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3-Aryl Pyridone Derivatives. Potent and Selective Kappa Opioid Receptor Agonists

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Abstract—A new series of 3-aryl pyridone based kappa opioid receptor agonists was designed and synthesised, based on an understanding of the classical kappa opioid receptor pharmacophore. The most potent of the new compounds were comparable to U-69,593 in receptor affinity, selectivity and functional agonist effect at the cloned human kappa opioid receptor.

Non-peptide ligands of the kappa opioid receptor (KOR) have been known for many years. The first selective agonist compounds were described by Upjohn in the 1980s[1] (e.g., **1**, Fig. 1) and were rapidly followed by related structures, in particular from ICI (**2**)[2] and later Glaxo (**3**), SmithKlineBeecham (**4**) and others.[3] All of these compounds were initially targeted towards various pain indications but preliminary clinical studies showed that they produced severe centrally-mediated side effects, such as diuresis, sedation and dysphoria,[4] and as a result were all dropped from development. Despite the implication from several sources that KOR agonists may still be useful in mediating various peripherally mediated pain states, attempts to restrict access of KOR agonists to the CNS have thus far been only partly successful[5] and no selective KOR agonist compound has yet reached the market.

We have been interested in the design of new KOR agonist scaffolds, which could eventually be modified to act selectively in the periphery as a potential treatment for visceral pain. A simple comparison across structural series of known KOR agonists led us to the obvious conclusion that several different conformational restrictions when applied to the classical N–C–C–N–CO pharmacophore, retain good KOR binding affinity and agonist activity. Our analysis of these clearly implied that the global active conformation was of an extended nature. We next applied simple conformational modelling techniques to explore the core structure of the open series (**2**, the most flexible example) to try and find new, restrained molecules which would mimic the active conformation. Amongst the classical KOR agonist series, the substituted phenyl acetic group and mimetics thereof, are an important determinant for receptor affinity. Perhaps as a result, this region has been much less well explored as a site of conformational restriction and so we began by modelling a number of cyclic bridged structures involving the *N*-methyl group and the phenyl acetyl carbon (Fig. 2). Delving further into the literature,

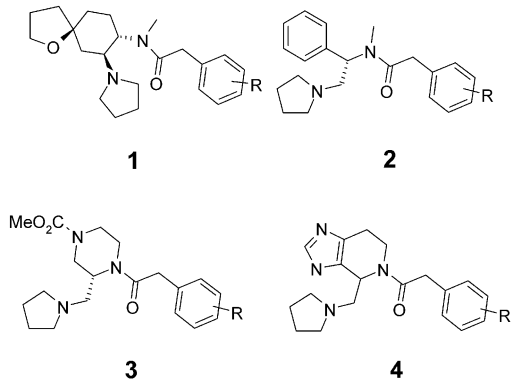

Figure 1. Known kappa agonists.

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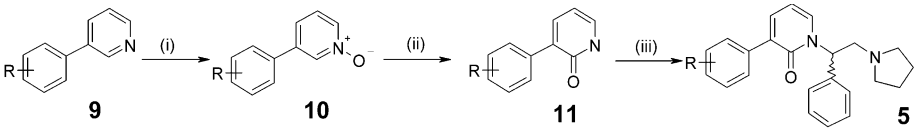
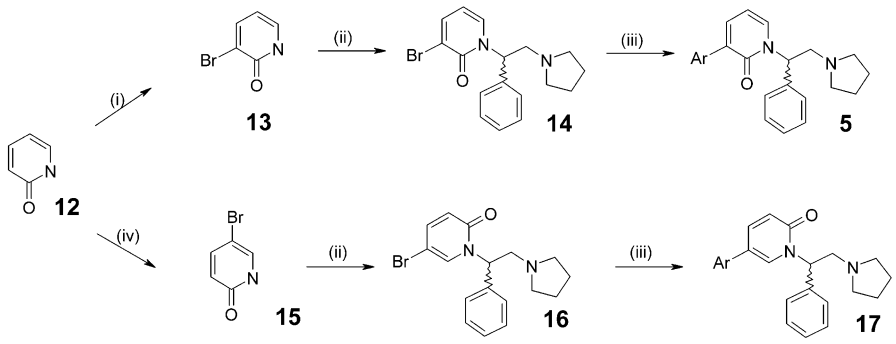


Scheme 1. Reagents and conditions: (i) H_2O_2, AcOH, 80 °C, 18 h, 90%; (ii) Ac_2O, 80 °C, 43%; (iii) (a) NaH, DMF, 0 °C, 1 h; (b) 1-(2-chloro-2-phenylethyl) pyrrolidine, rt 60% (two steps).



Scheme 2. Reagents and conditions: (i) Br_2, 1MKBr, rt 22%; (ii) (a) NaH, DMF, 0 °C, 1 h; (b) 1-(2-chloro-2-phenylethyl) pyrrolidine, rt 60%; (iii) $ArB(OH)_2$, PdOAc, dioxan, $NaHCO_3$, 80 °C, 4 h, 40–90%; (iv) NBS, AcOH, rt 4 h, 55%.

we found that cyclic urea compounds with sub-nanomolar affinity for the kappa receptor[6] and saturated lactam analogues related to earlier series[7] have both been described (Fig. 2). We were encouraged by the reported activity of these types of compounds, and as the conformation of these five-membered rings was very flat in our models, we decided to investigate the pyridone **5**, which we surmised would be a close mimic of these known active series.

We initially synthesised compounds of this type by the route shown in Scheme 1. Pyridone **11a** (R = H) was synthesised in two steps from commercially available 3-phenyl pyridine **9a** by oxidation to the *N*-oxide and acid catalysed rearrangement as previously described.[8] The analogous pyridone (**11b**, R = 4-CF_3) was prepared in a similar manner from the appropriate substituted aryl pyridine prepared in turn from the Grignard mediated coupling of 3-bromopyridine and 4-(trifluoromethyl)-bromobenzene.[9]

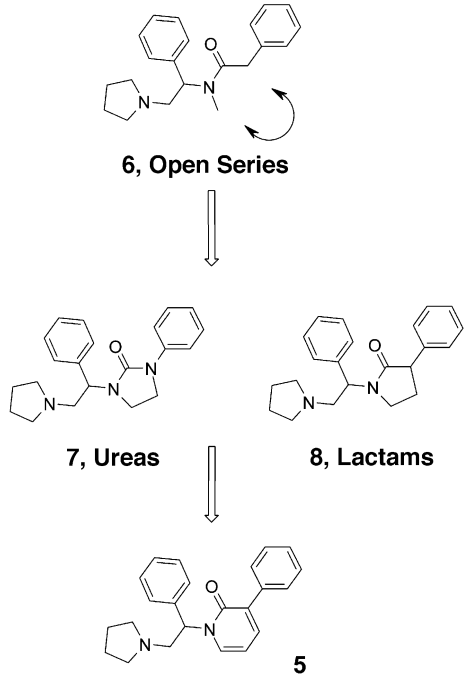


Figure 2. Design of pyridone-based kappa agonists.

These pyridones were readily alkylated by treatment with sodium hydride at 0 °C followed by 1-(2-chloro-2-phenylethyl) pyrrolidine,[10] prepared via the corresponding alcohol,[11] [**CAUTION**, the free base of 1-(2-chloro-2-phenylethyl) pyrrolidine is a potent mustard agent] providing the initial target compounds **5a** and **5b**.

The prototypical compound (**5a**) showed an IC_{50} of 56 nM for binding to the cloned human kappa opioid receptor,[12] and had no affinity for the related delta and mu opioid receptors. In addition, **5a** showed a clear full agonist effect (>95% E_{max} relative to U-69,593) in our in vitro functional test.[13] Substitution of the terminal phenyl ring with 4-CF_3, (**5b**), provided significantly improved kappa receptor binding (Table 1) and functional effects [$ED_{50} = 49.4 \pm 5.6$ nM ($E_{max} > 95\%$) c.f. 23.8 ± 1.76 nM for U-69,593] over the parent compound. As the corresponding substitution also provides an improvement in activity in the classical open series,[14] we were interested in expanding the available range of compounds in order to see how closely our new compounds would mimic the SAR of the classical agonist series. For this investigation we examined only the binding affinities of the new compounds for opioid receptors, having demonstrated in principle that the new series had functional agonist properties. In addition, we utilised an alternative synthetic route, making use of a palladium catalysed arylation as the final step to give more flexibility in the number and range of aryl groups that we could incorporate. This route is outlined in Scheme 2.

Table 1. Ligand binding data for kappa, delta and mu opioid receptors

Compd	Ar	κ-binding IC_{50} (nM)	δ-binding IC_{50} (nM)	μ-Binding IC_{50} (nM)
5a	Ph	56.3 (32.1–80.4)	> 10,000	> 10,000
5b	4-CF_3–Ph	8.7 (3.3–14.1)	> 10,000	2716
5c	4-Cl–Ph	5.5 (2.65–8.71)	> 10,000	4840 (677–9000)
5d	4-OMe–Ph	49.4 (22.6–76.2)[b]	5214[a]	1464[a]
5e	4-F–Ph	34.8 (19.4–45.2)	> 10,000[a]	> 10,000
5f	4-OCF_3–Ph	34.2 (27.5–43.8)	> 10,000	1100 (145–1790)
5g	2-OMe–Ph	19.5 (4.97–38.3)	> 10,000[a]	1200 (237–2170)
5h	2-CF_3–Ph	5.7 (2.64–7.9)	> 10,000	1680 (871–3250)
5i	3-NO_2–Ph	2.2 (1.72–2.67)[b]	> 10,000	3910 (1820–5510)
5j	3-Cl–Ph	2.4 (1.74–2.89)	> 10,000	308 (229–388)
5k	3-CN–Ph	5.3 (3.71–7.92)	> 10,000	4280 (2500–6540)
5l	3-Me–Ph	79.3 (52.9–92.9)	639 (120–1340)	> 10,000
5m	3,4-Cl_2–Ph	2.3 (2.1–2.5)[b]	> 10,000	2064[a]
5n	2-OMe, 5-F–Ph	3.4 (2.19–4.71)[b]	4350 (1250–7450)	3460 (1490–5050)
5o	2-OMe, 5-Cl–Ph	1.5 (0.66–2.26)	4170 (1220–5980)	1240 (318–2370)
5p	2,5-$(OMe)_2$–Ph	3.44 (1.73–5.3)	> 10,000	> 5000
5q	2,5-F_2–Ph	22.5 (16.6–26.3)	> 10,000	> 10,000
5r	2-Benzofuran	271[a]	n.d.	n.d.
5s	2-Thiophene	1177[a]	n.d.	n.d.
5t	2-Naphthalene	31.9 (17.7–56.4)	> 10,000	2680 (1630–4680)
17c	4-Cl–Ph	524[a]	n.d.	n.d.
17m	3,4-Cl_2–Ph	1494[a]	n.d.	n.d.
U-69,593	—	2.0 ± 0.1	5844 ± 1420	248 ± 23.8

Values for kappa binding are the arithmetical mean of at least three determinations (except [a]$n = 1$ and [b]$n = 2$) and are shown with 95% confidence limits (except for U-69,593 which is ± SEM). Values for delta and mu binding are the mean of at least two determinations (except [a] $n = 1$). n.d. = not determined.

3-Bromopyridone (**13**) was prepared by treatment of 2-hydroxypyridine (**12**) with bromine in KBr solution.[15] Alkylation with 1-(2-chloro-2-phenylethyl) pyrrolidine using the method outlined above, provided the key intermediate **14** in good yield. The Suzuki coupling reaction[16] was accomplished on a 10–15 mg scale (of substrate **14**) with a wide range of boronic acid derivatives. In a typical procedure, an excess of the boronic acid was reacted with **14** in the presence of 3 mol% of $Pd(OAc)_2$ and sodium bicarbonate at 80 °C in dioxan for 4 h, in a 96-well Robbins reaction block. The resultant products were isolated in good yield and > 85% purity (as determined by HPLC–MS) following parallel ion exchange purification on pre-packed SCX columns.

After screening in the KOR binding assay at a single concentration of either 1 or 10 μM, selected examples were further purified to homogeneity (> 96% purity) by parallel preparative HPLC. Full dose–response curves were then determined for binding to kappa, delta and mu opioid receptors and the data provided in Table 1 represents mean IC_{50} values for the fully purified material.

Substitution at the 4-position of the aryl ring with either trifluoromethyl- (**5b**) or chloro- (**5c**) groups provided an improvement in binding affinity for the KOR compared with the unsubstituted compound **5a**. Other 4-substituents had little effect. Substitution at the 3-position was also fruitful, with the 3-nitro (**5i**), 3-chloro (**5j**) and 3-cyano (**5k**) derivatives all having better KOR affinity than **5a**. The 3-chloro derivative however also showed significant binding to the mu opioid receptor. Incorporating two substituents onto this ring appeared to be beneficial. In particular, the 2-methoxy substituent, whilst having little effect on its own (**5g**), was able to assist in providing good affinity and selectivity for the KOR in combination with additional substituents in the 5-position. The most potent compound tested was **5o**, with an affinity for the KOR comparable to that of the literature standard compound, U-69,593 in our hands. Incorporation of either thiophene or fused aromatic rings lead to a significant decrease in affinity over the most potent substituted phenyl analogues. These data suggested to us that our pyridone analogues had a similar SAR to the classical open series[2] with regard to substitutions on the terminal aromatic ring inferring a similar mode of binding.

Finally, we also prepared the isomeric 5-aryl pyridone analogues **17**, in which the presumed pharmacophore is disrupted by arranging the carbonyl and aryl groups in a different relative orientation. An alternative bromination of 2-hydroxypyridine using NBS,[17] to provide **15** (Scheme 2), followed by alkylation and Suzuki arylation as described above, provided target compounds **17** in good yield.

The significantly poorer binding affinity of these analogues for the KOR (Table 1) is, we believe, due to the loss of a hydrogen bond interaction between the pyridone carbonyl and the receptor and we feel that, taken together, all the data validate our original hypothesis, that the above described 3-aryl pyridones bind to the KOR in a similar way to the classical open series.

In summary, we have designed and synthesised a new series of kappa opioid receptor ligands based on an understanding of the classical KOR pharmacophore. The new series provides a novel template with several potential points of attachment for functional groups,

for example, to one of the three aromatic rings, which may be used to restrict access to the CNS either by increasing polar surface area and/or decreasing logD. Their close similarity to the classical KOR agonists suggests we can exploit existing literature knowledge regarding the incorporation of such groups into our new series and such studies with compounds of this type will be reported in due course.

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