Bioorganic & Medicinal Chemistry Letters 28 (2018) 796–801

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Structural development of tetrachlorophthalimides as liver X receptor β (LXRβ)-selective agonists with improved aqueous solubility

Sayaka Nomura [a], Kaori Endo-Umeda [b], Shinya Fujii [a], Makoto Makishima [b], Yuichi Hashimoto [a], Minoru Ishikawa [a,*]

[a] Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan
[b] Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan

ARTICLE INFO

Article history:
Received 21 November 2017
Revised 8 December 2017
Accepted 11 December 2017
Available online 13 December 2017

Keywords:
Liver X receptor
LXR
Selective agonist

ABSTRACT

LXRβ-selective agonists are promising candidates to improve atherosclerosis without increasing plasma or hepatic TG levels. We have reported a series of tetrachlorophthalimide analogs as an LXRβ-selective agonist. However, they exhibited poor aqueous solubility probably due to its high hydrophobicity and highly rigid and plane structure. In this report, we present further structural development of tetrachloro(styrylphenyl)phthalimides as the LXRβ-selective agonists with improved aqueous solubility.

Liver X receptors (LXRs) are members of the nuclear receptor (NR) superfamily,[1,2] and ligand-dependent transcription factors. The physiological ligands for LXRα/β are oxysterols, including 22(*R*)-hydroxycholesterol (**1**) and 24(*S*),25-epoxycholesterol (**2**) (Fig. 1).[3] Upon binding of an agonist to the ligand-binding domain (LBD) of LXR, gene transcription occurs. The products of LXR-regulated genes, such as *ABCA1*, *ABCG1*, *ABCG5*, *ABCG8*, *ApoE* and *GLUT4*[4–6] are involved in lipid metabolism, reverse cholesterol transport,[7] and glucose transport, so LXRs are considered to be potential drug targets for atherosclerosis, hyperlipidemia, and metabolic syndrome.[8] However, LXRs agonists also induce genes involved in lipogenesis, such as *SREBP-1c* (sterol regulatory binding element proten 1c)[9] and *FAS* (fatty acid synthase),[8] resulting in increased plasma and hepatic triglyceride levels,[2] which in turn might lead to fatty liver and atherosclerosis as possible side effects.

LXRs include two subtypes with different tissue distribution, LXRα and LXRβ. LXRα is highly expressed in liver, intestine and macrophages, while LXRβ has a more widespread pattern of expression, being almost ubiquitous. LXRα contributes to lipogenesis in liver, while selective LXRβ activation improves RCT in LXRα-knockout mouse.[10,11] Therefore, LXRβ-selective agonists are expected to improve atherosclerosis via induction of RCT and cholesterol efflux from liver, without increasing plasma or hepatic TG levels. However, LXRα and LXRβ are highly related and share 78% amino acid sequence identity in the ligand-binding domains (LBDs), especially in the vicinity of the ligand-binding pocket.[12] Consequently, most LXR ligands, including T0901317 (**3**)[1] and GW3965 (**4**)[13,14] do not show subtype selectivity.

To date, a few LXRβ-selective agonists **5**–**8** have been reported (Fig. 1).[15] During our continual research of LXR ligands,[16] we have also found that **9** exhibited >100-fold selective LXRβ agonistic activity in a full-length LXRβ reporter gene assay system.[17] Compound **9** showed high selectivity over other NRs, and induced only *ABCA1* mRNA expression but not *SREBP-1c* mRNA expression. However, **9** exhibited poor aqueous solubility. In this report, we present further structural development of tetrachloro(styrylphenyl)phthalimides as the LXRβ-selective agonists with improved aqueous solubility.

Styrylphenylphthalimide analogues were synthesized as shown in Scheme 1. Benzyl bromides **10**, **11** were treated with PPh_3 to generate phosphonium ylides **11**, **13**. Wittig reaction of ylides **11** and aldehydes **14a**–**g**, and ylide **13** and aldehyde **15** afforded *ortho*-stilbenes **16a**–**h**. Reduction of the nitro group of **16a**–**h** with $SnCl_2{\cdot}2H_2O$, cyclization with tetrachlorophthalic anhydride, and separation of the *EZ* isomers gave the *E*-isomers **9** and **18a**–**g**, and *Z*-isomer **19h**. Various amines **20**, **22**–**24** were cyclized with tetrachlorophthalic anhydride to give **21**, **25**–**27**.

Our previous SAR studies indicated that chloro atoms at phthalimide are necessary for selective LXRβ agonistic activity. In addition, introduction of various substituents or changing position of methoxy substituent of the terminal benzene ring at styryl group did not lead to improve LXRβ agonistic activity. These results indicated that substituent(s) at the terminal benzene ring would inter-

* Corresponding author.
E-mail address: m-ishikawa@iam.u-tokyo.ac.jp (M. Ishikawa).

https://doi.org/10.1016/j.bmcl.2017.12.024
0960-894X/

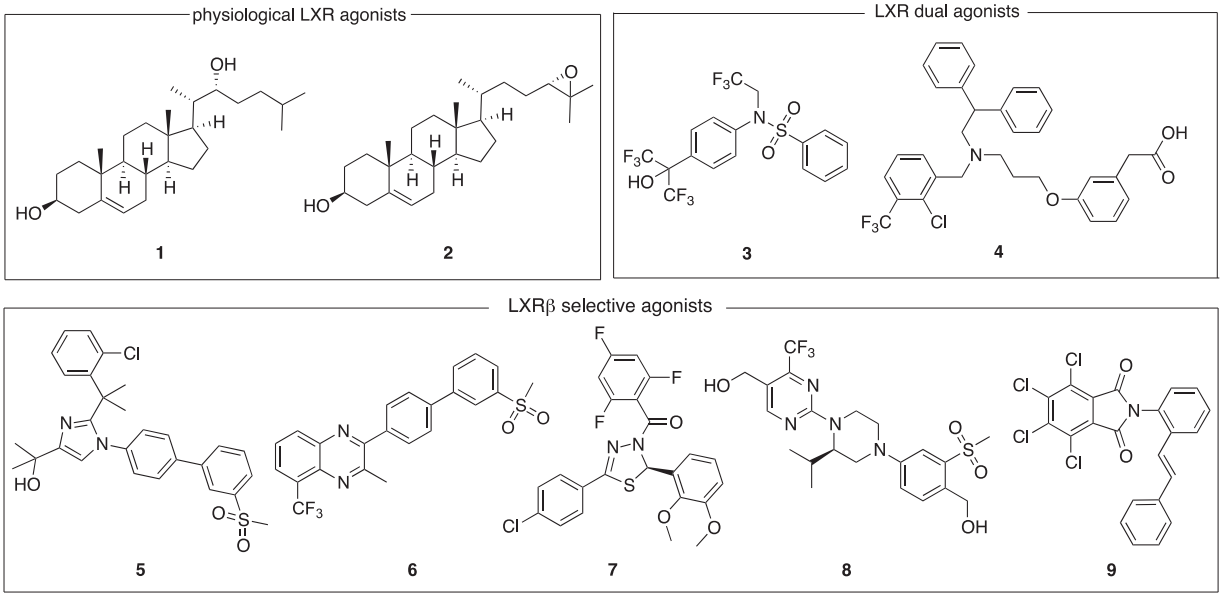
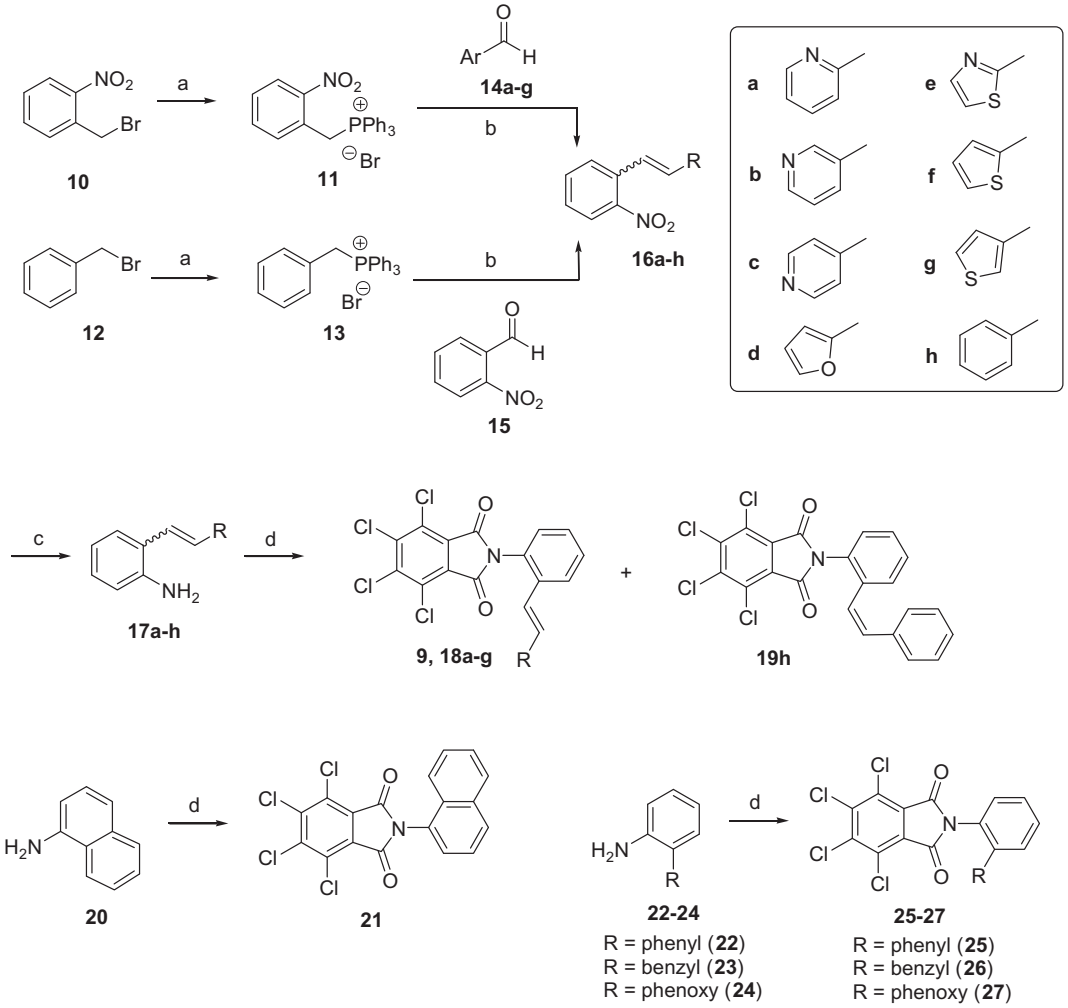


Fig. 1. Chemical structures of LXR agonists.



Scheme 1. Reagents and conditions: (a) PPh_3, CH_3CN, reflux; (b) benzaldehydes, 18-crown-6, K_2CO_3, DCM, reflux; (c) $SnCl_2{\cdot}2H_2O$, AcOEt, reflux; (d) tetrachlorophthalic anhydride, AcOH, reflux.