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Spiroazetidine–piperidine bromoindane as a key modular template to access a variety of compounds via C–C and C–N bond-forming reactions

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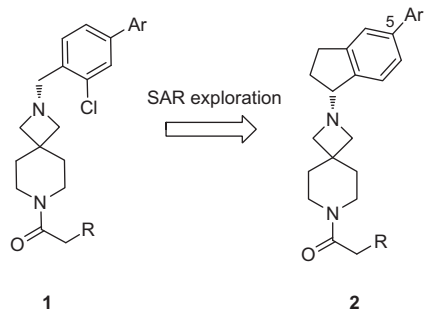
ABSTRACT

In the context of our ghrelin inverse agonist program, a functionalized bromoindane **3** provided a versatile intermediate for structure–activity relationship studies. After developing operationally simple cross-coupling reactions, a broad spectrum of chemical space was successfully explored. Optimization of a one-pot borylation/Suzuki sequence provided the desired products in high yield with low loading of the palladium catalyst. High yields of N-linked heterocyclic analogues were obtained through palladium catalyzed C–N bond formation. In addition, carboxylation of the bromoindane provided an indane carboxylic acid for further diversification.

Modular intermediates are key components of any drug discovery program. They can provide efficient access to analogues and allow for rapid structure–activity relationship (SAR) exploration. Points of diversity within an intermediate combined with a robust synthesis allow the discovery team to make rational decisions on the structures they wish to pursue for their program. Our team was interested in the structural diversity of spiroazetidine–piperidines **1** and **2** (Fig. 1) as ghrelin[1] inverse agonists and their use as therapeutic agents to treat type 2 diabetes.[2] We recently disclosed the SAR work around scaffold **1**,[3] the synthesis of the chiral spiroazetidine–piperidines,[4] and now wish to report the synthetic enablement of the heteroaromatic region of scaffold **2**.

To access various structural analogues of **2**, synthetic enablement was required to effectively vary the heteroaryl group off the indane ring. It was envisioned that intermediate **3** could be a modular starting point conducive to chemical space expansion and SAR exploration. The *N*-Boc protected piperidine ring would allow for orthogonal piperidine amide SAR development, while the aryl halide would allow for exploration of a variety of aryl groups at C5 (Scheme 1).

The bromoindane **3** was prepared as described previously from a chirally pure bromoindane amine and *N*-Boc-piperidine chloroaldehyde under reductive amination/cyclization conditions.[4] Reaction of **3** with a variety of boronic acids was demonstrated; however, the limited availability of heteroaryl boronic acid monomers impacted the diversity of chemical space that could be explored.[5] In comparison, a diverse pool of heteroaryl halides are available and we therefore reasoned that conversion of **3** to the intermediate boronate **4** followed by Suzuki coupling with a variety of aryl halides would allow us to probe broader chemical space.



1 2

Figure 1. Core structures of ghrelin inverse agonists for SAR exploration.

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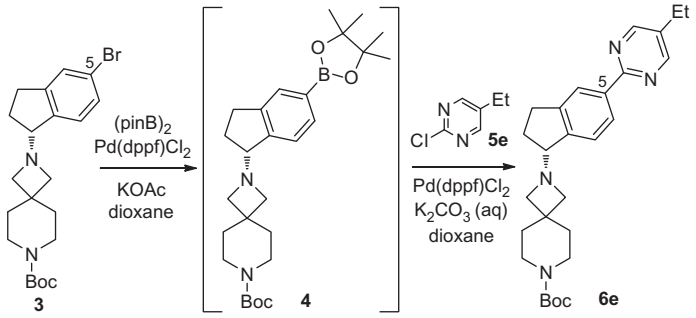


Scheme 1. One-pot borylation/Suzuki reaction of bromoindane **3**.

The intermediate **4** was isolated in 64% yield and was subjected to the Suzuki coupling, but the overall yield over the two-steps was low (~50%) and **4** was not stable for storage (prone to hydrolysis and further decomposition). Thus, the one-pot approach seemed more appealing. Initial conditions for the one-pot two-step Suzuki sequence involved heating **3** with 5 mol % of 1,1′-bis(diphenylphosphino)ferrocene)dichloro palladium ($Pd(dppf)Cl_2$), bis(pinacolato)diboron ($(pinB)_2$) (1.1 equiv), and potassium acetate (4 equiv) in 1,4-dioxane at 80–110 °C for 4–6 h, followed by addition of the heteroaryl chloride such as **5e**, additional 5 mol % of $Pd(dppf)Cl_2$, and aqueous potassium carbonate (7 equiv) and heating the mixture in 1,4-dioxane at 110 °C for 18 h to give 68% yield of **6e** after silica gel chromatography. Several analogues were made following this protocol (Table 1, conditions A) and they tended to have dark color even after several chromatographic purifications. The relatively large amount of palladium used over the two-steps was considered to be the cause of the discoloration.

To avoid additional chromatography and to increase purity, the two-step one-pot Suzuki process was optimized using 2-chloro-5-ethylpyrimidine as the coupling partner. Each step was studied separately by following the course of the reaction by HPLC. First, the temperature and time of the borylation reaction were studied. With 5 mol % of the Pd-catalyst the reaction did not proceed at all at room temperature. Increasing the temperature to 110 °C for 1 h with the same catalyst loading showed full conversion to the intermediate boronate **4**. The catalyst loading was reduced to 3 mol % and finally to 1 mol % at 110 °C resulting in full conversion to **4** in 1 h. To this reaction mixture was added 2-chloro-5-ethylpyrimidine (**5e**), potassium carbonate (7 equiv), various amounts of catalyst (1–5 mol %) and the reactions were monitored by HPLC. After 3 h at 110 °C, the reactions with 2–5 mol % catalyst had reached completion, whereas the reaction with just 1 mol % was 90% complete. This reaction did not proceed further even after heating for 18 h. However, the total catalyst loading was reduced from 10 to 3 mol % and the reaction time was reduced from 24 to 4 h. In addition, the purity increased to 98% (HPLC) to produce **6e** as an off-white solid.[6]

Several other heteroaryl halides were tested in this reaction and the results are shown in Table 1. In general, the reaction works well with six-membered heteroaryl chlorides **5a**–**5i** (yields between 63% and 94%, entries 1–9). When a hydrolytically labile group (i.e., nitrile or ester) is present, the yield drops due to partial hydrolysis of the final product under the reaction conditions (entries 10–12). A similar result was observed for compound **6v** which was obtained in 24% yield from the boronic acid **5v** under standard Suzuki conditions with 5 mol % of $Pd(PPh_3)_4$ (entry 22). In contrast, compound **6m** (entry 13) and the starting material **5m** seemed to be stable toward hydrolysis and the product was isolated in quantitative yield.

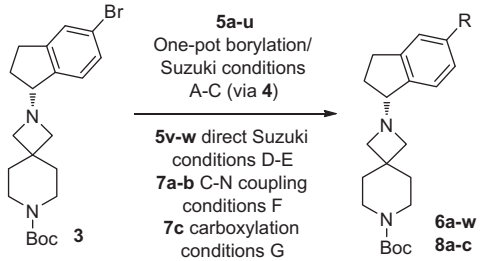
The primary amide containing halide **5n** also gave the desired product under conditions A (entry 14); however, the reaction did not go to completion (21% conversion by HPLC), even after prolonged heating and isolation of **6n** was unsuccessful. Compound **6w** was made from the boronic acid **5w** (entry 23) in quantitative yield under direct Suzuki coupling of **3** with 5 mol % of $Pd(OAc)_2$ and trisodium triphenylphosphine-3,3′,3″-trisulfonate (TPPTS) ligand (20 mol %). Five-membered heteroaryl analogues were obtained from the bromides **5o**–**5t** under conditions A to give **6o**–**6t** between 32–96% yields (entries 15–20). The yield of **6u** from 2-iodooxazole[7] (**5u**) (entry 21) was rather low due to the instability of 2-iodooxazole under aqueous conditions.

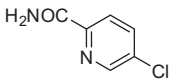
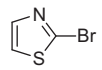
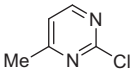
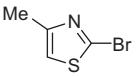
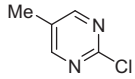
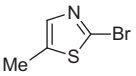
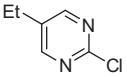
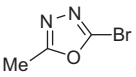
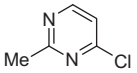
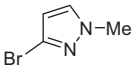
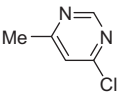
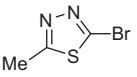
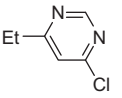
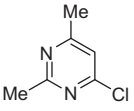
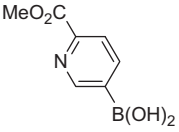
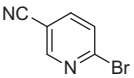
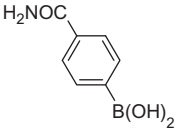
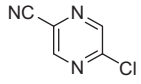
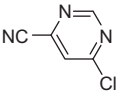
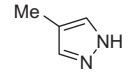
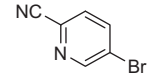
Upon scale-up of **6f** and **6g**, the one-pot Suzuki procedure was further optimized using only one portion of 2.5 mol % of Pd $(PPh_3)_2Cl_2$ to give the desired products in high purity without chromatographic purification. The solvent was exchanged to toluene to avoid potential peroxide generating 1,4-dioxane on larger scale. Using NaOH in place of K_2CO_3 also improved the reaction, presumably by effecting a more efficient in-situ boronate ester hydrolysis reaction. An aqueous acid–base work up followed by treatment with Isolute® Ultra pure thiol silica gel gave >99% pure material.[8] Both **6f** and **6g** were scaled up (>100 g) via this method in almost quantitative yields.

In addition to one-pot borylation/Suzuki couplings and direct Suzuki couplings, the bromoindane **3** can be subjected to Buchwald-type couplings with NH-containing heterocycles **7a**–**7b** (entries 24 and 25).[9] Using 4 mol % of tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) catalyst and 8 mol % of 5-(di-*tert*-butylphosphino)-1′3′5′-triphenyl-1′*H*-[1,4]bipyrazole (BippyPhos) ligand[10] products **8a** and **8b** were isolated in great yields and purity. Carboxylation of bromoindane **3** provided an additional handle for structural diversity and was achieved with $Mo(CO)_6$ and 5 mol % of Herrmann's catalyst[11] (trans-bis(acetate)bis[*o*-(di-*o*-tolylphosphine)benzyl]dipalladium(II)) in the presence of aqueous sodium carbonate to give carboxylic acid **8c** in moderate yield. Removal of the *N*-Boc-group of compounds **6a–w** and **8a–c** using standard acidic conditions (TFA or HCl) followed by amide coupling with a variety of carboxylic acids provided a number of potent ghrelin inverse agonists. A description of these compounds along with key data will be provided in a separate communication.

In conclusion we have discovered smooth and operationally simple methods for efficient delivery of a number of heteroaryl analogues **2** from a key intermediate **3**. These include a one-pot two-step Suzuki protocol, a Buchwald-type coupling reaction, and a carboxylation reaction. Optimization of the Suzuki reaction for lower catalyst loading provided final products in high yield and purity on small as well as on large scale. The synthetic methods identified enabled rapid SAR exploration of the indane scaffold **3** in the context of the drug discovery program.

Table 1
Examples of compounds accessible from bromoindane **3**



Entry	Reactant	Conditions[a]	Product (yield)[b] (%)	Entry	Reactant	Conditions[a]	Product (yield)[b] (%)
1	**5a** 	B	**6a** (99)	14	**5n** 	A	**6n** (21)[c]
2	**5b** 	A	**6b** (63)	15	**5o** 	A	**6o** (80)
3	**5c** 	B	**6c** (94)	16	**5p** 	A	**6p** (60)
4	**5d** 	A	**6d** (81)	17	**5q** 	A	**6q** (32)
5	**5e** 	B	**6e** (>99)	18	**5r** 	A	**6r** (47)
6	**5f** 	C	**6f** (84)	19	**5s** 	A	**6s** (78)
7	**5g** 	C	**6g** (86)	20	**5t** 	A	**6t** (96)
8	**5h** 	A	**6h** (88)	21	**5u** 	A	**6u** (20)
9	**5i** 	A	**6i** (82)	22	**5v** 	D	**6v** (24)
10	**5j** 	A	**6j** (19)	23	**5w** 	E	**6w** (>99)
11	**5k** 	A	**6k** (54)	24	**7a** 	F	**8a** (82)
12	**5l** 	A	**6l** (20)	25	**7b** 	F	**8b** (79)
13	**5m** 	B	**6m** (>99)	26	**7c** $Mo(CO)_6$	G	**8c** (51)

[a] Conditions: (A) (i) $Pd(dppf)Cl_2$ (5 mol %), $(pinB)_2$ (1.1 equiv), KOAc (4 equiv), dioxane, 110 °C, 4–6 h; (ii) Ar-X (1.2 equiv), $Pd(dppf)Cl_2$ (5 mol %), K_2CO_3 (7 equiv), dioxane, 110 °C, 18 h. (B) (i) $Pd(dppf)Cl_2$ (1.6 mol %), $(pinB)_2$ (1.1 equiv), KOAc (4 equiv), dioxane, 110 °C, 1 h; (ii) Ar-X (1.2 equiv), $Pd(dppf)Cl_2$ (2.5 mol %), K_2CO_3 (7 equiv), dioxane, 110 °C, 3 h. (C) (i) $Pd(PPh_3)_2Cl_2$ (2.5 mol %), $(pinB)_2$ (1.1 equiv), KOAc (4 equiv), toluene, 100 °C, 1.5 h; (ii) Ar-X (1.2 equiv), NaOH (5 equiv), toluene, 90 °C, 5 h; (iii) HCl, isolute® ultra pure thiol silica gel. (D) $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (2 equiv), dioxane, 95 °C, 18 h. (E) $Pd(OAc)_2$ (5 mol %), TPPTS (20 mol %), iPrNH (2.4 equiv), H_2O/MeCN, 90 °C, 2 h. (F) Pd_2dba_3 (4 mol %), BiPPyPhos (8 mol %), Cs_2CO_3 (1.5 equiv), dioxane, 100 °C, 18 h. (G) Herrmann's catalyst (5 mol %), Na_2CO_3 (3 equiv), 155 °C, μwave, 20 min.

[b] Yield refers to isolated product and is reported as an average of minimum of two experiments.

[c] HPLC conversion, not isolated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.047. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For ghrelin background, see: (a) Kojima, M.; Hosoda, H.; Date, Y.; Nakazato, M.; Matsuo, H.; Kangawa, K. *Nature* **1999**, 656–660; (b) Leite-Moreira, A. F.; Soares, J.-B. *Drug Discovery Today* **2007**, *12*, 276–288; (c) Dezaki, K.; Sone, H.; Yada, T. *J. Biochem.* **2008**, *118*, 239–249; (d) Sato, T.; Nakamura, Y.; Shiimura, Y.; Ohgusu, H.; Kangawa, K.; Kojima, M. *J. Biochem.* **2012**, *151*, 119–128.
2. Bhattacharya, S. K.; Cameron, K. O.; Fernando, D. P.; Kung, D.W.; Londregan, A. T.; McClure, K. F.; Simila, S. T. M. PCT Int. Appl. WO2011114271, 2011; PCT/1B2011/051035; *Chem. Abstr*. **2011**, *155*, 483976.
3. Kung, D. W.; Coffey, S. B.; Jones, R. M.; Cabral, S.; Jiao, W.; Fichtner, M.; Carpino, P. A.; Rose, C. R.; Hank, R. F.; Lopaze, M. G.; Swartz, R.; Chen, H.; Hendsch, Z.; Posner, B.; Wielis, C. F.; Manning, B.; Dubins, J.; Stock, I. A.; Varma, S.; Campbell, M.; DeBartola, D.; Kosa-Maines, R.; Steyn, S. J.; McClure, K. F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4281–4287.
4. Orr, S. T. M.; Cabral, S.; Fernando, D. P.; Makowski, T. *Tetrahedron Lett.* **2011**, *52*, 3618–3620.
5. Based on search and comparison of commercially available heteroaryl boronic acids and heteroaryl halides by SciFinder®.
6. General procedure for conditions **B**: To a vial with septa containing *tert*-butyl 2-[(*R*)-5-bromo-2,3-dihydro-1*H*-inden-1-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate **3** (2.42 mmol) were added bis(pinacolato)diboron (2.61 mmol), potassium acetate (12.12 mmol), and Pd(dppf)Cl_2 (0.039 mmol). The vial was purged with a stream of nitrogen, and anhydrous 1,4-dioxane (12 mL) was added. The resulting mixture was purged with nitrogen for three times, and the mixture was heated at 95 °C for 1 h. The aryl halide **5** (2.61 mmol), Pd(dppf)Cl_2 (0.062 mmol), and 9 ml of 2 M aqueous potassium carbonate solution (de-oxygenated by bubbling through N_2 for 15 min) were added. The mixture was purged with N_2 three times and heated at 95 °C for 17 h. The mixture was cooled to room temperature and the organic layer was separated from the aqueous layer. The organic layer was filtered through a thin plug of silica gel, and rinsed with 5 mL of isopropyl alcohol followed by 5 mL of MeOH. The filtrate and the washings were concentrated under reduced pressure to give the crude product that was purified by silica gel chromatography eluting with a gradient of 0–10% MeOH in CH_2Cl_2 to give the desired product. Spectral data for compound **6a**: ^{1}H NMR (500 MHz, C*d*$_3$O*d*): δ 8.83 (d, *J* = 5.0 Hz, 2 H), 8.29 (s, 1 H), 8.24 (d, *J* = 10.0 Hz, 1 H), 7.48 (d, *J* = 10.0 Hz, 1 H), 7.34 (t, *J* = 5.0 Hz, 1 H), 4.10–4.08 (m, 1 H), 3.37 (s, 4 H), 3.32–3.30 (m, 2 H), 3.29–3.28 (m, 2 H), 3.17–3.11 (m, 1 H), 2.94–2.88 (m, 1 H), 2.31–2.24 (m, 1 H), 1.97–1.91 (m, 1 H), 1.74–1.72 (m, 4 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, C*d*$_3$O*d*): δ 164.7, 157.5, 155.3, 145.6, 145.2, 137.6, 126.4, 124.5, 119.5, 99.9, 79.8, 71.7, 62.3, 51.0, 35.6, 33.9, 30.0, 29.3, 27.5; HRMS (CI): *m*/*z* 421.2587 (Calculated 421.2598 for $C_{25}H_{32}N_4O_2$+H).
7. Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarga, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190–5196.
8. Exemplary procedure for conditions **C**: To a 50 mL flask containing *tert*-butyl 2-[(*R*)-5-bromo-2,3-dihydro-1*H*-inden-1-yl]-2,7-diazaspiro[3.5]nonane-7-carb oxylate **3** (4.0 g, 9.49 mmol) were added bis(triphenylphosphine)palla dium(II) chloride (0.17 g, 0.24 mmol), potassium acetate (3.73 g, 37.97 mmol), and bis(pinacolato)diboron (2.65 g, 10.44 mmol) followed by degassing via vacuum then backfilling with nitrogen five times. De-oxygenated (N_2 stream for 30 min) toluene (40 mL) was added to the mixture and the reaction was heated at 100 °C for 1.5 h. The reaction was monitored for completion by HPLC. Upon formation of the boronic ester intermediate, the reaction was cooled to 40 °C and charged with a degassed solution of 4 M sodium hydroxide (11.87 mL, 47.46 mmol) followed by the addition of 4-chloro-6-methylpyrimidine **5g** (1.53 g, 11.87 mmol). The resulting mixture was then heated to 90 °C for 5 h under nitrogen. The reaction was cooled to room temperature and charged with water (25 mL). After stirring for 20 min, the mixture was filtered to remove black solids. The organic layer was extracted to an aqueous solution containing HCl (40 mL). The organic layer was removed and the resulting solution was treated with (4 g) ISOLUTE® Ultra Pure Si-Thiol silica gel for 1.5 h and filtered. The pH of the aqueous solution was then adjusted with 4 N NaOH to pH 7.8 and extracted to toluene (40 mL). The toluene layer was concentrated to approximately 15 mL under reduced pressure at 45 °C and heptane (75 mL) was added slowly with stirring at 20 °C for 1 h. The product was then filtered and dried under vacuum at 45 °C for 8 h to afford **6g** (3.56 g, 86%) as a white solid. ^{1}H NMR (500 MHz, C*d*$_3$O*d*): δ 9.00 (s, 1 H), 8.03 (s, 1 H), 7.98 (d, *J* = 5.0 Hz, 1 H), 7.86 (s, 1 H), 7.49 (d, *J* = 10.0 Hz, 1 H), 4.07–4.04 (m, 1 H), 3.36 (s, 4 H), 3.32–3.29 (m, 2 H), 3.26 (d, *J* = 5.0 Hz, 2 H), 3.16–3.10 (m, 1 H), 2.93–2.87 (m, 1 H), 2,57 (s, 3 H), 2.29–2.23 (m, 1 H), 1.96–1.90 (m, 1 H), 1.72–1.67 (m, 4 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, C*d*$_3$O*d*): δ 167.9, 164.4, 157.9, 155.3, 146.2, 145.7, 136.4, 125.6, 125.0, 123.7, 116.9, 79.8, 71.6, 62.3, 48.0, 35.6, 33.9, 30.1, 29.3, 27.5, 22.7; HRMS (CI): *m*/*z* 435.2753 (Calculated 435.2755 for $C_{26}H_{34}N_4O_2$ + H). Spectral data for compound **6f**: ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.70 (d, *J* = 5.4 Hz, 1 H), 8.04 (s, 1 H), 7.96 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.82 (d, *J* = 5.4 Hz, 1 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 3.87 (dd, *J* = 6.5, 3.5 Hz, 1 H), 3.30–3.20 (m, 4 H), 3.08 (d, *J* = 6.6 Hz, 2 H), 3.03–2.93 (m, 3 H), 2.81 (ddd, *J* = 15.9, 8.7, 4.4 Hz, 1 H), 2.66 (s, 3 H), 2.11–2.01 (m, 1 H), 1.85 (ddt, *J* = 12.5, 8.4, 4.1 Hz, 1 H), 1.60–1.53 (m, 4 H), 1.37 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 167.3, 162.8, 157.9, 153.9, 146.5, 144.9, 135.6, 125.0, 124.9, 123.2, 113.9, 99.3, 78.5, 70.2, 61.5, 35.3, 33.8, 30.0, 28.9, 28.1, 25.9; HRMS (CI): *m*/*z* 435.2759 (Calculated 435.2755 for $C_{26}H_{34}N_4O_2$+H).
9. Yin, J.; Buchwald, S. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048.
10. (a) Singer, R. A.; Withbroe, G. J.; Sieser, J. E. *Org. Process Res. Dev.* **2008**, *12*, 480–489; (b) Singer, R. A.; Doré, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* **2006**, *47*, 3727–3731; (c) Singer, R. A.; Tom, N. J.; Frost, H. N.; Simon, W. M. *Tetrahedron Lett.* **2004**, *45*, 4715–4718.
11. Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327–3329.