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# Discovery and optimization of a series of liver X receptor antagonists

XianYun Jiao [a,*], David J. Kopecky [a], Ben Fisher [a], Derek E. Piper [b], Marc Labelle [a], Sharon McKendry [a], Martin Harrison [b], Stuart Jones [b], Juan Jaen [a], Andrew K. Shiau [c], Patrick Escaron [c], Jean Danao [c], Anne Chai [c], Peter Coward [c], Frank Kayser [a]

[a] Department of Medicinal Chemistry, Amgen Inc., 1120 Veterans Blvd., South San Francisco, CA 94080, USA
[b] Department of Molecular Structure & Characterization, Amgen Inc., 1120 Veterans Blvd., South San Francisco, CA 94080, USA
[c] Department of Metabolic Disorders, Amgen Inc., 1120 Veterans Blvd., South San Francisco, CA 94080, USA

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ABSTRACT

The present report describes our efforts to convert an existing LXR agonist into an LXR antagonist using a structure-based approach. A series of benzenesulfonamides was synthesized based on structural modification of a known LXR agonist and was determined to be potent dual liver X receptor (LXR α/β) ligands. Herein we report the identification of compound **54** as the first reported LXR antagonist that is suitable for pharmacological in vivo evaluation in rodents.



The liver X receptors (LXRs), LXRα (NR1H3) and LXRβ (NR1H2), are members of the nuclear receptor (NR) superfamily of ligand-regulated, DNA-binding transcription factors.[1] Both LXRs bind to their cognate response elements as heterodimers with the retinoid X receptors (RXRs, NR2B1-3) and play important roles in lipid biology.[2a] Mammalian endogenously occurring LXR ligands include the oxysterols 24(*S*),25-epoxycholesterol which is mainly found in the liver, 22(*R*)-hydroxycholesterol which is present in steroidogenic tissues, and 24(*S*)-hydroxycholesterol which is prevalent in brain tissue and plasma.[2] Several synthetic agonists (Fig. 1) have been reported and have served as valuable tools to elucidate the role of LXRs in mammalian biology.[3,4] LXR activation results in an increase in transcription of genes involved in the catabolism (Cyp7a)[5] and transport (ABCA1, ABCG1, ABCG5, ABCG8)[6] of cholesterol. In mouse models of atherosclerosis, LXR agonists increase plasma HDL- cholesterol and decrease atherosclerotic lesions,[7] suggesting a potential utility in treating cardiovascular disease.[8] Moreover, there is evidence that LXR agonists are effective in suppression of inflammation, play an important role in the regulation of glucose metabolism and might be useful for the treatment of Alzheimer's disease and other neurodegenerative diseases of the CNS.[4,9]

However, current LXR agonists also increase plasma and hepatic triglyceride levels in mice and hamsters, which results from LXR-regulated induction of transcription factors involved in lipogenesis, such as sterol regulatory element-binding protein 1c (SREBP-1c)[10] and the carbohydrate responsive binding protein (ChREBP).[11] Thus, limiting the potential utility of LXR agonists in a clinical setting. One strategy to overcome this limitation centers on the use of LXRβ-selective agonists. This is based on evidence that while activation of either LXRα or LXRβ provides relatively similar positive effects on atherosclerosis, activation of LXRβ is responsible for hypertriglyceridemia.[10b,12] However, the high level of similarity in the LXRα and LXRβ ligand binding pockets has limited the feasibility of this approach and prevented the development of LXRβ-selective ligands. Another approach relies on the observation that expression of certain LXR target genes is repressed in the basal state. For example, in LXRα/β double knockout mice, although hepatic expression of SREBP1c, FAS, SCD1, and ACC is decreased compared to wild-type mice, expression of hepatic and intestinal

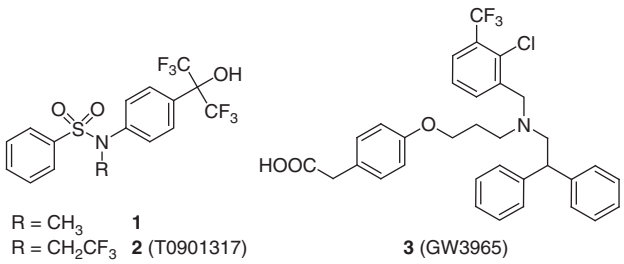


**Figure 1.** Examples of LXR agonists described in the literature.

* Corresponding author. Tel.: +1 650 244 2103; fax: +1 650 837 9369.
*E-mail address:* xjiao@amgen.com (XianYun Jiao).

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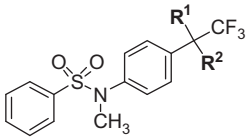
**Table 1**
Binding affinities of derivatives **1**, **4–14**



| Compd | $R^1$ | $R^2$ | LXRβ SPA binding,[19] $IC_{50}$ (μM) |
|---|---|---|---|
| **1** | OH | $CF_3$ | 0.02 |
| **4** | $OCH_3$ | $CF_3$ | 2.2 |
| **5** | OH | $CF_2CF_3$ | 0.16 |
| **6** | OH | H | >10 |
| **7** | OH | $CH_3$ | >10 |
| **8** | OH | Bn | >10 |
| **9** | OH | Thien-2-yl | 1.5 |
| **10** | OH | Phenyl | 3.6 |
| **11** | OH | Thiazol-2-yl | 7.5 |
| **12** | OH | 1*H*-Imidazol-2-yl | >10 |
| **13** | OH | 4*H*-1,2,4-Triazol-3-yl | >10 |
| **14** | OH | 1*H*-Tetrazol-5-yl | >10 |

ABCG5 and ABCG8 and macrophage ABCA1 and ABCG1 is either unchanged or elevated.[6a] In addition, LXRα/β null mice exhibited significantly reduced levels of VLDL plasma triglycerides relative to their wild type littermates.[10a]

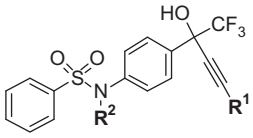
Taken together, these data suggest that an LXRα/β dual antagonist could downregulate the SREBP-1c pathway to reduce triglyceride levels in hypertriglyceridemic patients without affecting cholesterol homeostasis. Several synthetic LXR antagonists have been reported in the literature,[13] and only one report describes a compound which is potent in cellular assays.[13d] No LXR antagonist which is suitable for pharmacological in vivo evaluation in rodents has been reported.

*N*-Methylsulfonamide **1** and *N*-trifluoroethylsulfon-amide **2** (e.g., T0901317) are dual LXRα/β agonists that have been described previously.[3a] Both molecules activated LXRα in a luciferase reporter gene assay (GAL4) tested in HEK-293 cells.[14] Furthermore a scintillation proximity ligand binding assay (SPA) in which the triturated **1** was used as a competitive binder showed that these compounds displayed strong affinities for either LXR isoform[3a] A ligand-bound co-crystal structure of **2** with LXRα elucidated that helix 12 of ligand binding domain (LBD) of LXRα seals off the ligand binding pocket. A hydrogen bond between His421 and the acidic hydroxyl group of the 1,1,1,3,3,3-hexafluoro-isopropanol (HFIP) group is observed.[15] However, we reported recently that when one of the trifluoromethyl groups of **1** is replaced by a bulky heteroaromatic group, a new agonist binding mode characterized by the lack of a hydrogen bond is observed.[16] Thus, the acidity and spatial orientation of the hydroxyl group as well as the steric environment around the hydroxyl group influence which agonist binding mode is favored.

The approach we used for converting agonist **1** into an antagonist was to substitute one of the trifluoromethyl groups of **1** with a moiety that will push helix 12 away from the binding site, preventing the ligand-bound receptor from adopting a conformation which can undergo transcription. Similar strategies for the conversion of agonists to both partial agonists as well as antagonists have been reported previously (for e.g., the conversion of full agonist diethylstilbestrol to antagonist 4-hydroxytamoxifen by preventing helix 12 from adopting an agonist-bound conformation through steric interference).[17]

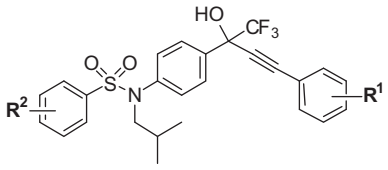
Our initial efforts focused on whether groups of different size and shape might be attached to either the alcohol moiety or one of the trifluoromethyl groups of **1**. Not surprisingly, replacing the acidic hydroxyl group of the HFIP moiety with a methyl ether (Table 1, compound 4) compromises binding affinity to LXRβ. Maintaining the capability of the hydroxyl group to form a hydrogen bond with His435 was crucial to binding of the compounds, thus we left the alcohol in place during further analoging efforts. The replacement of one or both of the trifluoromethyl groups of **1** with simple alkyl groups also resulted in loss of binding (Table 1).[18] Replacement of one of the trifluoromethyl groups with

**Table 2**
Binding affinities of derivatives **15–28**



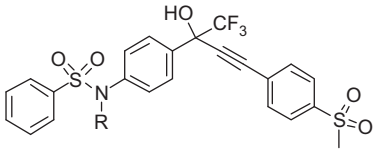
| Compound | $R^1$ | $R^2$ | LXRβ SPA binding, $IC_{50}$ (μM) | LXRβ GAL4, $IC_{50}$ μM (% of basal)[20] |
|---|---|---|---|---|
| **15** | $CF_3$ | Me | 4.1 | >10 |
| **16** | iBu | Me | >30 | - |
| **17** | Ph | Me | 1.4 | >10 |
| **18** | 4-F-Ph | $CF_3CH_2$ | 1.1 | >10 |
| **19** | Ph | $(CH_3)_2CHCH_2$ | 0.6 | 8 (28) |
| **20** | tBu | $(CH_3)_2CHCH_2$ | 1.1 | >10 |
| **21** | Bn | $(CH_3)_2CHCH_2$ | 0.6 | >10 |
| **22** | Cyclohexenyl | $(CH_3)_2CHCH_2$ | 1.1 | >10 |
| **23** | 2-Pyridyl | $(CH_3)_2CHCH_2$ | 3.8 | >10 |
| **24** | 3-Pyridyl | $(CH_3)_2CHCH_2$ | 0.4 | 10 |
| **25** | 3,5-Pyrimidinyl | $(CH_3)_2CHCH_2$ | 2.1 | 10 |
| **26** | 1-Methyl-1H-imidazol-5-yl | $(CH_3)_2CHCH_2$ | 5.1 | >10 |
| **27** | 3,5-Dimethyl-isoxazol-4-yl | $(CH_3)_2CHCH_2$ | 3.2 | >10 |
| **28** | 1-Ethyl-1H-pyrazol-4-yl | $(CH_3)_2CHCH_2$ | 1.7 | >10 |

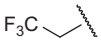
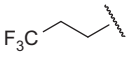
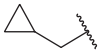
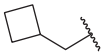
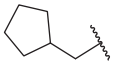
**Table 3**
Binding affinities of derivatives **19**, **29–50**



| Compound | $R^1$ | $R^2$ | LXRβ SPA binding, $IC_{50}$ (μM) | LXRβ GAL4, $IC_{50}$ μM (% of basal) |
|---|---|---|---|---|
| **19** | H | H | 0.6 | 8 (28) |
| **29** | H | 3-CN | 0.3 | 10 (34) |
| **30** | H | 2,5-$Cl_2$ | 1.4 | 10 (81) |
| **31** | 4-Cl | 3-CN | 0.6 | >10 |
| **32** | 3-$CF_3$ | H | 0.5 | >10 |
| **33** | 4-$CF_3$ | H | 2.5 | >10 |
| **34** | 3-MeO | H | 1.0 | >10 |
| **35** | 4-MeO | H | 0.7 | >10 |
| **36** | 4-EtO | H | 0.7 | >10 |
| **37** | 4-Me | H | 0.6 | >10 |
| **38** | 4-Bu | H | 3.5 | >10 |
| **39** | 2,4-$F_2$ | H | 0.8 | 8 (0) |
| **40** | 2-Me, 4-$NO_2$ | H | 2.8 | 10 (47) |
| **41** | 3-CN | H | 0.6 | >10 |
| **42** | 4-CN | 3-CN | 0.6 | >10 |
| **43** | 3-$CH_3SO_2$ | H | 0.6 | 5 (0) |
| **44** | 3-$CH_3SO_2$ | 3-CN | 0.4 | 7 (0) |
| **45** | 4-$CH_3SO_2$ | H | 0.6 | 2 (0) |
| **46** | 4-$CH_3SO_2$ | 3-CN | 0.6 | 2 (0) |
| **47** | 4-$CF_3SO_2$ | 3-CN | 4.3 | >10 |
| **48** | 4-$PhSO_2$ | 3-CN | >10 | >10 |
| **49** | 3-COOH | H | 1.8 | >10 |
| **50** | 4-COOH | 3-CN | 0.5 | 10 (0) |

**Table 4**
*N*-Alkyl modification of compound **45**




| Compound | R | RLM% rem[a] | LXRβ SPA binding, $IC_{50}$ (μM) | LXRβ GAL4, $IC_{50}$ (μM) |
|---|---|---|---|---|
| **45** |  | <5 | 0.6 | 2 |
| **51** |  | 85 | 1.0 | 9 |
| **52** |  | 42 | 0.5 | 4 |
| **53** |  | 36 | 1.2 | 6 |
| **54** |  | >95 | 0.5 | 2 |
| **55** |  | <5 | 0.3 | 7 |
| **56** |  | <5 | 0.15 | 1.5 |

[a] Compound percentage remaining after incubation in rat liver microsomes at 1.0 μM for 30 min.

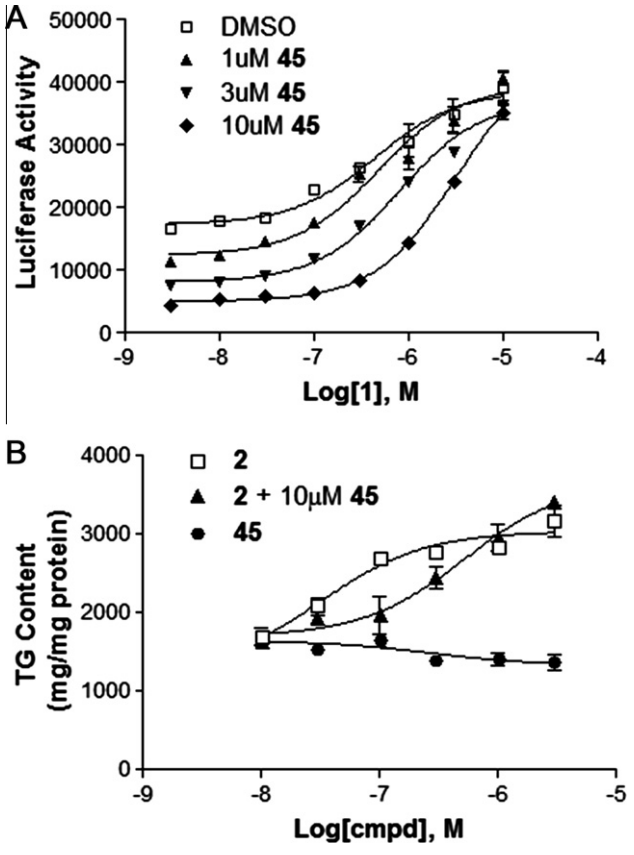



**Figure 2.** (A) Compound **45** reduces basal activity and antagonizes the dose response of compound **1** in a transient transfection assay in HEK-293 cells using the mSREBP-1c promoter. (B) Compound **45** antagonizes compound **2** in a triglyceride accumulation assay in HepG2 cells.

a variety of aryl and heterocyclic moieties generated compounds with generally diminished binding, consistent with our previous observations.[16]

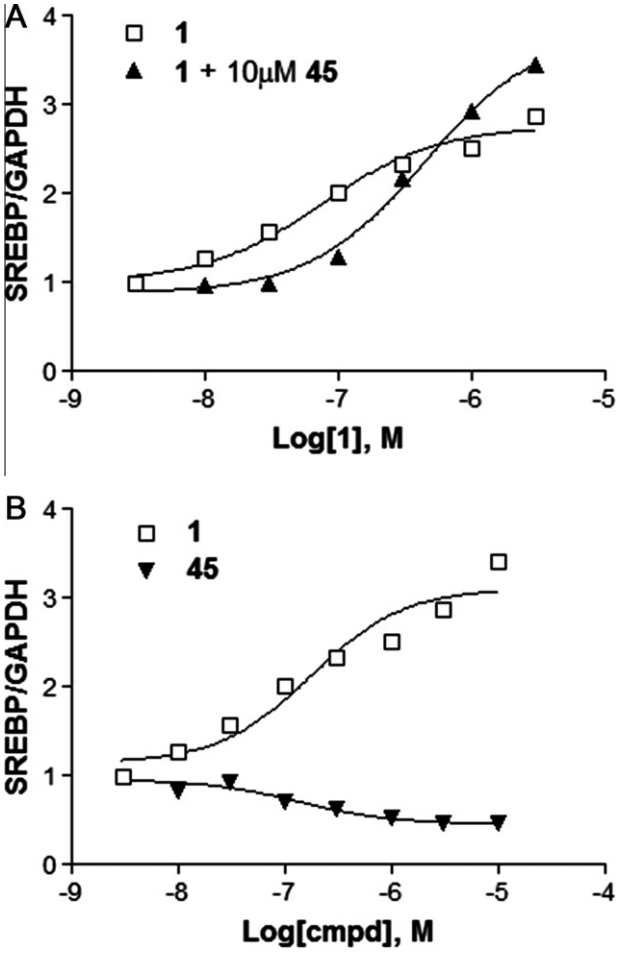



**Figure 3.** (A) Compound **45** antagonizes compound **1** in a QuantiGene Assay measuring endogenous SREBP-1 expression in Caco2 cells. Expression level is normalized by expression of the housekeeping gene GAPDH. (B) Compound **45** reduces the basal expression level of SREBP-1 by approximately 50%.

However, replacement of one of the trifluoromethyl groups with alkyne substituents (Table 2) resulted in compounds with good binding properties. In addition, changing the *N*-methyl group of the sulfonamide to a larger trifluoroethyl or isobutyl group was mostly beneficial (Table 2). These compounds were evaluated for antagonist activity in a GAL4 reporter gene assay using transiently transfected HEK293 cells.[20] **19** showed the most robust activity, decreasing the activation by the agonist **1** by 72%, with an $IC_{50}$ of 8 μM.

Table 3 summarizes the results from a broad survey of substituents around the benzenesulfonamide and phenylacetylene moiety. Consistent with previous results obtained in the agonist series, small substituents in the *meta* position of the benzenesulfonamide, such as a 3-CN group, conferred equal or better binding properties over the unsubstituted counterparts (see e.g., **19** vs **29**, **43** vs **44**, **45** vs **46**).[3a] In the phenylacetylene region, a broad range of small substituents, such as methoxy-, cyano-, methylsulfonyl or carboxylic acid were tolerated without significantly affecting binding, though larger, lipophilic groups were less preferred (**33**, **38**, **47**, and **48**). A 3- or 4-methylsulfonyl substituent gave compounds with good affinity to the receptor while also showing very robust antagonist activity in the GAL4 reporter gene assay, decreasing the activation by the agonist **1** completely with an $IC_{50}$ of 2–5 μM (**43**–**46**). When directly comparing **45** with **46**, we saw no additional benefit from the modification of the benzenesulfonyl moiety with a 3-cyano substituent. Both *p*-methyl sulfonylphenyl-

**Table 5**
Pharmacokinetic parameters following iv dosing in male Sprague–Dawley rats. [a,b]

| Compound | CL (L/h/kg) | $V_{ss}$ (L/kg) | MRT (h) | AUC (μgh/L) |
|---|---|---|---|---|
| **45** | 4.8 | 4.4 | 1.3 | 102 |
| **54** | 1.1 | 2.3 | 2.2 | 885 |

[a] $n = 3$ animals per study.
[b] Dosed at 0.5 mg/kg iv.

**Table 6**
Pharmacokinetic parameters following po dosing in male Sprague–Dawley rats[a,b]

| Compound | F (%) | AUC (μgh/L) |
|---|---|---|
| **45** | 9 | 86 |
| **54** | 31 | 1380 |

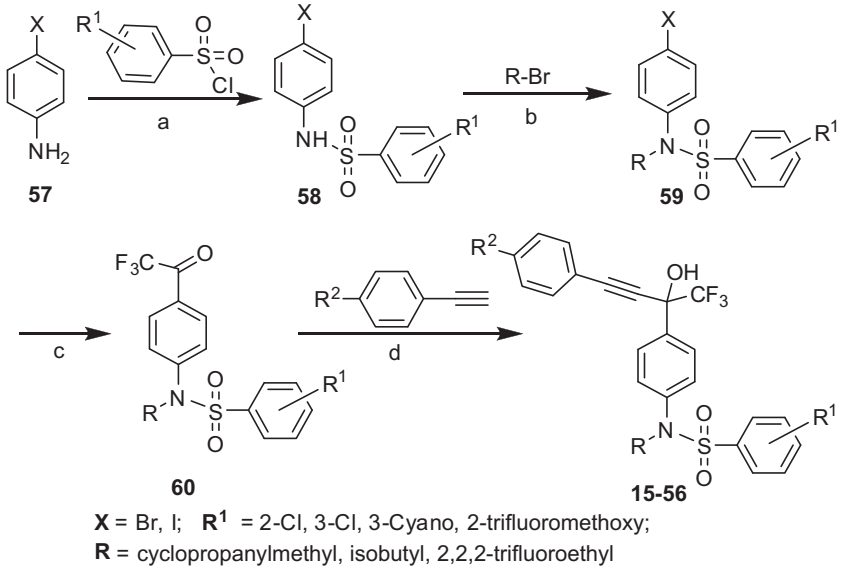
[a] $n = 3$ animals per study.
[b] Dosed at 5 mg/kg po.

acetylene derivatives **45** and **46** demonstrated potent antagonism (GAL4 $IC_{50} = 2$ μM) with no evidence of cell toxicity.

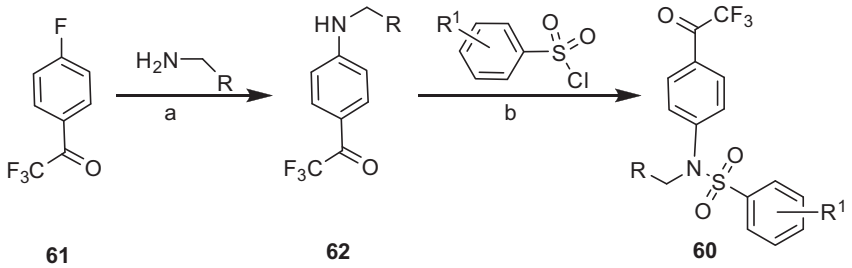
The functional activity of **45** was further characterized in an mSREBP reporter assay in HEK-293 cells and in a triglyceride accumulation assay in HepG2 cells (Fig. 2). **45** shows antagonism on an mSREBP-1c reporter, lowering the basal activity of the reporter and right-shifting the agonist dose response. **45** also shows antagonism in a triglyceride accumulation assay and at 10 μM causes a 15 fold right shift in the agonist dose response. **45** was also tested for its ability to block induction of endogenous SREBP-1c by the agonist **1**. Consistent with data in Figure 2A, **45** lowers the basal level of SREBP-1 transcript by 50%, and right-shifts the agonist dose response (Fig. 3).

Unfortunately, **45** displayed a poor pharmacokinetic profile in male Sprague–Dawley rats making it unsuitable as a tool compound for in vivo proof-of-concept studies (Table 5). Metabolite ID studies with rat liver microsomes revealed hydroxylation and oxidative cleavage of the isobutyl group to be the major clearance pathway. Hence we turned our attention towards the structure-metabolism relationship of a number of *N*-alkyl derivatives, as shown in Table 4. While the cyclobutylmethyl- and cyclopentylmethyl groups (**55** and **56**) were still metabolically labile, consistent with their possibility to undergo cytochrome p450 mediated oxidative cleavage, **51** and **52** had dramatically improved microsomal stability. This is most likely due to the reduced acidity of the hydrogen atoms on the carbon next to the nitrogen. The cyclopropylmethyl derivative **54** displayed the best balance of potency and microsomal stability. We were pleased to see that this translated into an improved in vivo pharmacokinetic profile with significantly lower rat clearance of **54** (1.1 L/h/kg) compared to **45** (4.8 L/h/kg), and about eight-fold higher AUC following *i.v.* dosing. (Table 5).

The oral PK profile of **54** was also significantly improved (Table 6) displaying good oral availability and good exposure following oral dosing at 5 mg/kg in rats (Table 6) and was suitable for in vivo pharmacological investigations in rodents (data not shown).




**Scheme 1.** Reagents and conditions: (a) pyridine, rt; (b) NaH, DMF, rt; (c) *n*-BuLi / TBME, −78 °C, then ethyl trifluoroacetate; (d) *n*-BuLi / THF, −78 °C.




**Scheme 2.** Reagents and conditions: (a) $Et_3N$, acetonitrile, reflux; (b) pyridine, rt.

The general synthetic route to compounds with LXR antagonistic properties is shown in Scheme 1. Sulfonylation of **57** with the corresponding sulfonyl chloride in pyridine afforded **58** in excellent yield. Aklylation of sulfonamide **58** with an appropriate alkyl bromide or iodide in the presence of 60% sodium hydride in mineral oil yielded **59** which was further transformed into **60** by generating the lithium salt of **59** and quenching with ethyl trifluoroacetate. Finally, the anion of the substituted acetylene was generated by *n*-butyllithium in THF at −78 °C which was then added to **60** to form **15–56** in good to excellent yields. The synthesis of **1**–**14** has been described previously.[18]

An alternative route to **60** (**Scheme 2**) started with the reaction of **61** with a corresponding alkylamine to provide the *N*-alkylaniline derivative **62**. Sulfonylation of **62** with the appropriate sulfonyl chloride in pyridine furnished **60**.

In conclusion, we were able to design a series of LXR antagonists starting from the LXR agonist **1** via structural modification of one of the trifluoromethyl groups. **54** is the first potent cell-active LXR antagonist reported to date and is suitable for pharmacological in vivo evaluation in rodents.[21]

## Acknowledgements

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## References and notes

1. Willy, P. J.; Umesono, K.; Ong, E. S.; Evans, R. M.; Heyman, R. A.; Mangelsdorf, D. J. *Genes Dev.* **1995**, ***1033***, 9.
2. (a) Bjorkhem, I. *J. Lipid Res.* **2009**, *50*(Suppl), S213; (b) Janowski, B. A.; Grogan, M. J.; Jones, S. A.; Wisely, G. B.; Kliewer, S. A.; Corey, E. J.; Mangelsdorf, D. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 266; (c) Lehmann, J. M.; Kliewer, S. A.; Moore, L. B.; Smith-Oliver, T. A.; Oliver, B. B.; Su, J. L.; Sundseth, S. S.; Winegar, D. A.; Blanchard, D. E.; Spencer, T. A.; Wilson, T. M. *J. Biol. Chem.* **1997**, *272*, 3137; (d) Fu, X.; Menke, J. G.; Chen, Y.; Zhou, G.; MacNaul, K. L.; Wright, S. D.; Sparrow, C. P.; Lund, E. G. *J. Biol. Chem.* **2001**, *276*, 38378.
3. (a) Li, L.; Liu, J.; Zhu, L.; Cutler, S.; Hasegawa, H.; Shan, B.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1638; (b) Collins, J. L.; Fivush, A. M.; Watson, M. A.; Galardi, C. M.; Lewis, M. C.; Moore, L. B.; Parks, D. J.; Wilson, J. G.; Tippin, T. K.; Binz, J. G.; Plunket, K. D.; Morgan, D. G.; Beaudet, E. J.; Whitney, K. D.; Kliewer, S. A.; Willson, T. M. *J. Med. Chem.* **1963**, *2002*, 45.
4. For recent reviews, see (a) Collins, J. L. *Curr. Opin. Drug Discov. Dev.* **2004**, *7*, 692; (b) Li, X.; Yeh, V.; Molteni, V. *Expert Opin. Ther. Pat.* **2010**, *20*, 535.
5. Chiang, J. Y.; Kimmel, R.; Stroup, D. *Gene* **2001**, *262*, 257.
6. (a) Repa, J. J.; Turley, S. D.; Lobaccaro, J.-M. A.; Medina, J.; Li, L.; Lustig, K.; Shan, B.; Heyman, R. A.; Dietschy, J. M.; Mangelsdorf, D. J. *Science* **2000**, *289*, 1524; (b) Costet, P.; Luo, Y.; Wang, N.; Tall, A. R. *J. Biol. Chem.* **2000**, *275*, 28240; (c) Schwartz, K.; Lawn, R. M.; Wade, D. P. *Biochem. Biophys. Res. Commun.* **2000**, *274*, 794; (d) Kennedy, M. A.; Venkateswaran, A.; Tarr, P. T. *J. Biol. Chem.* **2001**, *276*, 39438; (e) Repa, J. J.; Berge, K. E.; Pomajzl, C.; Richardson, J. A.; Hobbs, H.; Mangelsdorf, D. J. *J. Biol. Chem.* **2002**, *277*, 18793; (f) Yu, L.; York, J.; von Bergmann, K.; Lutjohann, D.; Cohen, J. C.; Hobbs, H. H. *J. Biol. Chem.* **2003**, *278*, 15565.
7. (a) Joseph, S. B.; McKilligin, E.; Pei, L.; Watson, M. A.; Collins, A. R.; Laffitte, B. A.; Chen, M.; Noh, G.; Goodman, J.; Hagger, G. N.; Tran, J.; Tippin, T. K.; Wang, X.; Lusis, A. J.; Hsueh, W. A.; Law, R. E.; Collins, J. L.; Willson, T. M.; Tontonoz, P. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 7604; (b) Terasaka, N.; Hiroshima, A.; Koieyama, T.; Ubukata, N.; Morikawa, Y.; Nakai, D.; Inaba, T. *FEBS Lett.* **2003**, *536*, 6; (c) Levin, N.; Bischoff, E. D.; Daige, C. L.; Thomas, D.; Vu, C. T.; Heyman, R. A.; Tangirala, R. K.; Schulman, I. G. *Arterioscl. Throm. Vas.* **2005**, *25*, 135; (d) Zhao, C.; Karin, D.-W. *J. Endocrinol.* **2010**, *204*, 233.
8. (a) Tontonoz, P.; Mangelsdorf, D. J. *Mol. Endocrinol.* **2003**, *17*, 985; (b) Bennet, J.; Cooke, A.; McKinnon, H. J.; Nimz, O. *Ann. Reports Med. Chem.* **2008**, *43*, 103.
9. For recent reviews, see (a) Michael, L. F.; Schkeryantz, J. M.; Burris, T. P. *Mini-Rev. Med. Chem.* **2005**, *5*, 729; (b) Viennois, E.; Pommier, A. J. C.; Mouzat, K.; Oumeddour, A.; El Hajjaii, F. Z.; Dufour, J.; Caira, F.; Volle, D. H.; Baron, S.; Lobaccaro, J. M. A. *Expert Opin. Ther. Targets* **2011**, *15*, 219.
10. (a) Schultz, J. R.; Tu, H.; Luk, A.; Repa, J. J.; Medina, J. C.; Li, L.; Schwendner, S.; Wang, S.; Thoolen, M.; Mangelsdorf, D. J.; Lustig, K. D.; Shan, B. *Genes Dev.* **2000**, *14*, 2831; (b) Repa, J. J.; Liang, G.; Ou, J.; Bashmakov, Y.; Lobaccaro, J.-M. A.; Shimomura, I.; Shan, B.; Brown, M. S.; Goldstein, J. L.; Mangelsdorf, D. J. *Genes Dev.* **2000**, *14*, 2819; (c) Yoshikawa, T.; Shimno, H.; Amemiya-Kudo, M.; Yahagi, N.; Hasty, A. H.; Matsuzaka, T.; Okazaki, H.; Tamura, Y.; Iizuka, Y.; Ohashi, K.; Osuga, J.-I.; Harada, K.; Gotoda, T.; Kimura, S.; Ishibashi, S.; Yamada, N. *Mol. Cell Biol.* **2001**, *21*, 2991.
11. Cha, J. Y.; Repa, J. J. *J. Biol. Chem.* **2007**, *282*, 743.
12. (a) Quinet, E. M.; Savio, D. A.; Halpern, A. R.; Chen, L.; Schuster, G. U.; Gustafsson, J. A.; Basso, M. D.; Nambi, P. *Mol. Pharmacol.* **2006**, *70*, 1340; (b) Lund, E. G.; Peterson, L. B.; Adams, A. D.; Lam, M. H.; Burton, C. A.; Chin, J.; Guo, Q.; Huang, S.; Latham, M.; Lopez, J. C.; Menke, J. G.; Milot, D. P.; Mitnaul, L. J.; Rex-Rabe, S. E.; Rosa, R. L.; Tian, J. Y.; Wright, S. D.; Sparrow, C. P. *Biochem. Pharmacol.* **2006**, *71*, 453.
13. See e.g.: (a) Noguchi-Yachide, T.; Aoyama, A.; Makishima, M.; Miyachi, H.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3957; (b) Motoshima, K.; Noguchi-Yachide, T.; Sugita, K.; Hashimoto, Y.; Ishikawa, M. *Bioorg. Med. Chem.* **2009**, *17*, 5001; (c) Aoyama, A.; Aoyama, H.; Dodo, K.; Makishima, M.; Hashimoto, Y.; Miyachi, H. *Heterocycles* **2008**, *76*, 137; (d) Zuercher, W. J.; Buckholz, R. G.; Campobasso, N.; Collins, J. L.; Galardi, C. M.; Gampe, R. T.; Hyatt, S. M.; Merrihew, S. L.; Moore, J. T.; Oplinger, J. A.; Reid, P. R.; Spearing, P. K.; Stanley, T. B.; Stewart, E. L.; Willson, T. M. *J. Med. Chem.* **2010**, *53*, 3412.
14. Menke, J. G.; Macnaul, N. S.; Hayes, N. S.; Baffic, J.; Chao, Y.-S.; Elbrecht, A.; Kelly, L. J.; Lam, M.-H.; Schmidt, A.; Sahoo, S.; Wang, J.; Wright, S. D.; Xin, P.; Zhou, G.; Moller, D. E.; Sparrow, C. P. *Endrocrinology* **2002**, *143*, 2548.
15. Svensson, S.; Ostberg, T.; Jacobsson, M.; Norstrom, C.; Stefansson, K.; Hallen, D.; Johansson, I. C.; Zachrisson, K.; Ogg, D.; Jendeberg, L. *EMBO* **2003**, *22*, 4625.
16. Kopecky, D. J.; Jiao, X.; Fisher, B.; McKendry, S.; Labelle, M.; Piper, D. E.; Coward, P.; Shiau, A. K.; Escaron, P.; Danao, J.; Chai, A.; Jaen, J.; Kayser, F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2407.
17. (a) De Lera, A. R.; Bourguet, W.; Altucci, L.; Gronemeyer, H. *Nat. Rev. Drug Discov.* **2007**, *6*, 811; (b) Shiau, A. K.; Barstad, D.; Radek, J. T.; Meyers, M. J.; Nettles, K. W.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A.; Agard, D. A.; Greene, G. L. *Nat. Struct. Biol.* **2002**, *9*, 359.
18. All data presented are for LXRβ unless otherwise noted. Results for LXRα were similar for this series.
19. SPA Assay: (scintillation proximity ligand binding assay): Binding assays were performed with glutathione S-transferase-LXR fusion proteins and glutathione-coated scintillation proximity assay beads. triturated compound **1** was used as the radioligand. Protein and beads were incubated for 2 h prior to addition of test compound at concentrations ranging from 30 μM to 1 nM for 1 h. Radioligand (50 nM) was then added for an additional hour. Data are expressed as $IC_{50}$ values in μM.
20. GAL4 assay: CBTT (Reporter gene assay) HEK-293 cells were co-transfected with a luciferase reporter construct and DNA encoding a fusion of the DNA-binding domain of the yeast transcription factor GAL4 and the LXR ligand-binding domain. A CMV-β-galactosidase reporter construct was included as a control for transfection efficiency. Compounds were dosed in the presence of 500 nM of compound **1**, and treatment lasted for 20 h. Data are expressed as $IC_{50}$ values in μM, which is the molar concentration of the test compound that affords a 50% decrease in the maximum reporter activity of compound **1**.
21. Previously disclosed: Abstracts of papers, 235th ACS National Meeting, New Orleans, LA, United States, April 6–10, 2008 (2008), MEDI-2.