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Synthesis and fungicidal activity of novel pimprinine analogues

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ABSTRACT

A simple and efficient synthetic protocol for 5-(3-indolyl)-oxazoles has been developed and further used to synthesize a series of novel analogues of natural product pimprinine. All new compounds were identified by ^{1}H NMR, high resolution mass spectrometry, and the structures of **10** and **18o** were further confirmed by X-ray crystallographic diffraction analysis. Bioassay conducted at Syngenta showed that several of the synthesized compounds exhibited fungicidal activity. Compounds **10**, **17**, **18h**, **18o**, **19h**, **19i** and **19l** all showed effective control of three out of the seven tested phytopathogenic fungi at the highest rate screened. Compounds **17** and **19h** in particular showed activity against the four pathogens screened in artificial media; *Pythium dissimile*, *Alternaria solani*, *Botryotinia fuckeliana* and *Gibberella zeae*.

1. Introduction

Natural products are well known as one of the most important sources for lead discovery in medicinal and agricultural chemistry, because their novel scaffolds can afford an opportunity to discover novel candidates with different action modes from the existing agents. Pimprinine **1** is an indole alkaloid produced by many species of *Streptomyces*, first isolated from the filtrates of *Streptomyces pimprina* cultures in 1963 [1], and belonging to the class of naturally occurring 5-(3-indolyl)oxazoles. Members of this family, as shown in Fig. 1, display a range of biological activities. For example, pimprinine itself is a monoamine oxidase (MAO) inhibitor and is reported to have anti-epileptic effects [2,3]. Screening conducted at Syngenta showed that pimprinine is active against the phytopathogenic fungi *Aureobasidium pullulans*, *Botrytis cinerea*, *Magnaporthe grisea* and *Septoria tritici* when tested in liquid culture assays (unpublished data). WS-30581 A **4** and WS-30581 B **5** have potent inhibitory effects on platelet aggregation, labradorin 1 **6** and labradorin 2 **7** were found to be potent inhibitors of the growth of human cancer cells [4,5], martefragin A **8** was reported to be a very potent inhibitor of lipid peroxidation [6,7], and the complex marine natural product diazonamide A **9** exhibited pronounced cytotoxic activities [8–10]. 4-Chloro -5-(3-indolyl)oxazole **10**, called streptochlorin, is a natural product with a structure similar to that of pimprinine, and it has been reported to show broad fungicidal activity against *Pythium*, *Botrytis cinerea*, *S. tritici*, *Pyricularia oryzae*, *Fusarium culmorum* and *Rhizoctonia solani* [11–14]. However, its potency is too low to be used as agricultural fungicide.

As a continuation of our extensive research program to discover novel bioactive lead compounds, pimprinine was used as the parent structure to carry out structural optimization with the aim of discovering synthetic analogues with simpler chemical structures and improved fungicidal activity. We describe structure–activity relationships around pimprinine, including analogues in which the indole nitrogen has been derivatised.

2. Materials and methods

2.1. Chemistry

The reagents were all analytically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. *p*-Toluene-sulfonylmethyl isocyanide (TosMIC) and Ambersep® 900(OH) ion exchange resin were bought from the Alfa Aesar Company (Tianjin, China). Yields were not optimized. ^{1}H NMR spectra were recorded on a VARIAN Mercury-Plus 600 or Mercury-Plus 400 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal reference. High resolution mass spectra (HRMS) were acquired in positive mode on a WATERS MALDI SYNAPT G2 HDMS

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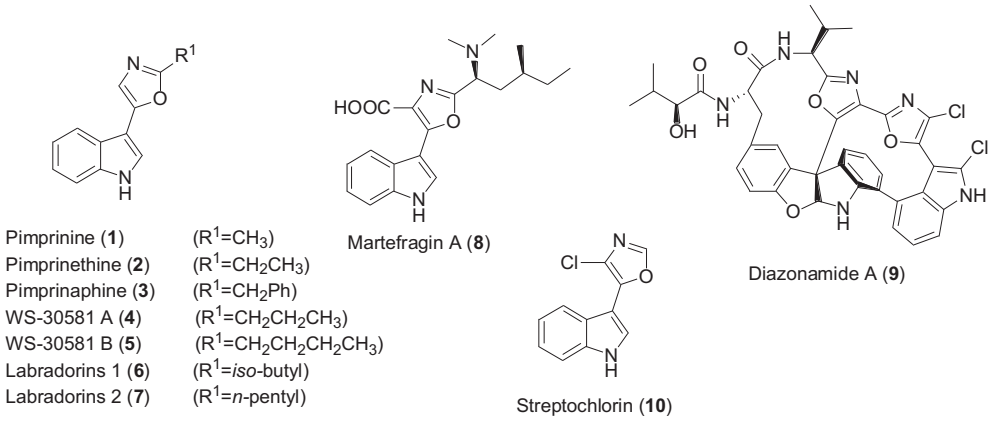


Fig. 1. Chemical structure of pimprinine and its analogues.

(MA, USA) or an Agilent 6520 Accurate-Mass Q-TOF liquid chromatography/mass spectrometry (LC/MS) (USA). FTIR was recorded on a Thermo Nicolet Avatar 360 FTIR Spectrometer, and melting points were taken on a Büchi B-545 melting point apparatus and are uncorrected. Microwave syntheses were carried out on a Smith synthesizer.

*2.1.1. Preparation of 1-(phenylsulfonyl)-3-indolecarboxaldehyde **12***

NaH (60% dispersion in mineral oil, 40.00 mmol, 0.96 g) was added portionwise to a stirred solution of indole-3-carboxaldehyde **11** (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 $PhSO_2Cl$ (24.00 mmol, 4.24 g) in anhydrous THF was added dropwise. When TLC monitoring showed that the starting material **11** had disappeared, the reaction mixture was evaporated under reduced pressure to remove the solvent and then diluted with ice water (300 mL). Solid products were filtrated off and recrystallized from acetone/petroleum ether (60–90 °C) to give the desired intermediate **12** in a yield of 97%, mp 151–153 °C ^{1}H NMR (600 MHz, $CDCl_3$): δ: 7.37 (*t*, *J* = 7.2 Hz, 1H), 7.42 (*dd*, *J* = 11.4, 4.2 Hz, 1H), 7.52 (*t*, *J* = 7.8 Hz, 2H), 7.62 (*t*, *J* = 7.2 Hz, 1H), 7.97 (*t*, *J* = 7.8 Hz, 3H), 8.20–8.31 (*m*, 2H), 10.11 (*s*, 1H). HRMS (MALDI): *m*/*z* 286.0515. Calcd. $C_{15}H_{11}NO_3S$: 286.0538 $[M + H]^+$.

*2.1.2. Preparation of 5-(3-indolyl)oxazole **13***

A solution of 1-(phenylsulfonyl)-3-indole- carboxaldehyde (8.76 mmol, 2.50 g) and p-toluene-sulfonylmethyl isocyanide (TosMIC) (9.64 mmol, 1.88 g) in 1:1 DME/MeOH (100 mL, both anhydrous) was refluxed with Ambersep® 900(OH) ion exchange resin (17.5 g, exchange capacity 1.18 meq/mL) for 2 h. The reaction mixture was filtered, the resin was washed (MeOH, 3 × 20 mL), and the combined filtrates were concentrated to give the crude product, which was purified by flash column chromatography using 20–30% acetone/petroleum ether (60–90 °C) as eluent to give the pure product **13** in a yield of 66%, mp 167–169 °C ^{1}H NMR (600 MHz, DMSO-d_6): δ: 7.16 (*t*, *J* = 7.2 Hz, 1H), 7.22 (*t*, *J* = 7.2 Hz, 1H), 7.41–7.54 (*m*, 2H), 7.82 (*s*, 1H), 7.87 (*d*, *J* = 7.8 Hz, 1H), 8.34 (*s*, 1H), 11.60 (*s*, 1H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 105.6, 111.6, 119.5, 119.9, 121.0, 122.1, 123.1, 124.0, 136.2, 147.9, 148.2. HRMS (MALDI): *m*/*z* 185.0753. Calcd. for $C_{11}H_8N_2O$: 185.0715 $[M + H]^+$.

*2.1.3. Preparation of 5-(1-(phenylsulfonyl)-1H-indol-3-yl)oxazole **14***

NaH (60% dispersion in mineral oil, 40.00 mmol, 0.96 g) was added portionwise to a stirred solution of 5-(3-indolyl)oxazole **13** (20.00 mmol, 3.68 g) in anhydrous THF (50 mL), cooled in an ice bath, then slowly allowed to warm to r.t. After 30 min of stirring, $PhSO_2Cl$ (24.00 mmol, 4.24 g) in anhydrous THF was added dropwise. When TLC monitoring showed that the starting material **13** had disappeared, the reaction mixture was evaporated under reduced pressure to remove the solvent, the residue was quenched by slowly adding cold water and neutralized to pH = 7 by the addition of dilute hydrochloric acid, and then extracted with 60 mL CH_2Cl_2. 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 desired intermediate compound **14** in a yield of 69%, mp 147–149 °C ^{1}H NMR (600 MHz, $CDCl_3$): δ: 7.36 (*t*, *J* = 7.2 Hz, 1H), 7.39–7.44 (*m*, 2H), 7.47 (*t*, *J* = 7.2 Hz, 2H), 7.57 (*t*, *J* = 6.6 Hz, 1H), 7.78 (*d*, *J* = 7.8 Hz, 1H), 7.94 (*d*, *J* = 6.6 Hz, 3H), 7.97 (*s*, 1H), 8.06 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 102.1, 111.0, 119.6, 120.5, 121.7, 124.1, 125.4, 126.5, 126.9, 127.6, 128.5, 128.8, 129.5, 133.5, 135.5, 138.1, 150.6. HRMS (MALDI): *m*/*z* 325.0635. Calcd. for $C_{17}H_{12}N_2O_3S$: 325.0647 $[M + H]^+$.

*2.1.4. Preparation of 4-halogen-5-(1-(phenylsulfonyl)-1H-indol-3-yl) oxazole **15** and **16***

To a stirred solution of **14** (1.33 g, 4.10 mmol) in THF–CCl_4 (50 mL, 1:1) was added NCS/NBS (4.51 mmol) and the resulting mixture was heated at 50 °C for 8 h and then allowed to cool. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using 15–25% acetone/petroleum ether (60–90 °C) as eluent to give the desired intermediate compounds **15** and **16** in yields of 88% and 75%, respectively.

Data for **15**: mp, 155–157 °C. IR (KBr) cm^{-1}: IR (KBr) cm^{-1}: 621 (C–Cl), 1135 (C–O–C), 1372 (–SO_2–), 1643 (C=N), 3124 (Ar–CH), 3442 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 7.34 (*t*, *J* = 7.8 Hz, 1H), 7.42 (*t*, *J* = 7.8 Hz, 1H), 7.48 (*t*, *J* = 7.8 Hz, 2H), 7.57 (*t*, *J* = 7.8 Hz, 1H), 7.91 (*s*, 1H), 7.95 (*d*, *J* = 7.8 Hz, 2H), 8.01 (*d*, *J* = 8.4 Hz, 1H), 8.05 (*d*, *J* = 8.4 Hz, 1H), 8.16 (*s*, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 102.0, 111.0, 119.6, 120.5, 121.7, 124.3, 125.5, 125.8, 126.9, 127.6, 128.5, 128.6, 128.9, 129.5, 135.5, 138.2, 150.7. HRMS (MALDI): *m*/*z* 359.0241. Calcd. for $C_{17}H_{11}ClN_2O_3S$: 359.0257 $[M + H]^+$.

Data for **16**: mp, 160–162 °C. IR (KBr) cm^{-1}: 593 (C–Br), 1134 (C–O–C), 1373 (–SO_2–), 1617 (C=N), 3124 (Ar–CH), 3443 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 7.34 (*t*, *J* = 7.6 Hz, 1H), 7.41 (*t*, *J* = 7.8 Hz, 1H), 7.48 (*t*, *J* = 7.9 Hz, 2H), 7.57 (*t*, *J* = 7.5 Hz, 1H), 7.92–7.98 (*m*, 3H), 8.00 (*d*, *J* = 7.9 Hz, 1H), 8.05 (*d*, *J* = 8.3 Hz, 1H), 8.27 (*s*, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 102.3, 109.5, 111.4, 113.6, 121.6, 124.2, 124.3, 125.7, 126.9, 127.3, 128.5, 129.5, 134.3, 134.5, 137.6, 143.4, 149.6. HRMS (MALDI): *m*/*z* 424.9922. Calcd. for $C_{17}H_{11}BrN_2O_3S$: 424.9571 $[M + Na]^+$.

*2.1.5. Preparation of 4-halogen-5-(3-indolyl)oxazoles **10** and **17***

To a stirred solution of **15** or **16** (4.00 mmol) in EtOH–H_2O (50 mL, 1:1) was added NaOH (20.00 mmol) and the resulting mixture was heated under reflux for 2 h, then allowed to cool. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using 15–25% acetone/petroleum ether (60–90 °C) as eluent to give the desired intermediate compounds **10** and **17** in yields of 64% and 56%, respectively. From **13**. To a stirred solution of **13** (0.74 g, 4.00 mmol) in THF–CCl_4 (30 mL, 1:1) was added NCS/NBS (4.40 mmol) and the resulting mixture was heated for 8 h at 50 °C, cooled, The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using 15–25% acetone/petroleum ether (60–90 °C) as eluent to give the desired intermediate compounds **10** and **17** in yields of 72% and 84%, respectively.

Data for **10**: Yield, 66%. mp, 167–169 °C. IR (KBr) cm^{-1}: 641 (C–Cl), 1127 (C–O–C), 1629 (C=N), 3045 (Ar–CH), 3206 (NH), 3443 (Pyrrolyl-CH). ^1H NMR (600 MHz, DMSO-d_6): δ: 7.17 (*t*, J = 7.5 Hz, 1H), 7.23 (*t*, J = 7.5 Hz, 1H), 7.51 (*d*, J = 8.0 Hz, 1H), 7.92 (*d*, J = 7.7 Hz, 2H), 8.50 (*s*, 1H), 11.81 (*s*, 1H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 103.7, 111.5, 120.8, 121.2, 121.6, 123.2, 123.3, 124.4, 135.6, 143.2, 147.6. HRMS (MALDI): *m/z* 219.0364. Calcd. for $C_{11}H_7ClN_2O$: 219.0325 $[M + H]^+$.

Data for **17**: Yield, 47%. mp, 147–149 °C. IR (KBr) cm^{-1}: 639 (C–Br), 1123 (C–O–C), 1607 (C=N), 3045 (Ar–CH), 3129 (NH), 3454 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 7.25–7.26 (*t*, J = 7.2 Hz, 1H), 7.32 (*t*, J = 7.2 Hz, 1H), 7.45–7.47 (*d*, J = 8.4 Hz, 1H), 7.94 (*s*,1H), 7.95 (*s*, 1H), 8.09–8.11 (*d*, J = 8.4 Hz, 1H), 8.51 (*bs*, 1H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 103.8, 107.9, 111.5, 120.8, 121.2, 123.3, 123.6, 124.5, 135.6, 145.7, 148.6. HRMS (MALDI): *m/z* 262.9766. Calcd. for $C_{11}H_7BrN_2O$: 262.9820 $[M + H]^+$.

*2.1.6. General procedure for the synthesis of target compounds **18** and **19***

NaH (60% dispersion in mineral oil, 4.00 mmol) was added portionwise to a stirred solution of **10** or **17** (2.00 mmol) in anhydrous THF (50 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 (2.40 mmol) as a solution in anhydrous THF was then added dropwise. When TLC monitoring showed that the starting material **11** had disappeared, the reaction mixture was evaporated under reduced pressure to remove the solvent and was then diluted with ice water (300 mL). The solid products were filtered off and recrystallized from acetone/petroleum ether (60–90 °C) to give the target compounds **18** and **19**.

*2.1.7. Microwave-assisted synthesis of compounds **18r** and **19o***

NaH (60% dispersion in mineral oil, 0.40 mmol) was added dropwise into a stirred solution of **10** (0.20 mmol) in anhydrous THF (5 mL) for 30 min, cyclopropylmethyl bromide (0.24 mmol) was then added dropwise. The mixture was sealed in a microwave tube, synthesized, and irradiated at 90 °C for 15 min. The resulted mixture was cooled and diluted with 10 mL of ice water, and neutralized to pH = 7 by the addition of dilute hydrochloric acid, and then extracted with 10 mL CH_2Cl_2. 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 desired intermediate compound **18r** in a yield of 87%. For **19o**: From compound **17**, as described for the synthesis of compound **18r**.

Data for **18a**: Yield, 96%. mp, 117–119 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1111 (C–O–C), 1623 (C=N), 3124 (Ar–CH), 3443 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 3.88 (*s*, 3H), 7.25 (*d*, J = 7.8 Hz, 1H), 7.33 (*t*, J = 7.8 Hz, 1H), 7.39 (*d*, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.86 (*s*, 1H), 8.08 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 33.3, 102.1, 109.7, 120.8, 120.9, 121.1, 122.8, 125.0, 127.6, 128.5, 136.6, 147.3. HRMS (MALDI): *m/z* 233.0522. Calcd. for $C_{12}H_9ClN_2O$: 233.0482 $[M + H]^+$.

Data for **18b**: Yield, 66%. mp, 42–44 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1108 (C–O–C), 1626 (C=N), 3129 (Ar–CH), 3446 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 1.51 (*t*, J = 7.2 Hz, 3H), 4.22 (*q*, J = 7.2 Hz, 2H), 7.24 (*dd*, J = 9.6, 5.4 Hz, 1H), 7.29–7.32 (*t*, J = 7.2 Hz, 1H), 7.31–7.32 (*m*, J = 8.4 Hz, 1H), 7.71 (*s*, 1H), 7.83 (*s*, 1H), 8.06 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 15.3, 41.5, 103.4, 109.7, 119.9, 120.8, 121.0, 121.3, 122.7, 125.0, 125.9, 139.0, 147.3. HRMS (MALDI): *m/z* 247.0686. Calcd. for $C_{13}H_{11}ClN_2O$: 247.0638 $[M + H]^+$.

Data for **18c**: Yield, 99%. mp, 72–74 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 993 (C=C), 1102 (C–O–C), 1624 (C=N), 3127 (Ar–CH), 3450 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 4.81 (*d*, J = 5.4 Hz, 2H), 5.16 (*d*, J = 16.8 Hz, 1H), 5.24–5.35 (*m*, 1H), 6.03 (*m*, 1H), 7.24 (*d*, J = 7.2 Hz, 1H), 7.31 (*t*, J = 7.8 Hz, 1H), 7.38 (*d*, J = 8.4 Hz, 1H), 7.87 (*s*, 1H), 7.71 (*s*, 1H), 8.09 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 49.1, 102.5, 110.0, 118.0, 120.9, 121.0, 122.8, 125.1, 126.6, 128.5, 132.5, 135.9, 143.1, 147.4. HRMS(ESI): *m/z* 259.0617. Calcd. for $C_{14}H_{11}ClN_2O$: 259.0638 $[M + H]^+$.

Data for **18d**: Yield, 39%. mp, 83–85 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1110 (C–O–C), 1620 (C=N), 3117 (Ar–CH), 3446 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 4.93–4.92 (*d*, J = 6.6 Hz, 1H), 6.09–6.07 (*t*, J = 6.6 Hz, 1H), 7.38–7.26 (*t*, J = 7.8 Hz, 1H), 7.38–7.34 (*m*, 2H), 7.69 (*s*, 1H), 7.87 (*s*, 1H), 8.09 (*d*, J = 7.8 Hz, 2H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 45.3, 103.2, 109.6, 121.2, 121.3, 121.6, 123.3, 124.4, 124.5, 125.2, 126.0, 135.6, 142.7, 147.5. HRMS (MALDI): *m/z* 326.9835. Calcd. for $C_{14}H_9Cl_3N_2O$: 326.9859 $[M + H]^+$.

Data for **18e**: Yield, 76%. mp, 158–160 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1113 (C–O–C), 1620 (C=N), 1720 (C=O), 3111 (Ar–CH), 3444 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 2.73 (*s*, 3H), 7.40 (*t*, J = 7.8 Hz, 1H), 7.46 (*d*, J = 8.4 Hz, 1H), 7.96 (*s*, 1H), 8.01 (*s*, 1H), 8.07 (*d*, J = 7.2 Hz, 1H), 8.52 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 24.0, 109.1, 116.7, 120.9, 123.0, 124.4, 126.3, 126.8, 135.4, 140.8, 141.2, 148.6, 168.5. HRMS (MALDI): *m/z* 261.0390. Calcd. for $C_{13}H_9ClN_2O_2$: 261.0431 $[M + H]^+$.

Data for **18f**: Yield, 65%. mp, 120–122 °C. IR (KBr) cm^{-1}: 619 (C–Cl), 1118 (C–O–C), 1615 (C=N), 1695 (C=O), 3127 (Ar–CH), 3443 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 1.39 (*t*, J = 7.2 Hz, 3H), 3.05 (*q*, J = 7.2 Hz, 2H), 7.39 (*t*, J = 7.2 Hz, 1H), 7.46 (*t*, J = 8.4 Hz, 1H), 7.95 (*s*, 1H), 8.06 (*m*, 2H), 8.54 (*d*, J = 9.0 Hz, 1H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 8.5, 29.2, 108.8, 116.6, 120.8, 122.2, 124.3, 124.4, 126.1, 126.6, 135.4, 141.3, 148.5, 172.0. HRMS (ESI): *m/z* 275.0599. Calcd. for $C_{14}H_{11}ClN_2O_2$: 275.0587 $[M + H]^+$.

Data for **18g**: Yield, 63%. mp, 113–115 °C. IR (KBr) cm^{-1}: 614 (C–Cl), 1136 (C–O–C), 1364 (–SO_2–), 1570 (C=N), 3141 (Ar–CH), 3443 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 1.28 (*t*, J = 7.2 Hz, 3H), 3.40 (*q*, J = 7.2 Hz, 2H), 7.42 (*t*, J = 7.2 Hz, 1H), 7.46 (*t*, J = 7.8 Hz, 1H), 7.92–8.00 (*m*, 2H), 8.03 (*s*, 1H), 8.11 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (600 MHz, DMSO-d_6): δ: 7.8, 48.5, 107.0, 113.3, 119.8, 121.2, 124.1, 124.7, 125.8, 126.2, 134.4, 139.8, 151.1. HRMS (MALDI): *m/z* 311.0238. Calcd. $C_{13}H_{11}ClN_2O_3S$: 311.0257 $[M + H]^+$.

Data for **18h**: Yield, 62%. mp, 157–159 °C. IR (KBr) cm^{-1}: 614 (C–Cl), 1121 (C–O–C), 1570 (C=N), 1713 (C=O), 3130 (Ar–CH), 3444 (Pyrrolyl-CH). ^1H NMR (600 MHz, $CDCl_3$): δ: 4.66 (*s*, 2H), 7.44 (*t*, J = 7.2 Hz, 1H), 7.50 (*t*, J = 7.2 Hz, 1H), 7.97 (*s*, 1H), 8.03 (*s*, 1H), 8.08 (*d*, J = 8.4 Hz, 1H), 8.51 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (600 MHz, $CDCl_3$): δ: 42.3, 102.1, 111.0, 119.6, 120.5, 121.3, 121.9, 124.1, 125.3, 126.8, 127.6, 135.5, 164.1. HRMS (MALDI): *m/z* 295.0115. Calcd. $C_{13}H_8Cl_2N_2O_2$: 295.0041 $[M + H]^+$.

Data for **18i**: Yield, 59%. mp, 129–131 °C. IR (KBr) cm^{-1}: 621 (C–Cl), 1126 (C–O–C), 1571 (C=N), 1726 (C=O), 3139 (Ar–CH),

3456 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, DMSO-d_6): δ: 7.50 (*t*, J = 7.2 Hz, 1H), 7.56 (*t*, J = 7.2 Hz, 1H), 8.02 (*t*, J = 4.2 Hz, 2H), 8.43–8.45 (*m*, 2H), 8.71 (*s*, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 65.6, 102.1, 110.9, 117.1, 121.3, 122.0, 125.7, 126.7, 127.1, 135.9, 140.6, 149.0, 160.7. HRMS (MALDI): *m/z* 328.9620. Calcd. $C_{13}H_7Cl_3N_2O_2$: 328.9651 $[M + H]^+$.

Data for **18j**: Yield, 54%. mp, 155–157 °C. IR (KBr) cm^{-1}: 623 (C–Cl), 1120 (C–O–C), 1570 (C=N), 1719 (C=O), 3135 (Ar–CH), 3446 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, DMSO-d_6): δ: 7.57 (*t*, J = 7.2 Hz, 1H), 7.63 (*t*, J = 7.2 Hz, 1H), 8.08 (*d*, J = 8.4 Hz, 1H), 8.43 (*d*, J = 8.4 Hz, 1H), 8.58 (*s*, 1H), 8.75 (*s*, 1H). ^{13}C NMR (600 MHz, DMSO-d_6): δ: 79.7, 101.8, 112.7, 120.2, 120.4, 120.9, 122.9, 124.4, 125.1, 127.2, 136.3, 143.2, 149.9. HRMS(ESI): *m/z* 362.9283. Calcd. $C_{13}H_6Cl_4N_2O_2$: 362.9262 $[M + H]^+$.

Data for **18k**: Yield, 60%. mp, 137–139 °C. IR (KBr) cm^{-1}: 617 (C–Cl), 1125 (C–O–C), 1571 (C=N), 1705 (C=O), 3127 (Ar–CH), 3446 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.91 (*d*, J = 6.6 Hz, 3H), 5.11 (*q*, J = 6.6 Hz, 1H), 7.43 (*t*, J = 8.4 Hz, 1H), 7.49 (*t*, J = 7.2 Hz, 1H), 7.97 (*s*, 1H), 8.06 (*d*, J = 8.4 Hz, 1H), 8.16 (*s*, 1H), 8.55 (*d*, J = 9.0 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ: 20.1, 51.8, 108.2, 116.4, 120.8, 124.4, 124.9, 126.4, 126.6, 127.6, 135.1, 139.9, 151.4, 168.0. HRMS (MALDI): *m/z* 309.0170. Calcd. $C_{14}H_{10}Cl_2N_2O_2$: 309.0198 $[M + H]^+$.

Data for **18l**: Yield, 65%. mp, 114–116 °C. IR (KBr) cm^{-1}: 614 (C–Cl), 1119 (C–O–C), 1571 (C=N), 1744 (–CO_2–), 3126 (Ar–CH), 3447 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 4.14 (*s*, 3H), 7.33 (*t*, J = 7.2 Hz, 1H), 7.37–7.44 (*t*, J = 7.2 Hz, 1H), 7.52 (*d*, J = 7.8 Hz, 1H), 8.01 (*s*, 1H), 8.03 (*s*, 1H), 8.13 (*d*, J = 9.0 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ: 54.8, 106.4, 115.5, 119.2, 124.2, 124.4, 125.6, 125.7, 127.7, 134.4, 137.1, 150.0, 153.3. HRMS (MALDI): *m/z* 314.9988. Calcd. $C_{13}H_9ClN_2O_3$: 314.9939 $[M + K]^+$.

Data for **18m**: Yield, 50%. mp, 103–105 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1127 (C–O–C), 1571 (C=N), 1719 (C=O), 3108 (Ar–CH), 3443 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 3.58 (*s*, 3H), 4.65 (*s*, 2H), 7.40–7.42 (*t*, J = 7.8 Hz, 1H), 7.46–7.48 (*t*, J = 7.8 Hz, 1H), 7.95 (*s*, 1H), 8.05 (*d*, J = 8.4 Hz, 1H), 8.11 (*s*, 1H), 8.52 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (600 MHz, DMSO-d_6): δ: 59.7, 72.4, 109.7, 116.5, 116.7, 121.1, 121.6, 124.7, 126.3, 135.4, 141.0, 147.5, 148.8, 167.7. HRMS (MALDI): *m/z* 291.0515. Calcd. $C_{14}H_{11}ClN_2O_3$: 291.0536 $[M + H]^+$.

Data for **18n**: Yield, 40%. mp, 60–62 °C. IR (KBr) cm^{-1}: 617 (C–Cl), 1121 (C–O–C), 1571 (C=N), 1747 (C=O), 3134 (Ar–CH), 3446 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.27 (*t*, J = 7.2 Hz, 3H), 4.23 (*q*, J = 7.2 Hz, 2H), 4.89 (*s*, 2H), 7.25 (*dd*, J = 13.2, 5.4 Hz, 2H), 7.30–7.37 (*m*, 1H), 7.71 (*s*, 1H), 7.85 (*s*, 1H), 8.08 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 14.1, 48.0, 62.0, 103.5, 109.4, 121.2, 121.3, 123.4, 125.0, 127.2, 127.6, 136.3, 142.9, 127.6, 167.8. HRMS: *m/z* 305.0678. Calcd. for $C_{15}H_{13}ClN_2O_3$: 305.0693 $[M + H]^+$.

Data for **18o**: Yield, 56%. mp, 111–113 °C. IR (KBr) cm^{-1}: 616 (C–Cl), 1122 (C–O–C), 1570 (C=N), 1746 (COCO), 3125 (Ar–CH), 3445 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.50–1.53 (*t*, J = 7.2 Hz, 3H), 4.54–4.58 (*q*, J = 7.2 Hz, 2H), 7.44–7.47 (*t*, J = 7.8 Hz, 1H), 7.48–7.51 (*t*, J = 7.8 Hz, 1H), 7.96 (*d*, J = 7.8 Hz, 1H), 8.08 (*d*, J = 7.8 Hz, 1H), 8.31 (*s*, 1H), 8.50 (*s*, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ: 14.0, 63.7, 111.1, 116.9, 121.3, 123.3, 125.5, 126.7, 127.2, 128.5, 135.4, 140.7, 148.9, 157.0, 159.6. HRMS (MALDI): *m/z* 319.0634. Calcd. $C_{15}H_{11}ClN_2O_4$: 319.0486 $[M + H]^+$.

Data for **18p**: Yield, 92%. mp, 102–104 °C. IR (KBr) cm^{-1}: 642 (C–Cl), 1113 (C–O–C), 1140 (C–F), 1604 (C=N), 3128 (Ar–CH), 3444 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 5.40 (*s*, 2H), 6.78 (*t*, J = 7.8 Hz, 1H), 6.88 (*t*, J = 9.0 Hz, 1H), 6.90–6.98 (*m*, 1H), 7.27 (*t*, J = 7.8 Hz, 2H), 7.30 (*t*, J = 7.8 Hz, 1H), 7.36 (*d*, J = 8.4 Hz, 1H), 7.77 (*s*, 1H), 7.88 (*s*, 1H), 8.10 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 43.8, 104.0, 104.2, 104.5, 109.9, 111.7, 111.9, 121.1, 121.2, 123.3, 125.2, 124.1, 126.8, 129.8, 135.9, 147.5, 160.8, 164.5. HRMS (MALDI): *m/z* 345.0569. Calcd. for $C_{18}H_{11}ClF_2N_2O$: 345.0606 $[M + H]^+$.

Data for **18q**: Yield, 61%. mp, 85–87 °C. IR (KBr) cm^{-1}: 616 (C–Cl), 1122 (C–O–C), 1570 (C=N), 3131 (Ar–CH), 3452 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 2.52 (*t*, J = 4.2 Hz, 1H), 2.86 (*t*, J = 4.2 Hz, 1H), 3.34 (*m*, 1H), 4.55–4.23 (*dd*, J = 15.0, 5.4 Hz, 2H), 7.27 (*t*, J = 9.0 Hz, 1H), 7.34 (*t*, J = 7.2 Hz, 1H), 7.45 (*d*, J = 8.4 Hz, 1H), 7.75 (*s*, 1H), 7.87 (*s*, 1H), 8.09 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 45.2, 48.2, 50.6, 109.8, 121.1, 121.2, 121.7, 123.2, 124.1, 127.0, 127.6, 128.3, 135.5, 147.5. HRMS (MALDI): *m/z* 275.0603. Calcd. for $C_{14}H_{11}ClN_2O_2$: 275.0587 $[M + H]^+$.

Data for **18r**: Yield, 87%. mp, 91–93 °C. IR (KBr) cm^{-1}: 634 (C–Cl), 1117 (C–O–C), 1571 (C=N), 3138 (Ar–CH), 3444 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 0.43 (*d*, J = 4.8 Hz, 2H), 0.69 (*d*, J = 7.8 Hz, 2H), 1.34 (*m*, 1H), 4.05 (*d*, J = 6.6 Hz, 2H), 7.24 (*m*, 1H), 7.31 (*t*, J = 7.8 Hz, 1H), 7.42 (*d*, J = 8.4 Hz, 1H), 7.88 (*s*, 1H), 7.94 (*s*, 1H), 8.08 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 4.2, 11.1, 51.0, 102.2, 107.5, 109.9, 120.8, 121.0, 122.7, 125.2, 126.6, 137.6, 136.0, 148.3. HRMS (MALDI): *m/z* 273.0819. Calcd. for $C_{15}H_{13}ClN_2O$: 273.0795 $[M + H]^+$.

Data for **19a**: Yield, 99%. mp, 131–133 °C. IR (KBr) cm^{-1}: 540 (C–Br), 1110 (C–O–C), 1571 (C=N), 3122(Ar–CH), 3454 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 3.88 (*s*, 3H), 7.24 (*t*, J = 7.8 Hz, 1H), 7.33 (*t*, J = 7.8 Hz, 1H), 7.38 (*d*, J = 8.4 Hz, 1H), 7.78 (*s*, 1H), 7.89 (*s*, 1H), 8.08 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 33.2, 102.2, 107.4, 109.6, 120.8, 120.9, 122.8, 125.1, 127.8, 136.5, 147.3, 148.3. HRMS (MALDI): *m/z* 276.9927. Calcd. for $C_{12}H_9BrN_2O$: 276.9976 $[M + H]^+$.

Data for **19b**: Yield, 99%. mp, 68–70 °C. IR (KBr) cm^{-1}: 539 (C–Br), 1122 (C–O–C), 1572 (C=N), 3135 (Ar–CH), 3450 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.54 (*t*, J = 7.2 Hz, 3H), 4.25 (*q*, J = 7.2 Hz, 2H), 7.24 (*t*, J = 7.8 Hz, 1H), 7.31 (*t*, J = 7.8 Hz, 1H), 7.41 (*d*, J = 7.8 Hz, 1H), 7.84 (*s*, 1H), 7.89 (*s*, 1H), 8.08 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 15.3, 41.5, 102.5, 106.8, 109.7, 120.8, 121.1, 122.7, 126.2, 127.5, 136.7, 147.6, 148.3. HRMS (MALDI): *m/z* 291.0088. Calcd. for $C_{13}H_{11}BrN_2O$: 291.0133 $[M + H]^+$.

Data for **19c**: Yield, 47%. mp, 65–67 °C. IR (KBr) cm^{-1}: 538 (C–Br), 993 (C=C), 1101 (C–O–C), 1573 (C=N), 3130 (Ar–CH), 3444 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 4.81 (*d*, J = 4.2 Hz, 2H), 5.16 (*d*, J = 16.2 Hz, 1H), 5.28 (*d*, J = 9.6 Hz, 1H), 6.17–5.90 (*m*, 1H), 7.24 (*t*, J = 7.8 Hz, 1H), 7.32 (*t*, J = 7.2 Hz, 1H), 7.38 (*d*, J = 7.8 Hz, 1H), 7.90 (*s*, 1H), 7.83 (*s*, 1H), 8.09 (*d*, J = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 49.1, 102.5, 107.6, 110.0, 117.9, 120.9, 121.0, 122.8, 125.2, 126.8, 132.4, 135.9, 145.5, 148.3. HRMS (ESI): *m/z* 303.0149. Calcd. for $C_{14}H_{12}BrN_2O$: 303.0133 $[M + H]^+$.

Data for **19d**: Yield, 43%. mp, 95–97 °C. IR (KBr) cm^{-1}: 539 (C–Br), 1123 (C–O–C), 1571 (C=N), 3110 (Ar–CH), 3441 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 4.94–4.93 (*d*, J = 6.0 Hz, 1H), 6.11–6.08 (*t*, J = 6.6 Hz, 1H), 7.28–7.30 (*t*, J = 6.6 Hz, 1H), 7.35–7.39 (*m*, 2H), 7.81 (*s*, 1H), 7.90 (*s*, 1H), 8.08–8.10 (*d*, J = 8.4 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ: 45.4, 103.4, 108.1, 109.7, 121.2, 121.3, 123.4, 124.5, 125.4, 126.4, 132.4, 135.7, 145.2, 148.5. HRMS (MALDI): *m/z* 370.9328. Calcd. for $C_{14}H_9BrCl_2N_2O$: 370.9354 $[M + H]^+$.

Data for **19e**: Yield, 99%. mp, 150–152 °C. IR (KBr) cm^{-1}: 540 (C–Br), 1109 (C–O–C), 1570 (C=N), 1719 (C=O), 3105 (Ar–CH), 3445 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 2.73 (*s*, 3H), 7.40 (*t*, J = 7.8 Hz, 1H), 7.46 (*t*, J = 7.8 Hz, 1H), 7.97 (*s*, 1H), 8.06 (*d*, J = 7.8 Hz, 1H), 8.14 (*s*, 1H), 8.51 (*d*, J = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ: 23.9, 107.4, 110.9, 116.2, 120.6, 124.2, 125.2, 125.8, 126.5, 134.7, 142.6, 152.0, 169.6. HRMS (MALDI): *m/z* 304.9926. Calcd. $C_{13}H_9BrN_2O_2$: 304.9926 $[M + H]^+$.

Data for **19f**: Yield, 84%. mp, 135–137 °C. IR (KBr) cm^{-1}: 538 (C–Br), 1114 (C–O–C), 1573 (C=N), 1709 (C=O), 3124 (Ar–CH), 3445 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.38–1.41

(*t*, *J* = 7.2 Hz, 3H), 3.02–3.06 (*q*, *J* = 7.2 Hz, 2H), 7.38–7.40 (*t*, *J* = 7.8 Hz, 1H), 7.96 (*s*, 1H), 8.04–8.05 (*d*, *J* = 7.8 Hz, 1H), 8.17 (*s*, 2H), 8.53–8.54 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 8.3, 28.4, 107.4, 110.6, 116.1, 120.5, 124.2, 125.8, 126.3, 128.5, 134.8, 142.6, 151.8, 172.6. HRMS (MALDI): *m*/*z* 319.0063. Calcd. $C_{14}H_{11}BrN_2O_2$: 319.0082 $[M + H]^+$.

Data for **19g**: Yield, 54%. mp, 132–135 °C. IR (KBr) cm^{-1}: 545 (C–Br), 1118 (C–O–C), 1363 (–SO_2–), 1572 (C=N), 3140 (Ar–CH), 3446 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 1.28 (*t*, *J* = 7.2 Hz, 3H), 3.40 (*q*, *J* = 7.2 Hz, 2H), 7.40–7.43 (*t*, *J* = 7.2 Hz, 1H), 7.45–7.47 (*t*, *J* = 7.2 Hz, 1H), 7.97–7.98 (*m*, 2H), 8.11 (*d*, *J* = 7.8 Hz, 1H), 8.14 (*s*, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 7.8, 48.5, 107.3, 111.1, 113.3, 121.3, 124.1, 124.9, 125.8, 126.4, 134.3, 142.2, 152.0. HRMS (MALDI): *m*/*z* 354.9735. Calcd. $C_{13}H_{11}BrN_2O_3S$: 354.9752 $[M + H]^+$.

Data for **19h**: Yield, 62%. mp, 98–100 °C. IR (KBr) cm^{-1}: 539 (C–Br), 1125 (C–O–C), 1571 (C=N), 1731 (C=O), 3138 (Ar–CH), 3444 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 4.66 (*s*, 2H), 7.44 (*t*, *J* = 7.2 Hz, 1H), 7.50 (*t*, *J* = 7.2 Hz, 1H), 8.00 (*s*, 1H), 8.07 (*d*, *J* = 7.8 Hz, 1H), 8.18 (*s*, 1H), 8.51 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 42.3, 107.5, 110.6, 111.9, 116.8, 121.2, 122.2, 125.2, 126.8, 128.5, 135.5, 149.8, 164.1. HRMS (ESI): *m*/*z* 338.9558. Calcd. $C_{13}H_8BrClN_2O_2$: 338.9536 $[M + H]^+$.

Data for **19i**: Yield, 41%. mp, 114–116 °C. IR (KBr) cm^{-1}: 540 (C–Br), 1147 (C–O–C), 1571 (C=N), 1724 (C=O), 3141 (Ar–CH), 3442 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 6.61 (*s*, 1H), 7.46–7.47 (*t*, *J* = 7.8 Hz, 1H), 7.50–7.51 (*t*, *J* = 7.8 Hz, 1H), 7.91–7.92 (*d*, *J* = 7.8 Hz, 1H), 8.01 (*s*, 1H), 8.07–8.08 (*d*, *J* = 7.8 Hz, 1H), 8.49 (*s*, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 65.7, 111.1, 112.3, 117.0, 121.3, 122.4, 125.7, 126.9, 127.1, 128.6, 135.8, 149.9, 160.7. HRMS (MALDI): *m*/*z* 372.9133. Calcd. for $C_{13}H_7BrCl_2N_2O_2$: 372.9146 $[M + H]^+$.

Data for **19j**: Yield, 55%. mp, 143–145 °C. IR (KBr) cm^{-1}: 554 (C–Br), 1123 (C–O–C), 1572 (C=N), 1704 (C=O), 3124 (Ar–CH), 3444 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 1.91 (*d*, *J* = 6.6 Hz, 3H), 5.10 (*q*, *J* = 6.6 Hz, 1H), 7.43 (*t*, *J* = 7.2 Hz, 1H), 7.48–7.52 (*t*, *J* = 7.2 Hz, 1H), 7.99 (*s*, 1H), 8.06 (*d*, *J* = 8.4 Hz, 1H), 8.30 (*s*, 1H), 8.54 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 20.1, 51.8, 108.5, 111.5, 120.8, 121.1, 124.9, 126.4, 126.7, 128.4, 135.1, 142.2, 152.3, 167.9. HRMS (MALDI): *m*/*z* 352.9699. Calcd. for $C_{14}H_{10}BrClN_2O_2$: 352.9692 $[M + H]^+$.

Data for **19k**: Yield, 72%. mp, 149–151 °C. IR (KBr) cm^{-1}: 539 (C–Br), 1113 (C–O–C), 1571 (C=N), 1740 (CO_2-), 3127 (Ar–CH), 3445 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 4.11 (*s*, 3H), 7.37 (*t*, *J* = 7.8 Hz, 1H), 7.44 (*t*, *J* = 7.8 Hz, 1H), 7.95 (*s*, 1H), 8.05 (*d*, *J* = 7.2 Hz, 1H), 8.26 (*d*, *J* = 8.4 Hz, 1H), 8.29 (*s*, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 54.6, 107.4, 110.7, 114.9, 120.8, 123.2, 123.8, 125.6, 126.2, 134.3, 142.5, 151.7, 161.1. HRMS (MALDI): *m*/*z* 320.9850. Calcd. for $C_{13}H_9BrN_2O_3$: 320.9875 $[M + H]^+$.

Data for **19l**: Yield, 63%. mp, 101–103 °C. IR (KBr) cm^{-1}: 540 (C–Br), 1126 (C–O–C), 1572 (C=N), 1717 (C=O), 3128 (Ar–CH), 3443 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 3.58 (*s*, 3H), 4.66 (*s*, 2H), 7.44 (*t*, *J* = 7.2 Hz, 1H), 7.47 (*t*, *J* = 7.2, 1H), 7.98 (*s*, 1H), 8.05–8.06 (*d*, *J* = 7.8 Hz, 1H), 8.27 (*s*, 1H), 8.54 (*d*, *J* = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 58.8, 71.1, 112.2, 116.1, 119.9, 120.5, 120.7, 122.5, 123.7, 124.5, 124.8, 126.1, 150.4, 169.0. HRMS (MALDI): *m*/*z* 335.0038. Calcd. $C_{14}H_{11}BrN_2O_3$: 335.0031 $[M + H]^+$.

Data for **19m**: Yield, 74%. mp, 116–118 °C. IR (KBr) cm^{-1}: 541 (C–Br), 1115 (C–O–C), 1572 (C=N), 1703 (COCO), 3127 (Ar–CH), 3444 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, DMSO-d_6): *δ*: 1.37–1.40 (t, *J* = 7.2 Hz, 3H), 4.44–4.47 (*q*, *J* = 7.2 Hz, 2H), 7.51–7.55 (*m*, 2H), 8.04–8.05 (*s*, 1H), 8.40 (*s*, 1H), 8.53 (*s*, 1H), 8.69–8.70 (*d*, *J* = 7.8 Hz,,1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 13.8, 63.4, 109.3, 111.4, 116.2, 121.0, 125.5, 126.4, 126.6, 128.5, 134.9, 142.0, 152.0, 156.5, 158.7. HRMS (MALDI): *m*/*z* 362.9973. Calcd. for $C_{15}H_{11}BrN_2O_4$: 362.9980 $[M + H]^+$.

Data for **19n**: Yield, 97%. mp, 101–103 °C. IR (KBr) cm^{-1}: 539 (C–Br), 1119 (C–O–C), 1572 (C=N), 3129 (Ar–CH), 3442 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 2.51 (*s*, 1H), 2.85 (*s*, 1H), 3.34 (*s*, 1H), 4.19–4.22 (*dd*, *J* = 15.0, 3.6 Hz, 1H), 4.54 (*d*, *J* = 15.0 Hz, 1H), 7.26 (*t*, *J* = 7.8 Hz, 1H), 7.33 (*t*, *J* = 7.2 Hz, 1H), 7.45 (*d*, *J* = 7.8 Hz, 1H), 7.85 (*s*, 1H), 7.88 (*s*, 1H), 8.08 (*d*, *J* = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): *δ*: 45.1, 48.0, 50.6, 103.1, 107.9, 109.8, 121.0, 121.2, 123.1, 125.2, 127.3, 128.5, 136.2, 148.5. HRMS (MALDI): *m*/*z* 319.0320. Calcd. for $C_{14}H_{11}BrN_2O_2$: 319.0289 $[M + H]^+$.

Data for **19o**: Yield, 87%. mp, 78–80 °C. IR (KBr) cm^{-1}: 539 (C–Br), 1109 (C–O–C), 1572 (C=N), 3111 (Ar–CH), 3454 (Pyrrolyl-CH). ^{1}H NMR (600 MHz, $CDCl_3$): *δ*: 0.43 (*d*, *J* = 7.2 Hz, 2H), 0.69 (*d*, *J* = 7.2 Hz, 2H), 1.34 (*m*, 1H), 4.05 (*d*, *J* = 6.6 Hz, 2H), 7.24 (*t*, *J* = 6.6 Hz, 1H), 7.31 (*t*, *J* = 7.2 Hz, 1H), 7.43 (*d*, *J* = 7.2 Hz, 1H), 7.89 (*s*, 1H), 7.95 (*s*, 1H), 8.08 (*d*, *J* = 7.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): *δ*: 4.0, 4.1, 11.0, 51.0, 102.5, 107.8, 109.8, 120.8, 121.0, 122.7, 125.7, 126.6, 136.2, 148.3, 150.4. HRMS (MALDI): *m*/*z* 317.0249. Calcd. $C_{15}H_{13}BrN_2O$: 317.0289 $[M + H]^+$.

2.2. X-ray diffraction analysis

Colourless crystals of compound **10** (0.26 mm × 0.20 mm × 0.10 mm) were mounted on a quartz fibre with protection oil. Cell dimensions and intensities were measured at 299 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo K_α radiation (*λ* = 0.71073 Å); θ_{max} = 20.30; 3172 measured reflections; 1809 independent reflections (R_{int} = 0.0275) of which 557 had [$I > 2\sigma_{(I)}$]. The structure was solved by direct methods using SHELXS-97; all other calculations were performed with Bruker SAINT System and Bruker SMART programs. Full-matrix least-squares refinement based on F^2 using the weight of $\omega = 1/[\sigma^2(Fo^2) + (0.0659P)^2 + 0.0500P]$ gave final values of $R = 0.0644$, $\omega R = 0.1363$, and GOF(F) = 1.065 for 139 restraints and 1174 parameters reflections. Maximum shift/error = 0.000(3), max/min residual electron density = 0.270/−0.195 eÅ^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter. In compound **10**, $C_{11}H_7ClN_2O$, the benzene and pyrrole rings are almost coplanar [dihedral angle = 0.8 (0)°]. The dihedral angle between the indole and oxazole rings is 18.7 (1)°. The crystal structure is stabilized by N–H···N hydrogen bonds and there are also π–π stacking interactions.

Colourless crystals of compound **18o** (0.16 mm × 0.12 mm × 0.10 mm) were mounted on a quartz fibre with protection oil. Cell dimensions and intensities were measured at 297 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo Kα radiation (*λ* = 0.71073 Å); θ_{max} = 23.48; 8953 measured reflections; 5043 independent reflections (R_{int} = 0.0349) of which 2235 had [$I > 2\sigma_{(I)}$]. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.9551; T_{max} = 0.9716). The structure was solved by direct methods using SHELXS-97; all other calculations were performed with Bruker SAINT System and Bruker SMART programs. Full-matrix least-squares refinement based on F^2 using the weight of $\omega = 1/[\sigma^2(Fo^2) + (0.0633P)^2 + 0.4557P]$ gave final values of $R = 0.0615$, $\omega R = 0.1387$, and GOF(F) = 1.105 for 200 restraints and 2131 parameters reflections. Maximum shift/error = 0.000(3), max/min residual electron density = 0.261/−0.163 eÅ^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter. In compound **18o**, $C_{15}H_{11}ClN_2O_4$, the benzene and pyrrole rings are almost coplanar [dihedral angle = 0.2 (5)°]. The dihedral angle between the indole and oxazole rings is 6.8 (2)°. The crystal structure is stabilized by Van der Waals forces and there are also π–π stacking interactions.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre with the deposition No.

Table 1
Details of the primary-level leaf-piece assays.

Pathogen	Host	Chemical rates[a]	Replicates[b]	Spore rates[c]
Phytophthora infestans	Tomato	200, 60	2	150,000
Septoria tritici	Wheat	100	3	1,000,000
Uromyces viciae-fabae	Field bean	100	2	0.3[c]

[a] Rates are given as parts per million a.i. in the formulated sample applied to the leaf-piece.
[b] Number of replicates per rate.
[c] Spore rates are sporangia per ml for *P. infestans*, conidia per ml for *S. tritici*, and mg per ml for *U. viciae-fabae*.

CCDC-835955 (compound **10**) and 835956 (compound **18o**). Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/.

2.3. Biological assays

2.3.1. Leaf-piece assays

200–300 μl water agar per well was dispensed into the 96-well assay plates, and 6 mm diameter leaf pieces (6 mm length for wheat) were cut and placed on the surface of the agar. Compounds to be tested were formulated to the appropriate rate, and 10 μl samples were dispensed onto the leaf pieces.

The plates were inoculated with spore suspensions of the appropriate pathogen at a set rate (Table 1), using a handheld spray gun. The plates were covered with lids and placed in controlled environment cabinets for between 5 and 14 days, depending on the species being tested.

2.3.2. Artificial media assays

Spore suspensions were prepared from stock plates of the target pathogens (Table 2) for all species apart from *Pythium dissimile*, for which a suspension of fragmented mycelia was used. These suspensions were made into a 3% agar, and dispensed into 96-well plates containing formulated samples of the compounds to be tested (10 μl formulated sample and 90 μl spore suspension, to give the chemical rates detailed in Table 2).

The plates were then stored in controlled environments set to appropriate conditions, until assessment between 5 and 14 days later, depending on the species.

2.3.3. Assessment of biological assays

Assessment for all assays was carried out by eye, with each individual well scored on a three-band pattern with additional result types for assay failure and phytotoxic activity on the leaf piece (Table 3). The resulting data were collated for each compound, and averages across replicates were used to make a judgement of the overall activity level of the compound.

Table 2
Details of the primary-level assays conducted in artificial media.

Pathogen	Chemical rates[a]	Replicates[b]	Spore rate[c]
Pythium dissimile	20, 2	2	0.5[c]
Alternaria solani	20, 2	2	20,000
Botryotinia fuckeliana (*Botrytis cinerea*)	20, 2	2	15,000
Gibberella zeae (*Fusarium graminearum*)	20, 2	2	10,000

[a] Rates are given as parts per million a.i. in the final artificial media mixture.
[b] Number of replicates per rate.
[c] Spore rates are given in spores per ml, with the exception of *P. dissimile* which is given as an optical density reading at 425 nm.

Table 3
Assessment criteria for the biological assays.

Scoring band	Well condition
0	0–49% control of disease or pathogen
55	50–80% control of disease or pathogen
99	81–100% control of disease or pathogen
NCH	Not captured (too phytotoxic)
NC	Not captured (test failure)

3. Results and discussion

3.1. Synthetic chemistry

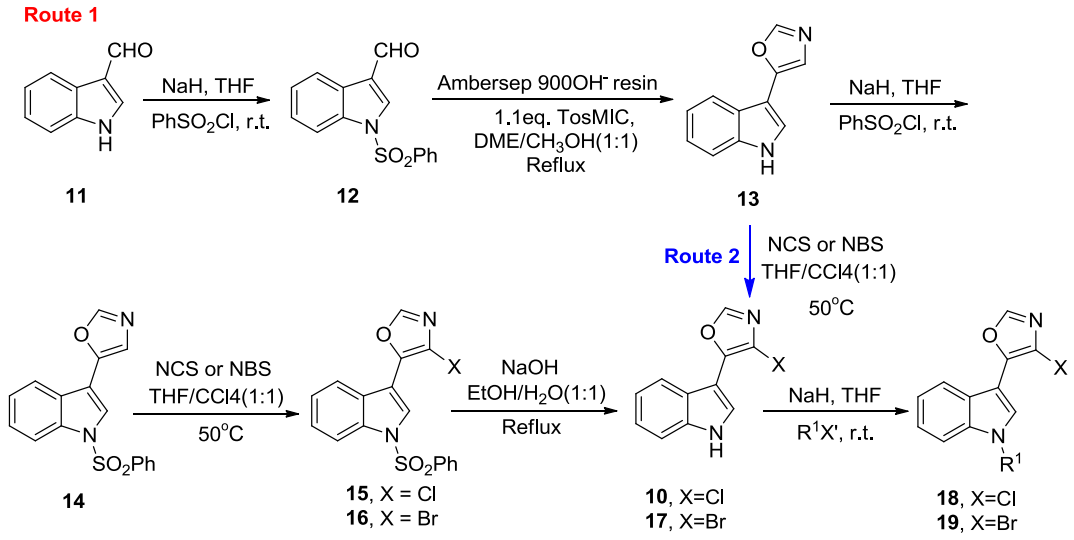
The synthetic route to the target compounds **18** and **19** is shown in Scheme 1. The commercially available indole-3-carboxaldehyde **11** was used as the starting material. Following protection of the indole nitrogen with a phenylsulfonyl group [15,16], reaction with *p*-toluene-sulfonylmethyl isocyanide (TosMIC) in the presence of the ion exchange resin of Ambersep® 900(OH) in a mixture of DME and methanol (*v*/*v*, 1:1) as solvent afforded 5-(1*H*-indol-3-yl)oxazole **13** in a yield of 66%. Compared to the previous method, cyclization protocol used herein shortened the reaction time from 8 h to 2 h, and meanwhile N-deprotection occurred as well that would be very convenient for the subsequent substitution to the NH group [17,18]. Originally, we were concerned that the free NH group would interfere with the subsequent halogenation of the oxazole ring, so we reprotected compound **13** to give the intermediate **14**, which was chlorinated or brominated with NCS or NBS, respectively, and then deprotected under basic conditions to afford the key intermediates **10** and **17** (Route **1**) [15,19]. In fact, this transformation of compound **13** into compound **10** involves three steps and the overall yield was very low. In order to prepare sufficient intermediate **10** to continue with the sequence, we then made the improvement that compound **13** could be converted directly into **10** or **17** without N-protection (Route **2**). After optimization, we found that intermediate **13** can be treated directly with NBS/NCS (1.1 equivalents) in a mixture of THF and CCl_4 at 50 °C to afford **17**/**10** in a good yield of 84% and 72%, respectively. In addition, this new synthetic route would complete within 8 h and afford about 46% yield, whereas the three-step route (Protection-Halogenation-Deprotection) usually require more than 48 h and lead to lower yield (25%). Finally, the target compounds **18** and **19** were easily prepared by the reaction between the intermediate **10**/**17** and various electrophiles. The reaction conditions and yields for the target compounds **18** and **19** are listed in Table 4.

The structures of all the intermediates and final target compounds were confirmed by ^{1}H NMR and HRMS spectral data. In addition, the crystal structures of the intermediate **10** and the target compound **18o** were determined by X-ray diffraction analysis, as shown in Fig. 2.

3.2. Fungicidal activity and the structure–activity relationships

The results of the biological testing against seven phytopathogenic fungi are given in Table 5. For the purposes of the structure–activity relationship analysis, compound **13**, compounds (**10**, **18a**–**r**) and compounds (**17**, **19a**–**o**) were defined as indole-oxazole, 4-chloroindole-oxazole derivatives and 4-bromoindole-oxazole derivatives, respectively. It is noticeable that any activity present is mainly in the artificial media assays, and rarely extends to those pathogens tested on leaf pieces. It is also noticeable that the fungicidal activity lacks potency, rarely extending to the lower rates tested.

Although it is difficult to extract clear structure–activity relationships from the biological data, the first conclusion that can be

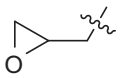
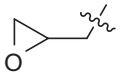


Scheme 1. Synthetic route to the compounds **18** and **19**.

drawn is that the spectrum of fungicidal activity is improved by substituting a halogen onto the 4-position of the oxazole ring. For example, compared with compound **13**, compounds **10** and **17** displayed a broader spectrum of activity in the artificial media assays and some moderate activity on the leaf-piece assays. Compound **10** was also the only analogue to show clear activity at a low rate, in this case against *Alternaria solani*. However, when derivatives with equivalent substitutions are compared it is not possible to determine a consistent difference in biological activity between the 4-chloroindoleoxazoles and the 4-bromoindoleoxazoles. This may in part be due to limitations inherent in the test method and it is possible that biological assays with a greater number of rates and species and a more nuanced scoring system would detect a difference.

Substitution on the nitrogen of the indole ring was also found to clearly affect fungicidal activity. Compounds with alkyl substituents (**18a**, **18b**, **19a**, **19b**) had dramatically reduced activity compared to the unsubstituted equivalents, and compounds with acetyl or propionyl substituents at this position (**18e**, **18f**, **19e**, **19f**) were completely inactive. Substitutions with aromatic groups also tended to reduce fungicidal activity (*e.g.* **18p**, **18q**). By contrast, certain *N*-acyl derivatives showed activity similar to that of the unsubstituted compounds on the artificial media assays, and the 4-bromoindoxazole with a chloro-acetyl substituent (**19h**) matched

Table 4
Conditions and yields for the synthesis of compounds of **18** and **19**.

Entry	R^1	Time[a] (h)	Yield[b] (%)	Entry	R^1	Time[a] (h)	Yield[b] (%)
18a	CH_3	3	96	**18r**		0.25[c]	87
18b	CH_3CH_2	3	66	**19a**	CH_3	3	99
18c	CH_2:$CHCH_2$	6	99	**19b**	CH_3CH_2	3	99
18d	CCl_2:$CHCH_2$	3	39	**19c**	CH_2:$CHCH_2$	6	47
18e	CH_3CO	3	76	**19d**	CCl_2:$CHCH_2$	3	43
18f	CH_3CH_2CO	6	65	**19e**	CH_3CO	3	99
18g	$CH_3CH_2SO_2$	3	63	**19f**	CH_3CH_2CO	6	84
18h	$ClCH_2CO$	3	62	**19g**	$CH_3CH_2SO_2$	6	54
18i	Cl_2CHCO	6	59	**19h**	$ClCH_2CO$	6	62
18j	CCl_3CO	6	54	**19i**	Cl_2CHCO	6	41
18k	$CH_3CHClCO$	3	60	**19j**	$CH_3ClCHCO$	3	55
18l	CH_3OCO	3	65	**19k**	CH_3OCO	6	72
18m	CH_3OCH_2CO	3	50	**19l**	CH_3OCH_2CO	3	63
18n	$CH_3CH_2OCOCH_2$	6	40	**19m**	CH_3CH_2OCOCO	3	74
18o	CH_3CH_2OCOCO	3	56	**19n**		3	59
18p	2,4-di-F-$C_6H_3CH_2$	3	92	**19o**		0.25[c]	87
18q		3	61				

[a] Time to finish the reaction monitored by TLC.
[b] Isolated yields.
[c] Microwave-assisted synthesis was employed.

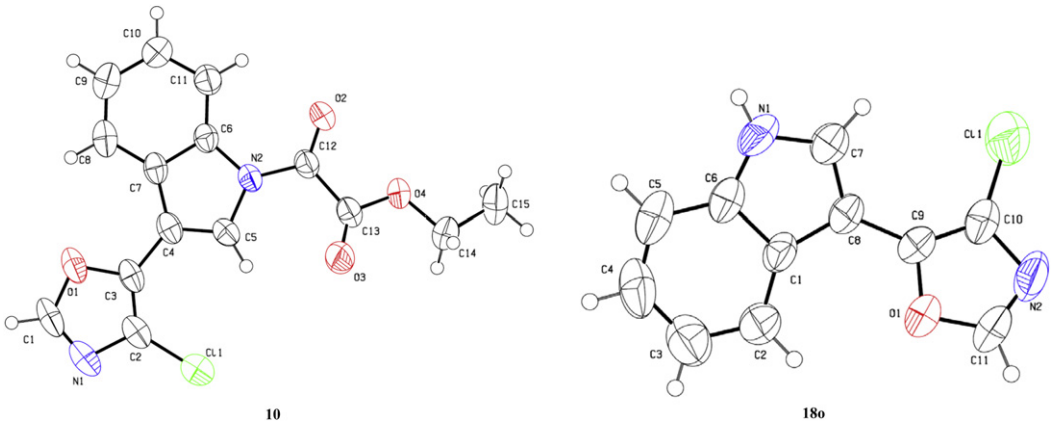


Fig. 2. Crystal structures of compounds **10** and **18o**.

or even slightly improved upon the activity of the equivalent unsubstituted compound (**17**) on the leaf-piece assays, although the 4-chloroindoxazole with a similar substitution lacked this activity (**18h**).

Table 5
Fungicidal activities of pimprinine analogues. Data are presented as means of the assessment scores (Table 4) across two replicates unless otherwise stated.

No.	Species	PHY[a]	SEP[a,b]	URO [a]	PYT[a]	ALT[a]	BOT[a]	GIB[a]
	Rate (ppm)	200/60	100	100	20/2	20/2	20/2	20/2
	10	0/49	36	55	**99**/0	**99**/**99**	**99**/0	**99**/0
	13	0/0	0	0	**99**/0	**77**/0	0/0	0/0
	17	49/0	0	**77**	**99**/0	**99**/0	**99**/0	**99**/0
	18a	0/0	0	**77**	0/0	0/0	0/0	0/0
	18b	0/0	0	**99**	55/0	0/0	0/0	0/0
	18c	0/0	0	**99**	0/0	0/0	0/0	0/0
	18d	–[c]	–	–	–	–	–	–
	18e	0/0	0	0	0/0	0/0	0/0	0/0
	18f	0/0	0	0	0/0	0/0	0/0	0/0
	18g	0/0	0	55	27/0	0/0	0/0	0/0
	18h	27/0	0	49	**99**/0	55/0	**99**/0	**99**/0
	18i	0/0	0	0	**99**/0	**99**/0	**99**/0	**99**/0
	18j	0/0	0	55	**99**/0	**99**/0	**99**/0	**99**/0
	18k	0/0	0	55	0/0	55/0	0/0	0/0
	18l	0/0	0	0	0/0	0/0	–/–	0/0
	18m	0/0	0	55	55/0	**99**/0	**77**/0	0/0
	18n	49/0	0	0	0/0	0/0	0/0	0/0
	18o	0/0	33	0	**77**/0	**99**/0	**99**/0	**99**/0
	18p	0/49	0	27	0/0	0/0	0/0	0/0
	18q	0/0	0	**77**	0/0	0/0	0/0	0/0
	18r	49/0	33	55	**99**/0	0/0	0/0	0/0
	19a	49/0	0	55	0/0	0/0	0/0	0/0
	19b	0/0	0	**99**	55/49	55/0	0/0	0/49
	19c	49/0	18	49	0/0	0/0	27/0	0/0
	19d	0/0	0	0	0/0	0/0	0/0	0/0
	19e	0/0	0	0	0/0	0/0	0/0	0/0
	19f	0/0	0	0	0/0	0/0	0/0	0/0
	19g	0/0	0	0	0/0	0/0	0/0	0/0
	19h	**99**/0	18	49	**99**/0	**99**/27	**99**/0	**99**/0
	19i	0/0	0	27	**77**/0	**99**/0	**99**/0	**99**/0
	19j	0/0	0	27	0/0	55/0	0/0	0/0
	19k	0/0	0	0	0/0	0/0	–/–	0/0
	19l	0/0	0	**77**	**77**/0	**99**/0	**99**/0	**99**/0
	19m	–[c]	–	–	–	–	–	–
	19n	–[c]	–	–	–	–	–	–
	19o	27/0	0	0	55/0	0/0	0/0	0/0

[a] PHY, *Phytophthora infestans* (on tomato leaf pieces); SEP, *Septoria 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] The data are the mean of three replicates.
[c] Not tested.

4. Conclusion

In summary, we have synthesized a series of pimprinine analogues and measured their fungicidal activities. Biological testing showed that some of the analogues exhibited broad-spectrum fungicidal activity against plant pathogens growing in artificial media. The seven most active compounds **10**, **17**, **18h**, **18o**, **19h**, **19i** and **19l** were identified as the most promising candidates for further study. Further structural optimization of pimprinine analogues is well under way, alongside more detailed biological testing of the most active compounds, in order to better define their levels of fungicidal activity.

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