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Efficient microwave-assisted synthesis of 4-amino-2-benzazepin-3-ones as conformationally restricted dipeptide mimetics

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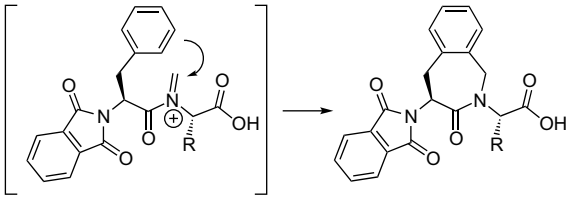
ABSTRACT

In this paper, we describe the synthesis of conformationally constrained dipeptide mimetic derivatives. Microwave flash heating was used in several synthetic steps providing the opportunity to perform the reactions in dramatically shortened time as well as to increase the obtained yields. The efficiency of the methodology makes it useful in order to prepare other dipeptides containing the 4-amino-tetrahydro-2-benzazepin-3-one motif.

1. Introduction

Introduction of conformational restrictions into the sequence of bioactive peptides is one of the most useful strategies in the design and preparation of more selective and/or more potent peptide mimetics as enzyme inhibitors or receptor agonists and/or antagonists.[1] Moreover, the so-obtained pseudopeptides display several important advantages compared to natural peptides such as increased bio-stability and improved selectivity toward the natural biological target. Due to the flexibility of the peptide side chains, the proper topography during receptor interaction can only be studied by constraining or fixing of the side-chain conformers.[2] A reduced conformational flexibility of phenylalanine-containing peptides can be obtained embodying a rigidified skeleton deriving from the cyclization of the aromatic side chain that is anchored to the α-amine of the next residue by means of a methylene bridge. This structural modification leads to the 4-amino-tetrahydro-2-benzazepin-3-one (Aba) nucleus, which has proven to be an excellent tool for the design and preparation of several different peptide mimetics such as renin inhibitors,[3] opioid peptides,[2,4] and human melanocortin-3 receptor ligands.[5] The previously reported synthetic strategy adopted for the preparation of this kind of moiety is based on the reaction, in acidic conditions, of an intermediate oxazolidinone that affords the benzazepinone nucleus by means of an intramolecular Friedel–Crafts cyclization via an *N*-acyliminium ion (Scheme 1).[3,6,7] Several laboratories have exploited *N*-acyliminium ion cyclization, especially for the synthesis of natural products.[8,9] *N*-Acyliminium species, in fact, have demonstrated a high reactivity toward a wide variety of π-nucleophiles including alkenes, allenes, alkynes, and aromatic or heteroaromatic systems.[9] Benzazepinone ring formation has been performed using acid, such as trifluoromethanesulfonic acid (TFMSA), or Lewis acids, such as titanium(IV) chloride or tin(IV) chloride, at room temperature or under reflux, and required several hours (usually 12–24 h). In later years, microwave irradiation in chemical reaction enhancement has been widely applied in various synthetic fields.[10] Replacing the oil bath with a dedicated microwave reactor allows using conditions not attainable under



Scheme 1. Formation of benzazepinone nucleus via an *N*-acyliminium ion.

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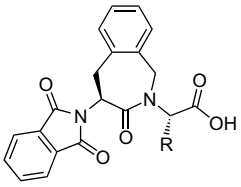
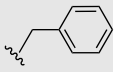
Table 1
Structures of dipeptide mimetics **6a–f**

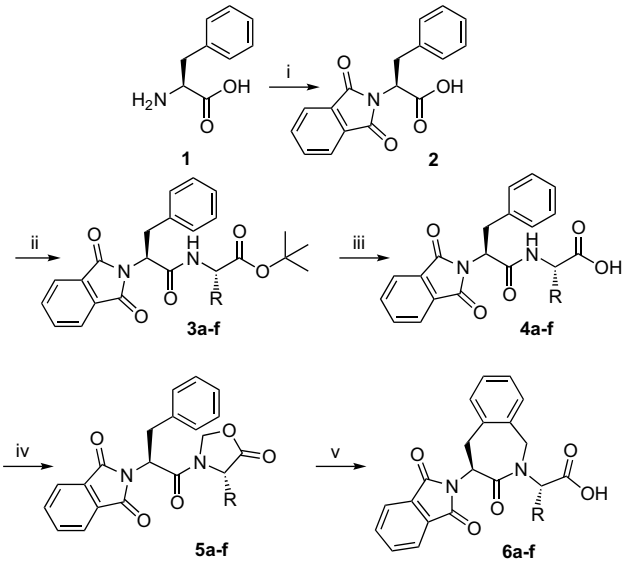


Compound	R	Compound	R
6a	–H	**6d**	
6b		**6e**	
6c		**6f**	

conventional heating, providing the opportunity to perform reactions in dramatically shortened time as well as increasing yields. Enhancements of the reaction rate and product selectivity under microwave dielectric heating have been attributed to thermal effects, which may result because of differences between the real reaction temperature at the reaction sites and the observed average temperature. Our special interest in applying the potential of microwave irradiation to the synthesis of peptide and peptide mimetic structures[11] prompted us to use this technology for the preparation of several dipeptide mimetics with the general structure Pht-Aba-X-OH, where X is represented by the amino acids Gly, Ala, Val, Leu, Ile and Phe, in order to develop new series of compounds in our ongoing research for novel protease activated receptor-1 (PAR-1) antagonists;[12] particularly, we planned the replacement of the Phe[2] of the sequence of PAR-1AP (human SFLLRN or rat SFFLRN) by these conformationally restricted derivatives. In this paper, we describe the application of microwave flash heating to the synthesis of conformationally constrained dipeptide mimetic derivatives. The efficiency of the methodology makes it useful in order to prepare other dipeptides containing the 4-amino-tetrahydro-2-benzazepin-3-one motif.

2. Results and discussion

In short peptides, different orientation of the side-chain group of an L-amino acid residue in terms of χ^1 space can lead to a relevant difference of the chemical surfaces, often corresponding to a dramatically different biological profile. The staggered conformations around C_α–C_β for Phe, such as *gauche* (+) (χ^1=60°) and *trans* (χ^1=180°), can be fixed by means of the 4-amino-tetrahydro-2-benzazepin-3-one nucleus. The dipeptide mimetic derivatives **6a–f**, reported in Table 1, have been prepared following a previously described procedure[2–7] summarized in Scheme 2. Phthaloylation of Phe, the –*t*-Bu removal from intermediates **3a–f**, and the crucial cyclization of oxazolidinones **5a–f** to benzazepinones **6a–f** have been performed by microwave flash heating. In recent years, the application of microwave-assisted reactions in organic synthesis has received considerable attention. Microwave irradiation commonly increases the reaction rates above those obtained by conventional heating and leads to the production of fewer by-products, making necessary minimum efforts for the purification of the final products. In contrast to conventional heating performed in blocks or ovens, where heat must initially be transferred to the medium via metal parts, air, or vessels, microwave irradiation directly heats the medium, resulting in significant time savings in several fields.



Scheme 2. (i) Phthalic anhydride, TEA, toluene, μυ; (ii) H-aa-O-*t*-Bu, DCC, HOBt, DMAP, DMF; (iii) 40% TFA in DCM, μυ; (iv) $(CH_2O)_n$, *p*-TsOH, toluene; (v) Methods A–D.

The synthetic procedure started with the protection of phenylalanine α-amino group obtained using phthalic anhydride in the presence of TEA. The reaction has been performed in several different anhydrous solvents, such as dioxane, DMF, and toluene, obtaining the best results (yield 85%) when using anhydrous toluene and irradiating the solution at 500 W (temperature 120 °C) for 1 h. Pht-Phe-OH **2** was then condensed with the appropriate *tert*-butyl ester amino acid, employing standard solution-phase peptide synthesis method (such as DCC/HOBt/TEA), affording the intermediates **3a–f**. The *tert*-butyl protection was removed by 40% TFA in DCM; the irradiation at 500 W (temperature 60 °C) for 10 min gave excellent yields (ranging between 80 and 98%) of the desired acids **4a–f**. The oxazolidinones **5a–f** were formed by reaction of the starting acids **4a–f** with paraformaldehyde in the presence of catalytic *p*-toluenesulfonic acid. Attempts to perform this step under microwave irradiation furnished low yields because it was impossible for us to achieve the water azeotropic removal needed to reach the completion of the reaction. Compounds **5c** and **5e** were obtained with yields lower than those accomplished with the other derivatives (32% and 25%, respectively); this result could be addressed to the β-branch of Val and Ile that hinders the oxazolidinone formation. No detectable epimerization occurred at the chiral centers during these transformations as measured by ^{1}H NMR spectroscopy. The crucial cyclization needed for obtaining the desired final dipeptide mimetic analogues **6a–f** was performed employing several acidic conditions such as TFMSA, $BF_3 \cdot OEt_2$, $AlCl_3$, and $ZnCl_2$ achieving the best results when titanium(IV) and tin(IV) chloride were used. The obtained yields and the reaction conditions are summarized in Table 2. As shown, the cyclization reaction, based on the key formation of an *N*-acyliminium ion that evolves through a Friedel–Crafts intramolecular reaction to the desired benzazepinone derivative, was accomplished with high yields using $TiCl_4$ (10 equiv of 1 M solution in anhydrous DCM) using microwave irradiation at 600 W for 1 h (temperature 80 °C in method A and 50 °C in method C). The final products were obtained with yields ranging between 10% and 89% when the reaction was performed at 80 °C, and 6%–89% when the reaction was performed at 50 °C. The accomplished yields, reported in Table 2, show that the operative temperature does not have a critical effect in the preparation of **6a**, **6d**, and **6f** (that were obtained with comparable yields when performing the reaction both at 50 °C and at 80 °C) while method A (80 °C) affords better results for compounds **6b** and **6c**.

Table 2
Comparison of $TiCl_4$ and $SnCl_4$ in the synthesis of 4-amino-2-benzazepin-3-ones **6a–f** from oxazolidinones **5a–f**

Reaction conditions	Products formed (% yield)					
	6a	**6b**	**6c**	**6d**	**6e**	**6f**
Method A[a]	82	68	62[b]	89	10[b]	85
Method B[a]	58	64	78	56	61[b]	56
Method C[a]	88	53	16[b]	86	6[b]	89
Method D[a]	70	42	48	69	58[b]	46

[a] Method A: $TiCl_4$ (1 M in CH_2Cl_2), 80 °C, 600 W, 1 h; method B: $SnCl_4$ (1 M in CH_2Cl_2), 80 °C, 600 W, 1 h; method C: $TiCl_4$ (1 M in CH_2Cl_2), 50 °C, 600 W, 1 h; method D: $SnCl_4$ (1 M in CH_2Cl_2), 50 °C, 600 W, 1 h.
[b] The reaction was run for 2 h.

The same reaction, performed with $SnCl_4$ (10 equiv of 1 M solution in anhydrous DCM), irradiating at 600 W for 1 h (temperature 80 °C in method B and 50 °C in method D), afforded yields lower than $TiCl_4$, except for compounds **6c** and **6e**. In these cases, the Lewis acids show specific reactivity; in fact, the preparation of **6c** using $SnCl_4$ furnished yields higher than those obtained with $TiCl_4$ (78% vs 62% at 80 °C and 48% vs 16% at 50 °C) while compound **6e** was prepared with satisfactory yields (61% at 80 °C and 58% at 50 °C) only when $SnCl_4$ was employed as catalyst. The efficiency of the here-described microwave-assisted synthesis was also confirmed by examining the extent of racemization occurring during the final Friedel–Crafts intramolecular cyclization. An additional diastereomer was observed in the synthesis of compound **6b**, performed employing both $SnCl_4$ and $TiCl_4$, while compounds **6c** and **6e** furnished the diastereomeric peak by only carrying out the reaction via $SnCl_4$. It was detected by ^{1}H NMR spectroscopy and its amount was quantified by HPLC. In all the observed cases, the measured epimerization was less than 5%, placing the microwave-assisted approach as an advantageous alternative to the previously described synthetic procedure.

3. Conclusion

We have described the synthesis of dipeptide mimetic analogues **6a–f** as useful scaffolds to be introduced in different biologically active peptide sequences. Some synthetic steps have been accomplished by microwave flash heating in order to explore the application of this methodology to this kind of reaction. Even in this case, microwave irradiation has shown its potential as technological tool able to improve on the reaction conditions allowing the synthesis of the final compounds **6a–f** with high selectivity and less than 5% racemization, occurring during the final synthetic step, as judged by HPLC profile and ^{1}H NMR spectroscopy. The previously reported synthesis of compound **6a**,[1,3] although characterized with high yields, required several hours (12–16 h). Using our methods, we obtained very good yields (82% at 80 °C and 88% at 50 °C) in just 1 h, and good results were obtained in the preparation of the other derivatives. $TiCl_4$ was the best catalyst in most of the cases except for compounds **6c** and **6e** that were prepared in acceptable yields only when $SnCl_4$ was used. Further development regarding the synthesis of several substituted benzazepinone derivatives is currently in progress in our laboratory for potential applications in medicinal chemistry and peptide mimetics synthesis.

4. Experimental

4.1. General

All solvents were purchased from Carlo Erba (Rodano, Milan, Italy). Extraction solvents were dried over sodium sulfate. Solvents used for reactions were dried over 3 Å molecular sieves. All solvents were filtered and degassed prior the use. Reagent grade materials were purchased from Bachem (Bubendorf, Switzerland) and from Aldrich (Milan, Italy) and were used without further purification. All reactions were followed both by TLC, carried out on precoated silica gel Kieselgel 60F254 (Merck, A.G., Darmstadt, Germany) plates with fluorescent indicator, and by RP-HPLC using a Beckman C_{18} column (5 μm, 4.6×250 mm) employing the following conditions: A, 0.05% TFA (v/v) in water; B, 0.05% TFA (v/v) in acetonitrile; UV detection at 220 nm, flow rate 1 mL/min. Preparative chromatographic purifications were performed using a Kieselgel 60 silica gel column and, when necessary, RP-HPLC purifications were performed on a Waters Delta Prep 4000 system equipped with a Waters 484 multi-wavelength detector on a Vydac C_{18} column (15–20 μm, 22×5000 mm). The operational flow rate was 30 mL/min. Capacity factor (K') and homogeneity of the final compounds were assessed by analytical RP-HPLC using both Vydac C_{18} column (5 μm, 4.6×250 mm) and Beckman C_{18} column (5 μm, 4.6×250 mm) employing the following conditions: eluent A, 0.05% TFA (v/v) in water; eluent B, 0.05% TFA (v/v) in acetonitrile; gradient 20–50% B over 25 min on the Vydac C_{18} column (system 1) and 30–60% B over 25 min on the Beckman C_{18} column (system 2), UV detection at 254 nm, flow rate 1 mL/min. The column was connected to a Rheodyne model 7725 injector, a Waters 600 HPLC system, a Waters 486 tunable absorbance detector, and a Waters 746 chart recorder. The melting points, measured on a Buchi B-540 instrument, represent values obtained on recrystallized or chromatographically purified material. Elemental analyses were carried out on a Carlo Erba model 1106. Specific rotations were measured on a Perkin–Elmer 243 B polarimeter. High resolution ESI-MS spectra were performed with a Micromass QTOF Micromass spectrometer. ESI-MS experiments were performed on an Applied Biosystem API 2000 triple-quadrupole mass spectrometer. IR spectra were recorded on Thermo Nicolet 5700 FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 MHz instrument. Chemical shifts are reported in parts per million using Me_4Si as an internal standard.

4.2. Microwave equipment and conditions

The synthetic steps performed by microwave irradiation were carried out using a microwave oven (ETHOS 1600 Milestone) especially designed for organic synthesis. Microwave reactions were performed in sealed tubes and a microwave program that was composed by appropriate ramping and holding steps was selected. The temperature of the stirred reaction mixture was monitored directly by a microwave-transparent fluoroptic probe inserted into the reaction mixture; irradiation time and power were monitored with the 'easyWAVE' software package.

4.3. N^{α}-Phthaloyl-L-phenylalanine (2)

A solution of L-phenylalanine **1** (2.5 g, 0.015 mol), phthalic anhydride (2.2 g, 0.015 mol), and triethylamine (3.6 mL, 0.026 mol) in 30 mL of anhydrous toluene over molecular sieves (3 Å) was placed in a closed reaction vessel, equipped with temperature control unit, and irradiated according to the following parameters: initial power, 500 W; initial time, 1 min (ramping); final power, 500 W; T, 120 °C; reaction time, 1 h. The reaction mixture was filtered and the obtained solution was extracted with 1 N HCl (3×40 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a residue, which was crystallized with ethyl acetate/*n*-hexane furnishing the desired product **2** as a white solid (3.8 g, 85%); mp 183–185 °C (lit.[13] mp 183–185 °C); $[\alpha]_D^{20}$ −164 (c 1.1, EtOH) (lit.[13] $[\alpha]_D^{20}$ −212); ν_{max} (KBr) 3300, 1780, 1760, 1690, 1400 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 3.56 (d, 2H, J=8.2 Hz), 5.11

(dd, 1H, *J*=10, 6.8 Hz), 7.10–7.15 (m, 5H), 7.63–7.66 (m, 2H), 7.73–7.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.8, 53.6, 123.6, 126.9, 128.7, 129.0, 131.9, 134.2, 137.4, 167.8, 171.3. Anal. Calcd (%) for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found C, 69.27; H, 4.43; N, 4.75. ESI-MS: calcd 295.3; found $[M+H]^+$ 296, $[M+Na]^+$ 318. HRMS (ESI): calcd 295.0845; found 295.0846.

4.4. General procedure for the synthesis of intermediates 3a–f

Pht-Phe-OH (**2**, 1.0 mmol), DCC (1.1 mmol), and HOBt (1.1 mmol) were dissolved in DMF (20 mL) and the solution was ice cooled. After 30 min the opportune H-aa-O-*t*-Bu···HCl and TEA (1.0 mmol) were added and the reaction mixture was stirred for 4 h at room temperature. After DCU removal, the filtrate was dried in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The organic layer was extracted with 5% $NaHCO_3$ (3×10 mL), 10% citric acid (3×10 mL), and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The desired products **3a–f** were obtained by crystallization with diethyl ether/*n*-hexane with yield ranging between 87% and 95%.

4.5. Procedure for the microwave-assisted synthesis of intermediates 4a–f

*4.5.1. Pht-Phe-Gly-OH (**4a**)*

N^{α}-Phthaloyl-phenylalanylglycine *tert*-butyl ester **3a** (500 mg, 1.2 mmol) was dissolved in 10 mL of 40% TFA in CH_2Cl_2, and the mixture was placed in a closed reaction vessel, equipped with temperature and pressure control units, and irradiated according to the following parameters: initial power, 500 W; initial time, 1 min (ramping); final power, 500 W; *T*, 60 °C; reaction time, 10 min. After evaporation of the solvent, the desired product **4a** was obtained by precipitation with diethyl ether as a white solid. Yield 385 mg, 91%; mp 177–179 °C (lit.[7] mp 184–185 °C); R_f 0.13 (DCM/MeOH 9/1); $[\alpha]_D^{20}$ −155 (*c* 0.8, EtOH) (lit.[7] $[\alpha]_D^{20}$ −153.7); ν_{max} (KBr) 1730, 1705, 1665, 1630, 1600, 750 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.31 (d, 1H, *J*=14.0 Hz), 3.49 (dd, 1H, *J*=14.0, 4.4 Hz), 3.61 (dd, 1H, *J*=17.2, 5.6 Hz), 3.77 (dd, 1H, *J*=17.2, 6.4 Hz), 4.96 (dd, 1H, *J*=12.0, 4.4 Hz), 7.05–7.14 (m, 5H), 7.76–7.78 (m, 4H), 8.59 (d, 1H, *J*=8.4 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) δ 34.4, 42.3, 54.9, 123.8, 127.2, 128.9, 129.3, 131.9, 135.2, 138.2, 168.0, 168.9, 174.6. Anal. Calcd (%) for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.83; H, 4.42; N, 7.96. ESI-MS: calcd 352.3; found $[M+H]^+$ 353.3, $[M+Na]^+$ 375.2, $[M+K]^+$ 391.2. HRMS (ESI): calcd 352.1059; found 352.1062.

Using the procedure described above for the preparation of **4a**, the following additional intermediates were synthesized using as starting material compounds **3b–f**.

*4.5.2. Pht-Phe-Ala-OH (**4b**)*

Yield 386 mg, 89%; white solid, mp 197–199 °C; R_f 0.19 (DCM/MeOH 9/1); $[\alpha]_D^{20}$ −130.1 (*c* 1.1, MeOH); ν_{max} (KBr) 1706, 1648, 1524, 1449, 1382, 712 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, 3H, *J*=7.2 Hz), 3.48 (t, 2H, *J*=5.2 Hz), 4.48–4.51 (m, 1H), 5.04 (dd, 1H, *J*=10.0, 6.4 Hz), 7.05–7.10 (m, 5H), 7.62–7.63 (m, 2H), 7.64–7.71 (m, 2H), 8.50 (d, 1H, *J*=8.4 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) δ 18.4, 34.9, 48.7, 55.6, 123.6, 127.0, 128.7, 129.1, 131.7, 134.3, 137.1, 168.0, 168.4, 174.7. Anal. Calcd (%) for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.43; H, 4.95; N, 7.65. ESI-MS: calcd 366.4; found $[M+H]^+$ 367.3, $[M+Na]^+$ 389.3, $[M+K]^+$ 405.3. HRMS (ESI): calcd 366.1216; found 366.1218.

*4.5.3. Pht-Phe-Val-OH (**4c**)*

Yield 403 mg, 92%; white solid, mp 127–133 °C; R_f 0.36 (DCM/MeOH 9/1); $[\alpha]_D^{20}$ −44.3 (*c* 1.0, MeOH); ν_{max} (KBr) 1707, 1666, 1534, 1378, 718 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 (d, 3H, *J*=6.4 Hz), 0.84 (d, 3H, *J*=6.8 Hz), 1.97–2.01 (m, 1H), 3.29 (t, 1H, *J*=14.0 Hz), 3.48 (dd, 1H, *J*=14.0, 4.4 Hz), 4.17 (t, 1H, *J*=7.4 Hz), 4.99 (dd, 1H, *J*=11.6, 4.4 Hz), 7.04–7.14 (m, 5H), 7.76–7.78 (m, 4H), 8.40 (d, 1H, *J*=8.8 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) δ 19.1, 19.9, 30.3, 34.8, 54.9, 58.6, 123.7, 127.1, 128.9, 129.4, 132.0, 135.1, 138.3, 168.2, 168.6, 173.6. Anal. Calcd (%) for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.87; H, 5.61; N, 7.09. ESI-MS: calcd 394.4; found $[M+H]^+$ 395.4, $[M+Na]^+$ 417.4, $[M+K]^+$ 433.4. HRMS (ESI): calcd 394.1529; found 394.1532.

*4.5.4. Pht-Phe-Leu-OH (**4d**)*

Yield 419 mg, 95%; white solid, mp 163–165 °C; R_f 0.33 (DCM/MeOH 9/1); $[\alpha]_D^{20}$ −73.3 (*c* 1.1, MeOH); ν_{max} (KBr) 1702, 1663, 1514, 1382, 716 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, 6H, *J*=5.2 Hz), 1.43–1.52 (m, 3H), 3.24 (t, 1H, *J*=13.6 Hz), 3.47 (dd, 1H, *J*=14.0, 4.4 Hz), 4.29–4.31 (m, 1H), 4.92 (dd, 1H, *J*=11.6, 4.4 Hz), 7.05–7.13 (m, 5H), 7.77–7.84 (m, 4H), 8.41 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) δ 21.8, 23.6, 24.7, 34.7, 51.2, 54.8, 123.7, 127.1, 128.9, 129.4, 132.0, 135.1, 138.3, 168.1, 168.5, 174.7. Anal. Calcd (%) for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.71; H, 5.91; N, 6.86. ESI-MS: calcd 408.4; found $[M+H]^+$ 409.4, $[M+Na]^+$ 431.4, $[M+K]^+$ 447.4. HRMS (ESI): calcd 408.1685; found 408.1672.

*4.5.5. Pht-Phe-Ile-OH (**4e**)*

Yield 397 mg, 90%; white solid, mp 151–153 °C; R_f 0.32 (DCM/MeOH 9/1); $[\alpha]_D^{20}$ −86.0 (*c* 1.0, MeOH); ν_{max} (KBr) 1698, 1651, 1517, 1376, 1359, 1100 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 (t, 3H, *J*=7.4 Hz), 0.82 (d, 3H, *J*=6.8 Hz), 1.08–1.12 (m, 2H), 1.32–1.34 (m, 1H), 3.30 (t, 1H, *J*=12.8 Hz), 3.47 (dd, 1H, *J*=14.0, 4.4 Hz), 4.22 (t, 1H, *J*=7.6 Hz), 4.99 (dd, 1H, *J*=11.6, 4.4 Hz), 7.06–7.12 (m, 5H), 7.73–7.75 (m, 4H), 8.39 (d, 1H, *J*=8.4 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.6, 16.2, 25.3, 34.8, 36.6, 54.9, 57.4, 123.7, 127.1, 128.9, 129.4, 132.0, 135.1, 138.3, 168.2, 168.6, 173.7. Anal. Calcd (%) for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.52; H, 5.92; N, 6.87. ESI-MS: calcd 408.4; found $[M+H]^+$ 409.4, $[M+Na]^+$ 431.4, $[M+K]^+$ 447.4. HRMS (ESI): calcd 408.1685; found 408.1671.

*4.5.6. Pht-Phe-Phe-OH (**4f**)*

Yield 420 mg, 95%; white solid, mp 166–168 °C; R_f 0.30 (DCM/MeOH 9/1); $[\alpha]_D^{20}$ −77.4 (*c* 1.2, MeOH); ν_{max} (KBr) 1706, 1511, 1374, 1179, 1093, 861, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.82–2.88 (m, 1H), 2.97 (dd, 1H, *J*=13.8, 5.0 Hz), 3.24 (t, 1H, *J*=13.6 Hz), 3.41 (dd, 1H, *J*=14.2, 4.4 Hz), 4.39–4.42 (m, 1H), 4.91 (dd, 1H, *J*=11.6, 4.4 Hz), 7.03–7.20 (m, 10H), 7.76–7.78 (m, 4H), 8.53 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) δ 34.5, 36.9, 54.8, 56.6, 123.7, 126.9, 127.1, 128.8, 128.9, 129.4, 129.7, 131.9, 135.1, 138.2, 138.3, 167.9, 168.5, 173.5. Anal. Calcd (%) for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33. Found: C, 70.49; H, 5.02; N, 6.33. ESI-MS: calcd 442.5, found $[M+H]^+$ 443.4, $[M+Na]^+$ 465.4, $[M+K]^+$ 481.4. HRMS (ESI): calcd 442.1529; found 442.1536.

4.6. Procedure for the synthesis of intermediates 5a–f

*4.6.1. (S)-2-(1-Oxo-1-(5-oxooxazolidin-3-yl)-3-phenylpropan-2-yl) isoindoline-1,3-dione (**5a**)*

A solution of Pht-Phe-Gly-OH **4a** (2.5 g, 7.1 mmol), paraformaldehyde (4.3 g, 20 equiv), and *p*-toluenesulfonic acid (270 mg, 0.2 equiv) in anhydrous toluene (75 mL) was refluxed in a Dean–Stark apparatus for 4 h and then the solvent was evaporated. The residue was dissolved in EtOAc (100 mL), washed with $NaHCO_3$ saturated (2×30 mL), saturated NaCl (1×30 mL), and then the collected organic phase was dried over Na_2SO_4. After evaporation, the solid was crystallized as a white solid in toluene. Yield 2.1 g, 80%, mp 165–167 °C (lit.[4] mp 176–178 °C); R_f 0.19 (*n*-hexane/EtOAc, 7/3); $[\alpha]_D^{20}$ −139.2 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1805, 1706, 1664, 1374, 1238, 1167, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (dd, 1H, *J*=14.2, 8.8 Hz), 3.63 (dd, 1H, *J*=14.0, 6.8 Hz), 3.80–4.05 (m, 2H), 4.97 (t, 1H,

J=8.0 Hz), 5.40–5.58 (m, 2H), 7.17–7.26 (m, 5H), 7.73–7.75 (m, 2H), 7.80–7.82 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 34.9, 51.7, 53.6, 79.8, 124.0, 127.6, 129.0, 129.4, 131.3, 134.9, 136.3, 167.5, 168.9, 170.3. Anal. Calcd (%) for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.82; H, 4.42; N, 7.70. ESI-MS: calcd 364.3; found $[M+H]^+$ 365.0, $[M+Na]^+$ 387.1, $[M+K]^+$ 403.0. HRMS (ESI): calcd 364.1059; found 364.1061.

Using the procedure described above for the preparation of **5a**, the following additional intermediates were synthesized using as starting material compounds **4b–f**.

*4.6.2. 2-((S)-1-((S)-4-Methyl-5-oxooxazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione (**5b**)*

Yield 1.7 g, 65%, white powder, mp 180–182 °C; R_f 0.31 (*n*-hexane/EtOAc, 7/3); $[\alpha]_D^{20}$ −137.9 (*c* 1.1, $CHCl_3$); ν_{max} (KBr) 1792, 1708, 1678, 1379, 1238, 952 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 3H), 3.30–3.45 (m, 1H), 3.58–3.70 (m, 1H), 4.52–4.61 (m, 1H), 4.98 (dd, 1H, J=8.6, 6.6 Hz), 5.05–5.10 (m, 1H), 5.20–5.29 (m, 1H), 7.16–7.17 (m, 5H), 7.74–7.80 (m, 2H), 7.81–7.82 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.7, 35.2, 50.6, 53.5, 78.9, 124.1, 127.4, 128.9, 129.5, 131.2, 134.9, 136.4, 167.9, 170.0, 172.4. Anal. Calcd (%) for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.53; H, 4.80; N, 7.40. ESI-MS: calcd 378.4; found $[M+H]^+$ 379.3, $[M+Na]^+$ 401.3, $[M+K]^+$ 417.1. HRMS (ESI): calcd 378.1216; found 378.1223.

*4.6.3. 2-((S)-1-((S)-4-Isopropyl-5-oxooxazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione (**5c**)*

Yield 0.82 g, 32%, white powder, mp 192–194 °C; R_f 0.40 (*n*-hexane/EtOAc, 7/3); $[\alpha]_D^{20}$ −121 (*c* 1.1, MeOH); ν_{max} (KBr) 1796, 1714, 1681, 1508, 1380, 1243, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (dd, 6H, J=6.8 Hz), 2.08–2.12 (m, 1H), 3.33–3.41 (m, 1H), 3.59–3.61 (m, 1H), 4.58–4.63 (m, 1H), 4.95–4.99 (m, 1H), 5.01 (t, 1H, J=6.8 Hz), 5.15–5.20 (m, 1H), 7.16–7.28 (m, 5H), 7.76–7.81 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.2, 31.6, 35.3, 53.4, 56.2, 59.6, 124.1, 127.2, 128.7, 129.5, 131.3, 134.5, 136.4, 168.2, 168.6, 171.7. Anal. Calcd (%) for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 68.01; H, 5.45; N, 6.90. ESI-MS: calcd 406.4; found $[M+H]^+$ 407.3, $[M+Na]^+$ 429.1, $[M+K]^+$ 445.1. HRMS (ESI): calcd 406.1529; found 406.1531.

*4.6.4. 2-((S)-1-((S)-4-Isobutyl-5-oxooxazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione (**5d**)*

Yield 1.9 g, 76%, white powder, mp 129–131 °C; R_f 0.46 (*n*-hexane/EtOAc, 7/3); $[\alpha]_D^{20}$ −126.4 (c 0.9, $CHCl_3$); ν_{max} (KBr) 1800, 1711, 1676, 1380, 1194, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 6H, J=6.8 Hz), 1.66 (t, 2H, J=6.6 Hz), 1.81 (m, 1H), 3.36 (t, 2H, J=11.6 Hz), 3.58–3.63 (m, 1H), 4.60–4.68 (m, 1H), 5.01 (t, 1H, J=6.0 Hz), 5.25–5.30 (m, 1H), 7.15–7.31 (m, 5H), 7.73–7.82 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.5, 22.8, 24.5, 35.2, 39.3, 53.0, 53.3, 124.1, 127.4, 128.9, 129.5, 131.1, 134.9, 136.4, 166.5, 167.0, 172.1. Anal. Calcd (%) for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.51; H, 5.75; N, 6.67. ESI-MS: calcd 420.5; found $[M+H]^+$ 421.3, $[M+Na]^+$ 443.1, $[M+K]^+$ 459.1. HRMS (ESI): calcd 420.1685; found 420.1696.

*4.6.5. 2-((S)-1-((S)-4-sec-Butyl-5-oxooxazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione (**5e**)*

Yield 0.64 g, 25%, white powder, mp 156–158 °C; R_f 0.70 (*n*-hexane/EtOAc, 7/3); $[\alpha]_D^{20}$ −86.9 (*c* 0.9, $CHCl_3$); ν_{max} (KBr) 1801, 1710, 1674, 1375, 1048, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, J=5.4 Hz), 0.91 (d, 3H, J=7.2 Hz), 1.54–1.56 (m, 2H), 2.50–2.55 (m, 1H), 3.25–3.33 (m, 1H), 3.50–3.55 (m, 1H), 4.64 (m, 1H), 4.94–4.97 (m, 1H), 5.02 (t, 1H, J=7.8 Hz), 5.25–5.29 (m, 1H), 7.13–7.31 (m, 5H), 7.73–7.83 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.0, 15.1, 25.2, 35.3, 37.6, 53.4, 58.7, 78.3, 124.1, 127.4, 128.9, 129.3, 131.0, 135.0, 136.4, 166.9, 167.0, 172.2. Anal. Calcd (%) for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.61; H, 5.74; N, 6.66. ESI-MS: calcd 420.5; found $[M+H]^+$ 421.3, $[M+Na]^+$ 443.2, $[M+K]^+$ 459.3. HRMS (ESI): calcd 420.1685; found 420.1695.

*4.6.6. 2-((S)-1-((S)-4-Benzyl-5-oxooxazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)isoindoline-1,3-dione (**5f**)*

Yield 1.4 g, 56%, white powder, mp 124–126 °C; R_f 0.42 (*n*-hexane/EtOAc, 7/3); $[\alpha]_D^{20}$ +7.7 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1802, 1710, 1680, 1377, 1238, 1181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34–3.37 (m, 2H), 3.48–3.53 (m, 1H), 3.60–3.64 (m, 2H), 4.86–4.89 (m, 1H), 5.00 (t, 1H, J=7.6 Hz), 5.10–5.15 (m, 1H), 7.00–7.26 (m, 10H), 7.78–7.81 (m, 2H), 7.83–7.84 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 34.6, 35.4, 53.0, 56.6, 78.2, 124.0, 127.4, 127.5, 128.7, 128.9, 129.4, 130.1, 131.1, 134.7, 134.9, 136.3, 167.6, 169.3, 171.6. Anal. Calcd (%) for $C_{27}H_{22}N_2O_5$: C, 71.35; H, 4.88; N, 6.16. Found: C, 71.41; H, 4.89; N, 6.16. ESI-MS: calcd 454.5; found $[M+H]^+$ 455.3, $[M+Na]^+$ 477.2, $[M+K]^+$ 493.3. HRMS (ESI): calcd 454.1529; found 454.1512.

4.7. Procedure for the synthesis of final compounds 6a–f

4.7.1. Reaction with $TiCl_4$ (methods A and C)

The appropriate oxazolidinone (**5a–f**, 100 mg) was dissolved in 10 mL of anhydrous CH_2Cl_2; subsequent addition of 1 M $TiCl_4$ in CH_2Cl_2 (10 equiv) gave a fluorescent yellow solution that was placed in a closed reaction vessel, equipped with temperature and pressure control units, and irradiated according to the following parameters: initial power, 600 W; initial time, 3 min (ramping); final power, 600 W; *T*, 80 °C (method A) or 50 °C (method C); reaction time, 1 h. The mixture was cooled down to 0 °C in an ice bath and quenched with 0.5 N HCl_{aq}. The two phases were separated and the water phase was extracted twice with CH_2Cl_2 (10 mL). By addition of acetone (10 mL) to the combined organic phases, a clear solution was obtained, which was dried over $MgSO_4$, filtered, and evaporated.

4.7.2. Reaction with $SnCl_4$ (methods B and D)

The appropriate oxazolidinones (**5a–f**, 100 mg) were dissolved in 10 mL of anhydrous CH_2Cl_2; after addition of 1 M $SnCl_4$ in CH_2Cl_2 (10 equiv), the solution was placed in a closed reaction vessel, equipped with temperature and pressure control units, and irradiated according to the following parameters: initial power, 600 W; initial time, 3 min (ramping); final power, 600 W; *T*, 80 °C (method B) or 50 °C (method D); reaction time, 1 h. The mixture was cooled down to 0 °C in an ice bath and quenched with 0.5 N HCl_{aq}. The two phases were separated and the water phase was extracted twice with CH_2Cl_2 (10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated.

The desired final products **6a–f** were recovered by crystallization from diethyl ether/*n*-hexane or, when necessary, by purification on silica gel column employing CH_2Cl_2/EtOH/CH_3COOH (9.5/0.5/0.25) as eluent. The yields obtained for compounds **6a–f** employing methods A–D are reported in Table 2.

*4.7.3. (S)-2-(4-(1,3-Dioxoisoindolin-2-yl)-3-oxo-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)acetic acid (**6a**)*

White solid; mp 203–205 °C (lit.[2] mp 197–200 °C); R_f 0.10 (DCM/MeOH, 9/1); *K′* (HPLC): 5.1 (system 1), 4.3 (system 2); $[\alpha]_D^{20}$ +6.6 (*c* 1.1, MeOH); ν_{max} (KBr) 2922, 1704, 1666, 1383, 1339, 1195, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (dd, 1H, J=15.2, 4.4 Hz), 4.08 (t, 1H, J=14.0 Hz), 4.22 (m, 2H), 4.63 (m, 2H), 5.32 (dd, 1H, J=12.8, 4.4 Hz), 7.19–7.31 (m, 4H), 7.71–7.73 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 34.5, 51.7, 52.2, 53.6, 123.9, 127.6, 128.7, 129.2, 130.1, 132.0, 134.6, 135.0, 135.9, 168.1, 170.4, 171.2. Anal. Calcd (%) for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.81; H, 4.42; N, 7.67. ESI-MS: calcd 364.4; found $[M+H]^+$ 365.0. HRMS (ESI): calcd 364.1059; found 364.1065.

*4.7.4. (S)-2-((S)-4-(1,3-Dioxoisoindolin-2-yl)-3-oxo-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)propanoic acid (**6b**)*

White solid; mp 165–167 °C; R_f 0.18 (DCM/MeOH, 9/1); K' (HPLC): 5.6 (system 1), 4.6 (system 2); $[\alpha]_D^{20}$ −36.3 (*c* 0.9, MeOH); ν_{max} (KBr) 2913, 1706, 1637, 1391, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, 3H, *J*=6.8 Hz), 3.04 (dd, 1H, *J*=14.8, 4.8 Hz), 3.93 (t, 1H, *J*=13.6 Hz), 4.40 (d, 1H, *J*=15.6 Hz), 4.81 (d, 1H, *J*=16 Hz), 5.16 (dd, 1H, *J*=12.8, 4.8 Hz), 5.29–5.31 (m, 1H), 7.23–7.31 (m, 4H), 7.72–7.73 (m, 2H), 7.86–7.88 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.8, 34.9, 47.9, 52.8, 54.9, 123.9, 127.9, 128.2, 129.1, 129.9, 132.1, 134.5, 136.1, 136.6, 168.1, 169.4, 171.3. Anal. Calcd (%) for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.81; H, 4.78; N, 7.38. ESI-MS: calcd 378.4; found $[M+H]^+$ 379.3. HRMS (ESI): calcd 378.1216; found 378.1227.

*4.7.5. (S)-2-((S)-4-(1,3-Dioxoisoindolin-2-yl)-3-oxo-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-3-methylbutanoic acid (**6c**)*

White solid; mp 224–226 °C; R_f 0.32 (DCM/MeOH, 9/1); K' (HPLC): 7.7 (system 1), 6.8 (system 2); $[\alpha]_D^{20}$ −39.6 (*c* 1.0, MeOH);ν_{max} (KBr) 2935, 1703, 1656, 1391, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, 3H, *J*=6.8 Hz), 1.03 (d, 3H, *J*=6.4 Hz), 2.39–2.50 (m, 1H), 3.15 (dd, 1H, *J*=15.8, 4.4 Hz), 4.11 (m, 2H), 4.58 (d, 1H, *J*=14.8 Hz), 4.79 (d, 1H, *J*=16.4 Hz), 5.44 (dd, 1H, *J*=10.0, 4.4 Hz), 7.21–7.26 (m, 4H), 7.70–7.73 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.4, 31.8, 34.2, 51.1, 55.9, 58.6, 123.8, 127.9, 128.2, 128.9, 130.2, 132.3, 134.5, 136.2, 136.5, 168.2, 169.6, 171.4. Anal. Calcd (%) for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 68.15; H, 5.45; N, 6.91. ESI-MS: calcd 406.4; found $[M+H]^+$ 407.3. HRMS (ESI): calcd 406.1529; found 406.1537.

*4.7.6. (S)-2-((S)-4-(1,3-Dioxoisoindolin-2-yl)-3-oxo-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-4-methylpentanoic acid (**6d**)*

White solid; mp 232–234 °C; R_f 0.33 (DCM/MeOH, 9/1); K' (HPLC): 9.3 (system 1), 8.0 (system 2); $[\alpha]_D^{20}$ −43.1 (*c* 1.0, MeOH); ν_{max} (KBr) 2958, 1709, 1645, 1389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (dd, 6H, *J*=6.4 Hz), 1.26–1.33 (m, 1H), 1.84 (t, 2H, *J*=7.2 Hz), 3.02 (dd, 1H, *J*=15.2, 4.8 Hz), 3.96 (t, 1H, *J*=14.0 Hz), 4.32 (d, 1H, *J*=15.6 Hz), 4.86 (d, 1H, *J*=15.2 Hz), 5.16 (dd, 1H, *J*=12.8, 4.8 Hz), 5.33 (t, 1H, *J*=7.6 Hz), 7.19–7.33 (m, 4H), 7.71–7.73 (m, 2H), 7.86–7.89 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.7, 23.2, 24.9, 34.9, 37.6, 48.0, 52.8, 57.5, 124.0, 127.8, 128.2, 129.2, 130.0, 132.0, 134.6, 136.1, 136.3, 168.1, 169.3, 171.2. Anal. Calcd (%) for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.44; H, 5.76; N, 6.68. ESI-MS: calcd 420.5; found $[M+H]^+$ 421.2. HRMS (ESI): calcd 420.1685; found 420.1679.

*4.7.7. (2S,3S)-2-((S)-4-(1,3-Dioxoisoindolin-2-yl)-3-oxo-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-3-methylpentanoic acid (**6e**)*

White solid; mp 220–222 °C; R_f 0.34 (DCM/MeOH, 9/1); K' (HPLC): 8.7 (system 1), 7.5 (system 2); $[\alpha]_D^{20}$ −32.2 (*c* 1.7, MeOH); ν_{max} (KBr) 2961, 1708, 1671, 1395 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, 3H, *J*=7.2 Hz), 0.93 (d, 3H, *J*=7.6 Hz), 1.25–1.32 (m, 2H), 2.22–2.24 (m, 1H), 3.13 (dd, 1H, *J*=15.8, 4.4 Hz), 4.16 (t, 1H, *J*=14.6 Hz), 4.60 (d, 1H, *J*=15.6 Hz), 4.73 (d, 1H, *J*=10.8 Hz), 4.78 (d, 1H, *J*=15.6 Hz), 5.43 (dd, 1H, *J*=13.2, 4.4 Hz), 7.16–7.29 (m, 4H), 7.73–7.75 (m, 2H), 7.86–7.88 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.7, 15.8, 25.2, 33.3, 34.3, 49.4, 52.3, 62.1, 123.9, 127.3, 128.9, 129.0, 130.2, 132.1, 134.5, 134.6, 135.8, 168.1, 170.7, 172.4. Anal. Calcd (%) for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.60; H, 5.76; N, 6.66. ESI-MS: calcd 420.5; found $[M+H]^+$ 421.2. HRMS (ESI): calcd 420.1685; found 420.1678.

*4.7.8. (S)-2-((S)-4-(1,3-Dioxoisoindolin-2-yl)-3-oxo-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-3-phenylpropanoic acid (**6f**)*

White solid; mp 180–182 °C; R_f 0.24 (DCM/MeOH, 9/1); K' (HPLC): 8.8 (system 1), 7.0 (system 2); $[\alpha]_D^{20}$ −161 (*c* 1.1, MeOH); ν_{max} (KBr) 2932, 2855, 1709, 1650, 1425, 1384, 1200, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (dd, 1H, *J*=15.2, 6.4 Hz), 3.21 (dd, 1H, *J*=15.2, 5.2 Hz), 3.52–3.58 (m, 2H), 4.49 (s, 2H), 5.20 (t, 1H, *J*=5.4 Hz), 5.43–5.44 (m, 1H), 6.81 (d, 1H, *J*=7.6 Hz), 6.87–7.26 (m, 8H), 7.64–7.70 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 30.3, 35.1, 45.7, 53.0, 53.4, 123.6, 125.7, 126.9, 127.2, 127.8, 128.5, 128.8, 129.4, 131.5, 132.1, 132.7, 134.4, 136.9, 167.5, 167.8, 172.3. Anal. Calcd (%) for $C_{27}H_{22}N_2O_5$: C, 71.35; H, 4.88; N, 6.16. Found: C, 71.48; H, 4.88; N, 6.14. ESI-MS: calcd 454.5; found $[M+H]^+$ 455.3. HRMS (ESI): calcd 454.1529; found 454.1538.

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References and notes

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