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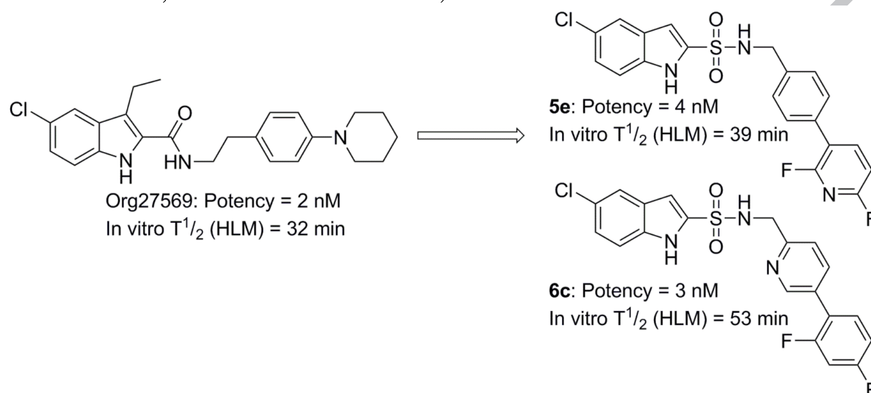

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Development of indole sulfonamides as cannabinoid receptor negative allosteric modulators.

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ABSTRACT

Existing CB1 negative allosteric modulators (NAMs) fall into a limited range of structural classes. In spite of the theoretical potential of CB1 NAMs, published *in vivo* studies have generally not been able to demonstrate the expected therapeutically-relevant CB1-mediated effects. Thus, a greater range of molecular tools are required to allow definitive elucidation of the effects of CB1 allosteric modulation. In this study, we show a novel series of indole sulfonamides. Compounds **5e** and **6c** (**ABD1075**) had potencies of 4 and 3 nM respectively, and showed good oral exposure and CNS penetration, making them highly versatile tools for investigating the therapeutic potential of allosteric modulation of the cannabinoid system.

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Drugs which block cannabinoid receptor activation were expected to find a huge market for the treatment of obesity, addiction and metabolic syndromes (e.g. type-2 diabetes). However, rejection by the FDA and eventual withdrawal in Europe of the first such drug to reach the market (rimonabant) effectively terminated this line of approach, in spite of the apparent therapeutic utility.[1] There are a number of different approaches now being taken to harness the potential of the cannabinoid system, whilst avoiding the side-effects of previous approaches that entailed global antagonism.[2] Such approaches include the use of neutral antagonists, negative allosteric modulators and peripheral restriction.[1,2]

CB1 receptors and endocannabinoids are present in peripheral tissues involved in metabolic dysfunction associated with obesity, including adipose tissue, liver, skeletal muscle and pancreas, and there is evidence for the upregulation of the endocannabinoid system in these tissues in experimental and human obesity.[3] Activation of CB1 receptors in peripheral tissues promotes lipogenesis, lipid storage, insulin secretion, glucagon secretion and adiponectin modulation.[4-6] Furthermore, a peripherally-restricted CB1 receptor antagonist does not affect behavioural responses in mice with genetic or diet-induced obesity, but it does cause weight-independent improvements in glucose homeostasis, fatty liver, and plasma lipid profile.[7] These findings confirm a prominent role for peripheral CB1 receptors on the modulation of metabolism and the potential for therapeutic benefit in the absence of CNS-mediated side-effects.[1]

Allosteric modulators are playing an increasingly prominent role in therapeutics, having the advantage of more subtle modulation of receptor activity than intervention at the orthosteric site, the normal binding site for the endogenous ligand Furthermore, the allosteric sites of many receptors offer greater opportunities for selectivity, whereas the orthosteric sites of many receptors and subtypes can be too similar to allow a drug to distinguish between them, as they often must bind the same endogenous ligand.[8] In 2005, the first evidence was published indicating that the cannabinoid CB1 receptor contains an allosteric binding site and compounds such as Org27569 were identified that unexpectedly were allosteric enhancers of agonist binding affinity, but functionally were allosteric inhibitors of agonist signalling efficacy.[9] Related analogues of Org27569[10-14] and the diphenylurea PSNCBAM-1[15] were subsequently found to display similar pharmacological profiles. Org27569 and analogues have been widely studied and photo-activated derivatives of Org27569 have been highly effective for mapping of the CB1 allosteric binding site.[16,17] However, *in vivo* studies using Org27569 gave unexpected results: Org27569 did not modulate agonist-induced catalepsy or nociception,[18,19] though it did antagonize reinstatement of extinguished cocaine and methamphetamine seeking behaviours,[20] and showed conflicting effects on agonist-induced hypothermia.[18,19] Thus, both Gamage *et al.* and Ding *et al.* have been led to conclude that Org27569 does not function as a CB1 NAM *in vivo* and is acting by non-CB1 mediated mechanisms.[18,19]

In view of these unexpected results, it is clear that a wider range of potent tool compounds is required in order to provide more definitive evaluation of the effects of CB1 allosteric modulation and therapeutic potential Our studies focused on bioisosteric replacement of the amide bond in Org27569 (Figure 1) with a sulfonamide, with the expectation of increasing metabolic stability and perhaps giving access to a greater range of structural motifs, and consequently better control of physiochemical properties than is afforded by the limited range of existing compounds: for example, the preparation of highly-polar peripherally-restricted structures.

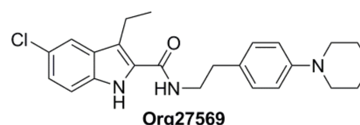
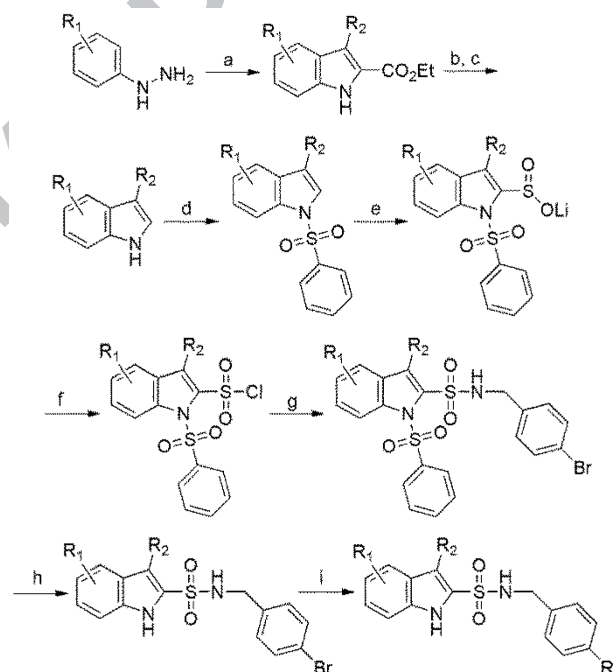


Figure 1. Structure of Org27569

We set about synthesising a range of sulfonamide analogues of Org27569, using the methodology shown in Scheme 1.[21] Substituted indoles were commercially-available or prepared as described previously.[22] The indole products were *N*-protected, deprotonated at the 2-position with *n*-butyllithium in THF, and reacted with sulfur dioxide to give the corresponding lithium sulfinates. Reaction with *N*-chlorosuccinimide in DCM gave the corresponding sulfonyl chlorides, which were subsequently coupled with the amine of choice and *N*-deprotected (to generate compounds **1a** – **1w**, **2a**, **2b**, **2t** and **2u**) or with the required 4-bromobenzylamine, *N*-deprotected, and further Suzuki coupling performed (to give compounds **2c** – **2u** and **2v** – **2z**).



Scheme 1. Synthesis of indole-2-sulfonamides **2a** – **2z**: Reagents and conditions (a) 2-oxovaleric acid PTSA, EtOH (reflux, 20 h); (b) 5% NaOH, EtOH (40 °C, overnight); (c) Cu, quinoline (microwaved for 25 min at 250 °C); (d) NaH, $BzSO_2Cl$, DMF (rt, 18 h); (e) 1.6 M *n*-BuLi, THF, SO_2, (-78 ºC to rt, 2 h); (f) NCS, DCM (0 ºC to rt, 2 h); (g) 4-bromobenzylamine, pyridine, DCM (0 ºC to rt, 18 h); (h) 10 % NaOH, EtOH, (reflux, 2 h); (i) substituted benzeneboronic acid, $(PPh_3)_4Pd$, ethanol, toluene, 2 M Na_2CO_3, (reflux, 3 h).

Initial studies, on compounds closely related to Org27569, suggested that the sulfonamide analogues were around 100-fold less potent than their amide counterparts and had very low metabolic stability, and thus were of limited developmental value (Table 1 and Table 3). However, a breakthough in potency was seen when 4-phenylbenzylamine was used as the side chain, giving compounds **2a** and **2b**, with IC_{50} values of 8 and 2 nM respectively in the PathHunter hCB1 β-Arrestin assay,[12] comparable to that of Org27569 (Figure 2, Tables 1 - 3).

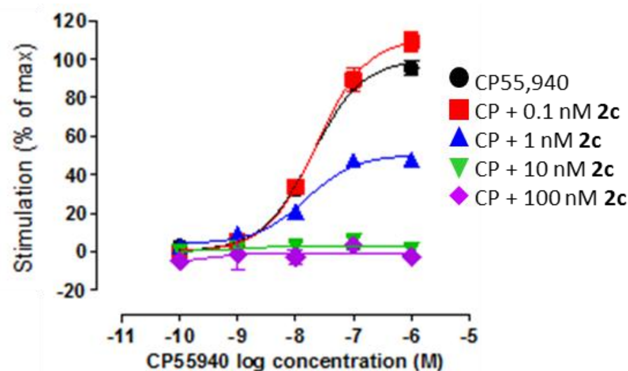
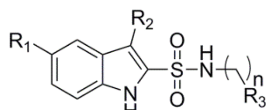


Figure 2. Allosteric modulation by **2c** in PathHunter hCB1 β-Arrestin assay

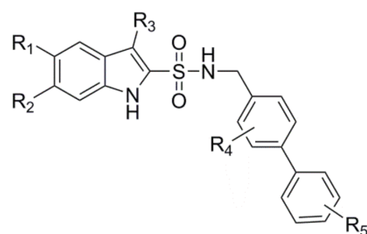


	R_1	R_2	R_3	n	IC_{50}, nM[a]
Org27569					2
1a	Cl	Et	4-(Piperidino)phenyl	2	120
1b	Cl	Et	4-(Dimethylamino)phenyl	2	130
1c	H	Me	4-(Piperidino)phenyl	2	200
1d	H	Me	4-(Dimethylamino)phenyl	2	300
1e	Cl	Et	4-(Morpholino)phenyl	2	500
1f	H	Me	4-(Morpholino)phenyl	2	>1000
1g	H	Me	Phenyl	1	>1000
1h	H	Me	Phenyl	2	>1000
1i	H	Me	4-Methylphenyl	1	200
1j	H	Me	4-Methoxyphenyl	1	200
1k	H	H	4-Methoxyphenyl	1	200
1l	H	Me	4-Chlorophenyl	1	400
1m	OMe	H	4-Methoxyphenyl	1	400
1n	Cl	Me	4-Methoxyphenyl	1	500
1o	H	Me	4-(Trifluoromethyl)phenyl	1	250
1p	H	Me	3-Chlorophenyl	1	800
1q	H	Me	3,4-Dichlorophenyl	1	800
1r	Cl	Et	4-Chlorophenyl	1	>1000
1s	H	Me	2-Pyridyl	1	>1000
1t	H	Me	3-Pyridyl	1	>1000
1u	H	Me	Cyclohexyl	1	>1000
1v	H	Me	*N*-Morpholino	2	>1000
1w	H	Me	*N*-Morpholino	3	>1000

Table 1. Structures and potencies of compounds **1a** – **1w**, [a]Potency in PathHunter™ hCB1 β-Arrestin assay (DiscoveRx, Fremont, USA) performed in triplicate.

Additional substituents could be introduced on the outer phenyl ring by reacting the sulfonyl chloride with 4-bromobenzylamine to give an intermediate that could be coupled with the required benzeneboronic acid by standard Suzuki coupling methods. This was used to give further potent compounds: 4'-fluoro, 4'-methoxy, 4'-dimethylamino and 4'-methyl groups, all with potencies of <5 nM (compounds **2c** – **2f,** Table 2). Modifications to other parts of the structure gave a similarly flat SAR: 6-chloro, 5-bromo, 6-fluoro and 5-methoxyindole derivatives all having very similar potencies (compounds **2g** – **2i** and **2p,** Table 2). The use of indoles bearing more polar substituents, including cyano and substituted amines (e.g. sulfonamides and amides, accessible via the nitroindole), was precluded by the reactivity of these groups to butyllithium under these reaction conditions.

As one of our aims was to make more polar compounds with no loss of potency, this insensitive SAR seemed ideal. However, very polar groups were not tolerated on the outer ring: addition of 4'-carboxy or 3'-carboxamide groups (**2j**, and **2k,** Table 2) gave poorly active compounds. Less polar substituents and arrangements such as 4'-methanesulfonyl, 4'-hydroxymethyl, 4'-hydroxy-3'-methoxy, 4'cyano and 2,4-dimethoxy (**2l** – **2p**), gave smaller losses in potency and demonstrated that some degree of polarity could be introduced here (most notably with a cyano group).



	R_1	R_2	R_3	R_4	R_5	IC_{50}, nM[a]
2a	H	H	Me	H	H	8
2b	H	H	H	H	H	2
2c	H	H	H	H	4-F	1
2d	H	H	H	H	4-OMe	2
2e	H	H	H	H	4-NMe_2	3
2f	H	H	H	H	4-Me	3
2g	Br	H	H	H	H	6
2h	H	F	H	H	H	5
2i	H	Cl	H	H	H	4
2j	H	H	H	H	4-CO_2H	>1000
2k	H	H	H	H	3-$CONH_2$	300
2l	H	H	H	H	4-SO_2Me	15
2m	H	H	H	H	4-OH-3-OMe	33
2n	H	H	H	H	2,4-OMe	22
2o	OMe	H	H	H	4-CH_2OH	112
2p	OMe	H	H	H	4-CN	8
2q	Br	H	H	H	4-F	12
2r	Cl	H	H	H	2,4-FF	4
2s	Cl	H	H	H	4-SO_2Me	15
2t	H	H	CH_2OMe	H	H	10
2u	H	H	CH_2OH	H	H	12
2v	Cl	H	H	2-F	4-F	21
2w	OMe	H	H	2-F	OCF_3	40
2x	Cl	H	H	2-Me	4-F	>1000
2y	Cl	H	H	3-Me	4-F	>1000
2z	H	H	H	(thiophen-3-yl)phenyl		12

Table 2. Structures of compounds and potencies of compounds **2a** – **2z.** [a]Potency in PathHunter™ hCB1 β-Arrestin assay (DiscoveRx, Fremont, USA) performed in triplicate.

Modifications at position-3 of the indole were also investigated. Addition of a hydroxymethyl group at position-3 was considered as a promising means by which polarity might be increased. The expected route to introduction of a hydroxymethyl was via Vilsmeier-Haack formylation of the relevant final compound or its 1-*N*-benzenesulfonyl-protected precursor. However, we were not able to optimise the reaction conditions and either the reaction did not occur or multiple products were obtained. Instead we found it necessary to introduce the hydroxymethyl prior to sulfonylation. This could be achieved from reduction of the indole-3-carboxaldehyde to give the alcohol (see Suppprting Information). The alcohol was protected with a *tert*-butyldimethylsilyl group and scheme 1 followed to give compound **2u**, which showed only a small reduction in potency (IC_{50} = 12 nM). Addition of a methoxymethyl group at position-3 was also a promising means to increase polarity. This could be achieved via the required gramine derivative (indol-3-yl-*N*,*N*-dimethylmethanamine, see Supporting Information). The 3-CH_2NMe_2 group was introduced by a Mannich amination,[23] and then converted into the 3-methoxymethyl derivative by reaction with methyliodide in the presence of sodium methoxide.[24] The 3-methoxymethylindole was then sulfonylated as described in scheme 1, to give compound **2t**, which again showed only a small reduction in potency (IC_{50} = 10 nM). Thus

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the nature of the 3-substituent appeared to have little impact, with H, Me, CH_2OMe and CH_2OH all showing similar potencies (compounds **2a**, **2b**, **2t** and **2u,** Table 2).

Stability studies in human liver microsomes (HLM) gave disappointing results: compounds **2c, 2g** and **2i** were metabolised very rapidly (T½ <15 min, Table 3), apparently by ring oxidation, suggesting that at least two of the aromatic rings needed to be protected. The electron-donating influence of the amine on the inner ring of the biphenyl made it also seem a likely candidate for metabolism. Reduction of electron density on this ring, via addition of electron-withdrawing groups on the adjacent outer ring, was an effective strategy: compounds **2q** and **2r**, bearing two or three strongly electron-withdrawing groups, a 5-bromo or 5-chloro on the indole and a 4'-fluoro or 2',4'-difluoro on the biphenyl, both showed a promising improvement in stability (**2r**: T½ >110 min in the HLM assay).

We also investigated the influence of substitution on the middle ring, both to block metabolism and for its affects on potency. The required bromobenzylamine could be prepared by Suzuki coupling of the substituted 4-bromobenzonitrile with an appropriate benzeneboronic acid, and reduction with lithium aluminium hydride to give the substituted 4-phenylbenzylamine (see Supporting Information), and compounds **2v** – **2y** were prepared. The methyl derivatives **2x** and **2y** showed a reduction in potency (IC_{50} = 1100 and 123 nM respectively), but **2v** and **2w** had reasonable potency (IC_{50} = 21 and 40 nM respectively); the addition of the fluoro group also had the effect of blocking metabolism on the middle ring and compound **2v** was stable in the HLM assay (T½ >140 min), either by blocking the site of metabolism or reducing electron density to make the ring less susceptible to metabolism. Replacement of the 5-chloro with a 5-methoxy, in an effort to increase polarity, gave compounds with reduced metabolic stability (**2p** and **2w**). Replacement of the outer phenyl with a 3-thiophene, a common bioisteric replacement, gave only a small loss of potency (compound **2z**).

Further modifications were made to the structure, including addition of an α-methyl onto the benzylamine side chain and changing the connectivity of the biphenylamine (compounds **3** and **4** respectively, Figure 3), using commercially-available α-methyl-4-bromobenzylamine and 3-bromobenzylamine respectively; both additions gave reductions in potency (IC_{50} = 41 and 137 nM respectively).

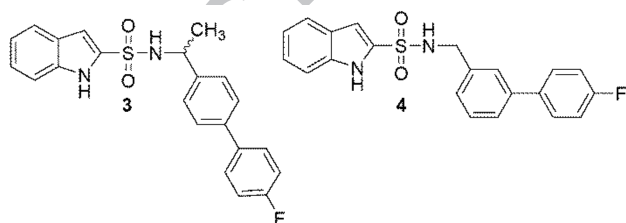

Figure 3. Structures of compounds **3** and **4**

Derivatives bearing an outer-ring pyridine (Figure 4) could be prepared by the same methodology as shown in scheme 1 followed by Suzuki coupling of the 4-bromobenzyl intermediate with a suitable pyridylboronic acid as the final step. The unsubstitued 3-pyridyl derivative (**5a**) was found to be very unstable in the HLM assay, and we sought to place a 2-fluoro group (**5b** and **5c**) or a 2,6-difluoro group (**5e**) on the pyridine to block metabolism. All of the compounds showed excellent potency (IC_{50} <10 nM) but only **5e** showed acceptable metabolic stability. Attempts to increase polarity by introduction of an amino group (**5f**) gave a reduction in potency to 85 nM.

	IC_{50}, nM[a]	HLM $T_{1/2(min)}$[b]	RLM $T_{1/2(min)}$[b]	Permeability $P_{app}(cm^{-6}/s)$[c]	TPSA (A^2)	Brain : Blood
Org27569	2	32	28	1.23	44	1.1[19]
1a	120	14	-	-	-	-
1d	300	13	-	-	-	-
1e	500	10	-	-	-	-
1h	200	3	-	-	-	-
1i	200	7	-	-	-	-
1k	400	2	-	-	-	-
2c	1	-	<15	-	58	-
2g	6	-	<15	-	58	-
2i	4	-	<15	-	58	-
2j	>1000	-	-	-	96	-
2k	300	-	-	-	101	-
2p	8	-	26	-	91	-
2q	12	-	130	-	58	-
2r	4	111	84	-	58	-
2s	15	41	36	-	92	-
2v	21	146	112	-	78	-
2w	40	-	<15	-	58	-
5a	7	-	<15	-	71	-
5b	3	<15	<15	-	80	-
5c	5	22	23	-	71	2.7[d]
5d	10	-	-	-	80	-
5e	4	39	48	141	71	0.8[d]
5f	85	-	-	-	97	-
6a	9	-	25	-	71	-
6b	4	53	33	-	71	-
6c	3	56	32	53.8	71	3.3[d]

Table 3. *In vitro* potency, pharmacokinetic and physiocochemical properties of selected compounds, [a]Potency in PathHunter™ β-Arrestin assay (DiscoveRx, Fremont, USA) performed in triplicate, [b]human and rat liver microsomal stability assays conducted by Cyprotex Ltd and performed in triplicate, [c]PAMPA assay conducted by Cyprotex Ltd and performed in triplicate. [d]Brain penetration studies conducted by the Dundee Drug Discovery Unit, in female NMRI mouse and performed in triplicate and samples taken at ~T_{max} (T = 2 h for **5c** and **6c**; 4 h for **5e**).

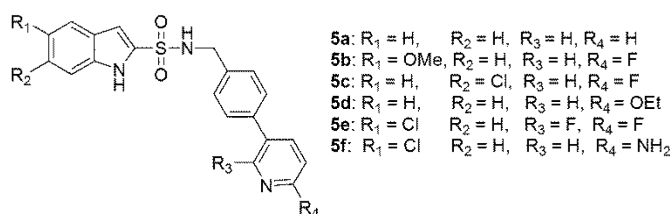

Figure 4. Structures of compounds **5a** – **5f**

Compounds with a pyridyl middle ring (Figure 5) could be prepared by Suzuki coupling of 5-bromo-2-pyridinecarbonitrile with the appropriate benzeneboronic acid and subsequent reduction with $LiAlH_4$ at low temperatures. The resultant (5-(phenyl)pyridin-2-yl)methanamine could be coupled with the indole-2-sulfonyl choride in THF in the presence of a stoichiometric quantity of DMAP (see Supporting Information). Compound **6a** was prepared by this method and found to be highly potent (IC_{50} = 9 nM); however it showed only modest stability in mouse liver microsomes (T½ = 25 min). As the 2,4-difluorophenyl had previously been found to stabilise a middle-ring phenyl (**2r**), it was hoped that it might also stabilise a middle-ring pyridyl, and compounds **6b** and **6c** were prepared. These were found to be highly potent (IC_{50} = 4 and 3 nM respectively), to have good stability in human liver microsomes (T½ = 53 and 56 min respectively) and reasonable stability in rat liver microsomes (T½ = 33 and 32 min respectively).

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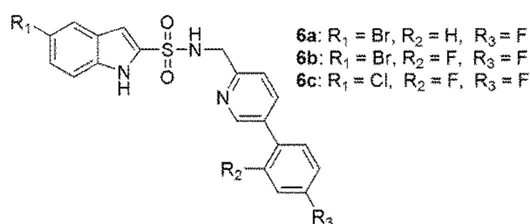

Figure 5. Structures of compounds **6a – 6c** bearing a middle ring pyridine

Table 3 demonstrates that it is possible to generate derivatives with fairly high TPSA with no loss of potency. Compounds **2p** and **2s** both have TPSA of >90 Å^2, which is above the threshold for passive CNS penetration suggested in most studies.[25] However, it was not possible to achieve significantly higher TPSA while retaining stability and potency. Unexpectedly, whilst compounds **5e** and **6c** both have significantly higher TPSA than Org27569, the also have a much higher *in vitro* permeability than Org27569 (Table 3), whilst at the same time retaining similar *in vivo* brain penetration. In spite of predicted low permeability, and anticipated poor stability caused by the central amide group, Org27569 has in fact been shown to have both excellent brain penetration and stability.[19] It is not understood as to why there is little or no *in vitro* : *in vivo* correlation in this case. Thus, for these compounds it is not clear that we will be able to predict or achieve peripheral restriction.

Having the best balance of properties, compounds **5e** (ABD1085[26]) and **6c** (ABD1075[26]) were selected for further PK evaluation. Both compounds showed acceptable mouse oral exposure and *in vivo* stability (10 mg/kg oral, female NMRI, N = 3). **5e**: Blood C_{max} = 672 ng/mL, T_{max} = 4 h, T½ = 7.9 h AUC_{0-8} = 263 µg/mL*min. **6c**: Blood C_{max} = 848 ng/mL, T_{max} = 1 h, T½ = 3 h, AUC_{0-8} =282 µg/mL*min.

In conclusion, we have demonstrated a novel class of highly potent CB1 negative allosteric modulators with excellent metabolic stability and membrane permeability. These show a wide scope for variation of physicochemical parameters whilst retaining potency. Thus, these may provide highly-versatile tools for investigating the therapeutic potential of the cannabinoid system.

Acknowledgments

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