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Synthesis and SAR of novel imidazoles as potent and selective cannabinoid CB_2 receptor antagonists with high binding efficiencies

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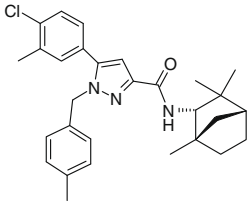
ABSTRACT

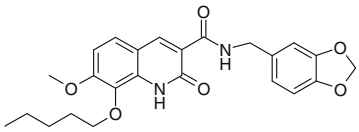
The synthesis and structure–activity relationship studies of imidazoles are described. The target compounds **6**–**20** represent a novel chemotype of potent and CB_2/CB_1 selective cannabinoid CB_2 receptor antagonists/inverse agonists with very high binding efficiencies in combination with favourable log *P* and calculated polar surface area values. Compound **12** exhibited the highest CB_2 receptor affinity (K_i = 1.03 nM) in this series, as well as the highest CB_2/CB_1 subtype selectivity (>9708-fold).

The cannabinoid CB_2 receptor was cloned[1] in 1993 and is almost exclusively expressed in cells of the immune system, spleen, pancreas, tonsils and thymus.[2] Under certain circumstances the CB_2 receptor is also expressed[3,4] in astrocytes, microglia and the brainstem.[5] CB_2 receptor ligands have potential in the therapeutic treatment of several diseases[6] such as inflammation, multiple sclerosis, neuropathic pain,[7] immune regulation,[8] osteoporosis and certain types of cancer. Recently, CB_2 receptor inverse agonists were also shown to block[9] leucocyte recruitment in vivo.

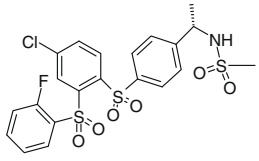
The amino acid sequence of the CB_2 receptor has an overall identity[1] of 44% with the CB_1 receptor. Their homology in the GPCR transmembrane domain amounts to 68%, thereby providing good prospects for the design of CB subtype selective ligands. Intense research efforts have indeed led to the discovery of subtype selective human cannabinoid CB_1 receptor antagonists/inverse agonists,[10] selective CB_2 receptor agonists such as JWH133,[11] HU-308,[12] L759656,[13] AM-1241,[14] A-796260 and A-836339[15] as well as selective CB_2 receptor antagonists/inverse agonists from different chemical series such as the pyrazolecarboxamide[16,17] SR144528 (**1**), the 2-oxoquinoline[18] JTE-907 (**2**) and the triarylbissulfone[19] SCH-356036 (**3**).



SR144528 (**1**)



JTE-907 (**2**)



SCH-356036 (**3**)

Several reviews described[20–25] the medicinal chemistry of CB_2 receptor ligands. Although many efforts have concentrated on the modelling of the CB_2 receptor and their ligands[20] as well as on receptor mutations,[26] it can be concluded that the design of novel CB_2 selective antagonists or agonists by CB_2 receptor modelling or virtual screening is still a challenging task.[27–30] It is interesting

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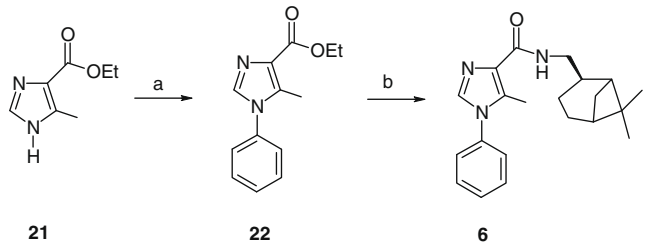
to note that both the selective CB_1 receptor antagonist rimonabant[31] and the selective CB_2 receptor antagonist **1** contain a 5-arylpyrazole-3-carboxamide scaffold. This intriguing observation prompted us to start CB_2 receptor antagonist design efforts based on our[32] CB_1 antagonistic 1,2-diarylimidazoles **4** which can be considered as bioisosters of rimonabant (Scheme 1). The preference for the imidazoles as a starting point for the design of CB_2 selective antagonists was fuelled by the generally observed[31,32] slightly higher CB_2 receptor affinities in the 1,2-diarylimidazole series as compared to the corresponding 1,5-diarylpyrazoles.

It was noted that the 1-arylmethyl moiety of **1** adds significant molecular weight and lipophilicity[33] to the molecule. Since, we were particularly interested in novel CB_2 receptor antagonist chemotypes with high ligand efficiencies[34] and favourable log *P* values, attention was given to the chemotype **5** wherein the large arylmethyl group of **1** is replaced by a considerably smaller substituent[35] R^1 at the corresponding imidazole 2-position. Removal of the original 2-aryl moiety in **4** was furthermore anticipated to have a detrimental effect on the CB_1 activity of the compounds, based on our extensive CB_1 SAR knowledge, thereby increasing CB_2/CB_1 subtype selectivity[36,37] In addition, the carboxamide *N*-piperidinyl substituent in **4** was replaced by a lipophilic substituent comparable to the trimethylbicyclo[2.2.1]heptane group in **1**.

In concreto, these design considerations led to a series of fifteen novel imidazole derivatives **6**–**20**. The synthesis of compound **6** is depicted in Scheme 2. The commercially available ester **21** was reacted with benzeneboronic acid in the presence of a catalytic amount of CuI to afford **22** in a modest yield. Weinreb amidation[38] of **22** with (−)-*cis*-myrtanylamine gave the imidazole **6** in 65% yield.

The synthesis of the imidazoles **7**–**13** is depicted in Scheme 3. The commercially available oxo-esters **23**–**25** were reacted with $NaNO_2$ to furnish the oximes **26**–**28**. Subsequent catalytic reductive acetylation with acetic anhydride afforded the crude compounds **29**–**31** which were cycloaromatized with aniline in butyronitrile in the presence of trifluoroacetic acid to the imidazoles **32**–**34**. This sequence of reactions constitutes a powerful route to the synthesis of 1-aryl-2,5-dialkylimidazole-4-carboxylates. It is interesting to note that our optimized reaction conditions led to considerable higher yields as well as less by-product formation as compared with the original procedure[39] which consisted of heating in xylene. Ester hydrolysis of **32**–**34** delivered the corresponding acids **35**–**37** in quantitative yield. The target compounds **7**–**13** were obtained from **35**–**37** via amidation reactions in the presence of a coupling reagent (either HBTU or CIP) in yields ranging from 60–72%.

The target compounds **14** and **15** were prepared[40] according to Scheme 4. The nitroacrylates **38** and **39** were cycloaromatized under reductive conditions with triethylorthopropionate to the 2-ethylimidazoles **40** and **41**, respectively. Ester **40** was hydrolyzed under basic conditions to the carboxylic acid **42**, which was then amidated with 1-adamantamine·HCl to provide target compound **14**. Compound **41** was converted in a straightforward Weinreb amidation[38] to **15**.



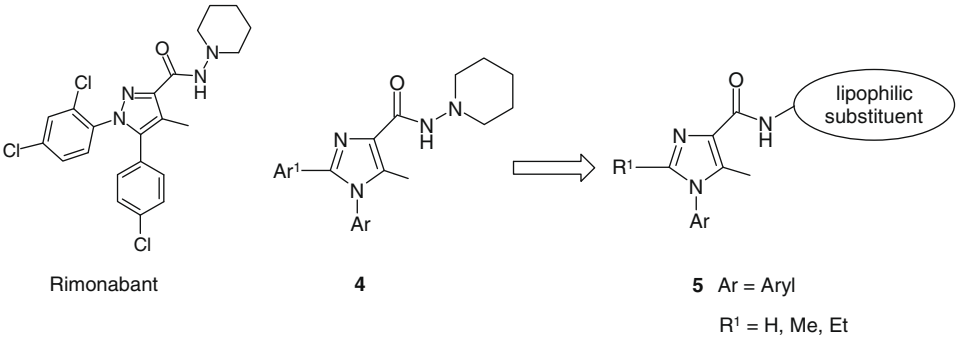
Scheme 2. Reagents and conditions: (a) $C_6H_5B(OH)_2$, CuI, EtOH/H_2O, reflux, 60 h (26%); (b) (−)-*cis*-myrtanylamine, $Al(CH_3)_3$, CH_2Cl_2, 35 °C, 16 h (65%).

The synthesis of the imidazoles **16**–**18** is depicted in Scheme 5. The ester intermediate **43** was prepared from the corresponding nitroacrylate analogously[40] to the method described in Scheme 4. Ester hydrolysis of **43**, followed by amidation with 1-adamantamine·HCl led to the carboxamide **44**. Subsequent regioselective lithiation of **44** with the strong non-nucleophilic base LDA, followed by treatment with an electrophile led to the target compounds **16**–**18** in reasonable yields. It is interesting to note that this strategy provides a nice alternative for the synthesis of 4-alkylated imidazoles such as **8** and **12**. Compounds **8** and **12** were obtained from **44** via the reaction with CH_3I and C_2H_5I in 70% and 41% yields, respectively.

The 2,5-dichloroimidazole derivative **19** was prepared as shown in Scheme 6. The dicarboxylic acid **45** was mono-decarboxylated in acetic anhydride and subsequently esterified with sulfuric acid in ethanol to **46**. N-Arylation with benzeneboronic acid in the presence of CuCl gave a regioisomeric mixture from which **47** was separated by flash chromatography. Basic hydrolysis of the ester group and subsequent amidation with adamantamine·HCl afforded **48**. Prolonged chlorination[41] of **48** with *N*-chlorosuccinimide eventually led to the incorporation of two chloro atoms at the imidazole nucleus and thereby produced the target compound **19**.

The cyclohexylimidazole analogue **20** was prepared according to Scheme 7. The nitroacrylate[40] **49** was reacted with cyclohexylamine to produce the corresponding cyclohexylamino derivative **50** in low yield. Subsequent cycloaromatization under reductive conditions with triethylorthoacetate gave the imidazole ester **51** which was efficiently converted via a Weinreb amidation[38] with 1-adamantamine·HCl to **20**.

The pharmacological data of the reference compounds **1**–**3** and target compounds **6**–**20** are depicted in Table 1. The observed order of CB_2 receptor affinities and CB_1/CB_2 receptor subtype selectivities of the reference compounds **1**–**3** matches the reported data.[16,18,19]



Scheme 1. Design concept of novel imidazoles **5** as selective cannabinoid CB_2 receptor antagonists from CB_1 receptor antagonists **4**.