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Research paper

Synthesis and biological evaluation of new curcumin analogues as antioxidant and antitumor agents: Molecular modeling study

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ABSTRACT

New curcumin analogues have been synthesized and their antioxidant activities were investigated by measuring their free radical scavenging capacities. The *in vitro* and *in vivo* antitumor activities of the synthesized compounds on Ehrlich ascites carcinoma (EAC) cell line were evaluated. 4-(4-Chlorophenyl)-2-(5-ethyl-7-(4-methoxybenzylidene)-3-(4-methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-2-yl)thiazole **7h** showed excellent antineoplastic activity in both *in vitro* and *in vivo* studies more than that of tested compounds and reference drug, cisplatin. Different molecular modeling studies were performed, where docking of compound **7h** into telomerase active site suggested that it could exert its antitumor potential by telomerase inhibition.

1. Introduction

Despite significant progress achieved in anticancer therapy, high systemic toxicity and drug resistance remain a major challenge for contemporary medicine in the management of cancers. Chemotherapy causes severe side-effects, which may be due to its cytotoxic effect on normal cells [1]. Therefore, it is important that anticancer drugs display antiproliferative and cytotoxic activity in tumor cells without affecting normal tissues. Reactive oxygen species (ROS) have been linked with cancer, coronary heart disease, and neurodegenerative diseases. Furthermore, their presence in the body causes damage to the DNA of cells. Antioxidants exert their effects by scavenging or preventing the generation of ROS, thus can protect against the formation of free radicals and retard the progress of many chronic diseases, including cancer [1].

Curcumin **(A)** is one of the most potent and multi-targeting phytochemicals against a variety of cancers. The cancer preventive capability of curcumin is linked to its direct antioxidant ability to eliminate free radicals and to reduce oxidative stress [2]. However, the clinical application of curcumin has been significantly limited by its instability and poor metabolic property. A number of synthetic modifications of curcumin have been studied intensively in order to develop a molecule with enhanced bioactivities. A number of curcumin analogues have partial structural resemblance to curcumin motif but are appended with different pharmacophores for targeting proteins that are crucial for survival of tumor cells in question. For example, monocarbonyl 5-carbon spacer, curcumin analogues having cycloalkanone or piperidone central motifs **(B)** were reported to exert good antioxidant and antitumor activities [3,4].

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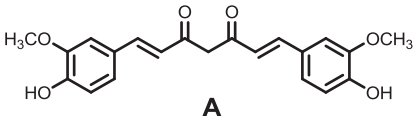
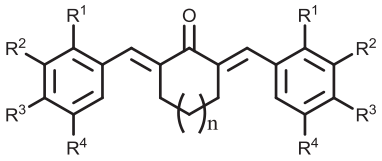
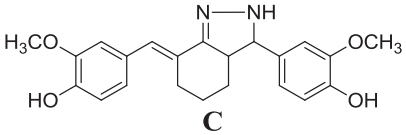


A

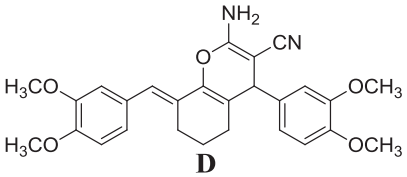


B

Our previous study also showed the incorporation of the shortened carbon linker in heterocyclic parts as hexahydro-2*H*-indazole ring **(C)** and tetrahydro-4*H*-chromene ring **(D)** and reported their promising activities [4].



C



D

Telomere is a non-coding DNA sequence, repeating (5′-TTAGGG-3′), located at the ends of the chromosomes. It functions by preventing chromosomes from losing base pair sequences at their ends. Telomerase, a reverse transcriptase, has been found to be activated in more than 80% of human cancers and, therefore, can be considered as a potential marker for tumorigenesis [5]. Several studies comprising a variety of mechanistic approaches, like mutations and RNA interference of the telomerase enzyme activity, provided the proof of concept for this form of cancer treatment [6–8]. Telomerase provides a good target not only for cancer diagnosis, but also for the development of novel therapeutic agents [9]. Regulation of telomerase activity of cancerous cells by curcumin was estimated and found beneficial to human beings [10,11].

Drug design in the area of cancer therapeutics has used curcumin and its analogues for developing a trend toward more precise mechanisms of cancer cell destruction [12]. So in our research program for novel antitumor agents, we designed and synthesized a series of curcumin analogues based on chalcone scaffold. We chose chalcone moiety as it represents an important pharmacophore of both natural products and synthetic precursors that were found to possess our beseeched biological activity, including antioxidants, and antitumor activities. Recently there is a strong link between curcumin cancer potential and telomerase inhibition [11–18]. So it was quite interesting to make *in silico* study on the most active antitumor curcumin analogue to investigate the mechanistic way for its antiumor potential, and compare it against the least active one.

2. Results and discussion

2.1. Chemistry

The reaction sequences employed for synthesis of the target derivatives are illustrated in Schemes 1–3.

2.1.1. Synthesis of compounds 3 and 4 (Scheme 1)

Thiocarbamoyl pyrazole derivatives **3a,b** were obtained by refluxing equimolar amounts of thiosemicarbazide and the corresponding chalcone **2a,b** in hot ethanolic NaOH solution. The reaction involved nucleophilic attack of the amino group on the polarized carbonyl group, followed by intramolecular cyclization. The spectral and microanalytical data of the formed products were consistent with their structures. The amino functional group was observed at 3280–3463 cm^{-1} in the IR spectra. The evidence for the formation of 4,5-dihydropyrazole ring was obtained from ^{1}H NMR spectrum which provided the diagnostic tool for the positional elucidation of protons. The geminal pyrazoline protons at C4 appeared in the region of 3.20–4.10 ppm as doublet of doublets in all compounds. In addition, CH proton at C5 also appeared as doublet of doublets in the region of 6.10–6.23 ppm due to vicinal coupling with the two non-magnetically equivalent geminal protons of C4. ^{13}C NMR spectrum of compound **3a** confirmed its proposed structure, since the C4 and C5 of pyrazoline ring resonated at 45.11 and 70.20 ppm, respectively. Moreover, the aforementioned compounds **3a,b** were cyclized to pyrazolothiazole derivatives **4a,b** through reaction with phenacyl bromide in ethanol. Analytical and spectral data of the prepared compounds **4a,b** were in agreement with the proposed structure.

2.1.2. Synthesis of compounds 5–8 (Scheme 2)

The key chalcone intermediates **5a–d** were synthesized through condensation of *p*-methoxybenzaldehyde with different cyclic ketones in accordance with the method described in the literature [3]. Heating at reflux equimolar amounts of thiosemicarbazide and the key chalcones **5a–d** in ethanol in the presence of NaOH afforded the corresponding 1-thiocarbamoyl pyrazole derivatives **6a–d**. The thiocarbamoyl moiety in the latter compounds was cyclized to 4-(substituted phenyl)thiazole ring, affording compounds **7a–h** in a good yield. The structures of the new compounds **7a–h** were confirmed using ^{1}H NMR spectra which revealed the presence of 5-H of thiazole in the aromatic region. Moreover, ^{13}C NMR for compound **7c** confirmed the proposed structure due to the appearance of a characteristic peak at δ169.20 corresponding to C_2 of thiazole. In addition, compounds **8a–d** were obtained by the reaction of 1-thiocarbamoyl pyrazole derivative **6b** with chloroacetic acid and different aromatic aldehydes in ethanol. The spectral and microanalytical data of compounds **8a–d** were consistent with their structures. For example, IR spectrum of compound **8a** showed a strong absorption band at 1696 cm^{-1} due to carbonyl group. In addition, ^{13}C NMR confirmed the proposed structure due to the appearance of a signal at 165.11 ppm for the carbonyl group as well as a signal assignable to C2 of thiazole at 160.21 ppm.