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Synthesis and evaluation of anilinohexafluoroisopropanols as activators/modulators of LXRα and β

Narendra Panday,* Jörg Benz, Denise Blum-Kaelin, Vanessa Bourgeaux, Henrietta Dehmlow, Peter Hartman, Bernd Kuhn, Hassen Ratni, Xavier Warot and Matthew B. Wright

F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Preclinical Research, CH-4070 Basel, Switzerland

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Abstract—A series of branched and unbranched anilinohexafluoroisopropanols related to the known sulfonamide T0901317 were prepared and evaluated as activators/modulators of both LXRα and LXRβ. A structure–activity relationship was established and compounds with high potency on both the receptors were identified. Many compounds showed a tendency toward selectivity for LXRβ versus LXRα. Several analogues were evaluated for effects on plasma lipoprotein levels in mice. A few of these significantly raised HDL-cholesterol levels in plasma but showed markedly different effects on liver triglyceride content, suggesting that this series may yield candidates with improved efficacy/safety profiles compared to existing molecules.

The Liver-X-receptors, LXRα and LXRβ, are nuclear hormone receptors that function as oxysterol regulated transcription factors and activate the expression of genes regulating cholesterol and lipid metabolism.[1] The LXRs directly induce the expression of the transmembrane lipid/cholesterol transporters ABCA1 and ABCG1 in cholesterol-loaded macrophages, liver, and intestinal cells, promoting cholesterol efflux and formation of high density lipoprotein particles (HDL).[2] Numerous clinical and epidemiological studies have shown that HDL-cholesterol levels are inversely related to the risk for coronary artery disease (CAD).[3] Drugs that activate LXR have the potential to increase HDL-C and cellular cholesterol efflux and are thus expected to be atheroprotective.[4] Full LXR agonism however leads to the undesired activation of triglyceride synthesis in the liver by upregulation of Srebp-1c.[5] The identification of LXR modulators, devoid of this undesired side effect remains a major challenge for drug development. Current efforts focus on the identification of LXRβ-selective agonists, partial or gene-specific LXR activators, or compounds with more favorable PK/PD properties.[5c,6]

One of the most extensively studied LXR activators is T0901317 (Fig. 1), a potent but pathway unselective LXRα/β coagonist developed by Tularik.[7] T0901317 has been shown to increase HDL-C and to reduce atherosclerotic plaques in mouse models[4,8] and thus was considered a starting point for the design of new analogues with potentially improved properties. The X-ray structure of T0901317 complexed with the LXRβ-ligand binding domain revealed the key contacts of the ligand required to stabilize the active conformation of the receptor.[9] Apart from a strong hydrogen bond between the hydroxyl group of the ligand and His435 ($d = 2.6$ Å), numerous lipophilic receptor–ligand contacts exist that lead to strong binding. The structure revealed that the trifluoroethyl and the phenylsulfonyl groups reach into two pockets marked as P1 and P2 in Figure 1. A third pocket P3 could be discerned at the opposite end of the ligand which was unoccupied and could offer opportunities for the introduction of additional functionalities. As illustrated in Figure 1, we reasoned that replacing the –SO_2– moiety of T0901317 by a methine group –CHR^a– would allow the positioning of a new functional group R^a into P3 and possibly improved affinity and activity. However, according to molecular modeling[10] the aniline resulting from a replacement of –SO_2– by a –CHR^a– (R^a = H or functional group) has a significantly smaller dihedral angle τ of approximately 27° compared to the experimentally observed $\tau = 62°$ for T0901317, which

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* Corresponding author. Tel.: +41 0 61 688 26 72; fax: +41 0 61 688 64 59; e-mail: npanday@epo.org

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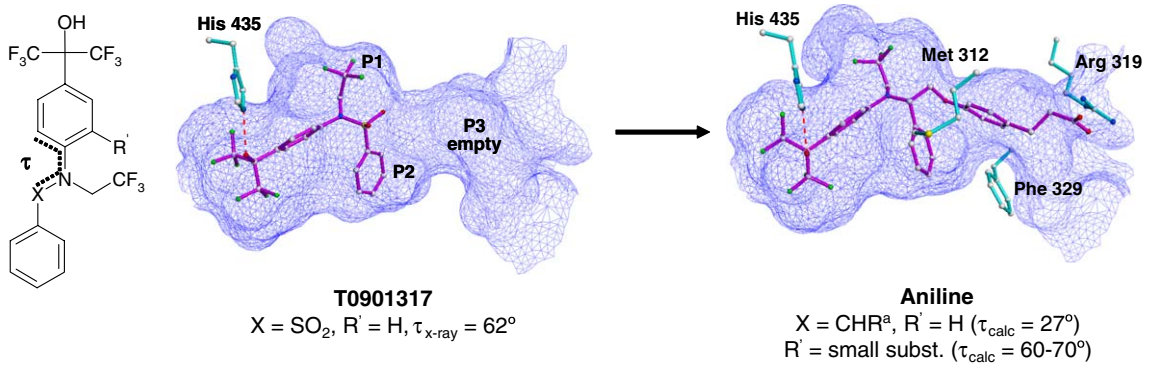
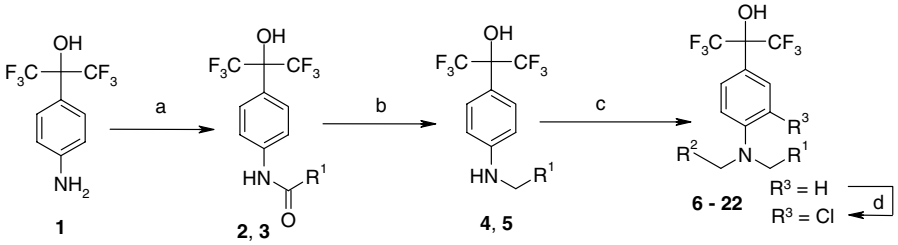


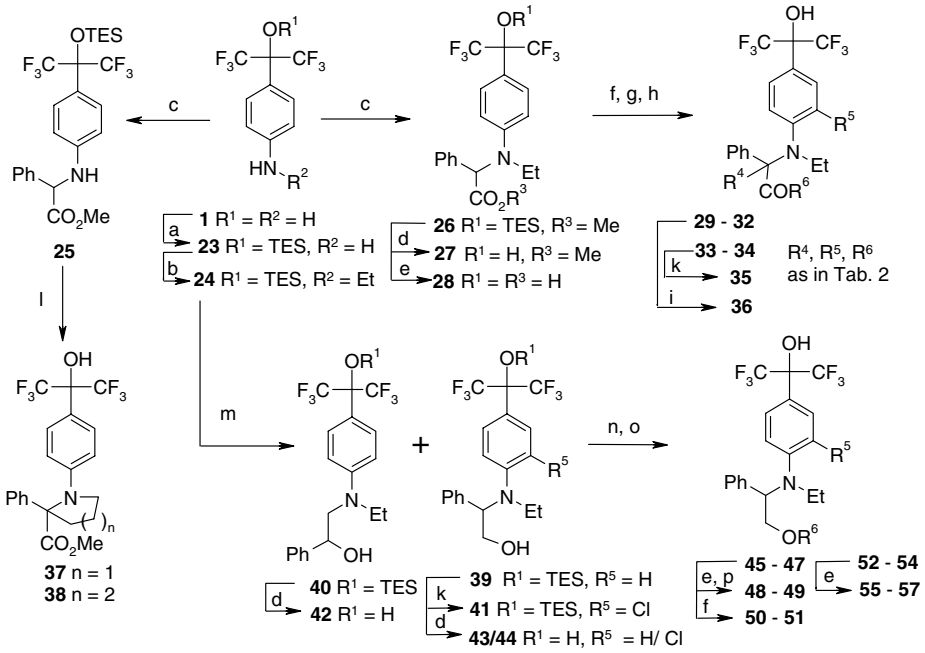
Figure 1. Left: definition of the dihedral angle τ discussed in the text. Middle: binding mode of T0901317 complexed to LXRβ. The hydrogen bond between the OH group of the ligand and His 435 is shown as a red, dashed line. Right: model of anilines illustrating the possibility to reach the P3 pocket and interact with different hydrophobic and polar side chains. R^a is a suitably chosen substituent reaching into the P3 pocket.

could result in a potentially detrimental reorientation of the N-substituents. To compensate for this, introduction of a substituent R′ in the *ortho* position to the aniline-nitrogen or the quaternization of the –CHR^a– to a –CR^aR^b– may be necessary to increase the τ angle and prevent loss of affinity/activity. We report here the synthesis and SAR of (i) 'unbranched' anilines for which X is –CH_2– and (ii) 'branched' anilines for which X is –CR^aR^b– with at least one of R^a or R^b not being H.[11] In both series, analogues with a chloro substituent *ortho* to the aniline-nitrogen were prepared.

The syntheses started from the commercially available 2-(4-amino-phenyl)-1,1,1,3,3,3-hexafluoro-propan-2-ol **1**.[12] The unbranched analogues (Scheme 1) were obtained by acetylation or trifluoroacetylation (**2** and **3**) followed by BH_3–THF-complex promoted reduction (**4** and **5**). Heating in the presence of an arylalkylhalogenide[13] optionally followed by *o*-chlorination of the aniline with NCS led to the final compounds (**6**–**22**). For the synthesis of the branched analogues (Scheme 2), we used the *O*-silyl protected derivative **23** of **1** which was converted to the *N*-ethyl derivative **24** using the same method as for the conversion of unprotected **2**–**4**. Treatment of either **23** or **24** with α-phenylbromoacetic acid methyl ester led to phenylmethylesters **25** and **26**, respectively, of which the latter was deprotected with TBAF to give **27**. Lithium hydroxide mediated hydrolysis of **26** was accompanied by desilylation and gave the deprotected acid **28**, which was converted to amides **29**–**32** by EDCI/HOBT-promoted coupling.[14] LiHMDA-promoted deprotonation in α position to the ester functionality of **26** followed by quenching with iodomethane or -ethane, led, after TBAF-mediated deprotection, to the quaternary derivatives **33** and **34**. Using the same method, the re-O-silylated derivative of dimethylamide **30** was converted to the α-methyl analogue **36**. Treatment of ester **34** with *N*-chloro succinimide gave the *o*-chloroaniline **35**. The bridged derivatives **37** and **38** were obtained by a double deprotonation of **25** with LiHMDA, treatment with either 1,3-diiodopropane or 1,4-diiodobutane, followed by TBAF-mediated deprotection. In the presence of lithiumperchlorate,[15] the O-protected *N*-ethyl aniline **24** reacted with styrene epoxide mainly to give the racemic hydroxymethyl derivative **39**, though small amounts of the alcohol **40** resulting from nucleophilic attack of the aniline on the β-carbon of the epoxide were also isolated. The enantiomerically pure *S*- or *R*-derivatives of **39** were obtained by using the corresponding optically pure styrene epoxides. The *o*-chloroaniline **41** was prepared from **39** by treatment with *N*-chlorosuccinimide. TBAF-mediated deprotection of **39**–**41** yielded the corresponding diols **42**–**44**. Both **39** and its o-chlorinated analogue **41** were further converted to a series of O-functionalized derivatives (**45**–**54**) by either O-alkylation or Mitsunobu-type substitution reactions and optional subsequent transformations (e.g., $LiAlH_4$-mediated reduction of **47** to **48**, LiOH-promoted hydrolysis of **47** to **49** and **52**–**54** to **55**–**57**, and amide couplings of **49** to **50** and **51**).



Scheme 1. Reagents and conditions: (a) for $R^1 = CH_3$/Ac_2O, Py, followed by treatment with aq NaOH, >90% of **2**. For $R^1 = CF_3$, TFAA, CH_2Cl_2, DIPEA, >90% of **3**; (b) BH_3·THF, 96% of **4** ($R^1 = CH_3$), 73% of **5** ($R^1 = CF_3$); (c) R^2-Cl or R^2-Br, DMF or ^{t}BuOH, heating, 11–90%; (d) NCS, *n*-propanol, >64%.



Scheme 2. Reagents and conditions: (a) TESCl, DBU, DMF, >90%; (b) (1) Ac_2O, Py, 2—BH_3·THF, 96%; (c) α-phenylbromoaceticacidmethylester, NaOAc, ^{t}BuOH, >90%; (d) TBAF, >90%; (e) LiOH in THF/H_2O 1:1, >90% of **28** from **26**, of **49** from **47**, of **55**–**57** from **52**–**54**; (f) amine or amine hydrogen chloride salt, EDCI, HOBt, NMO, from **28**: 73 % of **29**, 70% of **30**, 27% of **31**, 44% of **32**, from **49**: >90% of **50**, 76% of **51**; (g) (1) LiHMDA, (2) MeI, (3) TBAF, 67% of **33** from **26**; (h) (1) LiHMDA, (2) EtI, (3) TBAF, 30% of **34** from **26**; (i) (1) TESCl, DBU, DMF, >90% of o-silylated **30**, (2) LiHMDA, (3) MeI, (4) TBAF, 30% of **36** from **30**; (k) NCS, propanol, 50% of **35** from **34**, 69% of **41** from **39**; (l) (1) 2 equiv LiHMDA, (2) 1,3-diiodopropane or 1,4-diiodobutane, (3) TBAF, ca. 90% of **37**, 3% of **38**; (m) Li_2ClO_4, *rac*-, *R*-, or *S*-styreneoxide, 50–63% of *rac*-, *R*- or *S*-**39**, 5% of *rac*-**40**; (n) (1) BuLi, (2) MeI, BnBr or $BrCH_2CO_2Me$, (3) TBAF, 56–95% of **45**, **46** or **47** from **39**; (o) (1) methyl-4-hydroxybenzoate, methyl-4-hydroxyphenylacetate or methyl-3-(4-hydroxyphenyl)-propionate, DIAD, Ph_3P, (2) TBAF, 7–13% of **52**–**54**; (p) $LiAlH_4$, >90% of **48** from **47**.

The compounds were evaluated for binding affinity and the ability to transcriptionally activate LXRα and LXRβ in in vitro radioligand displacement and cellular transcriptional transactivation assays.[16]

Comparison of potency in binding and transactivation of the sulfonamide T0901317 and the benzyl analogue **6** showed that a slight decrease in affinity and activity toward LXRα (but not β) resulted from the replacement of the SO_2-moiety by a $–CH_2–$. It is likely that the unfavorable reorientation of the phenyl group due to the smaller τ-angle in **6** is compensated by improved interactions with the more lipophilic methylene group as compared to those with the rather polar SO_2-moiety of T0901317. Quite remarkably, there was no marked difference in potency between the trifluoroethyl and the ethyl anilines **6** and **8**. Introduction of an ethylene spacer (**15**) instead of the methylene (**8**) did not significantly affect the affinity and activity. Replacement of the phenyl ring of **7** by a less lipophilic heterocycle (**10**–**14**) resulted in loss of affinity and activity, with the 3-pyridyl proving particularly unfavorable. On the other hand, introduction of a thiazolyl group (**10** and **11**) led to two compounds with modest selectivity for LXRβ versus LXRα. The importance of the τ-angle and, hence, of the proper orientation of the aniline substituents toward the P1 and P2 pockets is evidenced by the marked increase in affinity and activity of the *o*-chloro anilines **7**, **9**, **11**, and **16**, as compared to the corresponding unchlorinated counterparts **6**, **8**, **10**, and **15**. Very significantly, however, the *o*-chloro substituent did not further improve the potency of the already highly potent phenyloxadiazolyl derivatives (**17/20** vs **18/21**). The phenyloxadiazolyl substituent is predicted to be too large to fit into the P2 pocket and presumably reaches instead into the P3 pocket both in the non-chlorinated and the o-chlorinated analogues. Favorable interactions between the phenyloxadiazole moiety and hydrophobic/aromatic amino acid side chain surrounding the P3 pocket probably account for the very high affinity and activity observed for **17**–**22**. Moreover, the values for **17/20** and **18/21** also suggest that interactions of the receptor with the chlorine contribute little if anything to the binding affinity. Thus, the improvement in affinity observed for the *o*-chloro derivatives **7**, **9**, **11**, and **16** indeed results primarily from the reorientation of the N-substituents. Quite interestingly, the trifluoroethyl group led to a significant loss in affinity and activity of the phenyloxazolyl series (**17/20** vs **19/22**). Perhaps the reorientation of the N-substituents to properly accommodate the large phenyloxazolyl group forces the trifluoroethyl group into repulsive interactions with the receptor, while the slightly smaller ethyl group is tolerated (Table 1).

The receptor binding and transactivation data for the branched anilines are presented in Tables 2 and 3. As compared to the parent aniline **8** the derivative with a methoxycarbonyl substituent on the methylene moiety (**27**) showed reduced affinity and activity. The loss in affinity/activity was even more pronounced for **28**–**32**

Table 1. Binding affinity (IC_{50}) and transactivation potency (EC_{50}) of unbranched anilines

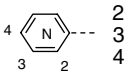
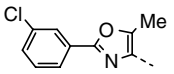
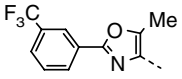
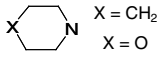
Compound	R^1	R^2	R^3	LXRα		LXRβ	
				IC_{50}, μM	EC_{50}, μM (% eff)	IC_{50}, μM	EC_{50}, μM (% eff)
T0901317	—	—	—	0.03	0.25 (100)	0.07	0.3 (100)
6	CF_3		H	0.07	0.9 (87)	0.06	0.2 (79)
7	CF_3		Cl	0.001	0.1 (89)	0.003	0.02 (55)
8	CH_3		H	0.05	1.1 (100)	0.03	0.4 (71)
9	CH_3		Cl	0.003	0.2 (88)	0.003	0.08 (91)
10	CH_3		H	0.6	3.3 (132)	0.05	0.2 (84)
11	CH_3		Cl	0.02	0.5 (122)	0.002	0.16 (112)
12	CH_3		H	1.5	0.7 (70)	0.46	0.3 (74)
13	CH_3		H	2.7	4.3 (88)	2.32	2.3 (106)
14	CH_3		H	1.7	2.1 (108)	1.68	0.5 (93)
15	CH_3		H	0.12	1.0 (80)	0.61	0.2 (76)
16	CH_3		Cl	0.006	0.8 (78)	0.003	0.09 (72)
17	CH_3		H	0.005	0.2 (90)	0.005	0.06 (86)
18	CH_3		Cl	0.002	0.3 (78)	0.004	0.04 (94)
19	CF_3		H	0.03	1.0 (117)	0.05	0.3 (89)
20	CH_3		H	0.006	0.2 (96)	0.003	0.06 (72)
21	CH_3		Cl	0.006	0.1 (130)	0.007	0.03 (100)
22	CF_3		H	0.013	0.7 (130)	0.02	0.1 (83)

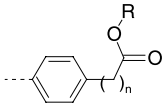
Table 2. Binding affinity (IC_{50}) and transactivation potency (EC_{50}) of branched anilines derived from N-alkylation with α-phenylbromoacetic acid methyl ester

Compound	R^4	R^5	R^6	LXR α		LXR β	
				IC_{50}, μM	EC_{50}, μM (% eff)	IC_{50}, μM	EC_{50}, μM (% eff)
rac-**27**	H	H	OMe	0.7	2.3 (33)	0.9	2.2 (50)
rac-**28**	H	H	OH	5.2	9.4 (77)	13.8	5.4 (95)
rac-**29**	H	H	NHMe	11.2	10.9 (24)	22	11 (32)
rac-**30**	H	H	NMe_2	13.8	9.3 (18)	6.3	2.3 (12)
rac-**31**	H	H	 X = CH_2	2.2	2.2 (49)	1.2	2.2 (26)
rac-**32**	H	H	X = O	5.4	8.5 (47)	1.4	2.3 (88)
rac-**33**	Me	H	OMe	0.05	0.1 (81)	0.008	0.03 (105)
rac-**34**	Et	H	OMe	0.05	0.3 (94)	0.04	0.07 (89)
rac-**35**	Et	Cl	OMe	0.06	0.5 (99)	0.03	0.07 (64)
rac-**36**	Me	H	NMe_2	0.2	0.4 (67)	0.06	0.07 (63)
rac-**37**	—	H	OMe	0.05	0.2 (92)	0.03	0.04 (58)
rac-**38**	—	H	OMe	0.06	0.09 (116)	0.03	0.04 (75)

bearing a polar carboxy or amido group. The lipophilic piperidino and morpholino moieties of amides **31** and **32**, respectively, are probably not properly oriented in the P3-pocket and therefore only slightly compensate for the repulsive interactions involving the amido functionality. An improvement of up to 100-fold in affinity was achieved by methylation or ethylation in the α-position to the ester or amide functionality (**33**–**36**). Analogous to the above-discussed '*o*-Cl-effect,' this is most likely due to the increased τ-angle resulting from the quaternization of the α-carbon with additional binding interactions between the receptor and the introduced alkyl group probably playing a minor role. This interpretation is supported by the similar increase in affinity observed upon o-chlorination of unquaternized anilines (see above and **43** vs **44**), in contrast to the lack of an effect when the *o*-chloro substituent was introduced after the α-carbon was already quaternized (**34** vs **35**). Quaternization of the α-carbon also proved effective when the α-substituent and the former *N*-ethyl substituent were fused to form a cycle (**37** and **38**).

Compared to the carboxy or amido groups of **28**–**30**, the still quite polar hydroxymethyl group of **43** was rather well tolerated. The isomeric diol **42**, obtained as side product, showed somewhat higher affinity and activity. Only minor differences were observed between the respective enantiomers *R*- and *S*-**43**, though the latter, in agreement to modeling predictions, was slightly more potent. Consistent with the mostly lipophilic character of the P3 pocket, O-methylation, O-benzylation or O-methoxycarbonylmethylation of **43**–**45**, **46**, and **47** slightly improved affinity. Modeling suggested that the benzyl group of **46** probably cannot orient in a way to

Table 3. Binding affinity (IC_{50}) and transactivation potency (EC_{50}) of branched anilines obtained by opening of styrene epoxide

Compound	R^5	R^6	LXRα		LXRβ	
			IC_{50}, μM	EC_{50}, μM (% eff)	IC_{50}, μM	EC_{50}, μM (% eff)
rac-**42**	—	—	0.5	1.0 (63)	0.5	0.2 (97)
rac-**43**	H	H	1.1	1.9 (87)	0.9	0.7 (53)
rac-**44**	Cl	H	0.2	0.4 (75)	0.09	0.2 (98)
R-**43**	H	H	1.3	1.5 (65)	0.5	0.4 (91)
S-**43**	H	H	0.5	0.5 (73)	0.4	0.1 (92)
rac-**45**	H	Me	0.4	0.9 (111)	0.3	0.1 (73)
rac-**46**	H	Bn	0.2	1.9 (55)	0.3	0.6 (85)
rac-**47**	H	CH_2CO_2Me	0.6	2.2 (54)	0.5	0.9 (65)
rac-**48**	H	CH_2CH_2OH	12	>40 (nd)	32	>40 (nd)
rac-**49**	H	CH_2CO_2H	61	10 (10)	90	>40 (nd)
rac-**50**	H	$CH_2CONHMe$	18	>40 (nd)	31	>40 (nd)
rac-**51**	H	CH_2CONMe_2	0.9	0.8 (87)	0.5	0.26 (67)
rac-**52**	Cl		n = 0, R = Me	0.06	0.7 (94)	0.02	0.2 (79)
rac-**53**	Cl		n = 1, R = Me	0.2	1.1 (65)	0.03	0.3 (98)
rac-**54**	Cl		n = 2, R = Me	0.1	1.4 (43)	0.05	0.6 (98)
rac-**55**	Cl		n = 0, R = H	0.1	3.7 (61)	0.02	1.1 (89)
rac-**56**	Cl		n = 1, R = H	0.1	5.5 (65)	0.02	2.4 (54)
rac-**57**	Cl		n = 2, R = H	0.06	4.5 (72)	0.007	1.2 (55)

optimally interact with the hydrophobic/aromatic side chains surrounding P3, explaining the only modest gain in affinity. The smaller but rather polar methoxycarbonyl and dimethylaminocarbonyl groups of **47** and **51**, respectively, are tolerated in P3, but further reduction of the lipophilicity in this position led to practically inactive compounds (**48**–**50**).

In contrast to an arylmethyl group (e.g. benzyl group in **46**), an aryl group attached to the hydroxymethyl moiety of **43** or **44** was expected to orient in a way to interact more favorably with the hydrophobic and aromatic side chains surrounding P3. In agreement with these expectations, most of the O-phenylated derivatives **52**–**57** showed an improved affinity compared to the parent **44**. This improvement was particularly pronounced for the propionic acid **57** and could well be due to interactions of the carboxy group with the Arg 319 side chain at the entrance to the binding pocket (see Fig. 1). The rather weak potencies measured for carboxylic acids **55**–**57** compared to those of the corresponding esters in the cellular transactivation assay were likely the result of reduced membrane permeability of these compounds.[17] Though **52**–**57** showed markedly improved affinities and activities compared to the other branched analogues, they did not reach the potency of the corresponding unbranched aniline **9**, indicating that the additional binding interactions in P3 were not sufficient to compensate for the entropically unfavorable fixation of the tested '–CH_2–O–R^6' groups and/or for the potentially reduced binding interactions of the other ligand moieties which could slightly reorient upon accommodation of a large '–CH_2–O–R^6' group in P3.

The anilines **9**, **20**, and **33** were selected for evaluation in animal studies. Since T0901317 has been reported to have significant crossreactivity with PXR and FXR, we evaluated these compounds in transcriptional transactivation assays for these receptors.[18] All three compounds showed significant PXR activity in a range similar to T0901317. However, none of the compounds activated FXR, in contrast to T0901317 which showed low but significant activation in our assay.

To evaluate the pharmacological effects on HDL-C and triglyceride levels, C57BL/6J mice were dosed once per day for five days with the compounds **9**, **20**, and **33**, and plasma and liver were collected 2 h following the final dose.[19] The choice of daily dose for each compound was based upon initial studies of compound stability during incubation in the presence of mouse microsomes. The results revealed distinct effects on plasma HDL-cholesterol levels and liver triglyceride content (Table 4). Compound **33**, at 100 mg/kg, significantly and dramatically increased liver triglyceride content by 520% compared to control, but surprisingly, produced only a marginal and insignificant increase in HDL-C. By contrast, compound **20**, at 10 mg/kg, significantly increased plasma HDL-C by 35% with a comparatively modest increase in liver triglyceride content (70%). Finally, the chloroaniline **9**, at 100 mg/kg, significantly increased HDL-C by 23% with almost no effect on liver triglyceride content. Plasma triglyceride levels were not significantly affected by any of the compounds. This is consistent with literature reports that the increase in plasma TGs after dosing with LXR agonists is transient and normalizes after repeated dosing.[20] Our experience suggests that this is due to a secondary increase in turnover of TG-rich lipoprotein particles which may be mediated by increased lipoprotein lipase expression, a direct target of LXR (unpublished data). Thus, steady-state plasma TG levels in mice appear not to reliably reflect the effects of LXR agonists on increased liver TG synthesis.

Compound levels were monitored by LC–MS in plasma and liver extracts (Table 4). All compounds were highly exposed, reaching plasma levels ranging between 6- and

Table 4. Effects on plasma HDL-C and triglyceride levels and liver triglyceride content in male C57Bl6J mice after 5 days treatment

Compound	Dose (mg/kg/day)	HDL-C	Plasma TG	Liver TG	Plasma exposure (ng/ml)	Liver exposure (ng/g)
9	100	+23%*	+7%	+28%	3400	13000
20	10	+35%*	−12%	+70%	700	8200
33	100	+12%	−11%	+520%*	2300	6300

Values are expressed as % change versus vehicle-treated group; $^{*}p > 0.05$; Anova followed by Student's *t*-test.

50-fold higher and liver levels between 30- and 150-fold higher than the EC_{50} in transcriptional transactivation assays. These compounds show significant binding to plasma proteins suggesting that the free fraction available for receptor activation may be somewhat lower. The contrast in the relative effects on HDL-C-raising versus the undesired induction of liver triglyceride synthesis for these compounds is striking, however it is currently unclear if this is due to differential activation of LXRα versus LXRβ or to gene-specific or tissue-specific regulatory functions. Further studies will be required to fully dissect these mechanisms.

In summary, the design of new LXR ligands, suggested partly by the published T091317/LXRβ-cocrystal structure, has led to the identification of unbranched and branched anilines with markedly improved affinity and activity compared to the sulfonamide T0901317. The modifications that led to improved potency were the introduction of suitable functional groups into the P2 and/or P3 pockets as well as proper orientation of the N-substituents. This was accomplished by either introduction of a chloro substituent *ortho* to the anilino nitrogen or by quaternizing the carbon atom that replaced the corresponding SO_2 group of T0901317. The identification of representative compounds that raised HDL-C with different effects on activation of liver triglyceride synthesis in mice, and of compounds with selectivity for LXRβ versus LXRα, suggests that this class may hold promise to find LXR modulators with reduced side effects.

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