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Synthesis and Biological Activity of Kappa Opioid Receptor Agonists. Part 2: Preparation of 3-Aryl-2-pyridone Analogues Generated by Solution- and Solid-Phase Parallel Synthesis Methods

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Abstract—New analogues of the previously described 3-aryl pyridone KOR agonists have been synthesised by parallel synthetic methods, both in solution- and with solid-phase chemistry, making use of the well known and versatile Mitsunobu, Suzuki and Buchwald reactions. Opioid receptor binding data for the compounds produced is reported.

We reported recently on the design and synthesis of potent and selective pyridone-based agonists of the kappa opioid receptor (KOR) based on our understanding of the mode of binding of the classical N–C–C–N–CO KOR agonist pharmacophore.[1] As part of our continuing examination of compounds of this type, we now wish to describe the synthetic strategy used to prepare, and the opioid receptor affinity of, a selection of related analogues. A key driver in these endeavours was to introduce more polar substituents to reduce lipophilicity and increase the polar surface area of the resultant compounds, the overall objective being to reduce their ability to cross the blood–brain barrier whilst hopefully maintaining efficacy at the receptor.[2] Such compounds may still act at peripherally located KORs and thus may be useful for the treatment of visceral pain, avoiding as they would the well-documented central side effects of previously known KOR agonists.[3] To this end, we have now developed highly flexible parallel synthesis methods amenable to the preparation of a wide variety of substituted analogues for further SAR exploration.

Our original synthesis of the 3-aryl-pyridin-2-one series of KOR agonists made use of a sodium hydride mediated alkylation of 3-aryl- or 3-bromo-pyridin-2-one with 1-(2-chloro-2-phenylethyl) pyrrolidine in DMF.[1] For the first stage of our initial SAR expansion, we employed the same synthetic step to investigate the effect of incorporating additional nitrogen atoms into the central heterocyclic portion of the molecule, as shown in Figure 1. In each case, the incorporation of a single nitrogen atom reduces the calculated logP of the resultant compound by 1.5–2 log units compared to the corresponding pyridone. The pyridones **4a**,**b** (Fig. 1, X,Y,Z = C) have been described previously.[1] The synthesis of the analogous pyrazinone **4e** (Y,Z = C; X = N) was achieved in two steps by condensation of phenyl glycinamide with glyoxal,[4] followed by alkylation of the resultant heterocycle **6** with 1-(2-chloro-2-phenylethyl) pyrrolidine regiospecifically and in good yield, using the same conditions as for the pyridone. The pyridazinone **4f** (X,Y = C; Z = N) was prepared by alkylation of 5-phenyl-4,5-dihydropyridazin-3-one **7**,[5] again under the same conditions. The major product of the reaction was the pyridazinone resulting from alkylation and concomitant oxidation of the heterocycle. Two minor non-oxidised alkylation products were also isolated, and HPLC-MS analysis indicated that they had arisen from direct alkylation of the dihydro- ring, suggesting that

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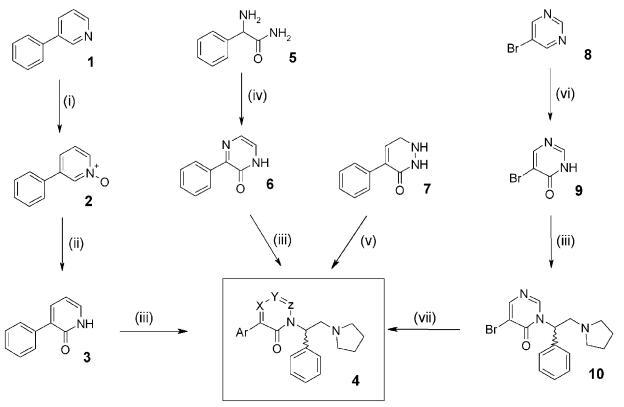


Figure 1. Reagents and conditions: (i) H_2O_2, AcOH, 80 °C, 18 h, 90%; (ii) Ac_2O, 80 °C, 43%; (iii) (a) NaH, DMF, 0 °C, 1 h; (b) 1-(2-chloro-2-phenylethyl) pyrrolidine, rt 55–60%; (iv) CHOCHO, methanol, 1 M NaOH, 69%; (v) (a) NaH, DMF, 0 °C, 1 h (b) 1-(2-chloro-2-phenylethyl) pyrrolidine, rt 32%; (vi) CH_3CO_3H, H_2SO_4, acetone, rt to reflux, 2 h, 88%; (vii) $ArB(OH)_2$, $Pd(OAc)_2$, dioxan, $NaHCO_3$, 80 °C, 4 h 60–70%.

the oxidation event may be secondary to alkylation. Neither of these purported dihydro- compounds showed any biological activity and were not further characterised.

The pyrimidinone analogues **4c**,**d** ((X,Z = C; Y = N) were prepared in three steps, the aryl group being appended in the final step by Suzuki coupling. Commercially available 5-bromopyrimidine **8** was converted to the bromopyrimidone **9** in one step by treatment with peracetic acid and sulfuric acid as described previously.[6] Alkylation of this bromo-heterocycle with 1-(2-chloro-2-phenylethyl) pyrrolidine to provide **10**, again proceeded in good yield. Suzuki coupling of the requisite boronic acid was carried out under the conditions previously described.[1] Purification of all the analogues in this phase of the study was by conventional column chromatography and the data provided in Table 1 represents mean IC_{50} values for the fully purified compounds.[7] It can be seen from these data that the inclusion of an additional nitrogen atom in the central heterocyclic portion of the molecule the parent structure, results in a decrease in affinity for the cloned human KOR by at least one order of magnitude. It appears however, that additional substituents to the terminal ring may provide a similar SAR to that for the pyridone, as the 2,4-dichloro substituted pyrimidone **4d**, showed a significant improvement in binding over **4c**. In addition, **4d** maintained good selectivity over the other opioid receptors tested and showed a clear full agonist effect ($ED_{50} = 615 \pm 66$ nM cf. 24 ± 1.8 nM for U-69,593. $E_{max} > 95\%$ relative to U-69593) in our in vitro functional test.[8] However, due to their 10–20-fold weaker activity when compared to **4b**, these structures were not pursued further.

Whilst the alkylation reactions outlined above proceed cleanly and in adequate yield, there are limitations to the range of chloro-amines that can be prepared for use in the alkylation step. This component was obtained by treatment of 2-pyrrolidino-1-phenylethanol with thionyl chloride under reflux,[9] and dehydration became a significant competing process when we tried to apply these conditions to other related examples. Moreover, such compounds are mustard agents and must be handled with extreme caution. Thus, as an alternative to the key C–N bond formation step we investigated the use of the Mitsunobu reaction, which can readily tolerate a wide range of functional groups and generally proceeds under mild conditions. The reaction has also been adapted to both solution and solid phase multiple parallel synthesis, and has also been described using solid supported reagents.[10] In addition, a wide variety of β-amino-alcohols, the considerably more benign building blocks required to couple to the pyridones, can be readily prepared in one or two steps from commercially available styrene oxides or aryl bromo-ketones as outlined in Figure 2. We found the latter route to be the most expedient, avoiding as it does the issue of regioselectivity in the epoxide ring opening, which can change significantly depending on the substituents on the Ar group.

Comins and co-workers have previously described conditions (triphenyl phosphine and diethylazodicarboxylate at rt in THF) under which they observed selective *O*-alkylation or mixtures of *O*- and *N*-alkylated products from the reaction of 2-pyridone with primary or secondary benzyl alcohols.[11] Undeterred, we investigated

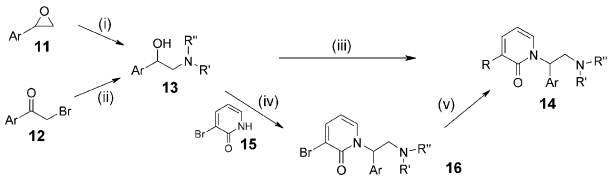


Figure 2. Reagents and conditions: (i) neat amine, reflux, or amine in methanol, reflux 15–90%; (ii) (a) amine, DIEA, DCM, rt; (b) $NaBH_4$, MeOH, water, rt 40–75%; (iii) Bu_3P, TMAD, THF, 18 h, 40–80%; (iv) Bu_3P, TMAD, THF, 18 h, 88%; (v) Suzuki, $ArB(OH)_2$, $Pd(OAc)_2$, dioxan, $NaHCO_3$, 80 °C, 4 h, 40–90% or Buchwald, $Pd_2(dba)_3$, R-BINAP, dioxan, 90 °C, 18 h, 40–90%.

Table 1.

No.	Ar	X	Y	Z	κ-Binding IC_{50} (nM ± SEM)[a]	δ-Binding IC_{50} (nM)	μ-Binding IC_{50} (nM)
4a	Ph	C	C	C	56 ± 18	> 10,000	> 10,000
4b	2,4-Cl_2Ph	C	C	C	2.3 ± 0.2	> 10,000	2100
4c	Ph	C	N	C	1760 ± 260	n.d.	n.d.
4d	2,4-Cl_2Ph	C	N	C	41 ± 7	> 10,000	9600
4e	Ph	N	C	C	2450 ± 520	n.d.	n.d.
4f	Ph	C	C	N	550 ± 70	n.d.	n.d.

Values for δ and μ binding are from single determinations. n.d., Value not determined.
[a]Values for κ binding are the arithmetical mean of at least three determinations ± SEM.

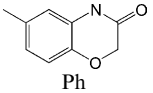
this, and a variety of alternative procedures and found that good yields for *N*-alkylation of 3-arylpyridin-2-ones with amino alcohols could be achieved using Bu_3P and 1,1′-azobis(*N*,*N*-dimethylformamide (TMAD) as the catalytic dehydrating system, with N versus O selectivities in general between 85:15 and 99:1. In addition, the combination of these reagents, and the presence of a basic amino group in our products allowed us to apply a rapid purification procedure using simple filtration, followed by ion-exchange on pre-packed SCX columns, facilitating the deployment of this chemistry in a parallel format. Having previously demonstrated in principle, that the pyridone series had functional agonist properties, we examined only the binding affinities of the new compounds for opioid receptors at this stage. After analysis by HPLC-MS, those mixtures that were of >85% purity (i.e., <15% *O*-alkylated product) were screened in the KOR binding assay at a single concentration of either 1 or 10 μM. In a typical run, a batch of 40 parallel Mitsonobu reactions resulted in only four examples where this criterion was not met [specifically 1-(2-hydroxy-3,4-dimethylbutyl] pyrrolidine in place of 2-pyrrolidino-1-arylethanols gave almost exclusive *O*-alkylation). First estimates of the IC_{50} for most compounds were made by determination of five-point dose–response curves at this stage. Selected examples, chosen to answer specific medicinal chemistry questions, were then further purified to homogeneity (>96% purity, leaving essentially no *O*-alkylated product) 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 2 represents mean IC_{50} values for the fully purified material.

Manipulation of the pyrrolidine group did not provide any improvement in the binding affinities of the resultant compounds when compared to the parent series. Other basic groups were tolerated however, with the 3-hydroxy-1-pyrrolidine replacement being the most promising, and providing some useful increase in polar surface area. Non-cyclic dialkyl amine groups in this position (e.g., 14, R,R'' = Et) resulted in significant loss in binding affinity (data not shown) as did incorporation of the less basic 1-imidazole moiety. In keeping with our previous observations, the SAR here is similar to that described for the classical ethylene diamine series of KOR agonists.[12]

The majority of substituents we looked at for our initial investigation of substitution on the Ar group, did not increase the polar surface area of the molecules. However, some of the examples that did are also shown in Table 2. Of these, the 3-carboxymethyl ether substituted analogue **14i** had disappointingly poor activity given that the same substitution has been used to confer peripheral selectivity in the classical series.[13] Again, there were no substituents tested which were better than the parent compound (with the exception of chloro substituted analogues which *increased* lipophilicity-data not shown), but the benzomorpholinone analogue **14j**, was only 7-fold poorer in binding affinity to the KOR than its parent compound and was considerably less lipophillic, giving us another useful pathway into more complex structures.

Crucially, the Mitsunobu procedure could also be applied to the bromopyridone **15** to provide intermediates of the type **16**. By the addition of a second parallel step to incorporate the substituent R, using our previously described Suzuki coupling methodology,[1] followed by a second parallel ion-exchange purification step, a wide variety of compounds of the type **14**, could be prepared in a matrix format whereby the SAR of substituents at three different positions could be examined

Table 2.

No.	R	Ar_2	NR′R″	κ-Binding IC_{50} (nM ± SEM)[a]	δ-Binding IC_{50} (nM)	μ-Binding IC_{50} (nM)
14a (=4a)	Ph	Ph	1-Pyrrolidine	56.3 ± 18	>10,000	>10,000
14b	4-CF_3–Ph	Ph	1-Pyrrolidine	8.7 ± 3.8	>10,000	2716
14c	4-CF_3–Ph	Ph	1-Morpholine	700 ± 400	>10,000	>10,000
14d	4-CF_3–Ph	Ph	1-Imidazole	>10,000	n.d.	n.d.
14e	4-CF_3–Ph	Ph	1-Diazepine	1400[b]	>10,000	>10,000
14f	Ph	Ph	1-(3-Hydroxy pyrrolidine)[c]	470 ± 140	>10,000	>10,000
14g	4-CF_3–Ph	4-(NEt_2)-Ph	1-Pyrrolidine	3080[b]	>10,000	>10,000
14h	4-CF_3–Ph	4-MeO-Ph	1-Pyrrolidine	320 ± 150	>10,000	>10,000
14i	4-CF_3–Ph	3-(OCH_2CO_2H)-Ph[d]	1-Pyrrolidine	420 ± 190	5600	>10,000
14j	4-CF_3–Ph		1-Pyrrolidine	57 ± 15	>10,000	>10,000
14k	Ph–NH–	Ph	1-Pyrrolidine	>1,000	n.d.	n.d.
14l	4-Me–Ph–NH–	Ph	1-Pyrrolidine	94 ± 29	>10,000	n.d.
14m	4-CF_3–Ph–NH–	Ph	1-Pyrrolidine	82 ± 22	>10,000	>10,000
14n	4-Me–Ph–$CH(CH_3)$NH–	Ph	1-Pyrrolidine	330 ± 110	>10,000	>10,000
U-69,593	—	—	—	2.0 ± 0.1	5800 ± 1420	250 ± 24

n.d., Value not determined.

[a]Values for κ binding are the arithmetical mean of at least two determinations ± SEM except where marked [b], which are from single determinations. All values for δ and μ binding are from single determinations.

[c]The hydroxy group of the 3-hydroxy pyrrolidine was protected as the TBDMS ether prior to reaction with styrene oxide. The final compound was isolated by treatment of the partially purified product (after SCX purification) with TFA in DCM for 24 h, followed by preparative HPLC.

[d]The acid group was protected as the methyl ester during the synthesis. The final compound was isolated by treatment of the partially purified product (after SCX purification) with LiOH in dioxan/water for 4 h, followed by preparative HPLC.

simultaneously. Furthermore, coupling of amines using the palladium-mediated coupling conditions described by Buchwald and coworkers[14] allowed preparation of amino substituted pyridones **14** (R = NH-aryl or NH-alkyl), a new class of potential kappa agonists. Again, purification was accomplished in parallel by ion exchange as outlined above. Representative examples of this latter series are shown in Table 2. In general the compounds were poorer KOR ligands than the parent series, but 4-substitution of the aryl ring in this case again provided an improvement in binding affinity, suggesting that they too bind in a manner similar to the classical series, and that the receptor pocket can accommodate substituents where the aryl ring is displaced from the pyridone ring. It was even more surprising to us that **14n**, in which these two rings are further separated, also retained weaker but significant binding affinity for the KOR.

At this stage, we opted to generate a small library of compounds with a hydroxyl group on the pyrrolidine ring. We already had an indication that this modification could be tolerated and we firmly believed that the SAR of the pyridone series and classical KOR agonist series, where such an addition can often provide significant improvements in potency,[15] are very closely related. However, as an alternative to protection of the alcohol function with TBDMS with the addition of a final deprotection step under our solution conditions described above, we decided to investigate the use of a solid phase approach, wherein the hydroxyl group was protected in a similar manner, but by a resin-bound silyl group (Fig. 3). Thus, 3-(*S*)-hydroxy pyrrolidine[15] was attached via the hydroxyl group to a Wang resin-bound benzylpropyl silyl linker, by treatment of the resin with the neat amine.

The resultant resin-bound amine could be heated with neat styrene oxide in a similar manner to the analogous solution phase reaction. Cleavage of a small portion of the resin showed that the ring opening of styrene oxide itself was completely regiospecific. Again, alkylation of aryl bromoketones followed by reduction with sodium borohydride was a more generally applicable route to ensure the required regiochemistry of the resultant amino-alcohol, and substituted analogues could be

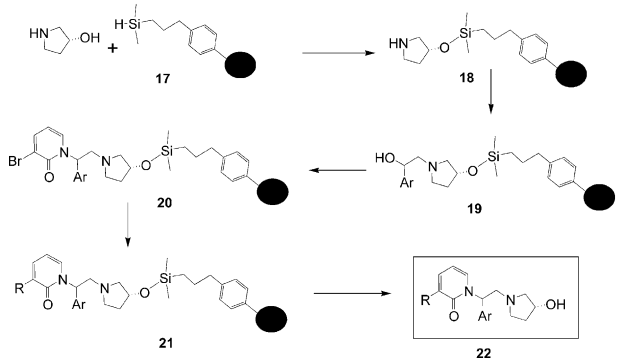


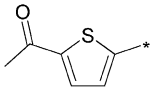
Figure 3. Reagents and conditions: (i) neat amine, 80 °C; (ii) styrene-oxide, 80 °C or (a) $ArCOCH_2Br$, DIEA, rt; (b) $NaBH_4$, MeOH, water, rt; (iii) Bu_3P, TMAD, THF, 18 h; (iv) $ArB(OH)_2$, $Pd(PPh_3)_4$, dioxan, $NaHCO_3$, 80 °C; (v) DCM, TFA.

readily prepared in this way. Having demonstrated that the Mitsunobu reaction of the amino alcohols with 3-bromo-2-pyridone gave predominantly *N*-alkylation in solution, we were pleased to find, following cleavage of a small portion of the resin produced here, that the same was true when the reaction was performed on solid phase, albeit with some minor modifications to the reaction conditions. Finally, Suzuki coupling of a commercially available set of 80 boronic acid derivatives, and acid catalysed cleavage of the final resin bound product, provided the 3-aryl-2-pyridone series **22**. The overall synthesis closely mirrored the optimised solution-phase route, but had the advantage of removing the two parallel purification stages required for the full application of that method. After analysis of the cleaved products by HPLC-MS (typical purity of mixtures of diastereomers > 85%, with the major impurities in each case arising from *O*-alkylation in the Mitsunobu reaction) and screening at 1 μM in the KOR binding assay (68 of 80 examples showed > 50% inhibition of ligand binding at this concentration) selected examples were purified to homogeneity by parallel preparative HPLC. The data provided in Table 3, where we again report only selected results mainly from the more hydrophilic substituents, represents mean IC_{50} values for the fully purified material.

In general, it appeared that most substitutions on the aryl ring had positive effects, although those substituents that provided the largest improvement in affinity in the unsubstituted pyrrolidine series,[1] were not necessarily those that were most beneficial here. The inclusion of oxygen containing groups was of clear benefit in the case of 2-formyl, 3-acetyl or 3-hydroxymethyl, but had a detrimental effect when the group was 3-carboxy (**20m**). 3- or 4-Trifluoromethoxy substitutions also gave good improvements in binding affinity. As with the unsubstituted pyrrolidine series however, incorporation of two substituents onto the aromatic ring provided a further improvement in affinity for the KOR. In particular, the 2-methoxy substituent, whilst having only a modest effect on its own (**20b**), was able to assist in providing good affinity for the KOR in combination with additional substituents (**20d–g**) although there was a notable reduction in receptor selectivity in a couple of examples. A similar combination of substituent effects was seen with the 4-Fluoro analogue **20j**, the affinity of which was improved 4-fold by addition of a 3-methyl group (**20k**). The most potent compound of this type was **20e**, with an affinity for the KOR comparable to that of the literature standard compound, U-69,593 in our hands, and a significant reduction in lipophilicity compared to the pyridone **4a**. In addition, we were able to confirm that the compound was a full agonist at the KOR ($ED_{50} = 32 \pm 9$nM in the GTPγS binding assay[8]).

Incorporation of either thiophene or fused aromatic rings lead to a significant decrease in affinity in comparison to the most potent substituted phenyl analogues (e.g., **20**, R = 2-thiophene showed only 31% inhibition of radioligand binding @ 1 μM). Reasonable activity could be rescued in this case though by incorporation of a 5-acetyl substituent (**20p**).

Table 3.

No.	R	κ-Binding IC_{50} (nM ± SEM)[a]	δ-Binding IC_{50} (nM)	μ-Binding IC_{50} (nM)
20a (=**14f**)	Ph	465 ± 135	> 10,000	> 10,000
20b	2-OMe–Ph	94 ± 29	> 10,000	n.d.
20c	3-NH_2–Ph	25 ± 19	> 10,000	2910
20d	2-OMe, 5-Cl–Ph	53 ± 11	> 10,000	190 ± 23
20e	2-OMe, 5-F–Ph	5.5 ± 1.3	460 ± 230	> 10,000
20f	2,6-$(OMe)_2$–Ph	9.8 ± 7.8	> 10,000	3910
20g	2,5-$(Ome)_2$–Ph	6.9 ± 7.1	> 10,000	2220
20h	4-OCF_3–Ph	7.6 ± 5.7	> 10,000	> 5000
20i	3-OCF_3–Ph	22 ± 13	> 10,000	> 5000
20j	4-F–Ph	33 ± 27	> 10,000	> 10,000
20k	3-Me, 4-F–Ph	8.4 ± 6.9	> 10,000	> 5000
20l	3-(CH_2OH)–Ph	9.6 ± 2.6	> 10,000	> 5000
20m	3-(CO_2H)–Ph	41% @ 1 μM	n.d.	n.d.
20n	4-$(COCH_3)$–Ph	14 ± 5.8	> 10,000	1750
20o	2-(CHO)–Ph	13 ± 10	> 10,000	n.d.
20p		38 ± 11	> 10,000	> 10,000
U–69,593	—	2.0 ± 0.1	5800 ± 1420	250 ± 24

n.d., Value not determined.
[a]Values for κ binding are the arithmetical mean of at least two determinations ± SEM except where marked [b], which are from single determinations. All values for δ and μ binding are from single determinations.

These data clearly demonstrate the advantage of running multiple parallel reactions in lead expansion, as the SAR was far from predictable. Indeed data from the unsubstituted pyrrolidine series inferred that the chloro analogue, **20d** would be most potent here, when in fact it was one order of magnitude weaker in binding affinity to the KOR then **20e**.

In summary, we have prepared a number of new analogues of our previously described 3-aryl pyridone KOR agonists. We have concentrated our efforts on changes to the structure aimed at reducing the lipohilicity and increasing the polar surface area of the resultant molecules. To expand the range of accessible derivatives we have developed parallel synthetic procedures, both in solution and on solid phase, making use of the well known and versatile Mitsunobu, Suzuki and Buchwald reactions. Although we have herein reported on the individual chemistry steps developed, the serial use of such parallel methods clearly provides a powerful tool for the exploration of the SAR of the resultant KOR agonist series. Using these techniques, we have been able to uncover interesting new structures that have served to direct our further work in this area and these efforts will be reported in due course.

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