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Pyridine-3-carboxamides as novel CB_2 agonists for analgesia

William L. Mitchell *, Gerard M. P. Giblin, Alan Naylor, Andrew J. Eatherton, Brian P. Slingsby, Anthony D. Rawlings, Karamjit S. Jandu, Carl P. Haslam, Andrew J. Brown, Paul Goldsmith, Nick M. Clayton, Alex W. Wilson, Iain P. Chessell, Richard H. Green, Andrew R. Whittington, Ian D. Wall

GlaxoSmithKline PLC, Neurosciences Centre of Excellence for Drug Discovery, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

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4-Cyclopropyl-6-[(2,4-dichlorophenyl)amino]-*N*-[(tetrahydro-2H-pyran-4-yl)methyl]-3-pyridinecarboxamide

ABSTRACT

We describe herein the medicinal chemistry approach which led to the discovery of a novel pyridine-3-carboxamide series of CB_2 receptor agonists. The SAR of this new template was evaluated and culminated in the identification of analogue **14a** which demonstrated efficacy in an in vivo model of inflammatory pain.

Cannabis sativa has been used as an analgesic as early as 2800 BC in China.[1] Cannabinoids are the pharmacologically[2] active components of cannabis, and are known to mediate some of their actions through the cannabinoid receptors[3] CB_1 and CB_2, both of which are G-protein coupled receptors. The CB_1 receptor is found in the central nervous system (CNS),[4] as well as in the periphery,[5] whereas the CB_2 receptor is found mainly in the periphery,[6] particularly in the immune system.[7] There is also increasing recent evidence of CB_2 receptor expression in the CNS.[8] Whilst stimulation of the CB_1 receptor mediates analgesia,[9] this receptor also mediates other undesirable CNS side-effects.[10] CB_2 agonists, on the other hand, have shown efficacy in preclinical models of inflammatory and neuropathic pain.[11]

We have therefore sought to design selective CB_2 agonists to avoid the undesirable psychoactive effects and abuse potential associated with agonism of the CB_1 receptor. Recently our research into a novel class of selective CB_2 agonists culminated in the discovery of **1** (GW842166X, Fig. 1),[12] which has entered human clinical studies for the treatment of pain. In this letter we describe our attempts to de-

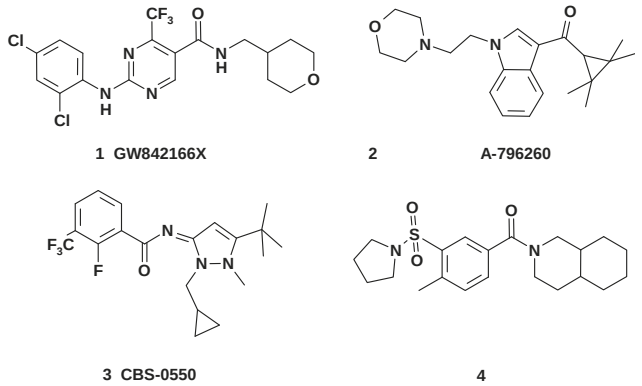

Figure 1. Recent lead CB_2 agonists.

* Corresponding author. Tel.: +44 7791634273.
E-mail address: bill.mitchell777@tiscali.co.uk (W.L. Mitchell).

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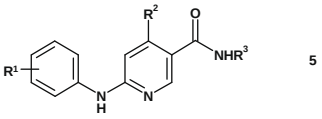
sign a new series of selective CB_2 agonists with improved aqueous solubility over GW842166X (solubility at pH 7.4 is 2 μg/mL).

Interest in selective CB_2 agonists has been growing, and, in addition to **1**, a number of other groups have reported novel selective CB_2 agonists. Abbott[13] have disclosed the morpholine **2**, A-796260, whilst Taisho[14] have revealed their lead compound, an iminopyrazole **3**, CBS-0550, and Boehringer Ingelheim-Evotec[15] have published a novel series of selective CB_2 agonists, exemplified by the sulphonamide **4**.

Following the identification of **1** as a clinical candidate, we began to look for a CB_2 agonist back-up candidate with improved aqueous solubility over **1**. As part of this programme, we investigated replacing the central pyrimidine core with a pyridine core, since the basic pK_a of pyridines (5.2) is higher[16] than pyrimidines (1.3), and molecular overlays suggested good alignment[17] of key features of the pyridine **5** with **1**. In the current research presented here, we describe the structure–activity-relationships (SAR), the pharmacokinetics, and efficacy in a pain model of these novel pyridine CB_2 agonists.



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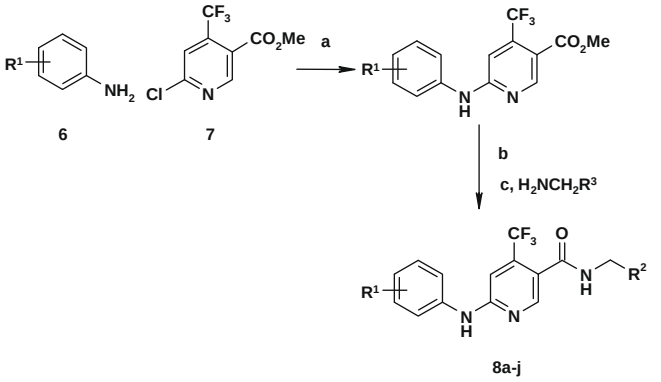
Initially we chose to prepare the 4-(trifluoromethyl)pyridines **8a–j**, which retained the 4-(trifluoromethyl)-substituent, so that the direct effects of changing the pyrimidine core to a pyridine core could be compared with our earlier SAR evaluation which led to the discovery of **1**. Condensation[18] of the anilines **6** with the chloropyridine **7**, followed by hydrolysis and amide formation gave the final products **8a–j** (Scheme 1).

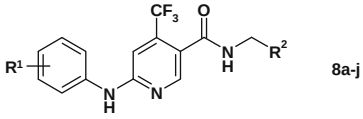
All but one (**8j**) of the analogues **8a–j** were found to be CB_2 agonists with an efficacy not significantly different from the reference CB_2 agonist HU210 (Table 1—the assay for CB_2 was run using a yeast CB_2 reporter assay in yeast cells, *Saccharomyces cerevisiae*, expressing the human CB_2 receptor[18]). Initially the amide nitrogen substituent was kept fixed as a (4-tetrahydropyranyl)methyl group, **8a–e**, whilst the aniline substituent R^1 was varied. This revealed that a 2,4-dichloro-substituent, as in **8a,** was optimal for CB_2 potency. However, variation of the amide N-substituent was well tolerated and other cycloalkyl groups, **8f–h**, gave CB_2 agonists of comparable potency and efficacy to the tetrahydropyranyl group. Indeed, the cyclohexyl group improved CB_2 potency, (**8h** cf **8b**). A 4-fluorobenzyl group **8i** was similarly tolerated on the amide nitrogen, but the 4-carboxamidobenzyl group in **8j** was not.

All of the analogues showed selectivity over CB_1 with a pEC_{50} of less than 5.5 and/or an efficacy of less than 10% at CB_1.



Scheme 1. Reagents and conditions: (a) Neat, 120 °C; (b) KOH, H_2O, reflux; (c) EDC, HOBT or HATU, PS-carbodiimide, HOBT or PS-diisopropylethylamine, 1-butyl-3-methylimidazolium hexafluorophosphate.

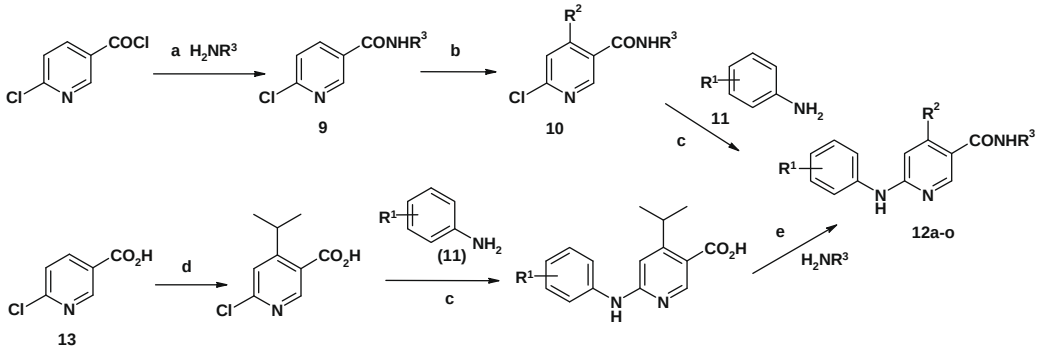
Table 1
CB_2 Agonist potencies[18] and efficacies for compounds (**8a**–**j**).



Compound	R^1	R^2	pEC_{50}[a]	SD[b]	*E* %[c]
8a	2,4-di-Cl	4-Tetrahydropyranyl	7.3	0.3	100
8b	3-Cl	4-Tetrahydropyranyl	6.6	0.3	95
8c	3-F	4-Tetrahydropyranyl	6.0	0.1	90
8d	4-Cl,2-dMe	4-Tetrahydropyranyl	6.6	0.1	94
8e	2-MeO,5-Cl	4-Tetrahydropyranyl	6.4	0.2	89
8f	2-MeO,5-Cl	Cyclobutyl	6.7	0.05	87
8g	2,4-di-Cl	Cyclopentyl	7.0	0.2	86
8h	3-Cl	Cyclohexyl	7.5	0.3	84
8i	3-Br	4-Fluorophenyl	7.1	0.05	84
8j	3-Cl	4-H_2NCO-Phenyl	5.8	0.1	10

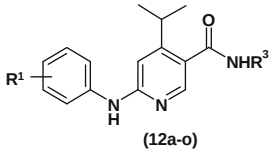
[a] CB_2 assay data is the mean of at least two determinations, see Ref. 18 for the method, HU210 had pEC_{50} 8.6 SD 0.2 and was used as a reference.
[b] Standard deviation.
[c] Efficacy (*E*) is expressed as a percentage relative to the efficacy of HU210 (an unselective CB_1/CB_2 agonist. All analogues show little or no activity at the human CB_1 receptor, that is, CB_1 pEC_{50} < 5.5 and/or *E* < 10% (data not shown).

The aqueous solubility[19] of the 4-(trifluoromethyl)pyridines **8a-j** was investigated, but it was not improved compared to **1**: for example, **8a** has a solubility of <1 μg/ml at pH 7.4. We therefore sought to improve the solubility by synthesizing[18] the 4-(isopropyl)pyridines **12a–o** (R^2 = ^{i}Pr, Scheme 2, Table 2), as the pK_a of 4-(isopropyl)pyridine[20] is 6.02 compared to the pK_a of 2.63 for 4-(trifluoromethyl)pyridine.[21]



Scheme 2. Reagents and conditions: (a) Et_3N, 0 °C; (b) R^2MgBr, 0 °C → rt, then DDQ.; (c) microwave 150–180 °C or microwave, MsOH, 180 °C; (d) ^{i}PrMgBr, 0 °C → rt, then $Mn(OAc)_3$ −60 °C → rt; microwave, 120 °C; (e) EDC, HOBT.

Table 2
CB_2 agonist potencies[18] and efficacies for compounds **12a–o**



(12a-o)

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Compound	R^1	R^{3a}	pEC_{50}[b]	SD[b]	E %[b]
12a	3-Cl	(4-THP)methyl–	6.9	0.15	101
12b	3-Br	(4-THP)methyl–	7.2	0.1	105
12c	3-MeO–	(4-THP)methyl–	6.4	0.1	82
12d	3-Me–	(4-THP)methyl–	6.3	0.2	88
12e	3-NC–	(4-THP)methyl–	6.4	0.1	100
12f	2,4-di-Cl–	(4-THP)methyl–	7.3	0.04	80
12g	3-Cl, 4-NC–	(4-THP)methyl–	7.1	0.15	75
12h	2-F,3-CF_3–	(4-THP)methyl–	7.2	0.1	98
12i	3-Cl	Cyclopentylmethyl–	7.4	0.15	105
12j	3-Me	Cyclobutylmethyl–	7.3	0.2	87
12k	3-Cl	4-Fluorobenzyl–	7.0	0.1	89
12l	3-Cl	4-THP–	6.3	0.2	85
12m	3-Cl	^{i}PrCH$_2$–	7.4	0.1	121
12n	3-Cl	^{t}BuCH$_2$–	6.6	0.4	97
12o	3-Cl	Et_2CHCH_2–	6.4	0.25	86

[a] THP, tetrahydropyranyl.
[b] See footnotes in Table 1 for definition of these terms. All analogues show little or no activity at the human CB1 receptor, that is, CB_1 pEC_{50} < 5.5 and/or $E \leqslant 7\%$ (data not shown).

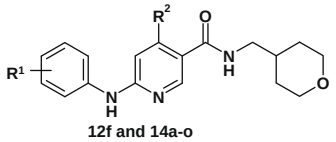
The 4-(isopropyl)pyridines **12a–o** (R^2 = ^{i}Pr) were prepared[18] by addition of a Grignard reagent to the pyridinecarboxamide **9**, followed by reaction of **10** with an aniline **11**. Alternatively, addition of isopropylmagnesium chloride to the nicotinic acid **13**, followed by reaction with an aniline **11**, and standard amide formation also gave the desired 4-(isopropyl)pyridines **12a–o** (R^2 = ^{i}Pr).

The in vitro data (Table 2) showed that these 4-isopropylpyridines **12a–o** were potent CB_2 agonists with an efficacy not significantly different from the reference CB_2 agonist HU210. Exploration of the aniline substituent R^1 to investigate the electronic requirements showed that the optimal 3-substituent for CB_2 potency was a halogen, either chlorine or bromine **12a**,**b**. However, di-substitution was tolerated, **12f–h**, and yielded analogues of similar potency to **12a**. Modification of the amide N-substituent showed that the cyclobutyl ring increased the CB_2 potency, **12j** cf **12d**, and that a number of other rings, but not all (e.g., **12l**), were tolerated **12i–k.** The isobutyl group gave a potent CB_2 agonist, **12m,** with a supramaximal response. Other *N*-alkyl substituents were less potent **12n**,**o**. All analogues in this series were selective over CB_1, with CB_1 $pEC_{50} \leqslant 5.5$ and/or an efficacy of <7%.

However, the solubility of the 4-(isopropyl)pyridine series, despite a small improvement, was still unacceptably low, for example, **12f** has a solubility of 5 μg/mL at pH 7.4. In addition, preliminary in vitro rat clearance[22] for many of the more potent analogues, where measured, was also unacceptably high (e.g., for **12b,f,i,m**, rat CLi >5 mL m^{-1} g^{-1} liver), and so further optimization was undertaken.

Our attention turned to investigate the SAR of the 4-substituent, that is, R^2, (Table 3). Analogues with an R^2 cycloalkyl group **14a,b** were prepared[23] by the routes previously used (Scheme 2), however, the introduction of a 4-(2-hydroxyprop-2-yl)-group or a 4-(*tert*-butyl) group required new syntheses (Scheme 3). Ortholithiation of the acid **13**, followed by treatment with acetone gave the lactone **15**. Displacement of the chlorine with an aniline gave the precursor **16**. Reaction[23] of **16** with an amine using the conditions described by Weinreb,[24] effected ring opening to give the 4-(2-hydroxyprop-2-yl)-analogue **14c**. The isopropyl intermediate **17**, (prepared by the routes shown in Scheme 2) was alkylated[25a] to give the *tert*-butylpyridine **18**, and this converted by the usual methods into the final *tert*-butyl analogue **14d**.

Table 3
CB_2 potencies, in vitro and in vivo pharmacokinetics, and aqueous solubility



12f and 14a-o

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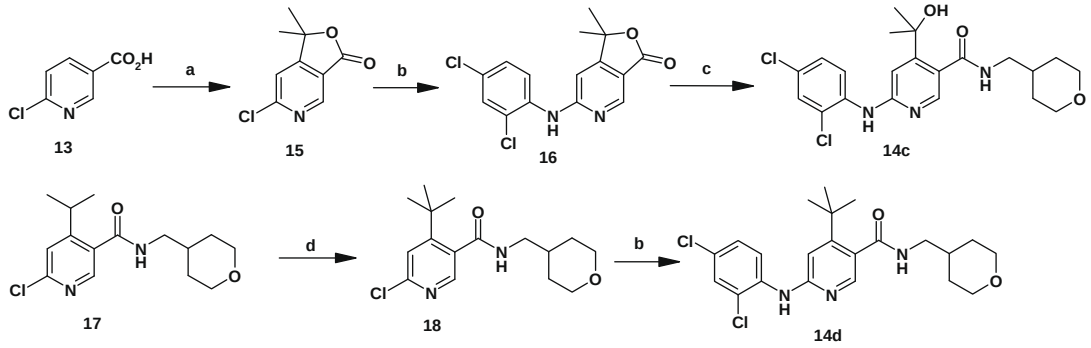
Compound	R^1	R^2	CB_2			rCLi[b]	hCLi[b]	CYP450 IC_{50} (μM)					AUC	Solubility
			pEC_{50} [a]	SD[a]	E%[a]			1A2	2C9	2C19	2D6	3A4	$(0-t)$/dose (min kg/L)[c]	μg/mL at pH 7.4
12f	2,4-dichloro	^{i}Pr	7.3	0.04	80	7.6	4.0	60	40	43	28	58	nd	5
14a	2,4-dichloro	Cyclopropyl	7.1	0.2	90	4.3	1.7	nd	43	82[e]	55	>100	15	7
14b	2,4-dichloro	Cyclopentyl	6.8	0.1	61	nd	nd	nd	nd	nd	nd	nd	nd	<1
14c	2,4-dichloro	$-C(OH)Me_2$	5.9	0.05	79	nd	nd	nd	nd	nd	nd	nd	nd	150
14d	2,4-dichloro	^{t}Bu	7.9	0.1	100	2.3	<0.5	22	17	28	>100	64	16	23
14e	3-Cl	Cyclopropyl	6.8	0.1	82	nd	nd	nd	nd	nd	nd	nd	nd	91
14f	3-Br	Cyclopropyl	6.7	0.1	93	1.6	<0.5	23	24	29	16	>100[e]	5	45
14g	3-CF_3	Cyclopropyl	6.7	0.3	76	nd	nd	nd	nd	nd	nd	nd	nd	19
14h	3-OCF_3	Cyclopropyl	6.6	0.1	87	3.5	1.0	NT	16	65	24	57[d]	3	<1
14i	3-NC	Cyclopropyl	6.1	0.2	78	nd	nd	nd	nd	nd	nd	nd	nd	4
14j	3-MeO	Cyclopropyl	5.7	0.3	65	nd	nd	nd	nd	nd	nd	nd	nd	168
14k	3-Me	Cyclopropyl	5.8	0.2	76	nd	nd	nd	nd	nd	nd	nd	nd	26
14l	3-F	Cyclopropyl	5.6	0.1	87	nd	nd	nd	nd	nd	nd	nd	nd	125
14m	2,5-dichloro	Cyclopropyl	6.4	0.1	92	12.0	2.4	53	27	49	42	>100	nd	12
14n	3,4-dichloro	Cyclopropyl	6.8	0.1	70	nd	nd	nd	nd	nd	nd	nd	nd	6
14o	3,5-dichloro	Cyclopropyl	7.2	0.4	57	nd	nd	nd	nd	nd	nd	nd	nd	7

[a] See footnotes in Table 1 for definition of these terms. All analogues show little or no activity at the human CB_1 receptor, that is, CB_1 pEC_{50} < 5.5 and/or $E \leqslant 5\%$ (data not shown).
[b] In vitro clearance, mL min^{-1} g^{-1} liver; r, rat; h, human; see Ref. 22 for procedures.
[c] Administered to rats as a suspension in aqueous 1% methylcellulose.
[d] Interference in the assay. nd, not determined.



Scheme 3. Reagents and conditions: (a) LiTMP, −55 °C, then Me_2CO, −71 °C → rt; (b) 2,4-dichloroaniline, MsOH, microwave, 180 °C; (c) (4-THP)methylamine (5 equiv), Me_3Al (5 equiv), CH_2Cl_2, 40 °C; (d) *n*-BuLi (2 equiv) −65 °C, MeI.

Modification of the R^2 substituent had a significant effect on the CB_2 potency of these analogues (Table 3). A cyclopropyl group in **14a** maintained the same level of CB_2 potency as an isopropyl group in **12f**, and the *tert*-butyl group in **14d** increased CB_2 potency. However, the cyclopentyl group in **14b** reduced CB_2 efficacy and the (2-hydroxyprop-2-yl) group in **14c** reduced CB_2 potency.

Following preliminary in vitro pharmacokinetic analysis, we noticed that the rat in vitro clearance[22] for the cyclopropylpyridine **14a** was significantly lower than that of the isopropylpyridine **12f**. A final round of optimization of this 4-(cyclopropyl)pyridine sub-series was therefore undertaken prior to evaluation in vivo to ensure the best chance of a compound with high oral bioavailability and also activity in vivo.

Further 4-(cyclopropyl)pyridine analogues **14e–o** (Table 3) were prepared[25b] as shown in Scheme 2. Amongst the substituents investigated at the 3-position of the aniline, the halogen containing substituents appeared to give the more potent analogues **14e–h** but 2,4- and 3,5-dichloro-substitution, gave the most potent CB_2 agonists **14a**,**o**.

The solubility data for this series revealed that two of the oxygen-containing analogues, **14c** and **14j**, as expected, had the greatest aqueous solubility at pH 7.4. Some of the less lipophilic analogues, for example, **14l**, also had improved solubility. However these three analogues also had weaker CB_2 potency and were thus not progressed any further.

The in vitro clearance and inhibition of cytochrome P450 for 4-(cyclopropyl)pyridines with CB_2 $pEC_{50} \geqslant 6.4$ and $E > 85\%$ was further assessed to prioritise them for in vivo pharmacokinetic analysis. Gratifyingly, a number of these, **14a,d,f,h,** appeared to have low in vitro clearance in both rat and human microsomes, combined with no significant P450 interactions.

These four analogues were next evaluated in a pharmacokinetic study in conscious rats, to assess their exposure in the blood up to 6 h after an oral dose of 3 mg/kg. Two of these, **14a,d**, had good oral exposure [as expressed by dose normalised area under the curve, $(AUC(0-t)/dose)$] despite having low aqueous solubility.

Since **14a** showed no activity at CB_1 at concentrations up to 30 μM (cf **14d**[26]), further pharmacokinetic studies were undertaken. In conscious rats, following an oral dose of 3 mg/kg of **14a**, the bioavailability was 39%, whilst an iv dose of 1 mg/kg of **14a** produced a clearance of 14 mL/min/kg, a volume of distribution of 2.4 L/kg, and a half life of 3.1 h.

14a has high in vitro CB_2 potency and efficacy, with excellent selectivity over CB_1, and good in vitro and in vivo pharmacokinetic properties. Despite its low aqueous solubility, it was selected for further evaluation in an in vivo model to give encouragement for further research around this template in the future. In the established Complete Freund's Adjuvant (CFA) model of inflammatory pain[27], **14a** has high potency with an oral ED_{50} of 0.07 mg/kg po,

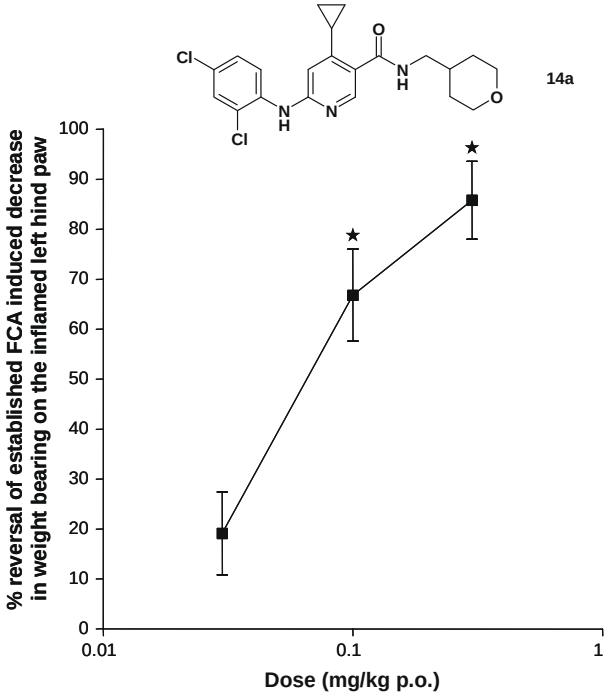


Figure 2. CFA model of inflammatory pain.

and shows full reversal of hyperalgesia at a dose of 0.3 mg/kg po as determined by the weight bearing protocol (Fig. 2).

In conclusion, a novel series of potent, selective pyridine-3-carboxamide CB_2 agonists has been discovered. One of these, **14a**, has good oral bioavailability, low clearance, and potent oral activity in the CFA model of inflammatory pain. Whilst some pyridine analogues have improved aqueous solubility, the lower solubility of **14a** is not a barrier to good oral bioavailability and oral activity in the CFA model of inflammatory pain.

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