Generation of Secondary Alkyl Amines on Solid Support by Borane Reduction: Application to the Parallel Synthesis of PPAR Ligands

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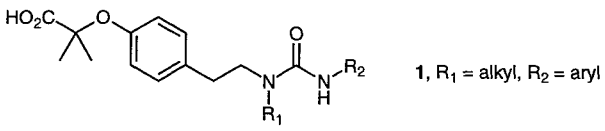
A solid phase parallel synthesis of fibrate PPAR ligands **1** has been developed. The key reaction is a novel borane reduction of resin bound amides that generates secondary amines not accessible by reductive alkylation of primary amines. The FMOC-protected amino-fibrate **2** was loaded onto Sasrin resin *via* the carboxylic acid. The amine was elaborated by amide bond formation followed by reduction with borane. The resulting secondary amines reacted with aryl isocyanates to generate the fibrates **1** in high yield and purity following cleavage from the solid support.

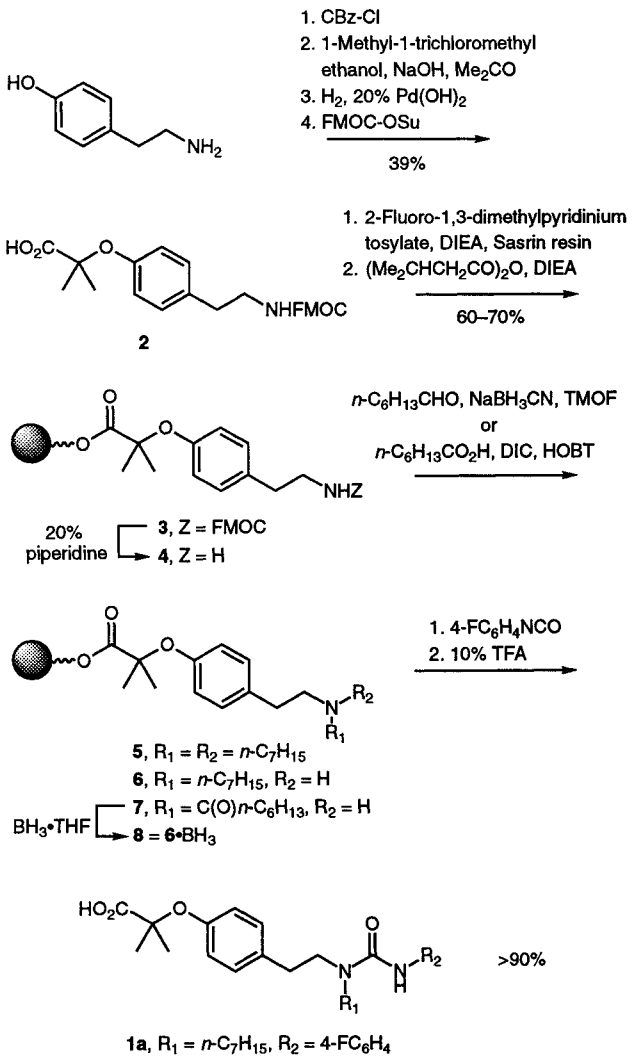
The solid phase synthesis (SPS) of small molecule libraries has the potential to speed significantly the discovery and optimization of chemical leads in the pharmaceutical industry.[1,2] In particular, the parallel synthesis of discrete analogs is well suited to the lead optimization process, provided that synthetic methods can be developed which deliver milligram quantities of high purity products.[3–6] The Borch reductive alkylation[7] of amines with aldehydes and ketones is a popular method for the generation of compound libraries.[8,9] However, as in solution, certain substrates are known to give low yields or mixtures of products.[7,10] Overalkylation of unhindered aldehydes or amines is a problem in SPS, where resin bound impurities cannot be removed without the addition of a final purification step. Despite these limitations, reductive alkylation is a mainstay of many library schemes because of the importance of the amine pharmacophore in many drugs (e.g. tertiary amines, verapamil and terfenadine; secondary amines, fluoxetine and salmeterol).[11] Herein, we disclose our preliminary studies toward the parallel synthesis of analogs of **1**, a recently identified ligand for the peroxisome proliferator-activated receptor (PPAR),[12] which resulted in the development of an alternate SPS of unhindered secondary alkyl amines.



1, R_1 = alkyl, R_2 = aryl

Our initial strategy for the synthesis of **1** was to load an amino-substituted fibrate[13] molecule onto a resin *via* the carboxylic acid, elaborate the primary amine with an alkyl substituent, and finally cap the resulting secondary amine as an aryl urea. The FMOC-protected amino-fibrate **2** was prepared in four steps from tyramine (Scheme). The key step involved a Bargellini reaction between a phenol and 1-methyl-1-trichloromethylethanol to generate the 2-phenoxyisobutyric acid.[14] The functionalized resin **3** was generated by the coupling of **2** onto Sasrin polystyrene resin.[15] Formation of the hindered ester bond was achieved using a 4-fold excess of **2** with Mukaiyama's reagent[16] as the coupling agent. Routine loadings of > 0.4 mmol/g (60–70%) were obtained as monitored by FMOC analysis of the resin **3**. Unreacted sites were capped with isovaleric anhydride.

To explore the elaboration of resin **3**, the free amine **4** was generated by piperidine deprotection. Standard methods for the generation of secondary amines on solid phase by reductive alkylation have employed excess aldehyde and a borohydride reducing agent under mildly acidic conditions.[7,8,17] Unfortunately, as in solution,[9,10] dialkylated products are often observed in reductive alkylations of primary amines with unhindered aryl and alkyl aldehydes.[7,17,18] Recently, the use of trimethyl orthoformate (TMOF) to generate the intermediate imine under neutral conditions was reported to minimize the



Scheme

formation of overalkylated products.[18] Under these conditions, amine **4** was successfully reacted with a series of benzaldehydes to generate the corresponding secondary amines in high yield.[19] However, when the amine **4** was reacted with heptaldehyde the dialkylated amine **5** was obtained exclusively even under the neutral conditions employing TMOF. Attempts at intercepting the monoalkylated amine **6** by modification of the reaction conditions met with limited success; for example, use of limiting quantities of aldehyde or changing the reaction solvent gave variable amounts of the monoalkylated amine **6** in only low to moderate yield contaminated with dialkylated amine **5** and starting amine **4**.

The solution to this synthetic problem came through the development of a novel two-step sequence for the generation of secondary alkyl amines on solid-phase (Scheme).[20] The amine resin **4** was coupled to heptanoic acid to generate the amide **7**. Chemoselective reduction of the amide was accomplished by treating resin **7** with excess borane–THF solution at room temperature under an inert atmosphere. Under these conditions, there was no evidence of reaction with the polystyrene resin or the ester linkage. Workup of the resin through a standard wash cycle generated the borane–amine complex **8**. The free amine **6** could be liberated from **8** by shaking the resin with excess ethylamine. For the purpose of our synthesis, however, it was found that the borane–amine complex **8** could be reacted directly with aryl isocyanates to generate the corresponding ureas. Thus, treatment of resin **8** with 4-fluorophenyl isocyanate followed by cleavage of the resin with 10% TFA gave the fibrate **1a** in 60–80% purity as measured by ^{1}H NMR or HPLC in comparison with an authentic sample.[21] The major impurities could be removed by loading the sample onto a solid phase extraction column (SPE) and eluting with diethyl ether. In four parallel experiments, the product **1a** was isolated in > 90% yield and 90–95% purity by ^{1}H NMR and HPLC analysis.

To demonstrate the utility of this chemistry for the synthesis of parallel arrays of PPAR ligands, a 4 × 4 matrix of fibrates was synthesized in which the urea substituents were varied (Table). Three alkyl carboxylic acids and one benzoic acid[22] were individually coupled to resin **4** and the resulting amides reduced with borane–THF. After washing to remove excess reagents, each resin was split into four reaction vessels and coupled with one of four aryl isocyanates.[22] Cleavage of the 16 individual resins and purification by SPE yielded 3–6 mg of the fibrates **1a–p**. HPLC analysis indicated that the fibrates **1a–l** derived from the alkyl acids were isolated in > 90% purity, while the fibrates **1m–p** derived from the benzoic acid were isolated in 80–90% purity.[23] As noted above, the fibrates **1m–p** can be synthesized in high yield and purity by reductive alkylation of **4** using the corresponding benzaldehyde.[19] Thus, the coupling/reduction SPS and the reductive alkylation SPS provide complementary access to a wide range of secondary amines for the synthesis of small molecule libraries.

In summary, a solid phase parallel synthesis of fibrate PPAR ligands has been developed. The key reaction is a novel borane reduction of resin bound amides that generates secondary amines not accessible by reductive alkylation of primary amines. Since the building blocks employed in this synthesis are readily available FMOC-protected amino acids, carboxylic acids and aryl isocyanates, the potential exists to expand this chemistry to the synthesis of large arrays of substituted ureas. The biological activity of these compounds as well as other approaches to the solid phase synthesis of PPAR ligands will be disclosed in due course.

Table. Parallel Synthesis of Fibrates **1a–p**

Product	R_1	R_2	Yield[a] (%)	Purity[b] (%)
1a	C_7H_{15}	4-FC_6H_4	96	90
1b	C_7H_{15}	2,4-$(OMe)_2C_6H_3$	56	98
1c	C_7H_{15}	4-AcC_6H_4	91	98
1d	C_7H_{15}	2,3-$Cl_2C_6H_3$	63	99
1e	$(CH_2)_2Ph$	4-FC_6H_4	91	91
1f	$(CH_2)_2Ph$	2,4-$(OMe)_2C_6H_3$	62	98
1g	$(CH_2)_2Ph$	4-AcC_6H_4	80	98
1h	$(CH_2)_2Ph$	2,3-$Cl_2C_6H_3$	77	99
1i	$CH_2CH(Me)OPh$	4-FC_6H_4	85	90
1j	$CH_2CH(Me)OPh$	2,4-$(OMe)_2C_6H_3$	54	95
1k	$CH_2CH(Me)OPh$	4-AcC_6H_4	91	98
1l	$CH_2CH(Me)OPh$	2,3-$Cl_2C_6H_3$	82	95
1m	$CH_2[3,5\text{-}(CF_3)_2]C_6H_3$	4-FC_6H_4	93	87
1n	$CH_2[3,5\text{-}(CF_3)_2]C_6H_3$	2,4-$(OMe)_2C_6H_3$	62	80
1o	$CH_2[3,5\text{-}(CF_3)_2]C_6H_3$	4-AcC_6H_4	94	80
1p	$CH_2[3,5\text{-}(CF_3)_2]C_6H_3$	2,3-$Cl_2C_6H_3$	62	90

[a] Yields are reported for the products isolated after SPE purification based on the initial resin loading.
[b] Purity was measured by C-18 reverse phase analytical HPLC monitored at 220 nm and confirmed by ^{1}H NMR spectroscopy.

All reagents and solvents were commercial grade. Carbobenzyloxytyramine was synthesized from tyramine by the literature procedure.[24] Sasrin resin was purchased from Bachem at an initial loading of 0.89 mmol/g. All solid phase reactions were conducted in Whatman polypropylene reaction vessels. For the borane reductions, the polypropylene cap was replaced with a septum and pierced with a needle attached to a nitrogen line. Solid phase extractions were performed on 3 mL Bakerbond SPE 40 μm SiOH columns. Analytical HPLC was performed on a 100 × 4.6 mm C-18 5 μm ODS Hypersil column at a flow rate of 2 mL/min with a gradient of 0–100% MeCN/0.1% TFA-H_2O over 5 min, monitoring at 220 nm. Mass spectra were obtained on a Fisons VG Platform I instrument run in positive ion mode using a flow injection in 90% MeOH/H_2O. ^{1}H NMR were recorded on a Varian Unity 300 MHz instrument in CD_3OD unless stated.

2-{4-[2-(9-Fluorenylmethoxycarbonyl)aminoethyl]phenoxy}-2-methylpropionic Acid (2):

A solution of carbobenzyloxytyramine (10.0 g, 36.9 mmol) and 1-methyl-1-trichloromethylethanol (15.4 g, 86.8 mmol) in acetone (180 mL) was cooled to 5°C. Solid NaOH (3.8 g, 95 mmol) was added and the mixture was allowed to warm to r.t. over 20 min. Acetone (30 mL) was added and the mixture stirred for 90 min. The mixture was cooled to 5°C and additional NaOH (3.8 g, 95 mmol) was added. After warming to r.t., the mixture was stirred for 60 min before acetone (60 mL) was added and the mixture was heated at reflux for 18 h. After cooling to r.t., the solvent was removed *in vacuo*. The residue was dissolved in water (1 L) and acidified to pH 3 with 6 N HCl. The solution was extracted with Et_2O and the ethereal extract was back-extracted with aqueous 10% $NaHCO_3$.

The resulting aqueous extract was acidified to pH 3 with 6 N HCl and extracted with Et_2O. The ethereal extract was washed with H_2O, dried ($MgSO_4$) and concentrated to yield 10.2 g (77%) of 2-{4-[2-(carbobenzyloxy)aminoethyl]phenoxy}-2-methylpropionic acid as an orange oil.

A suspension of 2-{4-[2-carbobenzyloxy)aminoethyl]phenoxy}-2-methylpropionic acid (73.0 g, 0.20 mol) and 20% $Pd(OH)_2/C$ (2.5 g) in MeOH (450 mL) was hydrogenated at 50 psi on a Parr apparatus for 18 h. The reaction mixture was diluted with EtOH (300 mL) and filtered. The resulting solid mixture of catalyst and product was suspended in a solution of H_2O (500 mL), DMF (500 mL) and concd HCl (17.5 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was triturated with EtOAc to yield 44.0 g (85%) of 2-[4-(2-aminoethyl)phenoxy]-2-methylpropionic acid hydrochloride as an off-white solid; mp 157–160°C.

^{1}H NMR (DMSO-d_6): δ = 8.15 (br, 3 H), 7.16 (d, J = 8 Hz, 2 H), 6.78 (d, J = 8 Hz, 2 H), 2.90 (m, 4 H), 1.49 (s, 6 H).

Na_2CO_3 (53.9 g, 0.50 mol) was added to a solution of 2-[4-(2-aminoethyl)phenoxy]-2-methylpropionic acid hydrochloride (44.0 g, 0.17 mol) and *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (FMOC-OSu) (57.1 g, 0.17 mol) in 1:1 dioxane/H_2O (500 mL). The resulting solution was stirred at r.t. for 4 h. The dioxane was removed *in vacuo*, the residue was diluted with H_2O (100 mL) and washed with EtOAc. The aqueous extract was acidified to pH 2 with concd HCl and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and concentrated. The resulting oil was dissolved in hot EtOAc (400 mL), cooled to r.t. and stored at 5°C for 18 h. The resulting solid was collected by filtration and dried under high vacuum to yield 44.0 g (60%) of **2** as a white powder; mp 113–114°C.

^{1}H NMR (DMSO-d_6): δ = 12.82 (br, 1 H), 7.87 (m, 2 H), 7.65 (m, 2 H), 7.35 (m, 4 H), 7.04 (d, J = 8 Hz, 2 H), 6.72 (d, J = 8 Hz, 2 H), 4.24 (m, 3 H), 3.15 (m, 2 H), 2.62 (m, 2 H), 1.45 (s, 6 H).

Anal. Calcd. for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.73; H, 6.13, N, 3.16.

Resin 3:

A solution of **2** (6.6 g, 15.3 mmol), *N,N*-diisopropylethylamine (7.5 mL, 43.3 mmol) and 2-fluoro-1,3-dimethylpyridinium *p*-toluenesulfonate (4.4 g, 14.8 mmol) in CH_2Cl_2 (30 mL) was stirred at r.t. for 15 min. Sasrin resin (3.3 g, 0.89 mmol/g) was added and the mixture stirred at r.t. for 4 h. The solution was drained and the resin washed with CH_2Cl_2, NMP and CH_2Cl_2. The resin was suspended in CH_2Cl_2 (30 mL), *N,N*-diisopropylethylamine (DIEA) (4.0 mL, 23.0 mmol) and isovaleric anhydride (3.0 mL, 15.1 mmol). After stirring at r.t. for 1 h, the solution was drained, the resin was washed with CH_2Cl_2 and dried under high vacuum for 12 h to yield resin **3**. FMOC analysis showed a loading of 0.43 mmol/g.

2-(4-[2-(3-[4-Fluorophenyl]-1-heptylureido)ethyl]phenoxy)-2-methylpropionic Acid (1a):

Solution Synthesis: 4-Fluorophenyl isocyanate (1.6 g, 11.7 mmol) was added to a solution of of ethyl 2-[4-(heptylaminoethyl)phenoxy]-2-methylpropionate [WO 92/10468, example 2, intermediate (d)][21a] (3.3 g, 9.5 mmol) in CH_2Cl_2 (50 mL). The resulting solution was stirred at r.t. for 18 h and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 2:1:1 hexane/CH_2Cl_2/EtOAc) to yield 4.8 g (87%) of ethyl 2-(4-{2-[3-(4-fluorophenyl)-1-heptylureido]ethyl}phenoxy)-2-methylpropionate as a light brown oil.

Ethyl 2-(4-[2-(3-[4-fluorophenyl]-1-heptylureido)ethyl]phenoxy)-2-methylpropionate (2.4 g, 5.1 mmol) was dissolved in EtOH (50 mL) and 1 N aq NaOH (30 mL) was added. The resulting solution was heated at reflux for 30 min, cooled to r.t. acidified with 2 N aq HCl (100 mL) and extracted with CH_2Cl_2. The organic extract was washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was recrystallized from Et_2O/hexane to yield 1.1 g (49%) of **1a** as a white powder; mp 162–164°C; HPLC: R_t 3.46 min (> 99%).

^{1}H NMR: δ = 7.82 (br, 1 H), 7.25–6.80 (m, 8 H), 3.55 (t, J = 7 Hz, 2 H), 3.31 (t, J = 7 Hz, 2 H), 2.83 (t, J = 7 Hz, 2 H), 1.53 (m, 2 H), 1.51 (s, 6 H), 1.30 (m, 8 H), 0.86 (m, 3 H).

Anal. Calcd for $C_{26}H_{35}FN_2O_4$: C, 68.10; H, 7.69; N, 6.11. Found: C, 68.15; H, 7.82; N, 6.10.

MS (ESI+): m/z = 459 (MH^+).

Solid Phase Synthesis: Resin **3** (40 mg, 0.43 mmol/g) was suspended in 20% piperidine in DMF (1 mL) for 30 min. The solution was drained and the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, THF, and DMF. A solution of heptanoic acid (1 M in DMF, 0.17 mL), HOBT (1-hydroxybenzotriazole hydrate) (1 M in DMF, 0.17 mL), and DIC (2-dimethylaminoisopropyl chloride hydrochloride) (1 M in DMF, 0.17 mL) was added. The suspension was mixed and kept at r.t. for 2 h. The solution was drained and the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, and THF. Under a N_2 atmosphere, a solution of $BH_3 \cdot$ THF (1 M in THF, 1.0 mL) was added to the resin. The suspension was mixed and kept at r.t. for 1 h. The solution was drained and the resin was washed with THF, CH_2Cl_2, DMF, MeOH, CH_2Cl_2 and DMF. A solution of 4-fluorophenyl isocyanate (1 M in CH_2Cl_2, 0.52 mL) was added. The suspension was mixed and left aside at r.t. for 18 h. The solution was drained and the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, THF, and CH_2Cl_2. The resulting resin was suspended in 10% TFA in CH_2Cl_2 (1 mL) for 30 min. The solution was filtered and the filtrate evaporated. The crude product was dissolved in a small volume of $CHCl_3$ and loaded onto an SPE column (Bakerbond, SiOH). The SPE column was washed with two column volumes of $CHCl_3$ and one column volume of Et_2O. The Et_2O fraction was evaporated to yield 7.1 mg (91%) of **1a**; HPLC: R_t 3.46 min (95%).

^{1}H NMR: δ = 7.82 (br, 1 H), 7.25–6.80 (m, 8 H), 3.55 (t, J = 7 Hz, 2 H), 3.31 (t, J = 7 Hz, 2 H), 2.83 (t, J = 7 Hz, 2 H), 1.53 (m, 2 H), 1.51 (s, 6 H), 1.30 (m, 8 H), 0.86 (m, 3 H).

MS (ESI+): m/z = 459 (MH^+).

Parallel Synthesis of Fibrates 1a–1p; General Procedure:

4 Batches of resin **3** (95 mg, 0.42 mmol/g) were suspended in 20% piperidine in DMF (2 mL) for 30 min. The solutions were drained and the resins were washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, THF, and DMF. To each resin, a solution of the respective carboxylic acid (Table, 1 M in DMF, 0.4 mL), HOBT (1 M in DMF, 0.4 mL), and DIC (1 M in DMF, 0.4 mL) was added. The suspensions were mixed and left aside at r.t. for 2 h. The solutions were drained and the resins were washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, and THF. Under a N_2 atmosphere, a solution of $BH_3 \cdot$ THF (1 M in THF, 2.0 mL) was added to each resin. The suspensions were mixed and kept at r.t. for 1 h. The solutions were drained and the resins were washed with THF, CH_2Cl_2, DMF, MeOH, CH_2Cl_2 and DMF. Each resin was suspended in CH_2Cl_2/DMF (1:1, 2 mL) and split into 4 equal aliquots. The resulting 16 suspensions were drained and washed with CH_2Cl_2. A solution of the appropriate aryl isocyanate (Table, 1 M in CH_2Cl_2, 0.4 mL) was added to each resin. The suspensions were mixed and allowed to stand at r.t. for 18 h. The solutions were drained and the resins were washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, THF, and CH_2Cl_2. The resulting resins were suspended in 10% TFA in CH_2Cl_2 (1 mL) for 30 min. The solutions were filtered and the filtrates evaporated. The crude products were dissolved in a small volume of $CHCl_3$ and loaded onto SPE columns (Bakerbond, SiOH). The SPE columns were each washed with two column volumes of $CHCl_3$ and one column volume of Et_2O. The Et_2O fractions were evaporated to yield the 2-{4-[2-(3-aryl-1-alkylureido)ethyl]phenoxy}-2-methylpropionic acids **1a–1p.**

2-(4-[2-(3-[4-Fluorophenyl]-1-heptylureido)ethyl]phenoxy)-2-methylpropionic Acid **(1a)**: Yield 4.4 mg (96%); HPLC: R_t 3.46 min (90%).

^{1}H NMR: δ = 7.82 (br, 1 H), 7.25–6.80 (m, 8 H), 3.55 (t, J = 7 Hz, 2 H), 3.31 (t, J = 7 Hz, 2 H), 2.83 (t, J = 7 Hz, 2 H), 1.53 (m, 2 H), 1.51 (s, 6 H), 1.30 (m, 8 H), 0.86 (m, 3 H).

MS (ESI+): m/z = 459 $(MH)^+$, 481 $(M+Na)^+$.

2-(4-[2-(3-[2,4-Dimethoxyphenyl]-1-heptylureido)ethyl]phenoxy)-2-methylpropionic Acid (**1b**): Yield 2.8 mg (56%); HPLC: R_t 3.60 min (98%).

^{1}H NMR: δ = 7.41 (d, J = 8 Hz, 1 H), 7.09 (d, J = 8 Hz, 2 H), 6.78 (d, J = 8 Hz, 2 H), 6.50 (s, 1 H), 6.40 (m, 1 H), 4.82 (s, 3 H), 3.71 (s, 3 H), 3.44 (t, J = 7 Hz, 2 H), 3.12 (t, J = 7 Hz, 2 H), 2.79 (t, J = 7 Hz, 2 H), 1.48 (m, 2 H), 1.45 (s, 6 H), 1.24 (m, 8 H), 0.84 (m, 3 H).

MS (ESI+): m/z = 501 $(MH)^+$, 523 $(M+Na)^+$.

2-(4-[2-(3-[4-Acetylphenyl]-1-heptylureido)ethyl]phenoxy)-2-methylpropionic Acid (**1c**): Yield 4.4 mg (91%); HPLC: 4.26 min (98%).

^{1}H NMR: δ = 7.90 (d, J = 8 Hz, 2 H), 7.44 (d, J = 8 Hz, 2 H), 7.14 (d, J = 8 Hz, 2 H), 6.83 (d, J = 8 Hz, 2 H), 3.59 (t, J = 7 Hz, 2 H), 3.27 (t, J = 7 Hz, 2 H), 3.27 (t, J = 7 Hz, 2 H), 2.55 (s, 3 H), 1.55 (m, 2 H), 1.49 (s, 6 H), 1.30 (m, 8 H), 0.89 (m, 3 H).

MS (ESI+): m/z = 483 $(MH)^+$, 505 $(M+Na)^+$.

2-(4-[2-(3-[2,3-Dichlorophenyl]-1-heptylureido)ethyl]phenoxy)-2-methylpropionic Acid (**1d**): Yield 3.2 mg (63%); HPLC: R_t 3.33 min (99%).

^{1}H NMR: δ = 7.53 (d, J = 8 Hz, 1 H), 7.20 (m, 2 H), 7.10 (d, J = 8 Hz, 2 H), 6.78 (d, J = 8 Hz, 2 H), 3.50 (t, J = 7 Hz, 2 H), 3.19 (t, J = 7 Hz, 2 H), 2.80 (t, J = 7 Hz, 2 H), 1.54 (m, 2 H), 1.44 (s, 3 H), 1.25 (m, 8 H), 0.84 (m, 3 H).

MS (ESI+): m/z = 531 $(M+Na)^+$.

2-(4-[2-(3-[4-Fluorophenyl]-1-[2-phenethyl]ureido)ethyl]phenoxy)-2-methylpropionic Acid (**1e**): Yield 4.2 mg (91%); HPLC: R_t 3.00 min (91%).

^{1}H NMR: δ = 7.30–6.80 (m, 13 H), 3.44 (m, 4 H), 2.80 (m, 4 H), 1.53 (s, 6 H).

MS (ESI+): m/z = 465 $(MH)^+$, 487 $(M+Na)^+$.

2-(4-[2-(3-[2,4-Dimethoxyphenyl]-1-[2-phenethyl]ureido)ethyl]-phenoxy)-2-methylpropionic Acid (**1f**): Yield 3.1 mg (62%); HPLC: R_t 3.07 min (98%).

^{1}H NMR: δ = 7.40 (d, J = 8 Hz, 1 H), 7.18 (m, 5 H), 7.05 (d, J = 8 Hz, 2 H), 6.77 (d, J = 8 Hz, 2 H), 6.51 (s, 1 H), 6.40 (m, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.33 (m, 4 H), 2.75 (m, 4 H), 1.42 (s, 6 H).

MS (ESI+): m/z = 507 $(MH)^+$, 529 $(M+Na)^+$.

2-(4-[2-(3-[4-Acetylphenyl]-1-[2-phenethyl]ureido)ethyl]phenoxy)-2-methylpropionic Acid (**1g**): Yield 3.9 mg (80%); HPLC: R_t 2.87 min (98%).

^{1}H NMR: δ = 7.88 (d, J = 8 Hz, 2 H), 7.37 (d, J = 8 Hz, 2 H), 7.21 (m, 5 H), 7.10 (d, J = 8 Hz, 2 H), 6.81 (d, J = 8 Hz, 1 H), 3.48 (m, 4 H), 2.80 (m, 4 H), 2.55 (s, 3 H), 1.46 (s, 6 H).

MS (ESI+): m/z = 489 $(MH)^+$, 511 $(M+Na)^+$.

2-(4-[2-(3-[2,3-Dichlorophenyl]-1-[2-phenethyl]ureido)ethyl]phenoxy)-2-methylpropionic Acid (**1h**): Yield 4.0 mg (77%); HPLC: R_t 3.51 min (99%).

^{1}H NMR: δ = 7.48 (d, J = 8 Hz, 1 H), 7.18 (m, 7 H), 7.12 (d, J = 8 Hz, 2 H), 6.77 (d, J = 8 Hz, 2 H), 3.40 (m, 4 H), 2.80 (m, 4 H), 1.42 (s, 6 H).

MS (ESI+): m/z = $(MH)^+$, 537 $(M+Na)^+$.

2-(4-[2-(3-[4-Fluorophenyl]-1-[2-phenoxypropyl]ureido)ethyl]-phenoxy)-2-methylpropionic Acid (**1i**): Yield 4.2 mg (85%); HPLC: R_t 3.11 min (90%).

^{1}H NMR: δ = 7.25–6.80 (m, 13 H), 4.63 (m, 1 H), 3.63 (t, J = 7 Hz, 2 H), 3.45 (m, 2 H), 2.83 (t, J = 7 Hz, 2 H), 1.51 (s, 6 H), 1.24 (d, J = 7 Hz, 3 H).

MS (ESI+): m/z = 495 $(MH)^+$, 517 $(M+Na)^+$.

2-(4-[2-(3-[2,4-Dimethoxyphenyl]-1-[2-phenoxypropyl]ureido)-ethyl]phenoxy)-2-methylpropionic Acid (**1j**): Yield 2.9 mg (54%); HPLC: R_t 3.46 min (95%).

^{1}H NMR: δ = 7.41 (d, J = 8 Hz, 1 H), 7.20 (t, J = 8 Hz, 2 H), 7.08 (d, J = 8 Hz, 2 H), 6.87 (m, 3 H), 6.77 (d, J = 8 Hz, 2 H), 6.50 (s, 1 H), 6.40 (m, 1 H), 4.58 (m, 1 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.50 (t, J = 7 Hz, 2 H), 3.38 (m, 2 H), 2.80 (t, J = 7 Hz, 2 H), 1.47 (s, 6 H), 1.20 (d, J = 7 Hz, 3 H).

MS (ESI+): m/z = 537 $(MH)^+$, 559 $(M+Na)^+$.

2-(4-[2-(3-[4-Acetylphenyl]-1-[2-phenoxypropyl]ureido)ethyl]phenoxy)-2-methylpropionic Acid (**1k**): Yield 4.7 mg (91%); HPLC: R_t 3.00 min (98%).

^{1}H NMR: δ = 7.91 (d, J = 8 Hz, 2 H), 7.42 (d, J = 8 Hz, 2 H), 7.25 (t, J = 8 Hz, 2 H), 7.12 (d, J = 8 Hz, 2 H), 6.92 (m, 3 H), 6.82 (d, J = 8 Hz, 2 H), 4.68 (m, 1 H), 3.63 (m, 2 H), 3.50 (m, 2 H), 2.86 (d, J = 7 Hz, 2 H), 2.55 (s, 3 H), 1.49 (s, 6 H), 2.60 (d, J = 7 Hz, 3 H).

MS (ESI+): m/z = 541 $(M+Na)^+$.

2-(4-[2-(3-[2,3-Dichlorophenyl]-1-[2-phenoxypropyl]ureido)ethyl]-phenoxy)-2-methylpropionic Acid (**1l**): Yield 4.2 mg (82%); HPLC: R_t 3.70 min (95%).

^{1}H NMR: δ = 7.61 (m, 1 H), 7.20 (m, 4 H), 7.10 (d, J = 8 Hz, 2 H), 6.87 (m, 3 H), 6.78 (d, J = 8 Hz, 2 H), 4.62 (m, 1 H), 3.56 (m, 2 H), 3.39 (m, 2 H), 2.83 (m, 4 H), 1.45 (s, 6 H), 1.21 (d, J = 7 Hz, 3 H).

MS (ESI+): m/z = 545 $(MH)^+$, 567 $(M+Na)^+$.

2-(4-[2-(4-[4-Fluorophenyl]-1-[3,5-ditrifluoromethylbenzyl]ureido)-ethyl]phenoxy)-2-methylpropionic Acid (**1m**): Yield 5.4 mg (93%); HPLC: 3.36 min (87%).

^{1}H NMR: δ = 7.82 (m, 3 H), 7.23–6.80 (m, 8 H), 4.67 (s, 2 H), 3.61 (m, 2 H), 2.86 (m, 2 H), 1.50 (s, 6 H).

MS (ESI+): m/z = 587 $(MH)^+$, 609 $(M+Na)^+$.

2-(4-[2-(3-[2,4-Dimethoxyphenyl]-1-[3,5-ditrifluoromethylbenzyl]-ureido)ethyl]phenoxy)-2-methylpropionic Acid (**1n**): Yield 3.9 mg (62%); HPLC: R_t 3.40 min (80%).

^{1}H NMR: δ = 7.87 (m, 3 H), 7.33 (d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 2 H), 6.86 (d, J = 8 Hz, 2 H), 6.55 (s, 1 H), 6.46 (m, 1 H), 4.62 (s, 2 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.59 (t, J = 7 Hz, 2 H), 2.88 (m, 2 H), 1.51 (s, 6 H).

MS (ESI+): m/z = 629 $(MH)^+$, 651 $(M+Na)^+$.

2-(4-[2-(3-[4-Acetylphenyl]-1-[3,5-ditrifluoromethylbenzyl]ureido)-ethyl]phenoxy)-2-methylpropionic Acid (**10**): Yield 5.7 mg (94%); HPLC: R_t 3.22 min (80%).

^{1}H NMR: δ = 7.85 (m, 5 H), 7.35 (d, J = 8 Hz, 2 H), 7.07 (m, 2 H), 6.77 (m, 2 H), 4.65 (s, 2 H), 3.63 (t, J = 7 Hz, 2 H), 2.80 (m, 2 H), 2.48 (s, 3 H), 1.41 (s, 6 H).

MS (ESI+): m/z = 611 $(MH)^+$, 633 $(M+Na)^+$.

2-(4-[2-(3-[2,3-Dichlorophenyl]-1-[3,5-ditrifluoromethylbenzyl]ureido)ethyl]phenoxy)-2-methylpropionic Acid (**1p**): Yield 3.9 mg (62%); HPLC: R_t 3.79 min (90%).

^{1}H NMR: δ = 7.81 (m, 3 H), 7.25 (m, 3 H), 7.08 (m, 2 H), 6.89 (m, 2 H), 4.62 (s, 2 H), 3.59 (t, J = 7 Hz, 2 H), 2.83 (t, J = 7 Hz, 2 H), 1.45 (s, 6 H).

MS (ESI+): m/z = 531 $(M+Na)^+$.

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