Bioorganic & Medicinal Chemistry Letters 26 (2016) 1292–1295

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological evaluation of novel orally available 1-phenyl-6-aminouracils containing dimethyldihydrobenzofuranol structure for the treatment of allergic skin diseases

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ARTICLE INFO

Article history:
Received 7 September 2015
Revised 30 December 2015
Accepted 8 January 2016
Available online 8 January 2016

Keywords:
CX-659S
1-Phenyl-6-aminouracils
Dimethyldihydrobenzofuranol
Contact hypersensitivity reaction
Pruritus

ABSTRACT

We have designed and efficiently synthesized novel 1-phenyl-6-aminouracils by replacing the chroman moiety in CX-659S, a nonsteroidal dermatologic candidate, with dimethyldihydrobenzofuranol to cancel CX-659S asymmetric center. Medicinal chemistry effort culminated in the discovery of **13d** bearing a 3-methyl group at the 1-phenyl group as a promising compound. Compound **13d**, having good in vitro ADME profile and moderate oral bioavailability in mice, showed potent anti-inflammatory activity against hapten-induced contact hypersensitivity reaction in mice following topical and oral administration. The effects of **13d** were equipotent to that of tacrolimus or prednisolone. In addition, compound **13d**, having potent hydroxyl radical-scavenging activity, showed more potent suppressive effect on substance P-induced pruritus in mice than oxatomide.

Atopic dermatitis (AD) and allergic contact dermatitis are well-known allergic skin diseases that cause serious inflammation and pruritus, and subsequently lower patient quality of life. Especially, AD is a chronic disease with alternating remission and recurrence that affects both children and adults in industrialized countries.[1,2] Glucocorticoids are widely used in the treatment of allergic skin diseases and work by suppressing allergic responses. However, these steroids produce severe side effects, including steroid withdrawal syndrome, skin atrophia, and increased susceptibility to infection. As current treatment of allergic skin diseases relies mainly on the use of steroids, there is a great need for new dermatologic drugs that can alleviate both inflammation and pruritus without inducing undesirable side effects.

We have previously disclosed that CX-659S (**1**, Fig. 1) inhibits hapten-induced acute and chronic contact hypersensitivity reaction (CHR) in mice.[3] In addition, we have shown that CX-659S acts as antioxidant in lipid peroxidation in rat brain homogenate and as scavenger of reactive oxygen species, which can contribute to skin inflammation.[4,5] As shown in Figure 1, CX-659S has an antioxidative chroman moiety that resembles the structure of vitamin E. This moiety plays an important role in CX-659S anti-inflammatory activity,[4] while generating an asymmetric center in the molecule. Development of chiral drug requires overcoming several hurdles, including separation of stereoisomers, determination of absolute stereochemistry and compliance with US Food and Drug Administration guidance for stereoisomeric drugs.[6]

To overcome these drawbacks, we aimed to cancel the asymmetric center of CX-659S, while maintaining its anti-inflammatory activity. Chugai (**2**) and Ono (**3**) scientists have independently reported that the dimethyldihydrobenzofuranol (DDB) acts as a potent antioxidant (Fig. 1).[7] As the structure of DDB shows no asymmetry, we extracted it from compounds **2** and **3**, and designed a novel structural class of 1-phenyl-6-aminouracils by replacing CX-659S chroman moiety with DDB (Fig. 1). In this Letter, we established the large-scale synthetic method of the DDB part and synthesized a series of novel 1-phenyl-6-aminouracils containing the DDB structure. In addition, we evaluated the anti-inflammatory activities of these compounds in mice hapten-induced CHR and assessed the suppressive effects of one of the selected compounds on pruritus in mice.

The general synthetic pathway to the 1-phenyl-6-aminouracils **13a**–**13i** is shown in Scheme 1. First, the 5,6-diaminouracils **6a**–**6i**

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http://dx.doi.org/10.1016/j.bmcl.2016.01.019
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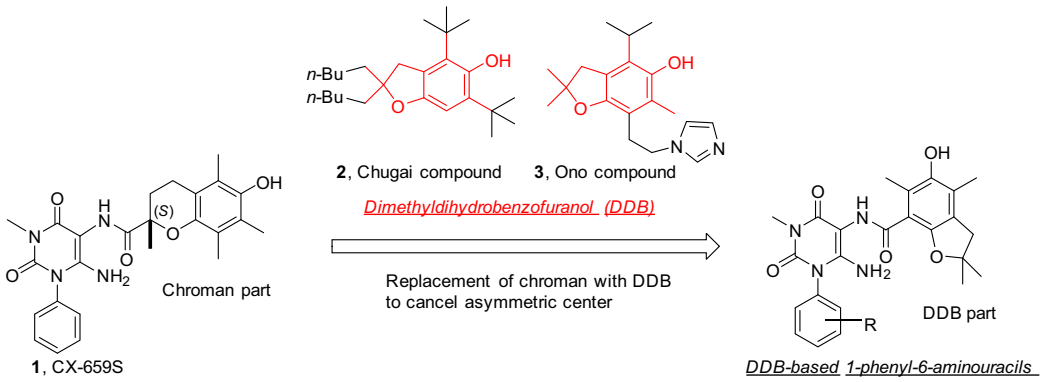
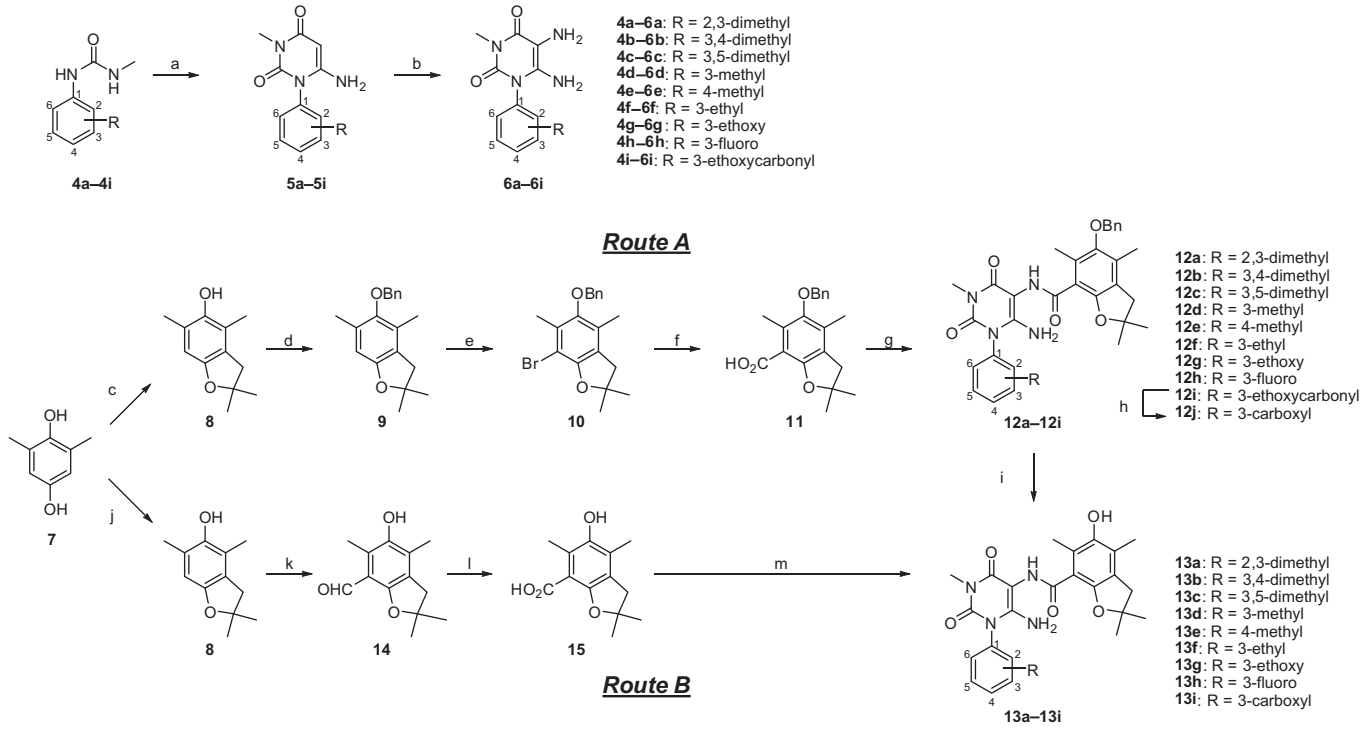


Figure 1. Design of DDB-based 1-phenyl-6-aminouracils using CX-659S.



Scheme 1. Reagents and conditions: (a) (i) cyanoacetic acid, acetic anhydride, toluene, 80 °C; (ii) 3 M NaOH or DBU, THF, 60–89% (2 steps); (b) (i) $NaNO_2$, 12 M HCl; (ii) 10% Pd/C, H_2, MeOH, 28–98% (2 steps); (c) β-methallyl alcohol, $ZnCl_2$, 12 M HCl, silica gel, 1,2-dichloroethane, reflux, 25%; (d) NaH, BnBr, DMF, 90%; (e) Br_2, CF_3CO_2Ag, CH_2Cl_2, 72%; (f) *n*-BuLi, Et_2O, −78 °C then dry ice, 45%; (g) **6a–6i**, diphenylphosphoryl chloride, Et_3N, EtOAc; (h) 3 M NaOH, EtOH; (i) 10% Pd/C, H_2, MeOH, 32–89% (from **11**); (j) isobutyraldehyde, 6 M HCl, toluene, reflux, 74%; (k) Cl_2CHOMe, $TiCl_4$, chlorobenzene, 89%; (l) $NaClO_2$, NaH_2PO_4, 1,4-dioxane, *t*-BuOH, H_2O, 83%; (m) (i) **6a–6i**, diphenylphosphoryl chloride, Et_3N, EtOAc, 18–64%; (ii) 2 M NaOH, MeOH, 70% (only for the synthesis of **13i**).

were synthesized based on a previous method.[3,8] Next, as shown in Route A, 2,6-dimethylhydroquinone **7** was reacted with β-methallyl alcohol and zinc chloride under acidic conditions to afford the dimethyldihydrobenzofuranol **8**.[9] After the protection and bromination, the bromo group in **10** was converted to a carboxyl group via lithiation and dry ice trapping. Condensation of **11** with **6a–6i** followed by deprotection of the benzyl group led to **13a–13h**, respectively. As for synthesis of the carboxylic acid **13i**, alkaline hydrolysis of **12i**, followed by deprotection of the benzyl group gave **13i**.

Although we managed to synthesize this series of compounds according to Route A, it was necessary to improve the route for large-scale synthesis. Especially, the synthetic steps of both **8** and the carboxylic acid **11** were problematic due to their low yield (25% and 45%, respectively), troublesome work-up, and necessity of column chromatography. To improve these problems, we conducted an optimization and found the efficient scalable synthetic route shown as Route B in Scheme 1. Using isobutyraldehyde and hydrogen chloride instead of zinc chloride, the large-scale synthesis of **8** was successfully achieved (155.2 g, 74% yield). Next, formylation of **8** by Rieche reaction,[10] followed by Pinnick oxidation afforded the carboxylic acid **15** (98 g, 74% yield for two steps). These synthetic methods were easy to handle and applicable to the large-scale preparation of **15**.[11] Condensation of **15** with **6a–6i**, followed by hydrolysis (only for the synthesis of **13i**) gave **13a–13i**, respectively. This condensation step needed no protection of the phenolic hydroxy group in **15**. Thus, establishment of Route B for a facile synthesis of the 1-phenyl-6-aminouracils enabled us to shorten the synthetic route by two steps compared to Route A.

The 1-phenyl-6-aminouracils listed in Table 1 were evaluated for their topical anti-inflammatory activity against picryl chloride