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Discovery and structure–activity relationship studies of indole derivatives as liver X receptor (LXR) agonists

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Abstract—A structurally novel liver X receptor (LXR) agonist (**1**) was identified from internal compound collection utilizing the combination of structure-based virtual screening and high-throughput gene profiling. Compound **1** increased ABCA1 gene expression by eightfold and SREBP1c by threefold in differentiated THP-1 macrophage cell lines. Confirmation of its agonistic activity against LXR was obtained in the co-factor recruitment and reporter transactivation assays. Structure–activity relationship studies on compound **1** are described.
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Liver X receptors (LXRα and LXRβ) belong to the type 2 family of the nuclear hormone receptor superfamily that function as transcription factors.[1] LXRα is expressed at high levels in liver, adipose tissue, and macrophages, while LXRβ is ubiquitously expressed. LXRs function as heterodimers with the retinoid X receptors (RXR) and regulate the expression of a number of genes involved in cholesterol and fatty acid metabolism.[2,3] Upon agonist binding, the DNA binding domain (DBD) of LXR interacts with LXR response elements on target genes to initiate transcription. One LXR target gene is the ATP-binding cassette transporter ABCA1, which is involved in reverse cholesterol transport (RCT) from macrophages in the atherosclerotic plaques to high-density lipoproteins (HDL) in the plasma.[4,5] As such, increasing RCT by LXR agonism is a potential therapeutic approach for a number of pathophysiological states including dyslipidemia, atherosclerosis, and diabetes.[6] To date, several distinct classes of agonists have been described in the literature[7–9] and patents[10] which include natural ligands 24(*S*),25-epoxycholesterol (EPC, I), *N*,*N*-dimethyl-3β-hydroxy-cholenamide (DMHCA, II), and non-steroidal synthetic ligands: GW3965 (III) and T0901317 (IV) (Fig. 1). Both natural and synthetic

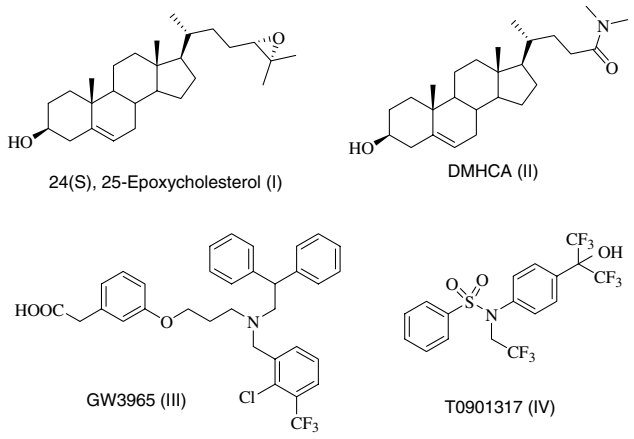

Figure 1. Natural and synthetic LXR agonists.

Keywords: Virtual screening; High-throughput gene profiling; LXR agonist; Liver X receptor.
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LXR agonists have been shown to increase the expression of ABCA1. Synthetic LXR agonists raise plasma HDL levels in mice and show anti-diabetic activity in rodent models of type 2 diabetes.[11,12] However, LXR agonists also activate sterol response element binding protein-1c (SREBP1c) expression, which controls the entire fatty acid biosynthetic pathway and promotes hyperlipidemia and hepatic steatosis. Thus, there is a clear need for selective LXR modulators that are devoid of lipogenic activity and could offer potential pharmacological benefits.[13]

In the search for novel LXR modulators with appropriate gene regulation profiles, we adopted a high-throughput gene profiling platform for our primary screening. Fifteen hundred compounds were selected from an internal compound collection through a homology-based virtual screening[14] and subsequently evaluated by high-throughput genomic technology (HTG, Inc., Tucson, AZ)[15] for gene expression profiling including 12 LXR target genes. Boc-indole compound (**1**) was identified as an initial hit that showed an excellent induction ratio of ABCA1 over SREBP1c genes in the differentiated THP-1 macrophages. It was further confirmed to be an LXR agonist with a cofactor peptide recruitment study using homogeneous time-resolved fluorescence energy transfer (HTRF) assay.[16] Herein, we describe the structure–activity relationship (SAR) studies on this novel chemotype, as LXR agonists. Strategically, compound **1** was divided into three portions: *N*-Boc-indole (left portion), indane (linker), and benzene sulfonamide (right portion), and systematic SAR studies were conducted in each portion (Fig. 2).

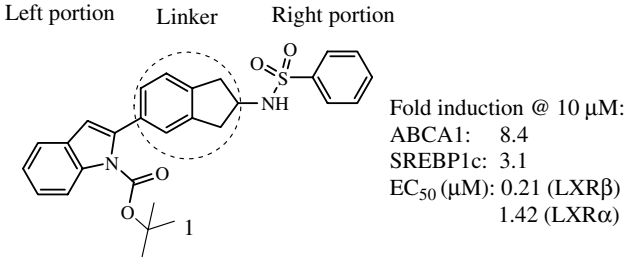
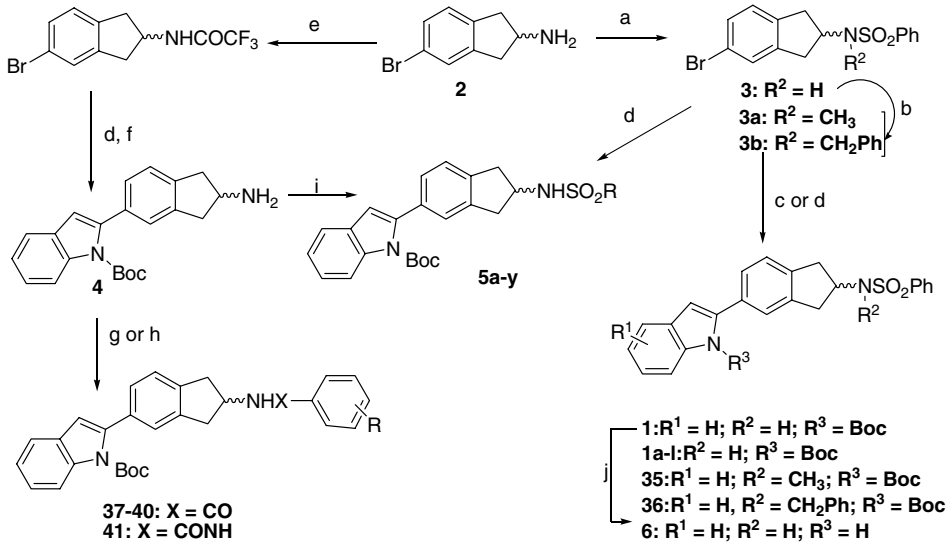


Figure 2. Initial HTG hit and SAR strategy.

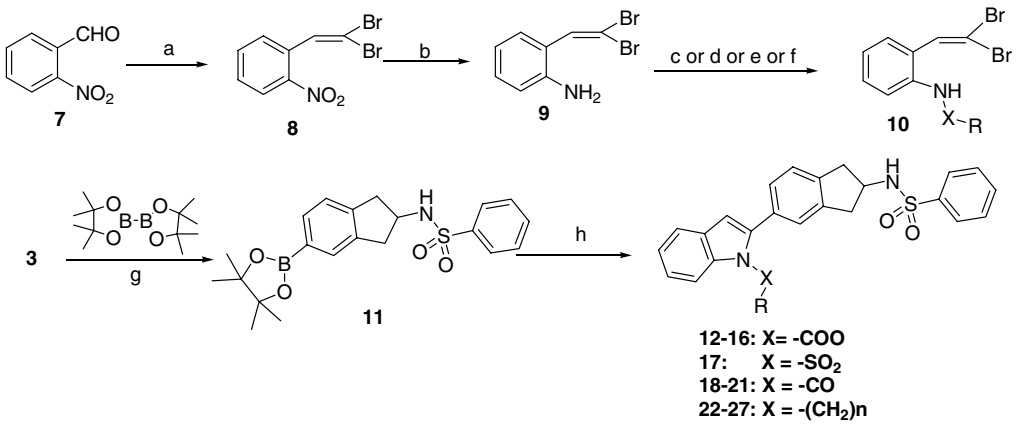
A general synthesis for initial hit **1** and its analogs is shown in Scheme 1. The amine **2** was converted to the requisite sulfonamides (**3** and **3a**–**b**) followed by Suzuki coupling leading to the indole sulfonamides (**1**, **1a**–**l**, **35**, and **36**). Alternatively, **2** was protected as the trifluoroacetamide that was coupled with *N*-Boc-indole-boronic acid followed by de-protection to yield the amine intermediate **4**. Compound **4** was derivatized to yield various targets (**5a**–**y** and **37**–**41**). The enantiomerically pure isomers, **1m** (*R*) and **1n** (*S*), were synthesized from the corresponding chiral amines **2a** (*R*)- and **2b** (*S*), which in turn were obtained in excellent optical purity by co-crystallization of **2** with (*S*)- and (*R*)-camphorsulfonic acids, respectively.[17]

A convergent synthesis was also developed to explore the N-1 substitution on the indole ring of compound **1** (Scheme 2).[18] Thus, 2-nitrobenzaldehyde was converted into dibromovinyl aniline **9** in two steps in high yields. The aniline was functionalized (**10**) to yield the desired *N*-alkyl (X = CH_2), *N*-acyl (X = CO), and urea (X = CONH) compounds which were subsequently reacted with the indane boronic ester **11** to provide the corresponding N-substituted indole derivatives.

Compounds wherein the linker attachment position was moved from the 2-position on the *N*-Boc-indole moiety (**1**) to the 4- and 6-positions (**28** and **29**, Fig. 3), respectively, were synthesized from requisite boronic acids according to Scheme 1. The *N*-Boc-pyrrole and *N*-Boc-



Scheme 1. Reagents and conditions: (a) $PhSO_2Cl$, DIEA, DCM, quantitative; (b) R^2X, NaH, DMF; (c) *N*-Boc-indole-2-boronic acid (optionally substituted), $Pd[(Ph)_3P]_4$, Na_3PO4, DMF, 100 °C, 20–40%; (d) *N*-Boc-indole-2-boronic acid (optionally substituted), $PdCl_2(PPh_3)_2$, K_2CO_3, toluene/ethanol/water (10:1:1), microwave, 10 min; (e) TFAA, DIEA, DCM, 91%; (f) 10% Na_2CO_3, MeOH, rt, 83%; (g) RCOCl, DIEA, DCM, 70–80%; (h) RNCO, DIEA, DCM, 50%; (i) similar to (a) with substituted $PhSO_2Cl$; (j) TFA, DCM.



Scheme 2. Reagents and conditions: (a) CBr_4, PPh_3, DCM; (b) $SnCl_2$, ethanol, 100 °C, 2 h, 82%; (c) RCH_2Br, K_2CO_3, THF; (d) RCOCl, Et_3N, DCM, 0 °C–rt, 18 h, 50–70%; (e) RNCO, Et_3N, DCM; (f) RSO_2Cl, Et_3N, DMAP, DCM, 0 °C–rt, 18 h, 50–70%; (g) KOAc, Et_3N, $Pd(dppf)Cl_2$, dioxane, 100 °C, 90%; (h) **10**, $Pd[(Ph_3P)]_4$, Cs_2CO_3, toluene/ethanol/water (10:1:1), 10–20%.

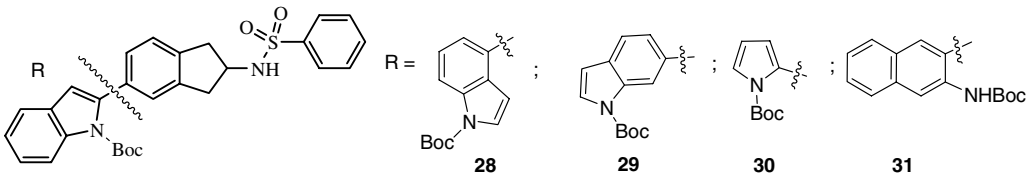


Figure 3. Linker attachment position.

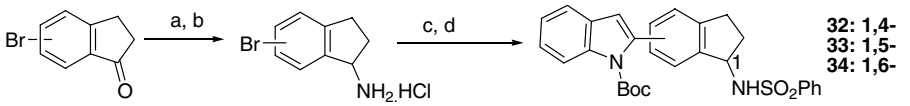
naphthalene compounds (**30** and **31**, Fig. 3) were prepared in an analogous manner.

Compounds **32**–**34** with three different 1-aminoindane linkers (1,4;1,5, and 1,6) were prepared in two steps from the requisite bromoindan-1-ylamine (Scheme 3), which in turn were prepared from the corresponding 1-indanone via a modified Leuckart reaction in excellent yields.[19]

SAR compounds prepared above were tested in the cofactor recruitment assay and were rank-ordered based on EC_{50} values. Those compounds tend to have slight selectivity for LXRβ over LXRα. Initial SAR studies indicated that only small groups such as methyl or hydroxy at the 6-position of the indole ring were tolerated (compare **1k** and **1l** with **1**, Table 1). Replacement of the 6-hydroxy in **1l** with 6-methoxy group (**1j**) reduced ~2-fold potency, whereas total loss of activity was observed with the corresponding benzyloxy analog **1i**. Any group at the C-5 position, even a fluorine atom (**1e**), decreased the binding activity, indicating that the interaction of **1** with the LXR binding site is tight around the indole ring. Compound **1n** (*S*-) isomer was fivefold more potent than the (*R*-) isomer **1m**.

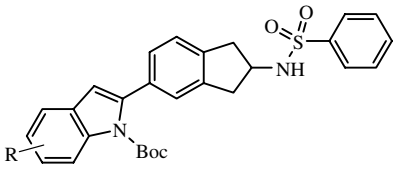
As indicated in Table 2, removal of the *t*-Boc group at the indole N-1 position (**6**) resulted in the complete loss of activity. Other carbamates such as ethyl, isobutyl, and neopentyl (**13**–**15**) were 8- to 10-fold less potent than the parent *tert*-butyl carbamate (*t*-Boc) derivative **1**. Methyl carbamate (**12**) or more bulky alkyl carbamates such as **16** were inactive. No activity was seen with the phenyl sulfonamide compound **17**. While cyclopentyl, *n*-pentyl or cyclopropyl methyl carboxamides (**18**–**20**) retained micromolar potency, *tert*-butylmethyl amide **21** wherein a methylene group substituted an oxygen atom in **1** was completely inactive. The alkyl modifications (**22**–**27**) were inactive indicating that either the pocket size is limited around this area or the carbonyl group is critical for activity.

The attachment point of the indole ring on the aminoindan linker seems to play a critical role. Switching the aminoindan linker from the 2-position in **1** to the 4- or 6-positions (**28** and **29**, Fig. 3), respectively, was detrimental to the potency ($EC_{50} > 30$ μM). Replacement of *N*-Boc-indole with *N*-Boc-pyrrole or *N*-Boc-naphthalene resulted in a complete loss of activity (**30** and **31**).



Scheme 3. Reagents and conditions: (a) $HCOONH_4/NaCNBH_3$, MeOH, 65%; (b) 10% concd HCl in MeOH, quantitative; (c) $PhSO_2Cl$, DIEA, DCM, 90%; (d) *N*-Boc-indole-2-boronic acid, $Pd[(Ph_3P)]_4$, DMF, 100 °C or K_2CO_3, toluene/ethanol/water (10:1:1), microwave, 10 min, 20–40%.

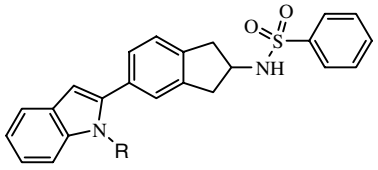
Table 1. Effect of substitution on the indole ring

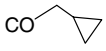
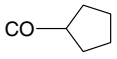


Compound	R	EC_{50}[a] (μM) LXRβ
1	H	0.21
1a	4-OH	>30
1b	4-OBn	>30
1c	5-OH	>30
1d	5-OBn	>30
1e	5-F	1.5
1f	5-CN	26
1g	5-OMe	28
1h	5-Me	18
1i	6-OBn	>30
1j	6-OMe	1.6
1k	6-Me	0.3
1l	6-OH	0.67
1m(*R*)-isomer	H	0.66
1n(*S*)-isomer	H	0.13

[a] Results shown are mean values of duplicate samples in a single experiment.

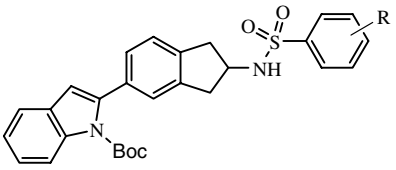
Table 2. SAR of N-substitution of indole



Compound	R	EC_{50}[a] (μM) LXRβ
6	H	>30
12	COOMe	>30
13	COOEt	1.6
14	$COOCH_2$(*i*-Bu)	1.3
15	$COOCH_2$(*t*-Bu)	1.4
16	$COOCH_2CH(Me)(CH_2)_3Me$	>30
17	SO_2Ph	>30
18		1.16
19		0.9
20	$CO(CH_2)_4Me$	2.1
21	$COCH_2$*t*-Bu	>30
22	Me	>30
23	CH_2COO *t*-Bu	>30
24	$(CH_2)_3OBn$	>30
25	CH_2Ph	>30
26	CH_2Ph(4-OMe)	>30
27	$(CH_2)_2Ph$	>10

[a] Results shown are mean values of duplicate samples in a single experiment.

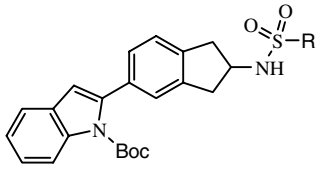
Table 3. SAR of the sulfonamide moiety

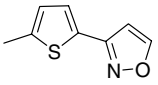
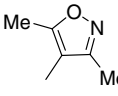
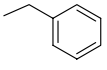


Compound	R	EC_{50}[a] (μM) LXRβ
5a	4-Cl	1.16
5b	4-F	0.46
5c	4-Et	0.65
5d	4-Me	0.43
5e	4-CF_3	0.73
5f	3-Cl	1.81
5g	3-Me	1.33
5h	3-OMe	0.96
5i	3-CN	0.46
5j	2-CO_2Me	0.6
5k	2-CO_2H	3.35
5l	2-Me	0.2
5m	2-OMe	0.6
5n	2-CF_3	0.8
5o	2-CN	0.06
5p	2-F	0.10
5q	2,6-DiF	0.09
5r	2-Cl	0.76

[a] Results shown are mean values of duplicate samples in a single experiment.

Table 4. SAR of additional sulfonamides

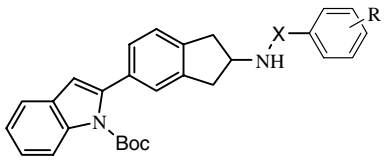


Compound	R	EC_{50}[a] (μM) LXRβ
5s		0.11
5t		0.67
5u		0.13
5v	Ph–Ph(4)	2.1
5w		0.52
5x	Me	0.21
5y	Et	0.40
1	Ph	0.19

[a] Results shown are mean values of duplicate samples in a single experiment.

The importance of the relative position of the right portion and left portion on the central indan ring (2,5 in compound **1**) was explored. Compound **33** with a 1,5 linker retained potency (EC_{50} = 0.22 μM), while compounds with 1,4 (**32**) and 1,6 (**34**) linkers were not toler-

Table 5. SAR of the carboxamide/urea analogs



Compound	X	R	EC_{50}[a] (μM) LXRβ
37	CO	H	0.19
38	CO	2-F	0.17
39	CO	2-OMe	0.47
40	CO	2-OH	0.53
41	CONH	H	1.5

[a] Results shown are mean values of duplicate samples in a single experiment.

ated (EC_{50} > 30 μM) indicating the importance of overall shape of the compounds for binding.

Unlike the *N*-Boc-indole moiety, the sulfonamide region could tolerate a wide range of structural variations (Tables 3–5). In general, small substitutions (Me, F, CN) on the phenyl sulfonamide were tolerated although the *ortho* position was favored over the *meta* or *para* (**5l**, **5o**, **5p**, and **5r** vs **5g**, **5i**, **5b**, and **5f**, respectively) positions. Addition of a second fluorine atom at the 6-position of the phenyl ring in **5p** did not improve the potency any further (**5q** vs **5p**). The 2-CN analog (**5o**) was the most potent one with an EC_{50} value of 60 nM. The corresponding carboxylic acid analog (**5k**) lost ~17-fold potency. The heterocyclic analogs **5s** (2-thienyl) and **5u** (isoxazolyl) increased potency slightly(Table 4). Intriguingly, even the methyl sulfonamide (**5x**) retained potency similar to the phenyl analog **1**. Substitution on the sulfonamide nitrogen in **1** was not tolerated. While the *N*-Me analog **35** retained weak activity (EC_{50} = 2.65 μM), the corresponding *N*-Bn analog **36** was inactive (EC_{50} > 30 μM) implying the requirement of an H-bond donor at this site for binding.

While the replacement of the sulfonamide moiety with the corresponding carboxamides (**37**–**40**) was tolerated, the urea analogs (e.g., **41**) were not favored (Table 5), indicating the sulfonamide group may be able to interact with the protein in the active site.

Selected compounds were tested for their ability to activate LXRβ in a reporter transactivation assay[20] and the regulation of LXR target genes such as ABCA1 and SREBP1c in either THP-1 differentiated macrophages or HepG2 cells with RT-qPCR assays (Table 6). In general, those compounds maintained good potency in the reporter assay. It is worth noting that those selected compounds demonstrated somewhat better gene expression profiles than known LXR agonists such as GW3965 and T0901317. For instance, compound **5b** caused 11-fold increases in ABCA1 gene expression while the SREBP1c gene induction was only twofold. Cell-based functional assays, such as cholesterol efflux and lipogenesis assays,[21,22] also indicated that these indole-based compounds induced lipogenesis to a lesser extent than did T0901317 or GW3965 (Table 6). It is interesting to point out that compound 5t, which showed an activity against LXRα, stimulated ABCA1 gene expression and induced significant cholesterol efflux in the THP-1 cells, indicating LXRβ activity might be the determining factor for this cellular activity. However, correlation between LXRβ activity and ABCA1 gene regulation is not straightforward (**5b** vs **5q**), partially due to compound properties.

Docking studies suggested that compound **1** fits nicely in the LXRβ ligand binding domain. The indole aromatic ring system is close to Trp457 in the AF-2 (helix 12) and forms a π–π interaction, while the Boc carbonyl group forms a hydrogen bond with the conserved His435 in helix 10/11, thereby locking it into an agonistic conformation.[23] The binding mode is very similar to that of GW3965. The plausible binding mode is consistent with the limited room for modification around the Boc-indole moiety. The sulfonamide group may have an interaction with Arg319 (Fig. 4).

In summary, a structurally novel series of LXR agonists was identified utilizing the combination of two powerful technologies, virtual screening and high-throughput gene profiling. Systematic SAR studies were conducted and several potent and efficacious LXRβ agonists were identified. The docking study revealed that the indole moiety in these compounds may interact with conserved histidine 435 in helix 10/10 and tryptophan 437 in the helix 12 (AF-2) to lock

Table 6. In vitro and cell functional activities for selected LXR agonists

Compound	HTRF EC_{50}[a] LXRα	HTRF EC_{50}[a] LXRβ	Reporter EC_{50}[a] LXRβ	ABCA1 induction[b] (THP-1)	SREBP-1c induction[b] (HepG2)	Efflux EC_{50}[a] (THP-1)	Maximum efflux[c]	Lipogenesis Induction[c] (HepG2)
1	1.5	0.21	0.065	8.4	3.1	0.680	1.6	3.1
5b	4.3	0.464	0.12	11.4	2.0	0.570	1.7	2.0
5t	>30	0.666	0.336	7.5	2.1	0.590	1.7	1.2
5s	0.54	0.108	0.363	7.3	2.9	0.570	1.5	1.7
5q	0.57	0.093	0.052	7.5	3.0	0.21	1.7	3.2
GW3965	0.367	0.035	0.015	10.7	5.2	0.010	1.8	2.7
T0901317	0.04	0.015	0.011	8.4	6.7	0.033	1.6	3.6

[a] Values shown are in μM.
[b] Values shown are in ratio of compound (10 μM) versus control (vehicle only).
[c] Values shown are in ratio of compound (10 μM) versus control (vehicle only).

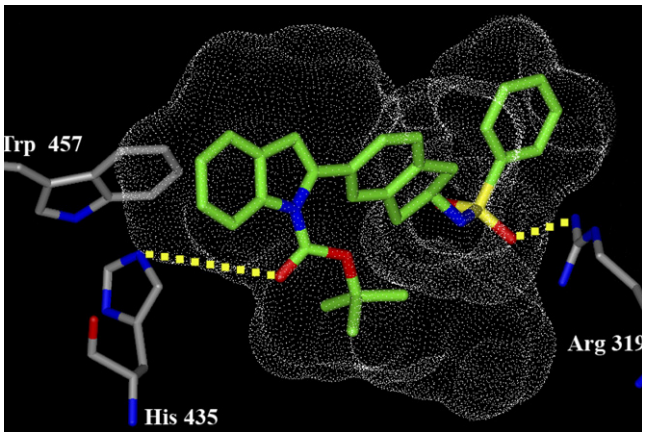


Figure 4. Plausible binding mode of compound **1** in LXRβ LBD.

LXR into the agonistic conformation. Selected indole compounds were shown to regulate LXR target genes and they tended to show slightly improved profiles in cell based functional assays as compared to GW3965 and T0901317.

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15. High-throughput genomics screening was performed using the ArrayPlate technology in a contract service provided by HTG, Inc. The ArrayPlate technology is a quantitative nuclease protection assay for multiplex gene profiling (http://www.htgenomics.com/).
16. The HTRF cofactor peptide recruitment assay was modified from a previous report.[24] Polyhistidine-tagged human LXRα (2 nM) or β (1 nM) ligand-binding domain (Roche Diagnostics, Indianapolis, IN) was mixed with the test compound, 20 nM biotin-SRC1 peptide (Synpep, Dublin, CA), 5 nM streptavidin–allophycocyanin, and europium-labeled anti-polyhistidine antibody (1 and 0.5 nM for α and β, respectively) in 50 mM Tris, pH 7.5, 50 mM KCl, 1 mM EDTA, 0.1% BSA, and 1 mM DTT. The final volume of the mixture was 40 μL in a 384-well assay plate. The mixture was incubated at room temperature for 1 h with shaking. Time-resolved fluorescence was measured at 615 and 665 nm on a LJL Analyst plate reader. The ratio of 665/615 was used to calculate EC_{50} values of test compounds.
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20. COS-7 cells were transfected for 24 h with plasmids of the human LXRβ receptor (OriGene, Rockville, MD), the LXR reporter +-GACCAGCAGTAACCTTGACCAG CAGTAACCTTGACCAGCAGTAACCT (prepared in house), and the RXRα receptor (OriGene, Rockville, MD). Subsequently, cells were treated with vehicle or compound for 16 h. LXR reporter activation was monitored by quantifying the luciferase activity in the cell lysate. EC_{50} values were calculated from mean values of quadruplicate samples in a single experiment.
21. Compound induction of cholesterol efflux was measured as described previously[25] with small modifications. THP-1 cells were differentiated into macrophages in a 48-well tissue culture plate using 30 h treatment with 200 nM PMA. The cells were then labeled with 0.6 μCi of 1,2-^{3}H (*N*)-cholesterol for 18 h in the presence of 16 μg/ml acLDL and 200 nM PMA. Cells were then incubated with vehicle or compound for 6 h in serum-free medium containing 2 mg/ml BSA. Subsequently, 5 μg/ml of APO-AI was added in fresh serum-free medium along with vehicle or compound for additional 18 h incubation. Cholesterol efflux was monitored by quantifying the radioactivity in the cell supernatant and presented as fold-induction versus control (vehicle only). Results shown are mean values of triplicate samples in a single experiment.

22. To measure compound induction of lipogenesis, HepG2 cells in 48-well tissue culture plates were pre-treated with vehicle or compound for 24 h. One microcurie of [^{14}C]glycerol was added and cells were cultured for another 48 h. Cellular triglycerides were extracted, separated by TLC, and quantified on a Storm 820 phosphorimager (GE Healthcare, Giles, UK). Lipogenesis was presented as fold-induction versus control (vehicle only). Results shown are mean values of triplicate samples in a single experiment.
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