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# Structural modifications of *N*-arylamide oxadiazoles: Identification of *N*-arylpiperidine oxadiazoles as potent and selective agonists of $CB_2$

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ABSTRACT

Structural modifications to the central portion of the *N*-arylamide oxadiazole scaffold led to the identification of *N*-arylpiperidine oxadiazoles as conformationally constrained analogs that offered improved stability and comparable potency and selectivity. The simple, modular scaffold allowed for the use of expeditious and divergent synthetic routes, which provided two-directional SAR in parallel. Several potent and selective agonists from this novel ligand class are described.



The cannabinoid G-protein coupled receptors, $CB_1$ and $CB_2$, play important roles in the transduction and perception of pain.[1] The contribution of $CB_1$ to the modulation of antinociception has been well established.[1] However, agonism of $CB_1$, which is predominantly expressed in the CNS, results in undesirable psychotropic effects, sedation, and catalepsy.[2] Selective agonism of $CB_2$, which is predominantly expressed in immune cells and tissues, presents an opportunity for pain management without the unfavorable CNS side effects. Indeed, a number of $CB_2$-selective agonists have shown efficacy in rodent models of inflammatory and neuropathic pain at doses that do not cause sedation or locomotor impairment.[3]

In accordance with our ongoing efforts to identify small molecule agonists of $CB_2$ for use as therapeutic agents in the treatment of pain, we recently disclosed the *N*-arylamide oxadiazoles.[4] This series is represented by **1** (Scheme 1), which exhibits full agonism[5] of the $CB_2$ receptor at low nanomolar concentrations with >200-fold selectivity over $CB_1$ in a functional GTP-Eu binding assay (Table 1).[6] Unfortunately, **1** suffered from high clearance in vivo (rat i.v. CL = 5.7 L/h/kg). High clearance was also observed for several of its analogs, and hydrolysis of the amide bond was identified as a major metabolic pathway in rats (Scheme 1).[7]

In an effort to improve the metabolic stability without compromising the agonist potency and efficacy, we investigated reversed amide **3** and propylamines **4**–**6** (Table 1).[8] The reversed amide **3** proved to be significantly less potent and efficacious than **1**. Next, we explored the removal of the amide carbonyl leading to propylamine **4**,[4] which was only 5-fold less potent and selective than the corresponding amide (**1**). Unfortunately, **4** was metabolically unstable in liver microsomes.[7] Accordingly, α-methyl substituents were introduced to block the potential oxidative metabolism, affording secondary and tertiary propylamines ((±)-**5** and **6**). In the case of the mono-methyl analog (±)-**5** only a modest 7-fold loss of potency was observed. The gem di-methyl analog **6** led to a more significant 20-fold loss of potency and provided only a partial agonist ($E_{max}$ = 52%). Also, both compounds were still rapidly metabolized in liver microsomes.

The data from propylamines **4**–**6** suggested that the carbonyl functionality was not essential for potency and efficacy. Furthermore, the 20- to 100-fold selectivity afforded by **4**–**6** was unanticipated since the vast majority of $CB_2$-selective functional agonists contain amide or sulfone moieties.[3c–f,9] Encouraged by this discovery, we sought to explore cyclic tethers that could presumably improve the metabolic stability and intrinsic potency through

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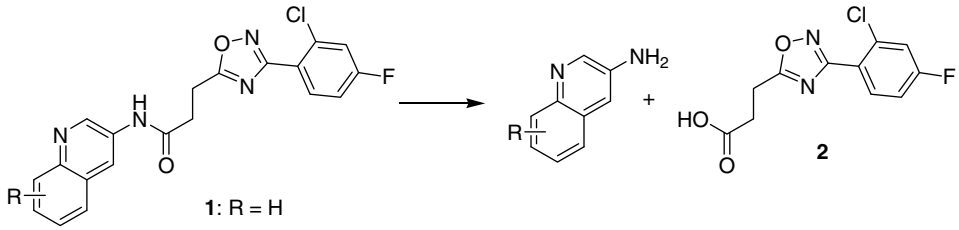
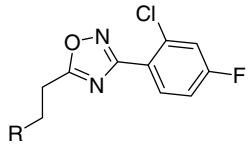
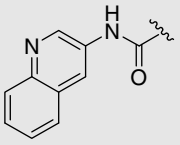
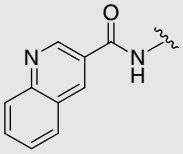
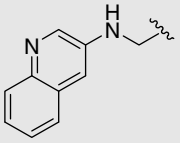
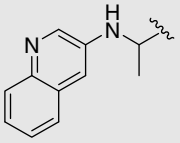
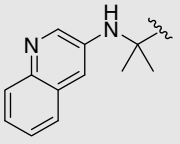



**Scheme 1.** Amide oxadiazoles and hydrolysis products.

**Table 1**
Functional GTP-Eu assay results for compounds **1**–**6** ($EC_{50}$, μM; $E_{max}$, %) and $CL_{int}$. in rat and human liver microsomes (RLM, HLM)[a]




| Compound | R | $CB_2$ $EC_{50}$ ($E_{max}$) | $CB_1$ $EC_{50}$ ($E_{max}$) | $CL_{int.}$ (μL/min/mg) | |
|---|---|---|---|---|---|
| | | | | RLM | HLM |
| **1** |  | 0.002 (115) | 0.403 (51) | 126 | 49 |
| **2** |  | NA (10) | NA (0.3) | — | — |
| **3** |  | 1.55 (87) | NA (−1) | — | — |
| **4** |  | 0.011 (104) | 0.472 (103) | 614 | 179 |
| (±)-**5** |  | 0.015 (112) | 1.56 (69) | >399 | 142 |
| **6** |  | 0.053 (52) | 1.30 (70) | 775 | 429 |

[a] The results are expressed as the means SEM for $n$ = 2–20 independent measurements, and were calculated in Prism by use of a logistic fit. $E_{max}$, % is given in parentheses (NA, not active).

increased conformational rigidity (Table 2). The cyclopentyl amine derivatives, (±)-**7** and (±)-**8**, displayed decreased potency and efficacy. However, the *trans*-cyclopropyl amine (±)-**9**, pyrrolidines **10** and **11**, and piperidine **12a** all showed promising functional activity and selectivity. Of these, **12a** afforded the best combination of potency, selectivity, and low intrinsic clearance in vitro.

In light of the in vitro profile of lead compound **12a**, we set out to explore the structure–activity relationships around this novel *N*-arylpiperidine oxadiazole scaffold. Molecular modeling revealed that **1** and **12a** adopt similar low energy conformations (Fig. 1),[10] suggesting that these two series of molecules share similar binding modes, and may therefore exhibit parallel SAR.[4]