Journal of Saudi Chemical Society (2017) **21**, S153–S162

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

A microwave-assisted facile synthesis of novel coumarin derivatives containing cyanopyridine and furan as antimicrobial agents

N.C. Desai *, H.M. Satodiya, K.M. Rajpara, V.V. Joshi, H.V. Vaghani

Division of Medicinal Chemistry, Department of Chemistry, UGC NON-SAP & DST-FIST Sponsored Department, Maharaja Krishnakumarsinhji Bhavnagar University, Mahatma Gandhi Campus, Bhavnagar 364 002, India

Received 17 March 2013; revised 19 November 2013; accepted 11 December 2013
Available online 13 January 2014

KEYWORDS

Microwave-assisted synthesis;
Coumarin;
Cyanopyridine;
Antimicrobial agents

Abstract In this paper, we have described the microwave-assisted method for the synthesis of novel 4-(substitutedphenyl)-2-(furan-2-ylmethyleneamino)-6-(2-oxo-2*H*-chromen-3-yl)nicotinonitriles (**5a**–**m**). Compound (I) 3-acetyl-2*H*-chromen-2-one was reacted with aromatic aldehydes, malononitrile and ammonium acetate in microwave conditions afforded compounds **3a**–**m**, which on further microwave irradiation at 300 W for 8–10 min in the presence of trace amount of $ZnCl_2$ furnished **5a**–**m**. Structures of synthesized compounds have been confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. Antimicrobial activity of the compounds was studied against several bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*) and fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus*) by using the serial broth dilution method. Five compounds **5d**, **5f**, **5j**, **5k** and **5l** were found to possess high activity comparable to ampicillin at 50 μg/ml against *E. coli* and *P. aeruginosa*.

1. Introduction

There is an urgent need for a new class of antimicrobial agents having new and diverse structures from those of existing agents due to the development from resistance and adverse reactions toward existing antimicrobial drugs. Coumarin is an important privileged structure for the development of antimicrobial agents and Novobiocin is a shining example (Fig. 1). There are a number of reports which show that natural and synthetic coumarin derivatives possess antimicrobial activity [2,11]. Novobiocin and chlorobiocin have been established as antimicrobials containing a coumarin skeleton [5]. The biological effects of coumarins include anti-inflammatory [1], anti-HIV [20] and anti-tumorigenic [16]. Coumarins having pyridine substitution at C3 are reported to have interesting biological activity. Many 3-(2-pyridyl)coumarins and 3-(3-pyridyl)coumarins are known for their useful bioactivities viz. antifungal [12] and bactericidal [19] activities. In addition, Schiff bases

* Corresponding author. Tel./fax: +91 278 2439852.
E-mail address: dnisheeth@rediffmail.com (N.C. Desai).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2013.12.005

incorporated heterocycles which are important class of compounds in the medicinal and pharmaceutical field [10,17,3,15]. On the basis of previous work of our group [8,9], Schiff bases of various heterocyclic compounds showed biological properties including antibacterial and antifungal [6]. In continuation to this, we have reported the synthesis and antimicrobial activity of 4-(substitutedphenyl)-2-(furan-2-ylmethyleneamino)-6-(2-oxo-2*H*-chromen-3-yl)nicotinonitriles (**5a**–**m**). The coumarin nucleus in these compounds is attached to pyridine moieties at C3 position and second position of pyridine ring has been linked with furfural ring via Schiff base.

In the present communication, we have focused on microwave-assisted synthesis because this technique has gained popularity over non-conventional techniques for the rapid synthesis [21,7,4,18]. With the help of this technique many researchers have accelerated organic synthesis and since last couple of years a large number of research papers have appeared in the scientific journals. This has proved the utility of microwave-assisted synthesis in various branches of chemistry. Microwave-assisted organic synthesis may be helpful to increase the yield, decrease the reaction time and minimize the formation of hazardous by-products. With the help of this technique solvent free reactions can be easily carried out for eliminating toxicity and flammability issues which are a major concern with classical solvents. Considering these facts and several applications of microwave in organic and pharmaceutical chemistry we report here microwave-assisted synthesis and antimicrobial activity of 4-(substitutedphenyl)-2-(furan-2-ylmethyleneamino)-6-(2-oxo-2*H*-chromen-3-yl)nicotinonitriles. The structures of compounds synthesized were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. These compounds were evaluated for their antibacterial and antifungal screening on different strains of microorganism.

2. Experimental

2.1. Materials and physical measurements

Melting points are determined on an electro thermal melting point apparatus and are reported uncorrected. Completion of reaction and purity of all compounds are checked on aluminum coated TLC plates 60 F_{245} (E. Merck) using n-hexane: ethyl acetate (8:2 V/V) as the mobile phase and visualized under ultraviolet (UV) light, or iodine vapor. Elemental analysis (% C, H, N) is carried out by a Perkin–Elmer 2400 CHN analyser. IR spectra of all compounds have been recorded on a Perkin–Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR and ^{13}C NMR spectra are recorded on a Bruker (400 MHz) and (100 MHz) spectrometer, respectively, using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Anhydrous reactions are carried out in oven-dried glassware in nitrogen atmosphere. Microwave-assisted reactions were carried out in a Synthos-3000.

2.2. Preparation methods and physical data of synthesized compounds

2.2.1. General procedure for the synthesis of 2-amino-4-(substitutedphenyl)-6-(2-oxo-2H-chromen-3-yl)nicotinonitrile derivatives (*3a*–*m*)

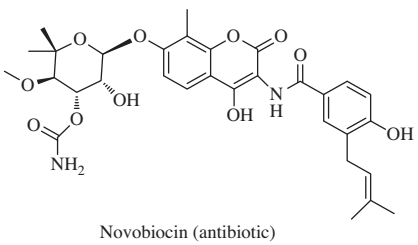
A mixture of 3-acetyl-2*H*-chromen-2-one (1) (2 mmol), malononitrile (2 mmol), substituted aromatic aldehydes (2 mmol) (**2a**–**m**) and ammonium acetate (8 mmol) in ethanol (99.5%) (10 mL) was introduced into microwave reaction vessel equipped with a magnetic stirrer. The vessel was sealed and the reaction mixture was irradiated by 350 W for 6–10 min at 130 °C and performed twice successively. The formed solid was filtered, washed with cold methanol and crystallized from methanol/chloroform (1:1).

2.2.2. General procedure for the synthesis of 4-(substitutedphenyl)-2-(furan-2-ylmethyleneamino)-6-(2-oxo-2H-chromen-3-yl)nicotinonitriles (*5a*–*m*)

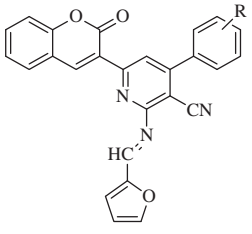
A mixture of compounds **3a**–**m** (3 mmol), 2-furfuraldehyde (3 mmol), acetic acid (10 mL) and catalytic amount of $ZnCl_2$ was introduced into reaction vessel equipped with a magnetic stirrer. The vessel was sealed and the reaction mixture was irradiated by 300 W for 8–10 min at 100 °C. The completion of the reaction was monitored by TLC (n-hexane: ethyl acetate, 3:7). The reaction mass was cooled to room temperature and neutralized with ammonium hydroxide to obtained a solid product. The resultant solid was filtered and washed with chloroform and methanol/water (1:1), respectively.

2.2.3. 2-Amino-6-(2-oxo-2H-chromen-3-yl)-4-phenylnicotinonitrile (*3a*)

This was obtained as light yellow solid; yield: 85%, m.p. 170–172 °C. IR (KBr, cm^{-1}): v 3117 (N–H stret., primary amine), 2220 (CN), 1688 (C═O, stret.), 1645 (C═N), 1598 (–N–H bending), 1519–1512 (C═C), 1260 (C–O–C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H, C_4 proton of coumarin), 8.09 (s, 1H, C_5 proton of pyridine), 7.58–7.80 (m, 5H, phenyl ring), 7.41–7.55 (m, 4H, C_5, C_6, C_7 and C_8 proton of coumarin), 6.90 (s, 2H, –NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ



Novobiocin (antibiotic)



R= Different substituents

Structure of synthesized compound **(5a-m)**

Figure 1 Structural similarity between targeted compound and commercially available drugs.