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Synthesis and Evaluation of Various Heteroaromatic Benzamides as Analogues of –Ylidene-Benzamide Cannabinoid Type 2 Receptor Agonists

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The authors declare no competing financial interest

Abstract

The CB_2 receptor is an attractive target for the treatment of a wide range of diseases and pathological conditions. Compounds that selectively activate the CB_2 receptor are desirable as this avoids CB_1-mediated psychoactive effects. Heteroarylidene-benzamides have demonstrated efficacy as selective CB_2 receptor agonists. We aimed to expand the structure-activity relationship studies of this series of compounds by investigating the heteroaromatic core via the synthesis and *in vitro* evaluation of a small library of various heteroaromatic benzamide analogues. As heteroaromatic amides are privileged scaffolds in drug design, methods to synthesise them are of interest. Concise and reliable synthetic strategies were developed to access these novel analogues. The –ylidene-benzamide moiety is shown to be essential for CB activity as all amide derivatives exhibit no functional activity at either CB_2 or CB_1 receptors.

Keywords: Cannabinoid receptor, CB_2, heterocyclic chemistry, synthesis.

Introduction

Since the identification of the cannabinoid (CB) receptors and their endogenous ligands, there has been great interest in the endocannabinoid system and its regulatory functions in health and disease. The cannabinoid type 1 (CB_1) receptor is found in high levels in the central nervous system, but also in a number of peripheral tissues, while the cannabinoid type 2 (CB_2) receptor is expressed primarily on cells of the immune system such as astrocytes and microglia.[1] The CB_2 receptor has become a promising target for a number of diseases that contain an inflammatory component.[2] One of the caveats of cannabinoid-based drug design is that activation of the CB_1 receptor results in undesirable psychoactive effects. Therefore there is a need to develop compounds that selectively activate the CB_2 receptor to avoid CB_1 mediated side effects. There have been a number of potent and selective CB_2 receptor agonists developed by academic laboratories and pharmaceutical companies.[3] Despite this, no drugs that target the CB_2 receptor have progressed through clinical trials and there is still an unmet need to develop novel CB_2 receptor agonists.[4]

A class of compounds originally developed by Taisho Pharmaceuticals Co. Ltd.[5-6] and then Abbott Laboratories[7-8] are heteroarylidene-benzamide derivatives such as **1**. These compounds are potent agonists of the CB_2 receptor and generally exhibit no measureable activity at the CB_1 receptor. Extensive structure-activity relationship studies (SARs) of the pendant groups are summarised in **Figure 1**, **A**.[8] We aimed to expand on the minimal SAR focused on the core of this class of compounds by modifying the heteroaromatic unit. As the –ylidene-benzamide moiety is only applicable to certain heterocycles we decided to explore isosteric amides. In light of results from previous SAR studies,[8-9] simplified pendent groups (achiral tetrahydropyran and 4-trifluoromethylbenzamide) were also chosen (**Figure 1**, **B**). The study aimed to investigate the number, position and identity of heteroatoms as well as the size of the aromatic ring. Synthetic strategies have been developed to access these compounds, many of which do not have reliable established syntheses, and their *in vitro* activity at the cannabinoid receptors evaluated.

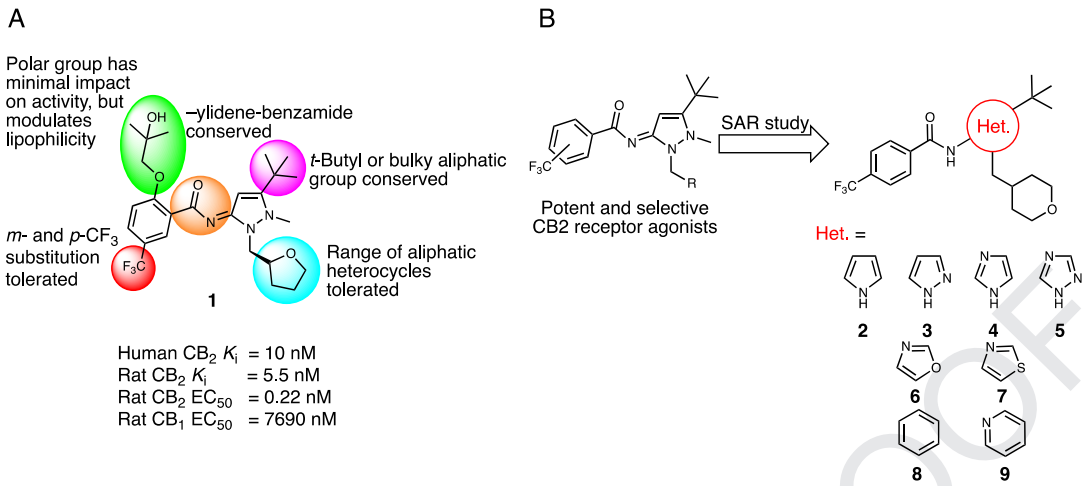
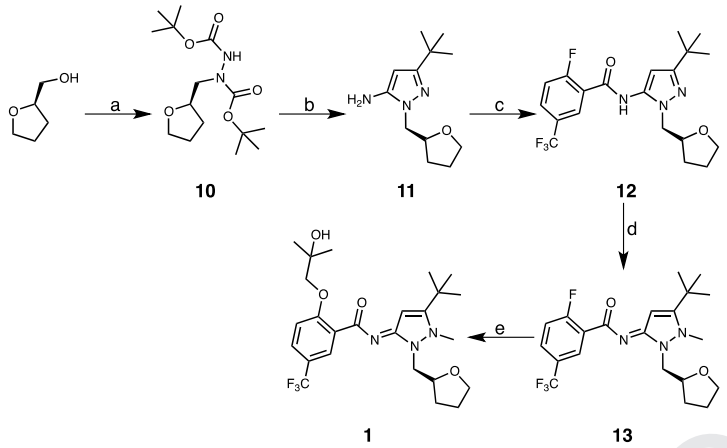


Figure 1: (A) Summary of SAR of heteroarylidene-benzamide derivatives such as **1**; (B) Strategy to explore the heterocyclic core of known heteroarylidene-benzamide agonists (**2**-**9**).

Results and Discussion

Synthesis Heteroaromatic Amides

The synthesis of lead compound **1** followed modified procedures reported by Carroll and co-workers (**Scheme 1**).[8] Starting with commercially available chiral alcohol, (*R*)-(tetrahydrofuran-2-yl)methanol, a Mitsunobu reaction using di-Boc protected hydrazine as the nucleophile afforded the requisite protected monosubstituted hydrazine **10**. Deprotection under acidic conditions followed by condensation with 4,4-dimethyl-3-oxopentanenitrile yielded amino-pyrazole **11**. Amide coupling via the requisite acid chloride and methylation under neutral conditions using methyl triflate afforded pyrazolylidene-benzamide derivative **13**. Finally, a nucleophilic aromatic substitution reaction provided the lead compound **1** in good overall yield.

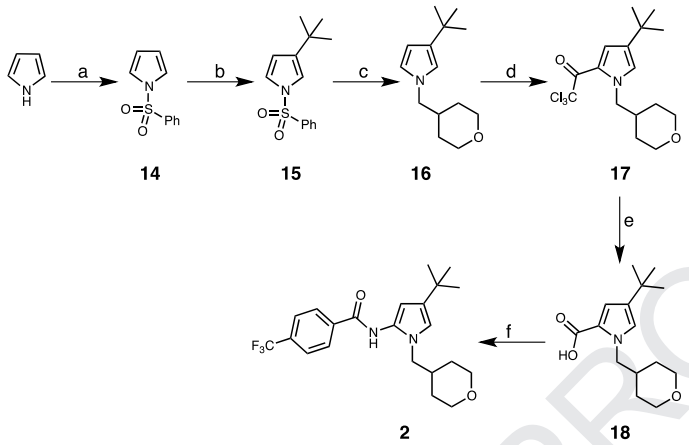


Scheme 1: Synthesis of lead compound **1**. *Reagents and conditions*: (a) Di-*tert*-butyl hydrazine-1,2-dicarboxylate, PPh_3, di-*tert*-butyl azodicarboxylate, THF, 0 °C-rt, 16 h, 72%; (b) i) HCl, dioxane, rt, 16 h, ii) 4,4-dimethyl-3-oxopentanenitrile, EtOH, reflux, 4 h, 75%; (c) i) 2-Fluoro-5-(trifluoromethyl)benzoic acid, oxalyl chloride, DMF, CH_2Cl_2, rt, 3 h, ii) $(i\text{Pr})_2\text{EtN}$, CH_2Cl_2, rt, 4 h, 67%; (d) MeOTf, MePh, 100 °C, 16 h, 72%; (e) 2-Methylpropane-1,2-diol, KO*t*Bu, 0 °C-rt, 2 h, 60%.

The synthesis of the heteroaromatic amide derivatives (**2-9**) was achieved via two main approaches: either direct synthesis of the requisite amino-heterocycle followed by amide coupling, or synthesis of the corresponding carboxylic acid followed by a Curtius rearrangement and quenching of the isocyanate with an aryl Grignard reagent to afford the desired heteroaromatic benzamides.

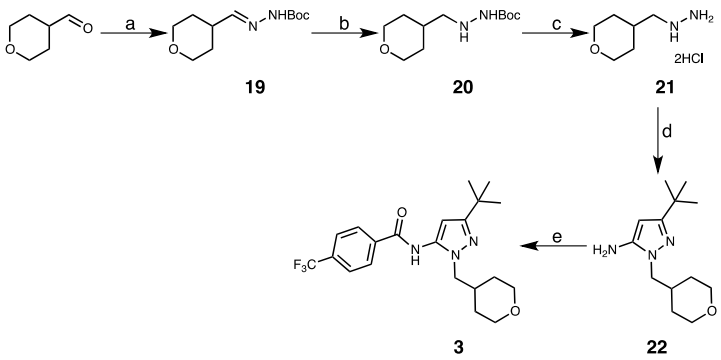
Pyrroles are notoriously capricious heterocycles and are prone to undergo degradation under a variety of conditions. The presence of an electron-donating group on an already electron-rich nucleus makes 2-aminopyrroles unstable unless the ring is substituted with electron withdrawing groups.[10] The known instability of electron-rich pyrroles meant that access to the requisite 2-aminopyrrole was not possible. An alternative approach was taken whereby a Curtius rearrangement of a stable pyrrole-2-carboxylic acid precursor could afford the challenging molecular synthon. Protection of freshly distilled pyrrole with a benzene sulfonyl group allowed regioselective aluminium chloride mediated Friedel-Crafts alkylation to install the *tert*-butyl group at the 3-positon (**Scheme 2**).[11] Removal of the protecting group using magnesium under ultrasonic irradiation,[12] followed by alkylation with tetrahydro-2*H*-pyran-4-yl)methyl tosylate afforded *N*-alkylpyrrole **16**. Reaction with trichloroacetyl chloride followed by hydrolysis under basic conditions gave the 2-substituted carboxylic acid **18**. The amide was formed via a Curtius rearrangement using a three-step procedure. Formation of the acyl azide with diphenylphosphoryl azide followed

by heating at 90 °C for 1.5 hours gave clean conversion to the corresponding isocyanate. The isocyanate was quenched with 4-trifluoromethylmagnesium chloride to afford the desired amide **2** in moderate yield (45% over 3 steps).



Scheme 2: Synthesis of pyrrole derivative **2**. *Reagents and conditions*: (a) Bu_4NHSO_4, benzene sulfonyl chloride, NaOH (aq.), CH_2Cl_2, rt, 24 h, 99%; (b) *t*-BuCl, $AlCl_3$, CH_2Cl_2, rt, 2 h, 81%; (c) i) Mg, NH_4Cl, MeOH, 1 h, ii) NaH, Bu_4NBr, tetrahydro-*2H*-pyran-4-yl)methyl tosylate, DMF, 0-50 °C, 16 h, 52%; (d) Trichloroacetyl chloride, pyridine, THF, rt, 6 h, 97%; (e) NaOH (aq.), MeOH, reflux, 16 h, 92%; (f) i) DPPA, Et_3N, CH_2Cl_2, rt, 16 h, ii) MePh, 90 °C, 1.5 h, iii) (4-(Trifluoromethyl)phenyl)magnesium chloride, 0 °C-rt, 1 h, 45%.

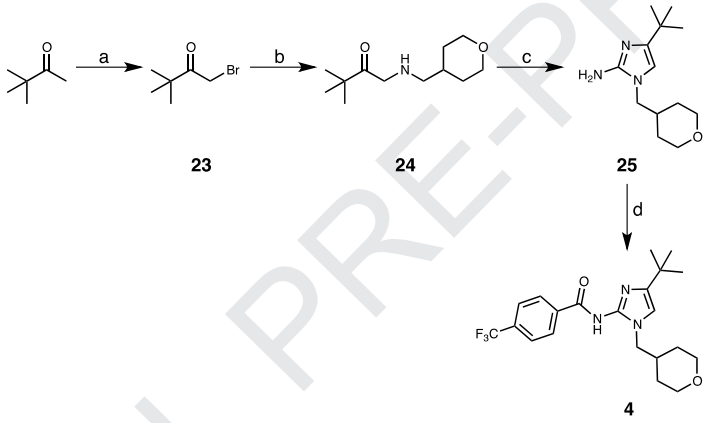
Pyrazole derivative **3** was synthesised via amino pyrazole **22** (**Scheme 3**). Mono-substituted hydrazine **21** was by synthesised by hydrazone formation from tetrahydro-2*H*-pyran-4-carbaldehyde and *tert*-butyl carbazate followed by sodium cyanoborohydride reduction and Boc group deprotection.[13] Reaction of the hydrazine hydrochloride salt **21** and 4,4-dimethyl-3-oxopentanenitrile afforded 5-aminopyrazole **22.** Finally, amide coupling with 4-trifluoromethylbenzoyl chloride yielded the desired amide **3**.



Scheme 3: Synthesis of pyrazole derivative **3**. *Reagents and conditions*: (a) *t*-Butyl carbazate, $MgSO_4$, MeOH, rt, 16 h, 63%; (b) $NaCNBH_3$, $TsOH.H_2O$, THF, rt, 16 h, 87%; (c) HCl, dioxane, MeOH rt, 16

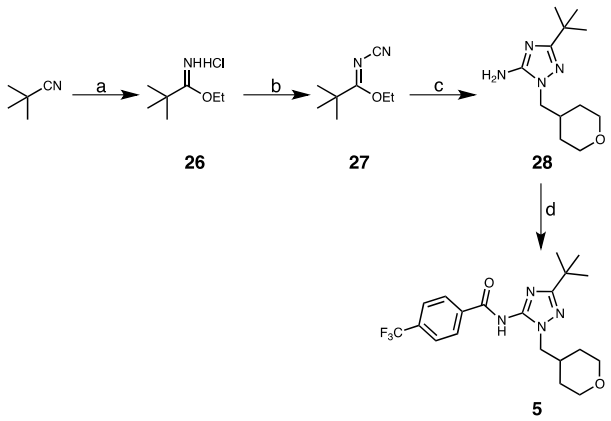
h, 100%; (d) 4,4-Dimethyl-3-oxopentanenitrile, EtOH, reflux, 16 h, 52%; (d) i) 4-Trifluoromethylbenzoic acid, oxalyl chloride, DMF, CH_2Cl_2, rt, 4 h, ii) (iPr)$_2$EtN, CH_2Cl_2, rt, 16 h, 72%.

Imidazole derivative **4** was synthesised via amino imidazole **25** (**Scheme 4**). Bromination of pinacolone gave α-bromoketone **23** which was added slowly to an excess of 4-methanamine tetrahydropyran at -78 °C to afford the secondary amine **24** in moderate yield.[14] Condensation with cyanamide gave the requisite 2-aminoimidazole **25**, which was converted to amide **4** via an acid chloride amide coupling.



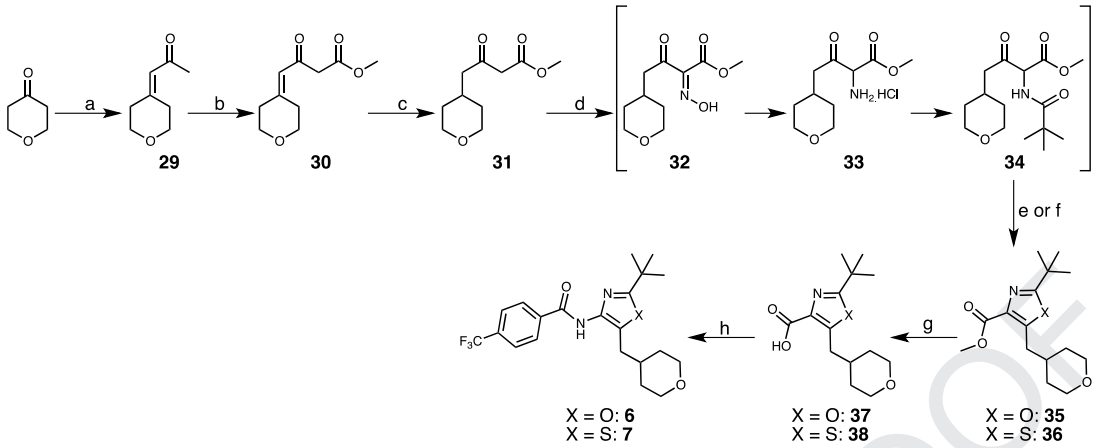
Scheme 4: Synthesis of imidazole derivative **4**. *Reagents and conditions*: (a) Br_2, MeOH, -40 °C-rt, 30 min, 83%; (b) 4-methanamine tetrahydropyran, diethyl ether, -78 °C-rt, 16 h, 43%; (c) Cyanamide, EtOH, reflux, 16 h, 94%; (d) 4-Trifluoromethylbenzoic acid, oxalyl chloride, DMF, CH_2Cl_2, rt, 4 h, ii) iPr$_2$EtN, CH_2Cl_2, rt, 16 h, 65%.

In a similar fashion triazole **5** was synthesised via the amino species **28** (**Scheme 5**). A Pinner reaction with pivalonitrile afforded the imidate salt which reacted with cyanamide to form cyanoimidate **27** under buffered conditions.[15] Reaction with hydrazine **21** afforded the poorly nucleophilic 5-aminotriazole **28**, which required deprotonation with sodium hydride and elevated temperatures to react with 4-trifluoromethylbenzoyl chloride to yield amide **5**.



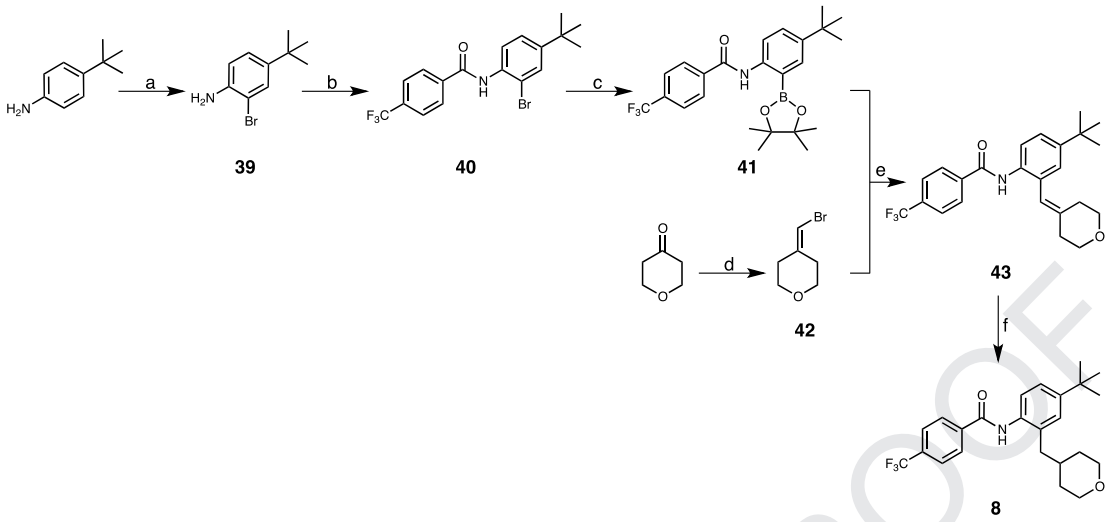
Scheme 5: Synthesis of triazole derivative **5**. *Reagents and conditions*: (a) EtOH, AcCl, 0 °C-rt, 16 h, 79%; (b) Cyanamide, $Na(OH)_2PO_2.H_2O$, $Na_2HPO_4.7H_2O$, MeCN, rt, 72 h, 51%; (c) Hydrazine **21**, DBU, MeOH, reflux, 16 h, 78%; (d) 4-Trifluoromethylbenzoic acid, oxalyl chloride, DMF, CH_2Cl_2, rt, 4 h, ii) NaH, MePh, reflux, 3 h, 75%.

Oxazole **6** and thiazole **7** could be formed from a common intermediate **34** (**Scheme 6**). A Horner-Wadsworth-Emmons olefination of dihydro-2*H*-pyran-4(3*H*)-one with 2-oxopropyl dimethyl ester phosphonic acid followed by reaction of the enolate with Mander's reagent afforded the β-ketoester **31** after selective hydrogenation of the alkene under hydrogen transfer conditions.[16] Oxime formation using sodium nitrite followed by hydrogenation under acidic conditions afforded the stable amine hydrochloride salt which reacted cleanly with pivalic anhydride to yield the amide common intermediate **34**. Cyclodehydration of the β-ketoamide using triphenylphosphine, iodine and triethylamine[17] afforded substituted oxazole **35** while the thiazole **36** was formed by reaction with Lawesson's reagent under elevated temperatures.[18] Basic ester hydrolysis followed by reaction with diphenylphosphoryl azide afforded the requisite acyl azides, which underwent Curtius rearrangements at elevated temperatures. Quenching with the appropriate Grignard reagent afforded amides **6** and **7**.



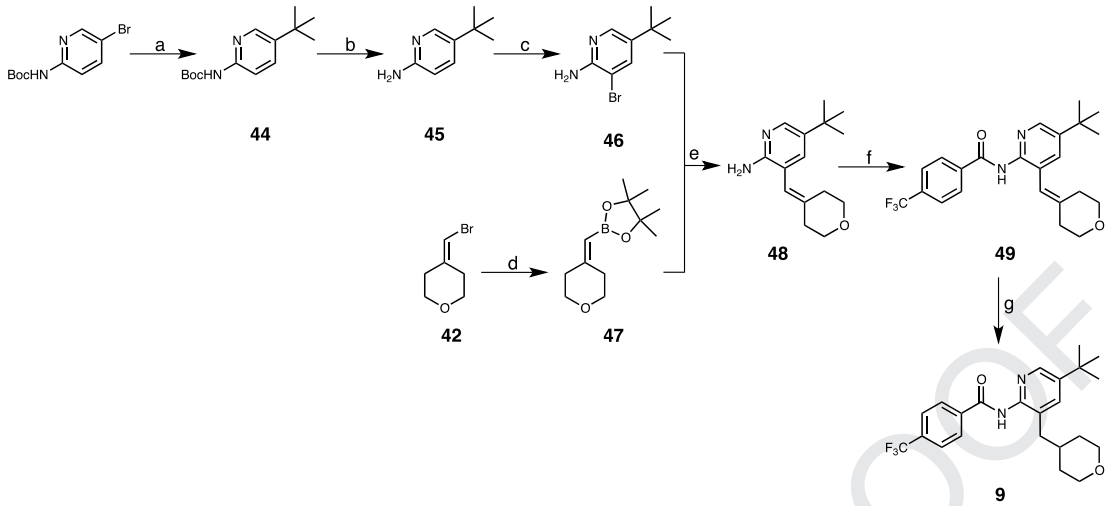
Scheme 6: Synthesis of oxazole and thiazole derivatives **6** and **7**. *Reagents and conditions*: (a) KOH, 2-oxopropyl dimethyl ester phosphonic acid, EtOH, 0 °C-rt, 5 h, 95%; (b) LDA, methyl cyanoformate, THF, -78 to -40 °C, 1 h, 58%; (c) NH_4HCO_2, Pd/C, MeOH, rt, 3 h, 95%; (d) i) $NaNO_2$, AcOH, H_2O, -5 °C-rt, 2 h, ii) HCl, Pd/C, H_2, EtOH, rt, 16 h, iii) Pivalic anhydride, Et_3N, CH_2Cl_2, rt, 16 h; (e) PPh_3, I_2, Et_3N, CH_2Cl_2, rt, 3 h, to give **35** 60% over 4 steps; (f) Lawesson's reagent, THF, reflux, 3 h, to give **36** 40% over 4 steps; (g) NaOH (aq.), THF, MeOH, rt, 4 h, 78-95%; (h) i) DPPA, Et_3N, CH_2Cl_2, rt, 16 h, ii) MePh, 90 °C, 1.5 h, iii) (4-(Trifluoromethyl)phenyl)magnesium chloride, 0 °C-rt, 1 h, 22-30%.

For the synthesis of phenyl derivative **8** it was envisioned that the tetrahydropyran group could be incorporated by cross-coupling chemistry (**Scheme 7**). Bromination of commercially available 4-(*tert*-butyl)aniline, amide coupling and finally a Miyaura borylation afforded cross-coupling partner **41**. A Suzuki cross-coupling with 4-(bromomethylene)tetrahydro-2*H*-pyran (**42**), which was formed by a Wittig-type reaction of dihydro-2*H*-pyran-4(3*H*)-one with (bromomethyl)triphenylphosphonium bromide,[19] achieved the key carbon-carbon bond formation. Hydrogenation of the alkene gave the final product **8**.



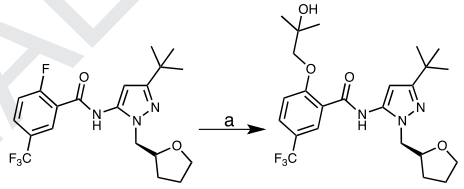
Scheme 7: Synthesis of phenyl derivative **8**. *Reagents and conditions*: (a) NBS, DMF, 0 °C-rt, 16 h, 78%; (b) 4-Trifluoromethylbenzoic acid, oxalyl chloride, DMF, CH_2Cl_2, rt, 4 h, ii) $(iPr)_2EtN$, CH_2Cl_2, rt, 16 h, 75%; (c) KOAc, $Pd(dppf)Cl_2$, $(Bpin)_2$, MePh, 90 °C, 16 h, 79%; (d) i) CH_2Br_2, PPh_3, MePh, reflux, 16 h, ii) KO^{t}Bu, THF, -78 ° to -40 °C, 3 h, 37%; (e) K_2CO_3, $Pd(PPh_3)_4$, DMF, H_2O, 80 °C, 4 h, 92%; (f) Pd/C, H_2, EtOAc, 16 h, 86%.

tert-Butyl-substituted aminopyridine **45** is not readily available and hence required synthesis to access pyridine derivative **9** (**Scheme 8**). Reaction of Boc-protected 2-amino-5-bromopyridine with an excess of *tert*-butyl magnesium chloride and copper cyanide afforded the desired alkylated product **44** in low yield.[8] Unlike in the case of the phenyl derivative **8**, it was found that the Suzuki cross-coupling reaction was most successful when the coupling partners were reversed and performed before the amide was formed. Optimised conditions using $Pd(dppf)Cl_2$ and aqueous potassium hydroxide as the base yielded the final product **9** after hydrogenation of the alkene.



Scheme 8: Synthesis of pyridine derivative **9**. *Reagents and conditions*: (a) *t*-BuMgCl, CuCN, THF, -78 °C-rt, 16 h, 19%; (b) TFA, CH_2Cl_2, rt, 2h, 100%; (c) NaOAc, Br_2, AcOH, rt, 3 h, 69%; (d) *t*-BuLi, isopropyl pinacol borate, THF, -78 °C-rt, 2.5 h, 63%; (e) KOH (aq.), Pd(dppf)Cl_2, THF, 60 °C, 16 h, 69%; (f) (i) 4-Trifluoromethylbenzoic acid, oxalyl chloride, DMF, CH_2Cl_2, rt, 4 h, ii) NaOH (aq.), CH_2Cl_2, 0 °C-rt, 2 h, iii) Bu_4N, THF, rt, 16 h, 87%; (g) Pd/C, H_2, EtOAc, 16 h, 91%.

The amide analogue of the lead compound **1** could be accessed from previously synthesised intermediate **12** by a simple nucleophilic aromatic substitution reaction using methylpropane-1,2-diol to afford **50** (**Scheme 9**).



Scheme 9: Synthesis of amide derivative of lead compound **50**. *Reagents and conditions*: (a) 2-Methylpropane-1,2-diol, KO*t*Bu, 0 °C-reflux, 4 h, 72%.

Functional activity at the CB_1 and CB_2 receptors

The heteroaromatic amides were assessed for their ability to activate the CB_1 and CB_2 receptors using a Fluorescence Imaging Plate Reader (FLIPR) membrane potential assay in AtT-20 cells expressing human CB_1 or CB_2 receptors as previously described.[20-21] The assay measures activation of endogenously expressed G protein-gated inwardly rectifying K^+ channels (GIRKs) at the CB_1 or CB_2 receptors.[22] Compounds displaying more than 40% activation at 10 μM in the assay were

evaluated further in dose−response studies. Their half maximal effective concentrations (EC_{50}) and maximal effect relative to high efficacy CB_1/CB_2 receptor agonist CP 55,940 (E_{max}),[23-24] which produced a maximal decrease in fluorescence at a concentration of 1 μM, corresponding to cellular hyperpolarization, were calculated as listed in **Table 1**. Further experimental details are provided in the Supplementary Information.

The lead pyrazoylidene-benzamide **1** exhibited potent and selective activation of the CB_2 receptor as expected. About a ten-fold decrease in potency was observed compared to the data reported for rat CB_2 receptor activation (**Figure 1**, **A**). Unfortunately, the heteroaromatic amide derivatives displayed no activity at the either of the CB receptors. Pyrrole derivative **2** was the only exception, possessing micromolar activity at CB_2. We consequently decided to investigate the structural basis for the observed loss of activity. We assumed the dramatic loss of activity was due to either substitution of the –ylidene-benzamide functionality for a benzamide or the particular combination of pendant groups used. We therefore synthesised the direct amide analogue of lead compound **1** with identical pendant groups to probe the importance of the linkage between the heterocycle and substituted phenyl group. Surprisingly amide **50** exhibited no functional activity at both cannabinoid receptors, confirming the –ylidene functional group is key for functional activity at the CB_2 receptor for this class of compounds. It is possible that amide **50** and its simplified analogues **2-9** may still bind to the CB_2 receptor but not have functional activity in the FLIPR membrane potential assay. To investigate the molecular basis for the differing functional activity at the CB_2 receptor of lead compound **1** and direct amide analogue **50** we performed docking simulations. For the docking study we used the first and only reported crystal structure of the CB_2 receptor, recently published by Li and co-workers.[25] A caveat to the simulations performed is that the inactive cannabinoid receptor structure, solved with an antagonist bound, is not ideal for predicting agonist interactions. Similar docking scores and near identical binding poses were observed for both –ylidene-benzamide **1** and amide **50** (see Supplementary Information, **Figure S1**). More in depth molecular dynamics and mutagenesis studies would be required to elucidate the molecular basis for the lack of functional activity of amide **50** despite its structural similarity to the lead compound **1**.[26] This finding has led us to further

explore the subtle SAR of this class of compounds, the results of which will be disclosed in due course.

Table 1: Agonist activities of lead compound (**1**) and heteroaromatic amide derivatives (**2**-**9** and **50**) in AtT-20 cells expressing human CB_1 or CB_2 receptors by a FLIPR membrane potential assay[a]

	CB_1		CB_2	
Compound	pEC_{50} ± SEM (EC_{50} nM)	E_{max} (%)	pEC_{50} ± SEM (EC_{50} nM)	E_{max} (%)
1	NA	ND	7.72 ± 0.08 (19)	93
2	NA	ND	5.61 ± 0.24 (2470)	45
3	NA	ND	NA	ND
4	NA	ND	NA	ND
5	NA	ND	NA	ND
6	NA	ND	NA	ND
7	NA	ND	NA	ND
8	NA	ND	NA	ND
9	NA	ND	NA	ND
50	NA	ND	NA	ND
CP 55,940	7.67 ± 0.04 (21)	99	7.50 ± 0.05 (32)	101

[a]See Supplementary Information for more details. Data represent mean values ± SEM from at least three independent experiments each performed in duplicate, with CP 55,940 used as a positive control. [b]NA: Not active, defined as <40% activation at 10 μM in the assay. [c]ND: Not determined; for compounds defined as not active, their maximal effects were not determined.

Conclusion

We report herein the design and synthesis of a small library of heteroaromatic amides as proposed CB_2 receptor agonists. Heteroaromatic amides are privileged scaffolds in drug design and the synthetic strategies developed here offer concise and reliable methods to access these products. The absence of functional activity at the cannabinoid receptors observed for these compounds has highlighted the importance of the –ylidene-benzamide moiety within this series of compounds. Preliminary docking studies were unsuccessful in determining the molecular basis for the lack of functional activity of the amide derivatives in this study. We have therefore refocused our efforts on further investigating the –ylidene-benzamide moiety and why it is crucial for functional activity.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online

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Highlights

- Synthetic routes to access heterocyclic benzamides are developed.
- Functional activity at the cannabinoid receptors is evaluated.
- –Ylidene benzamide moiety is determined to be imperative for activity.