Supporting Information

1-Aryl-3-(1-acylpiperidin-4-yl)urea Inhibitors of Human and Murine Soluble Epoxide Hydrolase: Structure-Activity Relationships, Pharmacokinetics, and Reduction of Inflammatory Pain

Tristan E. Rose, Christophe Morisseau, Jun-Yan Liu, Bora Inceoglu, Paul D. Jones, James R. Sanborn, Bruce D. Hammock*

Department of Entomology and University of California Davis Cancer Center, University of California, One Shields Avenue, Davis, California 95616 USA

Supporting Information – Table of Contents

Figures

Tables

Text

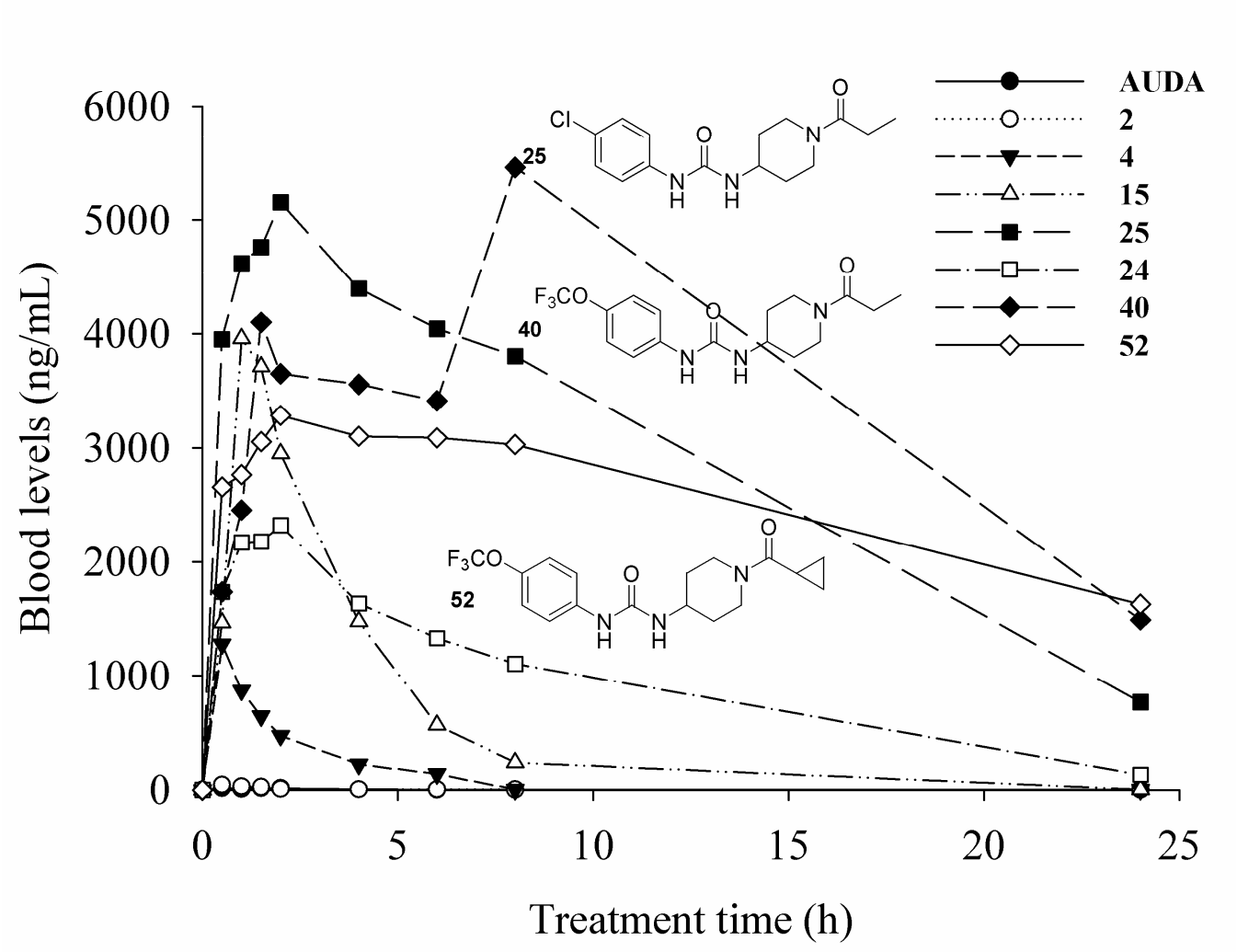


Figure S1. Relative blood pharmacokinetic profiles of key compounds. The compounds were dosed orally to CFW mice at 5 mg per kg. In this figure compounds 2 and AUDA have blood levels that are indistinguishable from baseline. The standard deviation of repeated injections of the same extract averages 3% and of repeated extracts average 5%, and they are not shown in this figure for clarity. The standard deviation shown in the subsequent figures thus represents variation among replicate mice. The pharmacokinetic parameters determined from cassette dosing are very similar to those for select compounds that were dosed individually. Blood levels of all compounds are shown with an expanded scale in S2. AUDA in this figure and APAU in Figure S5 are bridging compounds to compare potency[1-8] and pharmacokinetic data[9-11] to previous studies.

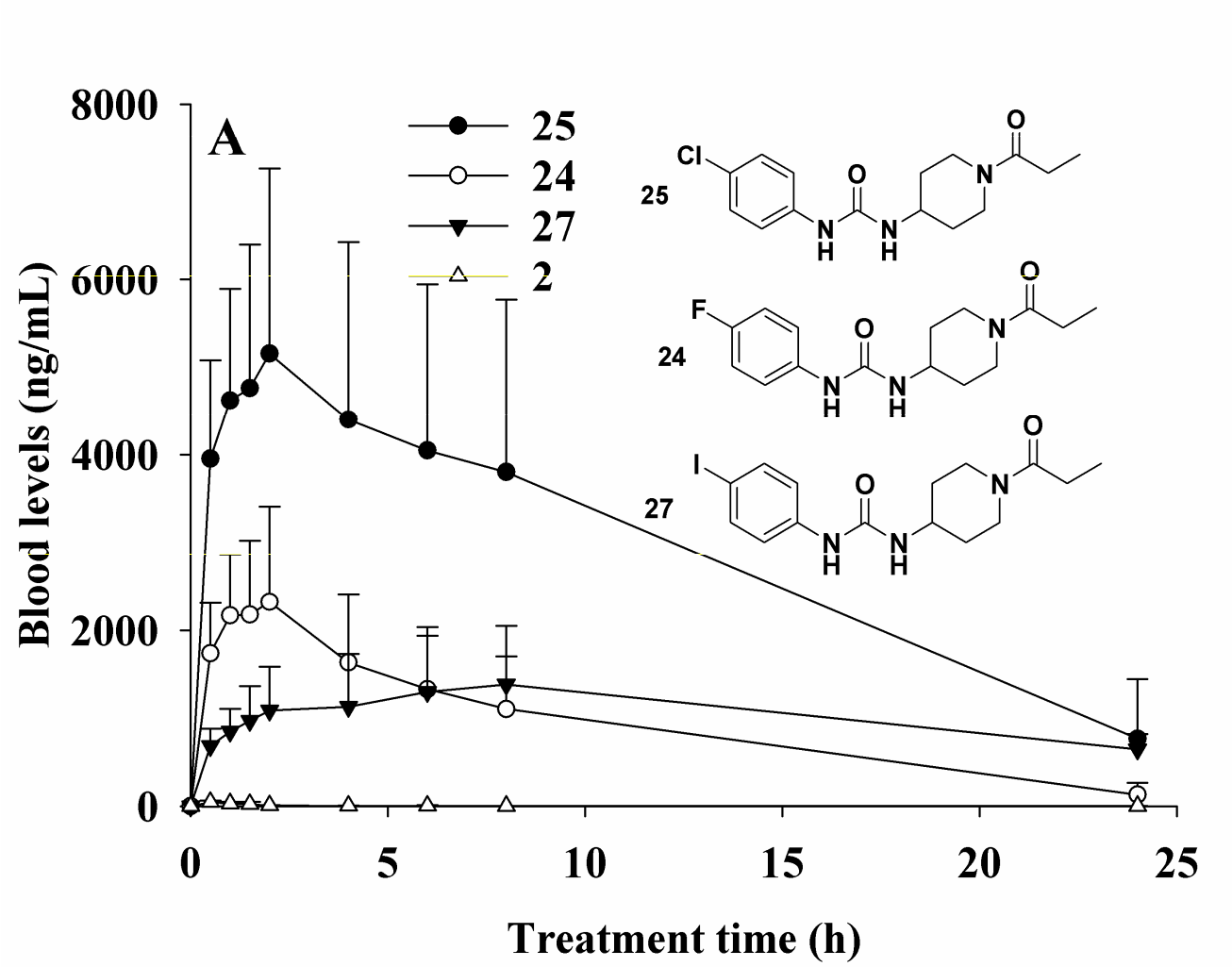


Figure S2. Blood pharmacokinetic profiles of sEH inhibitors. AUDA, APAU, 2, 3, 4, 12, 13, 14, 15, 24, 25, 27, 35 and 40 were dosed orally in mice at 5 mg per kg. The blood levels for inhibitors with similar pharmacokinetic values are shown on separate graphs for clarity. The standard deviation indicates variation among the 3-4 mice used for each cassette. Pharmacokinetic parameters are shown on Table 5. **S2A.** Blood pharmacokinetic profiles of halogenated phenyl sEH inhibitors compared to compound 2.

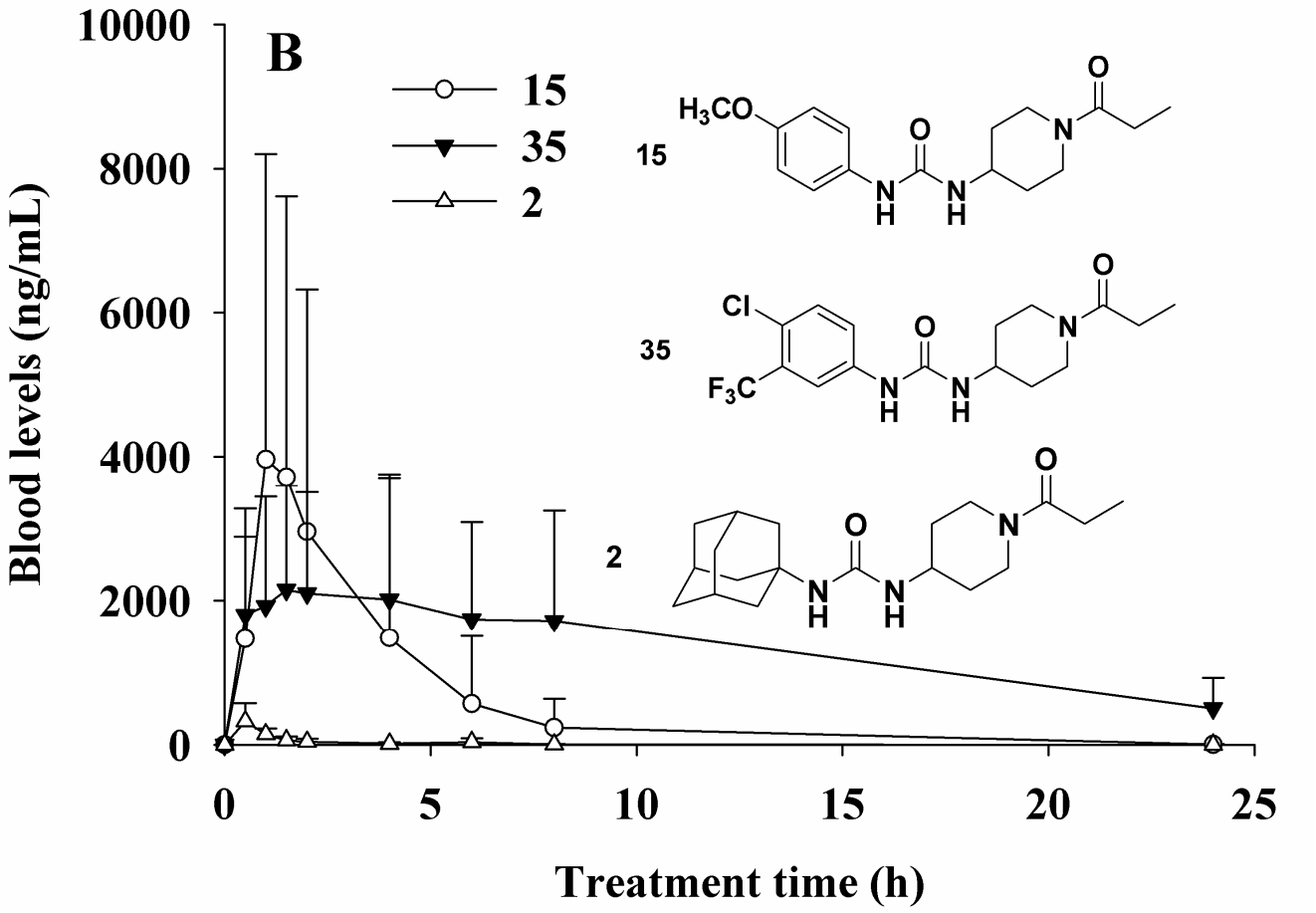


Figure S2B. Blood pharmacokinetic profiles of two substituted phenyl sEH inhibitors compared to the standard sEH inhibitor **2**. These data and data in figure 1 and S2E indicate that the adamantane is a metabolic liability in this class of compounds based on blood concentrations. The adamantane moiety has been used extensively in previous studies due to ease of monitoring adamantane containing compounds in the blood by LC-MS and due to the high potency and selectivity associated with it as a substituent. The 4-chloro-3-trifluoromethylphenyl derivative **35** has a phenyl substituent identical to the anti-cancer urea Sorafenib (Nexavar).[12] The very long half-life of **35** is consistent with an increase in logP and suggests very slow metabolism or enterohepatic circulation. Alkoxy derivatives such as **15** are commonly metabolized rapidly by O-dealkylation, but this sEH inhibitor is surprisingly stable *in vivo* and is more stable than alkyl groups in the *para*-position .

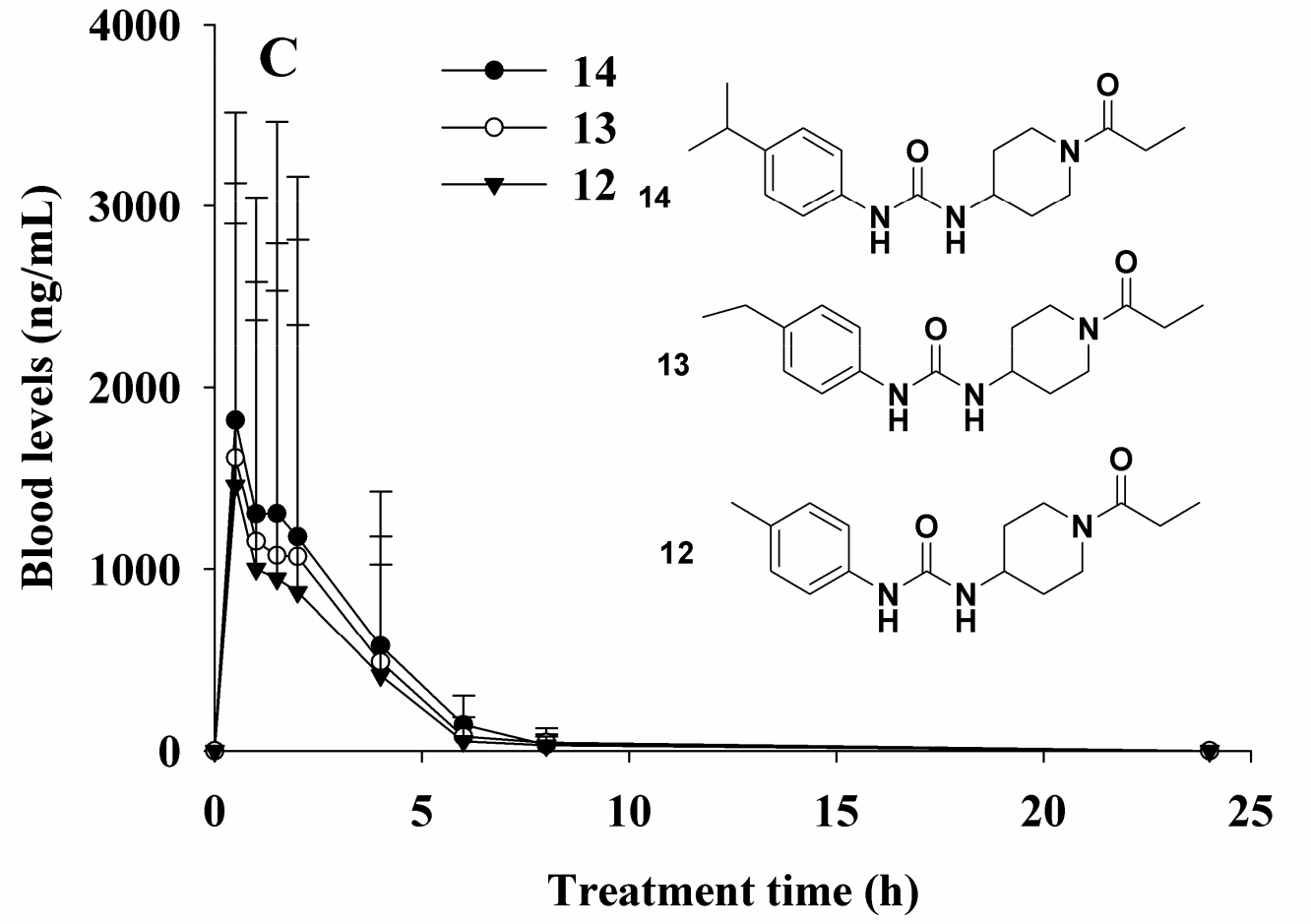


Figure S2C. Blood pharmacokinetic profiles of alkyl phenyl sEH inhibitors. All three sEH inhibitors appear to be cleared quickly from the blood, presumably largely by ω and ω-1 hydroxylation. The potency of the compounds increases with the lipophilicity and size of the alkyl group with the perfluoroisopropylphenyl derivative **38** the most active.

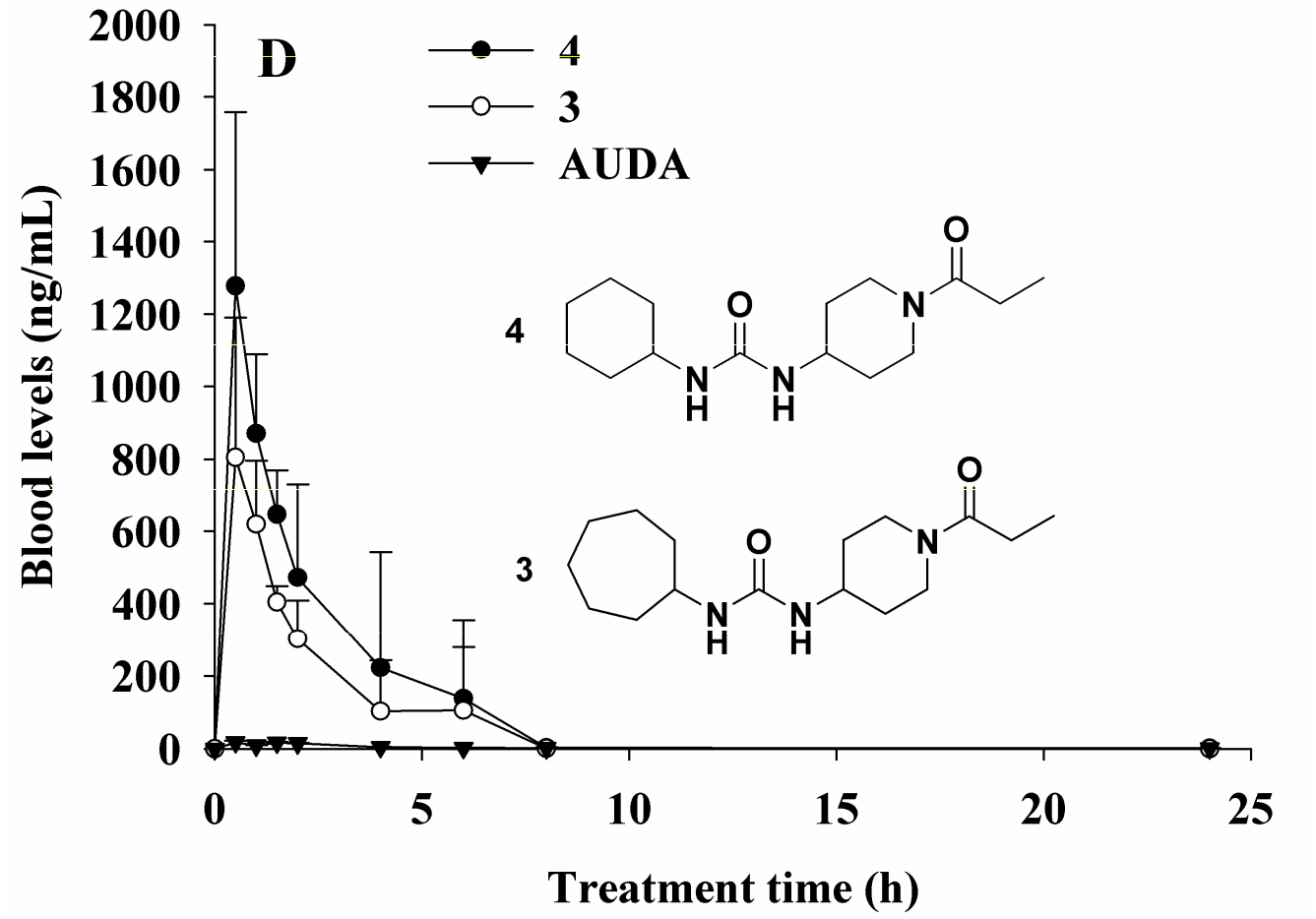


Figure S2D. Blood pharmacokinetic profiles of two cycloalkyl ureas compared to the commercial sEH inhibitor **AUDA.** Note that blood levels are higher for these cycloalkyl compounds than the corresponding adamantane derivative (**2**) in Figure **S2**E below.

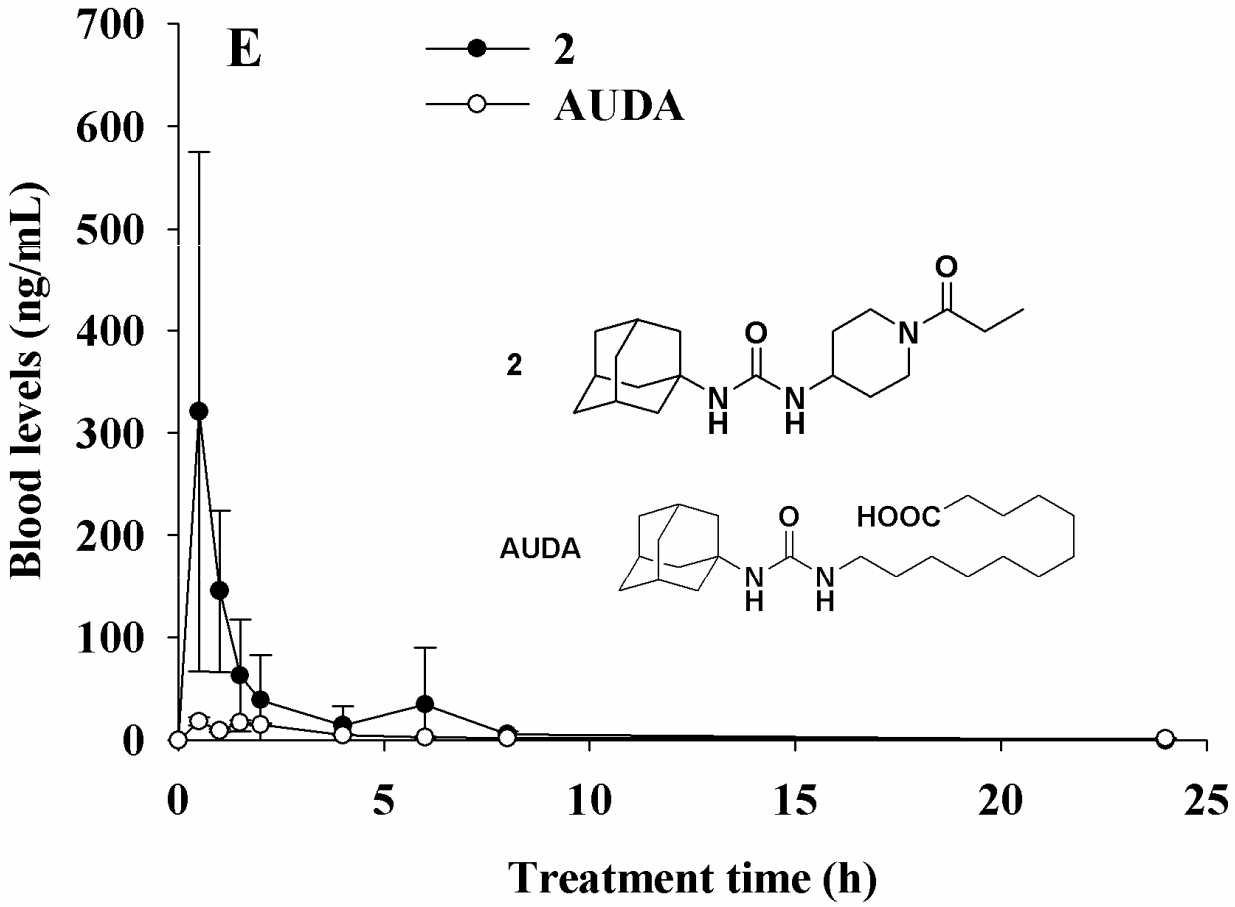


Figure S2E. Blood pharmacokinetic profiles of the standard sEH inhibitor for this study **2** compared to the commercially available sEH inhibitor **AUDA.** Compound **2** illustrates the use of the piperidine as a 'secondary pharmacophore' which increases water solubility and decreases the logP of the sEH inhibitors as illustrated earlier for the piperidines by Jones and associates.[4] In other series a polar group placed 7-8 Å from the carbonyl of the central pharmacophore has provided improved selectivity and water solubility without loss of potency. A variety of polar substituents have been used in other studies as the secondary pharmacophore. These data show a significant improvement in pharmacokinetics with a similar IC_{50} on the murine and human recombinant enzymes. **AUDA** data presented here and in Table 5 are very similar to previously published data but were generated specifically for this study to aid in comparison of different publications.[9,10]

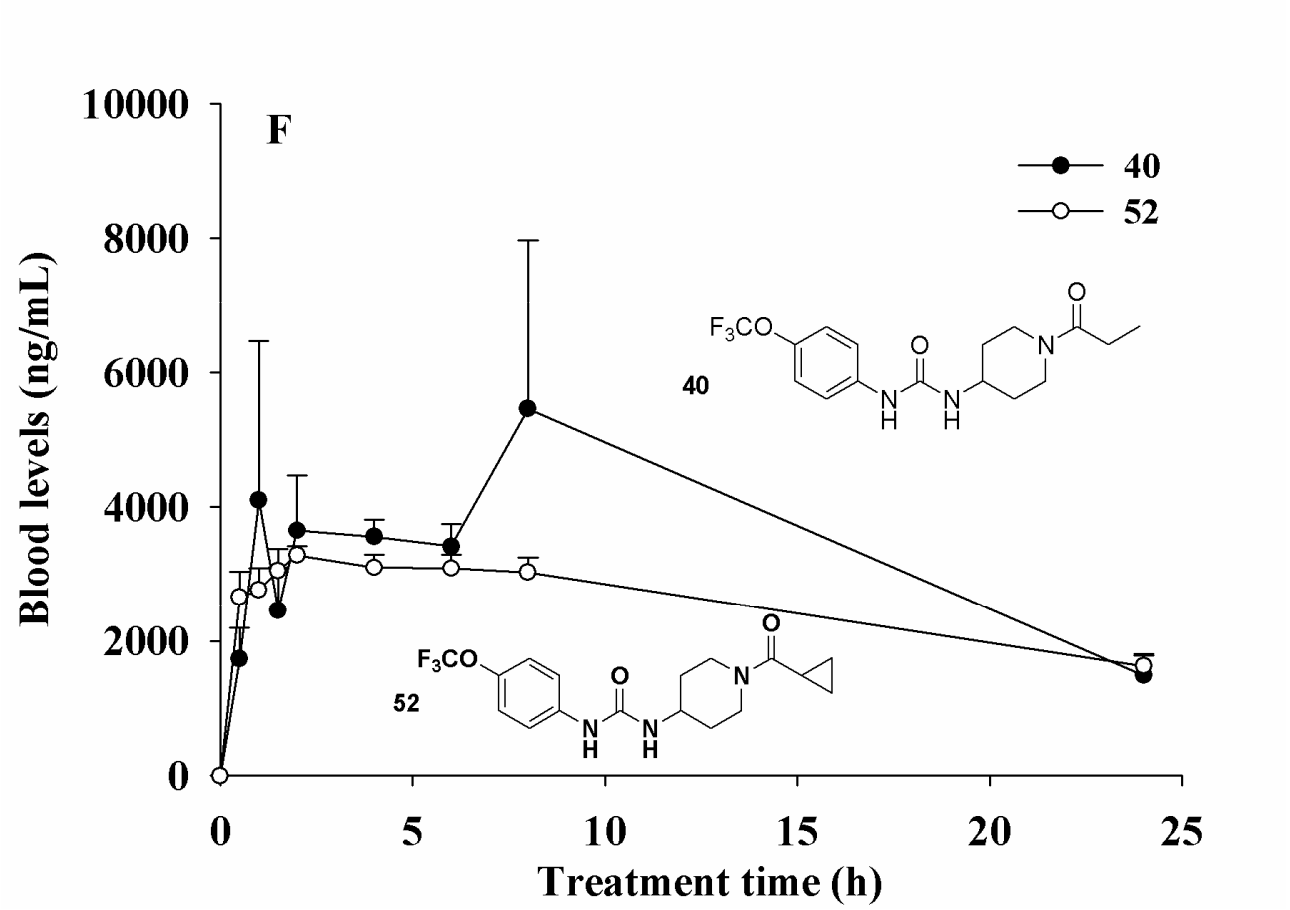


Figure S2F. Blood pharmacokinetic profiles of two highly potent and stable sEH inhibitors. Compound **40** (also known at 1770 or TPPU) is approximately 10 times less potent, has a slightly higher Cmax, slightly shorter half life and smaller AUC than the cyclopropyl compound **52**.

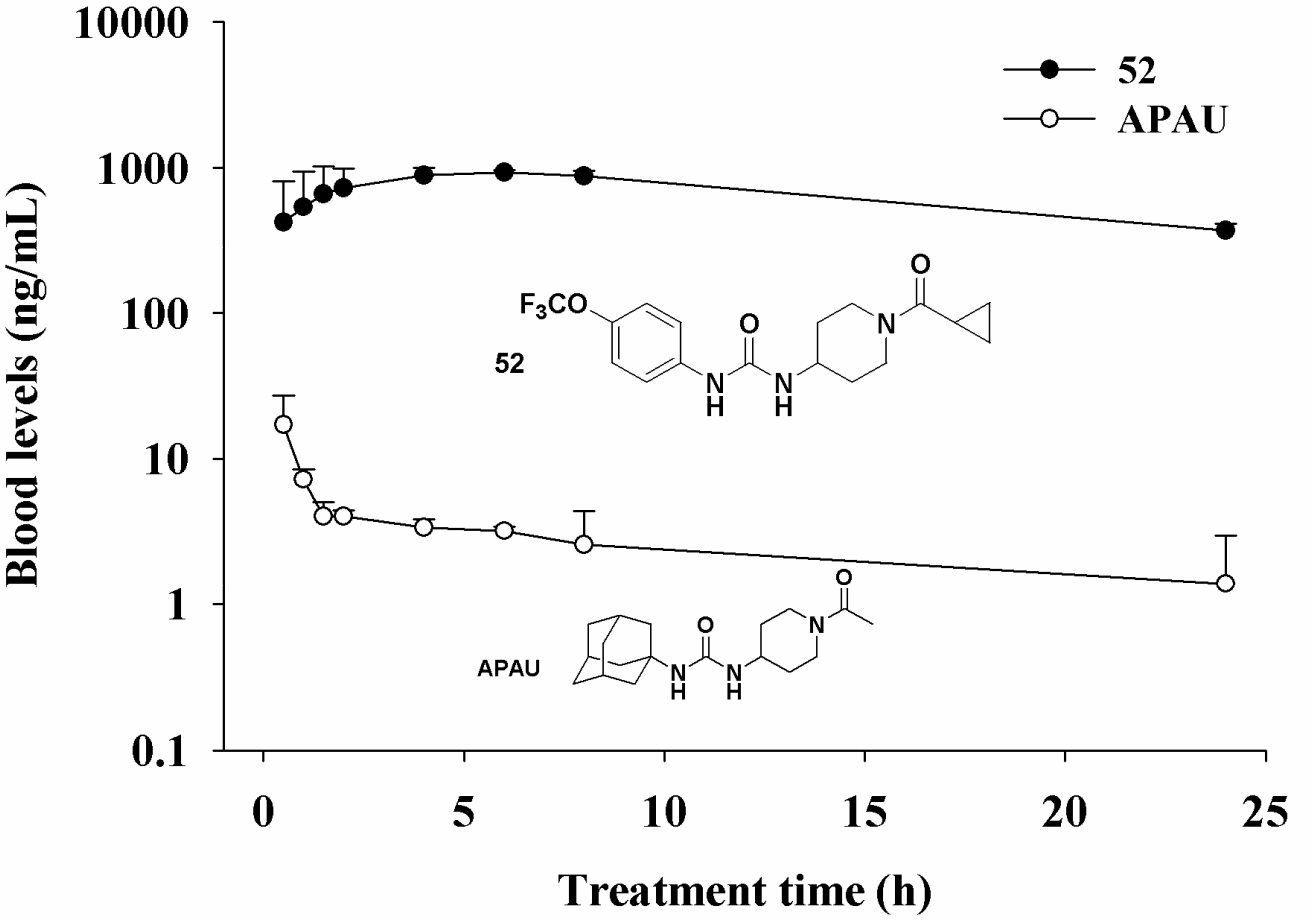


Figure S3. Blood pharmacokinetic profiles of compounds **52** and the bridging compound **APAU**[4] after single oral dosing to mice at a dose of 1 mg/kg. Please note that this figure is on a log scale. Compound **52** showed AUC_t/IC_{50} ($x10^4$ min) for the human and murine enzymes of 935 (note that AUC_t is from the mouse in both cases) while the chemically related **APAU** (1-(1-acetypiperidin-4-yl)-3-adamantanylurea) resulted in ratios of only 0.17 and 0.13 respectively. For more detailed pharmacokinetic data on APAU see Liu et al.[9] for murine and Tsai et al.[11] for canine data.

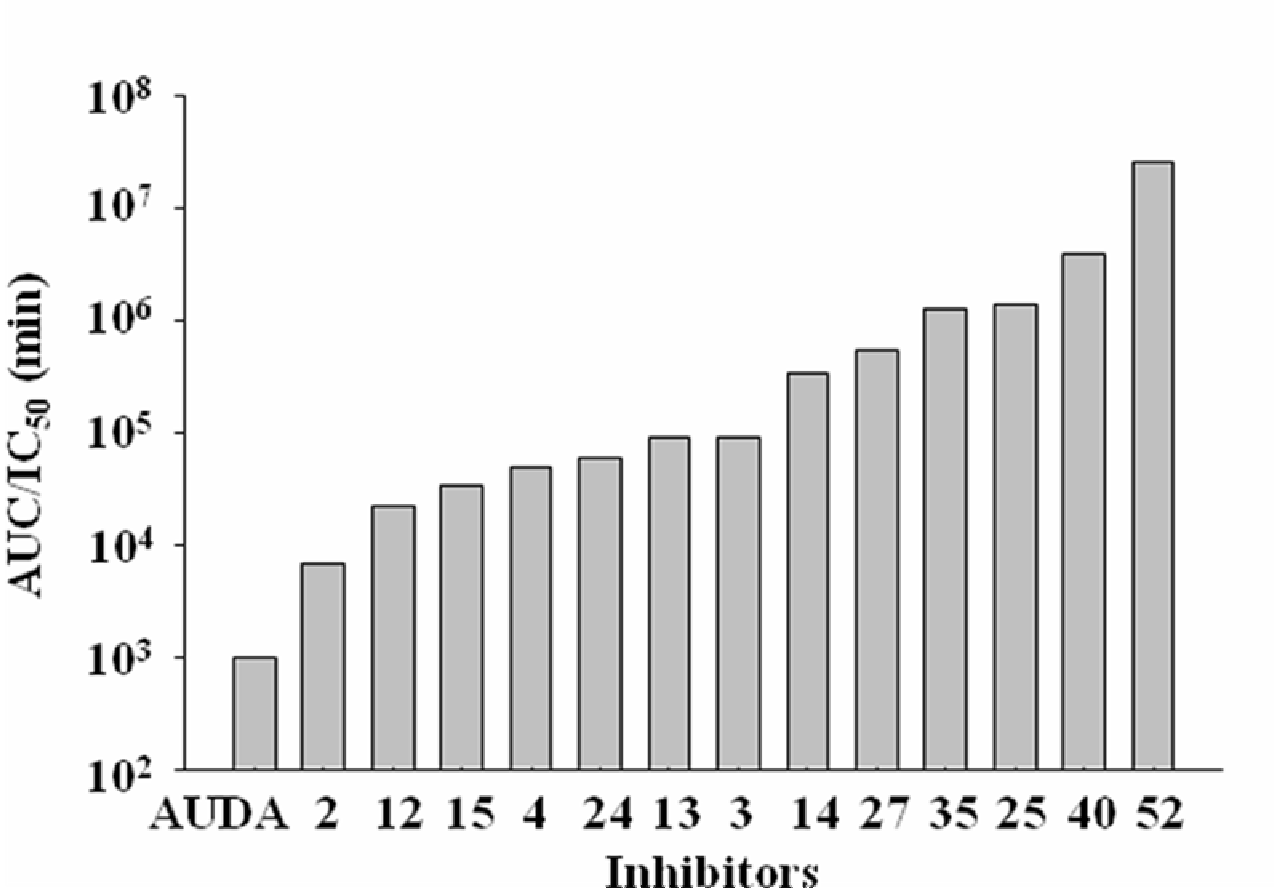


Figure S4. *In vivo* exposure (estimated as area under the curve from Figure S2, Table 5) as a function of potency (-log IC_{50}) on the homogenous, recombinant human sEH (IC_{50} from Table S2). AUDA bridges to earlier studies and compound **2** bridges to recent murine and canine pharmacokinetic studies.[9,11]

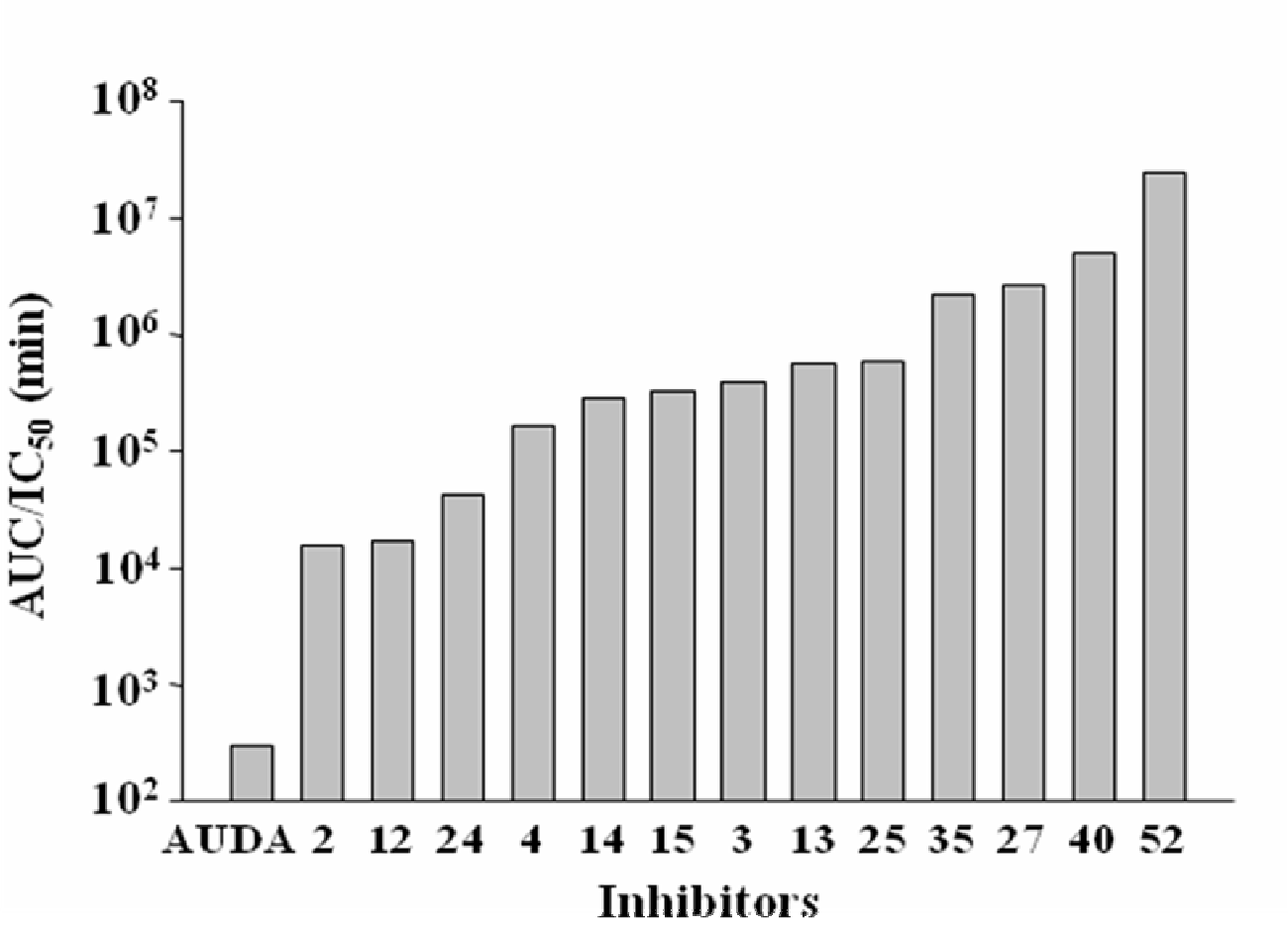


Figure S5. *In vivo* exposure (estimated as area under the curve from Figure S2, Table 5) as a function of potency (-log IC_{50}) on the homogenous, recombinant murine sEH (IC_{50} from Table S2)

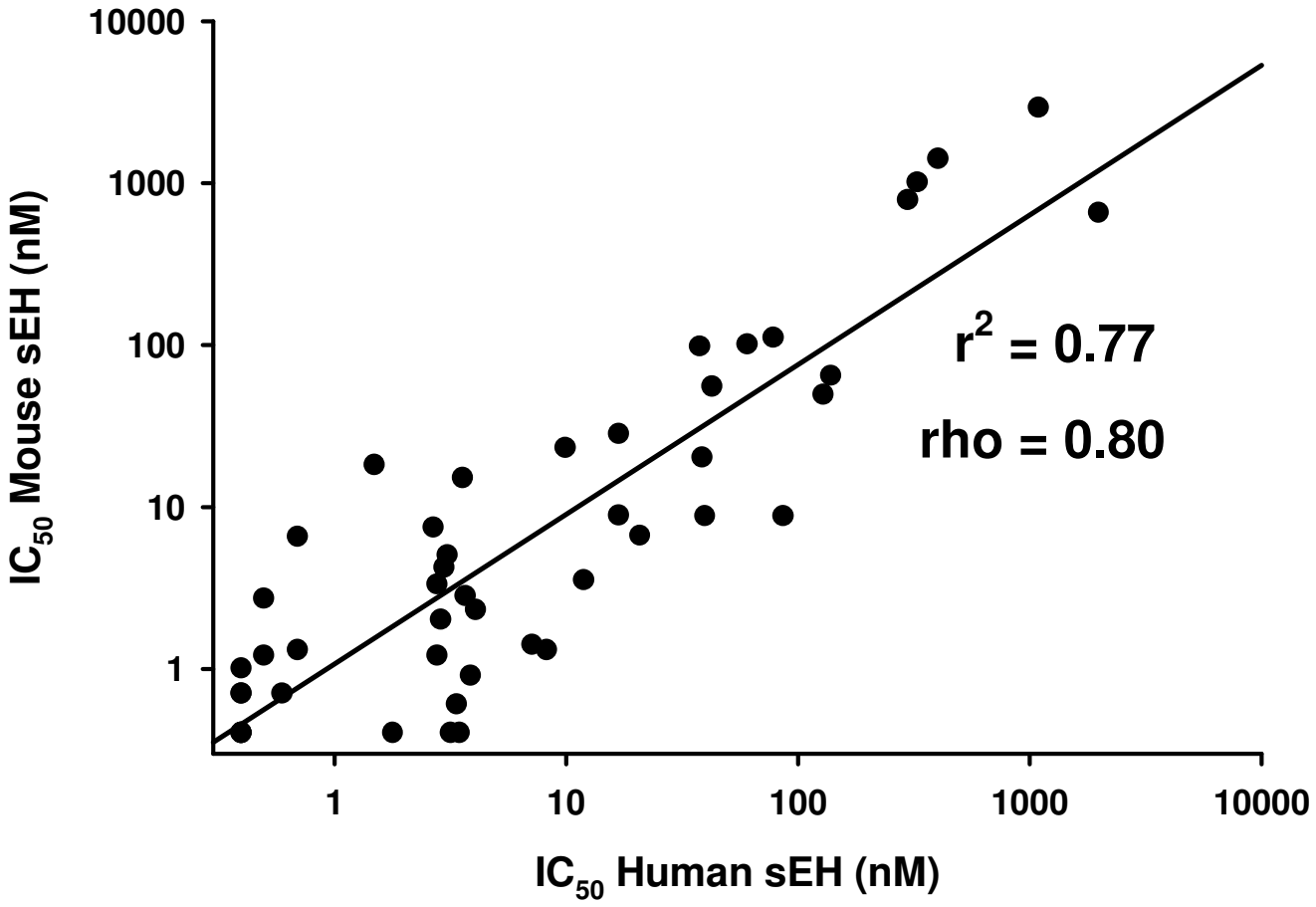


Figure S6. There is a high correlation between the IC_{50} determined on the affinity purified human and murine soluble epoxide hydrolase using CMNPC as substrate. Two statistics were used to evaluate the data including a linear regression or r^2 and a Spearman rank correlation or rho. Although the correlation is high there are clear outliers indicating that the fine structure of the catalytic site of the human and murine sEHs have some clear differences. This correlation is particularly poor with compounds similar to those reported here for canine vs human and rodent enzymes.[11]

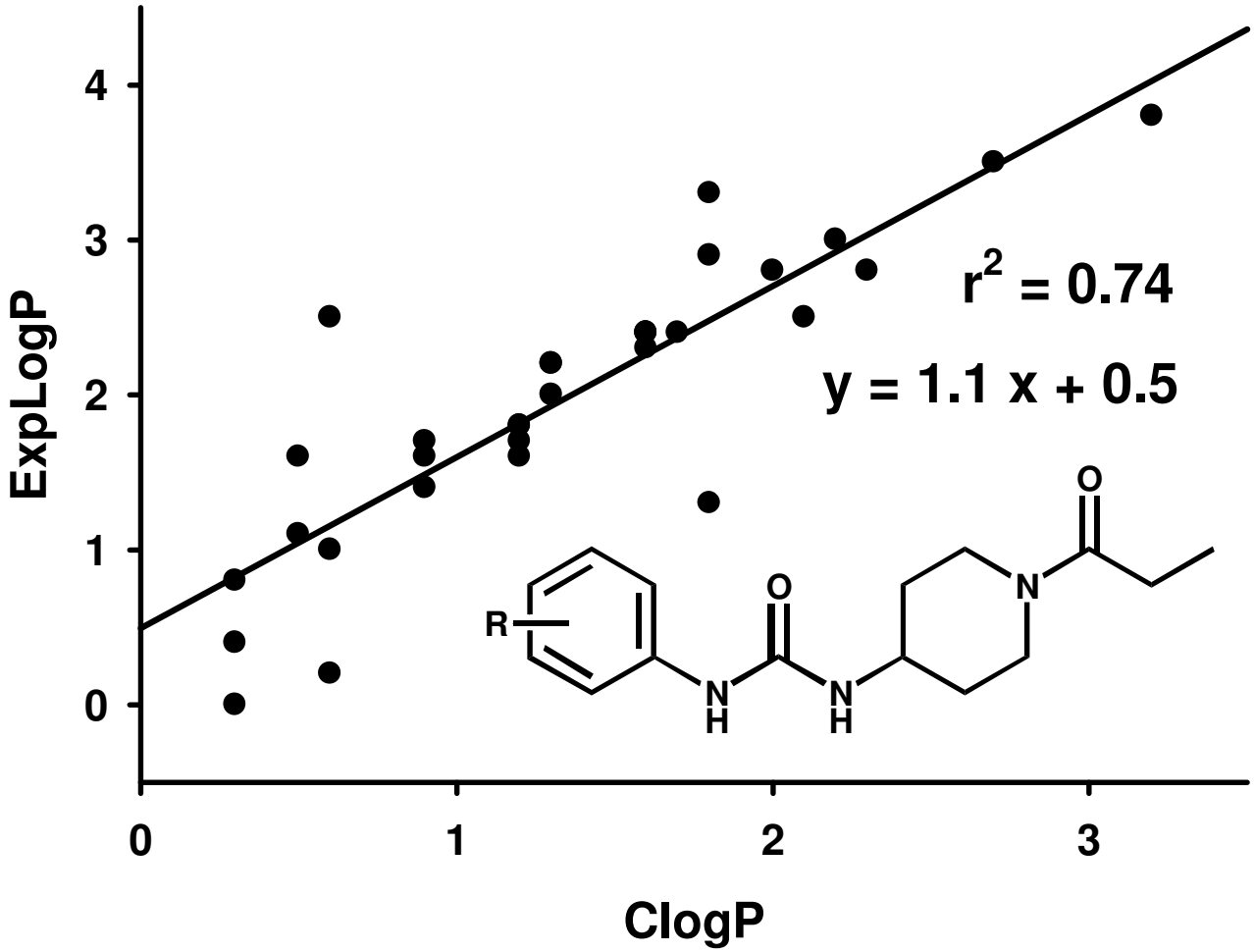


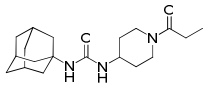
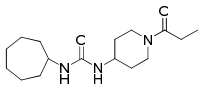
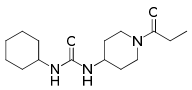
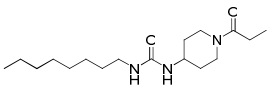
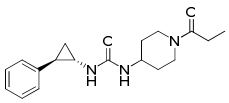
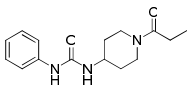
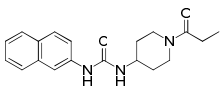
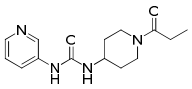
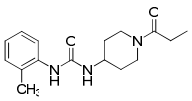
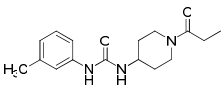
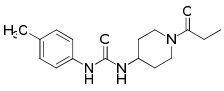
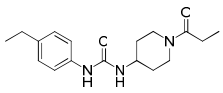
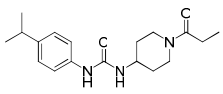
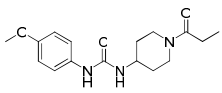
Figure S7. There is a reasonable correlation between the experimental logP and calculated logP for a series 1-(1-proprionylpiperidin-4-yl)-3-phenylureas (compounds **7** and **10** to **40**). This correlation drops dramatically ($r^2 < 0.3$) when including other urea inhibitors (n = 73). Alogrithms for predicting logP values generally are poor at predicting the behavior of urea compounds unless adjusted for this series of compounds.

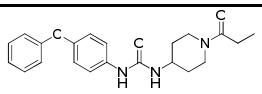
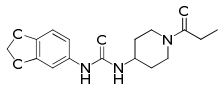
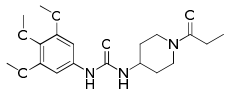
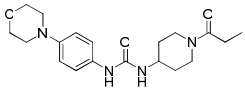
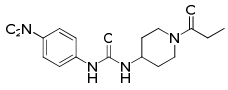
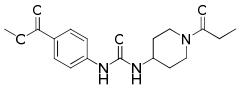
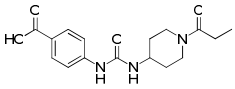
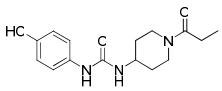
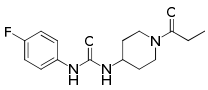
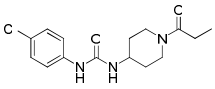
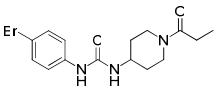
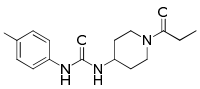
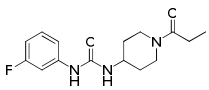
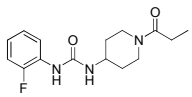
Table S1. Optimum mass spectrometer conditions and key fragmentation of the sEH inhibitors.

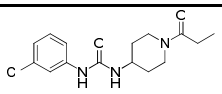
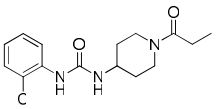
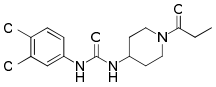
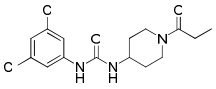
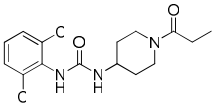
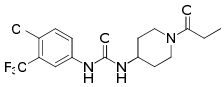
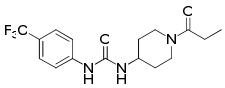
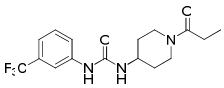
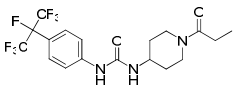
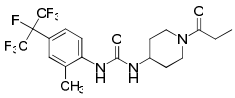
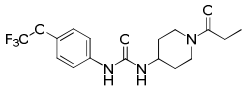
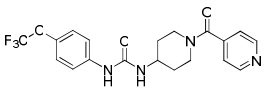
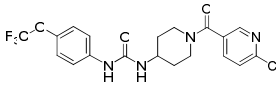
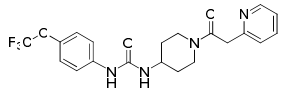
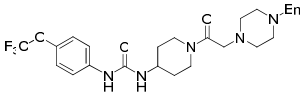
Compound ID	Precursor ions *m/z* $[M+H]^+$	Predominant product ion *m/z*	DP (V)	CE (V)	CXP (V)
CUDA[a]	341.2	216.2	76	25	10
2	334.2	157.1	51	15	6
3	296.1	157.1	51	21	8
4	282.1	157.1	61	19	12
12	290.1	183.1	56	19	14
13	304.4	122.1	56	29	6
14	318.1	183.1	51	21	14
15	305.8	84.1	51	55	4
24	293.7	183.1	31	19	8
25	310.0	183.0	66	21	16
27	402.1	183.1	77	19	12
35	378.1	183.1	66	23	12
40	358.2	175.9	-125	-22	-11
52	370.2	176.1	-90	-22	-9
APAU[b]	320.2	143.1	71	19	10
AUDA	393.2	135.1	81	37	10

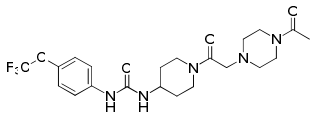
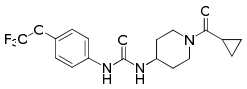
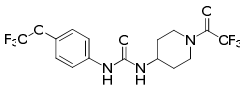
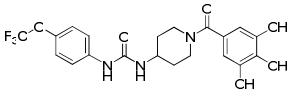
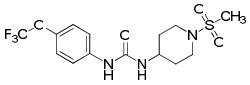
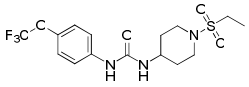
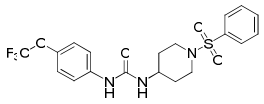
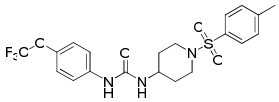
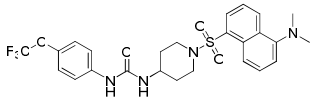
[a]12-(3-cyclohexan-1-yl-ureido)-dodecanoic acid (CUDA) was used as an internal standard to track instrument stability. [b]1-(1-acetypiperidin-4-yl)-3-adamantanylurea (APAU) was used as an internal standard added after thawing samples but before extraction to track the extraction efficiency of structurally similar target analytes.

Table S2. Cumulative table of inhibitor structures, results and properties.

		IC_{50} (nM)[b]				
Compound ID	Structure	Human	Murine	logP (±0.5)	MP (ºC)	Synthetic Method(s)
2		2.8	1.2	3.1	201 - 221	Ref.13
3		3.9	0.9	2.3	164 - 172	B
4		12	3.5	1.8	177 - 179	B
5		3.2	0.4	3.5	131 - 132	A, B
6		2.7	7.4	1.8	155 - 158	B
7		130	49	1.3	169 - 171	B
8		3.0	4.2	2.4	213 - 215	A, B
9		3,800	12,000	< 0	Oil	B
10		1,700	5,100	1.6	178 - 183	A, B
11		40	8.7	1.8	173 - 175	A, B
12		43	55	1.8	180 - 182	A, B
13		8.3	1.3	2.3	164 - 165	A, B
14		2.8	3.3	2.8	173 - 174	A, B
15		87	8.7	1.0	164 - 165	A, B

		IC_{50} (nM)[b]				
Compound ID	Structure	Human	Murine	logP (±0.5)	MP (ºC)	Synthetic Method(s)
16		3.5	0.4	2.8	153 - 154	A, B
17		61	100	1.1	195 - 197	C
18		>5,000	25,000	0.8	173 - 175	A, B
19		2,000	650	0.2	221 - 225	A, B
20		38	97	1.7	240 - 241	B
21		140	64	1.6	192 - 204	B
22		330	1,000	0.4	201 - 204	From 21
23		15	1,400	0.0	229 - 230	A, B
24		79	110	1.4	183 - 184	B
25		10	23	2.2	225 - 226	B
26		3.6	15	2.4	233 - 239	B
27		7.2	1.4	2.5	246 - 247	A, B
28		39	20	1.7	158 - 164	B
29		300	780	1.6	127 - 130	B

		IC_{50} (nM)[b]				
Compound ID	Structure	Human	Murine	logP (±0.5)	MP (ºC)	Synthetic Method(s)
30		21	6.6	2.2	165 - 166	B
31		1100	2900	2.0	150 - 157	C
32		3.4	0.6	2.9	198 - 200	A, B
33		0.4	1.0	3.3	196 - 198	A, B
34		>50,000	38,000	1.3	170 - 174	B
35		4.1	2.3	3.0	182 - 184	B
36		0.7	6.5	2.4	224 - 228	B
37		17	8.8	2.4	153 - 154	B
38		0.4	0.7	3.5	160 - 164	A, B
39		17	28	3.8	226 - 229	A, B
40		3.7	2.8	2.5	195 - 196	B
47		0.7	1.3	2.4	210 - 212	D
48		0.6	0.7	2.9	208 - 209	D
49		3.1	5.0	2.6	183 - 187	D
50		1.5	18	3.8	178 - 183	D

		IC_{50} (nM)[b]				
Compound ID	Structure	Human	Murine	logP (±0.5)	MP (ºC)	Synthetic Method(s)
51		0.5	1.2	2.4	111 - 122	From 50
52		0.4	0.4	2.7	195 - 196	D
53		0.4	0.4	3.1	150 - 154	See text
54		0.5	2.7	2.0	168 - 175	D
55		2.9	2.0	2.2	233 - 234	E
56		0.4	0.7	2.6	235 - 239	E
57		1.8	0.4	3.1	188 - 189	E
58		0.4	0.4	3.5	205 - 207	E
59		0.8	nd[a]	4.3	102 - 107	E

[a] nd = Not Determined

[b] IC_{50} values are based on at least 3 replicates of each point with at least two values above and two values below the IC_{50} value. The fluorescent substrate Cyano(2-methoxynaphthalen-6-yl)methyl *trans*-(3-phenyl-oxyran-2-yl) methyl carbonate (CMNPC). A caution is that this assay can over estimate the potency of sEH inhibitors in the piperidine and some other classes of compounds relative to assays based on other surrogate substrates or epoxyeicosanoids.[11]

Detailed synthetic methods

1-(4-Aminopiperidin-1-yl)propan-1-one (1). 4-Aminopiperidine (4.01g, 40mmol) and benzaldehyde (4.251g, 40mmol) were dissolved in toluene (70mL) and refluxed on a Dean-Stark trap until water ceased to evolve. The solvent was evaporated and the residue was reconstituted in dry THF (75mL). Triethylamine (4.04g, 40mmol) was added and the reaction was cooled in an ice bath. With vigorous stirring, propionyl chloride (3.70g, 40mmol) was added and the reaction continued for 1.5 hours at rt. The reaction was filtered, and the filtrate was evaporated and treated with 1N HCl (50mL) for 1 hour.

The aqueous phase was washed with Et_2O (3x50mL), basified to pH >10 with NaOH, saturated with sodium chloride and extracted with DCM (5x75mL). The combined DCM extract was evaporated and azeotropically dried with toluene to give intermediate **1** (4.74g, 64%) as a light brown oil: ^{1}H NMR (500MHz, DMSO-d_6) δ 4.18 (d, *J* = 11.8 Hz, 1H), 3.74 (d, *J* = 11.8 Hz, 1H), 3.00 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.89 (brs, 2H), 2.82-2.15 (m, 1H), 2.67 (dd, *J* = 11.8 Hz, 11.8Hz, 1H), 2.28 (q, *J* = 7.1 Hz, 2H), 1.72 (d, *J* = 11.8 Hz, 1H), 1.67 (d, *J* = 11.8Hz, 1H), 1.14 (q, *J* = 10.2Hz, 1H), 1.04 (q, *J* = 10.2 Hz, 1H), 0.98 (t, *J* = 7.1 Hz, 3H).

1-(1-Adamantyl)-3-(1-propionylpiperidin-4-yl)urea (2).[4] Mp 217–221 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 5.67 (d, *J* = 7.6 Hz, 1H), 5.41 (s, 1H), 4.10 (dd, *J* = 12.5 Hz, 1H), 3.69 (d, *J* = 12.5 Hz, 1H), 3.55-3.46 (m, 1H), 3.07 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.79-2.72 (m, 1H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.98 (s, 3H), 1.84 (s, 6H), 1.76 (d, *J* = 12.5 Hz, 1H), 1.70 (d, *J* = 12.5 Hz, 1H), 1.60 (brs, 6H), 1.16 (q, *J* = 11.0 Hz, 1H), 11.06 (q, *J* = 11.0 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H). Purity 95%. HRMS calculated for $C_{19}H_{31}N_3O_2 + H^+$ 334.2494; found (ESI(+), [M + H]) 334.2489.

1-Cycloheptyl-3-(1-propionylpiperidin-4-yl)urea (3). Cycloheptyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH afforded compound **3** (66mg, 22%) as a white solid: Mp 164–172 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 5.69 (d, *J* = 7.7 Hz, 1H), 5.66 (d, *J* = 7.8 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H), 3.71 (d, *J* = 13.4 Hz, 1H), 3.61-3.52 (m, 2H), 3.07 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.74 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.80-1.68 (m, 4H), 1.58-1.42 (m, 6H), 1.42-1.28 (m, 4H), 1.25-1.04 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). Purity 92%. HRMS calculated for $C_{16}H_{29}N_3O_2 - H^+$ 294.2182; found (ESI(-), [M-H]) 294.2205.

1-Cyclohexyl-3-(1-propionylpiperidin-4-yl)urea (4). Cyclohexyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc:MeOH (15:1, v:v) afforded compound **4** (63mg, 22%) as a white solid: Mp 177–179 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 5.70 (d, *J* = 7.6 Hz, 1H), 5.62 (d, *J* = 7.9 Hz, 1H), 4.13 (d, *J* = 13.2 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.61-3.52 (m, 1H), 3.34 (s, 1H), 3.07 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.74 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.81-

1.67 (m, 4H), 1.66-1.57 (m, 2H), 1.54-1.46 (m, 1H), 1.30-1.00 (m, 7H), 0.97 (t, *J* = 7.4 Hz, 3H). Purity 97%. HRMS calculated for $C_{15}H_{27}N_3O_2 + H^+$ 282.2181; found (ESI(+), [M+H]) 282.2146.

1-Octyl-3-(1-propionylpiperidin-4-yl)urea (5). Octyl isocyanate was prepared from octylamine by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc:MeOH (15:1, v:v) afforded compound **5** (145mg, 47%) as a white solid: Mp 131–132 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 5.76 (d, *J* = 7.7 Hz, 1H), 5.69 (t, *J* = 5.2 Hz, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 3.72 (d, *J* = 13.5 Hz, 1H), 3.61-3.52 (m, 1H), 3.07 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.95 (q, *J* = 6.6 Hz, 2H), 2.73 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.75 (d, *J* = 10.5Hz, 1H), 1.70 (d, *J* = 10.5Hz, 1H), 1.38-1.05 (m, 14H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 6.6 Hz, 3H). HRMS calculated for $C_{17}H_{33}N_3O_2 + H^+$ 312.2651; found (ESI(+), [M+H]) 312.2601.

1-(*trans*-2-Phenylcyclopropyl)-3-(1-propionylpiperidin-4-yl)urea (6). *trans*-2-Phenylcyclopropyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc:MeOH (15:1, v:v) and recrystallization from EtOAc:acetone afforded compound **6** (178mg, 57%) as a white solid: Mp 155–158 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.24 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.14 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 2H), 6.23 (s, 1H), 5.77 (d, *J* = 7.0 Hz, 1H), 4.16 (d, *J* = 12.9 Hz, 1H), 3.72 (d, *J* = 13.6 Hz, 1H), 3.64-3.54 (m, 1H), 3.06 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.71 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.62 (ddd, *J* = 6.8, 6.8, 3.3 Hz, 1H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.87 (ddd, *J* = 9.0, 6.0, 3.3 Hz, 1H), 1.77 (d, *J* = 11.7 Hz, 1H), 1.72 (d, *J* = 11.7 Hz, 1H), 1.23 (q, *J* = 11.6 Hz, 1H), 1.13 (q, *J* = 11.6 Hz, 1H), 1.11-1.01 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). Purity 94%. HRMS calculated for $C_{18}H_{25}N_3O_2$ - H^+ 314.1869; found (ESI(-), [M-H]) 314.1877.

1-Phenyl-3-(1-propionylpiperidin-4-yl)urea (7). Phenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH afforded compound **6** (112mg, 41%) as a white solid: Mp 169-171 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.21 (dd, *J* = 7.9, 7.9 Hz, 2H), 6.88 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.16 (d, *J* = 7.6 Hz, 1H), 4.18 (d, *J* = 12.7 Hz, 1H), 3.76 (d, *J* = 13.2 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.79 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.30 (q, *J* = 12.0

Hz, 1H), 1.20 (q, *J* = 12.0 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 95%. HRMS calculated for $C_{15}H_{21}N_3O_2 + H^+$ 276.1712; found (ESI(+), [M+H]) 276.1658.

1-(Naphthalen-2-yl)-3-(1-propionylpiperidin-4-yl)urea (8). 2-Naphthyl isocyanate was prepared from 2-naphthylamine by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 17:1 EtOAc:MeOH afforded compound **8** (159mg, 49%) as a white solid: Mp 213-215 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.98 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.40 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.30 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.22 (d, *J* = 7.4 Hz, 1H), 4.17 (brs, 1H), 3.80-3.66 (m, 2H), 3.21-3.10 (m, 1H), 2.89-2.79 (m, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.93-1.79 (m, 2H), 1.42-1.19 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). Purity 96%. HRMS calculated for $C_{19}H_{23}N_3O_2 - H^+$ 324.1712; found (ESI(-), [M-H]) 324.1683.

1-(1-Propionylpiperidin-4-yl)-3-(pyridin-3-yl)urea (9). Pyridine-3-isocyanate was reacted with **1** by Method B. Flash chromatography eluted with 9:1 EtOAc:MeOH afforded compound **9** (266mg, 96%) as a colorless oil: ^{1}H NMR (500MHz, DMSO-d_6) δ 8.52 (d, *J* = 2.3 Hz, 1H), 8.47 (s, 1H), 8.11 (d, *J* = 4.5 Hz, 1H), 7.86 (brd, *J* = 8.5 Hz, 1H), 7.24 (dd, *J* = 8.5, 4.5 Hz, 1H), 6.29 (d, *J* = 7.5 Hz, 1H), 4.18 (d, *J* = 11.9 Hz, 1H), 3.81-3.67 (m, 2H), 3.19-3.09 (m, 1H), 2.80 (dd, *J* = 11.6, 11.6 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.86 (d, *J* = 12.3, 1H), 1.81 (d, *J* = 12.3 Hz, 1H), 1.39-1.20 (m, 2H), 1.18 (t, *J* = 7.4 Hz, 3H). Purity 83% by ^{1}H-NMR. The purity of **9** was assessed by ^{1}H-NMR due to co-elution of a contaminant with the compound of interest. This contaminant, N,N'-bis-(3-pyridyl)urea, was made separately and is inactive against sEH. HRMS calculated for $C_{14}H_{20}N_4O_2 - H^+$ 275.1508; found (ESI(-), [M-H]) 275.1511.

1-(1-Propionylpiperidin-4-yl)-3-*o*-tolylurea (10). *o*-Tolyl isocyanate was prepared from *o*-toluidine by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 16:1 EtOAc:MeOH afforded compound **10** (88mg, 30%) as a white solid: Mp 178-183 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.55 (s, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.07 (dd, *J* = 7.7, 7.7Hz, 1H), 6.85 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 4.16 (d, *J* = 13.1 Hz, 1H), 3.75 (d, *J* = 13.8 Hz, 1H), 3.72-3.65 (m, 1H), 3.14 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.82 (dd, *J* = 11.4, 11.4 Hz,

1H), 2.32 (q, *J* = 7.4 Hz, 2H), 2.17 (s, 3H), 1.87 (d, *J* = 11.4Hz, 1H), 1.82 (d, *J* = 11.4Hz, 1H), 1.30 (q, *J* = 11.5Hz, 1H), 1.20 (q, *J* = 11.5Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H). Purity 95%. HRMS calculated for $C_{16}H_{23}N_3O_2 + H^+$ 290.1868; found (ESI(+), [M+H]) 290.1822.

1-(1-Propionylpiperidin-4-yl)-3-*m*-tolylurea (11). *m*-Tolyl isocyanate was prepared from *m*-toluidine by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH and recrystallization from EtOAc:MeOH afforded compound **11** (74mg, 26%) as a white solid: Mp 173-175 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.20 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.13 (d, *J* = 7.3 Hz, 1H), 4.17 (d, *J* = 13.0 Hz, 1H), 3.75 (d, *J* = 13.8 Hz, 1H), 3.72-3.63 (m, 1H), 3.12 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.79 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 2.23 (s, 3H), 1.84 (d, *J* = 11.8 Hz, 1H), 1.79 (d, *J* = 11.8 Hz, 1H), 1.30 (q, *J* = 11.8Hz, 1H), 1.19 (q, *J* = 11.8Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 98%. HRMS calculated for $C_{16}H_{23}N_3O_2 - H^+$ 288.1712; found (ESI(-), [M-H]) 288.1693.

1-(1-Propionylpiperidin-4-yl)-3-*p*-tolylurea (12). *p*-Tolyl isocyanate was prepared from *p*-toluidine by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **12** (81mg, 28%) as a white solid: Mp 180-182 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.09 (d, *J* = 7.5 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.75 (d, *J* = 12.9 Hz, 1H), 3.71-3.63 (m, 1H), 3.12 (dd, *J* = 11.6, 11.6 Hz, 1H), 2.78 (dd, *J* = 11.6, 11.6 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 2.21 (s, 3H), 1.84 (d, *J* = 11.6 Hz, 1H), 1.78 (d, *J* = 11.6 Hz, 1H), 1.30 (q, *J* = 11.8Hz, 1H), 1.20 (q, *J* = 11.8Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 97%. HRMS calculated for $C_{16}H_{23}N_3O_2 - H^+$ 288.1712; found (ESI(-), [M-H]) 288.1716.

1-(4-Ethylphenyl)-3-(1-propionylpiperidin-4-yl)urea (13). 4-Ethylphenyl isocyanate was prepared from 4-ethylaniline by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 17:1 EtOAc:MeOH and recrystallization from acetone afforded compound **13** (46mg, 15%) as a white solid: Mp 164-165 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.10 (d, *J* = 7.9, Hz, 1H), 4.17 (d, *J* = 13.2 Hz, 1H), 3.75 (d, *J* = 12.9 Hz, 1H), 3.72-3.63 (m, 1H), 3.12 (dd, *J* = 12.0 Hz, 1H), 2.79 (dd, *J* = 12.0 Hz, 1H), 2.54-

2.47 (m, 2H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.84 (dd, *J* = 12.0 Hz, 1H), 1.79 (dd, *J* = 12.0 Hz, 1H) 1.29 (ddd, *J* = 12.0, 12.0, 4.1 Hz, 1H), 1.19 (ddd, *J* = 12.0, 12.0, 4.1 Hz, 1H), 1.13 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 97%. HRMS calculated for $C_{17}H_{25}N_3O_2$ + H^+ 304.2025; found (ESI(+), [M+H]) 304.2005.

1-(4-Isopropylphenyl)-3-(1-propionylpiperidin-4-yl)urea (14). 4-Isopropylphenyl isocyanate was prepared from 4-isopropylaniline by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH and recrystallization from acetone afforded compound **14** (44mg, 14%) as a white solid. Mp 173-174 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.25-8.18 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.10 (d, *J* = 7.3 Hz, 1H), 4.17 (brd, *J* = 12.6 Hz, 1H), 3.75 (brd, *J* = 13.2 Hz, 1H), 3.71-3.63 (m, 1H), 3.12 (dd, *J* = 12.0 Hz, 1H), 2.83-2.75 (m, 2H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.34-1.18 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 6H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 98%. HRMS calculated for $C_{18}H_{27}N_3O_2$ - H^+ 316.2025; found (ESI(-), [M-H]) 316.1981.

1-(4-Methoxyphenyl)-3-(1-propionylpiperidin-4-yl)urea (15). 4-Methoxyphenyl isocyanate was prepared from *p*-anisidine by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH afforded compound **15** (82mg, 27%) as a white solid: Mp 164-165 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.04 (d, *J* = 7.6 Hz, 1H), 4.17 (brd, *J* = 12.9 Hz, 1H), 3.75 (brd, *J* = 13.2 Hz, 1H), 3.69 (s, 3H), 3.68-3.63 (m, 1H, obscured by s δ 3.69), 3.11 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.78 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.31 (q, *J* = 7.3 Hz, 2H), 1.84 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.78 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.34-1.14 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). Purity 95%. HRMS calculated for $C_{16}H_{23}N_3O_3$ + H^+ 306.1817; found (ESI(+), [M+H]) 306.1780.

1-(4-Phenoxyphenyl)-3-(1-propionylpiperidin-4-yl)urea (16). 4-Phenoxyphenyl isocyanate was prepared from 4-phenoxyaniline by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **16** (191mg, 52%) as a white solid: Mp 153-154 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.34 (dd, *J* = 7.9, 7.9 Hz,

2H), 7.07 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.92 (brd, *J* = 7.2 Hz, 4H), 6.14 (d, *J* = 7.5 Hz, 1H), 4.18 (d, *J* = 12.1 Hz, 1H), 3.76 (d, *J* = 12.8 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.79 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.31 (q, *J* = 12.0 Hz, 1H), 1.20 (q, *J* = 12.0 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 96%. HRMS calculated for $C_{21}H_{25}N_3O_3 + H^+$ 368.1974; found (ESI(+), [M+H]) 368.1937.

1-(3,4-Methylenedioxyphenyl)-3-(1-propionylpiperidin-4-yl)urea (17). 3,4-Methylenedioxyaniline (274mg, 2mmol) was subject to Method C to give the desired urea via an intermediate 4-nitrophenyl carbamate. Flash chromatography eluted with EtOAc afforded compound **17** (238mg, 37%) as a white solid: Mp 195-197 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.14 (d, *J* = 1.5 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.65 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 5.92 (s, 2H), 4.16 (brd, *J* = 12.3 Hz, 1H), 3.74 (d, *J* = 12.5 Hz, 1H), 3.71-3.62 (m, 1H), 3.12 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.79 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 11.7 Hz, 1H), 1.78 (d, *J* = 11.7 Hz, 1H), 1.30 (q, *J* = 11.7 Hz, 1H), 1.20 (q, *J* = 11.7 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H). Purity 98%. HRMS calculated for $C_{16}H_{21}N_3O_4 + H^+$ 320.1610; found (ESI(+), [M+H]) 320.1634.

1-(1-Propionylpiperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)urea (18). 3,4,5-Trimethoxyphenyl isocyanate was prepared from 3,4,5-trimethoxyaniline by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH and recrystallization from EtOAc afforded compound **18** (56mg, 15%) as a white solid: Mp 173-175 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.28 (s, 1H), 6.72 (s, 2H), 6.10 (d, *J* = 7.6 Hz, 1H), 4.18 (d, *J* = 13.3 Hz, 1H), 3.76 (d, *J* = 13.9 Hz, 1H), 3.71 (s, 6H), 3.69-3.63 (m, 1H), 3.58 (s, 3H), 3.11 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.78 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.83 (d, *J* = 11.4 Hz, 1H), 1.78 (d, *J* = 11.4 Hz, 1H), 1.30 (ddd, *J* = 11.4, 11.4, 3.5 Hz, 1H), 1.20 (ddd, *J* = 11.4, 11.4, 3.5 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 99%. HRMS calculated for $C_{18}H_{27}N_3O_2 - H^+$ 364.1873; found (ESI(-), [M-H]) 364.1906.

1-(4-Morpholinophenyl)-3-(1-propionylpiperidin-4-yl)urea (19). 4-Morpholinophenyl isocyanate was prepared from 4-morpholinoaniline by Method A using 1M NaOH in brine as the base and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 9:1 EtOAc:MeOH

afforded compound **19** (61mg, 17%) as a white solid: Mp 221-225 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.03 (d, *J* = 7.6 Hz, 1H), 4.17 (d, *J* = 13.5 Hz, 1H), 3.79-3.73 (m, 1H, obscured by d), 3.71 (appt. t, *J* = 12.2 Hz, 4H), 3.69-3.62 (m, 1H), 3.11 (dd, *J* = 11.7 Hz, 1H), 2.98 (appt. t, *J* = 4.5 Hz, 4H), 2.78 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.83 (d, *J* = 11.7Hz, 1H), 1.78 (d, *J* = 11.7Hz, 1H), 1.29 (q, *J* = 11.7 Hz, 1H), 1.17 (q, *J* = 11.7 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 93%. HRMS calculated for $C_{19}H_{28}N_4O_3 + H^+$ 359.2083; found (ESI(+), [M+H]) 359.2068.

1-(4-Nitrophenyl)-3-(1-propionylpiperidin-4-yl)urea (20). 4-Nitrophenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH afforded compound **20** (122mg, 38%) as a white solid: Mp 240-241 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.14 (d, *J* = 9.2 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 2H), 6.49 (d, *J* = 7.5 Hz, 1H), 4.20 (brd, *J* = 13.2 Hz, 1H), 3.80-3.68 (m, 2H), 3.13 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.79 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.86 (d, *J* = 11.9 Hz, 1H), 1.81 (d, *J* = 11.9 Hz, 1H), 1.34 (q, *J* = 11.9 Hz, 1H), 1.24 (q, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 95%. HRMS calculated for $C_{15}H_{20}N_4O_4 - H^+$ 319.1407; found (ESI(-), [M-H]) 319.1410.

Methyl 4-(3-(1-propionylpiperidin-4-yl)ureido)benzoate (21). Methyl 4-isocyanatobenzoate was reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH afforded compound **21** (271mg, 82%) as a white solid: Mp 201-204 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 7.5 Hz, 1H), 4.18 (brd, *J* = 13.0 Hz, 1H), 3.80 (s, 3H), 3.78-3.65 (m, 2H), 3.13 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.79 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.83 (d, *J* = 11.9 Hz, 1H), 1.78 (d, *J* = 11.9 Hz, 1H), 1.31 (q, *J* = 11.9 Hz, 1H), 1.20 (q, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 96%. HRMS calculated for $C_{17}H_{23}N_3O_4 - H^+$ 332.1611; found (ESI(-), [M-H]) 332.1595.

4-(3-(1-Propionylpiperidin-4-yl)ureido)benzoic acid (22). Compound **21** (85mg, 0.25mmol) was refluxed in ethanol (10mL) containing 1M NaOH (300µl, 1.2eq) for 5 hours. Additional base (300µl) was added and the reaction continued for 2 hours before cooling to RT The reaction was quenched with

1N HCl (20mL), the organic solvent removed and the remaining suspension filtered to give compound **22** (49mg, 60%) as a white solid: MP 201-204 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.73 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 7.6 Hz, 1H), 4.18 (brd, *J* = 13.2 Hz, 1H), 3.76 (brd, *J* = 13.5 Hz, 1H), 3.73-3.66 (m, 1H), 3.13 (dd, *J* = 11.9 Hz, 1H), 2.80 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.85 (dd, *J* = 11.9 Hz, 1H), 1.80 (dd, *J* = 11.9 Hz, 1H), 1.32 (q, *J* = 11.9 Hz, 1H), 1.22 (q, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 94%. HRMS calculated for $C_{16}H_{21}N_3O_4$ - H^+ 318.1454; found (ESI(-), [M-H]) 318.1498.

1-(4-Hydroxyphenyl)-3-(1-propionylpiperidin-4-yl)urea (23). 4-Benzyloxyphenyl isocyanate was prepared from 4-benzyloxyanline by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc gave intermediate 1-(4-benzyloxyphenyl)-3-(1-propionylpiperidin-4-yl)urea, which was dissolved in ethanol and hydrogenolyzed with 10% palladium on charcoal under an atmosphere of hydrogen. Flash chromatography eluted with 15:1 DCM:MeOH gave compound **23** (13mg, 5% overall) as a white solid: Mp 229-230 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.92 (s, 1H), 7.97 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.98 (d, *J* = 7.4 Hz, 1H), 4.17 (brd, *J* = 12.1 Hz, 1H), 3.75 (brd, *J* = 13.2 Hz, 1H), 3.70-3.62 (m, 1H), 3.11 (dd, *J* = 12.1, 12.1 Hz, 1H), 2.78 (dd, *J* = 12.1, 12.1 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.83 (dd, *J* = 12.1, 12.1 Hz, 1H), 1.76 (dd, *J* = 12.1, 12.1 Hz, 1H), 1.28 (q, *J* = 12.1 Hz, 1H), 1.18 (q, *J* = 12.1 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 100%. HRMS calculated for $C_{15}H_{21}N_3O_3$ + H^+ 292.1661; found (ESI(+), [M+H]) 292.1618.

1-(4-Fluorophenyl)-3-(1-propionylpiperidin-4-yl)urea (24). 4-Fluorophenyl isocyanate was prepared from 4-fluoroaniline by Method A and was subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **24** (106mg, 36%) as a white solid: Mp 183-184 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.40-7.35 (m, 2H), 7.05 (t, *J* = 8.8 Hz, 2H), 6.14 (d, *J* = 7.6 Hz, 1H), 4.18 (brd, *J* = 13.1 Hz, 1H), 3.75 (brd, *J* = 13.3 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.78 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 12.0 Hz,

1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.30 (q, *J* = 12.0 Hz, 1H), 1.20 (q, *J* = 12.0 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 100%. HRMS calculated for $C_{15}H_{20}FN_3O_2$ - H^+ 292.1462; found (ESI(-), [M-H]) 292.1444.

1-(4-Chlorophenyl)-3-(1-propionylpiperidin-4-yl)urea (25). 4-Chlorophenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with 15:1 EtOAc:MeOH and recrystallization from acetone:hexane afforded compound **25** (53mg, 17%) as a white solid: Mp 225-226 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.26 (d, *J* = 7.6 Hz, 1H), 4.17 (brd, *J* = 13.0 Hz, 1H), 3.75 (brd, *J* = 13.6 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* = 11.1, 11.1 Hz, 1H), 2.79 (dd, *J* = 11.1, 11.1 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.84 (brd, *J* = 11.1 Hz, 1H), 1.79 (brd, *J* = 11.1 Hz, 1H), 1.31 (ddd, *J* = 11.1, 11.1, 4.0 Hz, 1H), 1.21 (ddd, *J* = 11.1, 11.1, 4.0 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 96%. HRMS calculated for $C_{15}H_{20}ClN_3O_2$ - H^+ 308.1166; found (ESI(-), [M-H]) 308.1152.

1-(4-Bromophenyl)-3-(1-propionylpiperidin-4-yl)urea (26). 4-Bromophenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **26** (201mg, 57%) as a white solid: Mp 233-239 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 6.21 (d, *J* = 7.6 Hz, 1H), 4.18 (brd, *J* = 13.0 Hz, 1H), 3.75 (brd, *J* = 13.8 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.78 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.82 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.30 (ddd, *J* = 12.0, 12.0, 3.5 Hz, 1H), 1.20 (ddd, *J* = 12.0, 12.0, 3.5 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 94%. HRMS calculated for $C_{15}H_{20}BrN_3O_2$ + H^+ 354.0817; found (ESI(+), [M+H]) 354.0774.

1-(4-Iodophenyl)-3-(1-propionylpiperidin-4-yl)urea (27). 4-Iodophenyl isocyanate was prepared on a 2mmol scale from 4-iodoaniline by Method A and was subsequently reacted with **1** by Method B. Trituration twice from 1:1 EtOAc:MeOH, flash chromatography eluted with 8:1 EtOAc:MeOH and recrystallization from acetone:MeOH afforded compound **27** (39mg, 5%) as a white solid: Mp 246-247 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.21 (d, *J* = 7.6 Hz, 1H), 4.17 (brd, *J* = 12.9 Hz, 1H), 3.75 (brd, *J* = 14.3 Hz, 1H), 3.72-3.63 (m, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.78 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* =

12.0 Hz, 1H), 1.78 (d, *J* = 12.0 Hz, 1H), 1.30 (q, *J* = 12.0 Hz, 1H), 1.20 (q, *J* = 12.0 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 95%. HRMS calculated for $C_{15}H_{20}IN_3O_2$ - H^+ 400.0522; found (ESI(-), [M-H]) 400.0488.

1-(3-Fluorophenyl)-3-(1-propionylpiperidin-4-yl)urea (28). 3-Fluorophenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **28** (231mg, 79%) as a white solid: Mp 158-164 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.44 (d, J_{HF} = 12.2 Hz, 1H), 7.23 (appt. q, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.69 (ddd, *J* = 8.1, 8.1, 1.4 Hz, 1H), 6.25 (d, *J* = 7.5 Hz, 1H), 4.18 (brd, *J* = 13.0 Hz, 1H), 3.76 (brd, *J* = 13.3 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.78 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.32 (q, *J* = 7.3 Hz, 2H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.31 (q, *J* = 12.0 Hz, 1H), 1.21 (q, *J* = 12.0 Hz, 1H), 0.98 (t, *J* = 7.3 Hz, 3H). Purity 97%. HRMS calculated for $C_{15}H_{20}FN_3O_2$ - H^+ 294.1608; found (ESI(-), [M-H]) 294.1587.

1-(2-Fluorophenyl)-3-(1-propionylpiperidin-4-yl)urea (29). The reaction of 2-fluorophenyl isocyanate with **1** in the same manner as for compound **27** afforded compound **29** (118mg, 40%) as a white solid: Mp 127-130 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.19 (d, *J* = 1.3 Hz, 1H), 8.12 (ddd, *J* = 1.0, 8.2, 8.2 Hz, 1H), 7.17 (dd, J_{HH} = 8.2 Hz, J_{HF} = 11.6, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.91 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 4.12 (brd, *J* = 13.1 Hz, 1H), 3.77-3.66 (m, 2H), 3.15 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.86 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.86 (d, *J* = 11.5 Hz, 1H), 1.80 (d, *J* = 11.5 Hz, 1H), 1.30 (ddd, *J* = 11.5, 11.5, 3.3 Hz, 1H), 1.20 (ddd, *J* = 11.5, 11.5, 3.3 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 94%. HRMS calculated for $C_{15}H_{20}FN_3O_2$ - H^+ 294.1608; found (ESI(-), [M-H]) 294.1589.

1-(3-Chlorophenyl)-3-(1-propionylpiperidin-4-yl)urea (30). 3-Chlorophenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **30** (116mg, 38%) as a white solid: Mp 165-166 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.66 (t, *J* = 1.9 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.93 (dq, *J* = 8.0, 1.0 Hz, 1H), 6.26 (d, *J* = 7.6 Hz, 1H), 4.19 (brd, *J* = 13.3 Hz, 1H), 3.76 (brd, *J* = 13.3 Hz, 1H), 3.72-3.64 (m, 1H), 3.12 (dd, *J* =

11.4, 11.4 Hz, 1H), 2.78 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 11.4, 1H), 1.79 (d, *J* = 11.4 Hz, 1H), 1.33 (dq, *J* = 3.8, 11.4 Hz, 1H), 1.21 (dq, *J* = 3.8, 11.4 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 97%. HRMS calculated for $C_{15}H_{20}ClN_3O_2$ - H^+ 308.1166; found (ESI(-), [M-H]) 308.1111.

1-(2-Chlorophenyl)-3-(1-propionylpiperidin-4-yl)urea (31). 2-Chloroaniline (128mg, 1mmol) was subject to Method C. Flash chromatography eluted with EtOAc afforded compound **31** (48mg, 16%) as a white solid: Mp 150-157 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.91 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.05 (d, *J* = 6.9 Hz, 1H), 6.94 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.12 (brd, *J* = 11.7 Hz, 1H), 3.79-3.67 (m, 2H), 3.16 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.88 (dd, *J* = 11.7, 11.7 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.88 (d, *J* = 11.7, 1H), 1.82 (d, *J* = 11.7 Hz, 1H), 1.37-1.16 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). Purity 92%. HRMS calculated for $C_{15}H_{20}ClN_3O_2$ + H^+ 310.1322; found (ESI(+), [M+H]) 310.1311.

1-(3,4-Dichlorophenyl)-3-(1-propionylpiperidin-4-yl)urea (32). 3,4-Dichlorophenyl isocyanate was prepared from 3,4-dichloroaniline by Method A (using NaOH and brine as the base) and was subsequently reacted with **1** by Method B. Flash chromatography eluted with 17:1 EtOAc:MeOH and recrystallization from EtOAc afforded compound **32** (68mg, 20%) as a white solid: Mp 198-200 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.23 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 4.19 (brd, *J* = 13.1 Hz, 1H), 3.76 (brd, *J* = 13.8 Hz, 1H), 3.73-3.64 (m, 1H), 3.11 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.77 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 11.9 Hz, 1H), 1.79 (d, *J* = 11.9 Hz, 1H), 1.32 (d, *J* = 11.9 Hz, 1H), 1.22 (d, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.3 Hz, 3H). Purity 98%. HRMS calculated for $C_{15}H_{19}Cl_2N_3O_2$ + H^+ 342.0776; found (ESI(+), [M+H]) 342.0757.

1-(3,5-Dichlorophenyl)-3-(1-propionylpiperidin-4-yl)urea (33). 3,5-Dichlorophenyl isocyanate was prepared from 3,5-dichloroaniline by Method A and subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc and recrystallization from EtOAc:acetone afforded compound **33** (22mg, 6%) as a white solid: Mp 196-198 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.46 (d, *J*

= 1.5 Hz, 2H), 7.07 (t, *J* = 1.5 Hz, 1H), 6.40 (d, *J* = 7.6 Hz, 1H), 4.20 (d, *J* = 13.0 Hz, 1H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.73-3.64 (m, 1H), 3.11 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.75 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.32 (d, *J* = 12.0 Hz, 1H), 1.22 (d, *J* = 12.0 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 100%. HRMS calculated for $C_{15}H_{19}Cl_2N_3O_2$ + H^+ 344.0932; found (ESI(+), [M+H]) 344.0897.

1-(2,6-Dichlorophenyl)-3-(1-propionylpiperidin-4-yl)urea (34). 2,6-Dichlorophenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc afforded compound **34** (229mg, 67%) as a white solid: Mp 170-174 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.25 (t, *J* = 8.1 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 4.20 (brd, *J* = 13.2 Hz, 1H), 3.77 (brd, *J* = 13.0 Hz, 1H), 3.70-3.60 (m, 1H), 3.10 (dd, *J* = 12.0 Hz, 1H), 2.75 (dd, *J* = 12.0 Hz, 1H), 2.31 (q, *J* = 7.3 Hz, 2H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.79 (d, *J* = 12.0 Hz, 1H), 1.32 (dq, *J* = 3.8, 12.0 Hz, 1H), 1.22 (dq, *J* = 3.8, 12.0 Hz, 1H), 0.98 (t, *J* = 7.4, 3H). Purity 95%. HRMS calculated for $C_{15}H_{19}Cl_2N_3O_2$ - H^+ 342.0776; found (ESI(-), [M-H]) 342.0801.

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(1-propionylpiperidin-4-yl)urea (35). 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc and recrystallization from EtOAc afforded compound **35** (89mg, 24%) as a white solid: Mp 182-184 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.06 (s, 1H), 7.54 (d, *J* = 1 Hz, 2H), 6.37 (d, *J* = 7.6 Hz, 1H), 4.20 (brd, *J* = 13.2 Hz, 1H), 3.77 (brd, *J* = 13.9 Hz, 1H), 3.70 (s, 1H), 3.11 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.76 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.84 (d, *J* = 11.9 Hz, 1H), 1.79 (d, *J* = 11.9 Hz, 1H), 1.34 (q, *J* = 11.9 Hz, 1H), 1.24 (q, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 95%. HRMS calculated for $C_{16}H_{19}ClF_3N_3O_2$ + H^+ 378.1196; found (ESI(+), [M+H]) 378.1198.

1-(1-Propionylpiperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea (36). 4-Trifluoromethylphenyl isocyanate was reacted with **1** by Method B. Recrystallization from EtOAc:hexanes afforded compound **36** (166mg, 48%) as a white solid: Mp 224-228 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.61-7.54 (m, 4H), 6.33 (d, *J* = 7.5 Hz, 1H), 4.19 (brd, *J* = 12.9 Hz, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.74-3.66 (m, 1H), 3.13 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.79 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H),

1.85 (d, *J* = 11.8 Hz, 1H), 1.80 (d, *J* = 11.8 Hz, 1H), 1.33 (q, *J* = 11.8 Hz, 1H), 1.22 (q, *J* = 11.8 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 94%. HRMS calculated for $C_{16}H_{20}F_3N_3O_2$ - H^+ 342.1430; found (ESI(-), [M-H]) 342.1404.

1-(1-Propionylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)urea (37). 3-Trifluoromethylphenyl isocyanate was reacted with **1** by Method B. Flash chromatography eluted with EtOAc and recrystallization from EtOAc:hexanes afforded compound **37** (30mg, 9%) as a white solid: Mp 153-154 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.96 (s, 1H), 7.50-7.41 (m, 2H), 7.22 (d, *J* = 6.9 Hz, 1H), 6.31 (d, *J* = 7.4 Hz, 1H), 4.20 (brd, *J* = 13.1 Hz, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 3.74-3.65 (m, 1H), 3.12 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.77 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.85 (d, *J* = 11.9 Hz, 1H), 1.80 (d, *J* = 11.9 Hz, 1H), 1.33 (q, *J* = 11.9 Hz, 1H), 1.22 (q, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 98%. HRMS calculated for $C_{16}H_{20}F_3N_3O_2$ - H^+ 342.1430; found (ESI(-), [M-H]) 342.1419.

1-(4-Perfluoroisopropylphenyl)-3-(1-propionylpiperidin-4-yl)urea (38). 4-Perfluoroisopropyl-aniline was prepared as described[14] and converted to the corresponding isocyanate by Method A using NaOH in brine as the base and was subsequently reacted with **1** by Method B. Flash chromatography eluted with EtOAc and recrystallization from EtOAc:hexanes afforded compound **38** (43mg, 10%) as a white solid: Mp 160-164 ºC dec. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 6.32 (d, *J* = 7.4 Hz, 1H), 4.19 (brd, *J* = 12.6 Hz, 1H), 3.76 (brd, *J* = 13.6 Hz, 1H), 3.73-3.66 (m, 1H), 3.13 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.79 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.80 (d, *J* = 12.0 Hz, 1H), 1.37-1.17 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 100%. HRMS calculated for $C_{18}H_{20}F_7N_3O_2$ + H^+ 444.1522; found (ESI(+), [M+H]) 444.1505.

1-(2-Methyl-4-perfluoroisopropylphenyl)-3-(1-propionylpiperidin-4-yl)urea (39). 2-Methyl-4-perfluoroisopropylaniline[14] and compound **39** (41mg, 9%) were prepared as for compound **38**: Mp 226-229 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.6 Hz, 1H), 7.84 (s, 1H), 7.40-7.35 (m, 2H), 6.87 (d, *J* = 7.2 Hz, 1H), 4.16 (brd, *J* = 12.8 Hz, 1H), 3.80-3.67 (m, 2H), 3.15 (dd, *J* = 12.1, 12.1 Hz, 1H),

2.84 (dd, *J* = 12.1, 12.1 Hz, 1H), 2.33 (q, *J* = 7.4 Hz, 2H), 2.26 (s, 3H), 1.88 (d, *J* = 12.1 Hz, 1H), 1.83 (d, *J* = 12.1 Hz, 1H), 1.33 (q, *J* = 12.1 Hz, 1H), 1.22 (q, *J* = 12.1 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H). Purity 100%. HRMS calculated for $C_{19}H_{22}F_7N_3O_2$ - H^+ 456.1522; found (ESI(-), [M-H]) 456.1512.

1-(1-Propionylpiperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (40). To an ice cold solution of intermediate **41** (242mg, 0.84mmol) in DCM (5mL) was added triethylamine (250µL, 1.8mmol) followed by propionyl chloride (95µL, 1.1mmol). The reaction was allowed to warm to rt and was stirred for 5 hours. Flash chromatography eluted with 15:1 EtOAc:MeOH afforded compound **40** (178mg, 63%) as a white solid: Mp 195-196 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.23 (d, *J* = 7.6 Hz, 1H), 4.18 (brd, *J* = 12.8 Hz, 1H), 3.76 (brd, *J* = 13.6 Hz, 1H), 3.73-3.65 (m, 1H), 3.12 (dd, *J* = 11.9 Hz, 1H), 2.78 (t, *J* = 11.9 Hz, 1H), 2.32 (q, *J* = 7.4 Hz, 2H), 1.85 (d, *J* = 11.9 Hz, 1H), 1.79 (d, *J* = 11.9 Hz, 1H), 1.31 (q, *J* = 11.9 Hz, 1H), 1.21 (q, *J* = 11.9 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). Purity 97%. HRMS calculated for $C_{16}H_{20}F_3N_3O_3$ - H^+ 358.1379; found (ESI(-), [M-H]) 358.1404.

***tert*-Butyl 4-(3-(4-(trifluoromethoxy)phenyl)ureido)piperidine-1-carboxylate (41)**. 4-Trifluoromethoxyphenyl isocyanate (1.03g, 5mmol) was dissolved in dry THF (10mL) and cooled in an ice bath. A solution of N-BOC-4-aminopiperidine (781mg, 5mmol) in dry THF (10mL) was slowly added. The reaction was allowed to warm to RT and stir for 12 hours. The solvent was removed and the residue chromatographed from ethyl acetate to give intermediate **41** (1.71g, 95%) as a white solid: Mp 160–162 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 7.6 Hz, 1H), 3.81 (brd, *J* = 13.0 Hz, 2H), 3.67-3.59 (m, 1H), 2.90 (brs, 2H), 1.79 (dd, *J* = 12.1, 3.3 Hz, 2H), 1.40 (s, 9H), 1.25 (dq, *J* = 3.3, 12.1, Hz, 2H). HRMS calculated for $C_{18}H_{24}F_3N_3O_4$ - H^+ 402.1641; found (ESI(-), [M-H]) 402.1612.

1-(Piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (42). Intermediate **41** (2.02g, 5.0mmol) was treated with 1M HCl in methanol (35mL) and refluxed for 3 hours. The solvent was evaporated and the residue diluted with 1N NaOH. The resulting precipitate was removed by filtration and further dried under high vacuum to give intermediate **42** (1.35g, 89%) as a white solid: Mp 169-173 ºC. ^{1}H NMR

(500MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.15 (d, *J* = 7.7 Hz, 1H), 3.55-3.45 (m, 1H), 2.89 (dt, *J* = 12.3, 3.5 Hz, 2H), 2.49-2.45 (m, 2H), 2.13 (brs, 1H), 1.74 (dd, *J* = 10.7, 3.0 Hz, 2H), 1.21 (dq, *J* = 3.0, 10.7 Hz, 2H). HRMS calculated for $C_{13}H_{16}F_3N_3O_2$ - H^+ 302.1117; found (ESI(-), [M-H]) 302.1114.

Propyl 3,4,5-tribenzyloxybenzoate (43).[15] ^{1}H NMR (500MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 4H), 7.41-7.30 (m, 10H), 7.30-7.23 (m, 3H), 5.14 (s, 4H), 5.12 (s, 2H), 4.24 (t, *J* = 6.7 Hz, 2H), 1.81-1.72 (sxt, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

3,4,5-Tribenzyloxybenzoic acid (44).[15] Not characterized.

Ethyl (4-benzyl-piperazin-1-yl)acetate (45).[16] ^{1}H NMR (500MHz, DMSO-d_6, 50 ºC) δ 7.33-7.19 (m, 5H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.45 (s, 2H), 3.17 (s, 2H), 2.51 (dd, *J* = 4.5, 4.5 Hz, 2H) 2.50-2.45 (m, 2H), 2.37 (dd, *J* = 4.5, 4.5 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 3H).

(4-Benzyl-piperazin-1-yl)acetic acid (46).[24] ^{1}H NMR (500MHz, DMSO-d_6) δ 7.32 (tt, *J* = 6.9, 1.4, 2H) 7.29 (d, *J* = 6.9 Hz, 2H) 7.24 (t, *J* = 6.9 Hz, 1H), 3.46 (s, 2H), 3.13 (s, 2H), 2.64 (brs, 4H), 2.42 (brs, 4H).

1-(1-Isonicotinoylpiperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (47). Intermediate **42** (152mg, 0.5mmol) was reacted with isonicotinic acid by Method E. Flash chromatography eluted with 9:1 DCM:MeOH afforded compound **47** (204mg, 100%) as a white solid: Mp 210-212 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.67 (dd, *J* = 4.4, 1.4 Hz, 2H), 8.59 (s, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.38 (dd, *J* = 4.4, 1.4 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 7.6 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 3.76 (s, 1H), 3.41 (d, *J* = 12.3 Hz, 1H), 3.16 (dd, *J* = 11.7, 11.7 Hz, 1H), 3.05 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.92 (d, *J* = 11.7 Hz, 1H), 1.79 (d, *J* = 11.7 Hz, 1H), 1.47-1.29 (m, 2H). Purity 92%. HRMS calculated for $C_{19}H_{19}F_3N_4O_3$ - H^+ 407.1331; found (ESI(-), [M-H]) 407.1316.

1-(1-(6-Chloronicotinoyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (48). The reaction of **42** with 6-chloronicotinic in the same manner as for compound **46** afforded compound **48** (220mg, 100%) as a white solid: Mp 208-209 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.46 (d, *J* = 2.2 Hz, 1H), 7.90 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* =

8.8 Hz, 2H), 6.22 (d, *J* = 7.6 Hz, 1H), 4.28 (brs, 1H), 3.71-3.81 (m, 1H), 3.50 (brs, 1H), 3.26-3.02 (m, 2H), 1.87 (brs, 2H), 1.40 (brs, 2H). Purity 94%. HRMS calculated for $C_{19}H_{18}ClF_3N_4O_3$ - H^+ 441.0942; found (ESI(-), [M-H]) 441.0942.

1-(((Pyridin-2-yl)acetyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (49). The reaction of **42** with 2-pyridyl acetic acid in the same manner as for compound **46** afforded compound **49** (196mg, 93%) as a white solid: Mp 183-187 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.48 (d, *J* = 4.3 Hz, 1H), 8.43 (s, 1H), 7.73 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.26-7.22 (dd, *J* = 5.0, 7.7 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.17 (d, *J* = 7.5 Hz, 1H), 4.16 (brd, *J* = 12.0 Hz, 1H), 3.91 (brd, *J* = 13.3 Hz, 1H), 3.87 (s, 2H), 3.74-3.65 (m, 1H), 3.18 (dd, *J* = 11.8 Hz, 1H), 2.86 (dd, *J* =11.8, 11.8 Hz, 1H), 1.84-1.75 (m, 2H), 1.27-1.15 (m, 2H). Purity 91%. HRMS calculated for $C_{20}H_{21}F_3N_4O_3$ - H^+ 421.1488; found (ESI(-), [M-H]) 421.1477.

1-(1-(2-(4-Benzylpiperazin-1-yl)acetyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (50). Intermediate **42** (303mg, 1mmol) was reacted with carboxylic acid **46** by Method E. Flash chromatography eluted with 9:1 DCM:MeOH afforded compound **50** (379mg, 73%) as a white solid: Mp 178-183 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.34-7.26 (m, 4H), 7.26-7.19 (m, 3H), 6.25 (d, *J* = 7.5 Hz, 1H), 4.14 (brd, *J* = 13.4 Hz, 1H), 3.95 (brd, *J* = 12.5 Hz, 1H), 3.75-3.66 (m, 1H), 3.45 (s, 2H), 3.23 (d, *J* = 13.1 Hz, 1H), 3.12 (dd, *J* = 11.9, 11.9 Hz, 1H), 3.00 (d, *J* = 13.1 Hz, 1H), 2.78 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.47-2.30 (m, 8H), 1.85 (d, *J* = 11.9 Hz, 1H), 1.80 (d, *J* = 11.9 Hz, 1H), 1.35 (q, *J* = 11.9 Hz, 1H), 1.17 (q, *J* = 11.9 Hz, 1H). Purity 90%. HRMS calculated for $C_{26}H_{32}F_3N5O_3$ - H^+ 518.2379; found (ESI(-), [M-H]) 518.2365.

1-(1-((4-Acetylpiperazin-1-yl)acetyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (51). Compound **50** (110mg, 0.21mmol) was deprotected by stirring overnight with 10% Pd/C in ethanol (15mL) under a hydrogen atmosphere. The reaction was filtered through a bed of celite and the filtrate evaporated to give intermediate 1-(1-((piperazin-1-yl)acetyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (103mg, quantitative) as a clear oil, which was used without purification and coupled with acetic acid by Method E. Flash chromatography eluted with 9:1 DCM:MeOH and

recrystallization from EtOAc:hexanes afforded compound **51** (73mg, 74% over 2 steps) as a white solid: Mp 111-122 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.25 (d, *J* = 7.7 Hz, 1H), 4.15 (brd, J = 13.1 Hz, 1H), 3.92 (brd, *J* = 13.2 Hz, 1H), 3.76-3.67 (m, 1H), 3.47-3.38 (m, 4H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.14 (dd, *J* = 11.8, 11.8Hz, 1H) 3.09 (d, *J* = 13.5 Hz, 1H), 2.81 (dd, *J* = 11.8, 11.8 Hz, 1H), 2.42 (t, *J* = 4.0 Hz, 2H), 2.37 (t, *J* = 4.0 Hz, 2H), 1.98 (s, 3H), 1.86 (d, *J* = 11.8 Hz, 1H), 1.81 (d, *J* = 11.8 Hz, 1H), 1.37 (q, *J* = 11.8 Hz, 1H), 1.21 (q, *J* = 11.8 Hz, 1H). Purity 90%. HRMS calculated for $C_{21}H_{28}F_3N_5O_4$ - H^+ 470.2015; found (ESI(-), [M-H]) 470.2009.

1-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (52). Intermediate **42** (76mg, 0.25mmol) was reacted with cyclopropane carboxylic acid by Method E. Flash chromatography eluted with EtOAc and recrystallization from EtOAc:hexane afforded compound **52** (47mg, 51%) as a white solid: Mp 195-196 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 7.7 Hz, 1H), 4.21-4.09 (m, 2H), 3.77-3.68 (m, 1H), 3.25 (dd, *J* = 11.5,11.5 Hz, 1H), 2.81 (dd, *J* = 11.5, 11.5 Hz, 1H), 1.98 (m, 1H), 1.93-1.75 (m, 2H), 1.41-1.17 (m, 2H), 0.75-0.65 (m, 4H). Purity 100%. HRMS calculated for $C_{17}H_{20}F_3N_3O_3$ + H^+ 372.1535; found (ESI(+), [M+H]) 372.1546.

1-(1-(Trifluoroacetyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (53). Intermediate **42** (100mg, 0.33mmol) was dissolved in dry THF (1mL), ethyl trifluoroacetate (30µl, 0.39mmol) was added and the reaction was refluxed for 18 hours. The reaction was cooled to RT, evaporated and the residue chromatographed from EtOAc to give compound **53** (49mg, 37%) as a white solid: Mp 150-154 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.27 (d, *J* = 7.6 Hz, 1H), 4.15 (brd, *J* = 13.1 Hz, 1H), 3.84-3.75 (m, 2H), 3.38 (dd, *J* = 11.9, 11.9 Hz, 1H), 3.11 (dd, *J* = 11.9, 11.9 Hz, 1H), 1.98 (d, *J* = 11.9 Hz, 1H) 1.90 (d, *J* = 11.9 Hz,1H), 1.46-1.34 (m, 2H). Purity 100%. HRMS calculated for $C_{15}H_{15}F_6N_3O_3$ + H^+ 400.1096; found (ESI(+), [M+H]) 400.1078.

1-(4-(Trifluoromethoxy)phenyl)-3-(1-(3,4,5-trihydroxybenzoyl)piperidin-4-yl)urea (54). Intermediate **42** (152mg, 0.5mmol) was reacted with **44** by Method E. The reaction was diluted in ethyl

acetate and washed with 1M NaOH, 1N HCl and finally water. The organic phase was dried and evaporated and the residue recrystallized from EtOAc:acetone to give intermediate 1-(4-(trifluoromethoxy)phenyl)-3-(1-(3,4,5-tris(benzyloxy)benzoyl)piperidin-4-yl)urea (304mg, 84%). This intermediate (145mg, 0.20mmol) was hydrogenated in the same manner as for compound **51** and recrystallized from EtOAc:acetone to afford compound **54** (51mg, 47% over 2 steps) as a white solid: Mp 168-175 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 9.07 (s, 2H), 8.56 (s, 1H), 8.45 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 6.31 (s, 2H), 6.26 (d, *J* = 7.6 Hz, 1H), 4.20-3.80 (brs, 2H), 3.77-3.68 (m, 1H), 3.03 (brs, 2H), 1.83 (d, *J* = 10.2 Hz, 2H), 1.31 (dd, *J* = 10.2, 10.2 Hz, 2H). Purity 94%. HRMS calculated for $C_{20}H_{20}F_3N_3O_6$ - H^+ 454.1226; found (ESI(-), [M-H]) 454.1241.

1-(1-(Methylsulfonyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (55). Intermediate **42** (152mg, 0.5mmol) was reacted with methanesulfonyl chloride by Method E. Recrystallization from EtOAc:acetone afforded compound **55** (160mg, 84%) as a white solid: Mp 233-234 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.29 (d, *J* = 7.5 Hz, 1H), 3.64-3.55 (m, 1H), 3.47 (brd, *J* = 12.2 Hz, 2H), 2.91-2.84 (m, 5H), 1.91 (dd, *J* = 12.6, 3.2 Hz, 2H), 1.45 (dq, *J* = 3.5, 11.2 Hz, 2H). Purity 98%. HRMS calculated for $C_{14}H_{18}F_3N_3O_4S$ - H^+ 380.0892; found (ESI(-), [M-H]) 380.0931.

1-(1-(Ethylsulfonyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (56). The reaction of **42** with ethanesulfonyl chloride in the same manner as for compound **55** afforded compound **56** (122mg, 62%): Mp 235-239 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.47 (d, *J* = 9.1 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 7.6 Hz, 1H), 3.66-3.58 (m, 1H), 3.52 (brd, *J* = 12.6 Hz, 2H), 3.05 (q, *J* = 7.3 Hz, 2H), 2.96 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 2H), 1.89 (dd, *J* = 12.6, 2.5 Hz, 2H), 1.41 (dq, *J* = 11.5, 2.5 Hz, 2H), 1.21 (t, *J* = 7.3 Hz, 3H). Purity 100%. HRMS calculated for $C_{15}H_{20}F_3N_3O_4S$ + H^+ 396.1205; found (ESI(+), [M+H]) 396.1179.

1-(1-(Phenylsulfonyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (57). The reaction of **42** with benzenesulfonyl chloride in the same manner as for compound **55** afforded compound **57** (183mg, 82%): Mp 188-189 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (s, 1H), 7.80-7.62 (m, 5H), 7.41 (d, *J* =

9.4Hz, 2H), 7.19 (d, *J* = 9.4Hz, 2H), 6.21 (d, *J* = 7.5 Hz, 1H), 3.55-3.39 (m, 3H), 2.54 (appt. t, *J* = 10.5Hz, 2H), 1.92-1.80 (m, 2H), 1.35-1.53 (m, 2H). Purity 95%. HRMS calculated for $C_{19}H_{20}F_3N_3O_4S$ - H^+ 442.1049; found (ESI(-), [M-H]) 442.1046.

1-(1-Tosylpiperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (58). The reaction of **42** with tosyl chloride in the same manner as for compound **55** afforded compound **58** (119mg, 52%): Mp 205-207 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.64 (d, *J* = 7.9 Hz, Hz, 2H), 7.45 (d, *J* = 9.4 Hz, 2H), 7.43 (d, *J* = 9.4 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.18 (d, *J* = 7. Hz, 1H), 3.52-3.45 (m, 1H), 3.41 (brd, *J* = 11.7 Hz, 2H), 2.56 (dd, *J* = 11.0, 11.0 Hz, 2H), 2.42 (s, 3H), 1.87 (brd, *J* = 11.7 Hz, 2H), 1.45 (q, *J* = 11.0 Hz, 2H). Purity 95%. HRMS calculated for $C_{20}H_{22}F_3N_3O_4S$ - H^+ 456.1205; found (ESI(-), [M-H]) 456.1247.

1-(1-(5-(Dimethylamino)naphthalen-1-ylsulfonyl)piperidin-4-yl)-3-(4-(trifluoromethoxy)phenyl)urea (59). Intermediate **42** (200mg, 0.7mmol) was dissolved in DCM (7mL) and triethylamine (100µL, 0.7mmol) added followed by 5-(dimethylamino)-1-naphthalenesulfonyl chloride (207mg, 0.77mmol). The reaction was evaporated, reconstituted in EtOAc and washed with 1N HCl and 1N K_2CO_3. Flash chromatography eluted with 2:1 EtOAc:hexanes afforded compound **59** (338mg, 93%) as a tan solid: Mp 102-107 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (d, *J* = 8.6 Hz, 1H), 8.45 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 7.2 Hz, 1H), 7.67 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.43 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.24 (d, *J* = 7.5 Hz, 1H), 3.60-3.53 (m, 3H), 2.88 (dd, *J* = 11.2, 11.2 Hz, 2H, obscured by s δ 2.84), 2.84 (s, 6H), 1.84 (dd, *J* = 12.9, 3.0 Hz, 2H), 1.38 (dq, *J* = 10.6, 3.6 Hz, 2H). Purity 97%. HRMS calculated for $C_{25}H_{27}F_3N_4O_4S$ + H^+ 537.1783; found (ESI(+), [M+H]) 537.1785.

References

(1) Morisseau, C.; Hammock, B. D. Epoxide hydrolases: Mechanisms, inhibitor designs, and biological roles. *Annu. Rev. Pharmacol. Toxicol.* **2005,** 45, 311-333.

(2) Morisseau, C.; Goodrow, M. H.; Dowdy, D.; Zheng, J.; Greene, J. F.; Sanborn, J. R.; Hammock, B. D. Potent urea and carbamate inhibitors of soluble epoxide hydrolases *Proc. Natl. Acad. Sci. USA* **1999,** 96, 8849-8854.

(3) Kim, I. H.; Heirtzler, F. R.; Morisseau, C.; Nishi, K.; Tsai, H. J.; Hammock, B. D. Optimization of amide-based inhibitors of soluble epoxide hydrolase with improved water solubility. *J. Med. Chem.* **2005,** 48, 3621-3629.

(4) Jones, P. D.; Tsai, H. J.; Do, Z. N.; Morisseau, C.; Hammock, B. D. Synthesis and SAR of conformationally restricted inhibitors of soluble epoxide hydrolase. *Bioorg. Med. Chem. Lett.***, 2006**, 16, 5212-5216.

(5) Hwang, S. H.; Tsai, H. J.; Liu, J. Y.; Morisseau, C.; Hammock, B. D. Orally bioavailable potent soluble epoxide hydrolase inhibitors. *J. Med. Chem.* **2007,** 50, 3825-3840.

(6) Morisseau, C.; Goodrow, M. H.; Newman, J. W.; Wheelock, C. E.; Dowdy, D. L.; Hammock, B. D. Structural refinement of inhibitors of urea-based soluble epoxide hydrolases. *Biochem. Pharmacol.* **2002,** 63, 1599-1608.

(7) McElroy, N. R.; Jurs, P. C.; Morisseau, C.; Hammock, B. D. QSAR and classification of murine and human soluble epoxide hydrolase inhibition by urea-like compounds. *J. Med. Chem.* **2003,** 46, 1066-1080.

(8) Hwang, S. H.; Morisseau, C.; Do, Z.; Hammock, B. D. Solid-phase combinatorial approach for the optimization of soluble epoxide hydrolase inhibitors. *Bioorg. Med. Chem. Lett.* **2006,** 16, 5773-5777.

(9) Liu, J. Y.; Tsai, H. J.; Hwang, S. H.; Jones, P. D.; Morisseau, C.; Hammock, B. D. Pharmacokinetic optimization of four soluble epoxide hydrolase inhibitors for use in a murine model of inflammation. *Br. J. Pharmacol.* **2009,** 156, 284-296.

(10) Watanabe, T.; Schulz, D.; Morisseau, C.; Hammock, B. D. High-throughput pharmacokinetic method: Cassette dosing in mice associated with minuscule serial bleedings and LC/MS/MS analysis. *Anal. Chim. Acta.* **2006**, 559, 37-44.

(11) Tsai, H. J.; Hwang, S. H.; Morisseau, C.; Yang, J.; Jones, P. D.; Kim, I. H.; Hammock, B. D. Pharmacokinetic Screening of Soluble Epoxide Hydrolase Inhibitors in Dogs. *Eur. J. Pharm. Sci*. **2010**, 40, 222-238.

(12) Liu, J. Y.; Park, S. H.; Morisseau, C; Hwang, S. H.; Hammock, B. D.; Weiss, R. H. Sorafenib has soluble epoxide hydrolase inhibitory activity, which contributes to its effect profile *in vivo. Mol. Cancer Ther*. **2009**, 8, 2193-203.

(13) Xie, Y. L.; Liu, Y. D.; Gong, G. L.; Smith, D. H.; Yan, F.; Rinderspacher, A.; Feng, Y.; Zhu, Z. X.; Li, X. P.; Deng, S. X.; Branden, L.; Vidovic, D.; Chung, C.; Schurer, S.; Morisseau, C.; Hammock, B. D.; Landry, D. W. Discovery of potent non-urea inhibitors of soluble epoxide hydrolase. *Bioorg. Med. Chem. Lett.* **2009,** 19, 2354-2359.

(14) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S. L. Synthesis of peptide isocyanates and isothiocyanates. *J. Org. Chem.* **1996,** 61, 3929-3934.

(15) Ren, Y.; Himmeldirk, K.; Chen, X. Synthesis and Structure-Activity Relationship Study of *J. Med. Chem.* **2006,** 49, 2829-2837.

(16) Weber, D.; Berger, C.; Eickelmann, P.; Antel, J.; Kessler, H. Design of Selective Peptidomimetic Agonists for the Human Orphan Receptor BRS-3#. *J. Med. Chem.* **2003,** 46, 1918-1930.