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Assembly of Four Diverse Heterocyclic Libraries Enabled by Prins Cyclization, Au-Catalyzed Enyne Cycloisomerization, and Automated Amide Synthesis

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Abstract

We describe a unified synthetic strategy for efficient assembly of four new heterocyclic libraries. The synthesis began by creating a range of structurally diverse pyrrolidinones or piperidinones. Such compounds were obtained in a simple one-flask operation starting with readily available amines, ketoesters, and unsaturated anhydrides. The use of tetrahydropyran-containing ketoesters, which were rapidly assembled by our Prins cyclization protocol, enabled efficient fusion of pyran and piperidinone cores. A newly developed Au(I)-catalyzed cycloisomerization of alkyne-containing enamides further expanded heterocyclic diversity by providing rapid entry into a wide range of bicyclic and tricyclic dienamides. The final stage of the process entailed diversification of each of the initially produced carboxylic acids using a fully automated platform for amide synthesis, which delivered 1872 compounds in high diastereomeric and chemical purity.

INTRODUCTION

The amide-bond formation plays a central role in organic synthesis, chemical biology, and pharmaceutical research.¹ According to a recent survey, *N*-acylation of amines represents the most frequently employed reaction in drug discovery.² Thus, it is not surprising that amide synthesis has been extensively used for assembly of small-molecule libraries designed

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ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures as well as analytical characterization data. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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to deliver pharmacological probes and drugs.³ While early work in this area has relied almost exclusively on solid-phase synthesis,⁴ much of the recent effort has shifted to generating nonpeptide small-molecule libraries in solution.⁵ The most attractive feature of solution-based methods is the high efficiency of monitoring and optimizing chemical reactions. Indeed, many innovative strategies have been developed to enable high-throughput organic synthesis in solution, including the use of soluble polymeric supports,⁶ phase-separation tags,⁷ scavenging agents,⁸ or automated preparative LCMS methods.⁹ Another attractive purification tactic is a liquid–liquid extraction, which takes advantage of the differences in aqueous solubility of reagents, reactants, and products under either basic or acidic conditions. This method is particularly well suited for amide-bond formation and can completely avoid chromatographic purification, use of scavenging agents or attachment of phase-separation tags. Boger and co-workers were the first to recognize the value of parallel solution-phase amide synthesis followed by a simple liquid–liquid extraction, and employed this strategy for preparation of several amide-containing libraries.^{10,11} While small libraries were produced as individual compounds,¹⁰ larger libraries were typically generated as compound mixtures presumably due to the manual nature of the assembly process.¹¹

As the amide-bond formation continues to play a dominant role in organic, bioorganic, and medicinal chemistry, the automation of this important process could greatly improve its efficiency, enabling rapid access to large nonpeptide amide-containing libraries of individual, pure compounds. Herein, we report the development of a fully automated, chromatography-free protocol for parallel amide synthesis in solution, which was employed for the preparation of four representative heterocyclic libraries. The first stage of the assembly process entailed the synthesis of a range of structurally diverse pyrrolidinones or piperidinones. Such compounds were obtained in a one-flask operation starting with readily available amines, ketoesters, and unsaturated anhydrides. The use of tetrahydropyran-containing ketoesters, which were rapidly assembled by our Prins cyclization protocol, enabled efficient fusion of pyran and piperidinone cores. To further expand heterocyclic diversity, we developed Au(I)-catalyzed cycloisomerization of alkyne-containing enamides to afford a wide range of bicyclic and tricyclic dienamides. The final stage of the parallel assembly process entailed diversification of the initially produced heterocyclic cores via a solution-phase amide synthesis, which was readily performed by a conventional liquid-handling robot. This automation platform delivered 1872 new heterocyclic compounds, which were obtained with high efficiency and excellent chemical purity without chromatographic purification.

RESULTS AND DISCUSSION

Library Design

Our previous work demonstrated that reactions of vinylogous carbamates with maleic anhydride delivered a library of functionalized pyrrolidinones, which yielded two noncompetitive inhibitors of facilitative glucose transport.^{12a,b} While this library was produced using a short and efficient reaction sequence, chromatographic purification of all final compounds was required in order to ensure their high chemical purity prior to the biological evaluation.^{12a,b} Building on this precedent, the objectives of our present study were 2-fold. First, we aimed to increase the size and skeletal diversity of newly designed heterocyclic libraries based on five- and six-membered lactams. Second, we set out to develop a fully automated protocol for solution-phase amide synthesis that could be efficiently employed for final-stage diversification of such libraries. Such an automation platform would deliver a large number of individual compounds in high purity without chromatographic purification.

Our general synthetic strategy is depicted in Figure 1. The assembly process begins with a condensation of primary amines **1** and ketoesters **2** to deliver the corresponding vinylogous carbamates **3**. Subsequent reaction of **3** with maleic anhydride **4** would afford pyrrolidinones **7**.¹² A similar transformation employing itaconic anhydride **5** is expected to give ring-expanded piperidinones **8**.¹³ Structural diversity can be readily introduced into **7** and **8** by selecting a variety of amines **1** and ketoesters **2**. The use of alkyne-containing primary amines (R^1 = propargyl) could further expand skeletal diversity of lactams **7** and **8** via a transition-metal-catalyzed enyne cycloisomerization¹⁴ to deliver tetrahydro-oxindolizines **9** and hexahydrooxoquinolizines **10**. The final stage of the synthesis would rely on the development of an automated amide-bond forming protocol that would convert the initial set of core structures **7–10** to the final amide-containing libraries **12–15**, which would be produced on 10–20 mg scale and subjected to rigorous purity analysis. The use of cheminformatics methods would facilitate selection of the appropriate building blocks at each stage of the diversification process in order to produce all final compounds with favorable physicochemical properties *en route* to subsequent identification of new pharmacological probes.

Automation of the Solution-Phase Amide Synthesis

Our initial objective was to develop a general protocol for efficient, automated amide synthesis in solution that would employ readily available amide-coupling agents followed by a simple liquid–liquid extraction to purify final amide products (Figure 2). Such an automation platform was expected to possess excellent throughput capabilities by avoiding chromatographic purification using scavenging agents or attaching and detaching tags for phase separation. For purification, we intended to employ a single extraction step that would entail partitioning the reaction mixture between an organic phase and an acidic aqueous solution. This procedure would efficiently separate the amide-containing product, which would be collected in the organic phase, from an excess of starting amine, amide-coupling reagent and other coproducts, which would all partition into the acidic aqueous layer. In order to develop and validate this protocol, we prepared several pyrrolidinone-containing carboxylic acids **7** by reaction of amines **1** with ketoesters **2**, followed by cyclization with maleic anhydride **4** (Figure 2A). Evaluation of a number of existing amide-coupling protocols revealed that 1,1'-carbonyldiimidazole (CDI, **16**) served as the best reagent not only to promote efficient *N*-acylation but also to afford highest purity of the resulting amides following a single liquid–liquid extraction step. During the optimization studies, the efficiency of the initial acyl imidazole formation was conveniently monitored by ¹H NMR spectroscopy. This transformation proceeded to completion typically within 2–4 h at 20 °C in chloroform using a slight excess of CDI (1.05 equiv). The resulting acyl imidazole **17** was next treated with 3 equiv of either primary or secondary amines **11**. The excess of amine ensured complete conversion of acyl imidazole **17** to the corresponding amide **12**. The final reaction mixture was treated with a 1.2 M solution of hydrochloric acid. The two phases were thoroughly mixed and allowed to separate. Retrieval of the chloroform layer and evaporation produced several representative amide-containing products **12a–d** (Figure 2B) in high efficiency. High chemical purity of each of the products was established independently by LCMS analysis and 500 MHz ¹H NMR spectroscopy. We found that amide-bond formation and liquid–liquid extraction could be readily performed using a typical robotic liquid handler, followed by parallel evaporation. The use of this protocol can yield 1–100 mg of individual final products depending on the amount of carboxylic acid used for the amide-coupling step.

Synthesis of a Pyrrolidinone Library

Having developed an automated amide-coupling protocol, we next examined its first application to a larger set of pyrrolidinone-containing compounds. Our goal was to prepare a

216-membered library **12** on 20 mg scale starting from 3 primary amines **1**, 3 ketoesters **2**, and 24 amines **11** (Figure 3). We wanted to ensure that all reactions would produce final products **12** in high chemical purity without chromatographic purification of any of the final compounds. Selection of each of the building blocks shown in Figure 3B–D was guided by Accelrys Pipeline Pilot, which enabled virtual enumeration of the target library and estimation of various molecular properties *in silico*. Specifically, during the design process, we applied appropriate filters in order to select building blocks that would produce the target library **12** with molecular weight below 600 and calculated logarithmic value of *n*-octanol/water partition coefficient (cLogP) within a range of 1–5.¹⁵ The distribution of both parameters for this library is shown in the Supporting Information (Figure S1).¹⁶

The synthesis began with condensations of three primary amines **1** (Figure 3B) with three ketoesters **2** (Figure 3C), followed by reactions of the resulting vinylogous carbamates **3** with maleic anhydride **4** to afford nine pyrrolidinone-containing carboxylic acids **7**. Each of the acids **7** was obtained as a single diastereomer approximately on a 500 mg scale in a single-flask operation starting with the corresponding amines **1** and ketoesters **2**. In order to ensure their high chemical purity, all pyrrolidinone-containing carboxylic acids **7** were purified by conventional chromatography. The second stage of the assembly process entailed a fully automated synthesis of the target library **12** using a set of 24 amines **11** (Figure 3D). To this end, each acid **7** was first treated with a slight excess of CDI (**16**) in chloroform at room temperature and divided into 24 equal batches. Upon completion of the acyl imidazole formation, each batch was treated for 48 h with a solution of amine **11** in chloroform at the same temperature, followed by addition of a 1.2 M aqueous solution of HCl. The organic and aqueous layers were thoroughly mixed and allowed to separate. The amides **12** were obtained by removal of the chloroform layer and parallel solvent evaporation. We determined the yields of all final compounds by automated weighing, which established that 216 *N*-acylations proceeded with high efficiency with an average isolated yield of $87.2 \pm 7.2\%$. The high purity of each library member was established using LCMS.¹⁶ In addition, we acquired 500 MHz ¹H NMR spectra of 18 randomly selected amides, which independently confirmed their high diastereomeric and chemical purities.¹⁶

Synthesis of a Piperidinone Library

The reactions of vinylogous carbamates with maleic anhydride provided efficient and fully diastereoselective entry into the 2-pyrrolidinone core **7** (Figure 3) via a tandem reaction sequence including conjugate addition and anhydride opening. We next examined the construction of ring-expanded 2-piperidinones **8** (Table 1) via the corresponding reaction of vinylogous carbamates **3** with itaconic anhydride **5**. A representative reaction of amine **1a** with ketoester **2a** cleanly afforded enamine **3**, which was subsequently treated with anhydride **5** to give piperidinone **8a** with high efficiency and diastereoselectivity (Table 1, entry 1). The structure of **8a** was determined by X-ray crystallography.¹⁶ Investigation of the scope of this transformation revealed that both six- and seven-membered ketoesters **2b** and **2c** efficiently afforded the corresponding pyrrolidinones **8b** and **8c** (Table 1, entries 2 and 3). The use of furan-containing primary amine **1d** was also tolerated (Table 1, entry 4). High diastereoselectivity was observed in all cases. Interestingly, the opposite stereochemical outcome was observed during the formation of six-membered lactams **8** compared to the corresponding cyclizations leading to five-membered 2-pyrrolidiones **7**.

The high level of diastereoselectivity of both reactions can be rationalized by examining conjugate addition and anhydride-opening steps (Figure 4). The two initial transition states **A** and **E** have one common feature: they both entail the approach of unsaturated anhydride, which facilitates subsequent lactam formation by placing the imine moiety in close spatial proximity to the carbonyl group of the anhydride for its subsequent opening. In the case of

maleic anhydride, this process predicts the formation of intermediates **B** and **C** and explains the observed stereochemistry of the product **7**. For itaconic anhydride, similar logic predicts the intermediacy of anhydride **F** and *N*-acyliminium ion **G** *en route* to the observed six-membered lactam **8**.

Because a number of 2-piperidinones **8** were prepared with good efficiency and high diastereoselectivity (Table 1), we next employed this process for generating a 768-membered library **13** starting with 8 primary amines **1**, 4 ketoesters **2**, and 24 amines **11** (Figure 5). Analysis of the enumerated library *in silico* identified structures of 8 commercially available amines **1** (Figure 5B), 4 ketoesters **2** (Figure 5C), and the same set of 24 amines **11** (Figure 5D), which would deliver this chemical library with favorable molecular weight and a narrow cLogP distribution (Figure S2 in the Supporting Information). The synthesis began with parallel reactions of 8 amines **1** with each of the four ketoesters **2**. The resulting vinylogous carbamates **3** were not isolated but directly reacted with itaconic anhydride **5** to give 32 piperidinone-containing carboxylic acids **8**. Following this one-flask protocol, each of the acids **8** was obtained approximately on a 500 mg scale as a single diastereomer with good efficiency following conventional chromatographic purification in order to ensure their high purity. The final stage entailed CDI-promoted coupling of each of the 32 carboxylic acids **8** with 24 amines **11**. This operation was fully automated and conducted under the same conditions used for generating library of 2-pyrrolidinones **12**. This process delivered 768 amides **13**, which were prepared on a 15–20 mg scale. Parallel LCMS analysis of all library members established their high chemical purity, which was independently confirmed by obtaining 500 MHz ¹H NMR spectra of 64 randomly selected compounds.¹⁶

Synthesis of a Library of Fused Dihydropyrans and Piperidinones

Assembly of pyrrolidinones **12** and 2-piperidinones **13** thus far relied on the use of readily available carbocyclic ketoesters **2**, which limited the extent of their skeletal diversification. We next examined the ability of tetrahydropyran-containing ketoesters to participate in such lactam-forming reactions. This process would enable fusion of oxygen- and nitrogen-containing heterocyclic platforms, expanding both the skeletal and heteroatom diversity of the resulting libraries while maintaining their favorable physico-chemical properties. Our previously developed Prins cyclization of β -hydroxy dioxinones enabled efficient assembly of a range of highly functionalized tetrahydropyranones.¹⁷ Validated through several applications in the synthesis of complex polyketide natural products,¹⁸ this method could afford a variety of 3-carbomethoxy-4-tetrahydropyranones **24** diversified at both the C(2) and the C(6) positions (Table 2).

The synthesis began with the Mukaiyama aldol reaction of silyl dienol ether **19** with aldehyde **20** to give β -hydroxy dioxinones **21**. The next step entailed the Lewis acid promoted Prins cyclization of dioxinones **21** with aldehydes **22**, which proceeded efficiently in all cases. Finally, treatment of dihydropyrans **23** with methanol at 150 °C afforded four requisite 3-carbomethoxy-4-tetrahydropyranones **24** with high diastereoselectivity. Erosion of diastereoselectivity in the final product was observed only in one case at the final methanolysis stage (Table 2, entry 3). However, the major diastereomer **24c** was readily obtained in good overall yield and high diastereomeric purity by chromatographic purification.

We next examined reactions of vinylogous carbamates **25** derived from tetrahydropyran-containing ketoesters **24** with unsaturated anhydrides **4** and **5**. While the reaction of maleic anhydride **4** with **25** proved low yielding, the corresponding condensation with itaconic anhydride successfully delivered the expected piperidinone-containing products **26**. The

results of the initial scope study of this transformation are summarized in Table 3. The four ketoesters **24a–d** afforded the corresponding oxabicyclic piperidinones **26a–d** with high efficiency as single observed diastereomers. Excellent diastereoselectivity of this transformation, which affords products containing four stereogenic centers, is particularly noteworthy. Stereochemistry of the final products was determined by extensive NMR analysis and can be explained by considering a transition state model **E** (Figure 4) with the approach of itaconic anhydride **5** expected to occur opposite to the R² substituent, corresponding to a sterically more accessible face of the pyran moiety.

Having established efficient and fully diastereoselective access to dihydropyrans fused with piperidinones, we next examined the possibility of generating a large library of such heterocyclic compounds from four tetrahydropyran-containing ketoesters **24a–d** and the same two sets of amines **1** and **11**, which were used to prepare library **13**. This process would produce 768 compounds starting with 4 ketoesters **24**, 8 primary amines **1**, and 24 primary and secondary amines **11** (Figure 6). Analysis of the enumerated library *in silico* revealed that such compounds would display favorable molecular properties, including molecular weight and cLogP (Figure S3 in the Supporting Information).

The synthesis began with reactions of 8 amines **1** with each of the 4 ketoesters **24**, followed by treatment of the resulting vinylogous carbamates with itaconic anhydride **5**. This one-flask operation successfully delivered 32 expected carboxylic acids **26**, which were obtained with good efficiency and high purity following a single parallel chromatographic purification. Using the same automated liquid-handling platform employed for syntheses of libraries **12** and **13**, each of the acids **26** was activated using CDI (**16**) and coupled to 24 amines **11**, followed by liquid–liquid extraction and solvent evaporation. This process successfully delivered the target 768-membered library **27** on 15–20 mg scale in high efficiency and excellent purity, which was determined by LCMS.¹⁶ The NMR analysis of 64 randomly selected compounds once again confirmed their high chemical and diastereomeric purity.¹⁶

Development of Au-Catalyzed Enynamide Cycloisomerization

The efficient access to a series of structurally diverse bicyclic lactams prompted us to further expand their skeletal diversity by examining the ability of such compounds to participate in enyne cycloisomerizations in the presence of an appropriate metal catalyst. Among transition metals that catalyze enyne cycloisomerizations, Au- and Pt-based complexes are particularly noteworthy for their ability to chemoselectively activate the alkyne moiety and provide access to various reaction topologies depending on the structure of the starting enyne.¹⁴ Such reactions typically proceed under mild conditions, tolerate a wide variety of commonly used functional groups, and provide powerful methods for structural diversification in organic synthesis. Despite significant advances in Au- and Pt-catalyzed cycloisomerizations of 1,5-enynes, the vast majority of such reactions typically afford carbocyclic products.^{14b} Only a few examples of Au-catalyzed syntheses of nitrogen heterocycles are known. Indeed, we reported a series of Au(I)-catalyzed double cyclizations that produced a number of oxygen and nitrogen heterocycles.¹⁹ While such reactions efficiently proceeded under mild conditions, they were limited to the synthesis of several unique heterobicyclic products.¹⁹ Recently, Schaus and co-workers described Au(III)-catalyzed cycloisomerizations of alkyne-tethered dihydropyrimidones.²⁰ While this new catalytic process yielded a number of pyridopyrimidones, such reactions were conducted at high temperatures presumably due to the requirement for the initial isomerization of a vinylogous imide. Furthermore, only internal alkynes participated in such cycloisomerizations.²⁰

Prompted by the lack of general studies of transition-metal-catalyzed cycloisomerizations of enynes containing stable enamide fragments, we prepared several potential cyclization substrates **28a–c** by reactions of the corresponding primary propargyl amines **27a–c** with ketoester **2a**, followed by treatment of the resulting vinylogous carbamates with itaconic anhydride **5** (Table 4). Having examined several commonly employed transition metal complexes, we found that treatment of phenyl-substituted enyne **28a** with 5 mol % of PPh₃AuCl in the presence of a number of Ag-based additives produced cycloisomerization product **29a** (Table 1, entries 1–3). The reaction efficiency considerably decreased in the absence of PPh₃AuCl (Table 4, entry 4). Initially, the best results were obtained by combining PPh₃AuCl with AgSbF₅ in either dichloromethane or chloroform (Table 4, entries 1 and 5). The use of acetonitrile as a reaction solvent resulted in a further increase in efficiency and enabled nearly quantitative conversion of **28a** to **29a** (Table 4, entry 6). However, this set of conditions did not give successful results when applied to enamide **28b** containing a terminal alkyne. Indeed, the conversion level dropped to 20% (Table 4, entry 7). We next examined the effect of the various phosphine ligands on the reaction outcome. While electron deficient phosphines did not provide much improvement (Table 4, entry 8), the use of sterically hindered or electron-rich phosphines substantially improved the efficiency of cycloisomerization of **28b** to **29b** (Table 4, entries 9–12). Interestingly, a similar trend was recently attributed to a more efficient protodemetalation step in the presence of bulky or electron rich phosphines when this step became turnover limiting.²¹ Continuing to explore this trend, we evaluated a number of cationic gold complexes **30**, **31** and **32** containing bulky carbene or phosphine ligands (Table 4, entries 13–15). The best results were obtained using either **31** or **32**. In both cases, cycloisomerization of **28b** proceeded with quantitative efficiency. In addition, complex **31** proved superb at promoting cyclizations of **28a** and **28c** (Table 4, entries 16 and 17).

The high efficiency of this catalytic system, which operates at low catalyst loadings at room temperature to promote cyclizations of enamides containing both terminal and internal alkynes is highly noteworthy. Furthermore, this reaction tolerates a number of functional groups present in cycloisomerization substrates **28**, including unprotected carboxylic acids. The latter feature of the reaction is particularly important in maximizing synthetic efficiency of subsequent elaboration of cycloisomerization products (vide infra) despite the known reactivity of carboxylic acids in a number of other Au-catalyzed reactions.²²

We next examined the utility of cationic gold-phosphine complex **31** in promoting cycloisomerizations of other structurally diverse alkyne-containing enamides **33**, which originated from propargyl amines **27**, ketoesters **2**, and itaconic anhydride **5** (Table 5). We found that enynes **33a** and **33b** successfully underwent cycloisomerizations to deliver the corresponding dienamides **34a** and **34b** in high yields (Table 5, entries 1 and 2). Such transformations further expanded the skeletal diversity of the tricyclic products that can be efficiently prepared by this approach. Furthermore, acyclic ketoesters **2e** or **2f** could be efficiently converted to the corresponding enynes **33c** and **33d**, which upon treatment with Au complex **31** afforded bicyclic dienamides **34c** and **34d** (Table 5, entries 3 and 4).

While all enyne cycloisomerization products obtained thus far contained six-membered 2-piperidinones, we next examined the ability of this reaction to produce 1,3-dienamides incorporating five-membered lactams **36** (Table 6). The requisite alkyne-containing enamides **35** were prepared by the same one-pot procedure starting with propargyl amines **27**, ketoesters **2**, and maleic anhydride **4**. Subjections of enynes **35a** and **35b** to the general cycloisomerization protocol cleanly afforded the expected products **36a** and **36b** with quantitative efficiency (Table 6, entries 1 and 2). Similarly, cycloisomerizations of enynes **35c** and **35d**, which were derived from a seven-membered ketoester **2c**, successfully

afforded dienamides **36c** and **36d** (Table 6, entries 3 and 4). The structure of tricyclic lactam **36d** was confirmed by X-ray crystallography.¹⁶

Having established synthetic access to a variety of five- and six-membered lactams **34** and **36**, we next examined the preparation of a skeletally diverse chemical library using this newly uncovered enyne cycloisomerization and our previously developed automated amide synthesis protocol. Our initial studies established that chemical stability of the dienamide moiety found in **34** and **36** proved to be inadequate. Slow degradation of such compounds was observed upon their dissolution in either DMSO or MeOH. We found that this problem can be solved by partial hydrogenation of the dienamide fragment. We next subjected five enynes shown in Figure 7A to Au-catalyzed cycloisomerization, followed by immediate heterogeneous hydrogenation (H₂, Pd/C, EtOH). This one-pot operation efficiently delivered the corresponding tricyclic lactams **37–41** (Figure 7B) as a result of chemo-selective hydrogenation of disubstituted alkenes. The structure of **38** was established by X-ray crystallography.¹⁶ Such partially hydrogenated lactams proved to be stable and were next diversified by coupling each of them with the same set of 24 amines **11** (Figure 7C), which were employed for synthesis of other libraries discussed above. This fully automated process delivered a 120-membered amide-containing library containing five heterotryclic cores (Figure 7D) with favorable distributions of molecular weight and cLogP (Figure S4 in the Supporting Information). The library was produced on a 15–20 mg scale with good efficiency and excellent chemical purity, which was established by LCMS analysis.¹⁶ Diastereomeric purity of 10 randomly selected compounds was further confirmed by ¹H NMR.¹⁶

CONCLUSIONS

We have described a unified strategy for efficient synthesis of four new heterocyclic libraries. The first stage of the process entailed creation of a range of skeletally diverse pyrrolidinones or piperidinones in a single-flask operation starting with readily available amines, ketoesters and unsaturated anhydrides. In the course of this investigation, we employed our Lewis acid-promoted Prins cyclization protocol for efficient fusion of pyran and piperidinone cores and developed Au(I)-catalyzed cycloisomerization of alkyne-containing enamides to provide access into a wide range of bicyclic and tricyclic dienamides. Such catalytic processes substantially expanded heterocyclic diversity of the resulting libraries. For final diversification of each library, we developed a fully automated, chromatography-free protocol for parallel amide synthesis, which was applied to prepare 1870 heterocyclic products with favorable physicochemical properties. Because of the prominent role played by the amide-bond formation in high-throughput synthesis, chemical biology, and medicinal chemistry, the development of this automation platform represents an important and enabling synthetic advance that will facilitate access to a variety of new amide-containing libraries for subsequent biomedical applications. Results of the expansion of this automation platform to other commonly employed reactions, as well as the broad biological evaluation of the four new heterocyclic libraries will be reported in due course.²³

EXPERIMENTAL PROCEDURES

General Procedure A: Synthesis of Pyrrolidinones and Piperidinones

A solution of ketoester (**2** or **24**, 5.0 mmol) in CHCl₃ (8.0 mL) was treated with primary amine (**1** or **27**, 5.0 mmol) and 4 Å molecular sieves. The reaction mixture was stirred at 70 °C. The completion of the reaction monitored by ¹H NMR spectroscopy, which typically required 12–18 h. The resulting mixture was treated with anhydrous MgSO₄, filtered, and concentrated under reduced pressure to a 20 mL volume. The resulting solution was then

treated with either maleic anhydride (**4**, 1.1 equiv) or itaconic anhydride (**5**, 1.1 equiv) and stirred overnight at room temperature. The removal of the solvent under reduced pressure followed by silica gel chromatographic purification afforded pyrrolidinones (**7** or **35**) or piperidinones (**8**, **26**, **28**, or **34**).

Pyrrolidinone-Containing Carboxylic Acid 7a (2-((3*SR*,3*aRS*)-1-Allyl-3a-(ethoxycarbonyl)-2-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indol-3-yl)acetic Acid)

Compound **7a** was prepared according to general procedure A from primary amine **1a**, ketoester **2a**, and maleic anhydride **4**: yield 661 mg, 43%; ¹H NMR (500 MHz, CDCl₃) δ 10.18 (s, 1H), 4.94 (dddd, *J* = 17.5, 10.3, 6.1, 5.1 Hz, 1H), 4.46 (d, *J* = 17.2 Hz, 1H), 4.37 (d, *J* = 10.4 Hz, 1H), 4.26 (t, *J* = 3.8 Hz, 1H), 3.53–3.45 (m, 1H), 3.40–3.28 (m, 2H), 3.15 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.28 (dd, *J* = 8.5, 5.7 Hz, 1H), 2.10 (ddd, *J* = 17.5, 5.7, 1.0 Hz, 1H), 1.79 (dd, *J* = 9.5, 3.6 Hz, 1H), 1.53 (ddd, *J* = 17.5, 8.5, 1.0 Hz, 1H), 1.45–1.36 (m, 1H), 1.36–1.27 (m, 1H), 1.08–0.98 (m, 1H), 0.76–0.63 (m, 2H), 0.43 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.5, 173.5, 171.4, 138.2, 131.4, 117.9, 102.2, 61.7, 52.2, 47.5, 43.1, 31.7, 30.6, 22.9, 19.7, 14.2; HRMS (ESI-TOF) *m/z* [M + H]⁺ calcd for C₁₆H₂₂NO₅ 308.1498, found 308.1498.

Pyrrolidinone-Containing Carboxylic Acid 7b

Compound **7b** was prepared according to general procedure A from primary amine **1b**, ketoester **2a**, and maleic anhydride **4**: yield 1259 mg, 70%; ¹H NMR (500 MHz, CDCl₃) δ 7.27–7.22 (m, 1H), 6.88–6.83 (m, 1H), 5.06 (t, *J* = 3.7 Hz, 1H), 4.79 (d, *J* = 15.2 Hz, 1H), 4.48 (d, *J* = 15.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.03 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.79 (s, 2H), 3.01 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.80 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.59 (dt, *J* = 12.2, 2.9 Hz, 1H), 2.47 (dd, *J* = 16.5, 5.9 Hz, 1H), 2.20–2.12 (m, 1H), 2.12–2.03 (m, 1H), 1.83 (ddd, *J* = 14.6, 6.6, 3.6 Hz, 1H), 1.58–1.40 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.8, 173.9, 171.3, 159.1, 138.2, 129.2, 127.9, 113.9, 102.2, 61.6, 55.4, 52.1, 47.5, 43.9, 31.6, 30.6, 22.8, 19.6, 14.2; HRMS (ESI-TOF) *m/z* [M + H]⁺ calcd for C₂₁H₂₆NO₆ 388.1760, found 388.1753.

Pyrrolidinone-Containing Carboxylic Acid 7c

Compound **7c** was prepared according to general procedure A from primary amine **1c**, ketoester **2a**, and maleic anhydride **4**: yield 1319 mg, 50%; ¹H NMR (500 MHz, CDCl₃) δ 11.21 (s, 1H), 7.24–7.18 (m, 2H), 7.17–7.10 (m, 2H), 5.02 (t, *J* = 3.7 Hz, 1H), 4.15–4.02 (m, 2H), 3.85 (ddd, *J* = 13.7, 10.6, 6.4 Hz, 1H), 3.38 (ddd, *J* = 13.8, 10.5, 5.1 Hz, 1H), 2.99 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.90–2.81 (m, 2H), 2.77 (ddd, *J* = 13.6, 10.5, 6.4 Hz, 1H), 2.60–2.53 (m, 1H), 2.30 (dd, *J* = 17.4, 8.4 Hz, 1H), 2.20 (ddd, *J* = 17.8, 6.6, 4.0 Hz, 1H), 2.14–2.03 (m, 1H), 1.86–1.76 (m, 1H), 1.52–1.41 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 176.0, 173.0, 171.3, 164.1, 138.0, 136.9, 132.2, 130.0, 128.6, 101.1, 77.4, 61.4, 52.2, 47.2, 41.3, 32.0, 31.2, 30.5, 22.7, 19.5, 14.0; MS (ESI) calcd for C₂₁H₂₄ClNO₅ 405.13 (M⁺), found 406.19 (M + H)⁺.

Pyrrolidinone-Containing Carboxylic Acid 7d

Compound **7d** was prepared according to general procedure A from primary amine **1a**, ketoester **2b**, and maleic anhydride **4**: yield 1076 mg, 65%; ¹H NMR (500 MHz, CDCl₃) δ 6.41–6.31 (m, 1H), 5.69 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H), 5.25–5.12 (m, 3H), 4.20 (ddt, *J* = 16.3, 4.9, 1.8 Hz, 1H), 4.03 (ddt, *J* = 16.4, 5.0, 1.8 Hz, 1H), 3.69 (s, 3H), 3.06 (t, *J* = 6.9 Hz, 1H), 2.78 (dd, *J* = 17.0, 6.8 Hz, 1H), 2.53–2.44 (m, 1H), 2.37 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.26–2.15 (m, 1H), 1.96–1.84 (m, 2H), 1.76–1.62 (m, 2H), 1.62–1.52 (m, 1H), 1.37–1.27 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 175.7, 173.3, 171.3, 142.7, 130.9, 130.2, 117.2,

105.9, 55.5, 52.3, 48.3, 42.9, 36.1, 32.1, 27.7, 27.4, 26.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_5$ 308.1498, found 308.1496.

Pyrrolidinone-Containing Carboxylic Acid 7e

Compound **7e** was prepared according to general procedure A from primary amine **1b**, ketoester **2b**, and maleic anhydride **4**: yield 1588 mg, 82%; 1H NMR (500 MHz, $CDCl_3$) δ 7.21–7.14 (m, 2H), 6.89–6.81 (m, 2H), 5.20 (dd, J = 8.8, 4.4 Hz, 1H), 4.78 (d, J = 15.4 Hz, 1H), 4.55 (d, J = 15.4 Hz, 1H), 3.80 (d, J = 1.2 Hz, 3H), 3.66 (s, 3H), 3.04 (dd, J = 9.3, 4.8 Hz, 1H), 2.71 (ddd, J = 16.2, 9.3, 1.2 Hz, 1H), 2.56–2.41 (m, 2H), 2.22–2.09 (m, 1H), 1.95–1.79 (m, 2H), 1.79–1.64 (m, 2H), 1.62–1.52 (m, 1H), 1.34–1.21 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 173.8, 171.3, 158.9, 142.5, 128.4, 127.6, 114.0, 106.3, 55.4, 55.3, 52.3, 48.4, 43.8, 36.0, 32.0, 27.6, 27.4, 26.1; MS (ESI) calcd for $C_{21}H_{26}NO_6$ 388.1760 ($M + H$), found 388.1768.

Pyrrolidinone-Containing Carboxylic Acid 7f

Compound **7f** was prepared according to general procedure A from primary amine **1c**, ketoester **2b**, and maleic anhydride **4**: yield 1766 mg, 79%; 1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.20–7.14 (m, 2H), 5.22 (dd, J = 8.9, 4.4 Hz, 1H), 3.79 (ddd, J = 13.8, 9.8, 6.4 Hz, 1H), 3.70 (s, 3H), 3.56 (ddd, J = 13.8, 9.8, 5.6 Hz, 1H), 3.01 (t, J = 6.9 Hz, 1H), 2.86 (ddd, J = 13.5, 9.8, 5.6 Hz, 1H), 2.82–2.72 (m, 2H), 2.49 (ddd, J = 13.6, 4.7, 2.6 Hz, 1H), 2.35 (dd, J = 17.2, 7.2 Hz, 1H), 2.31–2.22 (m, 1H), 2.01–1.89 (m, 2H), 1.80–1.64 (m, 2H), 1.61–1.53 (m, 1H), 1.37–1.26 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 173.1, 171.3, 142.7, 136.8, 132.5, 130.3, 128.7, 104.9, 55.5, 52.3, 48.2, 41.6, 36.1, 32.1, 31.7, 27.7, 27.4, 26.1; MS (ESI) calcd for $C_{21}H_{24}ClNO_5$ 405.13 (M^+), found 406.23 ($M + H$) $^+$.

Pyrrolidinone-Containing Carboxylic Acid 7g

Compound **7g** was prepared according to general procedure A from primary amine **1a**, ketoester **2c**, and maleic anhydride **4**: yield 838 mg, 65%; 1H NMR (500 MHz, $CDCl_3$) δ 5.74–5.64 (m, 1H), 5.22–5.11 (m, 2H), 4.89–4.79 (m, 1H), 4.22–4.10 (m, 4H), 3.02 (t, J = 7.0 Hz, 1H), 2.87–2.77 (m, 1H), 2.62–2.51 (m, 1H), 2.40 (dd, J = 16.9, 7.3 Hz, 1H), 2.10–2.00 (m, 1H), 2.00–1.86 (m, 1H), 1.76–1.61 (m, 2H), 1.61–1.49 (m, 3H), 1.48–1.30 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 173.5, 171.4, 140.5, 130.7, 117.1, 104.0, 61.7, 53.9, 48.2, 42.8, 39.5, 32.8, 27.9, 26.1, 23.1, 22.7, 14.1; MS (ESI) calcd for $C_{18}H_{25}NO_5$ 335.17 (M^+), found 336.33 ($M + H$) $^+$.

Pyrrolidinone-Containing Carboxylic Acid 7h

Compound **7h** was prepared according to general procedure A from primary amine **1b**, ketoester **2c**, and maleic anhydride **4**: yield 1641 mg, 87%; 1H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, J = 8.4, 1.5 Hz, 2H), 6.85–6.78 (m, 2H), 4.85–4.73 (m, 1H), 4.66 (s, 2H), 4.21–4.05 (m, 2H), 3.76 (s, 3H), 3.08 (t, J = 7.0 Hz, 1H), 2.89 (dd, J = 16.9, 6.5 Hz, 1H), 2.57 (dd, J = 12.9, 6.6 Hz, 1H), 2.49–2.40 (m, 1H), 2.01–1.84 (m, 2H), 1.73–1.62 (m, 1H), 1.61–1.42 (m, 3H), 1.35–1.23 (m, 1H), 1.23–1.15 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 173.8, 171.3, 158.9, 140.3, 128.2, 127.5, 114.0, 104.5, 61.6, 55.3, 53.9, 48.2, 43.6, 39.3, 32.8, 27.8, 25.8, 23.0, 22.6, 14.0; MS (ESI) calcd for $C_{23}H_{29}NO_6$ 415.20 (M^+), found 416.29 ($M + H$) $^+$.

Pyrrolidinone-Containing Carboxylic Acid 7i

Compound **7i** was prepared according to general procedure A from primary amine **1c**, ketoester **2c**, and maleic anhydride **4**: yield 1519 mg, 70%; 1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 2H), 7.19–7.11 (m, 2H), 4.88 (dd, J = 10.6, 7.7 Hz, 1H), 4.23–4.14 (m, 2H), 3.79–3.66 (m, 2H), 2.94 (t, J = 7.0 Hz, 1H), 2.84 (t, J = 7.6 Hz, 2H), 2.77 (dd, J = 16.9, 6.7

Hz, 1H), 2.57 (dd, $J = 13.1, 6.2$ Hz, 1H), 2.37 (dd, $J = 16.9, 7.2$ Hz, 1H), 2.15–2.06 (m, 1H), 2.04–1.93 (m, 1H), 1.76–1.64 (m, 3H), 1.64–1.49 (m, 3H), 1.48–1.38 (m, 1H), 1.37–1.29 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.5, 173.4, 171.4, 140.7, 136.7, 132.6, 130.3, 128.8, 103.0, 61.7, 54.0, 48.1, 41.6, 39.7, 32.8, 31.8, 27.9, 26.0, 23.1, 22.6, 14.1; MS (ESI) calcd for $\text{C}_{23}\text{H}_{28}\text{ClNO}_5$ 433.17 (M^+), found 434.24 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8a (2-((3*RS*,4*aSR*)-1-(3,4-Dimethoxyphenethyl)-4a-(ethoxycarbonyl)-2-oxo-2,3,4,4a,5,6-hexahydro-1*H*-cyclopenta[*b*]pyridin-3-yl)acetic Acid)

Compound **8a** (1.59 g, 55%) was obtained according to general procedure A. ^1H NMR (500 MHz, CDCl_3) δ 6.77 (m, 3H), 5.11 (t, $J = 2.5$ Hz, 1H), 4.15 (m, 2H), 3.95 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.68 (m, 1H), 2.79 (m, 4H), 2.67 (m, 1H), 2.50 (m, 2H), 2.34 (m, 2H), 1.86 (dt, $J = 12.8, 9.3$ Hz, 1H), 1.69 (t, $J = 12.8$ Hz, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 173.9, 169.7, 149.0, 147.7, 140.9, 131.5, 120.7, 112.2, 111.4, 106.8, 61.5, 56.0, 56.0, 54.4, 46.0, 36.9, 36.7, 36.4, 35.7, 32.3, 29.0, 14.2; MS (ESI) calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_7$ 431.2 (M^+), found 414.3 ($\text{M} - \text{OH}$) $^+$, 432.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8b

Compound **8b** (1.12 g, 51%) was obtained according to general procedure A: ^1H NMR (500 MHz, CDCl_3) δ 5.42 (m, 1H), 5.32 (dd, $J = 5.1, 2.8$ Hz, 1H), 4.14 (m, 2H), 3.82 (m, 1H), 3.70 (m, 1H), 2.77 (dd, $J = 16.2, 6.9$ Hz, 1H), 2.67 (m, 1H), 2.52 (dd, $J = 16.2, 4.9$ Hz, 1H), 2.32 (dd, $J = 13.0, 5.7$ Hz, 1H), 2.25 (m, 3H), 2.14 (m, 1H), 2.05 (m, 1H), 1.95 (m, 5H), 1.68 (m, 1H), 1.58 (m, 3H), 1.50 (m, 4H), 1.37 (m, 1H), 1.27 (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.3, 173.9, 170.3, 135.8, 135.2, 122.7, 108.1, 61.7, 46.4, 43.2, 37.5, 36.8, 36.1, 34.9, 34.8, 28.6, 25.3, 24.5, 22.9, 22.4, 18.6, 14.3; MS (ESI) calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_5$ 389.2 (M^+), found 372.3 ($\text{M} - \text{OH}$) $^+$, 390.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8c

Compound **8c** (814 mg, 37%) was obtained according to general procedure A: ^1H NMR (500 MHz, CDCl_3) δ 7.29 (m, 2H), 7.20 (m, 1H), 7.14 (d, $J = 6.7$ Hz, 2H), 5.42 (t, $J = 7.0$ Hz, 1H), 5.17 (d, $J = 16.0$ Hz, 1H), 4.75 (d, $J = 16.1$ Hz, 1H), 3.77 (s, 3H), 2.84 (m, 2H), 2.62 (m, 1H), 2.15 (dd, $J = 13.2, 4.1$ Hz, 1H), 2.05 (m, 2H), 1.93 (m, 2H), 1.69 (m, 3H), 1.57 (m, 1H), 1.24 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 174.2, 171.1, 140.6, 137.3, 128.6, 126.8, 126.4, 116.1, 52.6, 51.6, 49.5, 39.5, 36.6, 35.6, 35.6, 26.3, 25.3, 24.8; MS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_5$ 371.2 (M^+), found 354.2 ($\text{M} - \text{OH}$) $^+$, 372.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8d

Compound **8b** (582 mg, 57%) was obtained according to general procedure A: ^1H NMR (500 MHz, CDCl_3) δ 7.33 (dd, $J = 1.7, 0.8$ Hz, 1H), 6.32 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.26 (d, $J = 3.2$ Hz, 1H), 5.51 (t, $J = 4.1$ Hz, 1H), 5.28 (d, $J = 15.8$ Hz, 1H), 4.57 (d, $J = 15.8$ Hz, 1H), 3.65 (s, 3H), 2.77 (dd, $J = 16.3, 7.5$ Hz, 1H), 2.63 (m, 2H), 2.28 (dd, $J = 12.9, 5.7$ Hz, 1H), 2.22 (d, $J = 13.6$ Hz, 1H), 2.00 (d, $J = 4.1$ Hz, 2H), 1.69 (t, $J = 12.9$ Hz, 1H), 1.43 (d, $J = 13.6$ Hz, 1H), 0.97 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.1, 174.8, 170.6, 150.8, 141.7, 135.6, 110.7, 109.3, 108.3, 52.8, 47.2, 45.6, 42.6, 38.8, 38.7, 37.3, 36.0, 31.7, 28.7, 25.3; MS (ESI) calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_6$ 375.2 (M^+), found 358.2 ($\text{M} - \text{OH}$) $^+$, 376.2 ($\text{M} + \text{H}$) $^+$, 398.2 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8e

Compound **8e** was prepared according to general procedure A from primary amine **1d**, ketoester **2d**, and itaconic anhydride **5**: yield 1144 mg, 63%; ^1H NMR (500 MHz, CDCl_3) δ 5.04 (s, 1H), 4.13 (m, 2H), 3.79 (m, 1H), 3.42 (m, 1H), 2.77 (m, 2H), 2.61 (m, 1H), 2.50 (dd,

$J = 12.6, 5.2$ Hz, 1H), 2.43 (dd, $J = 16.1, 9.3$ Hz, 1H), 2.31 (dd, $J = 12.7, 7.4$ Hz, 2H), 1.82 (dt, $J = 12.8, 9.2$ Hz, 1H), 1.64 (t, $J = 12.7$ Hz, 1H), 1.53 (m, 2H), 1.21 (m, 15H), 0.83 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 174.0, 169.9, 140.9, 107.1, 61.5, 54.3, 44.2, 36.9, 36.9, 36.4, 35.9, 31.9, 29.4, 29.3, 29.0, 27.1, 26.5, 22.7, 14.2, 14.2, 14.2; MS (ESI) calcd for $\text{C}_{21}\text{H}_{33}\text{NO}_5$ 379.2 (M^+), found 362.3 ($\text{M} - \text{OH}$) $^+$, 380.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8f

Compound **8f** was prepared according to general procedure A from primary amine **1e**, ketoester **2d**, and itaconic anhydride **5**: yield 626 mg, 55%; ^1H NMR (500 MHz, CDCl_3) δ 7.25 (m, 5H), 5.00 (m, 2H), 4.84 (m, 1H), 4.14 (m, 2H), 2.91 (m, 2H), 2.81 (m, 1H), 2.56 (dd, $J = 12.9, 5.8$ Hz, 1H), 2.36 (m, 2H), 2.26 (m, 1H), 1.85 (m, 2H), 1.19 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.3, 174.1, 170.2, 141.2, 136.7, 128.4, 127.0, 126.9, 108.2, 61.5, 54.4, 54.4, 47.9, 36.9, 36.5, 36.4, 35.5, 29.0, 14.2, 14.1; MS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_5$ 357.2 (M^+), found 340.2 ($\text{M} - \text{OH}$) $^+$, 358.2 ($\text{M} + \text{H}$) $^+$, 380.2 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8g

Compound **8g** was prepared according to general procedure A from primary amine **1f**, ketoester **2d**, and itaconic anhydride **5**: yield 855 mg, 55%; ^1H NMR (500 MHz, CDCl_3) δ 6.74 (m, 3H), 5.91 (s, 2H), 5.06 (dd, $J = 3.2, 1.8$ Hz, 1H), 4.81 (m, 2H), 4.14 (m, 2H), 2.92 (dq, $J = 12.8, 5.6$ Hz, 1H), 2.81 (dd, $J = 5.6, 1.6$ Hz, 2H), 2.55 (dd, $J = 12.7, 5.6$ Hz, 1H), 2.33 (m, 3H), 1.83 (m, 2H), 1.20 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.5, 174.0, 170.4, 147.9, 146.7, 141.2, 130.6, 120.5, 108.4, 108.3, 107.8, 101.1, 61.6, 54.5, 47.7, 37.0, 36.6, 36.6, 35.8, 29.1, 14.2; MS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_7$ 401.1 (M^+), found 402.2 ($\text{M} + \text{H}$) $^+$, 424.2 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8h

Compound **8h** was prepared according to general procedure A from primary amine **1g**, ketoester **2d**, and itaconic anhydride **5**: yield 705 mg, 42%; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (dd, $J = 1.8, 0.9$ Hz, 1H), 6.28 (m, 1H), 5.27 (t, $J = 2.5$ Hz, 1H), 4.92 (m, 1H), 4.81 (m, 1H), 4.12 (m, 2H), 2.90 (m, 1H), 2.81 (m, 1H), 2.70 (m, 1H), 2.54 (dd, $J = 12.7, 5.6$ Hz, 1H), 2.46 (m, 1H), 2.34 (m, 2H), 1.86 (dt, $J = 13.2, 9.2$ Hz, 1H), 1.71 (t, $J = 12.8$ Hz, 1H), 1.18 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.0, 173.9, 170.3, 150.2, 141.9, 140.9, 110.6, 108.4, 108.3, 61.6, 54.5, 41.2, 37.0, 36.9, 36.5, 35.9, 29.2, 14.2; MS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_6$ 347.1 (M^+), found 330.2 ($\text{M} - \text{OH}$) $^+$, 348.2 ($\text{M} + \text{H}$) $^+$, 370.2 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8i

Compound **8i** was prepared according to general procedure A from primary amine **1h**, ketoester **2d**, and itaconic anhydride **5**: yield 571 mg, 47%; ^1H NMR (500 MHz, CDCl_3) δ 5.41 (t, $J = 3.4$ Hz, 1H), 5.10 (t, $J = 2.4$ Hz, 1H), 4.14 (m, 2H), 3.82 (m, 1H), 3.59 (m, 1H), 2.80 (m, 2H), 2.60 (m, 1H), 2.52 (dd, $J = 12.3, 5.4$ Hz, 1H), 2.46 (m, 1H), 2.34 (m, 2H), 2.19 (m, 1H), 2.11 (m, 1H), 1.95 (m, 4H), 1.85 (dt, $J = 12.6, 9.3$ Hz, 1H), 1.65 (m, 1H), 1.59 (m, 2H), 1.52 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.5, 173.9, 169.9, 140.8, 135.0, 122.9, 107.1, 61.5, 54.3, 43.2, 37.1, 37.0, 36.4, 35.9, 34.6, 29.0, 28.5, 25.3, 23.0, 22.4, 14.2; MS (ESI) calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_5$ 375.2 (M^+), found 358.3 ($\text{M} - \text{OH}$) $^+$, 376.3 ($\text{M} + \text{H}$) $^+$, 398.3 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8j

Compound **8j** was prepared according to general procedure A from primary amine **1j**, ketoester **2d**, and itaconic anhydride **5**: yield 1277 mg, 49%; ^1H NMR (500 MHz, CDCl_3) δ 7.98 (m, 2H), 7.87 (m, 1H), 7.74 (d, $J = 8.2$ Hz, 1H), 7.53 (ddd, $J = 8.4, 6.8, 1.7$ Hz, 1H), 7.49 (td, $J = 8.6, 6.9, 1.5$ Hz, 1H), 7.35 (d, $J = 7.0$ Hz, 1H), 5.48 (d, $J = 16.4$ Hz, 1H), 5.36

(d, $J = 16.1$ Hz, 1H), 4.87 (dd, $J = 3.2, 1.6$ Hz, 1H), 4.23 (m, 2H), 4.14 (m, 1H), 3.01 (m, 2H), 2.83 (dd, $J = 16.8, 3.9$ Hz, 1H), 2.63 (dd, $J = 12.7, 5.4$ Hz, 1H), 2.36 (m, 2H), 2.22 (m, 1H), 1.95 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.3, 174.2, 170.3, 141.3, 133.7, 130.8, 130.8, 128.9, 127.4, 126.1, 125.6, 125.5, 122.9, 122.5, 108.6, 61.5, 54.5, 45.9, 37.0, 36.6, 36.2, 35.5, 28.9, 14.2; MS (ESI) calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_5$ 407.2 (M^+), found 390.2 ($\text{M} - \text{OH}$) $^+$, 408.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8k

Compound **8k** was prepared according to general procedure A from primary amine **1k**, ketoester **2d**, and itaconic anhydride **5**: yield 568 mg, 35%; ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, $J = 1.9$ Hz, 1H), 7.16 (m, 2H), 5.01 (d, $J = 16.9$ Hz, 1H), 4.86 (d, $J = 16.9$ Hz, 2H), 4.20 (m, 2H), 2.98 (dd, $J = 17.4, 5.3$ Hz, 1H), 2.91 (m, 1H), 2.76 (dd, $J = 17.0, 4.4$ Hz, 1H), 2.56 (dd, $J = 12.7, 5.5$ Hz, 1H), 2.37 (m, 2H), 2.26 (m, 1H), 1.91 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.6, 174.1, 170.2, 141.0, 133.3, 133.2, 132.4, 129.2, 128.4, 127.4, 108.3, 61.7, 54.5, 45.4, 37.1, 36.5, 36.0, 35.4, 29.0, 14.3; MS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{Cl}_2\text{NO}_5$ 425.1 (M^+), found 408.2 ($\text{M} - \text{OH}$) $^+$, 426.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8l

Compound **8l** was prepared according to general procedure A from primary amine **1d**, ketoester **2a**, and itaconic anhydride **5**: yield 1018 mg, 88%; ^1H NMR (500 MHz, CDCl_3) δ 5.25 (dd, $J = 5.2, 2.8$ Hz, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.64 (t, $J = 8.0$ Hz, 2H), 2.76 (dd, $J = 16.3, 6.1$ Hz, 1H), 2.66 (dq, $J = 11.9, 5.8$ Hz, 3H), 2.52 (dd, $J = 16.3, 5.6$ Hz, 1H), 2.30 (dd, $J = 12.9, 5.7$ Hz, 1H), 2.22 (m, 2H), 2.12 (m, 1H), 1.65 (m, 1H), 1.55 (t, $J = 13.0$ Hz, 1H), 1.46 (m, 2H), 1.34 (m, 1H), 1.24 (m, 12H), 1.18 (t, $J = 7.1$ Hz, 3H), 0.82 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 173.9, 169.9, 135.9, 107.8, 61.5, 46.3, 44.0, 37.2, 36.6, 36.1, 34.9, 31.8, 29.3, 29.3, 27.1, 26.7, 24.4, 22.6, 18.5, 14.2, 14.1; MS (ESI) calcd for $\text{C}_{22}\text{H}_{35}\text{NO}_5$ 393.3 (M^+), found 376.3 ($\text{M} - \text{OH}$) $^+$, 394.3 ($\text{M} + \text{H}$) $^+$, 416.3 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8m

Compound **8m** was prepared according to general procedure A from primary amine **1e**, ketoester **2a**, and itaconic anhydride **5**: yield 858 mg, 79%; ^1H NMR (500 MHz, CDCl_3) δ 7.30 (m, 2H), 7.21 (m, 3H), 5.39 (d, $J = 16.0$ Hz, 1H), 5.21 (dd, $J = 5.2, 2.8$ Hz, 1H), 4.55 (d, $J = 16.0$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.47 (s, 1H), 2.81 (m, 3H), 2.40 (m, 1H), 2.27 (dt, $J = 12.9, 3.4$ Hz, 1H), 2.15 (m, 1H), 2.04 (m, 1H), 1.81 (t, $J = 12.8$ Hz, 1H), 1.66 (m, 1H), 1.52 (td, $J = 13.6, 13.2, 2.8$ Hz, 1H), 1.37 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 174.2, 170.4, 137.4, 136.9, 128.6, 128.5, 126.7, 126.2, 109.1, 61.6, 48.9, 46.6, 36.5, 36.4, 36.3, 34.8, 24.2, 18.5, 14.3; MS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_5$ 371.2 (M^+), found 354.2 ($\text{M} - \text{OH}$) $^+$, 372.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8n

Compound **8n** was prepared according to general procedure A from primary amine **1f**, ketoester **2a**, and itaconic anhydride **5**: yield 1014 mg, 83%; ^1H NMR (500 MHz, CDCl_3) δ 6.69 (m, 3H), 5.89 (s, 2H), 5.22 (m, 2H), 4.47 (d, $J = 15.8$ Hz, 1H), 4.16 (m, 2H), 2.78 (m, 3H), 2.36 (dd, $J = 12.9, 5.5$ Hz, 1H), 2.25 (dt, $J = 13.1, 3.3$ Hz, 1H), 2.14 (m, 1H), 2.05 (m, 1H), 1.79 (t, $J = 13.0$ Hz, 1H), 1.64 (dd, $J = 14.0, 5.2$ Hz, 1H), 1.50 (td, $J = 13.6, 13.1, 2.8$ Hz, 1H), 1.36 (m, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.7, 174.2, 170.3, 147.9, 146.4, 136.8, 131.3, 119.4, 109.0, 108.3, 107.1, 100.9, 61.6, 48.5, 46.6, 36.5, 36.4, 36.3, 34.8, 24.3, 18.5, 14.3; MS (ESI) calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_7$ 415.2 (M^+), found 398.2 ($\text{M} - \text{OH}$) $^+$, 416.3 ($\text{M} + \text{H}$) $^+$, 438.2 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8o

Compound **8o** was prepared according to general procedure A from primary amine **1g**, ketoester **2a**, and itaconic anhydride **5**: yield 583 mg, 55%; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (m, 1H), 6.27 (m, 2H), 5.51 (dd, $J = 5.2, 2.8$ Hz, 1H), 5.24 (d, $J = 15.8$ Hz, 1H), 4.54 (d, $J = 15.8$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.82 (dd, $J = 16.1, 5.8$ Hz, 1H), 2.75 (dq, $J = 12.9, 5.6$ Hz, 1H), 2.65 (dd, $J = 16.1, 5.3$ Hz, 1H), 2.37 (dd, $J = 13.0, 5.7$ Hz, 1H), 2.25 (m, 2H), 2.13 (m, 1H), 1.66 (m, 2H), 1.50 (td, $J = 13.6, 13.1, 2.6$ Hz, 1H), 1.38 (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.2, 174.0, 170.2, 150.9, 141.6, 136.7, 110.6, 109.0, 108.0, 61.7, 46.6, 42.2, 37.0, 36.7, 36.2, 34.9, 24.4, 18.6, 14.3; MS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_6$ 361.2 (M^+), found 344.2 ($\text{M} - \text{OH}$) $^+$, 362.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8p

Compound **8p** was prepared according to general procedure A from primary amine **1i**, ketoester **2a**, and itaconic anhydride **5**: yield 914 mg, 58%; ^1H NMR (500 MHz, CDCl_3) δ 6.76 (m, 3H), 5.33 (dd, $J = 5.2, 2.8$ Hz, 1H), 4.12 (q, $J = 7.0$ Hz, 2H), 3.86 (m, 2H), 3.84 (s, 4H), 3.81 (s, 3H), 2.85 (m, 1H), 2.76 (dd, $J = 16.0, 5.7$ Hz, 1H), 2.69 (m, 2H), 2.62 (dd, $J = 16.1, 5.6$ Hz, 1H), 2.32 (dd, $J = 13.0, 5.6$ Hz, 1H), 2.25 (m, 2H), 2.14 (m, 1H), 1.67 (m, 1H), 1.61 (t, $J = 12.8$ Hz, 1H), 1.48 (td, $J = 13.4, 12.9, 2.6$ Hz, 1H), 1.38 (m, 1H), 1.18 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 173.9, 169.8, 148.9, 147.5, 135.9, 131.7, 120.5, 112.1, 111.3, 107.6, 61.5, 55.9, 55.9, 46.4, 45.6, 36.8, 36.4, 36.1, 34.8, 32.4, 24.4, 18.5, 14.2; MS (ESI) calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_7$ 445.2 (M^+), found 428.3 ($\text{M} - \text{OH}$) $^+$, 446.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8q

Compound **8q** was prepared according to general procedure A from primary amine **1j**, ketoester **2a**, and itaconic anhydride **5**: 1040 mg, 84%; ^1H NMR (500 MHz, CDCl_3) δ 7.99 (d, $J = 8.2$ Hz, 1H), 7.88 (m, 1H), 7.74 (d, $J = 8.2$ Hz, 1H), 7.51 (m, 3H), 7.33 (d, $J = 7.1$ Hz, 1H), 5.90 (d, $J = 16.7$ Hz, 1H), 5.07 (dd, $J = 5.1, 2.9$ Hz, 1H), 5.02 (d, $J = 16.7$ Hz, 1H), 4.25 (m, 2H), 3.03 (dd, $J = 16.6, 5.1$ Hz, 1H), 2.85 (m, 2H), 2.47 (dd, $J = 12.9, 5.4$ Hz, 1H), 2.31 (dt, $J = 13.3, 3.3$ Hz, 1H), 2.03 (m, 3H), 1.66 (m, 1H), 1.58 (td, $J = 13.5, 2.8$ Hz, 1H), 1.40 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.1, 174.2, 170.1, 137.0, 133.6, 131.3, 130.3, 128.8, 127.1, 125.9, 125.7, 125.5, 122.4, 122.4, 109.1, 61.6, 47.4, 46.7, 36.3, 36.2, 36.1, 34.7, 24.1, 18.5, 14.3; MS (ESI) calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_5$ 421.2 (M^+), found 404.3 ($\text{M} - \text{OH}$) $^+$, 422.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8r

Compound **8r** was prepared according to general procedure A from primary amine **1k**, ketoester **2a**, and itaconic anhydride **5**: yield 861 mg, 67%; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (s, 1H), 7.13 (m, 2H), 5.26 (d, $J = 17.1$ Hz, 1H), 4.91 (dd, $J = 5.1, 2.8$ Hz, 1H), 4.56 (d, $J = 17.1$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.00 (dd, $J = 16.9, 5.1$ Hz, 1H), 2.69 (m, 2H), 2.35 (dd, $J = 12.9, 5.6$ Hz, 1H), 2.25 (dt, $J = 13.2, 3.2$ Hz, 1H), 2.11 (m, 1H), 2.00 (m, 1H), 1.90 (t, $J = 12.9$ Hz, 1H), 1.64 (m, 1H), 1.51 (td, $J = 13.7, 2.8$ Hz, 1H), 1.34 (m, 1H), 1.24 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.3, 174.2, 170.3, 136.7, 133.0, 133.0, 132.7, 129.1, 128.3, 127.4, 109.0, 61.8, 46.8, 46.8, 36.2, 36.1, 35.8, 34.8, 24.2, 18.5, 14.4; MS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{Cl}_2\text{NO}_5$ 439.1 (M^+), found 422.2 ($\text{M} - \text{OH}$) $^+$, 440.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8s

Compound **8s** was prepared according to general procedure A from primary amine **1d**, ketoester **2b**, and itaconic anhydride **5**: yield 443 mg, 38%; ^1H NMR (500 MHz, CDCl_3) δ 5.54 (t, $J = 7.1$ Hz, 1H), 3.76 (s, 4H), 3.60 (m, 1H), 2.80 (dd, $J = 16.1, 7.5$ Hz, 1H), 2.70 (m, 1H), 2.40 (dd, $J = 16.1, 5.1$ Hz, 1H), 2.23 (m, 1H), 2.05 (m, 3H), 1.79 (m, 1H), 1.70 (m,

4H), 1.56 (m, 2H), 1.40 (m, 1H), 1.26 (m, 11H), 0.86 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.3, 174.1, 171.3, 140.3, 115.1, 52.7, 51.6, 51.6, 45.5, 40.0, 37.0, 36.6, 35.6, 31.9, 29.4, 29.4, 27.1, 26.9, 26.5, 25.5, 25.0, 22.8, 14.2; MS (ESI) calcd for $\text{C}_{22}\text{H}_{35}\text{NO}_5$ 393.3 (M^+), found 376.3 ($\text{M} - \text{OH}$) $^+$, 394.4 ($\text{M} + \text{H}$) $^+$, 416.4 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8t

Compound **8t** was prepared according to general procedure A from primary amine **1f**, ketoester **2b**, and itaconic anhydride **5**: yield 595 mg, 33%; ^1H NMR (500 MHz, CDCl_3) δ 6.74 (d, $J = 7.9$ Hz, 1H), 6.64 (d, $J = 1.7$ Hz, 1H), 6.62 (dd, $J = 8.0, 1.8$ Hz, 1H), 5.92 (d, $J = 1.7$ Hz, 2H), 5.46 (t, $J = 7.0$ Hz, 1H), 5.04 (d, $J = 15.8$ Hz, 1H), 4.69 (d, $J = 15.8$ Hz, 1H), 3.77 (s, 3H), 2.88–2.76 (m, 2H), 2.63–2.56 (m, 1H), 2.19–2.07 (m, 2H), 2.07–2.00 (m, 1H), 2.00–1.92 (m, 1H), 1.88 (t, $J = 13.2$ Hz, 1H), 1.78–1.54 (m, 4H), 1.33–1.23 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 174.2, 171.3, 148.0, 146.5, 140.6, 131.2, 119.6, 116.2, 108.4, 107.1, 101.0, 52.7, 51.6, 49.4, 39.6, 36.7, 35.9, 35.6, 26.3, 25.3, 24.9; HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_7$ 416.1709, found 416.1714.

Piperidinone-Containing Carboxylic Acid 8u

Compound **8u** was prepared according to general procedure A from primary amine **1g**, ketoester **2b**, and itaconic anhydride **5**: yield 452 mg, 28%; ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 1.7, 0.9$ Hz, 1H), 6.28 (dd, $J = 3.1, 1.8$ Hz, 1H), 6.18 (d, $J = 3.2$ Hz, 1H), 5.68 (t, $J = 7.1$ Hz, 1H), 5.08 (d, $J = 15.9$ Hz, 1H), 4.69 (d, $J = 15.9$ Hz, 1H), 3.74 (s, 3H), 2.86 (dd, $J = 16.7, 6.0$ Hz, 1H), 2.76 (dt, $J = 6.8, 4.4$ Hz, 1H), 2.48 (dd, $J = 16.7, 6.4$ Hz, 1H), 2.17 (m, 1H), 2.11 (dd, $J = 13.2, 4.4$ Hz, 1H), 2.00 (m, 2H), 1.78 (m, 2H), 1.64 (m, 2H), 1.27 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.6, 174.1, 171.0, 150.8, 141.5, 140.5, 116.3, 110.5, 108.1, 52.6, 51.8, 42.9, 39.5, 36.6, 35.6, 35.6, 26.4, 25.3, 24.9; MS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_6$ 361.2 (M^+), found 344.2 ($\text{M} - \text{OH}$) $^+$, 362.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8v

Compound **8v** was prepared according to general procedure A from primary amine **1h**, ketoester **2b**, and itaconic anhydride **5**: yield 438 mg, 38%; ^1H NMR (500 MHz, CDCl_3) δ 5.54 (t, $J = 7.2$ Hz, 3H), 5.39 (m, 3H), 3.98 (m, 3H), 3.74 (s, 9H), 3.60 (m, 3H), 2.80 (dd, $J = 16.3, 6.9$ Hz, 3H), 2.68 (m, 3H), 2.37 (dd, $J = 16.3, 5.7$ Hz, 3H), 2.19 (m, 9H), 2.03 (m, 9H), 1.95 (m, 13H), 1.79 (m, 3H), 1.68 (m, 13H), 1.57 (m, 6H), 1.50 (m, 6H), 1.36 (m, 2H), 1.23 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 174.1, 171.1, 140.2, 135.0, 123.0, 114.9, 52.6, 51.6, 43.3, 39.7, 37.0, 36.2, 35.5, 34.8, 28.4, 26.8, 25.6, 25.3, 25.0, 22.9, 22.4; HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_5$ 390.2280, found 390.2280.

Piperidinone-Containing Carboxylic Acid 8w

Compound **8w** was prepared according to general procedure A from primary amine **1i**, ketoester **2b**, and itaconic anhydride **5**: yield 1090 mg, 42%; ^1H NMR (500 MHz, CDCl_3) δ 6.77 (m, 3H), 5.64 (t, $J = 7.2$ Hz, 1H), 4.06 (m, 1H), 3.88 (s, 3H), 3.85 (s, 4H), 3.76 (s, 3H), 2.85 (dt, $J = 9.4, 5.6$ Hz, 2H), 2.78 (dd, $J = 16.4, 7.1$ Hz, 1H), 2.72 (dt, $J = 12.6, 6.0$ Hz, 1H), 2.40 (dd, $J = 15.9, 4.8$ Hz, 1H), 2.26 (m, 1H), 2.05 (m, 3H), 1.80 (m, 1H), 1.67 (m, 3H), 1.60 (t, $J = 13.3$ Hz, 1H), 1.39 (m, 1H), 1.24 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.3, 174.0, 170.8, 148.8, 147.5, 140.4, 131.3, 120.6, 114.6, 112.0, 111.2, 77.4, 77.2, 76.9, 55.9, 52.5, 51.5, 46.1, 39.4, 36.7, 35.6, 35.5, 32.4, 26.6, 25.5, 24.9; MS (ESI) calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_7$ 445.2 (M^+), found 428.2 ($\text{M} - \text{OH}$) $^+$, 446.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid 8x

Compound **8x** was prepared according to general procedure A from primary amine **1j**, ketoester **2b**, and itaconic anhydride **5**: yield 791 mg, 32%; ^1H NMR (500 MHz, CDCl_3) δ

7.94 (d, $J = 8.3$ Hz, 1H), 7.88 (m, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.52 (m, 2H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.20 (d, $J = 7.1$ Hz, 1H), 5.56 (d, $J = 16.4$ Hz, 1H), 5.36 (t, $J = 7.0$ Hz, 1H), 5.27 (d, $J = 16.6$ Hz, 1H), 3.81 (s, 3H), 2.89 (m, 2H), 2.71 (m, 1H), 2.20 (dd, $J = 13.2, 4.2$ Hz, 1H), 2.03 (m, 3H), 1.89 (m, 1H), 1.69 (m, 3H), 1.57 (m, 1H), 1.24 (m, 1H); MS (ESI) calcd for $C_{25}H_{27}NO_5$ 421.2 (M^+), found 404.3 ($M - OH$)⁺, 422.3 ($M + H$)⁺.

Piperidinone-Containing Carboxylic Acid **8y**

Compound **8y** was prepared according to general procedure A from primary amine **1k**, ketoester **2b**, and itaconic anhydride **5**: yield 1118 mg, 46%; 1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, $J = 2.1$ Hz, 1H), 7.19 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 5.18 (t, $J = 6.9$ Hz, 1H), 4.98 (d, $J = 17.2$ Hz, 1H), 4.86 (d, $J = 17.0$ Hz, 1H), 3.79 (s, 3H), 2.77 (m, 3H), 2.11 (m, 3H), 1.98 (m, 2H), 1.80 (m, 2H), 1.63 (m, 2H), 1.34 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 174.2, 170.8, 140.8, 133.1, 133.0, 129.2, 128.3, 127.5, 115.4, 52.8, 51.7, 47.9, 39.2, 36.9, 35.6, 35.3, 26.1, 25.3, 24.9; HRMS (ESI-TOF) m/z [$M + H$]⁺ calcd for $C_{21}H_{24}Cl_2NO_5$ 440.1032, found 440.1037.

Piperidinone-Containing Carboxylic Acid **8z**

Compound **8z** was prepared according to general procedure A from primary amine **1d**, ketoester **2e**, and itaconic anhydride **5**: yield 479 mg, 41%; 1H NMR (500 MHz, $CDCl_3$) δ 5.19 (t, $J = 4.1$ Hz, 1H), 3.66 (m, 2H), 3.61 (s, 3H), 2.70 (m, 1H), 2.53 (m, 2H), 2.19 (m, 2H), 1.97 (d, $J = 4.1$ Hz, 2H), 1.59 (m, 2H), 1.47 (m, 1H), 1.38 (d, $J = 13.7$ Hz, 1H), 1.23 (m, 11H), 0.92 (s, 3H), 0.82 (t, $J = 6.7$ Hz, 3H), 0.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 175.1, 169.8, 134.9, 107.4, 52.4, 47.2, 45.3, 44.5, 38.7, 38.4, 37.1, 35.9, 31.8, 31.6, 29.3, 29.3, 28.5, 27.2, 26.7, 25.3, 22.6, 14.1, 14.1; MS (ESI) calcd for $C_{23}H_{37}NO_5$ 407.3 (M^+), found 390.3 ($M - OH$)⁺, 408.3 ($M + H$)⁺.

Piperidinone-Containing Carboxylic Acid **8aa**

Compound **8aa** was prepared according to general procedure A from primary amine **1e**, ketoester **2e**, and itaconic anhydride **5**: yield 474 mg, 76%; 1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.22 (m, 3H), 5.50 (d, $J = 16.1$ Hz, 1H), 5.14 (t, $J = 4.1$ Hz, 1H), 4.49 (d, $J = 16.0$ Hz, 1H), 3.67 (s, 3H), 2.90 (m, 1H), 2.74 (dd, $J = 17.0, 5.2$ Hz, 1H), 2.63 (dt, $J = 18.5, 5.4$ Hz, 1H), 2.29 (dd, $J = 12.8, 5.8$ Hz, 1H), 2.22 (d, $J = 13.5$ Hz, 1H), 1.88 (m, 3H), 1.46 (d, $J = 13.6$ Hz, 1H), 0.94 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 175.4, 170.3, 137.5, 137.5, 136.0, 128.6, 126.8, 126.3, 108.8, 52.6, 49.5, 47.2, 45.6, 38.6, 38.3, 36.5, 36.1, 31.7, 28.6, 25.4; MS (ESI) calcd for $C_{22}H_{27}NO_5$ 385.2 (M^+), found 368.2 ($M - OH$)⁺, 386.3 ($M + H$)⁺.

Piperidinone-Containing Carboxylic Acid **8ab**

Compound **8ab** was prepared according to general procedure A from primary amine **1f**, ketoester **2e**, and itaconic anhydride **5**: yield 890 mg, 76%; 1H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.74 (m, 2H), 6.69 (m, 1H), 5.92 (d, $J = 1.8$ Hz, 2H), 5.34 (d, $J = 15.8$ Hz, 1H), 5.19 (m, 1H), 4.45 (dd, $J = 15.7, 3.4$ Hz, 1H), 3.67 (s, 3H), 2.82 (m, 1H), 2.74 (m, 1H), 2.63 (dt, $J = 13.1, 5.5$ Hz, 1H), 2.28 (dd, $J = 12.8, 5.8$ Hz, 1H), 2.22 (d, $J = 13.6$ Hz, 1H), 1.91 (t, $J = 3.0$ Hz, 2H), 1.82 (td, $J = 13.0, 3.0$ Hz, 1H), 1.44 (d, $J = 13.6$ Hz, 1H), 0.94 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 175.4, 170.4, 147.9, 146.4, 136.0, 131.4, 119.6, 108.8, 108.4, 107.2, 101.0, 66.0, 52.6, 49.2, 47.2, 45.6, 38.7, 38.3, 36.6, 36.1, 31.7, 28.6, 25.5, 15.3; MS (ESI) calcd for $C_{23}H_{27}NO_7$ 429.2 (M^+), found 412.2 ($M - OH$)⁺, 430.2 ($M + H$)⁺.

Piperidinone-Containing Carboxylic Acid **8ac**

Compound **8ac** was prepared according to general procedure A from primary amine **1h**, ketoester **2e**, and itaconic anhydride **5**: yield 420 mg, 38%; ^1H NMR (500 MHz, CDCl_3) δ 5.46 (m, 1H), 5.32 (m, 1H), 3.90 (m, 1H), 3.72 (m, 1H), 3.67 (s, 3H), 2.74 (dd, $J = 15.7, 7.3$ Hz, 1H), 2.53 (m, 2H), 2.31 (td, $J = 12.3, 11.6, 5.6$ Hz, 1H), 2.23 (m, 2H), 2.11 (m, 1H), 2.00 (m, 7H), 1.61 (m, 3H), 1.55 (m, 2H), 1.43 (d, $J = 13.7$ Hz, 1H), 1.21 (m, 1H), 0.97 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.3, 175.1, 170.2, 135.2, 134.9, 122.6, 107.7, 52.6, 47.2, 45.3, 43.8, 38.8, 38.5, 37.4, 35.9, 34.8, 31.7, 28.6, 28.6, 25.4, 25.3, 22.9, 22.4; MS (ESI) calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_5$ 403.2 (M^+), found 386.2 ($\text{M} - \text{OH}$) $^+$, 404.2 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid **8ad**

Compound **8ad** was prepared according to general procedure A from primary amine **1i**, ketoester **2e**, and itaconic anhydride **5**: yield 570 mg, 46%; ^1H NMR (500 MHz, CDCl_3) δ 6.80 (m, 3H), 5.39 (dd, $J = 5.0, 3.2$ Hz, 1H), 3.96 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.68 (s, 3H), 2.94 (m, 1H), 2.77 (m, 2H), 2.62 (m, 1H), 2.53 (dd, $J = 16.0, 3.4$ Hz, 1H), 2.26 (m, 2H), 2.06 (m, 2H), 1.63 (t, $J = 13.0$ Hz, 1H), 1.45 (d, $J = 13.6$ Hz, 1H), 1.00 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.7, 175.1, 169.8, 148.9, 147.5, 135.0, 131.8, 120.6, 112.1, 111.3, 107.4, 55.9, 55.9, 52.4, 47.1, 46.2, 45.3, 38.7, 38.2, 36.8, 35.9, 32.5, 31.6, 28.5, 25.3; MS (ESI) calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_7$ 459.2 (M^+), found 442.3 ($\text{M} - \text{OH}$) $^+$, 460.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Carboxylic Acid **8ae**

Compound **8ae** was prepared according to general procedure A from primary amine **1j**, ketoester **2e**, and itaconic anhydride **5**: yield 715 mg, 60%; ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, $J = 8.3$ Hz, 1H), 7.88 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.53 (m, 2H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 7.2$ Hz, 1H), 5.99 (d, $J = 16.7$ Hz, 1H), 5.03 (dd, $J = 5.1, 2.9$ Hz, 1H), 4.93 (d, $J = 16.7$ Hz, 1H), 3.74 (s, 3H), 3.05 (m, 1H), 2.73 (m, 2H), 2.36 (dd, $J = 12.8, 5.6$ Hz, 1H), 2.27 (dd, $J = 13.7, 1.9$ Hz, 1H), 2.05 (m, 1H), 1.85 (m, 2H), 1.52 (d, $J = 13.7$ Hz, 1H), 0.95 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.8, 175.6, 170.2, 136.3, 133.8, 131.6, 130.4, 128.9, 127.3, 126.1, 125.8, 125.6, 122.7, 122.6, 109.0, 77.4, 77.2, 76.9, 52.7, 48.3, 47.2, 45.7, 38.5, 38.3, 36.3, 36.2, 31.7, 28.6, 25.4; HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{26}\text{H}_{30}\text{NO}_5$ 436.2124, found 436.2120.

Piperidinone-Containing Carboxylic Acid **8af**

Compound **8af** was prepared according to general procedure A from primary amine **1k**, ketoester **2e**, and itaconic anhydride **5**: yield 944 mg, 77%; ^1H NMR (500 MHz, CDCl_3) δ 7.35 (d, $J = 1.9$ Hz, 1H), 7.15 (m, 2H), 5.41 (d, $J = 17.2$ Hz, 1H), 4.89 (dd, $J = 4.8, 3.2$ Hz, 1H), 4.49 (d, $J = 17.1$ Hz, 1H), 3.71 (s, 3H), 3.09 (dd, $J = 17.2, 4.9$ Hz, 1H), 2.60 (m, 2H), 2.25 (m, 2H), 1.98 (t, $J = 13.0$ Hz, 1H), 1.89 (t, $J = 4.1$ Hz, 2H), 1.48 (d, $J = 13.7$ Hz, 1H), 0.94 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.3, 175.4, 170.1, 136.0, 133.2, 133.0, 132.7, 129.1, 128.3, 127.4, 108.5, 52.7, 47.6, 47.1, 45.6, 38.5, 37.9, 36.1, 35.7, 31.7, 28.6, 25.4; MS (ESI) calcd for $\text{C}_{22}\text{H}_{25}\text{Cl}_2\text{NO}_5$ 453.1 (M^+), found 436.2 ($\text{M} - \text{OH}$) $^+$, 454.2 ($\text{M} + \text{H}$) $^+$.

Carbomethoxytetrahydropyranone **24a** ((*2RS,6RS*)-Methyl 6-*tert*-Butyl-2-methyl-4-oxotetrahydro-2H-pyran-3-carboxylate)

Compound **24a** was prepared according to reported procedures.¹⁷ ^1H NMR (500 MHz, CDCl_3) δ 3.96 (dd, $J = 10.4, 6.0$ Hz, 1H), 3.77 (s, 3H), 3.31 (dd, $J = 11.8, 2.3$ Hz, 1H), 3.17 (dd, $J = 10.4, 0.7$ Hz, 1H), 2.45 (dd, $J = 13.9, 2.3$ Hz, 1H), 2.29 (ddd, $J = 13.9, 11.9, 0.9$ Hz, 1H), 1.32 (d, $J = 6.0$ Hz, 3H), 0.93 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 203.8, 168.9,

84.4, 75.0, 64.6, 52.2, 42.2, 34.4, 25.6, 20.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{12}H_{20}O_4Na$ 251.1259, found 251.1267.

Carbomethoxytetrahydropyranone 24b

Compound **24b** was prepared according to reported procedures:¹⁷ 1H NMR (500 MHz, $CDCl_3$) δ 3.97 (dq, J = 10.4, 6.0 Hz, 1H), 3.76 (s, 3H), 3.43 (ddd, J = 11.5, 7.9, 2.3 Hz, 1H), 3.19 (dd, J = 10.4, 0.8 Hz, 1H), 2.50 (dd, J = 14.2, 2.3 Hz, 1H), 2.27 (ddd, J = 14.2, 11.6, 0.9 Hz, 1H), 1.97 (q, J = 8.3 Hz, 1H), 1.87–1.81 (m, 1H), 1.69–1.51 (m, 6H), 1.45–1.40 (m, 1H), 1.32 (d, J = 6.0 Hz, 3H), 1.21–1.14 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 168.8, 81.2, 75.0, 64.6, 52.3, 46.2, 45.5, 29.3, 28.6, 25.62, 25.43, 21.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{20}O_4Na$ 263.1259, found 263.1266.

Carbomethoxytetrahydropyranone 24c

Compound **24c** was prepared according to reported procedures:¹⁷ 1H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.39–3.33 (m, 2H), 3.33–3.27 (m, 1H), 2.46 (dd, J = 14.3, 2.3 Hz, 1H), 2.27–2.22 (m, 1H), 1.79 (dq, J = 13.4, 6.7 Hz, 1H), 0.99–0.93 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.57–0.49 (m, 2H), 0.48–0.43 (m, 1H), 0.40–0.35 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 168.8, 81.6, 81.4, 63.9, 52.2, 44.3, 33.4, 18.5, 18.1, 15.7, 2.9, 2.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{20}O_4Na$ 263.1259, found 263.1258.

Carbomethoxytetrahydropyranone 24d

Compound **24d** was prepared according to reported procedures:¹⁷ 1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 4.60 (q, J = 9.9 Hz, 2H), 4.04 (dq, J = 10.5, 6.0 Hz, 1H), 3.94–3.89 (m, 1H), 3.77 (s, 3H), 3.60–3.53 (m, 2H), 3.23 (dd, J = 10.5, 0.7 Hz, 1H), 2.53–2.41 (m, 2H), 1.36 (d, J = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 168.6, 137.8, 128.6, 127.95, 127.85, 76.1, 75.2, 73.6, 71.9, 64.3, 52.3, 43.4, 20.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}O_5Na$ 315.1208, found 315.1211.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26a (2-((3*SR*,4*aRS*,5*RS*,7*RS*)-1-Benzyl-7-*tert*-butyl-4a-(methoxycarbonyl)-5-methyl-2-oxo-2,3,4,4a,5,7-hexahydro-1*H*-pyrano[4,3-*b*]pyridin-3-yl)acetic Acid)

Compound **26a** (428 mg, 82%) was obtained according to general procedure A: 1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 1H), 7.25–7.20 (m, 1H), 5.43 (s, 1H), 5.27 (d, J = 15.5 Hz, 1H), 4.47 (d, J = 15.5 Hz, 1H), 3.84 (q, J = 6.4 Hz, 1H), 3.72 (s, 1H), 3.59 (s, 3H), 3.14–3.06 (m, 1H), 3.00 (dd, J = 17.0, 5.3 Hz, 1H), 2.78 (dd, J = 17.0, 5.2 Hz, 1H), 2.47 (dd, J = 12.6, 7.4 Hz, 1H), 1.79 (t, J = 12.6 Hz, 1H), 1.18 (d, J = 6.3 Hz, 3H), 0.73 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 172.7, 170.9, 138.3, 137.4, 128.7, 127.2, 127.0, 111.6, 82.1, 74.6, 52.8, 51.4, 49.4, 37.5, 36.5, 34.7, 28.8, 25.5, 16.2; MS (ESI) calcd for $C_{24}H_{31}NO_6$ 429.2 (M^+), found 412.2 ($M - OH$)⁺, 430.2 ($M + H$)⁺, 452.2 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26b

Compound **26b** (366 mg, 74%) was obtained according to general procedure A: 1H NMR (500 MHz, $CDCl_3$) δ 5.43 (s, 1H), 5.41–5.38 (m, 1H), 4.05 (d, J = 7.6 Hz, 1H), 3.98 (q, J = 6.6 Hz, 1H), 3.82–3.72 (m, 1H), 3.67 (s, 2H), 3.64–3.55 (m, 1H), 3.02–2.91 (m, 1H), 2.75 (dd, J = 16.8, 5.9 Hz, 1H), 2.71–2.63 (m, 1H), 2.38 (dd, J = 12.8, 7.2 Hz, 1H), 2.30–2.20 (m, 1H), 2.06–1.99 (m, 1H), 1.99–1.92 (m, 5H), 1.77–1.66 (m, 2H), 1.66–1.56 (m, 5H), 1.56–1.47 (m, 4H), 1.44–1.34 (m, 1H), 1.34–1.24 (m, 1H), 1.19 (dd, J = 6.6, 2.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 172.6, 170.5, 170.5, 136.4, 135.0, 123.0, 111.0, 78.1, 74.5, 52.9, 51.3, 44.8, 43.4, 37.9, 37.9, 36.3, 34.9, 29.3, 28.7, 28.6, 28.5, 25.9, 25.8, 25.4, 23.0, 22.4, 16.6; MS (ESI) calcd for $C_{26}H_{37}NO_6$ 459.3 (M^+), found 460.4 ($M + H$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26c

Compound **26c** (609 mg, 81%) was obtained according to general procedure A: ^1H NMR (500 MHz, CDCl_3) δ 6.77–6.68 (m, 3H), 5.27 (d, J = 1.9 Hz, 1H), 3.91 (dd, J = 6.2, 1.8 Hz, 1H), 3.89–3.82 (m, 1H), 3.81 (s, 3H), 3.81–3.76 (m, 4H), 3.78–3.72 (m, 1H), 3.62 (s, 3H), 3.30 (d, J = 8.0 Hz, 1H), 3.02–2.91 (m, 1H), 2.84–2.71 (m, 4H), 2.48 (dd, J = 12.8, 6.7 Hz, 1H), 1.85 (t, J = 12.1 Hz, 1H), 1.83–1.72 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.48 (d, J = 8.3 Hz, 2H), 0.45–0.36 (m, 1H), 0.18–0.11 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.6, 172.7, 170.3, 148.9, 147.5, 136.2, 131.5, 120.6, 111.9, 111.3, 108.9, 81.5, 78.7, 55.8, 55.8, 52.7, 51.6, 45.8, 37.1, 36.4, 33.2, 32.5, 29.8, 18.3, 18.0, 11.7, 3.5, 2.4; MS (ESI) calcd for $\text{C}_{28}\text{H}_{37}\text{NO}_8$ 515.3 (M^+), found 498.4 ($\text{M} - \text{OH}$) $^+$, 516.4 ($\text{M} + \text{H}$) $^+$, 538.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26d

Compound **26d** (293 mg, 54%) was obtained according to general procedure A: ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.27 (m, 5H), 6.30 (dd, J = 3.3, 1.8 Hz, 1H), 6.23 (d, J = 3.2 Hz, 1H), 5.58 (d, J = 1.7 Hz, 1H), 4.91 (d, J = 15.7 Hz, 1H), 4.75 (d, J = 15.7 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.48 (td, J = 6.0, 1.7 Hz, 1H), 4.07 (q, J = 6.5 Hz, 1H), 3.61 (s, 2H), 3.54 (dd, J = 9.9, 6.5 Hz, 1H), 3.40 (dd, J = 9.8, 5.6 Hz, 1H), 3.05–2.95 (m, 1H), 2.80 (dd, J = 16.9, 5.4 Hz, 1H), 2.72 (dd, J = 16.9, 6.2 Hz, 1H), 2.39 (dd, J = 12.8, 6.7 Hz, 1H), 1.71 (t, J = 12.1 Hz, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.3, 172.4, 170.3, 150.1, 141.8, 138.1, 136.6, 128.5, 128.5, 127.8, 127.8, 127.8, 110.6, 108.8, 108.7, 74.4, 73.5, 73.3, 72.7, 53.0, 51.2, 51.2, 41.0, 37.2, 36.4, 29.2, 16.8; MS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{NO}_8$ 483.2 (M^+), found 484.3 ($\text{M} + \text{H}$) $^+$, 506.3 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26e

Compound **26e** was prepared according to general procedure A from primary amine **1d**, ketoester **24a**, and itaconic anhydride **5**: yield 454 mg, 93%; ^1H NMR (500 MHz, CDCl_3) δ 5.46 (s, 1H), 3.88 (q, J = 6.4 Hz, 1H), 3.82 (s, 1H), 3.76–3.68 (m, 1H), 3.65 (s, 3H), 3.48–3.39 (m, 1H), 3.06–2.97 (m, 1H), 2.78 (dd, J = 16.9, 6.0 Hz, 1H), 2.67 (dd, J = 16.9, 5.2 Hz, 1H), 2.41 (dd, J = 12.7, 7.7 Hz, 1H), 1.60 (dd, J = 12.6, 10.7 Hz, 2H), 1.48–1.38 (m, 1H), 1.33–1.18 (m, 12H), 1.15 (d, J = 6.5 Hz, 3H), 0.91–0.81 (m, 12H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.8, 172.6, 170.4, 138.0, 110.0, 82.2, 74.6, 52.7, 51.4, 44.5, 37.8, 36.3, 34.7, 31.9, 29.3, 29.3, 28.6, 27.2, 26.8, 25.6, 22.7, 16.2, 14.2; MS (ESI) calcd for $\text{C}_{25}\text{H}_{41}\text{NO}_6$ 451.3 (M^+), found 434.4 ($\text{M} - \text{OH}$) $^+$, 452.4 ($\text{M} + \text{H}$) $^+$, 474.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26f

Compound **26f** was prepared according to general procedure A from primary amine **1f**, ketoester **24a**, and itaconic anhydride **5**: yield 431 mg, 77%; ^1H NMR (500 MHz, CDCl_3) δ 6.77–6.72 (m, 2H), 6.70 (dd, J = 7.8, 1.8 Hz, 1H), 5.94–5.90 (m, 2H), 5.49 (d, J = 1.6 Hz, 1H), 5.06 (d, J = 15.3 Hz, 1H), 4.48 (d, J = 15.3 Hz, 1H), 3.85 (q, J = 6.4 Hz, 1H), 3.74 (d, J = 1.5 Hz, 1H), 3.61 (s, 3H), 3.12–3.05 (m, 1H), 2.96 (dd, J = 17.0, 5.4 Hz, 1H), 2.75 (dd, J = 17.0, 5.3 Hz, 1H), 2.45 (dd, J = 12.6, 7.4 Hz, 1H), 1.76 (dd, J = 12.7, 11.1 Hz, 1H), 1.18 (d, J = 6.5 Hz, 3H), 0.78 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.0, 172.6, 170.9, 148.0, 146.7, 138.3, 131.2, 120.4, 111.5, 108.3, 107.9, 101.1, 82.1, 77.4, 77.4, 77.2, 76.9, 74.6, 52.8, 51.4, 49.0, 37.4, 36.5, 34.7, 28.7, 25.6, 16.2; MS (ESI) calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_8$ 473.2 (M^+), found 474.2 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26g

Compound **26g** was prepared according to general procedure A from primary amine **1g**, ketoester **24a**, and itaconic anhydride **5**: yield 219 mg, 46%; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (dd, J = 1.7, 0.9 Hz, 1H), 6.30 (dd, J = 3.1, 1.8 Hz, 1H), 6.23 (d, J = 3.1 Hz, 1H), 5.69

(d, $J = 1.5$ Hz, 1H), 5.07 (d, $J = 15.6$ Hz, 1H), 4.47 (d, $J = 15.6$ Hz, 1H), 3.85 (q, $J = 6.3$ Hz, 1H), 3.79 (d, $J = 1.6$ Hz, 1H), 3.61 (s, 3H), 3.07–2.99 (m, 1H), 2.86 (dd, $J = 17.0$, 6.1 Hz, 1H), 2.70 (dd, $J = 17.0$, 4.6 Hz, 1H), 2.43 (dd, $J = 12.7$, 7.5 Hz, 1H), 1.66 (dd, $J = 12.7$, 10.9 Hz, 1H), 1.16 (d, $J = 6.4$ Hz, 3H), 0.83 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.0, 172.7, 170.4, 150.6, 141.7, 138.1, 111.1, 110.7, 108.6, 82.1, 74.5, 52.8, 51.3, 42.2, 37.4, 36.4, 34.7, 28.5, 25.5, 16.1; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_7$ 420.2022, found 420.2000.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26h

Compound **26h** was prepared according to general procedure A from primary amine **1h**, ketoester **24a**, and itaconic anhydride **5**: yield 363 mg, 71%; ^1H NMR (500 MHz, CDCl_3) δ 5.54 (s, 1H), 5.47 (s, 1H), 3.90 (q, $J = 6.5$ Hz, 1H), 3.84 (s, 1H), 3.77 (ddd, $J = 13.4$, 11.3, 5.0 Hz, 1H), 3.68 (s, 3H), 3.62 (ddd, $J = 13.5$, 11.1, 5.5 Hz, 1H), 3.09–3.01 (m, 1H), 2.77–2.67 (m, 2H), 2.45 (dd, $J = 12.7$, 7.6 Hz, 1H), 2.31 (td, $J = 12.3$, 11.3, 5.4 Hz, 1H), 2.07–1.92 (m, 5H), 1.66–1.59 (m, 3H), 1.58–1.51 (m, 2H), 1.19 (d, $J = 6.5$ Hz, 3H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.1, 172.5, 170.9, 137.9, 135.0, 123.1, 110.4, 82.2, 74.7, 52.8, 51.4, 44.0, 38.2, 36.3, 35.2, 34.8, 29.1, 28.6, 25.7, 25.4, 23.0, 22.4, 16.2; MS (ESI) calcd for $\text{C}_{25}\text{H}_{37}\text{NO}_6$ 447.3 (M^+), found 448.3 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26i

Compound **26i** was prepared according to general procedure A from primary amine **1i**, ketoester **24a**, and itaconic anhydride **5**: yield 460 mg, 80%; ^1H NMR (500 MHz, CDCl_3) δ 6.78 (d, $J = 7.9$ Hz, 1H), 6.76–6.71 (m, 2H), 5.42 (d, $J = 1.5$ Hz, 1H), 3.88 (q, $J = 6.4$ Hz, 2H), 3.86–3.80 (m, 7H), 3.80–3.72 (m, 1H), 3.62 (s, 3H), 3.07–3.00 (m, 1H), 2.90–2.81 (m, 2H), 2.79–2.72 (m, 1H), 2.69 (dd, $J = 16.9$, 4.9 Hz, 1H), 2.44 (dd, $J = 12.7$, 7.6 Hz, 1H), 1.63 (dd, $J = 12.6$, 10.5 Hz, 1H), 1.15 (d, $J = 6.5$ Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.9, 172.5, 170.4, 149.0, 147.6, 138.3, 131.7, 120.6, 111.9, 111.4, 110.3, 82.1, 74.5, 55.9, 55.9, 52.7, 51.4, 47.2, 37.6, 36.4, 34.6, 32.8, 28.5, 25.5, 16.1; MS (ESI) calcd for $\text{C}_{27}\text{H}_{37}\text{NO}_8$ 503.3 (M^+), found 486.4 ($\text{M} - \text{OH}$) $^+$, 504.4 ($\text{M} + \text{H}$) $^+$, 526.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26j

Compound **26j** was prepared according to general procedure A from primary amine **1j**, ketoester **24a**, and itaconic anhydride **5**: yield 395 mg, 72%; ^1H NMR (500 MHz, CDCl_3) δ 8.04–7.98 (m, 1H), 7.89–7.83 (m, 1H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.56–7.51 (m, 1H), 7.48 (ddd, $J = 8.0$, 6.7, 1.2 Hz, 1H), 7.43 (dd, $J = 8.2$, 7.1 Hz, 1H), 7.36 (dd, $J = 7.2$, 1.3 Hz, 1H), 5.50 (d, $J = 1.4$ Hz, 1H), 5.46 (d, $J = 16.0$ Hz, 1H), 5.26 (d, $J = 16.0$ Hz, 1H), 3.82 (q, $J = 6.4$ Hz, 1H), 3.72 (d, $J = 1.5$ Hz, 1H), 3.28 (s, 3H), 3.21–3.13 (m, 2H), 2.85–2.78 (m, 1H), 2.49 (dd, $J = 12.6$, 7.2 Hz, 1H), 1.92 (dd, $J = 12.7$, 10.8 Hz, 1H), 1.18 (d, $J = 6.4$ Hz, 3H), 0.77 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.7, 172.7, 170.4, 138.1, 133.8, 131.5, 131.0, 128.8, 127.8, 126.3, 125.7, 125.4, 123.2, 111.8, 82.0, 74.5, 52.4, 51.4, 47.0, 37.0, 36.5, 34.6, 28.4, 25.5, 16.1; MS (ESI) calcd for $\text{C}_{28}\text{H}_{33}\text{NO}_6$ 479.2 (M^+), found 480.4 ($\text{M} + \text{H}$) $^+$, 502.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26k

Compound **26k** was prepared according to general procedure A from primary amine **1k**, ketoester **24a**, and itaconic anhydride **5**: yield 468 mg, 82%; ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, $J = 2.0$ Hz, 1H), 7.24–7.14 (m, 2H), 5.26 (d, $J = 1.5$ Hz, 1H), 5.23 (d, $J = 16.8$ Hz, 1H), 4.48 (d, $J = 16.8$ Hz, 1H), 3.83 (q, $J = 6.4$ Hz, 1H), 3.71 (d, $J = 1.5$ Hz, 1H), 3.68 (s, 3H), 3.22 (dd, $J = 17.7$, 5.2 Hz, 1H), 3.01 (ddt, $J = 11.9$, 7.3, 4.6 Hz, 1H), 2.69 (dd, $J = 17.7$, 4.2 Hz, 1H), 2.43 (dd, $J = 12.6$, 7.2 Hz, 1H), 1.91 (t, $J = 12.1$ Hz, 1H), 1.20 (d, $J = 6.4$ Hz,

3H), 0.75 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.1, 172.7, 170.4, 138.4, 133.3, 133.0, 132.8, 129.2, 129.1, 127.2, 111.2, 82.0, 74.6, 52.9, 51.4, 47.4, 36.3, 36.2, 34.7, 28.1, 25.5, 16.1; MS (ESI) calcd for $\text{C}_{24}\text{H}_{29}\text{Cl}_2\text{NO}_6$ 497.1 (M^+), found 480.3 ($\text{M} - \text{OH}$) $^+$, 498.3 ($\text{M} + \text{H}$) $^+$, 520.3 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26l

Compound **26l** was prepared according to general procedure A from primary amine **1d**, ketoester **24b**, and itaconic anhydride **5**: yield 357 mg, 76%; ^1H NMR (500 MHz, CDCl_3) δ 5.37 (d, $J = 1.7$ Hz, 1H), 4.06 (dd, $J = 7.5, 1.6$ Hz, 1H), 3.97 (q, $J = 6.5$ Hz, 1H), 3.77 (ddd, $J = 13.6, 10.2, 6.1$ Hz, 1H), 3.67 (s, 3H), 3.50–3.40 (m, 1H), 3.00 (ddt, $J = 11.1, 7.2, 5.7$ Hz, 1H), 2.75 (dd, $J = 16.8, 5.7$ Hz, 1H), 2.69 (dd, $J = 16.9, 6.1$ Hz, 1H), 2.39 (dd, $J = 12.7, 7.2$ Hz, 1H), 2.02–1.92 (m, 1H), 1.78–1.34 (m, 12H), 1.33–1.21 (m, 12H), 1.19 (d, $J = 6.5$ Hz, 3H), 0.86 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.3, 172.6, 170.5, 136.5, 111.1, 78.2, 74.6, 52.8, 51.3, 44.7, 44.0, 37.8, 36.3, 31.9, 29.4, 29.3, 29.1, 28.6, 28.4, 27.2, 26.7, 25.9, 25.8, 22.7, 16.5, 14.2; MS (ESI) calcd for $\text{C}_{26}\text{H}_{41}\text{NO}_6$ 463.3 (M^+), found 446.4 ($\text{M} - \text{OH}$) $^+$, 464.4 ($\text{M} + \text{H}$) $^+$, 486.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26m

Compound **26m** was prepared according to general procedure A from primary amine **1e**, ketoester **24b**, and itaconic anhydride **5**: yield 368 mg, 68%; ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.28 (m, 2H), 7.26–7.20 (m, 3H), 5.35 (d, $J = 1.6$ Hz, 1H), 5.15 (d, $J = 15.5$ Hz, 1H), 4.63 (d, $J = 15.5$ Hz, 1H), 4.00–3.93 (m, 2H), 3.59 (s, 3H), 3.10–3.03 (m, 1H), 2.90 (dd, $J = 16.9, 5.3$ Hz, 1H), 2.81 (dd, $J = 17.0, 5.7$ Hz, 1H), 2.43 (dd, $J = 12.7, 6.9$ Hz, 1H), 1.92–1.85 (m, 1H), 1.81 (dd, $J = 12.7, 11.6$ Hz, 1H), 1.69–1.60 (m, 1H), 1.55–1.37 (m, 5H), 1.32–1.23 (m, 1H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.18–1.11 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 172.7, 170.9, 137.1, 136.7, 128.7, 127.3, 127.1, 112.2, 77.9, 74.5, 52.9, 51.3, 48.6, 44.5, 37.4, 36.4, 29.2, 28.6, 28.2, 25.9, 25.8, 16.6.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26n

Compound **26n** was prepared according to general procedure A from primary amine **1f**, ketoester **24b**, and itaconic anhydride **5**: yield 353 mg, 68%; ^1H NMR (500 MHz, CDCl_3) δ 6.77–6.66 (m, 3H), 5.93 (s, 2H), 5.39 (d, $J = 1.6$ Hz, 1H), 4.97 (d, $J = 15.3$ Hz, 1H), 4.61 (d, $J = 15.4$ Hz, 1H), 3.99 (dd, $J = 7.3, 1.6$ Hz, 1H), 3.96 (q, $J = 6.8$ Hz, 1H), 3.61 (s, 3H), 3.09–3.01 (m, 1H), 2.88 (dd, $J = 17.0, 5.3$ Hz, 1H), 2.79 (dd, $J = 16.9, 5.8$ Hz, 1H), 2.41 (dd, $J = 12.6, 6.9$ Hz, 1H), 1.96–1.87 (m, 1H), 1.79 (dd, $J = 12.7, 11.6$ Hz, 1H), 1.72–1.62 (m, 1H), 1.61–1.41 (m, 5H), 1.34–1.25 (m, 1H), 1.20 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 172.7, 171.0, 148.0, 146.8, 136.7, 131.0, 120.5, 112.2, 108.3, 107.9, 101.1, 78.0, 74.5, 52.9, 51.3, 48.3, 44.5, 37.4, 36.4, 29.2, 28.6, 28.3, 25.9, 25.8, 16.6; MS (ESI) calcd for $\text{C}_{26}\text{H}_{31}\text{NO}_8$ 485.2 (M^+), found 486.2 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26o

Compound **26o** was prepared according to general procedure A from primary amine **1g**, ketoester **24b**, and itaconic anhydride **5**: yield 283 mg, 60%; ^1H NMR (500 MHz, CDCl_3) δ 7.29 (dd, $J = 1.7, 0.9$ Hz, 1H), 6.28 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.21 (d, $J = 3.2$ Hz, 1H), 5.56 (d, $J = 1.6$ Hz, 1H), 4.98 (d, $J = 15.6$ Hz, 1H), 4.58 (d, $J = 15.7$ Hz, 1H), 4.03 (d, $J = 7.3$ Hz, 1H), 3.93 (q, $J = 6.5$ Hz, 1H), 3.59 (s, 2H), 3.03–2.95 (m, 1H), 2.80 (dd, $J = 17.0, 6.2$ Hz, 1H), 2.73 (dd, $J = 17.1, 4.9$ Hz, 1H), 2.39 (dd, $J = 12.6, 7.1$ Hz, 1H), 1.99–1.90 (m, 1H), 1.69 (dd, $J = 12.7, 11.1$ Hz, 3H), 1.58–1.41 (m, 4H), 1.38–1.20 (m, 2H), 1.16 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.9, 172.6, 170.3, 150.3, 141.6, 136.7, 111.8, 110.6, 108.5, 78.0, 74.4, 52.8, 51.2, 44.4, 41.5, 37.2, 36.3, 28.8, 28.5, 28.1, 25.8, 25.8, 16.4; MS

(ESI) calcd for $C_{23}H_{29}NO_7$ 431.2 (M^+), found 414.3 ($M - OH$)⁺, 432.3 ($M + H$)⁺, 454.3 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26p

Compound **26p** was prepared according to general procedure A from primary amine **1i**, ketoester **24b** and itaconic anhydride **5**: yield 457 mg, 73%; ¹H NMR (500 MHz, CDCl₃) δ 6.78 (d, *J* = 7.9 Hz, 1H), 6.76–6.72 (m, 2H), 5.35 (d, *J* = 1.6 Hz, 1H), 4.05 (d, *J* = 7.4 Hz, 1H), 3.98 (q, *J* = 6.5 Hz, 1H), 3.84 (d, *J* = 10.2 Hz, 7H), 3.73 (ddd, *J* = 13.5, 10.4, 5.0 Hz, 1H), 3.64 (s, 3H), 2.98 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.88–2.81 (m, 1H), 2.80–2.70 (m, 2H), 2.40 (dd, *J* = 12.7, 7.1 Hz, 1H), 1.97–1.89 (m, 1H), 1.76–1.63 (m, 2H), 1.63–1.47 (m, 3H), 1.41–1.34 (m, 1H), 1.32–1.23 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 176.6, 172.6, 170.3, 149.0, 147.6, 136.7, 131.6, 120.6, 111.9, 111.3, 111.0, 78.0, 74.5, 55.9, 55.9, 52.8, 51.3, 46.3, 44.7, 37.5, 36.4, 32.6, 28.9, 28.6, 28.4, 25.8, 25.7, 16.5; MS (ESI) calcd for $C_{28}H_{37}NO_8$ 515.3 (M^+), found 516.4 ($M + H$)⁺, 538.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26q

Compound **26q** was prepared according to general procedure A from primary amine **1j**, ketoester **24b**, and itaconic anhydride **5**: yield 379 mg, 63%; ¹H NMR (500 MHz, CDCl₃) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.57–7.49 (m, 1H), 7.48 (ddd, *J* = 8.0, 6.7, 1.2 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.1 Hz, 1H), 5.40 (d, *J* = 16.1 Hz, 1H), 5.36 (d, *J* = 1.4 Hz, 1H), 5.33 (d, *J* = 16.0 Hz, 1H), 4.01 (dd, *J* = 6.6, 1.5 Hz, 1H), 3.91 (q, *J* = 6.5 Hz, 1H), 3.29 (s, 3H), 3.12 (dt, *J* = 17.6, 4.0 Hz, 1H), 3.07 (d, *J* = 5.9 Hz, 1H), 2.85 (dd, *J* = 16.9, 4.3 Hz, 1H), 2.46 (dd, *J* = 12.6, 6.8 Hz, 1H), 1.98–1.86 (m, 2H), 1.67–1.58 (m, 1H), 1.53–1.38 (m, 5H), 1.31–1.22 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 177.4, 172.7, 170.4, 136.8, 133.8, 131.3, 131.1, 128.8, 127.8, 126.3, 125.7, 125.4, 125.2, 123.1, 112.6, 77.7, 74.5, 52.5, 51.3, 46.4, 44.3, 37.0, 36.5, 28.8, 28.2, 28.1, 25.9, 25.8, 16.4; MS (ESI) calcd for $C_{29}H_{33}NO_6$ 491.2 (M^+), found 492.4 ($M + H$)⁺, 514.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26r

Compound **26r** was prepared according to general procedure A from primary amine **1k**, ketoester **24b**, and itaconic anhydride **5**: yield 360 mg, 56%; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.33 (m, 1H), 7.16 (s, 2H), 5.16 (d, *J* = 16.8 Hz, 1H), 5.13 (d, *J* = 1.7 Hz, 1H), 4.60 (d, *J* = 16.7 Hz, 1H), 4.00–3.92 (m, 2H), 3.68 (s, 3H), 3.11 (dd, *J* = 17.5, 5.5 Hz, 1H), 3.01–2.91 (m, 1H), 2.72 (dd, *J* = 17.5, 4.4 Hz, 1H), 2.38 (dd, *J* = 12.7, 6.7 Hz, 1H), 1.93 (t, *J* = 12.3 Hz, 1H), 1.92–1.82 (m, 1H), 1.66–1.56 (m, 1H), 1.55–1.46 (m, 2H), 1.46–1.38 (m, 4H), 1.32–1.23 (m, 2H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.19–1.13 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 177.6, 172.8, 170.3, 136.6, 133.3, 132.9, 132.8, 129.1, 129.1, 129.0, 127.3, 111.5, 77.6, 77.4, 74.4, 53.0, 51.3, 46.4, 44.4, 36.3, 36.2, 28.6, 28.3, 28.1, 25.9, 25.8, 16.6; MS (ESI) calcd for $C_{25}H_{29}Cl_2NO_6$ 509.1 (M^+), found 492.3 ($M - OH$)⁺, 510.3 ($M + H$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26s

Compound **26s** was prepared according to general procedure A from primary amine **1d**, ketoester **24c**, and itaconic anhydride **5**: yield 461 mg, 73%; ¹H NMR (500 MHz, CDCl₃) δ 5.30 (d, *J* = 1.8 Hz, 1H), 3.93 (dd, *J* = 6.1, 1.7 Hz, 1H), 3.80–3.70 (m, 1H), 3.64 (s, 2H), 3.50–3.40 (m, 1H), 3.31 (d, *J* = 7.9 Hz, 1H), 3.02–2.92 (m, 1H), 2.73 (dd, *J* = 16.9, 5.2 Hz, 1H), 2.67 (dd, *J* = 16.9, 6.4 Hz, 1H), 2.48 (dd, *J* = 12.8, 6.8 Hz, 1H), 1.87–1.76 (m, 2H), 1.57–1.48 (m, 1H), 1.47–1.39 (m, 1H), 1.27–1.17 (m, 9H), 1.15 (t, *J* = 7.1 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.82 (t, *J* = 6.9 Hz, 3H), 0.52–0.45 (m, 2H), 0.44–0.36 (m, 1H), 0.18–0.11 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 176.6, 172.8, 170.3, 136.2, 108.9, 81.6, 78.8, 52.7, 51.6, 43.5, 37.4, 36.3, 33.2, 31.8, 29.9, 29.3, 29.2, 27.1, 26.5,

22.6, 18.3, 18.0, 14.1, 11.8, 3.4, 2.4; MS (ESI) calcd for $C_{26}H_{41}NO_6$ 463.3 (M^+), found 446.5 ($M - OH$)⁺, 464.5 ($M + H$)⁺, 486.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26t

Compound **26t** was prepared according to general procedure A from primary amine **1e**, ketoester **24c**, and itaconic anhydride **5**: yield 343 mg, 68%; ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.23 (m, 2H), 7.23–7.16 (m, 3H), 5.28 (d, *J* = 1.8 Hz, 1H), 5.15 (d, *J* = 15.7 Hz, 1H), 4.66 (d, *J* = 15.7 Hz, 1H), 3.83 (dd, *J* = 6.4, 1.8 Hz, 1H), 3.59 (s, 3H), 3.30 (d, *J* = 8.1 Hz, 1H), 3.09–2.99 (m, 1H), 2.92 (dd, *J* = 17.1, 6.1 Hz, 1H), 2.81 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.50 (dd, *J* = 12.9, 6.4 Hz, 1H), 2.06 (t, *J* = 12.4 Hz, 1H), 1.75–1.65 (m, 1H), 0.88–0.83 (m, 1H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H), 0.57–0.50 (m, 1H), 0.50–0.44 (m, 1H), 0.44–0.37 (m, 1H), 0.22–0.13 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 177.2, 172.9, 170.6, 137.0, 136.0, 128.5, 127.1, 126.8, 109.9, 81.6, 78.6, 52.8, 51.6, 47.9, 36.8, 36.4, 33.2, 29.9, 18.1, 11.9, 3.9, 2.5; MS (ESI) calcd for $C_{25}H_{31}NO_6$ 441.2 (M^+), found 424.4 ($M - OH$)⁺, 442.4 ($M + H$)⁺, 464.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26u

Compound **26u** was prepared according to general procedure A from primary amine **1f**, ketoester **24c**, and itaconic anhydride **5**: yield 361 mg, 66%; ¹H NMR (500 MHz, CDCl₃) δ 6.74–6.64 (m, 3H), 5.89 (s, 2H), 5.32 (d, *J* = 1.9 Hz, 1H), 4.94 (d, *J* = 15.5 Hz, 1H), 4.67 (d, *J* = 15.5 Hz, 1H), 3.85 (dd, *J* = 6.4, 1.9 Hz, 1H), 3.61 (s, 3H), 3.31 (d, *J* = 8.2 Hz, 1H), 3.07–2.97 (m, 1H), 2.89 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.79 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.48 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.02 (t, *J* = 12.4 Hz, 1H), 1.81–1.68 (m, 1H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.57–0.44 (m, 2H), 0.44–0.37 (m, 1H), 0.22–0.13 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 177.0, 172.9, 170.7, 147.9, 146.6, 136.0, 130.9, 120.2, 109.8, 108.2, 107.6, 101.0, 81.6, 78.7, 52.8, 51.6, 47.5, 36.8, 36.4, 33.2, 29.9, 18.3, 18.2, 11.9, 3.9, 2.5; MS (ESI) calcd for $C_{26}H_{31}NO_8$ 485.2 (M^+), found 486.4 ($M + H$)⁺, 508.3 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26v

Compound **26v** was prepared according to general procedure A from primary amine **1g**, ketoester **24c**, and itaconic anhydride **5**: yield 373 mg, 63%; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.28 (m, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 5.52 (d, *J* = 1.7 Hz, 1H), 5.00 (d, *J* = 15.8 Hz, 1H), 4.64 (d, *J* = 15.8 Hz, 1H), 3.91 (dd, *J* = 6.0, 1.8 Hz, 1H), 3.61 (s, 3H), 3.30 (d, *J* = 8.0 Hz, 1H), 3.02 (dq, *J* = 11.9, 6.0 Hz, 1H), 2.77 (d, *J* = 5.7 Hz, 2H), 2.51 (dd, *J* = 12.9, 6.8 Hz, 1H), 1.90 (t, *J* = 12.2 Hz, 1H), 1.80 (h, *J* = 6.7 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 4H), 0.84 (d, *J* = 6.6 Hz, 4H), 0.50 (dq, *J* = 7.6, 4.7 Hz, 2H), 0.44–0.37 (m, 1H), 0.19–0.12 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 176.8, 172.8, 170.4, 150.4, 141.6, 136.2, 110.6, 109.9, 108.3, 81.5, 78.8, 52.8, 51.6, 41.0, 37.0, 36.4, 33.2, 29.8, 18.1, 18.1, 11.7, 3.5, 2.5; MS (ESI) calcd for $C_{23}H_{29}NO_7$ 431.2 (M^+), found 432.4 ($M + H$)⁺, 454.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26w

Compound **26w** was prepared according to general procedure A from primary amine **1h**, ketoester **24c**, and itaconic anhydride **5**: yield 520 mg, 77%; ¹H NMR (500 MHz, CDCl₃) δ 5.39 (s, 1H), 5.33 (s, 1H), 3.91 (dd, *J* = 6.0, 1.8 Hz, 1H), 3.74 (ddd, *J* = 13.0, 10.6, 5.4 Hz, 1H), 3.64 (s, 3H), 3.30 (d, *J* = 8.0 Hz, 1H), 2.97–2.87 (m, 1H), 2.74 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.64 (dd, *J* = 16.8, 6.3 Hz, 1H), 2.44 (dd, *J* = 12.9, 6.6 Hz, 1H), 2.23–2.13 (m, 1H), 2.06–1.97 (m, 1H), 1.95–1.88 (m, 4H), 1.87–1.78 (m, 2H), 1.59–1.52 (m, 2H), 1.52–1.45 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 4H), 0.88 (d, *J* = 6.7 Hz, 4H), 0.51–0.46 (m, 2H), 0.44–0.37 (m, 1H), 0.20–0.12 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 176.5, 172.8, 170.2, 135.9, 134.9, 122.9, 108.5, 81.6, 78.7, 52.7, 51.6, 42.7, 37.2, 36.3, 34.7, 33.3, 29.9, 28.4, 25.2,

22.9, 22.3, 18.4, 18.1, 11.9, 3.7, 2.4; MS (ESI) calcd for $C_{26}H_{37}NO_6$ 459.3 (M^+), found 460.4 ($M + H$)⁺, 482.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26x

Compound **26x** was prepared according to general procedure A from primary amine **1j**, ketoester **24c**, and itaconic anhydride **5**: yield 436 mg, 61%; ¹H NMR (500 MHz, CDCl₃) δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.45–7.38 (m, 1H), 7.32 (d, *J* = 7.0 Hz, 1H), 5.42 (d, *J* = 16.1 Hz, 1H), 5.36 (d, *J* = 16.0 Hz, 1H), 5.31 (d, *J* = 1.8 Hz, 1H), 3.86 (dd, *J* = 5.9, 1.8 Hz, 1H), 3.32 (s, 3H), 3.29 (d, *J* = 7.8 Hz, 1H), 3.23–3.13 (m, 1H), 3.04 (dd, *J* = 17.1, 5.9 Hz, 1H), 2.87 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.60 (dd, *J* = 12.9, 6.8 Hz, 1H), 2.12 (t, *J* = 12.3 Hz, 1H), 1.77–1.66 (m, 1H), 0.95–0.86 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H), 0.55–0.45 (m, 2H), 0.47–0.38 (m, 1H), 0.18–0.11 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 177.3, 172.8, 170.6, 136.3, 133.8, 131.3, 131.1, 128.9, 127.8, 126.4, 125.8, 125.4, 125.0, 123.0, 110.9, 81.5, 78.8, 52.5, 51.7, 45.8, 37.0, 36.6, 33.1, 29.9, 18.2, 17.8, 11.7, 3.3, 2.5; MS (ESI) calcd for $C_{29}H_{33}NO_6$ 491.2 (M^+), found 492.4 ($M + H$)⁺, 514.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26y

Compound **26y** was prepared according to general procedure A from primary amine **1k**, ketoester **24c**, and itaconic anhydride **5**: yield 450 mg, 60%; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, *J* = 2.0 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.14–5.08 (m, 2H), 4.75 (d, *J* = 16.8 Hz, 1H), 3.82 (dd, *J* = 6.6, 1.9 Hz, 1H), 3.70 (s, 3H), 3.34 (d, *J* = 8.1 Hz, 1H), 3.04 (dd, *J* = 17.1, 5.6 Hz, 1H), 3.01–2.93 (m, 1H), 2.77 (dd, *J* = 17.1, 4.2 Hz, 1H), 2.47 (dd, *J* = 12.9, 6.0 Hz, 1H), 2.16 (t, *J* = 12.5 Hz, 1H), 1.79–1.69 (m, 1H), 0.96–0.87 (m, 1H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.61–0.49 (m, 2H), 0.49–0.41 (m, 1H), 0.27–0.18 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 177.6, 173.0, 170.5, 135.8, 133.4, 133.0, 132.7, 129.2, 128.8, 127.4, 109.5, 81.5, 78.5, 53.0, 51.7, 45.5, 36.3, 36.1, 33.3, 29.7, 18.4, 18.3, 12.0, 4.1, 2.5; MS (ESI) calcd for $C_{25}H_{29}Cl_2NO_6$ 509.1 (M^+), found 492.3 ($M - OH$)⁺, 510.3 ($M + H$)⁺, 532.3 ($M + Na$)⁺.

Tetrahydropyran-fused Piperidinone-Containing Carboxylic Acid 26z

Compound **26z** was prepared according to general procedure A from primary amine **1d**, ketoester **24d**, and itaconic anhydride **5**: yield 351 mg, 65%; ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.23 (m, 5H), 5.34 (d, *J* = 1.8 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.49 (td, *J* = 6.0, 1.7 Hz, 1H), 4.08 (q, *J* = 6.6 Hz, 1H), 3.85–3.75 (m, 1H), 3.67 (s, 3H), 3.54 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.47–3.37 (m, 2H), 3.01–2.91 (m, 1H), 2.76 (dd, *J* = 16.8, 5.5 Hz, 1H), 2.64 (dd, *J* = 16.8, 6.2 Hz, 1H), 2.36 (dd, *J* = 12.7, 6.8 Hz, 1H), 1.64 (t, *J* = 12.1 Hz, 1H), 1.60–1.51 (m, 1H), 1.49–1.39 (m, 1H), 1.28–1.18 (m, 13H), 0.85 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 176.3, 172.4, 170.2, 137.9, 136.4, 128.5, 127.8, 127.8, 107.6, 74.4, 73.5, 73.3, 72.6, 52.9, 51.1, 43.6, 37.5, 36.2, 31.8, 29.3, 29.3, 29.2, 27.1, 26.5, 22.7, 16.8, 14.2; MS (ESI) calcd for $C_{29}H_{41}NO_7$ 515.3 (M^+), found 516.4 ($M + H$)⁺, 538.4 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26aa

Compound **26aa** was prepared according to general procedure A from primary amine **1e**, ketoester **24d**, and itaconic anhydride **5**: yield 257 mg, 63%; ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.27 (m, 5H), 7.25–7.19 (m, 5H), 5.39 (s, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.82 (d, *J* = 15.6 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.41 (td, *J* = 6.1, 1.8 Hz, 1H), 4.10 (q, *J* = 6.4 Hz, 1H), 3.58 (s, 3H), 3.48 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.29 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.09–2.99 (m, 1H), 2.85–2.78 (m, 2H), 2.40 (dd, *J* = 12.8, 6.5 Hz, 1H), 1.80 (t,

$J = 12.0$ Hz, 1H), 1.20 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.4, 172.6, 170.6, 138.0, 136.8, 136.4, 128.6, 128.5, 128.5, 127.8, 127.8, 127.2, 127.1, 126.6, 108.5, 74.3, 73.5, 73.0, 72.7, 52.9, 51.3, 47.8, 37.0, 36.4, 29.4, 17.0; MS (ESI) calcd for $\text{C}_{28}\text{H}_{31}\text{NO}_7$ 493.2 (M^+), found 494.3 ($\text{M} + \text{H}$) $^+$, 516.3 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26ab

Compound **26ab** was prepared according to general procedure A from primary amine **1f**, ketoester **24d**, and itaconic anhydride **5**: yield 393 mg, 68%; ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.23 (m, 5H), 6.75–6.65 (m, 3H), 5.90 (d, $J = 1.4$ Hz, 1H), 5.90 (d, $J = 1.4$ Hz, 1H), 5.37 (d, $J = 1.9$ Hz, 1H), 4.86 (d, $J = 15.6$ Hz, 1H), 4.74 (d, $J = 15.5$ Hz, 1H), 4.51 (q, $J = 12.1$ Hz, 2H), 4.42 (td, $J = 6.1, 1.8$ Hz, 1H), 4.10 (q, $J = 6.4$ Hz, 1H), 3.62 (s, 3H), 3.49 (dd, $J = 9.8, 6.4$ Hz, 1H), 3.32 (dd, $J = 9.8, 5.7$ Hz, 1H), 3.05–2.95 (m, 1H), 2.81 (dd, $J = 5.7, 2.1$ Hz, 2H), 2.37 (dd, $J = 12.7, 6.5$ Hz, 1H), 1.80 (t, $J = 12.3$ Hz, 1H), 1.20 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.3, 172.5, 170.6, 147.9, 146.7, 138.0, 136.4, 130.6, 128.5, 128.5, 127.8, 127.8, 127.8, 120.4, 108.5, 108.3, 107.8, 101.1, 74.3, 73.5, 73.1, 72.7, 53.0, 51.2, 47.5, 37.0, 36.4, 29.3, 17.0; MS (ESI) calcd for $\text{C}_{29}\text{H}_{31}\text{NO}_9$ 537.2 (M^+), found 538.3 ($\text{M} + \text{H}$) $^+$, 560.2 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26ac

Compound **26ac** was prepared according to general procedure A from primary amine **1h**, ketoester **24d**, and itaconic anhydride **5**: yield 555 mg, 70%; ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.31 (m, 4H), 7.31–7.27 (m, 1H), 5.45–5.41 (m, 1H), 5.40 (d, $J = 1.9$ Hz, 1H), 4.61 (d, $J = 12.2$ Hz, 1H), 4.56 (d, $J = 12.2$ Hz, 1H), 4.50 (td, $J = 6.1, 1.7$ Hz, 1H), 4.11 (q, $J = 6.5$ Hz, 1H), 3.82 (ddd, $J = 13.5, 10.5, 5.2$ Hz, 1H), 3.70 (s, 3H), 3.67–3.59 (m, 1H), 3.57 (dd, $J = 9.7, 6.4$ Hz, 1H), 3.43 (dd, $J = 9.7, 5.8$ Hz, 1H), 2.99–2.89 (m, 1H), 2.78 (dd, $J = 16.7, 6.1$ Hz, 1H), 2.63 (dd, $J = 16.7, 5.8$ Hz, 1H), 2.36 (dd, $J = 12.7, 6.7$ Hz, 1H), 2.28–2.17 (m, 1H), 2.10–2.00 (m, 1H), 1.99–1.92 (m, 4H), 1.64 (t, $J = 11.5$ Hz, 1H), 1.61–1.56 (m, 2H), 1.56–1.48 (m, 2H), 1.22 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 172.4, 170.3, 138.0, 136.2, 134.9, 128.6, 127.9, 127.9, 123.0, 107.6, 74.4, 73.5, 73.2, 72.7, 53.0, 51.2, 42.9, 37.6, 36.3, 34.7, 29.5, 28.6, 25.3, 23.0, 22.4, 17.0; MS (ESI) calcd for $\text{C}_{29}\text{H}_{37}\text{NO}_7$ 511.3 (M^+), found 512.3 ($\text{M} + \text{H}$) $^+$, 534.3 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26ad

Compound **26ad** was prepared according to general procedure A from primary amine **1i**, ketoester **24d**, and itaconic anhydride **5**: yield 339 mg, 53%; ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.28 (m, 4H), 7.28–7.23 (m, 1H), 6.77–6.68 (m, 3H), 5.37 (d, $J = 1.9$ Hz, 1H), 4.59 (d, $J = 12.0$ Hz, 1H), 4.54 (d, $J = 12.1$ Hz, 1H), 4.50 (td, $J = 6.2, 1.9$ Hz, 1H), 4.09 (q, $J = 6.5$ Hz, 1H), 3.97–3.87 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78–3.68 (m, 1H), 3.65 (s, 3H), 3.53 (dd, $J = 9.7, 6.4$ Hz, 1H), 3.38 (dd, $J = 9.7, 5.9$ Hz, 1H), 3.01–2.91 (m, 1H), 2.88–2.77 (m, 1H), 2.77–2.70 (m, 2H), 2.70–2.64 (m, 1H), 2.37 (dd, $J = 12.7, 6.7$ Hz, 1H), 1.68 (t, $J = 12.1$ Hz, 1H), 1.21 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.1, 172.4, 170.1, 149.0, 147.6, 137.9, 136.5, 131.4, 128.5, 127.8, 127.8, 120.6, 112.0, 111.3, 107.7, 74.4, 73.5, 73.2, 72.6, 55.9, 55.9, 52.9, 51.2, 45.7, 37.2, 36.3, 32.4, 29.2, 16.8; MS (ESI) calcd for $\text{C}_{31}\text{H}_{37}\text{NO}_9$ 567.2 (M^+), found 568.4 ($\text{M} + \text{H}$) $^+$, 590.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid 26ae

Compound **26ae** was prepared according to general procedure A from primary amine **1j**, ketoester **24d**, and itaconic anhydride **5**: yield 277 mg, 46%; ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, $J = 8.4$ Hz, 1H), 7.86 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.75 (d, $J = 8.3$ Hz, 1H), 7.56–7.45 (m, 2H), 7.42–7.35 (m, 1H), 7.27 (d, $J = 7.1$ Hz, 1H), 7.25–7.20 (m, 3H), 7.17–7.11 (m, 2H), 5.45 (d, $J = 16.2$ Hz, 1H), 5.34 (d, $J = 1.8$ Hz, 1H), 5.28 (d, $J = 16.1$ Hz, 1H), 4.45 (d, $J =$

12.0 Hz, 1H), 4.40 (d, J = 12.2 Hz, 1H), 4.37 (td, J = 5.5, 3.0 Hz, 1H), 4.04 (q, J = 6.4, 5.8 Hz, 1H), 3.45 (dd, J = 9.8, 6.4 Hz, 1H), 3.29 (s, 3H), 3.28–3.24 (m, 1H), 3.14–3.04 (m, 1H), 2.92 (dd, J = 17.0, 5.7 Hz, 1H), 2.84 (dd, J = 17.0, 5.2 Hz, 1H), 2.42 (dd, J = 12.8, 6.6 Hz, 1H), 1.91 (t, J = 12.3 Hz, 1H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.8, 172.4, 170.3, 137.8, 136.4, 133.8, 131.0, 130.9, 128.8, 128.3, 127.8, 127.7, 127.7, 126.3, 125.7, 125.4, 124.8, 123.0, 108.8, 74.3, 73.3, 73.1, 72.5, 52.5, 51.2, 45.7, 36.7, 36.4, 29.1, 16.8; MS (ESI) calcd for $\text{C}_{32}\text{H}_{33}\text{NO}_7$ 543.2 (M^+), found 544.4 ($\text{M} + \text{H}$) $^+$, 566.4 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Carboxylic Acid **26af**

Compound **26af** was prepared according to general procedure A from primary amine **1k**, ketoester **24d**, and itaconic anhydride **5**: yield 392 mg, 62%; ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, J = 2.1 Hz, 1H), 7.34–7.26 (m, 3H), 7.23–7.20 (m, 2H), 7.16 (dd, J = 8.4, 2.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 5.15 (d, J = 1.9 Hz, 1H), 5.08 (d, J = 16.9 Hz, 1H), 4.74 (d, J = 16.9 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 4.38 (td, J = 5.9, 1.9 Hz, 1H), 4.13 (q, J = 6.4 Hz, 1H), 3.72 (s, 3H), 3.47 (dd, J = 9.7, 6.4 Hz, 1H), 3.30 (dd, J = 9.7, 5.6 Hz, 1H), 3.03–2.89 (m, 2H), 2.76 (dd, J = 16.8, 4.0 Hz, 1H), 2.36 (dd, J = 12.7, 5.8 Hz, 1H), 1.94 (t, J = 12.3 Hz, 1H), 1.24 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.9, 172.7, 170.3, 137.9, 136.2, 133.4, 133.1, 132.4, 129.3, 128.7, 128.5, 127.8, 127.8, 127.8, 127.4, 108.0, 74.3, 73.5, 72.9, 72.6, 53.1, 51.2, 45.9, 36.4, 36.2, 29.2, 17.1; MS (ESI) calcd for $\text{C}_{28}\text{H}_{29}\text{Cl}_2\text{NO}_7$ 561.1 (M^+), found 562.4 ($\text{M} + \text{H}$) $^+$, 584.3 ($\text{M} + \text{Na}$) $^+$.

Enynamide **28a** (2-((3*RS*,4*aSR*)-4*a*-(Ethoxycarbonyl)-2-oxo-1-(3-phenylprop-2-yn-1-yl)-1,2,3,4,4*a*,5,6,7-octahydroquinolin-3-yl)acetic Acid)

Compound **28a** was prepared according to general procedure A from primary amine **27a**, ketoester **2a**, and itaconic anhydride **5** (3.16 g, 80%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.35 (2H, m), 7.22–7.19 (3H, m), 5.59 (1H, dd, J = 4.5, 2.5 Hz), 5.02 (1H, d, J = 17.0 Hz), 4.27 (1H, d, J = 17.5 Hz), 4.09 (2H, 7.0 Hz), 2.83 (1H, dd, J = 16.0, 6.0 Hz), 2.71 (1H, m), 2.48 (1H, dd, J = 16.5, 5.5 Hz), 2.29–2.10 (3H, m), 1.65 (1H, br), 1.59 (1H, t, J = 13.0 Hz), 1.47 (1H, dt, J = 14.0, 2.5 Hz), 1.37 (1H, m), 1.15 (3H, t, J = 6.5 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.6, 173.7, 169.9, 136.0, 131.8, 128.3, 128.2, 122.8, 109.3, 84.3, 83.4, 61.6, 46.4, 37.0, 36.7, 36.2, 35.2, 34.6, 24.3, 18.5, 14.1; HRMS-ESI m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5$ 396.1811, found 396.1818.

Enynamide **28b**

Compound **28b** was prepared according to general procedure A from primary amine **27b**, ketoester **2a** and itaconic anhydride **5** (3.19 g, quant): ^1H NMR (CDCl_3 , 500 MHz) δ 5.47 (1H, dd, J = 5.0, 3.0 Hz), 4.80 (1H, dd, J = 17.0, 2.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 4.05 (1H, dd, J = 17.5, 2.5 Hz), 2.81 (1H, dd, J = 16.5, 6.0 Hz), 2.69 (1H, m), 2.53 (1H, dd, J = 6.0 Hz), 2.33 (1H, dd, J = 13.0, 6.0 Hz), 2.27–2.09 (5H, m), 1.65 (1H, br), 1.59 (1H, t, J = 13.0 Hz), 1.47 (1H, dt, J = 14.0, 2.5 Hz), 1.39–1.29 (1H, m), 1.17 (3H, t, J = 7.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 176.1, 173.7, 169.6, 136.0, 108.8, 78.8, 71.7, 61.6, 46.4, 36.7, 36.6, 36.1, 34.6, 34.2, 24.2, 18.5, 14.1; HRMS-ESI m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_5$ 320.1498, found 320.1497.

Enynamide **28c**

Compound **28c** was prepared according to general procedure A from primary amine **27c**, ketoester **2a** and itaconic anhydride **5** (2.40 g, 72%): ^1H NMR ($\text{DMSO}-d_6$, 500 MHz) δ 5.40 (1H, dd, J = 4.5, 3.0 Hz), 4.66 (1H, dd, J = 17.0, 2.5 Hz), 4.11 (2H, q, J = 7.0 Hz), 4.03 (1H, dd, J = 17.0, 2.0 Hz), 2.65 (1H, dd, J = 16.5, 4.5 Hz), 2.50 (1H, m), 2.42 (1H, dd, J = 16.5, 7.0 Hz), 2.23–2.12 (4H, m), 1.17 (3H, s), 1.70 (1H, s, J = 13.0 Hz), 1.65 (1H, m), 1.51 (1H,

dt, $J = 13.5, 2.0$ Hz), 1.26 (1H, m), 1.15 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ 173.4, 172.7, 168.3, 136.2, 106.5, 78.4, 75.2, 60.8, 45.9, 36.0, 35.8, 35.7, 33.9, 33.5, 23.7, 18.2, 13.9, 3.1; HRMS-EI m/z $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5$ 333.1576, found 333.1569

Enynamide 33a (2-((3*RS*,4*aSR*)-4*a*-(Ethoxycarbonyl)-2-oxo-1-(prop-2-yn-1-yl)-2,3,4,4*a*,5,6-hexahydro-1*H*-cyclopenta[*b*]-pyridin-3-yl)acetic Acid)

Compound **33a** was prepared according to general procedure A from primary amine **27b**, ketoester **2d**, and itaconic anhydride **5** (1.71 g, 56%): ^1H NMR (CDCl_3 , 500 MHz) δ 5.28 (1H, s), 4.60 (1H, dd, $J = 17.5, 2.5$ Hz), 4.36 (1H, dd, $J = 17.5, 2.5$ Hz), 4.18 (2H, m), 2.91–2.81 (2H, m), 2.70 (1H, dd, $J = 6.0, 16.5$ Hz), 2.59–2.50 (2H, m), 2.43–2.36 (2H, m), 2.21 (1H, t, $J = 2.0$ Hz), 1.91 (1H, m), 1.73 (1H, t, $J = 12.5$ Hz), 1.25 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 176.7, 173.7, 169.3, 140.3, 107.9, 77.9, 71.5, 61.5, 54.2, 36.8, 36.4, 36.3, 35.6, 33.4, 29.0, 14.1; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_5$ 306.1341, found 306.1339.

Enynamide 33b

Compound **33b** was prepared according to general procedure A from primary amine **27a**, ketoester **2b** and itaconic anhydride **5** (1.62 g, 41%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.35 (2H, m), 7.22 (3H, m), 5.78 (1H, t, $J = 7.0$ Hz), 4.86 (1H, d, $J = 17.5$ Hz), 4.45 (1H, d, $J = 17.5$ Hz), 3.70 (3H, s), 2.83 (1H, dd, $J = 16.5, 6.5$ Hz), 2.71 (1H, m), 2.38 (1H, dd, $J = 16.5, 6.0$ Hz), 2.23 (1H, m), 2.10–1.98 (4H, m), 1.76–1.61 (5H, m), 1.42–1.34 (1H, m); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.9, 173.9, 170.7, 139.8, 131.8, 128.3, 128.2, 122.7, 116.3, 84.4, 83.4, 52.6, 51.6, 39.5, 36.5, 36.0, 35.7, 35.5, 26.3, 25.3, 24.9; HRMS-EI m/z $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5$ 395.1733, found 395.1734.

Enynamide 33c

Compound **33c** was prepared according to general procedure A from primary amine **27a**, ketoester **2e**, and itaconic anhydride **5** (1.85 g, 50%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.34 (2H, m), 7.21 (3H, m), 4.95 (1H, d, $J = 2.5$ Hz), 4.87 (1H, d, $J = 17.0$ Hz), 4.62 (1H, d, $J = 2.5$ Hz), 4.53 (1H, d, $J = 17.0$ Hz), 4.07 (2H, q, $J = 7.5$ Hz), 2.98 (1H, m), 2.81 (1H, dd, $J = 17.0, 5.5$ Hz), 2.53 (1H, dd, $J = 17.0, 6.5$ Hz), 2.29 (1H, dd, $J = 13.5, 6.0$ Hz), 1.61 (1H, t, $J = 13.0$ Hz), 1.43 (3H, s), 1.14 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 176.3, 173.6, 170.3, 146.0, 131.8, 128.3, 128.1, 122.7, 96.2, 83.9, 83.4, 61.6, 46.5, 36.5, 36.4, 36.1, 35.4, 24.8, 14.0; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_5$ 370.1654, found 370.1652.

Enynamide 33d

Compound **33d** was prepared according to general procedure A from primary amine **27b**, ketoester **2f**, and itaconic anhydride **5** (1.47 g, 50%): ^1H NMR (CDCl_3 , 500 MHz) δ 5.01 (1H, d, $J = 2.0$ Hz), 4.76 (1H, d, $J = 2.0$ Hz), 4.62 (1H, dd, $J = 17.5, 1.5$ Hz), 4.35 (1H, dd, $J = 17.5, 1.5$ Hz), 4.20 (2H, m), 4.14 (2H, q, $J = 7.0$ Hz), 3.14 (1H, m), 2.90 (1H, dd, $J = 17.0, 5.5$ Hz), 2.61 (1H, dd, $J = 17.0, 6.5$ Hz), 2.41–2.25 (5H, m), 2.18–2.12 (1H, m), 1.62 (1H, t, $J = 13.0$ Hz), 1.27 (3H, dt, $J = 7.0, 1.0$ Hz), 1.26 (3H, dt, $J = 7.0, 1.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.7, 172.6, 170.4, 144.4, 97.6, 78.2, 72.0, 72.0, 61.8, 60.7, 49.7, 35.8, 35.7, 34.7, 33.0, 32.9, 29.5, 14.2, 14.0; HRMS-EI m/z $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_7$ 379.1631, found 379.1623.

Enynamide 35a (2-((3*SR*,3*aRS*)-3*a*-(Ethoxycarbonyl)-2-oxo-1-(prop-2-yn-1-yl)-2,3,3*a*,4,5,6-hexahydro-1*H*-indol-3-yl)acetic Acid)

Compound **35a** was prepared according to general procedure A from primary amine **27b**, ketoester **2a**, and maleic anhydride **4** (2.53 g, 83%): ^1H NMR (CDCl_3 , 500 MHz) δ 5.19 (1H, t, $J = 7.5$ Hz), 4.23 (2H, dq, $J = 17.5, 2.5$ Hz), 4.13–4.03 (2H, m), 2.96 (1H, t, $J = 7.0$

(Hz), 2.80 (1H, dd, $J = 17.5, 6.5$ Hz), 2.54 (1H, m), 2.29 (1H, dd, $J = 17.5, 8.0$ Hz), 2.22–2.07 (3H, m), 1.81 (1H, m), 1.55–1.42 (2H, m), 1.17 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.9, 172.5, 171.1, 137.3, 102.4, 76.8, 71.7, 61.5, 52.0, 47.3, 31.2, 30.3, 29.6, 22.7, 19.5, 14.0; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_5$ 306.1341, found 306.1339.

Enynamide 35b

Compound **35b** was prepared according to general procedure A from primary amine **27a**, ketoester **2a**, and maleic anhydride **4** (1.95 g, 51%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.33 (2H, m), 7.25–7.19 (3H, m), 5.28 (1H, t, $J = 3.5$ Hz), 4.45 (2H, q, $J = 11.5$ Hz), 4.05 (2H, m), 2.98 (1H, t, $J = 7.0$ Hz), 2.79 (1H, dd, $J = 17.0, 6.5$ Hz), 2.53 (1H, m), 2.31 (1H, dd, $J = 17.5, 7.5$ Hz), 2.22–2.08 (2H, m), 1.80 (1H, m), 1.56–1.42 (2H, m), 1.13 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.5, 172.8, 171.1, 137.4, 131.8, 128.5, 128.2, 122.5, 102.7, 83.4, 82.3, 61.5, 52.0, 47.4, 31.3, 30.6, 30.2, 22.8, 19.5, 14.0; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_5$ 382.1654, found 382.1647.

Enynamide 35c

Compound **35c** was prepared according to general procedure A from primary amine **27b**, ketoester **2b**, and maleic anhydride **4** (2.63 g, 86%): ^1H NMR (CDCl_3 , 500 MHz) δ 5.40 (1H, dd, $J = 9.0, 4.5$ Hz), 4.40 (1H, d, $J = 17.0$ Hz), 4.20 (1H, d, $J = 17.0$ Hz), 3.71 (3H, s), 3.09 (1H, t, $J = 6.5$ Hz), 2.80 (1H, dd, $J = 17.0, 6.5$ Hz), 2.50 (1H, d, $J = 11.5$ Hz), 2.40–2.27 (2H, m), 2.21 (1H, s), 2.01–1.94 (2H, m), 1.78–1.60 (3H, m), 1.38 (1H, q, $J = 12.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.9, 172.4, 171.1, 141.7, 106.2, 76.8, 71.6, 55.4, 52.3, 48.1, 35.6, 31.6, 30.0, 27.5, 27.2, 26.1; HRMS-EI m/z $[\text{M} - \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_5$ 304.1185, found 304.1179.

Enynamide 35d

Compound **35d** was prepared according to general procedure A from primary amine **27a**, ketoester **2b**, and maleic anhydride **4** (1.95 g, 51%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.34 (2H, m), 7.23 (3H, m), 5.42 (1H, dd, $J = 8.5, 4.0$ Hz), 4.55 (1H, d, $J = 17.5$ Hz), 4.32 (1H, d, $J = 17.5$ Hz), 3.61 (3H, s), 3.02 (1H, t, $J = 7.0$ Hz), 2.66 (1H, dd, $J = 17.0, 7.5$ Hz), 2.41 (1H, d, $J = 15.0$ Hz), 2.34 (1H, dd, $J = 17.0, 6.5$ Hz), 2.24 (1H, m), 1.94–1.84 (2H, m), 1.67 (2H, m), 1.55 (1H, t, $J = 13.5$ Hz), 1.29 (1H, m); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.1, 172.8, 171.0, 141.6, 131.7, 128.4, 128.3, 122.4, 106.7, 83.4, 82.1, 55.4, 52.3, 48.2, 35.5, 31.6, 30.9, 27.4, 27.2, 26.1; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_5$ 382.1654, found 382.1653.

General Procedure B: Au-Catalyzed Enynamide Cycloisomerization

A solution of enyne-containing piperidinones (**28** or **33**, 5.00 mmol) or pyrrolidinones (**35**, 5.00 mmol) in CH_3CN (8.2 mL) was treated with JohnPhos-Au-NCMe-SbF₆ (**31**, 0.15 mmol, 3 mol %). The resulting solution was stirred overnight at room temperature under inert nitrogen atmosphere. Removal of solvent under reduced pressure afforded crude dienamides (**29**, **34**, or **36**), which were used for subsequent hydrogenation without purification.

Cycloisomerization product 29a (2-((2*RS*,10*aSR*)-10*a*-(Ethoxycarbonyl) - 3 - oxo-7-phenyl - 1, 2, 3, 5, 8, 9, 10, 10*a*-octahydropyrido[3,2,1-*ij*]quinolin-2-yl)acetic Acid)

Compound **29a** was prepared according to general procedure B from enynamide **28a** (quantative yield by ^1H NMR using mesitylene as an internal standard): ^1H NMR (CDCl_3 , 500 MHz) δ 7.34 (3H, m), 7.20 (2H, m), 5.66 (1H, dd, $J = 6.0, 2.5$ Hz), 5.22 (1H, dd, $J = 17.5, 6.0$ Hz), 4.24 (2H, m), 3.88 (1H, d, $J = 17.5$ Hz), 2.98 (1H, dd, $J = 16.5, 6.5$ Hz), 2.60 (1H, dd, $J = 16.5, 6.0$ Hz), 2.34 (1H, d, $J = 13.0$ Hz), 2.15 (1H, m), 1.89 (1H, dd, $J = 18.0, 4.5$ Hz), 1.70 (2H, m), 1.55–1.42 (2H, m), 1.30 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 125

MHz) δ 175.6, 173.9, 169.3, 139.0, 138.7, 131.3, 128.4, 128.0, 127.3, 118.9, 116.8, 61.8, 46.5, 41.3, 37.3, 36.5, 36.1, 34.3, 27.0, 19.0, 14.2; HRMS-ESI m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO_5$ 395.1733, found 395.1724.

Cycloisomerization Product 29b

Compound **29b** was prepared according to general procedure B from enynamide **28b** (quantative yield by 1H NMR using mesitylene as an internal standard): 1H NMR ($CDCl_3$, 500 MHz) δ 5.70 (2H, m), 5.03 (1H, dd, J = 18.0, 5.5 Hz), 4.20 (2H, m), 3.85 (1H, d, J = 18.0 Hz), 2.89 (1H, dd, J = 16.0, 6.0 Hz), 2.77 (1H, m), 2.54 (1H, dd, J = 16.5, 6.5 Hz), 2.39 (1H, dd, J = 13.0, 6.0 Hz), 2.30 (1H, m), 2.19 (2H, m), 1.70 (1H, m), 1.61 (1H, t, J = 13.0 Hz), 1.47 (2H, m), 1.26 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 173.9, 169.1, 129.8, 125.5, 120.4, 115.1, 61.7, 45.7, 42.2, 37.0, 36.0, 35.9, 34.4, 27.3, 18.8, 14.2; HRMS-ESI m/z $[M + H]^+$ calcd for $C_{17}H_{22}NO_5$ 320.1498, found 320.1506.

Cycloisomerization Product 29c

Compound **29c** was prepared according to general procedure B from enynamide **28c** (90% yield by 1H NMR using mesitylene as an internal standard): 1H NMR ($CDCl_3$, 500 MHz) δ 5.49 (1H, m), 5.01 (1H, dd, J = 17.0, 6.0 Hz), 4.21 (2H, m), 3.70 (1H, dq, J = 17.5, 2.5 Hz), 2.89 (1H, dd, J = 16.5, 7.0 Hz), 2.78 (1H, m), 2.50 (1H, dd, J = 16.0, 5.0 Hz), 2.43 (1H, dd, J = 6.0, 13.0 Hz), 2.33–2.29 (2H, m), 2.23–2.16 (1H, m), 1.86–1.77 (1H, m), 1.77 (3H, m), 1.60 (1H, t, J = 12.5 Hz), 1.50–1.41 (2H, m), 1.27 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 173.9, 169.4, 129.0, 117.8, 61.5, 46.0, 40.9, 37.7, 37.0, 35.6, 34.6, 29.7, 27.9, 21.6, 18.9, 14.2; HRMS-EI m/z $[M]^+$ calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1569.

Cycloisomerization Product 34a (2-((2*RS*,9*aSR*)-9*a*-(Ethoxy-carbonyl)-3-oxo-2,3,5,8,9,9*a*-hexahydro-1*H*-cyclopenta[*ij*]-quinolizin-2-yl)acetic Acid)

Compound **34a** (98% yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 5.94 (1H, dt, J = 2.0, 10.0 Hz), 5.60 (1H, m), 4.85 (1H, dd, J = 19.5, 4.5), 4.16–4.28 (3H, m), 2.89 (2H, m), 2.60 (3H, m), 2.37 (2H, m), 1.89 (1H, dt, J = 18.5, 9.0 Hz), 1.67 (1H, t, J = 12.5 Hz), 1.28 (3H, t, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.3, 173.7, 168.5, 134.6, 121.2, 120.5, 116.0, 61.6, 53.0, 44.1, 36.6, 36.4, 36.3, 35.0, 29.8, 14.2; HRMS-ESI m/z $[M + H]^+$ calcd for $C_{16}H_{20}NO_5$ 306.1341, found 306.1343.

Cycloisomerization Product 34b

Compound **34b** (75% yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.29 (3H, m), 7.18 (2H, m), 5.71 (1H, dd, J = 5.5, 4.5 Hz), 4.86 (1H, dd, J = 15.5, 5.5 Hz), 4.00 (1H, dd, J = 15.5, 4.0 Hz), 3.87 (3H, s), 2.97–2.86 (2H, m), 2.45 (1H, dd, J = 16.0, 6.0 Hz), 2.20 (3H, m), 2.02 (1H, m), 1.86–1.66 (5H, m), 1.35 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 174.0, 171.1, 142.2, 139.1, 136.3, 128.2, 128.1, 127.3, 126.0, 117.2, 52.7, 51.9, 40.2, 40.0, 36.6, 35.7, 35.5, 29.5, 26.6, 25.6; HRMS-EI m/z $[M]^+$ calcd for $C_{23}H_{25}NO_5$ 395.1733, found 395.1736.

Cycloisomerization Product 34c

Compound **34c** (90% yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.29 (5H, m), 5.88 (1H, m), 5.74 (1H, d, J = 1.5 Hz), 5.05 (1H, dd, J = 18.0, 5.5 Hz), 4.31–4.20 (3H, m), 3.09 (1H, m), 2.95 (1H, dd, J = 16.5, 6.0 Hz), 2.60 (1H, dd, J = 17.0, 6.5 Hz), 2.43 (1H, dd, J = 13.5, 6.0 Hz), 1.73 (1H, t, J = 13.0 Hz), 1.58 (3H, s), 1.29 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.3, 173.6, 169.7, 139.4, 138.5, 134.2, 128.6,

127.7, 125.5, 115.8, 106.7, 61.8, 45.9, 42.8, 36.6, 36.2, 36.2, 24.0, 14.1; HRMS-ESI m/z $[M]^+$ calcd for $C_{21}H_{23}NO_5$ 369.1576, found 369.1585.

Cycloisomerization Product 34d

Compound **34d** (quantitative yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 5.95 (1H, m), 5.68 (1H, m), 5.48 (1H, d, $J = 5.5$ Hz), 4.55 (1H, dd, $J = 17.5$, 4.0 Hz), 4.40 (1H, d, $J = 17.5$ Hz), 4.22 (2H, m), 4.15 (2H, q, $J = 7.0$ Hz), 3.13 (1H, m), 2.90 (1H, dd, $J = 17.0$, 6.5 Hz), 2.54 (1H, dd, $J = 16.5$, 6.0 Hz), 2.39 (2H, t, $J = 8.0$ Hz), 2.31 (2H, m), 2.16–2.10 (1H, m), 1.58 (1H, t, $J = 13.0$ Hz), 1.30–1.25 (6H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 172.7, 172.6, 170.5, 136.8, 122.2, 120.5, 107.3, 61.9, 60.8, 48.9, 41.6, 36.1, 35.8, 32.9, 32.8, 29.6, 14.2, 14.0; HRMS-EI m/z $[M - H]^+$ calcd for $C_{19}H_{24}NO_7$ 378.1553, found 378.1558.

Cycloisomerization Product 36a (2-((1*SR*,9*aRS*)-9*a*-(Ethoxy-carbonyl)-2-oxo-2,4,7,8,9,9*a*-hexahydro-1*H*-pyrrolo[3,2,1-*ij*]-quinolin-1-yl)acetic Acid)

Compound **36a** (quantitative yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 5.81 (1H, dq, $J = 10.0$, 1.5 Hz), 5.51 (1H, ddd, $J = 9.5$, 5.0, 2.0 Hz), 4.72 (1H, dd, $J = 17.5$, 5.0 Hz), 4.2 (2H, m), 4.1 (1H, d, $J = 17.5$), 3.01–2.93 (2H, m), 2.65 (1H, dt, $J = 12.5$, 3.0 Hz), 2.37 (1H, dd, $J = 17.0$, 8.0 Hz), 2.22 (1H, dd, $J = 17.5$, 6.5 Hz), 2.07 (1H, m), 1.92 (1H, m), 1.57 (1H, m), 1.46 (1H, td, $J = 13.0$, 2.5 Hz), 1.28 (3H, t, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 173.0, 170.7, 133.5, 124.8, 117.9, 109.0, 61.5, 51.8, 47.3, 41.3, 31.3, 30.2, 24.3, 19.8, 13.9; HRMS-ESI m/z $[M - H]^+$ calcd for $C_{16}H_{18}NO_5$ 304.1185, found 304.1186.

Cycloisomerization Product 36b

Compound **36b** (quantitative yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (3H, m), 7.21 (2H, m), 5.41 (1H, dd, $J = 5.0$, 2.5 Hz), 4.83 (1H, dd, $J = 17.5$, 5.5 Hz), 4.84 (3H, m), 3.08 (1H, t, $J = 7.5$ Hz), 2.96 (1H, dd, $J = 17.0$, 6.5 Hz), 2.65 (1H, d, $J = 10.5$ Hz), 2.43 (1H, dd, $J = 17.5$, 8.0 Hz), 2.09 (1H, dd, $J = 16.5$, 6.0 Hz), 1.89 (2H, m), 1.51 (2H, m), 1.32 (3H, 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 173.1, 170.8, 138.9, 138.2, 134.1, 128.3, 128.0, 127.3, 116.8, 109.8, 61.8, 52.5, 47.4, 41.2, 31.5, 29.9, 23.9, 20.2, 14.1; HRMS-ESI m/z $[M - H]^+$ calcd for $C_{22}H_{22}NO_5$ 380.1498, found 380.1494.

Cycloisomerization Product 36c

Compound **36c** (72% yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 5.76 (1H, dt, $J = 10.0$, 2.0 Hz), 5.46 (1H, m), 4.56 (1H, dd, $J = 18.0$, 4.5 Hz), 4.22 (1H, dq, $J = 18.0$, 2.5 Hz), 3.76 (3H, s), 3.05 (1H, t, $J = 6.5$ Hz), 2.80 (1H, dd, $J = 17.0$, 7.0 Hz), 2.52 (1H, m), 2.40 (1H, dd, $J = 17.5$, 7.0 Hz), 2.21–2.10 (2H, m), 1.94–1.91 (1H, m), 1.79–1.74 (1H, m), 1.60–1.70 (2H, m), 1.36–1.45 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.3, 173.1, 170.9, 136.2, 128.2, 116.7, 113.1, 55.8, 52.5, 47.5, 42.0, 35.7, 31.9, 31.9, 27.3, 26.9; HRMS-EI m/z $[M - H]^+$ calcd for $C_{16}H_{18}NO_5$ 304.1185, found 304.1187.

Cycloisomerization Product 36d

Compound **36d** (77% yield determined by 1H NMR using mesitylene as an internal standard) was prepared according to the general procedure B: 1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (3H, m), 7.18 (2H, m), 5.40 (1H, dd, $J = 5.0$, 2.5 Hz), 4.71 (1H, dd, $J = 17.5$, 5.5 Hz), 4.24 (1H, d, $J = 17.0$ Hz), 3.79 (3H, s), 3.16 (1H, t, $J = 6.5$ Hz), 2.84 (1H, dd, $J = 17.0$, 7.0

Hz), 2.56 (1H, m), 2.43 (1H, 17.0, 7.0 Hz), 2.18 (1H, dd, J = 15.5, 6.5 Hz), 1.94–1.66 (5H, m), 1.40 (1H, m); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.5, 173.1, 171.0, 140.3, 139.8, 138.4, 128.2, 127.3, 115.6, 114.2, 56.3, 52.5, 47.8, 41.5, 35.3, 31.8, 28.2, 27.3, 26.7; HRMS-ESI m/z $[\text{M} - \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_5$ 380.1498, found 380.1505.

General Procedure C: Diene Hydrogenations

To a round-bottom flask was added 10% Pd/C (0.30 mmol, 0.10 equiv) and the corresponding crude acid solution (prepared from general procedure B, 3.00 mmol, 1.00 equiv) in EtOH (30.0 mL). The mixture was stirred overnight at room temperature under H_2 atmosphere (1 atm). The mixture was filtered over Celite and concentrated under reduced pressure. The product was isolated after purification by Combi-flash column chromatography (DCM: (EtOAc + 1% HCOOH) = 95:5 to 30:70).

Tricyclic Carboxylic Acid 37 (2-((2*RS*,10*aSR*)-10*a*-(ethoxycarbonyl)-3-oxo-1,2,3,5,6,7,8,9,10,10*a*-decahydropyrido[3,2,1-*ij*]-quinolin-2-yl)acetic Acid)

Compound **37** (771 mg, 80%) was prepared according to the general procedure C: ^1H NMR (CDCl_3 , 500 MHz) δ 4.62 (1H, dt, J = 13.0, 3.5 Hz), 4.24–4.13 (2H, m), 2.97 (1H, dt, J = 12.0, 2.5 Hz), 2.82 (1H, dd, J = 16.0, 7.5), 2.36 (1H, dd, J = 13.0, 5.5 Hz), 2.27 (1H, m), 2.20–2.13 (1H, m), 2.09 (2H, m), 2.01–1.90 (2H, m), 1.80–1.71 (2H, m), 1.61 (1H, t, J = 13.0 Hz), 1.54–1.39 (2H, m), 1.26 (3H, t, J = 7.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.1, 173.9, 169.4, 132.1, 130.1, 118.0, 116.2, 61.7, 46.1, 41.4, 37.5, 36.5, 35.9, 34.1, 25.2, 18.8, 18.1, 14.2; HRMS-ESI m/z $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_5$ 321.1576, found 321.1584.

Tricyclic Carboxylic Acid 38

Compound **38** (645 mg, 70%) was prepared according to the general procedure C: ^1H NMR (CD_3CN , 500 MHz) δ 4.18–4.08 (2H, m), 3.85 (1H, m), 3.56 (1H, br), 3.31–3.26 (1H, m), 2.73–2.65 (2H, m), 2.57–2.52 (1H, m), 2.48–2.41 (2H, m), 2.29–2.22 (2H, m), 2.09 (2H, m), 1.97 (1H, quintet, J = 2.5 Hz), 1.88–1.78 (3H, m), 1.69 (1H, t, J = 12.5 Hz), 1.21 (3H, t, J = 7.0 Hz); ^{13}C NMR (CD_3CN , 125 MHz) δ 174.8, 174.0, 168.6, 133.5, 118.8, 61.3, 53.4, 40.1, 36.4, 35.6, 35.3, 35.2, 32.1, 22.4, 21.3, 13.4; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ 308.1498, found 308.1503.

Tricyclic Carboxylic Acid 39

compound **39** (882 mg, 77%) was prepared according to the general procedure C: ^1H NMR (CDCl_3 , 500 MHz) δ 5.19 (1H, t, J = 4.0 Hz), 4.23–4.13 (4H, m), 3.87 (1H, m), 3.65 (1H, m), 3.08 (1H, m), 2.85 (1H, dd, J = 16.0, 7.0 Hz), 2.56 (1H, dd, J = 16.0, 5.0 Hz), 2.38–2.24 (4H, m), 2.19 (2H, m), 2.14–2.08 (1H, m), 1.81 (2H, m), 1.59 (1H, t, J = 13.0 Hz), 1.28 (6H, m); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.3, 173.0, 172.7, 170.1, 135.8, 109.1, 61.7, 60.8, 48.6, 41.1, 36.8, 35.5, 33.2, 32.3, 29.4, 22.6, 21.5, 14.2, 14.1; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_7$ 382.1866, found 382.1864.

Tricyclic Carboxylic Acid 40

Compound **40** (600 mg, 65%) was prepared according to the general procedure C: ^1H NMR (CDCl_3 , 500 MHz) δ 4.22–4.11 (2H, m), 3.90 (1H, m), 3.31 (1H, dt, J = 10.5, 3.5 Hz), 2.96 (1H, t, J = 7.5 Hz), 2.84 (1H, dd, J = 17.0, 7.5 Hz), 2.61 (1H, t, J = 12.0, 2.5 Hz), 2.42 (1H, dd, J = 16.5, 6.5 Hz), 2.21–1.87 (6H, m), 1.71–1.80 (1H, m), 1.61–1.44 (2H, m), 1.26 (3H, t, J = 7.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 174.6, 172.5, 171.3, 131.4, 111.2, 61.4, 51.4, 48.0, 38.9, 32.0, 30.5, 26.8, 25.4, 20.9, 19.9, 14.1; HRMS-ESI m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ 308.1498, found 308.1507.

Tricyclic Carboxylic Acid 41

Compound **41** (645 mg, 70%) was prepared according to the general procedure C: ^1H NMR (CDCl_3 , 500 MHz) δ 3.79 (1H, m), 3.73 (3H, s), 3.30 (1H, m), 2.98 (1H, dd, $J = 9.0, 5.5$ Hz), 2.68 (1H, dd, $J = 16.5, 9.0$ Hz), 2.50–2.42 (2H, m), 2.20–2.08 (3H, m), 2.00 (1H, m), 1.93–1.88 (2H, m), 1.78–1.69 (3H, m), 1.59 (1H, dt, $J = 13.0, 3.5$ Hz), 1.38 (1H, m); ^{13}C NMR (CDCl_3 , 125 MHz) δ 173.6, 172.4, 171.2, 134.2, 116.8, 55.4, 52.3, 48.2, 38.8, 35.5, 33.2, 32.4, 29.2, 27.3, 26.7, 20.5; HRMS-ESI m/z $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_5$ 307.1420, found 307.1422.

General Procedure D: Automated Library Synthesis

A solution of a carboxylic acid (**7**, **8**, **26**, or **36**, 1.25 mmol) in 25 mL of CDCl_3 was treated with CDI (**16**, 212.8 mg, 1.31 mmol, 1.05 equiv). The reaction was stirred at room temperature until NMR indicated complete conversion of the carboxylic acid to the corresponding acylimidazole, which typically took 2–4 h. Using a Perkin-Elmer Multiprobe II liquid handler, the resulting solution was distributed into 24 1-dram glass vials, delivering 0.95 mL of the above solution into each vial. For reactions involving the coupling with secondary amines, the glass vials were precharged with imidazole hydrochloride (9.9 mg, 0.095 mmol, 2 equiv). For each vial, a solution of one of the 24 amines **11** (2 M, 2.7 equiv) in 0.065 mL of chloroform was added. The resulting reaction mixtures were capped and agitated on an orbital shaker at room temperature for 48 h. The vials were then returned to the deck of the liquid handler and treated with 1.9 mL of 1.2 N HCl solution followed by eight cycles of rapid aspiration and dispensing to ensure thorough mixing. After complete phase separation, which can be accelerated by centrifugation for 10 min at 500 g (versus ~2 h without centrifugation), the bottom layers were retrieved by the liquid handler and transferred to 24 empty barcoded, preweighed one-dram vials. The vials containing the product solutions were placed in a GeneVac centrifugal evaporator to remove solvent, and were weighed using an automated Mettler Toledo weigher to determine the yield of each final product. Each of the tips used for the above material transfer was then washed in another vial containing 0.5 mL of MeOH in order to dissolve the residual material present on the tip, which provided sufficient amount of material for purity analysis of each final compound using LC–MS equipped with an autosampler.

Pyrrolidinone-Containing Amide 12a ((3*SR*,3*aRS*)-Ethyl 1-(4-Methoxybenzyl)-2-oxo-3-(2-oxo-2-(prop-2-yn-1-ylamino)-ethyl)-2,3,3a,4,5,6-hexahydro-1*H*-indole-3*a*-carboxylate)

Compound **12a** (18.85 mg, 93%) was prepared according to the general procedure D: 93% yield; ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.17 (m, 2H), 6.87–6.78 (m, 2H), 4.99 (t, $J = 3.7$ Hz, 1H), 4.77 (d, $J = 15.2$ Hz, 1H), 4.44 (d, $J = 15.1$ Hz, 1H), 4.12–3.95 (m, 3H), 3.78 (s, 3H), 2.99 (dd, $J = 7.8, 5.6$ Hz, 1H), 2.65 (dd, $J = 15.1, 7.8$ Hz, 1H), 2.56 (dt, $J = 12.4, 3.1$ Hz, 1H), 2.26–2.17 (m, 2H), 2.17–2.00 (m, 2H), 1.85–1.74 (m, 1H), 1.57–1.36 (m, 2H), 1.12 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 171.4, 170.6, 159.1, 138.2, 129.2, 128.1, 113.9, 102.0, 79.7, 71.5, 61.4, 55.4, 52.3, 48.5, 43.8, 33.4, 30.3, 29.4, 22.9, 19.5, 14.2; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$ 425.2076, found 425.2066.

Pyrrolidinone-Containing Amide 12b

Compound **12b** (18.02 mg, 85%) was prepared according to the general procedure D: ^1H NMR (500 MHz, CDCl_3) δ 7.20–7.11 (m, 2H), 6.87–6.81 (m, 2H), 6.76 (t, $J = 5.7$ Hz, 1H), 5.08 (dd, $J = 8.6, 4.4$ Hz, 1H), 4.73 (d, $J = 15.4$ Hz, 1H), 4.52 (d, $J = 15.4$ Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.33–3.17 (m, 2H), 3.07 (dd, $J = 8.2, 4.8$ Hz, 1H), 2.56 (dd, $J = 15.0, 8.2$ Hz, 1H), 2.50–2.43 (m, 1H), 2.20–2.07 (m, 2H), 1.92–1.82 (m, 1H), 1.82–1.70 (m, 1H), 1.70–1.61 (m, 1H), 1.61–1.45 (m, 3H), 1.41–1.21 (m, 3H), 0.91 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 171.5, 170.6, 158.9, 142.5, 128.5, 127.9, 113.9, 105.8,

55.7, 55.4, 52.1, 49.3, 43.8, 39.6, 35.2, 33.9, 31.7, 27.4, 27.2, 26.2, 20.2, 13.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{35}N_2O_5$ 443.2546, found 443.2538.

Pyrrolidinone-Containing Amide 12c

Compound **12c** (19.75 mg, 88%) was prepared according to the general procedure D: 1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3H), 7.19–7.14 (m, 2H), 7.08 (t, J = 6.2 Hz, 1H), 5.15 (dd, J = 8.7, 4.4 Hz, 1H), 3.76 (ddd, J = 13.6, 10.0, 6.3 Hz, 1H), 3.70 (s, 3H), 3.54 (ddd, J = 13.7, 9.9, 5.5 Hz, 1H), 3.48–3.29 (m, 4H), 3.27–3.15 (m, 2H), 3.14–3.08 (m, 1H), 2.85 (ddd, J = 13.5, 10.1, 5.6 Hz, 1H), 2.77 (ddd, J = 13.5, 10.0, 6.3 Hz, 1H), 2.53 (dd, J = 15.4, 7.3 Hz, 1H), 2.50–2.44 (m, 1H), 2.41 (t, J = 8.1 Hz, 2H), 2.30–2.18 (m, 1H), 2.12 (dd, J = 15.4, 6.2 Hz, 1H), 2.09–2.00 (m, 2H), 1.99–1.84 (m, 2H), 1.82–1.63 (m, 5H), 1.56 (ddd, J = 13.7, 12.2, 3.4 Hz, 1H), 1.38–1.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 173.7, 171.5, 170.5, 142.9, 137.2, 132.4, 130.3, 128.7, 103.9, 55.5, 52.3, 48.7, 47.5, 41.5, 39.8, 36.2, 35.5, 33.7, 31.7, 31.1, 27.5, 27.4, 26.6, 26.2, 18.1. MS (ESI) calcd for $C_{28}H_{36}ClN_3O_5$ 529.23 (M^+), found 530.18 ($M + H$) $^+$.

Pyrrolidinone-Containing Amide 12d

Compound **12d** (22.01 mg, 72%) was prepared according to the general procedure D: 1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.20 (m, 6H), 5.71 (ddt, J = 17.3, 10.3, 5.1 Hz, 1H), 5.22–5.15 (m, 3H), 4.86 (t, J = 9.2 Hz, 1H), 4.48 (dd, J = 14.8, 5.9 Hz, 1H), 4.41 (dd, J = 14.8, 5.5 Hz, 2H), 4.19–4.10 (m, 3H), 3.04 (dd, J = 8.4, 4.6 Hz, 1H), 2.71 (dd, J = 15.3, 8.4 Hz, 1H), 2.61 (ddd, J = 14.4, 6.4, 2.2 Hz, 1H), 2.22 (dd, J = 15.3, 4.6 Hz, 1H), 2.07 (ddd, J = 9.1, 6.8, 3.5 Hz, 2H), 1.77–1.57 (m, 5H), 1.54–1.38 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 171.6, 170.6, 140.4, 138.4, 131.0, 128.7, 127.9, 127.4, 117.0, 104.1, 61.5, 54.7, 48.0, 43.9, 42.8, 34.7, 27.8, 26.5, 23.1, 22.6, 14.2; MS (ESI) calcd for $C_{25}H_{32}N_2O_4$ 424.24 (M^+), found 425.34 ($M + H$) $^+$.

Pyrrolidinone-Containing Amide 12e

Compound **12e** was prepared according to the general procedure D from carboxylic acid **7b** and amine **11x**: 1H NMR (500 MHz, $CDCl_3$) δ 7.33 (td, J = 7.5, 1.5 Hz, 2H), 7.29–7.18 (m, 5H), 6.89–6.82 (m, 2H), 4.98 (d, J = 3.8 Hz, 1H), 4.81 (dd, J = 15.2, 2.9 Hz, 2H), 4.47 (dd, J = 15.2, 7.9 Hz, 1H), 4.16–3.90 (m, 2H), 3.80 (s, 3H), 3.40 (dd, J = 8.6, 4.2 Hz, 1H), 3.22–3.10 (m, 1H), 3.01 (m, 1H), 2.81–2.59 (m, 2H), 2.33 (ddd, J = 17.0, 8.7, 2.4 Hz, 1H), 2.19–2.01 (m, 2H), 1.96–1.86 (m, 1H), 1.86–1.75 (m, 1H), 1.75–1.43 (m, 4H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.4, 172.1, 172.0, 168.6, 168.6, 158.9, 145.4, 145.3, 138.7, 129.2, 129.1, 128.7, 128.5, 126.9, 126.6, 113.9, 113.9, 101.2, 61.1, 61.1, 55.4, 52.5, 52.4, 47.9, 47.9, 46.3, 46.2, 43.7, 43.0, 43.0, 43.0, 43.0, 33.8, 33.7, 33.0, 33.0, 31.0, 30.2, 30.1, 22.9, 22.9, 19.8, 19.8, 14.3, 14.3. MS (ESI) calcd for $C_{32}H_{38}N_2O_5$ 530.28 (M^+), found 531.48 ($M + H$) $^+$.

Pyrrolidinone-Containing Amide 12f

Compound **12f** was prepared according to the general procedure D from carboxylic acid **7e** and amine **11u**. 1H NMR (500 MHz, $CDCl_3$) δ 7.20–7.14 (m, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.05 (dd, J = 8.9, 4.3 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 4.55 (d, J = 15.5 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 3.62–3.57 (m, 1H), 3.57–3.50 (m, 1H), 3.45–3.33 (m, 2H), 2.91 (dd, J = 16.7, 4.6 Hz, 1H), 2.64–2.56 (m, 1H), 2.31 (dd, J = 16.7, 7.3 Hz, 1H), 2.15–2.05 (m, 1H), 1.92–1.79 (m, 2H), 1.70–1.51 (m, 7H), 1.30–1.18 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 172.0, 168.2, 158.7, 143.1, 128.4, 128.3, 128.1, 113.9, 113.8, 104.9, 55.7, 55.2, 51.9, 48.5, 46.5, 43.6, 43.2, 35.8, 30.3, 27.6, 27.4, 26.3, 26.1, 25.5, 24.6; MS (ESI) calcd for $C_{26}H_{34}N_2O_5$ 454.25 (M^+), found 455.41 ($M + H$) $^+$.

Pyrrolidinone-Containing Amide 12g

Compound **12g** was prepared according to the general procedure D from carboxylic acid **7a** and amine **11d**: ^1H NMR (500 MHz, CDCl_3) δ 6.73 (t, J = 5.5 Hz, 1H), 5.81–5.69 (m, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.19 (dd, J = 10.3, 1.5 Hz, 1H), 5.02 (t, J = 3.7 Hz, 1H), 4.28 (dd, J = 15.9, 5.3 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.00–3.89 (m, 1H), 3.33–3.18 (m, 2H), 2.97 (dd, J = 7.6, 5.8 Hz, 1H), 2.63–2.52 (m, 2H), 2.27–2.06 (m, 3H), 1.89–1.79 (m, 1H), 1.69–1.58 (m, 1H), 1.57–1.36 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 171.6, 170.7, 138.3, 131.6, 117.7, 101.7, 61.4, 52.4, 48.6, 43.0, 38.4, 38.2, 33.6, 30.2, 26.0, 22.9, 22.6, 22.6, 19.6, 14.3; MS (ESI) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_4$ 376.24 (M^+), found 377.39 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12h

Compound **12h** was prepared according to the general procedure D from carboxylic acid **7a** and amine **11e**: ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.17 (m, 2H), 6.97 (dd, J = 3.4, 1.2 Hz, 1H), 6.93 (dd, J = 5.1, 3.4 Hz, 1H), 5.78–5.68 (m, 1H), 5.25 (d, J = 17.2 Hz, 1H), 5.17 (d, J = 10.3 Hz, 1H), 5.01 (t, J = 3.7 Hz, 1H), 4.67–4.53 (m, 2H), 4.26 (dd, J = 15.8, 5.3 Hz, 1H), 4.14–4.06 (m, 2H), 3.97–3.89 (m, 1H), 2.98 (dd, J = 7.6, 5.8 Hz, 1H), 2.63 (dd, J = 15.1, 7.7 Hz, 1H), 2.55 (dt, J = 12.5, 3.0 Hz, 1H), 2.24–2.15 (m, 1H), 2.15–2.05 (m, 1H), 1.87–1.78 (m, 1H), 1.58–1.39 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.9, 171.5, 170.5, 141.1, 138.2, 131.6, 126.9, 126.0, 125.1, 117.7, 101.8, 61.5, 52.4, 48.4, 43.0, 38.5, 33.5, 30.3, 22.9, 19.6, 14.2; MS(ESI) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ 402.16 (M^+), found 403.33 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12i

Compound **12i** was prepared according to the general procedure D from carboxylic acid **7h** and amine **11f**: ^1H NMR (500 MHz, CDCl_3) δ 7.15–7.08 (m, 3H), 6.90–6.77 (m, 5H), 4.80 (dd, J = 10.1, 8.2 Hz, 1H), 4.67 (d, J = 15.5 Hz, 1H), 4.59 (d, J = 15.5 Hz, 1H), 4.39 (d, J = 5.6 Hz, 2H), 4.15–4.01 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.08 (dd, J = 8.4, 4.6 Hz, 1H), 2.72 (dd, J = 15.2, 8.4 Hz, 1H), 2.58 (ddd, J = 14.6, 6.7, 2.3 Hz, 1H), 2.22 (dd, J = 15.2, 4.6 Hz, 1H), 2.05–1.91 (m, 2H), 1.77–1.49 (m, 3H), 1.39–1.23 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 171.5, 170.5, 158.9, 149.2, 148.4, 140.2, 131.1, 128.3, 127.7, 120.1, 114.0, 111.3, 111.2, 104.6, 61.5, 56.0, 56.0, 55.4, 54.6, 48.0, 43.7, 43.6, 37.5, 34.8, 27.8, 26.4, 23.1, 22.5, 14.2; MS (ESI) calcd for $\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_7$ 564.28 (M^+), found 565.4 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12j

Compound **12j** was prepared according to the general procedure D from carboxylic acid **7h** and amine **11g**: ^1H NMR (500 MHz, CDCl_3) δ 7.60 (t, J = 5.9 Hz, 1H), 7.57–7.48 (m, 3H), 7.47–7.41 (m, 1H), 7.16–7.10 (m, 2H), 6.86–6.79 (m, 2H), 4.83 (dd, J = 10.3, 8.1 Hz, 1H), 4.69 (d, J = 15.4 Hz, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.54 (dd, J = 15.2, 6.0 Hz, 1H), 4.46 (dd, J = 15.2, 5.8 Hz, 1H), 4.17–4.02 (m, 2H), 3.78 (s, 3H), 3.04 (dd, J = 8.8, 4.1 Hz, 1H), 2.77 (dd, J = 15.2, 8.8 Hz, 1H), 2.58 (ddd, J = 14.7, 6.3, 2.9 Hz, 1H), 2.25 (dd, J = 15.2, 4.1 Hz, 1H), 2.08–1.93 (m, 2H), 1.76–1.49 (m, 5H), 1.43–1.23 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.7, 171.4, 171.0, 159.0, 140.0, 139.7, 131.2 (q, $^1J_{\text{C-F}}$ = 1.3 Hz), 129.2, 128.3, 127.6, 131.0 (q, $^2J_{\text{C-F}}$ = 32.2 Hz), 124.4 (q, $^3J_{\text{C-F}}$ = 3.8 Hz), 124.2 (q, $^3J_{\text{C-F}}$ = 3.8 Hz), 124.2 (q, $^1J_{\text{C-F}}$ = 273.4 Hz), 114.0, 105.0, 61.5, 55.4, 54.8, 47.9, 43.6, 43.3, 37.1, 34.7, 27.7, 26.5, 23.1, 22.5, 14.2; MS(ESI) calcd for $\text{C}_{31}\text{H}_{35}\text{F}_3\text{N}_2\text{O}_5$ 572.25 (M^+), found 573.37 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12k

Compound **12k** was prepared according to the general procedure D from carboxylic acid **7i** and amine **11r**: ^1H NMR (500 MHz, CDCl_3) δ 7.51 (dd, J = 1.8, 0.9 Hz, 1H), 7.29–7.23 (m, 2H), 7.22–7.15 (m, 2H), 7.07 (dd, J = 3.5, 0.9 Hz, 1H), 6.51 (dd, J = 3.5, 1.8 Hz, 1H), 4.86 (dd, J = 10.7, 7.5 Hz, 1H), 4.23–4.07 (m, 2H), 3.94–3.63 (m, 7H), 3.61–3.48 (m, 2H), 3.48–3.41 (m, 1H), 3.18 (dd, J = 8.3, 4.7 Hz, 1H), 2.92–2.79 (m, 2H), 2.75–2.63 (m, 2H), 2.34 (dd, J = 16.6, 8.4 Hz, 1H), 2.15–2.07 (m, 1H), 2.05–1.94 (m, 1H), 1.81–1.72 (m, 1H), 1.72–1.50 (m, 4H), 1.50–1.39 (m, 1H), 1.40–1.30 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.9, 172.2, 169.2, 159.3, 147.7, 144.1, 141.4, 136.8, 132.5, 130.6, 128.7, 117.3, 111.6, 102.2, 61.3, 54.2, 48.7, 45.5, 42.1, 41.3, 39.5, 31.9, 31.8, 28.4, 25.9, 23.2, 23.0, 14.3; MS (ESI) calcd for $\text{C}_{32}\text{H}_{38}\text{ClN}_3\text{O}_6$ 595.24 (M^+), found 596.34 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12l

Compound **12l** was prepared according to the general procedure D from carboxylic acid **7i** and amine **11o**: ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.23 (m, 2H), 7.19–7.13 (m, 2H), 6.87 (t, J = 5.5 Hz, 1H), 6.11 (d, J = 3.1 Hz, 1H), 5.90 (dd, J = 3.1, 1.3 Hz, 1H), 4.86 (dd, J = 10.0, 8.3 Hz, 1H), 4.43 (dd, J = 15.4, 5.8 Hz, 1H), 4.36–4.28 (m, 1H), 4.20–4.07 (m, 2H), 3.76 (dt, J = 13.9, 8.0 Hz, 1H), 3.66 (dt, J = 14.1, 7.1 Hz, 1H), 2.96 (dd, J = 8.0, 5.2 Hz, 1H), 2.83 (t, J = 7.7 Hz, 2H), 2.64–2.53 (m, 2H), 2.27 (s, 3H), 2.18–2.03 (m, 3H), 1.71–1.58 (m, 5H), 1.48–1.37 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 171.6, 170.3, 151.9, 149.5, 140.7, 136.9, 132.6, 130.4, 128.8, 108.3, 106.4, 103.0, 61.5, 54.7, 47.9, 41.5, 37.8, 37.0, 34.6, 31.8, 27.9, 26.5, 23.1, 22.6, 14.2, 13.7; MS(ESI) calcd for $\text{C}_{29}\text{H}_{35}\text{ClN}_2\text{O}_5$ 526.22 (M^+), found 527.33 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12m

Compound **12m** was prepared according to the general procedure D from carboxylic acid **7g** and amine **11m**: ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.18 (m, 1H), 7.14 (dd, J = 7.4, 1.8 Hz, 1H), 6.92–6.82 (m, 3H), 6.72 (t, J = 5.5 Hz, 1H), 5.72 (ddt, J = 17.2, 10.2, 5.0 Hz, 1H), 5.22–5.14 (m, 2H), 4.84 (dd, J = 10.0, 8.4 Hz, 1H), 4.21–3.99 (m, 3H), 3.83 (s, 4H), 3.60–3.38 (m, 2H), 3.00 (dd, J = 7.4, 5.7 Hz, 1H), 2.92–2.76 (m, 3H), 2.70–2.53 (m, 2H), 2.16–1.97 (m, 3H), 1.74–1.53 (m, 5H), 1.52–1.37 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.2, 171.7, 170.4, 157.6, 140.6, 131.0, 130.8, 127.9, 127.5, 120.7, 116.9, 110.5, 103.7, 61.4, 55.4, 54.6, 48.0, 42.7, 40.0, 34.7, 30.3, 27.9, 26.4, 23.1, 22.6, 14.2; MS (ESI) calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_5$ 468.26 (M^+), found 469.38 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12n

Compound **12n** was prepared according to the general procedure D from carboxylic acid **7f** and amine **11b**: ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.23 (m, 3H), 7.22–7.13 (m, 2H), 6.82 (t, J = 5.9 Hz, 1H), 5.18 (dd, J = 8.6, 4.4 Hz, 1H), 3.85–3.71 (m, 1H), 3.68 (s, 3H), 3.60–3.49 (m, 1H), 3.21–3.10 (m, 1H), 3.09–3.01 (m, 1H), 2.98–2.92 (m, 1H), 2.91–2.82 (m, 1H), 2.81–2.74 (m, 1H), 2.54–2.45 (m, 2H), 2.33–2.19 (m, 1H), 2.14 (dd, J = 15.0, 4.8 Hz, 1H), 2.03–1.84 (m, 2H), 1.84–1.60 (m, 1H), 1.56 (ddd, J = 14.1, 12.3, 3.5 Hz, 1H), 1.51–1.41 (m, 1H), 1.40–1.28 (m, 1H), 1.28–1.09 (m, 4H), 1.00–0.86 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.0, 171.4, 170.6, 142.6, 137.0, 132.5, 130.3, 128.8, 104.5, 55.9, 52.2, 49.1, 46.2, 41.6, 38.0, 35.2, 33.8, 31.7, 31.0, 27.4, 27.2, 26.6, 26.2, 26.0; MS(ESI) calcd for $\text{C}_{28}\text{H}_{37}\text{ClN}_2\text{O}_4$ 500.24 (M^+), found 501.14 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12o

Compound **12o** was prepared according to the general procedure D from carboxylic acid **7d** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 6.97–6.88 (m, 1H), 5.70 (ddt, J = 17.3, 10.3, 5.1 Hz, 1H), 5.21 (ddd, J = 17.3, 1.6 Hz, 1H), 5.16 (ddd, J = 10.3, 1.5 Hz, 1H), 5.12 (dd, J =

8.6, 4.4 Hz, 1H), 4.19 (ddt, J = 16.4, 5.1, 1.8 Hz, 1H), 4.04 (ddt, J = 16.2, 5.2, 1.7 Hz, 1H), 3.67 (s, 3H), 3.02–2.95 (m, 2H), 2.88 (dd, J = 13.4, 6.0 Hz, 1H), 2.54 (dd, J = 15.0, 8.4 Hz, 1H), 2.51–2.45 (m, 1H), 2.25–2.12 (m, 2H), 1.99–1.92 (m, 4H), 1.92–1.83 (m, 1H), 1.82–1.64 (m, 6H), 1.64 (s, 0H), 1.50–1.45 (m, 7H), 1.37–1.24 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 171.4, 170.8, 142.6, 131.2, 117.1, 105.4, 55.7, 52.2, 51.5, 49.3, 42.9, 40.3, 37.1, 35.2, 33.8, 33.8, 28.4, 27.4, 27.2, 26.1; MS(ESI) calcd for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_4$ 454.28 (M^+), found 455.36 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12p

Compound **12p** was prepared according to the general procedure D from carboxylic acid **7d** and amine **11q**: ^1H NMR (500 MHz, CDCl_3) δ 5.69 (ddt, J = 17.2, 10.3, 5.0 Hz, 1H), 5.20 (ddd, J = 17.3, 1.6 Hz, 1H), 5.17–5.09 (m, 2H), 4.20–4.13 (m, 1H), 4.09–4.00 (m, 1H), 3.78–3.59 (m, 9H), 3.58–3.37 (m, 1H), 3.29 (dd, J = 7.0, 5.0 Hz, 1H), 2.83 (dd, J = 16.5, 5.1 Hz, 1H), 2.55 (dd, J = 11.3, 5.0 Hz, 1H), 2.30 (dd, J = 16.5, 6.9 Hz, 1H), 2.24–2.14 (m, 1H), 1.96–1.84 (m, 3H), 1.75–1.65 (m, 3H), 1.65–1.54 (m, 2H), 1.35–1.24 (m, 1H), 1.01–0.95 (m, 2H), 0.81–0.73 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 172.4, 172.2, 171.9, 171.1, 169.0, 142.9, 131.2, 116.7, 105.6, 104.8, 55.6, 52.0, 48.5, 48.2, 45.2, 42.7, 41.9, 41.7, 36.1, 30.1, 27.6, 27.4, 26.1, 11.0, 7.6; MS(ESI) calcd for $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_5$ 443.24 (M^+), found 444.35 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12q

Compound **12q** was prepared according to the general procedure D from carboxylic acid **7c** and amine **11v**: ^1H NMR (500 MHz, CDCl_3) δ 7.30–7.22 (m, 3H), 7.17 (dq, J = 9.1, 4.0, 3.3 Hz, 3H), 5.01 (t, J = 3.7 Hz, 1H), 4.13–4.05 (m, 2H), 3.94–3.82 (m, 2H), 3.72 (q, J = 4.0 Hz, 2H), 3.42 (ddd, J = 13.8, 10.4, 4.9 Hz, 1H), 3.28 (dd, J = 8.6, 4.4 Hz, 1H), 2.93–2.72 (m, 3H), 2.66–2.53 (m, 7H), 2.28–2.08 (m, 3H), 1.88–1.80 (m, 1H), 1.60–1.43 (m, 2H), 1.34–1.22 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.6, 172.2, 168.8, 138.6, 137.2, 132.4, 130.2, 128.8, 100.6, 61.2, 52.7, 48.4, 47.7, 45.0, 41.4, 32.2, 31.0, 30.2, 27.7, 27.5, 23.0, 19.9, 14.4; MS (ESI) calcd for $\text{C}_{25}\text{H}_{31}\text{ClN}_2\text{O}_4\text{S}$ 490.17 (M^+), found 491.28 ($\text{M} + \text{H}$) $^+$.

Pyrrolidinone-Containing Amide 12r

Compound **12r** was prepared according to the general procedure D from carboxylic acid **7c** and amine **11l**: ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.23 (m, 5H), 7.22–7.13 (m, 7H), 6.77 (t, J = 5.7 Hz, 1H), 5.05 (t, J = 3.7 Hz, 1H), 4.17–4.06 (m, 2H), 3.88 (ddd, J = 13.8, 10.7, 6.3 Hz, 1H), 3.44 (ddd, J = 13.8, 10.6, 5.2 Hz, 1H), 3.35–3.19 (m, 3H), 2.98–2.76 (m, 3H), 2.68–2.51 (m, 5H), 2.31–2.20 (m, 1H), 2.21–2.08 (m, 2H), 1.87 (ddt, J = 13.6, 6.5, 3.3 Hz, 1H), 1.74–1.63 (m, 2H), 1.62–1.50 (m, 3H), 1.46 (ddd, J = 15.4, 10.1, 2.9 Hz, 1H), 1.35–1.25 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 171.5, 170.8, 142.3, 138.2, 137.1, 132.5, 130.2, 128.8, 128.5, 128.4, 125.9, 101.0, 61.5, 52.6, 48.5, 41.5, 39.7, 35.6, 33.5, 32.2, 30.2, 29.2, 28.8, 23.0, 19.7, 14.3; MS (ESI) calcd for $\text{C}_{31}\text{H}_{37}\text{ClN}_2\text{O}_4$ 536.24 (M^+), found 537.47 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13a ((3*RS*,4*aSR*)-Ethyl 1-Benzyl-3-(2-(4-(furan-2-carbonyl)piperazin-1-yl)-2-oxoethyl)-2-oxo-2,3,4,4*a*,5,6-hexahydro-1*H*-cyclopenta[*b*]pyridine-4*a*-carboxylate)

Compound **13a** was prepared according to the general procedure D from carboxylic acid **8f** and amine **11r**: ^1H NMR (500 MHz, CDCl_3) δ 7.50 (dd, J = 1.7, 0.8 Hz, 1H), 7.29 (d, J = 4.3 Hz, 4H), 7.24–7.18 (m, 1H), 7.04 (dd, J = 3.5, 0.9 Hz, 1H), 6.49 (dd, J = 3.5, 1.8 Hz, 1H), 5.00 (dd, J = 3.2, 1.8 Hz, 1H), 4.95 (d, J = 15.5 Hz, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.19–4.05 (m, 2H), 3.81 (s, 4H), 3.74–3.63 (m, 2H), 3.57 (t, J = 5.2 Hz, 2H), 2.99–2.90 (m,

2H), 2.79–2.73 (m, 1H), 2.54 (dd, J = 12.7, 5.1 Hz, 1H), 2.44–2.35 (m, 1H), 2.32 (dd, J = 12.7, 7.0 Hz, 1H), 2.25 (ddd, J = 15.4, 8.6, 3.2 Hz, 1H), 2.05–1.98 (m, 1H), 1.91–1.81 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 170.7, 169.6, 159.3, 147.7, 144.1, 141.5, 137.2, 128.5, 127.1, 127.0, 127.0, 119.4, 117.2, 111.6, 107.8, 61.4, 54.5, 47.8, 45.5, 43.8, 41.8, 37.0, 36.8, 35.9, 35.1, 29.1, 14.3; HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{29}\text{H}_{34}\text{N}_3\text{O}_6$ 520.2448, found 520.2452.

Piperidinone-Containing Amide 13b

Compound **13b** was prepared according to the general procedure D from carboxylic acid **8f** and amine **11m**: ^1H NMR (500 MHz, CDCl_3) δ 7.32–7.27 (m, 2H), 7.25–7.19 (m, 3H), 7.18 (dd, J = 6.8, 1.4 Hz, 1H), 7.11 (dd, J = 7.4, 1.8 Hz, 1H), 6.90–6.82 (m, 2H), 6.08 (t, J = 5.6 Hz, 1H), 4.98 (dd, J = 3.2, 1.7 Hz, 1H), 4.92–4.86 (m, 2H), 4.19–4.07 (m, 2H), 3.82 (s, 3H), 3.53–3.37 (m, 2H), 2.92–2.85 (m, 1H), 2.78 (t, J = 6.9 Hz, 2H), 2.68 (dd, J = 14.7, 5.6 Hz, 1H), 2.59–2.48 (m, 2H), 2.42–2.29 (m, 2H), 2.24 (ddd, J = 14.9, 8.6, 3.2 Hz, 1H), 1.90–1.82 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.2, 170.9, 170.7, 157.6, 141.5, 136.9, 130.7, 128.5, 127.9, 127.5, 127.1, 127.0, 120.7, 110.5, 107.8, 61.4, 55.4, 54.6, 47.8, 39.8, 38.5, 37.5, 37.0, 35.7, 30.4, 29.0, 14.3; MS(ESI) calcd for $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_5$ 490.25 (M^+), found 491.28 ($\text{M} + \text{H}$) $^+$, 513.24 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13c

Compound **13c** was prepared according to the general procedure D from carboxylic acid **8g** and amine **11e**: ^1H NMR (500 MHz, CDCl_3) δ 7.19 (dd, J = 4.8, 1.5 Hz, 1H), 6.95–6.89 (m, 2H), 6.76–6.69 (m, 3H), 5.91 (s, 2H), 5.03 (t, J = 2.3 Hz, 1H), 4.83 (d, J = 15.4 Hz, 1H), 4.70 (d, J = 15.3 Hz, 1H), 4.57 (d, J = 5.5 Hz, 2H), 4.19–4.07 (m, 2H), 3.47 (s, 1H), 2.91 (dq, J = 13.1, 5.4 Hz, 1H), 2.81 (dd, J = 14.6, 5.0 Hz, 1H), 2.56 (ddd, J = 14.4, 7.8, 5.5 Hz, 2H), 2.46–2.31 (m, 2H), 2.27 (ddd, J = 15.3, 8.7, 3.3 Hz, 1H), 1.93–1.81 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 170.9, 170.8, 147.9, 146.7, 141.2, 141.1, 130.7, 127.0, 126.0, 125.2, 120.4, 108.2, 107.7, 101.1, 61.5, 54.6, 47.5, 38.4, 38.2, 37.6, 37.0, 35.7, 29.1, 14.2; HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_6\text{S}$ 497.1746, found 497.1740.

Piperidinone-Containing Amide 13d

Compound **13d** was prepared according to the general procedure D from carboxylic acid **8g** and amine **11k**: ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.26 (m, 2H), 7.24 (td, J = 6.5, 1.7 Hz, 3H), 6.76–6.69 (m, 3H), 5.89 (s, 2H), 5.03 (dd, J = 3.2, 1.8 Hz, 1H), 4.81 (d, J = 15.3 Hz, 1H), 4.69 (d, J = 15.3 Hz, 1H), 4.40 (d, J = 5.6 Hz, 2H), 4.18–4.08 (m, 2H), 3.46 (s, 1H), 2.95–2.88 (m, 1H), 2.83 (dd, J = 14.7, 5.0 Hz, 1H), 2.57 (ddd, J = 14.7, 5.5, 2.6 Hz, 2H), 2.45–2.36 (m, 1H), 2.33 (dd, J = 12.7, 7.0 Hz, 1H), 2.27 (ddd, J = 15.3, 8.7, 3.2 Hz, 1H), 1.92–1.82 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 171.2, 170.9, 147.9, 146.7, 141.2, 138.4, 130.6, 128.8, 127.8, 127.5, 120.4, 108.3, 108.2, 107.7, 101.1, 61.5, 54.5, 47.6, 43.7, 38.2, 37.6, 37.0, 35.7, 29.1, 14.2; MS(ESI) calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_6$ 490.21 (M^+), found 491.22 ($\text{M} + \text{H}$) $^+$, 513.21 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13e

Compound **13e** was prepared according to the general procedure D from carboxylic acid **8h** and amine **11a**: ^1H NMR (500 MHz, CDCl_3) δ 7.33 (d, J = 0.9 Hz, 1H), 6.37 (s, 1H), 6.32–6.29 (m, 1H), 6.28–6.25 (m, 1H), 5.23 (t, J = 2.4 Hz, 1H), 4.94 (d, J = 15.5 Hz, 1H), 4.78 (d, J = 15.7 Hz, 1H), 4.17–4.08 (m, 2H), 4.05–3.97 (m, 1H), 3.96–3.87 (m, 1H), 3.48 (s, 1H), 2.90–2.82 (m, 1H), 2.75–2.68 (m, 1H), 2.58–2.51 (m, 2H), 2.49–2.40 (m, 1H), 2.38–2.28 (m, 2H), 2.21–2.17 (m, 1H), 1.91–1.82 (m, 1H), 1.77 (dd, J = 13.5, 12.5 Hz, 1H), 1.21–1.15 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 170.8, 170.4, 150.4, 141.9, 141.1, 110.5,

108.2, 108.0, 79.8, 71.5, 61.5, 54.6, 41.2, 38.3, 37.6, 36.9, 35.8, 29.2, 29.1, 14.2; MS(ESI) calcd for $C_{21}H_{24}N_2O_5$ 384.17 (M^+), found 407.16 ($M + Na$)⁺.

Piperidinone-Containing Amide 13f

Compound **13f** was prepared according to the general procedure D from carboxylic acid **8h** and amine **11n**: ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.27 (m, 1H), 6.73 (s, 1H), 6.28 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.25 (dd, *J* = 3.3, 1.0 Hz, 1H), 5.16 (dd, *J* = 3.2, 1.8 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.82 (d, *J* = 15.6 Hz, 1H), 4.15–4.05 (m, 2H), 3.46 (s, 1H), 3.36 (t, *J* = 7.1 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 3.21–3.07 (m, 2H), 2.90–2.81 (m, 1H), 2.66–2.55 (m, 2H), 2.49 (dd, *J* = 12.8, 5.7 Hz, 1H), 2.46–2.35 (m, 5H), 2.34–2.24 (m, 2H), 2.09–1.96 (m, 2H), 1.88–1.73 (m, 2H), 1.69–1.59 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 175.9, 174.2, 171.1, 170.2, 150.7, 141.7, 141.3, 110.5, 107.9, 107.3, 61.4, 54.6, 47.5, 41.1, 39.9, 38.5, 37.2, 37.0, 36.0, 35.9, 31.1, 29.1, 26.7, 18.1, 14.2; MS(ESI) calcd for $C_{25}H_{33}N_3O_6$ 471.24 (M^+), found 472.25 ($M + H$)⁺, 494.24 ($M + Na$)⁺.

Piperidinone-Containing Amide 13g

Compound **13g** was prepared according to the general procedure D from carboxylic acid **8i** and amine **11f**: ¹H NMR (500 MHz, CDCl₃) δ 6.85–6.74 (m, 3H), 5.42–5.37 (m, 1H), 5.06 (t, *J* = 2.4 Hz, 1H), 4.40 (dd, *J* = 14.4, 6.0 Hz, 1H), 4.27 (dd, *J* = 14.6, 5.4 Hz, 1H), 4.19–4.09 (m, 2H), 3.91–3.81 (m, 7H), 3.77 (ddd, *J* = 13.2, 10.6, 5.8 Hz, 1H), 3.47 (ddd, *J* = 13.2, 10.7, 5.3 Hz, 1H), 2.85–2.77 (m, 1H), 2.69 (dd, *J* = 14.6, 4.8 Hz, 1H), 2.61–2.41 (m, 3H), 2.38–2.27 (m, 2H), 2.09 (m, 2H), 2.00–1.89 (m, 4H), 1.85 (dt, *J* = 13.0, 9.4 Hz, 1H), 1.74 (t, *J* = 13.0 Hz, 1H), 1.64–1.56 (m, 2H), 1.56–1.48 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.1, 171.1, 170.1, 149.2, 148.4, 141.0, 135.0, 131.2, 122.8, 120.1, 111.2, 111.1, 106.8, 61.5, 56.0, 56.0, 54.4, 43.5, 43.1, 38.7, 37.6, 37.0, 35.9, 34.5, 29.1, 28.6, 25.4, 23.0, 22.4, 14.3; MS(ESI) calcd for $C_{30}H_{40}N_2O_6$ 524.29 (M^+), found 525.29 ($M + H$)⁺.

Piperidinone-Containing Amide 13h

Compound **13h** was prepared according to the general procedure D from carboxylic acid **8i** and amine **11s**: ¹H NMR (500 MHz, CDCl₃) δ 5.43 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.07 (t, *J* = 2.3 Hz, 1H), 4.21–4.08 (m, 4H), 3.88 (ddd, *J* = 13.3, 10.7, 5.6 Hz, 1H), 3.66–3.31 (m, 9H), 2.85–2.70 (m, 3H), 2.55–2.41 (m, 2H), 2.39–2.26 (m, 3H), 2.25–2.08 (m, 2H), 2.05–1.92 (m, 4H), 1.91–1.77 (m, 2H), 1.66–1.56 (m, 2H), 1.56–1.48 (m, 2H), 1.32–1.18 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 174.3, 169.7, 169.4, 155.3, 141.1, 135.1, 122.5, 106.0, 61.6, 61.2, 54.2, 45.1, 43.5, 43.0, 41.3, 37.5, 36.9, 36.5, 35.8, 35.2, 34.4, 28.9, 28.4, 25.2, 22.9, 22.3, 14.6, 14.2; MS(ESI) calcd for $C_{28}H_{41}N_3O_6$ 515.30 (M^+), found 516.32 ($M + H$)⁺, 538.3 ($M + Na$)⁺.

Piperidinone-Containing Amide 13i

Compound **13i** was prepared according to the general procedure D from carboxylic acid **8a** and amine **11l**: ¹H NMR (500 MHz, CDCl₃) δ 7.24 (m, 2H), 7.14 (m, 3H), 6.79 (m, 3H), 6.03 (s, 1H), 5.09 (t, *J* = 2.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.01 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.64 (m, 1H), 3.23 (m, 2H), 2.79 (m, 3H), 2.66 (m, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.55 (dd, *J* = 13.0, 5.8 Hz, 1H), 2.48 (dd, *J* = 14.5, 5.3 Hz, 2H), 2.35 (m, 2H), 1.87 (m, 1H), 1.78 (t, *J* = 13.0 Hz, 1H), 1.60 (m, 2H), 1.50 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.2, 171.0, 170.2, 149.1, 147.8, 142.2, 141.1, 131.7, 128.5, 128.4, 125.9, 120.8, 112.3, 111.5, 106.6, 61.5, 56.1, 56.1, 54.5, 45.9, 39.4, 38.5, 37.6, 36.9, 35.8, 35.6, 32.5, 29.4, 29.0, 28.7, 14.3; MS(ESI) calcd for $C_{33}H_{42}N_2O_6$ 562.30 (M^+), found 563.37 ($M + H$)⁺.

Piperidinone-Containing Amide 13j

Compound **13j** was prepared according to the general procedure D from carboxylic acid **8a** and amine **11w**: ^1H NMR (500 MHz, CDCl_3) δ 6.80 (m, 3H), 5.09 (t, $J = 2.2$ Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.00 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.71 (m, 1H), 3.42 (m, 4H), 2.82 (m, 4H), 2.61 (dd, $J = 15.9, 2.9$ Hz, 1H), 2.49 (m, 2H), 2.35 (m, 2H), 1.90 (m, 6H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 170.5, 169.2, 149.0, 147.6, 141.5, 132.1, 120.7, 112.3, 111.4, 105.8, 61.3, 56.0, 56.0, 54.5, 46.6, 45.9, 45.7, 37.0, 36.6, 36.5, 36.0, 32.4, 29.1, 26.2, 24.5, 14.3; MS(ESI) calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_6$ 484.26 (M^+), found 485.32 ($\text{M} + \text{H}$) $^+$, 507.31 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13k

Compound **13k** was prepared according to the general procedure D from carboxylic acid **8j** and amine **11w**: ^1H NMR (500 MHz, CDCl_3) δ 8.03–7.94 (m, 1H), 7.92–7.77 (m, 4H), 7.71 (d, $J = 8.1$ Hz, 1H), 7.59–7.32 (m, 7H), 7.25–7.20 (m, 1H), 6.29 (t, $J = 5.1$ Hz, 1H), 5.10 (d, $J = 16.5$ Hz, 1H), 5.03 (dd, $J = 14.4, 6.5$ Hz, 1H), 4.75 (d, $J = 16.4$ Hz, 1H), 4.72–4.65 (m, 2H), 4.18 (dq, $J = 11.0, 7.2$ Hz, 1H), 4.10 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.02–2.89 (m, 2H), 2.65 (dd, $J = 13.0, 5.5$ Hz, 1H), 2.51 (dd, $J = 14.0, 4.6$ Hz, 1H), 2.39–2.28 (m, 2H), 2.25–2.16 (m, 1H), 2.01 (t, $J = 13.0$ Hz, 1H), 1.96–1.85 (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 170.7, 170.5, 140.9, 134.1, 134.0, 133.8, 131.5, 130.9, 130.9, 129.0, 128.8, 128.6, 127.5, 127.0, 126.7, 126.1, 126.1, 125.7, 125.6, 125.6, 123.9, 122.8, 122.6, 108.3, 61.5, 54.5, 45.1, 41.6, 38.3, 38.0, 37.1, 35.5, 29.0, 14.3; MS(ESI) calcd for $\text{C}_{35}\text{H}_{34}\text{N}_2\text{O}_4$ 546.25 (M^+), found 547.28 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13l

Compound **13l** was prepared according to the general procedure D from carboxylic acid **8j** and amine **11w**: ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, $J = 8.3$ Hz, 1H), 7.90–7.84 (m, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.55–7.39 (m, 4H), 5.45 (d, $J = 16.4$ Hz, 1H), 5.38 (d, $J = 16.4$ Hz, 1H), 4.84 (dd, $J = 3.4, 1.7$ Hz, 1H), 4.23–4.15 (m, 1H), 4.14–4.05 (m, 1H), 3.57–3.48 (m, 1H), 3.47–3.38 (m, 3H), 3.03–2.93 (m, 2H), 2.69–2.60 (m, 1H), 2.57 (dd, $J = 12.7, 5.4$ Hz, 1H), 2.40–2.30 (m, 2H), 2.28–2.15 (m, 2H), 1.99–1.88 (m, 3H), 1.88–1.78 (m, 2H), 1.26–1.19 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.7, 171.2, 169.2, 141.8, 133.8, 131.4, 131.0, 128.9, 127.3, 126.0, 125.8, 125.5, 123.5, 122.7, 107.8, 61.3, 54.6, 46.6, 46.0, 45.7, 37.2, 36.8, 36.5, 36.0, 29.1, 26.2, 24.5, 14.3; MS(ESI) calcd for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4$ 460.24 (M^+), found 461.26 ($\text{M} + \text{H}$) $^+$, 483.25 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13m

Compound **13m** was prepared according to the general procedure D from carboxylic acid **8k** and amine **11a**: ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.33 (m, 1H), 7.23–7.16 (m, 2H), 6.16 (t, $J = 5.4$ Hz, 1H), 4.99–4.90 (m, 2H), 4.85 (dd, $J = 3.2, 1.7$ Hz, 1H), 4.27–4.12 (m, 2H), 4.07–3.94 (m, 2H), 2.95–2.87 (m, 1H), 2.82 (dd, $J = 15.1, 5.0$ Hz, 1H), 2.60–2.50 (m, 2H), 2.42–2.32 (m, 2H), 2.29–2.21 (m, 1H), 2.20 (t, $J = 2.5$ Hz, 1H), 1.98 (t, $J = 13.0$ Hz, 1H), 1.94–1.85 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.1, 170.8, 170.6, 141.1, 133.3, 133.3, 132.4, 129.2, 128.5, 127.4, 108.1, 79.6, 71.7, 61.6, 54.6, 45.3, 37.8, 37.4, 37.1, 35.6, 29.3, 29.0, 14.4; MS(ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_4$ 462.11 (M^+), found 533.39 ($\text{M} + \text{H}$) $^+$, 555.38 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13n

Compound **13n** was prepared according to the general procedure D from carboxylic acid **8k** and amine **11n**: ^1H NMR (500 MHz, CDCl_3) δ 7.34 (d, $J = 2.1$ Hz, 1H), 7.27–7.23 (m, 1H), 7.17 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.74 (t, $J = 6.2$ Hz, 1H), 4.96–4.88 (m, 2H), 4.79 (dd, $J = 3.2, 1.7$ Hz, 1H), 4.24–4.11 (m, 2H), 3.38–3.26 (m, 4H), 3.21–3.11 (m, 2H), 2.92–2.85 (m, 1H),

2.78 (dd, $J = 15.4, 5.6$ Hz, 1H), 2.58–2.47 (m, 2H), 2.41–2.30 (m, 4H), 2.25–2.17 (m, 1H), 2.06–1.95 (m, 3H), 1.91–1.82 (m, 1H), 1.67–1.59 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 174.2, 170.9, 170.8, 141.4, 133.2, 133.1, 132.8, 129.0, 128.8, 127.4, 107.3, 61.5, 54.6, 47.5, 45.2, 39.8, 37.9, 37.1, 37.0, 35.8, 35.8, 31.0, 29.0, 26.6, 18.1, 14.4; MS(ESI) calcd for $\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{N}_3\text{O}_5$ 549.18 (M^+), found 550.18 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13o

Compound **13o** was prepared according to the general procedure D from carboxylic acid **8l** and amine **11a**: ^1H NMR (500 MHz, CDCl_3) δ 6.69 (t, $J = 5.4$ Hz, 1H), 5.25 (dd, $J = 5.3, 2.8$ Hz, 1H), 4.16 (dd, $J = 7.0, 2.0$ Hz, 1H), 4.14 (dd, $J = 7.1, 1.9$ Hz, 1H), 4.05–3.94 (m, 2H), 3.71 (ddd, $J = 13.6, 10.5, 5.2$ Hz, 1H), 3.64 (ddd, $J = 13.7, 10.7, 5.7$ Hz, 1H), 2.68–2.59 (m, 2H), 2.56–2.49 (m, 1H), 2.34 (dd, $J = 13.1, 5.4$ Hz, 1H), 2.31–2.21 (m, 2H), 2.17 (t, $J = 2.6$ Hz, 1H), 2.16–2.09 (m, 1H), 1.72–1.58 (m, 3H), 1.55–1.45 (m, 2H), 1.43–1.35 (m, 1H), 1.34–1.20 (m, 13H), 0.87 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.2, 171.0, 170.0, 136.2, 107.3, 79.8, 71.4, 61.6, 46.6, 44.2, 38.8, 37.3, 36.7, 35.0, 32.0, 29.5, 29.4, 29.2, 27.3, 27.0, 24.5, 22.8, 18.7, 14.4, 14.2; MS(ESI) calcd for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_4$ 430.28 (M^+), found 431.29 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13p

Compound **13p** was prepared according to the general procedure D from carboxylic acid **8l** and amine **11o**: ^1H NMR (500 MHz, CDCl_3) δ 6.46 (t, $J = 5.7$ Hz, 1H), 6.04 (d, $J = 3.0$ Hz, 1H), 5.85 (dd, $J = 3.1, 1.3$ Hz, 1H), 5.22 (dd, $J = 5.3, 2.8$ Hz, 1H), 4.35 (dd, $J = 15.5, 5.6$ Hz, 1H), 4.29 (dd, $J = 15.4, 5.4$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.71–3.58 (m, 2H), 2.70–2.60 (m, 2H), 2.56–2.49 (m, 1H), 2.39–2.32 (m, 1H), 2.31–2.20 (m, 5H), 2.18–2.09 (m, 1H), 1.73–1.64 (m, 2H), 1.62–1.54 (m, 1H), 1.54–1.34 (m, 3H), 1.33–1.18 (m, 13H), 0.87 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 170.9, 169.9, 151.8, 149.7, 136.3, 108.1, 107.1, 106.3, 61.5, 46.6, 44.1, 38.7, 37.4, 36.7, 36.5, 35.0, 32.0, 29.5, 27.3, 26.8, 24.5, 22.8, 18.7, 14.3, 14.2, 13.7; MS(ESI) calcd for $\text{C}_{28}\text{H}_{42}\text{N}_2\text{O}_5$ 486.31 (M^+), found 487.32 ($\text{M} + \text{H}$) $^+$, 509.3 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13q

Compound **13q** was prepared according to the general procedure D from carboxylic acid **8m** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 8.2, 6.9$ Hz, 2H), 7.23–7.17 (m, 3H), 6.38 (t, $J = 5.7$ Hz, 1H), 5.39 (d, $J = 16.0$ Hz, 1H), 5.13 (dd, $J = 5.2, 2.8$ Hz, 1H), 4.54 (d, $J = 16.1$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.44–3.29 (m, 3H), 3.28 (s, 3H), 3.27–3.20 (m, 1H), 2.79–2.68 (m, 2H), 2.59–2.51 (m, 1H), 2.42 (dd, $J = 13.1, 5.3$ Hz, 1H), 2.29–2.22 (m, 1H), 2.17–2.08 (m, 1H), 2.06–1.95 (m, 1H), 1.91 (t, $J = 13.0$ Hz, 1H), 1.76–1.67 (m, 2H), 1.68–1.60 (m, 1H), 1.52 (td, $J = 13.6, 2.7$ Hz, 1H), 1.40–1.30 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 170.9, 170.7, 137.7, 137.2, 128.6, 126.8, 126.2, 108.5, 71.4, 61.5, 58.8, 48.8, 46.8, 38.6, 37.8, 37.6, 36.6, 34.9, 29.3, 24.4, 18.7, 14.4; MS(ESI) calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_5$ 442.25 (M^+), found 443.27 ($\text{M} + \text{H}$) $^+$, 465.23 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13r

Compound **13r** was prepared according to the general procedure D from carboxylic acid **8m** and amine **11n**: ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 8.2, 6.9$ Hz, 2H), 7.23–7.17 (m, 3H), 6.38 (t, $J = 5.7$ Hz, 1H), 5.39 (d, $J = 16.0$ Hz, 1H), 5.13 (dd, $J = 5.2, 2.8$ Hz, 1H), 4.54 (d, $J = 16.1$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.44–3.29 (m, 3H), 3.28 (s, 3H), 3.27–3.20 (m, 1H), 2.79–2.68 (m, 2H), 2.59–2.51 (m, 1H), 2.42 (dd, $J = 13.1, 5.3$ Hz, 1H), 2.29–2.22 (m, 1H), 2.17–2.08 (m, 1H), 2.06–1.95 (m, 1H), 1.91 (t, $J = 13.0$ Hz, 1H), 1.76–1.67 (m, 2H), 1.68–1.60 (m, 1H), 1.52 (td, $J = 13.6, 2.7$ Hz, 1H), 1.40–1.30 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 170.9, 170.7, 137.7, 137.2, 128.6, 126.8,

126.2, 108.5, 71.4, 61.5, 58.8, 48.8, 46.8, 38.6, 37.8, 37.6, 36.6, 34.9, 29.3, 24.4, 18.7, 14.4; MS(ESI) calcd for $C_{28}H_{37}N_3O_5$ 495.27 (M^+), found 496.28 ($M + H$) $^+$.

Piperidinone-Containing Amide 13s

Compound **13s** was prepared according to the general procedure D from carboxylic acid **8n** and amine **11i**: 1H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, $J = 7.9$ Hz, 1H), 6.70 (d, $J = 1.6$ Hz, 1H), 6.67 (dd, $J = 7.9, 1.7$ Hz, 1H), 6.23 (t, $J = 6.3$ Hz, 1H), 5.92 (s, 2H), 5.23–5.13 (m, 2H), 4.57 (d, $J = 15.8$ Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.00 (dd, $J = 13.4, 6.8$ Hz, 1H), 2.87–2.67 (m, 3H), 2.56 (dd, $J = 13.8, 4.5$ Hz, 1H), 2.41 (dd, $J = 13.2, 5.4$ Hz, 1H), 2.30–2.22 (m, 1H), 2.15 (dt, $J = 18.3, 5.4$ Hz, 1H), 2.09–1.98 (m, 1H), 1.97–1.84 (m, 4H), 1.74–1.55 (m, 8H), 1.55–1.46 (m, 1H), 1.45–1.41 (m, 6H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 171.2, 170.9, 148.0, 146.5, 137.0, 131.5, 119.6, 108.7, 108.4, 107.3, 101.0, 61.6, 51.1, 48.3, 46.8, 40.3, 38.8, 37.8, 37.1, 36.6, 34.9, 33.7, 28.4, 24.4, 18.7, 14.4; MS(ESI) calcd for $C_{33}H_{42}N_2O_6$ 562.30 (M^+), found 563.31 ($M + H$) $^+$.

Piperidinone-Containing Amide 13t

Compound **13t** was prepared according to the general procedure D from carboxylic acid **8n** and amine **11w**: 1H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, $J = 1.6$ Hz, 1H), 6.80–6.70 (m, 2H), 5.95–5.87 (m, 2H), 5.31 (d, $J = 15.9$ Hz, 1H), 5.17 (dd, $J = 5.2, 2.7$ Hz, 1H), 4.42 (d, $J = 15.8$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.51 (dt, $J = 13.0, 6.8$ Hz, 1H), 3.41 (p, $J = 6.9, 6.3$ Hz, 3H), 2.90 (dd, $J = 16.5, 6.2$ Hz, 1H), 2.73 (dtd, $J = 12.4, 5.9, 3.3$ Hz, 1H), 2.62 (dd, $J = 16.4, 3.3$ Hz, 1H), 2.36 (dd, $J = 12.8, 5.8$ Hz, 1H), 2.28–2.18 (m, 1H), 2.18–1.97 (m, 3H), 1.97–1.89 (m, 2H), 1.87–1.78 (m, 2H), 1.67–1.58 (m, 1H), 1.52 (td, $J = 13.6, 2.7$ Hz, 1H), 1.42–1.30 (m, 1H), 1.24 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 171.1, 169.1, 148.0, 146.3, 137.6, 132.2, 119.5, 108.3, 108.2, 107.5, 100.9, 61.5, 48.9, 46.8, 46.6, 45.8, 36.7, 36.6, 36.4, 35.1, 26.2, 24.5, 24.5, 18.8, 14.4; MS(ESI) calcd for $C_{26}H_{32}N_2O_6$ 468.23 (M^+), found 469.23 ($M + H$) $^+$, 491.22 ($M + Na$) $^+$.

Piperidinone-Containing Amide 13u

Compound **13u** was prepared according to the general procedure D from carboxylic acid **8o** and amine **11g**: 1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2H), 7.42–7.37 (m, 2H), 7.27 (dd, $J = 1.8, 0.8$ Hz, 1H), 6.74 (d, $J = 6.0$ Hz, 1H), 6.27 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.22 (d, $J = 3.1$ Hz, 1H), 5.50 (dd, $J = 5.2, 2.8$ Hz, 1H), 5.22 (d, $J = 15.8$ Hz, 1H), 4.51 (d, $J = 15.9$ Hz, 1H), 4.43 (dd, $J = 15.3, 6.3$ Hz, 1H), 4.34 (dd, $J = 15.3, 5.8$ Hz, 1H), 4.15 (qd, $J = 7.1, 1.8$ Hz, 2H), 2.81–2.69 (m, 2H), 2.59–2.52 (m, 1H), 2.40 (dd, $J = 13.1, 5.4$ Hz, 1H), 2.30–2.20 (m, 2H), 2.12 (dddd, $J = 18.0, 11.1, 6.4, 2.9$ Hz, 1H), 1.78–1.64 (m, 2H), 1.50 (td, $J = 13.6, 13.2, 2.6$ Hz, 1H), 1.44–1.31 (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 171.3, 170.5, 151.2, 141.6, 139.8, 136.9, 131.0, 131.0, 129.1, 124.3 (q, $^3J_{C-F} = 3.6$ Hz), 124.2 (q, $^3J_{C-F} = 3.5$ Hz), 124.2 (q, $^1J_{C-F} = 272.8$ Hz), 110.6, 108.8, 107.9, 61.6, 46.8, 43.0, 42.1, 38.7, 37.6, 36.6, 34.8, 24.5, 18.6, 14.3; MS(ESI) calcd for $C_{27}H_{29}F_3N_2O_5$ 518.20 (M^+), found 519.21 ($M + H$) $^+$, 541.21 ($M + Na$) $^+$.

Piperidinone-Containing Amide 13v

Compound **13v** was prepared according to the general procedure D from carboxylic acid **8o** and amine **11n**: 1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, $J = 1.9$ Hz, 1H), 6.71 (t, $J = 6.0$ Hz, 1H), 6.30 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.25 (d, $J = 3.1$ Hz, 1H), 5.41 (dd, $J = 5.1, 2.7$ Hz, 1H), 5.24 (d, $J = 15.9$ Hz, 1H), 4.51 (d, $J = 15.9$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.36 (t, $J = 7.1$ Hz, 2H), 3.30 (t, $J = 6.5$ Hz, 2H), 3.22–3.06 (m, 2H), 2.78–2.70 (m, 1H), 2.60 (d, $J = 5.3$ Hz, 2H), 2.41–2.32 (m, 3H), 2.28–2.18 (m, 2H), 2.14–1.97 (m, 3H), 1.79–1.71 (m, 1H), 1.69–1.60 (m, 3H), 1.50 (td, $J = 13.6, 2.6$ Hz, 1H), 1.42–1.31 (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 174.3, 171.0, 170.2, 151.4, 141.4, 137.2, 110.6,

108.1, 107.7, 61.5, 47.4, 46.7, 42.2, 39.9, 38.6, 37.1, 36.7, 36.1, 34.9, 31.1, 26.8, 24.5, 18.7, 18.1, 14.3; MS(ESI) calcd for $C_{26}H_{35}N_3O_6$ 485.25 (M^+), found 486.26 ($M + H$)⁺, 508.24 ($M + Na$)⁺.

Piperidinone-Containing Amide 13w

Compound **13w** was prepared according to the general procedure D from carboxylic acid **8p** and amine **11r**: ¹H NMR (500 MHz, CDCl₃) δ 7.51–7.46 (m, 1H), 7.04 (d, *J* = 3.4 Hz, 1H), 6.82–6.78 (m, 3H), 6.49 (dt, *J* = 3.3, 1.4 Hz, 1H), 5.35 (dd, *J* = 5.2, 2.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.95–3.87 (m, 2H), 3.87–3.83 (m, 7H), 3.83–3.76 (m, 2H), 3.75–3.67 (m, 1H), 3.67–3.60 (m, 1H), 3.58–3.52 (m, 2H), 3.51–3.42 (m, 1H), 2.96–2.86 (m, 1H), 2.85–2.68 (m, 4H), 2.37 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.33–2.22 (m, 2H), 2.22–2.15 (m, 1H), 1.82 (t, *J* = 12.6 Hz, 1H), 1.73–1.65 (m, 1H), 1.54 (td, *J* = 13.5, 13.0, 2.6 Hz, 1H), 1.47–1.39 (m, 1H), 1.30–1.21 (m, 4H), 1.19 (t, *J* = 7.0 Hz, 3H), 0.90–0.81 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 174.5, 169.9, 169.5, 159.3, 149.0, 147.6, 144.1, 136.5, 132.2, 120.7, 117.2, 112.2, 111.6, 111.4, 106.8, 66.0, 61.5, 56.0, 56.0, 46.6, 45.6, 41.8, 36.8, 36.6, 35.3, 35.2, 32.6, 31.7, 24.6, 22.8, 18.8, 15.4, 14.4, 14.2; MS(ESI) calcd for $C_{33}H_{41}N_3O_8$ 607.29 (M^+), found 608.35 ($M + H$)⁺, 630.31 ($M + Na$)⁺.

Piperidinone-Containing Amide 13x

Compound **13x** was prepared according to the general procedure D from carboxylic acid **8p** and amine **11q**: ¹H NMR (500 MHz, CDCl₃) δ 6.80 (d, *J* = 3.2 Hz, 4H), 5.35 (dd, *J* = 5.3, 2.7 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.95–3.88 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.75–3.55 (m, 6H), 3.53–3.41 (m, 2H), 2.96–2.86 (m, 1H), 2.85–2.66 (m, 4H), 2.40–2.22 (m, 2H), 2.22–2.12 (m, 1H), 1.81 (t, *J* = 12.6 Hz, 1H), 1.70 (dq, *J* = 13.5, 5.3, 4.5 Hz, 2H), 1.54 (td, *J* = 13.5, 12.9, 2.6 Hz, 1H), 1.46–1.38 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.03–0.96 (m, 2H), 0.83–0.75 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 174.5, 172.4, 170.0, 169.5, 149.0, 147.6, 136.5, 132.1, 120.7, 112.2, 111.3, 106.9, 61.5, 56.0, 56.0, 46.6, 45.6, 45.3, 41.6, 36.8, 36.6, 35.3, 35.2, 32.6, 24.6, 18.8, 14.4, 11.1, 7.8; MS(ESI) calcd for $C_{32}H_{43}N_3O_7$ 581.31 (M^+), found 582.37 ($M + H$)⁺, 604.34 ($M + Na$)⁺.

Piperidinone-Containing Amide 13y

Compound **13y** was prepared according to the general procedure D from carboxylic acid **8q** and amine **11t**: ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.56–7.40 (m, 4H), 5.85 (d, *J* = 16.6 Hz, 1H), 5.04 (dd, *J* = 5.1, 2.8 Hz, 1H), 4.97 (d, *J* = 16.6 Hz, 1H), 4.27–4.14 (m, 2H), 3.64 (ddt, *J* = 9.2, 6.9, 4.7 Hz, 6H), 3.47 (dd, *J* = 6.1, 3.6 Hz, 2H), 2.97 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.87–2.80 (m, 1H), 2.75 (dd, *J* = 16.2, 3.2 Hz, 1H), 2.47 (dd, *J* = 12.8, 5.7 Hz, 1H), 2.29 (dt, *J* = 13.3, 3.3 Hz, 1H), 2.16 (t, *J* = 12.8 Hz, 1H), 2.06 (dt, *J* = 18.1, 5.5 Hz, 1H), 2.02–1.93 (m, 1H), 1.69–1.54 (m, 2H), 1.44–1.34 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.7, 170.7, 169.4, 137.7, 133.8, 132.0, 130.5, 128.9, 127.1, 126.0, 125.5, 123.0, 122.7, 108.8, 67.0, 66.6, 61.6, 47.8, 46.9, 45.9, 42.0, 36.9, 36.8, 35.1, 34.8, 24.4, 18.8, 14.5; MS(ESI) calcd for $C_{29}H_{34}N_2O_5$ 490.25 (M^+), found 491.28 ($M + H$)⁺, 513.27 ($M + Na$)⁺.

Piperidinone-Containing Amide 13z

Compound **13z** was prepared according to the general procedure D from carboxylic acid **8q** and amine **11p**: ¹H NMR (500 MHz, CDCl₃) δ 8.02–7.95 (m, 1H), 7.91–7.85 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.58–7.47 (m, 2H), 7.42 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.23 (dd, *J* = 7.1, 1.4 Hz, 1H), 6.38 (t, *J* = 5.5 Hz, 1H), 5.86 (d, *J* = 16.7 Hz, 1H), 5.01 (dd, *J* = 5.1, 2.8 Hz, 1H), 4.96 (d, *J* = 16.7 Hz, 1H), 4.26–4.19 (m, 2H), 3.45–3.36 (m, 3H), 3.31 (t, *J* = 6.6 Hz, 2H), 3.29–3.21 (m, 1H), 2.85–2.77 (m, 2H), 2.58–2.45 (m, 2H), 2.30 (dd, *J* = 13.2, 3.5 Hz, 1H), 2.11–2.01 (m, 2H), 2.01–1.92 (m, 1H), 1.78–1.62 (m, 4H), 1.58 (td, *J* = 13.6, 2.8 Hz, 1H),

1.53–1.45 (m, 2H), 1.42–1.33 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 4H), 0.87 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 170.8, 170.6, 137.4, 133.8, 131.7, 130.5, 129.0, 127.2, 126.1, 125.8, 125.7, 122.6, 122.5, 108.8, 71.0, 69.5, 61.6, 47.5, 47.0, 38.4, 38.1, 37.7, 36.6, 34.9, 31.9, 29.4, 24.3, 19.5, 18.7, 14.5, 14.0; MS(ESI) calcd for $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_5$ 490.25 (M^+), found 491.28 ($\text{M} + \text{H}$) $^+$, 513.27 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13aa

Compound **13aa** was prepared according to the general procedure D from carboxylic acid **8r** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, $J = 1.7$ Hz, 1H), 7.23–7.17 (m, 2H), 6.20 (t, $J = 5.9$ Hz, 1H), 5.26 (d, $J = 17.2$ Hz, 1H), 4.91 (dd, $J = 5.2, 2.8$ Hz, 1H), 4.61 (d, $J = 17.2$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.46–3.37 (m, 2H), 3.37–3.23 (m, 6H), 2.82 (dd, $J = 15.0, 5.4$ Hz, 1H), 2.74–2.67 (m, 1H), 2.47 (dd, $J = 15.0, 4.3$ Hz, 1H), 2.39 (dd, $J = 13.1, 5.7$ Hz, 1H), 2.27 (dd, $J = 13.0, 3.3$ Hz, 1H), 2.13 (dt, $J = 17.8, 5.6$ Hz, 1H), 2.08–1.97 (m, 2H), 1.77–1.63 (m, 2H), 1.54 (td, $J = 13.7, 2.8$ Hz, 1H), 1.35 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 170.8, 170.7, 137.1, 133.3, 133.0, 132.8, 129.1, 128.6, 127.5, 108.4, 71.6, 61.6, 58.9, 46.9, 46.7, 38.0, 37.8, 37.2, 36.4, 34.9, 29.3, 24.3, 18.7, 14.4; MS(ESI) calcd for $\text{C}_{25}\text{H}_{32}\text{Cl}_2\text{N}_2\text{O}_5$ 510.17 (M^+), found 511.19 ($\text{M} + \text{H}$) $^+$, 533.18 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ab

Compound **13ab** was prepared according to the general procedure D from carboxylic acid **8r** and amine **11q**: ^1H NMR (500 MHz, CDCl_3) δ 7.41 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 2.1$ Hz, 1H), 7.20 (dd, $J = 8.3, 2.2$ Hz, 1H), 5.32 (d, $J = 17.2$ Hz, 1H), 4.95 (dd, $J = 5.3, 2.7$ Hz, 1H), 4.54 (d, $J = 17.2$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.76–3.56 (m, 6H), 3.56–3.42 (m, 2H), 3.08 (dd, $J = 16.5, 5.7$ Hz, 1H), 2.77–2.68 (m, 1H), 2.61 (dd, $J = 16.6, 3.2$ Hz, 1H), 2.34 (dd, $J = 12.8, 5.7$ Hz, 1H), 2.30–2.22 (m, 1H), 2.20–2.10 (m, 2H), 2.07–1.97 (m, 1H), 1.76–1.62 (m, 2H), 1.55 (td, $J = 13.6, 2.8$ Hz, 1H), 1.44–1.33 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.04–0.96 (m, 2H), 0.84–0.75 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 172.5, 170.8, 169.4, 137.3, 133.6, 132.9, 132.7, 129.0, 127.5, 108.4, 61.6, 47.2, 46.9, 45.2, 41.9, 41.6, 36.6, 35.0, 34.6, 24.4, 18.7, 14.5, 11.2, 7.8; MS(ESI) calcd for $\text{C}_{29}\text{H}_{35}\text{Cl}_2\text{N}_3\text{O}_5$ 575.20 (M^+), found 576.22 ($\text{M} + \text{H}$) $^+$, 598.18 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ac

Compound **13ac** was prepared according to the general procedure D from carboxylic acid **8s** and amine **11b**: ^1H NMR (500 MHz, CDCl_3) δ 6.56 (t, $J = 6.0$ Hz, 1H), 5.49 (t, $J = 7.2$ Hz, 1H), 3.75 (s, 3H), 3.60 (ddd, $J = 14.2, 10.0, 5.4$ Hz, 1H), 3.06 (dt, $J = 13.2, 6.6$ Hz, 1H), 2.99 (dt, $J = 13.1, 6.3$ Hz, 1H), 2.65–2.58 (m, 1H), 2.50 (d, $J = 5.4$ Hz, 2H), 2.27–2.17 (m, 1H), 2.13 (dd, $J = 13.5, 4.2$ Hz, 1H), 2.08–1.95 (m, 1H), 1.77–1.60 (m, 10H), 1.60–1.49 (m, 1H), 1.49–1.34 (m, 1H), 1.34–1.08 (m, 18H), 0.95–0.83 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 171.0, 169.2, 141.1, 113.5, 52.5, 51.7, 46.6, 45.1, 42.9, 40.1, 37.0, 35.8, 34.3, 31.9, 29.5, 29.4, 27.2, 26.9, 26.6, 26.5, 25.7, 25.5, 25.2, 24.7, 22.8, 14.2; MS(ESI) calcd for $\text{C}_{29}\text{H}_{48}\text{N}_2\text{O}_4$ 488.36 (M^+), found 489.38 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13ad

Compound **13ad** was prepared according to the general procedure D from carboxylic acid **8s** and amine **11u**: ^1H NMR (500 MHz, CDCl_3) δ 5.47 (t, $J = 7.1$ Hz, 1H), 3.84–3.68 (m, 4H), 3.65–3.53 (m, 1H), 3.47–3.38 (m, 2H), 3.38–3.29 (m, 1H), 2.99 (dd, $J = 16.3, 3.8$ Hz, 1H), 2.82–2.73 (m, 1H), 2.33 (dd, $J = 16.4, 8.3$ Hz, 1H), 2.26–2.14 (m, 2H), 2.08–1.99 (m, 2H), 1.81–1.44 (m, 14H), 1.45–1.33 (m, 1H), 1.33–1.18 (m, 10H), 0.87 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 171.0, 169.2, 141.1, 113.5, 52.5, 51.7, 46.6, 45.1, 42.9, 40.1, 37.0, 35.8, 34.3, 31.9, 29.5, 29.4, 27.2, 26.9, 26.6, 26.5, 25.7, 25.5, 25.2, 24.7, 22.8,

14.2; MS(ESI) calcd for $C_{27}H_{44}N_2O_4$ 460.33 (M^+), found 461.35 ($M + H$)⁺, 483.32 ($M + Na$)⁺.

Piperidinone-Containing Amide 13ae

Compound **13ae** was prepared according to the general procedure D from carboxylic acid **8c** and amine **11d**: ¹H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, $J = 8.2, 6.9$ Hz, 2H), 7.24–7.19 (m, 1H), 7.15–7.10 (m, 2H), 6.32 (d, $J = 5.9$ Hz, 1H), 5.40 (t, $J = 7.1$ Hz, 1H), 5.14 (d, $J = 16.1$ Hz, 1H), 4.79 (d, $J = 16.1$ Hz, 1H), 3.78 (s, 3H), 3.27–3.14 (m, 2H), 2.81–2.74 (m, 1H), 2.56 (d, $J = 5.4$ Hz, 2H), 2.21 (dd, $J = 13.5, 4.4$ Hz, 1H), 2.12–2.02 (m, 2H), 1.96–1.85 (m, 2H), 1.77–1.62 (m, 3H), 1.62–1.52 (m, 2H), 1.33 (q, $J = 7.3$ Hz, 2H), 1.25–1.15 (m, 1H), 0.95–0.84 (m, 7H); ¹³C NMR (126 MHz, $CDCl_3$) δ 174.4, 171.7, 171.1, 140.9, 137.4, 128.7, 126.9, 126.3, 115.9, 52.7, 51.8, 49.4, 39.7, 38.5, 37.9, 37.8, 36.8, 36.8, 26.6, 26.0, 25.5, 24.9, 22.6, 22.6; MS(ESI) calcd for $C_{26}H_{36}N_2O_4$ 440.27 (M^+), found 441.27 ($M + H$)⁺, 463.24 ($M + Na$)⁺.

Piperidinone-Containing Amide 13af

Compound **13af** was prepared according to the general procedure D from carboxylic acid **8c** and amine **11l**: ¹H NMR (500 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 7.22–7.08 (m, 5H), 6.36 (s, 1H), 5.38 (t, $J = 7.1$ Hz, 1H), 5.08 (d, $J = 16.1$ Hz, 1H), 4.78 (d, $J = 16.1$ Hz, 1H), 3.76 (s, 3H), 3.25–3.16 (m, 2H), 2.77 (ddd, $J = 10.8, 8.8, 4.9$ Hz, 1H), 2.66–2.49 (m, 4H), 2.20 (dd, $J = 13.5, 4.3$ Hz, 1H), 2.12–1.98 (m, 2H), 1.95–1.84 (m, 2H), 1.78–1.52 (m, 8H), 1.51–1.43 (m, 2H), 1.26–1.14 (m, 1H); ¹³C NMR (126 MHz, $CDCl_3$) δ 174.3, 171.7, 171.1, 142.3, 140.9, 137.4, 128.7, 128.5, 128.4, 126.9, 126.3, 125.9, 115.9, 52.7, 51.7, 49.4, 39.7, 39.4, 37.8, 36.8, 36.8, 35.6, 29.3, 28.8, 26.6, 25.5, 24.9; MS(ESI) calcd for $C_{31}H_{38}N_2O_4$ 502.28 (M^+), found 503.28 ($M + H$)⁺, 505.3 ($M + Na$)⁺.

Piperidinone-Containing Amide 13ag

Compound **13ag** was prepared according to the general procedure D from carboxylic acid **8u** and amine **11j**: ¹H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, $J = 1.8, 0.9$ Hz, 1H), 6.33 (s, 1H), 6.30 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.19 (d, $J = 3.2$ Hz, 1H), 5.67 (t, $J = 7.1$ Hz, 1H), 5.11 (d, $J = 15.9$ Hz, 1H), 4.69 (d, $J = 15.9$ Hz, 1H), 3.76 (s, 3H), 3.21–3.14 (m, 2H), 2.75–2.67 (m, 1H), 2.58–2.48 (m, 2H), 2.22–2.12 (m, 2H), 2.06–1.93 (m, 2H), 1.83–1.73 (m, 2H), 1.73–1.57 (m, 2H), 1.45–1.38 (m, 2H), 1.36–1.23 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H); ¹³C NMR (126 MHz, $CDCl_3$) δ 174.3, 171.6, 171.1, 151.0, 141.6, 140.8, 116.1, 110.6, 108.0, 52.7, 51.8, 43.0, 39.6, 39.3, 37.7, 36.7, 36.6, 31.7, 26.6, 25.4, 24.9, 20.2, 13.9; MS(ESI) calcd for $C_{23}H_{32}N_2O_5$ 416.23 (M^+), found 417.27 ($M + H$)⁺, 439.26 ($M + Na$)⁺.

Piperidinone-Containing Amide 13ah

Compound **13ah** was prepared according to the general procedure D from carboxylic acid **8u** and amine **11o**: ¹H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, $J = 1.8, 0.9$ Hz, 1H), 6.56 (s, 1H), 6.30 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.19–6.16 (m, 1H), 6.05 (d, $J = 3.1$ Hz, 1H), 5.88–5.84 (m, 1H), 5.66 (t, $J = 7.2$ Hz, 1H), 5.06 (d, $J = 16.0$ Hz, 1H), 4.70 (d, $J = 15.9$ Hz, 1H), 4.34–4.29 (m, 2H), 3.76 (s, 3H), 2.78–2.71 (m, 1H), 2.60 (dd, $J = 14.4, 6.1$ Hz, 1H), 2.53 (dd, $J = 14.4, 5.0$ Hz, 1H), 2.27–2.21 (m, 3H), 2.21–2.12 (m, 2H), 2.06–1.92 (m, 2H), 1.83–1.72 (m, 2H), 1.72–1.57 (m, 3H), 1.31–1.22 (m, 1H); ¹³C NMR (126 MHz, $CDCl_3$) δ 174.3, 171.5, 170.9, 151.8, 151.0, 149.7, 141.6, 140.8, 116.0, 110.6, 108.1, 108.0, 106.3, 52.7, 51.8, 43.0, 39.6, 37.5, 36.7, 36.7, 36.6, 26.6, 25.4, 25.0, 13.7; MS(ESI) calcd for $C_{25}H_{30}N_2O_6$ 454.21 (M^+), found 455.26 ($M + H$)⁺, 477.24 ($M + Na$)⁺.

Piperidinone-Containing Amide 13ai

Compound **13ai** was prepared according to the general procedure D from carboxylic acid **8v** and amine **11f**: ^1H NMR (500 MHz, CDCl_3) δ 6.85–6.72 (m, 4H), 5.54–5.47 (m, 1H), 5.42–5.36 (m, 1H), 4.36 (dd, J = 14.6, 5.8 Hz, 1H), 4.31 (dd, J = 14.6, 5.6 Hz, 1H), 3.94–3.81 (m, 7H), 3.76 (s, 3H), 3.63–3.54 (m, 1H), 2.72–2.64 (m, 1H), 2.56 (dd, J = 14.2, 6.8 Hz, 1H), 2.45 (dd, J = 14.1, 4.2 Hz, 1H), 2.27–2.18 (m, 1H), 2.16–2.08 (m, 2H), 2.08–2.01 (m, 1H), 1.97 (s, 8H), 1.81 (dd, J = 11.2, 5.9 Hz, 1H), 1.75–1.62 (m, 3H), 1.62–1.56 (m, 2H), 1.56–1.48 (m, 2H), 1.40–1.30 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 171.3, 171.2, 149.2, 148.3, 140.6, 135.1, 131.3, 122.9, 120.0, 114.4, 111.1, 111.1, 56.0, 56.0, 52.6, 51.7, 43.5, 43.4, 39.9, 38.0, 37.1, 36.6, 34.9, 28.5, 27.0, 25.7, 25.4, 25.1, 23.0, 22.5; MS(ESI) calcd for $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_6$ 538.30 (M^+), found 539.35 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13aj

Compound **13aj** was prepared according to the general procedure D from carboxylic acid **8v** and amine **11m**: ^1H NMR (500 MHz, CDCl_3) δ 7.19 (td, J = 7.8, 1.8 Hz, 1H), 7.11 (dd, J = 7.4, 1.8 Hz, 1H), 6.90–6.82 (m, 2H), 6.44 (s, 1H), 5.51 (dd, J = 8.2, 6.2 Hz, 1H), 5.42 (dd, J = 4.2, 2.4 Hz, 1H), 4.00–3.87 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.60 (ddd, J = 14.2, 8.7, 5.9 Hz, 1H), 3.50–3.38 (m, 2H), 2.79 (t, J = 6.9 Hz, 2H), 2.67–2.59 (m, 1H), 2.56 (dd, J = 14.3, 6.3 Hz, 1H), 2.36–2.12 (m, 4H), 2.12–1.87 (m, 7H), 1.87–1.77 (m, 1H), 1.76–1.57 (m, 6H), 1.57–1.49 (m, 2H), 1.40–1.30 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 171.2, 171.2, 157.6, 140.7, 135.2, 130.7, 127.8, 127.5, 122.9, 120.7, 114.2, 110.4, 55.4, 52.6, 51.8, 43.4, 39.8, 39.7, 37.8, 37.1, 36.5, 35.0, 30.4, 28.5, 27.1, 25.7, 25.4, 25.1, 23.0, 22.5; MS(ESI) calcd for $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_5$ 522.31 (M^+), found 523.37 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13ak

Compound **13ak** was prepared according to the general procedure D from carboxylic acid **8w** and amine **11x**: ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.27 (m, 2H), 7.25–7.12 (m, 3H), 6.83–6.74 (m, 3H), 5.59 (t, J = 7.1 Hz, 1H), 4.75 (d, J = 12.8 Hz, 1H), 4.11–3.96 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.81–3.74 (m, 3H), 3.16–2.95 (m, 2H), 2.92–2.79 (m, 3H), 2.77–2.57 (m, 2H), 2.45–2.35 (m, 1H), 2.32–2.21 (m, 1H), 2.18 (dd, J = 13.0, 4.4 Hz, 1H), 2.12–1.99 (m, 2H), 1.91–1.83 (m, 3H), 1.82–1.75 (m, 1H), 1.75–1.54 (m, 6H), 1.46–1.38 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 171.2, 169.1, 149.0, 147.6, 145.3, 141.1, 131.9, 128.7, 126.8, 126.6, 120.8, 113.6, 112.2, 111.3, 56.0, 56.0, 52.6, 51.8, 46.5, 46.4, 46.2, 42.9, 42.8, 42.6, 42.5, 39.9, 36.9, 35.9, 34.2, 33.9, 33.1, 33.0, 32.7, 26.6, 25.5, 25.2; MS(ESI) calcd for $\text{C}_{35}\text{H}_{44}\text{N}_2\text{O}_6$ 588.32 (M^+), found 589.39 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13al

Compound **13al** was prepared according to the general procedure D from carboxylic acid **8w** and amine **11v**: ^1H NMR (500 MHz, CDCl_3) δ 6.82–6.73 (m, 3H), 5.58 (t, J = 7.1 Hz, 1H), 4.10–4.02 (m, 1H), 4.01–3.93 (m, 1H), 3.86 (d, J = 10.6 Hz, 7H), 3.78 (s, 4H), 3.74–3.64 (m, 2H), 2.91 (dd, J = 16.3, 4.0 Hz, 1H), 2.88–2.83 (m, 2H), 2.82–2.76 (m, 1H), 2.69–2.53 (m, 4H), 2.32 (dd, J = 16.3, 7.7 Hz, 1H), 2.25 (q, J = 7.9, 7.3 Hz, 1H), 2.12 (dd, J = 13.0, 4.4 Hz, 1H), 2.09–1.97 (m, 2H), 1.82–1.75 (m, 1H), 1.75–1.60 (m, 4H), 1.45–1.37 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 171.0, 169.3, 149.0, 147.7, 141.0, 131.9, 120.8, 113.8, 112.2, 111.3, 56.1, 56.0, 52.6, 51.8, 48.2, 46.3, 44.5, 39.9, 36.9, 35.8, 34.2, 32.7, 27.9, 27.5, 26.6, 25.6, 25.2; MS(ESI) calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_6\text{S}$ 530.25 (M^+), found 531.31 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13am

Compound **13am** was prepared according to the general procedure D from carboxylic acid **8x** and amine **11x**: ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, J = 8.2 Hz, 1H), 7.87 (dd, J = 8.0, 1.6 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.56–7.47 (m, 2H), 7.44 (t, J = 7.7 Hz, 1H), 7.36–7.26

(m, 3H), 7.24–7.13 (m, 3H), 5.58 (dd, J = 17.2, 6.7 Hz, 1H), 5.32 (t, J = 6.9 Hz, 1H), 5.26 (dd, J = 16.5, 8.5 Hz, 1H), 4.81 (d, J = 12.1 Hz, 1H), 4.06–3.99 (m, 1H), 3.83 (s, 3H), 3.16–3.06 (m, 1H), 3.05–2.93 (m, 2H), 2.77–2.58 (m, 3H), 2.34–2.27 (m, 1H), 2.14 (t, J = 13.1 Hz, 1H), 2.10–2.00 (m, 2H), 1.95–1.84 (m, 3H), 1.83–1.54 (m, 6H), 1.33–1.23 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.7, 171.3, 145.3, 141.4, 133.8, 132.0, 130.7, 128.9, 128.7, 127.2, 126.9, 126.6, 126.0, 125.9, 125.6, 123.6, 122.8, 115.3, 52.6, 51.9, 48.7, 46.2, 42.9, 42.7, 42.5, 40.0, 36.6, 36.1, 34.1, 33.8, 33.1, 26.1, 25.0; MS(ESI) calcd for $\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_4$ 564.30 (M^+), found 565.3 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13an

Compound **13an** was prepared according to the general procedure D from carboxylic acid **8x** and amine **11o**: ^1H NMR (500 MHz, CDCl_3) δ 7.93 (dd, J = 8.3, 1.3 Hz, 1H), 7.90–7.85 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.56–7.47 (m, 2H), 7.41 (dd, J = 8.3, 7.1 Hz, 1H), 7.14 (dd, J = 7.1, 1.3 Hz, 1H), 6.53 (s, 1H), 6.03 (d, J = 3.0 Hz, 1H), 5.85–5.82 (m, 1H), 5.45 (d, J = 16.4 Hz, 1H), 5.35–5.27 (m, 2H), 4.41–4.28 (m, 2H), 3.81 (s, 3H), 2.94–2.83 (m, 1H), 2.63 (d, J = 5.4 Hz, 2H), 2.30–2.23 (m, 1H), 2.22 (s, 3H), 2.10–1.98 (m, 3H), 1.91–1.83 (m, 1H), 1.78–1.62 (m, 3H), 1.62–1.52 (m, 1H), 1.26–1.15 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 171.4, 170.9, 151.8, 149.6, 141.1, 133.9, 131.5, 130.6, 129.0, 127.4, 126.1, 125.7, 123.2, 122.7, 116.0, 108.1, 106.3, 52.7, 51.8, 48.4, 39.6, 37.6, 36.9, 36.8, 36.8, 26.5, 25.4, 25.0, 13.7; MS(ESI) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_5$ 514.25 (M^+), found 515.25 ($\text{M} + \text{H}$) $^+$, 527.23 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ao

Compound **13ao** was prepared according to the general procedure D from carboxylic acid **8y** and amine **11d**: ^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, J = 2.1 Hz, 1H), 7.19 (dd, J = 8.3, 2.2 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.05 (s, 1H), 5.16 (t, J = 7.0 Hz, 1H), 4.91 (s, 2H), 3.80 (s, 3H), 3.26–3.14 (m, 2H), 2.81–2.72 (m, 1H), 2.59 (dd, J = 14.6, 4.8 Hz, 1H), 2.52 (dd, J = 14.6, 5.7 Hz, 1H), 2.21 (dd, J = 13.4, 4.6 Hz, 1H), 2.14–1.99 (m, 3H), 1.97–1.87 (m, 1H), 1.82–1.72 (m, 2H), 1.72–1.52 (m, 3H), 1.37–1.23 (m, 3H), 0.89 (d, J = 3.4 Hz, 3H), 0.87 (d, J = 3.3 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 171.5, 170.8, 141.0, 133.1, 133.0, 133.0, 129.3, 128.3, 127.5, 115.2, 52.8, 51.8, 47.8, 39.5, 38.5, 38.0, 37.4, 37.0, 36.6, 26.4, 26.0, 25.4, 25.0, 22.6, 22.6; MS(ESI) calcd for $\text{C}_{26}\text{H}_{34}\text{Cl}_2\text{N}_2\text{O}_4$ 508.19 (M^+), found 509.23 ($\text{M} + \text{H}$) $^+$, 531.22 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ap

Compound **13ap** was prepared according to the general procedure D from carboxylic acid **8y** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, J = 2.1 Hz, 1H), 7.18 (dd, J = 8.4, 2.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.28 (s, 1H), 5.17 (t, J = 7.0 Hz, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.82 (d, J = 17.2 Hz, 1H), 3.80 (s, 3H), 2.94–2.84 (m, 2H), 2.82–2.72 (m, 1H), 2.64 (dd, J = 14.1, 4.5 Hz, 1H), 2.56 (dd, J = 14.4, 5.9 Hz, 1H), 2.22 (dd, J = 13.5, 4.5 Hz, 1H), 2.15–1.98 (m, 3H), 1.98–1.86 (m, 4H), 1.83–1.64 (m, 6H), 1.64–1.54 (m, 4H), 1.45–1.39 (m, 6H), 1.32–1.24 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.3, 171.6, 171.1, 141.1, 133.1, 133.0, 132.9, 129.3, 128.3, 127.5, 115.2, 52.8, 51.8, 51.1, 47.8, 40.3, 39.5, 37.5, 37.1, 37.0, 36.7, 33.7, 28.3, 26.6, 25.5, 25.0; MS(ESI) calcd for $\text{C}_{32}\text{H}_{40}\text{Cl}_2\text{N}_2\text{O}_4$ 586.24 (M^+), found 587.28 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13aq

Compound **13aq** was prepared according to the general procedure D from carboxylic acid **8z** and amine **11v**: ^1H NMR (500 MHz, CDCl_3) δ 5.20 (t, J = 4.1 Hz, 1H), 3.98–3.89 (m, 1H), 3.79–3.66 (m, 5H), 3.65 (s, 3H), 2.78–2.64 (m, 2H), 2.62–2.48 (m, 5H), 2.25 (dd, J = 12.6, 5.9 Hz, 1H), 2.19 (d, J = 13.6 Hz, 1H), 2.00 (d, J = 4.1 Hz, 2H), 1.80 (t, J = 12.7 Hz, 1H),

1.69–1.61 (m, 1H), 1.59–1.51 (m, 1H), 1.43 (d, $J = 13.5$ Hz, 1H), 1.35–1.21 (m, 10H), 0.95 (s, 3H), 0.87 (t, $J = 6.9$ Hz, 3H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.8, 169.8, 169.2, 135.6, 106.4, 52.4, 48.3, 47.5, 45.5, 44.5, 44.5, 38.9, 38.7, 36.5, 35.4, 32.0, 31.9, 29.5, 29.5, 28.7, 27.9, 27.5, 27.4, 26.9, 25.5, 22.8, 14.2; MS(ESI) calcd for $\text{C}_{27}\text{H}_{44}\text{N}_2\text{O}_4\text{S}$ 492.30 (M^+), found 493.42 ($\text{M} + \text{H}$) $^+$, 515.4 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ar

Compound **13ar** was prepared according to the general procedure D from carboxylic acid **8z** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 7.30–7.23 (m, 3H), 7.21–7.13 (m, 3H), 6.29 (s, 1H), 5.16 (t, $J = 4.1$ Hz, 1H), 3.72–3.65 (m, 2H), 3.64 (s, 3H), 3.28–3.14 (m, 2H), 2.67–2.57 (m, 3H), 2.54–2.39 (m, 2H), 2.26 (dd, $J = 12.9, 5.7$ Hz, 1H), 2.19 (d, $J = 13.7$ Hz, 1H), 2.00–1.95 (m, 2H), 1.72 (t, $J = 13.1$ Hz, 1H), 1.68–1.56 (m, 3H), 1.55–1.45 (m, 2H), 1.42 (d, $J = 13.6$ Hz, 1H), 1.35–1.22 (m, 10H), 0.95 (s, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 171.1, 170.0, 142.3, 135.3, 128.5, 128.4, 125.9, 106.9, 52.5, 47.3, 45.5, 44.5, 39.4, 38.8, 38.4, 37.4, 35.6, 32.0, 31.8, 29.5, 29.5, 29.4, 28.7, 28.6, 27.4, 26.9, 25.4, 22.8, 14.2; MS(ESI) calcd for $\text{C}_{33}\text{H}_{50}\text{N}_2\text{O}_4$ 538.38 (M^+), found 539.49 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13as

Compound **13as** was prepared according to the general procedure D from carboxylic acid **8aa** and amine **11f**: ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.27 (m, 2H), 7.23–7.16 (m, 3H), 6.79–6.72 (m, 3H), 6.38 (s, 1H), 5.41 (d, $J = 16.1$ Hz, 1H), 5.09 (t, $J = 4.1$ Hz, 1H), 4.50 (d, $J = 16.1$ Hz, 1H), 4.42–4.34 (m, 1H), 4.25 (dd, $J = 14.4, 5.3$ Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 2.77 (dd, $J = 14.4, 5.0$ Hz, 1H), 2.65 (dt, $J = 18.4, 5.3$ Hz, 1H), 2.50 (dd, $J = 14.4, 4.9$ Hz, 1H), 2.34 (dd, $J = 12.9, 5.8$ Hz, 1H), 2.26–2.19 (m, 1H), 2.03 (t, $J = 13.2$ Hz, 1H), 1.90–1.85 (m, 2H), 1.47 (d, $J = 13.7$ Hz, 1H), 0.93 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.6, 170.8, 170.5, 149.2, 148.4, 137.7, 136.2, 131.1, 128.6, 126.8, 126.3, 120.1, 111.2, 111.2, 108.3, 56.0, 55.9, 52.6, 49.2, 47.2, 45.7, 43.4, 38.7, 38.6, 38.5, 37.4, 31.8, 28.6, 25.4; MS(ESI) calcd for $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_6$ 534.27 (M^+), found 535.34 ($\text{M} + \text{H}$) $^+$, 557.33 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13at

Compound **13at** was prepared according to the general procedure D from carboxylic acid **8aa** and amine **11g**: ^1H NMR (500 MHz, CDCl_3) δ 7.51–7.44 (m, 2H), 7.42–7.34 (m, 2H), 7.31–7.26 (m, 2H), 7.22–7.17 (m, 3H), 6.77 (t, $J = 6.1$ Hz, 1H), 5.39 (d, $J = 16.1$ Hz, 1H), 5.12 (t, $J = 4.1$ Hz, 1H), 4.56–4.44 (m, 2H), 4.31 (dd, $J = 15.2, 5.6$ Hz, 1H), 3.66 (s, 3H), 2.79 (dd, $J = 14.4, 4.8$ Hz, 1H), 2.69–2.60 (m, 1H), 2.54 (dd, $J = 14.4, 5.2$ Hz, 1H), 2.35 (dd, $J = 13.0, 5.8$ Hz, 1H), 2.23 (d, $J = 13.6$ Hz, 2H), 1.99 (t, $J = 13.2$ Hz, 1H), 1.91–1.86 (m, 2H), 1.48 (d, $J = 13.7$ Hz, 1H), 0.94 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.5, 171.2, 170.6, 139.7, 137.6, 136.2, 131.1, 131.0 (q, $^2J_{\text{C-F}} = 31.5$ Hz), 129.2, 128.6, 126.9, 126.3, 124.2 (q, $^1J_{\text{C-F}} = 272.2$ Hz), 124.4 (q, $^3J_{\text{C-F}} = 3.8$ Hz), 124.2 (q, $^3J_{\text{C-F}} = 3.8$ Hz), 108.6, 52.6, 49.3, 47.2, 45.7, 43.0, 38.7, 38.6, 38.5, 37.5, 31.8, 28.6, 25.4; MS(ESI) calcd for $\text{C}_{30}\text{H}_{33}\text{F}_3\text{N}_2\text{O}_4$ 542.24 (M^+), found 543.32 ($\text{M} + \text{H}$) $^+$, 565.3 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13au

Compound **13au** was prepared according to the general procedure D from carboxylic acid **8ab** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 6.77–6.72 (m, 2H), 6.71–6.65 (m, 1H), 6.36 (s, 1H), 5.94–5.89 (m, 2H), 5.36 (d, $J = 15.8$ Hz, 1H), 5.12 (t, $J = 4.1$ Hz, 1H), 4.42 (d, $J = 15.8$ Hz, 1H), 3.66 (s, 3H), 3.44–3.38 (m, 2H), 3.38–3.32 (m, 1H), 3.29 (s, 3H), 3.27–3.17 (m, 1H), 2.74 (dd, $J = 14.5, 5.3$ Hz, 1H), 2.63–2.54 (m, 1H), 2.49 (dd, $J = 14.6, 4.7$ Hz, 1H), 2.30 (dd, $J = 13.0, 5.8$ Hz, 1H), 2.20 (d, $J = 13.6$ Hz, 1H), 1.95 (t, $J = 13.1$ Hz, 1H),

1.90–1.86 (m, 2H), 1.77–1.68 (m, 2H), 1.45 (d, J = 13.6 Hz, 1H), 0.92 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.61, 170.76, 170.59, 148.00, 146.40, 136.34, 131.84, 119.49, 108.35, 108.17, 107.29, 101.01, 71.45, 58.84, 52.55, 49.13, 47.23, 45.65, 38.72, 38.43, 38.35, 37.86, 37.29, 31.85, 29.31, 28.63, 25.44; MS(ESI) calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_7$ 500.25 (M^+), found 501.33 ($\text{M} + \text{H}$) $^+$, 523.31 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13av

Compound **13av** was prepared according to the general procedure D from carboxylic acid **8ab** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 6.77–6.70 (m, 2H), 6.70–6.65 (m, 1H), 5.94–5.90 (m, 2H), 5.27 (d, J = 15.7 Hz, 1H), 5.17 (t, J = 4.1 Hz, 1H), 4.52 (d, J = 15.7 Hz, 1H), 3.65 (s, 3H), 3.03 (dd, J = 13.4, 6.8 Hz, 1H), 2.96–2.84 (m, 1H), 2.80 (dd, J = 13.4, 5.5 Hz, 1H), 2.63–2.50 (m, 2H), 2.34 (dd, J = 13.0, 5.6 Hz, 1H), 2.21 (d, J = 13.6 Hz, 1H), 1.97–1.91 (m, 3H), 1.89 (d, J = 4.0 Hz, 2H), 1.68 (d, J = 12.4 Hz, 4H), 1.65–1.55 (m, 4H), 1.49–1.39 (m, 7H), 0.93 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 171.4, 171.0, 148.0, 146.5, 136.1, 131.4, 119.7, 108.3, 107.4, 101.0, 52.5, 51.3, 49.0, 47.1, 45.6, 40.3, 40.2, 39.7, 38.7, 38.4, 37.4, 37.0, 36.5, 33.8, 31.8, 28.6, 28.3, 28.0, 25.4; MS(ESI) calcd for $\text{C}_{34}\text{H}_{44}\text{N}_2\text{O}_6$ 576.32 (M^+), found 577.39 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13aw

Compound **13aw** was prepared according to the general procedure D from carboxylic acid **8d** and amine **11r**: ^1H NMR (500 MHz, CDCl_3) δ 7.49 (dd, J = 1.6, 0.8 Hz, 1H), 7.32 (dd, J = 1.7, 0.9 Hz, 1H), 7.04 (dd, J = 3.5, 0.9 Hz, 1H), 6.49 (dd, J = 3.5, 1.8 Hz, 1H), 6.34–6.28 (m, 2H), 5.38 (t, J = 4.1 Hz, 1H), 5.29 (d, J = 15.9 Hz, 1H), 4.56 (d, J = 15.9 Hz, 1H), 3.79 (s, 4H), 3.64 (s, 4H), 3.54 (t, J = 5.0 Hz, 2H), 2.83 (dd, J = 16.4, 6.7 Hz, 1H), 2.75 (dd, J = 16.4, 3.6 Hz, 1H), 2.67–2.59 (m, 1H), 2.30 (dd, J = 12.7, 5.9 Hz, 1H), 2.20 (d, J = 13.6 Hz, 1H), 2.00–1.95 (m, 2H), 1.91 (t, J = 12.8 Hz, 1H), 1.44 (d, J = 13.7 Hz, 1H), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.7, 170.1, 169.4, 159.3, 151.4, 147.8, 144.1, 141.4, 136.2, 117.2, 111.6, 110.7, 108.0, 107.7, 52.6, 47.4, 45.7, 42.8, 38.8, 38.8, 36.6, 35.0, 31.8, 28.7, 25.4; MS(ESI) calcd for $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_7$ 537.25 (M^+), found 538.33 ($\text{M} + \text{H}$) $^+$, 560.31 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ax

Compound **13ax** was prepared according to the general procedure D from carboxylic acid **8d** and amine **11o**: ^1H NMR (500 MHz, CDCl_3) δ 7.31 (dd, J = 1.8, 0.9 Hz, 1H), 6.38–6.27 (m, 2H), 6.25 (dd, J = 3.2, 1.0 Hz, 1H), 6.03 (d, J = 3.0 Hz, 1H), 5.85 (dd, J = 2.7, 1.4 Hz, 1H), 5.40 (t, J = 4.1 Hz, 1H), 5.27 (d, J = 15.9 Hz, 1H), 4.53 (d, J = 15.9 Hz, 1H), 4.36 (dd, J = 15.4, 5.9 Hz, 1H), 4.17 (dd, J = 15.4, 5.1 Hz, 1H), 3.64 (s, 3H), 2.71 (dd, J = 14.4, 5.1 Hz, 1H), 2.62–2.53 (m, 1H), 2.50 (dd, J = 14.3, 4.9 Hz, 1H), 2.29 (dd, J = 13.0, 5.9 Hz, 1H), 2.24 (s, 3H), 2.20 (d, J = 13.6 Hz, 1H), 1.97 (d, J = 4.0 Hz, 2H), 1.80 (t, J = 13.1 Hz, 1H), 1.44 (d, J = 13.7 Hz, 1H), 0.95 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 170.6, 170.2, 151.8, 151.3, 149.6, 141.6, 136.0, 110.6, 108.2, 108.2, 107.9, 106.3, 52.6, 47.2, 45.6, 42.5, 38.8, 38.4, 38.4, 37.3, 36.7, 31.8, 28.7, 25.3, 13.7; MS(ESI) calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_6$ 468.23 (M^+), found 469.31 ($\text{M} + \text{H}$) $^+$, 491.28 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ay

Compound **13ay** was prepared according to the general procedure D from carboxylic acid **8ac** and amine **11h**: ^1H NMR (500 MHz, CDCl_3) δ 8.00 (dd, J = 6.8, 2.4 Hz, 1H), 7.87–7.81 (m, 1H), 7.77 (t, J = 4.8 Hz, 1H), 7.53–7.45 (m, 2H), 7.41–7.36 (m, 2H), 6.48 (t, J = 5.2 Hz, 1H), 5.34 (t, J = 3.5 Hz, 1H), 5.06 (dd, J = 14.5, 6.8 Hz, 1H), 4.94 (t, J = 4.0 Hz, 1H), 4.60 (dd, J = 14.5, 4.6 Hz, 1H), 3.59 (s, 3H), 3.42 (t, J = 8.3 Hz, 2H), 2.80 (dd, J = 13.9, 4.6 Hz, 1H), 2.51–2.38 (m, 2H), 2.25 (dd, J = 12.9, 5.7 Hz, 1H), 2.18 (d, J = 13.4 Hz, 1H), 2.05–

1.91 (m, 6H), 1.90–1.84 (m, 2H), 1.77–1.64 (m, 2H), 1.62–1.50 (m, 4H), 1.38 (d, J = 13.6 Hz, 1H), 0.97 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 170.5, 169.5, 135.3, 134.9, 134.0, 134.0, 131.5, 128.8, 128.6, 126.9, 126.6, 125.9, 125.5, 123.9, 122.4, 106.8, 52.4, 47.2, 45.4, 43.3, 41.5, 38.8, 38.5, 38.1, 37.5, 34.4, 31.9, 28.6, 28.6, 25.4, 25.4, 23.0, 22.5; MS(ESI) calcd for $\text{C}_{34}\text{H}_{42}\text{N}_2\text{O}_4$ 542.31 (M^+), found 543.38 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13az

Compound **13az** was prepared according to the general procedure D from carboxylic acid **8ac** and amine **11k**: ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.27 (m, 2H), 7.26–7.20 (m, 3H), 6.62 (t, J = 5.6 Hz, 1H), 5.44 (m, 1H), 5.21 (t, J = 4.1 Hz, 1H), 4.45 (dd, J = 14.6, 6.9 Hz, 1H), 4.32 (dd, J = 15.0, 5.5 Hz, 1H), 3.81–3.66 (m, 2H), 3.64 (s, 3H), 2.71 (dd, J = 13.7, 4.3 Hz, 1H), 2.57–2.45 (m, 2H), 2.28 (dd, J = 12.8, 5.6 Hz, 1H), 2.24–2.18 (m, 2H), 2.04–1.92 (m, 7H), 1.75 (t, J = 13.0 Hz, 1H), 1.65–1.51 (m, 4H), 1.45 (d, J = 13.7 Hz, 1H), 0.97 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 171.0, 169.8, 138.6, 135.4, 135.3, 128.7, 127.8, 127.4, 122.5, 106.9, 52.5, 47.3, 45.5, 43.6, 43.5, 38.9, 38.7, 38.4, 37.4, 34.8, 31.8, 28.7, 28.6, 25.5, 25.4, 23.1, 22.5; MS(ESI) calcd for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_4$ 492.30 (M^+), found 493.35 ($\text{M} + \text{H}$) $^+$, 515.34 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13ba

Compound **13ba** was prepared according to the general procedure D from carboxylic acid **8ad** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 6.84–6.78 (m, 3H), 5.27 (t, J = 4.1 Hz, 1H), 3.93 (t, J = 8.4 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 3.42 (t, J = 5.9 Hz, 2H), 3.35–3.27 (m, 5H), 2.98–2.88 (m, 1H), 2.81–2.71 (m, 1H), 2.66–2.59 (m, 1H), 2.59–2.47 (m, 4H), 2.27 (dd, J = 12.6, 5.3 Hz, 1H), 2.24–2.18 (m, 1H), 2.05–1.99 (m, 2H), 1.82–1.69 (m, 3H), 1.46 (d, J = 13.6 Hz, 1H), 0.97 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 170.8, 170.0, 149.0, 147.7, 135.4, 132.1, 120.7, 112.2, 111.4, 106.8, 71.4, 58.9, 56.1, 56.0, 52.5, 47.3, 46.1, 45.5, 38.9, 38.5, 38.4, 37.8, 37.1, 32.7, 31.8, 29.4, 28.7, 25.4; MS(ESI) calcd for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_7$ 530.30 (M^+), found 531.36 ($\text{M} + \text{H}$) $^+$, 553.35 ($\text{M} + \text{Na}$) $^+$.

Piperidinone-Containing Amide 13bb

Compound **13bb** was prepared according to the general procedure D from carboxylic acid **8ad** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 6.84–6.76 (m, 3H), 6.24 (s, 1H), 5.29 (t, J = 4.0 Hz, 1H), 4.07–3.97 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 2.97–2.83 (m, 3H), 2.81–2.71 (m, 2H), 2.58–2.45 (m, 2H), 2.29 (dd, J = 12.9, 5.6 Hz, 1H), 2.23 (dd, J = 13.6, 1.7 Hz, 1H), 2.05–1.99 (m, 2H), 1.96–1.91 (m, 3H), 1.80 (t, J = 13.0 Hz, 1H), 1.73–1.55 (m, 8H), 1.50–1.40 (m, 7H), 0.97 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 171.1, 170.1, 149.0, 147.7, 135.3, 132.0, 120.6, 112.1, 111.4, 107.1, 56.0, 56.0, 52.5, 51.1, 47.3, 45.9, 45.6, 40.3, 39.7, 38.9, 38.6, 38.3, 37.5, 37.0, 36.5, 33.7, 32.6, 31.8, 28.7, 28.3, 28.0, 25.5; MS(ESI) calcd for $\text{C}_{36}\text{H}_{50}\text{N}_2\text{O}_6$ 606.37 (M^+), found 607.42 ($\text{M} + \text{H}$) $^+$.

Piperidinone-Containing Amide 13bc

Compound **13bc** was prepared according to the general procedure D from carboxylic acid **8ae** and amine **11b**: ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, J = 8.2 Hz, 1H), 7.93–7.87 (m, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.54 (m, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.0 Hz, 1H), 5.94 (d, J = 16.7 Hz, 1H), 5.10 (t, J = 4.1 Hz, 1H), 4.97 (d, J = 16.7 Hz, 1H), 3.73 (s, 3H), 3.27 (s, 1H), 3.21 (dt, J = 13.2, 6.5 Hz, 1H), 2.99 (m, 1H), 2.74–2.66 (m, 1H), 2.63 (dd, J = 14.9, 7.0 Hz, 1H), 2.49 (dd, J = 13.2, 5.8 Hz, 1H), 2.28 (dd, J = 13.6, 1.8 Hz, 1H), 2.05 (t, J = 13.2 Hz, 1H), 1.91–1.77 (m, 2H), 1.71–1.57 (m, 6H), 1.51 (d, J = 13.8 Hz, 2H), 1.21–1.06 (m, 3H), 0.94 (s, 3H), 0.91–0.84 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.1, 172.1, 171.7, 135.9, 133.8, 131.0, 130.3, 129.1, 127.6, 126.4, 126.0, 125.7, 122.5,

122.2, 52.8, 48.5, 46.8, 45.6, 38.6, 38.5, 37.5, 37.0, 31.7, 30.9, 30.9, 30.4, 28.7, 26.4, 25.8, 25.8, 25.4, 25.3; MS(ESI) calcd for $C_{33}H_{42}N_2O_4$ 530.31 (M^+), found 531.4 ($M + H$) $^+$.

Piperidinone-Containing Amide 13bd

Compound **13bd** was prepared according to the general procedure D from carboxylic acid **8ae** and amine **11p**: 1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.58–7.47 (m, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.1 Hz, 1H), 6.38 (s, 1H), 5.97 (d, J = 16.7 Hz, 1H), 4.97 (dd, J = 5.1, 3.0 Hz, 1H), 4.89 (d, J = 16.7 Hz, 1H), 3.71 (s, 3H), 3.46–3.36 (m, 3H), 3.30 (t, J = 6.6 Hz, 2H), 3.27–3.17 (m, 1H), 2.83 (dd, J = 14.6, 5.4 Hz, 1H), 2.72–2.62 (m, 1H), 2.49 (dd, J = 14.6, 4.6 Hz, 1H), 2.39 (dd, J = 13.0, 5.8 Hz, 1H), 2.25 (dd, J = 13.7, 1.8 Hz, 1H), 2.14 (t, J = 13.2 Hz, 1H), 1.89–1.74 (m, 2H), 1.74–1.65 (m, 2H), 1.56–1.44 (m, 3H), 1.35–1.23 (m, 2H), 0.92 (s, 3H), 0.87 (t, J = 7.4 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 170.7, 170.4, 136.6, 133.8, 131.9, 130.5, 128.9, 127.2, 126.1, 125.8, 125.7, 122.8, 122.6, 108.5, 71.0, 69.5, 52.6, 48.2, 47.3, 45.8, 38.6, 38.5, 38.2, 38.1, 37.5, 31.9, 31.9, 29.3, 28.7, 25.4, 19.5, 14.0; MS(ESI) calcd for $C_{33}H_{44}N_2O_5$ 548.33 (M^+), found 549.41 ($M + H$) $^+$, 571.39 ($M + Na$) $^+$.

Piperidinone-Containing Amide 13be

Compound **13be** was prepared according to the general procedure D from carboxylic acid **8af** and amine **11e**: 1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 2.0 Hz, 1H), 7.26–7.21 (m, 1H), 7.21–7.14 (m, 2H), 6.94–6.88 (m, 2H), 6.31 (s, 1H), 5.31 (d, J = 17.2 Hz, 1H), 4.88 (t, J = 4.0 Hz, 1H), 4.63–4.44 (m, 3H), 3.71 (s, 3H), 2.88 (dd, J = 15.1, 5.0 Hz, 1H), 2.64–2.54 (m, 1H), 2.44 (dd, J = 15.1, 4.4 Hz, 1H), 2.30 (dd, J = 12.9, 5.8 Hz, 1H), 2.23 (d, J = 13.7 Hz, 1H), 2.14 (t, J = 13.1 Hz, 1H), 1.91–1.86 (m, 2H), 1.50 (d, J = 13.6 Hz, 1H), 0.94 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 170.6, 170.5, 141.0, 136.1, 133.3, 133.1, 132.8, 129.1, 128.6, 127.5, 127.0, 126.0, 125.2, 108.2, 52.7, 47.3, 47.2, 45.7, 38.6, 38.4, 38.2, 37.6, 37.1, 31.8, 28.7, 25.5; MS(ESI) calcd for $C_{27}H_{30}Cl_2N_2O_4S$ 548.13 (M^+), found 549.2 ($M + H$) $^+$.

Piperidinone-Containing Amide 13bf

Compound **13bf** was prepared according to the general procedure D from carboxylic acid **8af** and amine **11j**: 1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 1.8 Hz, 1H), 7.23–7.16 (m, 2H), 5.87 (s, 1H), 5.37 (d, J = 17.2 Hz, 1H), 4.87 (t, J = 4.1 Hz, 1H), 4.52 (d, J = 17.2 Hz, 1H), 3.71 (s, 3H), 3.28–3.17 (m, 1H), 3.16–3.05 (m, 1H), 2.85 (dd, J = 14.9, 5.0 Hz, 1H), 2.56 (dt, J = 15.0, 5.1 Hz, 1H), 2.40 (dd, J = 15.0, 4.3 Hz, 1H), 2.29 (dd, J = 12.9, 5.8 Hz, 1H), 2.22 (d, J = 13.7 Hz, 1H), 2.14 (t, J = 13.1 Hz, 1H), 1.90–1.85 (m, 2H), 1.49 (d, J = 13.7 Hz, 1H), 1.45–1.35 (m, 2H), 1.34–1.23 (m, 2H), 0.93 (s, 3H), 0.88 (t, J = 7.3 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 170.7, 170.7, 136.2, 133.3, 133.0, 132.8, 129.1, 128.5, 127.4, 108.2, 52.7, 47.5, 47.2, 45.7, 39.5, 38.6, 38.3, 37.7, 37.2, 31.8, 31.7, 28.7, 25.4, 20.2, 13.9; MS(ESI) calcd for $C_{26}H_{34}Cl_2N_2O_4$ 508.19 (M^+), found 509.23 ($M + H$) $^+$, 531.23 ($M + Na$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27a ((3*SR*,4*aRS*,5*RS*,7*RS*)-Methyl 7-*tert*-Butyl-5-methyl-1-octyl-2-oxo-3-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-2,3,4,4*a*,5,7-hexahydro-1*H*-pyrano[4,3-*b*]pyridine-4*a*-carboxylate)

Compound **27a** was prepared according to the general procedure D from carboxylic acid **26e** and amine **11a**: 1H NMR (500 MHz, $CDCl_3$) δ 5.48 (d, J = 1.8 Hz, 1H), 4.02 (ddd, J = 17.7, 5.2, 2.6 Hz, 1H), 3.96 (ddd, J = 17.5, 4.9, 2.6 Hz, 1H), 3.90 (q, J = 6.4 Hz, 1H), 3.83 (d, J = 1.6 Hz, 1H), 3.82–3.75 (m, 1H), 3.67 (s, 3H), 3.50–3.43 (m, 1H), 3.10–3.02 (m, 1H), 2.68–2.60 (m, 1H), 2.56 (dd, J = 14.8, 5.9 Hz, 1H), 2.46 (dd, J = 12.9, 7.6 Hz, 1H), 2.20 (t, J = 2.6 Hz, 1H), 1.69–1.58 (m, 2H), 1.50–1.41 (m, 1H), 1.34–1.20 (m, 12H), 1.17 (d, J = 6.5 Hz,

3H), 0.89 (d, $J = 15.2$ Hz, 12H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.6, 170.8, 170.7, 138.1, 110.0, 82.1, 74.7, 71.5, 52.7, 51.5, 44.5, 40.0, 37.5, 34.8, 31.9, 29.4, 29.4, 29.3, 29.1, 27.3, 27.0, 25.7, 22.8, 16.3, 14.2; MS(ESI) calcd for $\text{C}_{28}\text{H}_{44}\text{N}_2\text{O}_5$ 488.33 (M^+), found 489.42 ($\text{M} + \text{H}$) $^+$, 511.41 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27b

Compound **27b** was prepared according to the general procedure D from carboxylic acid **26e** and amine **11e**: ^1H NMR (500 MHz, CDCl_3) δ 7.19 (dd, $J = 5.0, 1.4$ Hz, 1H), 6.97–6.90 (m, 3H), 5.47 (s, 1H), 4.62–4.51 (m, 2H), 3.90 (q, $J = 6.4$ Hz, 1H), 3.83 (d, $J = 1.5$ Hz, 1H), 3.75 (ddd, $J = 13.5, 10.1, 6.0$ Hz, 1H), 3.67 (s, 3H), 3.42 (ddd, $J = 14.2, 10.0, 4.9$ Hz, 1H), 3.10–3.02 (m, 1H), 2.62–2.56 (m, 2H), 2.48 (dd, $J = 12.9, 7.6$ Hz, 1H), 1.67 (dd, $J = 12.9, 10.9$ Hz, 1H), 1.63–1.54 (m, 1H), 1.48–1.38 (m, 1H), 1.34–1.21 (m, 13H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 17.9$ Hz, 12H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.6, 170.9, 170.8, 138.0, 127.0, 126.2, 125.2, 110.1, 82.1, 74.8, 52.7, 51.5, 44.4, 39.8, 38.5, 37.5, 34.8, 34.8, 31.9, 29.4, 29.4, 29.1, 27.3, 26.9, 25.7, 22.8, 16.3, 14.2; MS(ESI) calcd for $\text{C}_{30}\text{H}_{46}\text{N}_2\text{O}_5\text{S}$ 546.31 (M^+), found 547.43 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27c

Compound **27c** was prepared according to the general procedure D from carboxylic acid **26a** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 7.30 (t, $J = 7.5$ Hz, 2H), 7.24–7.17 (m, 3H), 6.35 (s, 1H), 5.39 (d, $J = 1.6$ Hz, 1H), 5.20 (d, $J = 15.4$ Hz, 1H), 4.54 (d, $J = 15.5$ Hz, 1H), 3.84 (q, $J = 6.4$ Hz, 1H), 3.71 (d, $J = 1.5$ Hz, 1H), 3.57 (s, 3H), 3.43 (t, $J = 5.8$ Hz, 2H), 3.40–3.24 (m, 5H), 3.14–3.06 (m, 1H), 2.66 (dd, $J = 14.7, 4.9$ Hz, 1H), 2.59 (dd, $J = 14.9, 6.5$ Hz, 1H), 2.50 (dd, $J = 12.8, 7.4$ Hz, 1H), 1.84–1.70 (m, 3H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.74 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 171.1, 170.7, 138.4, 137.5, 128.7, 127.2, 127.0, 110.8, 82.0, 74.7, 71.5, 58.9, 52.7, 51.4, 48.9, 40.1, 37.9, 37.8, 34.7, 29.3, 29.1, 25.6, 16.4; MS(ESI) calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_6$ 500.29 (M^+), found 501.33 ($\text{M} + \text{H}$) $^+$, 523.32 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27d

Compound **27d** was prepared according to the general procedure D from carboxylic acid **26a** and amine **11t**: ^1H NMR (500 MHz, CDCl_3) δ 7.32–7.18 (m, 6H), 5.42 (d, $J = 1.4$ Hz, 1H), 5.17 (d, $J = 15.6$ Hz, 1H), 4.57 (d, $J = 15.5$ Hz, 1H), 3.85 (q, $J = 6.4$ Hz, 1H), 3.72 (d, $J = 1.5$ Hz, 1H), 3.70–3.52 (m, 8H), 3.46 (t, $J = 4.7$ Hz, 2H), 3.14–3.06 (m, 1H), 2.85 (dd, $J = 16.0, 3.5$ Hz, 1H), 2.76 (dd, $J = 16.0, 7.5$ Hz, 1H), 2.48 (dd, $J = 12.6, 7.3$ Hz, 1H), 1.84 (dd, $J = 12.6, 10.9$ Hz, 1H), 1.17 (d, $J = 6.4$ Hz, 3H), 0.76 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.2, 169.2, 138.6, 137.7, 128.5, 127.2, 127.0, 110.6, 82.1, 74.7, 67.0, 66.7, 52.6, 51.5, 48.9, 46.0, 42.0, 37.2, 36.5, 34.7, 29.1, 25.6, 16.4; MS(ESI) calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_6$ 498.27 (M^+), found 499.31 ($\text{M} + \text{H}$) $^+$, 521.31 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27e

Compound **27e** was prepared according to the general procedure D from carboxylic acid **26f** and amine **11j**: ^1H NMR (500 MHz, CDCl_3) δ 6.74 (d, $J = 7.8$ Hz, 1H), 6.71 (d, $J = 1.7$ Hz, 1H), 6.67 (dd, $J = 7.9, 1.8$ Hz, 1H), 6.00 (s, 1H), 5.92 (s, 2H), 5.45 (d, $J = 1.5$ Hz, 1H), 5.01 (d, $J = 15.3$ Hz, 1H), 4.53 (d, $J = 15.3$ Hz, 1H), 3.84 (q, $J = 6.4$ Hz, 1H), 3.72 (d, $J = 1.5$ Hz, 1H), 3.59 (s, 3H), 3.28–3.12 (m, 2H), 3.12–3.02 (m, 1H), 2.61 (dd, $J = 5.6, 3.1$ Hz, 2H), 2.48 (dd, $J = 12.8, 7.4$ Hz, 1H), 1.79 (dd, $J = 12.9, 11.1$ Hz, 1H), 1.49–1.39 (m, 2H), 1.37–1.26 (m, 2H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.90 (t, $J = 7.4$ Hz, 3H), 0.78 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 171.2, 170.6, 148.0, 146.7, 138.4, 131.4, 120.4, 110.8, 108.3, 107.9, 101.1, 82.0, 74.7, 52.7, 51.4, 48.5, 40.0, 39.4, 37.9, 34.7, 31.8, 29.0, 25.6, 20.2, 16.3, 13.9; MS(ESI) calcd for $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_7$ 528.28 (M^+), found 529.37 ($\text{M} + \text{H}$) $^+$, 551.37 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27f

Compound **27f** was prepared according to the general procedure D from carboxylic acid **26f** and amine **11u**: ^1H NMR (500 MHz, CDCl_3) δ 6.79 (s, 1H), 6.73 (s, 2H), 5.91 (d, J = 1.6 Hz, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.44 (d, J = 1.5 Hz, 1H), 5.02 (d, J = 15.4 Hz, 1H), 4.54 (d, J = 15.4 Hz, 1H), 3.85 (q, J = 6.5 Hz, 1H), 3.75–3.72 (m, 2H), 3.59 (s, 3H), 3.58–3.52 (m, 1H), 3.52–3.44 (m, 1H), 3.44–3.33 (m, 2H), 3.12–3.03 (m, 1H), 2.87 (dd, J = 15.9, 3.2 Hz, 1H), 2.77–2.67 (m, 1H), 2.47 (dd, J = 12.6, 7.3 Hz, 1H), 1.80 (dd, J = 12.8, 10.7 Hz, 1H), 1.66–1.58 (m, 2H), 1.58–1.47 (m, 4H), 1.17 (d, J = 6.4 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 171.5, 168.6, 147.9, 146.5, 138.7, 131.8, 120.5, 110.3, 108.2, 108.1, 101.0, 82.1, 74.8, 52.6, 51.5, 48.5, 46.6, 42.8, 37.3, 36.9, 34.7, 29.1, 26.5, 25.7, 25.6, 24.7, 16.4; MS(ESI) calcd for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_7$ 540.28 (M^+), found 541.37 ($\text{M} + \text{H}$) $^+$, 563.35 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27g

Compound **27g** was prepared according to the general procedure D from carboxylic acid **26g** and amine **11s**: ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.30 (m, 1H), 6.33–6.29 (m, 2H), 5.67 (s, 1H), 5.03 (d, J = 15.7 Hz, 1H), 4.57 (d, J = 15.7 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.87 (q, J = 6.4 Hz, 1H), 3.80 (d, J = 1.6 Hz, 1H), 3.60 (s, 3H), 3.59–3.49 (m, 1H), 3.49–3.37 (m, 6H), 3.13–3.05 (m, 1H), 2.84 (dd, J = 16.0, 3.5 Hz, 1H), 2.67 (dd, J = 15.9, 7.8 Hz, 1H), 2.48 (dd, J = 12.6, 7.4 Hz, 1H), 1.70 (t, J = 11.6 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.9, 169.2, 155.5, 150.9, 141.6, 138.5, 110.7, 110.6, 108.4, 82.1, 74.7, 61.8, 52.8, 51.5, 45.3, 43.6, 42.0, 41.5, 37.2, 36.8, 34.8, 29.1, 25.6, 16.3, 14.8; MS(ESI) calcd for $\text{C}_{29}\text{H}_{41}\text{N}_3\text{O}_8$ 559.29 (M^+), found 560.44 ($\text{M} + \text{H}$) $^+$, 582.43 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27h

Compound **27h** was prepared according to the general procedure D from carboxylic acid **26g** and amine **11w**: ^1H NMR (500 MHz, CDCl_3) δ 7.31 (s, 1H), 6.31 (d, J = 1.4 Hz, 2H), 5.64 (d, J = 1.7 Hz, 1H), 5.04 (d, J = 15.7 Hz, 1H), 4.58 (d, J = 15.7 Hz, 1H), 3.86 (q, J = 6.4 Hz, 1H), 3.79 (s, 1H), 3.60 (s, 3H), 3.43 (t, J = 6.9 Hz, 2H), 3.37 (t, J = 6.8 Hz, 2H), 3.10 (dtd, J = 10.9, 7.7, 3.5 Hz, 1H), 2.76 (dd, J = 16.2, 3.5 Hz, 1H), 2.60 (dd, J = 16.2, 7.9 Hz, 1H), 2.52 (dd, J = 12.6, 7.3 Hz, 1H), 1.97–1.87 (m, 2H), 1.83 (q, J = 6.8 Hz, 2H), 1.72 (dd, J = 12.7, 10.7 Hz, 1H), 1.18 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.2, 169.0, 151.1, 141.5, 138.6, 110.7, 110.2, 108.3, 82.1, 74.8, 52.7, 51.5, 46.6, 45.8, 42.0, 38.2, 37.0, 34.8, 29.2, 26.2, 25.7, 24.5, 16.4; MS(ESI) calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_6$ 472.26 (M^+), found 473.4 ($\text{M} + \text{H}$) $^+$, 495.38 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27i

Compound **27i** was prepared according to the general procedure D from carboxylic acid **26h** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 6.37 (t, J = 5.7 Hz, 1H), 5.48 (d, J = 1.5 Hz, 1H), 5.47–5.43 (m, 1H), 3.89 (q, J = 6.5 Hz, 1H), 3.83 (d, J = 1.5 Hz, 1H), 3.79 (ddd, J = 13.4, 11.2, 5.0 Hz, 1H), 3.66 (s, 3H), 3.57 (ddd, J = 13.4, 11.0, 5.3 Hz, 1H), 3.43 (t, J = 5.9 Hz, 2H), 3.32 (s, 2H), 3.29 (q, J = 6.4, 5.5 Hz, 2H), 3.07–2.97 (m, 1H), 2.58 (dd, J = 14.7, 5.1 Hz, 1H), 2.53–2.39 (m, 2H), 2.36–2.24 (m, 1H), 2.08–1.91 (m, 5H), 1.80–1.68 (m, 3H), 1.66–1.57 (m, 3H), 1.57–1.49 (m, 2H), 1.17 (d, J = 6.5 Hz, 3H), 0.90 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 170.7, 170.6, 138.3, 135.1, 122.9, 109.5, 82.1, 74.7, 71.5, 58.9, 52.7, 51.5, 43.7, 40.4, 37.8, 37.7, 35.3, 34.8, 29.4, 29.4, 29.0, 28.6, 25.7, 25.7, 25.4, 23.0, 22.4, 16.4; MS(ESI) calcd for $\text{C}_{29}\text{H}_{46}\text{N}_2\text{O}_6$ 518.34 (M^+), found 519.43 ($\text{M} + \text{H}$) $^+$, 541.43 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27j

Compound **27j** was prepared according to the general procedure D from carboxylic acid **26h** and amine **11m**: ^1H NMR (500 MHz, CDCl_3) δ 7.20 (td, $J = 7.8, 1.7$ Hz, 1H), 7.11 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.93–6.81 (m, 2H), 6.07 (t, $J = 5.6$ Hz, 1H), 5.50–5.44 (m, 2H), 3.89 (q, $J = 6.5$ Hz, 1H), 3.87–3.79 (m, 4H), 3.81–3.72 (m, 1H), 3.66 (s, 3H), 3.56 (ddd, $J = 13.4, 11.0, 5.4$ Hz, 1H), 3.50–3.36 (m, 2H), 3.05–2.95 (m, 1H), 2.79 (t, $J = 6.9$ Hz, 2H), 2.54 (dd, $J = 14.6, 5.0$ Hz, 1H), 2.50–2.40 (m, 2H), 2.35–2.22 (m, 1H), 2.07–1.93 (m, 5H), 1.67–1.58 (m, 3H), 1.58–1.50 (m, 2H), 1.17 (d, $J = 6.4$ Hz, 3H), 0.90 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 170.6, 170.6, 157.6, 138.3, 135.1, 130.7, 127.9, 127.5, 122.9, 120.8, 110.5, 109.5, 82.1, 74.7, 55.4, 52.7, 51.5, 43.8, 40.3, 39.8, 37.7, 35.3, 34.8, 30.4, 28.8, 28.6, 25.7, 25.4, 23.0, 22.5, 16.4; MS(ESI) calcd for $\text{C}_{34}\text{H}_{48}\text{N}_2\text{O}_6$ 580.35 (M^+), found 581.45 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27k

Compound **27k** was prepared according to the general procedure D from carboxylic acid **26i** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 6.80 (d, $J = 7.9$ Hz, 1H), 6.78–6.72 (m, 2H), 6.12 (t, $J = 6.4$ Hz, 1H), 5.38 (d, $J = 1.5$ Hz, 1H), 3.94–3.87 (m, 2H), 3.86 (s, 3H), 3.85 (s, 1H), 3.82 (d, $J = 1.4$ Hz, 1H), 3.78–3.70 (m, 1H), 3.65 (s, 3H), 3.10–3.02 (m, 1H), 2.96–2.88 (m, 2H), 2.88–2.83 (m, 1H), 2.83–2.76 (m, 1H), 2.64 (dd, $J = 14.7, 5.3$ Hz, 1H), 2.56–2.47 (m, 2H), 1.98–1.92 (m, 4H), 1.73–1.64 (m, 5H), 1.64–1.56 (m, 5H), 1.49–1.44 (m, 7H), 1.17 (d, $J = 6.5$ Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 171.0, 170.7, 149.2, 147.8, 138.6, 131.8, 120.7, 112.1, 111.5, 110.3, 82.1, 74.7, 56.0, 56.0, 52.7, 51.7, 51.1, 47.1, 40.6, 40.4, 40.3, 39.7, 37.9, 37.1, 37.0, 36.5, 34.7, 33.7, 33.0, 29.1, 28.4, 28.4, 28.0, 25.6, 16.3; MS(ESI) calcd for $\text{C}_{38}\text{H}_{54}\text{N}_2\text{O}_7$ 650.39 (M^+), found 651.54 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27l

Compound **27l** was prepared according to the general procedure D from carboxylic acid **26i** and amine **11s**: ^1H NMR (500 MHz, CDCl_3) δ 6.81–6.75 (m, 3H), 5.46 (d, $J = 1.5$ Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 3.94–3.89 (m, 1H), 3.88–3.82 (m, 8H), 3.77–3.69 (m, 1H), 3.65 (s, 3H), 3.59–3.53 (m, 2H), 3.51–3.40 (m, 7H), 3.10–3.03 (m, 1H), 2.91–2.75 (m, 3H), 2.69 (dd, $J = 16.1, 7.8$ Hz, 1H), 2.48 (dd, $J = 12.6, 7.5$ Hz, 1H), 1.72–1.61 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.9, 169.1, 155.5, 149.1, 147.7, 138.7, 132.0, 120.7, 112.2, 111.5, 109.8, 82.2, 74.7, 61.8, 56.0, 56.0, 52.7, 51.7, 46.8, 45.3, 43.6, 41.5, 37.2, 37.1, 34.8, 32.9, 29.1, 25.7, 16.4, 14.8; MS(ESI) calcd for $\text{C}_{34}\text{H}_{49}\text{N}_3\text{O}_9$ 643.35 (M^+), found 644.51 ($\text{M} + \text{H}$) $^+$, 666.47 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27m

Compound **27m** was prepared according to the general procedure D from carboxylic acid **26j** and amine **11l**: ^1H NMR (500 MHz, CDCl_3) δ 8.06–8.00 (m, 1H), 7.88 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 7.57–7.48 (m, 2H), 7.41 (dd, $J = 8.2, 7.1$ Hz, 1H), 7.31–7.25 (m, 3H), 7.24–7.14 (m, 4H), 6.08–6.02 (m, 1H), 5.46–5.39 (m, 2H), 5.28 (d, $J = 16.0$ Hz, 1H), 3.82 (q, $J = 6.4$ Hz, 1H), 3.71 (d, $J = 1.4$ Hz, 1H), 3.34–3.28 (m, 1H), 3.26 (s, 3H), 3.25–3.13 (m, 2H), 2.73 (dd, $J = 14.7, 6.0$ Hz, 1H), 2.67–2.58 (m, 4H), 2.52 (dd, $J = 12.9, 7.4$ Hz, 1H), 1.92 (dd, $J = 12.9, 11.2$ Hz, 1H), 1.68–1.60 (m, 3H), 1.56–1.48 (m, 2H), 1.18 (d, $J = 6.5$ Hz, 3H), 0.78 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 171.0, 170.7, 142.3, 138.1, 133.9, 131.6, 131.2, 128.9, 128.5, 128.5, 128.4, 127.9, 126.5, 125.9, 125.9, 125.8, 125.3, 125.2, 123.3, 111.3, 82.0, 74.7, 52.4, 51.4, 46.5, 39.9, 39.5, 38.0, 35.6, 34.7, 29.3, 29.1, 28.8, 25.6; MS(ESI) calcd for $\text{C}_{38}\text{H}_{46}\text{N}_2\text{O}_5$ 610.34 (M^+), found 611.48 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27n

Compound **27n** was prepared according to the general procedure D from carboxylic acid **26j** and amine **11n**: ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, J = 8.3 Hz, 1H), 7.85 (dd, J = 8.1, 1.4 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.54–7.49 (m, 1H), 7.49–7.45 (m, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 6.77 (t, J = 6.0 Hz, 1H), 5.45–5.40 (m, 2H), 5.26 (d, J = 16.0 Hz, 1H), 3.79 (q, J = 6.4 Hz, 1H), 3.69 (d, J = 1.5 Hz, 1H), 3.35–3.27 (m, 4H), 3.25 (s, 3H), 3.22–3.13 (m, 3H), 2.74 (dd, J = 15.0, 6.4 Hz, 1H), 2.67 (dd, J = 15.0, 4.8 Hz, 1H), 2.48 (dd, J = 12.7, 7.5 Hz, 1H), 2.38 (t, J = 8.1 Hz, 2H), 2.03–1.95 (m, 2H), 1.86 (dd, J = 12.8, 11.0 Hz, 1H), 1.69–1.61 (m, 2H), 1.16 (d, J = 6.5 Hz, 3H), 0.75 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.8, 172.7, 170.9, 170.8, 138.3, 133.9, 131.8, 131.2, 128.8, 127.7, 126.3, 125.7, 125.4, 125.4, 123.4, 110.9, 82.1, 74.7, 52.4, 51.4, 47.4, 46.5, 39.8, 39.8, 37.6, 36.0, 34.7, 31.1, 28.9, 26.7, 25.6, 18.0, 16.3; MS(ESI) calcd for $\text{C}_{35}\text{H}_{45}\text{N}_3\text{O}_6$ 603.33 (M^+), found 604.47 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27o

Compound **27o** was prepared according to the general procedure D from carboxylic acid **26k** and amine **11d**: ^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 8.4, 2.1 Hz, 1H), 5.71 (t, J = 5.7 Hz, 1H), 5.25 (d, J = 1.4 Hz, 1H), 5.19 (d, J = 16.7 Hz, 1H), 4.57 (d, J = 16.7 Hz, 1H), 3.84 (q, J = 6.5 Hz, 1H), 3.70 (d, J = 1.5 Hz, 1H), 3.67 (s, 3H), 3.29–3.13 (m, 3H), 3.05–2.96 (m, 1H), 2.78 (dd, J = 15.1, 5.7 Hz, 1H), 2.51 (dd, J = 15.1, 4.5 Hz, 1H), 2.44 (dd, J = 12.7, 7.1 Hz, 1H), 1.98 (t, J = 12.1 Hz, 1H), 1.63–1.53 (m, 1H), 1.38–1.30 (m, 2H), 1.21 (d, J = 6.5 Hz, 3H), 0.92–0.86 (m, 8H), 0.78 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.2, 170.3, 138.3, 133.3, 133.1, 133.0, 129.5, 129.2, 127.3, 110.5, 82.0, 74.8, 52.9, 51.5, 46.6, 38.9, 38.6, 38.0, 37.6, 34.7, 28.8, 26.0, 25.6, 22.6, 22.6, 22.6; MS(ESI) calcd for $\text{C}_{29}\text{H}_{40}\text{Cl}_2\text{N}_2\text{O}_5$ 566.23 (M^+), found 567.39 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27p

Compound **27p** was prepared according to the general procedure D from carboxylic acid **26k** and amine **11f**: ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 1.2 Hz, 1H), 7.14 (dd, J = 8.4, 2.1 Hz, 1H), 6.80–6.74 (m, 3H), 6.00 (t, J = 5.7 Hz, 1H), 5.25 (d, J = 1.5 Hz, 1H), 5.20 (d, J = 16.8 Hz, 1H), 4.53 (d, J = 16.8 Hz, 1H), 4.36–4.31 (m, 2H), 3.84 (d, J = 7.2 Hz, 4H), 3.80 (s, 3H), 3.71 (d, J = 1.5 Hz, 1H), 3.67 (s, 3H), 3.08–2.99 (m, 1H), 2.84 (dd, J = 15.3, 5.6 Hz, 1H), 2.54 (dd, J = 15.3, 4.4 Hz, 1H), 2.45 (dd, J = 12.6, 7.1 Hz, 1H), 2.06 (t, J = 12.1 Hz, 1H), 1.21 (d, J = 6.4 Hz, 3H), 0.78 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.1, 170.3, 149.3, 148.5, 138.4, 133.3, 133.0, 132.9, 131.0, 129.5, 129.2, 127.3, 120.0, 111.2, 111.1, 110.5, 82.0, 74.8, 56.0, 56.0, 52.9, 51.5, 46.8, 43.4, 38.7, 37.5, 34.7, 28.9, 25.6, 16.3; MS(ESI) calcd for $\text{C}_{33}\text{H}_{40}\text{Cl}_2\text{N}_2\text{O}_7$ 646.22 (M^+), found 647.38 ($\text{M} + \text{H}$) $^+$, 669.34 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27q

Compound **27q** was prepared according to the general procedure D from carboxylic acid **26l** and amine **11a**: ^1H NMR (500 MHz, CDCl_3) δ 6.54 (t, J = 5.6 Hz, 1H), 5.36 (d, J = 1.6 Hz, 1H), 4.08–3.93 (m, 4H), 3.79 (ddd, J = 13.6, 10.1, 5.9 Hz, 1H), 3.68 (s, 3H), 3.48 (ddd, J = 13.6, 10.1, 4.9 Hz, 1H), 3.02–2.92 (m, 1H), 2.63–2.52 (m, 2H), 2.40 (dd, J = 12.8, 7.1 Hz, 1H), 2.19 (t, J = 2.6 Hz, 1H), 2.03–1.92 (m, 1H), 1.81–1.35 (m, 11H), 1.35–1.22 (m, 10H), 1.20 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 170.7, 170.6, 136.4, 110.6, 79.8, 78.2, 74.6, 71.5, 52.8, 51.4, 44.9, 43.9, 39.7, 37.4, 31.9, 29.5, 29.4, 29.4, 29.3, 28.9, 28.6, 27.3, 26.8, 25.9, 25.8, 22.8, 16.7, 14.2; MS(ESI) calcd for $\text{C}_{29}\text{H}_{44}\text{N}_2\text{O}_5$ 500.33 (M^+), found 501.45 ($\text{M} + \text{H}$) $^+$, 524.44 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27r

Compound **27r** was prepared according to the general procedure D from carboxylic acid **26l** and amine **11j**: ^1H NMR (500 MHz, CDCl_3) δ 6.12 (s, 1H), 5.34 (d, J = 1.6 Hz, 1H), 4.07–3.95 (m, 2H), 3.79 (ddd, J = 13.5, 10.1, 6.0 Hz, 1H), 3.68 (s, 3H), 3.46 (ddd, J = 14.2, 10.0, 4.9 Hz, 1H), 3.29–3.11 (m, 2H), 2.99–2.89 (m, 1H), 2.55 (d, J = 5.6 Hz, 2H), 2.40 (dd, J = 12.9, 7.1 Hz, 1H), 2.02–1.92 (m, 1H), 1.80–1.65 (m, 4H), 1.65–1.37 (m, 5H), 1.35–1.22 (m, 16H), 1.20 (d, J = 6.5 Hz, 3H), 0.94–0.83 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 170.8, 170.7, 136.5, 110.4, 78.2, 74.7, 52.8, 51.4, 44.9, 43.8, 39.9, 39.4, 37.7, 31.9, 31.8, 29.4, 29.4, 29.3, 28.9, 28.6, 27.3, 26.8, 25.8, 25.8, 22.8, 20.2, 16.7, 14.2, 13.9; MS(ESI) calcd for $\text{C}_{30}\text{H}_{50}\text{N}_2\text{O}_5$ 518.37 (M^+), found 519.48 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27s

Compound **27s** was prepared according to the general procedure D from carboxylic acid **26m** and amine **11j**: ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.14 (m, 5H), 6.08 (s, 1H), 5.30 (d, J = 1.7 Hz, 1H), 5.12 (d, J = 15.6 Hz, 1H), 4.69 (d, J = 15.6 Hz, 1H), 3.99 (q, J = 6.5 Hz, 1H), 3.93 (dd, J = 7.8, 1.7 Hz, 1H), 3.60 (s, 3H), 3.28–3.15 (m, 2H), 3.06–2.96 (m, 1H), 2.64 (dd, J = 5.5, 2.4 Hz, 2H), 2.43 (dd, J = 12.9, 6.7 Hz, 1H), 1.90–1.82 (m, 2H), 1.72–1.62 (m, 1H), 1.53–1.45 (m, 4H), 1.45–1.38 (m, 4H), 1.38–1.25 (m, 3H), 1.20 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.1, 170.8, 137.2, 136.4, 128.6, 127.2, 127.0, 111.2, 77.9, 74.5, 52.8, 51.4, 48.0, 44.8, 39.5, 39.5, 37.8, 31.8, 29.5, 28.9, 28.4, 25.8, 25.7, 20.2, 16.9, 13.9; MS(ESI) calcd for $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_5$ 496.29 (M^+), found 497.33 ($\text{M} + \text{H}$) $^+$, 519.32 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27t

Compound **27t** was prepared according to the general procedure D from carboxylic acid **26m** and amine **11l**: ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.13 (m, 10H), 6.10 (t, J = 6.0 Hz, 1H), 5.29 (d, J = 1.6 Hz, 1H), 5.09 (d, J = 15.6 Hz, 1H), 4.68 (d, J = 15.6 Hz, 1H), 3.99 (q, J = 6.5 Hz, 1H), 3.93 (dd, J = 7.8, 1.8 Hz, 1H), 3.59 (s, 3H), 3.31–3.15 (m, 3H), 3.05–2.95 (m, 1H), 2.65–2.57 (m, 5H), 2.42 (dd, J = 12.9, 6.6 Hz, 1H), 1.90–1.81 (m, 2H), 1.71–1.58 (m, 2H), 1.55–1.40 (m, 6H), 1.35–1.23 (m, 1H), 1.19 (d, J = 6.5 Hz, 3H), 1.16–1.05 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.1, 170.8, 142.3, 137.2, 136.4, 128.6, 128.5, 128.4, 127.2, 127.0, 125.9, 111.2, 77.9, 74.5, 52.8, 51.4, 48.0, 44.8, 39.5, 39.5, 37.7, 35.6, 29.6, 29.3, 28.9, 28.8, 28.4, 25.8, 25.7, 16.9; MS(ESI) calcd for $\text{C}_{35}\text{H}_{44}\text{N}_2\text{O}_5$ 572.33 (M^+), found 573.37 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27u

Compound **27u** was prepared according to the general procedure D from carboxylic acid **26n** and amine **11g**: ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 6.9 Hz, 2H), 7.46 (d, J = 7.5 Hz, 1H), 7.44–7.39 (m, 1H), 6.75–6.69 (m, 2H), 6.66 (dd, J = 7.9, 1.7 Hz, 1H), 6.62 (t, J = 6.0 Hz, 1H), 5.93–5.89 (m, 2H), 5.34 (d, J = 1.6 Hz, 1H), 4.92 (d, J = 15.5 Hz, 1H), 4.63 (d, J = 15.4 Hz, 1H), 4.50 (dd, J = 15.2, 5.8 Hz, 1H), 4.45 (dd, J = 15.2, 6.0 Hz, 1H), 4.00 (q, J = 6.6 Hz, 1H), 3.95 (dd, J = 7.9, 1.6 Hz, 1H), 3.62 (s, 3H), 3.08–3.00 (m, 1H), 2.70 (dd, J = 15.0, 5.5 Hz, 1H), 2.65 (dd, J = 15.0, 5.7 Hz, 1H), 2.42 (dd, J = 12.8, 6.7 Hz, 1H), 1.94–1.82 (m, 2H), 1.74–1.64 (m, 1H), 1.59–1.41 (m, 5H), 1.37–1.28 (m, 1H), 1.23–1.12 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 171.1, 171.0, 148.0, 146.7, 139.7, 136.3, 131.2, 131.2, 131.0, 131.0 (q, $^2J_{\text{C-F}}$ = 31.8 Hz), 129.2, 124.4 (q, $^3J_{\text{C-F}}$ = 3.8 Hz), 124.3 (q, $^3J_{\text{C-F}}$ = 3.8 Hz), 124.2 (q, $^1J_{\text{C-F}}$ = 272.7 Hz), 120.3, 111.3, 108.3, 107.7, 101.1, 78.0, 74.5, 52.9, 51.3, 47.7, 44.8, 43.1, 39.4, 37.6, 29.7, 28.9, 28.5, 25.8, 16.8; MS(ESI) calcd for $\text{C}_{34}\text{H}_{37}\text{F}_3\text{N}_2\text{O}_7$ 642.26 (M^+), found 643.32 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27v

Compound **27v** was prepared according to the general procedure D from carboxylic acid **26n** and amine **11t**: ^1H NMR (500 MHz, CDCl_3) δ 6.78 (d, J = 1.5 Hz, 1H), 6.76–6.70 (m, 2H), 5.91 (s, 2H), 5.34 (d, J = 1.6 Hz, 1H), 4.95 (d, J = 15.4 Hz, 1H), 4.65 (d, J = 15.5 Hz, 1H), 4.01–3.93 (m, 2H), 3.70–3.63 (m, 4H), 3.62 (s, 5H), 3.46 (t, J = 4.9 Hz, 2H), 3.04–2.97 (m, 1H), 2.85–2.76 (m, 2H), 2.38 (dd, J = 12.5, 6.7 Hz, 1H), 1.95–1.86 (m, 2H), 1.74–1.64 (m, 1H), 1.60–1.41 (m, 5H), 1.33 (dq, J = 12.5, 7.9, 7.4 Hz, 1H), 1.22–1.13 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 171.1, 169.1, 147.9, 146.6, 136.8, 131.5, 120.4, 110.8, 108.2, 108.0, 101.0, 78.2, 74.6, 67.0, 66.7, 52.7, 51.4, 47.9, 45.9, 44.7, 42.1, 37.0, 35.9, 29.4, 28.9, 28.4, 25.8, 25.8, 16.8; MS(ESI) calcd for $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_8$ 554.26 (M^+), found 555.37 ($\text{M} + \text{H}$) $^+$, 577.33 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27w

Compound **27w** was prepared according to the general procedure D from carboxylic acid **26o** and amine **11n**: ^1H NMR (500 MHz, CDCl_3) δ 7.32 (dd, J = 1.8, 0.9 Hz, 1H), 6.74 (t, J = 6.3 Hz, 1H), 6.31 (dd, J = 3.2, 1.8 Hz, 1H), 6.26 (d, J = 3.2 Hz, 1H), 5.53 (d, J = 1.5 Hz, 1H), 5.00 (d, J = 15.8 Hz, 1H), 4.63 (d, J = 15.7 Hz, 1H), 3.99 (dd, J = 8.0, 1.6 Hz, 1H), 3.95 (q, J = 6.5 Hz, 1H), 3.61 (s, 3H), 3.37 (t, J = 7.0 Hz, 2H), 3.31 (td, J = 6.5, 2.6 Hz, 2H), 3.21–3.08 (m, 2H), 3.06–2.99 (m, 1H), 2.64 (dd, J = 15.0, 5.0 Hz, 1H), 2.55 (dd, J = 14.9, 6.6 Hz, 1H), 2.42–2.35 (m, 3H), 2.08–1.99 (m, 2H), 1.99–1.90 (m, 1H), 1.77–1.61 (m, 6H), 1.61–1.45 (m, 3H), 1.41–1.32 (m, 1H), 1.29–1.21 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 172.8, 170.8, 170.7, 150.8, 141.6, 136.8, 111.1, 110.7, 108.4, 78.2, 74.6, 52.8, 51.3, 47.5, 44.8, 41.4, 39.8, 39.5, 37.3, 36.0, 31.1, 29.2, 28.9, 28.4, 26.7, 25.8, 25.8, 18.1, 16.7; MS(ESI) calcd for $\text{C}_{30}\text{H}_{41}\text{N}_3\text{O}_7$ 555.29 (M^+), found 556.48 ($\text{M} + \text{H}$) $^+$, 578.46 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27x

Compound **27x** was prepared according to the general procedure D from carboxylic acid **26o** and amine **11s**: ^1H NMR (500 MHz, CDCl_3) δ 7.32 (dd, J = 1.7, 0.9 Hz, 1H), 6.31 (dd, J = 3.2, 1.8 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H), 5.55 (d, J = 1.5 Hz, 1H), 4.96 (d, J = 15.7 Hz, 1H), 4.69 (d, J = 15.7 Hz, 1H), 4.15 (q, J = 7.1 Hz, 3H), 4.00 (dd, J = 7.9, 1.5 Hz, 1H), 3.96 (q, J = 6.5 Hz, 1H), 3.64–3.57 (m, 4H), 3.56–3.37 (m, 6H), 3.07–2.99 (m, 1H), 2.84 (dd, J = 16.1, 3.5 Hz, 1H), 2.70 (dd, J = 16.2, 7.5 Hz, 1H), 2.42 (dd, J = 12.6, 6.9 Hz, 1H), 2.01–1.91 (m, 1H), 1.81–1.62 (m, 4H), 1.62–1.45 (m, 4H), 1.43–1.33 (m, 1H), 1.30–1.22 (m, 4H), 1.19 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.7, 169.2, 155.5, 150.8, 141.6, 136.9, 111.2, 110.7, 108.4, 78.3, 74.6, 61.8, 52.8, 51.4, 45.3, 44.7, 43.7, 41.5, 41.4, 37.0, 36.3, 29.4, 28.9, 28.4, 25.9, 25.8, 16.7, 14.8; MS(ESI) calcd for $\text{C}_{30}\text{H}_{41}\text{N}_3\text{O}_8$ 571.29 (M^+), found 572.48 ($\text{M} + \text{H}$) $^+$, 594.46 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27y

Compound **27y** was prepared according to the general procedure D from carboxylic acid **26b** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 6.25 (s, 1H), 5.45 (d, J = 3.3 Hz, 1H), 5.37 (d, J = 1.6 Hz, 1H), 4.07–3.97 (m, 2H), 3.89 (ddd, J = 13.4, 11.0, 5.3 Hz, 1H), 3.68 (s, 3H), 3.56 (ddd, J = 13.5, 10.8, 5.2 Hz, 1H), 3.04–2.79 (m, 3H), 2.60 (d, J = 5.7 Hz, 2H), 2.40 (dd, J = 12.9, 6.7 Hz, 1H), 2.25 (ddd, J = 15.2, 10.7, 5.1 Hz, 1H), 2.11–1.88 (m, 10H), 1.80–1.67 (m, 7H), 1.67–1.57 (m, 7H), 1.57–1.48 (m, 2H), 1.47–1.37 (m, 5H), 1.33–1.23 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 171.1, 170.6, 136.2, 135.1, 122.9, 110.2, 78.1, 74.5, 52.8, 51.4, 51.1, 45.1, 42.9, 40.3, 39.8, 37.8, 37.1, 36.5, 34.9, 33.7, 32.3, 29.5, 29.0, 28.7, 28.6, 28.4, 28.0, 25.8, 25.8, 25.4, 23.0, 22.4, 16.8; MS(ESI) calcd for $\text{C}_{37}\text{H}_{54}\text{N}_2\text{O}_5$ 606.40 (M^+), found 607.55 ($\text{M} + \text{H}$) $^+$, 609.57 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27z

Compound **27z** was prepared according to the general procedure D from carboxylic acid **26b** and amine **11p**: ^1H NMR (500 MHz, CDCl_3) δ 6.42 (t, J = 5.5 Hz, 1H), 5.45 (t, J = 3.4 Hz, 1H), 5.37 (d, J = 1.6 Hz, 1H), 4.08–3.95 (m, 2H), 3.81 (ddd, J = 13.4, 11.0, 5.2 Hz, 1H), 3.68 (s, 3H), 3.59 (ddd, J = 13.3, 10.9, 5.3 Hz, 1H), 3.47 (t, J = 5.8 Hz, 2H), 3.40 (t, J = 6.6 Hz, 3H), 3.35–3.26 (m, 2H), 2.97–2.87 (m, 1H), 2.59 (dd, J = 14.8, 5.1 Hz, 1H), 2.47 (dd, J = 14.8, 6.4 Hz, 1H), 2.38 (dd, J = 12.8, 6.9 Hz, 1H), 2.30–2.22 (m, 1H), 2.09–2.01 (m, 1H), 2.01–1.93 (m, 5H), 1.80–1.69 (m, 5H), 1.69–1.58 (m, 5H), 1.58–1.48 (m, 6H), 1.46–1.24 (m, 5H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.7, 170.5, 136.5, 135.2, 122.9, 109.9, 78.2, 74.6, 71.0, 69.7, 52.8, 51.4, 45.0, 43.0, 39.7, 38.1, 37.5, 35.0, 31.9, 29.4, 29.0, 28.7, 28.6, 25.8, 25.4, 23.0, 22.5, 19.5, 16.8, 14.1; MS(ESI) calcd for $\text{C}_{33}\text{H}_{52}\text{N}_2\text{O}_6$ 572.38 (M^+), found 573.53 ($\text{M} + \text{H}$) $^+$, 595.53 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27aa

Compound **27aa** was prepared according to the general procedure D from carboxylic acid **26p** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 6.83–6.73 (m, 3H), 6.32 (q, J = 5.9 Hz, 1H), 5.34 (d, J = 1.6 Hz, 1H), 4.05–3.98 (m, 2H), 3.94 (ddd, J = 13.5, 10.5, 6.2 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78–3.68 (m, 1H), 3.66 (s, 3H), 3.44 (t, J = 5.9 Hz, 2H), 3.37–3.27 (m, 6H), 3.01–2.91 (m, 1H), 2.91–2.81 (m, 1H), 2.81–2.72 (m, 1H), 2.61 (dd, J = 14.9, 5.1 Hz, 1H), 2.54 (dd, J = 14.8, 6.5 Hz, 1H), 2.41 (dd, J = 12.8, 7.0 Hz, 1H), 1.99–1.87 (m, 1H), 1.80–1.64 (m, 6H), 1.64–1.56 (m, 2H), 1.56–1.48 (m, 2H), 1.44–1.36 (m, 1H), 1.32–1.22 (m, 1H), 1.21 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.7, 170.6, 149.1, 147.7, 136.8, 131.8, 120.7, 112.2, 111.5, 110.4, 78.2, 74.6, 71.6, 58.9, 56.0, 56.0, 52.8, 51.5, 46.0, 45.0, 39.7, 38.0, 37.5, 32.8, 29.4, 29.3, 29.0, 28.7, 25.8, 25.7, 16.8; MS(ESI) calcd for $\text{C}_{32}\text{H}_{46}\text{N}_2\text{O}_8$ 586.33 (M^+), found 587.48 ($\text{M} + \text{H}$) $^+$, 609.47 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ab

Compound **27ab** was prepared according to the general procedure D from carboxylic acid **26p** and amine **11t**: ^1H NMR (500 MHz, CDCl_3) δ 6.83–6.74 (m, 3H), 5.37 (d, J = 1.6 Hz, 1H), 4.06–3.90 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79–3.69 (m, 1H), 3.66 (d, J = 5.8 Hz, 6H), 3.63–3.51 (m, 3H), 3.45 (t, J = 4.9 Hz, 2H), 3.03–2.93 (m, 1H), 2.91–2.73 (m, 3H), 2.70 (dd, J = 16.2, 7.5 Hz, 1H), 2.41 (dd, J = 12.6, 6.9 Hz, 1H), 2.01–1.89 (m, 1H), 1.80–1.73 (m, 2H), 1.72–1.65 (m, 1H), 1.65–1.49 (m, 4H), 1.49–1.36 (m, 1H), 1.34–1.23 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 170.7, 169.2, 149.1, 147.7, 136.9, 131.9, 120.7, 112.2, 111.4, 110.2, 78.3, 74.7, 67.0, 66.7, 56.0, 56.0, 52.8, 51.5, 45.9, 45.0, 42.1, 36.9, 36.3, 32.7, 29.4, 29.0, 28.7, 25.8, 25.8, 16.8; MS(ESI) calcd for $\text{C}_{32}\text{H}_{44}\text{N}_2\text{O}_8$ 584.31 (M^+), found 585.47 ($\text{M} + \text{H}$) $^+$, 607.45 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ac

Compound **27ac** was prepared according to the general procedure D from carboxylic acid **26q** and amine **11t**: ^1H NMR (500 MHz, CDCl_3) δ 8.06–8.00 (m, 1H), 7.85 (dd, J = 8.0, 1.5 Hz, 1H), 7.75 (dd, J = 7.7, 1.8 Hz, 1H), 7.52 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.47 (ddd, J = 8.0, 6.9, 1.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.40–7.37 (m, 1H), 5.41 (d, J = 16.0 Hz, 1H), 5.37–5.30 (m, 2H), 3.95 (dd, J = 7.4, 1.5 Hz, 1H), 3.91 (q, J = 6.5 Hz, 1H), 3.67 (dd, J = 5.4, 3.0 Hz, 4H), 3.64–3.57 (m, 2H), 3.48 (t, J = 4.8 Hz, 2H), 3.25 (s, 3H), 3.13–3.06 (m, 1H), 2.91 (dd, J = 16.2, 6.9 Hz, 1H), 2.81 (dd, J = 16.2, 3.4 Hz, 1H), 2.42 (dd, J = 12.5, 6.8 Hz, 1H), 2.00 (dd, J = 12.5, 11.4 Hz, 1H), 1.95–1.86 (m, 1H), 1.70–1.61 (m, 1H), 1.52–1.38 (m, 5H), 1.35–1.25 (m, 1H), 1.21–1.15 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 171.0, 169.2, 136.9, 133.9, 131.8, 131.3, 128.8, 127.7, 126.3, 125.7, 125.5, 125.5, 123.3, 111.7, 78.1, 74.6, 67.0, 66.7, 52.4, 51.4, 46.0, 45.9, 44.6, 42.1, 37.0, 35.9, 29.3, 28.6, 28.3, 25.9,

25.8, 16.6; MS(ESI) calcd for $C_{33}H_{40}N_2O_6$ 560.29 (M^+), found 561.44 ($M + H$)⁺, 583.44 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ad

Compound **27ad** was prepared according to the general procedure D from carboxylic acid **26q** and amine **11w**: ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.49–7.45 (m, 1H), 7.44–7.37 (m, 2H), 5.43 (d, *J* = 16.1 Hz, 1H), 5.36–5.30 (m, 2H), 3.96–3.88 (m, 2H), 3.51–3.44 (m, 2H), 3.44–3.38 (m, 2H), 3.27 (s, 3H), 3.09 (dtd, *J* = 10.5, 6.6, 3.2 Hz, 1H), 2.88 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.74 (dd, *J* = 16.3, 3.4 Hz, 1H), 2.42 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.06 (t, *J* = 12.1 Hz, 1H), 1.97–1.79 (m, 5H), 1.70–1.62 (m, 1H), 1.51–1.36 (m, 5H), 1.35–1.26 (m, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.16–1.08 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.1, 171.3, 169.0, 136.8, 133.8, 131.8, 131.3, 128.8, 127.6, 126.3, 125.6, 125.5, 125.5, 123.3, 111.3, 78.1, 74.6, 52.4, 51.4, 46.6, 45.8, 45.8, 44.7, 37.4, 37.0, 29.4, 28.8, 28.4, 26.2, 25.8, 25.8, 24.5, 16.8; MS(ESI) calcd for $C_{33}H_{40}N_2O_5$ 544.29 (M^+), found 545.44 ($M + H$)⁺, 567.43 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ae

Compound **27ae** was prepared according to the general procedure D from carboxylic acid **26r** and amine **11t**: ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.19 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.19–5.12 (m, 2H), 4.65 (d, *J* = 16.8 Hz, 1H), 3.98 (q, *J* = 6.5 Hz, 1H), 3.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.62–3.53 (m, 1H), 3.48–3.41 (m, 2H), 3.02–2.90 (m, 2H), 2.66 (dd, *J* = 16.2, 2.9 Hz, 1H), 2.32 (dd, *J* = 12.5, 6.2 Hz, 1H), 2.10 (t, *J* = 12.0 Hz, 1H), 1.94–1.85 (m, 1H), 1.71–1.61 (m, 1H), 1.55–1.40 (m, 6H), 1.33 (dt, *J* = 13.1, 7.4 Hz, 1H), 1.26–1.14 (m, 5H); ¹³C NMR (126 MHz, CDCl₃) δ 173.3, 171.2, 169.0, 136.7, 133.2, 133.1, 133.0, 129.6, 129.0, 127.3, 110.7, 78.0, 74.5, 67.0, 66.6, 52.9, 51.4, 46.1, 45.8, 44.7, 42.0, 36.8, 35.1, 29.1, 28.8, 28.4, 25.9, 25.8, 16.9; MS(ESI) calcd for $C_{29}H_{36}Cl_2N_2O_6$ 578.20 (M^+), found 579.36 ($M + H$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27af

Compound **27af** was prepared according to the general procedure D from carboxylic acid **26r** and amine **11v**: ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.18–5.11 (m, 2H), 4.64 (d, *J* = 16.8 Hz, 1H), 3.98 (q, *J* = 6.5 Hz, 2H), 3.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 3.92–3.78 (m, 1H), 3.75–3.66 (m, 5H), 3.02–2.90 (m, 2H), 2.69–2.55 (m, 5H), 2.31 (dd, *J* = 12.4, 6.3 Hz, 1H), 2.09 (t, *J* = 12.0 Hz, 1H), 1.95–1.85 (m, 1H), 1.71–1.62 (m, 1H), 1.56–1.40 (m, 6H), 1.37–1.27 (m, 1H), 1.27–1.14 (m, 4H); ¹³C NMR (126 MHz, CDCl₃) δ 173.3, 171.2, 168.7, 136.7, 133.2, 133.1, 132.9, 129.6, 129.0, 127.3, 110.7, 78.0, 74.5, 52.9, 51.4, 48.2, 46.1, 44.7, 44.4, 36.9, 35.3, 29.1, 28.8, 28.3, 27.9, 27.5, 25.9, 25.8, 16.8; MS(ESI) calcd for $C_{29}H_{36}Cl_2N_2O_5S$ 594.17 (M^+), found 595.33 ($M + H$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ag

Compound **27ag** was prepared according to the general procedure D from carboxylic acid **26s** and amine **11t**: ¹H NMR (500 MHz, CDCl₃) δ 5.34 (d, *J* = 1.8 Hz, 1H), 3.95 (dd, *J* = 6.6, 1.8 Hz, 1H), 3.82 (ddd, *J* = 13.8, 10.0, 6.3 Hz, 1H), 3.69 (s, 3H), 3.68–3.63 (m, 4H), 3.61–3.55 (m, 2H), 3.53–3.44 (m, 3H), 3.32 (d, *J* = 8.4 Hz, 1H), 3.05–2.98 (m, 1H), 2.86 (dd, *J* = 16.1, 3.5 Hz, 1H), 2.59 (dd, *J* = 16.1, 7.9 Hz, 1H), 2.52 (dd, *J* = 12.8, 6.6 Hz, 1H), 1.96–1.83 (m, 2H), 1.62–1.53 (m, 1H), 1.53–1.45 (m, 1H), 1.33–1.21 (m, 11H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 4H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.58–0.48 (m, 2H), 0.47–0.41 (m, 1H), 0.22–0.16 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.2, 170.7, 169.4, 136.3, 108.0, 82.2, 79.0, 67.0, 66.7, 52.7, 51.8, 46.0, 43.3, 42.1, 36.9, 36.2, 33.5, 31.9, 30.5, 29.4,

29.4, 27.3, 26.7, 22.8, 18.6, 18.5, 14.2, 12.1, 4.0, 2.7; MS(ESI) calcd for $C_{30}H_{48}N_2O_6$ 532.35 (M^+), found 533.53 ($M + H$)⁺, 555.5 ($M + Na$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ah

Compound **27ah** was prepared according to the general procedure D from carboxylic acid **26s** and amine **11n**: ¹H NMR (500 MHz, CDCl₃) δ 6.89 (s, 1H), 5.31 (d, *J* = 1.9 Hz, 1H), 3.93 (dd, *J* = 6.6, 1.9 Hz, 1H), 3.79 (ddd, *J* = 13.6, 10.0, 6.0 Hz, 1H), 3.68 (s, 3H), 3.56–3.45 (m, 1H), 3.38 (t, *J* = 7.0 Hz, 2H), 3.35–3.28 (m, 3H), 3.23–3.12 (m, 2H), 3.04–2.95 (m, 1H), 2.64 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.54–2.43 (m, 2H), 2.39 (t, *J* = 8.1 Hz, 2H), 2.10–1.99 (m, 2H), 1.92–1.81 (m, 2H), 1.67 (td, *J* = 6.4, 2.5 Hz, 2H), 1.61–1.52 (m, 1H), 1.52–1.43 (m, 1H), 1.35–1.18 (m, 10H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 4H), 0.89–0.84 (m, 3H), 0.57–0.47 (m, 2H), 0.47–0.40 (m, 1H), 0.23–0.15 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 175.9, 173.1, 171.0, 170.7, 136.2, 107.9, 82.0, 78.9, 52.8, 51.7, 47.5, 43.4, 39.8, 39.6, 37.1, 36.0, 33.5, 31.9, 31.1, 30.4, 29.4, 27.2, 26.7, 26.7, 22.8, 18.6, 18.5, 18.1, 14.2, 12.2, 4.0, 2.6; MS(ESI) calcd for $C_{33}H_{53}N_3O_6$ 587.39 (M^+), found 588.57 ($M + H$)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ai

Compound **27ai** was prepared according to the general procedure D from carboxylic acid **26t** and amine **11b**: ¹H NMR (500 MHz, CDCl₃) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.25–7.17 (m, 3H), 6.14 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 1.9 Hz, 1H), 5.10 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.7 Hz, 1H), 3.80 (dd, *J* = 7.2, 1.9 Hz, 1H), 3.62 (s, 3H), 3.32 (d, *J* = 8.5 Hz, 1H), 3.07 (t, *J* = 6.4 Hz, 2H), 3.02–2.95 (m, 1H), 2.69–2.60 (m, 2H), 2.49 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.11 (t, *J* = 12.7 Hz, 1H), 1.77–1.60 (m, 6H), 1.47–1.37 (m, 1H), 1.27–1.09 (m, 3H), 0.95–0.81 (m, 6H), 0.74 (d, *J* = 6.7 Hz, 3H), 0.60–0.53 (m, 1H), 0.51–0.40 (m, 2H), 0.25–0.19 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.1, 171.3, 170.8, 137.1, 135.6, 128.7, 127.2, 126.9, 109.1, 81.9, 78.5, 52.8, 51.7, 47.4, 45.9, 39.4, 38.0, 37.7, 33.5, 30.9, 30.6, 26.5, 26.0, 18.6, 18.5, 12.3, 4.6, 2.6; HRMS (ESI-TOF) *m/z* [$M + H$]⁺ calcd for $C_{32}H_{45}N_2O_5$ 537.3328, found 537.3327.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27aj

Compound **27aj** was prepared according to the general procedure D from carboxylic acid **26t** and amine **11n**: ¹H NMR (500 MHz, CDCl₃) δ 7.29 (dd, *J* = 8.6, 6.7 Hz, 2H), 7.23–7.18 (m, 3H), 6.85 (d, *J* = 6.3 Hz, 1H), 5.25 (d, *J* = 1.9 Hz, 1H), 5.12 (d, *J* = 15.8 Hz, 1H), 4.75 (d, *J* = 15.8 Hz, 1H), 3.79 (dd, *J* = 7.2, 1.9 Hz, 1H), 3.62 (s, 3H), 3.38–3.27 (m, 5H), 3.24–3.12 (m, 2H), 3.08–3.01 (m, 1H), 2.70 (dd, *J* = 15.1, 5.2 Hz, 1H), 2.60 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.44 (dd, *J* = 13.0, 6.2 Hz, 1H), 2.41–2.36 (m, 2H), 2.08 (t, *J* = 12.6 Hz, 1H), 2.06–1.99 (m, 2H), 1.68 (dp, *J* = 18.8, 6.5 Hz, 3H), 0.90–0.81 (m, 4H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.59–0.52 (m, 1H), 0.50–0.38 (m, 2H), 0.23–0.17 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 175.9, 173.1, 171.1, 170.9, 137.3, 135.7, 128.6, 127.0, 126.9, 108.6, 82.0, 78.6, 52.8, 51.7, 47.5, 47.4, 39.8, 39.2, 37.2, 36.0, 33.5, 31.1, 30.5, 26.7, 18.6, 18.5, 18.1, 12.3, 4.6, 2.6; HRMS (ESI-TOF) *m/z* [$M + H$]⁺ calcd for $C_{32}H_{44}N_3O_6$ 566.3230, found 566.3225.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ak

Compound **27ak** was prepared according to the general procedure D from carboxylic acid **26u** and amine **11e**: ¹H NMR (500 MHz, CDCl₃) δ 7.19 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.97–6.90 (m, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 1.6 Hz, 1H), 6.67 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 5.33 (d, *J* = 1.9 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.63–4.54 (m, 2H), 3.82 (dd, *J* = 7.2, 1.9 Hz, 1H), 3.64 (s, 3H), 3.33 (d, *J* = 8.5 Hz, 1H), 3.04–2.97 (m, 1H), 2.71 (dd, *J* = 14.9, 5.5 Hz, 1H), 2.65 (dd, *J* = 14.9, 5.5 Hz, 1H), 2.48 (dd, *J* = 13.1, 6.2 Hz, 1H), 2.09 (t, *J* = 12.7 Hz, 1H), 1.81–1.73 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89–0.83 (m, 2H), 0.60–0.53 (m, 1H), 0.53–0.47 (m, 1H), 0.47–0.39 (m, 1H), 0.25–0.18

(m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 171.3, 170.7, 148.0, 146.7, 141.2, 135.6, 130.8, 127.0, 126.1, 125.1, 120.2, 109.2, 108.3, 107.6, 101.1, 81.8, 78.6, 52.9, 51.6, 47.1, 38.9, 38.4, 37.5, 33.5, 30.5, 18.6, 18.6, 12.3, 4.5, 2.7; MS(ESI) calcd for $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_7\text{S}$ 580.22 (M^+), found 581.4 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27al

Compound **27al** was prepared according to the general procedure D from carboxylic acid **26u** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 7.29–7.23 (m, 3H), 7.19–7.13 (m, 3H), 6.73 (d, $J = 7.9$ Hz, 1H), 6.70 (d, $J = 1.6$ Hz, 1H), 6.66 (dd, $J = 8.0, 1.7$ Hz, 1H), 5.91 (s, 2H), 5.32 (d, $J = 2.0$ Hz, 1H), 4.91 (d, $J = 15.6$ Hz, 1H), 4.73 (d, $J = 15.5$ Hz, 1H), 3.82 (dd, $J = 7.1, 1.9$ Hz, 1H), 3.63 (s, 3H), 3.32 (d, $J = 8.5$ Hz, 1H), 3.27–3.21 (m, 2H), 3.02–2.94 (m, 1H), 2.68–2.57 (m, 4H), 2.48 (dd, $J = 13.1, 6.3$ Hz, 1H), 2.07 (t, $J = 12.7$ Hz, 1H), 1.80–1.72 (m, 1H), 1.68–1.59 (m, 2H), 1.56–1.48 (m, 2H), 0.90 (d, $J = 6.7$ Hz, 3H), 0.89–0.82 (m, 1H), 0.79 (d, $J = 6.7$ Hz, 3H), 0.59–0.52 (m, 1H), 0.51–0.40 (m, 2H), 0.24–0.17 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 171.4, 170.8, 148.0, 146.7, 142.3, 135.7, 130.9, 128.5, 128.4, 125.9, 120.2, 108.3, 107.6, 101.1, 81.9, 78.6, 52.9, 51.7, 47.2, 39.6, 39.1, 37.6, 35.6, 33.5, 30.5, 29.3, 28.8, 18.6, 18.6, 12.3, 4.5, 2.6; MS(ESI) calcd for $\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_7$ 616.31 (M^+), found 617.49 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27am

Compound **27am** was prepared according to the general procedure D from carboxylic acid **26v** and amine **11d**: ^1H NMR (500 MHz, CDCl_3) δ 7.31 (d, $J = 2.3$ Hz, 1H), 6.31 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.25 (d, $J = 3.2$ Hz, 1H), 5.99 (s, 1H), 5.56 (d, $J = 1.8$ Hz, 1H), 5.07 (d, $J = 15.8$ Hz, 1H), 4.66 (d, $J = 15.7$ Hz, 1H), 3.89 (dd, $J = 6.7, 1.8$ Hz, 1H), 3.64 (s, 3H), 3.32 (d, $J = 8.2$ Hz, 1H), 3.24–3.13 (m, 2H), 3.03–2.95 (m, 1H), 2.58 (d, $J = 5.3$ Hz, 1H), 2.52 (dd, $J = 13.1, 6.6$ Hz, 1H), 1.95 (dd, $J = 13.1, 11.8$ Hz, 1H), 1.87–1.78 (m, 1H), 1.62–1.53 (m, 1H), 1.36–1.29 (m, 2H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.92–0.85 (m, 1H), 0.57–0.46 (m, 2H), 0.46–0.39 (m, 1H), 0.22–0.16 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 171.1, 170.7, 150.7, 141.8, 136.2, 110.7, 109.4, 108.3, 81.8, 78.8, 52.9, 51.7, 41.0, 39.5, 38.6, 38.0, 37.7, 33.4, 30.3, 26.0, 22.6, 22.6, 22.6, 18.5, 18.4, 12.1, 4.0, 2.6; MS(ESI) calcd for $\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_6$ 500.29 (M^+), found 501.45 ($\text{M} + \text{H}$) $^+$, 523.44 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27an

Compound **27an** was prepared according to the general procedure D from carboxylic acid **26v** and amine **11q**: ^1H NMR (500 MHz, CDCl_3) δ 7.31 (dd, $J = 1.6, 0.9$ Hz, 1H), 6.31 (dd, $J = 3.1, 1.8$ Hz, 1H), 6.27 (d, $J = 3.2$ Hz, 1H), 5.52 (d, $J = 1.8$ Hz, 1H), 5.02 (d, $J = 15.8$ Hz, 1H), 4.73 (d, $J = 15.8$ Hz, 1H), 3.90 (dd, $J = 6.7, 1.8$ Hz, 1H), 3.74–3.65 (m, 6H), 3.64 (s, 3H), 3.60 (s, 2H), 3.47 (s, 1H), 3.31 (d, $J = 8.3$ Hz, 1H), 3.12–3.03 (m, 1H), 2.89 (dd, $J = 16.2, 3.7$ Hz, 1H), 2.69 (s, 1H), 2.52 (dd, $J = 12.8, 6.5$ Hz, 1H), 1.98 (t, $J = 11.6$ Hz, 1H), 1.83 (h, $J = 6.7$ Hz, 1H), 1.70 (s, 1H), 1.00 (dt, $J = 6.3, 3.2$ Hz, 2H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.79 (dt, $J = 8.0, 3.5$ Hz, 2H), 0.56–0.46 (m, 2H), 0.45–0.39 (m, 1H), 0.21–0.14 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 170.8, 150.8, 141.6, 136.3, 110.7, 108.2, 81.9, 52.8, 51.8, 45.3, 42.0, 41.7, 40.9, 37.0, 36.0, 33.4, 30.5, 18.5, 18.5, 12.1, 11.2, 7.8, 4.0, 2.6; MS(ESI) calcd for $\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_7$ 567.29 (M^+), found 568.48 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ao

Compound **27ao** was prepared according to the general procedure D from carboxylic acid **26w** and amine **11e**: ^1H NMR (500 MHz, CDCl_3) δ 7.18 (dd, $J = 5.0, 1.3$ Hz, 1H), 6.96–6.88 (m, 2H), 6.61 (t, $J = 5.8$ Hz, 1H), 5.43 (t, $J = 3.3$ Hz, 1H), 5.36 (d, $J = 1.9$ Hz, 1H), 4.63 (dd, $J = 15.2, 5.9$ Hz, 1H), 4.51 (dd, $J = 15.3, 5.3$ Hz, 1H), 3.92 (dd, $J = 7.0, 1.9$ Hz, 1H), 3.78 (ddd, $J = 13.5, 10.7, 5.4$ Hz, 1H), 3.69 (s, 3H), 3.67–3.58 (m, 1H), 3.34 (d, $J = 8.4$ Hz,

1H), 2.95–2.86 (m, 1H), 2.62 (dd, $J = 14.7, 5.6$ Hz, 1H), 2.56 (dd, $J = 14.7, 5.6$ Hz, 1H), 2.47 (dd, $J = 13.0, 6.3$ Hz, 1H), 2.23–2.13 (m, 1H), 2.09–2.00 (m, 1H), 2.00–1.90 (m, 5H), 1.87 (dt, $J = 13.5, 6.8$ Hz, 1H), 1.61 (dq, $J = 6.4, 4.1, 3.7$ Hz, 2H), 1.57–1.49 (m, 2H), 0.99 (d, $J = 6.7$ Hz, 3H), 0.96–0.86 (m, 4H), 0.60–0.49 (m, 2H), 0.46 (dq, $J = 10.2, 4.8$ Hz, 1H), 0.26–0.18 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 170.7, 170.6, 141.4, 135.7, 135.0, 126.9, 125.9, 125.0, 123.0, 108.0, 81.9, 78.7, 52.9, 51.7, 42.5, 39.4, 38.3, 37.5, 34.9, 33.7, 30.5, 28.6, 25.4, 23.0, 22.4, 18.8, 18.7, 12.3, 4.4, 2.7; MS(ESI) calcd for $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_5\text{S}$ 554.28 (M^+), found 555.44 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ap

Compound **27ap** was prepared according to the general procedure D from carboxylic acid **26w** and amine **11o**: ^1H NMR (500 MHz, CDCl_3) δ 6.36 (t, $J = 5.3$ Hz, 1H), 6.06 (d, $J = 3.0$ Hz, 1H), 5.86 (d, $J = 2.6$ Hz, 1H), 5.47–5.41 (m, 1H), 5.35 (d, $J = 1.9$ Hz, 1H), 4.36 (dd, $J = 15.4, 5.5$ Hz, 1H), 4.29 (dd, $J = 15.4, 5.1$ Hz, 1H), 3.93 (dd, $J = 6.9, 1.8$ Hz, 1H), 3.79 (ddd, $J = 13.5, 10.7, 5.3$ Hz, 1H), 3.69 (s, 3H), 3.67–3.59 (m, 1H), 3.33 (d, $J = 8.4$ Hz, 1H), 2.96–2.88 (m, 1H), 2.62 (dd, $J = 14.8, 5.4$ Hz, 1H), 2.54 (dd, $J = 14.7, 5.9$ Hz, 1H), 2.47 (dd, $J = 13.0, 6.4$ Hz, 1H), 2.24 (s, 3H), 2.22–2.15 (m, 1H), 2.10–2.02 (m, 1H), 2.01–1.89 (m, 5H), 1.86 (dt, $J = 13.5, 6.8$ Hz, 1H), 1.65–1.57 (m, 2H), 1.57–1.49 (m, 2H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.95–0.86 (m, 4H), 0.58–0.48 (m, 2H), 0.48–0.42 (m, 1H), 0.24–0.18 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 170.6, 170.6, 151.9, 149.7, 135.9, 135.1, 123.0, 108.2, 108.0, 106.3, 81.9, 78.7, 52.8, 51.8, 42.6, 39.5, 37.5, 36.8, 34.9, 33.6, 30.4, 28.6, 25.4, 23.0, 22.4, 18.7, 18.6, 13.7, 12.3, 4.2, 2.6; MS(ESI) calcd for $\text{C}_{32}\text{H}_{44}\text{N}_2\text{O}_6$ 552.32 (M^+), found 553.49 ($\text{M} + \text{H}$) $^+$, 575.47 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27aq

Compound **27aq** was prepared according to the general procedure D from carboxylic acid **26c** and amine **11d**: ^1H NMR (500 MHz, CDCl_3) δ 6.82–6.74 (m, 3H), 6.02 (s, 1H), 5.31 (d, $J = 1.8$ Hz, 1H), 3.98–3.90 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.79 (ddd, $J = 13.6, 9.8, 5.6$ Hz, 1H), 3.68 (s, 3H), 3.33 (d, $J = 8.3$ Hz, 1H), 3.29–3.18 (m, 2H), 2.98–2.90 (m, 1H), 2.87–2.74 (m, 2H), 2.56 (dd, $J = 9.4, 5.7$ Hz, 1H), 2.50 (dd, $J = 12.9, 6.5$ Hz, 1H), 1.93 (dd, $J = 13.1, 11.6$ Hz, 1H), 1.86–1.78 (m, 1H), 1.63–1.54 (m, 1H), 1.37 (q, $J = 7.3$ Hz, 2H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.94–0.85 (m, 11H), 0.58–0.48 (m, 2H), 0.48–0.41 (m, 1H), 0.24–0.17 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 170.9, 170.6, 149.1, 147.8, 136.2, 131.7, 120.7, 112.2, 111.5, 108.4, 81.9, 78.8, 56.0, 56.0, 52.9, 51.9, 45.6, 39.6, 38.6, 38.0, 37.6, 33.5, 32.7, 30.4, 26.0, 22.6, 22.6, 22.6, 18.6, 18.5, 12.2, 4.1, 2.6; MS(ESI) calcd for $\text{C}_{33}\text{H}_{48}\text{N}_2\text{O}_7$ 584.35 (M^+), found 585.51 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ar

compound **27ar** was prepared according to the general procedure D from carboxylic acid **26c** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 8.27 (s, 1H), 6.82–6.72 (m, 3H), 6.15 (t, $J = 6.4$ Hz, 1H), 5.31 (d, $J = 1.9$ Hz, 1H), 4.00 (ddd, $J = 13.7, 9.7, 7.0$ Hz, 1H), 3.92 (dd, $J = 7.1, 1.9$ Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.76 (ddd, $J = 13.9, 9.5, 5.5$ Hz, 1H), 3.68 (s, 3H), 3.34 (d, $J = 8.4$ Hz, 1H), 2.98 (dd, $J = 13.6, 6.4$ Hz, 1H), 2.92 (dd, $J = 11.8, 6.1$ Hz, 1H), 2.89–2.75 (m, 3H), 2.62 (dd, $J = 5.6, 2.0$ Hz, 2H), 2.49 (dd, $J = 13.1, 6.4$ Hz, 1H), 2.06–1.89 (m, 5H), 1.86–1.78 (m, 1H), 1.74–1.55 (m, 10H), 1.45 (d, $J = 2.9$ Hz, 6H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.92–0.84 (m, 5H), 0.58–0.48 (m, 2H), 0.48–0.42 (m, 1H), 0.25–0.19 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 170.9, 170.8, 149.1, 147.8, 136.0, 131.7, 120.7, 112.2, 111.5, 108.2, 81.8, 78.7, 56.0, 56.0, 52.9, 51.8, 51.3, 51.0, 45.5, 40.4, 40.3, 39.7, 39.6, 37.7, 37.1, 37.0, 36.5, 33.8, 33.6, 32.6, 32.3, 30.4, 28.4, 28.3, 28.0, 18.7, 18.6, 12.3, 4.3, 2.7; MS(ESI) calcd for $\text{C}_{39}\text{H}_{54}\text{N}_2\text{O}_7$ 662.39 (M^+), found 663.55 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27as

Compound **27as** was prepared according to the general procedure D from carboxylic acid **26x** and amine **11t**: ^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.53 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.48 (ddd, J = 7.9, 6.8, 1.2 Hz, 1H), 7.44–7.35 (m, 2H), 5.47 (d, J = 16.0 Hz, 1H), 5.32 (d, J = 16.3 Hz, 1H), 5.29 (d, J = 1.8 Hz, 1H), 3.86–3.79 (m, 1H), 3.71–3.63 (m, 5H), 3.63–3.55 (m, 2H), 3.54–3.43 (m, 2H), 3.32 (s, 3H), 3.27 (d, J = 8.2 Hz, 1H), 3.20–3.12 (m, 1H), 2.86 (d, J = 5.2 Hz, 2H), 2.54 (dd, J = 12.7, 6.5 Hz, 1H), 2.19 (t, J = 12.2 Hz, 1H), 1.78–1.68 (m, 1H), 0.99–0.87 (m, 1H), 0.85 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H), 0.55–0.44 (m, 2H), 0.44–0.36 (m, 1H), 0.19–0.10 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 171.2, 169.3, 136.3, 133.9, 131.7, 131.2, 128.9, 127.7, 126.3, 125.7, 125.5, 125.2, 123.2, 109.8, 78.8, 67.0, 66.7, 52.4, 51.8, 46.0, 45.3, 42.1, 37.1, 35.7, 33.4, 30.4, 18.4, 18.2, 12.0, 3.9, 2.6; MS(ESI) calcd for $\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_6$ 560.29 (M^+), found 561.46 ($\text{M} + \text{H}$) $^+$, 583.44 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27at

Compound **27at** was prepared according to the general procedure D from carboxylic acid **26x** and amine **11n**: ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.53 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.48 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.28 (dd, J = 7.2, 1.3 Hz, 1H), 6.82 (t, J = 6.3 Hz, 1H), 5.42 (d, J = 16.2 Hz, 1H), 5.35 (d, J = 16.2 Hz, 1H), 5.23 (d, J = 1.8 Hz, 1H), 3.80 (dd, J = 6.5, 1.8 Hz, 1H), 3.38 (s, 3H), 3.36–3.24 (m, 5H), 3.23–3.09 (m, 3H), 2.70 (d, J = 5.6 Hz, 2H), 2.52 (dd, J = 13.0, 6.5 Hz, 1H), 2.37 (t, J = 8.1 Hz, 2H), 2.14 (t, J = 12.4 Hz, 1H), 2.04–1.93 (m, 2H), 1.83 (s, 1H), 1.76–1.60 (m, 3H), 0.99–0.86 (m, 1H), 0.83 (d, J = 6.7 Hz, 3H), 0.68 (d, J = 6.7 Hz, 3H), 0.61–0.43 (m, 2H), 0.44–0.36 (m, 1H), 0.21–0.12 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 173.0, 171.1, 170.9, 136.1, 133.8, 131.5, 131.1, 128.9, 127.7, 126.3, 125.7, 125.5, 124.7, 123.1, 109.5, 81.9, 78.7, 52.5, 51.7, 47.4, 45.3, 39.8, 39.3, 37.4, 36.0, 33.4, 31.1, 30.4, 26.7, 18.4, 18.3, 18.0, 12.1, 4.1, 2.6; MS(ESI) calcd for $\text{C}_{36}\text{H}_{45}\text{N}_3\text{O}_6$ 615.33 (M^+), found 616.51 ($\text{M} + \text{H}$) $^+$, 638.49 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27au

Compound **27au** was prepared according to the general procedure D from carboxylic acid **26y** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 7.37 (t, J = 1.2 Hz, 1H), 7.21 (d, J = 1.2 Hz, 2H), 6.21 (t, J = 5.6 Hz, 1H), 5.10 (d, J = 2.0 Hz, 1H), 5.05 (d, J = 16.8 Hz, 1H), 4.88 (d, J = 16.8 Hz, 1H), 3.78 (dd, J = 7.4, 2.0 Hz, 1H), 3.71 (s, 3H), 3.44 (t, J = 5.8 Hz, 2H), 3.38–3.27 (m, 5H), 2.99–2.89 (m, 1H), 2.70 (dd, J = 15.2, 5.8 Hz, 1H), 2.59 (dd, J = 15.2, 4.8 Hz, 1H), 2.43 (dd, J = 13.0, 6.0 Hz, 1H), 2.24 (t, J = 12.8 Hz, 1H), 1.83–1.67 (m, 4H), 0.90 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H), 0.59 (td, J = 8.8, 4.1 Hz, 1H), 0.55–0.41 (m, 2H), 0.30–0.21 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.2, 171.2, 170.5, 135.4, 133.3, 133.1, 132.8, 129.2, 129.0, 127.5, 108.3, 81.8, 78.5, 71.7, 58.9, 53.0, 51.7, 44.9, 38.4, 38.1, 37.3, 33.6, 30.4, 29.3, 18.7, 18.7, 12.4, 4.8, 2.6; MS(ESI) calcd for $\text{C}_{29}\text{H}_{38}\text{Cl}_2\text{N}_2\text{O}_6$ 580.21 (M^+), found 581.39 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27av

Compound **27av** was prepared according to the general procedure D from carboxylic acid **26y** and amine **11p**: ^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, J = 1.7 Hz, 1H), 7.24–7.18 (m, 2H), 6.28 (t, J = 5.4 Hz, 1H), 5.09 (d, J = 2.0 Hz, 1H), 5.06 (d, J = 16.8 Hz, 1H), 4.87 (d, J = 16.8 Hz, 1H), 3.78 (dd, J = 7.4, 2.0 Hz, 1H), 3.71 (s, 3H), 3.48 (t, J = 5.8 Hz, 2H), 3.39 (t, J = 6.6 Hz, 2H), 3.36–3.30 (m, 2H), 2.99–2.89 (m, 1H), 2.70 (dd, J = 15.2, 5.8 Hz, 1H), 2.58 (dd, J = 15.2, 4.6 Hz, 1H), 2.42 (dd, J = 13.0, 5.9 Hz, 1H), 2.24 (t, J = 12.7 Hz, 1H), 1.80–1.69 (m, 3H), 1.59–1.49 (m, 2H), 1.40–1.31 (m, 2H), 0.96–0.86 (m, 8H), 0.77 (d, J = 6.7 Hz, 3H), 0.59 (dtd, J = 10.1, 5.6, 4.8, 2.8 Hz, 1H), 0.54–0.41 (m, 2H), 0.29–0.22 (m, 1H); ^{13}C

NMR (126 MHz, CDCl₃) δ 173.2, 171.2, 170.4, 133.3, 133.1, 132.8, 129.2, 129.1, 127.5, 108.3, 81.8, 78.5, 71.1, 69.9, 53.0, 51.7, 44.9, 38.4, 38.3, 37.2, 33.6, 31.9, 30.3, 29.3, 19.5, 18.7, 18.7, 14.1, 12.4, 4.8, 2.6; MS(ESI) calcd for C₃₂H₄₄Cl₂N₂O₆ 622.26 (M⁺), found 623.44 (M + H)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27aw

Compound **27aw** was prepared according to the general procedure D from carboxylic acid **26z** and amine **11a**: ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.32 (m, 4H), 7.32–7.28 (m, 1H), 6.46 (t, *J* = 5.4 Hz, 1H), 5.35 (d, *J* = 1.7 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.50 (td, *J* = 6.0, 1.8 Hz, 1H), 4.11 (q, *J* = 6.5 Hz, 1H), 4.03 (ddd, *J* = 17.6, 5.4, 2.5 Hz, 1H), 3.95 (ddd, *J* = 17.4, 5.0, 2.5 Hz, 1H), 3.85–3.75 (m, 2H), 3.70 (s, 3H), 3.56 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.52–3.45 (m, 1H), 3.43 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.93 (m, 1H), 2.59 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.54 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.37 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.19 (t, *J* = 2.6 Hz, 1H), 1.71 (t, *J* = 12.3 Hz, 1H), 1.65–1.53 (m, 1H), 1.53–1.42 (m, 1H), 1.36–1.23 (m, 10H), 1.22 (d, *J* = 6.6 Hz, 3H), 0.91–0.84 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.6, 170.7, 170.5, 138.1, 136.4, 128.6, 127.9, 127.9, 107.3, 79.8, 74.5, 73.6, 73.3, 72.8, 71.5, 52.9, 51.3, 43.6, 39.3, 37.3, 31.9, 29.5, 29.5, 29.4, 29.3, 27.3, 26.7, 22.8, 17.0, 14.2; MS(ESI) calcd for C₃₂H₄₄N₂O₆ 552.32 (M⁺), found 553.5 (M + H)⁺, 575.48 (M + Na)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ax

Compound **27ax** was prepared according to the general procedure D from carboxylic acid **26z** and amine **11f**: ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.30 (m, 4H), 7.30–7.27 (m, 1H), 6.84–6.75 (m, 3H), 6.33 (t, *J* = 5.7 Hz, 1H), 5.32 (d, *J* = 1.8 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.50 (td, *J* = 5.9, 1.7 Hz, 1H), 4.32 (dd, *J* = 14.1, 5.4 Hz, 2H), 4.11 (q, *J* = 6.6 Hz, 1H), 3.96 (d, *J* = 12.6 Hz, 2H), 3.89–3.85 (m, 3H), 3.85–3.82 (m, 3H), 3.68 (s, 3H), 3.56 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.43 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.95 (m, 1H), 2.60 (dd, *J* = 14.8, 5.5 Hz, 1H), 2.53 (dd, *J* = 14.8, 5.9 Hz, 1H), 2.37 (dd, *J* = 12.8, 6.6 Hz, 1H), 1.72 (t, *J* = 12.2 Hz, 1H), 1.61–1.50 (m, 1H), 1.49–1.40 (m, 1H), 1.33–1.22 (m, 10H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 191.1, 172.6, 170.7, 170.5, 149.2, 148.5, 138.1, 136.5, 131.2, 128.6, 127.9, 127.9, 127.0, 120.1, 119.8, 111.3, 111.3, 111.2, 110.9, 110.5, 109.1, 107.0, 74.5, 73.6, 73.3, 72.9, 56.3, 56.1, 56.1, 56.1, 56.0, 56.0, 56.0, 56.0, 52.9, 44.6, 43.5, 43.5, 39.5, 37.4, 31.9, 29.6, 29.5, 29.4, 29.4, 27.3, 26.7, 22.8, 17.0, 14.2; MS(ESI) calcd for C₃₈H₅₂N₂O₈ 664.37 (M⁺), found 665.55 (M + H)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ay

Compound **27ay** was prepared according to the general procedure D from carboxylic acid **26aa** and amine **11h**: ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.80 (dd, *J* = 6.3, 3.3 Hz, 1H), 7.56–7.45 (m, 2H), 7.43–7.36 (m, 2H), 7.34–7.26 (m, 4H), 7.26–7.15 (m, 6H), 6.20 (t, *J* = 5.6 Hz, 1H), 5.27 (d, *J* = 1.9 Hz, 1H), 4.91–4.78 (m, 3H), 4.74 (d, *J* = 15.8 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.43 (d, *J* = 12.1 Hz, 1H), 4.40 (td, *J* = 5.6, 2.8 Hz, 1H), 4.13 (q, *J* = 6.5 Hz, 1H), 3.59 (s, 3H), 3.47 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.31 (dd, *J* = 9.8, 5.7 Hz, 1H), 3.04–2.96 (m, 1H), 2.70–2.58 (m, 2H), 2.38 (dd, *J* = 12.8, 6.3 Hz, 1H), 1.87 (t, *J* = 12.4 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.7, 170.8, 170.4, 138.1, 136.8, 136.2, 134.0, 133.7, 131.5, 128.9, 128.7, 128.6, 128.5, 127.8, 127.8, 127.2, 127.0, 126.8, 126.8, 126.1, 125.5, 123.7, 107.7, 74.2, 73.5, 72.9, 72.9, 52.9, 51.4, 47.4, 41.8, 39.0, 37.5, 29.6, 17.2; MS(ESI) calcd for C₃₉H₄₀N₂O₆ 632.29 (M⁺), found 633.45 (M + H)⁺.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27az

Compound **27az** was prepared according to the general procedure D from carboxylic acid **26aa** and amine **11u**: ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.27 (m, 5H), 7.26–7.19 (m, 5H), 5.29 (d, J = 1.8 Hz, 1H), 4.98 (d, J = 15.7 Hz, 1H), 4.87 (d, J = 15.7 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 4.41 (td, J = 6.6, 1.5 Hz, 1H), 4.12 (q, J = 6.6 Hz, 1H), 3.64–3.56 (m, 4H), 3.48 (dd, J = 9.9, 6.6 Hz, 1H), 3.45–3.32 (m, 1H), 3.30 (dd, J = 9.8, 5.7 Hz, 1H), 3.01–2.93 (m, 1H), 2.87 (dd, J = 16.2, 3.4 Hz, 1H), 2.76 (dd, J = 16.2, 7.5 Hz, 1H), 2.37 (dd, J = 12.7, 6.2 Hz, 1H), 1.94 (t, J = 12.2 Hz, 1H), 1.68–1.59 (m, 3H), 1.59–1.47 (m, 5H), 1.20 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 171.2, 168.6, 138.2, 137.2, 136.7, 128.6, 128.5, 127.8, 127.8, 127.2, 127.0, 107.1, 74.4, 73.5, 73.0, 52.8, 51.4, 47.5, 46.6, 42.9, 37.0, 35.9, 29.8, 26.5, 25.7, 24.7, 17.2; MS(ESI) calcd for $\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_6$ 560.29 (M^+), found 561.46 ($\text{M} + \text{H}$) $^+$, 583.44 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27ba

Compound **27ba** was prepared according to the general procedure D from carboxylic acid **26ab** and amine **11a**: ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.31 (m, 2H), 7.31–7.26 (m, 2H), 7.25 (d, J = 1.4 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 6.67 (dd, J = 7.9, 1.8 Hz, 1H), 6.28 (t, J = 5.0 Hz, 1H), 5.92 (s, 2H), 5.34 (d, J = 1.8 Hz, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.41 (td, J = 6.1, 1.8 Hz, 1H), 4.12 (q, J = 6.5 Hz, 1H), 4.00 (dd, J = 5.3, 2.6 Hz, 2H), 3.64 (s, 3H), 3.49 (dd, J = 9.8, 6.3 Hz, 1H), 3.33 (dd, J = 9.8, 5.7 Hz, 1H), 2.97 (m, 1H), 2.66 (dd, J = 14.9, 5.6 Hz, 1H), 2.60 (dd, J = 15.0, 5.4 Hz, 1H), 2.37 (dd, J = 12.9, 6.4 Hz, 1H), 2.20 (t, J = 2.5 Hz, 1H), 1.84 (t, J = 12.4 Hz, 1H), 1.64 (s, 1H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 171.0, 170.5, 148.0, 146.7, 138.1, 136.3, 130.7, 128.5, 127.9, 127.8, 120.3, 108.4, 108.0, 107.7, 101.1, 79.7, 74.3, 73.5, 72.9, 72.8, 71.6, 53.0, 51.4, 47.4, 38.8, 37.4, 29.6, 29.3, 17.1; MS(ESI) calcd for $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_8$ 574.23 (M^+), found 575.35 ($\text{M} + \text{H}$) $^+$, 597.34 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bb

Compound **27bb** was prepared according to the general procedure D from carboxylic acid **26ab** and amine **11w**: ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.24 (m, 5H), 6.79 (d, J = 1.1 Hz, 1H), 6.72 (t, J = 1.1 Hz, 2H), 5.90 (d, J = 1.2 Hz, 2H), 5.30 (d, J = 1.7 Hz, 1H), 4.86 (d, J = 15.6 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.3 Hz, 1H), 4.42 (td, J = 6.6, 6.2, 1.7 Hz, 1H), 4.12 (q, J = 6.4, 6.0 Hz, 1H), 3.64 (s, 3H), 3.54–3.48 (m, 2H), 3.43 (m, 4H), 3.33 (dd, J = 9.8, 5.7 Hz, 1H), 2.99–2.91 (m, 1H), 2.82 (dd, J = 16.4, 6.6 Hz, 1H), 2.68 (dd, J = 16.5, 3.5 Hz, 1H), 2.33 (dd, J = 12.6, 6.2 Hz, 1H), 2.02 (t, J = 12.3 Hz, 1H), 1.93 (m, 2H), 1.87–1.80 (m, 2H), 1.21 (d, J = 6.4 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 171.3, 168.9, 147.9, 146.5, 138.2, 136.8, 131.2, 128.5, 127.8, 127.8, 120.3, 108.2, 107.9, 107.0, 101.0, 74.4, 73.5, 73.1, 73.0, 52.8, 51.4, 47.3, 46.6, 45.8, 36.9, 36.7, 29.6, 26.2, 24.5, 17.2; MS(ESI) calcd for $\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_8$ 590.26 (M^+), found 591.38 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bc

Compound **27bc** was prepared according to the general procedure D from carboxylic acid **26d** and amine **11d**: ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.26 (m, 5H), 6.30 (dd, J = 3.2, 1.9 Hz, 1H), 6.24 (d, J = 3.2 Hz, 1H), 5.91 (t, J = 5.4 Hz, 1H), 5.56 (d, J = 1.8 Hz, 1H), 4.95 (d, J = 15.8 Hz, 1H), 4.72 (d, J = 15.8 Hz, 1H), 4.58 (d, J = 12.1 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.46 (td, J = 6.0, 1.8 Hz, 1H), 4.09 (q, J = 6.5 Hz, 1H), 3.62 (s, 3H), 3.54 (dd, J = 9.7, 6.4 Hz, 1H), 3.40 (dd, J = 9.8, 5.7 Hz, 1H), 3.20–3.14 (m, 2H), 2.94 (m, 1H), 2.55 (dd, J = 5.6, 2.0 Hz, 2H), 2.38 (dd, J = 12.9, 6.6 Hz, 1H), 1.75 (dd, J = 12.9, 11.6 Hz, 1H), 1.61–1.51 (m, 1H), 1.43–1.34 (m, 1H), 1.34–1.27 (m, 2H), 1.19 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 1.2

Hz, 3H), 0.87 (d, $J = 1.2$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.6, 170.8, 170.6, 150.4, 141.8, 138.2, 136.6, 128.5, 127.8, 127.8, 110.6, 108.5, 108.3, 74.4, 73.6, 73.2, 72.8, 53.0, 51.4, 41.0, 39.2, 38.5, 38.0, 37.6, 29.4, 26.0, 22.6, 22.6, 17.0; MS(ESI) calcd for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_7$ 552.28 (M^+), found 553.46 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bd

Compound **27bd** was prepared according to the general procedure D from carboxylic acid **26d** and amine **11x**: ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.27 (m, 6H), 7.25–7.17 (m, 4H), 6.32–6.27 (m, 2H), 5.53 (d, $J = 1.8$ Hz, 1H), 4.95–4.79 (m, 2H), 4.76–4.70 (m, 1H), 4.60 (d, $J = 12.2$ Hz, 1H), 4.54 (d, $J = 12.1$ Hz, 1H), 4.51–4.47 (m, 1H), 4.10 (dd, $J = 6.6$, 4.7 Hz, 1H), 4.00–3.92 (m, 1H), 3.62 (d, $J = 2.6$ Hz, 3H), 3.60–3.53 (m, 1H), 3.42 (dd, $J = 9.8$, 5.5 Hz, 1H), 3.14–3.05 (m, 1H), 3.04–2.96 (m, 1H), 2.90 (ddd, $J = 17.2$, 14.2, 3.4 Hz, 1H), 2.80–2.67 (m, 2H), 2.66–2.57 (m, 1H), 2.46–2.37 (m, 1H), 1.86 (q, $J = 12.1$, 11.6 Hz, 3H), 1.69–1.56 (m, 3H), 1.28–1.18 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 170.9, 168.8, 168.7, 150.6, 145.3, 141.6, 138.2, 137.0, 128.9, 128.7, 128.6, 128.5, 128.5, 127.9, 127.8, 127.8, 127.2, 126.9, 126.8, 126.8, 126.6, 110.6, 108.4, 108.3, 107.7, 107.6, 74.5, 73.5, 73.4, 73.3, 73.0, 52.9, 51.4, 51.4, 46.2, 44.7, 42.9, 42.6, 42.6, 40.9, 40.8, 40.7, 37.0, 36.9, 36.1, 36.1, 33.9, 33.8, 33.0, 33.0, 30.0, 29.6, 17.0, 17.0; MS(ESI) calcd for $\text{C}_{37}\text{H}_{42}\text{N}_2\text{O}_7$ 626.30 (M^+), found 627.47 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27be

Compound **27be** was prepared according to the general procedure D from carboxylic acid **26ac** and amine **11g**: ^1H NMR (500 MHz, CDCl_3) δ 7.56–7.48 (m, 2H), 7.48–7.38 (m, 2H), 7.38–7.31 (m, 4H), 7.31–7.27 (m, 1H), 6.73 (q, $J = 6.5$, 6.0 Hz, 1H), 5.44–5.40 (m, 1H), 5.37 (d, $J = 1.7$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 4.55 (d, $J = 12.1$ Hz, 1H), 4.53–4.46 (m, 2H), 4.40 (dd, $J = 15.2$, 5.7 Hz, 1H), 4.14 (q, $J = 6.3$ Hz, 1H), 3.80 (ddd, $J = 13.1$, 10.8, 5.3 Hz, 1H), 3.69 (s, 3H), 3.61–3.51 (m, 2H), 3.44 (dd, $J = 9.7$, 5.8 Hz, 1H), 2.96–2.86 (m, 1H), 2.62 (dd, $J = 14.7$, 5.8 Hz, 1H), 2.55 (dd, $J = 15.0$, 5.5 Hz, 1H), 2.36 (dd, $J = 12.7$, 6.4 Hz, 1H), 2.23–2.13 (m, 1H), 2.08–1.99 (m, 1H), 1.99–1.91 (m, 4H), 1.70 (t, $J = 12.4$ Hz, 1H), 1.64–1.56 (m, 2H), 1.56–1.48 (m, 2H), 1.21 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.6, 171.1, 170.5, 139.7, 138.1, 136.0, 134.9, 131.2, 129.2, 128.6, 127.9, 127.9, 124.4 (q, $^3J_{\text{C-F}} = 3.6$ Hz), 124.3 (q, $^3J_{\text{C-F}} = 3.5$ Hz), 124.2 (q, $^1J_{\text{C-F}} = 273.3$ Hz), 123.0, 107.0, 74.3, 73.6, 73.0, 72.9, 53.0, 51.3, 43.1, 42.6, 39.5, 37.4, 34.7, 29.8, 28.6, 25.4, 23.0, 22.4, 17.1; MS(ESI) calcd for $\text{C}_{37}\text{H}_{43}\text{F}_3\text{N}_2\text{O}_6$ 668.31 (M^+), found 669.42 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bf

Compound **27bf** was prepared according to the general procedure D from carboxylic acid **26ac** and amine **11t**: ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.32 (m, 4H), 7.31–7.27 (m, 1H), 5.50–5.40 (m, 1H), 5.37 (d, $J = 1.8$ Hz, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.55 (d, $J = 12.1$ Hz, 1H), 4.52 (td, $J = 6.1$, 1.6 Hz, 1H), 4.12 (q, $J = 6.5$ Hz, 1H), 3.86 (ddd, $J = 13.5$, 11.0, 5.4 Hz, 1H), 3.70 (s, 3H), 3.68–3.62 (m, 4H), 3.62–3.49 (m, 4H), 3.47–3.39 (m, 3H), 2.96–2.88 (m, 1H), 2.83 (dd, $J = 16.2$, 3.4 Hz, 1H), 2.62 (dd, $J = 16.2$, 7.7 Hz, 1H), 2.37 (dd, $J = 12.6$, 6.5 Hz, 1H), 2.28–2.18 (m, 1H), 2.12–2.02 (m, 1H), 1.99–1.91 (m, 4H), 1.75 (t, $J = 12.0$ Hz, 1H), 1.63–1.56 (m, 2H), 1.56–1.49 (m, 2H), 1.23 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 170.3, 169.3, 138.1, 136.7, 135.1, 128.5, 127.9, 127.8, 122.8, 106.4, 74.5, 73.5, 73.3, 73.0, 67.0, 66.6, 52.9, 51.4, 45.9, 42.6, 42.1, 36.8, 35.9, 34.7, 29.6, 28.6, 25.4, 23.0, 22.5, 17.1; MS(ESI) calcd for $\text{C}_{33}\text{H}_{44}\text{N}_2\text{O}_7$ 580.31 (M^+), found 581.45 ($\text{M} + \text{H}$) $^+$, 603.42 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bg

Compound **27bg** was prepared according to the general procedure D from carboxylic acid **26ad** and amine **11g**: ^1H NMR (500 MHz, CDCl_3) δ 7.58–7.37 (m, 4H), 7.36–7.30 (m, 4H), 7.30–7.27 (m, 1H), 6.78–6.69 (m, 3H), 6.56 (t, J = 6.0 Hz, 1H), 5.37 (d, J = 1.8 Hz, 1H), 4.60 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.3 Hz, 1H), 4.53–4.49 (m, 1H), 4.46 (dd, J = 18.7, 5.8 Hz, 1H), 4.14 (q, J = 6.5 Hz, 1H), 3.94 (ddd, J = 13.5, 10.4, 6.2 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.76–3.69 (m, 1H), 3.69 (s, 3H), 3.55 (dd, J = 9.7, 6.3 Hz, 1H), 3.41 (dd, J = 9.7, 6.0 Hz, 1H), 2.96 (m, 1H), 2.85–2.77 (m, 1H), 2.77–2.69 (m, 1H), 2.65–2.56 (m, 2H), 2.38 (dd, J = 12.8, 6.5 Hz, 1H), 1.75 (t, J = 12.3 Hz, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.6, 171.0, 170.6, 149.1, 147.8, 139.7, 138.1, 136.3, 131.5, 131.2, 131.1, 131.1 ($^2J_{\text{C-F}}$ = 32.4 Hz), 129.2, 128.6, 127.9, 127.9, 124.4 ($^3J_{\text{C-F}}$ = 3.8 Hz), 124.3 ($^3J_{\text{C-F}}$ = 3.8 Hz), 124.2 ($^1J_{\text{C-F}}$ = 272.9 Hz), 120.7, 74.4, 73.6, 73.1, 72.9, 56.1, 56.0, 53.0, 51.4, 45.4, 43.1, 39.4, 37.4, 32.6, 29.7, 17.1; MS(ESI) calcd for $\text{C}_{39}\text{H}_{43}\text{F}_3\text{N}_2\text{O}_8$ 724.30 (M^+), found 725.46 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bh

Compound **27bh** was prepared according to the general procedure D from carboxylic acid **26ad** and amine **11q**: ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.30 (m, 4H), 7.29 (s, 1H), 6.77 (d, J = 10.7 Hz, 3H), 5.37 (d, J = 1.8 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.58–4.49 (m, 2H), 4.11 (q, J = 6.6 Hz, 1H), 3.98 (ddd, J = 13.3, 10.6, 6.2 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78–3.71 (m, 1H), 3.71–3.60 (m, 8H), 3.56 (dd, J = 9.7, 6.6 Hz, 1H), 3.41 (dd, J = 9.7, 5.9 Hz, 1H), 3.01–2.91 (m, 1H), 2.89–2.81 (m, 2H), 2.81–2.71 (m, 3H), 2.38 (dd, J = 12.6, 6.6 Hz, 1H), 1.84–1.76 (m, 1H), 1.72 (s, 1H), 1.23 (d, J = 6.6 Hz, 3H), 1.01 (dq, J = 6.6, 3.9 Hz, 3H), 0.83–0.76 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.8, 170.5, 149.1, 147.7, 138.1, 136.9, 131.8, 128.6, 127.9, 120.7, 112.2, 111.4, 74.6, 73.5, 73.3, 72.9, 56.0, 56.0, 52.9, 51.4, 45.5, 45.3, 41.9, 41.7, 36.8, 36.0, 32.6, 29.5, 17.0, 11.2, 7.8; MS(ESI) calcd for $\text{C}_{39}\text{H}_{49}\text{N}_3\text{O}_9$ 703.35 (M^+), found 704.5 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bi

Compound **27bi** was prepared according to the general procedure D from carboxylic acid **26ae** and amine **11i**: ^1H NMR (500 MHz, CDCl_3) δ 8.27 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.87 (dd, J = 7.9, 1.7 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.58–7.46 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.24 (dd, J = 6.4, 2.7 Hz, 3H), 7.14 (dd, J = 6.6, 3.0 Hz, 2H), 6.10 (s, 1H), 5.53 (d, J = 16.2 Hz, 1H), 5.30–5.20 (m, 2H), 4.45 (d, J = 12.1 Hz, 1H), 4.39 (d, J = 12.2 Hz, 1H), 4.36 (td, J = 6.4, 6.0, 2.3 Hz, 1H), 4.11 (q, J = 6.5 Hz, 1H), 3.44 (dd, J = 9.8, 6.5 Hz, 1H), 3.35 (s, 3H), 3.27 (dd, J = 9.8, 5.5 Hz, 1H), 3.07–3.00 (m, 1H), 2.92 (d, J = 6.2 Hz, 2H), 2.75 (dd, J = 14.6, 5.8 Hz, 1H), 2.70–2.62 (m, 3H), 2.43 (dd, J = 12.9, 6.3 Hz, 1H), 2.06–2.01 (m, 2H), 2.01–1.90 (m, 2H), 1.75–1.56 (m, 8H), 1.51–1.39 (m, 3H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 171.0, 170.9, 138.0, 136.2, 133.9, 131.2, 131.0, 128.9, 128.5, 127.8, 127.8, 127.8, 126.4, 125.8, 125.5, 124.6, 123.0, 108.2, 74.2, 73.5, 72.9, 72.8, 52.7, 51.4, 51.3, 51.1, 45.4, 40.4, 40.3, 39.8, 39.2, 37.9, 37.1, 37.1, 36.5, 33.7, 32.3, 29.7, 28.4, 28.3, 28.0, 17.1; MS(ESI) calcd for $\text{C}_{43}\text{H}_{50}\text{N}_2\text{O}_6$ 690.37 (M^+), found 691.53 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bj

Compound **27bj** was prepared according to the general procedure D from carboxylic acid **26ae** and amine **11n**: ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.53 (ddd, J = 8.5, 6.8, 1.6 Hz, 1H), 7.49 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.1 Hz, 1H), 7.25–7.18 (m, 3H), 7.16–7.10 (m, 2H), 6.80 (t, J = 6.3 Hz, 1H), 5.43 (d, J = 16.4 Hz, 1H), 5.32 (d, J = 16.5 Hz, 1H), 5.23 (d, J = 1.8 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 4.40–4.34 (m, 2H), 4.09 (q, J = 6.5 Hz,

1H), 3.44 (dd, $J = 9.8, 6.7$ Hz, 1H), 3.39 (s, 3H), 3.35–3.24 (m, 5H), 3.18 (q, $J = 6.2$ Hz, 2H), 3.10–3.03 (m, 1H), 2.70 (t, $J = 5.7$ Hz, 1H), 2.37 (dd, $J = 9.5, 7.0$ Hz, 3H), 2.03–1.93 (m, 3H), 1.65 (tt, $J = 6.4$ Hz, $J = 6.4$ Hz, 2H), 1.21 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.9, 172.8, 170.9, 170.8, 138.1, 136.6, 133.9, 131.2, 131.1, 128.9, 128.4, 127.8, 127.7, 127.7, 126.4, 125.8, 125.6, 124.6, 123.1, 107.7, 74.3, 73.4, 73.0, 72.9, 52.7, 51.4, 47.5, 45.6, 39.8, 38.9, 37.3, 37.2, 36.0, 31.1, 29.6, 26.7, 18.0, 17.1; MS(ESI) calcd for $\text{C}_{39}\text{H}_{45}\text{N}_3\text{O}_7$ 667.33 (M^+), found 668.51 ($\text{M} + \text{H}$) $^+$, 690.45 ($\text{M} + \text{Na}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bk

Compound **27bk** was prepared according to the general procedure D from carboxylic acid **26af** and amine **11o**: ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.27 (m, 4H), 7.25–7.21 (m, 2H), 7.19–7.13 (m, 2H), 6.06 (d, $J = 3.0$ Hz, 1H), 6.02 (t, $J = 5.3$ Hz, 1H), 5.88–5.84 (m, 1H), 5.10 (d, $J = 1.9$ Hz, 1H), 5.01 (d, $J = 16.9$ Hz, 1H), 4.79 (d, $J = 16.9$ Hz, 1H), 4.51 (d, $J = 12.3$ Hz, 1H), 4.45 (d, $J = 12.1$ Hz, 1H), 4.38 (td, $J = 6.2, 1.9$ Hz, 1H), 4.33 (d, $J = 5.2$ Hz, 2H), 4.16 (q, $J = 6.6$ Hz, 1H), 3.72 (s, 3H), 3.48 (dd, $J = 9.8, 6.4$ Hz, 1H), 3.31 (dd, $J = 9.8, 5.6$ Hz, 1H), 2.96–2.86 (m, 1H), 2.77 (dd, $J = 15.2, 5.8$ Hz, 1H), 2.58 (dd, $J = 15.3, 4.6$ Hz, 1H), 2.34 (dd, $J = 12.9, 6.1$ Hz, 1H), 2.24 (s, 3H), 2.02 (t, $J = 12.6$ Hz, 1H), 1.23 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.9, 170.2, 152.0, 149.4, 138.1, 136.1, 133.4, 133.1, 132.5, 129.2, 128.8, 128.5, 128.5, 127.8, 127.8, 127.5, 108.4, 107.2, 106.4, 74.2, 73.5, 72.8, 72.8, 53.1, 51.4, 45.5, 38.0, 37.2, 36.8, 29.5, 17.3, 13.7; MS(ESI) calcd for $\text{C}_{34}\text{H}_{36}\text{Cl}_2\text{N}_2\text{O}_7$ 654.19 (M^+), found 655.37 ($\text{M} + \text{H}$) $^+$.

Tetrahydropyran-Fused Piperidinone-Containing Amide 27bl

Compound **27bl** was prepared according to the general procedure D from carboxylic acid **26af** and amine **11p**: ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.27 (m, 4H), 7.25–7.14 (m, 4H), 6.27 (t, $J = 5.5$ Hz, 1H), 5.08 (d, $J = 1.9$ Hz, 1H), 5.04 (d, $J = 17.0$ Hz, 1H), 4.79 (d, $J = 17.0$ Hz, 1H), 4.51 (d, $J = 12.2$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.38 (td, $J = 5.8, 1.9$ Hz, 1H), 4.16 (q, $J = 6.5$ Hz, 1H), 3.72 (s, 3H), 3.51–3.43 (m, 3H), 3.39 (t, $J = 6.6$ Hz, 2H), 3.35–3.26 (m, 2H), 2.93–2.83 (m, 1H), 2.73 (dd, $J = 15.3, 5.8$ Hz, 1H), 2.54 (dd, $J = 15.3, 4.4$ Hz, 1H), 2.32 (dd, $J = 12.8, 6.0$ Hz, 1H), 2.04 (t, $J = 12.5$ Hz, 1H), 1.73 (tt, $J = 6.0$ Hz, 2H), 1.58–1.49 (m, 2H), 1.40–1.30 (m, 2H), 1.23 (d, $J = 6.5$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 170.9, 170.3, 138.1, 136.2, 133.3, 133.1, 132.6, 129.2, 128.9, 128.5, 127.8, 127.8, 127.5, 107.0, 74.2, 73.5, 72.9, 72.8, 71.1, 70.0, 53.1, 51.4, 45.6, 38.5, 38.0, 37.2, 31.9, 29.6, 29.2, 19.5, 17.3, 14.1; MS(ESI) calcd for $\text{C}_{35}\text{H}_{44}\text{Cl}_2\text{N}_2\text{O}_7$ 674.25 (M^+), found 675.41 ($\text{M} + \text{H}$) $^+$.

Tricyclic Amide 42 ((6*RS*,7*aSR*)-Ethyl 6-(2-((3,4-Dimethoxybenzyl)amino)-2-oxoethyl)-5-oxo-2,3,5,6,7,7*a*,8,9-octahydro-1*H*-cyclopenta[*i*]quinolizine-7*a*-carboxylate)

Compound **42** was prepared according to the general procedure D from carboxylic acid **38** and amine **11f**: ^1H NMR (500 MHz, CDCl_3) δ 6.81 (s, 1H), 6.77 (s, 2H), 6.58 (t, $J = 5.9$ Hz, 1H), 4.40 (dd, $J = 14.6, 6.2$ Hz, 1H), 4.25 (dd, $J = 14.6, 5.4$ Hz, 1H), 4.18–4.07 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 (ddd, $J = 13.1, 6.9, 4.0$ Hz, 1H), 3.36 (ddd, $J = 12.7, 8.6, 3.7$ Hz, 1H), 2.84–2.74 (m, 1H), 2.65 (dd, $J = 14.5, 4.9$ Hz, 1H), 2.58–2.41 (m, 2H), 2.27 (dd, $J = 12.9, 6.9$ Hz, 1H), 2.20 (dd, $J = 15.3, 8.7$ Hz, 1H), 2.15–2.06 (m, 1H), 2.03 (dt, $J = 17.2, 5.6$ Hz, 1H), 1.86–1.65 (m, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 171.2, 168.7, 149.2, 148.4, 133.9, 131.4, 120.0, 118.5, 111.2, 111.2, 61.3, 56.0, 56.0, 53.6, 43.3, 40.3, 38.4, 37.7, 36.0, 35.9, 32.6, 23.0, 21.7, 14.3; MS(ESI) calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6$ 456.23 (M^+), found 457.11 ($\text{M} + \text{H}$) $^+$.

Tricyclic Amide 43

Compound **43** was prepared according to the general procedure D from carboxylic acid **38** and amine **11p**: ^1H NMR (500 MHz, CDCl_3) δ 6.49 (s, 1H), 4.20–4.08 (m, 2H), 3.94 (ddd, $J = 13.0, 6.2, 4.3$ Hz, 1H), 3.44 (t, $J = 6.0$ Hz, 2H), 3.41–3.21 (m, 5H), 2.75 (dt, $J = 12.9, 5.5$ Hz, 1H), 2.61–2.41 (m, 3H), 2.27 (dd, $J = 12.9, 6.9$ Hz, 1H), 2.19 (dd, $J = 15.3, 8.7$ Hz, 1H), 2.15–1.99 (m, 2H), 1.90–1.75 (m, 3H), 1.75–1.64 (m, 3H), 1.53 (tt, $J = 8.1, 6.4$ Hz, 2H), 1.39–1.29 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 171.2, 168.7, 134.1, 118.2, 71.0, 69.4, 61.3, 53.6, 40.3, 38.3, 37.8, 37.5, 36.0, 35.8, 32.6, 31.9, 29.5, 23.0, 21.8, 19.5, 14.3, 14.0; MS(ESI) calcd for $\text{C}_{23}\text{H}_{36}\text{N}_2\text{O}_5$ 420.26 (M^+), found 421.52 ($\text{M} + \text{H}$) $^+$.

Tricyclic Amide 44

Compound **44** was prepared according to the general procedure D from carboxylic acid **37** and amine **11h**: ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.98 (m, 1H), 7.86–7.80 (m, 1H), 7.77 (dd, $J = 5.8, 3.7$ Hz, 1H), 7.48 (m, 2H), 7.41–7.35 (m, 2H), 6.66–6.58 (m, 1H), 5.08 (dd, $J = 14.6, 6.9$ Hz, 1H), 4.61 (dd, $J = 14.6, 4.5$ Hz, 1H), 4.33–4.24 (m, 1H), 4.16–4.03 (m, 2H), 2.84–2.71 (m, 2H), 2.64–2.54 (m, 1H), 2.50 (dd, $J = 14.1, 5.4$ Hz, 1H), 2.35 (dd, $J = 13.0, 5.6$ Hz, 1H), 2.23–2.15 (m, 1H), 2.01–1.91 (m, 3H), 1.75–1.58 (m, 3H), 1.46–1.29 (m, 2H), 1.18 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 170.8, 168.6, 134.2, 133.9, 131.4, 129.3, 128.7, 128.5, 126.6, 126.5, 125.9, 125.5, 123.9, 116.3, 61.4, 46.1, 41.5, 40.6, 38.6, 37.3, 36.5, 34.7, 29.8, 28.1, 21.5, 19.1, 14.3; MS(ESI) calcd for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4$ 460.24 (M^+), found 461.30 ($\text{M} + \text{H}$) $^+$.

Tricyclic Amide 45

Compound **45** was prepared according to the general procedure D from carboxylic acid **37** and amine **11j**: ^1H NMR (500 MHz, CDCl_3) δ 6.45 (s, 1H), 4.63–4.49 (m, 1H), 4.22–4.00 (m, 2H), 3.30–3.08 (m, 2H), 3.00–2.83 (m, 1H), 2.63–2.53 (m, 2H), 2.53–2.45 (m, 1H), 2.34 (dd, $J = 13.1, 5.5$ Hz, 1H), 2.20 (ddd, $J = 12.3, 3.9, 2.3$ Hz, 1H), 2.16–2.05 (m, 1H), 2.05–1.97 (m, 2H), 1.97–1.83 (m, 2H), 1.73–1.61 (m, 2H), 1.52–1.35 (m, 4H), 1.35–1.25 (m, 2H), 1.21 (t, $J = 7.1$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 171.2, 169.0, 129.7, 116.3, 61.4, 46.2, 40.8, 39.2, 38.9, 37.3, 36.8, 34.7, 31.8, 29.8, 28.1, 21.9, 20.2, 19.1, 14.3, 13.8; MS(ESI) calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_4$ 376.24 (M^+), found 377.47 ($\text{M} + \text{H}$) $^+$.

Tricyclic Amide 46

Compound **46** was prepared according to the general procedure D from carboxylic acid **40** and amine **11c**: ^1H NMR (500 MHz, CDCl_3) δ 6.96 (t, $J = 5.7$ Hz, 1H), 4.18–4.03 (m, 2H), 3.83 (dt, $J = 12.6, 4.7$ Hz, 1H), 3.44 (t, $J = 6.0$ Hz, 2H), 3.36–3.27 (m, 5H), 3.27–3.18 (m, 1H), 2.90 (t, $J = 6.8$ Hz, 1H), 2.62 (dd, $J = 15.2, 7.1$ Hz, 1H), 2.54 (dt, $J = 12.6, 3.2$ Hz, 1H), 2.18–1.64 (m, 8H), 1.60–1.47 (m, 1H), 1.41 (ddd, $J = 13.7, 12.4, 3.0$ Hz, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 172.1, 171.1, 132.0, 110.4, 71.4, 61.4, 59.0, 51.8, 49.5, 39.1, 37.9, 34.0, 30.7, 29.6, 27.3, 25.9, 21.4, 20.3, 14.5; MS(ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_5$ 378.22 (M^+), found 379.10 ($\text{M} + \text{H}$) $^+$.

Tricyclic Amide 47

Compound **47** was prepared according to the general procedure D from carboxylic acid **40** and amine **11m**: ^1H NMR (500 MHz, CDCl_3) δ 7.21–7.16 (m, 1H), 7.14 (dd, $J = 7.4, 1.7$ Hz, 1H), 6.90–6.81 (m, 2H), 6.75 (t, $J = 5.6$ Hz, 1H), 4.16–4.01 (m, 2H), 3.88–3.75 (m, 4H), 3.55–3.39 (m, 2H), 3.28–3.18 (m, 1H), 2.91–2.77 (m, 3H), 2.61 (dd, $J = 15.2, 7.1$ Hz, 1H), 2.54 (dt, $J = 12.7, 3.2$ Hz, 1H), 2.17–1.78 (m, 6H), 1.77–1.65 (m, 1H), 1.60–1.45 (m, 1H), 1.40 (ddd, $J = 13.8, 12.5, 3.0$ Hz, 1H), 1.19 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz,

CDCl₃) δ 172.8, 171.8, 170.8, 157.7, 131.7, 130.7, 127.8, 127.5, 120.6, 110.4, 110.1, 61.1, 55.3, 51.6, 49.2, 39.8, 38.8, 33.6, 30.4, 30.4, 27.0, 25.6, 21.2, 20.0, 14.2; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₅H₃₃N₂O₅ 441.2389, found 441.2384.

Tricyclic Amide 48

Compound 48 was prepared according to the general procedure D from carboxylic acid **41** and amine **11t**: ¹H NMR (500 MHz, CDCl₃) δ 3.77–3.69 (m, 1H), 3.69–3.60 (m, 7H), 3.60–3.52 (m, 1H), 3.50–3.43 (m, 1H), 3.43–3.37 (m, 1H), 3.28–3.18 (m, 2H), 2.79 (dd, J = 16.6, 5.0 Hz, 1H), 2.59–2.50 (m, 1H), 2.22 (dd, J = 16.6, 7.3 Hz, 1H), 2.16–2.03 (m, 3H), 1.98–1.90 (m, 1H), 1.89–1.80 (m, 2H), 1.75–1.63 (m, 2H), 1.64–1.54 (m, 2H), 1.34 (dddd, J = 13.2, 10.5, 8.0, 2.8 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 172.5, 172.1, 169.2, 135.0, 114.8, 67.0, 66.6, 55.7, 52.1, 48.7, 46.0, 42.4, 38.7, 36.0, 33.5, 30.1, 29.6, 27.6, 26.9, 20.9; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₀H₂₉N₂O₅ 377.2076, found 377.2086.

Tricyclic Amide 49

Compound 49 was prepared according to the general procedure D from carboxylic acid **41** and amine **11k**: ¹H NMR (500 MHz, CDCl₃) δ 7.39 (t, J = 5.8 Hz, 1H), 7.36–7.29 (m, 3H), 7.29–7.23 (m, 1H), 4.50 (dd, J = 14.9, 5.9 Hz, 1H), 4.42 (dd, J = 14.9, 5.5 Hz, 1H), 3.76 (dt, J = 12.8, 4.8 Hz, 1H), 3.65 (s, 3H), 3.25–3.14 (m, 1H), 2.98 (dd, J = 8.5, 4.8 Hz, 1H), 2.56 (dd, J = 15.1, 8.5 Hz, 1H), 2.47 (dt, J = 13.8, 4.0 Hz, 1H), 2.21 (dd, J = 15.1, 4.8 Hz, 1H), 2.17–2.03 (m, 3H), 2.02–1.94 (m, 1H), 1.90–1.81 (m, 2H), 1.80–1.65 (m, 1H), 1.56 (ddd, J = 13.8, 12.2, 4.0 Hz, 1H), 1.44–1.32 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 172.5, 171.8, 170.7, 138.6, 134.5, 128.7, 127.8, 127.3, 115.5, 55.6, 52.2, 49.2, 43.8, 38.6, 35.2, 33.9, 33.3, 29.5, 27.2, 26.9, 20.8; MS(ESI) calcd for C₂₃H₂₈N₂O₄ 396.20 (M⁺), found 397.13 (M + H)⁺.

Tricyclic Amide 50

Compound 50 was prepared according to the general procedure D from carboxylic acid **39** and amine **11a**: ¹H NMR (500 MHz, CDCl₃) δ 6.68 (t, J = 5.3 Hz, 1H), 5.11 (t, J = 4.0 Hz, 1H), 4.21–4.08 (m, 4H), 4.05 (ddd, J = 17.5, 5.6, 2.6 Hz, 1H), 3.95 (ddd, J = 17.5, 5.1, 2.5 Hz, 1H), 3.72 (dd, J = 6.9, 4.3 Hz, 2H), 3.05–2.92 (m, 1H), 2.63–2.51 (m, 2H), 2.36–2.28 (m, 2H), 2.28–2.17 (m, 2H), 2.17–2.11 (m, 2H), 2.11–2.01 (m, 1H), 1.82–1.71 (m, 2H), 1.60 (t, J = 13.1 Hz, 1H), 1.24 (t, J = 7.1 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 173.3, 172.9, 171.0, 170.2, 136.2, 108.7, 79.9, 71.3, 61.7, 60.8, 48.8, 41.1, 38.0, 36.7, 33.1, 32.8, 29.6, 29.2, 22.8, 21.8, 14.3, 14.2; MS(ESI) calcd for C₂₂H₃₀N₂O₆ 418.21 (M⁺), found 419.36 (M + H)⁺.

Tricyclic Amide 51

Compound 51 was prepared according to the general procedure D from carboxylic acid **39** and amine **11w**: ¹H NMR (500 MHz, CDCl₃) δ 5.04 (t, J = 4.0 Hz, 1H), 4.21–4.04 (m, 4H), 3.90 (ddd, J = 12.7, 6.3, 4.2 Hz, 1H), 3.53 (ddd, J = 12.3, 7.4, 4.4 Hz, 1H), 3.42 (m, 4H), 3.03 (m, 1H), 2.73 (dd, J = 16.4, 4.2 Hz, 1H), 2.57 (dd, J = 16.3, 6.8 Hz, 1H), 2.34 (ddd, J = 8.9, 6.1, 2.1 Hz, 2H), 2.28–2.17 (m, 2H), 2.17–2.00 (m, 3H), 1.97–1.86 (m, 2H), 1.86–1.70 (m, 4H), 1.28–1.17 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 173.6, 173.1, 170.2, 169.4, 136.7, 107.4, 61.5, 60.7, 48.8, 46.6, 45.7, 40.9, 36.2, 35.8, 33.3, 32.3, 29.7, 26.2, 24.5, 22.9, 21.7, 14.3, 14.2; MS (ESI) calcd for C₂₃H₃₄N₂O₆ 434.24 (M⁺), found 435.5 (M + H)⁺.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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23. The libraries are being evaluated in a number of high-throughput screening biological assays which are performed in our laboratories as well as the NIH Molecular Libraries Screening Centers Network since all of the compounds have been provided to the NIH *Molecular Libraries Small Molecule Repository*.

Figure 1. General Synthetic Strategy to Skeletally Diverse Heterocyclic Libraries. The assembly process is divided into two stages. First, a number of skeletally diverse lactams **7–10** are produced starting with readily available primary amines **1**, ketoesters **2** and unsaturated anhydrides **4** or **5**. Second, each of the lactams **7–10** is coupled to amines **11** in a fully automated fashion to deliver the resulting amide-containing heterocyclic libraries **12–15**.

Figure 2. Development of an automation platform for solution-phase amide synthesis and liquid–liquid extraction. (A) Synthetic scheme used for the development of automated amide synthesis and extractive purification. Carboxylic acids **7** were manually prepared from primary amines **1**, ketoesters **2**, and anhydride **4** as previously described.¹² Automated amide synthesis entailed activation of each carboxylic acid **7** with 1,1'-carbonyldiimidazole (CDI, **16**), followed by treatment of the resulting acyl imidazole **17** with 3 equivalents of amines **11** for 48 h at 20 °C and washing the resulting chloroform solution with 1.2 M aqueous solution of HCl. (B) Structures and isolated yields of four representative amides, which were prepared by the above protocol following solvent evaporation. The purity of each compound was established by LCMS analysis and confirmed by ¹H NMR spectroscopy.

Figure 3.

Synthesis of a 216-membered library of bicyclic pyrrolidinones. (A) Two-stage assembly process entailed preparation of nine carboxylic acids **7** starting with 3 amines **1** and 3 ketoesters **2**, followed by automated amide-bond synthesis using a set of 24 amines **11**. (B) Structures of 3 amines **1**. (C) Structures of 3 ketoesters **2**. (D) Structures of 24 amines **11**.

Figure 4.

Proposed explanation of the diastereoselective formation of 2-pyrrolidinones **7** and 2-piperidinones **8**. In both cases, the tandem reaction sequence entails a conjugate addition of the enamine to unsaturated anhydride followed by a ring-opening and a proton transfer. Initial approach of each anhydride facilitates subsequent lactam formation by placing the reactive imine and carbonyl moieties in close spatial proximity, as shown in intermediates **B** and **F**.

Figure 5.

Synthesis of a 768-membered library of bicyclic piperidinones. (A) Two-stage assembly process entailed preparation of 32 carboxylic acids **8** starting with 8 amines **1** and 4 ketoesters **2**, followed by automated amide-bond synthesis using a set of 24 amines **11**. (B) Structures of 8 amines **1**. (C) Structures of 4 ketoesters **2**. (D) Structures of 24 amines **11**.

Figure 6.

Synthesis of a 768-membered library of 2-piperidinones fused to dihydropyrans. (A) Assembly process entailed preparation of 32 carboxylic acids **26** starting with 8 amines **1** and 4 ketoesters **2**, followed by automated amide-bond synthesis using a set of 24 amines **11**. (B) Structures of 8 amines **1**. (C) Structures of 4 ketoesters **2**. (D) Structures of 24 amines **11**.

Figure 7.

Synthesis of a 120-Membered Library of Tetrahydro-oxo-indolizines and Hexahydro-oxo-quinolizines. (A) Structures of five enamides employed for the Au-catalyzed cycloisomerization, followed by alkene hydrogenation. (B) Structures of tetrahydro-oxo-indolizines **37**, **38** and **39** and hexahydro-oxo-quinolizines **40** and **41**. (C) Structures of 24 amines **11** used for automated amide synthesis. (D) Final amide-containing library incorporating five skeletally diverse lactams.

Table 1

Synthesis of Bicyclic 2-Piperidinones

Entry	Amine	Ketoester	Product	Yield, % ^a	dr ^b
1				55%	>95:5
2				51%	>95:5
3				41%	>95:5
4				57%	>95:5

^aYields refer to those of isolated compounds following chromatographic purification.^bDiastereomeric ratios (dr) were determined by ¹H NMR analysis of unpurified reaction mixtures.

Table 2

Synthesis of Carbomethoxytetrahydropyranones

Entry	R ¹	R ²	Ketoester	Yield, % (3 steps) ^a	dr ^b
1	<i>i</i> -Bu	Me	24a	60	>95:5
2		Me	24b	57	>95:5
3	<i>i</i> -Pr		24c	60	85:15 ^c
4		Me	24d	53	>95:5

^aYields refer to those of isolated compounds following chromatographic purification.^bDiastereomeric ratios (dr) were determined by ¹H NMR analysis of unpurified reaction mixtures.^cMajor diastereomer was obtained in diastereomerically pure form after chromatographic purification.

Table 3

Synthesis of Pyrrolidinones Fused to Dihydropyrans

Entry	Amine	Ketoester	Product	Yield, % ^a	dr ^b	
1				82%	>95:5	
2				75%	>95:5	
3				81%	>95:5	
4				54%	>95:5	

^aYields refer to those of isolated compounds following chromatographic purification.^bDiastereomeric ratios (dr) were determined by ¹H NMR analysis of unpurified reaction mixtures.

Table 4

Discovery and Optimization of Enyne Cycloisomerization

entry	R ¹	enyne	catalyst(s), (mol %)	solvent	product	yield ^a (%)
1	Ph	28a	Ph ₃ PAuCl (5), AgSbF ₆ (10)	CH ₂ Cl ₂	29a	85
2	Ph	28a	Ph ₃ PAuCl (5), AgBF ₄ (10)	CH ₂ Cl ₂	29a	75
3	Ph	28a	Ph ₃ PAuCl (5), AgOTf (10)	CH ₂ Cl ₂	29a	60
4	Ph	28a	AuSbF ₆ (10)	CH ₂ Cl ₂	29a	45
5	Ph	28a	Ph ₃ PAuCl (5), AgSbF ₆ (10)	CHCl ₃	29a	85
6	Ph	28a	Ph ₃ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29a	95
7	H	28b	Ph ₃ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29b	20
8	H	28b	(<i>p</i> -CF ₃ Ph) ₃ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29b	30
9	H	28b	Cy ₃ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29b	95
10	H	28b	<i>t</i> -Bu ₃ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29b	95
11	H	28b	Ph (Me) ₂ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29b	87
12	H	28b	Et ₃ PAuCl (5), AgSbF ₆ (10)	CH ₃ CN	29b	98
13	H	28b	complex 30 (3)	CH ₃ CN	29b	95
14	H	28b	complex 31 (3)	CH ₃ CN	29b	100
15	H	28b	complex 32 (3)	CH ₃ CN	29b	100
16	Ph	28a	complex 31 (3)	CH ₃ CN	29a	100
17	Me	28c	complex 31 (3)	CH ₃ CN	29c	100

^aYields were determined by 500 MHz ¹H NMR analysis of unpurified reaction mixtures using an internal standard. Each of the products 29 was subsequently isolated and fully characterized.

Table 5

Au-Catalyzed Cycloisomerizations of Enyne-Containing 2-Piperidinones

Entry	Ketoester	R ¹	Enyne	Yield, %	Product	Yield, % ^a	dr ^b
1		H		98		98	>95:5
2		Ph		75		75	>95:5
3		Ph		90		90	>95:5
4		H		100		100	>95:5

^aYields were determined by 500 MHz ¹H NMR analysis of unpurified reaction mixtures using an internal standard. Each of the products 34 was subsequently isolated and fully characterized.

Table 6

Au-Catalyzed Cycloisomerizations of Enyne-Containing 2-Pyrrolidinones

Entry	Ketoester	R ¹	Enyne	Yield, %	Product	Yield, % ^a	dr ^b
1		H		100		100	>95:5
2		Ph		100		100	>95:5
3		H		72		72	>95:5
4		Ph		77		77	>95:5

^aYields were determined by 500 MHz ¹H NMR analysis of unpurified reaction mixtures using an internal standard. Each of the products 36 was subsequently isolated and fully characterized.