiquzzaman et al., 2012). Alkylation of compound **10** with the bromomethylcoumarin derivative **3a** in tetrahydrofuran using triethylamine as a base afforded the intermediate alkylsulfanyl pyrimidine carbonitrile **11**, which was subsequently halogenated by the reaction with phosphorous oxychloride to give the reactive chloro intermediate **12**. The chloro group in compound **12** was replaced with different aliphatic and aromatic amines in ethanol to afford the final compounds **13a-d** in good yield.

2.2. Antitumor activity

Twenty-four newly synthesized compounds were tested for their cytotoxic activity against human breast cancer cell line (MCF-7) and hepatocellular carcinoma cell line (HepG-2) using

Download English Version:

https://daneshyari.com/en/article/5551438

Download Persian Version:

https://daneshyari.com/article/5551438

Daneshyari.com