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Original article

Synthesis and antifungal activity of 3-(1,3,4-oxadiazol-5-yl)-indoles and 3-(1,3,4-oxadiazol-5-yl)methyl-indoles

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ABSTRACT

On the basis of the principle of combination of active structural moieties, a modified and efficient synthetic method for three series of novel indole-based 1,3,4-oxadiazoles is described. Bioassays conducted at Syngenta showed that several of the synthesized compounds exhibit higher antifungal activity than pimprinine, the natural product which inspired this synthesis. Two main structural alterations were found to broaden the spectrum of biological activity in most cases. Compounds **3g**, **6c**, **6e**, **6h**, **9d**, **9e**, **9h** and **9m** (Fig. 1) were identified as the most active on the biological assays, and will be studied further.

1. Introduction

Indole derivatives are an important class of heterocyclic compounds with a wide range of biological activities [1]. Indole is a substructural element of many natural products, and is widely used as a scaffold in agricultural and medicinal chemistry. For example, indole-3-acetic acid, also known as IAA, is a key plant growth hormone [2], and tryptophan, an essential amino acid, participates in many essential biological processes [3]. Indomethacin is a non-steroidal anti-inflammatory drug [4]. Sumatriptan, Frovatriptan and Zolmitriptan are used to treat acute migraine attacks and headaches [5]. Reserpine, an indole alkaloid, is an antipsychotic and antihypertensive drug that has been used for the control of high blood pressure and for the relief of psychotic symptoms [6]. And vinblastine is an antimicrotubule drug used to treat certain kinds of cancer, including Hodgkin's lymphoma and non-small cell lung cancer [7] (Fig. 2).

Pimprinine, an indole alkaloid originally isolated in 1963 from the filtrates of cultures of *Streptomyces pimprina* [8], belongs to the class of naturally occurring 5-(3-indolyl)oxazoles. It was screened on bioassays at Syngenta, where it demonstrated weak antifungal activity. In addition, a 4-chloro-analogue of pimprinine called streptochlorin, also a natural product, has a good spectrum of antifungal activity, but low potency (Table 4).

Compounds containing a 1,3,4-oxadiazole ring display a broad spectrum of biological activities, including anticancer [9], antimicrobial [10], antineoplastic [11], antifungal [12,13], antibacterial [14] and anti-HIV [15] activities. For example, Oxadiazon is the first oxadiazole herbicide developed by Rhone-Poulenc and launched in 1969, Metoxadiazone is a widely used household insecticide developed by Sumitomo Chemical and launched in 1978, (S)-9b is reported to exhibit highly selective and potent inhibitory activity against glycogen synthase kinase 3β (GSK-3β) [16], MK-0633 *p*-toluenesulfonate was identified as a potent and selective inhibitor of 5-lipoxygenase (5-LO) [17], 3(H) is reported to be a human neutrophil elastase inhibitor and is in clinical evaluation [18], Zibotentan is an endothelin receptor antagonist as an anticancer candidate [19], and Raltegravir, also called MK-0518, was the first HIV-integrase inhibitor approved by the FDA in October 2007 for the treatment of HIV/AIDS-infected patients [15,20] (Fig. 3).

1,3,4-Oxadiazole is a very good bioisostere of amide and ester functional groups and is reported to contribute substantially to pharmacological activity by participating in hydrogen bonding interactions with various receptors [21]. On the basis of the principle

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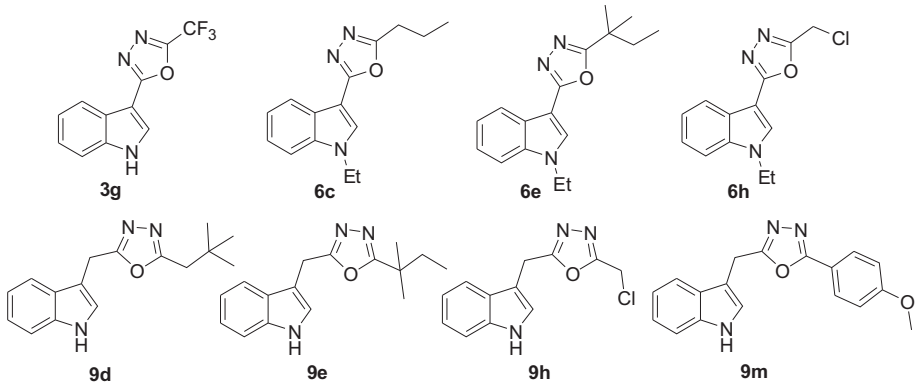


Fig. 1. Structures of the most active synthetic pimprinine derivatives.

of combination of active structural moieties, it has been reported that the substitution by oxadiazoles at the 3-position of the indole nucleus enhances these activities [22,23].

As a continuation of our extensive research program aimed at the discovery of novel bioactive compounds, we have described our use of pimprinine as a lead structure on which to carry out optimization with the aim of discovering synthetic analogues with simple structures and improved antifungal activity [24]. In the work described in this paper, our focus has been on the replacement of the oxazole ring of pimprinine with an oxadiazole ring. In addition, the structure–activity relationships of 3-(1,3,4-oxadiazol-5-yl)-indoles and analogues are also described.

Although many synthetic approaches to 1,3,4-oxadiazoles have been described [25], few of these are suitable for the preparative synthesis of indole-based 1,3,4-oxadiazole derivatives for a number of reasons. Modifying a method described by Hai-Liang Zhu [26], we have efficiently synthesized three series of indole-based 1,3,4-oxadiazole derivatives, some of which showed antifungal activity, and the structure–activity relationships within a series of such compounds is summarized.

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. Methyl indole-3-carboxylate and ethyl indole-3-acetate were bought from the Alfa Aesar Company (Tianjin, China). Yields were not optimized. ^{1}H NMR spectra were recorded on a VARIAN Mercury-Plus 400/600 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal reference. ^{13}C NMR and ^{13}C DEPT spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury-Plus 400/600 (100/150 MHz) spectrometer and chemical shifts (δ) are given in ppm relative to the centre line of a triplet at 77.0 ppm of $CDCl_3$ or 39.5 ppm of DMSO-d_6. High resolution mass spectra (HRMS) were acquired in positive mode on a WATERS MALDI SYNAPT G2 HDMS (MA, USA) or Agilent 6224 TOF LC/MS (ESI). MS spectra were determined using a Trace MS 2000 organic mass spectrometry, and the signals were given in m/z. Melting points were taken on a Büchi B-545 melting point apparatus and are uncorrected.

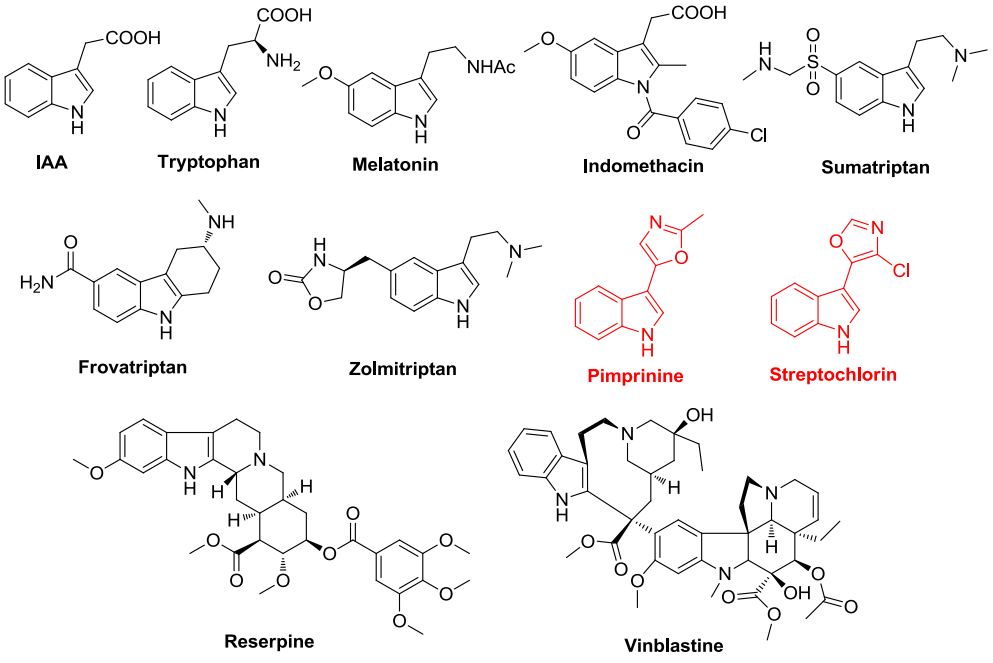


Fig. 2. Structures of indole-containing drugs and natural products.

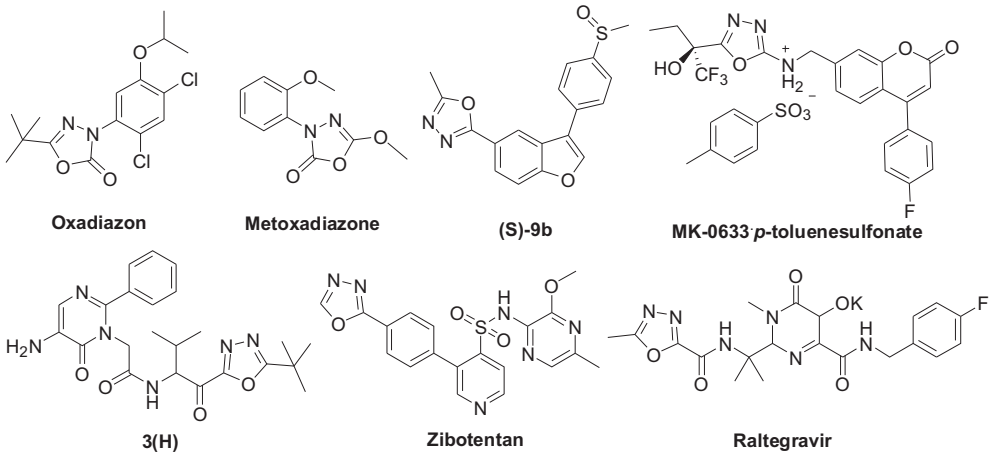


Fig. 3. Structures of 1,3,4-oxadiazole-containing agrochemicals, enzyme inhibitors and drugs.

*2.1.1. Preparation of 1H-indole-3-carbohydrazide **2** (Scheme 1)*

Hydrazine hydrate (99%, 2 mL, 40 mmol) was added in one portion to methyl indole-3-carboxylate **1** (10 mmol, 1.75 g) dissolved in dry ethanol (50 mL) at room temperature, and the resulting solution was heated under reflux for 8 h. The reaction mixture was allowed to cool and the solid obtained was filtered off and washed with a small quantity of ethanol to give the 1*H*-indole-3-carbohydrazide **2**. Yield: 1.66 g, 95%, white solid, mp 234–236 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.34 (s, 2H), 7.10–7.11 (m, 2H), 7.43 (t, J = 3.6 Hz, 2H), 7.98 (s, 1H), 8.15 (d, J = 7.2 Hz, 3H), 9.18 (s, 1H), 11.55 (s, 1H); EI-MS: m/z (%) 175 (M^+, 22), 144 (100), 116 (17), 89 (11).

*2.1.2. General procedure for the synthesis of target compounds **3** (Scheme 1)*

Equimolar quantities of compound **2** (1 mmol) and a substituted carboxylic acid were dissolved in phosphoryl chloride (5 mL) and heated at 80 °C for 3–6 h, the progress of reaction being monitored by TLC. The reaction mixture was then heated under reduced pressure to allow excess phosphoryl chloride to distill off, and the residue was subjected to flash chromatography on silica gel using 15–25% acetone in petroleum ether as eluent to give the target compounds **3a**–**m** (Table 1).

*2.1.2.1. Data for **3a**.* White solid, mp 236–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (m, 3H), 7.32–7.35 (m, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.90 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.5, 99.7, 112.4, 120.3, 121.1, 122.8, 124.1, 127.7, 136.5, 161.4, 161.8. HRMS (MALDI): m/z 222.0648. Calcd. for $C_{11}H_9N_3O$: 222.0643 $[M + Na]^+$.

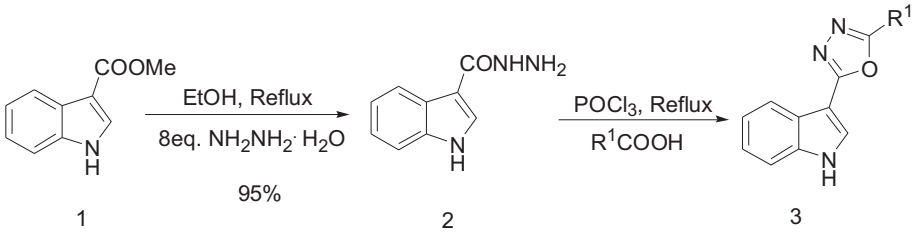
*2.1.2.2. Data for **3b**.* White solid, mp 205–207 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.47 (t, J = 7.8 Hz, 3H), 2.98 (q, J = 7.8 Hz, 2H), 7.32 (t, J = 3.6 Hz, 1H), 7.49 (t, J = 6.6 Hz, 1H), 7.91 (s, 1H), 8.27 (d, J = 6.0 Hz, 1H), 9.00 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.6, 18.3, 99.7, 112.4, 120.3, 121.1, 122.8, 124.1, 127.7, 136.4, 161.7, 165.3. HRMS (MALDI): m/z 214.0980. Calcd. for $C_{12}H_{11}N_3O$: 214.0980 $[M + H]^+$.

*2.1.2.3. Data for **3c**.* White solid, mp 144–146 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.09 (t, J = 7.8 Hz, 3H), 1.87–1.93 (m, 2H), 2.93 (t, J = 7.8 Hz, 3H), 7.31 (t, J = 3.6 Hz, 1H), 7.48 (t, J = 5.4 Hz, 1H), 7.92 (s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 9.10 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4 19.6, 26.4, 99.7, 112.4, 120.2, 121.1, 122.7, 124.1, 127.7, 136.4, 161.7, 164.2. HRMS (MALDI): m/z 250.0944. Calcd. for $C_{13}H_{13}N_3O$: 250.0956 $[M + Na]^+$.

*2.1.2.4. Data for **3d**.* White solid, mp 167–169 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.05 (s, 9H), 2.72 (s, 2H), 7.25–7.30 (m, 2H), 7.58 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H), 12.04 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 29.0, 31.2, 38.1, 99.7, 112.4, 120.1, 122.8, 124.1, 127.8, 136.5, 161.8, 163.0. HRMS (MALDI): m/z 294.0982. Calcd. for $C_{15}H_{17}N_3O$: 294.1009 $[M + K]^+$.

*2.1.2.5. Data for **3e**.* White solid, mp 148–150 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.83 (t, J = 7.2 Hz, 3H), 1.42 (s, 6H), 1.77 (q, J = 7.2 Hz, 2H), 7.26–7.39 (m, 2H), 7.56 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 7.2 Hz, 1H), 8.19 (s, 1H), 12.05 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 9.0, 25.3, 33.6, 35.6, 99.7, 112.4, 120.1, 121.1, 122.8, 124.1, 127.9, 136.5, 161.8, 169.5. HRMS (MALDI): m/z 256.1449. Calcd. for $C_{15}H_{17}N_3O$: 256.1450 $[M + H]^+$.

*2.1.2.6. Data for **3f**.* White solid, mp 151–152 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.86 (s, 9H), 1.04 (d, J = 4.8 Hz, 3H), 1.14–1.17 (m, 3H), 1.35 (d, J = 13.8 Hz, 1H), 2.06–2.07 (m, 1H), 2.80–2.83 (m, 2H), 7.24–7.28 (m, 2H), 7.54 (t, J = 7.8 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 8.15 (s, 1H), 12.00 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.6, 27.9, 29.6, 30.7,



Scheme 1. Synthesis of 2-indolyl-5-substituted-1,3,4-oxadiazoles **3**.

Table 1
Reaction times and yields in the synthesis of compounds **3**.

Entry	R^1	Time	Yield
3a	CH_3	6 h	81%
3b	CH_3CH_2	6 h	83%
3c	$CH_3CH_2CH_2$	3 h	81%
3d	$(CH_3)_3CCH_2$	3 h	71%
3e	$CH_3CH_2(CH_3)_2C$	3 h	74%
3f	$(CH_3)_3CCH_2(CH_3)CHCH_2$	3 h	71%
3g	CF_3	6 h	63%
3h	CH_2Cl	6 h	70%
3i	2-F-C_6H_4	5 h	45%
3j	2-I-C_6H_4	5 h	37%
3k	2-Cl-C_6H_4	6 h	47%
3l	3-Cl-C_6H_4	6 h	49%
3m	4-Me-C_6H_4	5 h	67%

33.7, 49.4, 98.6, 112.4, 120.2, 121.1, 122.8, 124.1, 127.8, 136.4, 161.7, 163.5. ^{13}C DEPT (100 MHz, DMSO-d_6): CH_3 (methyl): 22.6, 29.6; CH_2 (methylene): 33.8, 49.4; CH (methine): 27.9, 112.4, 120.2, 121.1, 122.8, 127.7. HRMS (MALDI): *m/z* 298.1941. Calcd. for $C_{18}H_{23}N_3O$: 298.1919 $[M + H]^+$.

2.1.2.7. Data for ***3g***. White crystal, mp 219–221 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.31–7.36 (m, 2H), 7.61 (d, J = 7.2 Hz, 1H), 8.13 (d, J = 6.6 Hz, 1H), 8.43 (s, 1H), 12.35 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 97.8–97.0 (d, J_{C-F} = 5.7 Hz, 1C), 112.7–112.8 (d, J_{C-F} = 23.0 Hz, 1C), 115.7, 117.5, 120.0, 120.1, 124.1, 130.4, 136.6, 151.7–152.0 (d, J_{C-F} = 42.6 Hz, 1C), 164.1. HRMS (MALDI): *m/z* 254.0503. Calcd. for $C_{11}H_6F_3N_3O$: 254.0541 $[M + H]^+$.

2.1.2.8. Data for ***3h***. White solid, mp 204–206 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.16 (s, 2H), 7.27–7.32 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 12.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.5, 98.9, 112.6, 120.2, 121.4, 123.0, 124.1, 128.7, 136.5, 160.5, 163.0. HRMS (MALDI): *m/z* 234.0415. Calcd. for $C_{11}H_8ClN_3O$: 234.0434 $[M + H]^+$.

2.1.2.9. Data for ***3i***. Pale pink solid, mp 226–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26–7.29 (m, 2H), 7.32–7.52 (m, 3H), 7.73 (t, J = 7.2 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 8.17–8.19 (m, 1H), 8.30 (s, 1H), 12.11 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.2, 105.8, 111.7–112.5 (t, J_{C-F} = 41.8 Hz, 1C), 111.9–112.5 (d, J_{C-F} = 20.6 Hz, 1C), 120.2, 121.4, 122.9, 124.9, 125.2, 128.6, 129.4, 133.6, 136.5, 157.9, 162.9, 169.2. HRMS (MALDI): *m/z* 280.0878. Calcd. for $C_{16}H_{10}FN_3O$: 280.0886 $[M + H]^+$.

2.1.2.10. Data for ***3j***. White solid, mp 197–199 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.27–7.31 (m, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 8.17 (t, J = 8.4 Hz, 1H), 8.27 (s, 1H), 12.12 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 95.7, 99.2, 112.5, 120.2, 121.4, 122.9, 124.1, 128.6, 129.1, 131.3, 132.7, 136.5, 140.7, 145.7, 161.8, 162.3. HRMS (MALDI): *m/z* 387.9927. Calcd. for $C_{16}H_{10}IN_3O$: 387.9947 $[M + H]^+$.

2.1.2.11. Data for ***3k***. Light yellow solid, mp 209–211 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.27–7.28 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 8.13–8.17 (m, 2H), 8.29 (s, 1H), 12.11 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.2, 112.6, 120.1, 121.4, 122.9, 124.1, 128.8, 129.4, 131.1, 131.7, 132.2, 132.8, 136.5, 140.7, 161.0, 162.3. HRMS (MALDI): *m/z* 296.0562. Calcd. for $C_{16}H_{10}ClN_3O$: 296.0591 $[M + H]^+$.

2.1.2.12. Data for ***3l***. White solid, mp 244–246 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.29–7.30 (m, 2H), 7.58 (d, J = 9.0 Hz, 1H), 7.66–7.72 (m, 2H), 8.10 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 8.39 (s, 1H), 12.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.3, 112.5, 120.3, 121.3, 122.9, 124.1, 124.9, 125.6, 125.8, 128.9, 131.3, 134.0, 136.5, 152.0, 160.7, 162.3. HRMS (MALDI): *m/z* 296.0597. Calcd. for $C_{16}H_{10}ClN_3O$: 296.0591 $[M + H]^+$.

2.1.2.13. Data for ***3m***. White solid, mp 226–228 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.42 (s, 3H), 7.29 (t, J = 3.6 Hz, 1H), 7.46 (d, J = 3.6 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 7.2 Hz, 1H), 8.18 (d, J = 6.6 Hz, 1H), 8.32 (s, 1H), 12.09 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1, 99.5, 112.5, 120.3, 121.0, 121.2, 122.8, 124.2, 126.3, 128.4, 129.9, 136.5, 141.5, 161.7, 161.9. HRMS (MALDI): *m/z* 298.0961. Calcd. for $C_{17}H_{13}N_3O$: 298.0956 $[M + Na]^+$.

2.1.3. Preparation of 1-ethyl-1H-indole-3-carboxylic acid methyl ester ***4*** *(Scheme 2) [27]*

NaH (60% dispersion in mineral oil, 0.96 g, 40.00 mmol) was added in portions to a stirred solution of methyl indole-3-carboxylate **1** (3.50 g, 20.00 mmol) in anhydrous THF (50 mL) cooled in an ice bath. The resulting mixture was then allowed slowly to warm to r.t. After stirring for 30 min, ethyl bromide (2.62 g, 24.0 mmol) in anhydrous THF (5 mL) was added dropwise. When TLC monitoring showed complete consumption of the starting material, the reaction mixture was evaporated under reduced pressure to leave a residue that was treated with ice water (300 mL). The resulting solid was filtrated off and recrystallized from acetone/petroleum ether (60–90 °C) to give the desired intermediate **4**. Yield: 4.02 g, 99%.

2.1.4. Preparation of 1-ethyl-1H-indole-3-carbohydrazide ***5*** *(Scheme 2)*

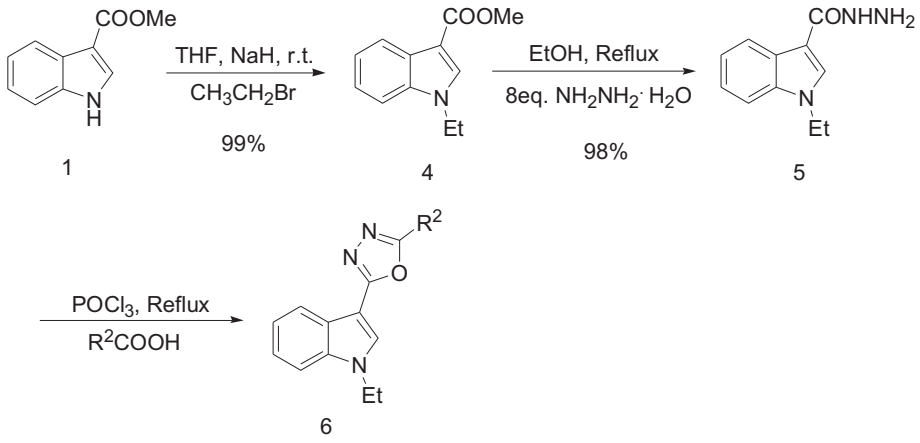
Hydrazine hydrate (99%, 2 mL, 40 mmol) was added in one portion to a solution of compound **4** (2.03 g, 10 mmol) in dry ethanol (50 mL) and the mixture was then heated at reflux for 10 h. The reaction mixture was cooled and the solid obtained was filtered off and washed with a small quantity of ethanol to give the desired intermediate **2**. Yield: 1.99 g, 98%, white solid, mp 144–146 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.39 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.35 (s, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.52 (d, J = 8.4, Hz, 1H), 8.01 (s, 1H), 8.13 (d, J = 7.2 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.1, 40.7, 108.2, 110.1, 120.5, 121.2, 121.8, 126.6, 129.4, 135.6, 164.9. HRMS (ESI): *m/z* 226.0959. Calcd. for $C_{11}H_{13}N_3O$: 226.0956 $[M + Na]^+$.

2.1.5. General procedure for the synthesis of target compounds ***6*** *(Scheme 2)*

Equimolar quantities of compound **5** (1 mmol) and a substituted carboxylic acid were dissolved in phosphoryl chloride (5 mL) and heated under reflux for 3–6 h, the progress of reaction being monitored by TLC. The reaction mixture was then heated under reduced pressure to allow excess phosphoryl chloride to distill off, and the residue was purified by flash chromatography on silica gel using 15–25% acetone in petroleum ether as eluent to give the target compounds **6a**–**z** (Table 2).

2.1.5.1. Data for ***6a***. White solid, mp 129–131 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.54 (t, J = 7.2 Hz, 3H), 2.61 (s, 3H), 4.24 (q, J = 7.2 Hz, 2H), 7.30–7.33 (m, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 10.5, 15.3, 41.0, 98.9, 110.8, 120.6, 121.3, 122.8, 124.6, 130.0, 136.0, 161.4, 161.5. HRMS (MALDI): *m/z* 250.0930. Calcd. for $C_{13}H_{13}N_3O$: 250.0956 $[M + Na]^+$.

2.1.5.2. Data for ***6b***. White solid, mp 62–64 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.45 (t, J = 7.8 Hz, 3H), 1.55 (t, J = 7.2 Hz, 3H), 2.96 (q, J = 7.8 Hz, 2H), 4.25 (q, J = 7.2 Hz, 2H), 7.30–7.34 (m, 2H), 7.41 (d,



Scheme 2. Synthesis of 2-(1-ethyl-indolyl)-5-substituted-1,3,4-oxadiazoles **6**.

J = 7.8 Hz, 1H), 7.83 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 10.6, 15.3, 18.3, 41.0, 98.9, 110.8, 120.6, 121.3, 122.8, 124.6, 130.0, 136.0, 161.4, 165.2. HRMS (MALDI): m/z 264.1100. Calcd. for $C_{14}H_{15}N_3O$: 264.1113 $[M + Na]^+$.

2.1.5.3. Data for ***6c****.* Light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08 (t, J = 7.2 Hz, 3H), 1.54 (t, J = 7.2 Hz, 3H), 1.89–1.92 (m, 2H), 2.91 (t, J = 7.2 Hz, 3H), 4.25 (q, J = 7.2 Hz, 2H), 7.32 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 13.4, 15.2, 19.6, 26.4, 41.0, 98.9, 110.7, 120.6, 121.3, 122.7, 124.6, 129.9, 136.0, 161.4, 164.2. HRMS (MALDI): m/z 294.1003. Calcd. for $C_{15}H_{17}N_3O$: 294.1009 $[M + K]^+$.

2.1.5.4. Data for ***6d****.* Light yellow oil. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.11 (s, 9H), 1.54 (t, J = 7.2 Hz, 3H), 2.84 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 7.30–7.34 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 8.24 (d, J = 7.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.2, 29.0, 31.0, 38.0, 40.9, 98.9, 111.7, 120.4, 121.2, 122.7, 124.6, 126.3, 127.9, 129.9, 135.9, 161.4, 162.9. HRMS (MALDI): m/z 284.1744. Calcd. for $C_{17}H_{21}N_3O$: 284.1763 $[M + H]^+$.

Table 2
Reaction times and yields in the synthesis of compounds **6**.

Entry	R^2	Time	Yield
6a	CH_3	6 h	72%
6b	CH_3CH_2	6 h	61%
6c	$CH_3CH_2CH_2$	6 h	71%
6d	$(CH_3)_3CCH_2$	4 h	73%
6e	$CH_3CH_2(CH_3)_2C$	5 h	45%
6f	$(CH_3)_3CCH_2(CH_3)CHCH_2$	6 h	78%
6g	CF_3	5 h	71%
6h	CH_2Cl	6 h	43%
6i	CCl_3	6 h	70%
6j	C_6H_5	6 h	54%
6k	2-F-C_6H_4	6 h	49%
6l	2-Cl-C_6H_4	6 h	59%
6m	2-I-C_6H_4	3 h	22%
6n	3-Cl-C_6H_4	6 h	60%
6o	3-NO_2-C_6H_4	6 h	28%
6p	3-Pyridyl	6 h	51%
6q	4-Cl-C_6H_4	6 h	55%
6r	4-Br-C_6H_4	6 h	62%
6s	4-NO_2-C_6H_4	3 h	43%
6t	4-Me-C_6H_4	6 h	68%
6u	4-MeO-C_6H_4	6 h	60%
6v	3,5-Di-Me-C_6H_3	6 h	55%
6w	3,4,5-Tri-MeO-C_6H_2	6 h	63%
6x	$C_6H_5CH_2$	5 h	48%
6y	2-Me-$C_6H_5CH_2$	5 h	42%
6z	(E)-C_6H_5CH:CH	6 h	53%

2.1.5.5. Data for ***6e****.* White solid, mp 78–80 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.84 (t, J = 7.2 Hz, 3H), 1.42 (s, 6H), 1.45 (t, J = 7.2 Hz, 3H), 1.78 (t, J = 7.2 Hz, 3H), 4.35 (t, J = 7.2 Hz, 2H), 7.31–7.34 (m, 2H), 7.64 (d, J = 7.2 Hz, 1H), 8.15 (t, J = 7.8 Hz, 2H), 8.27 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 8.1, 15.2, 25.2, 33.5, 35.5, 40.9, 98.9, 110.7, 120.4, 121.2, 122.7, 124.6, 130.0, 135.9, 161.4, 169.4. HRMS (MALDI): m/z 322.1313. Calcd. for $C_{17}H_{21}N_3O$: 322.1322 $[M + K]^+$.

2.1.5.6. Data for ***6f****.* Red oil. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.88 (s, 9H), 1.05 (d, J = 3.0 Hz, 3H), 1.14–1.19 (m, 1H), 1.38 (d, J = 14.4 Hz, 1H), 1.45 (t, J = 6.6 Hz, 3H), 2.08–2.09 (m, 1H), 2.78–2.82 (m, 1H), 2.84–2.88 (m, 1H), 4.36 (q, J = 6.6 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.33–7.34 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 7.8 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.2, 22.4, 27.9, 29.5, 30.6, 33.7, 40.9, 49.4, 98.8, 110.8, 120.5, 121.2, 122.7, 124.5, 126.3, 129.9, 135.9, 161.4, 163.4. HRMS (MALDI): m/z 364.1778. Calcd. for $C_{20}H_{27}N_3O$: 364.1791 $[M + K]^+$.

2.1.5.7. Data for ***6g****.* White crystal, mp 140–142 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.45 (t, J = 6.6 Hz, 3H), 4.36 (q, J = 6.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 8.48 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.2, 41.3, 97.0, 111.2, 115.7, 120.3, 122.0, 123.2, 124.5, 132.4, 136.1, 151.7, 151.9, 163.8. HRMS (MALDI): m/z 282.0820. Calcd. for $C_{13}H_{10}F_3N_3O$: 282.0854 $[M + H]^+$.

2.1.5.8. Data for ***6h****.* White solid, mp 116–118 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.56 (t, J = 7.2 Hz, 3H), 4.27 (q, J = 7.2 Hz, 2H), 4.49 (s, 2H), 7.32–7.37 (m, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.92 (s, 1H), 8.26 (d, J = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 33.5, 41.1, 98.1, 111.0, 120.5, 121.6, 123.0, 124.6, 130.9, 136.0, 160.5, 162.7. HRMS (MALDI): m/z 284.0539. Calcd. for $C_{13}H_{12}ClN_3O$: 284.0567 $[M + Na]^+$.

2.1.5.9. Data for ***6i****.* White solid, mp 131–133 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.48 (t, J = 7.2 Hz, 3H), 4.37 (q, J = 7.2 Hz, 2H), 7.31–7.36 (m, 2H), 7.68 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.51 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.3, 96.9, 111.2, 120.3, 122.0, 124.5, 132.3, 136.1, 160.9, 164.3. HRMS (MALDI): m/z 329.9986. Calcd. for $C_{13}H_{10}Cl_3N_3O$: 329.9968 $[M + H]^+$.

2.1.5.10. Data for ***6j****.* White solid, mp 170–171 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.47 (t, J = 7.2 Hz, 3H), 4.37 (q, J = 7.2 Hz, 1H), 7.32–7.35 (m, 2H), 7.65–7.66 (m, 3H), 7.69 (d, J = 7.8 Hz, 1H), 8.13–8.14 (m, 2H), 8.21 (d, J = 7.8 Hz, 1H), 8.41 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.2, 41.1, 98.6, 110.9, 120.5, 120.6, 121.5, 123.7,

124.6, 126.2, 126.4, 129.4, 130.8, 131.5, 136.1, 161.8. HRMS (MALDI): *m*/*z* 290.1268. Calcd. for $C_{18}H_{15}N_3O$: 290.1293 $[M + H]^+$.

2.1.5.11. Data for ***6k***. White solid, mp 160–162 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.58 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.2 Hz, 2H), 7.29–7.36 (m, 4H), 7.45 (t, J = 7.2 Hz, 1H), 7.53–7.54 (m, 1H), 8.00 (s, 1H), 8.20 (t, J = 7.2 Hz, 1H), 8.35–8.36 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 98.4, 110.8–111.1 (t, J_{C-F} = 247 Hz, 1C), 109.9, 111.7–111.9 (d, J_{C-F} = 213 Hz, 1C), 111.1, 116.0, 120.7, 123.6, 124.6, 129.3, 136.1, 148.8, 159.2, 160.6, 162.7, 163.0. HRMS (MALDI): *m*/*z* 346.0753. Calcd. for $C_{18}H_{141}FN_3O$: 346.0758 $[M + K]^+$.

2.1.5.12. Data for ***6l***. White solid, mp 140–142 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.57 (t, J = 7.2 Hz, 3H), 4.28 (q, J = 7.2 Hz, 2H), 7.34–7.35 (m, 2H), 7.44–7.48 (m, 3H), 7.58 (d, J = 7.8 Hz, 1H), 7.97 (s, 1H), 8.13 (d, J = 7.2 Hz, 1H), 8.35 (d, J = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 98.3, 110.0, 120.5, 121.6, 122.8, 122.9, 124.6, 127.9, 131.0, 131.1, 131.2, 131.6, 132.8, 136.0, 160.0, 162.1. HRMS (MALDI): *m*/*z* 324.0925. Calcd. for $C_{18}H_{14}ClN_3O$: 324.0904 $[M + H]^+$.

2.1.5.13. Data for ***6m***. White solid, mp 155–157 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.57 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.8 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.33–7.36 (m, 2H), 7.45 (d, J = 7.3 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 98.4, 111.0, 120.5, 121.6, 124.6, 128.6, 127.7, 129.1, 130.8, 131.3, 131.4, 132.8, 136.1, 140.7, 161.8, 162.0. HRMS (MALDI): *m*/*z* 438.0074. Calcd. for $C_{18}H_{14}IN_3O$: 438.0079 $[M + Na]^+$.

2.1.5.14. Data for ***6n***. White solid, mp 162–164 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.47 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 7.31–7.36 (m, 2H), 7.65–7.71 (m, 3H), 8.09 (d, J = 7.2 Hz, 1H), 8.11 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.45 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 98.4, 111.0, 120.6, 121.6, 122.9, 124.6, 125.0, 125.6, 125.8, 131.1, 131.3, 131.4, 134.1, 136.1, 160.7, 162.0. HRMS (MALDI): *m*/*z* 346.0706. Calcd. for $C_{18}H_{14}ClN_3O$: 346.0723 $[M + Na]^+$.

2.1.5.15. Data for ***6o***. Light yellow solid, mp 163–164 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.62 (t, J = 7.2 Hz, 3H), 4.33 (q, J = 7.2 Hz, 2H), 7.38–7.46 (m, 3H), 7.77 (t, J = 7.8 Hz, 1H), 8.02 (s, 1H), 8.34 (d, J = 7.2 Hz, 1H), 8.40 (d, J = 7.8 Hz, 1H), 8.54 (d, J = 6.6 Hz, 1H), 8.95 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 98.3, 111.0, 120.5, 122.9, 124.5, 125.1, 125.8, 127.3, 130.5, 131.2, 132.2, 135.4, 147.8, 160.3, 165.5. HRMS (MALDI): *m*/*z* 335.1149. Calcd. for $C_{18}H_{14}N_4O_3$: 335.1144 $[M + H]^+$.

2.1.5.16. Data for ***6p***. Light yellow solid, mp 138–140 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.60 (t, J = 7.2 Hz, 3H), 4.32 (q, J = 7.2 Hz, 2H), 7.37–7.38 (m, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.97 (s, 1H), 8.32–8.33 (m, 1H), 8.50 (d, J = 7.8 Hz, 1H), 8.78–8.80 (m, 1H), 9.38 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.2, 41.1, 98.4, 111.1, 120.4, 120.6, 121.4, 121.8, 122.7, 124.4, 130.9, 131.0, 133.6, 136.1, 147.0, 160.0, 162.1. HRMS (MALDI): *m*/*z* 291.1218. Calcd. for $C_{17}H_{14}N_4O$: 291.1246 $[M + H]^+$.

2.1.5.17. Data for ***6q***. White solid, mp 139–141 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.59 (t, J = 7.8 Hz, 3H), 4.31 (q, J = 7.2 Hz, 2H), 7.34–7.36 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.7, 41.5, 99.0, 111.4, 121.0, 122.0, 123.0, 123.4, 125.0, 128.5, 130.0, 131.3, 136.5, 136.7, 161.5, 162.3. HRMS (MALDI): *m*/*z* 324.0869. Calcd. for $C_{18}H_{14}ClN_3O$: 324.0904 $[M + H]^+$.

2.1.5.18. Data for ***6r***. White solid, mp 158–160 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.47 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 7.30–7.36 (m, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.86 (t, J = 7.2 Hz, 2H), 8.04–8.06 (m, 2H), 8.19 (d, J = 7.8 Hz, 1H), 8.42 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 98.5, 111.0, 120.6, 121.6, 122.9, 124.6, 125.1, 128.2, 131.0, 131.3, 132.5, 136.1, 161.2, 161.9. HRMS (MALDI): *m*/*z* 390.0191. Calcd. for $C_{18}H_{14}BrN_3O$: 390.0218 $[M + Na]^+$.

2.1.5.19. Data for ***6s***. Yellow solid, mp 191–193 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.48 (t, J = 7.2 Hz, 3H), 4.37 (q, J = 6.6 Hz, 2H), 7.31–7.36 (m, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.98 (s, 1H), 8.31–8.32 (m, 3H), 8.39 (d, J = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.2, 99.0, 111.1, 116.0, 120.7, 123.6, 124.6, 129.3, 136.1, 148.8, 159.2, 160.6, 162.7, 163.0. HRMS (MALDI): *m*/*z* 357.0997. Calcd. for $C_{18}H_{14}N_4O_3$: 357.0964 $[M + Na]^+$.

2.1.5.20. Data for ***6t***. White solid, mp 163–165 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.46 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 4.39 (q, J = 6.6 Hz, 2H), 7.31–7.35 (m, 2H), 7.45 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 7.8 Hz, 2H), 8.21 (d, J = 7.8 Hz, 1H), 8.41 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.3, 21.1, 41.1, 98.7, 120.5, 120.7, 121.0, 124.6, 126.2, 126.3, 129.3, 130.0, 130.5, 136.1, 141.6, 161.5, 161.9. HRMS (MALDI): *m*/*z* 326.1249. Calcd. for $C_{19}H_{17}N_3O$: 326.1269 $[M + Na]^+$.

2.1.5.21. Data for ***6u***. White solid, mp 85–87 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.56 (t, J = 7.2 Hz, 3H), 3.87 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.32–7.34 (m, 2H), 7.40–7.41 (m, 1H), 7.89 (s, 1H), 8.04 (d, J = 9.0 Hz, 2H), 8.32 (t, J = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.6, 41.5, 55.8, 99.2, 111.2, 115.2, 116.5, 121.0, 121.8, 123.2, 125.1, 128.5, 130.8, 136.5, 150.1, 154.6, 161.6, 162.1. HRMS (MALDI): *m*/*z* 320.1369. Calcd. for $C_{19}H_{17}N_3O_2$: 320.1399 $[M + H]^+$.

2.1.5.22. Data for ***6v***. White solid, mp 110–112 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.59 (t, J = 7.2 Hz, 3H), 2.43 (s, 6H), 4.29 (q, J = 7.2 Hz, 2H), 7.17 (s, 1H), 7.24–7.25 (m, 1H), 7.37 (t, J = 3.6 Hz, 2H), 7.45 (t, J = 5.4 Hz, 1H), 8.00–8.01 (m, 2H),8.33–8.34 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.2, 20.7, 41.0, 98.7, 110.9, 120.6, 123.5, 124.6, 127.0, 130.7, 134.1, 136.0, 137.7, 161.5. HRMS (MALDI): *m*/*z* 356.1151. Calcd. for $C_{20}H_{19}N_3O$: 356.1165 $[M + K]^+$.

2.1.5.23. Data for ***6w***. White solid, mp 115–117 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.59 (t, J = 7.2 Hz, 3H), 3.92 (s, 3H), 3.99 (s, 6H), 4.29 (q, J = 6.6 Hz, 2H), 7.35–7.38 (m, 4H), 7.45 (d, J = 7.2 Hz, 1H), 7.95 (s, 1H), 8.33 (d, J = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 41.1, 56.1, 56.2, 60.3, 98.7, 103.7, 104.2, 110.9, 118.5, 119.0, 120.7, 121.6, 122.9, 124.6, 130.8, 136.1, 140.2, 153.5, 161.6, 161.8. HRMS (MALDI): *m*/*z* 402.1447. Calcd. for $C_{21}H_{21}N_3O_4$: 402.1430 $[M + Na]^+$.

2.1.5.24. Data for ***6x***. Light yellow solid, mp 112–114 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.41 (t, J = 6.0 Hz, 3H), 4.32 (q, J = 6.6 Hz, 2H), 4.36 (s, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.31–7.33 (m, 2H), 7.41 (t, J = 7.2 Hz, 4H), 7.64 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.21 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 30.7, 41.0, 98.6, 110.9, 120.5, 121.4, 122.8, 124.6, 127.2, 128.7, 128.8, 130.2, 134.9, 135.9, 161.8, 163.1. ^{13}C DEPT (100 MHz, DMSO-d_6): CH_3 (methyl): 15.3; CH_2 (methylene): 30.8, 41.0; CH (methine):110.9, 120.5, 121.4, 122.8, 127.2, 128.7, 128.8, 130.2. HRMS (MALDI): *m*/*z* 342.0990. Calcd. for $C_{19}H_{17}N_3O$: 342.1009 $[M + K]^+$.

2.1.5.25. Data for ***6y***. White solid, mp 127–129 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.53 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 4.24 (q, J = 7.2 Hz, 2H), 4.27 (s, 2H), 7.20–7.21 (m, 3H), 7.27–7.31 (m, 3H), 7.40 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H). ^{13}C NMR

(150 MHz, DMSO-d_6): δ 15.3, 19.1, 28.8, 41.0, 98.6, 110.8, 120.5, 121.3, 122.8, 124.6, 126.2, 127.4, 129.6, 130.2, 130.3, 133.3, 135.9, 136.6, 161.7, 162.8. HRMS (MALDI): *m/z* 340.1406. Calcd. for $C_{20}H_{19}N_3O$: 340.1426 $[M + Na]^+$.

2.1.5.26. Data for ***6z***. White solid, mp 105–107 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.48 (t, J = 6.6 Hz, 3H), 4.38 (q, J = 6.6 Hz, 2H), 7.32–7.34 (m, 2H), 7.39 (m, 2H), 7.49 (t, J = 6.6 Hz, 2H), 7.68–7.70 (m, 2H), 7.81 (d, J = 7.2 Hz, 1H), 8.25 (d, J = 7.2 Hz, 1H), 8.36 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.2, 41.0, 98.7, 110.4, 110.8, 120.6, 121.5, 122.9, 124.6, 127.6, 127.7, 128.8, 129.0, 129.7, 130.6, 134.9, 136.0, 137.5, 161.0, 161.9. HRMS (MALDI): *m/z* 354.0992. Calcd. for $C_{20}H_{17}N_3O$: 354.1009 $[M + K]^+$.

2.1.6. Preparation of (1H-indol-3-yl)-acetic acid hydrazide ***8*** *(Scheme 3)*

Hydrazine hydrate (99%, 2 mL, 40 mmol) was added to a solution of compound **7** (2.03 g, 10 mmol) in dry ethanol (50 mL) and the resulting mixture was heated under reflux for 8 h. The reaction mixture was cooled to room temperature and the solid obtained was filtered off and washed with a small quantity of ethanol to give the desired intermediate **8**. Yield: 1.80 g, 95%, white solid, mp 125–127 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.46 (s, 2H), 4.20 (s, 2H), 6.98 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 9.16 (s, 1H), 10.87 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 30.8, 108.7, 111.3, 118.3, 118.7, 120.8, 123.6, 127.2, 136.1, 170.3. EI-MS: *m/z* (%) 189 (M^+, 26), 144 (14), 130 (100), 77 (7).

2.1.7. General procedure for the synthesis of target compounds ***9*** *(Scheme 3)*

Equimolar quantities of compound **5** (1 mmol) and a substituted carboxylic acid were dissolved in phosphoryl chloride (5 mL) and heated under reflux at 80 °C for 3–6 h, the progress of reaction being monitored by TLC. The reaction mixture was then heated under reduced pressure to allow excess phosphoryl chloride to distill off, and the residue was purified by flash chromatography on silica gel using 15–25% acetone in petroleum ether as eluent to give the target compounds **9a**–**p** (Table 3).

2.1.7.1. Data for ***9a***. White solid, mp 84–86 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.31 (s, 3H), 7.15 (t, J = 7.2 Hz, 1H), 7.18 (s, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 8.36 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.9, 22.0, 108.2, 111.2, 118.6, 122.3, 123.0, 123.1, 126.7, 136.1, 163.9, 165.9. HRMS (ESI): *m/z* 214.0970. Calcd. for $C_{12}H_{11}N_3O$: 214.0980 $[M + H]^+$.

2.1.7.2. Data for ***9b***. White solid, mp 65–67 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (t, J = 7.8 Hz, 3H), 2.81 (d, J = 7.8 Hz, 2H), 4.32 (s, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4, 18.9, 21.9, 107.6, 111.4, 118.3, 119.5, 122.0, 123.2, 126.6, 136.1, 165.9, 168.0. HRMS (ESI): *m/z* 228.1127. Calcd. for $C_{13}H_{13}N_3O$: 228.1137 $[M + H]^+$.

Table 3
Reaction times and yields in the synthesis of compounds **9**.

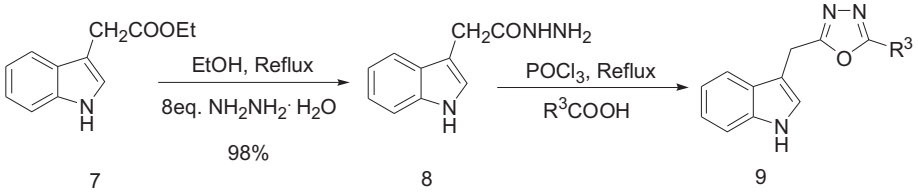
Entry	R^3	Time	Yield
9a	CH_3	5 h	73%
9b	CH_3CH_2	5 h	66%
9c	$CH_3CH_2CH_2$	6 h	71%
9d	$(CH_3)_3CCH_2$	5 h	60%
9e	$CH_3CH_2(CH_3)_2C$	5 h	76%
9f	$(CH_3)_3CCH_2(CH_3)CHCH_2$	5 h	66%
9g	CF_3	5 h	45%
9h	CH_2Cl	5 h	53%
9i	CCl_3	5 h	44%
9j	2-F-C_6H_4	3 h	53%
9k	3-Cl-C_6H_4	3 h	48%
9l	4-Br-C_6H_4	6 h	51%
9m	4-MeO-C_6H_4	6 h	66%
9n	4-Me-C_6H_4	6 h	71%
9o	3,5-Di-MeO-C_6H_3	3 h	57%
9p	3,4,5-Tri-MeO-C_6H_2	5 h	62%

2.1.7.3. Data for ***9c***. White solid, mp 82–84 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.98 (t, J = 7.8 Hz, 3H), 1.74–1.78 (m, 2H), 2.75 (t, J = 7.8 Hz, 2H), 4.32 (s, 2H), 7.12–7.13 (m, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 8.40 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.8, 19.9, 22.1, 27.2, 108.3, 111.2, 118.6, 119.7, 122.9, 123.3, 126.7, 136.1, 165.8, 167.1. HRMS (ESI): *m/z* 242.1285. Calcd. for $C_{14}H_{15}N_3O$: 242.1293 $[M + H]^+$.

2.1.7.4. Data for ***9d***. White solid, mp 109–111 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.90 (s, 9H), 2.50 (s, 2H), 4.32 (s, 2H), 7.00 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.31 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 11.04 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.5, 29.0, 31.1, 38.0, 107.1, 111.6, 118.2, 118.7, 121.3, 123.9, 126.6, 136.2, 165.2, 165.8. HRMS (MALDI): *m/z* 270.1581. Calcd. for $C_{16}H_{19}ClN_3O$: 270.1606 $[M + H]^+$.

2.1.7.5. Data for ***9e***. White solid, mp 103–105 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.69 (t, J = 7.8 Hz, 3H), 1.26 (s, 6H), 1.63 (t, J = 7.2 Hz, 2H), 4.31 (s, 2H), 7.01 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.30 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 11.03 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 8.7, 21.5, 25.2, 33.5, 35.5, 107.1, 111.6, 118.3, 118.6, 121.3, 123.9, 126.6, 136.2, 165.7, 171.7. ^{13}C DEPT (100 MHz, DMSO-d_6): CH_3 (methyl): 8.8, 25.2; CH_2 (methylene): 21.5, 33.5; CH (methine):111.6, 118.3, 118.7, 121.3, 123.9. HRMS (MALDI): *m/z* 270.1571. Calcd. for $C_{16}H_{19}ClN_3O$: 270.1606 $[M + H]^+$.

2.1.7.6. Data for ***9f***. Red oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (s, 9H), 1.01 (d, J = 6.6 Hz, 3H), 1.14–1.16 (m, 1H), 1.28–1.30 (m, 1H), 2.02–2.03 (m, 1H), 2.64–2.79 (m, 2H), 4.36 (s, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.22–7.26 (m, 2H), 7.30 (s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 8.28 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 22.3, 27.8, 29.5, 30.5, 33.6, 49.2, 107.0, 111.5, 118.2, 118.6, 121.2, 123.9, 126.6, 136.2, 165.7, 169.9. HRMS (MALDI): *m/z* 312.2060. Calcd. for $C_{19}H_{25}N_3O$: 312.2076 $[M + H]^+$.



Scheme 3. Synthesis of 2-(3-indolyl)-methyl-5-substituted-1,3,4-oxadiazoles **9**.

2.1.7.7. Data for ***9g***. White solid, mp 103–105 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.46 (s, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.24–7.25 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 8.18 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 105.6, 110.7, 111.6, 114.8, 118.1–118.8 (d, J_{C-F} = 108 Hz, 1C), 121.4, 124.5, 126.5, 136.5, 161.2, 168.7. HRMS (MALDI): m/z 290.0529. Calcd. for $C_{12}H_8F_3N_3O$: 290.0517 $[M + Na]^+$.

2.1.7.8. Data for ***9h***. White solid, mp 110–112 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.39 (s, 2H), 5.00 (s, 2H), 7.01 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.35–7.39 (m, 2H), 7.52 (d, J = 7.8 Hz, 1H), 11.08 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.4, 33.2, 106.5, 111.6, 118.2, 118.8, 121.4, 124.2, 126.6, 136.2, 163.8, 167.2. HRMS (MALDI): m/z 286.0131. Calcd. for $C_{12}H_{10}ClN_3O$: 286.0149 $[M + K]^+$.

2.1.7.9. Data for ***9i***. White solid, mp 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (s, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.23–7.25 (m, 2H), 7.41 (d, J = 6.8 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 8.22 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.6, 18.3, 99.7, 111.4, 120.3, 121.1, 122.8, 124.1, 127.7, 136.4, 161.7, 165.3. HRMS (MALDI): m/z 315.9833. Calcd. for $C_{12}H_8Cl_3N_3O$: 315.9811 $[M + H]^+$.

2.1.7.10. Data for ***9j***. Pale pink solid, mp 116–118 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.47 (s, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.36–7.38 (m, 1H), 7.39–7.47 (m, 5H), 7.62 (d, J = 7.8 Hz, 1H), 7.98 (t, J = 7.2 Hz, 1H), 11.10 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.5, 106.8, 111.6, 111.7, 111.8, 116.3, 118.3–118.8 (d, J_{C-F} = 71.3 Hz, 1C), 124.6, 125.3, 126.7, 129.4, 130.2, 134.1, 136.2, 158.2, 160.6, 163.2. HRMS (MALDI): m/z 294.1023. Calcd. for $C_{17}H_{12}FN_3O$: 294.1043 $[M + H]^+$.

2.1.7.11. Data for ***9k***. White solid, mp 141–143 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.46 (s, 2H), 7.05 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.41–7.44 (m, 2H), 7.57–7.66 (m, 3H), 7.71 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.5, 106.7, 111.6, 118.3, 118.8, 121.4, 124.3, 125.0, 125.3, 125.8, 126.7, 131.6, 134.0, 136.2, 162.9, 166.5, 168.0. HRMS (MALDI): m/z 332.0549. Calcd. for $C_{17}H_{12}ClN_3O$: 332.0567 $[M + Na]^+$.

2.1.7.12. Data for ***9l***. White solid, mp 158–160 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.45 (s, 2H), 7.04 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.39–7.42 (m, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 9.0 Hz, 2H), 7.86 (d, 2H), 11.10 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.6, 106.7, 111.6, 118.3, 118.8, 121.4, 122.6, 124.3, 125.4, 126.7, 128.2, 132.5, 136.2, 163.4, 166.3. HRMS (MALDI): m/z 354.0229. Calcd. for $C_{17}H_{12}BrN_3O$: 354.0242 $[M + H]^+$.

2.1.7.13. Data for ***9m***. Light yellow solid, mp 116–118 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.82 (s, 3H), 4.43 (s, 2H), 7.06 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.41–7.42 (m, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 11.11 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.6, 55.4, 107.0, 111.6, 114.8, 115.8, 118.3, 118.8, 121.4, 124.2, 126.7, 128.1, 136.2, 161.8, 163.9, 165.5. HRMS (MALDI): m/z 306.1218. Calcd. for $C_{18}H_{15}N_3O_2$: 306.1243 $[M + H]^+$.

2.1.7.14. Data for ***9n***. White solid, mp 147–149 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.35 (s, 3H), 4.44 (s, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.41–7.43 (m, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 11.11 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.1, 21.6, 55.4, 106.9, 111.7, 118.3, 118.8, 120.7, 121.4, 124.2, 126.3, 126.7, 129.9, 136.3, 141.9, 164.1, 165.8. HRMS (MALDI): m/z 290.1273. Calcd. for $C_{18}H_{15}N_3O$: 290.1293 $[M + H]^+$.

2.1.7.15. Data for ***9o***. White solid, mp 124–126 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.82 (s, 6H), 4.44 (s, 2H), 6.57 (s, 1H), 7.13 (s, 2H), 7.18 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 7.82 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.6, 55.5, 103.7, 104.1, 106.8, 111.6, 118.3, 118.8, 121.4, 124.2, 126.7, 136.3, 161.0, 163.8, 166.2. HRMS (MALDI): m/z 336.1352. Calcd. for $C_{19}H_{17}N_3O_3$: 336.1348 $[M + H]^+$.

2.1.7.16. Data for ***9p***. White solid, mp 182–184 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.73 (s, 3H), 3.85 (s, 3H), 4.44 (s, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.41 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 11.10 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.7, 56.0, 60.2, 103.6, 106.9, 111.6, 118.4, 118.6, 118.7, 121.4, 124.2, 126.7, 136.3, 140.3, 153.4, 163.9, 166.0. HRMS (MALDI): m/z 388.1272. Calcd. for $C_{20}H_{19}N_3O_4$: 388.1273 $[M + Na]^+$.

2.2. X-ray diffraction analysis

Crystal structures of compound **3h**, **6g** and **9k** are shown in Fig. 4.

Colourless crystals of compound **3h** (0.23 mm × 0.20 mm × 0.20 mm) were mounted on a quartz fibre with protection oil. Cell dimensions and intensities were measured at 299 K on a Bruker CCD DUO area detector diffractometer with graphite monochromated Mo K_α radiation (λ = 0.71073 Å); θ_{max} = 32.00; 9126 measured reflections; 2955 independent reflections (R_{int} = 0.0169) of which 6320 had [$I > 2\sigma_{(I)}$]. The structure was solved by direct methods using SHELXS-97. Collected data were corrected for absorbance by using SADABS based upon the Laue symmetry using equivalent reflections with the multi-scan method. Structure solution and refinement were carried out with the SHELXTL software package and the structure was solved by the direct method. Full-matrix least-squares refinement based on F^2 using the weight of $\omega = 1/[\sigma^2(Fo^2) + (0.0485P)2 + 0.3358P]$ gave final values of R_1 = 0.0300, ωR_2 = 0.0869 [$I > 2\sigma_{(I)}$], and GOF(F) = 1.084 for 149

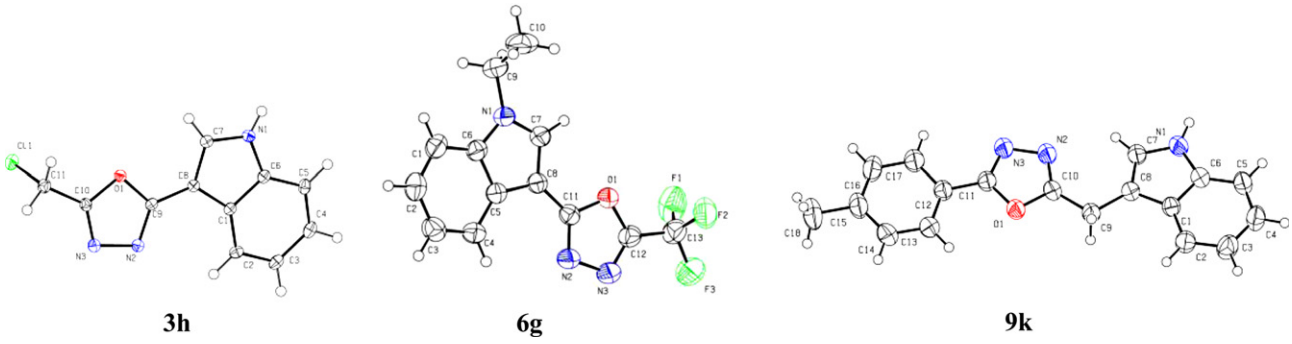


Fig. 4. Crystal structures of compound **3h**, **6g** and **9k**.

restraints and 2955 parameters reflections. Maximum shift/error = 0.001(3), max/min residual electron density = 0.420/−0.227 e Å^{-3}. Hydrogen atoms were observed and placed at their ideal positions, then they were refined with a fixed value of their isotropic displacement parameter being equal to 1.2–1.5 times of U_{eq} of their parent atoms. In compound **3h**, $C_{11}H_8ClN_3O$, the benzene and pyrrole rings are almost coplanar [dihedral angle = 2.8 (2)°]. The dihedral angle between the pyrrole and oxadiazole rings is 4.7 (5)°. The crystal structure is stabilized by N–H···N hydrogen bonds and there are also weak N–H···C interactions.

Colourless crystals of compound **6g** (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 299 K on a Bruker CCD DUO area detector diffractometer with graphite monochromated Mo K_α radiation ($\lambda = 0.71073$ Å); $\theta_{max} = 28.97$; 16,840 measured reflections; 4878 independent reflections ($R_{int} = 0.0297$) of which 5281 had [$I > 2\sigma_{(I)}$]. The structure was solved by direct methods using SHELXS-97. Collected data were corrected for absorbance by using SADABS based upon the Laue symmetry using equivalent reflections with the multi-scan method. Structure solution and refinement were carried out with the SHELXTL software package and the structure was solved by the direct method. Full-matrix least-squares refinement based on F^2 using the weight of $\omega = 1/[\sigma^2(Fo^2) + (0.1040P)^2 + 0.3447P]$ gave final values of $R_1 = 0.0524$, $\omega R_2 = 0.1604$ [$I > 2\sigma_{(I)}$], and GOF(F) = 1.083 for 384 restraints and 4878 parameters reflections. Maximum shift/error = 0.001(3), max/min residual electron density = 0.388/−0.266 e Å^{-3}. Hydrogen atoms were observed and placed at their ideal positions, then they were refined with a fixed value of their isotropic displacement parameter being equal to 1.2–1.5 times of U_{eq} of their parent atoms. In compound **6g**, $C_{13}H_{10}F_3N_3O$, the benzene and pyrrole rings are almost coplanar [dihedral angle = 9.2 (0)°]. The dihedral angle between the indole and oxadiazole rings is 3.7 (8)°. The crystal structure is stabilized by F···F interactions.

Colourless crystals of compound **9k** (0.20 mm × 0.15 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 CCD DUO area detector diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å); $\theta_{max} = 31.09$; 12,814 measured reflections; 4289 independent reflections ($R_{int} = 0.0256$) of which 4054 had [$I > 2\sigma_{(I)}$]. The structure was solved by direct methods using SHELXS-97. Collected data were corrected for absorbance by using SADABS based upon the Laue symmetry using equivalent reflections with the multi-scan method. Structure solution and refinement were carried out with the SHELXTL software package and the structure was solved by the direct method. Full-matrix least-squares refinement based on F^2 using the weight of $\omega = 1/[\sigma^2(Fo^2) + (0.0872P)2 + 0.0890P]$ gave final values of $R_1 = 0.0467$, $\omega R_2 = 0.1368$ [$I > 2\sigma_{(I)}$], and GOF(F) = 1.050 for 204 restraints and 4289 parameters reflections. Maximum shift/error = 0.001(3), max/min residual electron density = 0.262/−0.171 e Å^{-3}. Hydrogen atoms were observed and placed at their ideal positions, then they were refined with a fixed value of their isotropic displacement parameter being equal to 1.2–1.5 times of U_{eq} of their parent atoms. In compound **9k**, $C_{17}H_{13}N_3O$, the benzene and pyrrole rings of the indole are almost coplanar [dihedral angle = 0.1 (9)°], and the same is true for the toluene and oxadiazole rings [dihedral angle = 0.4 (0)°]. The dihedral angle between the pyrrole and oxadiazole rings is 5.7 (0)°. The crystal structure is stabilized by N–H···N hydrogen bonds and there are also weak C–H···π interactions.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre with the deposition No. CCDC-859394 (compound **3h**), CCDC-859392 (compound **6g**) and CCDC-859393 (compound **9k**). Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/.

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 [24]. The results of the biological testing against seven phytopathogenic fungi are shown in Table 4.

3. Results and discussion

3.1. Chemistry

Three series of indole derivatives containing the 1,3,4-oxadiazole ring were efficiently synthesized in moderate to good yields, and were screened for antifungal activity. The first series of compounds **3** were prepared in a two-step process involving conversion of a carboxylic acid into the corresponding hydrazide and then condensation with a different carboxylic acid and ring closure with dehydration. We observed that many of this first series of indole derivatives (**3a**–**m**) have high melting points, a feature often associated with low solubility and hence limited bioavailability. Two strategies were therefore used in attempts to make analogues with lower melting points and improved bioavailability. First, we synthesized the compounds **6a**–**z** in which the indole ring nitrogen had been substituted with an ethyl group, and second, we prepared the compounds **9a**–**p** in which a methylene bridge had been introduced between the indole and oxadiazole rings.

Treatment of the indole esters (**1**, **4**, **7**) with hydrazine hydrate in ethanol overnight afforded the corresponding hydrazides (**2**, **5**, **8**) in almost quantitative yields. Subsequent condensation between the hydrazide and a variety of substituted benzoic or aliphatic carboxylic acids followed by dehydrative ring closure in the same pot was achieved by treatment with phosphoryl chloride at 80 °C under reflux and led to the target 1,3,4-oxadiazoles (**3**, **5**, **9**). It is worth noting that the excess phosphoryl chloride could easily be distilled out of the reaction mixture and recycled.

We observed that in the key 1,3,4-oxadiazole-forming reaction, the unsubstituted indole compounds (**3a**–**m** and **9a**–**p**) were more readily prepared (80 °C, 3–6 h) than their N-substituted counterparts (**6a**–**z**) (reflux, 3–6 h).

We also noted that, although the yields were not optimized, the oxadiazole-forming reaction was sensitive to the nature of the substituents. It was found that electron-donating substituents such as MeO-groups increase the rate of reaction and lead to moderate or good yields of products. Similarly, reactions with aliphatic acids proceed smoothly. By contrast, examples with electron-withdrawing substituents gave lower isolated yields, *e.g.* just 28% for compound **6o** (3-NO_2-C_6H_4) and 22% for **6m** (2-I-C_6H_4).

3.2. Antifungal activity and the structure–activity relationships

The oxadiazoles that have been synthesized are bioisosteres of pimprinine. We speculated that the additional nitrogen atom of the oxadiazole ring in comparison to the oxazole ring would participate in hydrogen bonding interactions and contribute substantially to the antifungal activity. Indeed, several of the synthesized compounds displayed patterns of activity with improved spectrum and/or potency compared to that of pimprinine. For the purposes of structure–activity relationship analysis, the antifungal activity of derivatives of compound **3** can be compared to their equivalents of compounds **6** and **9**. It was noticeable that where compounds were active it was most commonly against *Pythium dissimile*, and that the antifungal activity lacked potency, rarely extending to the lower

Table 4
Antifungal activities of pimprinine derivatives.

Species	PHY[a]		SEP[b]	URO	PYT		ALT		BOT		GIB	
Compound	Rate											
	200	60	100	100	20	2	20	2	20	2	20	2
Pimprinine	0	0	51	27	0	0	0	0	0	0	0	0
Streptochlorin	0	49	36	55	**99**	0	**99**	**99**	**99**	0	**99**	0
3a	0	0	0	0	0	0	0	0	0	0	0	0
3b	0	0	0	0	0	0	0	0	0	0	0	0
3c	49	0	0	0	55	0	0	0	0	0	0	0
3d	0	–	0	0	**99**	0	0	0	0	0	0	0
3e	0	–	0	0	**99**	0	0	0	0	0	0	0
3f	0	–	0	0	**99**	49	0	0	0	0	0	0
3g	0	–	0	**99**	**99**	27	0	0	0	0	0	0
3h	0	0	0	0	0	0	0	0	0	0	0	0
3i	0	0	55	0	0	0	0	0	0	0	0	0
3j	0	0	0	0	0	0	0	0	0	0	0	0
3k	0	0	18	0	0	0	0	0	0	0	0	0
3l	0	0	0	0	0	0	0	0	0	0	0	0
3m	0	0	0	0	0	0	0	0	0	0	0	0
6a	0	0	18	0	0	0	0	0	0	0	0	0
6b	0	0	36	0	0	0	0	0	0	0	0	0
6c	0	0	18	27	55	0	55	0	0	0	0	0
6d	0	0	0	0	0	0	0	0	0	0	0	0
6e	0	–	**66**	**99**	**99**	0	0	0	0	0	0	0
6f	0	0	0	0	0	0	0	0	0	0	0	0
6g	0	–	0	0	0	0	0	0	0	0	0	0
6h	0	–	0	49	**99**	**99**	27	0	0	0	0	0
6i	0	–	0	0	**99**	0	0	0	0	0	0	0
6j	0	–	0	0	27	0	0	0	0	0	0	0
6k	0	–	0	0	**77**	0	0	0	0	0	0	0
6l	0	–	0	0	27	0	0	0	0	0	0	0
6m	0	–	0	0	**99**	0	0	0	0	0	0	0
6n	0	0	0	0	0	0	0	0	0	0	0	0
6o	0	0	0	0	0	0	0	0	0	0	0	0
6p	0	–	0	55	**99**	0	0	0	0	0	0	0
6q	0	–	0	0	**99**	49	0	0	0	0	0	0
6r	0	–	0	27	**99**	0	0	0	0	0	0	0
6s	0	–	0	0	27	27	0	0	0	0	0	0
6t	0	–	0	0	27	0	0	0	0	0	0	0
6u	0	–	0	55	0	0	0	0	0	0	0	0
6v	0	–	0	0	**99**	0	0	0	0	0	0	0
6w	0	–	0	0	49	55	0	0	0	0	0	0
6x	0	–	0	0	**99**	**77**	0	0	0	0	0	0
6y	0	–	0	0	**99**	49	0	0	0	0	0	0
6z	27	–	0	0	**99**	0	0	0	0	0	0	0
9a	0	0	0	0	0	0	0	0	0	0	0	0
9b	0	0	NC	0	0	0	0	0	0	0	0	0
9c	0	0	0	0	0	0	27	0	27	0	0	0
9d	0	–	0	27	**99**	49	0	0	49	0	0	0
9e	49	–	0	**99**	55	27	27	0	49	0	0	0
9f	0	–	0	0	0	0	0	0	0	0	0	0
9g	0	–	0	0	**99**	0	0	0	49	0	0	0
9h	49	0	0	49	**99**	0	0	0	0	0	0	0
9i	0	0	0	55	0	0	55	0	0	0	0	0
9j	49	0	0	0	27	0	0	0	0	0	0	0
9k	0	0	0	49	0	0	0	0	0	0	0	0
9l	0	0	0	0	0	0	0	0	0	0	0	0
9m	49	0	18	0	55	0	0	0	55	0	0	0
9n	0	0	0	0	55	55	0	0	0	0	0	0
9o	0	0	0	0	0	0	0	0	0	0	0	0
9p	0	0	0	0	0	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] Mean of three replicates.

rates tested. Although the generally weak activity makes a detailed analysis of structure–activity relationships difficult, some broad conclusions can be drawn.

The spectrum of antifungal activity is generally improved by substituting an ethyl group onto the indole ring nitrogen, or by introducing a methylene bridge between the indole and the oxadiazole rings. For example, while compound **3e** was only active against *P. dissimile* at 20 ppm, the equivalent **6e** also displayed activity against *Septoria tritici* and *Uromyces viciae-fabae* at 100 ppm, and **9e** was less active against *P. dissimile* but was active against *U. viciae-fabae*, and gave weak activity against other species. Similarly, while **3h** was entirely inactive, compound **6h** produced strong activity against *P. dissimile*, and **9h** was also active against the species at high rates. Both **6h** and **9h** also showed weak activity against other species.

This improvement in activity is not seen with all derivatives, however. **3g** was active against *P. dissimile* and *U. viciae-fabae*, while **6g** was inactive and **9g** lost the activity against *U. viciae-fabae*. **3d** was only active against *P. dissimile*, while **6d** was inactive on all assays and **9d** showed a broader spectrum, although with weak activity.

More generally, it is noticeable that almost all the derivatives of compound **3** with substitution on the benzene ring were inactive, while equivalent derivatives of compounds **6** and **9** were usually active against *P. dissimile*, and sometimes display a broader spectrum of activity (*e.g.* **9j**).

4. Conclusions

In conclusion, we have efficiently synthesized three series of indole-based 1,3,4-oxadiazole derivatives, designed as analogues of the antifungal natural product pimprinine, and evaluated their antifungal activities.

Biological testing showed that the synthesized derivatives displayed an altered pattern of biological activity compared to the natural product pimprinine and that in most cases biological activity is improved by N-ethylation of the indole nitrogen to give compounds **6**, or by introducing a methylene bridge between the indole and oxadiazole rings to give compounds **9**. The compounds **3g**, **6c**, **6e**, **6h**, **9d**, **9e**, **9h** and **9m** (Fig. 1) were identified as the most promising candidates for further study.

Further structural optimization of indole-based 1,3,4-oxadiazole derivatives is well under way, alongside more detailed biological testing of the most active compounds, with the aim of improving their levels of antifungal activity.

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