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# Bioisosteric replacement of the pyrazole 3-carboxamide moiety of rimonabant. A novel series of oxadiazoles as CB1 cannabinoid receptor antagonists†

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Based on the bioisosteric replacement of the pyrazole C3-carboxamide of rimonabant with a 5-alkyl oxadiazole ring, a novel class of oxadiazole derivatives with promising biological activity towards CB1 receptors was discovered. Among them, compounds with an alkyl linker containing a strong electron-withdrawing group (*e.g.*, $CF_3$) and a sterically favorable bulky group (*e.g.*, *t*-butyl) exhibited excellent CB1 antagonism and selectivity, and thus might serve as potential candidates for further development as anti-obesity agents.

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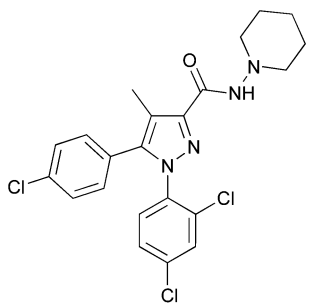
## Introduction

Obesity, a cause of major morbidity and mortality,[1–3] has become a global epidemic and is recognized as a chronic disease by the World Health Organization (WHO). Accordingly, obesity and its associated co-morbidities, such as type 2 diabetes, hypertension, dyslipidemia, and cancers, pose a serious threat to the public health, and constitute a substantial healthcare burden in modern society. Therefore, finding effective pharmacological therapeutics to treat obesity is becoming an urgent necessity, especially considering that the current two major anti-obesity drugs, Orlistat and Sibutramine, only meet with moderate success in weight reduction, but the accompanying adverse effects are many.[4–8]

The endocannabinoid signaling system has been shown to be involved in both neuronal and peripheral physiological processes, including feeding behavior, intestinal motility, nociception, locomotive activity, and immune responses.[9] These activities are mediated by the combined action of three components such as receptors, lipid-like endocannabinoids and proteins involved in the production and removal of endocannabinoids.[10] Two cannabinoid receptors CB1[11] and CB2[12], which belong to the G protein-coupled receptor family, have been identified as responding to endocannabinoids, plant derived cannabinoids (*e.g.* $\Delta^9$-tetrahydrocannabinol) or synthetic ligands (*e.g.* CP55,940 and *R*-(+)-WIN55,212). CB1 receptors are predominantly expressed in neurons to inhibit the release of neurotransmitters, and CB2 receptors are abundantly expressed in immune cells and potentially participate in cytokine release and function.[9] Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) derived from phospholipid precursors are the two most studied endocannabinoids.[13,14] Physiologically, these endocannabinoids are not prestored in secretary vesicles, but are synthesized on demand by enzymes such as *N*-acyl-phosphatidyl-ethanolamine-selective phospholipase D (NAPE-PLD) and the sn-1-selective diacylglycerol (DAG) lipases.

During the past two decades, intensive studies on the cannabinoid-CB1 receptor axis have been fulfilled, showing that appetite control and weight loss in animals could be significantly induced through CB1 blockers,[15–18] leading to the discovery of SR141716A (Fig. 1; rimonabant, Acomplia™), the first anti-obesity drug behaving as a selective CB1 inverse agonist[19] and launched in Europe in 2006. Although rimonabant has been shown to afford weight reduction and improvements in cardiometabolic risk factors after one year and two years of treatment,[20–23] a higher incidence of psychiatric adverse events was observed with patients of depressive illness. Most recently, however, the two-year studies of RIO-Europe (rimonabant in obesity and related metabolic disorders-Europe) demonstrated that with rimonabant therapy, the clinically significant weight loss and improvements in several cardiometabolic risk factors, including triglycerides, high-density lipoprotein cholesterol, insulin resistance and fasting glucose levels, were sustained over two years with favorable tolerability and safety for overweight/obese patients without a history of severe depressive disorder or anxiety.[24]




**1**

**Fig. 1** SR141716A (rimonabant, Acomplia™).

The aforementioned encouraging results stimulated our long-lasting efforts in pursuing a new generation of rimonabant-mimicking molecules as anti-obesity agents with less CNS toxicity.[25] Herein, we wish to report that the bioisosteric

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† Electronic supplementary information (ESI) available: Table of $K_i$ values of all compounds, including **4a–k**, **8a–h**, and **SR141716A,** toward CB1 and CB2 receptors.[30] See DOI: 10.1039/b807648k

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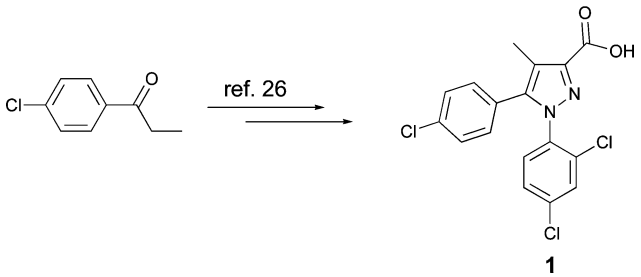
replacement of the pyrazole C3-carboxamide of rimonabant with an oxadiazole moiety has been envisioned and experimentally realized to afford an array of novel analogues, several of which exhibited high binding affinity and potent activity towards CB1 receptors with excellent CB2/1 selectivity. Detailed description of the synthetic design and structure–activity relationship (SAR) studies of these newly developed compounds is presented as follows.




**Scheme 2**

## Results and discussion

### Synthesis

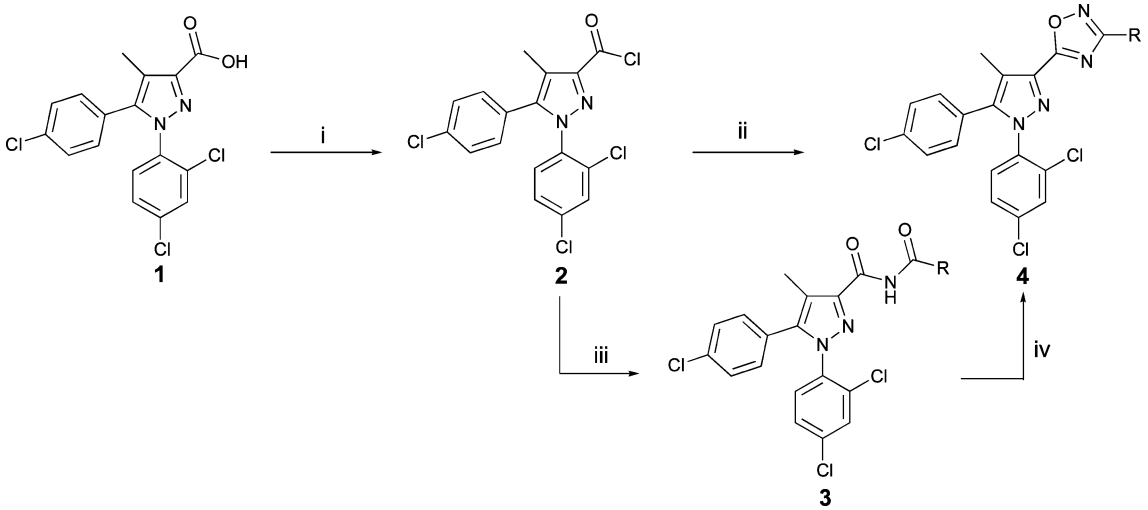
The procedures employed in our laboratory for the synthesis of 3-alkyl oxadiazoles, as represented by the generic formula **4**, are depicted in Scheme 1. The synthesis began with carboxylic acid **1**, readily accessible through a four-step sequence reported in the literature (Scheme 2).[26] Under treatment with thionyl chloride, intermediate **1** was converted to the corresponding acyl chloride **2** in 98% yield which, without purification, was coupled with various amide oximes ($R(C{=}NOH)NH_2$) followed by thermal annulation to afford the desired products **4a–k** (Table 1) in 30–80% yields over the two steps. The required amide oximes were previously prepared in moderate to good yields (50–80%) by treatment of the corresponding alkyl nitriles with hydroxylamine.[27] Alternatively, acid chloride **2** was individually treated with the deprotonated amides, formed *in situ* by treatment with LiHMDS, to afford the corresponding imides which in turn underwent condensation with hydroxylamine to generate the desired 3-alkyl oxadiazoles in 36–60% yields over the two steps.

For the synthesis of 5-alkyl oxadiazoles, as represented by the generic formula **8**, the synthetic sequence illustrated in Scheme 3 was fulfilled. Carboxylic acid **1** was first converted to the primary amide **5** by coupling with ammonia in the presence of EDCI and HOBT as a pair of coupling reagents. The compound **5** thus obtained was subjected to dehydration under standard conditions to give nitrile **6**, which was sequentially reacted with hydroxylamine to afford amide oxime **7**, followed by treatment with the required acid chloride in refluxing toluene to generate the desired 5-alkyl oxadiazoles **8a–h** in 40–52% yields over four steps.

### Biological studies

All the oxadiazole compounds, including **4a–k** and **8a–h**, were subjected to biological evaluations towards CB1 and CB2 receptors, the results of which are compiled in Table 1.

As shown, though the initial test compound, 3-methyl oxadiazole **4a**, exhibited poorer binding affinity and less potency toward the CB1 receptor ($IC_{50}$ = 509.6 nM; $EC_{50}$ = 552.1 nM) than rimonabant ($IC_{50}$ = 13.6 nM; $EC_{50}$ = 17.3 nM), which was constantly employed as the reference in our assay systems, the submicromolar activities observed with **4a** implied that when a hydrophobic substituent was appropriately positioned, the oxadiazole ring might serve as a potential bioisostere for the pyrazole C3-carboxamide moiety. Based on the binding mode of rimonabant in the proposed CB1-receptor homology model (Fig. 2),[18a] further structural modifications aiming to enhance the hydrophobic interaction by extending the alkyl chain were then carried out. When the methyl side chain was replaced with an ethyl or *n*-propyl group, the corresponding 3-ethyl oxadiazole **4b** ($IC_{50}$ = 225.1 nM; $EC_{50}$ = 75.5 nM) and 3-propyl oxadiazole **4c** ($IC_{50}$ = 291.2 nM; $EC_{50}$ = 59.1 nM) resulted in considerable improvements in the CB1 biological activities, with particularly remarkable increases of *ca.* 10-fold in the functional activity ($EC_{50}$). However, further extension of the linear alkyl chain to




**Scheme 1** *Reagents and conditions*: (i) $SOCl_2$, toluene, reflux, 2 h; (ii) $RC(NOH)NH_2$, toluene, reflux, 2 h; (iii) $RCONH_2$, LiHMDS, THF, −78 °C then −10 °C, 2 h; (iv) $NH_2OH$ then pyridine, reflux, 4 h.

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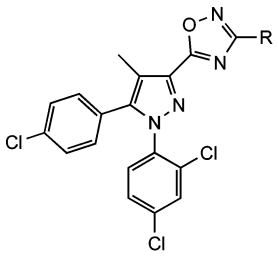
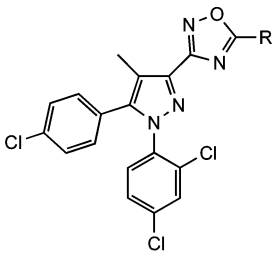
**Table 1** Biological evaluation of 3-alkyl oxadiazoles and 5-alkyl oxadiazoles on hCB1 and hCB2 receptors



**4a-k**



**8a-h**

| Compd | R | $EC_{50}$[a,c] | hCB1 $IC_{50}$[a,b]/nM | hCB2 $IC_{50}$[a,b]/nM | Selectivity (hCB2/hCB1) |
|---|---|---|---|---|---|
| **4a** | $CH_3$ | 552.1 ± 109.6 | 509.6 ± 101.3 | >10000 | > 20 |
| **4b** | $CH_2CH_3$ | 75.5 ± 12.1 | 225.1 ± 44.9 | 6507.5 ± 509.8 | 29 |
| **4c** | $CH_2CH_2CH_3$ | 59.1 ± 23.1 | 291.2 ± 87.5 | 7518.1 ± 1047.0 | 26 |
| **4d** | $CH_2(CH_2)_2CH_3$ | 141.1 ± 8.8 | 255.8 ± 13.7 | >10000 | > 39 |
| **4e** | $CH_2(CH_2)_3CH_3$ | 128.5 ± 36.3 | 220.7 ± 27.9 | >10000 | > 45 |
| **4f** | $CH(CH_3)_2$ | 55.3 ± 8.5 | 80.2 ± 19.5 | 6924.8 ± 724.9 | 86 |
| **4g** | $CH(C_2H_5)_2$ | 39.1 ± 19.3 | 62.2 ± 14.7 | 3490.8 ± 1273.9 | 56 |
| **4h** | $C(CH_3)_3$ | 25.8 ± 6.2 | 64.7 ± 8.6 | 5198.5 ± 95.5 | 80 |
| **4i** | *c*-$C_3H_5$ | 95.0 ± 77.7 | 114.5 ± 9.3 | 6794.7 ± 122.4 | 59 |
| **4j** | $CH_2CH(CH_3)_2$ | 95.8 ± 32.7 | 317.6 ± 9.2 | 9207.0 ± 833.6 | 29 |
| **4k** | $CH_2$(*c*-$C_3H_5$) | 155.5 ± 17.6 | 435.1 ± 204.1 | 9926.7 ± 824.8 | 21 |
| **8a** | $CH_3$ | 435.5 ± 21.7 | 924.8 ± 106.1 | >10000 | > 11 |
| **8b** | $CH_2CH_3$ | 365.3 ± 38.2 | 270.7 ± 47.6 | >10000 | > 37 |
| **8c** | $CH_2CH_2CH_3$ | 163.9 ± 18.3 | 160.2 ± 40.9 | 9965.6 ± 398.3 | 62 |
| **8d** | $CH(CH_3)_2$ | 150.1 ± 69.3 | 77.8 ± 24.1 | 9021.7 ± 1316.9 | 116 |
| **8e** | $CH(C_2H_5)_2$ | 131.5 ± 61.1 | 55.1 ± 17.6 | 1329.5 ± 168.4 | 24 |
| **8f** | $C(CH_3)_3$ | 56.1 ± 24.1 | 30.5 ± 8.7 | 9790.6 ± 268.7 | 321 |
| **8g** | $CF_3$ | 64.6 ± 5.1 | 37.1 ± 5.0 | >10000 | > 269 |
| **8h** | $C(CH_3)_2CF_3$ | 8.2 ± 3.9 | 14.2 ± 4.0 | 3544.5 ± 1374.4 | 247 |
| | **SR141716A** | 17.3 ± 1.8 | 13.6 ± 1.0 | 1643.7 ± 107.0 | 121 |

[a] Data are expressed as the mean ± SD of at least three independent experiments. [b] The binding affinity determined by inhibition of [$^3$H]-CP55940 binding to the hCB1 or hCB2-transfected HEK 293 membrane is expressed as $IC_{50}$. [c] The functional activity determined by inhibition of Eu-GTP binding to hCB1-transfected HEK 293 membrane is expressed as $EC_{50}$.

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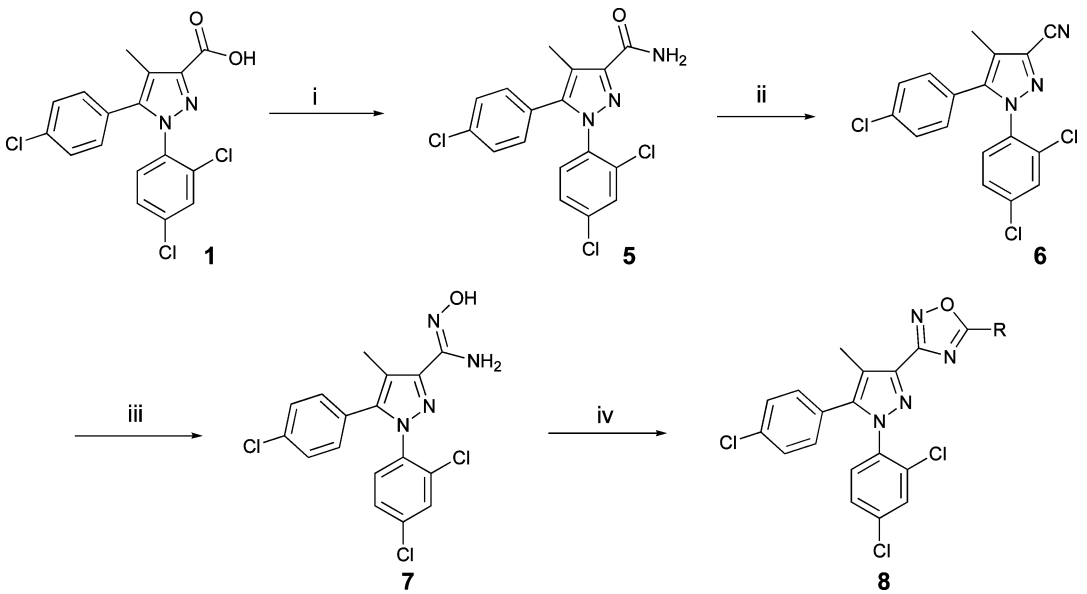


**Scheme 3** *Reagents and conditions*: (i) EDCI, HOBT, $CH_2Cl_2$, r.t., 40 min, then $NH_{3(aq.)}$, r.t., 30 min; (ii) TFAA, $Et_3N$, $CH_2Cl_2$, 0 °C, 1h; (iii) 50% $NH_2OH_{(aq.)}$, MeOH, 40 °C, 16 h; (iv) RCOCl, toluene, reflux, 2 h.

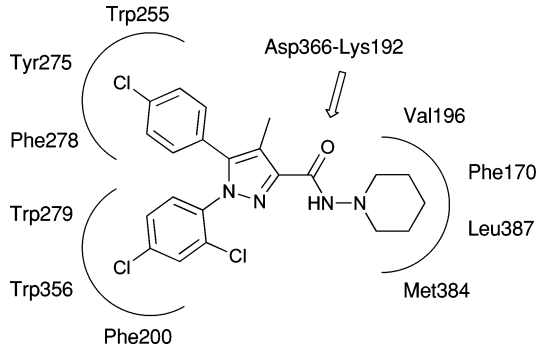
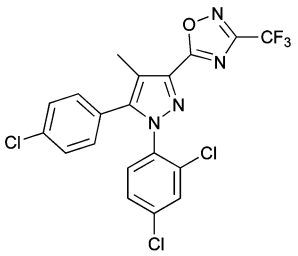


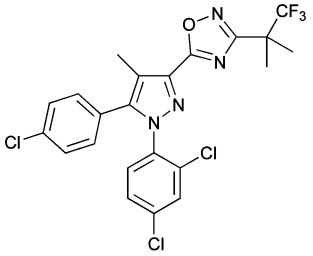

**Fig. 2** The binding mode of rimonabant in the proposed CB1-receptor homology model.

3 and 4 methylene units gave rise to compounds **4d** and **4e**, respectively, with no improvements in either the binding affinity or the potency towards the CB1 receptor, indicating that the hydrophobic cavity of the CB1 receptor around the pyrazole C-3 substitution might be shallow.

As such, analogues with a branched alkyl group, instead of a linear linker, were then explored. As illustrated in Table 1, compounds **4f–i** thus obtained apparently supported the aforementioned inference of CB1 receptor with a shallow cavity surrounding the C-3 position, leading to an enhancement of both the functional activity and the binding affinity by up to 20- and 8-fold (*i.e.*, **4h**), respectively. Further expanding the dimensions of the branched alkyl group seemed not to be tolerated, as demonstrated by **4j–k** whose biological activities are inferior to those of **4f–i**. Though the array of 3-alkyl oxadiazoles described above revealed great potential as bioisosteres of rimonabant, all its compounds share the liability of poor CB2/1 selectivity (CB2/1 = 20∼86). For comparison purposes, attempts were also made to explore 5-alkyl oxadiazoles, in which a 1,2-transposition of the heteroatoms O and N was implemented. As a result, not unexpectedly, the corresponding compounds **8a–f** displayed similar binding and functional behaviors towards CB1 receptors as did the 3-alkyl oxadiazoles **4a–c** and **4f–h**, suggesting that the binding mode against CB1 receptors was little influenced by this minor structural modification. However, it was observed that the CB2/1 selectivity of compound **8f** (CB2/1 = 321) was dramatically enhanced as compared to **4h** (CB2/1 = 80). This finding is hard to rationalize by the current results and is worth studying further. Also encouraging is the finding that when the methyl group was substituted with a trifluoromethyl moiety, the resulting **8g** ($IC_{50}$ = 37.1 nM; $EC_{50}$ = 64.6 nM; CB2/1 = >269) exhibited a substantial improvement relative to **8a** ($IC_{50}$ = 924.8 nM; $EC_{50}$ = 435.5 nM; CB2/1 = >11) in all biological aspects, including binding affinity, potency, and selectivity towards CB1 receptors, presumably due to the enhancement of the Asp366–Lys192 salt bridge-stabilizing capacity in the presence of a strong electron-withdrawing group (see Fig. 2).[18a] By this inference, a hybrid with an alkyl chain combining both the favored trifluoromethyl and bulky *t*-butyl motifs was designed, leading to the desired compound **8h** ($IC_{50}$ = 14.2 nM; $EC_{50}$ = 8.2 nM; CB2/1 = 247), the biological profile of which is comparable to SR141716A and which might serve as an advanced lead for further development for the treatment of obesity. Based on these encouraging results, attempts were also made to synthesize compounds **4l** and **4m**, which are highly expected to behave the same as compounds **8g** and **8h** with desirable receptor–ligand interactions. Unfortunately, these efforts turned out to be fruitless due to the labile intermediates formed following the synthetic Scheme 1. Also, following the protocol reported in the literature,[28] the intrinsic properties of all the compounds in Table 1 were identified, leading to the finding that these rimonabant-mimicking molecules, without exception, behaved as inverse agonists as does rimonabant.




**4l**




**4m**

## Conclusions

In conclusion, based on the bioisosteric replacement of the pyrazole C3-carboxamide of rimonabant with a 5-alkyl oxadiazole ring, a novel class of oxadiazole derivatives with promising biological activity towards CB1 receptors was discovered. Among them, compounds with an alkyl linker containing a strong electron-withdrawing group (*e.g.*, $CF_3$) and a sterically favorable bulky group (*e.g.*, *t*-butyl) have shown potent CB1 antagonism and excellent selectivity, and thus might serve as potential candidates for further development as anti-obesity agents. Further structural modifications and *in vivo* efficacy studies on the series are currently under active investigation and the results will be reported elsewhere in due course.

## Experimental

### General methods for chemistry

All reactions were performed in oven-dried glassware and some reactions were carried out under a positive pressure of argon or nitrogen when the reactions were sensitive to moisture or oxygen. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by the use of E. Merck silica gel 60 (230–400 mesh). Fourier transform infrared spectra (IR) were recorded on a Perkin-Elmer spectrum RX-1. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Aavance EX 400 FT NMR or a Bruker DMX-600. Chloroform-*d* was used as the solvent and TMS ($\delta$ = 0.00 ppm) as an internal standard. Chemical shift values are reported in ppm relative to the TMS in delta ($\delta$) units. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), dd (doublet of doublets), dt (doublet of triplets), br (broadened) and m (multiplet). Coupling constants ($J$) are expressed in Hz. MS and HRMS were measured by JEOL JMS-D300 and JEOL JMS-HX110 spectrometers, respectively; electrospray mass spectra (ESMS) were recorded using an Agilent 1100MSD spectrometer. Spectral data were recorded as $m/z$ values.

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### General procedure for the synthesis of compounds 4a, 4b, 4f, 4g, 4h and 4k

The general procedure is illustrated immediately below with compound **4a** as a specific example.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-methyl-1,2,4-oxadiazole (4a).** To a stirred solution of the acid **1** (0.150 g, 0.39 mmol) in toluene (5 mL) was added thionyl chloride (0.17 mL, 2.36 mmol) at room temperature. The mixture was heated to reflux for 2 h and then cooled to room temperature. This was followed by concentration *in vacuo* to afford the crude carbonyl chloride **2** (0.153 g, 98% yield) as a white solid. To a stirred solution of *N*-hydroxyacetimidamide (0.087 g, 1.18 mmol) in toluene (2 mL) was added the carbonyl chloride **2** in toluene (2 mL) in one portion. The resulting mixture was heated to reflux for 2 h and then cooled to room temperature. Water (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with dichloromethane (3 × 10 mL); the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1 : 12) to give compound **4a** (0.042 g, 31% yield) as a white solid: mp 92–93 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3085, 2958, 2927, 2856, 1605, 1569, 1497, 1487 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.42–7.30 (m, 5H), 7.13 (d, $J = 8.2$ Hz, 2H), 2.51 (s, 3H), 2.43 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.6, 167.5, 143.1, 138.3, 136.2, 135.6, 135.2, 132.8, 130.8, 130.5, 130.2, 129.0, 127.8, 126.6, 117.6, 11.6, 9.5; MS (EI, 70 eV) *m*/*z* (% intensity) 417.9 ($M^+$, 28.3); HRMS calcd for $C_{19}H_{13}Cl_3N_4O$ 418.0155, found 418.0143.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-ethyl-1,2,4-oxadiazole (4b).** Compound **4b** was obtained by a similar procedure to that used for compound **4a**. Treatment of acid **1** (0.155 g, 0.40 mmol) with thionyl chloride (0.18 mL, 2.50 mmol), and *N*-hydroxypropionimidamide (0.105 g, 1.20 mmol) gave compound **4b** (0.064 g, 38% yield) as a white solid: mp 129–130 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3052, 2959, 2928, 2871, 1604, 1569, 1498, 1490 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 7.45–7.27 (m, 5H), 7.13 (d, $J = 8.4$ Hz, 2H), 2.88 (q, $J = 7.6$ Hz, 2H), 2.44 (s, 3H), 1.40 (t, $J = 7.6$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.9, 170.5, 143.1, 138.4, 136.1, 135.6, 135.2, 132.8, 130.7, 130.5, 130.1, 128.9, 127.8, 126.6, 117.5, 19.7, 11.4, 9.5; MS (EI, 70 eV) *m*/*z* (% intensity) 432.0 ($M^+$, 33.8); HRMS calcd for $C_{20}H_{15}Cl_3N_4O$ 432.0311, found 432.0298.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-isopropyl-1,2,4-oxadiazole (4f).** Compound **4f** was obtained by a similar procedure to that used for compound **4a**. Treatment of acid **1** (0.155 g, 0.40 mmol) with thionyl chloride (0.18 mL, 2.50 mmol), and *N*-hydroxyisobutyramidine (0.122 g, 1.20 mmol) gave compound **4f** (0.084 g, 46% yield) as a white solid: mp 130–132 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3086, 2972, 2932, 2874, 1606, 1569, 1497, 1486 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.47–7.25 (m, 5H), 7.13 (d, $J = 8.2$ Hz, 2H), 3.21 (quint, $J = 6.9$ Hz, 1H), 2.45 (s, 3H), 1.43 (d, $J = 6.9$ Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.3, 170.4, 143.1, 138.5, 136.1, 135.6, 135.1, 132.8, 130.7, 130.6, 130.0, 128.9, 127.7, 126.6, 117.6, 26.7, 20.4, 9.4; MS (EI, 70 eV) *m*/*z* (% intensity) 446.0 ($M^+$, 36.9); HRMS calcd for $C_{21}H_{17}Cl_3N_4O$ 446.0468, found 446.0481.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-(pentan-3-yl)-1,2,4-oxadiazole (4g).** Compound **4g** was obtained by a similar procedure to that used for compound **4a**. Treatment of acid **1** (0.150 g, 0.39 mmol) with thionyl chloride (0.17 mL, 2.36 mmol), and 2-ethyl-*N*-hydroxybutanamidine (0.153 g, 1.18 mmol) gave compound **4g** (0.086 g, 46%): mp 173–174 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3087, 2964, 2932, 2876, 1606, 1568, 1496, 1486 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.27 (m, 5H), 7.13 (d, $J = 8.4$ Hz, 2H), 2.82 (quint, $J = 5.5$ Hz, 1H), 2.44 (s, 3H), 1.89–1.73 (m, 4H), 0.89 (t, $J = 7.4$ Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.3, 170.5, 143.1, 138.6, 136.1, 135.7, 135.2, 132.9, 130.7, 130.6, 130.1, 128.9, 127.8, 126.7, 117.6, 40.6, 25.9, 11.7, 9.5; MS (EI, 70 eV) *m*/*z* (% intensity) 474.0 ($M^+$, 25.4); HRMS calcd for $C_{23}H_{21}Cl_3N_4O$ 474.0781, found 474.0786.

**3-*tert*-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (4h).** Compound **4h** was obtained by a similar procedure to that used for compound **4a**. Treatment of acid **1** (0.150 g, 0.39 mmol) with thionyl chloride (0.17 mL, 2.36 mmol), and *N*-hydroxypivalamidine (0.137 g, 1.18 mmol) gave compound **4h** (0.143 g, 79% yield) as a white solid: mp 155–156 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3086, 2970, 2930, 2870, 1608, 1569, 1497, 1487 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.28 (m, 5H), 7.12 (d, $J = 8.4$ Hz, 2H), 2.44 (s, 3H), 1.46 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 177.8, 170.3, 143.0, 138.5, 136.1, 135.6, 135.1, 132.9, 130.7, 130.6, 130.0, 128.9, 127.7, 126.6, 117.6, 32.4, 28.3, 9.5; MS (EI, 70 eV) *m*/*z* (% intensity) 460.0 ($M^+$, 15.4); HRMS calcd for $C_{22}H_{19}Cl_3N_4O$ 460.0624, found 460.0634.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-(cyclopropylmethyl)-1,2,4-oxadiazole (4k).** Compound **4k** was obtained by a similar procedure to that used for compound **4a**. Treatment of acid **1** (0.155 g, 0.40 mmol) with thionyl chloride (0.18 mL, 2.50 mmol), and 2-cyclopropyl-*N*-hydroxyacetamidine (0.120 g, 1.20 mmol) gave compound **4k** (0.104 g, 56% yield) as a white solid: mp 120–121 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3082, 2959, 2925, 2871, 1605, 1569, 1496, 1486 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43–7.27 (m, 5H), 7.14 (d, $J = 8.4$ Hz, 2H), 2.76 (d, $J = 7.0$ Hz, 2H), 2.45 (s, 3H), 1.25 (m, 1H), 0.58 (m, 2H), 0.32 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 170.4, 143.1, 138.4, 136.1, 135.6, 135.2, 132.8, 130.7, 130.5, 130.1, 128.9, 127.8, 126.6, 117.6, 30.8, 9.4, 8.71, 4.70; MS (EI, 70 eV) *m*/*z* (% intensity) 458.0 ($M^+$, 28.6); HRMS calcd for $C_{22}H_{17}Cl_3N_4O$ 458.0468, found 458.0457.

### General procedure for the synthesis of compounds 4c, 4d, 4e, 4i and 4j

The general procedure is illustrated immediately below with compound **4c** as a specific example.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-propyl-1,2,4-oxadiazole (4c).** To a stirred solution of the acid **1** (0.150 g, 0.39 mmol) in toluene (5 mL) was added thionyl chloride (0.17 mL, 2.36 mmol) at room temperature. The mixture was heated to reflux for 2 h and then cooled to room temperature. This was followed by concentration *in vacuo* to afford the crude carbonyl chloride **2** (0.153 g, 98% yield) as a white solid. A stirred solution of butyramide (0.072 g, 0.83 mmol) in THF (5 mL) was treated with lithium bis(trimethylsilyl)amide (1 M solution in THF, 1.0 mL, 1.00 mmol) at −78 °C. The

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mixture was stirred for 50 min then carbonyl chloride **2** in THF (5 ml) was added dropwise. The resulting mixture was allowed to warm to −10 °C and stirred for 2 h. Water (10 mL) was added and the aqueous layer was separated and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude imide product, which in turn, without purification, was treated with hydroxylamine hydrochloride (125 mg, 1.81 mmol) in pyridine (3 mL) under reflux conditions for 4 h. This was followed by a usual work-up procedure to afford the crude oxadiazole product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1 : 12) to give compound **4c** (0.073 g, 41% yield) as a white solid: mp 98–99 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3086, 2964, 2933, 2874, 1605, 1570, 1497, 1487 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.50–7.29 (m, 5H), 7.13 (d, $J = 8.4$ Hz, 2H), 2.82 (t, $J = 7.6$ Hz, 2H), 2.44 (s, 3H), 1.88 (sext, $J = 7.6$ Hz, 2H), 1.03 (t, $J = 7.6$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.8, 170.5, 143.1, 138.5, 136.2, 135.7, 135.2, 132.8, 130.7, 130.6, 130.1, 128.9, 127.8, 126.7, 117.6, 27.9, 20.4, 13.6, 9.5; MS (EI, 70 eV) *m/z* (% intensity) 445.9 ($M^+$, 32.2); HRMS calcd for $C_{21}H_{17}Cl_3N_4O$ 446.0468, found 446.0469.

**3-Butyl-5-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (4d).** Compound **4k** was obtained by a similar procedure to that used for compound **4c**. Treatment of acid **1** (0.155 g, 0.40 mmol) with thionyl chloride (0.18 mL, 2.50 mmol), lithium bis(trimethylsilyl)amide (1.0 mL, 1.00 mmol) and pentanamide (0.084 g, 0.83 mmol) gave compound **4d** (0.071 g, 38% yield) as a white solid: mp 136–137 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3085, 2959, 2931, 2872, 1605, 1569, 1497, 1487 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.42–7.28 (m, 5H), 7.13 (d, $J = 8.2$ Hz, 2H), 2.84 (t, $J = 7.5$ Hz, 2H), 2.44 (s, 3H), 1.82 (quint, $J = 7.5$ Hz, 2H), 1.45 (sext, $J = 7.5$ Hz, 2H), 0.96 (t, $J = 7.5$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.9, 170.4, 143.0, 138.4, 136.1, 135.6, 135.1, 132.8, 130.7, 130.5, 130.0, 128.9, 127.7, 126.6, 117.5, 29.0, 25.6, 22.1, 13.5, 9.4; MS (EI, 70 eV) *m/z* (% intensity) 460 ($M^+$, 55.0); HRMS calcd for $C_{22}H_{19}Cl_3N_4O$ 460.0619, found 460.0636.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-pentyl-1,2,4-oxadiazole (4e).** Compound **4e** was obtained by a similar procedure to that used for compound **4c**. Treatment of acid **1** (0.150 g, 0.39 mmol) with thionyl chloride (0.17 mL, 2.36 mmol), lithium bis(trimethylsilyl)amide (1.0 mL, 1.00 mmol) and hexanamide (0.095 g, 0.83 mmol) gave compound **4e** (0.110 g, 59% yield) as a white solid: mp 150–152 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3086, 2957, 2930, 2860, 1605, 1568, 1497, 1486 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.27 (m, 5H), 7.13 (d, $J = 8.4$ Hz, 2H), 2.83 (t, $J = 7.5$ Hz, 2H), 2.44 (s, 3H), 1.86–1.80 (m, 2H), 1.50–1.26 (m, 4H), 0.91 (t, $J = 6.7$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.9, 170.5, 143.1, 138.4, 136.1, 135.6, 135.2, 132.8, 130.7, 130.5, 130.1, 128.9, 127.7, 126.6, 117.5, 31.2, 26.6, 25.9, 22.2, 13.8, 9.5; MS (EI, 70 eV) *m/z* (% intensity) 474.0 ($M^+$, 31.8); HRMS calcd for $C_{23}H_{21}Cl_3N_4O$ 474.0781, found 474.0769.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-cyclopropyl-1,2,4-oxadiazole (4i).** Compound **4i** was obtained by a similar procedure to that used for compound **4c**. Treatment of acid **1** (0.150 g, 0.39 mmol) with thionyl chloride (0.17 mL, 2.36 mmol), lithium bis(trimethylsilyl)amide (1.0 mL, 1.00 mmol) and cyclopropane-carboxamide (0.070 g, 0.83 mmol) gave compound **4i** (0.063 g, 36% yield) as a white solid: mp 110–111 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3087, 2959, 2928, 2871, 1605, 1569, 1497, 1487 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.28 (m, 5H), 7.11 (d, $J = 8.2$ Hz, 2H), 2.40 (s, 3H), 2.25–2.15 (m, 1H), 1.23–1.05 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.8, 170.4, 143.2, 138.5, 136.2, 135.7, 135.3, 133.0, 130.8, 130.7, 130.2, 129.0, 127.8, 126.7, 117.7, 9.6, 7.8, 6.9; MS (EI, 70 eV) *m/z* (% intensity) 443.9 ($M^+$, 27.8); HRMS calcd for $C_{21}H_{15}Cl_3N_4O$ 444.0311, found 444.0309.

**5-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-3-isobutyl-1,2,4-oxadiazole (4j).** Compound **4j** was obtained by a similar procedure to that used for compound **4c**. Treatment of acid **1** (0.150 g, 0.39 mmol) with thionyl chloride (0.17 mL, 2.36 mmol), lithium bis(trimethylsilyl)amide (1.0 mL, 1.00 mmol) and 3-methylbutanamide (0.084 g, 0.83 mmol) gave compound **4j** (0.067 g, 37% yield) as a white solid: mp 126–127 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3093, 2960, 2926, 2855, 1607, 1569, 1497, 1487 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43–7.28 (m, 5H), 7.13 (d, $J = 8.4$ Hz, 2H), 2.72 (d, $J = 6.8$ Hz, 2H), 2.44 (s, 3H), 2.26 (m, $J = 6.8$ Hz, 1H), 1.03 (d, $J = 6.8$ Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.46, 170.16, 143.12, 138.50, 136.18, 135.68, 135.22, 132.84, 130.77, 130.60, 130.14, 128.97, 127.82, 126.69, 117.61, 34.72, 27.02, 22.30, 9.54; MS (EI, 70 eV) *m/z* (% intensity) 460.0 ($M^+$, 31.8); HRMS calcd for $C_{22}H_{19}Cl_3N_4O$ 460.0624, found 460.0640.

**5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (5).** To a solution of acid **1** (1.290 g, 3.38 mmol) in $CH_2Cl_2$ (20 mL) was added 1-hydroxybenzotriazole (HOBT, 0.550 g, 4.06 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 0.900 g, 5.07 mmol) in sequence. The resulting mixture was stirred at room temperature for 40 min and then ammonia (30% in $H_2O$, 10 eq.) was added dropwise. The reaction mixture was stirred for an additional 30 min at room temperature. The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (3 : 10) gave carboxamide **5** (1.160 g, 90% yield) as a white solid: mp 185–186 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3458, 3287, 1678, 1592, 1573, 1494, 1484 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.39 (d, $J = 2.0$ Hz, 1H), 7.27–7.23 (m, 4H), 7.04–7.02 (m, 2H), 6.82 (br s, 1H), 5.80 (br s, 1H), 2.33 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 164.7, 144.2, 143.0, 135.9, 135.7, 134.8, 132.8, 130.7, 130.4, 130.2, 128.8, 127.8, 127.0, 117.9, 9.4; ESMS *m/z*: 380.1 ($MH^+$).

**5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbonitrile (6).** To a stirred solution of carboxamide **5** (1.160 g, 3.05 mmol) in $CH_2Cl_2$ (20 mL) was added triethylamine (1.28 mL, 9.15 mmol) and trifluoroacetic anhydride (0.85 mL, 6.10 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h. Water (15 mL) was added to quench the reaction. The aqueous layer was separated and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and

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concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1 : 10) gave carbonitrile **6** (1.050 g, 95% yield) as a white solid: mp 90–92 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3089, 2239, 1604, 1560, 1496, 1487 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.40 (d, $J$ = 2.0 Hz, 1H), 7.30–7.23 (m, 4H), 7.04–7.02 (m, 2H), 2.22 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 142.1, 136.5, 135.5, 135.1, 132.6, 130.4, 130.3, 130.2, 129.1, 127.6, 125.9, 120.9, 113.1, 8.7; ESMS $m/z$: 362.0 ($MH^+$).

**(*Z*)-5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N′-hydroxy-4-methyl-1*H*-pyrazole-3-carboximidamide (7).** To a stirred solution of compound **6** (0.863 g, 2.28 mmol) in MeOH (20 ml) was added 50% aqueous hydroxylamine solution (4.56 ml, 2.99 mmol) at room temperature. The mixture was heated to 40 °C and stirred for 16 h. The resulting solution was then cooled to room temperature and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1 : 1) to give carboximidamide **7** (0.753 g, 80% yield) as a white solid: mp 218–221 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3501, 3390, 1644, 1567, 1496, 1485 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (br s, 1H), 7.32–7.25 (m, 5H), 7.08 (d, $J$ = 8.3 Hz, 2H), 5.26 (br s, 2H), 2.25 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 148.9, 143.8, 142.7, 136.1, 135.6, 134.7, 133.0, 130.8, 130.6, 130.2, 128.8, 127.7, 127.5, 114.6, 10.3; ESMS $m/z$: 395.0 ($MH^+$).

### General procedure for the synthesis of compounds 8a–8f

The general procedure is illustrated immediately below with compound **8a** as a specific example.

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-methyl-1,2,4-oxadiazole (8a).** To a stirred solution of carboximidamide **7** (0.150 g, 0.38 mmol) in anhydrous toluene (5 mL) was added a solution of acetyl chloride (0.036 g, 0.49 mmol). The resulting mixture was heated to reflux and stirred for 2 h. The reaction was subsequently cooled to room temperature and water (5 mL) was added. The aqueous layer was separated and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1 : 6) to give compound **8a** (0.111 g, 70% yield) as a white solid: mp 112–115 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3085, 2975, 2931, 2870, 1579, 1561, 1497, 1486 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.36–7.34 (m, 2H), 7.28–7.24 (m, 3H), 7.09 (d, $J$ = 8.3 Hz, 2H), 2.63 (s, 3H), 2.35 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 176.2, 164.0, 142.7, 140.4, 135.9, 135.7, 134.8, 132.9, 130.7, 129.9, 128.8, 127.6, 127.1, 116.2, 12.2, 9.8; ESMS $m/z$: 419.0 ($MH^+$).

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-ethyl-1,2,4-oxadiazole (8b).** Compound **8b** was obtained by a similar procedure to that used for compound **8a**. Treatment of carboximidamide **7** (0.16 g, 0.41 mmol) with propionyl chloride (0.048 g, 0.53 mmol) gave compound **8b** (0.126 g, 71% yield) as a white solid: mp 145–147 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3086, 2977, 2934, 2876, 1580, 1567, 1497, 1486 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.37–7.35 (m, 2H), 7.29–7.25 (m, 3H), 7.09 (d, $J$ = 8.3 Hz, 2H), 2.98 (q, $J$ = 7.7 Hz, 2H), 2.36 (s, 3H), 1.43 (t, $J$ = 4.4 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 180.4, 164.0, 142.8, 140.6, 136.0, 135.7, 134.8, 133.0, 130.8, 130.7, 129.9, 128.8, 127.6, 127.2, 116.3, 20.2, 10.8, 9.8; ESMS $m/z$: 433.1 ($MH^+$).

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-propyl-1,2,4-oxadiazole (8c).** Compound **8c** was obtained by a similar procedure to that used for compound **8a**. Treatment of carboximidamide **7** (0.16 g, 0.41 mmol) with butyryl chloride (0.057 g, 0.53 mmol) gave compound **8c** (0.133 g, 74% yield) as a white solid: mp 163–165 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3085, 2985, 2942, 2881, 1583, 1567, 1496, 1486 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.37–7.34 (m, 2H), 7.28–7.25 (m, 3H), 7.09 (d, $J$ = 8.4 Hz, 2H), 2.92 (t, $J$ = 7.6 Hz, 2H), 2.36 (s, 3H), 1.90–1.85 (m, 2H), 1.00 (t, $J$ = 7.5 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 180.4, 164.0, 142.8, 140.6, 136.0, 135.7, 134.8, 133.0, 130.8, 130.7, 129.9, 128.8, 127.6, 127.2, 116.3, 20.2, 10.8, 9.8; ESMS $m/z$: 447.0 ($MH^+$).

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-isopropyl-1,2,4-oxadiazole (8d).** Compound **8d** was obtained by a similar procedure to that used for compound **8a**. Treatment of carboximidamide **7** (0.15 g, 0.38 mmol) with isobutyryl chloride (0.052 g, 0.49 mmol) gave compound **8d** (0.125 g, 74% yield) as a white solid: mp 155–157 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 2977, 2934, 2876, 1580, 1567, 1497, 1486 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.38–7.34 (m, 2H), 7.29–7.25 (m, 3H), 7.09 (d, $J$ = 8.3 Hz, 2H), 3.31 (quint, $J$ = 6.9 Hz, 1H), 2.36 (s, 3H), 1.44 (d, $J$ = 6.8 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 183.6, 163.9, 142.8, 140.7, 136.0, 135.7, 134.8, 133.0, 130.9, 130.8, 129.9, 128.8, 127.6, 127.2, 116.4, 27.5, 20.1, 9.8; ESMS $m/z$: 447.0 ($MH^+$).

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(pentan-3-yl)-1,2,4-oxadiazole (8e).** Compound **8e** was obtained by a similar procedure to that used for compound **8a**. Treatment of carboximidamide **7** (0.155 g, 0.39 mmol) with 2-ethylbutanoyl chloride (0.066 g, 0.49 mmol) gave compound **8e** (0.137 g, 76% yield) as a white solid: mp 195–197 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3084, 2966, 2933, 2876, 1578, 1567, 1497, 1486 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.39–7.34 (m, 2H), 7.29–7.25 (m, 3H), 7.09 (d, $J$ = 8.4 Hz, 2H), 3.00–2.95 (m, 1H), 2.37 (s, 3H), 1.91–1.85 (m, 2H), 1.81–1.76 (m, 2H), 0.88 (t, $J$ = 7.4 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 182.5, 163.9, 142.8, 140.7, 136.0, 135.7, 134.8, 133.0, 130.9, 130.7, 129.9, 128.8, 127.6, 127.2, 116.4, 41.8, 26.1, 11.7, 9.9; ESMS $m/z$: 475.1 ($MH^+$).

**5-*tert*-Butyl-3-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (8f).** Compound **8f** was obtained by a similar procedure to that used for compound **8a**. Treatment of carboximidamide **7** (0.155 g, 0.39 mmol) with pivaloyl chloride (0.059 g, 0.49 mmol) gave compound **8f** (0.146 g, 75% yield) as a white solid: mp 178–180 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3088, 2962, 2928, 2853, 1587, 1566, 1497, 1486 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.35 (m, 2H), 7.29–7.24 (m, 3H), 7.09 (d, $J$ = 8.0 Hz, 2H), 2.36 (s, 3H), 1.49 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 183.6, 163.8, 142.8, 140.7, 136.0, 135.7, 134.8, 133.1, 130.9, 130.8, 129.9, 128.8, 127.6, 127.2, 116.4, 33.6, 28.4, 9.9; ESMS $m/z$: 461.1 ($MH^+$).

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### General procedure for the synthesis of compounds 8g and 8h

The general procedure is illustrated immediately below with compound **8g** as a specific example.

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole (8g).** To a stirred solution of 2,2,2-trifluoroacetic acid (0.061 g, 0.53 mmol) in anhydrous $CH_2Cl_2$ (0.5 mL) was added oxalyl chloride (0.06 mL, 0.68 mmol). The resulting solution was stirred at room temperature for 2 h and concentrated *in vacuo* to afford the crude carbonyl chloride. To a stirred solution of carboximidamide **7** (0.100 g, 0.25 mmol) in toluene (2 mL) was added the above crude carbonyl chloride in toluene (2 mL). The mixture was heated to reflux for 2 h and then cooled to room temperature. Water (15 mL) was added to quench the reaction. The aqueous layer was separated and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1 : 10) to give compound **8g** (0.111 g, 70% yield) as a white solid: mp 128–129 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3090, 2969, 2930, 2876, 1582, 1569, 1497, 1486, 1178 $cm^{-1}$;$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.30 (m, 5H), 7.14–7.12 (m, 2H), 2.41 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.9 (q, $J_{C\text{-}F}$ = 44 Hz), 164.8, 143.3, 138.8, 136.2, 135.7, 135.2, 133.0, 130.8, 130.7, 130.1, 129.0, 127.8, 126.7, 117.3 (q, $J_{C\text{-}F}$ = 272 Hz), 117.0, 9.8; ESMS *m*/*z*: 474.0 ($MH^+$).

**3-(5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl)-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2,4-oxadiazole (8h).** Compound **8h** was obtained by a similar procedure to that used for compound **8g**. Treatment of 3,3,3-trifluoro-2,2-dimethylpropanoic acid (0.078 g, 0.5 mmol) with oxalyl chloride (0.06 mL, 0.65 mmol) and carboximidamide **7** (0.090 g, 0.23 mmol) gave compound **8h** (0.071 g, 60% yield) as a white solid: mp 176–177 °C; IR ($CH_2Cl_2$, cast) $\nu_{max}$ 3094, 2929, 2870, 1588, 1566, 1498, 1486, 1215, 1178, 1157 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42–7.37 (m, 2H), 7.34–7.28 (m, 3H), 7.13 (d, $J$ = 8.4 Hz, 2H), 2.39 (s, 3H), 1.76 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.7, 164.2, 143.0, 140.1, 135.9, 135.9, 135.0, 133.1, 130.8, 130.8, 130.0, 128.9, 127.7, 127.3 (q, $J_{C\text{-}F}$ = 280 Hz), 127.1, 116.8, 43.6 (q, $J_{C\text{-}F}$ = 28 Hz), 20.7 (× 2, q, $J_{C\text{-}F}$ = 6 Hz), 9.8; ESMS *m*/*z*: 516.0 ($MH^+$).

### General methods for biological evaluation

Establishment of human CB1 (hCB1) and CB2 (hCB2) stable cell lines and membrane purification: either hCB1 cDNA tagged with Flag at the N terminus or hCB2 cDNA was subcloned into the pIRES2-EGFP vector (Clontech Laboratories, Inc., Mountain View, CA). After being transfected into HEK 293 cells, clones stably expressing either hCB1 or hCB2 were selected by GFP and G418 sulfate, and maintained in DMEM supplemented with 10% fetal bovine serum and 0.5 mg $ml^{-1}$ G418 sulfate under 5% $CO_2$ at 37 °C. For membrane purification, cells were homogenized in ice-cold buffer A (50 mM Tris, 5 mM $MgCl_2$, 2.5 mM EDTA, pH 7.4, 10% sucrose) with 1 mM PMSF. The homogenate was centrifuged for 15 min at 2000*g* at 4 °C. The resulting supernatant was centrifuged for another 30 minutes at 43000*g* at 4 °C. The final pellet was resuspended in buffer A and stored at −80 °C.

### Radioligand binding assay

0.2–8 μg of the purified membrane was incubated with 0.75 nM [$^3$H] CP55,940 and the compound of interest in the incubation buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 1 mM EDTA, 0.3% BSA, pH 7.4). The non-specific binding was defined in the presence of 1 μM of CP55,940. The reactions were incubated for one and a half hours at 30 °C in Multiscreen microplates (Millipore Corp., Billerica, MA). The reactions were terminated by manifold filtration and washed four times with ice-cold wash buffer (50 mM Tris, pH 7.4, 0.25% BSA). The radioactivity bound to the filters was measured by Topcount (PerkinElmer Inc., Waltham, MA). The $IC_{50}$ was determined as the concentration of compound required to inhibit 50% of the binding of [$^3$H] CP55,940 and calculated by non-linear regression (GraphPad software, San Diego, CA).[29] Alternatively, the $K_i$ was measured according to the standard protocol reported in the literature[30]; these binding affinity values are compiled in Table 2 as exhibited in the ESI.†

### Eu-GTP binding assay

The Eu-GTP binding assay was performed using the DELFIA Eu-GTP binding kit (Perkin Elmer Inc., Waltham, MA) based on methods developed by Frang *et al.*,[31] with minor modifications as described in the following: 1–4 μg of purified membrane was incubated with the compound of interest and 20 nM CP55,940 in the assay buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 100 μg $mL^{-1}$ saponin, 5 mM $MgCl_2$, 2 μM GDP, 0.5% BSA) at 30 °C for 60 minutes in acroplates (Pall Life Sciences, Ann Arbor, Mich.). Following the addition of Eu-GTP and incubation for 30 minutes at 30 °C, the assay was terminated by washing four times with the washing buffer provided in the kit. The fluorescence signal of the Eu-GTP was determined with a Victor 2 multilabel reader (Perkin Elmer Inc., Waltham, MA). The $EC_{50}$ of the tested compounds at inhibiting 50% of the CP55,940-stimulated Eu-GTP binding was determined from the dose–response curves using non-linear regression (GraphPad software, San Diego, CA).

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