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Design and synthesis of 3,5-disubstituted 1,2,4-oxadiazole containing retinoids from a retinoic acid receptor agonist

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ABSTRACT

We previously synthesized novel retinoid libraries, and after screening for bioactivity found one compound **BT10** that functions as a specific agonist for retinoic acid receptors. This lead compound was further derivatized using SAR and LRD to obtain 3,5-disubstituted-1,2,4-oxadiazole-containing retinoids. The new oxadiazole (amide bioisosters)-containing retinoids (compounds **1**, **2**, **3**, **4**, **5**, and **6**) were synthesized in 42–65% yield by reacting with (*E*)-4-((3-ethyl,2-4,4,4-trimethylcyclohex-2-enylidene)methyl)benzoic acid and phenyl substituted amidoxime in DMF using CDI as the coupling reagent. The biological activities of the synthesized compounds are currently being evaluated.

Retinoids (retinol [vitamin A] and its biologically active metabolites) are essential signaling molecules that control various developmental pathways and influence the proliferation and differentiation of a variety of cell types in the adult.[1,2] A number of synthetic retinoids have been synthesized that interact selectively with their receptors.[3] Considering the importance of the retinoids, we were interested in synthesizing a small library of new retinoids.

In the context of our ongoing chemical biology project, studying the role of retinoic acid signaling pathways during zebrafish embryogenesis, we synthesized novel retinoid libraries.[4a–f]

This small library of compounds was screened for bioactivity in living zebrafish embryos. We found that several structurally related compounds significantly affect development. Distinct phenotypes are generated depending on time of exposure, and we characterized one compound **BT10** (Fig. 1) that produces specific cardiovascular defects when added 1 day post fertilization. When compared to all-trans retinoic acid (atRA), **BT10** shows similar but not identical changes in the expression pattern of embryonic genes that are known targets of the retinoid pathway. Reporter assays determined that **BT10** interacts with all three RAR receptor sub-types, but has no activity for RXR receptors, at all concentrations tested.[4g]

This lead compound may be useful for manipulating components of retinoid signaling networks, and may be further derivatized to enhance activity and selectivity. For that purpose we undertook this project to synthesize oxadiazole-containing novel retinoids as **BT10** analogues.

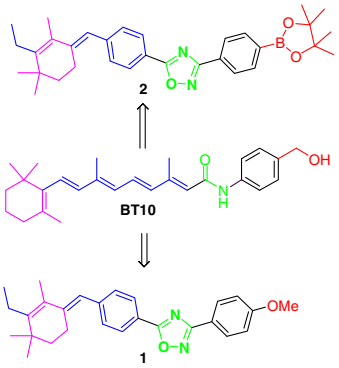

Figure 1.

Our lead molecule **BT10** is an amide derivative of retinoic acid (containing polyene alkene spacers and amide linkage). Attempting to increase efficacy and receptor subtype specificity, we tried to synthesize new retinoic acid analogues by (a) introducing a constrained phenyl ring system in place of the conjugated alkene backbone (spacers in atRA) to avoid the metabolism of atRA into its isomers, 9-cis-RA and 13-cis-RA, (b) bio-isosterically replacing the amide linkage with oxadiazoles[5] to prevent the in vivo protease cleavage of the amide groups, and (c) introducing the methoxy group by replacing the methyl alcohol group of **BT10** to increase

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the efficacy. Here, we report success at synthesizing novel oxadiazole-containing retinoids, which may provide new tools for probing retinoic acid signaling pathways.

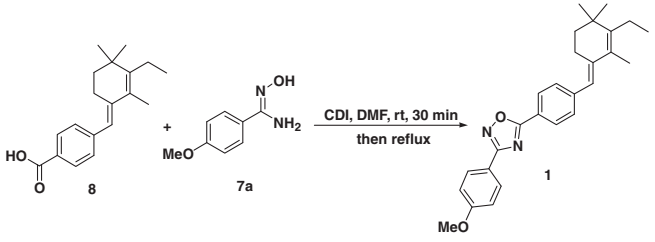
To synthesize our lead compound **1** (Fig. 1), we first synthesized the acid; (*E*)-4-((3-ethyl,2-4,4,4-trimethylcyclohex-2-enylidene)methyl)benzoic acid **8**. The acid **8**[4d,e] was synthesized starting from β-cyclocitral in a manner reported by us previously.[4d] Next we synthesized different substituted amidoximes by refluxing an ethanolic solution of substituted phenyl nitriles and hydroxylamine hydrochloride using NaOH as base.[6] The oxadiazole-containing retinoid **1** was synthesized by an amide coupling strategy[7] using methoxy amidoxime **7** and acid **8**, which were readily available though simple transformations, as the substrates. The corresponding acid **8** was treated with 1.2 equiv of CDI in DMF for 30 min at room temperature, then the methoxy amidoxime **7** was added and the resulting reaction mixture was heated under reflux for about 12 h (or until the acid was consumed completely as monitored by TLC) (Scheme 1).[8a] After purification by silica-gel chromatography (Hexanes/EtOAc: 3:1) compound **1** was obtained as a white solid, melting point 133–135 °C with 48% yield.

To validate the generality of the coupling reaction, we synthesized compounds **3**, **4**, **5**, and **6** using acid **8** and various substituted amidoximes (**7b–7e**) using CDI as coupling reagent in DMF (Scheme 2). Compounds **3**,**4**[8b],**5**, and **6** were also successfully synthesized in 42–65% yield. Derivatives may have useful additional features. For example, compound **5** contains free acetylene, which could be further converted in vivo into a triazole derivative for target identification purposes. Compounds **3** and **6** could be further derivatized to ^{18}F and ^{11}C PET (Positron Emission Tomography) agents for noninvasive diagnostic agents, for diseases with over expressed RAR-alpha receptors.

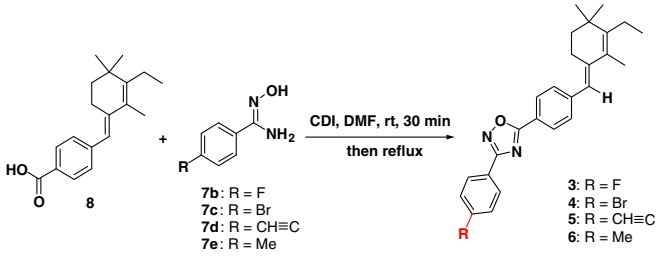
We further envisioned developing a boron-based oxadiazole-containing small molecule retinoid library (Fig. 1), based on the hypothesis that introducing a boron atom in a biologically active framework might allow interaction with a target protein, not only through hydrogen bonds but also through covalent bonds. Such interactions could produce potent biological activity.[9] With this in mind, we synthesized compound **2**.

To synthesize compound **2** we first tried to synthesize **10** ((*Z*)-*N*′-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidamide) and planned to attach it with acid **8** using CDI as a coupling reagent in DMF. To synthesize **10** we started with nitrile **9** (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile) and hydroxylamine hydrochloride **11**. But unfortunately, we failed to synthesize **10** in spite of using different bases [like NaOH/EtOH, K_2CO_3/DMSO, Et_3N/EtOH, and $(iPr)_2NH$/EtOH)] and reaction conditions (Scheme 3).[10]

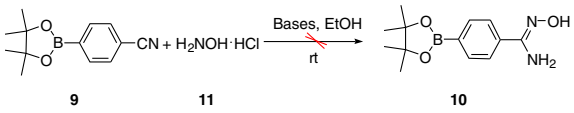
As we failed to synthesize **10**, a separate reaction scheme was devised. A Suzuki coupling reaction was introduced using bromide compound **4**[8b] and B_2Pin_2 (Bis-pinocolatodiboron) as the substrates to give the boronic ester containing compound **2** in 45% yield as a white solid (Scheme 4).[11]



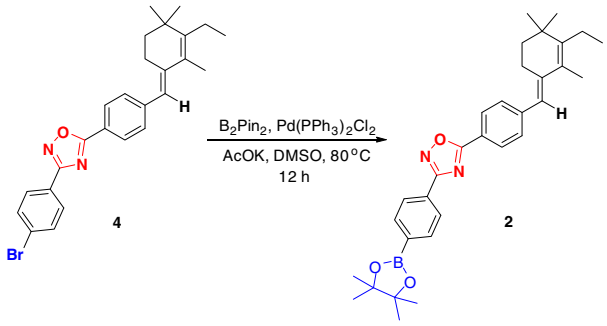
Scheme 1. Reagents and conditions: Compound **1** (42% yield, white solid, mp 133–135 °C).



Scheme 2. Reagents and conditions: compound **3**: R═F, (42% yield, white solid, mp 135–137 °C); compound **4**: R═Br, (65% yield, white solid, mp 130–132 °C); compound **5**: R═C═CH, (52% yield, brown solid; mp 124–126 °C); compound **6**: R═CH_3, (46% yield, yellow solid, mp120–122 °C).



Scheme 3.



Scheme 4.

In conclusion, we report for the first time the synthesis of 3,5-disubstituted-1,2,4-oxadiazole-containing retinoids. The detailed biological evaluation of these compounds as possible RA pathway modulators is currently ongoing in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data ((copies of ^1H, ^{13}C NMR and Mass spectra) are available online with this paper in Science Direct)associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.011.

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8. (a) *General procedure for synthesis of compound* ***1***: Acid **8** (0.5 mmol) and CDI (carbonyl diimidazole) (0.6 mmol) were dissolved in 3 mL of DMF and stirred at room temperature. After 30 min, amidoxime **7a** was added and the reaction mixture was heated under reflux for about 24 h (Monitored by TLC). Then the mixture was poured into water (20.0 mL), extracted by $CHCl_3$ (3 × 15.0 mL), and the combined organic solvent was dried over Na_2SO_4, filtered, and concentrated in vacumn. The crude product was purified by silica-gel chromatography to give a white solid mp 133–135 °C with 48% yield.
   ^{1}H NMR (300 MHz, Acetone, TMS) δ 1.10 (t, J = 7.5 Hz, 3H, CH_3), 1.13 (s, 6H, $2CH_3$), 1.52–1.58 (m, 2H, CH_2), 1.96 (s, 3H, CH_3), 2.25–2.33 (m, 2H, CH_2), 2.65–2.62 (m, 2H, CH_2), 2.83 (s, 3H, CH_3), 6.59 (s, 1H, CH), 7.13–7.16 (m, 2H, Ar), 7.59 (d, J = 6.0 Hz, 2H, Ar), 8.10–8.13 (m, 2H, Ar), 8.18 (d, J = 6.0 Hz, 2H, Ar); ^{13}C NMR (75 MHz, Acetone, TMS) 14.6, 15.0, 23.0, 24.6, 27.4, 36.0, 39.0, 55.3, 114.8, 119.7, 120.8, 121.7, 127.5, 128.0, 129.3, 130.4, 142.8, 144.3, 149.1, 162.7, 168.8, 175.8; HRMS (EI) Calcd for C27H30N2O2 $[M+H]^+$ requires 415.2386. Found 415.2408.
   (**8b**) *Analytical data's of compound* ***4***. Compound **4** (65%). A white solid. mp 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.10 (t, J = 7.5 Hz, 3H, CH_3), 1.12 (s, 6H, $2CH_3$), 1.52–1.58 (m, 2H, CH_2), 1.96 (s, 3H, CH_3), 2.26 (q, J = 7.5 Hz, 2H, CH_2), 2.62–2.68 (m, 2H, CH_2), 6.50 (s, 1H, CH), 7.46 (d, J = 8.1 Hz, 2H, Ar), 7.67 (d, J = 8.1 Hz, 2H, Ar), 8.08 (d, J = 8.1 Hz, 2H, Ar), 8.17 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.7, 15.2, 23.0, 24.4, 27.6, 35.9, 38.8, 120.3, 121.0, 125.6, 126.1, 127.0, 127.8, 129.0, 129.9, 132.1, 142.8, 144.0, 149.3, 168.2, 176.0. Anal. Calcd for $C_{26}H_{27}BrN_2O$: C, 67.39%; H, 5.87%; N, 6.05%. Found: C, 67.13%; H, 6.08%; N, 5.68%.
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11. *General procedure for synthesis of compound* ***2***: The desired bromide compound (0.2 mmol) together with B_2Pin_2 (0.44 mmol, 111.7 mg), AcOK (1.0 mmol, 98.1 mg), $Pd(PPh_3)_2Cl_2$ (0.02 mmol, 14.0 mg), and DMSO (3 mL) was added into a 15.0 mL three-necked RBF under N_2. The resulting mixture was stirred at rt for 10 min then heat at 80 °C for about 12 h under N_2. After the reaction was complete (Monitored by TLC), the reaction mixture was poured into 10 mL of water and extracted by DCM (3 × 10.0 mL). The combined organic solvent was dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica-gel chromatography to give the boron-containing compound **2**.
    Compound **2** (45%). A white solid. mp 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.11 (t, J = 7.5 Hz, 3H, CH_3), 1.12 (s, 6H, $2CH_3$), 1.53–1.57 (m, 2H, CH_2), 1.96 (s, 3H, CH_3), 2.25 (q, J = 7.5 Hz, 2H, CH_2), 2.67 (t, J = 5.7 Hz, 2H, CH_2), 6.50 (s, 1H, CH), 7.46 (d, J = 8.4 Hz, 2H, Ar), 7.97 (d, J = 8.4 Hz, 2H, Ar), 8.19 (dd, J = 8.4 Hz, 4H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.7, 15.2, 22.9, 24.4, 24.9, 27.6, 35.9, 38.8, 84.1, 120.3, 121.1, 126.6, 127.0, 127.8, 129.4, 129.8, 135.1, 142.7, 143.9, 149.2, 168.9, 175.8. HRMS (EI) Calcd for $C_{32}H_{40}BN_2O_3$ $[M+H]^+$ requires 511.3132. Found 511.3131.