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Letter

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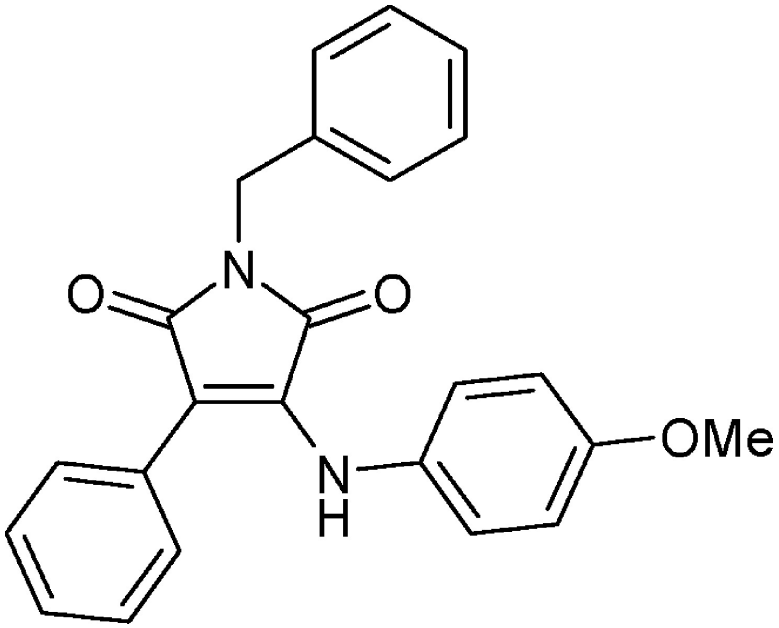

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Discovery of Substituted Maleimides as Liver X Receptor Agonists and Determination of a Ligand-Bound Crystal Structure

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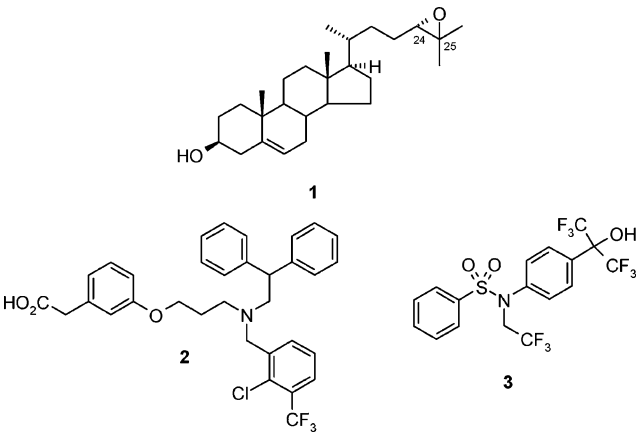
Abstract: Substituted 3-(phenylamino)-1*H*-pyrrole-2,5-diones were identified from a high throughput screen as inducers of human ATP binding cassette transporter A1 expression. Mechanism of action studies led to the identification of GSK3987 (**4**) as an LXR ligand. **4** recruits the steroid receptor coactivator-1 to human LXRα and LXRβ with EC_{50}s of 40 nM, profiles as an LXR agonist in functional assays, and activates LXR though a mechanism that is similar to first generation LXR agonists.

The ATP binding cassette transporter ABCA1 plays a critical role in cholesterol homeostasis and HDL-c metabolism. ABCA1 is required for efflux of cellular free cholesterol to poorly lipidated apoA-I and other apolipoprotein acceptors in plasma and is considered to be the first step in reverse cholesterol transport (RCT). Genetic deficiency in ABCA1 results in Tangier disease, a condition that leads to massive cholesterol accumulation in peripheral tissues and extremely low plasma HDL-c levels. Its critical role in atherosclerosis is supported by the observation that patients with mutations in one or both ABCA1 alleles have an increased risk for coronary artery disease.[1] Agents that increase ABCA1 expression, stimulate cellular cholesterol efflux, and increase RCT should decrease atherosclerotic plaque cholesterol and decrease the incidence of coronary heart disease.

Liver X receptors (LXR) α and β are ligand-activated transcription factors belonging to the superfamily of nuclear hormone receptors.[2] To date, several distinct structural classes of ligands have been described which include a natural ligand 24(*S*),25-epoxycholesterol (**1**, EPC) as well as two synthetic, nonsteroidal ligands GW3965 (**2**) and T0901317 (**3**) (Chart 1).[3−5] Both natural and synthetic LXR agonists have been shown to increase the expression of ABCA1.[6] Synthetic LXR agonists have demonstrated efficacy in mouse models of atherosclerosis, presumably as a consequence of upregulated expression of genes *abca1*, *abcg1*, *abcg5*, *abcg8*, *cyp7a*, and *apoE* leading to increased RCT.[7] Synthetic LXR agonists inhibit LPS-induced expression of proinflammatory genes and decrease inflammation in mouse models, which may also contribute to the antiatherosclerotic activity of LXR agonists.[8] Synthetic LXR agonists also regulate the expression of several genes involved in glucose metabolism and show antidiabetic activity in rodent models of type 2 diabetes.[9] However, the therapeutic potential of LXR agonists is compromised by LXR-mediated increases in plasma and hepatic triglycerides, which results from LXR-regulated induction of lipogenic genes including sterol response element binding protein-1c (SREBP-1c) and fatty acid synthase (FAS). There is a clear need for new LXR chemotypes which retain the antiinflammatory, antidiabetic, or antiatherosclerotic efficacy of current LXR agonists but are devoid of lipogenic activity. In this report, we describe the identification of substituted 3-(phenylamino)-1*H*-pyrrole-2,5-diones (maleimides) as dual LXRα/β agonists.

Chart 1. Structures of 24(*S*),25-Epoxycholesterol (**1**), GW3965 (**2**), and T0901317 (**3**)



To identify compounds that upregulate the expression of ABCA1 gene in macrophages, we conducted a high throughput screen of the GSK compound collection using human monocytic THP-1 cells stably transfected with a luciferase reporter construct driven by a 1.5 kb segment of the human ABCA1 proximal promoter. Nonspecific transcriptional upregulators were eliminated by examining activity of compounds in an unrelated control reporter assay (data not shown). Compounds showing specificity for induction of the ABCA1 reporter gene were further characterized using an in vitro ligand-sensing assays (LiSA) employing the purified LXRα and LXRβ ligand binding domains.[10] In this manner, several LXR chemotypes were identified along with the known LXR agonist **3**.

Nine maleimide compounds, previously reported as inhibitors of glycogen synthase kinase-3 (GSK-3), showed activity in both the ABCA1 reporter and LXRα/β SRC-1 LiSA, with **4** being the most potent and efficacious

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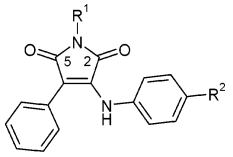
Table 1. ABCA1 Reporter Gene, LXRα/β LiSA, and GSK-3β Activity of Substituted Maleimides[a]



			ABCA1		LXRα-SRC1		LXRβ-SRC1		GSK-3β
compd	R^1	R^2	EC_{50} (μM)	RE	EC_{50} (nM)	RE	EC_{50} (nM)	RE	IC_{50} (nM)
2	–	–	0.17 ± 0.01	1.0	80 ± 45	1.0	20 ± 10	1.0	NT
3	–	–	0.07 ± 0.03	1.0	55 ± 15	1.1	30 ± 10	0.8	NT
4	Bn	OMe	0.08 ± 0.03	0.9	50 ± 7	0.9	40 ± 9	0.9	>5000
5	Bn	H	1.32 ± 0.3	0.6	100 ± 25	0.3	70 ± 25	0.5	>5000
6	Bn	Cl	1.42 ± 0.24	0.4	130 ± 30	0.3	110 ± 40	0.4	>5000
7	Et	OMe	10.17 ± 1.17	0.4	300 ± 75	1.1	200 ± 50	0.9	>5000
8	Ph	OMe	1.12 ± 0.06	0.7	275 ± 60	0.7	260 ± 90	0.6	>5000
9	Me	OMe	0.84 ± 0.05	1.4	575 ± 130	0.9	300 ± 80	0.9	>2000
10	Et	H	1.79 ± 0.36	0.5	890 ± 215	0.7	560 ± 155	0.7	>5000
11	Et	Cl	4.55 ± 0.55	0.4	725 ± 135	0.5	575 ± 150	0.6	>5000
12	Me	H	4.65 ± 2.84	0.3	1590 ± 385	0.5	850 ± 95	0.6	>5000

[a] EC_{50} = concentration of compound that leads to half-maximal activity ± standard error, $n > 4$. RE = relative efficacy compared to GW3965 (**2**). NT = not tested.

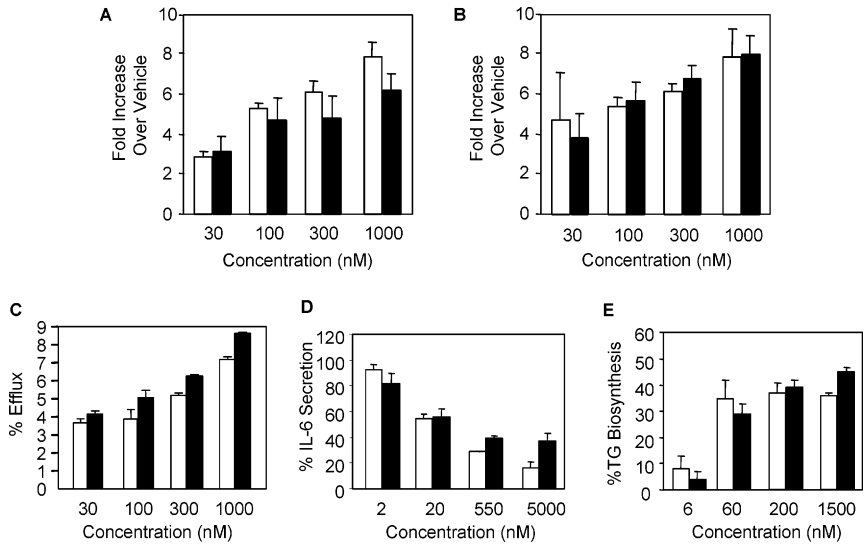


Figure 1. Effects of **2** (white bars) and **4** (black bars) on (A) ABCA1 mRNA expression in primary human macrophages, (B) SREBP-1c mRNA expression in HepG2 cells, (C) ^{3}H-cholesterol efflux to apoA1 in primary human macrophages, (D) IL-6 secretion in THP-1 cells, and (E) percent triglyceride biosynthesis over basal in HepG2 cells.

compound (Table 1).[11] Consistent with the high level of amino acid identity within the LXRα and LXRβ ligand-binding pockets, all of the analogues profiled as dual agonists with no significant subtype selectivity.[12] Importantly, maleimide **4** showed >50-fold selectivity when tested against a panel of nuclear receptors (FXR, PPARα/γ/δ, PXR, AR, ERα/β, GR, PR). While analogues containing an *N*-benzyl moiety were the most potent analogues in the LXRα/β LiSA, incorporation of this *N*-alkyl group dramatically reduced activity at GSK-3 (Table 1). The fact that LXR potency decreased as the size of the *N*-benzyl group was reduced suggested that this substituent occupied a hydrophobic pocket (see structure discussion below). Interestingly, incorporation of a methoxy group at the para position of the aniline ring consistently increased efficacy relative to hydrogen or chlorine substituents at this position. With the exception of **7**, the general rank order of potencies in the LiSA paralleled that from the ABCA1 assay, consistent with the role of LXR as a primary transcriptional regulator of ABCA1 expression.

In line with its activity in the ABCA1 reporter gene assay, **4** increased the expression of ABCA1 in primary human macrophages (Figure 1A) and induced cellular cholesterol efflux to apoA1 particles in a dose-dependent manner (Figure 1C). **2** has been reported to decrease the expression of several proinflammatory genes in stimulated macrophages such as interleukin-6 (IL-6), inducible nitric oxide synthase, and cyclooxygenase-2.[8] We therefore employed an ELISA to determine whether LXR agonists would affect secretion of IL-6 protein from activated THP-1 macrophages. In this assay, **2** inhibited LPS-stimulated IL-6 secretion in a dose-dependent manner by up to 80%. Maleimide **4** profiled similarly albeit with reduced efficacy at the highest concentration tested (Figure 1D). First generation LXR agonists also increase the expression of genes that control fatty acid and triglyceride biosynthesis such as SREBP-1c and FAS. Maleimide **4** increased the expression of SREBP-1c and induced triglyceride accumulation in human hepatoma (HepG2) cells in a dose-dependent manner (Figure 1B and 1E). The activities in the gene expression

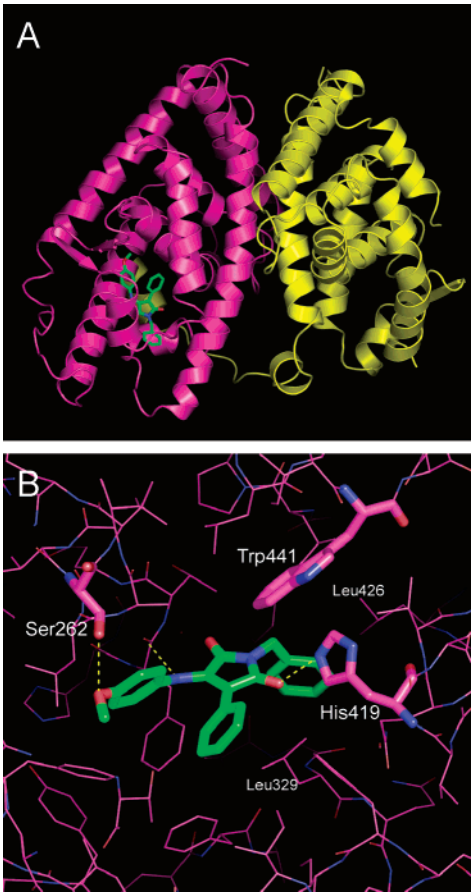


Figure 2. X-ray crystal structure of **4** bound to mLXRα. (A) View of **4**-mLXRα (magenta)/9cRA-RXRα (yellow) ligand-binding domain heterodimer structure. (B) A closeup view highlighting key recognition elements for binding of **4** to mLXRα. A hydrogen bond interaction between the 2-carbonyl of **4** and His^{419} on helix 10/11 promotes an electrostatic interaction between His^{419} and Trp^{441} on AF-2 which, in turn, leads to stabilization of AF-2 and activation of LXRα. Figures made using the program PYMOL.[15]

and cellular assays are consistent with **4** profiling as a nonselective LXR agonist.

To date, ligand-bound LXR crystal structures have been published for **1**−**3**.[13] The X-ray structures reveal ligand-binding pockets that vary in size and shape depending on the nature of the bound ligand. Whereas **1**−**3** show different interactions with residues in the pocket that are distal to AF-2, they each activate the receptor by promoting similar electrostatic interactions between a conserved histidine on helix 10/11 and tryptophan on the C-terminal activation function-2 (AF-2) helix.[12] Maleimide **4** provided a structurally distinct LXR chemotype to explore ligand−receptor contacts and alternative mechanisms for receptor activation. Cocrystallization of **4** with mouse LXRα (mLXRα) in complex with human retinoid X receptor α (RXRα) and 9-*cis*-retinoic acid generated crystals that diffracted to a resolution of 2.8 Å (Figure 2). The crystals were in a P1 space group with four heterodimers in each asymmetric unit. The standard three-layered α-helical fold was observed for both mLXRα and hRXRα, and the receptors were involved in a heterodimer interaction involving helices 7 and 10. The AF-2 helix of each LXRα is packed against the LBP in an active conformation. Interestingly, the AF-2 helix of each RXRα molecule binds in the coactivator binding groove of its mLXRα heterodimer partner. While the functional relevance of this interaction is not known, the LXXML residues in the AF-2 helix of RXRα most likely mimic a natural LXXLL sequence of known coactivators such as SRC-1.[14]

The orientation of **4** is guided by multiple interactions with residues that line the pocket (Figure 2B). The 2-oxo group is involved in a strong hydrogen bond with His^{419} which stabilizes the receptor in an active conformation by promoting an interaction between His^{419} and Trp^{441}. In contrast, the 5-oxo functionality is not involved in any interaction with the receptor, suggesting that removal of this group would not be detrimental to LXR binding. The *N*-benzyl moiety fills a hydrophobic pocket near the *gem*-dimethyl group in **1**, the 2-chloro-3-trifluoromethylbenzyl group in **2**, and the bis-trifluoromethyl groups in **3**. Unlike those ligands, the *N*-benzyl group in **4** protrudes much deeper into the hydrophobic pocket, which expands by a shift in the helix 6−7 loop (Leu^{329}) and the C-terminus of helix 10/11 (Leu^{426}). Filling this hydrophobic pocket with the *N*-benzyl group appears to make the compounds more potent (Table 1, compounds **4**−**6**). The 4-phenyl group occupies a similar hydrophobic pocket as compared to the trifluoroethyl group in **3** and one of the phenyl rings in the diphenethyl moiety in **2**. The aniline NH appears to be involved in a weak 3.4 Å hydrogen bonding interaction with the backbone carbonyl of Phe^{255} in helix 3. A similar interaction was not observed in the crystal structures of **1**−**3** bound to LXR and may constitute a unique ligand-LXR interaction. The 4-methoxy ether oxygen is involved in a hydrogen bond interaction with the hydroxyl in Ser^{262}. It is not obvious from the cocrystal structure why replacement of the methoxy group with chlorine or hydrogen decreases efficacy in the LXRα/β LiSAs.

In summary, substituted 3-(phenylamino)-1*H*-pyrrole-2,5-diones (maleimides) were identified from a high throughput screen as inducers of ABCA1 with compound **4** proving to be the most potent, dual LXRα/β agonist. While analysis of the ligand-bound cocrystal structure reveals unique interactions between **4** and mLXRα as compared to previously reported structures, the molecular basis for receptor activation appears to be conserved. This may, in part, explain the observed similarities between **4** and **2** in gene expression and cellular functional assays in human macrophages and hepatoma cells**.** While **4** shows a favorable profile in cellular cholesterol efflux and antiinflammatory assays, induction of triglyceride accumulation remains a liability. The identification of this new LXR chemotype facilitated the determination of key interactions which are required for receptor activation, but also provides insight into the plasticity of the LBP and highlights regions to be probed for future development of LXR modulators with improved therapeutic indices.

Supporting Information Available: Experimental procedures and crystallographic data (PDB ID code ZACL) for the research described in this letter are available free of charge via the Internet at http://pubs.acs.org.

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