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Solid-phase synthesis of 4-biaryl-piperidine-4-carboxamides

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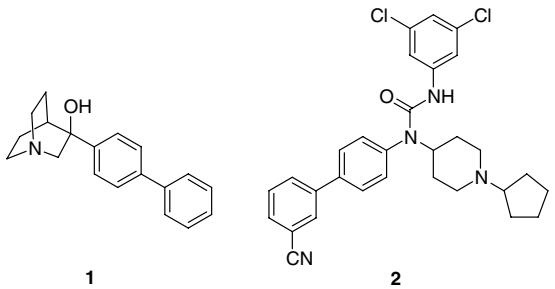
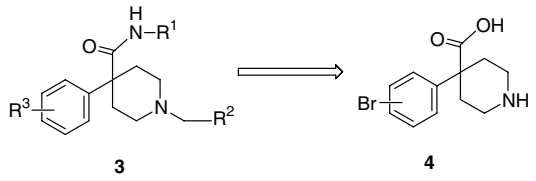
Abstract—A novel solid-phase synthesis of 4-biaryl-piperidine-4-carboxamides has been developed using FDMP resin with a carboxamide as the anchor point. With this approach, three points of diversity were incorporated into a GPCR-directed scaffold. Final products were obtained in good purity and yield.

Two common structural motifs that are found in G-protein coupled receptor (GPCR) ligands contain either biaryl or piperidinyl groups, which are considered to be privileged structures for GPCR ligands.[1] Examples of these include compound **1**, an SQS inhibitor,[2a] and compound **2**, an MCH antagonist (Fig. 1).[2b] The fact that these moieties frequently appear in different GPCR ligands is attributed to their binding to conserved regions of target proteins. In efforts to discover potent ligands for GPCR targets based on the structural motifs of the biaryl and piperidinyl groups, compound **3**, featuring three points of diversity, was designed (Fig. 2). Compound **3** could be derived from scaffold **4**, which would allow for a structurally diverse set of compounds through solid-phase chemistry. As the first point of diversity, a variety of amines (for R^1 in **3**) would serve as an anchor point to immobilize scaffold **4** onto a solid support. The piperidinyl end of the scaffold could allow for reductive amination, acylation, or N-arylation[3] to introduce the second diversity point. Finally, the third



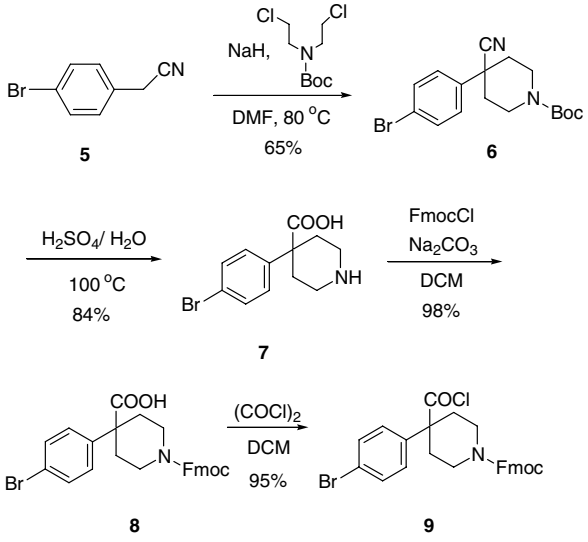
1 2

Figure 1. Biologically important molecules featuring biaryl or piperidino moieties.



3 4

Figure 2. Design of compound **3** with three points of diversity.



Scheme 1. Synthesis of scaffold material.

Keywords: Solid-phase; Suzuki coupling; Biaryl-piperidine.
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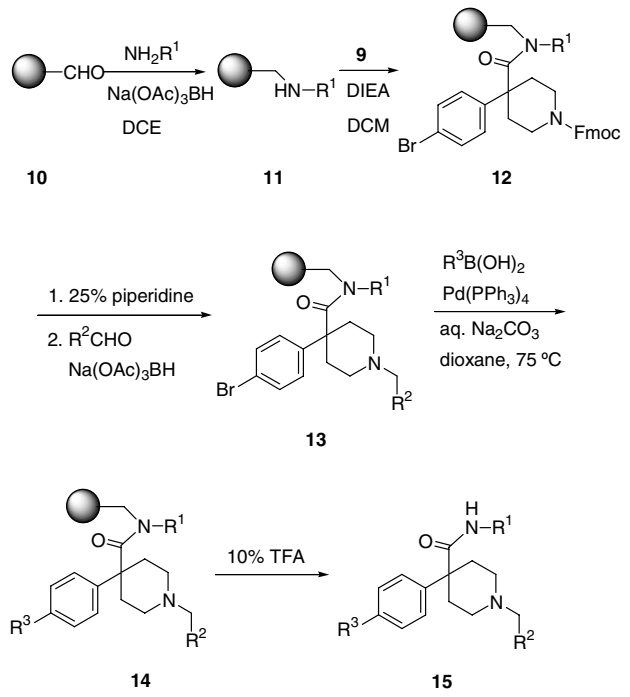


Scheme 2. Solid-phase synthesis of biaryl-piperidines.

diversity point could be incorporated through a Suzuki coupling reaction on the aromatic ring.

The synthesis of scaffold **8** commenced with dialkylation of **5** yielding Boc protected piperidine **6** (Scheme 1),[4] which upon hydrolysis,[5] provided the free amine **7**. Subsequent protection with FmocCl provided acid **8**.

FDMP resin (loading 1.5 mmol/g), known for its versatility in solid-phase chemistry,[6] was employed in the chemistry development process. Amines were first attached to this solid support through a reductive amination reaction[7] with $NaBH(OAc)_3$ in 1,2-dichloroethane (Scheme 2). Direct coupling of acid **8** to the solid bound amine **11** via coupling reagents was problematic, presumably due to the steric hindrance involved. However, conversion of the acid to the corresponding acid chloride **9** allowed for smooth acylation with **11** in the presence of Hunig's base. Deprotection of **12** was effected with 25% piperidine in DMF, followed by a second round of reductive amination leading to **13**.

Finally, the third diversity point was introduced through a Suzuki coupling of **13**. The coupling reaction did not go to completion upon a catalytic amount of $PdCl_2(PPh_3)_2$. However, when $Pd(PPh_3)_4$ was used, the reaction went to completion in both high yields and

Table 1. Solid-phase synthesis of biaryl-piperidines

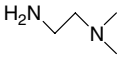
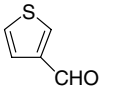
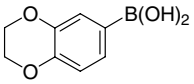
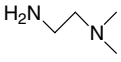
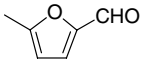
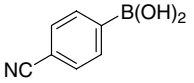
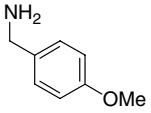
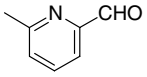
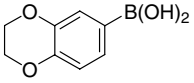
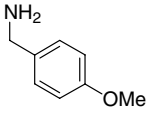
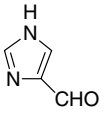
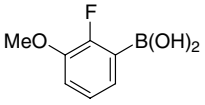
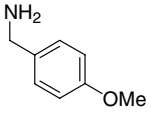
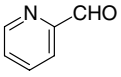
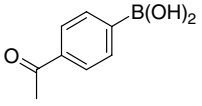
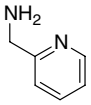
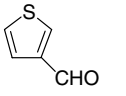
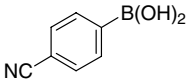
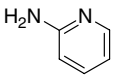
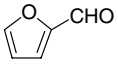
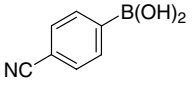
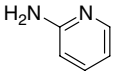
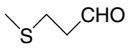
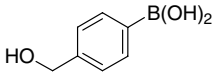
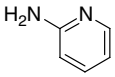
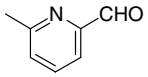
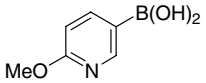
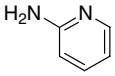
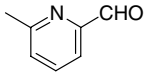
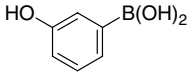
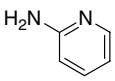
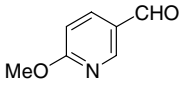
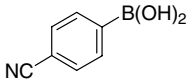
Entry	Amine R^1NH_2	Aldehyde R^2CHO	Boronic acid $R^3B(OH)_2$	Purity of **15**[a] (%)	Yield[b] (%)
1				94	45
2				93	42
3				96	66 61[c]
4				90	62
5				99	70 64[c]
6				95	42
7				100	72 66[c]

Table 1 (*continued*)

Entry	Amine R^1NH_2	Aldehyde R^2CHO	Boronic acid $R^3B(OH)_2$	Purity of **15**[a] (%)	Yield[b] (%)
8				100	86
9				96	85 80[c]
10				96	67
11				91	66

[a] Determined by LC–MS with both UV and ELSD detectors; further confirmed with ^1H NMR analysis.
[b] Determined by weight of the crude products based on the loading of the resins.
[c] Isolated yield.

purity. In addition, the purity of the final products appeared to be better when dioxane was used as the solvent rather than with DMF or THF. Cleavage with 10% TFA in DCM afforded the desired product **15**.

As shown in Table 1, a variety of amines were examined. Some amines led to a low yield of the final products, though the purity was found to be satisfactory (entries 1 and 2).[8] Heterocyclic aldehydes were incorporated to further increase structural diversity. Examples include thiophenyl, furanyl, and pyridinyl groups (entries 1, 2, and 3). Both electron-donating groups and electron-withdrawing groups on the aryl moiety of boronic acids led to the expected products in good purity. Functional groups such as alcohols, phenols, cyano, and carbonyl groups are tolerated in the final coupling reaction (entries 2, 5, 9, and 11).

In conclusion, an efficient solid-phase synthesis of bi-aryl-piperidines has been developed.[9] The immobilized bromo-aryl scaffold could allow not only for manipulation of the nitrogen, but also incorporation of various groups on the aryl moiety.

Acknowledgments

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8. Analytical data for selected compounds. Compound **15-1**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.60–6.88 (m, 10H), 4.28 (s, 2H), 4.26 (s, 2H), 4.21 (s, 1H), 3.61–3.44 (m, 4H), 3.15–2.82 (m, 4H), 2.68 (s, 3H), 2.58 (s, 3H), 2.40–2.16 (m, 6H); MS (ELS): 506.2 ($M+H^+$). Compound **15-2**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.38 (m, 9H), 6.02–5.98 (m, 1H), 4.12 (s, 1H), 3.80–3.62 (m, 4H), 3.18–2.80 (m, 2H), 2.76 (s, 3H), 2.58 (s, 3H), 2.24 (s, 3H), 2.25–1.90 (m, 8H); MS (ELS): 471.6 ($M+H^+$). Compound **15-3**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–6.75 (m, 14H), 4.92 (bs, 1H), 4.32 (s, 4H), 4.28 (s, 2H), 3.78 (s, 3H), 3.42 (br s, 2H), 2.59 (s, 3H), 2.58–2.42 (m, 8H); MS (ELS): 564.7 ($M+H^+$).
9. Typical procedures. Attachment of amines to solid support: To a suspension of FDMP (2-(3,5-dimethoxy-4-formyl-phenoxy)ethoxymethyl) resin (1.5 mmol/g) in 2% acetic acid in DCE was added the amine (6 equiv, 0.4 M). The reaction mixture was shaken for 2 h, followed with the addition of $NaBH(OAc)_3$ (10 equiv). The mixture was shaken overnight at room temperature. After quenching the excess of $NaBH(OAc)_3$ with methanol, the resin was washed with MeOH, DCM, then DMF (2×), MeOH, and DCM successively, and then dried in vacuo overnight.

Acylation of solid bound amines and deprotection: To a suspension of resin **10** in DCM was added DIEA (5 equiv), followed with acid chloride **9** (2 equiv). The mixture was shaken at room temperature for 5 h. The resin was washed with DCM, MeOH, DMF, and MeOH successively. A solution of 20% piperidine in DMF was added to the resin. The mixture was shaken for 30 min. After draining the solvent, a fresh solution of piperidine in DMF was added to the resin, and the mixture was shaken for another 30 min. The solvent was then drained. The resin was washed successively with DMF, MeOH, and DCM, and then dried in vacuo overnight. Reductive amination: To a suspension of the resin (1.5 mmol/g) in 2% acetic acid in DCE was added the aldehyde (6 equiv, 0.4 M). The reaction mixture was shaken for 2 h, followed with the addition of $NaBH(OAc)_3$ (10 equiv). The mixture was shaken overnight at room temperature. After quenching the excess of $NaBH(OAc)_3$ with methanol, the resin was washed with MeOH, DCM, then twice with DMF, MeOH, and DCM successively, and then dried in vacuo overnight. Suzuki coupling: To a suspension of resin **13** in dioxane was added $Pd(PPh_4)_3$ (5 mol %), aqueous Na_2CO_3 (2 M, 20 equiv), and boronic acid (10 equiv). The mixture was flushed with argon, and the reaction vessel was then sealed. The reaction vessel was heated at 75 °C for 20 h. The resin was washed with water, DMF, MeOH, DCM, and MeOH, and then dried in vacuo overnight. Cleavage of product from the resin: The resin was treated with 10% TFA in DCM for 30 min. After the solvent was evaporated, the compounds were analyzed with proton NMR and LC–MS. The LC–MS instrument was equipped with an analytical HPLC column and a UV detector in determining the purity of the products. NMR data was also collected on the crude products. To further confirm on the yield and purity of the products, a small set of compounds (out of those in Table 1) were purified. The yields of the purified compounds were consistent with the reported yields of the crude products.