

A Novel Purification Method in Organic Synthesis Using Hydrogen Bonding

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A new workup and purification method based on quadruple hydrogen-bonding interactions is reported. Substrates containing a hydrogen-bonding affinity tag – either directly connected or through a cleavable linker – were conveniently separated from a reaction mixture and purified using a resin containing self-complementary affinity tags. Several Ugi

products and nucleophilic aromatic substitution products were successfully purified by this hydrogen-bonding-based affinity-separation protocol.

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Introduction

The ever increasing demand of the pharmaceutical industry for small drug-like organic molecules has resulted in the development of a range of synthetic tools, which contribute to the speed, efficiency and selectivity of synthesis routes.^[1] An important aspect therein is the ability to separate the desired products from side-products and impurities. Therefore, not only new efficient chemical transformations have to be developed, but novel, broadly applicable purification protocols as well.

A disadvantage of solution-phase synthesis is the fact that reactions are labour-intensive in terms of workup and purification of products. Another drawback of the aqueous workup and purification is that these operations are not easily automated, rendering solution-phase synthesis in principle less suited for automated library synthesis. These drawbacks of solution-phase synthesis for pharmaceutical purposes led to the development of robust alternatives such as solid-phase synthesis.^[2,3] More recently, alternative workup and purification strategies have been developed based on affinity separation.^[4] In the latter approaches, chemical reactions are performed in solution phase so that the process can be monitored by standard analytical tools. After completion, an additional medium, immiscible with the reaction mixture, is added. The additional phase is either a solvent or a solid that has a distinct affinity for the tagged compound, but no affinity whatsoever for the other reagents and products. This way, affinity binding will lead

to transfer of the tagged compounds to the affinity medium, while other reactants will remain in the initial phase. Affinity separation has been recognized as a welcome tool in organic synthesis, and has been explored by different groups in recent years.^[5] A range of suitable tags has been developed, utilising all kinds of affinity interactions, such as for example fluororous interactions,^[6,7] hydrophobic interactions,^[8–10] ionic interactions between crown ethers and ammonium ions,^[11,12] metal chelation between diacid moieties and Cu^{II} ions,^[13,14] and a combination of fluororous interactions and hydrogen bonding.^[15] A first example of purification solely by hydrogen bonding was developed by Fukase and co-workers.^[16,17] They used the host–guest interaction of bis(2,6-diamidopyridine)amide of isophthalic acid and barbituric acid, which form a strong complex through the formation of six hydrogen bonds.^[18] The binding constant of the complex ($2.8 \times 10^4 \text{ M}^{-1}$), however, is too small to bind all types of tagged products.^[19] We aimed to explore the possibilities of the latter affinity purification method using the robust self-complementary hydrogen bonding ureidopyrimidinone (UPy) unit (Figure 1), which displays significantly larger binding constants (UPy dimerization constant is $6 \times 10^7 \text{ M}^{-1}$ in chloroform, $6 \times 10^8 \text{ M}^{-1}$ in toluene)^[20] and therefore might be more widely applicable.

In a previous account, we already demonstrated the viability of a similar hydrogen-bonding-based affinity-separation strategy for catalyst recycling.^[21] We envisioned that the same affinity separation might be used in a synthetic sense, where a substrate connected to a UPy affinity tag (AT) can undergo modification in solution phase (Figure 1). The UPy moiety forms dimers by generating four hydrogen bonds in apolar solvents, and dissociates again in polar solvents.^[22] Hence, subsequent treatment with a resin containing a self-complementary UPy affinity unit (viz. **1**) will lead to the corresponding dimeric complex. After washing of the complex and transfer to a polar solvent, the hy-

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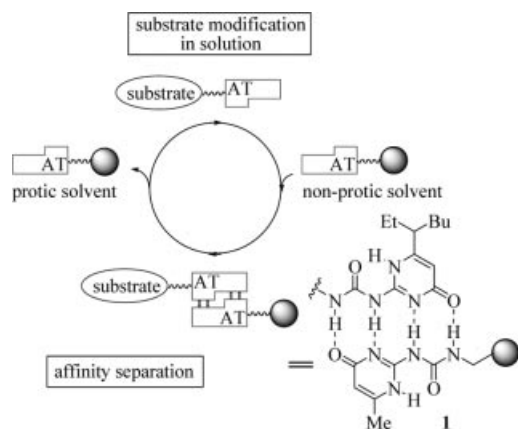


Figure 1. Schematic representation of purification by hydrogen bonding.

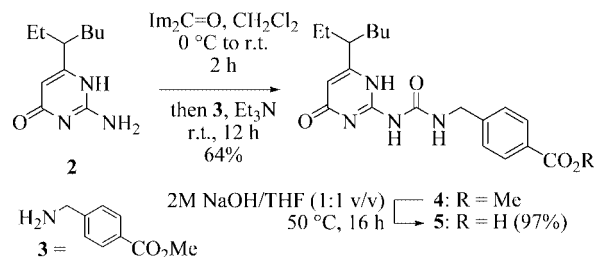
drogen bonds are broken and the tagged compound dissociates from the resin and dissolves again. Subsequent filtration of the polymer beads and evaporation of the solvent leads again to the tagged compound in pure form, which can be subjected to a next reaction. Because this method in principle combines the advantages of solution-phase synthesis and solid-phase purification, and therefore might be potentially useful for automated synthesis, we set out to realize a proof of this concept.

Results and Discussion

Initially, we chose to equip a benzoate with the UPy AT, which yielded a compound that could be used in Ugi 4-component reactions (U-4CRs).^[23] This versatile multi-component reaction (MCR) has been studied extensively, and applications in organic synthesis include the formation of peptides,^[24] glycopeptides,^[25] β -lactams,^[26] iminohydantoins^[27] and various other biologically active compound classes.

The isocytosine **2**, obtained by two high-yielding steps,^[28] was treated with carbonyl diimidazole^[29] and subsequently with the benzylamine derivative **3** in a one-pot procedure to give compound **4** in modest yield (Scheme 1). Saponification of the methyl ester gave the desired UPy-tagged benzoic acid **5** in excellent yield. Compound **5** was subjected to standard U-4CR conditions using readily available reagents (Table 1). Due to the rather poor solubility of UPy-tagged compound **5** in methanol, a 1:1 mixture of methanol/chloroform was used as the solvent. All reactions proceeded smoothly, which showed the compatibility of U-4CRs with the UPy AT. Clearly, the tolerance of the UPy tag towards chemical transformations is a strict requirement for our purposes.

As can be read from Table 1, products **6** to **10** were isolated in good yields using standard column chromatography. Isolation of the same products using the hydrogen-bonding properties of the tag (affinity separation) as described above, provided the same products in slightly higher yields. In all cases, the ArgoPore resin-bound tag **1** was ap-



Scheme 1. Synthesis of UPy-tagged U-4CR precursor **5**.

Table 1. U-4CRs and comparison of purification methods.

Entry	Substrate	R	R ¹	R ²	Yield [%] CC ^[a]	Yield [%] AS ^[b]
1	6	HC≡CCH ₂	<i>n</i> Bu	<i>t</i> Bu	77	83
2	7	HC≡CCH ₂	<i>n</i> Bu	<i>c</i> Hex	82	87
3	8	HC≡CCH ₂	3-butenyl	<i>t</i> Bu	84	89
4	9	PMB ^[c]	3-butenyl	<i>t</i> Bu	76	84
5	10	PMB ^[c]	3-butenyl	<i>c</i> Hex	75	84

[a] CC = column chromatography. [b] AS = affinity separation. [c] PMB = *p*-methoxybenzyl.

plied, which was previously optimized for catalyst recycling.^[20] The presence of methanol in the reaction mixture forced us to evaporate the solvent after completion of the reaction, and redissolve the crude product in chloroform before affinity binding. The purity of the products appeared to be similar, albeit that in some cases the compounds that were purified through AS appeared to be slightly yellow, while the products purified by column chromatography were always colorless. Simple treatment of the products obtained by affinity separation with activated charcoal was sufficient to yield colorless compounds as well. These results demonstrate that our assumption on the applicability of the UPy tags in organic synthesis was justified, and indicate that this methodology may be more widely applicable to purify products obtained by other organic reactions.

To further expand the value of this purification protocol, it was decided to investigate whether substrate molecules could be equipped with a cleavable linker bearing the UPy AT. This would offer the possibility of isolating the pure product after the linker is removed in the final synthesis step by an additional AS cycle (Figure 2).

After the product is freed from the tagged linker, it has no longer affinity for the UPy-equipped resin. Addition of the resin will therefore abstract only the linker that still bears the UPy functionality from solution, so filtration and subsequent solvent evaporation should yield the substrate in pure form. We decided to use *p*-hydroxybenzyl alcohol as the starting compound for the synthesis of linker **15** (Scheme 2). This alkoxybenzyl alcohol based linker offers a handle to couple substrates with, and can be cleaved under

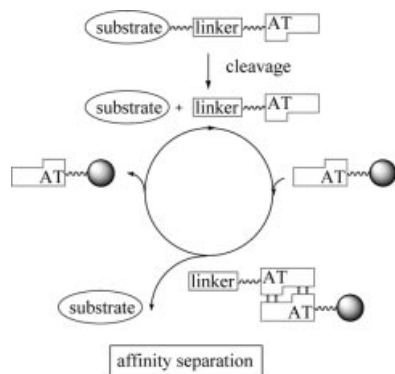
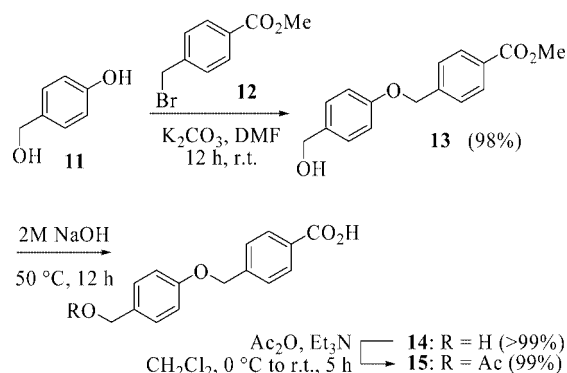


Figure 2. Release and separation of substrate molecules from the AT.

mild, acidic conditions.^[30] Hence, this moiety enables facile acid-mediated cleavage of substrates from the tag after purification by our method.

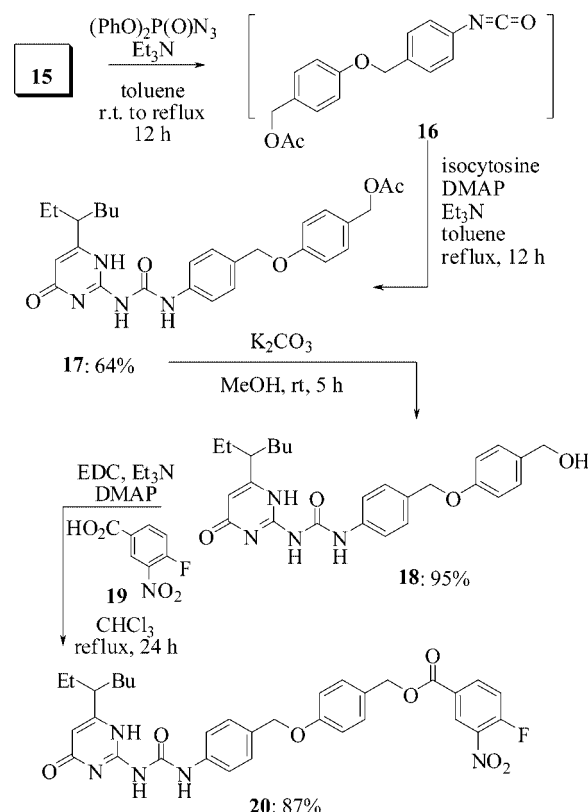


Scheme 2. Synthesis of cleavable linker **15**.

Alkylation of *p*-hydroxybenzyl alcohol **11** with bromide **12** under basic conditions went smoothly to give adduct **13** in excellent yield. After saponification of the methyl ester, and subsequent protection of the benzylic hydroxy group, compound **15** was obtained without difficulties.

The benzoic acid **15** was treated with DPPA to give the corresponding acyl azide, which was transformed into the intermediate isocyanate **16** at elevated temperatures. After addition of (2-ethylpentyl)isocytosine and a catalytic amount of DMAP, the mixture was heated again to give tagged linkers **17** in reasonable yield. The same procedure was also carried out using adamantyl-substituted isocytosine, but this resulted in virtually insoluble adducts, which could not be fully characterized by common spectroscopic methods. Next, the deprotection of the benzylic alcohol and coupling of this linker with a simple substrate was pursued (Scheme 3). Deacetylation was performed under standard conditions to give the alcohol **18** in excellent yield. It was decided to couple the linkers with benzoic acid derivative **19**, since the resulting compound **20** was anticipated to easily undergo nucleophilic aromatic substitutions with amines to give the aniline derivatives. Coupling of **19** with linkers **18** was performed using EDC and DMAP in chloroform to provide compound **20** in a yield of 87%. Next, **20** was subjected to aromatic substitution reactions, which are well de-

scribed.^[31] Thus, treatment of the AT-equipped substrate **20** with an excess of a nucleophilic amine and triethylamine as a base at room temperature, gave indeed substitution products **21–23** after 24 h (Table 2). A large excess of amine was used to force the reactions to go to completion, which is a necessity for successful application of our new purification protocol. All compounds functionalized with the UPy-based AT will be bound by the tagged resin, so that discrimination between starting material and product is not possible. According to TLC, full conversion was obtained in all cases and the products were again purified both by column chromatography and affinity separation.



Scheme 3. Completion of acid-labile linker **17**.

The results are shown in Table 2. In case column chromatography was applied, an extraction was performed prior to the purification, while during affinity separation, the crude mixture was directly subjected to the resin without any workup. Again, the yields of the products that were purified by column chromatography were lower than the yields encountered with affinity separation, but the purity of the compounds isolated was comparable according to NMR spectroscopy. The next step, cleavage of the tagged linker and purification of the products using the tagged resin, was carried out with compounds **21** to **23** which were obtained after affinity separation. A 95:5 mixture of trifluoroacetic acid/water was used to cleave the Wang-type linker and products **24–26** were formed as anticipated. The cleaved linker was separated by affinity separation and products **24–26** were isolated in excellent yield (Table 2).^[32] The purity of isolated compounds **24** and **25** was compar-

Table 2. Aromatic substitution, followed by purification.

Entry	R	Compound	Yield (CC) ^[a]	Yield (AS)	Product	Yield (AS)
1	H ₂ C=CHCH ₂	21	75%	>95%	24	>95%
2	HC≡CCH ₂	22	73%	>95%	25	>95%
3	<i>p</i> -MeOC ₆ H ₄ CH ₂	23	>95%	>95%	26	86% ^[b]

[a] Prior to CC an extraction was carried out. [b] To obtain a pure sample, treatment with activated charcoal was required.

able to the products isolated by column chromatography, but treatment of **26** with activated charcoals was required to obtain the product in pure form. Nevertheless, this approach offers the possibility of carrying out multiple solution-phase steps with a straightforward purification by the hydrogen-bonding protocol to yield the products in excellent purity.

Conclusions

We have successfully developed a new workup and purification method based on quadruple hydrogen-bonding interactions. Products of Ugi multicomponent reactions were selectively bound by a tagged resin, and were isolated in high yield and purity. Installation of a cleavable linker offered the possibility of isolating products after linker removal using the same affinity protocol, as was successfully demonstrated in nucleophilic aromatic substitution reactions.

Experimental Section

General: All reactions were carried out under dry argon. Standard syringe techniques were applied to the transfer of dry solvents and air- or moisture-sensitive reagents. *R_f* values were obtained using thin layer chromatography (TLC) on silica gel coated plates (Merck 60 F254) with the indicated solvent mixture, and compounds were detected with UV light or with aqueous potassium permanganate. Melting points were determined with a Büchi melting point apparatus B-545. IR spectra were recorded with an ATI Mattson Genesis Series FTIR spectrometer, equipped with a Harrick Split Pea ATR apparatus. Absorptions are reported in cm⁻¹. NMR spectra were recorded with a Bruker DMX 300 (300 MHz), and a Varian 400 (400 MHz) spectrometer in CDCl₃ solutions (unless otherwise reported) using tetramethylsilane (TMS) as internal standard; chemical shifts are given in ppm. Coupling constants are reported as *J* values in Hz. Column or flash chromatography was carried out

using ACROS silica gel (0.035–0.070 mm and ca. 6 nm pore diameter). Mass spectra and accurate mass measurements were carried out using a Fisons (VG) Micromass 7070E or a Finnigan MAT900S instrument. Solvents were distilled from appropriate drying agents prior to use. Unless otherwise noted, all chemicals were purchased and used as such.

4-{3-[6-(1-Ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureido-methyl}benzoic Acid (5**):** To a stirred solution of the (ethylpentyl)-isocytosine **2** (3.00 g, 14.3 mmol) in DMF (75 mL) were added Et₃N (6.1 mL, 35 mmol), carbonyl diimidazole (2.55 g, 15.7 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temp. for 2 h, then amine **3** (HCl salt, 5.86 g, 29.0 mmol) and Et₃N (5.2 mL, 30 mmol) were added. The mixture was stirred at room temp. for an additional 20 h, and the solvent was removed under reduced pressure. The residue was taken up in H₂O/CH₂Cl₂ (1:1 v/v, 250 mL), and the layers were separated. The aqueous phase was back-extracted with CH₂Cl₂ (2 × 100 mL), and the combined organic layers were washed with aqueous NH₄Cl (150 mL), dried (MgSO₄), and concentrated to give a light yellow solid. Precipitation in Et₂O gave compound **4** (3.64, 64%) as a white solid. FTIR (ATR): $\tilde{\nu}$ = 2951, 2931, 2853, 1720, 1693, 1650, 1572, 1522, 1276, 1253, 1105, 848, 786 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 13.07 (s, 1 H), 12.11 (s, 1 H), 10.96 (t, *J* = 5.6 Hz, 1 H), 8.00 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 5.81 (s, 1 H), 4.51 (d, *J* = 5.8 Hz, 2 H), 3.89 (s, 3 H), 2.31–2.27 (m, 1 H), 1.69–1.49 (m, 4 H), 1.33–1.18 (m, 4 H), 0.89 (t, *J* = 7.4 Hz, 3 H), 0.52 (t, *J* = 7.4 Hz, 3 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 172.7, 166.5, 156.6, 155.3, 154.3, 143.7, 129.6 (2 C), 128.7, 127.0 (2 C), 106.1, 52.0, 45.4, 43.2, 32.9, 29.4, 26.7, 22.6, 14.0, 11.9 ppm. Without further purification, compound **4** (400 mg, 1.00 mmol) was dissolved in aqueous NaOH (2 M)/THF (1:1 v/v, 10 mL). The mixture was heated to 50 °C overnight, and then concentrated in vacuo. The resulting solution was then carefully acidified using concentrated HCl, upon which a white solid precipitated from the solution. The white solid was filtered off, washed with water and dried in vacuo to give the desired acid **5** (379 mg, 97%) in pure form. M.p. 164 °C. FTIR (ATR): $\tilde{\nu}$ = 2955, 2928, 2861, 1691, 1650, 1575, 1523, 1422, 1258, 850, 738 cm⁻¹. ¹H NMR ([D₆]DMSO, 400 MHz): δ = 8.26 (br. s, 1 H), 7.91 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 5.75 (s, 1 H), 4.45 (d, *J* = 5.8 Hz, 2 H), 2.24–2.17 (m, 1 H), 1.47–

1.36 (m, 4 H), 1.25–1.02 (m, 4 H), 0.79 (t, $J = 7.1$ Hz, 3 H), 0.72 (t, $J = 7.4$ Hz, 3 H) ppm. ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, 75 MHz): $\delta = 170.2, 167.0, 161.6, 154.7, 151.7, 144.0, 129.5, 129.4$ (2 C), 127.1 (2 C), 104.9, 47.6, 42.5, 32.9, 29.0, 26.4, 22.1, 13.8, 11.7 ppm. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{27}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 387.2032, found 387.2025.

General Procedure for the Purification of Compounds 6–10 by Affinity Separation: To a solution of 1 equiv. of compounds 6–10 in chloroform (2 mL) were added 10 equiv. of Et_3N and 10 equiv. of the amine. The mixture was stirred for 24 h. The tagged resin (10 equiv. of binding sites relative to the amount of 6–10) was added to the crude mixture, and the flask was put in a shaking apparatus for 16 h. The solvent was filtered off, and the resin was washed with CHCl_3 . After transferring the resin to a flask, a 2:1 mixture of DMF/MeOH (10 mL) was added, and the mixture was shaken for 3 h. The solvent was filtered off and evaporated to give the desired compound with high purity and yield as indicated in Table 1.

***N*-[1-(*tert*-Butylcarbamoyl)pentyl]-4-{3-[6-(1-ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureidomethyl}-*N*-(prop-2-ynyl)benzamide (6):** A mixture of propargylamine (14 mg, 0.25 mmol), *tert*-butyl isocyanide (21 mg, 0.25 mmol), pentanal (22 mg, 0.25 mmol) and acid 5 (39 mg, 0.10 mmol) in MeOH/ CHCl_3 (1:1 v/v, 2 mL) was stirred for 3 d. The solvent was evaporated, and the residue was purified by column chromatography (1→3% MeOH in CHCl_3) to give the desired adduct in 77% yield as a colorless oil, or purified with the tagged resin (83% yield). FTIR (ATR): $\tilde{\nu} = 3309, 3218, 2954, 2924, 2872, 1697, 1949, 1580, 1519, 1450, 1411, 1308, 1251, 845, 728, 603\text{ cm}^{-1}$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 13.09$ (s, 1 H), 12.11 (s, 1 H), 10.93 (t, $J = 4.8$ Hz, 1 H), 7.61–7.51 (br. s, 2 H), 7.45 (d, $J = 8.0$ Hz, 2 H), 6.51–6.37 (br. s, 1 H), 5.81 (s, 1 H), 4.80–4.70 (br. s, 1 H), 4.50 (d, $J = 5.8$ Hz, 2 H), 4.23–4.08 (m, 1 H), 4.02–3.89 (m, 1 H), 2.33–2.24 (m, 1 H), 2.27 (t, $J = 2.4$ Hz, 1 H), 2.07–1.93 (m, 2 H), 1.72–1.47 (m, 6 H), 1.38–1.17 (m, 6 H), 1.33 (s, 9 H), 0.90–0.84 (m, 9 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 173.1, 169.6, 162.6, 156.8, 155.6, 154.6, 141.4, 133.9$ (2 C), 127.5 (2 C), 106.2, 80.1, 72.7, 59.1, 51.1, 45.3, 43.1, 37.0, 36.4, 32.8, 29.2, 28.6, 28.5, 27.9, 26.5, 22.4, 13.9, 13.8, 11.6 ppm. HRMS (ESI): calcd. for $\text{C}_{33}\text{H}_{48}\text{N}_6\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 615.3635, found 615.3599.

***N*-[1-(Cyclohexylcarbamoyl)pentyl]-4-{3-[6-(1-ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureidomethyl}-*N*-(prop-2-ynyl)benzamide (7):** A mixture of acid 5 (39 mg, 0.10 mmol), propargylamine (14 mg, 0.25 mmol), cyclohexyl isocyanide (27 mg, 0.25 mmol), and pentanal (22 mg, 0.25 mmol) was treated as described above to give 51 mg (82% yield) of the desired adduct as a colorless oil by column chromatography, and 54 mg (87%) as a light yellow oil by resin purification. FTIR (ATR): $\tilde{\nu} = 3304, 3228, 3023, 2954, 2929, 2855, 1695, 1655, 1640, 1583, 1527, 1446, 1411, 1305, 1254, 851, 806, 731, 668, 649\text{ cm}^{-1}$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 13.08$ (s, 1 H), 12.10 (s, 1 H), 10.92 (s, 1 H), 7.61–7.51 (m, 2 H), 7.43 (d, $J = 7.9$ Hz, 2 H), 6.54 (br. s, 1 H), 5.81 (s, 1 H), 4.79 (m, 1 H), 4.50 (d, $J = 5.7$ Hz, 2 H), 4.20–4.09 (m, 1 H), 3.99–3.88 (m, 1 H), 3.79–3.70 (m, 1 H), 2.33–2.26 (m, 1 H), 2.29 (t, $J = 2.4$ Hz, 1 H), 2.07–1.99 (m, 2 H), 1.90–1.80 (m, 2 H), 1.71–1.50 (m, 8 H), 1.38–1.15 (m, 12 H), 0.90–0.84 (m, 9 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 173.1, 169.5, 156.9, 155.7, 154.7, 141.5, 133.9, 127.5$ (2 C), 127.4 (2 C), 106.3, 80.1, 72.7, 58.7, 47.9, 45.3, 43.1, 37.2, 32.8, 32.7, 29.7, 29.3, 28.5, 28.0, 26.6, 25.5, 24.6, 22.4, 13.9, 13.8, 11.7 ppm. HRMS (ESI): calcd. for $\text{C}_{35}\text{H}_{50}\text{N}_6\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 641.3791, found 641.3742.

***N*-[1-(*tert*-Butylcarbamoyl)pent-4-enyl]-4-{3-[6-(1-ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureidomethyl}-*N*-(prop-2-ynyl)benzamide (8):** A mixture of compound 5 (39 mg, 0.10 mmol), propar-

gylamine (14 mg, 0.25 mmol), 4-pentenal (21 mg, 0.25 mmol) and *tert*-butyl isocyanide (21 mg, 0.25 mmol) was treated as described above, to give 51 mg (84% yield) of the desired compound as a colorless oil by column chromatography, and 54 mg (89%) as a light yellow oil by resin purification. FTIR (ATR): $\tilde{\nu} = 3300, 3218, 2958, 2924, 2868, 1692, 1640, 1575, 1524, 1446, 1416, 1364, 1308, 1247, 1143, 1022, 910, 849, 806, 728, 646\text{ cm}^{-1}$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 13.08$ (s, 1 H), 12.10 (s, 1 H), 10.92 (s, 1 H), 7.55 (br. s, 2 H), 7.45 (d, $J = 8.0$ Hz, 2 H), 6.42 (br. s, 1 H), 5.86–5.08 (m, 2 H), 5.06–4.98 (m, 2 H), 4.79 (m, 1 H), 4.49 (d, $J = 5.8$ Hz, 2 H), 4.17–4.12 (m, 1 H), 3.97–3.93 (m, 1 H), 2.30–2.26 (m, 2 H), 2.16–2.11 (m, 4 H), 1.68–1.48 (m, 4 H), 1.32 (s, 9 H), 1.30–1.22 (m, 4 H), 0.89–0.83 (m, 6 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 172.7, 169.0, 156.6, 155.3, 154.4, 141.3, 137.1, 133.6, 127.3$ (2 C), 127.2 (2 C), 115.4, 106.1, 80.1, 72.9, 65.8, 58.4, 51.3, 45.4, 43.2, 37.2, 33.0, 30.7, 29.4, 28.8 (3 C), 27.6, 26.8, 22.6, 14.1, 11.9 ppm. HRMS (ESI): calcd. for $\text{C}_{33}\text{H}_{46}\text{N}_6\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$ 613.3478, found 613.3445.

***N*-[1-(*tert*-Butylamino)-1-oxohex-5-en-2-yl]-4-{3-[6-(hept-3-yl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureido}methyl)-*N*-(4-methoxybenzyl)-benzamide (9):** A mixture of 39 mg (0.10 mmol) of compound 5, 34 mg (0.25 mmol) of 4-methoxybenzylamine, 21 mg (0.25 mmol) of 4-pentenal, and 21 mg (0.25 mmol) of *tert*-butyl isocyanide was treated as described above, to give 51 mg (76% yield) of the desired compound as a colorless oil by column chromatography, and 54 mg (84%) as a light yellow oil by resin purification. FTIR (ATR): $\tilde{\nu} = 3218, 3023, 2958, 2924, 2868, 1692, 1645, 1580, 1519, 1450, 1256, 1148, 1053, 910, 845, 728\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 13.07$ (s, 1 H), 12.07 (s, 1 H), 10.90 (s, 1 H), 7.37 (br. s, 4 H), 7.18–7.14 (m, 1 H), 6.75–6.60 (m, 4 H), 5.78 (s, 1 H), 5.77–5.70 (m, 1 H), 5.00–4.93 (m, 2 H), 4.62–4.56 (m, 3 H), 4.46–4.44 (m, 2 H), 3.74 (s, 3 H), 2.31–2.24 (m, 1 H), 2.14–1.83 (m, 4 H), 1.69–1.48 (m, 4 H), 1.33–1.13 (m, 13 H), 0.87 (t, $J = 7.5$ Hz, 3 H), 0.85 (t, $J = 7.3$ Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 173.5, 173.0, 169.3, 159.7, 156.8, 155.6, 154.6, 140.8, 137.3, 134.9, 129.6$ (2 C), 127.6 (2 C), 126.9 (2 C), 119.6, 115.6 (2 C), 113.1, 112.8, 106.2, 60.2, 55.1, 51.7, 51.0, 45.3, 43.0, 32.8, 30.5, 29.2, 28.5 (3 C), 26.5, 22.4, 13.8, 11.6 ppm. HRMS (ESI): calcd. for $\text{C}_{38}\text{H}_{52}\text{N}_6\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$ 695.3897, found 695.3839.

***N*-[1-(Cyclohexylamino)-1-oxohex-5-en-2-yl]-4-{3-[6-(hept-3-yl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureido}methyl)-*N*-(4-methoxybenzyl)-benzamide (10):** A mixture of compound 5 (39 mg, 0.10 mmol), 4-methoxybenzylamine (34 mg, 0.25 mmol), 4-pentenal (21 mg, 0.25 mmol) and cyclohexyl isocyanide (27 mg, 0.25 mmol) was treated as described above, to give 51 mg (75% yield) of the desired compound as a colorless oil by column chromatography, and 54 mg (84%) as a light yellow oil by resin purification. FTIR (ATR): $\tilde{\nu} = 3309, 3049, 2924, 2855, 1653, 1584, 1528, 1446, 1333, 1251, 1148, 1048, 910, 728, 690\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 13.06$ (s, 1 H), 12.06 (s, 1 H), 10.88 (s, 1 H), 7.36 (br. s, 4 H), 7.23–7.14 (m, 1 H), 6.84–6.59 (m, 4 H), 5.77 (s, 1 H), 5.75–5.70 (m, 1 H), 5.02–4.90 (m, 2 H), 4.58–4.49 (m, 3 H), 4.45–4.32 (m, 2 H), 3.73 (s, 3 H), 3.62–3.58 (m, 1 H), 2.31–2.23 (m, 1 H), 2.15–1.49 (m, 12 H), 1.32–1.00 (m, 10 H), 0.86 (t, $J = 7.5$ Hz, 3 H), 0.84 (t, $J = 7.3$ Hz, 3 H) ppm. HRMS (ESI): calcd. for $\text{C}_{40}\text{H}_{55}\text{N}_6\text{O}_5\text{Na}$ $[\text{M} + \text{H}]^+$ 699.4233, found 699.4169.

Methyl 4-[4-(Hydroxymethyl)phenoxy]methyl]benzoate (13): To a solution of *p*-hydroxybenzyl alcohol (5.00 g, 40.3 mmol) in acetone (150 mL) were added methyl 4-(bromomethyl)benzoate (8.30 g, 36.3 mmol) and K_2CO_3 (5.60 g, 40.3 mmol). The mixture was refluxed overnight, cooled to room temp. and concentrated in vacuo. The residue was taken up in a 1:1 mixture of aqueous NaOH

(0.625 M)/EtOAc (300 mL), and the layers were separated. The aqueous phase was back-extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with water, dried (MgSO₄) and the solvents evaporated. The residue was precipitated in aqueous NaOH (0.625 M) to give the desired product (9.70 g, 98%) as a white solid. M.p. 115–116 °C. FTIR (ATR): $\tilde{\nu}$ = 3304, 2958, 2915, 2959, 1714, 1282 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 8.04 (d, *J* = 7.8 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 5.13 (s, 2 H), 4.62 (s, 2 H), 3.92 (s, 3 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 166.1, 157.7, 141.9, 133.5, 129.7 (2 C), 128.4 (2 C), 126.7 (2 C), 114.7 (2 C), 69.4, 65.0, 52.2 ppm. HRMS (EI) calcd. for C₁₆H₁₆O₄ [M⁺] 272.1049, found 272.1049.

4-{[4-(Hydroxymethyl)phenoxy]methyl}benzoic Acid (14): A suspension of **13** (6.45 g, 23.7 mmol) in aqueous NaOH (2.0 M, 150 mL) was stirred at 50 °C for 12 h. After cooling the mixture to room temp., it was acidified with aqueous HCl (5.0 M, 75 mL) and the solid was filtered off. After washing (0.01 M HCl, 50 mL) and drying in vacuo, compound **14** (6.12 g, >99%) was obtained as a white solid. M.p. 197–198 °C. FTIR (ATR): $\tilde{\nu}$ = 3396, 2930, 2803, 1690, 1236 cm⁻¹. ¹H NMR ([D₆]DMSO, 400 MHz): δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 5.17 (s, 2 H), 4.41 (s, 2 H) ppm. ¹³C NMR ([D₆]DMSO, 75 MHz): δ = 167.0, 156.8, 141.8, 134.8, 129.3 (2 C), 127.8 (2 C), 127.1 (2 C), 114.4 (2 C), 68.7, 62.6 ppm. HRMS (EI) calcd. for C₁₅H₁₄O₄ [M⁺] 258.0892, found 258.0893.

4-{[4-(Acetoxymethyl)phenoxy]methyl}benzoic Acid (15): A solution of **14** (4.00 g, 15.5 mmol) and Et₃N (10.8 mL, 77.4 mmol) in CH₂Cl₂ (100 mL) was cooled to 0 °C, and Ac₂O (4.40 mL, 46.5 mmol) was added dropwise. The mixture was warmed to room temp. and stirred for 5 h. After diluting the mixture with aqueous HCl (1.0 M, 100 mL), the layers were separated, and the aqueous phase was back-extracted with CHCl₃ (2 × 100 mL). The combined organic layers were washed with water (250 mL), and the solvents evaporated. The residue was precipitated from water (100 mL) to give **15** (4.59 g, 99%) as a white solid. ¹H NMR (400 MHz, [D₆]DMSO): δ = 12.90 (br. s, 1 H), 7.92 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 5.17 (s, 2 H), 4.95 (s, 2 H), 1.99 (s, 3 H) ppm. ¹³C NMR ([D₆]DMSO, 75 MHz): δ = 170.5, 161.7, 158.1, 142.8, 130.3 (2 C), 130.0 (2 C), 128.6, 128.5, 126.8 (2 C), 114.8 (2 C), 69.3, 66.1, 21.3 ppm. HRMS (EI) calcd. for C₁₇H₁₆O₅ [M⁺] 300.0998, found 300.0999.

1-([4-(4-(Acetoxymethyl)phenoxy]methyl]phenyl)-3-[6-(1-ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]urea (17): To a solution of **15** (2.00 g, 6.66 mmol) and Et₃N (1.90 mL, 13.3 mmol) in CHCl₃ (150 mL), (PhO)₂P(O)N₃ (1.70 mL, 8.00 mmol) was added dropwise. The mixture was stirred at room temp. for 6 h, then refluxed for 12 h. After cooling the solution to room temp., the (ethylpentyl)-isocytosine **2** (3.01 g, 14.4 mmol) and a catalytic amount of DMAP were added, and the mixture was refluxed for another 5 h. After cooling the mixture to room temp., the solution was concentrated in vacuo. The residue was taken up in CHCl₃/H₂O (1:1 v/v, 200 mL). The layers were separated, and the aqueous phase was back-extracted with CHCl₃ (2 × 100 mL). The combined organic layers were washed with water, dried and the solvents evaporated. The residue was precipitated in MeOH and dried to give **17** (2.16 g, 64%) as a white solid. FTIR (ATR): $\tilde{\nu}$ = 3022, 2956, 2925, 2866, 1737, 1648, 1605, 1581, 1508, 1321, 1219, 1173, 1017, 822 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 13.11 (s, 1 H), 12.27 (s, 1 H), 12.25 (s, 1 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 5.92 (s, 1 H), 5.01 (br. s, 4 H), 2.36–2.31 (m, 1 H), 2.05 (s, 3 H), 1.68–1.55 (m, 4 H),

1.33–1.25 (m, 4 H), 0.94–0.84 (m, 6 H) ppm. HRMS (ESI) calcd. for C₂₈H₃₅N₄O₅ [M + H⁺] 507.2607, found 507.2653.

1-[6-(1-Ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]-3-(4-((4-hydroxymethyl)phenoxy)methyl]phenyl]urea (18): To a suspension of **17** (0.795 g, 1.57 mmol) in methanol (20 mL) was added K₂CO₃ (1.08 g, 7.85 mmol). The mixture was stirred at room temp. for 5 h, and brought to neutral pH using aqueous NH₄Cl. The methanol was evaporated, and the residue was precipitated in water (25 mL). After filtration, the crude product was washed with Et₂O (15 mL) and dried to give **18** as a white solid (0.693 g, 95%). FTIR (ATR): $\tilde{\nu}$ = 2956, 2925, 2862, 1640, 1605, 1508, 1445, 1406, 1227, 1009, 818 cm⁻¹. ¹H NMR (CDCl₃/CD₃OD, 400 MHz): δ = 7.65 (br. s, 1 H), 7.46 (br. s, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 8.3 Hz, 2 H), 5.94 (s, 1 H), 5.06 (s, 2 H), 4.57 (s, 2 H), 2.44–2.35 (m, 1 H), 1.69–1.58 (m, 4 H), 1.36–1.22 (m, 4 H), 0.96–0.85 (m, 6 H) ppm. HRMS (ESI) calcd. for C₂₆H₃₂N₄O₄Na [M + Na⁺] 487.2321, found 487.2321.

4-(4-{3-[6-(1-Ethylpentyl)-4-oxo-1,4-dihydropyrimidin-2-yl]ureido}-benzyloxy)benzyl 4-Fluoro-3-nitrobenzoate (20): To a solution of **18** (0.204 g, 0.439 mmol) and Et₃N in (0.60 mL, 4.40 mmol) in CHCl₃ (25 mL) were added 4-fluoro-3-nitrobenzoic acid (**19**, 0.814 g, 4.40 mmol), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (0.555 g, 4.40 mmol) and a catalytic amount of DMAP. The mixture was refluxed for 24 h, and cooled to room temp. The solvent was evaporated, and the residue was precipitated in methanol (15 mL). After filtration, washing with methanol (10 mL) and drying, **20** (0.241 g, 87%) was isolated as a yellow solid. FTIR (ATR): $\tilde{\nu}$ = 3023, 2952, 2924, 2868, 1719, 1694, 1649, 1606, 1571, 1539, 1508, 1321, 1278, 1222, 1176, 1112, 1011, 909, 824 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 13.11 (s, 1 H), 12.32 (s, 1 H), 12.29 (s, 1 H), 8.73 (dd, *J* = 7.2, 2.2 Hz, 1 H), 8.32 (ddd, *J* = 8.7, 4.2, 2.2 Hz, 1 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.34 (d, *J* = 8.9 Hz, 1 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 5.94 (d, *J* = 1.5 Hz, 1 H), 5.32 (s, 2 H), 5.07 (s, 2 H), 2.39–2.31 (m, 1 H), 1.75–1.55 (m, 4 H), 1.36–1.19 (m, 4 H), 0.92 (t, *J* = 7.6 Hz, 3 H), 0.88 (t, *J* = 7.6 Hz, 3 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 172.64, 163.16, 159.49, 158.79, 155.91, 155.49, 154.44, 137.64, 136.41, 136.28, 132.03, 130.23, 127.98, 127.66, 127.14, 120.70, 118.66, 188.38, 114.97, 106.45, 69.78, 67.65, 45.56, 33.08, 29.50, 26.84, 22.68, 14.11, 11.94 ppm. HRMS (FAB) calcd. for C₃₃H₃₅FN₅O₇ [M + H⁺] 632.2521, found 632.2495.

General Procedure for Nucleophilic Aromatic Substitution on Compounds 20 and Subsequent Purification Using the Tagged Resin: To a solution of compound **20** (20 mg, 32 μmol, 1 equiv.) in chloroform (2 mL) were added 10 equiv. of Et₃N and 10 equiv. of the amine. The mixture was stirred for 24 h. The tagged resin (10 equiv. of binding sites relative to the amount of **20**) was added to the crude mixture, and the flask was put in a shaking apparatus for 16 h. The resin was filtered off and washed with CHCl₃. After transferring the resin to a flask, a 2:1 mixture of DMF/MeOH (10 mL) was added, and the mixture was shaken for 3 h. The solvent was filtered off and evaporated to give the desired compound with high purity and yield as indicated in Table 2. The compounds were then directly subjected to the cleavage conditions as described for compound **24**.

4-(Allylamino)-3-nitrobenzoic Acid (24): Reaction of **20** according to the general procedure with allylamine provided **21**. M.p. dec. >200 °C. FTIR (ATR): $\tilde{\nu}$ = 3373, 2924, 1697, 1619, 1506, 1256, 1217, 1096, 1014, 798, 759 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 13.12 (s, 1 H), 12.31 (s, 1 H), 12.25 (s, 1 H), 8.89 (dd, *J* = 4.4, 2.0 Hz, 1 H), 8.47 (br. t, *J* = 5.3 Hz, 1 H), 8.07–8.03 (m, 1 H), 7.71

(d, $J = 8.5$ Hz, 2 H), 7.41–7.30 (m, 3 H), 6.96 (dd, $J = 8.8$, 2.2 Hz, 2 H), 6.83 (d, $J = 9.1$ Hz, 2 H), 5.98–5.89 (m, 2 H), 5.33–5.27 (m, 4 H), 5.01 (s, 2 H), 4.04–4.01 (m, 2 H), 2.39–2.32 (m, 1 H), 1.73–1.57 (m, 4 H), 1.35–1.24 (m, 4 H), 0.92 (t, $J = 7.3$ Hz, 3 H), 0.88 (t, $J = 7.2$ Hz, 3 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 173.1$, 165.0, 158.9, 155.8, 154.8, 147.6, 136.4, 132.3, 131.5, 130.1 (2 C), 129.5, 128.9, 128.6, 128.4, 128.2 (2 C), 120.9, 120.7, 117.7 (2 C), 115.0 (2 C), 113.8, 106.6, 77.2, 69.8, 69.7, 66.6, 45.4, 32.9, 29.7, 29.3, 26.7, 22.5, 13.9, 11.7 ppm. Without further purification compound **21** (9.8 mg, 14.6 μmol) was dissolved in TFA/ H_2O (95:5 v/v, 2 mL) and the mixture stirred for 90 min. The solvent was evaporated, and the residue was taken up in 20 mL of CHCl_3 . To the resulting solution 0.50 g of the tagged resin was added (0.14 mmol AT groups), and the mixture was shaken gently overnight. After filtering off the resin, the filtrate was concentrated to give **24** (3.2 mg, >99%) as a yellow solid. FTIR (ATR): $\tilde{\nu} = 3343$, 3101, 2902, 2855, 1675, 1614, 1563, 1537, 1437, 1364, 1277, 1230, 1152, 1083, 932, 759, 703, 543, 521 cm^{-1} . ^1H NMR ($[\text{D}_6]\text{DMSO}$, 400 MHz): $\delta = 8.65$ (t, $J = 5.9$ Hz, 1 H), 8.58 (d, $J = 2.1$ Hz, 1 H), 7.91 (dd, $J = 9.0$, 1.7 Hz, 1 H), 6.98 (d, $J = 9.1$ Hz, 1 H), 5.93–5.84 (m, 1 H), 5.21–5.13 (m, 2 H), 4.08–4.05 (m, 2 H) ppm. ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, 75 MHz): $\delta = 165.8$, 147.2, 135.7, 133.8, 130.5, 128.3, 117.1, 116.2, 115.0, 44.5 ppm.^[33]

3-Nitro-4-(prop-2-ynylamino)benzoic Acid (25): Reaction of **20** according to the general procedure with propargylamine provided **22**. FTIR (ATR): $\tilde{\nu} = 2954$, 2924, 2868, 1718, 1692, 1649, 1619, 1571, 1511, 1316, 1216, 1113, 1009, 910, 819, 806, 741 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 13.12$ (s, 1 H), 12.32 (s, 1 H), 12.27 (s, 1 H), 8.91 (d, $J = 1.7$ Hz, 1 H), 8.43 (br. t, $J = 5.3$ Hz, 1 H), 8.14 (dd, $J = 8.9$, 1.4 Hz, 1 H), 7.72 (d, $J = 8.3$ Hz, 2 H), 7.41 (d, $J = 7.7$ Hz, 2 H), 7.37 (d, $J = 8.1$ Hz, 2 H), 6.98 (d, $J = 8.6$ Hz, 2 H), 5.94 (s, 1 H), 5.29 (s, 2 H), 5.06 (s, 2 H), 4.17 (d, $J = 5.7$ Hz, 2 H), 2.37–2.32 (m, 2 H), 1.72–1.58 (m, 4 H), 1.35–1.24 (m, 4 H), 0.92 (t, $J = 7.2$ Hz, 3 H), 0.89 (t, $J = 7.1$ Hz, 3 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 172.66$, 164.53, 158.60, 155.49, 154.47, 146.29, 137.63, 136.32, 132.16, 130.26, 129.97, 129.17, 128.02, 120.73, 115.01, 114.88, 113.55, 106.48, 77.98, 72.94, 69.83, 67.68, 66.74, 45.59, 33.11, 32.94, 29.87, 29.52, 26.86, 22.70, 14.13, 11.96 ppm. HRMS (FAB): calcd. for $\text{C}_{10}\text{H}_9\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 221.0562, found 221.0559.

4-[(4-Methoxybenzyl)amino]-3-nitrobenzoic Acid (26): Reaction of **20** according to the general procedure with (*p*-methoxybenzyl)-amine provided **23**. FTIR (ATR): $\tilde{\nu} = 3373$, 3045, 2954, 2829, 1697, 1649, 1618, 1576, 1511, 1325, 1264, 1217, 1109, 1009, 910, 798, 737 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 13.12$ (s, 1 H), 12.31 (s, 1 H), 12.27 (s, 1 H), 8.91 (d, $J = 1.5$ Hz, 1 H), 8.70 (br. t, $J = 5.5$ Hz, 1 H), 8.00 (dd, $J = 9.0$, 2.0 Hz, 1 H), 7.72 (d, $J = 8.4$ Hz, 2 H), 7.40 (d, $J = 8.4$ Hz, 2 H), 7.35 (d, $J = 8.5$ Hz, 2 H), 7.30–7.28 (m, 1 H), 6.96 (d, $J = 8.4$ Hz, 2 H), 6.92–6.82 (m, 4 H), 5.94 (s, 1 H), 5.26 (s, 2 H), 5.05 (s, 2 H), 4.55 (d, $J = 5.6$ Hz, 2 H), 3.79 (s, 3 H), 2.38–2.32 (m, 1 H), 1.75–1.58 (m, 4 H), 1.43–1.24 (m, 4 H), 0.92 (t, $J = 7.3$ Hz, 3 H), 0.88 (t, $J = 7.2$ Hz, 3 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 172.65$, 164.60, 159.84, 158.57, 155.48, 154.49, 147.22, 137.80, 137.62, 136.25, 132.15, 131.48,

130.11, 129.93, 129.28, 128.24, 128.02, 120.70, 119.02, 117.72, 114.84, 113.78, 112.99, 112.68, 106.47, 69.82, 66.63, 55.33, 47.30, 45.57, 33.09, 29.51, 26.85, 22.69, 14.12, 11.95 ppm. HRMS (FAB): calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_8$ $[\text{M} + \text{H}]^+$ 443.1399, found 443.1399. Treatment of compound **23** without further purification with TFA/ H_2O as described above, gave acid **26** in quantitative yield. A pure sample of **26** was obtained after filtration through a short silica plug (86% yield). FTIR (ATR): $\tilde{\nu} = 3360$, 2950, 2920, 2850, 1718, 1619, 1454, 1437, 1260, 1212, 1156, 1044 cm^{-1} . ^1H NMR ($[\text{D}_6]\text{DMSO}$, 400 MHz): $\delta = 8.99$ (t, $J = 6.1$ Hz, 1 H), 8.60 (d, $J = 2.1$ Hz, 1 H), 7.86 (dd, $J = 9.1$, 2.1 Hz, 1 H), 7.23 (t, $J = 7.1$ Hz, 1 H), 6.96–6.79 (m, 4 H), 4.63 (d, $J = 6.1$ Hz, 2 H), 3.70 (s, 3 H) ppm. ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, 75 MHz): $\delta = 165.8$, 159.5, 147.1, 139.5, 135.8, 130.8, 129.7, 128.3, 118.9, 117.4, 115.0, 112.7, 112.4, 56.0, 54 ppm.^[33]

Acknowledgments

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- [1] See, e.g.: a) *Handbook of Combinatorial Chemistry* (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**; b) *Combinatorial Chemistry*, 2nd revised ed. (Eds.: W. Bannwarth, B. Hinzen), Wiley-VCH, Weinheim, **2006**.
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