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Original article

Synthesis and cannabinoid activity of 1-substituted-indole-3-oxadiazole derivatives: Novel agonists for the CB_1 receptor

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Abstract

An exploratory chemical effort has been undertaken to develop a novel series of compounds as selective CB_1 agonists. It is hoped that compounds of this type will have clinical utility in pain control, and cerebral ischaemia following stroke or traumatic head injury.

We report here medicinal chemistry studies directed towards the investigation of a series of 1-substituted-indole-3-oxadiazoles as potential CB_1 agonists.

Keywords: Cannabinoid CB_1 receptors; CB_1 agonists; Pain control; Aminoalkylindoles; Design; Synthesis

1. Introduction

There are two cannabinoid receptors designated neuronal (CB_1) and peripheral (CB_2) and both have recently been cloned [1,2]. Activation of both receptors leads to inhibition of adenylate cyclase and activation of mitogen-activated protein kinases. Activation of CB_1 receptors also leads to the gating of a variety of ion channels, including the inhibition of N-type voltage dependent calcium channels. As a consequence of these cellular effects, together with the distribution of the receptors in neuronal tissues, cannabinoid CB_1 agonists have been suggested to offer significant therapeutic potential in the management of glaucoma, motor dysfunction, appetite stimulation, emesis and, in particular, the treatment of chronic neuropathic pain [3–5]. In 1992, it was discovered that the endogenous ligand for the CB_1 receptor is anandamide [6]. Anandamide (**1**) and a range of other structurally unrelated cannabinoid agonists have been shown to block the N-type calcium channel. Given that blockade of these channels by certain conotoxin peptides has already demonstrated clinical potential for the treatment of neuropathic pain [7], there is considerable and ongoing interest for the development of more tractable, organic small molecules that can achieve the same therapeutic effect without the difficulties associated with the use of peptides as therapeutic agents. Not surprisingly, a number of studies have already investigated analogues of anandamide as one means for achieving such a goal [8–13]. Molecular modeling studies have been performed on anandamide [14] and these and other studies have resulted in a proposed conformation of anandamide (**1**) for activity at the CB_1 receptor Chart 1 [15,16].

In recent times it has been demonstrated that the activity of a series of aminoalkylindole (AAI) antinociceptive agents, originally designed as non-ulcerogenic, non-steroidal antiinflammatory drugs (NSAIDS) is associated with a second mechanism of action manifested by potent activity at

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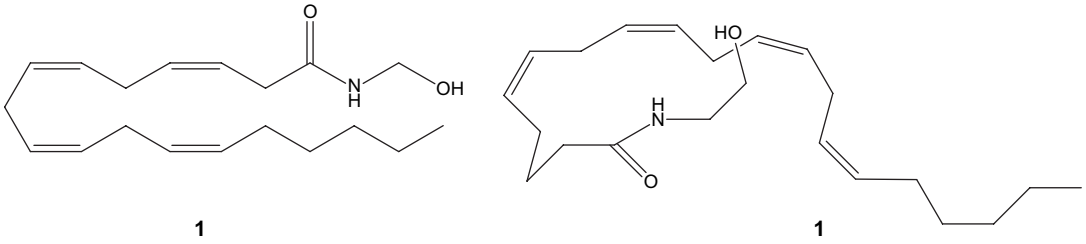


1 1

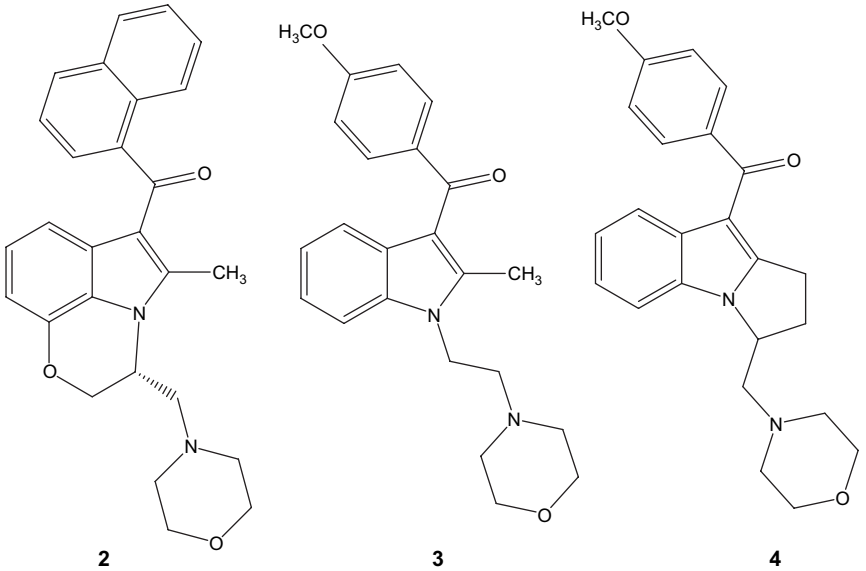
Chart 1.

inhibiting electrically induced contractions of mouse vas deferens (MVD) [12,17–20]. Studies on WIN-55,212-2 (**2**), pravadoline (**3**), and related compounds have shown that compounds from this structurally unrelated indole based series (relative to the non-classical cannabinoids or to anandamide (**1**) and other arachadonic acid derivatives) are capable of producing pharmacological responses in a fashion resembling the profile exhibited by (−)-Δ^9-THC. Additionally the AAI drug class produces its cannabimimetic actions in a stereoselective manner as shown by the results for the optical isomers of WIN-55,212-2 [21].

WIN-55,212-2 (CB_1, $IC_{50} = 2.0$ nM) (**2**), pravadoline (CB_1, $IC_{50} = 453$ nM) (**3**), and (4-methoxyphenyl)(3-morpholinomethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)methanone (**4**) [15] (CB_1, $IC_{50} = 0.32$ nM) are all potent CB_1 receptor agonists, Chart 2 [2,17,22]. The key structural features for potent cannabinoid activity in this series are a 3-keto group, an aryl or bicyclic (naphthyl) substituent at the 3-position, a small (H or CH_3) substituent at the 2-position and an ethylene linked morpholine group at the 1-position. Molecular modeling studies have been performed to develop a pharmacophore and to compare AAI structures with those of classical cannabinoids [23]. Within this work a CB_1 antagonist WIN-54,461 (**5**) (or bromopravadoline) was also identified. A separate group identified a related compound AM630 (**6**) (or iodopravadoline) which is also found to be a competitive cannabinoid receptor antagonist [24].

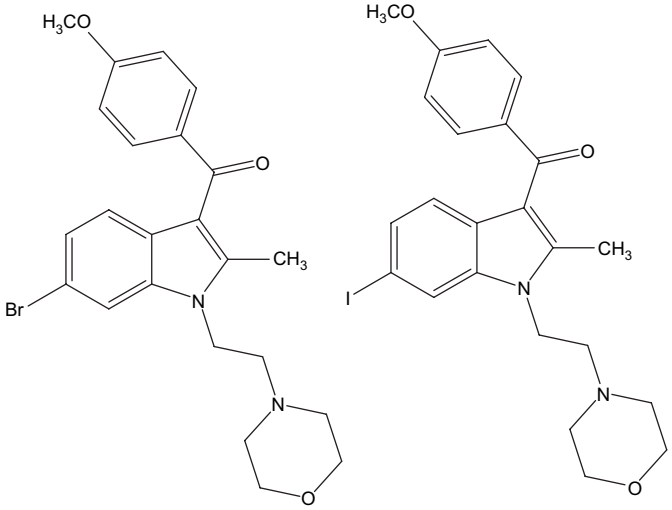
AM630 (**6**), Chart 3 behaved as a competitive antagonist of CP-55940 (**8**), WIN-55,212-2 (**2**), and anandamide (**1**) producing rightward shifts in the log concentration response curves of these cannabinoid receptor agonists and of (−)-Δ^9-THC that was concentration-dependent, essentially parallel and not accompanied by any decrease in the size of maximal response. AM630 (**6**) was markedly more potent as an antagonist of (−)-Δ^9-THC and CP-55940 (**8**) ($K_d = 14.0$ and 17.3 nM, respectively) than as an antagonist of WIN-55,212-2 (**2**) or anandamide (36.5 and 278.8 nM, respectively). These differences in dissociation constants imply that the mouse vas deferens may contain more than one type of cannabinoid receptor. The data also indicate that the receptors for which AM630 (**6**) has the highest affinity may not be CB_1 cannabinoid receptors as the CB_1-selective antagonist, SR141716A (**7**) is known to be equally potent in attenuating the inhibitory effects of CP-55940 (**8**) and anandamide (**1**) on the twitch response of the mouse vas deferens (Chart 4).

In 1993, a human peripheral cannabinoid (CB_2) receptor was disclosed [22]. Several workers have put forward the hypothesis that a selective and potent ligand for the CB_2 receptor would show therapeutically useful effects [19]. Gallant and colleagues submitted a large number of compounds to in vitro



2 3 4

Chart 2.



Bromopravadoline WIN-54,461.
5

AM630
6

Chart 3.

binding assays on the cannabinoid receptors. These compounds included a series of analogues selected through a topological similarity search using WIN-55,212-2 (**2**) as the template [17,18]. This work led to the discovery of a range of N^1-benzoyl and N^1-naphthoyl indole analogues [17,18]. Two of the more potent compounds from this work included L-768,242 (**9**) and L-759,787 [12] (**10**) ($K_i = 12$ and 8.5 nM, respectively, for the CB_2 receptor) Chart 5.

They exhibit good selectivity over the CB_1 receptor ($CB_1/CB_2 = 160$ for L-768,242 (**9**) and 103 for L-759,787 (**10**)). In conjunction with the synthesis of novel compounds as potential CB_1 agonists, we have performed preliminary modeling studies in an attempt to build up a pharmacophore for the CB_1 receptor. A comparison was made between the aminoalkylindoles, anandamide (**1**) and the classical and non-classical cannabinoids. We extrapolated from work carried out by Thomas and coworkers [15] using the proposed conformation anandamide adopts for binding. Chart 6 illustrates the four proposed important binding sites within the CB_1 pharmacophore using anandamide, (−)-Δ^9-THC, HU210 (**11**) and WIN-55,212-2 (**2**). The proposed binding sites are a hydrogen bond donor/acceptor site (1), and two further hydrogen bonding sites (2) and (3) and a hydrophobic pocket (4). The pharmacophore is further illustrated in Figs. 1–4. The proposed mode of binding of a low energy conformer of HU210 (**11**) and anandamide (**1**) are shown in Figs. 1 and 2, respectively.

2. Synthetic chemistry

The amideoxime derivatives required for the synthesis of the oxadiazole derivatives were prepared from nitrile derivatives, Scheme 1. Reaction with hydroxylamine hydrochloride in the presence of triethylamine afforded the amideoximes in good yield. Reaction of the amideoxime with indole-3-carboxylic acid afforded the desired indole-3-oxadiazoles, Scheme 2. The indole-3-oxadiazole derivatives were then alkylated with 1-(2-chloroethyl)morpholine hydrochloride, 1-(2-chloroethyl)-pyrrolidine hydrochloride, 2-bromo-1-(4-morpholinyl)-1-ethanone or other alkyl halides to afford the desired target molecules, Scheme 2. In our current study we have reported the synthesis and testing of one indole based compound with an alternative to the 3-oxadiazole substituent and that is 1-(2-(4-morpholino)ethyl)-3-aceto-1*H*-indole (**54**), which has an aceto group at the 3-position and this indole derivative was synthesized by alkylation of 3-indolyl acetate with 4-(2-chloroethyl)morpholine hydrochloride.

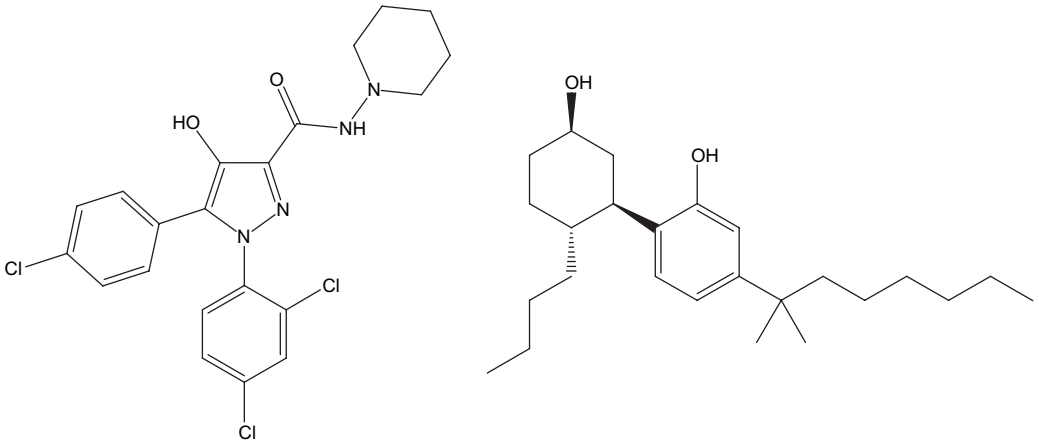
3. Results and discussion

The compounds investigated and their biological data are shown in Table 1. In order to explain the biological data we referred to our theoretical receptor model for the CB_1 receptor, shown in Fig. 1. using the preferred conformation of the cannabinoid mimetic HU210 (**11**) fitted to the proposed CB_1 receptor model. The theoretical receptor model is composed of four binding sites. To build our theoretical CB_1 receptor model we compared potential commonality between aminoalkylindoles and other cannabinoids. We initially built the structure for anandamide (**1**) and minimised the proposed conformation anandamide adopts for binding to the CB_1 receptor. We then recognized that when HU210 and anandamide (**1**) were compared it was possible to overlay the phenolic hydroxyl of HU210 with the amido ethyl alcohol of anandamide (binding site 1). Binding site 1 is represented by the red[1] sphere and is a hydrogen bonding site, which the phenolic group of HU210 can interact with, Fig. 1. Binding site 2 is represented by the purple sphere in Fig. 1. and the 9-hydroxymethyl group of HU210 interacts with this binding site and is an important binding site for the aminoalkylindole series [12,19,20] and our novel indole-3-oxadiazole series. Binding site 3 is a hydrogen bonding site and is represented by the orange sphere, Fig. 1 and is accessed by the pyran oxygen of HU210 and the amide carbonyl of anandamide (**1**), Fig. 2. Binding site 4 is represented by the large elongated yellow space and is a hydrophobic binding site, Fig. 1 and is the binding site which the aliphatic side chain of HU210 and (−)-Δ^9-THC can interact with as does the aliphatic side chain of anandamide (**1**), Fig. 2. A low energy conformation of HU210 and binding sites 1–4 are shown in Fig. 1.

The proposed conformation anandamide (**1**) adopts for binding to the CB_1 receptor and the binding sites 1–4 are shown in Fig. 2.

Our current series of indole-3-oxadiazole compounds were modelled on the aminoalkyl indole series [23]. In our current study a decision was made to replace the indole-3-linking group with an oxadiazole group, which is of the appropriate size to allow the phenyl group of the attached benzyl group to occupy a similar position in the CB_1 receptor like the keto linked phenyl group of the aminoalkylindole series. The

[1] For interpretation of the references to colour in text, the reader is referred to the web version of this article.



SR141716A **CP55940.**

7 **8**

Chart 4.

1,2,4-oxadiazole group also has an oxygen group ideally placed to act as a hydrogen bond acceptor if this is the function of the ketone oxygen of the aminoalkylindole series. The oxadiazole group is a stable bioisosteric replacement for ester and amide groups [19,25–27]. In our previous work in the serotonin area we successfully replaced the ester group with a 1,2,4-oxadiazole moiety while successfully retaining the desired pharmacological profile [29].

We have retained an alkyl linked morpholine side chain attached to the indole nitrogen because the literature suggests that the nitrogen of the morpholine ring is important for reasonable CB_1 potency.

As a part of our study to investigate important structural features in an effort to establish structure–activity relationships within our 1*H*-indole-3-oxadiazole series, the aminoalkylindole series of compounds and other cannabinoid mimetics we decided to study the hydrophobic pocket which we have designated as binding site 4, Chart 6. The hydrophobic pocket looks interesting as a variety of functional groups within the different classes of cannabinoid ligands have been used to interact with this binding site including a variety of substituted phenyl groups [30].

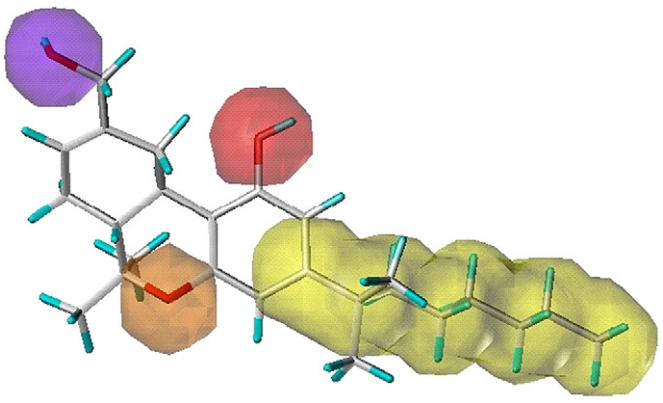


Fig. 1.

Several changes were made to the oxadiazole-3-aromatic group in our efforts to investigate whether CB_1 affinity could be enhanced with changes to this position of the molecule. We have investigated benzyl, phenyl, biphenyl, phenethyl and thiophene groups as well as varying substitution within the benzyl series. A comparison of compounds containing these aromatic groups attached to the 1,2,4-oxadiazole group revealed that the best aromatic groups were the benzyl group and the phenethyl group. From the benzyl series we can compare four compounds **37** (96.6% inhibition at 1.0 μM), **38** ($pK_b = 7.2$), **48** ($pK_b = 5.6$) and **50** (100% inhibition at 1.0 μM). The one compound we synthesized and evaluated from the phenethyl series was 1-(2-morpholin-4-yl-ethyl)-3-(3-phenethyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (**53**) (90% inhibition at 1.0 μM). It was interesting and informative to observe that the biphenyl derivative **41** was essentially inactive (11.4% inhibition at 1.0 μM).and the compounds, which contained more flexible aromatic substituents exhibited good CB_1 affinity. Our molecular modeling studies revealed that the biphenyl group was unable to access the hydrophobic pocket while the oxadiazole oxygen interacted with the hydrogen bonding site (binding site 1), Chart 6. It was also interesting to observe that replacement of the benzyl group with a methyl thiophene group to produce **45** (81% inhibition at 1.0 μM) resulted in an indole-3-oxadiazole derivative with good CB_1 affinity. Compound **45** was expected to have good CB_1 potency as our modeling studies suggested that the thiophene moiety would be able to orientate itself so as to easily access the hydrophobic pocket while the other binding sites were being interacted with. It was not surprising to observe that an alternative aromatic group could interact successfully with the hydrophobic pocket given that we have witnessed that the aliphatic side chains of anandamide (**1**), (−)-Δ^9-THC and HU210 (**11**) interact with the hydrophobic pocket and the naphthyl groups of WIN-55212-2 (**2**) and L-759,787 (**10**) [12,17,18] interact with the hydrophobic pocket. The biological results presented in Table 1 confirm that the inclusion of a 2-naphthyl group attached to the 1,2,4-oxadiazole enhances CB_1 affinity. A proposed conformation and mode of interaction

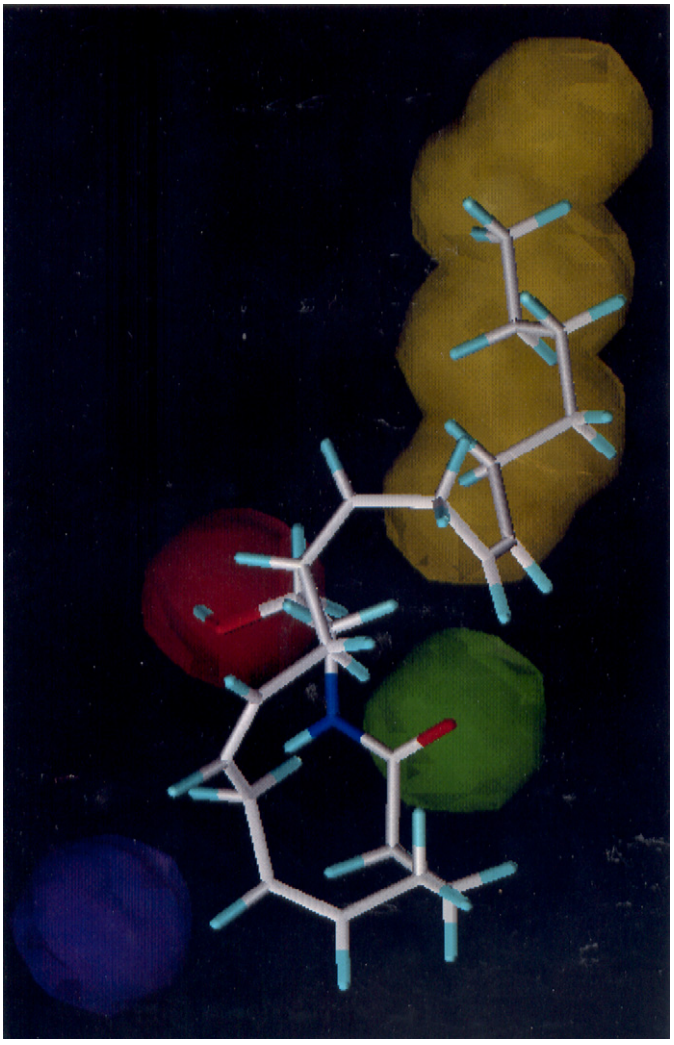


Fig. 2.

with the CB_1 receptor for **56**, (95.6% inhibition at 1.0 μM) is shown in Fig. 3. Published research conducted on the aminoalkylindole series [27,28] revealed the potency of derivatives containing a naphthyl group which have ability to interact

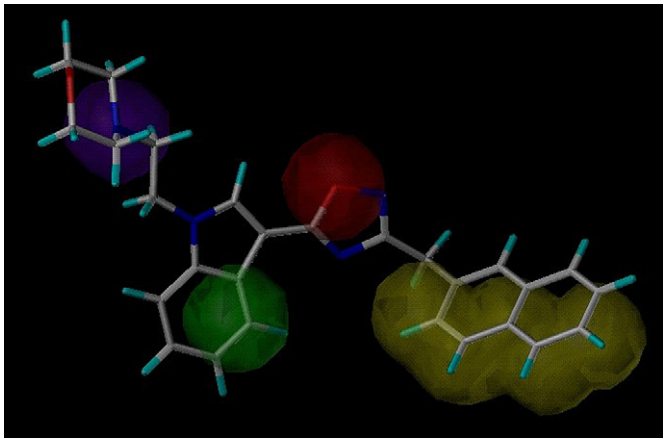


Fig. 3.

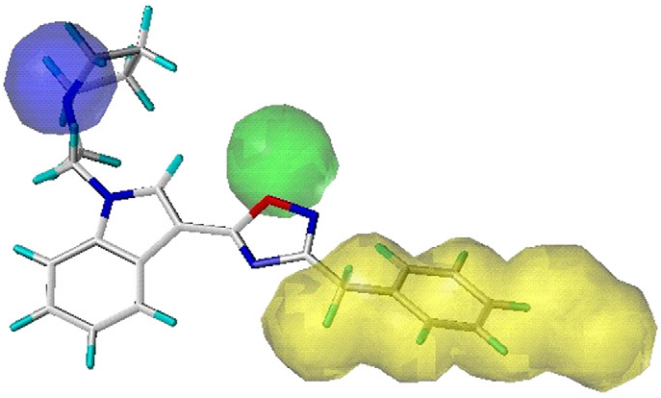
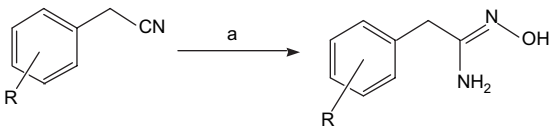
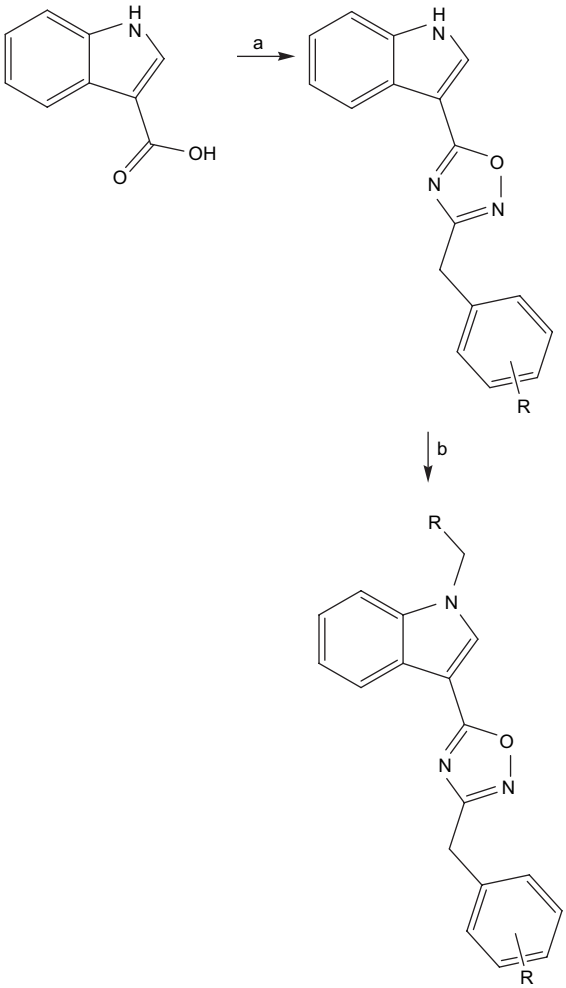


Fig. 4.



Reagent: (a) NH_2OH

Scheme 1.



Reagents: (a) CDI, amideoxime, THF. (b) NaH, DMF, alkyl halide.

Scheme 2.

Table 1

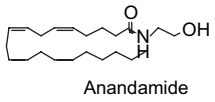
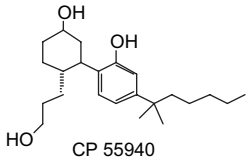
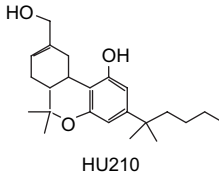
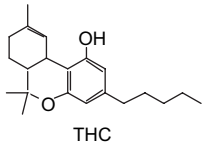
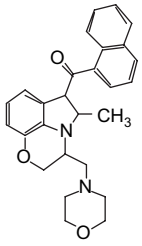
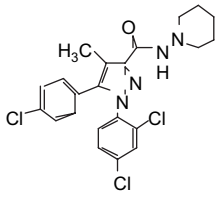
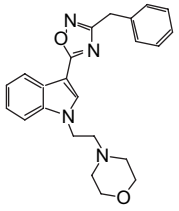
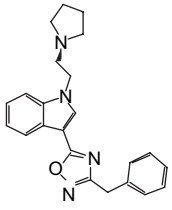
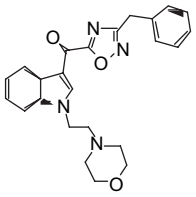
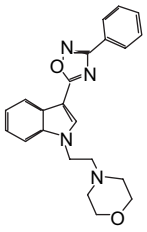
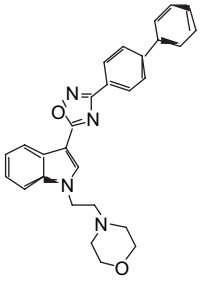
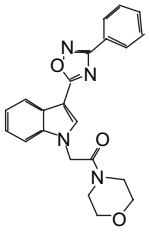
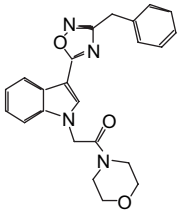
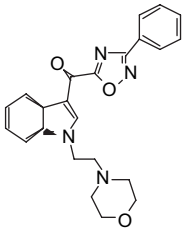
Compound number	Structure	CB_1 (MVD)[a,b]	CB_1 (binding)[c]	CB_2 (binding)[c]
Anandamide 1	 Anandamide	$pK_B = 8.52$		
CP-55940 8	 CP 55940			
HU210 11	 HU210		$IC_{50} = 3.22\ \mu M$	
(−)-Δ^9-THC	 THC	$pK_B = 8.74$		
WIN-55212 2		$pK_B = 8.6$	$IC_{50} = 0.43\ \mu M$	$IC_{50} = 2200$ nM
SR141716A 7		$pK_B = 8.4–8.6$	$IC_{50} = 3.92$ nM	
37		$pK_B = 7.0$	$IC_{50} = 2.62$ nM	$IC_{50} = 1.1\ \mu M$
38		$pK_B = 7.2$		

Table 1 (*continued*)

Compound number	Structure	CB_1 (MVD)[a,b]	CB_1 (binding)[c]	CB_2 (binding)[c]
39		22.4% inhibition at 1.0 μM		
40		$pK_B = 6.47$	$IC_{50} = 0.25$ μM	$IC_{50} = 4.03$ μM
41		11.4% inhibition at 1.0 μM	$IC_{50} = 1.52$ μM	14% inhibition at 10.0 μM
42		−5.29% inhibition at 1.0 μM		Inactive
43		17% inhibition at 1.0 μM		Inactive
44		44.3% inhibition at 1.0 μM		Inactive

(*continued on next page*)

Table 1 (*continued*)

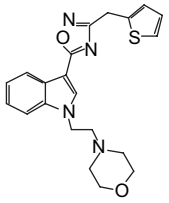
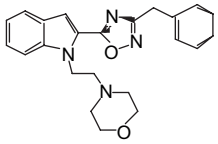
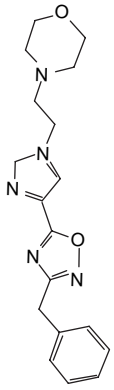
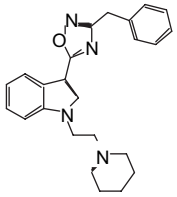
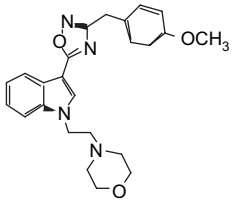
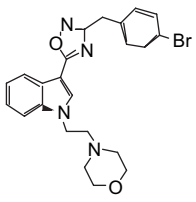
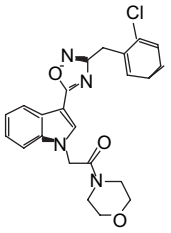
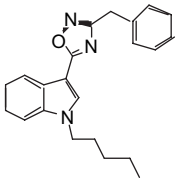
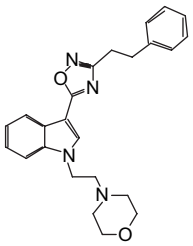
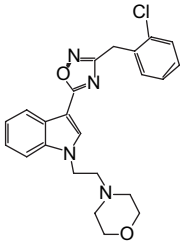
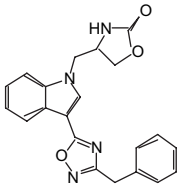
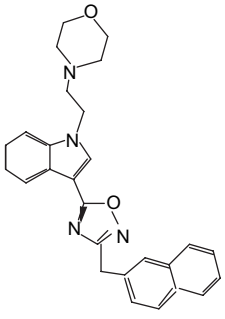
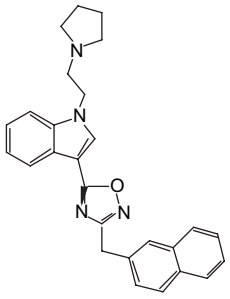
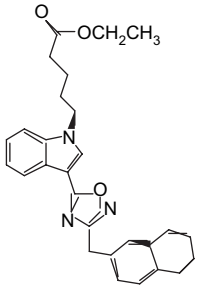
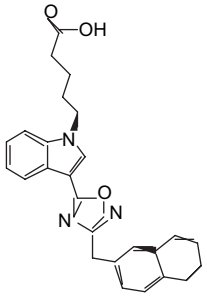
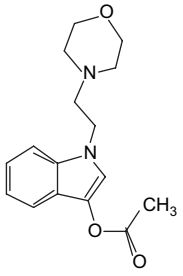
Compound number	Structure	CB_1 (MVD)[a,b]	CB_1 (binding)[c]	CB_2 (binding)[c]
45		81% inhibition at 1.0 μM	$IC_{50} = 6.8$ μM	
46		Inactive	Inactive	
47		46.8% inhibition at 1.0 μM	Inactive	
48		$pK_B = 5.6$ (partial agonist)	$IC_{50} = 5.6$ μM	
49		39.2% inhibition at 1.0 μM		$IC_{50} = 2.8$ μM
50		58% inhibition at 1.0 μM	$IC_{50} = 6.2$ μM	

Table 1 (*continued*)

Compound number	Structure	CB_1 (MVD)[a,b]	CB_1 (binding)[c]	CB_2 (binding)[c]
51		−21% inhibition at 1.0 μM	Inactive	
52		100% inhibition at 1.0 μM	$IC_{50} = 8.8$ μM	
53		90% inhibition at 1.0 μM	$IC_{50} = 6.8$ μM	
54		95% inhibition at 1.0 μM	$IC_{50} = 7.4$ μM	
55		15.8% inhibition at 1.0 μM	$IC_{50} = 6.1$ μM	
56		95.6% inhibition at 1.0 μM		

(*continued on next page*)

Table 1 (*continued*)

Compound number	Structure	CB_1 (MVD)[a,b]	CB_1 (binding)[c]	CB_2 (binding)[c]
57		78.6% inhibition at 1.0 μM		
58		41.6% inhibition at 1.0 μM. Non-specific		
59		53.6% inhibition at 1.0 μM. Non-specific		
60		81.8% inhibition at 1.0 μM		

[a] MVD – mouse vas deferens bioassay.

[b] Affinity ($pK_B = -\log_{10} K_B$ the dissociation equilibrium constant) estimates for novel compounds at the CB_1 receptor in the mouse vas deferens (MVD). Standard errors are omitted for clarity but in all cases were ≤ 0.2 $\log_{10}$ units.

[c] IC_{50} = negative logarithm of the concentration of compound required to inhibit 50% of the specific binding of the radioligand. Affinity values are the means of at least four different estimates. Negative values connote stimulation rather than inhibition.

intimately with the hydrophobic pocket. Other classes of cannabinoid ligands that possess a naphthyl group have been reported, which interacts with the hydrophobic pocket such as the N^1-naphthoyl indole derivative L-759,787 [17,18], Chart 5. In our current study we investigated two compounds, which contained an oxadiazole-3-methyl naphthyl group including (**57**), (78.6% inhibition), which contains a 1-ethyl linked pyrrole group as does the benzyl oxadiazole derivative (**38**). The second compound we investigated, which contains an oxadiazole-3-methyl naphthyl group was 3-[3-(2-methylnaphthyl)-[1,2,4]oxadiazol-5-yl]-1-(2-morpholin-4-yl-ethyl)-1*H*-indole (**56**), (95.6% inhibition), which contains a 1-ethyl linked morpholine group. A

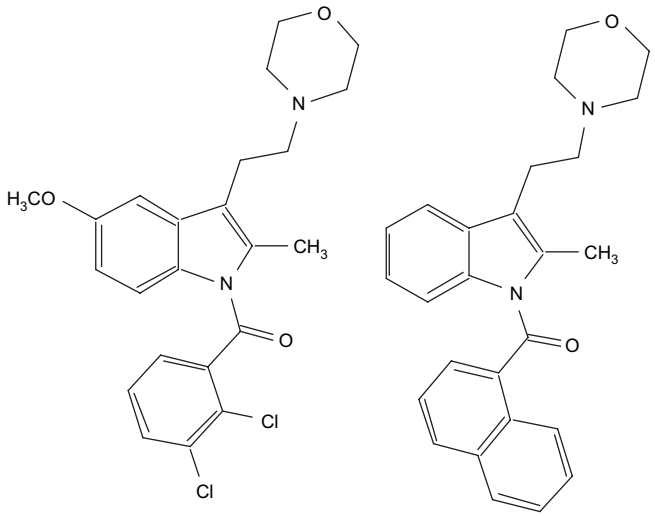


Chart 5.

proposed conformation and mode of interaction with the CB_1 receptor is shown for **56** in Fig. 3.

The importance of the hydrophobic pocket for good CB_1 potency is further illustrated with the total inactivity observed for the indole-2-substituted indole derivative **46**. When the 2-indole substituted analogue **46** adopts a conformation that allows the oxadiazole oxygen to interact with the hydrogen bonding site, the attached benzyl group is unable to access the hydrophobic pocket. The general substitution of the benzyl group did not enhance CB_1 affinity. The 4-bromobenzyl analogue **50** (58% inhibition at 1.0 μM) showed decreased CB_1 affinity compared with the unsubstituted analogues **37** and **38**. A similar situation was observed for the 4-methoxybenzyl derivative **49** (39% inhibition at 1.0 μM). Clearly substitution on the benzyl group was not detrimental to CB_1 affinity illustrated by the potency of the 2-chlorobenzyl derivative **54** (95.0% inhibition at 1.0 μM). The choice of inclusion of a chloro substituent at the 2-position of the benzyl group was based on the favourable CB_1 affinity observed for the chloro substituted N^1-benzoyl indole derivative L-768,242 (**9**), Chart 5 [17,18].

One of the most potent compounds from the indole-3-oxadiazole series was 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole (**38**), which possesses an 1-ethyl linked pyrrolidine group. The pyrrolidine nitrogen can interact with the hydrogen bonding site (binding site 3), Fig. 4.

Molecular modeling studies indicate that as the ethyl linking side chain orientates to allow the pyrrolidine nitrogen to interact with the hydrogen bonding site (binding site 2) the oxadiazole oxygen is able to interact with another hydrogen bonding site (binding site 1), which allows the attached benzyl group to interact with the proposed hydrophobic pocket, Fig. 4. When **38** adopts a conformation to interact with these proposed CB_1 binding sites the π electrons of the indole ring are able to interact with an extra binding site proposed for the pyran oxygen of HU210 (binding site 3), Chart 6.

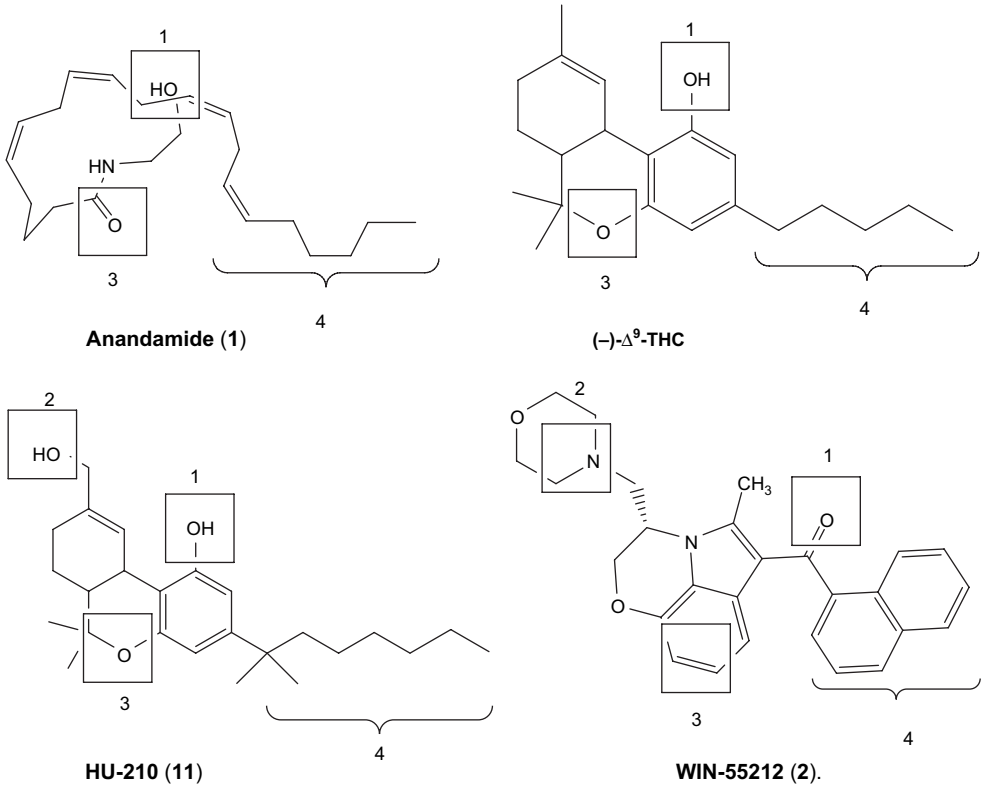


Chart 6.

3-[3-Benzyl-[1,2,4]oxadiazol-5-yl]-1-(2-morpholin-4-yl-ethyl)-1*H*-indole (**37**) was one of the first indole-3-oxadiazole derivatives designed, synthesized and evaluated. Like many of the compounds from our indole-3-oxadiazole series **37** possesses a 1-ethyl linked morpholine moiety. The 1-ethyl linked morpholine moiety was incorporated into the design of the indole-3-oxadiazole series based on the structure–activity relationships of the aminoalkylindole series previously published [27]. Compound **37** exhibited good affinity for the CB_1 receptor (96.6% inhibition) indicating that **37** was able to interact with the important binding sites within the CB_1 receptor including the hydrogen bonding site (binding site 3) that the morpholine nitrogen was able to interact with.

In the process of investigating a variety of indole based compounds incorporating an oxadiazole moiety at the 3-position of the indole in order to supply the molecule with the appropriate functionality to interact with the hydrogen bonding site (binding site 1) and to act as a suitable linking moiety between the central indole nucleus and the hydrophobic group, we investigated several compounds with a ketone bridging group between the indole ring at the 3-position and the oxadiazole group. The poor CB_1 affinity of (3-benzyl-1,2,4-oxadiazol-5-yl)(1-(2-morpholinoethyl)-1*H*-indol-3-yl)methanone (**39**) (18% inhibition at 1.0 μM) and [1-(2-morpholin-4-yl-ethyl)-1*H*-indol-3-yl]-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanone (**44**) (44% inhibition at 1.0 μM) indicates that the presence of the keto bridging group between the indole ring and the oxadiazole moiety is detrimental to interaction with the CB_1 binding sites as the oxygen of the bridging ketone preferentially interacts with the hydrogen bonding site (binding site 1), which results in the terminal aromatic group not being able to access the hydrophobic pocket accurately.

The biological results presented in Table 1 reveal that there are CB_1 binding sites that must be interacted with in order for the compound to exhibit good CB_1 potency and there are less important binding sites. This observation is evident when we observe that 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1-pentyl-1*H*-indole (**52**), exhibits 100% inhibition at 1.0 μM. Compound **52** has a pentyl chain attached to the indole nitrogen and thus has no attached heterocyclic ring system containing a protonatable nitrogen such as a morpholine or pyrrolidine ring to interact with the hydrogen bonding site (binding site 2). An examination of the expected conformation **52** adopts to interact with the CB_1 receptor reveals that the oxadiazole oxygen can interact with binding site 1, the benzyl group can interact with the hydrophobic pocket and the π electrons of the indole ring system is able to interact with the extra binding site (binding site 3), Chart 6. Clearly interaction with the hydrogen bonding site (binding site 2) is not a requirement for optimal CB_1 affinity. This proposal on the relative importance of the CB_1 receptor binding sites appears to be confirmed when an inspection is made on the preferred conformations of potent cannabinoids such as anandamide (**1**), Fig. 2 and (−)-Δ^9-THC. An inspection of anandamide (**1**) and (−)-Δ^9-THC reveals that both molecules do not possess functionality to interact with the hydrogen bonding site (binding site 2). The importance of being able to access all the CB_1 receptor binding sites is illustrated when we observe the highly potent cannabinoid mimetic HU210 (**11**), which has the pyran ring oxygen to interact with the extra binding site (binding site 3) and is able to interact with all the proposed binding sites 1–4, Fig. 1.

An examination of some of the compounds from the various classes of CB_1 agonists including the aminoalkylindoles and our novel 1-substituted-1*H*-indole-3-oxadiazole derivatives reveals an area of space between the indole nitrogen and the morpholine nitrogen or the pyrrolidine nitrogen (binding site 2). There may be a requirement for hydrophobicity in this region. It is interesting to compare the aminoalkylindoles and our novel 1-substituted-1*H*-indole-3-oxadiazole derivatives with (−)-Δ^9-THC and HU210. This proposed hydrophobic region may be where the six membered rings of (−)-Δ^9-THC and HU210 are placed when these compounds are interacting with the CB_1 receptor. The good CB_1 potency of 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1-pentyl-1*H*-indole (**52**) may be partially explained by the ability of the 1-pentyl side chain to interact with this proposed hydrophobic region near the indole nitrogen.

For **37** and **38** the 1-ethyl linking chain may be in this area. It was of interest to us to design new compounds with different functionality in this area of the molecule. To investigate this region of the receptor we synthesized 2-[3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-indol-1-yl]-1-morpholin-4-yl-ethanone (**43**), 2-{3-[3-(2-chlorobenzyl)-[1,2,4]oxadiazol-5-yl]-indol-1-yl}-1-morpholin-4-yl-ethanone (**51**) and 1-morpholin-4-yl-2-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-indol-1-yl]-ethanone (**42**). When a comparison is made with the unsubstituted analogues **37**, **54** and **40** it became clear that inclusion of a carbonyl group in this region within these classes of molecules was detrimental to CB_1 potency.

Inclusion of a carbonyl group into the 1-ethyl linking chain of **40** resulted in the formation of **42**, which has been converted from a potent CB_1 inhibitor (83%) to a compound with no significant potency at all (−5.29%). (4-(2-(3-(2-Chlorobenzyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**54**) is a potent inhibitor (95%) and conversion to the carbonyl analogue **51** results in a significant decrease in potency (21%). 3-[3-Benzyl-[1,2,4]oxadiazol-5-yl]-1-(2-morpholin-4-yl-ethyl)-1*H*-indole (**37**) is one of the compounds we first designed and synthesized within the oxadiazole family and **37** exhibited good potency (96.6% inhibition). Compound **43** the carbonyl analogue of **37** exhibited only 17% inhibition at the same concentration.

Clearly the inclusion of a carbonyl group in the 1-ethyl linking chain neighbouring the morpholine nitrogen impedes the ease with which the morpholine or pyrrolidine nitrogen can interact with the proposed hydrogen bonding site in the position (binding site 2).

In a second effort to explore the proposed hydrophobic region between the indole nitrogen and the proposed hydrogen bonding site (binding site 2) we synthesized the two compounds which have the 1-ethyl morpholine or 1-ethyl pyrrolidine side chain replaced with either a pentanoic acid side chain (**59**) or an ethyl pentanoate side chain (**58**) substituent attached to the indole nitrogen. Inspection of the biological

results for **58** and **59** reveals that both compounds do exhibit CB_1 potency but not as potent as **38**, which possesses a 1-ethyl pyrrolidine side chain. Molecular modeling studies suggest that the pentanoic acid and the ethyl pentanoate side chains are not able to adopt a conformation to easily access the hydrogen bonding site 2 while interacting with binding site 1. It is possible that the terminal carboxylic and ethyl carboxylate groups are detrimental to good CB_1 affinity given that the unsubstituted 1-pentyl analogue **52** displays high CB_1 potency.

4. Conclusions

In this study we have identified a novel series of indole-3-oxadiazole derivatives as agonists of the CB_1 receptor. 3-(3-Benzyl-[1,2,4]oxadiazol-5-yl)-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole (**38**) exhibited high CB_1 receptor affinity ($pK_B = 7.2$) and showed that the 1,2,4-oxadiazole group can successfully replace the keto linking group common to the aminoalkyl indole series [23] and interact with the hydrogen bonding site designated as binding site 1, Chart 6. From this series the pyrrolidine ring system linked to the 1-ethyl side chain provided the most potent compound. Compounds **37**, **40** and **45** incorporating a morpholine moiety and compound **48** containing a piperidine moiety were also potent indicating that a ring system containing a basic nitrogen in the correct position would allow for interaction with binding site 2. The biological results presented in Table 1 support our proposed CB_1 binding sites shown in Chart 6 and by the individual figures for specific compounds, Figs. 1–4. Although we have not rigorously investigated additional properties of these compounds, such as ability to cross the blood brain barrier and their addictive potential (or lack thereof), the in vitro profile of compounds such as (3-benzyl-5-(1-(2-pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)-1,2,4-oxadiazole (**38**) suggests at the very least that we have identified useful pharmacological probes for the CB_1 receptor.

5. Experimental section

5.1. Biological methods

5.1.1. Pharmacological studies

The affinity of compounds at cannabinoid receptors is routinely assessed using ligand binding assays. Radioligand binding assays were conducted using rat cerebellum or rat spleen. The rationale for this approach is as follows: The rat cerebellum expresses predominantly, if not exclusively the CB_1 receptor subtype [31,32]. Thus binding constants obtained from these studies using the CB_1-selective antagonist [^{3}H]SR141716A are characterised by a single affinity value, as only one receptor type is labeled. This was found to be the case for all compounds tested thus the derived values represent binding affinity constants for the CB_1 receptor. The rat spleen possesses both CB_1 and CB_2 subtypes of cannabinoid receptor, with the latter being the predominating subtype [33,34]. Because of the lack of the general availability of a CB_2-selective antagonist we utilised instead the high affinity agonist [^{3}H]WIN-55212-2. Since this compound labels both CB_1 and CB_2, single affinity estimates would only be associated with compounds that showed no selectivity between the two subtypes in the rat spleen assay. In contrast biphasic binding curves in the spleen characterised by two affinity constants represent the profile of compounds showing selectivity for one receptor subtype over another. In order to determine the order of selectivity, the high and low affinity values obtained for these compounds in the spleen binding assays were compared to the single affinity estimates obtained for the cerebellum (CB_1) assays. Compounds for which the high affinity binding constant from the spleen correlated with the binding affinity constant from the cerebellum were concluded to be CB_1-selective. In contrast, compounds for which the low affinity binding constant from the spleen correlated the binding affinity constant from the cerebellum were concluded to be CB_2-selective and the high affinity constant from the spleen experiments was then taken as the measure of affinity for the CB_2 receptor.

Functional activity of the compounds was assayed using the mouse electrically-stimulated vas deferens bioassay, a measure of CB_1 receptor function [35,36]. Compounds showing appreciable activity in this assay and the ability to be antagonised by the CB_1-selective antagonist, SR141716A (**7**), were deemed to be CB_1 agonists. The remaining compounds were classed as cannabinoid ligands. CB_2 functionality may be investigated using assays, such as those described in (US 6,013,648) [37].

5.1.2. Radioligand binding assays

5.1.2.1. Rat cerebellum. Sprague Dawley rats of either sex (200–300 g) were killed by gassing with 80% CO_2 in O_2 and decapitation, and the entire brain excised rapidly and placed in ice-cold tris–HCl buffer (tris 50 mM, $MgCl_2$ 3 mM, EGTA 0.2 mM, pH to 7.4 with HCl). On ice the cerebellum was dissected away from the rest of the brain, weighed and homogenised (PT-DA 1205/2EC Polytron Aggregate; Kinematica, Luzernstrasse Switzerland) in 10 volumes of ice-cold Tris–HCl (buffer, Fullerton, CA, USA) and centrifuged at 31,000g for 15 min at 4 °C. Subsequently, the supernatant was discarded, the pellet then suspended in 20 volumes of buffer and assayed for protein content using the method of Bradford [38] in a Novaspec II spectrometer (Pharmacia Biotech) with bovine serum albumen (BSA, Homosafe BSA, c/o 'ScimaR' Templestowe, Australia) as a standard. The homogenate was then recentrifuged and the final pellet resuspended in tris–HCl buffer at a protein concentration of 5 mg/mL and stored in 500 μL aliquots at −80 °C until used in the binding assay.

5.1.2.2. Rat spleen. Sprague Dawley rats (200–300 g) were killed by gassing with 80% CO_2 in O_2 and decapitation and the spleen excised rapidly and placed in ice-cold tris–HCl buffer (tris 50 mM, $MgCl_2$ 3 mM, EGTA 0.2 mM, pH 7.4). The spleen was weighed and diced using a scalpel before homogenisation in 10 volumes of tris–HCl buffer. The

homogenate was then made up to 20 volumes and centrifuged (12,600g, 5 min, 4 °C) and the supernatant was retained and centrifuged (23,800g, 20 min, 4 °C). The pellet was resuspended in 10 volumes of buffer and assayed for protein content using the method of Bradford [38] with BSA as standard. The homogenate was then recentrifuged and the final pellet resuspended in tris–HCl buffer at a protein concentration of 5 mg/mL and stored in 500 μL aliquots at −80 °C until used for the binding assay.

5.1.2.3. Radioligand binding protocol. Ligand binding assays were performed in polypropylene tubes in a total volume of 1.0 mL containing tris–HCl buffer, a final concentration of 1.0 mg/mL BSA, and varying concentrations of drugs. Tubes contained 30.0 μg of membrane protein and incubation was started by the addition of 100 μL of either 0.5 nM [^{3}H]SR141716A or 0.2 nM [^{3}H]WIN-55,212-2. Experiments were carried out in triplicate at 30 °C for 90 min with non-specific binding being defined as radioligand binding in the presence of 1.0 μM unlabelled WIN-55,212-2. Incubations were terminated by rapid filtration with an M-24 Cell Harvester (Brandel; Gaithersburg, MD, USA) using ice-cold tris–HCl buffer containing 0.5 mg/mL BSA. Filters (Wattman GR/B) were soaked for 2 h prior to filtering in a solution of tris–HCl buffer containing 3.0 mg/mL BSA and 0.5% w/w polyethyleneimine (PEI). Filters were left to dry thoroughly before placement into scintillation vials with 5.0 mL of scintillation cocktail (Ultima Gold LSC-cocktail; Packard Bioscience, Meridian, CT, USA) being added. Vials were left to stand overnight before the radioactivity was determined using a Model 1409 DSA Liquid Scintillation counter (EG&E Wallac, Gaithersburg, Maryland, USA).

5.1.2.4. Data analysis. The resulting radioligand binding curves were analysed by nonlinear regression using the program PRISM 3.0 (Graphpad Software, San Diego, CA) in order to derive ligand affinity estimates for the cannabinoid receptor(s).

5.1.2.5. Drugs and chemicals. [^{3}H]SR141716A (Amersham Pharmacia Biotech Piscataway, NJ, USA), [^{3}H]WIN-55212-2 (Du Pont), Bio-Rad protein assay dye reagent concentrate (Bio-Rad, Hercules, CA, USA), ethylglycol-bis(β-aminethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA; Sigma Chemical Co., St Louis, MO, USA) and Tris Ultrapure (ICN Biomedicals Inc, Ohio, USA). All other reagents were obtained from Sigma Chemical Co.

5.1.3. Mouse isolated vas deferentia

Swiss white mice (35–50 g) were killed by exposure to 80% CO_2 in O_2 and exsanguination. Mouse vas deferentia were dissected with capsular connective tissue intact and set up in 20 mL organ baths at 37 °C in Mg^{2+}-free physiological salt solution [39]. The upper (epididymal) end was attached to an isometric force transducer (Grass FTO3C) and lower (prostatic) end tied to a fixed support between two parallel field electrodes (5 mm apart, 5 mm long). The tissue was initially stretched by 0.5 g force and allowed to equilibrate for 10 min. The tissues were stimulated (grass S88 stimulator) to contract using trains of electrical field stimulation of three pulses (4 Hz), 0.5 ms duration, 100 V (80% maximal voltage) every 20 s for 10 min. This electrical stimulation period was applied before and after both antagonist and agonist addition. Output from the transducer amplifier were recorded on a flat bed recorder (Gould BS 272, Cleveland, OH, USA) All drugs were dissolved in dimethyl sulfoxide (DMSO, Sigma, St Louis, MO, USA) and allowed to equilibrate with the tissue for 30 min before the responses to field stimulation were assessed. Drug effects were measured as the percentage decrease of the pre-drug twitch force. In experiments where only a single drug concentration was tested, the resulting effect was expressed as a percentage of that observed in the presence of vehicle. Binding data and data in the mouse vas deferens assay for some compounds are summarised in Table 1.

5.2. Chemical methods: general directions

Computational chemistry was performed on a Silicon Graphics Iris indigo II using the Sybyl [40] molecular modeling software.

Unless otherwise stated, all ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AM 300 spectrometer. Chemical shifts are in Δ ppm relative to TMS. Deuterated dimethylsulphoxide (99.9%) was used as solvent unless otherwise stated. Mass spectra and high resolution mass spectra (HRMS) were obtained on a Kratos Concept IS (EIMS), a Kratos MS50 (FAB) mass spectrometer or a Joel JMX DX-300 double focussing instrument. Melting points were determined on a Gallencamp melting point apparatus and are uncorrected. Methanol and ethanol were distilled from iodine and magnesium and stored over type 3 Å molecular sieves. Anhydrous THF was freshly distilled over potassium and benzophenone. Anhydrous DMF, diethyl ether and toluene were stored over type 4 Å molecular sieves. Triethylamine, diisopropylethylamine and pyridine were stored over sodium hydroxide. All solutions were dried over $MgSO_4$ or Na_2SO_4 and concentrated on a Buchi rotary evaporator. Column chromatography was performed on silica gel (Merck Kieselgel 60 F_{254}). Infra Red spectra were run in KBr discs on a Bruker IFS66 FTIR spectrometer. Microanalyses were performed on a VG Platform spectrometer and are within 0.4% of the theoretical values unless otherwise stated. HPLC was performed on a Waters Millenium system comprising a 490E multi-wavelength detector, 600 controller, a series 600 pump with a 717 plus autosampler. A Zorbax 4.6 mm × 250 mm, 5 μm column was used for analytical work while a 22.4 mm × 250 mm, 7 μm C18 column was used for preparative work. A 10% H_2O/AcCN (10–90% gradient elution) (A)/0.1 M NH_4OAc (pH 4) (90–10%) (B) solvent system was used.

*5.2.1. N-Hydroxy-2-(4-methoxyphenyl)acetamidine (**11**) [41]*

A mixture of (4-methoxyphenyl)acetonitrile (2.0 g, 14.0 mmol) and hydroxylamine hydrochloride (1.94 g, 28.0 mmol) in ethanol (25.0 mL) was treated with triethylamine (4.4 mL) and heated at

reflux for 16 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%, 100.0 mL) was added and the solution extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a green solid, which was recrystallised from ethyl acetate/hexane to afford (1.43 g, 57.0%) the desired *N*-hydroxy-2-(4-methoxy-phenyl)-acetamidine (**11**) as pale green prisms. M.p. = 109–111 °C, (lit [42] m.p. = 108–109 °C), M.S. *m/z* 181 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.17 (2H, s, CH_2), 3.7 (3H, s, CH_3), 5.29 (2H, s, NH_2), AA′BB′ system: 6.83 (2H, d, $J_{AB}+J_{AB'}=8.3$ Hz, H-3″), 7.17 (2H, d, $J_{AB}+J_{AB'}=8.3$ Hz, H-2″), 8.83 (1H, s, OH). ^{13}C NMR (DMSO-d_6) Δ 36.33, 55.02, 113.5, 129.7, 129.8, 152.3, 157.8.

5.2.2. N-Hydroxy-2-phenyl-acetamidine (**12**) [42]

A mixture of phenylacetonitrile (5.0 g, 42.7 mmol) and hydroxylamine hydrochloride (4.97 g, 71.5 mmol) in ethanol (75.0 mL) was treated with triethylamine (13.0 mL) and heated at reflux for 24 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%) was added and the solution extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford yellow oil, which on standing crystallised to afford a yellow crystalline solid, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (4.94 g, 77.0%) the desired *N*-hydroxy-2-phenyl-acetamidine (**12**) as a cream powder. M.p. = 63–64 °C, (lit [42] m.p. = 67 °C), M.S. *m/z* 151 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 3.47 (2H, s, CH_2), 4.45 (2H, s, NH_2), 6.88 (1H, s, OH), 7.22–7.38 (5H, m, 5 × ArH).

5.2.3. N-Hydroxy-2-naphthalen-2-yl-acetamidine (**13**) [43]

A mixture of naphthalene-2-acetonitrile (2.34 g, 14.0 mmol) and hydroxylamine hydrochloride (1.94 g, 28.0 mmol) in ethanol (40.0 mL) was treated with triethylamine (4.4 mL) and heated at reflux for 24 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%) was added and the solution extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow powder, which was recrystallised from ethyl acetate/hexane to afford (910.0 mg, 32.0%) the desired *N*-hydroxy-2-naphthalen-2-yl-acetamidine (**13**) as a cream powder. M.p. = 117–119 °C, M.S. *m/z* 201 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.46 (2H, s, CH_2), 5.45 (2H, s, NH_2), 7.4–7.5 (3H, m, 3 × ArH), 7.77–7.89 (4H, m, 4 × ArH), 8.97 (1H, s, OH). ^{13}C NMR (DMSO-d_6) Δ 37.36, 125.4, 126.0, 126.8, 127.3, 127.4, 127.4, 127.5, 131.8, 133.0, 135.6, 152.0. Found C, 71.95, H, 6.1, N, 13.95%, $C_{12}H_{12}N_2O$ requires C, 71.98, H, 6.04, N, 13.99%.

5.2.4. N-Hydroxyisonicotinamidine (**14**) [44]

A mixture of 4-cyanopyridine (4.48 g, 43.0 mmol) and hydroxylamine hydrochloride (2.97 g, 43.0 mmol) in ethanol (60.0 mL) was treated with triethylamine (13.0 mL) and heated at reflux for 24 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%) was added and the solution extracted with hot ethyl acetate. The combined ethyl acetate extracts (900.0 mL) were evaporated under reduced pressure to an approximate volume of 100.0 mL and the ethyl acetate was allowed to cool to room temperature and white crystals crystallised out to afford (2.85 g, 48.0%) the desired *N*-hydroxyisonicotinamidine (**14**) as fine white needles. M.p. = 175–176 °C, (lit [41] m.p. = 178–179 °C), M.S. *m/z* 138 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 5.97 (2H, s, NH_2), AA′BB′ system: 7.63 (2H, d, $J_{AB}+J_{AB'}=5.0$ Hz, H-3″), 8.56 (2H, d, $J_{AB}+J_{AB'}=5.0$ Hz, H-2″), 10.03 (1H, s, OH).

5.2.5. N-Hydroxybenzamidine (**15**) [45]

A mixture of benzonitrile (4.4 g, 42.7 mmol) and hydroxylamine hydrochloride (2.97 g, 42.7 mmol) in ethanol (40.0 mL) was treated with triethylamine (13.0 mL) and heated at reflux for 24 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%, 100.0 mL) was added and the solution extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford viscous colourless oil, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (3.5 g, 60.0%) the desired *N*-hydroxybenzamidine (**15**) as a cream coloured powder. M.p. = 75–77 °C, (lit [45] m.p. = 79–80 °C), ^{1}H NMR (DMSO-d_6) Δ 5.7 (2H, s, NH_2), 7.34 (3H, m, 3 × ArH), 7.65 (2H, m, 2 × ArH), 9.59 (1H, s, OH).

5.2.6. N-Hydroxy-2-(thiophen-2-yl)acetamidine (**16**) [43,45]

Sodium metal (380.0 mg, 17.0 mmol) was added in small pieces to methanol (12.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (1.14 g, 16.0 mmol) in methanol (20.0 mL). The reaction mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with thiophene-2-acetonitrile (1.74 mL, 16.0 mmol) and heated at gentle reflux for 48 h after which the methanol was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (1.07 g, 49%) the desired *N*-hydroxy-2-(thiophen-2-yl)acetamidine (**16**) as a cream solid. M.p. = 77 °C (lit [45] m.p. = 80 °C), M.S. *m/z* 157 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.45 (2H, s, CH_2), 5.37 (2H, s, NH_2), 6.9 (2H, m, 2 × ArH), 7.3 (1H, m, ArH), 8.89 (1H, s, OH).

5.2.7. N-Hydroxy-2-(4-nitrophenyl)acetamidine (**17**) [43]

Sodium metal (741.0 mg, 32.23 mmol) was added in small pieces to methanol (20.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (2.1 g, 30.3 mmol) in methanol (40.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with (4-nitrophenyl)acetonitrile (4.91 g, 30.3 mmol) and heated at gentle reflux for 48 h after which the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography eluting with (chloroform/methanol) (19/1) to afford (2.9 g, 49.0%) the desired *N*-hydroxy-2-(4-nitrophenyl)acetamidine (**17**) as a green powder.

M.p. = 154–156 °C, M.S. *m/z* 196 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.43 (2H, s, CH_2), 5.46 (2H, s, NH_2), AA′BB′ system: 7.54 (2H, d, $J_{AB}+J_{AB'}=8.7$ Hz, H-2″), 8.15 (2H, d, $J_{AB}+J_{AB'}=8.7$ Hz, H-3″), 8.93 (1H, s, OH).

5.2.8. 2-(4-Bromophenyl)-N-hydroxy-acetamidine (**18**) [43,46]

Sodium metal (590.0 mg, 25.6 mmol) was added in small pieces to methanol (20.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (1.77 g, 25.5 mmol) in methanol (40.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with 2-(4-bromophenyl)-*N*-hydroxyacetamidine (5.0 g, 25.5 mmol) and heated at gentle reflux for 16 h after which the solvent was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (1.9 g, 33.0%) the desired 2-(4-bromophenyl)-*N*-hydroxy-acetamidine (**18**) as a pale yellow powder. M.p. = 132–134 °C, M.S. *m/z* 229/231 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.22 (2H, s, CH_2), 5.4 (2H, s, NH_2), AA′BB′ system: 7.21 (2H, m, H-2″), 7.47 (2H, m, H-3″), 8.89 (1H, s, OH).

5.2.9. 2-(2-Chlorophenyl)-N-hydroxyacetamidine (**19**) [43]

Sodium metal (450.0 mg, 19.8 mmol) was added in small pieces to methanol (15.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (1.38 g, 19.8 mmol) in methanol (40.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with 2-chlorobenzylcyanide (3.0 g, 19.8 mmol) and heated at gentle reflux for 16 h after which the solvent was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (1.05 g, 58.0%) the desired 2-(2-chlorophenyl)-*N*-hydroxyacetamidine (**19**) as a white powder. M.p. = 112–114 °C, M.S. *m/z* 185/187 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.42 (2H, s, CH_2), 5.45 (2H, s, NH_2), 7.22–7.28 (2H, m, 2 × ArH), 7.33–7.41 (2H, m, 2 × ArH), 8.98 (1H, s, OH). Found: $(M+1)^+ = 185.0474$, $C_8H_9ClN_2O$ requires $(M+1)^+ = 185.0476$.

5.2.10. 2-(2,4-Dichlorophenyl)-N-hydroxyacetamidine (**20**) [43]

Sodium metal (120.0 mg, 5.2 mmol) was added in small pieces to methanol (4.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (370.0 mg, 5.38 mmol) in methanol (8.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with 2,4-dichlorophenylacetonitrile (1.0 g, 5.38 mmol) and heated at gentle reflux for 16 h after which the solvent was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (500.0 mg, 42.0%) the desired 2-(2,4-dichlorophenyl)-*N*-hydroxyacetamidine (**20**) as a yellow powder. M.S. *m/z* 219/221/223 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 3.57 (2H, s, CH_2), 4.55 (1H, s, OH), 5.42 (2H, s, NH_2), 7.24–7.43 (3H, m, 3 × ArH).

5.2.11. N-Hydroxy-2-(2-methoxyphenyl)acetamidine (**21**) [43,47]

Sodium metal (160.0 mg, 6.79 mmol) was added in small pieces to methanol (5.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (470.0 mg, 6.79 mmol) in methanol (8.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with (2-methoxyphenyl)acetonitrile (1.0 g, 6.79 mmol) and heated at gentle reflux for 16 h after which the solvent was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (570.0 mg, 47.0%) the desired 2-(2-methoxyphenyl)-*N*-hydroxyacetamidine (**21**) as a yellow oil. M.S. *m/z* 181 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 3.48 (2H, s, CH_2), 3.88 (3H, s, OCH_3), 4.77 (2H, s, NH_2), 6.95–6.88 (2H, m, 2 × ArH), 7.21–7.27 (2H, m, 2 × ArH), 7.3–7.9 (1H, br s, OH). Found C, 59.8, H, 6.68, N, 15.4%, $C_9H_{12}N_2O_2$ requires C, 59.99, H, 6.71, N, 15.55%.

5.2.12. 2-(4-Chlorophenyl)-N-hydroxyacetamidine (**22**) [42,43]

Sodium metal (150.0 mg, 6.6 mmol) was added in small pieces to methanol (5.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (460.0 mg, 6.6 mmol) in methanol (8.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with (4-chlorophenyl)acetonitrile (1.0 g, 6.6 mmol) and heated at gentle reflux for 16 h after which the solvent was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (200.0 mg, 16.0%) the desired 2-(4-chlorophenyl)-*N*-hydroxyacetamidine (**22**) as a yellow powder. M.p. = 103–104 °C, M.S. *m/z* 185, 187 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 3.56 (2H, s, CH_2), 5.3 (3H, s, NH_2 + OH), AA′BB′ system: 7.23 (2H, d, $J_{AB}+J_{AB'}=8.4$ Hz, H-2″), 7.34 (2H, d, $J_{AB}+J_{AB'}=8.7$ Hz, H-3″).

5.2.13. N-Hydroxy-3-phenyl-propionamidine (**23**) [43,48]

Sodium metal (880.0 mg, 38.0 mmol) was added in small pieces to methanol (40.0 mL), and once cooled, was treated with a solution of hydroxylamine hydrochloride (2.65 g, 38.0 mmol) in methanol (20.0 mL). The mixture was stirred at room temperature for 40 min and filtered. The filtrate was treated with hydrocinnamonitrile (5.0 g, 38.0 mmol) and heated at gentle reflux for 24 h after which the solvent was evaporated under reduced pressure to afford a residue, which was purified with column chromatography eluting with (chloroform/methanol) (19/1) to afford (3.73 g, 60.0%) the desired *N*-hydroxy-3-phenyl-propionamidine (**23**) as a viscous yellow oil. M.S. *m/z* 165 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 2.46 (2H, t, $J=7.8$ Hz, CH_2), 2.89 (2H, t, $J=7.8$ Hz, CH_2), 4.49 (2H, s, NH_2), 7.16–7.35 (5H, m, 5 × ArH), 7.92 (1H, s, OH). Found: $(M+1)^+ = 165.102$, $C_9H_{12}N_2O$ requires $(M+1)^+ = 165.1022$.

*5.2.14. N-Hydroxy-2-biphenylacetamidine (**24**) [43,49]*

A mixture of biphenyl-4-carbonitrile (1.0 g, 5.58 mmol) and hydroxylamine hydrochloride (769.0 mg, 11.16 mmol) in ethanol (10.0 mL) was treated with triethylamine (1.76 mL) and heated at reflux for 16 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%) was added and the solution extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a white solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (695.0 mg, 60.0%) the desired *N*-hydroxy-2-biphenyl-acetamidine (**24**) as a white powder. M.S. *m/z* 213 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 5.7 (2H, s, NH_2), 6.93 (1H, m, ArH), 7.26 (1H, m, ArH), 7.36 (2H, m, 2 × ArH), 7.57 (2H, m, 2 × ArH), 7.6 (1H, m, ArH), 7.65 (2H, d, $J = 8.2$ Hz, 2 × ArH), 9.54 (1H, s, OH). Found C, 73.58, H, 5.69, N, 13.18%, $C_{13}H_{12}N_2O$ requires C, 73.6, H, 5.66, N, 13.19%.

*5.2.15. 3-Benzyl-5-(1H-indol-3-yl)-1,2,4-oxadiazole (**25**) [43]*

Indole-3-carboxylic acid (820.0 mg, 5.1 mmol) and carbonyldiimidazole (914.0 mg, 5.6 mmol) were stirred in anhydrous DME (20.0 mL) for 16 h. To a stirred solution of *N*-hydroxy-2-phenyl-acetamidine (766.0 mg, 5.1 mmol) in anhydrous DME (20.0 mL), was added crushed molecular sieves (3Å, 900.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 205.0 mg, 5.1 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated at gentle reflux for 24 h. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate (50.0 mL) and sodium bicarbonate solution (5%, 50.0 mL). The entire mixture was filtered through a sintered glass funnel and the phases separated. The aqueous portion was extracted with ethyl acetate (2 × 20.0 mL), and the combined organic extracts were dried, filtered and evaporated under reduced pressure to afford an oily yellow solid, which was recrystallised from ethyl acetate/hexane to afford (720.0 mg, 51.0%) the desired 3-benzyl-5-(1*H*-indol-3-yl)-1,2,4-oxadiazole (**25**) as white crystals. M.p. = 198–199 °C, M.S. *m/z* 276 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 4.16 (2H, s, CH_2), 7.21–7.48 (8H, m, 8 × ArH), 8.02 (1H, m, ArH), 8.28 (1H, m, ArH), 8.7 (1H, s, NH). Found C, 74.15, H, 4.7, N, 15.2%, $C_{17}H_{13}N_3O$ requires C, 74.17, H, 4.76, N, 15.26%.

*5.2.16. 5-(1H-Indol-3-yl)-3-(thiophen-2-ylmethyl)-1,2,4-oxadiazole (**26**) [43]*

1*H*-Indole-3-carboxylic acid (505.5 mg, 3.13 mmol) and carbonyldiimidazole (562.0 mg, 3.44 mmol) were stirred in anhydrous DME (15.0 mL) for 16 h. To a stirred solution of *N*-hydroxy-2-thiophen-2-yl-acetamidine (470.0 mg, 3.13 mmol) in anhydrous DME (15.0 mL), was added crushed molecular sieves (3 Å, 500.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 126.0 mg, 3.13 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated at gentle reflux for 24 h. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and sodium bicarbonate solution (5%). The entire mixture was filtered through a sintered glass funnel and the phases separated. The aqueous portion was extracted with ethyl acetate and the combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford an oily black solid, which was purified with column chromatography eluting with chloroform to afford (124.0 mg, 14.0%) the desired 5-(1*H*-indol-3-yl)-3-(thiophen-2-ylmethyl)-1,2,4-oxadiazole (**26**) as a black powder. M.S. *m/z* 282 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 4.37 (2H, m, CH_2), 6.98 (1H, dd, $J = 3.6$, 5.1 Hz, H-4″), 7.07 (1H, m, H-3″), 7.23 (1H, dd, $J = 1.2$, 5.1 Hz, H-5″), 7.3–7.39 (2H, m, 2 × ArH), 7.44–7.5 (1H, m, ArH), 8.06 (1H, d, $J = 2.7$ Hz, ArH), 8.3–8.33 (1H, m, ArH), 8.64 (1H, br s, NH). Found: $(M+1)^+ = 282.0688$, $C_{15}H_{11}N_3OS$ requires $(M+1)^+ = 282.0696$.

*5.2.17. 5-(1H-Imidazol-4-yl)-3-(thiophen-2-ylmethyl)-1,2,4-oxadiazole (**27**)*

Imidazole-4-carboxylic acid (247.2 mg, 2.2 mmol) and carbonyldiimidazole (395.0 mg, 2.42 mmol) were stirred in anhydrous DME (8.0 mL) for 16 h. To a stirred solution of *N*-hydroxy-2-phenyl-acetamidine (331.2 mg, 2.2 mmol) in anhydrous DME (8.0 mL), was added crushed molecular sieves (3 Å, 360.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 88.2 mg, 2.2 mmol) was added. After stirring at room temperature for an additional 30 min, the imidamide/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated at gentle reflux for 24 h. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and sodium bicarbonate solution (5%). The entire mixture was filtered through a sintered glass funnel and the phases separated. The aqueous phase was extracted with ethyl acetate and the combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford an yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (469.0 mg, 94.0%) the desired 5-(1*H*-imidazol-4-yl)-3-(thiophen-2-ylmethyl)-1,2,4-oxadiazole (**27**) as a cream powder. M.S. *m/z* 227 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 4.09 (2H, s, CH_2), 7.02 (1H, s, NH), 7.19–7.35 (5H, m, 5 × ArH), 7.92 (1H, s, ArH), 8.08 (1H, s, ArH). Found: $(M+1)^+ = 227.0923$, $C_{12}H_{10}N_4O$ requires $(M+1)^+ = 2227.0927$.

*5.2.18. 3-(4-Bromobenzyl)-5-(1H-indol-3-yl)-1,2,4-oxadiazole (**28**) [43]*

1*H*-Indole-3-carboxylic acid (350.0 mg, 2.17 mmol) and carbonyldiimidazole (389.0 mg, 2.38 mmol) were stirred in anhydrous THF (20.0 mL) for 16 h. To a stirred solution of 4-bromobenzylamido oxime (1.0 g, 4.37 mmol) in anhydrous THF (20.0 mL) was added crushed molecular sieves (3 Å,

1.1 g). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 175.0 mg, 4.38 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated at gentle reflux for 24 h. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and sodium bicarbonate solution (5%). The entire mixture was filtered through a sintered glass funnel and the phases separated. The aqueous portion was extracted with ethyl acetate and the combined organic extracts were dried, filtered and evaporated under reduced pressure to afford an yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (46.0 mg, 6.0%) the desired 3-(4-bromobenzyl)-5-(1*H*-indol-3-yl)-1,2,4-oxadiazole (**28**) as a black solid. M.S. *m/z* 354/356 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 4.12 (2H, s, CH_2), 7.25 (3H, m, $3\times$ArH), AA′BB′ system: 7.34 (2H, d, $J_{AB}+J_{AB'}=8.4$ Hz, H-2″), 7.53 (2H, d, $J_{AB}+J_{AB'}=8.4$ Hz, H-3″), 8.04 (1H, m, ArH), 8.31 (1H, s, ArH), 12.17 (1H, s, NH). Found: $(M+1)^+=354.0223$, $C_{17}H_{12}BrN_3O$ requires $(M+1)^+=354.0236$.

5.2.19. 5-(1H-Indol-3-yl)-3-(4-methoxybenzyl)-1,2,4-oxadiazole (*29*) [43]

1*H*-Indole-3-carboxylic acid (89.0 mg, 0.55 mmol) and carbonyldiimidazole (99.0 mg, 0.61 mmol) were stirred in anhydrous THF (10.0 mL) under an atmosphere of nitrogen at room temperature for 2 h. To a stirred solution of *N*-hydroxy-2-(4-methoxyphenyl)acetamidine (200.0 mg, 1.11 mmol) in anhydrous THF (10.0 mL), was added crushed molecular sieves (3 Å, 250.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 44.0 mg, 1.11 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated at gentle reflux for 4 h After this the reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford an off white residue, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (41.0 mg, 24.3%) the desired 5-(1*H*-indol-3-yl)-3-(4-methoxybenzyl)-1,2,4-oxadiazole (**29**) as a grey solid. M.S. *m/z* 306 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.72 (3H, s, CH_3), 4.04 (2H, s, CH_2), 6.89 (2H, d, $J_{AB}+J_{AB'}=8.7$ Hz, H-2″), 7.3-7.23 (4H, m, $4\times$ArH), 7.51–7.53 (1H, m, ArH), 8.04 (1H, m, ArH), 8.3 (1H, s, ArH), 12.13 (1H, s, NH). ^{13}C NMR (methanol-d_4) Δ 32.26, 55.84, 102.2, 113.4, 115.3, 121.6, 123.1, 124.5, 126.2, 129.4, 131.1, 138.4, 160.4, 170.9, 175.2. Found: $(M+1)^+=306.1245$, $C_{18}H_{15}N_3O_2$ requires $(M+1)^+=306.1243$. Found C, 70.8, H, 4.92, N, 13.74%, $C_{18}H_{15}N_3O_2$ requires C, 70.81, H, 4.95, N, 13.76%. Found: $(M+1)^+=306.12449$ $C_{18}H_{15}N_3O_2$ requires $(M+1)^+=306.11643$.

5.2.20. 3-(2-Chlorobenzyl)-5-(1H-indol-3-yl)-1,2,4-oxadiazole (*30*) [43]

1*H*-Indole-3-carboxylic acid (440.0 mg, 2.71 mmol) and carbonyldiimidazole (480.0 mg, 2.98 mmol) were stirred in anhydrous DME (8.0 mL) under an atmosphere of nitrogen at 80 °C for 2 h. To a stirred solution of *N*-hydroxy-2-(2-chlorophenyl)acetamidine (500.0 mg, 2.71 mmol) in anhydrous DME (8.0 mL), was added crushed molecular sieves (3 Å, 550.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 108.0 mg, 2.71 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was stirred at 80 °C for 10 min followed by heating at gentle reflux for 18 h. After this the reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford an off white residue, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (182.3 mg, 36.0%) the desired 3-(2-chlorobenzyl)-5-(1*H*-indol-3-yl)-1,2,4-oxadiazole (**30**) as a pale brown powder. M.S. *m/z* 310/312 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 4.31 (2H, s, CH_2), 7.2–7.48 (7H, m, $7\times$ArH), 8.05 (1H, m, ArH), 8.28 (1H, s, ArH), 8.67 (1H, s, NH). Found: $(M+1)^+=310.0744$, $C_{17}H_{12}ClN_3O$ requires $(M+1)^+=310.0747$. Found C, 65.9, H, 3.86, N, 13.52%, $C_{17}H_{12}ClN_3O$ requires C, 65.92, H, 3.9, N, 13.57%.

5.2.21. 5-(1H-Indol-3-yl)-3-phenethyl-1,2,4-oxadiazole (*31*) [43]

1*H*-Indole-3-carboxylic acid (980.0 mg, 6.08 mmol) and carbonyldiimidazole (1.09 g, 6.7 mmol) were stirred in anhydrous DME (25.0 mL) under an atmosphere of nitrogen at 80 °C for 2 h. To a stirred solution of phenethylamidooxime (1.0 g, 6.08 mmol) in anhydrous DME (25.0 mL) was added crushed molecular sieves (3 Å, 1.0 g). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 240.0 mg, 6.08 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was stirred at 80 °C for 10 min followed by heating at gentle reflux for 18 h. After this the reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford a pink residue, which was purified with column chromatography eluting with chloroform to afford

(326.3 mg, 18.65%) the desired 5-(1*H*-indol-3-yl)-3-phenethyl-1,2,4-oxadiazole (**31**) as a pale pink powder. M.S. *m/z* 290 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 3.16 (4H, m, $2\times CH_2$), 7.18–7.4 (7H, m, $7\times$ ArH), 7.43–7.53 (1H, m, ArH), 8.06 (1H, d, $J=3.0$ Hz, ArH), 8.28–8.37 (1H, m, ArH), 8.67 (1H, s, NH). Found: $(M+1)^+=290.1279$, $C_{18}H_{15}N_3O$ requires $(M+1)^+=290.1288$. Found C, 74.7, H, 6.25, N, 13.72%, $C_{18}H_{15}N_3O$ requires C, 74.73, H, 6.27, N, 13.76%.

5.2.22. 3-(Biphenyl-4-yl)-5-(1H-indol-3-yl)-1,2,4-oxadiazole (**32**) [43]

1*H*-Indole-3-carboxylic acid (49.4 mg, 0.31 mmol) and carbonyldiimidazole (54.7 mg, 0.34 mmol) were stirred in anhydrous THF (15.0 mL) for 16 h. To a stirred solution of *N*-hydroxy-2-biphenyl-acetamidine (130.0 mg, 0.61 mmol) in anhydrous THF (15.0 mL) was added crushed molecular sieves (3 Å, 100.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 24.6 mg, 0.61 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated at gentle reflux for 24 h. After this the solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and sodium bicarbonate solution (5%). The entire mixture was filtered through a sintered glass funnel and the phases separated. The aqueous portion was extracted with ethyl acetate and the combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford an off white solid, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford a white solid, which was recrystallised from ethyl acetate/hexane to afford (78.0 mg, 75.4%) the desired 3-(biphenyl-4-yl)-5-(1*H*-indol-3-yl)-1,2,4-oxadiazole (**32**) as white crystals. M.p. = 236–238 °C, M.S. *m/z* 338 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 7.16–7.19 (2H, m, $2\times$ ArH), 7.29 (1H, m, ArH), 7.36 (2H, m, $2\times$ ArH), 7.43–7.46 (2H, m, $2\times$ ArH), 7.63 (2H, d, $J=6.0$ Hz, $2\times$ ArH), 7.76 (2H, d, $J=6.0$ Hz, $2\times$ ArH), 8.06–8.12 (3H, m, $3\times$ ArH), 8.31 (1H, s, H-2). Found C, 78.3, H, 4.5, N, 12.44%, $C_{22}H_{15}N_3O$ requires C, 78.32, H, 4.48, N, 12.46%. Found: $(M+1)^+=338.12672$, $C_{22}H_{15}N_3O$ requires $(M+1)^+=338.12151$.

5.2.23. (3-Benzyl-[1,2,4]oxadiazol-5-yl)(1H-indol-3-yl)-methanone (**33**)

Indole-3-glyoxylic acid (630.0 mg, 3.33 mmol) and carbonyldiimidazole (590.0 mg, 6.7 mmol) were stirred in anhydrous THF (20.0 mL) under an atmosphere of nitrogen at room temperature for 2 h. To a stirred solution of benzylamidooxime (1.0 g, 6.66 mmol) in anhydrous THF (20.0 mL) was added crushed molecular sieves (3 Å, 1.1 g). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 266.0 mg, 6.66 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was stirred at room temperature for 30 min followed by heating at gentle reflux for 4 h. After this the reaction mixture was allowed to cool to room temperature and the reaction mixture was allowed to stir at room temperature for 18 h. After this the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford a yellow residue, which was purified with column chromatography eluting with (chloroform/methanol) (99/1) to afford (308.6 mg, 31.0%) the desired (3-benzyl-[1,2,4]oxadiazol-5-yl)(1*H*-indol-3-yl)methanone (**33**) as a yellow powder. M.p. = 223–225 °C, M.S. *m/z* 304 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 4.28 (2H, s, CH_2), 7.3–7.51 (7H, m, $7\times$ ArH), 7.6 (1H, m, ArH), 8.25 (1H, m, ArH), 8.75 (1H, s, ArH), 12.5 (1H, s, NH). Found C, 71.08, H, 4.32, N, 13.46%, $C_{18}H_{13}N_3O_2$ requires C, 71.28, H, 4.32, N, 13.85%.

5.2.24. 5-(1H-Indol-3-yl)-3-phenyl-1,2,4-oxadiazole (**34**) [43,50]

1*H*-Indole-3-carboxylic acid (376.0 mg, 2.33 mmol) and carbonyldiimidazole (416.0 mg, 2.57 mmol) were stirred in anhydrous THF (8.0 mL) under an atmosphere of nitrogen at room temperature for 30 min. To a stirred solution of *N*-hydroxy-2-phenyl-acetamidine (635.0 mg, 4.67 mmol) in anhydrous DME (8.0 mL), was added crushed molecular sieves (3 Å, 770.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 187.0 mg, 4.67 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was stirred at 80 °C for 10 min followed by heating at gentle reflux for 18 h. After this the reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford an off white solid, which was purified with column chromatography eluting with chloroform to afford to afford a white solid, which was recrystallised from ethyl acetate/hexane to afford (400.0 mg, 65.61%) the desired 5-(1*H*-indol-3-yl)-3-phenyl-1,2,4-oxadiazole (**34**) as fine white crystals. M.p. = 172–173 °C, M.S. *m/z* 262 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 7.3 (2H, m, $2\times$ ArH), 7.6 (4H, m, $4\times$ ArH), 8.14 (2H, m, $2\times$ ArH), 8.23 (1H, m, ArH), 8.43 (1H, s, ArH), 12.27 (1H, s, NH). Found C, 73.54, H, 4.2, N, 16.06%, $C_{16}H_{11}N_3O$ requires C, 73.56, H, 4.24, N, 16.08%.

5.2.25. (1H-Indol-3-yl)(3-phenyl-1,2,4-oxadiazol-5-yl)-methanone (**35**)

Indole-3-glyoxylic acid (274.0 mg, 1.44 mmol) and carbonyldiimidazole (259.0 mg, 1.59 mmol) were stirred in anhydrous THF (10.0 mL) under an atmosphere of nitrogen at room temperature for 2 h. To a stirred solution of phenylamidooxime (394.0 mg, 2.89 mmol) in anhydrous THF (10.0 mL) was added crushed molecular sieves (3 Å, 479.0 mg). The

mixture was stirred at room temperature for 30 min and sodium hydride (60%, 116.0 mg, 2.89 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was stirred at room temperature for 30 min followed by heating at gentle reflux for 4 h. After this the reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (185.0 mg, 44.15%) the desired (1*H*-indol-3-yl) (3-phenyl-1,2,4-oxadiazol-5-yl)methanone (**35**) as a yellow powder. M.p. = 258–260 °C, M.S. *m/z* 290 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 7.31 (2H, m, 2 × ArH), 7.56–7.7 (4H, m, 4 × ArH), 8.17 (2H, m, 2 × ArH), 8.3 (2H, m, 2 × ArH), 8.98 (1H, s, ArH), 12.11 (1H, s, NH). Found C, 70.54, H, 3.81, N, 14.5%, $C_{17}H_{11}N_3O_2$ requires C, 70.56, H, 3.84, N, 14.53%.

5.2.26. 5-(1H-Indol-3-yl)-3-(naphthalene-2-ylmethyl)-1,2,4-oxadiazole (**36**) [43]

1*H*-Indole-3-carboxylic acid (80.0 mg, 0.49 mmol) and carbonyldiimidazole (89.0 mg, 0.54 mmol) were stirred in anhydrous THF (15.0 mL) under an atmosphere of nitrogen at room temperature for 2 h. To a stirred solution of *N*-hydroxy-2-(2-naphthalen-2-yl)acetamidine (200.0 mg, 0.55 mmol) in anhydrous THF (15.0 mL), was added crushed molecular sieves (3 Å, 500.0 mg). The mixture was stirred at room temperature for 30 min and sodium hydride (60%, 40.0 mg, 0.5 mmol) was added. After stirring at room temperature for an additional 30 min, the amidoxime/sieves/sodium hydride mixture was added in one portion to the acid/CDI mixture and the resulting mixture was heated to gentle reflux for 4 h. After this the reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure and the residue was taken up in water. The aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and water and dried, filtered and evaporated under reduced pressure to afford a yellow residue, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (140.0 mg, 86.7%) the desired 5-(1*H*-indol-3-yl)-3-(naphthalene-2-ylmethyl)-1,2,4-oxadiazole (**36**) as a yellow powder. M.S. *m/z* 326 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.62 (2H, s, CH_2), 7.25 (3H, m, 3 × ArH), 7.4–7.51 (3H, m, 3 × ArH), 7.7–7.81 (4H, m, 4 × ArH), 8.02 (1H, m, ArH), 8.29 (1H, s, ArH), 12.0 (1H, s, NH). Found C, 77.48, H, 4.64, N, 12.9%, $C_{21}H_{15}N_3O$ requires C, 77.52, H, 4.65, N, 12.91%.

5.2.27. 4-(2-(3-(3-Benzyl-[1,2,4]oxadiazol-5-yl)-1H-indol-1-yl)-ethyl)morpholine (**37**) [43]

To a stirred solution of 3-[3-benzyl-[1,2,4]oxadiazol-5-yl]-1*H*-indole (247.0 mg, 0.89 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 79.0 mg, 1.97 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (157.0 mg, 0.84 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 16 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to a yellow residue, which was taken up in water. The aqueous phase was basified with potassium carbonate and the basic aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (dichloromethane/ethanol/ammonia) (250/5/1) to afford (52.0 mg, 14.9%) the desired 4-(2-(3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**37**) as a yellow powder. M.S. *m/z* 389 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.42 (4H, m, 2 × NCH_2), 2.71 (2H, t, $J = 5.7$ Hz, CH_2), 3.49 (4H, m, 2 × OCH_2), 4.13 (2H, s, CH_2), 4.4 (2H, t, $J = 6.0$ Hz, CH_2), 7.25–7.36 (7H, m, 7 × ArH), 7.67 (1H, d, $J = 8.1$ Hz, ArH), 8.05 (1H, d, $J = 6.9$ Hz, H-5), 8.41 (1H, s, H-2). H.p.l.c. retention time = 5.39 min; (10% B/90% D) to (100% B) over 20 min (B = 90% CH_3CN/10% H_2O) (D = 0.05% aqueous TFA).

5.2.28. 3-Benzyl-5-(1-(2-pyrrolidin-1-yl)ethyl)-1H-indol-3-yl)-1,2,4-oxadiazole (**38**) [43]

To a stirred solution of 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (120.0 mg, 0.43 mmol) in anhydrous DMF (2.0 mL) was added sodium hydride (60%, 38.0 mg, 0.95 mmol). The mixture was stirred at room temperature for 30 min and 1-(2-chloroethyl)pyrrolidine hydrochloride (81.0 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 24 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%, 30.0 mL) was added and the solution was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow residue, which was purified by column chromatography eluting with (chloroform/methanol) (19/1), to afford (116.0 mg, 72.0%) the desired 3-benzyl-5-(1-(2-pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)-1,2,4-oxadiazole (**38**) as a viscous yellow oil. M.S. *m/z* 373 $(M+1)^+$. ^{1}H NMR (methanol-d_4) Δ 1.64 (4H, m, 2 × CH_2), 2.39 (4H, m, 2 × CH_2), 2.71 (2H, t, $J = 6.9$ Hz, CH_2), 4.01 (2H, s, CH_2), 4.14 (2H, t, $J = 6.9$ Hz, CH_2), 7.1–7.38 (8H, m, 8 × ArH), 7.94 (1H, s, H-2), 8.06 (1H, m, H-4). ^{13}C NMR (methanol-d_4) Δ 22.81, 31.53, 45.21, 53.59, 54.68, 100.0, 110.1, 120.5, 121.8, 123.0, 125.1, 126.5, 128.2, 128.6, 132.4, 135.9, 136.4, 169.1, 173.3. Found C, 70.7, H, 6.5, N, 14.24%, $C_{23}H_{24}N_4O \cdot 1H_2O$ requires C, 70.74, H, 6.66, N, 14.27%.

5.2.29. (3-Benzyl-1,2,4-oxadiazol-5-yl)(1-(2-morpholinoethyl)-1H-indol-3-yl)methanone (**39**)

To a stirred solution of (1*H*-indol-3-yl)-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanone (100.0 mg, 0.33 mmol) in anhydrous DMF (10.0 mL) was added sodium hydride (60%,

29.0 mg, 0.73 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (61.0 mg, 0.33 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 4 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. The yellow residue was taken up in water and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (120.0 mg, 87.6%) the desired 3-benzyl-5-(1-[2-(morpholine-4-yl)ethyl]-3-indoloyl)oxadiazole (**39**) as a yellow powder. M.S. *m/z* 417 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.42 (4H, t, $J = 4.5$ Hz, $2 \times CH_2$), 2.69 (2H, t, $J = 6.0$ Hz, CH_2), 3.49 (4H, t, $J = 4.5$ Hz, $2 \times CH_2$), 4.27 (2H, s, CH_2), 4.44 (2H, t, $J = 6.0$ Hz, CH_2), 7.28–7.39 (7H, m, $7 \times$ ArH), 7.68–7.74 (1H, m, H-7), 8.23–8.29 (1H, s, H-2). Found C, 69.2, H, 5.78, N, 14.4%, $C_{24}H_{24}N_4O_3$ requires C, 69.21, H, 5.81, N, 13.45%.

5.2.30. 4-(2-(3-(3-Phenyl-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)-ethyl)morpholine (**40**) [43]

To a stirred solution of 3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (100.0 mg, 0.38 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 34.0 mg, 0.84 mmol). The mixture was stirred at room temperature for 30 min and 1-(2-chloroethyl)morpholine hydrochloride (71.3 mg, 0.38 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 2 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. Sodium carbonate solution (10%, 30.0 mL) was added and the aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was recrystallised from ethyl acetate/hexane to afford (130.0 mg, 90.9%) the desired 4-(2-(3-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl) ethyl)morpholine (**40**) as yellow crystals. M.p. = 144–146 °C, M.S. *m/z* 375 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.52 (4H, t, $J = 4.5$ Hz, $2 \times CH_2$), 2.78 (2H, t, $J = 6.3$ Hz, CH_2), 3.55 (4H, t, $J = 4.5$ Hz, $2 \times CH_2$), 4.49 (2H, t, $J = 6.3$ Hz, CH_2), 7.33–7.44 (2H, m, $2 \times$ ArH), 7.58–7.69 (3H, m, $3 \times$ ArH), 7.76 (1H, m, ArH), 8.16 (2H, m, $2 \times$ ArH), 8.26 (1H, m, ArH), 8.56 (1H, s, ArH). Found C, 70.57, H, 5.9, N, 14.92%, $C_{22}H_{22}N_4O_2$ requires C, 70.57, H, 5.92, N, 14.96%.

5.2.31. 4-(2-(3-(3-Biphenyl-4-yl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (**41**) [43]

To a stirred solution of 3-(3-biphenyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (50.0 mg, 0.15 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 14.0 mg, 0.33 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (28.0 mg, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 18 h after which the solvent was evaporated under reduced pressure. Sodium carbonate solution (10%) was added and the solution was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a white solid, which was recrystallised from ethyl acetate/hexane to afford (45.0 mg, 67.5%) the desired 4-(2-(3-(3-biphenyl-4-yl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**41**) as white crystals. M.p. = 138–140 °C, M.S. *m/z* 451 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.57 (4H, m, $2 \times CH_2$), 2.8 (2H, t, $J = 6.3$ Hz, CH_2), 3.6 (4H, m, $2 \times CH_2$), 4.53 (2H, t, $J = 6.2$ Hz, CH_2), 7.41 (1H, m, ArH), 7.45 (1H, m, ArH), 7.59 (2H, m, $2 \times$ ArH), 7.77–7.86 (3H, m, $3 \times$ ArH), 7.98 (2H, d, $J = 8.4$ Hz, $2 \times$ ArH), 8.26 (2H, d, $J = 8.3$ Hz, $2 \times$ ArH), 8.27–8.28 (1H, m, ArH), 8.62 (1H, s, H-2). Found C, 74.63, H, 5.86, N, 12.11%, $C_{28}H_{26}N_4O_2$ requires C, 74.65, H, 5.82, N, 12.44%. Found: $(M+1)^+ = 451.21302$, $C_{28}H_{26}N_4O_2$ requires $(M+1)^+ = 451.20558$. Retention time = 27.51 min (Isocratic 50 B/50 D (B = CH_3CN/H_2O 9/1) (D = 0.05% TFA in H_2O).

5.2.32. 1-Morpholino-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethanone (**42**)

To a stirred solution of 3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (121.0 mg, 0.46 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 37.1 mg, 0.93 mmol). The mixture was stirred at room temperature for 30 min and 2-bromo-1-(4-morpholinyl)-1-ethanone (96.4 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 80 °C for 9 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. The yellow residue was taken up in water and the aqueous solution was basified with sodium carbonate. The basic aqueous solution was the extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (60.0 mg, 20.5%) the desired 1-morpholino-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethanone (**42**) as a white powder. M.p. = 174–175 °C, M.S. *m/z* 389 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.6 (6H, s, $3 \times CH_2$), 3.71 (2H, s, CH_2), 5.39 (2H, s, CH_2), 7.33 (2H, m, $2 \times$ ArH), 7.59 (4H, m, $4 \times$ ArH), 8.12 (2H, m, $2 \times$ ArH), 8.22 (1H, m, ArH), 8.39 (1H, s, ArH). Found C, 67.59, H, 5.16, N, 14.4%, $C_{22}H_{20}N_4O_3$ requires C, 68.03, H, 5.19, N, 14.42%.

5.2.33. 2-(3-(3-Benzyl-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)-1-morpholinoethanone (**43**)

To a stirred solution of 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (125.0 mg, 0.38 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 30.5 mg, 0.76 mmol). The mixture was stirred at room temperature for 30 min and 2-bromo-1-(4-morpholinyl)-1-ethanone (79.5 mg, 0.38 mmol) was added. The reaction mixture was stirred at room temperature

for 30 min and at 80 °C for 8 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. The yellow residue was taken up in water and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was then extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (80.7 mg, 44.12%) the desired 2-(3-(3-benzyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)-1-morpholinoethanone (**43**) as white needles. M.p. = 172–174 °C, M.S. *m/z* 403 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.44 (2H, s, CH_2), 3.59 (4H, s, $2\times CH_2$), 3.69 (2H, s, CH_2), 4.13 (2H, s, CH_2), 5.34 (2H, s, CH_2), 7.2–7.41 (7H, m, $7\times$ ArH), 7.53 (1H, m, ArH), 8.05 (1H, m, ArH), 8.27 (1H, s, ArH). Found C, 68.58, H, 5.49, N, 13.8%, $C_{23}H_{22}N_4O_3$ requires C, 68.64, H, 5.51, N, 13.92%.

5.2.34. (1-(2-Morpholinoethyl)-1H-indol-3-yl)(3-phenyl-1,2,4-oxadiazol-5-yl)methanone (**44**)

To a stirred solution of (1*H*-indol-3-yl)-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methanone (75.5 mg, 0.26 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 30.3 mg, 0.76 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (48.6 mg, 0.26 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 8 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. The yellow residue was taken up in water and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was then extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (27.0 mg, 25.76%) the desired (1-(2-morpholinoethyl)-1*H*-indol-3-yl)(3-phenyl-1,2,4-oxadiazol-5-yl) methanone (**44**) as a yellow powder. M.p. = 132–133 °C, M.S. *m/z* 403 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.49 (4H, t, $J=4.5$ Hz, $2\times CH_2$), 2.73 (2H, t, $J=5.9$ Hz, CH_2), 3.52 (4H, t, $J=4.5$ Hz, $2\times CH_2$), 4.51 (2H, t, $J=5.9$ Hz, CH_2), 7.21 (1H, m, ArH), 7.38 (2H, m, ArH), 7.64 (2H, m, $2\times$ ArH), 7.74, (1H, d, $J=7.2$ Hz, ArH), 8.18 (2H, m, $2\times$ ArH), 8.32 (1H, d, $J=7.8$ Hz, ArH), 9.08 (1H, s, ArH). Found C, 68.22, H, 5.63, N, 13.2%, $C_{23}H_{22}N_4O_3\cdot 0.1H_2O$ requires C, 68.27, H, 5.49, N, 13.8%.

5.2.35. 4-(2-(3-(3-(Thiophen-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (**45**) [43]

To a stirred solution of 5-(1*H*-indol-3-yl)-3-(thiophen-2-ylmethyl)-1,2,4-oxadiazole (210.0 mg, 0.75 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 66.0 mg, 1.6 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (139.0 mg, 0.75 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 22 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford brown oil. The brown oil was partitioned between aqueous sodium carbonate solution (10%, 30.0 mL) and ethyl acetate (30.0 mL). The ethyl acetate extract was then dried, filtered and evaporated under reduced pressure to afford brown oil, which was purified with column chromatography eluting with (chloroform/methanol) (98/2) to afford (127.0 mg, 43.13%) the desired 4-(2-(3-(3-(thiophen-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**45**) as a yellow gum. M.S. *m/z* 395 $(M+1)^+$. ^{1}H NMR (MeOH-d_4) Δ 2.5 (2H, m, CH_2), 2.58 (2H, m, CH_2), 2.81 (2H, t, $J=6.3$ Hz, CH_2), 3.63 (2H, t, $J=4.8$ Hz, CH_2), 3.69 (2H, m, CH_2), 4.34 (2H, s, CH_2), 4.45 (2H, m, CH_2), 6.91 (1H, m, ArH), 7.05, (1H, d, $J=3.6$ Hz, ArH), 7.27–7.34 (3H, m, $3\times$ ArH), 7.58 (1H, d, $J=7.8$ Hz, ArH), 8.17 (1H, m, ArH), 8.23 (1H, s, H-2). Found: $(M+1)^+=395.1516$, $C_{21}H_{22}N_4O_2S$ requires $(M+1)^+=395.1536$.

5.2.36. 4-(2-(3-(3-Benzyl-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)-ethyl)morpholine (**46**)

To a stirred solution of 2-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (230.0 mg, 0.84 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 74.0 mg, 1.9 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (171.0 mg, 0.92 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 24 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford an off white residue. The residue was taken up in water and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts ware then dried, filtered and evaporated under reduced pressure to afford an off white solid, which was purified with column chromatography eluting with (chloroform/methanol) (98/2) to afford (193.0 mg, 60.0%) the desired 4-(2-(3-(3-benzyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)morpholine (**46**) as a cream powder. M.S. *m/z* 389 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 2.35 (4H, m, $2\times CH_2$), 2.63 (2H, m, CH_2), 3.53 (4H, m, $2\times CH_2$), 4.15 (2H, s, CH_2), 4.78 (2H, m, CH_2), 7.18 (1H, dd, $J=7.2$, 7.8 Hz, ArH), 7.22–7.5 (8H, m, $8\times$ ArH), 7.7 (1H, d, $J=8.1$ Hz, ArH). ^{13}C NMR ($CDCl_3$) Δ 32.34, 42.21, 53.68, 57.58, 66.76, 109.2, 110.3, 121.0, 122.4, 123.7, 125.1, 126.9, 127.1, 128.6, 129.0, 135.5, 138.9, 169.5, 170.0. Found C, 65.0, H, 6.55, N, 13.15%, $C_{23}H_{24}N_4O_2\cdot 2H_2O$ requires C, 65.08, H, 6.59, N, 13.19%. Found: $(M+1)^+=389.1956$, $C_{23}H_{24}N_4O_2$ requires $(M+1)^+=389.1972$.

5.2.37. 4-(2-(4-(3-Benzyl-1,2,4-oxadiazol-5-yl)-1H-imidazol-1-yl)ethyl)morpholine and 4-(2-(5-(3-benzyl-1,2,4-oxadiazol-5-yl)-1H-imidazol-1-yl)ethyl)morpholine (1/1 mixture) (**47**)

To a stirred solution of 3-benzyl-5-(1*H*-imidazol-4-yl)-[1,2,4]oxadiazole (102.0 mg, 0.45 mmol) in anhydrous DMF (3.0 mL) was added sodium hydride (60%, 40.0 mg,

1.0 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (92.0 mg, 0.49 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 24 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford an off white residue. The residue was taken up in water and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were then dried, filtered and evaporated under reduced pressure to afford an off white solid, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (80.6 mg, 52.67%) the desired 4-(2-(4-(3-benzyl-1,2,4-oxadiazol-5-yl)-1*H*-imidazol-1-yl)ethyl)morpholine and 4-(2-(5-(3-benzyl-1,2,4-oxadiazol-5-yl)-1*H*-imidazol-1-yl)ethyl)morpholine (1/1 mixture, **47**) as a colourless solid. M.S. *m/z* 340 $(M+1)^+$. H.p.l.c. retention time = 21.39 min; (Isocratic 20 B/80 D (B = 90% CH_3CN/10% H_2O) (D = 0.05% aqueous TFA).

5.2.38. 3-Benzyl-5-1-(2-(piperidine-1-yl)ethyl)-1H-indol-3-yl)-1,2,4-oxadiazole (*48*) [43]

To a stirred solution of 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (180.0 mg, 0.65 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 58.0 mg, 1.43 mmol). The mixture was stirred at room temperature for 30 min and 1-(2-chloroethyl)piperidine hydrochloride (132.0 mg, 0.72 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 16 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. The residue was taken up in aqueous sodium carbonate solution (5%, 10.0 mL) and the basic aqueous solution was extracted with ethyl acetate. The combined ethyl acetate extracts were then dried, filtered and evaporated under reduced pressure to afford a yellow oil, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (175.7 mg, 70.0%) the desired 3-benzyl-5-1-(2-(piperidine-1-yl)ethyl)-1*H*-indol-3-yl)-1,2,4-oxadiazole (**48**) as a yellow oil. M.S. *m/z* 387 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 1.35–1.51 (2H, m, CH_2), 1.51–1.75 (4H, m, 2 × CH_2), 2.45 (4H, m, 2 × CH_2), 2.74 (2H, t, *J* = 6.9 Hz, CH_2), 4.16 (2H, s, CH_2), 4.29 (2H, t, *J* = 6.9 Hz, CH_2), 7.2–7.47 (8H, m, 8 × ArH), 8.0 (1H, s, H-2), 8.27 (1H, m, H-4). Found: $(M+1)^+ = 387.2175$, $C_{24}H_{26}N_4O$ requires $(M+1)^+ = 387.2179$.

5.2.39. 4-(2-(3-(3-(4-Methoxybenzyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (*49*) [43]

To a stirred solution of 3-[3-(4-methoxybenzyl)-[1,2,4]oxadiazol-5-yl]-1*H*-indole (40.0 mg, 0.13 mmol) in anhydrous DMF (10.0 mL) was added sodium hydride (60%, 12.0 mg, 0.29 mmol). The mixture was stirred at room temperature for 30 min and 1-(2-chloroethyl)morpholine hydrochloride (132.0 mg, 0.72 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 16 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to a yellow residue, which was taken up in water. The aqueous phase was basified with potassium carbonate and the basic aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (45.0 mg, 84.3%) the desired 4-(2-(3-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**49**) as a yellow powder. M.S. *m/z* 419 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.42 (4H, t, *J* = 4.2 Hz, 2 × CH_2), 2.7 (2H, t, *J* = 6.0 Hz, CH_2), 3.5 (4H, t, *J* = 4.5 Hz, 2 × CH_2), 3.82 (3H, s, OCH_3), 4.04 (2H, s, CH_2), 4.4 (2H, t, *J* = 6.0 Hz, CH_2), 6.89 (2H, d, *J* = 8.7 Hz, 2 × ArH), 7.27 (2H, d, *J* = 8.7 Hz, 2 × ArH), 7.3 (2H, m, 2 × ArH), 7.66 (1H, d, *J* = 7.5 Hz, ArH), 8.05 (1H, d, *J* = 8.1 Hz, ArH), 8.39 (1H, s, H-2). Found: $(M+1)^+ = 419.20616$, $C_{24}H_{26}N_4O_3$ requires $(M+1)^+ = 419.20049$.

5.2.40. 4-(2-(3-(3-(4-Bromobenzyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (*50*) [43]

To a stirred solution of 3-[3-(4-bromobenzyl)-[1,2,4]oxadiazol-5-yl]-1*H*-indole (200.0 mg, 0.54 mmol) in anhydrous DMF (10.0 mL) was added sodium hydride (60%, 47.0 mg, 1.18 mmol). The mixture was stirred at room temperature for 30 min and 1-(2-chloroethyl)morpholine hydrochloride (100.0 mg, 0.54 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 4 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to a yellow residue, which was taken up in water. The aqueous phase was basified with potassium carbonate and the basic aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (217.3 mg, 87.0%) the desired 4-(2-(3-(3-(4-bromobenzyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**50**) as a yellow solid. M.S. *m/z* 467 $(M+1)^+$ ^{1}H NMR ($CDCl_3$) Δ 2.52 (2H, s, CH_2), 2.82 (2H, s, CH_2), 3.7 (2H, s, CH_2), 4.09 (2H, s, CH_2), 4.33 (2H, s, CH_2), 7.29 (2H, d, *J* = 8.1 Hz, 2 × ArH), 7.25–7.5 (2H, m, H-5, H-6), 7.46 (1H, d, *J* = 8.1 Hz, H-2), 8.0 (1H, s, H-2), 8.27 (1H, d, *J* = 5.4 Hz, H-4). H.p.l.c. retention time = 16.7 min; (10% B/90% D) to (100% B) over 20 min (B = 90% CH_3CN/10% H_2O) (D = 0.05% aqueous TFA).

5.2.41. 2-(3-(3-(2-Chlorobenzyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)-1-morpholinoethanone (*51*)

To a stirred solution of 3-(3-(2-chlorobenzyl)-[1,2,4]oxadiazol-5-yl)-1*H*-indole (50.0 mg, 0.16 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 14.0 mg, 0.36 mmol). The mixture was stirred at room temperature for 30 min and 2-bromo-1-(4-morpholinyl)-1-ethanone (34.0 mg, 0.16 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for

15 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a grey residue. The grey residue was taken up in water and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was the extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a grey solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (18.0 mg, 25.5%) the desired 2-(3-(3-(2-chlorobenzyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)-1-morpholinoethanone (**51**) as a grey solid. M.S. *m/z* 437 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 3.51 (2H, m, CH_2), 3.68 (6H, m, $3\times CH_2$), 4.3 (2H, s, CH_2), 4.96 (2H, s, CH_2), 7.22–7.24 (2H, m, $2\times$ ArH), 7.32–7.43 (3H, m, $3\times$ ArH), 7.94 (1H, s, ArH), 8.28 (1H, m, ArH). Found: $(M+1)^+ = 437.13723$ and 439.13431, $C_{23}H_{21}ClN_4O_2$ requires $(M+1)^+ = 437.13022$ and 439.13022. H.p.l.c. retention time = 21.0 min; (50% A/50% B) (A = 90% CH_3CN/10% H_2O) (B = 0.05% aqueous TFA.

5.2.42. 3-Benzyl-5-(1-pentyl-1H-indol-3-yl)-1,2,4-oxadiazole (**52**) [43]

To a stirred solution of 3-(3-benzyl-[1,2,4]oxadiazol-5-yl)-1*H*-indole (100.0 mg, 0.36 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 16.0 mg, 0.4 mmol). The mixture was stirred at room temperature for 30 min and 1-bromopentane (50.0 μL, 0.65 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 18 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford an off white residue. Water was added to the residue and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was then extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford an off white solid, which was purified with column chromatography eluting with chloroform to afford (59.0 mg, 85.0%) the desired 3-benzyl-5-(1-pentyl-1*H*-indol-3-yl)-1,2,4-oxadiazole (**52**) as colourless needles. M.S. *m/z* 346 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 1.04 (3H, t, $J = 6.9$ Hz, CH_2), 1.44 (4H, s, $2\times CH_2$), 2.0 (2H, tt, $J = 7.2$, 7.2 Hz, CH_2), 4.25 (2H, t, $J = 7.2$ Hz, CH_2), 4.31 (2H, s, CH_2), 7.37–7.61 (8H, m, $8\times$ ArH), 8.04 (1H, s, ArH), 8.43 (1H, m, ArH). Found C, 76.46, H, 6.68, N, 12.14, $C_{22}H_{23}N_3O$ requires C, 76.49, H, 6.71, N, 12.16%.

5.2.43. 4-(2-(3-(3-Phenethyl-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (**53**) [43]

To a stirred solution of 3-(3-phenethyl-1,2,4-oxadiazol-5-yl)-1*H*-indole (250.0 mg, 0.86 mmol) in anhydrous DMF (10.0 mL) was added sodium hydride (60%, 76.0 mg, 1.9 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (161.0 mg, 0.86 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 18 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford a yellow residue. Water was added to the residue and the aqueous solution was basified with potassium carbonate. The basic aqueous solution was then extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (296.0 mg, 85.0%) the desired 4-(2-(3-(3-phenethyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**53**) as yellow needles. M.S. *m/z* 403 $(M+1)^+$. ^{1}H NMR ($CDCl_3$) Δ 2.5 (4H, t, $J = 4.7$ Hz, $2\times CH_2$), 2.82 (2H, t, $J = 6.6$ Hz, CH_2), 3.08–3.24 (4H, m, $2\times CH_2$), 3.7 (4H, t, $J = 4.7$ Hz, $2\times CH_2$), 4.31 (2H, t, $J = 6.6$ Hz, CH_2), 7.18–7.47 (8H, m, $8\times$ ArH), 8.03 (1H, s, ArH), 8.31 (1H, m, ArH). Found: $(M+1)^+ = 403.2125$, $C_{24}H_{26}N_4O_2$ requires $(M+1)^+ = 403.2129$.

5.2.44. 4-(2-(3-(3-(2-Chlorobenzyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (**54**) [43]

To a stirred solution of 3-[3-(2-chlorobenzyl)-[1,2,4]oxadiazol-5-yl]-1*H*-indole (70.0 mg, 0.23 mmol) in anhydrous DMF (12.0 mL) was added sodium hydride (60%, 20.0 mg, 0.5 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (42.1 mg, 0.23 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 15 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to a yellow residue, which was taken up in water. The aqueous phase was basified with potassium carbonate and the basic aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (12.1 mg, 12.6%) the desired 4-(2-(3-(3-(2-chlorobenzyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**54**) as a yellow solid. M.S. *m/z* 423 $(M+1)^+$. ^{1}H NMR (MeOH-d_4) Δ 2.0 (4H, m, $2\times CH_2$), 2.07 (2H, m, CH_2), 2.38 (2H, m, CH_2), 2.61 (4H, m, $2\times CH_2$), 2.97 (2H, s, CH_2), 5.84 (1H, m, ArH), 5.99 (2H, m, $2\times$ ArH), 6.1 (3H, m, $3\times$ ArH), 6.35 (1H, d, $J = 8.1$ Hz, ArH), 6.87 (1H, d, $J = .5$ Hz, ArH), 6.95 (1H, s, H-2). Found C, 65.28, H, 5.46, N, 13.22%, $C_{23}H_{23}ClN_4O_2$ requires C, 65.32, H, 5.48, N, 13.25%.

5.2.45. 4-((3-(3-Benzyl-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)-methyl)oxazolidine-2-one (**55**)

To a stirred solution of 3-[3-benzyl-[1,2,4]oxadiazol-5-yl]-1*H*-indole (123.0 mg, 0.45 mmol) in anhydrous DMF (12.0 mL) was added sodium hydride (60%, 17.0 mg, 0.45 mmol). The mixture was stirred at room temperature for 30 min and 5-(chloromethyl)oxazolidinone (60.6 mg, 0.45 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 4 h after which

the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to a white residue, which was taken up in water. The aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a white solid, which was purified with column chromatography eluting with (chloroform/methanol) (9/1) to afford (41.8 mg, 25.0%) the desired 4-((3-(3-benzyl-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)methyl) oxazolidine-2-one (**55**) as a yellow solid. M.S. *m/z* 375 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 3.78 (2H, d, CH_2), 3.86 (2H, d, CH_2), 4.12 (2H, s, CH_2), 4.82 (1H, m, CH), 7.23–7.26 (3H, m, 3 × ArH), 7.36 (2H, m, 2 × ArH), 7.52 (2H, m, 2 × ArH), 8.05 (1H, m, ArH), 8.31 (1H, s, H-2). Found C, 67.32, H, 4.82, N, 14.5%, $C_{21}H_{18}N_4O_3$ requires C, 67.37, H, 4.85, N, 14.96%.

5.2.46. 4-(2-(3-(3-(Naphthalene-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)ethyl)morpholine (**56**) [43]

To a stirred solution of 3-[3-(2-naphthalene)-[1,2,4]oxadiazol-5-yl]-1*H*-indole (125.7 mg, 0.38 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 30.9 mg, 0.77 mmol). The mixture was stirred at room temperature for 30 min and 4-(2-chloroethyl)morpholine hydrochloride (71.9 mg, 0.38 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 100 °C for 15 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to a yellow residue, which was taken up in water. The aqueous phase was basified with potassium carbonate and the basic aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a yellow solid, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (90.0 mg, 53.0%) the desired 4-(2-(3-(3-(naphthalene-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**56**) as a yellow powder. M.S. *m/z* 439 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.4 (4H, m, 2 × CH_2), 2.68 (2H, m, CH_2), 3.48 (4H, m, 2 × CH_2), 4.38 (2H, t, $J = 6.3$ Hz, CH_2), 4.59 (2H, s, CH_2), 7.27 (2H, m, 2 × ArH), 7.49–7.66 (6H, m, 6 × ArH), 7.86 (1H, d, $J = 7.5$ Hz, ArH), 7.94 (1H, d, $J = 7.2$ Hz, ArH), 8.01 (1H, d, $J = 77.2$ Hz, ArH), 8.2 (1H, d, $J = 78.4$ Hz, ArH), 8.37 (1H, s, H-2). Found C, 73.92, H, 5.96, N, 12.8%, $C_{27}H_{26}N_4O_2$ requires C, 73.95, H, 5.98, N, 12.78%.

5.2.47. (3-Naphthalen-2-ylmethyl)-5-(1-(2-(pyrrolidine-1-yl)-ethyl)-1H-indol-3-yl)-1,2,4-oxadiazole (**57**) [43]

To a stirred solution of 3-[3-(2-naphthalene)-[1,2,4]oxadiazol-5-yl]-1*H*-indole (58.9 mg, 0.18 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 25.0 mg, 0.18 mmol). The mixture was stirred at 60 °C for 30 min then allowed to cool to room temperature and 4-(2-chloroethyl)pyrrolidine hydrochloride (31.7 mg, 0.19 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 110 °C for 18 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to yellow oil, which was taken up in water. The aqueous phase was basified with potassium carbonate and the basic aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford yellow oil, which was purified with column chromatography eluting with (chloroform/methanol) (99/1) to afford (12.2 mg, 15.9%) the desired 4-(2-(3-(3-(naphthalene-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)ethyl)morpholine (**57**) as a yellow powder. M.S. *m/z* 423 $(M+1)^+$. ^{1}H NMR (methanol-d_4) Δ 1.45 (4H, m, 2 × CH_2), 1.7–1.75 (4H, m, 2 × CH_2), 4.29 (2H, t, $J = 6.6$ Hz, CH_2), 4.59 (2H, s, CH_2), 7.29 (4H, m, 4 × ArH), 7.46–7.62 (6H, m, 6 × ArH), 7.85 (2H, m, ArH), 8.19 (1H, m, ArH). Found C, 76.72, H, 6.1, N, 13.2%, $C_{27}H_{26}N_4O$ requires C, 76.75, H, 6.2, N, 13.26%.

5.2.48. Ethyl 5-(3-(3-(naphthalen-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)pentanoate (**58**) [43]

To a stirred solution of 3-[3-(2-naphthalene)-[1,2,4]oxadiazol-5-yl]-1*H*-indole (39.4 mg, 0.12 mmol) in anhydrous DMF (5.0 mL) was added sodium hydride (60%, 5.0 mg, 0.12 mmol). The mixture was stirred at 60 °C for 60 min then allowed to cool to room temperature and 5-bromovalerate (25.3 mg, 0.12 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 110 °C for 18 h after which the reaction mixture was allowed to cool to room temperature and the solvent was then evaporated under reduced pressure to afford white oil, which was taken up in water. The aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford white oil, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (30.0 mg, 54.6%) the desired ethyl 5-(3-(3-(naphthalen-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)pentanoate (**58**) as an off white oil. M.S. *m/z* 454 $(M+1)^+$. ^{1}H NMR (MeOH-d_4) Δ 1.14 (3H, t, $J = 7.2$ Hz, CH_3), 1.53 (2H, m, CH_2), 1.84 (2H, m, CH_2), 4.05 (2H, q, $J = 6.9$ Hz, CH_2), 4.21 (2H, m, CH_2), 4.56 (2H, s, CH_2), 7.19–7.3 (4H, m, 4 × ArH), 7.42–7.56 (6H, m, 6 × ArH), 7.8 (1H, d, $J = 8.1$ Hz, ArH), 7.87 (1H, d, $J = 7.8$ Hz, ArH), 8.1 (1H, s, ArH), 8.21 (1H, m, ArH). H.p.l.c. retention time = 21.51 min; (50% B/50% D) (B = 90% CH_3CN/10% H_2O) (D = 0.05% H_3PO_4 in water).

5.2.49. 5-(3-(3-(Naphthalene-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1H-indol-1-yl)pentanoic acid (**59**) [43]

3-[3-(2-Methylnaphthyl)-5-(ethyl-*N*-pentanoate)indol-3-yl) oxadiazole (10.9 mg, 0.024 mmol) was dissolved in methanolic potassium hydroxide (potassium hydroxide (2.0 mg), anhydrous methanol (5.0 mL)) and the reaction mixture was stirred at room temperature for 12 h. After this the methanol was evaporated under reduced pressure to grey gum, which was taken up in water. The aqueous phase was acidified with dilute hydrochloric acid and then extracted with ethyl

acetate. The combined ethyl acetate extracts were dried, filtered and evaporated under reduced pressure to afford a grey gum, which was purified with column chromatography eluting with (chloroform/methanol) (95/5) to afford (8.0 mg, 72.2%) the desired 5-(3-(3-(naphthalene-2-ylmethyl)-1,2,4-oxadiazol-5-yl)-1*H*-indol-1-yl)pentanoic acid (**59**) as a grey gum. M.S. *m/z* 426 $(M+1)^+$. ^{1}H NMR (MeOH-d_4) Δ 0.9 (2H, m, CH_2), 1.62 (2H, m, CH_2), 1.92 (2H, m, CH_2), 2.3 (2H, m, CH_2), 4.58 (2H, s, CH_2), 7.25–7.31 (4H, m, 4 × ArH), 7.46–7.51 (2H, m, 2 × ArH), 7.52–7.55 (4H, m, 4 × ArH), 7.82 (2H, d, $J = 8.1$ Hz, 2 × ArH), 7.88 (2H, d, $J = 8.7$ Hz, 2 × ArH), 8.11 (1H, m, ArH), 8.13 (1H, s, ArH), 8.22 (1H, m, ArH). H.p.l.c. retention time = 2.53 min; (100% B) (B = 90% CH_3CN/10% H_2O).

5.2.50. 1-(2-Morpholinoethyl)-1H-indol-3-yl acetate (*60*)

3-Indolyl acetate (1.0 g, 5.7 mmol) was dissolved in anhydrous DMF (10.0 mL) and sodium hydride (60% dispersion, 437.6 mg, 11.4 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. After this 4-(2-chloroethyl)morpholine hydrochloride (1.06 g, 5.7 mmol) was added and the reaction mixture was heated at 110 °C under the atmosphere of nitrogen for 18 h. After this the reaction mixture was allowed to cool to room temperature. The DMF was evaporated under reduced pressure to afford a purple gum, which was purified with column chromatography eluting with chloroform to afford (1.1 g, 67.0%) the desired 1-(2-(4-morpholino)ethyl)-3-aceto-1*H*-indole (**60**) as a purple solid. M.S. *m/z* 189 $(M+1)^+$. ^{1}H NMR (DMSO-d_6) Δ 2.41 (4H, t, $J = 4.5$ Hz, 2 × CH_2), 2.48 (2H, t, $J = 6.0$ Hz, CH_2), 3.55 (4H, t, $J = 4.5$ Hz, 2 × CH_2), 3.66 (2H, t, $J = 6.0$ Hz, CH_2), 7.24 (2H, m, 2 × ArH), 7.69 (2H, m, 2 × ArH), 8.44 (1H, s, ArH). H.p.l.c. retention time = 2.02 min; (100% B) (B = 90% CH_3CN/10% H_2O).

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