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Optimization of diarylpentadienones as chemotherapeutics for prostate cancer

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ABSTRACT

Our earlier studies indicate that (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones and (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-diene-3-ones exhibit up to 121-fold greater antiproliferative potency than curcumin in human prostate cancer cell models, but only 2–10 fold increase in mouse plasma concentrations. The present study aims to further optimize them as anti-prostate cancer agents with both good potency and bioavailability. (1*E*,4*E*)-1,5-Bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one, the potential metabolic product of (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones, was synthesized and evaluated for its anti-proliferative activity. The promising potency of 1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones was completely abolished by removing the 1-alkyl group, suggesting the critical role of an appropriate group on the N1 position. We then envisioned that *N*-aryl substitution to exclude the C–H bond on the carbon adjacent to the *N*1 position (*α*-H) may increase the metabolic stability. Consequently, seven (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones and three (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-ones, as well as three (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-pyrrolo[3,2-*b*]pyridine-2-yl)penta-1,4-dien-3-ones, were synthesized through a three-step transformation, including *N*-arylation via Ullmann condensation, formylation, and Horner-Wadsworth-Emmons reaction. Six optimal (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones exhibit 24- to 375-fold improved potency as compared with curcumin. Replacement of the imidazole with bulkier benzoimidazole and 4-azaindole results in a substantial decrease in the potency. (1*E*,4*E*)-1,5-Bis(1-(2-methoxyphenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**17d**) was established as an optimal compound with both superior potency and good bioavailability that is sufficient to provide the therapeutic efficacy necessary to suppress *in vivo* tumor growth.

1. Introduction

Diferuloylmethane (**1**, Fig. 1), commonly known as curcumin, is a naturally occurring diarylheptanoid from the rhizomes of *Curcuma longa* L (turmeric) of the Zingiberaceae family. Turmeric, with curcumin as its major and active chemical component, has long been used as curry ingredient and as traditional medicines in China and India.[1] Curcumin was first revealed by Dorai and co-workers to have the capability of suppressing human prostate cancer proliferation and inducing prostate cancer apoptosis.[2–4] Additionally, the safety profile of curcumin in humans has been validated by the Food and Drug Administration (FDA) in the USA.[4–5] However, the low bioavailability of curcumin together with its moderate potency has hindered its clinical advancement.[6,7] The reported IC_{50} values of curcumin in suppressing cell proliferation against three prostate cancer cell lines (LNCaP, DU145, and PC-3) range from 2.0 μM to 39.6 μM.[2] A phase I trial indicates that curcumin concentration in plasma falls below the detection limit after oral administration of 450–3600 mg of curcumin daily.[7] One way to address these weaknesses is to develop analogs with improved potency and/or bioavailability.[2,8] For example, replacement of the unstable diketone moiety with monokeone leads to a 10–20 fold increase in *in vitro* potency.[2,8] Our earlier studies have identified (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-diene-3-ones (**2–6**, Fig. 1) as the most impressive and promising class of curcumin-based anti-prostate cancer agents due to their superior *in vitro* potency in prostate cancer cell models.[9,10] The 1-alkyl-1*H*-imidazol-2-yl group in compounds **2–4**

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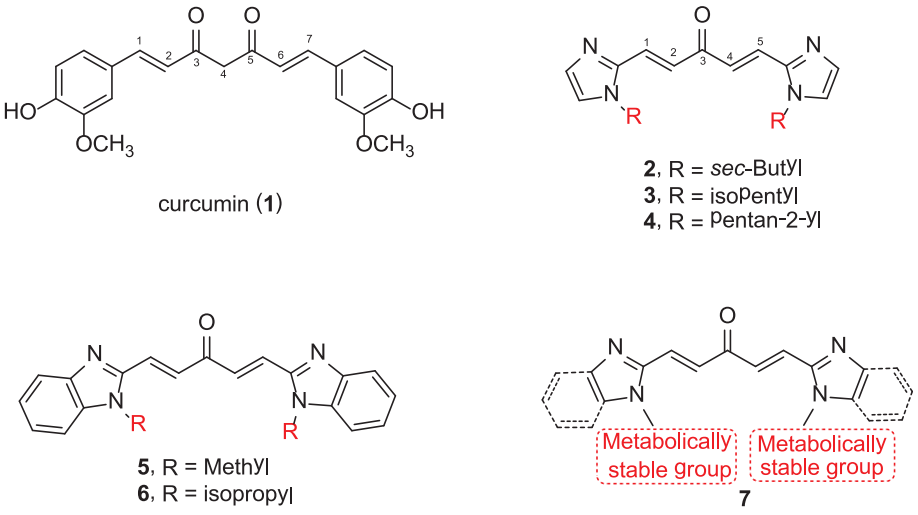


Fig. 1. Structures of curcumin and its mimics.

(Fig. 1) and the 1-alkyl-1*H*-benzo[*d*]imidazole-2-yl group in compounds **5–6** (Fig. 1) have been demonstrated to be significantly beneficial to the *in vitro* antiproliferative potency in three prostate cancer cell models.[10] The most potent compounds showed up to 121-fold improved antiproliferative potency towards both androgen-dependent and androgen-independent prostate cancer cells. However, their bioavailability is only slightly increased, as evidenced by the 2–10 fold increase in mouse plasma concentration.[9,10]

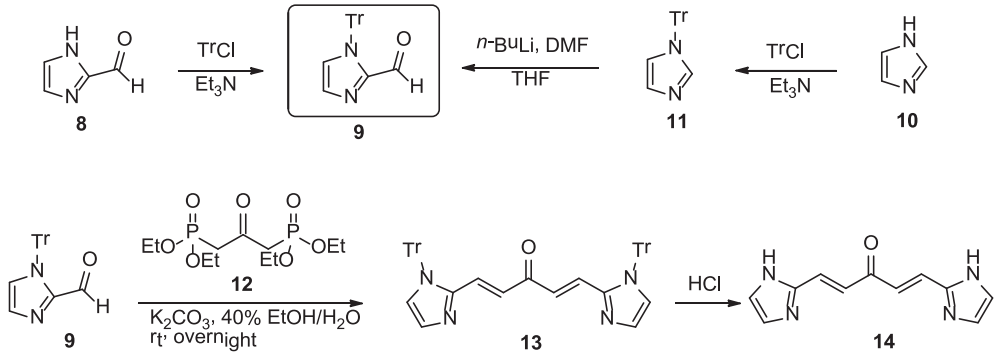
The present study aims to further optimize (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*)-imidzaole-2-yl)penta-1,4-diene-3-ones (e.g. **2–4**) and (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-benzo[*d*]imidazole-2-yl)penta-1,4-diene-3-ones (e.g. **5–6**). New groups of 1,5-diheretoarylpenta-1,4-dien-3-ones (**7**) with the hope of integrating optimal potency and pharmacokinetic profile were thus designed by incorporating a metabolically stable group to the *N*1 position of imidazole and benzoimidazole moiety.

2. Results and discussion

2.1. Design, synthesis, and antiproliferative activity of (1E,4E)-1,5-bis(1H-imidazol-2-yl)penta-1,4-diene-3-one (14)

To optimize the potency and bioavailability of 1,5-bis(1*H*-imidazol-2-yl)penta-1,4-dien-3-ones (**2–4**), we first evaluated the *in vitro* antiproliferative potency of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**). Compound **14** was first studied because it may be the metabolic product of 1,5-bis(1*H*-imidazol-2-yl)penta-1,4-dien-3-ones through *N*-dealkylation catalyzed by cytochrome P450[11] and it can be used to test the necessity of an 1-alkyl group for the *in vitro* potency. Consequently, we started our optimization with the synthesis and antiproliferative evaluation of (1*E*, 4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**). As shown in Scheme 1, potential metabolic product (**14**) of (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2–4**) was synthesized through the Horner-Wadsworth-Emmons reaction of 1-trityl-1*H*-imidazole-2-carbaldehyde (**9**) with 1,3-bis(diethylphosphonato)acetone (**12**) followed by removal of the trityl protecting group of **13** in the presence of hydrochloric acid. 1-Trityl-1*H*-imidazole-2-carbaldehyde (**9**) was initially synthesized by tritylation of 2-imidazolecarboxaldehyde (**8**) with trityl chloride using triethylamine as base in 20% yield. Replacement of triethylamine with potassium carbonate did not improve the yield. Alternately, aldehyde **9** was achieved in 60% yield by formylation of 1-trityl-1*H*-imidazole (**11**) that was derived from tritylation of imidazole (**10**).

The anti-proliferative activity of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl) penta-1,4-diene-3-one (**14**) against androgen-insensitive prostate cancer cell lines (PC-3 and DU145) and androgen-sensitive prostate cancer cell line (LNCaP) has been evaluated by WST-1 cell proliferation assay following the procedure as described in the experimental section. The IC_{50} values for (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**) towards three prostate cancer cell lines range from 73 μM to 305 μM, which indicates that (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**) is even less potent than curcumin (IC_{50}, 14–26 μM) and that removal of the 1-alkyl group diminishes the antiproliferative activity of (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2–4**). This suggests that introduction of an appropriate metabolically stable group to *N*1 position of imidazole moiety is indispensable for both potency and bioavailability.



Scheme 1. Synthesis of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**).