Synthesis and Antifungal Activity of Novel Streptochlorin Analogues

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Original article

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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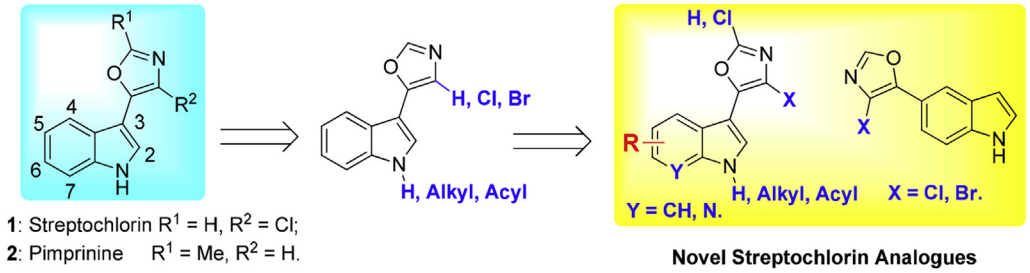


Scheme 1. Modification strategy – streptochlorin derivatives.

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^+).

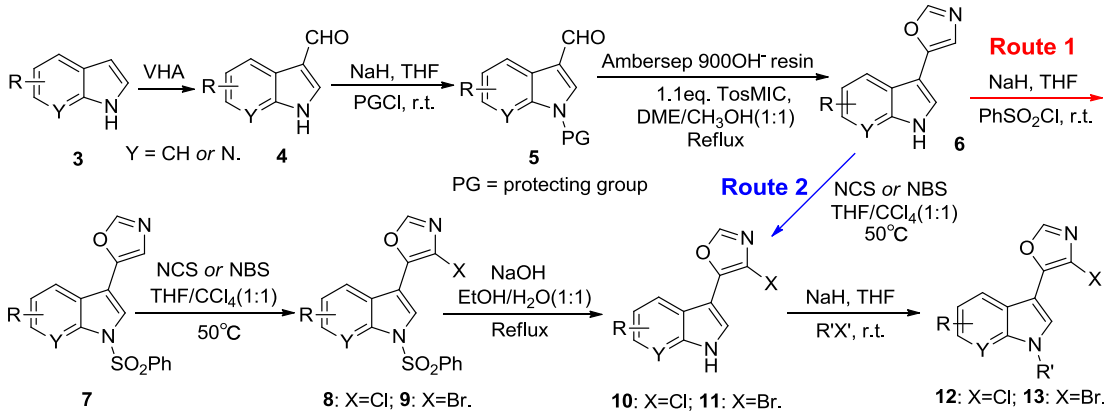
2.2.2.5. Data for 6-methyl-1-(phenylsulfonyl)-1H-indole-3-carbaldehyde ***(5e)***. White solid, yield 84%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.46 (*s*, 3H), 7.24 (*d*, J = 7.8 Hz, 1H), 7.69 (*t*, J = 7.8 Hz, 2H),7.76–7.79 (*m*, 2H), 7.99 (*d*, J = 7.8 Hz, 1H), 8.16 (*d*, J = 7.8 Hz, 2H), 8.83 (*s*, 1H),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

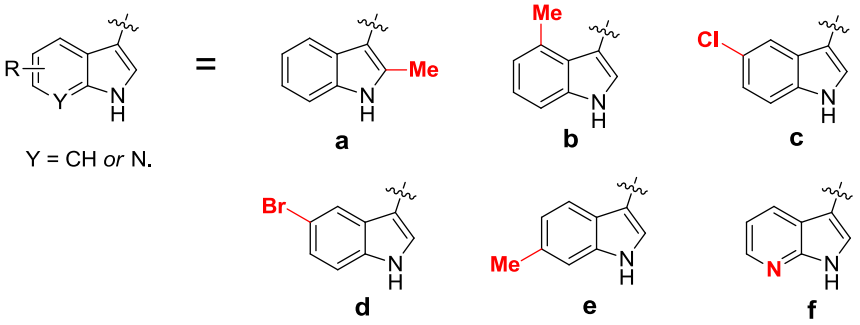
2.2.3. General procedure for the synthesis of compounds **6–13** (Schemes 2 and 3)

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;



Scheme 2. Synthetic routes for the preparation of analogues of streptochlorin.



Scheme 3. Structures of substituted indoles.

N, 14.10. EI-MS: *m/z* (%) 199.1 (MH^+).

2.2.3.2. Data for 5-(4-methyl-1H-indol-3-yl)oxazole ***(6b)***. White solid, yield 54%. mp, 124–126 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.35 (*s*, 3H), 6.85 (*d*, J = 6.6 Hz, 1H), 7.07 (*d*, J = 7.8 Hz, 1H), 7.18 (*s*, 1H), 7.30 (*t*, J = 8.4 Hz, 1H), 7.59 (*s*, 1H), 8.41 (*s*, 1H), 10.58 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.3, 98.7, 108.1, 119.7, 121.5, 121.7, 121.9, 128.6, 134.0, 135.6, 149.9, 150.7. Anal.Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13; Found: C, 72.62; H, 5.23; N, 14.15. EI-MS: *m/z* (%) 199.2 (MH^+).

2.2.3.3. Data for 5-(5-chloro-1H-indol-3-yl)oxazole ***(6c)***. White solid, yield 65%. mp, 130–132 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (*s*, 1H), 7.27 (*s*, 1H), 7.37 (*d*, J = 7.8 Hz, 1H), 7.58 (*d*, J = 7.8 Hz, 1H), 7.85 (*s*, 1H), 7.92 (*s*, 1H), 8.50 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 99.0, 114.7, 121.5, 121.7, 122.4, 125.6, 128.8, 129.9, 134.9, 149.7, 151.3. Anal.Calcd for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81; Found: C, 60.52; H, 3.28; N, 12.65. ESI-MS: *m/z* 219.5 (MH^+).

2.2.3.4. Data for 5-(5-bromo-1H-indol-3-yl)oxazole ***(6d)***. White solid, yield 57%. mp, 142–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19 (*s*, 1H), 7.28 (*s*, 1H), 7.35 (*d*, J = 7.2 Hz, 1H), 7.61 (*d*, J = 7.2 Hz, 1H), 7.90 (*s*, 1H), 7.98 (*s*, 1H), 8.46 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 99.1, 113.9, 121.4, 122.8, 124.7, 126.2, 128.6, 130.7, 135.6, 149.2, 150.7. Anal.Calcd for $C_{11}H_7BrN_2O$: C, 50.22; H, 2.68; N, 10.65; Found: C, 50.34; H, 2.73; N, 10.62. ESI-MS: *m/z* 263.4 (MH^+), 265.2 (MH^+).

2.2.3.5. Data for 5-(6-methyl-1H-indol-3-yl)oxazole ***(6e)***. White solid, yield 60%. mp, 118–120 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.42 (*s*, 3H), 6.98 (*d*, J = 7.8 Hz, 1H), 7.25 (*s*, 1H), 7.41 (*s*, 1H), 7.70–7.73 (*m*, 2H), 8.31 (*s*, 1H), 11.42 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.9, 97.8, 107.8, 120.3, 121.2, 121.7, 122.4, 128.4, 135.0, 135.2, 148.4, 149.9. Anal.Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13; Found: C, 72.80; H, 5.14; N, 14.07. ESI-MS: *m/z* 199.2 (MH^+).

2.2.3.6. Data for 5-(7-aza-1H-indol-3-yl)oxazole ***(6f)***. White solid, yield 45%. mp, 157–159 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.26 (*m*, 1H), 7.29 (*s*, 1H), 7.73 (*s*, 1H), 7.93 (*s*, 1H), 8.24 (*d*, J = 7.2 Hz, 1H), 8.43 (*d*, J = 4.2 Hz, 1H), 8.70 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 103.6, 116.6, 120.3, 123.6, 128.4, 142.5, 146.6, 148.7, 149.4, 151.1. Anal.Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69; Found: C, 64.77; H, 3.90; N, 22.72. EI-MS: *m/z* (%) 185 (100), 156 (23), 145 (46), 130 (39), 103 (19).

2.2.3.7. Data for 5-(2-methyl-1-(phenylsulfonyl)-1H-indol-3-yl)oxazole ***(7a)***. Grey solid, yield 77%. mp, 242–244 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.77 (*s*, 3H), 7.25 (*s*, 1H), 7.31 (*t*, J = 7.8 Hz, 1H), 7.36 (*t*, J = 7.8 Hz, 1H), 7.45–7.47 (*m*, 2H), 7.58 (*t*, J = 7.8 Hz, 1H), 7.71 (*d*, J = 7.8 Hz, 1H), 7.84–7.85 (*m*, 2H), 8.02 (*s*, 1H), 8.29 (*d*, J = 8.4 Hz, 1H). ESI-MS: *m/z* 339.4 (MH^+).

2.2.3.8. Data for 4-chloro-5-(2-methyl-1-(phenylsulfonyl)-1H-indol-3-yl)oxazole ***(8a)***. White solid, yield 17%. mp, 253–255 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ: 2.63 (*s*, 3H), 7.30 (*d*, J = 7.8 Hz, 1H), 7.38 (*t*, J = 7.8 Hz, 1H), 7.44–7.49 (*m*, 3H), 7.60 (*t*, J = 7.8 Hz, 1H), 7.86 (*d*, J = 7.8 Hz, 2H), 7.97 (*s*, 1H), 8.26 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.6, 99.8, 114.5, 119.7, 121.2, 124.6, 125.8, 127.7, 128.4, 129.7, 133.9, 134.0, 135.5, 139.8, 151.4, 154.2. Anal.Calcd for $C_{18}H_{13}ClN_2O_3S$: C, 57.99; H, 3.51; N, 7.51; Found: C, 57.85; H, 3.62; N, 7.50. ESI-MS: *m/z* 373.0 (MH^+).

*2.2.3.9. Data for 4-bromo-5-(2-methyl-1-(phenylsulfonyl)-1H-indol-3-yl)oxazole **(9a)**.* White solid, yield 28%, mp, 280–282 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.65 (*s*, 3H), 7.31 (*d*, *J* = 7.8 Hz, 1H), 7.34 (*t*, *J* = 7.8 Hz, 1H), 7.45–7.50 (*m*, 3H), 7.60 (*t*, *J* = 7.8 Hz, 1H), 7.83 (*d*, *J* = 7.8 Hz, 2H), 7.97 (*s*, 1H), 8.29 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 23.1, 98.9, 115.2, 118.8, 122.3, 124.4, 125.6, 126.9, 128.6, 129.7, 134.4, 134.8, 135.6, 138.7, 150.48, 152.1. Anal.-Calcd for $C_{18}H_{13}BrN_2O_3S$: C, 51.81; H, 3.14; N, 6.71; Found: C, 51.68; H, 3.16; N, 6.67. ESI-MS: *m/z* 419.2 (MH^+).

*2.2.3.10. Data for 4-chloro-5-(4-methyl-1H-indol-3-yl)oxazole **(10b)**.* White solid, yield 29%, mp, 256–258 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.32 (*s*, 3H), 6.96 (*d*, *J* = 7.2 Hz, 1H), 7.17 (*t*, *J* = 7.2 Hz, 1H), 7.20 (*t*, *J* = 7.8 Hz, 1H), 7.30 (*s*, 1H), 8.07 (*s*, 1H), 8.56 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 19.5, 98.6, 108.1, 119.8, 121.8, 125.4, 128.2, 128.5, 132.9, 135.4, 138.1, 151.4. Anal.Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04; Found: C, 62.05; H, 3.88; N, 12.05. ESI-MS: *m/z* 233.2 (MH^+).

*2.2.3.11. Data for 4-chloro-5-(5-chloro-1H-indol-3-yl)oxazole **(10c)**.* White solid, yield 38%, mp, 243–245 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1131 (C–O–C), 1634 (C=N), 3035 (Ar-CH), 3210 (NH), 3450 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 7.25 (*s*, 1H), 7.38 (*d*, *J* = 9.0 Hz, 1H), 7.85 (*d*, *J* = 9.0 Hz, 1H), 7.89 (*s*, 1H), 8.07 (*s*, 1H), 8.53 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 99.2, 115.1, 121.4, 122.4, 125.2, 125.8, 127.9, 130.0, 134.8, 138.7, 150.9. Anal.Calcd for $C_{11}H_6Cl_2N_2O$: C, 52.20; H, 2.39; N, 11.07; Found: C, 52.20; H, 2.39; N, 11.07. ESI-MS: *m/z* 253.1 (MH^+).

*2.2.3.12. Data for 4-chloro-5-(5-bromo-1H-indol-3-yl)oxazole **(10d)**.* White solid, yield 29%, mp, 252–254 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (*s*, 1H), 7.31 (*d*, *J* = 7.2 Hz, 1H), 7.78 (*d*, *J* = 7.2 Hz, 1H), 7.82 (*s*, 1H), 8.12 (*s*, 1H), 8.44 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 98.7, 114.2, 121.6, 122.8, 124.4, 125.6, 127.7, 131.1, 135.0, 137.7, 150.1. Anal.Calcd for $C_{11}H_6BrClN_2O$: C, 44.40; H, 2.03; N, 9.42; Found: C, 44.38; H, 2.13; N, 9.45. ESI-MS: *m/z* 299.4 (MH^+).

*2.2.3.13. Data for 4-chloro-5-(6-methyl-1H-indol-3-yl)oxazole **(10e)**.* White solid, yield 75%. mp, 225–227 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.47 (*s*, 3H), 7.09 (*d*, *J* = 7.8 Hz, 1H), 7.41 (*s*, 1H), 7.75 (*s*, 1H), 7.87 (*s*, 1H), 7.97 (*d*, *J* = 7.8 Hz, 1H), 8.37 (*s*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 102.1, 110.6, 119.6, 120.3, 121.3, 122.6, 123.2, 133.4, 134.7, 146.5, 149.2. Anal.Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04; Found: C, 61.87; H, 4.00; N, 12.11. ESI-MS: *m/z* 233.1 (MH^+).

*2.2.3.14. Data for 4-chloro-5-(7-aza-1H-indol-3-yl)oxazole **(10f)**.* White solid, yield 15%, mp, 234–236 °C. ^{1}H NMR (600 MHz, DMSO-d_6):δ: 7.36 (*s*, 1H), 7.69 (*s*, 1H), 8.33 (*s*, 1H), 8.43 (*s*, 1H), 8.51 (*s*, 1H),12.32 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 99.4, 111.8, 115.6, 122.2, 125.2, 127.5, 138.3, 143.5, 147.3, 151.4. Anal.Calcd for $C_{10}H_6ClN_3O$: C, 54.69; H, 2.75; N, 19.13; Found: C, 54.71; H, 2.69; N, 19.12. EI-MS: *m/z* (%) 219 (M^+, 100), 221 (32), 184 (4), 143(5), 117(8).

*2.2.3.15. Data for 4-bromo-5-(6-methyl-1H-indol-3-yl)oxazole **(11e)**.* White solid, yield 18%, mp, 228–230 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.48 (*s*, 3H), 7.07 (*d*, *J* = 7.8 Hz, 1H), 7.14 (*s*, 1H), 7.50 (*s*, 1H), 7.85 (*d*, *J* = 8.4 Hz, 1H), 8.00 (*s*, 1H), 8.31 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.2, 97.9, 107.8, 120.1, 121.7, 125.8, 128.5, 129.0, 133.3, 135.5, 137.9, 150.7. Anal.Calcd for $C_{12}H_9BrN_2O$: C, 52.01; H, 3.27; N, 10.11; Found: C, 52.11; H, 3.22; N, 10.09. ESI-MS: *m/z* 277.2 (MH^+).

*2.2.3.16. Data for4-bromo-5-(7-aza-1H-indol-3-yl)oxazole **(11f)**.* White solid, yield 27%, mp, 262–264 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.25 (*s*, 1H), 8.08 (*s*, 1H), 8.29 (*s*, 1H), 8.30 (*s*, 1H), 8.54 (*s*, 1H), 12.39 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 101.1, 115.7, 121.3, 124.2, 125.7, 128.1, 138.0, 142.8, 148.3, 150.7. Anal.Calcd for $C_{10}H_6BrN_3O$: C, 45.48; H, 2.29; N, 15.91; Found: C, 45.52; H, 2.31; N, 15.80. EI-MS: *m/z* (%) 263 (M^+, 100), 265 (100), 184 (4), 145(32), 146 (7).

*2.2.3.17. Data for 2-chloro-1-(5-chloro-3-(4-chlorooxazol-5-yl)-1H-indol-1-yl)ethanone **(12c)**.* White solid, yield 43%.mp, 215–217 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.32 (*s*, 2H), 7.08 (*d*, *J* = 7.8 Hz, 1H), 7.86 (*d*, *J* = 7.8 Hz, 1H), 7.98 (*s*, 1H), 8.05 (*s*, 1H), 8.18 (*s*, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 48.3, 112.5, 121.5, 121.9, 122.4, 125.4, 126.6, 129.3, 123.0, 133.8, 138.1, 151.4, 160.9. Anal.Calcd for $C_{13}H_7Cl_3N_2O_2$: C, 47.38; H, 2.14; N, 8.50; Found: C, 47.45; H, 2.09; N, 8.51. EI-MS: *m/z* (%) 329.1 (MH^+).

*2.2.3.18. Data for 2-chloro-1-(3-(4-chlorooxazol-5-yl)-6-methyl-1H-indol-1-yl)ethanone **(12e)**.* White solid, yield 55%. mp, 202–204 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.32 (*s*, 3H), 4.52 (*s*, 2H), 7.21 (*d*, *J* = 7.8 Hz, 1H), 7.97 (*s*, 1H), 8.20 (*s*, 1H), 8.28 (*s*, 1H), 8.31 (*d*, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.5, 46.5, 98.9, 111.2, 120.3, 122.0, 125.6, 126.2, 129.5, 132.1, 135.7, 138.2, 151.5, 160.5. Anal.Calcd for $C_{14}H_{10}Cl_2N_2O_2$: C, 54.39; H, 3.26; N, 9.06; Found: C, 54.37; H, 3.12; N, 9.11. EI-MS: *m/z* (%) 309.2 (MH^+).

*2.2.3.19. Data for 4-bromo-5-(1-(cyclopropylmethyl)-6-methyl-1H-indol-3-yl)oxazole **(13e)**.* White solid, yield, 63%. mp, 168–170 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.45 (*d*, *J* = 7.2 Hz, 2H), 0.67 (*d*, *J* = 7.2 Hz, 2H), 1.29–1.31 (*m*, 1H), 2.32 (*s*, 3H), 4.11 (*d*, *J* = 6.6 Hz, 2H), 7.31 (*d*, *J* = 7.2 Hz, 1H), 7.43 (*d*, *J* = 7.2 Hz, 1H), 7.89 (*s*, 1H), 7.95 (*s*, 1H), 8.08 (*s*, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 3.9, 4.0, 10.8, 22.3, 51.2, 102.5, 107.8, 109.8, 120.7, 121.3, 122.3, 125.4, 126.5, 137.2, 148.0, 151.2. Anal.Calcd for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.56; N, 8.46; Found: C, 58.11; H, 4.58; N, 8.50. EI-MS: *m/z* (%) 331.0 (MH^+).

*2.2.4. General procedure for the synthesis of compounds **15**–**21** (Scheme 4)*

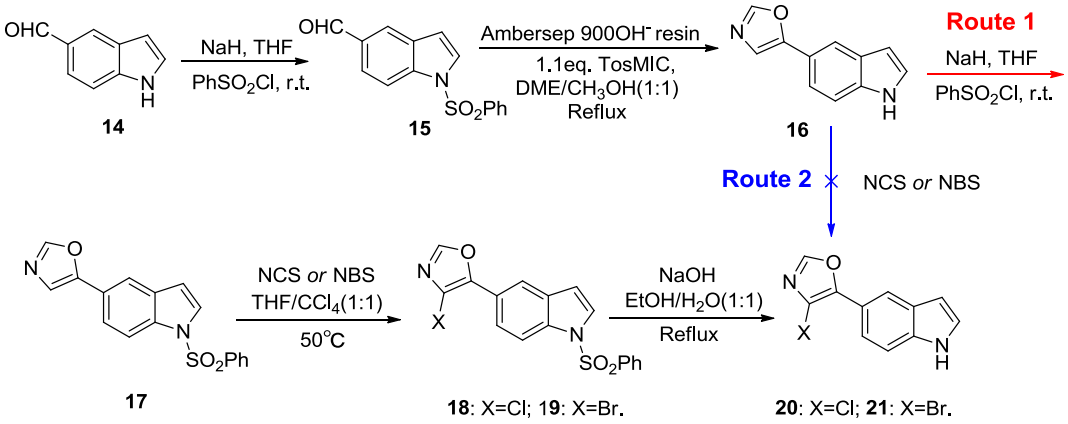
The synthetic procedures for compounds **15**–**21** are the same as those described in our previous work [12].

*2.2.4.1. Data for 1-(phenylsulfonyl)-1H-indole-5-carbaldehyde **(15)**.* White solid, yield 61%. IR (KBr) cm^{-1}: 731 (Pyrrolyl-HC=CH), 1699 (C=O), 3435 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.80 (*t*, *J* = 4.2 Hz, 1H), 7.46–7.49 (*m*, 2H), 7.59 (*t*, *J* = 7.8 Hz, 1H), 6.69 (*d*, *J* = 3.6 Hz, 1H), 7.86–7.88 (*m*, 2H), 7.92 (*d*, *J* = 7.2 Hz, 1H), 8.07 (*s*, 1H), 8.13 (*d*, *J* = 8.4 Hz, 1H), 10.03 (*s*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.5, 113.8, 124.7, 125.2, 126.7, 127.9, 129.4, 130.8, 132.2, 134.2, 137.8, 138.0, 191.7. ESI-MS: *m/z* 286.1 (MH^+).

*2.2.4.2. Data for 5-(1H-indol-5-yl)oxazole **(16)**.* White solid, yield 82%, mp, 211–213 °C. IR (KBr) cm^{-1}: 1114(C–O–C), 1622 (C=N), 3185 (NH), 3436 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.50 (*s*, 1H), 7.27 (*s*, 1H), 7.42 (*d*, *J* = 7.2 Hz, 1H), 7.48–7.49 (*m*, 2H), 7.53 (*d*, *J* = 7.2 Hz, 1H), 7.92 (*s*, 1H), 11.29 (*s*, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 101.8, 111.2, 115.8, 119.4, 121.7, 124.3, 128.3, 129.4, 135.5, 149.8, 151.2. Anal.Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21; Found: C, 71.82; H, 4.50; N, 15.19. ESI-MS: *m/z* 185.3 (MH^+).

*2.2.4.3. Data for 5-(1-(phenylsulfonyl)-1H-indol-5-yl)oxazole **(17)**.* White solid, yield 62%. mp, 218–220 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.71 (*d*, *J* = 3.0 Hz, 1H), 7.33 (*s*, 1H), 7.43–7.46 (*m*, 2H), 7.47 (*t*, *J* = 7.8 Hz, 2H), 7.61 (*d*, *J* = 3.6 Hz, 1H), 7.79 (*s*, 1H), 7.82–7.84 (*m*, 2H), 7.91 (*s*, 1H), 8.06 (*d*, *J* = 9.0 Hz, 1H). ESI-MS: *m/z* 325.1 (MH^+).

*2.2.4.4. Data for 4-chloro-5-(1-(phenylsulfonyl)-1H-indol-5-yl)oxazole **(18)**.* White solid, yield 24%. mp, 276–278 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.71 (*d*, *J* = 7.2 Hz, 1H). 7.33 (s, 1H), 7.46 (*t*,



Scheme 4. Synthetic routes for "reversed" streptochlorin analogues.

$J = 7.8$ Hz, 2H), 7.55 ($t, J = 7.8$ Hz, 1H), 7.61 ($d, J = 7.2$ Hz, 2H), 7.83 (s, 1H), 7.95–7.86 (m, 2H), 8.05 ($d, J = 8.4$ Hz, 1H). ESI-MS: m/z 359.2 (MH^+).

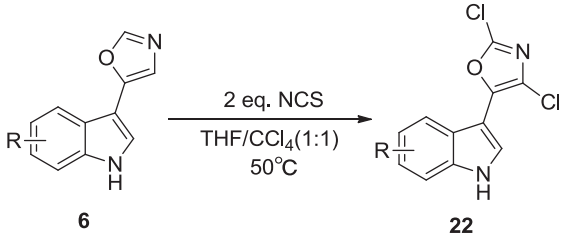
2.2.4.5. Data for 4-bromo-5-(1-(phenylsulfonyl)-1H-indol-5-yl)oxazole ***(19)***. White solid, yield 26%, mp, 254–256 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.67 ($d, J = 7.2$ Hz, 1H). 7.29 (s, 1H), 7.40 ($t, J = 7.8$ Hz, 2H), 7.51 ($t, J = 7.8$ Hz, 1H), 7.57 ($d, J = 7.2$ Hz, 2H), 7.80 (s, 1H), 7.89–7.91 (m, 2H), 8.02 ($d, J = 8.4$ Hz, 1H). ESI-MS: m/z 402.9 (MH^+).

2.2.4.6. Data for 4-chloro-5-(1H-indol-5-yl)oxazole ***(20)***. White solid, yield 40%, mp, 238–240 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, $J = 7.2$ Hz, 1H), 7.40 (s, 1H), 7.54 ($d, J = 7.2$ Hz, 1H), 7.61 ($d, J = 8.4$ Hz, 1H), 7.98 (s, 1H), 8.02 (s, 1H), 8.53 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 102.6, 111.7, 116.8, 119.2, 124.3, 125.7, 128.8, 129.7, 135.2, 149.8, 152.7. Anal.Calcd for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81; Found: C, 60.47; H, 3.31; N, 12.78. ESI-MS: m/z 219.1 (MH^+).

2.2.4.7. Data for 4-bromo-5-(1H-indol-5-yl)oxazole ***(21)***. White solid, yield 48%, mp, 246–248 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (d, $J = 7.2$ Hz, 1H), 7.38 (s, 1H), 7.43–7.47 (m, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.91 (s, 1H), 7.96 (s, 1H), 8.46 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 101.7, 111.6, 116.4, 120.1, 124.5, 125.6, 128.3, 129.9, 135.4, 148.3, 151.8. Anal.Calcd for $C_{11}H_7BrN_2O$: C, 50.22; H, 2.68; N, 10.65; Found: C, 50.31; H, 2.69; N, 10.68. ESI-MS: m/z 263.0 (MH^+).

2.2.5. General procedure for the synthesis of dichlorinated compounds ***22*** *(Scheme 5)*

To a stirred solution of **6** (4.10 mmol) in THF-CCl_4 (50 mL, 1:1) was added 2 equivalents of NCS (8.20 mmol) and the resulting mixture was heated at 50 °C until **6** had been completely consumed. The mixture was allowed to cool and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography using 15–25% acetone/petroleum ether (60–90 °C) as eluent to give the dichlorinated compounds **22**.



Scheme 5. Synthesis of dichlorinated analogues of streptochlorin.

2.2.5.1. Data for 2,4-dichloro-5-(5-chloro-1H-indol-3-yl)oxazole ***(22c)***. White solid, yield, 63%. mp, 257–259 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.23 ($d, J = 7.2$ Hz, 1H), 7.50 ($d, J = 7.2$ Hz, 1H), 7.81 (s, 1H), 8.65 (s, 1H), 10.28 (bs, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 99.7, 115.2, 122.7, 124.5, 125.8, 126.6, 129.4, 130.8, 136.7, 142.1, 153.6. Anal.Calcd for $C_{11}H_5Cl_3N_2O$: C, 45.95; H, 1.75; N, 9.74; Found: C, 46.01; H, 1.79; N, 9.68. EI-MS: m/z (%) 287.2 (MH^+).

2.2.5.2. Data for 2,4-dichloro-5-(6-methyl-1H-indol-3-yl)oxazole ***(22e)***. White solid, yield, 63%. mp, 243–245 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.41 (s, 3H), 7.11 ($d, J = 7.2$ Hz, 1H), 7.42 ($d, J = 7.2$ Hz, 1H), 7.75 (s, 1H), 8.35 (s, 1H), 10.57 (bs, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.9, 98.5, 114.9, 122.6, 124.6, 125.4, 126.2, 128.8, 130.9, 135.3, 139.1, 153.4. Anal.Calcd for $C_{12}H_8Cl_2N_2O$: C, 53.96; H, 3.02; N, 10.49; Found: C, 54.01; H, 3.09; N, 10.52. EI-MS: m/z (%) 267.0 (MH^+).

2.3. Biological assays

The materials and methods used in the biological assays conducted at Syngenta are the same as those described in our earlier work [12]. Screening consists of seven different high throughput assays covering a selection of economically important plant pathogenic fungi and is performed using both leaf pieces and artificial media. The results of the biological testing are shown in Table 1.

3. Results and discussion

3.1. Synthetic chemistry

A series of indole-substituted streptochlorin analogues was efficiently synthesized based on the methods we had developed in our previous work. The synthetic routes to the streptochlorin analogues are shown in Scheme 2, and the indole substituents are shown in Scheme 3. The required substituted indole-3-carboxaldehydes **4** were either commercially available, or could be made by Vilsmeier-Haack formylation of the corresponding substituted indoles **3** [16,17]. The indole nitrogen was then sulfonylated to give the protected indole-3-carboxaldehydes **5**. In the key step of this sequence, the 5-linked oxazole was then installed by Van Leusen's [3 + 2] cyclisation with TosMIC, under the catalytic influence of the ion exchange resin Ambersep® 900(OH) [18,19], to

Table 1
Antifungal activities of streptochlorin analogues. Data are presented as means of the assessment scores across two or three replicates unless otherwise stated.

Species		PHY[a]		SEP[a]	URO[a]	PYT[a]		ALT[a]		BOT[a]		GIB[a]	
Compound	Rate	200	60	100	100	20	2	20	2	20	2	20	2
Streptochlorin		0[b]	49	36	**55**	**99**	0	**99**	**99**	**99**	0	**99**	0
Pimprinine		0	0	51	27	0	0	0	0	0	0	0	0
6a		49	0	0	0	**99**	**55**	0	0	0	0	0	0
6b		0	0	0	**77**	**99**	0	27	0	0	0	0	0
7a		0	27	0	27	27	0	0	27	0	0	0	0
8a		0	0	0	49	0	0	0	0	0	0	0	0
9a		49	0	0	27	0	0	0	0	0	0	0	0
10b		0	0	0	49	**99**	0	27	0	49	0	0	0
10c		0	0	0	**77**	–	–	**77**	0	–	–	**99**	0
10d		–[c]	–	–	–	–	–	–	–	–	–	–	–
10e		0	0	0	0	–	0	0	0	–	0	**99**	0
10f		–	–	–	–	–	–	–	–	–	–	–	–
11d		–	–	–	–	–	–	–	–	–	–	–	–
11e		0	0	0	0	0	0	**99**	0	–	0	**99**	0
11f		–	–	–	–	–	–	–	–	–	–	–	–
12c		0	0	**55**	**55**	0	0	0	0	0	0	0	0
12e		0	0	0	0	**55**	0	0	0	0	0	0	0
13e		49	0	0	**99**	**77**	0	**99**	27	–	–	**55**	0
16		0	0	0	0	**55**	0	**99**	0	0	0	0	0
18		0	0	0	0	0	0	0	0	0	0	0	0
20		0	0	0	0	**77**	0	**55**	0	0	0	0	0
21		**99**	0	**66**	0	**77**	0	**55**	0	0	0	0	0
22c		0	0	0	**99**	–	–	**99**	0	–	–	**99**	0
22e		0	0	0	27	–	–	**99**	27	–	–	**99**	0

[a] PHY, Phytophthora infestans (on tomato leaf pieces); SEP, *Zymoseptoria tritici* (on wheat leaf pieces); URO, *Uromyces viciae-fabae* (on bean leaf pieces); PYT, *Pythium dissimile*; ALT, *Alternaria solani*; BOT, Botryotinia fuckeliana; GIB, *Gibberella zeae* (all in artificial media).
[b] 0 means 0–49% control of disease or pathogen; 55 means 50–80% control of disease or pathogen; 99 means 81–100% control of disease or pathogen.
[c] On testing or not tested.

give the 5-(3′-indolyl)-oxazoles **6**, with the sulfonyl protecting group lost during this cyclisation. For compounds with the indole substitution patterns **b**, **c**, **d**, **e** and **f**, varying from electron-donating groups to electron-withdrawing groups (shown in Scheme 3), compounds **6** could be treated with NCS/NBS to directly afford the chlorinated or brominated streptochlorin analogues **10**/**11**, respectively (Route **2** shown in Scheme 2) [12,20]. Some dichlorinated analogues of streptochlorin were also obtained when two equivalents of NCS were employed (Scheme 5). For compounds with the indole substitution patterns **a** (2-methylindole) and **14** (5-indolyl), streptochlorin analogues were synthesized by a sequence of protection, cyclization, reprotection, halogenation and hydrolysis (Route **1** shown in Scheme 2 and Scheme 4). On the basis of our previous work, further substituents were introduced to the indole NH of some streptochlorin derivatives.

Although the yields were not optimized, we noted that the step that led to the formation of the oxazole ring was sensitive to the nature of the steric effect of substituents on indole. For example, for a methyl substituent, the yields of oxazoles **6** from aldehydes **5** were highly dependent on the position of the methyl group, namely 17%, 43% and 50% for 5-(**2-methyl**-1*H*-indol-3-yl)oxazole **6a**, 5-(**4-methyl**-1*H*-indol-3-yl)oxazole **6b** and 5-(**6-methyl**-1*H*-indol-3-yl) oxazole **6e**, respectively. These results show that a methyl group at the 2-position of the indole offers greater steric hindrance than a methyl at the 4- or 6-positions.

It is worth noting that the 2-methyl streptochlorin derivatives **10a** and **11a** could not be synthesized using halogenation as the final step, since chlorination or bromination of the 2-methyl-indole **6a** using NCS or NBS afforded complex mixtures. A phenylsulfonyl group was therefore added to the indole nitrogen of **6a** to give intermediate **7a**, after which halogenation proceeded smoothly to generate the N-protected streptochlorin derivatives **8a** and **9a**. Hydrolysis of the phenylsulfonyl group from these intermediates to afford the final compounds **10a**, **11a** then proved to be problematic.

Direct halogenation on the oxazole ring of the reversed streptochlorin analogue **16** with NCS or NBS was also a problem, because halogenation also occurred at the 2- and 3-positions of the indole. Again, the solution was to add a phenylsulfonyl group to the indole nitrogen, after which halogenation took place exclusively on the oxazole ring. Hydrolysis of the phenylsulfonyl group then gave the required reversed analogues **20** and **21**.

3.2. Antifungal activity and the structure–activity relationships (SAR)

The results of the biological testing against seven phytopathogenic fungi are given in Table 1. For the purposes of an analysis of structure–activity relationships, the antifungal activities of compounds **6**–**13**, **16**, **18** and **20**–**22** were compared to the lead compounds, the natural products streptochlorin and pimprinine.

It was noticeable that where compounds were active it was most commonly against *Pythium dissimile*, *Uromyces viciae-fabae* and *Alternaria solani*, but the activity lacked potency, as illustrated by the absence of activity at the lower rates tested. Although the antifungal activity of some of the compounds has not yet been determined, making it difficult for a detailed structure–activity relationship analysis, some broad conclusions can still be drawn.

Some indole-modified derivatives **10** showed antifungal activity. For example, compounds **10b** and **10e** showed clear activity on *P. dissimile* and *Gibberella zeae*, respectively. **10c** exhibited clear activity on three out of five fungal species tested at the higher rates only (*U. viciae-fabae*, *A. solani*, *G. zeae*), therefore displaying a broader spectrum of activity. For the effect of indole ring substituents, compared to antifungal activity of electron-donating 4-methyl and 6-methyl equivalents (**10b** and **10e**), the electron-withdrawing 5-Cl derivative (**10c**) and the dichloro equivalent (**22c**) displayed higher antifungal activity on three out of five fungal species, though **10b** demonstrated a broader spectrum. Compound **21**, the reversed brominated analogue of streptochlorin, showed clear activity on *Phytophthora infestans* and *P. dissimile* and

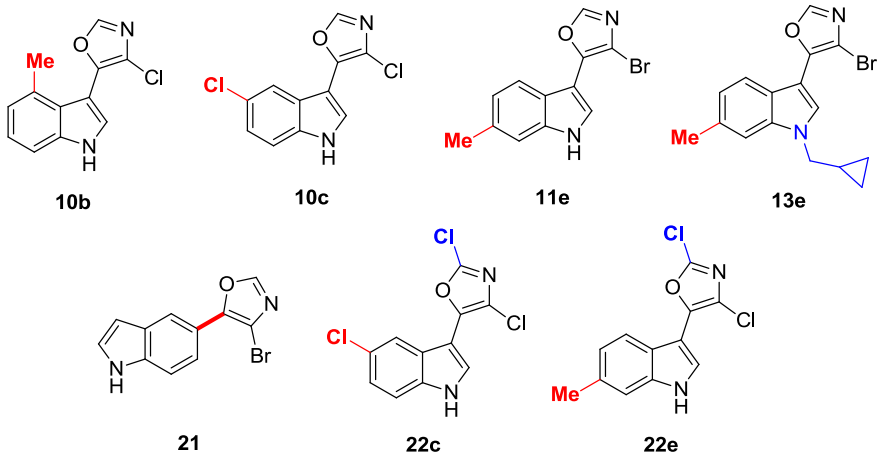


Fig. 1. Structures of the most active synthetic streptochlorin analogues.

moderate control of *Zymoseptoria tritici*, and *A. solani*. However, the indole-modified derivatives **10** were less active than the lead compound streptochlorin.

In our previous work we showed that antifungal activity could be improved by introducing a halogen atom (Cl, Br) at the 4-position of the oxazole ring. An additional halogen atom introduced at the 2-position of the oxazole ring can also further improve the antifungal activity. For example, the compound **10c** showed good control of *G. zeae*, *U. vicae-fabae and A. solani*, while the dichloro equivalent **22c** exhibited effective control of *U. viciae-fabae*, *A. solani*, and *G. zeae*. The situation is similar with compounds **10e** and its dichloro equivalent **22e**. A derivative with substitution on the nitrogen of the indole ring was also tested for the antifungal activity; compound **13e** showed effective control of *U. viciae-fabae*, *P. dissimile*, *A. solani*, and moderate control of *G. zeae*, but the activity lacks potency.

4. Conclusions

In summary, we have efficiently synthesized a novel series of indole-modified streptochlorin analogues based on the methods developed in our previous work. Biological testing showed that some of the derivatives have good antifungal activity in a series of primary assays. The compounds **10b**, **10c**, **11e**, **13e**, **21**, **22c** and **22e** were identified as the most active and therefore the most promising candidates for further study (shown in Fig. 1). Further structural optimization of indole-modified streptochlorin derivatives is well under way, with the aim of preparing analogues with improved antifungal activity.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.01.043.

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