

# Supporting Information

## Indazole-based Liver X Receptor (LXR) Modulators with Maintained Atherosclerotic Lesion Reduction Activity but Diminished Stimulation of Hepatic Triglyceride Synthesis.

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### Experimental Section

General experimental: Solvents and chemicals were purchased from EM Sciences, VWR, Oakwood, and Aldrich Chemical Co. and used without further purification. MS results were obtained on an Agilent MS. High-resolution mass spectra were obtained on a Waters LC-TOFMS instrument and were measured to within 5 ppm of calculated values. <sup>1</sup>H NMR spectra were obtained on a Varian (400 MHz) instrument. NMR data are given as delta values (δ) ppm using tetramethylsilane as an internal standard (δ = 0 ppm).

### Elemental analysis for experimental compounds

Cmpd	calc'd			found		
	C%	H%	N%	C%	H%	N%
<b>5</b>	71.58	4.29	7.95	71.82	4.08	7.97
<b>11</b>	69.34	4.55	7.03	69.49	4.41	6.96
<b>12</b>	59.66	2.86	6.63	59.71	2.62	6.55
<b>13</b>	64.95	3.37	7.21	64.84	3.32	7.30
<b>14</b>	62.31	3.24	6.92	62.27	3.25	6.99
<b>15</b>	64.95	3.37	7.21	64.83	3.26	7.13
<b>16</b>	62.31	3.24	6.92	62.40	3.28	6.90
<b>17</b>	57.42	2.75	6.38	57.73	2.82	6.21
<b>18</b>	57.42	2.75	6.38	57.74	2.89	6.22
<b>19</b>	59.88	3.11	6.65	59.78	3.09	6.56
<b>20</b>	62.31	3.24	6.92	62.20	3.13	6.88
<b>21</b>	58.10	2.88	6.16	58.05	2.82	6.10
<b>22</b>	58.10	2.88	6.16	58.28	2.82	6.06

**2-(2,4-dimethylbenzyl)-3-(4-fluorophenyl)-7-(trifluoromethyl)-2H-indazole (11)**

HRMS: calc'd for  $C_{23}H_{18}F_4N_2 + H^+$ , 399.1479; found (ESI,  $[M+H]^+$  Obs'd), 399.1481;

HRMS: calc'd for  $C_{23}H_{18}F_4N_2 + Na^+$ , 421.1298; found (ESI,  $[M+Na]^+$  Obs'd), 421.1303;

HPLC purity: 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt = 12.0 min.

**2-(2-chloro-4-fluorobenzyl)-3-(4-fluorophenyl)-7-(trifluoromethyl)-2H-indazole (12)**

HRMS: calc'd for  $C_{21}H_{12}ClF_5N_2 + H^+$ , 423.06819; found (ESI-FTMS,  $[M+H]^{1+}$ ),

423.0683; HPLC purity 100% at 210-370 nm, 11.5 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/min, 85/15-5/95 (ammonium. formate Buff. Ph=3.5/ACN+MeOH) for 10min, hold 4min.

**2-(2-fluorobenzyl)-3-(4-fluorophenyl)-7-(trifluoromethyl)-2H-indazole (13)**

HRMS: calc'd for  $C_{21}H_{13}F_5N_2 + H^+$ , 389.1072; found (ESI,  $[M+H]^+$  Obs'd), 389.1081;

HRMS: calc'd for  $C_{21}H_{13}F_5N_2 + Na^+$ , 411.0891; found (ESI,  $[M+Na]^+$  Obs'd), 411.0903;

HPLC purity 100.0% at 210-370 nm, 11.2 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/min, 85/15-5/95 (ammonium formate. Buff. Ph=3.5/ACN+MeOH) for 10min, hold 4min.

**2-(2-chlorobenzyl)-3-(4-fluorophenyl)-7-(trifluoromethyl)-2H-indazole (14)**

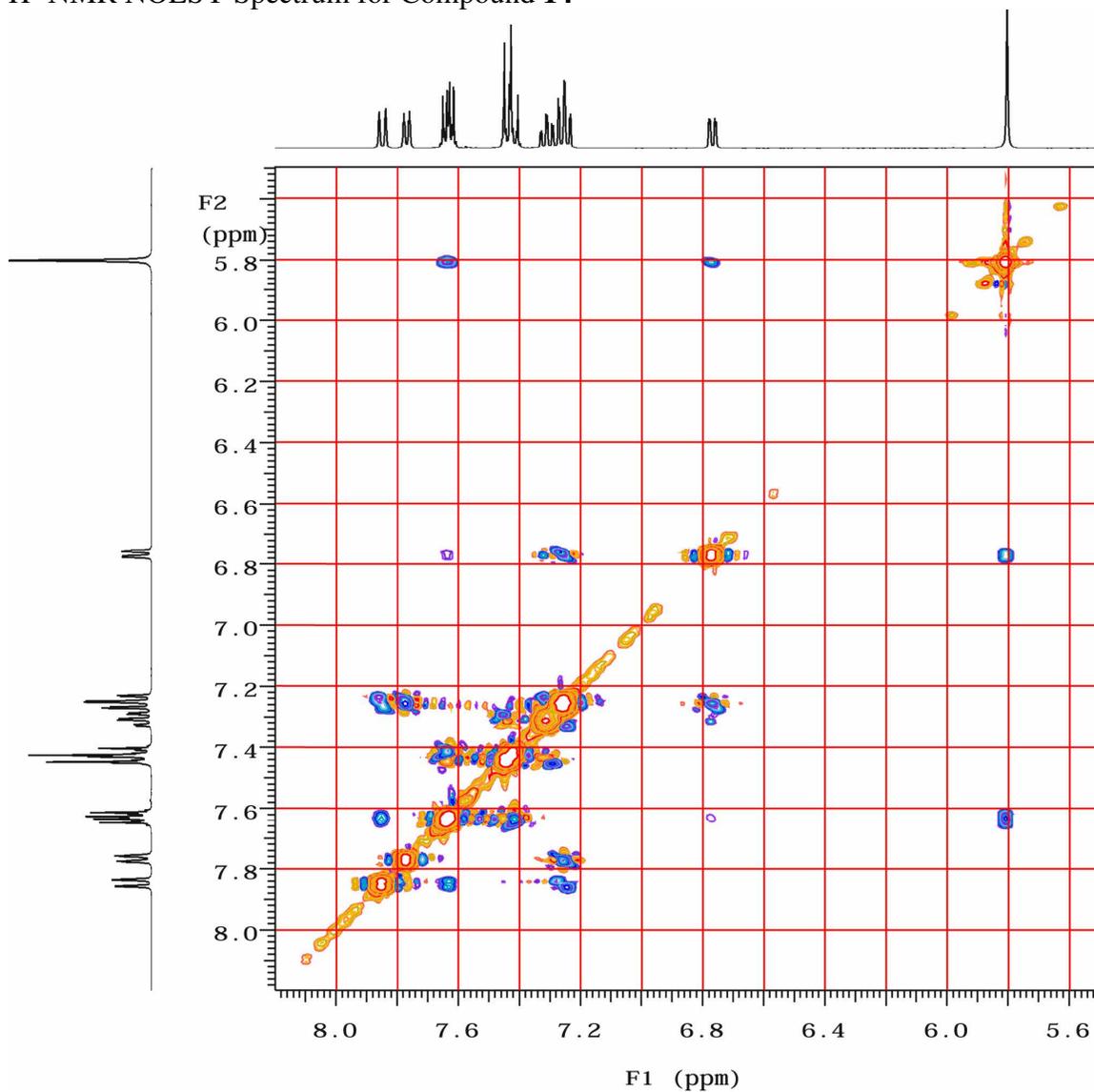
HRMS: calc'd for  $C_{21}H_{13}ClF_4N_2 + H^+$ , 405.0776; found (ESI,  $[M+H]^+$  Obs'd), 405.0782;

HRMS: calc'd for  $C_{21}H_{13}ClF_4N_2 + Na^+$ , 427.0596; found (ESI,  $[M+Na]^+$  Obs'd), 427.0602;

HPLC purity 100.0% at 210-370 nm, 11.5 min.; Xterra RP18, 3.5u, 150 x 4.6 mm

column, 1.2 mL/min, 85/15-5/95 (ammonium formate Buff. Ph=3.5/ACN+MeOH) for 10min, hold 4min.

### $^1\text{H}$ NMR NOESY Spectrum for Compound **14**



Obtained in DMSO- $d_6$  at 25°C on Varian Unity INOVA 400 MHz instrument

Pulse sequence:NOESY  
Relax. Delay 1.3 sec  
Acq. Time 0.177 sec  
Width 5797.1 Hz  
2D width 5797.1 sec  
16 repetitions

OBSERVE H1 399.789 MHz  
Data processing Gauss apodization 0.082 sec  
F1 data processing Gauss apodization 0.082 sec  
FT size 4096 x 4096

**2-(4-fluorobenzyl)-3-(4-fluorophenyl)-7-(trifluoromethyl)-2H-indazole (15)**

HRMS: calc'd for  $C_{21}H_{13}F_5N_2 + H^+$ , 389.1076; found (ESI,  $[M+H]^+$  Obs'd), 389.1072;

HRMS: calc'd for  $C_{21}H_{13}F_5N_2 + Na^+$ , 411.0895; found (ESI,  $[M+Na]^+$  Obs'd), 411.0891;

**2-(4-chlorobenzyl)-3-(4-fluorophenyl)-7-(trifluoromethyl)-2H-indazole (16)**

HRMS: calc'd for  $C_{21}H_{13}F_4N_2 + H^+$ , 405.0779; found (ESI,  $[M+H]^+$  Obs'd), 405.0776;

HRMS: calc'd for  $C_{21}H_{13}F_4N_2 + Na^+$ , 427.0592; found (ESI,  $[M+Na]^+$  Obs'd), 427.0596;

HPLC purity 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2

mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt =

11.8 min.

**2-(4-chloro-2-fluorobenzyl)-3-(4-chlorophenyl)-7-(trifluoromethyl)-2H-indazole (17)**

HRMS: calc'd for  $C_{21}H_{12}Cl_2F_4N_2 + H^+$ , 439.0386; found (ESI,  $[M+H]^+$  Obs'd), 439.0390;

HRMS: calc'd for  $C_{21}H_{12}Cl_2F_4N_2 + Na^+$ , 461.0206; found (ESI,  $[M+Na]^+$  Obs'd),

461.0212; HPLC purity 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column,

1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt =

12.2 min.

**2-(2-chloro-4-fluorobenzyl)-3-(4-chlorophenyl)-7-(trifluoromethyl)-2H-indazole (18)**

HRMS: calc'd for  $C_{21}H_{12}Cl_2F_4N_2 + H^+$ , 439.0386; found (ESI,  $[M+H]^+$  Obs'd), 439.0389;  
HRMS: calc'd for  $C_{21}H_{12}Cl_2F_4N_2 + Na^+$ , 461.0206; found (ESI,  $[M+Na]^+$  Obs'd),  
461.0210; HPLC purity 98.9% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column,  
1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt =  
12.2 min.

**2-(2-chlorobenzyl)-3-(4-chlorophenyl)-7-(trifluoromethyl)-2H-indazole (19)**

HRMS: calc'd for  $C_{21}H_{13}Cl_2F_3N_2 + H^+$ , 421.0483; found (ESI,  $[M+H]^+$  Obs'd),  
421.0481; HRMS: calc'd for  $C_{21}H_{13}Cl_2F_3N_2 + Na^+$ , 443.0307; found (ESI,  $[M+Na]^+$   
Obs'd), 443.0300; HPLC purity 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm  
column, 1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50  
ACN:MeOH; rt = 12.2 min

**3-(4-chlorophenyl)-2-(2-fluorobenzyl)-7-(trifluoromethyl)-2H-indazole (20)**

HRMS: calc'd for  $C_{21}H_{13}ClF_4N_2 + H^+$ , 405.0779; found (ESI,  $[M+H]^+$  Obs'd), 405.0776;  
HRMS: calc'd for  $C_{21}H_{13}ClF_4N_2 + Na^+$ , 427.0597; found (ESI,  $[M+Na]^+$  Obs'd),  
427.0596; HPLC purity 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column,  
1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt =  
11.8min.

**3-(4-chlorophenyl)-7-(trifluoromethyl)-2-[2-(trifluoromethyl)benzyl]-2H-indazole  
(21)**

HRMS: calc'd for  $C_{22}H_{13}ClF_6N_2 + H^+$ , 455.0751; found (ESI,  $[M+H]^+$  Obs'd), 455.0744;  
HRMS: calc'd for  $C_{22}H_{13}ClF_6N_2 + Na^+$ , 477.0565; found (ESI,  $[M+Na]^+$  Obs'd),  
477.0564; HPLC purity 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column,  
1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt =  
12.1 min.

**3-(4-chlorophenyl)-7-(trifluoromethyl)-2-[4-(trifluoromethyl)benzyl]-2H-indazole  
(22)**

HRMS: calc'd for  $C_{22}H_{13}ClF_6N_2 + H^+$ , 455.0744; found (ESI,  $[M+H]^+$  Obs'd), 455.0744;  
HRMS: calc'd for  $C_{22}H_{13}ClF_6N_2 + Na^+$ , 477.0564; found (ESI,  $[M+Na]^+$  Obs'd),  
477.0557; HPLC purity 100% at 210-370 nm; Xterra RP18, 3.5u, 150 x 4.6 mm column,  
1.2 mL/min, A: 10mM ammonium formate in water (ph 3.5); B: 50:50 ACN:MeOH; rt =  
12.1 min.

**2-benzyl-3-phenyl-7-(trifluoromethyl)-2H-indazole (5)**

Prepared identical as for the 4-fluoro and 4-chloro analogs starting from (2-fluoro-3-(trifluoromethyl)phenyl)(phenyl)methanone.

$^1H$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  5.75 (s, 2H), 7.0 (dd, 2H), 7.26 (m, 4H), 7.58 (m, 5H),  
7.75 (d, 1H,  $J=7.05$  Hz), 7.84 (d, 1H,  $J=8.46$ ); HRMS: calc'd for  $C_{21}H_{15}F_3N_2 + H^+$ ,  
353.1260; found (ESI,  $[M+H]^+$  Obs'd), 353.1267; HRMS: calc'd for  $C_{21}H_{15}F_3N_2 + Na^+$ ,  
375.1080; found (ESI,  $[M+Na]^+$  Obs'd), 375.1083; HPLC purity 100% at 210-370 nm;  
Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/min, A: 10mM ammonium formate in

water (pH 3.5); B: 50:50 ACN:MeOH; rt = 11.4 min.

### Cross-reactivity assays

PPAR and FXR Gal4 transactivation assays were performed as describe previously<sup>1</sup> using the agonist ligands in the table below.

Binding assays: All receptor constructs are of human receptors. All binding assays rely on competition between the test compound and a radioactively labeled reference binder. Some of the binding assays utilize the SPA or flash plate technology (PXR; RXR; ER $\alpha$  and  $\beta$ ), the others involve a step where free and bound radioactivity are separated by use of a filter (MR; AR; GR; PR; TR).

Receptor	Assay format	Reference binder / agonist	Compound 12 EC <sub>50</sub> ( $\mu$ M)	Compound 13 EC <sub>50</sub> ( $\mu$ M)
PPAR $\alpha$	Receptor LBD fused to GAL4 DBD used in transient transfection assays.	WY-14643	No agonist effect	No agonist effect
PPAR $\gamma$	Receptor LBD fused to GAL4 DBD used in transient transfection assays.	Rosiglitazone	No agonist effect	No agonist effect
PPAR $\delta$	Receptor LBD fused to GAL4 DBD used in transient transfection assays.	L-796449	No agonist effect	No agonist effect
FXR	Receptor LBD fused to GAL4 DBD used in transient transfection assays.	GW-4064	No agonist effect	No agonist effect
			Compound 12 IC <sub>50</sub> ( $\mu$ M)	Compound 13 IC <sub>50</sub> ( $\mu$ M)
PXR	Binding assay	T0901317	1.77	2.16
RXR	Binding assay	9- <i>cis</i> retinoic acid	>10	No binding
GR	Binding assay	Dexamethasone	1.0	7.2
MR	Binding assay	Aldosterone	No binding	>10
AR	Binding assay	Mibolerone	2.3	No binding
PR	Binding assay	Progesterone	>1	>10
ER $\alpha$	Binding assay	Estradiol	No binding	No binding
ER $\beta$	Binding assay	Estradiol	No binding	No binding
TR $\alpha$	Binding assay	T3	No binding	No binding

TR $\beta$	Binding assay	T3	No binding	No binding
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1. Hu, B.; Collini, M.; Unwalla, R.; Miller, C.; Singhaus, R.; Quinet, E.; Savio, D.; Halpern, A.; Basso, M.; Keith, J.; Clerin, V.; Chen, L.; Resmini, C.; Liu, Q.-Y.; Feingold, I.; Huselton, C.; Azam, F.; Farnegardh, M.; Enroth, C.; Bonn, T.; Goos-Nilsson, A.; Wilhelmsson, A.; Nambi, P.; Wrobel, J., Discovery of Phenyl Acetic Acid Substituted Quinolines as Novel Liver X Receptor Agonists for the Treatment of Atherosclerosis. *Journal of Medicinal Chemistry* **2006**, 49, 6151-6154.