Computer-Assisted Discovery and Structural Optimization of a Novel Retinoid X Receptor Agonist Chemotype

Pascal Heitel[†], Leonie Gellrich[†], Lena Kalinowsky[†], Jan Heering[‡], Astrid Kaiser[†], Julia Ohrndorf[†], Ewgenij Proschak[†], and Daniel Merk[*,†]

[†]Institute of Pharmaceutical Chemistry, Goethe University Frankfurt, Max-von-Laue-Str. 9, 60438 Frankfurt, Germany.

[‡]Project Group Translational Medicine and Pharmacology TMP, Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Theodor-Stern-Kai 7, D-60596, Frankfurt, Germany.

- Supporting Information -

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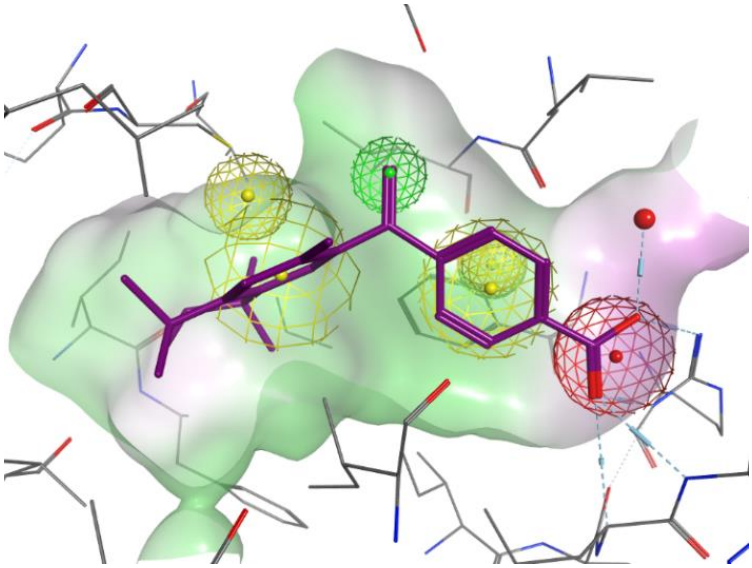

Figure S1: Pharmacophore Model of Bexarotene in Crystal Structure 4K6I. Pharmacophore features are colored by type: Aromatic centroids and corresponding pins in yellow, hydrophobic atom in green, bioisostere COO^- in red. The surface of the binding pocket is colored by lipophilicity (green: lipophilic, magenta: hydrophilic).

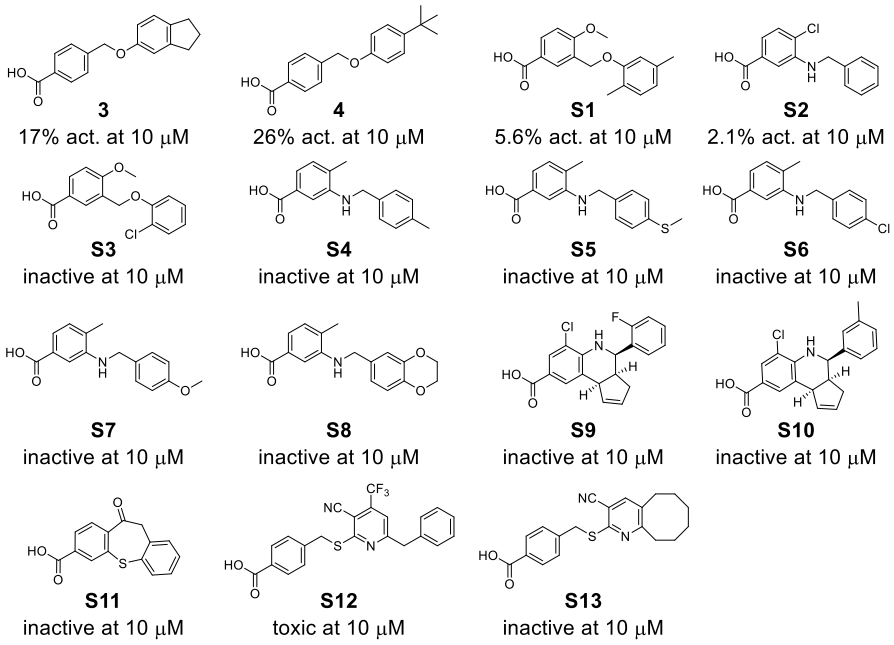

Figure S2: Screening Hits. Chemical structures of the 15 virtual screening hits that were tested *in vitro* in a RXRα-Gal4 hybrid reporter gene assay.

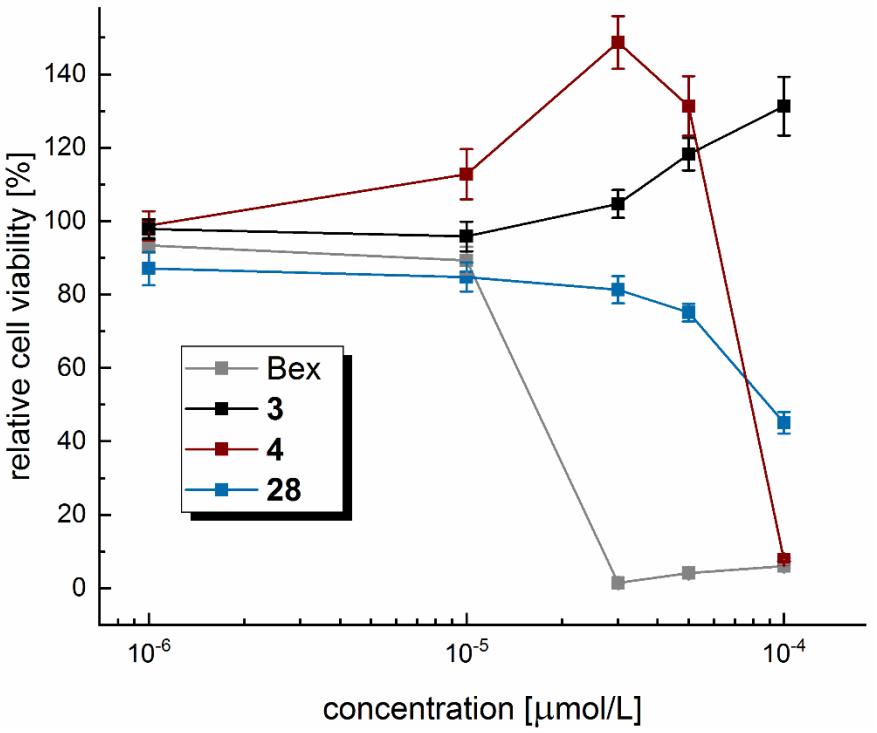

Figure S3**: **Water-Soluble Tetrazolium 1 Assay (WST-1) to Capture Test Compound Toxicity. After 48h incubation, screening hit **3** shows no toxicity in HepG2 cells and compound **4** demonstrates weak antiproliferative effects only at the highest concentration tested (100 µM). Compared to literature RXR agonist bexarotene (**1**, Bex), the optimized compound **28** exhibits markedly lower toxic effects. Results are mean ± SEM, n = 3.

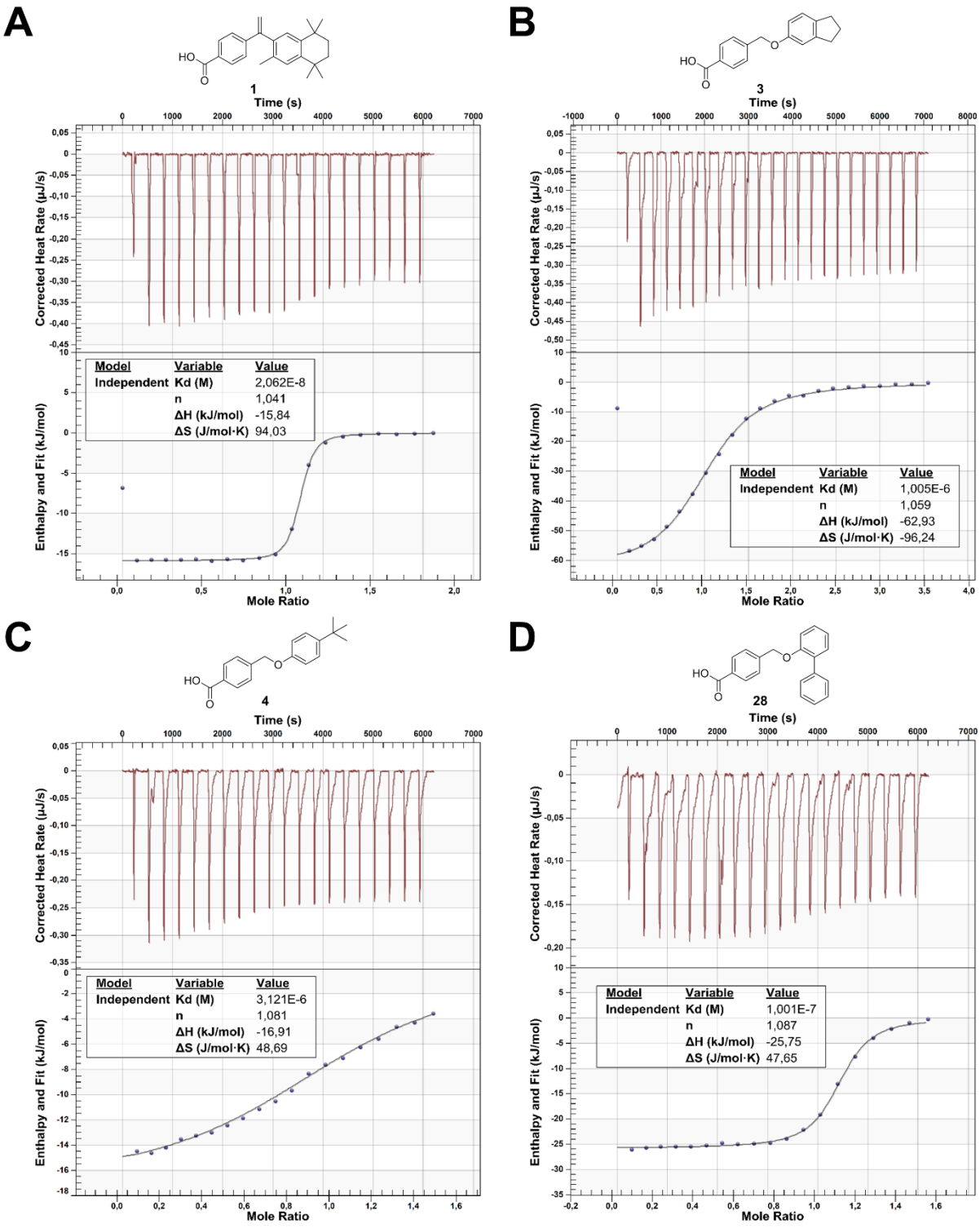

Figure S4: Isothermal Titration Calorimetry. Representative curves to determine binding affinity of literature RXR agonist bexarotene (**1**, A) and compounds **3** (B), **4** (C), and **28** (D).

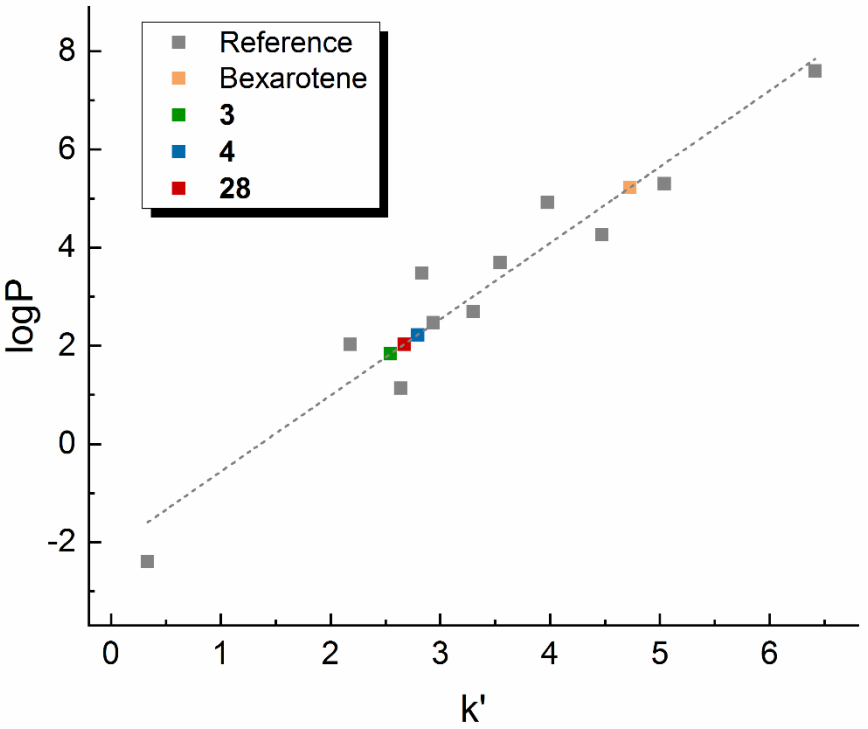

Figure S5: LogP Determination by HPLC. After calibration with eleven reference compounds (grey), test compounds **1**, **3**, **4**, and **28** were analyzed and logP was calculated relative to the references by regression. Compared to literature RXR agonist bexarotene (**1**), compounds **3**, **4**, and **28** are markedly less lipophilic.

Chemistry

General. All chemicals and solvents were obtained from commercial sources in reagent grade and used without further purification. TLC was performed using TLC-plates (silica gel 60 F254, 0.2 mm, Merck or Alugram Xtra Sil G/UV 0.2 mm, Machery-Nagel) with detection under UV-light (254 nm and 366 nm). Preparative column chromatography was performed using Silicagel 60 (Macherey-Nagel) and solvents of technical grade. Reactions with air- or moisture-sensitive compounds were carried out under argon atmosphere. NMR spectra were recorded on Bruker AM 250 XP, AV 300, AV 400, AV 500 spectrometers (Bruker Corporation, Billerica, MA, USA). Chemical shifts (δ) are reported in ppm relative to TMS, coupling constants (*J*) in Hz. Multiplicity of signals is indicated as s for singulet, d for duplet, t for triplet, q for quartet, and m for multiplet. Mass spectra were obtained on a VG Platform II (Thermo Fischer Scientific, Inc., Waltham, MA, USA) using electrospray ionization (ESI). High resolution mass spectra were recorded on a MALDI LTQ ORBITRAP XL instrument (Thermo Fisher Scientific) or on a Bruker maXis ESI-Qq-TOF-MS instrument (Bruker). Compound purity was analyzed on a Varian ProStar HPLC (SpectraLab Scientific Inc., Markham, ON, Canada) equipped with a MultoHigh100 Phenyl-5 µ 240+4 mm column (CS-Chromatographie Service GmbH, Langerwehe, Germany) using a gradient (H_2O/MeOH 80:20 + 0.1% formic acid isocratic for 5 min to MeOH + 0.1% formic acid after additional 45 min and MeOH + 0.1% formic acid for additional 10 min) at a flow rate of 1 mL/min and UV-detection at 245 nm and 280 nm. All final compounds for biological evaluation had a purity > 95%. Compounds **3-5**, **16-19**, **21**, **29**, and **S1-S13** were purchased from Specs (Zoetermeer, Netherlands).

General Procedures

(a) Esterification

The corresponding carboxylic acid (1.0 eq) was dissolved in a 20:1 (v/v) mixture of ethanol and concentrated sulfuric acid to a concentration of 0.5 mol/L and heated to reflux for 2 – 15 hours. After cooling to room temperature, the solution was neutralized with sodium carbonate and the crude product was extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated in vacuum. If required, the product was further purified by column chromatography on silica. Compounds **38a-d** and **49** were prepared according to this general procedure in 77 – 99% yield.

(b) Bromination Under Radical Conditions

The toluene derivative (1.0 eq), *N*-bromosuccinimide (1.0 eq) and 10-mol% AIBN were suspended in dry $CHCl_3$ (2 mL/mmol) under Ar. The suspension dissolved while heating to reflux, which was kept for one hour. After cooling to room temperature, the solvent was removed under reduced pressure and the purified product was obtained after column chromatography on silica. Compounds **39a-d** were prepared according to this general procedure in 15 – 86% yield.

(c) Williamson Ether Synthesis

The corresponding alcohol (1.0 eq), benzyl bromide or benzyl chloride (0.8 – 1.2 eq) and 2.0 equivalents of potassium carbonate were suspended in dry DMF (4 mL/mmol) and stirred for 10 min. to 18 hours at rt – 100 °C. After cooling to room temperature, ethyl acetate (30 mL) was added and organic layer was washed three times with water (30 mL). The organic layer was then dried over Na_2SO_4 and the solvents were evaporated in vacuum. Column chromatography on silica afforded the pure product. Compounds **41a-s**, **53**, **58**, and **61** were prepared according to this general procedure in 28 – 94% yield.

(d) Suzuki Reaction

The respective bromoarene (1.0 eq) and sodium carbonate (3.0 eq) were dissolved in a 4:1 mixture of 1,4-dioxane and water (c = 0.1 M) and the solvents were degassed. A catalytic amount of $Pd(PPh_3)_4$ (5.0 mol-%) and phenylboronic acid (1.2 eq) were added. The mixture was heated to reflux for 2 - 7 hours. After cooling to room temperature, 5 mL of 5% aqueous hydrochloric acid were added, the mixture was extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated in vacuum. The crude product was purified by column chromatography on silica. Compounds **40o-q** were prepared according to this general procedure in 40 – 64% yield.

(e) Alkaline Hydrolysis

An aqueous solution of lithium hydroxide (5.0 eq, c = 1.0 M) was added to a solution of the ester (1.0 eq) in THF (c = 0.05 M). The resulting mixture was either heated to 50 °C or stirred at ambient temperature until TLC indicated complete conversion. Subsequently, the solution was acidified with 5% aqueous hydrochloric acid and extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated in vacuum. If necessary, further purification was achieved by column chromatography on silica. Compounds **6-9**, **13-15**, **20**, **22-28**, and **30-36** were prepared according to this general procedure in 31 – 99% yield.

(f) Duff Reaction

To a solution of the corresponding arene (1.0) in trifluoroacetic acid (5 mL/mmol) hexamethylene-tetramine (1.1 eq) was added and the mixture was heated to 100 °C for 3 – 7 hours. After cooling to room temperature, the mixture was neutralized with saturated $NaHCO_3$. The mixture was extracted three times with ethyl acetate, the combined organic layers were dried over Na_2SO_4, and the solvent was

evaporated in vacuum. Purification by column chromatography afforded the pure product. Compounds **50** and **55** were prepared according to this general procedure in 18 – 60% yield.

(g) Aldehyde Reduction

Sodium borohydride (1.5 eq) was carefully added to a solution of the respective benzaldehyde (1.0 eq) in methanol (20 mL/mmol) at 0 °C. The mixture was allowed to warm to room temperature for 2 – 3 hours and then quenched with water and 5% aqueous hydrochloric acid. The mixture was extracted three times with ethyl acetate, the combined organic layers were dried over Na_2SO_4, and the solvents were removed under reduced pressure. The crude product was purified with column chromatography. Compounds **51** and **56** were prepared according to this general procedure in 55 – 59% yield.

(h) Chlorination of Benzyl Alcohols

Thionyl chloride (1.3 eq) was added dropwise to a solution of the corresponding benzyl alcohol (1.0 eq) in dry CH_2Cl_2 (15 mL/mmol) at 0 °C. The solution was stirred for 1 – 2 hours. Then, water was added to stop the reaction and the solution was neutralized with $NaHCO_3$ solution. Phases were separated and the organic layer was washed twice with water. The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuum. If required, the product was further purified by column chromatography. Compounds **52**, **57**, and **60** were prepared according to this general procedure in 41 – 80% yield.

List of Compounds

Table S1: List of Compounds.

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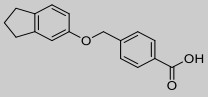
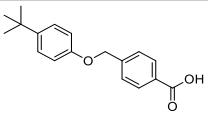
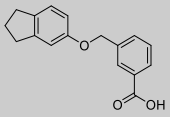
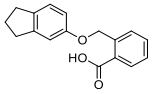
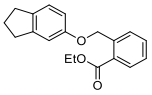
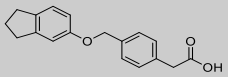
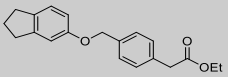
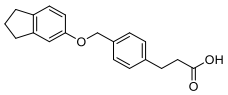
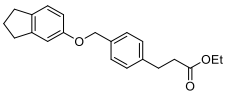
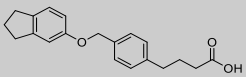
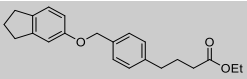
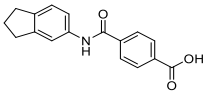
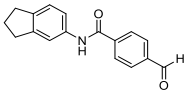
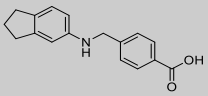
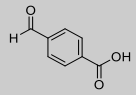
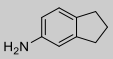
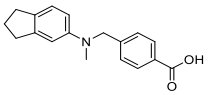
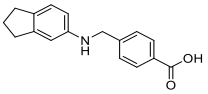
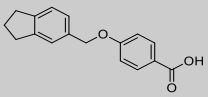
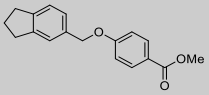
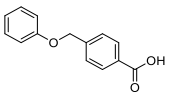
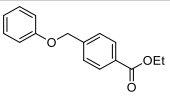
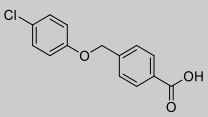
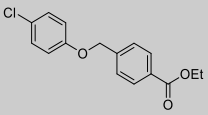
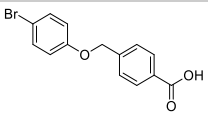
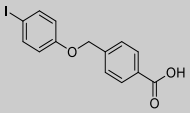
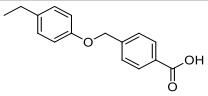
3		purchased	-	-	-	-
4		purchased	-	-	-	-
5		purchased	-	-	-	-
6		e	**41a**		-	-
7		e	**41b**		-	-
8		e	**41c**		-	-
9		e	**53**		-	-
10		-	**47**		-	-
11		-	**45**		**46**	
12		-	**10**		-	-
13		e	**58**		-	-
14		e	**41d**		-	-
15		e	**41e**		-	-
16		purchased	-	-	-	-
17		purchased	-	-	-	-
18		purchased	-	-	-	-

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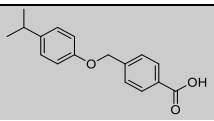
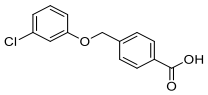
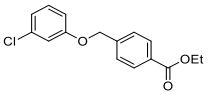
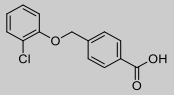
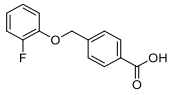
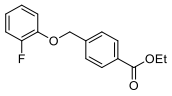
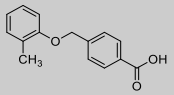
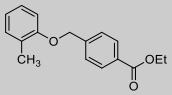
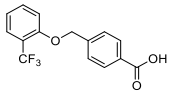
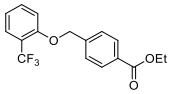
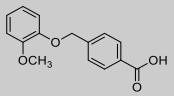
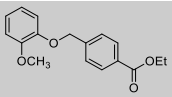
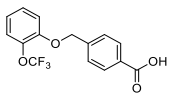
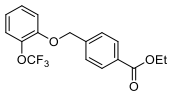
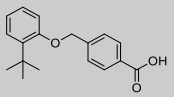
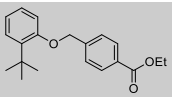
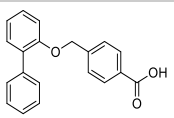
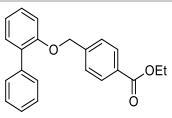
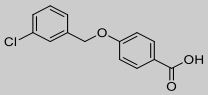
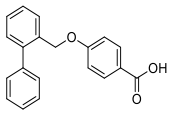
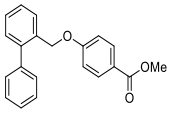
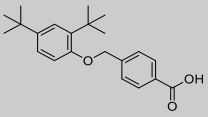
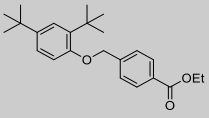
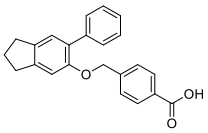
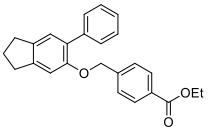
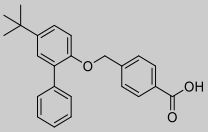
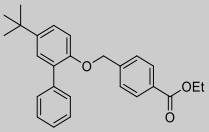
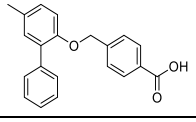
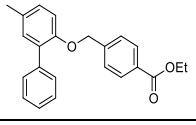
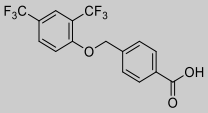
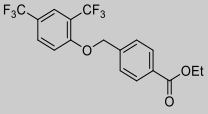
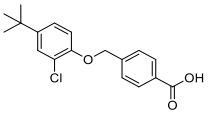
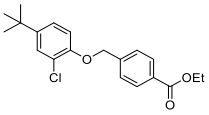
19		purchased	-	-	-	-
20		e	**41f**		-	-
21		purchased	-	-	-	-
22		e	**41g**		-	-
23		e	**41h**		-	-
24		e	**41i**		-	-
25		e	**41j**		-	-
26		e	**41k**		-	-
27		e	**41l**		-	-
28		e	**41m**		-	-
29		purchased	-	-	-	-
30		e	**61**		-	-
31		e	**41n**		-	-
32		e	**41o**		-	-
33		e	**41p**		-	-
34		e	**41q**		-	-

#	Structure	General Procedure	Precursor A	Structure	Precursor B	Structure
35		e	**41r**		-	-
36		e	**41s**		-	-
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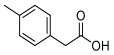
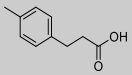
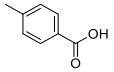
37b		purchased	-	-	-	-
37c		purchased	-	-	-	-
37d		purchased	-	-	-	-
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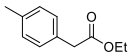
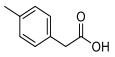
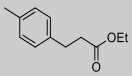
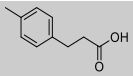
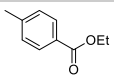
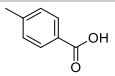
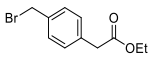
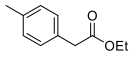
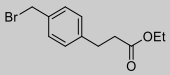
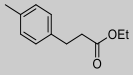
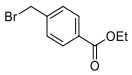
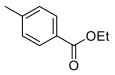
38b		a	**37b**		-	-
38c		a	**37c**		-	-
38d		a	**37d**		-	-
39a		b	**38a**		-	-
39b		b	**38b**		-	-
39c		b	**38c**		-	-
39d		b	**38d**		-	-
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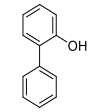
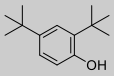
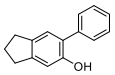
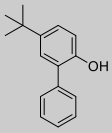
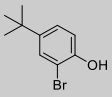
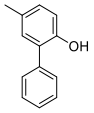
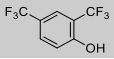
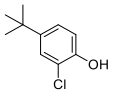
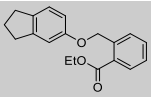
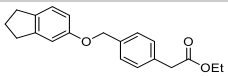
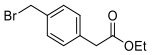
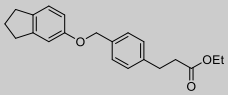
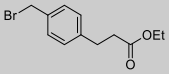
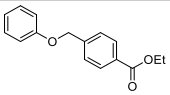
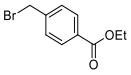
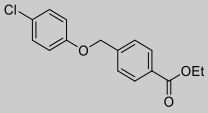
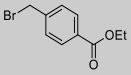
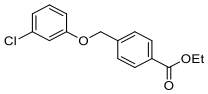
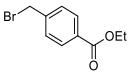
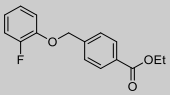
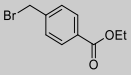
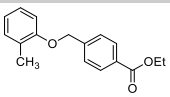
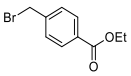
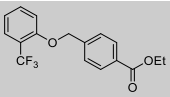
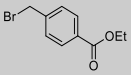
40f		purchased	-	-	-	-
40g		purchased	-	-	-	-
40h		purchased	-	-	-	-
40i		purchased	-	-	-	-
40j		purchased	-	-	-	-
40k		purchased	-	-	-	-
40l		purchased	-	-	-	-

#	Structure	General Procedure	Precursor A	Structure	Precursor B	Structure
40m		purchased	-	-	-	-
40n		purchased	-	-	-	-
40o		d	**42o**		**43**	
40p		d	**42p**		**43**	
40q		d	**42q**		**43**	
40r		purchased	-	-	-	-
40s		purchased	-	-	-	-
41a		c	**39a**		**44**	
41b		c	**39b**		**44**	
41c		c	**39c**		**44**	
41d		c	**39d**		**40d**	
41e		c	**39d**		**40e**	
41f		c	**39d**		**40f**	
41g		c	**39d**		**40g**	
41h		c	**39d**		**40h**	
41i		c	**39d**		**40i**	
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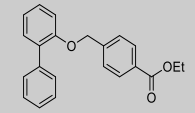
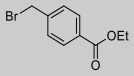
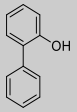
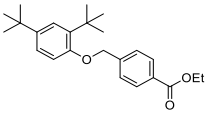
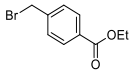
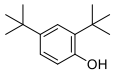
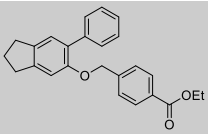
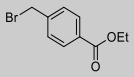
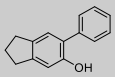
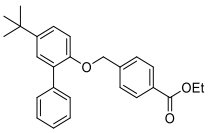
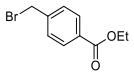
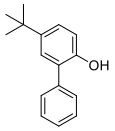
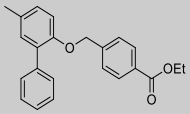
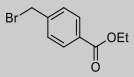
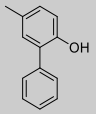
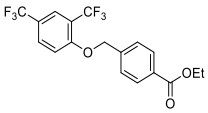
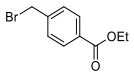
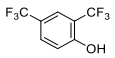
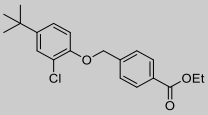
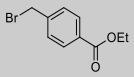
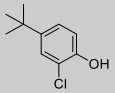
41l		c	**39d**		**40l**	

#	Structure	General Procedure	Precursor A	Structure	Precursor B	Structure
41m		c	**39d**		**40m**	
41n		c	**39d**		**40n**	
41o		c	**39d**		**40o**	
41p		c	**39d**		**40p**	
41q		c	**39d**		**40q**	
41r		c	**39d**		**40r**	
41s		c	**39d**		**40s**	
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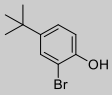
42p		purchased	-	-	-	-
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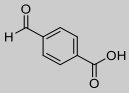
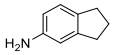
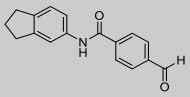
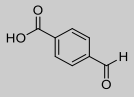
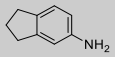
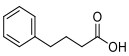
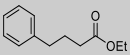
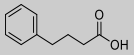
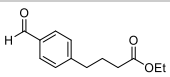
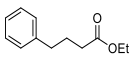
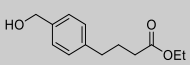
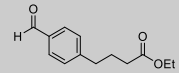
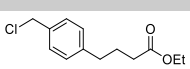
45		purchased	-	-	-	-
46		purchased	-	-	-	-
47		-	**45**		**46**	
48		purchased	-	-	-	-
49		a	**48**		-	-
50		f	**49**		-	-
51		g	**50**		-	-
52		h	**51**		-	-

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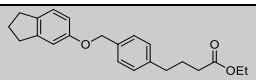
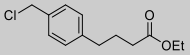
53		c	**52**		**44**	
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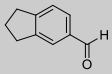
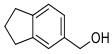
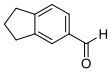
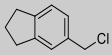
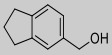
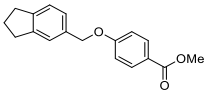
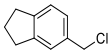
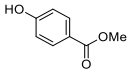
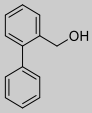
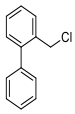
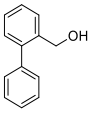
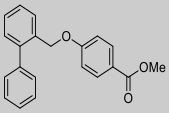
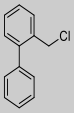
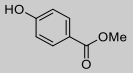
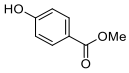
55		f	**54**		-	-
56		g	**55**		-	-
57		h	**56**		-	-
58		c	**57**		**62**	
59		purchased	-	-	-	-
60		h	**59**		-	-
61		c	**60**		**62**	
62		purchased	-	-	-	-

Analytical Characterization

2-([{5-Indanyl}oxy]methyl)benzoic acid (**6**): Preparation according to general procedure e using **41a**. Yield: 64%. Pale yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.99 (p, ^{3}J = 7.4 Hz, 2H), 2.76 (t, ^{3}J = 7.3 Hz, 2H), 2.80 (t, ^{3}J = 7.4 Hz, 2H), 5.40 (s, 2H), 6.71 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.84 (d, ^{4}J = 1.9 Hz, 1H), 7.10 (d, ^{3}J = 8.2 Hz, 1H), 7.43 (ddd, ^{3}J = 7.7, 7.7 Hz, ^{4}J = 1.2 Hz, 1H), 7.58 (ddd, ^{3}J = 7.6, 7.6 Hz, ^{4}J = 1.3 Hz, 1H), 7.63 (d, ^{3}J = 7.0 Hz, 1H), 7.92 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.1 Hz, 1H), 13.05 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.4, 31.4, 32.6, 67.7, 110.6, 112.7, 124.7, 127.5, 127.7, 129.3, 130.5, 132.1, 135.7, 138.8, 145.2, 157.2, 168.2 ppm. ESI-MS: *m/z* 267.11 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 291.09917 for $C_{17}H_{16}O_3Na$, found 291.09923 ([M+Na]$^+$).

4-([{5-Indanyl}oxy]methyl)phenylacetic acid (**7**): Preparation according to general procedure e using **41b**. Yield: 90%. Yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.99 (p, ^{3}J = 7.4 Hz, 2H), 2.76 (t, ^{3}J = 7.3 Hz, 2H), 2.80 (t, ^{3}J = 7.4 Hz, 2H), 3.56 (s, 2H), 5.02 (s, 2H), 6.74 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.87 (d, ^{4}J = 2.0 Hz, 1H), 7.09 (d, ^{3}J = 8.2 Hz, 1H), 7.26 (d, ^{3}J = 8.1 Hz, 2H), 7.36 (d, ^{3}J = 8.1 Hz, 2H), 12.33 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.4, 31.4, 32.6, 40.4, 69.0, 110.7, 112.8, 124.7, 127.5, 129.4, 134.5, 135.6, 135.7, 145.1, 157.2, 172.7 ppm. ESI-MS: *m/z* 281.12 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 305.11482 for $C_{18}H_{18}O_3Na$, found 305.11459 ([M+Na]$^+$).

3-([4-{(5-Indanyl)oxy}methyl]phenyl)propanoic acid (**8**): Preparation according to general procedure e using **41c**. Purification by preparative HPLC. Yield: 55%. Beige solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.99 (p, ^{3}J = 7.4 Hz, 2H), 2.53 (t, ^{3}J = 7.7 Hz, 2H), 2.76 (t, ^{3}J = 7.3 Hz, 2H), 2.78 – 2.86 (m, 4H), 5.00 (s, 2H), 6.73 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.87 (d, ^{4}J = 1.9 Hz, 1H), 7.09 (d, ^{3}J = 8.2 Hz, 1H), 7.23 (d, ^{3}J = 8.0 Hz, 2H), 7.33 (d, ^{3}J = 8.0 Hz, 2H), 12.13 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.4, 30.1, 31.4, 32.6, 35.2, 69.1, 110.7, 112.8, 124.6, 127.7, 128.3, 135.0, 135.6, 140.4, 145.1, 157.3, 173.7 ppm. ESI-MS: *m/z* 295.16 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 319.13047 for $C_{19}H_{20}O_3Na$, found 319.13035 ([M+Na]$^+$).

4-(4-[{(5-Indanyl)oxy}methyl]phenyl)butanoic acid (**9**): Preparation according to general procedure e using **53**. Yield: 99%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.79 (p, ^{3}J = 7.5 Hz, 2H), 1.98 (p, ^{3}J = 7.4 Hz, 2H), 2.21 (t, ^{3}J = 7.4 Hz, 2H), 2.58 (t, ^{3}J = 7.7 Hz, 2H), 2.76 (t, ^{3}J = 7.3 Hz, 2H), 2.80 (t, ^{3}J = 7.4 Hz, 2H), 5.00 (s, 2H), 6.73 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.87 (d, ^{4}J = 2.0 Hz, 1H), 7.09 (d, ^{3}J = 8.2 Hz, 1H), 7.19 (d, ^{3}J = 8.0 Hz, 2H), 7.33 (d, ^{3}J = 8.0 Hz, 2H), 12.07 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.4, 26.3, 31.4, 32.6, 33.1, 34.1, 69.2, 110.7, 112.8, 124.7, 127.7, 128.4, 134.9, 135.6, 141.1, 145.1, 157.3, 174.3 ppm. ESI-MS: *m/z* 309.23 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 333.14612 for $C_{20}H_{22}O_3Na$, found 333.14596 ([M+Na]$^+$).

4-([5-Indanyl]carbamido)benzoic acid (**10**): *N*-(5-Indanyl)-4-formylbenzamide (**47**, 111 mg, 419 µmol, 1.0 eq) and 129 mg oxone® (419 µmol, 1.0 eq) were suspended in dry DMF under argon atmosphere and stirred for 3 hours at ambient temperature. Another equivalent of oxone® was added and the reaction stirred overnight. Ethyl acetate (30 mL) was then added and the mixture was washed once with 5% HCl and twice with water (30 mL). The organic layer was dried over sodium sulfate, the solvent was evaporated in vacuum and the product obtained by column chromatography in a gradient of hex/EA (3:1) + 2% to EA + 2% HOAc as a beige solid (35 mg) with a yield of 29%. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.02 (p, ^{3}J = 7.4 Hz, 2H), 2.77 – 2.91 (m, 4H), 7.19 (d, ^{3}J = 8.1 Hz, 1H), 7.48 (d, ^{3}J = 8.0 Hz, 1H), 7.68 (s, 1H), 8.02 (d, ^{3}J = 8.4 Hz, 2H), 8.06 (d, ^{3}J = 8.4 Hz, 2H), 10.29 (s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.2, 31.9, 32.5, 116.7, 118.6, 124.1, 127.8, 129.3, 133.6, 137.1, 138.7, 139.2, 144.1, 164.7, 166.9 ppm. ESI-MS: *m/z* 280.11 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 282.11247 for $C_{17}H_{16}NO_3$, found 282.11271 ([M+H]$^+$).

4-([{5-Indanyl}amino]methyl)benzoic acid (**11**): 4-Formylbenzoic acid (**45**, 112 mg, 743 µmol, 1.0 eq) and 5-aminoindane (**46**, 109 mg, 818 µmol, 1.1 eq) were dissolved in 1,2-dichloroethane (5 mL) and acetic acid (85 µL, 1.5 mmol, 2.0 eq) under argon atmosphere. The mixture was stirred for two hours at room temperature. Subsequently, 221 mg $NaBH(OAc)_3$ (1.04 mmol, 1.4 eq) were added. After 17 h, the

reaction was quenched with water, followed by 5% aqueous hydrochloric acid and the mixture was extracted three times with ethyl acetate (3x 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. Purification by column chromatography in hexane/EA (3:2) + 2% HOAc afforded the title compound as a pale brown solid (182 mg, 91%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.90 (p, ^3J = 7.4 Hz, 2H), 2.61 – 2.74 (m, 4H), 4.31 (s, 2H), 6.10 (br s, 1H), 6.33 (dd, ^3J = 8.1 Hz, ^4J = 2.1 Hz, 1H), 6.43 (d, ^4J = 1.2 Hz, 1H), 6.87 (d, ^3J = 8.1 Hz, 1H), 7.45 (d, ^3J = 8.3 Hz, 2H), 7.88 (d, ^3J = 8.3 Hz, 2H), 12.71 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.3, 31.4, 32.6, 46.6, 108.3, 110.8, 124.3, 127.1, 129.1, 129.4, 130.9, 144.3, 146.2, 147.2, 167.3 ppm. ESI-MS: *m/z* 266.19 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 268.13321 for $C_{17}H_{18}NO_2$, found 268.13236 ([M+H]$^+$).

4-([{5-Indanyl}{methyl}amino]methyl)benzoic acid (**12**): To a mixture of **10** (50 mg, 0.19 mmol, 1.0 eq) in 3 mL formic acid at 0 °C was carefully added a 37% aqueous solution of formaldehyde (3 mL). Then, the solution was heated to 100 °C for 90 minutes. Ethyl acetate (30 mL) was added to the cooled mixture and the mixture was washed three times with water (30 mL each). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The product was isolated by column chromatography in hex/EA (3:1) + 2% HOAc as a yellow solid (28 mg, 54%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.94 (p, ^3J = 7.4 Hz, 2H), 2.68 – 2.77 (m, 4H), 2.97 (s, 3H), 4.58 (s, 2H), 6.48 (dd, ^3J = 8.3 Hz, ^4J = 2.4 Hz, 1H), 6.60 (d, ^4J = 1.9 Hz, 1H), 6.98 (d, ^3J = 8.3 Hz, 1H), 7.30 (d, ^3J = 8.3 Hz, 2H), 7.87 (d, ^3J = 8.3 Hz, 2H), 12.85 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.3, 31.3, 32.8, 39.0, 55.7, 108.3, 110.6, 124.4, 126.9, 129.2, 129.5, 131.2, 144.6, 144.9, 148.0, 167.2 ppm. ESI-MS: *m/z* 280.16 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 282.14886 for $C_{18}H_{20}NO_2$, found 282.14831 ([M+H]$^+$).

4-([5-Indanyl]methoxy)benzoic acid (**13**): Preparation according to general procedure e using **58**. Yield: 96%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.01 (p, ^3J = 7.4 Hz, 2H), 2.78 – 2.91 (m, 4H), 5.12 (s, 2H), 7.08 (d, ^3J = 8.9 Hz, 2H), 7.19 (d, ^3J = 7.7 Hz, 1H), 7.23 (d, ^3J = 7.7 Hz, 1H), 7.30 (s, 1H), 7.88 (d, ^3J = 8.9 Hz, 2H), 12.63 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.1, 32.1, 32.1, 69.7, 114.6, 123.0, 124.0, 124.2, 126.0, 131.4, 134.3, 143.7, 144.1, 162.0, 167.0 ppm. ESI-MS: *m/z* 267.33 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 269.11722 for $C_{17}H_{17}O_3$, found 269.11721 ([M+H]$^+$).

4-(Phenoxymethyl)benzoic acid (**14**): Preparation according to general procedure e using **41d**. Yield: 93%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.19 (s, 2H), 6.95 (dd, ^3J = 7.3, 7.3 Hz, 1H), 7.01 (d, ^3J = 8.0 Hz, 2H), 7.30 (dd, ^3J = 8.4, 7.5 Hz, 2H), 7.56 (d, ^3J = 8.1 Hz, 2H), 7.96 (d, ^3J = 8.2 Hz, 2H), 12.93 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 68.5, 114.8, 120.9, 127.4, 129.5, 129.6, 130.2, 142.2, 158.1, 167.1 ppm. ESI-MS: *m/z* 227.06 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 229.08592 for $C_{14}H_{13}O_3$, found 229.08549 ([M+H]$^+$).

4-([4-Chlorophenoxy]methyl)benzoic acid (**15**): Preparation according to general procedure e using **41e**. Yield: 66%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.02 (s, 2H), 7.04 (d, ^3J = 9.0 Hz, 2H), 7.34 (d, ^3J = 8.9 Hz, 2H), 7.55 (d, ^3J = 8.2 Hz, 2H), 7.96 (d, ^3J = 8.2 Hz, 2H), 12.95 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 68.9, 116.6, 124.6, 127.4, 129.3, 129.5, 130.2, 141.8, 157.0, 167.1 ppm. ESI-MS: *m/z* 261.01 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 262.03912 for $C_{14}H_{11}ClO_3$, found 262.03899 ($M^{+\bullet}$).

4-([3-Chlorophenoxy]methyl)benzoic acid (**20**): Preparation according to general procedure e using **41f**. Yield: 98%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.23 (s, 2H), 6.98 – 7.03 (m, 2H), 7.12 (dd, ^4J = 2.2, 2.2 Hz, 1H), 7.32 (dd, ^3J = 8.2, 8.2 Hz, 1H), 7.56 (d, ^3J = 8.3 Hz, 2H), 7.97 (d, ^3J = 8.3 Hz, 2H), 12.98 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 68.9, 114.0, 114.9, 120.9, 127.4, 129.5, 130.3, 130.9, 133.8, 141.7, 159.1, 167.1 ppm. ESI-MS: *m/z* 261.10 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 262.04695 for $C_{14}H_{12}ClO_3$, found 263.04687 ([M+H]$^+$).

4-([2-Fluorophenoxy]methyl)benzoic acid (**22**): Preparation according to general procedure e using **41g**. Yield: 86%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.27 (s, 2H), 6.96 (dddd, ^3J = 7.9,

7.9 Hz, ^4J = 4.7, 1.5 Hz, 1H), 7.12 (dd, ^3J = 7.8, 7.8 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.57 (d, ^3J = 8.3 Hz, 2H), 7.97 (d, ^3J = 8.3 Hz, 2H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 69.5, 115.5 (d, $^3J_{C-F}$ = 1.3 Hz), 116.2 (d, $^2J_{C-F}$ = 17.8 Hz), 121.5 (d, $^3J_{C-F}$ = 6.9 Hz), 124.8 (d, $^4J_{C-F}$ = 3.8 Hz), 127.5, 129.6, 130.5, 141.6, 146.0 (d, $^2J_{C-F}$ = 10.4 Hz), 151.9 (d, $^1J_{C-F}$ = 243.5 Hz), 167.1 ppm. ESI-MS: *m/z* 245.01 ([M-H]$^-$). HRMS (ESI-): *m/z* calculated 245.0619 for $C_{14}H_{10}FO_3$, found 245.0618 ([M-H]$^-$).

4-([2-Methylphenoxy]methyl)benzoic acid (**23**): Preparation according to general procedure e using **41h**. Yield: 32%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.22 (s, 3H), 5.21 (s, 2H), 6.85 (dd, ^3J = 7.3, 7.3 Hz, 1H), 6.98 (d, ^3J = 8.1 Hz, 1H), 7.10 – 7.20 (m, 2H), 7.58 (d, ^3J = 8.1 Hz, 2H), 7.97 (d, ^3J = 8.1 Hz, 2H), 12.98 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 16.1, 68.4, 111.6, 120.5, 125.9, 126.9, 127.0, 129.4, 130.0, 130.5, 142.5, 156.0, 167.1 ppm. ESI-MS: *m/z* 241.29 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 242.09375 for $C_{15}H_{14}O_3$, found 242.09368 ($M^{+\bullet}$).

4-([2-{Trifluoromethyl}phenoxy]methyl)benzoic acid (**24**): Preparation according to general procedure e using **41i**. Yield: 88%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.37 (s, 2H), 7.12 (dd, ^3J = 7.5, 7.5 Hz, 1H), 7.33 (d, ^3J = 8.3 Hz, 1H), 7.56 (d, ^3J = 8.1 Hz, 2H), 7.60 – 7.70 (m, 2H), 7.98 (d, ^3J = 8.1 Hz, 2H), 12.97 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 69.1, 114.0, 117.3 (q, $^2J_{C-F}$ = 30.0 Hz), 120.7, 123.9 (q, $^1J_{C-F}$ = 272.2 Hz), 126.9 (q, $^3J_{C-F}$ = 5.2 Hz), 127.0, 129.6, 130.3, 134.3, 141.5, 155.8, 167.1 ppm. ESI-MS: *m/z* 295.22 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 319.05525 for $C_{15}H_{11}F_3O_3Na$, found 319.05404 ([M+Na]$^+$).

4-([2-Methoxyphenoxy]methyl)benzoic acid (**25**): Preparation according to general procedure e using **41j**. Yield: 80%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.77 (s, 3H), 5.16 (s, 2H), 6.86 (ddd, ^3J = 7.7, 7.7 Hz, ^4J = 1.6 Hz,1H), 6.91 (ddd, ^3J = 7.7, 7.7 Hz, ^4J = 1.6 Hz, 1H), 6.97 – 7.04 (m, 2H), 7.55 (d, ^3J = 8.3 Hz, 2H), 7.96 (d, ^3J = 8.3 Hz, 2H), 12.94 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 55.6, 69.3, 112.3, 114.0, 120.7, 121.5, 127.4, 129.5, 130.2, 142.4, 147.6, 149.3, 167.2 ppm. ESI-MS: *m/z* 257.27 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 258.08866 for $C_{15}H_{14}O_4$, found 258.08806 ($M^{+\bullet}$).

4-([2-{Trifluoromethoxy}phenoxy]methyl)benzoic acid (**26**): Preparation according to general procedure e using **41k**. Yield: 98%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.31 (s, 2H), 7.04 (dd, ^3J = 7.7, 7.7 Hz, 1H), 7.29 (d, ^3J = 8.2 Hz, 1H), 7.32 – 7.42 (m, 2H), 7.55 (d, ^3J = 8.1 Hz, 2H), 7.98 (d, ^3J = 8.2 Hz, 2H), 12.99 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 69.3, 115.0, 120.3 (q, $^1J_{C-F}$ = 256.4 Hz), 121.3, 123.2, 127.2, 128.8, 129.6, 130.3, 137.1 (q, $^3J_{C-F}$ = 1.5 Hz), 141.5, 150.4, 167.1 ppm. ESI-MS: *m/z* 311.21 ([M-H]$^-$). HRMS (ESI-): *m/z* calculated 311.0537 for $C_{15}H_{10}F_3O_4$, found 311.0544 ([M-H]$^-$).

4-([2-tert-Butylphenoxy]methyl)benzoic acid (**27**): Preparation according to general procedure e using **41l**. Yield: 31%. Pale yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.35 (s, 9H), 5.23 (s, 2H), 6.89 (ddd, ^3J = 7.7, 7.7 Hz, ^4J = 0.9 Hz, 1H), 7.04 (d, ^3J = 7.5 Hz, 1H), 7.17 (dd, ^3J = 7.7, 7.7 Hz, 1H), 7.25 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H), 7.60 (d, ^3J = 8.2 Hz, 2H), 7.99 (d, ^3J = 8.2 Hz, 2H), 12.96 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 29.7, 34.5, 69.0, 112.9, 120.6, 126.4, 127.2, 127.4, 129.6, 130.1, 137.3, 142.4, 156.9, 167.1 ppm. ESI-MS: *m/z* 283.32 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 284.14070 for $C_{18}H_{20}O_3$, found 284.14164 ($M^{+\bullet}$).

4-([{(1,1'-Biphenyl)-2-yl}oxy]methyl)benzoic acid (**28**): Preparation according to general procedure e using **41m**. Yield: 80%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.22 (s, 2H), 7.06 (ddd, ^3J = 7.5, 7.5 Hz, ^4J = 0.8 Hz, 1H), 7.17 (d, ^3J = 8.1 Hz, 1H), 7.29 – 7.36 (m, 3H), 7.42 (dd, ^3J = 7.6, 7.6 Hz, 2H), 7.47 (d, ^3J = 8.3 Hz, 2H), 7.51 – 7.59 (m, 2H), 7.92 (d, ^3J = 8.3 Hz, 2H), 12.93 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 69.1, 113.2, 121.3, 127.0, 127.0, 128.0, 128.9, 129.4, 129.4, 130.0, 130.3, 130.6, 138.1, 142.3, 154.9, 167.1 ppm. ESI-MS: *m/z* 303.25 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 327.09917 for $C_{20}H_{16}O_3Na$, found 327.09959 ([M+Na]$^+$).

4-([{1,1'-Biphenyl}-2-yl]methoxy)benzoic acid (**30**): Preparation according to general procedure e using **61**. Yield: 92%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.01 (s, 2H), 6.96 (d, ^3J = 8.8 Hz,

2H), 7.32 – 7.50 (m, 8H), 7.61 (d, ^{3}J = 7.0 Hz, 1H), 7.85 (d, ^{3}J = 8.8 Hz, 2H), 12.60 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 67.9, 114.4, 123.2, 127.4, 127.7, 128.3, 128.6, 128.9, 129.9, 130.0, 131.3, 133.3, 139.9, 141.8, 161.7, 167.0 ppm. ESI-MS: *m/z* 303.12 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 305.11722 for $C_{20}H_{17}O_3$, found 305.11627 ([M+H]$^+$).

4-([2,4-Di-tert-butyl]phenoxymethyl)benzoic acid (**31**): Preparation according to general procedure e using **41n**. Yield: 99%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.26 (s, 9H), 1.37 (s, 9H), 5.20 (s, 2H), 6.95 (d, ^{3}J = 8.6 Hz, 1H), 7.16 (dd, ^{3}J = 8.5 Hz, ^{4}J = 2.4 Hz, 1H), 7.26 (d, ^{4}J = 2.4 Hz, 1H), 7.60 (d, ^{3}J = 8.2 Hz, 2H), 7.99 (d, ^{3}J = 8.2 Hz, 2H), 12.97 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 29.8, 31.4, 33.9, 34.6, 69.1, 112.5, 123.1, 123.5, 127.3, 129.6, 130.1, 136.4, 142.3, 142.6, 154.6, 167.1 ppm. ESI-MS: *m/z* 339.32 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 340.20330 for $C_{22}H_{28}O_3$, found 340.20294 ($M^{+\bullet}$).

4-([{6-Phenyl-5-indanyl}oxy]methyl)benzoic acid (**32**): Preparation according to general procedure e using **41o**. Yield: 90%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.03 (p, ^{3}J = 7.4 Hz, 2H), 2.83 (t, ^{3}J = 7.4 Hz, 2H), 2.87 (t, ^{3}J = 7.4 Hz, 2H), 5.16 (s, 2H), 7.06 (s, 1H), 7.15 (s, 1H), 7.26 – 7.33 (m, 1H), 7.39 (t, ^{3}J = 7.6 Hz, 2H), 7.44 (d, ^{3}J = 8.2 Hz, 2H), 7.48 – 7.53 (m, 2H), 7.90 (d, ^{3}J = 8.3 Hz, 2H), 12.92 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 25.4, 31.6, 32.7, 69.3, 109.6, 126.1, 126.6, 126.9, 127.9, 128.4, 129.3, 129.4, 130.0, 136.2, 138.7, 142.5, 144.4, 153.8, 167.1 ppm. ESI-MS: *m/z* 343.11 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 344.14070 for $C_{23}H_{20}O_3$, found 344.14070 ($M^{+\bullet}$).

4-([{(5-tert-Butyl-1,1'-biphenyl)-2-yl}oxy]methyl)benzoic acid (**33**): Preparation according to general procedure e using **41p**. Yield: 77%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.29 (s, 9H), 5.18 (s, 2H), 7.07 (d, ^{3}J = 8.6 Hz, 1H), 7.29 (d, ^{4}J = 2.5 Hz, 1H), 7.30 – 7.35 (m, 2H), 7.42 (dd, ^{3}J = 7.6, 7.6 Hz, 2H), 7.46 (d, ^{3}J = 8.3 Hz, 2H), 7.52 – 7.57 (m, 2H), 7.91 (d, ^{3}J = 8.3 Hz, 2H), 12.91 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 31.3, 33.9, 69.2, 112.9, 125.4, 126.8, 126.9, 127.5, 128.0, 129.4, 129.4, 129.6, 130.0, 138.5, 142.5, 143.4, 152.7, 167.1 ppm. ESI-MS: *m/z* 359.15 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 383.16177 for $C_{24}H_{24}O_3Na$, found 383.16135 ([M+Na]$^+$).

4-([{(5-Methyl-1,1'-biphenyl)-2-yl}oxy]methyl)benzoic acid (**34**): Preparation according to general procedure e using **41q**. Yield: 72%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.28 (s, 3H), 5.16 (s, 2H), 7.04 (d, ^{3}J = 8.2 Hz, 1H), 7.08 – 7.17 (m, 2H), 7.31 (dd, ^{3}J = 7.4, 7.4 Hz, 1H), 7.41 (dd, ^{3}J = 7.6, 7.6 Hz, 2H), 7.44 (d, ^{3}J = 8.2 Hz, 2H), 7.50 – 7.56 (m, 2H), 7.91 (d, ^{3}J = 8.2 Hz, 2H), 12.80 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 20.1, 69.2, 113.4, 126.9, 126.9, 128.0, 129.0, 129.3, 129.4, 130.0, 130.1, 130.1, 131.2, 138.2, 142.4, 152.8, 167.1 ppm. ESI-MS: *m/z* 317.21 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 319.13287 for $C_{21}H_{19}O_3$, found 319.13197 ([M+H]$^+$).

4-([{2,4-Bis(trifluoromethyl)}phenoxy]methyl)benzoic acid (**35**): Preparation according to general procedure e using **41r**. Yield: 99%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 5.48 (s, 2H), 7.50 - 7.59 (m, 3H), 7.94 (d, ^{4}J = 1.4 Hz, 1H), 7.99 (d, ^{3}J = 8.3 Hz, 2H), 8.05 (dd, ^{3}J = 8.9 Hz, ^{4}J = 1.8 Hz, 1H), 12.96 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 69.8, 115.0, 117.9 (q, $^{2}J_{C\text{-}F}$ = 31.3 Hz), 121.2 (q, $^{2}J_{C\text{-}F}$ = 33.2 Hz), 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.7 Hz), 123.7 (q, $^{1}J_{C\text{-}F}$ = 271.4 Hz), 124.2 (m), 127.1, 129.6, 130.5, 131.8 (d, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 140.7, 158.7, 167.0 ppm. ESI-MS: *m/z* 363.02 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 365.06069 for $C_{16}H_{11}F_6O_3$, found 365.06118 ([M+H]$^+$).

4-([{4-tert-Butyl-2-chloro}phenoxy]methyl)benzoic acid (**36**): Preparation according to general procedure e using **41s**. Yield: 89%. White solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.24 (s, 9H), 5.27 (s, 2H), 7.11 (d, ^{3}J = 8.7 Hz, 1H), 7.28 (dd, ^{3}J = 8.7 Hz, ^{4}J = 2.4 Hz, 1H), 7.41 (d, ^{4}J = 2.4 Hz, 1H), 7.57 (d, ^{3}J = 8.3 Hz, 2H), 7.97 (d, ^{3}J = 8.3 Hz, 2H), 12.95 (br s, 1H) ppm. ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 31.1, 34.0, 69.4, 114.0, 121.1, 124.9, 126.9, 127.1, 129.5, 130.3, 141.9, 144.6, 151.1, 167.1 ppm. ESI-MS: *m/z* 317.09 ([M-H]$^-$). HRMS (MALDI): *m/z* calculated 318.10172 for $C_{18}H_{19}ClO_3$, found 318.10206 ($M^{+\bullet}$).

Ethyl 2-methylbenzoate (**38a**): Preparation according to general procedure a using 2-methylbenzoic acid (**37a**). Yield: 77%. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, ^{3}J = 7.1 Hz, 3H), 2.60 (s, 3H), 4.36 (q, ^{3}J = 7.1 Hz, 2H), 7.18 – 7.31 (m, 2H), 7.39 (ddd, ^{3}J = 7.5, 7.5 Hz, ^{4}J = 1.4 Hz, 1H), 7.85 - 7.96 (m, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 21.8, 60.8, 125.8, 130.1, 130.6, 131.8, 131.9, 140.1, 167.9 ppm.

Ethyl 4-methylphenylacetate (**38b**): Preparation according to general procedure a using 4-methyl-phenylacetic acid (**37b**). Yield: 99%. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, ^{3}J = 7.1 Hz, 3H), 2.33 (s, 3H), 3.57 (s, 2H), 4.14 (q, ^{3}J = 7.1 Hz, 2H), 7.13 (d, ^{3}J = 8.0 Hz, 2H), 7.18 (d, ^{3}J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3, 21.2, 41.2, 60.9, 129.2, 129.4, 131.2, 136.8, 172.0 ppm.

Ethyl 3-(4-methylphenyl)propanoate (**38c**): Preparation according to general procedure a using 3-(4-methylphenyl)propanoic acid (**37c**). Yield: 90%. Pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^{3}J = 7.1 Hz, 3H), 2.32 (s, 3H), 2.60 (t, ^{3}J = 7.9 Hz, 2H), 2.91 (t, ^{3}J = 7.8 Hz, 2H), 4.13 (q, ^{3}J = 7.1 Hz, 2H), 7.10 (s, 4H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 21.1, 30.7, 36.2, 60.5, 128.3, 129.3, 135.8, 137.7, 173.1 ppm.

Ethyl 4-methylbenzoate (**38d**): Preparation according to general procedure a using 4-methylbenzoic acid (**37d**). Yield: 90%. Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, ^{3}J = 7.1 Hz, 3H), 2.40 (s, 3H), 4.36 (q, ^{3}J = 7.1 Hz, 2H), 7.23 (d, ^{3}J = 8.1 Hz, 2H), 7.94 (d, ^{3}J = 8.2 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.6, 21.9, 61.0, 128.0, 129.3, 129.8, 143.6, 167.0 ppm.

Ethyl 2-(bromomethyl)benzoate (**39a**): Preparation according to general procedure b using **38a**. Yield: 73%. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, ^{3}J = 7.1 Hz, 3H), 4.41 (q, ^{3}J = 7.1 Hz, 2H), 4.96 (s, 2H), 7.37 (dd, ^{3}J = 7.3, 7.3 Hz, 1H), 7.42 – 7.54 (m, 2H), 7.97 (d, ^{3}J = 7.8 Hz, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 31.7, 61.5, 128.6, 129.7, 131.4, 131.8, 132.5, 139.2, 166.8 ppm.

Ethyl 4-(bromomethyl)phenylacetate (**39b**): Preparation according to general procedure b using **38b**. Yield: 57%. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, ^{3}J = 7.1 Hz, 3H), 3.60 (s, 2H), 4.15 (q, ^{3}J = 7.1 Hz, 2H), 4.48 (s, 2H), 7.26 (d, ^{3}J = 8.1 Hz, 2H), 7.35 (d, ^{3}J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3, 33.3, 41.2, 61.1, 129.4, 129.8, 134.6, 136.7, 171.4 ppm.

Ethyl 3-([4-bromomethyl]phenyl)propanoate (**39c**): Preparation according to general procedure b using **38c**. Yield: 15%. Pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, ^{3}J = 7.1 Hz, 3H), 2.61 (t, ^{3}J = 7.8 Hz, 2H), 2.94 (t, ^{3}J = 7.8 Hz, 2H), 4.13 (q, ^{3}J = 7.1 Hz, 2H), 4.48 (s, 2H), 7.18 (d, ^{3}J = 8.1 Hz, 2H), 7.32 (d, ^{3}J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3, 30.8, 33.6, 35.8, 60.6, 128.9, 129.3, 135.9, 141.2, 172.9 ppm.

Ethyl 4-(bromomethyl)benzoate (**39d**): Preparation according to general procedure b using **38d**. Yield: 86%. Brown solid. Used for following reactions without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 4.49 (s, 2H), 7.45 (d, ^{3}J = 8.2 Hz, 2H), 8.01 (d, ^{3}J = 8.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 32.4, 61.2, 129.1, 130.2, 130.6, 142.6, 166.2 ppm.

6-Phenyl-5-indanol (**40o**): Preparation according to general procedure d using **42o**. Yield: 40%. Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.10 (p, ^{3}J = 7.4 Hz, 2H), 2.84 – 2.96 (m, 4H), 5.05 (s, 1H), 6.87 (s, 1H), 7.09 (s, 1H), 7.33 – 7.56 (m, 5H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.0, 32.2, 33.1, 111.8, 125.7, 127.7, 129.3, 129.4, 129.8, 136.5, 137.9, 145.8, 151.2 ppm.

4-tert-Butyl-2-phenylphenol (**40p**): Preparation according to general procedure d using 2-bromo-4-*tert*-butylphenol (**42p**). Yield: 64%. Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 5.06 (s, 1H), 6.93 (dd, ^{3}J = 8.4 Hz, ^{4}J = 0.4 Hz, 1H), 7.25 (d, ^{4}J = 2.5 Hz, 1H), 7.29 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.5 Hz, 1H), 7.37 – 7.45 (m, 1H), 7.47 – 7.52 (m, 4H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 31.7, 34.3, 115.4, 126.2, 127.3, 127.6, 127.9, 129.3, 129.4, 137.8, 143.7, 150.2 ppm.

4-Methyl-2-phenylphenol (**40q**): Preparation according to general procedure d using 2-bromo-4-methylphenol (**42q**). Yield: 63%. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 5.03 (br s, 1H), 6.87 – 6.92 (m, 1H), 7.05 – 7.10 (m, 2H), 7.36 – 7.44 (m, 1H), 7.45 – 7.52 (m, 4H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.6, 115.8, 127.9, 128.0, 129.2, 129.3, 129.7, 130.1, 130.8, 137.4, 150.3 ppm.

Ethyl 2-([{5-indanyl}oxy]methyl)benzoate (**41a**): Preparation according to general procedure c using **39a** and 5-indanol (**44**). Yield: 67%. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, ^{3}J = 7.1 Hz, 3H), 2.07 (p, ^{3}J = 7.4 Hz, 2H), 2.78 – 2.93 (m, 4H), 4.37 (q, ^{3}J = 7.1 Hz, 2H), 5.47 (s, 2H), 6.78 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.88 (d, ^{4}J = 1.9 Hz, 1H), 7.11 (d, ^{3}J = 8.2 Hz, 1H), 7.37 (dd, ^{3}J = 7.6, 7.6 Hz, 1H), 7.54 (ddd, ^{3}J = 7.7, 7.7 Hz, ^{4}J = 1.3 Hz, 1H), 7.77 (d, ^{3}J = 7.8 Hz, 1H), 8.03 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.2 Hz, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 26.0, 32.1, 33.3, 61.2, 68.5, 111.0, 113.0, 124.9, 127.2, 127.5, 128.1, 130.8, 132.6, 136.6, 140.1, 145.9, 157.8, 167.2 ppm.

Ethyl 4-([{5-indanyl}oxy]methyl)phenylacetate (**41b**): Preparation according to general procedure c using **39b** and 5-indanol (**44**) with caesium carbonate as a base instead of potassium carbonate. Yield: 34%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, ^{3}J = 7.1 Hz, 3H), 2.09 (p, ^{3}J = 7.4 Hz, 2H), 2.78 – 2.97 (m, 4H), 3.64 (s, 2H), 4.18 (q, ^{3}J = 7.1 Hz, 2H), 5.04 (s, 2H), 6.78 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.89 (d, ^{4}J = 1.8 Hz, 1H), 7.14 (d, ^{3}J = 8.2 Hz, 1H), 7.32 (d, ^{3}J = 8.1 Hz, 2H), 7.42 (d, ^{3}J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3, 25.9, 32.1, 33.3, 41.3, 61.0, 70.0, 111.0, 112.9, 124.8, 127.8, 129.5, 133.8, 136.4, 136.6, 145.8, 157.8, 171.6 ppm.

Ethyl 3-([4-{(5-indanyl)oxy}methyl]phenyl)propanoate (**41c**): Preparation according to general procedure c using **39c** and 5-indanol (**44**). Yield: 68%. Pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^{3}J = 7.1 Hz, 3H), 2.07 (p, ^{3}J = 7.4 Hz, 2H), 2.62 (t, ^{3}J = 7.8 Hz, 2H), 2.79 – 2.90 (m, 4H), 2.96 (t, ^{3}J = 7.8 Hz, 2H), 4.13 (q, ^{3}J = 7.1 Hz, 2H), 5.00 (s, 2H), 6.76 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.4 Hz, 1H), 6.86 (d, ^{4}J = 1.9 Hz, 1H), 7.11 (d, ^{3}J = 8.2 Hz, 1H), 7.22 (d, ^{3}J = 8.1 Hz, 2H), 7.35 (d, ^{3}J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 26.0, 30.8, 32.1, 33.3, 36.0, 60.6, 70.2, 111.1, 113.0, 124.9, 127.9, 128.6, 135.5, 136.6, 140.4, 145.9, 157.9, 173.0 ppm

Ethyl 4-(phenoxymethyl)benzoate (**41d**): Preparation according to general procedure c using **39d** and phenol (**40d**). Yield: 74%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.13 (s, 2H), 6.92 – 7.02 (m, 3H), 7.26 – 7.35 (m, 2H), 7.46 – 7.55 (m, 2H), 8.01 – 8.12 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 61.1, 69.3, 115.0, 121.3, 127.0, 129.6, 129.9, 130.1, 142.3, 158.6, 166.5 ppm.

Ethyl 4-([4-chlorophenoxy]methyl)benzoate (**41e**): Preparation according to general procedure c using **39d** and 4-chlorophenol (**40e**). Yield: 69%. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.09 (s, 2H), 6.84 – 6.94 (m, 2H), 7.20 – 7.26 (m, 2H), 7.48 (d, ^{3}J = 8.3 Hz, 2H), 8.06 (d, ^{3}J = 8.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 61.2, 69.8, 116.3, 126.3, 127.0, 129.6, 130.0, 130.3, 141.8, 157.2, 166.4 ppm.

Ethyl 4-([3-chlorophenoxy]methyl)benzoate (**41f**): Preparation according to general procedure c using **39d** and 3-chlorophenol (**40f**). Yield: 80%. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.39 (q, ^{3}J = 7.1 Hz, 2H), 5.11 (s, 2H), 6.82 – 6.88 (m, 1H), 6.93 – 7.00 (m, 2H), 7.20 (dd, ^{3}J = 8.1, 8.1 Hz, 1H), 7.48 (d, ^{3}J = 8.3 Hz, 2H), 8.07 (d, ^{3}J = 8.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 61.2, 69.7, 113.4, 115.5, 121.6, 127.1, 130.1, 130.4, 130.5, 135.1, 141.6, 159.3, 166.4 ppm.

Ethyl 4-([2-fluorophenoxy]methyl)benzoate (**41g**): Preparation according to general procedure c using **39d** and 2-fluorophenol (**40g**). Yield: 78%. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.20 (s, 2H), 6.88 – 7.05 (m, 3H), 7.10 (ddd, ^{3}J = 11.4 Hz, 8.0 Hz, ^{4}J = 1.6 Hz, 1H), 7.51 (d, ^{3}J = 8.4 Hz, 2H), 8.06 (d, ^{3}J = 8.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 61.1, 70.9, 116.0 (d, $^{3}J_{C\text{-}F}$ = 1.7 Hz), 116.6 (d, $^{2}J_{C\text{-}F}$ = 18.2 Hz), 122.0 (d,

$^{3}J_{C-F}$ = 6.9 Hz), 124.4 (d, $^{4}J_{C-F}$ = 4.0 Hz), 127.1, 130.0, 130.3, 141.8, 146.6 (d, $^{2}J_{C-F}$ = 10.6 Hz), 153.1 (d, $^{1}J_{C-F}$ = 246.0 Hz), 166.5 ppm.

Ethyl 4-([2-methylphenoxy]methyl)benzoate (**41h**): Preparation according to general procedure c using **39d** and 2-methylphenol (**40h**). Yield: 83%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 2.31 (s, 3H), 4.39 (q, ^{3}J = 7.1 Hz, 2H), 5.15 (s, 2H), 6.80 – 6.96 (m, 2H), 7.10 – 7.22 (m, 2H), 7.52 (d, ^{3}J = 8.6 Hz, 2H), 8.07 (d, ^{3}J = 8.4 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 16.5, 61.1, 69.4, 111.5, 121.0, 126.8, 126.9, 127.2, 129.9, 130.0, 131.0, 142.7, 156.7, 166.5 ppm.

Ethyl 4-([2-{trifluoromethyl}phenoxy]methyl)benzoate (**41i**): Preparation according to general procedure c using **39d** and 2-(trifluoromethyl)phenol (**40i**). Yield: 61%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.24 (s, 2H), 6.95 – 7.11 (m, 2H), 7.42 - 7.50 (m, 1H), 7.52 (d, ^{3}J = 8.6 Hz, 2H), 7.61 (dd, ^{3}J = 7.1 Hz, ^{4}J = 0.8 Hz, 1H), 8.07 (d, ^{3}J = 8.4 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 61.1, 69.8, 113.3, 119.4 (q, $^{2}J_{C-F}$ = 30.9 Hz), 120.7, 123.8 (q, $^{1}J_{C-F}$ = 272.4 Hz), 126.6, 127.4 (q, $^{3}J_{C-F}$ = 5.3 Hz), 130.0, 130.3, 133.4 (q, $^{4}J_{C-F}$ = 1.0 Hz), 141.4, 156.3 (q, $^{3}J_{C-F}$ = 1.8 Hz), 166.5 ppm.

Ethyl 4-([2-methoxyphenoxy]methyl)benzoate (**41j**): Preparation according to general procedure c using **39d** and 2-methoxyphenol (**40j**). Yield: 65%. Beige solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, ^{3}J = 7.1 Hz, 3H), 3.90 (s, 3H), 4.37 (q, ^{3}J = 7.1 Hz, 2H), 5.21 (s, 2H), 6.80 – 6.89 (m, 2H), 6.90 – 6.98 (m, 2H), 7.51 (dd, ^{3}J = 8.0 Hz, ^{4}J = 0.6 Hz, 2H), 8.04 (d, ^{3}J = 8.5 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 56.1, 61.1, 70.7, 112.2, 114.5, 120.9, 122.0, 126.9, 130.0, 130.1, 142.6, 148.0, 149.9, 166.5 ppm.

Ethyl 4-([2-{trifluoromethoxy}phenoxy]methyl)benzoate (**41k**): Preparation according to general procedure c using **39d** and 2-(trifluoromethoxy)phenol (**40k**). Yield: 73%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.20 (s, 2H), 6.93 – 7.01 (m, 2H), 7.17 – 7.31 (m, 2H), 7.46 – 7.55 (m, 2H), 8.04 – 8.12 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 61.2, 70.3, 114.7, 120.9 (q, $^{1}J_{C-F}$ = 257.3 Hz), 121.5, 123.5 (q, $^{4}J_{C-F}$ = 0.8 Hz), 126.8, 128.0, 130.0, 130.3, 138.6 (q, $^{3}J_{C-F}$ = 1.7 Hz), 141.6, 151.0, 166.5 ppm.

Ethyl 4-([2-tert-butylphenoxy]methyl)benzoate (**41l**): Preparation according to general procedure c using **39d** and 2-*tert*-butylphenol (**40l**). Yield: 72%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.37 – 1.44 (m, 12H), 4.40 (q, ^{3}J = 7.1 Hz, 2H), 5.18 (s, 2H), 6.87 – 6.97 (m, 2H), 7.17 (ddd, ^{3}J = 8.0, 7.4 Hz, ^{4}J = 1.7 Hz, 1H), 7.33 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, 1H), 7.51 – 7.57 (m, 2H), 8.06 – 8.12 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 30.0, 35.0, 61.1, 69.7, 112.6, 121.0, 127.0, 127.1, 127.2, 130.0, 130.1, 138.5, 142.6, 157.4, 166.5 ppm.

Ethyl 4-([{(1,1'-biphenyl)-2-yl}oxy]methyl)benzoate (**41m**): Preparation according to general procedure c using **39d** and 2-phenylphenol (**40m**). Yield: 94%. Pale yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.13 (s, 2H), 6.96 – 7.04 (m, 1H), 7.08 (ddd, ^{3}J = 7.5, 7.5 Hz, ^{4}J = 1.1 Hz, 1H), 7.22 – 7.47 (m, 5H), 7.47 – 7.52 (m, 2H), 7.55 – 7.63 (m, 2H), 8.01 (dd, ^{3}J = 8.4 Hz, ^{4}J = 1.7, 1.7 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 61.1, 70.0, 113.4, 121.8, 126.6, 127.2, 128.1, 128.7, 129.2, 129.4, 129.8, 129.8, 131.2, 138.5, 142.5, 155.4, 166.5 ppm.

Ethyl 4-([{2,4-di-tert-butyl}phenoxy]methyl)benzoate (**41n**): Preparation according to general procedure c using **39d** and 2,4-di-*tert*-butylphenol (**40n**). Yield: 51%. Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 1.43 (t, ^{3}J = 7.1 Hz, 3H), 1.46 (s, 9H), 4.42 (q, ^{3}J = 7.1 Hz, 2H), 5.18 (s, 2H), 6.86 (d, ^{3}J = 8.5 Hz, 1H), 7.20 (dd, ^{3}J = 8.5 Hz, ^{4}J = 2.5 Hz, 1H), 7.41 (d, ^{4}J = 2.5 Hz, 1H), 7.53 – 7.62 (m, 2H), 8.08 – 8.16 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 30.1, 31.7, 34.4, 35.2, 61.1, 69.7, 111.9, 123.5, 124.2, 127.0, 130.0, 130.0, 137.6, 142.9, 143.2, 155.2, 166.5 ppm.

Ethyl 4-([{6-phenyl-5-indanyl}oxy]methyl)benzoate (**41o**): Preparation according to general procedure c using **39d** and 6-phenyl-5-indanol (**40o**). Yield: 64%. Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.31 (t, ^{3}J = 7.1 Hz, 3H), 2.03 (p, ^{3}J = 7.5 Hz, 2H), 2.77 – 2.90 (m, 4H), 4.29 (q, ^{3}J = 7.1 Hz, 2H), 4.99 (s, 2H), 6.82 (s, 1H), 7.14 (s, 1H), 7.22 – 7.37 (m, 5H), 7.44 – 7.53 (m, 2H), 7.87 – 7.95 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 25.8, 32.3, 33.3, 61.0, 70.4, 110.0, 126.5, 126.7, 126.8, 128.0, 129.7, 129.7, 129.7, 129.8, 137.2, 139.1, 142.7, 144.9, 154.3, 166.5 ppm.

Ethyl 4-([{(5-tert-butyl-1,1'-biphenyl)-2-yl}oxy]methyl)benzoate (**41p**): Preparation according to general procedure c using **39d** and 4-*tert*-butyl-2-phenylphenol (**40p**). Yield: 58%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 9H), 1.42 (t, ^{3}J = 7.1 Hz, 3H), 4.40 (q, ^{3}J = 7.1 Hz, 2H), 5.13 (s, 2H), 6.96 (d, ^{3}J = 8.6 Hz, 1H), 7.30 – 7.51 (m, 7H), 7.63 (ddd, ^{3}J = 8.2 Hz, ^{4}J = 1.8, 1.8 Hz, 2H), 8.03 (d, ^{3}J = 8.4 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): (75 MHz, $CDCl_3$): δ = 14.4, 31.6, 34.3, 61.0, 70.1, 113.0, 125.4, 126.6, 127.0, 128.1, 128.4, 129.8, 129.8, 129.8, 130.9, 139.0, 142.7, 144.4, 153.2, 166.5 ppm.

Ethyl 4-([{(5-methyl-1,1'-biphenyl)-2-yl}oxy]methyl)benzoate (**41q**): Preparation according to general procedure c using **39d** and 4-methyl-2-phenylphenol (**40q**). Yield: 28%. Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, ^{3}J = 7.1 Hz, 3H), 2.35 (s, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.09 (s, 2H), 6.90 (d, ^{3}J = 8.3 Hz, 1H), 7.09 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1.8 Hz, 1H), 7.19 (d, ^{4}J = 1.9 Hz, 1H), 7.31 – 7.40 (m, 3H), 7.39 – 7.46 (m, 2H), 7.58 (d, ^{3}J = 7.1 Hz, 2H), 8.00 (d, ^{3}J = 8.3 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.5, 20.7, 61.1, 70.3, 113.7, 126.6, 127.1, 128.1, 129.0, 129.7, 129.8, 129.8, 131.1, 131.5, 131.9, 138.6, 142.7, 153.4, 166.5 ppm.

Ethyl 4-([{2,4-bis(trifluoromethyl)}phenoxy]methyl)benzoate (**41r**): Preparation according to general procedure c using **39d** and 2,4-bis(trifluoromethyl)phenol (**40r**). Yield: 78%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.30 (s, 2H), 7.09 (d, ^{3}J = 8.7 Hz, 1H), 7.44 – 7.55 (m, 2H), 7.73 (dd, ^{3}J = 8.7 Hz, ^{4}J = 2.2 Hz, 1H), 7.87 (d, ^{4}J = 1.4 Hz, 1H), 8.04 – 8.12 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 61.2, 70.1, 113.3, 119.9 (q, $^{2}J_{C\text{-}F}$ = 32.0 Hz), 123.0 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz), 123.2 (q, $^{2}J_{C\text{-}F}$ = 33.8 Hz), 123.7 (q, $^{1}J_{C\text{-}F}$ = 271.6 Hz), 125.1 (m), 126.6, 130.2, 130.6, 130.8 (q, $^{3}J_{C\text{-}F}$ = 2.9 Hz), 140.3, 158.7, 166.3 ppm.

Ethyl 4-([{4-tert-butyl-2-chloro}phenoxy]methyl)benzoate (**41s**): Preparation according to general procedure c using **39d** and 4-*tert*-butyl-2-chlorophenol (**40s**) with acetonitrile as solvent instead of dimethylformamide. Yield: 76%. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 1.40 (t, ^{3}J = 7.1 Hz, 3H), 4.38 (q, ^{3}J = 7.1 Hz, 2H), 5.19 (s, 2H), 6.85 (d, ^{3}J = 8.6 Hz, 1H), 7.17 (dd, ^{3}J = 8.6 Hz, ^{4}J = 2.3 Hz, 1H), 7.40 (d, ^{4}J = 2.3 Hz, 1H), 7.54 (d, ^{3}J = 8.0 Hz, 2H), 8.07 (d, ^{3}J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.5, 31.5, 34.4, 61.1, 70.5, 113.9, 122.9, 124.6, 126.8, 127.8, 130.0, 130.2, 142.0, 145.5, 151.7, 166.5 ppm.

6-Bromo-5-indanol (**42o**): 5-Indanol (**44**) (271 mg, 2.02 mmol, 1.0 eq) was dissolved in 5 mL dry DMF. A solution of NBS (360 mg, 2.02 mmol, 1.0 eq) in 3 mL dry DMF was added slowly and the resulting mixture was stirred for four hours at room temperature. Ethyl acetate (30 mL) was added and the mixture washed once with 5% $Na_2S_2O_3$ solution (30 mL) and twice with water (30 mL each). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. Column chromatography in hex/EA (19:1) afforded the pure product as a brown liquid (344 mg, 80%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.98 – 2.16 (m, 2H), 2.83 (t, ^{3}J = 7.4 Hz, 4H), 5.33 (s, 1H), 6.89 (s, 1H), 7.28 (s, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.1, 32.1, 32.9, 107.6, 112.0, 127.2, 137.9, 146.0, 150.6 ppm.

N-(5-Indanyl)-4-formylbenzamide (**47**): 4-Formylbenzoic acid (**45**, 166 mg, 1.10 mmol, 1.1 eq), EDC hydrochloride (250 mg, 1.30 mmol, 1.3 eq), and DMAP (25 mg, 201 µmol, 0.2 eq) were suspended in 7 mL dry CH_2Cl_2. A solution of 5-aminoindane (**46**, 134 mg, 1.00 mmol, 1.0 eq) in 3 mL dry CH_2Cl_2 was added and the mixture heated to reflux for 30 minutes. After cooling, diluted HCl was added and the product extracted three times with CH_2Cl_2. The combined organic layers were then dried over Na_2SO_4, the solvent evaporated and the crude product purified by column chromatography in a gradient of hex/EA (3:1 to 3:2) to afford the product as a pale yellow solid (168 mg, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.10 (p, ^{3}J = 7.5 Hz, 2H), 2.79 – 3.02 (m, 4H), 7.21 (d, ^{3}J = 8.0 Hz, 1H), 7.30 (d, ^{3}J = 7.7 Hz,

1H), 7.59 (s, 1H), 7.89 (s, 1H), 7.94 – 8.06 (m, 4H), 10.09 (s, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.8, 32.6, 33.2, 117.1, 118.7, 124.8, 127.9, 130.1, 135.7, 138.4, 140.5, 141.4, 145.6, 164.6, 191.6 ppm.

Ethyl 4-phenylbutanoate (**49**): Preparation according to general procedure a using 4-phenylbutanoic acid (**48**). Yield: 96%. Colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H), 1.89 – 2.04 (m, 2H), 2.32 (t, ^3J = 7.5 Hz, 2H), 2.66 (t, ^3J = 7.6 Hz, 2H), 4.13 (q, ^3J = 7.1 Hz, 2H), 7.15 - 7.22 (m, 3H), 7.25 – 7.32 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 26.7, 33.8, 35.3, 60.4, 126.1, 128.5, 128.6, 141.6, 173.7 ppm.

Ethyl 4-(4-formylphenyl)butanoate (**50**): Preparation according to general procedure f using **49**. Yield: 18%. Brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H), 1.98 (tt, ^3J = 7.5, 7.5 Hz, 2H), 2.33 (t, ^3J = 7.4 Hz, 2H), 2.73 (t, ^3J = 7.4 Hz, 2H), 4.13 (q, ^3J = 7.1 Hz, 2H), 7.34 (d, ^3J = 8.0 Hz, 2H), 7.81 (d, ^3J = 8.2 Hz, 2H), 9.96 (s, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3, 26.2, 33.7, 35.4, 60.7, 129.3, 130.2, 134.7, 149.2, 173.6, 192.4 ppm.

Ethyl 4-(4-[hydroxymethyl]phenyl)butanoate (**51**): Preparation according to general procedure g using **50**. Yield: 55%. Brown oil. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, ^3J = 7.1 Hz, 3H), 1.80 (tt, ^3J = 7.5, 7.5 Hz, 2H), 2.27 (t, ^3J = 7.4 Hz, 2H), 2.56 (t, ^3J = 7.6 Hz, 2H), 4.04 (q, ^3J = 7.1 Hz, 2H), 4.45 (s, 2H), 5.10 (br s, 1H), 7.13 (d, ^3J = 8.0 Hz, 2H), 7.22 (d, ^3J = 8.1 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.1, 26.4, 32.9, 34.0, 59.7, 62.8, 126.6, 128.0, 139.7, 140.1, 172.7 ppm.

Ethyl 4-(4-[chloromethyl]phenyl)butanoate (**52**): Preparation according to general procedure h using **51**. Yield: 41%. Pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H), 1.86 – 2.04 (m, 2H), 2.32 (t, ^3J = 7.4 Hz, 2H), 2.65 (t, ^3J = 7.6 Hz, 2H), 4.12 (q, ^3J = 7.1 Hz, 2H), 4.57 (s, 2H), 7.14 - 7.21 (m, 2H), 7.27 – 7.34 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 26.5, 33.7, 34.9, 46.3, 60.4, 128.8, 129.0, 135.3, 142.0, 173.5 ppm.

Ethyl 4-(4-[{(5-indanyl)oxy}methyl]phenyl)butanoate (**53**): Preparation according to general procedure c using **52** and 5-indanol (**44**). Yield: 82%. Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3H), 1.97 (p, ^3J = 7.5 Hz, 2H), 2.08 (p, ^3J = 7.4 Hz, 2H), 2.33 (t, ^3J = 7.5 Hz, 2H), 2.67 (t, ^3J = 7.6 Hz, 2H), 2.79 – 2.96 (m, 4H), 4.14 (q, ^3J = 7.1 Hz, 2H), 5.01 (s, 2H), 6.77 (dd, ^3J = 8.2 Hz, ^4J = 2.5 Hz, 1H), 6.88 (d, ^4J = 2.0 Hz, 1H), 7.12 (d, ^3J = 8.2 Hz, 1H), 7.20 (d, ^3J = 8.1 Hz, 2H), 7.36 (d, ^3J = 8.2 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4, 26.0, 26.6, 32.1, 33.3, 33.8, 35.0, 60.4, 70.3, 111.1, 113.0, 124.9, 127.8, 128.8, 135.2, 136.5, 141.3, 145.8, 158.0, 173.6 ppm.

5-Indanylcarbaldehyde (**55**): Preparation according to general procedure f using indane (**54**). Yield: 60%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.13 (p, ^3J = 7.6 Hz, 2H), 2.97 (t, ^3J = 7.5 Hz, 4H), 7.36 (d, ^3J = 7.8 Hz, 1H), 7.65 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H), 7.73 (s, 1H), 9.95 (s, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.5, 32.5, 33.3, 124.9, 125.3, 129.0, 135.4, 145.4, 152.2, 192.5 ppm.

5-Indanylmethanol (**56**): Preparation according to general procedure g using **55**. Yield: 59%. Yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.91 (br s, 1H), 2.10 (p, ^3J = 7.3 Hz, 2H), 2.92 (t, ^3J = 7.4 Hz, 4H), 4.64 (s, 2H), 7.13 (d, ^3J = 7.5 Hz, 1H), 7.17 – 7.27 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.6, 32.7, 32.9, 65.6, 123.4, 124.5, 125.3, 139.0, 143.9, 144.8 ppm.

5-(Chloromethyl)indane (**57**): Preparation according to general procedure h using **56**. Yield: 80%. Colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.08 (p, ^3J = 7.5 Hz, 2H), 2.85 – 2.96 (m, 4H), 4.58 (s, 2H), 7.15 (dd, ^3J = 7.8 Hz, ^4J = 1.3 Hz, 1H), 7.21 (d, ^3J = 7.6 Hz, 1H), 7.26 (s, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.6, 32.8, 32.9, 46.9, 124.7, 124.9, 126.8, 135.5, 144.9, 145.1 ppm.

Methyl 4-([5-indanyl]methoxy)benzoate (**58**): Preparation according to general procedure c with methyl 4-hydroxybenzoate (**62**) and **57**. Yield: 90%. White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.99 (p, ^3J = 7.5 Hz, 2H), 2.82 (t, ^3J = 7.4 Hz, 4H), 3.78 (s, 3H), 4.96 (s, 2H), 6.85 – 6.93 (m, 2H), 7.08 (dd, ^3J = 8.1 Hz, ^4J = 1.0 Hz, 1H), 7.14 (d, ^3J = 7.7 Hz, 1H), 7.19 (s, 1H), 7.86 – 7.93 (m, 2H) ppm. ^{13}C-NMR

(75 MHz, $CDCl_3$): δ = 25.6, 32.7, 32.9, 51.9, 70.5, 114.5, 122.8, 123.9, 124.6, 125.8, 131.7, 134.1, 144.6, 144.9, 162.7 166.9 ppm.

2-(Chloromethyl)-1,1'-biphenyl (**60**): Preparation according to general procedure h using [1,1'-biphenyl]-2ylmethanol (**59**). Yield: 58%. Colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.54 (s, 2H), 7.27 – 7.34 (m, 1H), 7.34 – 7.50 (m, 7H), 7.52 – 7.59 (m, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 44.6, 127.6, 128.1, 128.5, 128.7, 129.3, 130.5, 130.7, 135.1, 140.3, 142.2 ppm.

Methyl 4-([{1,1'-biphenyl}-2-yl]methoxy)benzoate (**61**): Preparation according to general procedure c using **60** and **62**. Yield: 93%. Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3H), 5.02 (s, 2H), 6.84 – 6.93 (m, 2H), 7.32 – 7.49 (m, 8H), 7.57 – 7.68 (m, 1H), 7.93 – 8.03 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 51.9, 68.3, 114.5, 122.9, 127.5, 127.8, 128.4, 128.4, 129.2, 129.3, 130.3, 131.6, 133.5, 140.4, 142.1, 162.4, 166.9 ppm.

Methods for in Vitro Characterization

Hybrid reporter gene assays for PPARα/γ/δ, LXRα/β, RXRα/β/γ, RARα/β/γ, FXR, VDR, CAR and PXR

Plasmids: The Gal4-fusion receptor plasmids pFA-CMV-hPPARα-LBD[1], pFA-CMV-hPPARγ-LBD[1], pFA-CMV-hPPARδ-LBD[1], pFA-CMV-hLXRα-LBD[2], pFA-CMV-hLXRβ-LBD[2], pFA-CMV-hRXRα-LBD[3], pFA-CMV-hRXRβ-LBD[3], pFA-CMV-hRXRγ-LBD[3], pFA-CMV-hRARα-LBD[3], pFA-CMV-hRARβ-LBD[3], pFA-CMV-hRARγ-LBD[3], pFA-CMV-hFXR-LBD[2], pFA-CMV-hVDR-LBD[3], pFA-CMV-hCAR-LBD[3] and pFA-CMV-hPXR-LBD[3] coding for the hinge region and ligand binding domain (LBD) of the canonical isoform of the respective nuclear receptor have been reported previously. pFR-Luc (Stratagene) was used as reporter plasmid and pRL-SV40 (Promega) for normalization of transfection efficiency and cell growth.

Assay procedure: HEK293T cells were grown in DMEM high glucose, supplemented with 10% FCS, sodium pyruvate (1 mM), penicillin (100 U/mL) and streptomycin (100 µg/mL) at 37 °C and 5% CO_2. The day before transfection, HEK293T cells were seeded in 96-well plates ($3 \cdot 10^4$ cells/well). Before transfection, medium was changed to Opti-MEM without supplements. Transient transfection was carried out using Lipofectamine LTX reagent (Invitrogen) according to the manufacturer's protocol with pFR-Luc (Stratagene), pRL-SV40 (Promega) and the corresponding Gal4-fusion nuclear receptor plasmid. 5 h after transfection, medium was changed to Opti-MEM supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), now additionally containing 0.1% DMSO and the respective test compound or 0.1% DMSO alone as untreated control. Each concentration was tested in duplicates and each experiment was repeated independently at least three times. Following overnight (12-14 h) incubation with the test compounds, cells were assayed for luciferase activity using Dual-Glo™ Luciferase Assay System (Promega) according to the manufacturer's protocol. Luminescence was measured with an Infinite M200 luminometer (Tecan Deutschland GmbH). Normalization of transfection efficiency and cell growth was done by division of firefly luciferase data by renilla luciferase data and multiplying the value by 1000 resulting in relative light units (RLU). Fold activation was obtained by dividing the mean RLU of a test compound at a respective concentration by the mean RLU of untreated control. Relative activation was obtained by dividing the fold activation of a test compound at a respective concentration by the fold activation of a respective reference agonist at 1 µM (PPARα: GW7647; PPARγ: pioglitazone; PPARδ: L165,041; LXRα/β: T0901317; RXRα/β/γ: bexarotene; RARα/β/γ: tretinoin; FXR: GW4064; VDR: calcitriol; CAR: CITCO; PXR: SR12813). All hybrid assays were validated with the above-mentioned reference agonists which yielded EC_{50} values in agreement with literature.

Reporter gene assays for the human full-length heterodimers RXR-PPARγ and RXR-LXR

HEK293T cells were grown in DMEM high glucose, supplemented with 10% FCS, sodium pyruvate (1 mM), penicillin (100 U/mL) and streptomycin (100 µg/mL) at 37 °C and 5% CO_2. The day before transfection, HEK293T cells were seeded in 96-well plates ($3 \cdot 10^4$ cells/well). Before transfection, medium was changed to Opti-MEM without supplements. Transient transfection was carried out using Lipofectamine LTX reagent (Invitrogen) according to the manufacturer's protocol with the reporter RXR-PPARγ responsive construct PPRE1-pGL3 or the RXR-LXR responsive construct ABCA1-pGL3 as well as pRL-SV40 (Promega). 5 h after transfection, medium was changed to Opti-MEM supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), now additionally containing 0.1% DMSO and the respective test compound or 0.1% DMSO alone as untreated control. Each concentration was tested in duplicates and each experiment was repeated independently at least three times. Following overnight (12-14 h) incubation with the test compounds, cells were assayed for

luciferase activity using Dual-Glo™ Luciferase Assay System (Promega) according to the manufacturer's protocol. Luminescence was measured with an Infinite M200 luminometer (Tecan Deutschland GmbH). Normalization of transfection efficiency and cell growth was done by division of firefly luciferase data by renilla luciferase data and multiplying the value by 1000 resulting in relative light units (RLU). Fold activation was obtained by dividing the mean RLU of a test compound at a respective concentration by the mean RLU of untreated control.

RXR target gene quantification (quantitative real-time PCR)

HepG2 cells were incubated with compound **28** (1 and 10 µM), bexarotene (1 µM), or 0.1% DMSO alone as untreated control for 8 h, harvested, washed with cold phosphate buffered saline (PBS) and then directly used for RNA extraction with the Total RNA Mini Kit (R6834-02, Omega Bio-Tek, Inc., Norcross, GA, USA). One microgram of total RNA was reverse-transcribed into cDNA using the High-Capacity cDNA Reverse Transcription Kit (4368814, Thermo Fischer Scientific, Inc.) according to the manufacturer's protocol. RXR target gene expression was evaluated by quantitative real time PCR analysis with a StepOnePlus™ System (Life Technologies, Carlsbad, CA, USA) using PowerSYBRGreen (Life Technologies; 12.5 µL per well). The following primers were used:

Table S2: Primers Used for RXR Target Gene Quantification.

Gene	Forward Primer (5' → 3')	Reverse Primer (5' → 3')
GAPDH	ATA TGA TTC CAC CCA TGG CA	GAT GAT GAC CCT TTT GGC TC
ADIPOQ	TGG CTA TGC TCA CAG TCT CAC ATC	CTC TGT GCC TCT GGT TCC ACA A
ANGPTL4	ATT CTT TCC AGC GGC TTC TG	GAG GAC TGG AGA CGC GGA G
APOE	GGT CGC TTT TGG GAT TAC CT	CTC CAG TTC CGA TTT GT

Each sample was set up in duplicates and repeated in four independent experiments. The expression was quantified by the comparative ΔΔCt method and glycerinealdehyde 3-phosphate dehydrogenase (GAPDH) served as reference gene. The obtained ΔCt values were compared to the mean ΔCt of the negative control. Results (expressed as mean fold activation ± SEM; n = 4): ADIPOQ: DMSO: 106 ± 21%; bexarotene (1 µM): 382 ± 144%; **28** (1 µM): 553 ± 122%; **28** (10 µM): 344 ± 72%. ANGPTL4: DMSO: 103 ± 14%; bexarotene (1 µM): 234 ± 44%; **28** (1 µM): 258 ± 14%; **28** (10 µM): 216 ± 47%. APOE: DMSO: 103 ± 14%; bexarotene (1 µM): 176 ± 29%; **28** (1 µM): 151 ± 30%; **28** (10 µM): 200 ± 18%.

Isothermal titration calorimetry (ITC)

Isothermal titration calorimetry (ITC) was conducted on an Affinity ITC (TA Instruments Affinity ITC). Recombinant RXRα ligand binding domain protein (100 µM) and **3**, **4**, **28**, and bexarotene (**1**, 20 µM) were each dissolved in a HEPES buffer (25 mM; adjusted to pH 7.5 with KOH; further containing 150 mM KF, 10% glycerol (w/w), 1% DMSO (v/v) and 5 mM DTT). The ITC instrument was adjusted to a temperature of 25 °C and the stirring rate was set at 75 rpm. 190 µL of tested compound were filled into the reaction cell and RXRα ligand binding domain solution was titrated in 20 - 23 injections (inverse titration). The first injection had a reduced volume of 1.0 µL and was followed by injections of 2.5 µL. An interval of 300 s was maintained between individual injections. The heats of dilution resulting from titrating RXRα ligand binding domain protein solution into the buffer solution were recorded in an additional ITC run and subtracted from the respective raw ITC data. ITC raw data was analyzed using

NanoAnalyze software package (version 3.7.5). An independent binding model was used to fit the reaction enthalpy (ΔH), binding affinity constant (K_d), and stoichiometry (n). Free energy change (ΔG) was calculated from the equation $\Delta G = -RT \ln K$ and the entropy (ΔS) was calculated from $\Delta G = \Delta H - T\Delta S$.

LogP Determination

LogP values of **3**, **4**, **28** and bexarotene were determined by HPLC analysis using a VWR Hitachi Chromaster System with DAD 5430. The HPLC column was a MultoHigh 100RP18 (4,6 mm I.D., 250 mm length, 5 µ particle size) from Chromatographie-Service GmbH (Langerwehe, Germany). A linear gradient was used with mobile phase A as 100% acetonitrile, and mobile phase B as 100% 10 mM ammonium acetate (adjusted to pH 7.4 with ammonium hydroxide and acetic acid). The gradient table was: 0 min/ 5% A, 2.0 min/ 5% A, 12.0 min/ 95% A, 20 min/ 95% A, 30 min/ 5% A, 35 min/ 5% A. Flow rate was 0.5 ml/min, and UV spectra were collected at 254 nm and 280 nm. The samples were dissolved in DMSO at 30 µM and 50 µL were injected.

The HPLC capacity factor k' was determined according to:

$$k' = \frac{t_R - t_0}{t_0},$$

Where t_R is the retention time and t_0 the retention time of the unretained reference compound (thiourea). The logP was calibrated to k' by running 11 reference compounds (see below) and plotting k' versus literature logP values.[5] All determinations were performed three times.

Reference compounds:

Table S3: List of Reference Compounds for LogP Determination.

Compound	t_R - t_0 [min.]	k'	logP (literature)	logP (calculated)	ΔlogP
Thiourea	0				
Levodopa	1.062	0.331979167	-2.39	-1.60	-0.79
Chloramphenicol	8.446	2.63921875	1.14	1.98	-0.84
Furosemide	6.972	2.17875	2.03	1.27	0.76
Phenytoin	9.392	2.935052083	2.47	2.44	0.03
Albendazole	10.550	3.296927083	2.7	3.00	-0.30
Propranolol	9.054	2.829479167	3.48	2.28	1.20
Amodiaquine	11.337	3.542760417	3.7	3.39	0.31
Lovastatin	14.311	4.4721875	4.26	4.83	-0.57
Amitriptyline	12.722	3.975625	4.92	4.06	0.86
Fenofibrate	16.129	5.040416667	5.3	5.71	-0.41
Clofazimine	20.525	6.414166667	7.6	7.84	-0.24
Bexarotene (**1**)	15.130	4.72817708		5.23	
3	8.143	2.5446875		1.84	
4	8.943	2.79479167		2.23	
28	8.542	2.66947917		2.03	

Aqueous solubility

Aqueous solubility of compounds **3**, **4**, **28** and bexarotene (**1**) was determined using Whatman Uniprep filters (Whatman plc, Maidstone, UK). 3 mg of each compound and 2 mL H_2O dest. were inserted into the Uniprep vessel and the mixture was shaken at 37 °C for 24 h. The mixture was then pressed through the Uniprep filter and the concentration of dissolved compound in filtrate was quantified by HPLC

(Waters 600 Controller and Waters 2487 Dual Absorbance Detector equipped with a MultoHigh100 Phenyl 5 µ 240+4 mm column, CS-Chromatographie Service GmbH) using external calibration.

WST-1 assay

WST-1 assay (Roche Diagnostics International AG, Rotkreuz, Schweiz) was performed according to manufacturer's protocol and as described previously.[4] In brief, HepG2 cells were seeded in DMEM high glucose, supplemented with sodium pyruvate (1 mM), penicillin (100 U/mL), streptomycin (100 µg/mL) and 10% FCS in 96-well plates ($3 \cdot 10^4$ cells/well). After 24 h, medium was changed to DMEM high glucose, supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL) and 1% charcoal stripped FCS and cells were incubated with **3**, **4**, **28**, and bexarotene (final concentrations 1 µM, 10 µM, 30 µM, 50 µM and 100 µM), Revlotron as positive control, and DMEM + 1% DMSO as negative control. After 48 h, WST reagent (Roche Diagnostics International AG) was added to each well according to manufacturer's instructions. After 35 min incubation, absorption (450 nm/ reference: 620 nm) was determined with a Tecan Infinite M200 (Tecan Deutschland GmbH). Each experiment was repeated three times in triplicates. Results are expressed as mean percent of untreated control ± SEM and the negative DMSO control was set to 100% cell viability.

Computational Methods

General

Calculations were conducted in Molecular Operating Environment (MOE,[6] v 2015.10, Chemical Computing Group Inc. Montreal, QC, Canada) and KNIME (KNIME AG, Zurich, Switzerland)[7] using default settings for each tool/function unless stated otherwise.

Pharmacophore Model

A pharmacophore model was developed based on the retinoid X receptor X-ray structure PDB code 4K6I. The protein-ligand complex was prepared in MOE. The complex was protonated using the *Protonate 3D*[8] function and complex energy was minimized using the *Energy Minimize* function with default settings. The *Pharmacophore Editor* tool was used to set pharmacophore features on the co-crystalized ligand bexarotene. The pharmacophore used for virtual screening consisted of two aromatic centroids, a hydrophobic atom and a bioisostere annotation for COO^- (O2) as illustrated in figure S1. In addition, excluded volume outlining the binding pocket was created. Poses invading the excluded volume were rejected.

Data set preparation

The Specs database[9] (version march 2016 (total of 212,452 unique compounds)) was used for screening. For library preparation, hydrogen atoms were added using the software package MOE. Only compounds containing an acidic functional group (including carboxylic acid, sulfonic acid or thiocarboxylic acid group) were collected, reducing the database to 6,298 compounds. Up to 250 3D conformers were generated per compound using the *Conformations node* (MOE; stochastic search algorithm, max. conformations: 250, energy window: 4.0, all other options default) in KNIME. In total, 46,059 conformers were generated with a median of 4 conformers per compound. Bexarotene and the corresponding pharmacophore model served as the reference for the database screening. On this account, a superimposition on bexarotene and shape-based filtering step of the filtered Specs conformer database was conducted. The ShaEP software was used to superimpose the conformers by the molecular electrostatic potential (MEP) field and volume overlap. This algorithm yielded a similarity index allowing a shape-based filtering step[10]. The 3,000 compounds (as a 3D conformer) with the highest similarity index to bexarotene were selected as the screening dataset.

Data set screening

The pharmacophore screening in the above described subset of the Specs library was realized using the *Pharmacophore Search* function in MOE with the pharmacophore model shown in figure S1. Within the 3000 screening compounds with high similarity to bexarotene, the screening retrieved a total of 29 hits. Those hits were manually inspected and 15 compounds (Figure S2) with maximum diversity were selected for *in vitro* characterization.

Molecular Docking

Docking was performed using MOE software suite (version 2018.0101, Chemical Computing Group Inc., Montreal, QC, Canada). X-ray structure of RXRα (PDB code 4K6I) was selected based on ligand similarity to bexarotene. Protonation state of the complex was adjusted using the Protonate3D tool.

Docking was performed using following settings from MOE Dock tool: Site: Ligand Atoms; Placement: Triangle Matcher; Score: London dG; Refinement: Induced Fit; Refinement Score: Alpha HB for compounds **27** and **28** and GBVI/WSA dG for compounds **3** and **4**. The top-ranked binding-mode was used. For the generation of the minimum energy conformation, the surrounding receptor was deleted and QM-based energy minimization was performed using the MOPAC engine built in MOE with the AM1 basis set. Pocket surfaces were colored violet for hydrophilic, white for neutral, and green for lipophilic areas.

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