Synthesis and Antibacterial Evaluation of Benzopyran Derivatives Based on Microwave-Mediated Molecular Cyclization

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Summary: Almost all of synthetic strategies of benzopyran derivatives suffer from some drawbacks such as multistep sequence, time consuming and expensive purification processes, by-products, low product yields, or longer reaction time. So we recently reported an efficient method that three new benzopyran derivatives were synthesized, 2-amidogen-3-phenylsulfonyl-4-tolyl-4H-benzochroene(4A), 2-amidogen-3-phenylsulfonyl-4-nitrophenyl-4H-benzochroene (4B) and 2-amidogen-3-phenylsulfonyl-4-ethylphenyl)-4H-benzochroene(4C) by the multicomponent reaction （MCR）of 1-naphthol , aromatic aldehydes and benzenesulfonyl acetonitrile s via solvent-free using piperidine as catalyst. This method has many advantages, such as high yield, wide range of substrates, simple experiment, short reaction time, and easy availability of raw materials. The prepared product was characterized and confirmed by ^{1}H NMR, HR-ESI-MS and ^{13}C NMR. At the same time, the antibacterial evaluation of three benzochromene derivatives was further screened for minimum bactericidal concentration.

Keywords: MCR, Reaction yields, Antibacterial evaluation, Minimum bactericidal concentration.

Introduction

Heterocyclic compounds, especially benzopyrans, are natural and synthetic compounds with important biological activities, including oxygen-containing molecules with antitumor, antibiotic and antioxidant properties. As a matter of fact, chromatin structure is an important pharmacophore, which can prevent cancer, cataract and coronary heart disease for its physical and chemical properties [1-3]. The literature also shows that tryptophan and benzotryptophan contain broad-spectrum active pharmacophore. They have antibacterial [4-7], hypolipidemic [8], antioxidant [9, 10], analgesic [11] and other effects.

There are many ways to synthesize benzochromene compounds, such as (MCR) [12-14] (Fig. 1), heterogeneous catalytic method [15], electrocatalytic process [16], microwave [17, 18] and ultrasonic technology [19], etc. Due to its inherent molecular diversity, efficiency and atom economy, the MCR has molecular diversity, high efficiency and economy. It is a synthetic fusion and powerful tool for heterocycles [20-23]. At the same time, The microwave assisted method can accelerate the reaction in organic synthesis , increase the purity of products , streamline the reaction process , and obtain better product yields [24].

As a comparison , Sachin Shinde [25] reported a very similar reaction of 2-amidogen-4H-chromene derivatives under classical conditions . The synthesis shows more environmental and facile. However , the results show that the reaction should take a long time and a more complex reaction procedure.

MCRs have proven to be a powerful tool for the synthesis of bioactive compounds and drug candidates from simple and readily available starting materials [26-29]. Due to their inherent molecular diversity, efficiency, and economy, MCRs are powerful tools for the fabrication of fused heterocyclic rings [30]. The desired product is produced at a high yield under simple and mild reaction conditions. These characteristics make MCRs very suitable for the easy construction of various heterocyclic scaffolds. In this context, as part of our research program for the synthesis of bioactive molecules by multi-component one-pot reaction , we report an efficient one-pot combination method for the preparation of benzopyran derivatives. Finally, the synthesized compounds were confirmed by three characterization methods of ^{1}H NMR , HR-ESI-MS and ^{13}C NMR.

The high circumstance of the persistence of

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diverse microorganisms to most of the antibacterial agents has been drawn a significant consideration . The international organization for world health organization and food, agriculture, and animal health organization haveclarified the drastic menace affected by antibacterial-persistent infective organisms to animal and human safety [30]. At the same time, the antibacterial evaluation of three benzochromene derivatives was further screened for minimum bactericidal concentration.

Experimental

Materials

1-naphthol (CAS: 90-15-3, ≥ 99.0% purity) , p-Tolualdehyde (CAS: 104-87-0, ≥ 97.0% purity) , 4-Ethylbenzaldehyde (CAS: 4748-78-1, ≥ 97.0% purity) , 4-Nitrobenzaldehyde (CAS: 555-16-8, ≥ 99.0% purity) , Benzene sulfonyl acetonitrile (CAS: 7605-28-9, ≥ 99.0% purity) , and piperidine (CAS:110-89-4, ≥99.5% purity) , were provided by Sigma (Shanghai, China) . The rest of the chemical products were supplied by Sinopharm Group (Beijing , China) . All other chemicalsused were of analytical grade .

General instrumentation details

We used Bruker DMX 500 spectrometer to record ^{1}H NMR and ^{13}C NMR spectra, which the chemical shifts (d) are reported in parts per million (ppm) and the value of J is in Hertz (Hz) . Aglient 6550 iFunnel Q-TOF was used for high-resolution mass spectrometry analysis . We used microwave reactor (MAS-II) for auxiliary heating in the synthesis. The melting point was mesured by X-4 digital display melting point meter.

Preparation of benzopyran derivatives

The reaction conditions of benzopyran derivative 4 (A-C) are the same as 4A. In order to synthesize 4A , we firstly added 1-naphthol (1) , 4-methylbenzaldehyde (2) and phenylsulfonyl acetonitrile (3, 1.0 mmol) to the three neck flask. The quantity of the above three ingredients is 1.0 mmol. Secondly, we added solvent ethanol (2 mL) to the three neck flask . And the obtained mixture was heated under microwave irradiation (80℃, 5 min). Subsequently cooled to room temperature after reaction (TLC monitoring) . The resulting product was rinsed with ethanol to obtain 4A. The synthesis of 4B and 4C was carried out according to the above operation . The characterization results of 4A , 4B and 4C are shown in the complementary material.

Determination of minimum inhibitory concentration

Staphylococcus aureus (*S. aureus* ATCC 29213) and *Escherichia coli* (*E. coli* ATCC 25922) were activated in Tryptic Soy Broth (TSB) medium and incubated at under aerobic conditions (37℃, 24 h). All the microorganisms came from ATCC . Broth dilution was used to evaluate the antimicrobial activity and minimum inhibitory concentration (MIC) of 4 (A-C) according to the M7-A6 reference guidelines of the Association of Clinical and laboratory standards (CLSI) [31]. Compound 4 (A-C) was dissolved in DMSO: H_2O (2: 8,V/V) to an initial concentration of 500 μg/mL. Two consecutive dilutions were performed to obtain the concentrations of 1.95 to 250 μg/mL described in ref [32].

Result and Discussion

The synthesis mechanism of 4(A-C)

The synthesis mechanism of 4 (A-C) is clarified (Fig . 2). Firstly, the adduct A1 was formed by the condensation reaction between benzene sulfonyl acetonitrile 3 and acetaldehyde 2. Next , the Michael reaction between the knoevenagel product A1 and 1 produces the intermediate A2. And then you get A3 by cyclization of an intermolecular N-intermediate. Finally, the target compound 4 was obtained by imine enamine tautomerism.

Synthetic products analysis

Initially, 4A was synthesized in the presence of piperidine, and 1 (1-naphthol) , 2a and 3 (benzenesulfonyl acetonitrile) reacted in three components in ethanol (Scheme 1). The reaction mixture was composed of 1, 2a and 3 in a ratio of 1: 1: 1. The experiment was carried out under microwave irradiation in ethanol as solvent for 5min. The yield of the reaction was 92.5%. The preparation method of benzopyran derivatives 4B and 4C is the same as 4A. Analysis of synthetic products is shown in Table 1. The detailed information on the characterization of synthetic products can be found in the supporting information .

Assessment of minimum inhibitory concentration (MIC)

The antibacterial activity of benzopyran derivative 4 (A-C) revealed that the maximum antibacterial activity was observed against S. aureus and E. coli. The bioactivity evaluation of benzopyran derivative 4 (A-C) was shown in table 2. These outcomes demonstrate that benzopyran derivative 4 (A-C) display relatively efficient antibacterial activity against *S. aureus* and *E. coli* at the highest

concentration (250μg/mL) , and the MIC ranged from 9.8 to 15.6 μg/mL , which are mostly lower to those reported in the relevant literature [33, 34, 35]. However, the synthetic products we used are relatively easy to prepare [36] . Interestingly, Compound 4B showed the best antibacterial activity against *E. coli* (MIC=7.8 μg/mL) . Compound 4B showed the best inhibitory activity against *S. aureus* and *E. coli* with MIC of 12.3 μg/mL and 9.8 μg/mL, respectively.

Conclusion

In conclusion, 2-amidogen-3-phenylsulfonyl-4-tolyl-4H-benzochromene derivatives have been designed and synthesized, using the multicomponent reaction strategy containing benzenesulfonyl acetonitrile, acetaldehyde and 1-naphthol. Compared with other synthesis methods, this new MCR has been proved to have a wide range of applications , and provides a general and effective strategy for building fused benzo pigment derivatives with diverse structures . The structure identity of the desired compounds was confirmed , using ^{1}H NMR and ^{13}C NMR . In addition , higher chemical yield has been achieved without traditional purification , chromatography and recrystallization processes. According to relevant literature , the special chemical structure of the benzochromene derivatives can increase the antibacterial activity . Evaluating the three compounds , they showed higher antimicrobial activity gainst both *E. coli* and *S. aureus*, and the minimum inhibitory concentration was reached .

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