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# Design, synthesis, and structure–activity relationship study of a novel class of ORL1 receptor antagonists based on *N*-biarylmethyl spiropiperidine

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ABSTRACT

Based on reported structures, a focused library of biarylmethyl bound to the nitrogen atom of spiropiperidine was designed. Systematic modifications allowed the discovery of a synthetically feasible and highly potent ORL1 antagonist **37**, 1′-{[1-(3-chloropyridin-2-yl)-1*H*-pyrazol-4-yl]methyl}-3*H*-spiro[2-benzofuran-1,4′-piperidine], which exhibits excellent selectivity to $\mu$, $\kappa$, and human ether-a-go-go related gene potassium channel.



A fourth opioid receptor (opioid receptor-like 1, ORL1) was discovered in 1994 based on its high degree of amino acid sequence homology to the classical opioid receptors.[1] Despite this homology, it was shown that this fourth member of the opioid receptor family did not bind to classical opioids with appreciable affinity. Soon after, its endogenous agonist was isolated from the brain, identified as a 17-amino acid peptide, and named as nociceptin or orphanin FQ (NC/OFQ).[2] Subsequently, a number of reports have demonstrated the possible involvement of the NC/OFQ-ORL1 system in pain regulation,[3] cognition,[4] anxiety,[5] and cardiovascular systems.[6] To date, however, the development of non-peptidic ORL1-antagonists with fairly good selectivity toward opioid receptors has resulted in merely a few classes:[7] benzimidazolyl piperidines,[8] benzimidazoles,[9] 4-aminoquinolines,[10] and spiropiperidines or 4-aryl piperidines.[11] Based on the latter class, we have recently developed a novel class of orally active ORL1-antagonists (**1**) that exhibits a wide safety window with regards to adverse cardiovascular effects.[12] Our initial concept of a back-up program to develop structurally diverse leads involved the synthesis of a feasible scaffold to facilitate structure–activity relationship (SAR) studies. In this report, we describe the design, synthesis, and SAR investigations of a synthetically feasible class of ORL1-antagonists based on 4-aryl piperidines (**1**–**4**)[7,12] resulting in the discovery of lead molecule **37**, which exhibits high affinity to the human ORL1-receptor, while possessing desirable in vitro features.

As shown in Figure 1, the pharmacophore of known ORL1-antagonists containing a 4-aryl piperidine ring typically possesses an aromatic ring that is connected to a basic nitrogen through a 3- or 4-atom linker. Among these, we focused our attention to compound **4** due to its simple and relatively rigid structure. Due to the limited availability of aldehydes that are bound to fused-biaromatic compounds (such as a naphthyl group), commercially available achiral biaryl aldehydes were chosen as alternative starting compounds to be introduced onto the basic nitrogen atom. To minimize the lipophilicity of the target molecules, biaryl aldehydes with one or more heteroatom(s) in the aromatic ring were favored (Fig. 1). Consequently, 78 commercially available biaryl aldehydes[13] were selected and subjected to parallel synthesis via a simple reductive amination reaction (Scheme 1). Upon purification via preparative LC–MS method, the resulting analogs were tested for their inhibitory effects on ligand binding to the human ORL1 receptor and on GTP$\gamma$S binding to proteins using membrane fractions of CHO cells expressing ORL1. Binding affinities for ORL1 were determined by displacement of [$^{125}$I]Tyr$^{14}$-NC/OFQ, and agonist/antagonist activities were measured by the [$^{35}$S]GTP$\gamma$S binding method.[14]

The binding affinities to the ORL1-receptor of selected biaryl groups ($Ar^1$–$Ar^2$) of the library (Fig. 2) are listed in Table 1. Among the 3-pyridyl substituted phenyl analogs (**5**, **6**, and **7**), which show weak binding activities, *m*-substituted analog **7** exhibited the highest binding affinity (45% inhibition at 1 $\mu$M) suggesting that the 4-atom is preferable over the 3- or 5-atom linker. Although 2-pyridyl analog **8** possessed moderate binding affinity ($IC_{50}$ 310 nM), 4-pyridyl analog **9** exhibited a drastic loss of the binding affinity. Among

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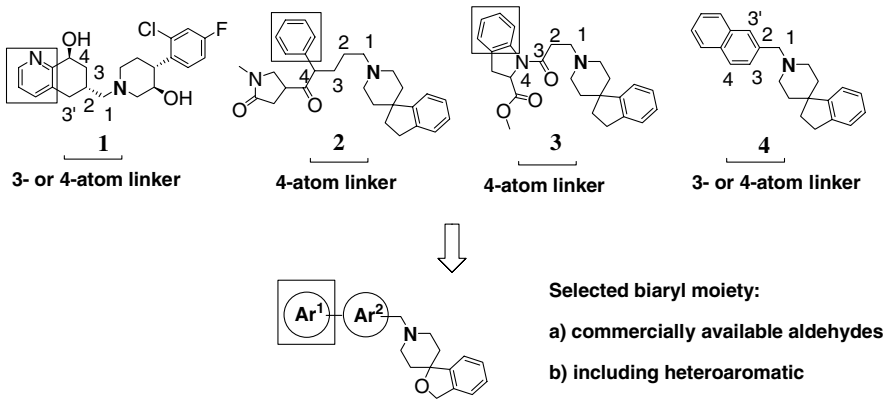
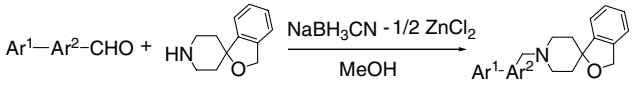



**Figure 1.** Design for biarylmethyl library based on our previous lead (**1**) and reported structures (**2**–**4**).




**Scheme 1.** Preparation of *N*-biarylmethyl spiropiperidines.

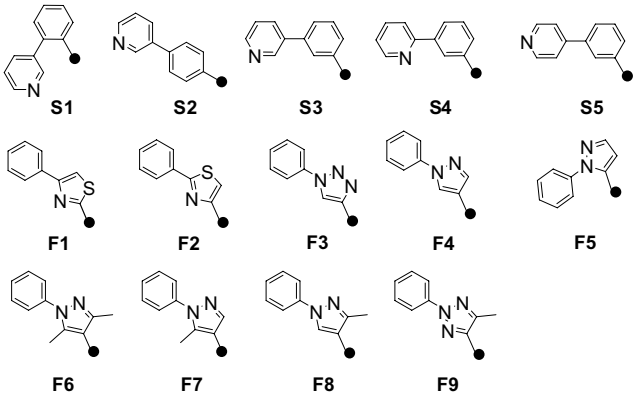
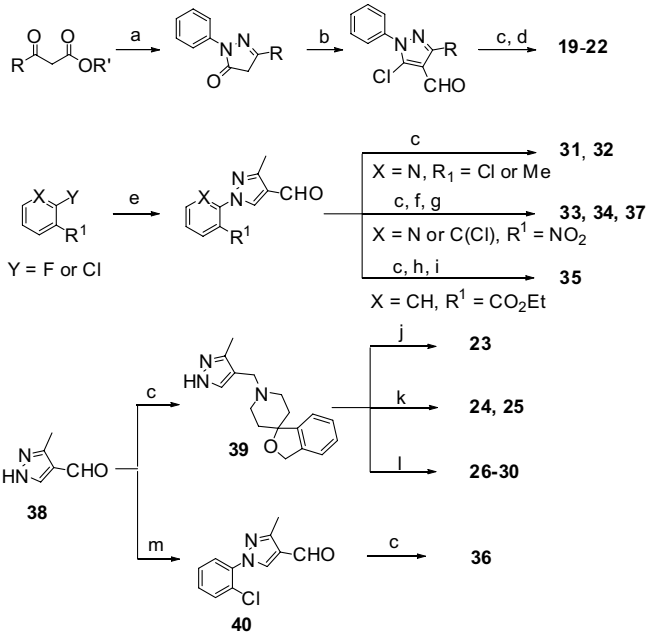


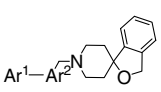

**Figure 2.** Biaryl groups (S1–S5 and F1–F9) listed in Table 1.

the 5-membered-$Ar^2$ analogs, the *N*-phenyl-1,2,3-triazole-4- (**12**) and *N*-phenylpyrazole-4- (**13**) analogs exhibited significantly higher binding affinities to ORL1 with $IC_{50}$ values of 190 and 40 nM, respectively. Introduction of a methyl group at the 3-position of the pyrazole ring resulted in a six- to eightfold increase in the binding affinities (**13** vs **17**, **15** vs **16**). In contrast, a methyl group at the 5-position resulted in 2.5-times loss in potency (**13** vs **16**), suggesting that a substituent at the 5-position is unfavorable in terms of




**Scheme 2.** Synthesis of *N*-biarylmethyl spiropiperidines. Reagents and conditions: (a) phenyl hydrazine, EtOH, 80 °C, 16–87%; (b) $POCl_3$, DMF, 110 °C, 59–80%; (c) 3H-spiro(2-benzofuran-1,4′-piperidine) hydrochloride, $NaBH_3CN$, $ZnCl_2$, MeOH, 60 °C, 50–98%; (d) $H_2$ (1 atm), Pd-C, MeOH-$Et_3N$, rt, 62–84%; (e) 3-methyl-4-formylpyrazole (**38**), NaH, DMF, rt, 64–67%; (f) $H_2$ (1 atm), Pd-C, MeOH for **33** and **34**, quant. or Fe, $NH_4Cl$ aq, MeOH, reflux for **37**, 78%; (g) $Ac_2O$, pyridine, 71% or MsCl, $Et_3N$, $CHCl_3$, 63–77%; (h) 5 N NaOH aq, THF, rt; (i) CDI, $MeNH_2$, $CHCl_3$, 50 °C, 6% in two steps; (j) 2-chloropyridine, $^t$BuOK, aliquot 336, DMSO, 37%; (k) $ArB(OH)_2$, $Cu(OAc)_2$, pyridine, MS4Å, DMF, rt, 7–24%; (l) halogenated heteroaromatics, $^t$BuOK, DMSO or NaH, THF, 4–48%; (*m*) 2-chlorophenylboronic acid, $Cu(OAc)_2$, MS4Å, air, dioxane, rt, 10%.

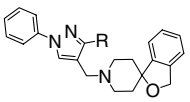
**Table 1**
Binding affinity to ORL1 of compounds **5**–**18**




| Compound | $Ar^1$–$Ar^2$ | Binding $IC_{50}$[a] (nM) | Compound | $Ar^1$–$Ar^2$ | Binding $IC_{50}$[a] (nM) |
|---|---|---|---|---|---|
| **5** | S1 | >1000 (31%) | **12** | F3 | 190 |
| **6** | S2 | >1000 (15%) | **13** | F4 | 40 |
| **7** | S3 | >1000 (45%) | **14** | F5 | >1000 (−2%) |
| **8** | S4 | 310 | **15** | F6 | 13 |
| **9** | S5 | >1000 (18%) | **16** | F7 | 100 |
| **10** | F1 | >1000 (−7%) | **17** | F8 | 6.9 |
| **11** | F2 | >1000 (3%) | **18** | F9 | >1000 (36%) |

[a] Binding affinity to ORL1 receptor. Numbers in parentheses indicate % inhibition at 1 μM. Values are calculated from a displacement of [$^{125}$I]Tyr$^{14}$-NC/OFQ ($n$ = 1, Ref. 15).

**Table 2**
Effect of substituent at 3-position on pyrazole ring



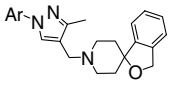
| Compound | R | Binding $IC_{50}$[a] (nM) | GTPγS (nM) $IC_{50}$[b] (nM) |
|---|---|---|---|
| **17** | -Me | 6.9 | 1.6 |
| **19** | -Et | 9.4 | 8.4 |
| **20** | -$^{i}$Pr | 21 | – |
| **21** | -$^{t}$Bu | 59 | – |
| **22** | -Benzyl | 30 | – |

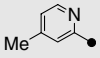
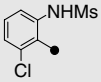
[a] Values are calculated from a displacement of [$^{125}$I]Tyr$^{14}$-NC/OFQ ($n$ = 1, Ref. 15).
[b] –, not tested.

the binding affinity. Replacement of the pyrazole ring with 4-phenylthiazole (**10**), 2-phenylthiazole (**11**), and 2-phenyl-4-methyltriazole (**18**) rings resulted in analogs with complete loss of the binding affinity.

Based on the favorable results of the *N*-phenyl-4-pyrazolyl group, several spiropiperidine analogs possessing *N*-substituted-4-pyrazolyl groups were prepared to extend our SAR studies. The synthetic scheme of *N*-biarylmethyl spiropiperidine derivatives **19**–**37** is outlined in Scheme 2. Target molecules with various substituents at the 3-position of the pyrazole ring were prepared from *N*-phenyl-4-formylpyrazoles, which was obtained via the Vilsmeier reaction of pyrazolones. Subsequent reductive amination via $NaBH_3CN$-$ZnCl_2$, followed by de-chlorination via hydrogenolysis in the presence of triethylamine provided the corresponding target molecules. Synthesis of the aromatic ring at the 1-position of the

**Table 3**
Effect of substituent at 1-position on pyrazole ring



| Compound | Ar | Binding $IC_{50}$[a] (nM) | Antagonism GTPγS[b] (nM) | log$D_{7.4}$[c] |
|---|---|---|---|---|
| **17** |  | 6.9 | 1.6 | >4 |
| **23** |  | 12 | 16 | 3.1 |
| **24** |  | 130 | – | 3.2 |
| **25** |  | 820 | – | 3.7 |
| **26** |  | 200 | – | 3.5 |
| **27** |  | 93 | – | 2.9 |
| **28** |  | 43 | – | 3.9 |
| **29** |  | 280 | – | 3.5 |
| **30** |  | 19 | 45 | 3.2 |
| **31** |  | 4.5 | 2.7 | 3.1 |
| **32** |  | 2.6 | 2.6 | 2.7 |
| **33** |  | 27 | – | 3.2 |
| **34** |  | 11 | – | 2.1 |
| **35** |  | 22 | – | 1.4 |
| **36** |  | 0.65 | 0.87 | 3.7 |
| **37** |  | 1.9 | 0.53 | 2.1 |

[a] Values are calculated from a displacement of [$^{125}$I]Tyr$^{14}$-NC/OFQ ($n$ = 1, Ref. 15).
[b] –, not tested.
[c] Measured by shake-flask method.

**Table 4**
Off-target activities ($\mu$, $\kappa$, and hERG $K^+$ channel) and in vitro metabolic stability of **17**, **31**, **32**, and **37**

| Compound | Binding affinity, $IC_{50}$ (nM) | | | | In vitro metabolic stability (%)[c] | |
|---|---|---|---|---|---|---|
| | ORL1 | $\mu$[a] | $\kappa$[a] | hERG $K^+$[b] | HM | RM |
| **17** | 6.9 | 6200 | 9700 | 740 | 28 | 4 |
| **31** | 4.5 | 7400 | >10,000 | 7800 | 60 | 6 |
| **32** | 2.6 | 4400 | >10,000 | 13,000 | 64 | 1 |
| **37** | 1.9 | >10,000 | >10,000 | 17,000 | 54 | 69 |

[a] Displacement of a [$^3$H]diprenorphin ($\mu$), and [3H]U-69593 ($\kappa$) binding to CHO cells stably expressing cloned human $\mu$-, and $\kappa$-opioid receptors, respectively.
[b] Displacement of a [$^{35}$S]-radiolabeled MK-499 in membranes derived from HEK 293 cells stably transfected with hERG gene and expressing the IKr channel protein.
[c] See Ref. 16 for detailed description.

pyrazole ring was based on one of two methods: (1) nucleophilic addition-elimination reaction of 3-methylpyrazolyl intermediates (**38** or **39**) with the corresponding halogenated aromatic compounds, followed by reductive amination, or (2) coupling reaction of intermediates **38** or **39** with the corresponding aryl boronic acids mediated by $Cu(OAc)_2$. The substituents of the aryl ring were further converted into the desired functional groups via conventional methods.

SAR studies were carried out to assess the effects of substituents at the 3-position of the pyrazole ring (Table 2). Substitution with a methyl group (**17**) resulted in, not only high binding affinity, but also good antagonist activity. In comparison, substitution with a longer ethyl group (**19**) exhibited similar binding affinity, but the antagonist activity decreased to 1/5 that of **17**. Introduction of bulkier substituents ($^i$Pr, $^t$Bu, and benzyl) decreased the binding affinity from 1/3 to 1/8 that of **17**. These results show that, in terms of the binding and antagonist activities, a methyl group is the optimal alkyl substituent at the 3-position of the pyrazole ring.

Next, the effects of the aryl group (Ar) at the 1-position of the pyrazole ring on the binding and antagonist activities were determined (Table 3). In terms of lipophilicity, analog **17** possesses a relatively high $\log D_{7.4}$ value (>4). We have previously reported that, for a lead structure possessing a 4-aryl piperidine group, adjustment of the lipophilicity was essential in removing its affinity to the hERG $K^+$ channel.[12] Indeed, **17** exhibited a sub-μM order binding affinity to the hERG $K^+$ channel (Table 4). To help identify a potential lead molecule, SAR studies were carried out using analogs with hydrophilic aryl groups. Although the 3- and 4- pyridine analogs (**24** and **25**, respectively) resulted in significantly decreased binding affinities, the 2-pyridine analog (**23**) retained the binding affinity while reducing the lipophilicity ($\log D_{7.4}$ value of 3.1) – its antagonist activity was 1/10 than that of **17**. The 2-pyrazine or 2-pyrimidine analogs (**26** and **27**, respectively) exhibited drastically decreased binding affinities.

Consequently, substituent effects were investigated using analogs that incorporated various groups on the 2-pyridine ring (**28**–**35**). Substitution at the 3-position of the pyridine ring with a methyl (**31**) or chloro (**32**) group resulted in a five- to sixfold increase in the antagonist potencies, while exhibiting comparable lipophilicity as that of **23**. Whereas analogs with an acetamide or an *N*-methylamide substituent (**33** and **35**, respectively) decreased the affinity by one half, incorporation of a methanesulfonamide group did not affect the binding affinity (**23** vs **34**). Based on these encouraging results, we revisited the benzene analog for further structural modification. Accordingly, introduction of a chlorine atom dramatically enhanced the in vitro potency (**36**). The combination of **36** with a methanesulfonamide group led to identification of analog **37**, which exhibited sub-nM antagonist activity while possessing a lower lipophilicity than that of **23**.

Because analogs **31**, **32**, and **37**[17] exhibited good in vitro potency while possessing reasonable lipophilicity, their off-target selectivities against $\mu$-, $\kappa$-opioid receptors, and hERG $K^+$ channel and in vitro metabolic stabilities were determined (Table 4). Analog **37** was shown to be a highly selective ORL1-antagonist against $\mu$-, and $\kappa$-opioid receptors, and hERG $K^+$ channel with moderate in vitro metabolic stability. Further studies revealed that analog **37** is not subject to human P-gp efflux (transport ratio of 1.8),[18] suggesting that its brain penetrability might be suitable for humans.

In conclusion, based on the structures of previous leads, a highly potent and selective class of compounds was investigated as novel ORL1-antagonists. SAR studies of this class of compounds have led to the identification of analog **37**, which exhibits high affinity to the human ORL1 receptor while possessing other desirable in vitro profiles that merit further developments. Further pharmacological studies of this compound and its analogs are currently under way.

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13. Seventy-eight kinds of aldehydes consist of the following structures: pyridine-substituted benzaldehydes (8 kinds), pyrimidine substituted benzaldehydes (4 kinds), 4-(1-pyrro)benzaldehyde, 4-(2-thiazolyl) benzaldehyde, 4-(1,2,3-thiadiazol-4-yl)benzaldehyde, 2-methyl-3-formyl-5-phenylfuran, 3-methyl-4-formyl-5-phenyl-1,2-oxazole, 2-methyl-3-formyl-4-phenyl-1,2-oxazole, 2-formyl-5-phenylthiophene, 2-formyl-5-(2-pyridyl) thiophene, 2-formyl-thiazoles with aromatic substituent (11 kinds), 4-formyl-2-phenylthiazole, 2-formylpyrroles with aromatic substituent at the 1-position (37 kinds), 1-(2-cyanophenyl)-3-formylpyrrole, 3-formylpyrazoles with aromatic substituent at the 1-position (6 kinds), 1-phenyl-5-formylpyrazole, 1-phenyl-4-formyl-1,2,3-triazole.
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16. Rat microsomal (RM) and human microsomal (HM) stabilities were determined by percentage parent compound (1 μM) remaining after 30 min (37 °C) incubation with rat/human liver microsomes (0.25 mg protein/ml).
17. Analytical data for HCl salt of compound **37**. $^1$H NMR(400 MHz, DMSO-$d_6$) $\delta$ [ppm] 1.82–1.86 (2H, m), 2.36 (3H, s), 2.36–2.39 (2H, m), 2.98 (3H, s), 3.18–3.22 (2H, m), 3.46–3.50 (2H, m), 4.28 (2H, s), 5.03 (2H, s), 7.13–7.15 (1H, m), 7.32–7.34 (3H, m), 7.52–7.56 (3H, m), 8.15 (1H, s), 9.18 (1H, s). MS (ESI+): *m*/*z* 487.3 $[M+H]^+$.
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