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Identification of a chromone-based retinoid containing a polyolefinic side chain via facile synthetic routes

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ABSTRACT

Attempts to prepare substituted chromones as novel retinoids revealed that some chromones were unstable under Wadsworth–Horner–Emmons reaction conditions. Hence, Wittig reactions were used to prepare chromone-based compounds as potential retinoids. Firstly, Wittig reagents prepared from 3-bromomethyl-chromen-4-one were reacted with olefinic-aldehydes to provide the target compounds with all-trans side chains in good yield. The approach supplies a useful general route to structurally diverse chromone-based compounds possessing a variety of side chains. Sequential Wittig reactions were used also to prepare a chromone-based retinoid. These novel compounds were evaluated in binding assays and a high affinity RAR ligand was identified. Crystal structures obtained for two key precursors aided the interpretation of binding data.

Vitamin A (retinol) and its biologically active derivatives, collectively called retinoids, are important in the regulation of a wide range of physiological and developmental processes. All-trans retinoic acid (ATRA) and 9-cis retinoic acid (9-cis RA) (Fig. 1) are endogenous ligands for the two families of retinoid nuclear receptors: retinoic acid receptors (RARs) and retinoic X receptors (RXRs).[1] Each family of receptors is further divided into alpha (α), beta (β), and gamma subtypes (γ). Numerous synthetic retinoids have been developed as pharmacological tools to dissect the complex molecular mechanism of RARs, as well as therapeutic agents for the treatment of cancer and hyperproliferative diseases.[2–4] A major concern regarding the use of currently available nonselective retinoids is an adverse effect profile that includes respiratory distress, fever, pulmonary edema, and pulmonary infiltrates.[5] In order to decrease the adverse effects of these agents and to provide improved pharmacological tools, ligands exhibiting more selectivity for retinoid receptor subtypes are required.[2]

Our early efforts in the development of subtype selective synthetic retinoids involved heterocyclic compounds that proved too bulky to bind to the target receptors. A search for more compact, planar nuclei for ligand design led to the chromone system as a potential scaffolding. Chromone-related flavonoids show activity at the nuclear aryl hydrocarbon receptor (AhR) and synthetic retinoids have been reported to bind and activate AhRs also.[6,7] Hence, the chromone nucleus was used to design synthetic retinoids possessing polyolefinic side chains that mimic the endogenous RAR ligand ATRA. Wittig and Wadsworth–Horner–Emmons (WHE) reaction conditions were seen as efficient routes to the target chromones. Initial attempts to prepare a retinoids by reacting commercially available 3-formylchromone or 6-*i*-propyl-3-formylchromone with triethyl 3-methyl-4-phosphonocrotonate under WHE reaction conditions led to a rearrangement/cyclization. The reactions products were benzophenones as shown in Scheme 1. The structures of the rearranged products were confirmed by NMR and X-ray crystal analysis.[8] Interestingly, no rearrangement was observed when 3-formylchromone was reacted with triethylphosphonoacetate (as seen in our hands and reported previously[9]).

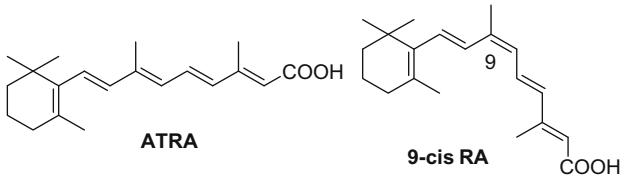

Figure 1. Structures of ATRA and 9-cis RA.

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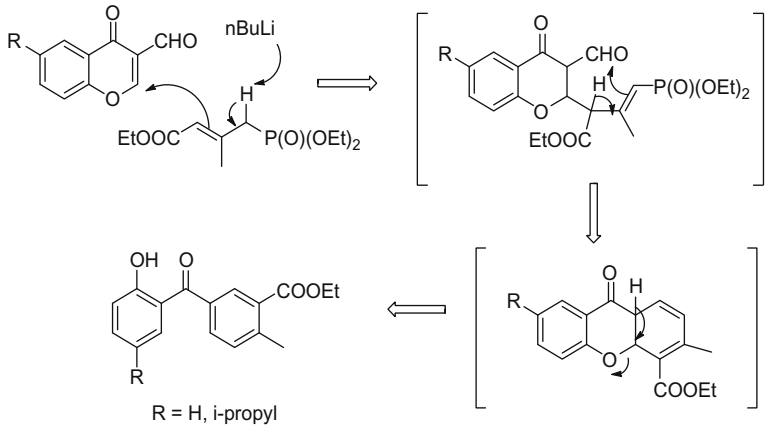
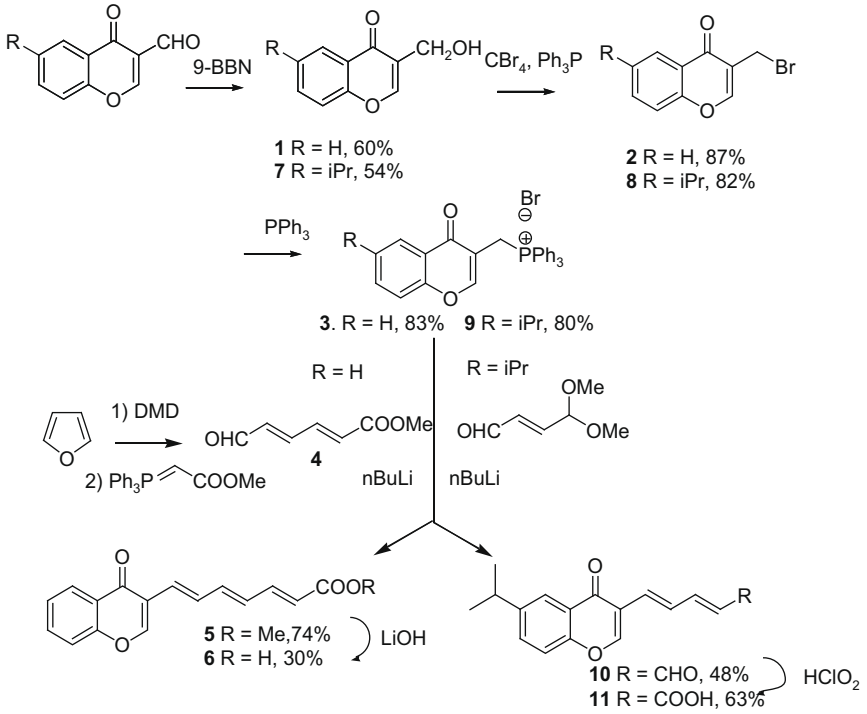


Scheme 1. Proposed mechanism for the formation of benzophenones via a rearrangement/cyclization.

In order to circumvent the rearrangement that leads to unwanted benzophenones, alternative routes to the target retinoids were devised. Firstly, a generally applicable approach was developed that involved the preparation of chromone-based Wittig reagents. Hence, 3-formylchromones were converted first to phosphorous ylides as described in Scheme 2. The ylide thus formed was then reacted with the appropriate aldehyde to afford the chromone-based precursor compounds (Scheme 2).

The phosphorous ylides **3** and **9** were prepared from the chromone-aldehydes by first reducing the aldehydes to the alcohols in moderate yield using 9-BBN. The alcohols were treated with tetrabromomethane in the presence of PPh_3 to afford the bromomethyl analogs **2** and **8**. The bromo analogs were reacted with PPh_3 to provide the corresponding phosphorous ylides (**3** and **9**) in good yield (Scheme 2). Ylides thus formed provide useful intermediates en route to a variety of substituted chromones. Reaction of ylides **3** and **9** with commercially available 4,4-dimethoxy-but-2-enal or aldehydic ester **4** provided chromones **6** and **11**, respectively (Scheme 2). The route to acid **6** involved the preparation of the aldehydic ester **4** (Scheme 2). Dimethyl dioxirane (DMD) was prepared by oxidizing acetone with Oxone in aqueous sodium bicarbonate solution.[10] Furan was oxidized in DMD solution to form the malealdehyde intermediate which reacted with methyl (triphenylphosphoranylidene) acetate to give **4** in the all-trans conformation.[11] The aldehyde **4** thus formed, was reacted with ylide **3** to provide the corresponding ester **5** as the mixture of trans and cis isomers in almost equal quantities which could not be separated by column chromatography. The trans isomer of **5** was isolated from the mixture through recrystalization. The ester was hydrolyzed to the corresponding acid **6** using LiOH. When compound **6** did not bind to the target RAR receptors, an isopropyl group was incorporated on the chromone nucleus in order to explore the effect of aliphatic groups on binding. As shown in Scheme 2, phosphorous ylide **9** was reacted with commercially available fumaraldehyde mono(dimethyl) acetal to afford aldehyde **10** in situ. The all trans stereochemistry of **10** was verified using



Scheme 2. Facile synthetic routes to chromone-based ligands **6** and **11**.

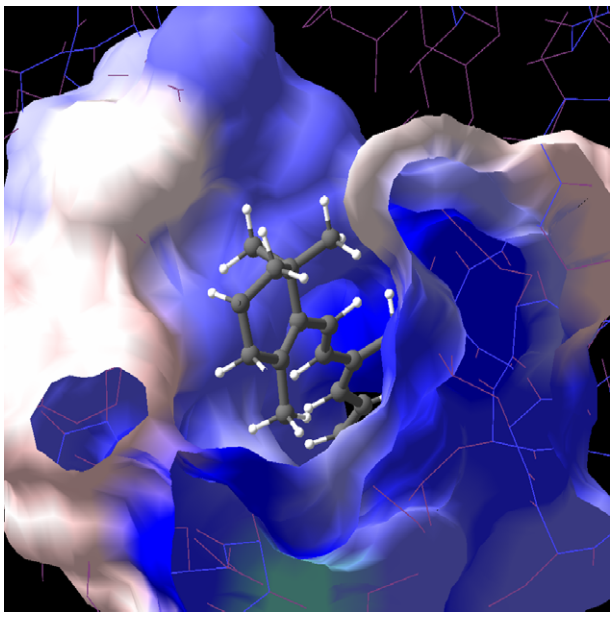


Figure 2. ATRA in the surface of RARγ binding pocket (adapted from 2lbd.pdb). Hydrophobic areas of the surface are tainted blue, hydrophilic areas are red and neutral portions are white.

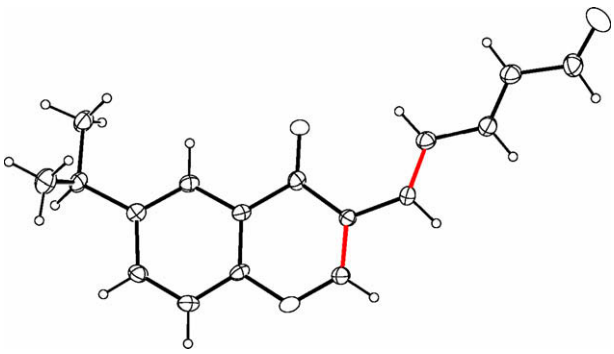


Figure 3. Ortep drawing of aldehyde **10**.

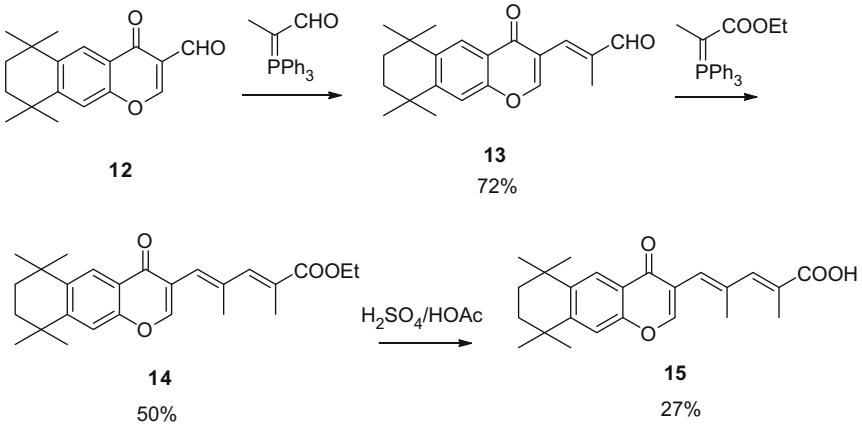
NMR and X-ray crystal data. Oxidation of this unsaturated aldehyde using sodium hypochlorite under mild acidic conditions yielded **11**.[12] Binding studies performed on acid **11** revealed that the compound had no affinity for RAR receptors. The negative results obtained in binding studies of compounds **6** and **11** led to a re-examination of the interaction between ATRA and retinoic acid receptors. The co-crystal structure of ATRA in RARγ (PDB:2lbd) reveals that the β-ionone ring of ATRA is sandwiched in a hydrophobic environment. Its dimethyl groups are reported to be involved in hydrophobic interactions with lipophilic residues of the protein (Fig. 2).[13]

Hence, the lack of affinity observed for **6** could be attributed, at least in part, to the need for properly positioned aliphatic groups on the aromatic ring. The isopropyl group of **11** was incorporated to mimic the methyl groups on the β-ionone ring of ATRA but did not lead to receptor affinity. In order to better understand these observations, the crystal structure of **10** (precursor of target acid **11**) was determined and is shown in Figure 3. The *s*-trans conformer (two double bonds in red) in **10**, rather than the *s*-cis found in ATRA helps to explain the lack of affinity observed for **11**.

Efforts to prepare ligands with *s*-cis geometry and appropriately positioned aliphatic groups led to the design and synthesis of acid **15** (Scheme 3). Aldehyde **12**[8] was prepared following a literature procedure and reacted with 2-(triphenylphosphoranylidene)-propionaldehyde to form intermediate **13**. Another Wittig reaction involving **13** and (carbethoxyethylidene)triphenyl-phosphorane provided **14** which was hydrolyzed under acidic conditions to furnish acid **15**. Compound **15** contains a tetramethyl alicyclic system and an olefinic side chain with two methyl groups.

The crystal structure of precursor **14** reveals that this compound has the *s*-cis conformation (Fig. 4; two double bonds in red) found in ATRA. The affinity of acid **15** for RARs was evaluated in preliminary radioligand binding assays using previously described methods[14] and found to have IC_{50} values of 15 nM, 40 nM, and 40 nM for RARα, RARβ and RARγ, respectively. These data suggest that the chromone nucleus provides a useful scaffold for RAR ligand design. Chromone-based retinoid **15** has been identified as a lead molecule for further ligand development.

In summary, initial efforts to prepare chromone-based retinoids with polyolefinic side chains involved the use of formylchromones and triethyl 3-methyl-4-phosphonocrotonate under WHE reaction conditions. These efforts consistently led to benzophenones following a rearrangement and cyclization. In order to avoid this rearrangement, alternative routes to the target ligands were devised. The first route involved conversion of 3-formylchromones to the corresponding phosphorous ylides in three steps. The Wittig reagents thus formed were reacted with olefinic aldehydes to yield the target chromone-based products with the trans conformation.[15] The approach supplies a useful general route to structurally diverse chromone-based compounds possessing a variety of side chains. A second route involving sequential Wittig reactions using



Scheme 3. Facile synthetic route to retinoid **15**.

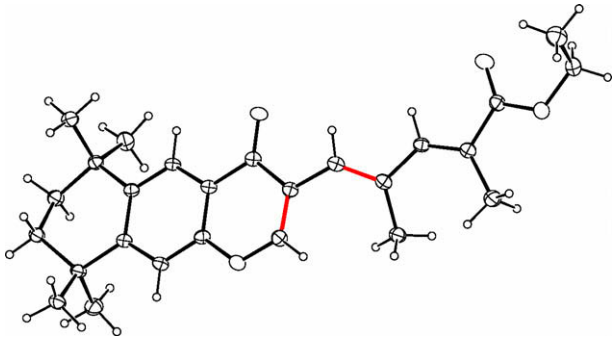


Figure 4. Ortep drawing of compound **14**.

a tetramethylcyclohexyl-chromone-based aldehyde yielded an olefinic ester with *s*-cis geometry similar to ATRA.[16,17] Crystal structures obtained for two key precursors aided the interpretation of binding data.[18] A novel chromone-based ligand was identified as a lead for the development of future RAR. Molecular modification of chromone-based acid **15** is underway in an effort to develop subtype selective RAR ligands.[19]

Acknowledgements

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15. *7-(4-Oxo-4H-chromen-3-yl)-hepta-2,4,6-trienoic acid methyl ester (trans isomer)* (**5**). To a chilled (−78 °C) solution of compound **3** (0.5 g, 1 mmol) in dry THF (15 mL) under N_2 was added *n*-butyllithium (2 M in heptane, 0.75 mL, 1.5 mmol) with stirring. After 30 min, aldehyde **4** (0.12 g, 0.86 mmol) in dry THF (5 mL) was added dropwise. After stirring at −78 °C for an additional 30 min, the resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (15 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$, concentrated and purified by flash chromatography (silica gel; 3:1, hexane/EtOAc) to afford a mixture of trans and cis isomers (1:1 based on NMR) (0.18 g, 74%). A solution of trans and cis isomers in EtOAc and hexane (15 mL; 5:1) was allowed to evaporate gradually at room temperature. Compound **5** precipitated as pale yellow crystals: mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.33–7.56 (m, 4H), 6.67 (dd, J = 14.8, 10.8 Hz, 1H), 6.55 (d, J = 15.4 Hz, 1H), 6.47 (dd, J = 14.8, 10.8 Hz, 1H), 5.93 (d, J = 15.4 Hz, 1H), 3.76 (s, 3H).
16. *(E)-2-methyl-3-(6,6,9,9-tetramethyl-4-oxo-6,7,8,9-tetrahydro-4H-benzo[g]chromen-3-yl)acrylaldehyde (13)*. An oven-dried flask was flushed with N_2 and charged with **12** (0.134 g, 0.47 mmol) and 2-(triphenylphosphoranylidene) propionaldehyde (0.605 g, 1.88 mmol) in 10 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature under N_2 for 48 h. The mixture was condensed under reduced pressure and the residue was purified by flash chromatography to yield **13** (0.11 g, 72%) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.65 (s, 1H), 8.21 (s, 1H), 8.19 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 2.01 (s, 2H), 1.75 (s, 2H), 1.37 (s, 6H), 1.35 (s, 6H).
17. Attempts to transform aldehyde **13** to a phosphorous ylide (see synthesis of **3** and **9** above) failed. Under Wittig reaction conditions, no reaction occurred between 3-formylchromones and 2-(triphenylphosphoranylidene)propionaldehyde.
18. Crystallographic data (excluding structure factors) for compounds **10** and **14** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 283693 (for **10**) and 722736 (for **14**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
19. The hydrolysis of chromone-based esters (**5** and **14**) under alkaline or acidic conditions was challenging due to the instability of the chromone nucleus (see: Kona, J.; Fabian, W.M.F.; Zahradnik, P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 422). No effort was made to optimize yields here but methods are available that report higher yields (for example see; He, X.; Li, Z.; You, Q. *Synth. Commun.* **2002**, *32*, 709).