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Synthesis and antifungal activity of novel streptochlorin analogues

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ABSTRACT

Streptochlorin, first isolated as a new antibiotic in 1988 from the lipophilic extracts of the mycelium of a *Streptomyces* sp, is an indole natural products with a variety of biological activities. Based on the methods developed for the synthesis of pimprinine in our laboratory, we have synthesized a series of indole-modified streptochlorin analogues and measured their activities against seven phytopathogenic fungi. Some of the analogues displayed good activity in the primary assays, and the seven compounds **10b**, **10c**, **11e**, **13e**, **21**, **22c** and **22e** (shown in Figure 1) were identified as the most promising candidates for further study. Structural optimization is still ongoing with the aim of discovering synthetic analogues with improved antifungal activity.

1. Introduction

Streptochlorin **1**, an indole alkaloid produced by many species of marine actinomycetes [1], was first isolated as a new antibiotic in 1988 from the lipophilic extracts of the mycelium of a *Streptomyces* sp. [2]. It belongs to the class of naturally occurring 5-(3-indolyl) oxazoles, which also includes the natural product pimprinine **2** [3]. Streptochlorin has been claimed to have a variety of biological activities, such as antibiotic [4], antiallergic [5], antiangiogenic [6,7], anticancer [6,7] antitumor [8], antiproliferative [1], antityrosinase [9], antinematodal [10] and pesticidal activity [11].

Biological activity screening conducted at Syngenta showed that streptochlorin demonstrates antifungal activity against *Pythium* spp., *Botrytis cinerea*, *Zymoseptoria tritici*, *Pyricularia oryzae*, *Fusarium culmorum* and *Rhizoctonia solani*, and its analogue pimprinine also exhibited weak antifungal activity. However, the potency of these two compounds is too low to be used as agricultural fungicides.

In our previous work, we have described various structural modifications to streptochlorin, including the introduction of different substituents at the nitrogen of the indole ring, replacement of Cl on the oxazole ring by Br or H [12], and replacement of the oxazole ring by oxadiazole [13]. In a continuation of our studies aimed at the discovery of novel analogues with improved antifungal activity, we now describe work which has focused on the optimization of the substituents on the indole ring of streptochlorin (shown in Scheme 1). Jong Seok Lee and co-workers have previously described the synthesis of two derivatives [14,15], but, other than this, further indole ring modification and biological activity of streptochlorin analogues have not been reported before.

2. Experimental

2.1. Chemicals and instruments

2-Methyl-1*H*-indole-3-carbaldehyde (**4a**), 5-chloro-1*H*-indole-3-carbaldehyde (**4c**), 5-bromo-1*H*-indole-3-carbaldehyde (**4d**), 7-aza-1*H*-indole-3-carbaldehyde (**4f**), 1*H*-indole-5-carbaldehyde (**14**) and other chemicals were purchased from commercial sources (e.g., Alfa Aesar Co.) and used without further purification unless otherwise stated. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. ^{1}H NMR spectra were recorded on a VARIAN Mercury-Plus 600 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian

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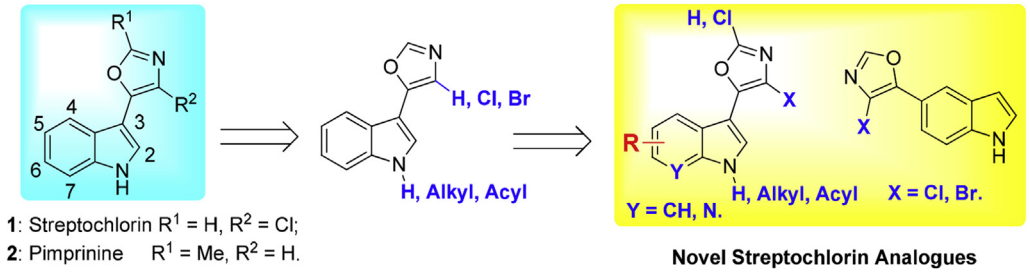

Scheme 1. Modification strategy – streptochlorin derivatives.

Mercury 400/600 (100/150 MHz) spectrometer and chemical shifts (δ) are given in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$ or 39.5 ppm of DMSO-d_6. Mass spectra were determined using a Trace MS 2000 organic mass spectrometry (EI-MS) or a ThermoFisher Mass platform DSQII by electrospray ionization (ESI-MS), and the signals are given in *m/z*. Melting points were taken on a Büchi B-545 melting point apparatus and are uncorrected. Reaction yields were not optimized.

2.2. General procedure

2.2.1. General procedure for the synthesis of 4-methyl-1H-indole-3-carbaldehyde (**4b**) and 6-methyl-1H-indole-3-carbaldehyde (**4e**) (Schemes 2 and 3)

The Vilsmeier-Haack reagent was prepared by adding $POCl_3$ (60 mmol, 6 mL) dropwise to ice-cold dry DMF (30 mL) whilst stirring. The mixture was then stirred for 10–15 min at 0 °C. Compound **3b** or **3e** (10 mmol) was added as a solution in DMF (5 mL) to the above Vilsmeier-Haack reagent. The stirred mixture was then heated at 35 °C for 1 h. After cooling, ice water (6 mL) and a 30% aqueous solution of NaOH (13 mL) were added successively, and the mixture was heated at reflux for 20 min and allowed to cool. The mixture was extracted with CH_2Cl_2 (20 mL*3). The extracts were dried over Na_2SO_4, evaporated under reduced pressure to remove the solvent, and the crude product was purified by flash column chromatography using 15–25% acetone/petroleum ether (60–90 °C) as eluent to give the corresponding intermediate compound **4b** or **4e**, respectively.

2.2.1.1. Data for 4-methyl-1H-indole-3-carbaldehyde ***(4b)***. White solid, yield 74%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.54 (*s*, 3H), 6,88 (*t*, J = 7.8 Hz, 1H), 7.03 (*d*, J = 7.2 Hz, 1H), 7.37 (*d*, J = 7.2 Hz, 1H), 7.55 (*s*, 1H), 9.83 (*s*, 1H), 10.52 (*bs*, 1H). ESI-MS: *m/z* 160.8 (MH^+).

2.2.1.2. Data for 6-methyl-1H-indole-3-carbaldehyde ***(4e)***. white solid, yield 79%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.45 (*s*, 3H), 7.16 (*d*, J = 8.4 Hz, 1H), 7.24 (*s*, 1H), 7.78 (*s*, 1H), 8.19 (*d*, J = 8.4 Hz, 1H), 8.80 (*s*, 1H), 10.03 (*s*, 1H). ESI-MS: *m/z* 160.2 (MH^+).

2.2.2. General procedure for the synthesis of compounds **5** (Schemes 2 and 3)

NaH (60% dispersion in mineral oil, 20.00 mmol, 0.48 g) was added portionwise to a stirred solution of the aldehyde **4** (10.00 mmol) in anhydrous THF (25 mL) cooled in an ice bath. The resulting mixture was then slowly allowed to warm to r.t. After stirring for 30 min, $PhSO_2Cl$ (12.00 mmol) (CH_3COCl 12.00 mmol for **5f**) in anhydrous THF (5 mL) was added dropwise. When TLC monitoring showed that the starting material **4** had disappeared, the reaction mixture was evaporated under reduced pressure to remove the solvent and was then diluted with ice water (50 mL). Solid products were filtered off and recrystallized from acetone/petroleum ether (60–90 °C) to give the desired intermediate **5**.

2.2.2.1. Data for 2-methyl-1-(phenylsulfonyl)-1H-indole-3-carbaldehyde ***(5a)***. White solid, yield 50%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.99 (*s*, 3H), 7.38 (*d*, J = 7.2 Hz, 1H), 7.41 (*d*, J = 8.4 Hz, 1H), 7.66 (*t*, J = 7.8 Hz, 2H), 7.77 (*d*, J = 7.8 Hz, 1H), 8.05 (*d*, J = 7.8 Hz, 2H), 8.12 (*d*, J = 8.4 Hz, 1H), 8.17 (*d*, J = 7.8 Hz, 1H), 10.27 (*s*, 1H). ESI-MS: *m/z* 300.2 (MH^+).

2.2.2.2. Data for 4-methyl-1-(phenylsulfonyl)-1H-indole-3-carbaldehyde ***(5b)***. White solid, yield 79%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.71 (*s*, 3H), 7.18 (*d*, J = 7.2 Hz, 1H), 7.35 (*t*, J = 7.8 Hz, 1H), 7.67 (*t*, J = 7.8 Hz, 2H), 7.76–7.81 (*m*, 2H), 8.14 (*m*, 2H), 8.84 (*s*, 1H), 10.07 (*s*, 1H). ESI-MS: *m/z* 300.6 (MH^+).

2.2.2.3. Data for 5-chloro-1-(phenylsulfonyl)-1H-indole-3-carbaldehyde ***(5c)***. White solid, yield 96%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.40 (*m*, 2H), 7.53–7.55 (*m*, 2H), 7.65 (*d*, J = 7.2 Hz, 1H), 7.89 (*d*, J = 8.4 Hz, 1H), 7.96 (*d*, J = 8.4 Hz, 1H), 8.24 (*s*, 1H), 8.27 (*s*, 1H), 10.09 (*s*, 1H). ESI-MS: *m/z* 320.2 (MH^+).

2.2.2.4. Data for 5-bromo-1-(phenylsulfonyl)-1H-indole-3-carbaldehyde ***(5d)***. White solid, yield 96%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.39 (*m*, 2H), 7.49–7.51 (*m*, 2H), 7.71 (*d*, J = 7.2 Hz, 1H), 7.90 (*d*, J = 8.4 Hz, 1H), 7.95 (*d*, J = 8.4 Hz, 1H), 8.24 (*s*, 1H), 8.27 (*s*, 1H), 10.07 (*s*, 1H). ESI-MS: *m/z* 365.9 (MH^+), 364.0 (MH^+).

2.2.2.5. Data for 6-methyl-1-(phenylsulfonyl)-1H-indole-3-carbaldehyde ***(5e)***. White solid, yield 84%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.46 (*s*, 3H), 7.24 (*d*, J = 7.8 Hz, 1H), 7.69 (*t*, J = 7.8 Hz, 2H),7.76–7.79 (*m*, 2H), 7.99 (*d*, J = 7.8 Hz, 1H), 8.16 (*d*, J = 7.8 Hz, 2H), 8.83 (*s*, 1H), 10.05 (*s*, 1H). ESI-MS: *m/z* 300.5 (MH^+).

2.2.2.6. Data for 1-acetyl-1H-7-aza-1H-indole-3-carbaldehyde ***(5f)***. White solid, yield 78%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.14 (*s*, 3H), 7.35 (*m*, 1H), 8.48 (*d*, J = 7.8 Hz, 1H), 8.44 (*m*, 2H), 10.10 (*s*, 1H). ESI-MS: *m/z* 189.3 (MH^+).

2.2.3. General procedure for the synthesis of compounds **6–13** (Schemes 2 and 3)

The synthetic procedures for compounds **6–13** are the same as those described in our previous work [12].

2.2.3.1. Data for 5-(2-methyl-1H-indol-3-yl)oxazole ***(6a)***. White solid, yield 34%. mp, 135–137 °C. IR (KBr) cm^{-1}: 1092 (C–O–C), 1461 (-CH_3), 1629 (C=N), 3180 (NH), 3413 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.90 (s, 3H), 7.21 (*t*, J = 7.2 Hz, 1H), 7.29 (*t*, J = 7.2 Hz, 1H), 7.36–7.38 (*m*, 2H), 7.82 (*s*, 1H), 7.97 (*s*, 1H), 10.60 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 13.0, 100.2, 111.1, 118.7, 119.3, 119.9, 121.3, 125.3, 134.4, 135.2, 148.1, 149.6. Anal.Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13; Found: C, 72.59; H, 5.22;