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Design and synthesis of boron containing 2,4-disubstituted-phthalazin-1(2*H*)-one and 3,7-disubstituted-2*H*-benzo[*b*][1,4] oxazine derivatives as potential HGF-mimetic agents

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ABSTRACT

We synthesized boron containing 2-(4-methoxybenzyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioaborolan-2-yl)phenyl) phthalazin-1(2*H*)-one **3** and 7-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2*H*-benzo**[***b***]**[1,4] oxazine **8.** The reaction of compound **2** with B_2pin_2 using potassium acetate as the base and $Pd(PPh_3)_2Cl_2$ as the catalyst, produced the corresponding boron-containing derivative **3** as a white solid in 65% yield. Alternatively, we have synthesized compound **8** as a yellow solid in 59% yield using the Miyaura borylation reaction. The potassium trifluoro(4-(-methyl-2*H*-benzo**[***b***]**[1,4]oxazine-3-yl)phenylborate **9** was then obtained after treatment of **8** with aqueous solution of KF_2H in methanol as white solid product in 60% yield. The biological activities of the synthetic compounds are currently being evaluated.

Hepatocyte growth factor (HGF) is a potent mitogen for hepatocytes that is required for liver development, regeneration, and also a critical factor in the two most common liver pathologies, hepatitis, and cirrhosis.[1–5] Exogenous supplementation of HGF has been shown to attenuate disease progression not only in the liver but also in animal models of renal and pulmonary fibrosis.[6,7] Thus, identifying the most effective strategies to administer its biological effects in injured tissues is of high priority. Previous approaches to HGF-therapies were focused on peptides and antibodies.[5–7] However, unfortunately, the half-life of proteins and peptides is short and easily degraded by proteases. Above all their production is costly. Thus, there is an urgent need to develop small molecule HGF mimetics that work with higher efficiency.

In the context of our ongoing chemical biology project, we sought to synthesize small molecules as HGF mimetics utilizing a limited rational design approach (LRD). To identify small molecule agonists, we searched web-based protein-ligand data banks (PDB and EBI) that store information on protein crystal structures and their predicted ligands in conjunction with the similarity search methods.[8] From the EMBL-EBI website using the PDB data bank code found protein id for HGF (pdb:1BHT), then we used similarity search methods (are based on Tanimoto similarity scores) to identify structurally similar small molecules with suitable drug properties. From our initial search we found phthalazin-1(2*H*)-one and 2*H*-benzo [*b*][1,4] oxazine based heterocyclic compounds are novel pharmacophore groups, formed a complex with HGF and also bound c-Met receptors. To fully elaborate the biological utilities of these scaffolds as HGF-mimetic agents, we synthesized compound **3**, **8**, and **9** based on these scaffolds.

From the literature search, we found that heterocyclic compounds bearing phthalazinone[9] and oxazine[10] scaffolds have been extensively used in synthetic medicinal chemistry against a plethora of biological targets, and introducing a boron atom in a biologically active framework allows interaction with a target protein, not only through hydrogen bonds but also through covalent bonds.[11] So, we undertook this project to synthesize boron containing phthalazinone and oxazine derivatives as potential HGF mimetic agents.

Unfortunately, the initial attempts to synthesize compound **1** via Miyaura borylation route using 4-(4-boromophenyl) phthalazin-1(2*H*)-one **4** as the substrate did not meet with success and the starting material was recycled (Scheme 1). We reasoned that protecting the amide group was necessary. Thus, the 4-(4-boromophenyl) phthalazin-1(2*H*)-one **4** was then treated with 4-methoxybenzyl chloride in anhydrous DMF in the presence of K_2CO_3 and stirred for about 3 h until all the phthalazinone compound was consumed as monitored by TLC. After work up, the resulting residue was recrystallized from ethylacetate and hexanes (95:5) to give a white solid **2** in 89% yield (Scheme 2).

With compound **2** in hand, a Miyaura borylation reaction was conducted. The reaction of compound **2** with B_2pin_2 using potassium acetate as the base and $Pd(PPh_3)_2Cl_2$ as the catalyst, delivered

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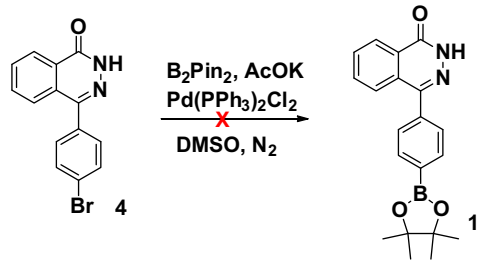
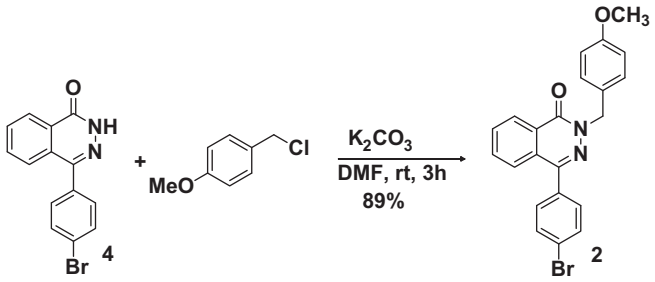
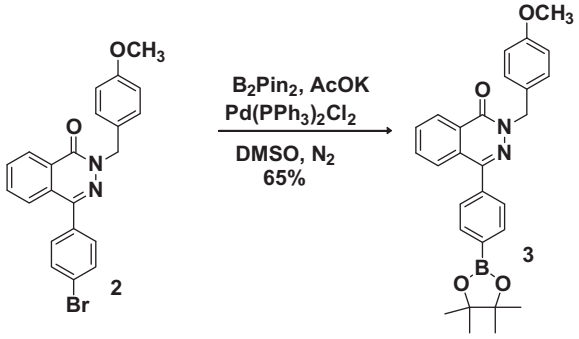


Scheme 1.



Scheme 2.



Scheme 3.

the corresponding boron-containing derivative **3** as a white solid in 65% yield (Scheme 3).[12]

After synthesizing boron containing phthalazinone derivative, we then planned to synthesize boron containing oxazine derivatives. The target compound **8** was syntheized from 6-amino-*m*-cresol **5** (Scheme 4). Compound **5** was treated with 2,4′-dibromoacetophenone **6** in DCM using K_2CO_3 as the base and Bu_4NHSO_4 as the phase transfer catalyst, compound **7** was obtained in 51% yield as a yellow solid. After Miyaura borylation reaction, boronic ester product **8** was synthesized from **7** as yellow solid in 59% yield.[16]

Organotrifluoroborates are used (a) as versatile intermediates in organic synthesis,[13] (b) as novel therapeutic agents (sodium/iodide symporter, antinociceptive, antiinfective),[14] and (c) as novel molecular imaging agents (positron emission tomography—PET).[15] We, therefore, further envisioned to derivatized **8** to the boronic salt **9** (Scheme 4). In brief, the compound **9** was syntheiszed as follows: compound **8** was dissolved in MeOH and KF_2H solution was added to it drop wise. The reaction mixture was stirred at room temperature for 2 h, then the solvent was removed in vacuo. Hot acetone was added and the solvent was removed in vacuo again. The resulting white solid was washed with ethyl acetate for three times to get a pure solid product **9** in 60% yield.[16]

In conclusion, we have synthesized boron containing phthalazinone and oxazine derivatives. To our knowledge, this is the first report on the synthesis boron containing phthalazinone and oxazine derivatives. To synthesize these compounds, we used Miyaura coupling reactions. It is our hope that these simple and elegant reaction procedures for obtaining boron containing products would find extensive use in organic synthesis and medicinal chemistry fields. These compounds could be used as synthetic intermediates for further metal mediated reactions, as novel imaging agents and useful biological active compounds for our ongoing chemical biology projects in particular as potential HGF mimetics agents. The biological activities of the synthetic compounds are currently being evaluated.

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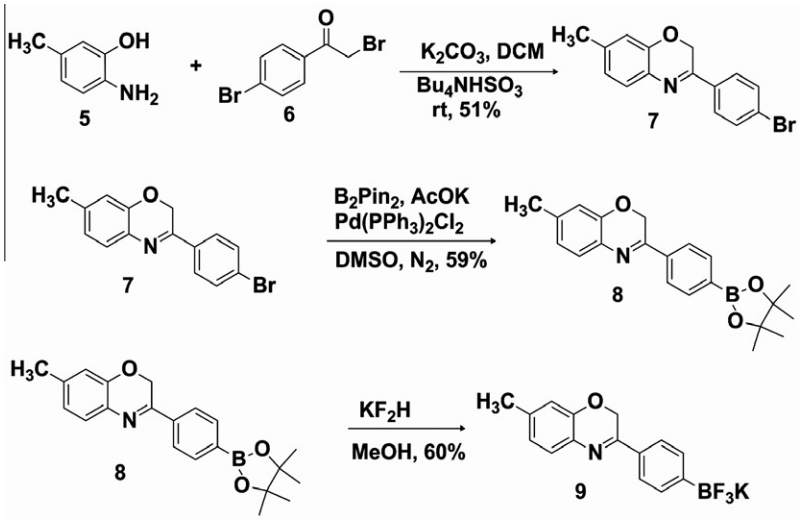

Scheme 4. Synthesis of compounds **7, 8,** and **9.**

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.032.

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12. **(a)** *General procedure for the synthesis of compound* **2.** Bromo phenyl phthalazinone **4** (500.0 mg, 1.65 mmol, 1.0 equiv), K_2CO_3 (460.0 mg, 3.3 mmol, 2.0 equiv) and anhydrous DMF (25.0 mL) were added into a 100 mL round bottom flask. To the above mixture was added 4-methoxybenzyl chloride (517.8 mg, 3.3 mmol) dropwise and the reaction mixture was stirred at room temperature for about 3 h. After the reaction completed, the solid was filtered and mother liquid was poured into water, the resulting mixture was extracted by ethylacetate, dried over Na_2SO4, filtered and concentrated in vacuo. The small amount of DMF remained was removed by high vacuum and the residue was recrystallized from ethylacetate and hexanes (95:5) to give a white solid **2** in 89% yield. A white solid. Mp 147–148 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 3.70 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.88 (d, J = 8.7 Hz, 2H, Ar), 7.33 (d, J = 8.7 Hz, 2H, Ar), 7.56 (d, J = 8.1 Hz, 2H, Ar), 7.67–7.70 (m, 1H, Ar), 7.76 (d, J = 8.1 Hz, 2H, Ar), 7.88–7.91 (m, 2H, Ar), 8.36–8.39 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 54.4, 55.9, 114.7, 123.6, 127.4, 128.4, 129.1, 130.0, 130.3, 132.4, 132.5, 133.0, 134.6, 134.8, 146.1, 158.8, 159.5. (b) *General procedure for the synthesis of compound* **3.**To a flame-dried 10 mL round bottom flask was added Bromide **2** (137.0 mg, 0.3 mmol, 1.0 equiv), B_2Pin_2 (167.6 mg, 0.66 mmol, 0.22 equiv), AcOK (147.2 mg, 1.5 mmol, 5.0 equiv) was added 3.0 mL of anhydrous DMSO under nitrogen. The resulting mixture was stirred at 80 °C for 12 h under nitrogen. Then the reaction mixture was diluted with water (10 mL), extracted by ethyl acetate (3 × 10 mL). The combined organic layer was dried over Na_2SO4, filtered and concentrated in vacuo. The resulting residue was subjected to a flash silica gel chromatography (Hexanes: EtOAc: 60:40) and then recrystallized from methanol to give a white crystal product **3** in 65% yield. A white solid. Mp 155–157 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.41 (s, 12H, $4CH_3$), 3.79 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 6.87 (d, J = 8.4 Hz, 2H, Ar), 7.52 (d, J = 8.4 Hz, 2H, Ar), 7.61 (d, J = 8.1 Hz, 2H, Ar), 7.72–7.78 (m, 3H, Ar), 7.99 (d, J = 8.1 Hz, 2H, Ar), 8.52–8.55 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 25.3, 55.0, 55.6, 84.4, 114.2, 126.9, 127.7, 128.8, 129.2, 129.5, 129.6, 130.7, 131.7, 133.1, 135.3, 138.3, 147.2, 159.3, 159.6; ^{11}B NMR ($CDCl_3$, 300 MHz, TMS) δ 30.9; HRMS (EI) calcd for $C_{28}H_{30}BN_2O_4$ $[M+H]^+$ requires 469.2299, found 469.2300.
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16. *General procedure for the synthesis of compound* **7**. 6-Amino-m-cresol **5** (1.23 g, 10.0 mmol, 1.0 equiv), Bu_4NHSO_3 (1.7 g, 5.0 mmol, 0.5 equiv), K_2CO_3 (2.76 g, 20.0 mmol, 2.0 equiv) in 10 mL water were added into a 100 mL of RBF. DCM (60 mL) was added and the resulting mixture was stirred for around 5 min. 2,4′-dibromoacetophenone in 20 mL of DCM was added dropwise over a period of 10 min. The reaction mixture was stirred at rt over night. After the reaction was completed, water (30 mL) was added and the mixture was extracted by DCM (3 × 25 mL). The combined organic layer was washed by 1 N HCl, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by a silica gel chromatography to give a yellow solid product **7** (1.5 g, 51%).
A yellow solid. Mp 141–143 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.36 (s, 3H, CH_3), 5.02 (s, 2H, CH_2), 6.75 (s, 1H, Ar), 6.85 (d, J = 7.8 Hz, 1H, Ar), 7.32 (d, J = 7.8 Hz, 1H, Ar), 7.61 (d, J = 8.4 Hz, 2H, Ar), 7.79 (d, J = 8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.5, 62.6, 116.0, 123.2, 125.5, 127.5, 127.8, 131.4, 131.9, 134.4, 139.5, 146.0, 156.3.
Synthesis of **8**: To a 10 mL round bottom flask charged with Bromide **7** (91.0 mg, 0.3 mmol, 1.0 equiv), B_2Pin_2 (167.6 mg, 0.66 mmol, 0.22 equiv), AcOK (147.2 mg, 1.5 mmol, 5.0 equiv) and $Pd(PPh_3)_2Cl_2$ (21.0 mg, 0.03 mmol, 0.1 equiv) was added 3.0 mL of anhydrous DMSO under nitrogen. The resulting mixture was stirred at 80 °C for 12 h under nitrogen. Then the reaction mixture was diluted with water, extracted with ethylacetate. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was subjected to a flash silica gel chromatography to give a yellow solid product **8** (62 mg, 59%). A yellow solid. Mp 120–122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 12H, $4CH_3$), 2.36 (s, 3H, CH_3), 5.07 (s, 2H, CH_2), 6.75 (s, 1H, Ar), 6.85 (dd, $J_{1,2}$ = 7.8, 1.2 Hz, 1H, Ar), 7.34 (d, J = 7.8 Hz, 1H, Ar), 7.91 (s, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 24.9, 62.9, 84.1, 116.0, 123.1, 125.4, 127.6, 131.6, 135.0, 137.8, 139.3, 146.1, 157.4; HRMS (EI) calcd for $C_{21}H_{25}BNO_3$ $[M+H]^+$ requires 350.1927, found 350.1933.
Synthesis of compound **9**: compound **8** (0.052 mmol, 18 mg) was dissolved in MeOH (1 mL). To the above solvent was added 4.5 M KF_2H aqueous solution drop wise (0.21 mmol, 47 μL). The reaction mixture was stirred at rt for 2 h, then the solvent was removed in vacuo. Hot acetone was added and the solvent was removed in vacuo again. The resulting white solid was washed with EA for (3 × 25 mL) to obtain a pure solid product **9** (10 mg, 60%). A yellow solid. Mp 166–168 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H, CH_3), 5.10 (s, 2H, CH_2), 6.73 (s, 1H, Ar), 6.82 (d, J = 8.1 Hz, 1H, Ar), 7.23 (d, J = 8.1 Hz, 1H, Ar), 7.63 (d, J = 8.1 Hz, 2H, Ar), 7.80 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 63.0, 116.1, 123.0, 124.9, 127.4, 132.2, 132.3, 132.6, 138.3, 146.9, 159.3.