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An efficient synthesis and antifungal evaluation of natural product streptochlorin and its analogues

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ABSTRACT

Streptochlorin, a small indole alkaloid isolated from marine *Streptomyces* sp., exhibits a wide range of potent biological activities. An efficient and economic synthetic protocol for streptochlorin has been developed and validated, 4 steps from indole in a total yield of 45%, and further applied for the synthesis of its analogues. Biological testing showed that most of the target compounds exhibited potential antifungal activity in the primary assays, especially compounds **6**, **7** and **9c** were the most active ones, representing effective activity against the phytopathogenic fungi screened in preliminary test and might be explored for the study of mode of action in the future.

1. Introduction

Natural products have been widely investigated in medicinal and agricultural chemistry for a long time, according to their chemically structural diversity, good biological activities and compatibility with the environment. Streptochlorin (Fig. 1) is a small molecule of indole alkaloid originally isolated from marine *Streptomyces* sp. [1], and it's considered as a promising drug for various biological activities, such as antimicrobial, anticancer, antioxidation, antiviral and cell proliferation [2–4].

Biological screening conducted at Syngenta showed that streptochlorin also has antifungal activity, however its lack of potency hampered its use as agriculture fungicide [5]. Meanwhile, the commercial available streptochlorin is not easy to be gained from marine *Streptomyces* sp. because of the relatively low yield and complex chromatographic steps, so the market price of streptochlorin is very expensive, and it remains challenging to develop an efficient and economic method to synthesize streptochlorin based on more versatile starting materials. Furthermore, the mechanism of action for antifungal activity of streptochlorin is not yet clear, only a few literatures reported it can inhibit the activity of monoamine oxidase [5]. Thus, we intend to develop effective synthetic strategies to the study of streptochlorin and its derivatives. Afterwards, process development for the novel streptochlorin analogues with excellent antifungal activities involved structural optimization and bioassay screening, help us to explore the mechanism of action for the biological activity of streptochlorin.

As alkynyl, ester, isoamyl groups can be widely found in a variety of fungicides. For examples (Fig. 1), **Mandipropamid** [6], which contains an alkynyl group, possesses high effective in preventing some important phytopathogens such as *Phytophthora infestans* (potato and tomato late blight), *Plasmopara viticola* (grape downy mildew) and *Pseudoperonospara cubensis* (cucumber downy mildew). **Osthole** is a natural coumarin occurring [7], containing an isoamyl group, has been broadly used as a fungicide in China for a long time. It is approved for the treatment of *Rhizoctonia solani* and other phytopathogenic fungi in 2005. **Azoxystrobin**, a member of strobilurin fungicides, displays a range of antifungal activities [8]. It was registered for controlling pepper anthracnose, cucumber downy mildew, and tomato early blight in China.

In contrast to the method we had developed in our previous study [5,9,10], here we developed and validated the effectiveness of this proposed approach by comparing with the published methods. And then, we led alkynyl, ester, isoamyl groups at the nitrogen of the streptochlorin indole ring and replaced the Cl on the oxazole ring by Br (Fig. 1). We now describe work which has focused on the optimization of the substituents of the streptochlorin structure.

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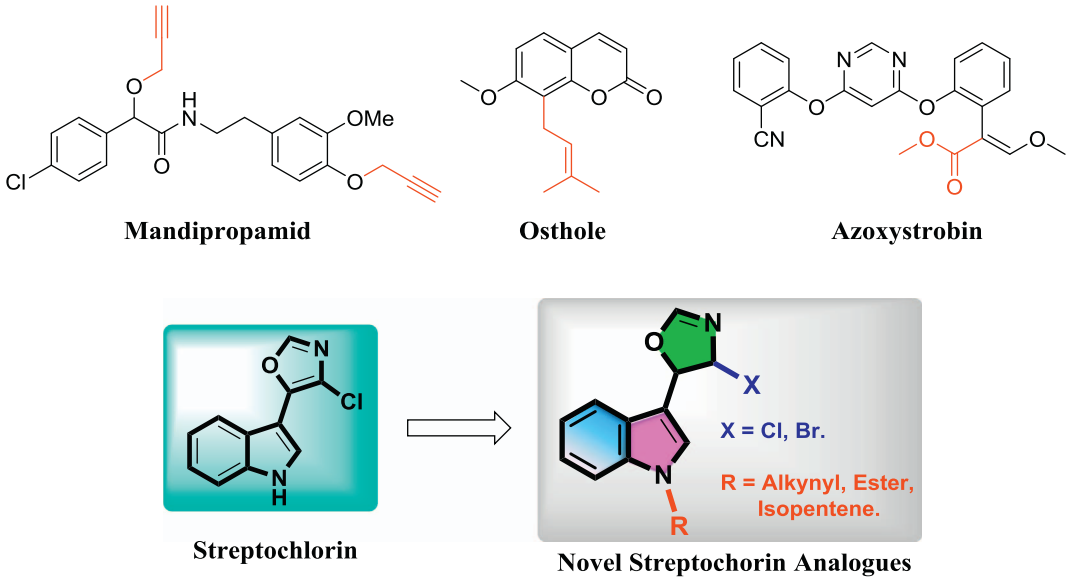

Fig. 1. Structural optimization to streptochlorin by alternative groups.

2. Materials and methods

2.1. Chemistry

All chemicals were purchased from commercial sources (e.g., Alfa Aesar Co.) and were all analytically pure. The solvents and liquid reagents were dried by standard methods in advance and distilled before use. Melting points were taken on a Büchi M-560 melting point apparatus (uncorrected), and FT-IR spectra were recorded on a Thermo Nicolet 380 FTIR Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker Avance 400 MHz spectrometer in DMSO-*d6* or $CDCl_3$ solution with TMS as an internal standard. HR-MS (ESI) spectra were carried out with a Thermo Exactive spectrometer. Reaction yields were not optimized.

2.1.1. Preparation of 1H-indole-3-carbaldehyde (2)

$POCl_3$ (2.0 mL) was added dropwise to a stirred solvent of DMF (14.0 mL) cooled at 0–5 °C and stirred it in an ice bath for 30 min. Then indole **1** (20.00 mmoL, 2.34 g) in DMF was added and reacted at 35 °C for an hour. Cooled the solution, joined H_2O (12 mL), NaOH (30%, 26 mL) in order and refluxed for 30 min. Allowed to cool slowly to r.t., a lot of crystal separated out from the solvent. The crude product was filtered and washed with water, then obtained the pure intermediate **2** after overnight vacuum drying.

2.1.2. Preparation of 1-(phenylsulfonyl)-1H-indole-3-carbaldehyde (3)

NaH (60% dispersion in mineral oil, 40.00 mmol, 0.96 g) was added portionwise to a stirred solution of indole-3-carboxaldehyde **2** (20.00 mmol, 2.90 g) in anhydrous THF (50 mL) cooled in an ice bath, then slowly allowed to warm to r.t. After stirring for 30 min, $PhSO_2Cl$ (36.00 mmol, 6.36 g) in anhydrous THF (3 mL) was added dropwise. When TLC monitoring showed that the starting material **2** had disappeared, the reaction mixture was evaporated under reduced pressure to remove the solvent and then washed with water, extracted with CH_2Cl_2 (50 mL × 3) and the extracts were dried over Na_2SO_4. Then the solvent was concentrated to recrystallize and gave the desired intermediate **3**.

2.1.3. Preparation of 5-(1H-indol-3-yl)oxazole (4)

A solution of 1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde **3** (6.39 mmol, 3.00 g) and *p*-toluene-sulfonylmethylisocyanide (TosMIC) (11.69 mmol, 2.28 g) in 1:1 THF/MeOH (120 mL, both anhydrous) was refluxed with Ambersep® 900(OH) ion exchange resin (21.0 g, exchange capacity 1.18 meq/mL) for 2 h. The reaction mixture was filtered, the resin was washed with acetone for several times, and the combined filtrates were evaporated under reduced pressure to remove the solvent, washed with water and extracted with CH_2Cl_2 (50 mL × 3) and the extracts were dried over Na_2SO_4. Then the solvent was concentrated to give the crude product and purified by flash column chromatography using 12–17% acetone/petroleum ether (60–90 °C) as eluent to give the pure product **4**.

2.1.4. Preparation of 4-halogen-5-(1H-indol-3-yl)oxazoles 6 and 7

To a stirred solution of compound **4** (0.50 g, 2.71 mmol) in THF–CCl_4 (20 mL, 1:1) was added NCS/NBS (2.98 mmol) and the resulting mixture was heated at 50 °C for 1 h and then monitored by TLC. The solvent was removed under reduced pressure and washed with water. Extracted with CH_2Cl_2 (30 mL × 3) and the extracts were dried over Na_2SO_4. After evaporating under reduced pressure, the crude product was purified by flash column chromatography using 12–17% acetone/petroleum ether (60–90 °C) as eluent to give the desired intermediate compounds **6** and **7**, respectively.

2.1.5. General procedure for the synthesis of target compounds 8 and 9

NaH (60% dispersion in mineral oil, 1.50 mmol) was added portionwise to a stirred solution of compound **6** or **7** (1.00 mmol) in anhydrous THF (10 mL). At first, the mixture was cooled in an ice bath, but it was then allowed to warm and was stirred at r.t. for 30 min. The appropriate electrophile R'X (1.20 mmol) in a solution of anhydrous THF was then added dropwise. When TLC monitoring showed that the reaction didn't continue any more, the reaction mixture was evaporated under reduced pressure to remove the solvent and was then diluted with water (30 mL). Extracted with CH_2Cl_2 (20 mL × 3) and the extracts were dried over Na_2SO_4. After evaporating under reduced pressure, the solid products were then purified by flash column chromatography using 2–7% acetone/petroleum ether (60–90 °C) as eluent to give the target compounds **8** and **9**, respectively.

2.2. Compounds data

2.2.1. 1H-indole-3-carbaldehyde (2)

A white crystal; Yield: 98%; Mp:195.8–198.7 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.14 (s, 1H), 9.94 (s, 1H), 8.29 (s, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.24 (dtd, J = 17.7, 7.2, 1.2 Hz, 2H). ^{13}C