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Synthesis, molecular docking, antimicrobial, antioxidant and toxicity assessment of quinoline peptides

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ABSTRACT

A series of quinoline based peptides were synthesized by a one-pot reaction through Ugi-four component condensation of lipoic acid, cyclohexyl isocyanide, aniline derivatives and 2-methoxy quinoline-3-carbaldehyde derivatives under microwave irradiation. The products were obtained in excellent yields and high purity. Solvent optimization and the effect of microwave irradiation with various powers were also observed. All the synthesized compounds were characterized by FTIR, NMR spectral data and elemental analysis. A total of eight peptides were subjected to antimicrobial, antioxidant and toxicity evaluation. Among them, four peptides showed potential towards antibacterial screening with *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis* and *Candida albicans*, *Candida utilis* and three peptides showed antioxidant test positive (DPPH). Besides, toxicity of all the peptides were evaluated by using brine shrimp and it was observed that four peptides showed mortality rate less than 50% up to 48 h. Molecular docking studies revealed that the higher binding affinity of the two peptides toward DNA gyrase than ciprofloxacin based on Libdock score. The described chemistry represents a facile tool to synthesize complex heterocycles of pharmaceutical relevance in a highly efficient and one-pot fashion. The advantages of this method are its green approach, inexpensive solvent, shorter reaction times and excellent yields.

1. Introduction

Microbial infections are one of the leading diseases which are responsible for millions of deaths every year because of lack of effective antimicrobial therapy and this situation becomes more complicated because of microbial resistance towards conventional antibiotics [1]. Occurrence of the antibiotic resistance pathogen has become a severe health issue and thus, numerous studies have been stated to improve the current antimicrobial therapies. It is known that over 70% of bacterial infections are resistant to one or more of the antibiotics that are generally used to eradicate the infection [2]. Recently, bioactive peptides have received close scientific attention for their broad scope of bioactivities, mainly including antioxidation, antihypertensive, anticancer, and antimicrobial properties. Peptides open up new perspectives in drug design by providing an entire range of highly selective and nontoxic pharmaceuticals. With growing applications of their synthesis and bioactivity, considerable attention has been focused on the research of peptide-based derivatives [3].

One-pot multi-component reactions (MCRs) are simple and efficient synthetic routes for sustaining diverse heterocycles. These reactions are straight forward one-step transformations which offer significant advantages over conventional linear type synthesis due to its flexible, convergent and atom efficient nature [4]. Among multicomponent condensation reactions, the Ugi reaction [5] is a highly convergent for the rapid generation of organic druglike molecule libraries and many different types of biologically active targets [6]. The Ugi four component reaction (Ugi-4CR) in which an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide combine to yield α-N-acylaminoamide [7] is particularly attractive because of the wide range of products obtainable through variation of the starting materials.

Quinoline is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities such as anti-inflammatory [8], antimalarial [9], antimicrobial [10], anticonvulsant [11], antineoplastic [12], vasorelaxing [13], antiproliferative [14] and platelet derived growth factor receptor tyrosine kinase inhibiting agents [15] which can be well illustrated by the large number of drugs in the market. Ugi four-component derivatives have also been found to have various applications (viz., anesthetics, antibiotics, natural product isolation, HIV protease inhibitor crixivan, [16–18] etc.). Therefore, it is of significance to develop novel

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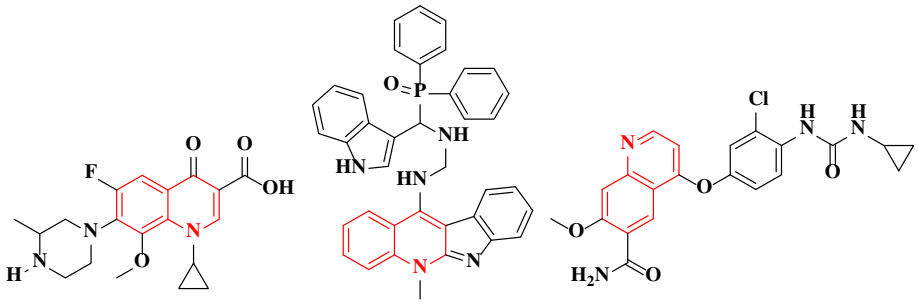

Fig. 1. Some typical examples of biologically active quinolines.

preparations for Ugi-4CR having a quinoline nucleus.

Compounds such as Neocryptolepine, Gatifloxacin and Lenvatinib (Fig. 1) are effective against Gram-positive and Gram-negative organisms, [19]. They inhibit the bacterial enzyme DNA gyrase [20] and are multi-kinase inhibitors for various types of cancer [21]. There is enough evidence that the pharmacological activity is due to the compounds intercalating between the base pair of DNA and interferes with normal functioning of the enzyme topoisomerase II which is involved in the breaking and releasing of DNA strands [22]. The interaction of peptides and nanoparticles with DNA constitutes a significant area of research which has attracted considerable attention from biochemists: studies have shown that they are related to the development of new DNA reagents for biotechnology and medicine [23–25]. The important pharmacological applications and essential quinoline ring system has sparked more interest in preparing new quinoline peptide conjugates.

Traditionally, the Ugi reaction was performed at room temperature or under reflux in methanol with reaction times up to 12–24 h or more using several catalysts [26–29]. However, most of these methods employ long reaction times and moderate yields of products are produced. Recently, a new, simple, and elegant synthesis of Ugi-4CR has been described using ionic liquids and water [30,31]. In view of the remarkable importance from pharmacological, industrial, and synthetic points of view, we report the one-pot synthesis of potentially biological active peptides via the Ugi-4CR under microwave irradiation within the framework of green chemistry protocol. Also, the antimicrobial, antioxidant and toxicity were evaluated: molecular docking of the novel peptides is presented.

2. Experimental

2.1. Materials and Methods

All chemicals were purchased from Sigma-Aldrich and used without further purification. Solvents used were of synthesis grade. CEM discover microwave reactor was used for reaction. Melting points were determined by Stuart SMP10 and are uncorrected. The IR spectra were recorded on Perkin Elmer 537 spectrophotometer instrument, using ATR disc and the absorption frequencies were expressed as ν_{max} cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on BRUKER 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in hertz. The progress of the reaction was monitored by TLC using aluminium plates with silica gel (Sigma-Aldrich). The Mass spectra were recorded by Waters Micromass LCT Premier TOF-MS. The elemental analyses (C, H, N) were obtained from a Perkin Elmer precisely 2400 analyser. The bacterial and yeast strains include *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis* and *Candida albicans*, *Candida utilis* were used in the present study and were collected from the culture collection at the Department of Biotechnology and Food Technology, Durban University of Technology, South Africa.

2.2. General Procedure for the Ugi Reaction

A mixture of arylamine (1 mmol), quinoline carbaldehyde (1 mmol), lipoic acid (1.5 mmol) and cyclohexyl isocyanide (1.5 mmol) was dissolved in MeOH (15 mL) and the reaction mixture was taken in a microwave tube (35 mL). The reaction tube was placed into a CEM microwave discover synthesizer and irradiated at 120 W with the temperature of 110 °C for 15 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to attain room temperature. The solvent was removed under vacuum, and the residue was purified by column chromatography (eluent ethyl acetate: petroleum ether, 25%) to give the corresponding Ugi product.

2.3. Synthesis of quinoline peptides through Ugi-4CR under microwave irradiation (**5a-5h**)

2.3.1. N-(2-(cyclohexylamino)-1-(2-methoxyquinolin-3-yl)-2-oxoethyl)-5-((R)-1,2-dithiolan-3-yl)-N-phenylpentanamide (**5a**)

IR ν_{max} (cm^{-1}): 1600 C═N, 1325 C–N, 2970 CH, 1493 C═C, 1625 C═O, 722 C–S, 3416 NH. ^1H NMR: (400 MHz, $CDCl_3$) δ (ppm) 7.88 (1H, s, Ar–H), 7.78 (1H, d, J = 8.32 Hz, Ar–H), 7.59 (2H, t, J = 1.32 Hz, Ar–H), 7.57 (1H, d, J = 2.28 Hz, Ar–H), 7.32 (2H, d, J = 8.56 Hz, Ar–H), 7.30 (1H, s, Ar–H), 7.12 (2H, d, J = 6.8 Hz, Ar–H), 6.35 (1H, s, CH), 5.90 (1H, d, J = 8.4 Hz, N–H), 4.09 (3H, s, OCH_3), 3.88 (1H, m, CH), 3.52 (1H, m, CH), 3.12–3.05 (2H, m, CH_2), 2.39–2.24 (2H, m, CH_2), 2.05 (2H, m, CH_2), 2.09 (2H, m, CH_2), 1.90–1.88 (2H, m, CH_2), 1.67–1.65 (2H, m, CH_2), 1.62 (2H, m, CH_2), 1.60–1.58 (2H, m, CH_2), 1.37–1.35 (2H, m, CH_2), 1.25 (2H, m, CH_2), 1.11 (2H, m, CH_2). ^{13}C NMR: (100 MHz, $CDCl_3$) δ (ppm) 177.24, 173.67, 168.72, 159.85, 145.84, 140.46, 139.84, 130.05, 128.91, 128.23, 127.85, 126.53, 124.56, 124.27, 119.01, 58.65, 56.38, 56.31, 53.94, 48.78, 40.22, 38.50, 38.43, 34.60, 33.60, 32.87, 32.84, 28.78, 25.49, 25.07, 24.84, 24.49. TOF-MS m/z: Calculated: 577.80 $[M]^+$, Found: 600.23 $[M + Na]^+$, 577.25 $[M]^+$. Elemental Analysis: Anal. Calc. for $C_{32}H_{39}N_3O_3S_2$: C, 66.52; H, 6.80; N, 7.27; %. Found: C, 66.54; H, 6.81; N, 7.25; %.

2.3.2. N-(2-(cyclohexylamino)-1-(2-methoxyquinolin-3-yl)-2-oxoethyl)-5-((R)-1,2-dithiolan-3-yl)-N-(o-tolyl)pentanamide (**5b**)

IR ν_{max} (cm^{-1}): 1625 C═N, 1360 C–N, 2949 CH, 1434 C═C, 1683 C═O, 764 C–S, 3456 NH. ^1H NMR: (400 MHz, CD_3OD-d_4) δ (ppm) 7.96 (1H, s, Ar–H), 7.90 (1H, d, J = 7.8 Hz, Ar–H), 7.69 (2H, t, J = 10.4 Hz, Ar–H), 7.53–7.50 (1H, m, Ar–H), 7.27 (1H, t, J = 7.32 Hz, Ar–H), 7.11 (1H, t, J = 7.68 Hz, Ar–H), 6.98 (2H, t, J = 9.28 Hz, Ar–H), 6.57 (1H, s, NH), 6.14 (1H, s, CH), 4.02 (3H, s, OCH_3), 3.32 (1H, m, CH), 3.12–3.10 (2H, m, CH_2), 3.10–3.07 (2H, m, CH_2), 2.44–2.37 (2H, m, CH_2), 2.32 (1H, t, J = 7.2 Hz, CH), 1.98–1.96 (2H, m, CH_2), 1.95 (2H, s, CH_2), 1.87–1.83 (2H, m, CH_2), 1.63–1.62 (2H, m, CH_2), 1.61–1.60 (2H, m, CH_2),1.60–1.58 (2H, m, CH_2), 1.32–1.30 (2H, m, CH_2), 1.29–1.28 (2H, m, CH_2), 1.11–1.09 (3H, m, CH_3). ^{13}C NMR: (100 MHz, $CDCl_3$) δ (ppm) 159.32, 159.29, 146.40,