Synthesis of Novel Thrombin Inhibitors. Use of Ring-Closing Metathesis Reactions for Synthesis of P2 Cyclopentene- and Cyclohexenedicarboxylic Acid Derivatives

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The thrombin inhibitory tripeptide D-Phe-Pro-Arg has been mimicked using either cyclopentenedicarboxylic derivatives or a cyclohexenedicarboxylic derivative as surrogate for the P2 proline. In the P3 position, tertiary amides were optimized as D-Phe P3 replacements. The P1 arginine was, in all compounds, substituted with the more rigid and biocompatible 4-aminomethylbenzamidine. One of the novel inhibitors was cocrystallized with α-thrombin and subjected to X-ray analysis. From analysis of the X-ray crystal structure, new ligands were designed leading to significantly improved binding affinity, the lead candidate exhibiting an in vitro IC_{50} of 49 nM.

Introduction

Thrombin is a key trypsin-like serine protease of the blood coagulation cascade, converting soluble fibrinogen to insoluble fibrin. Moreover, it is the most potent activator of platelet aggregation known.[1] Undesired blood clotting is one of the major underlying events in numerous cardiovascular diseases. Currently, intense efforts are under way to develop small-molecule thrombin inhibitor drugs to exploit the potential of regulating hemostasis and thrombosis in disease.[2] By use of the classical D-Phe-Pro-Arg motif of thrombin inhibitors[3] and aided by the X-ray crystal structure of the covalently bound inhibitor PPACK[4] in complex with thrombin, drug candidates and investigational drugs such as melagatran[5] have been developed (Figure 1). We have recently reported on cyclopentane- and cyclopentenedicarboxylic acid as novel P2-proline replacements yielding thrombin inhibitors in the ∼1 μM range.[6] Encouraged by these results, we now report on the further development of these P2-cyclopentene-1,5-dicarboxylic acid derivatives (series **1**). Moreover, we have also studied the homologous P2 proline replacement, cyclohexene-1,6-dicarboxylic derivatives (series **4**), as well as the isomeric cyclopentene rings (series **2** and **3**) (Figure 1). By usage of the second-generation Grubbs' catalyst, an efficient synthetic pathway to series **1**, **3**, and **4** was developed. The 3-D structure, determined for one of the inhibitors in complex with thrombin, guided the optimization process, eventually leading to inhibitor **1**{*22*} with an IC_{50} = 49 nM.

Results and Discussion

Commercially available 4-methyl itaconate was alkylated using 4-bromobutene or 5-bromopentene, lithium diisopropylamide (LDA) and lithium iodide in THF, *N*,*N*′-dimethylpropyleneurea (DMPU), 1:1, at −85 °C, yielding the dienes **5** and **6** in 48% and 42% yield, respectively (Scheme 1 and Table 2).[7] In the absence of DMPU, no product formation was detected and only unreacted starting material was recovered.[8] The dienes **5** and **6** underwent high-yield cyclization with 4 mol % tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV) dichloride[9] in refluxing DCM to yield the cyclopentene scaffold **7** in 98% yield and the cyclohexene scaffold **8** in 85% yield. Utilization of the first-generation Grubbs' catalyst bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride[10] failed to yield products, unless the electron-withdrawing carboxylic acid function in **5** was reduced. The benzoate ester derivative benzoic acid 3-methoxycarbonyl-2-methylenehept-6-enyl ester could be cyclized in 35% yield. After saponification followed by oxidation, **7** could be obtained. The direct use of the second-generation Grubbs' catalyst on **5** made these steps unnecessary.

The scaffold **9** was prepared in a straightforward manner in 90% yield from commercially available 1-cyclopentene-1,2-dicarboxylic anhydride in methanol in the presence of zinc chloride. The monoacids **7**−**9** (Scheme 1, Table 2) were coupled with the amines from reagent chemset **10** (Figure 2) using mainly BOP-Cl (bis-(2-oxo-3-oxazolidinyl)phosphinic chloride) at room temperature, yielding compounds in the series **11**−**13**. Some of the sterically hindered anilines in chemset **10** could only be coupled in DMF at elevated temperature with BOP-Cl as coupling reagent. Other attempted coupling conditions as PyBOP, HATU, DCC/HOBt, EDC/HOBt in THF or DMF failed at room temperature and with heat. These coupling tests were performed on compound **2**{*7*}. The use of HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate), one of the most versatile coupling reagents, resulted generally in sluggish reactions and low yields. The methyl esters from series **11**−**13** were hydrolyzed

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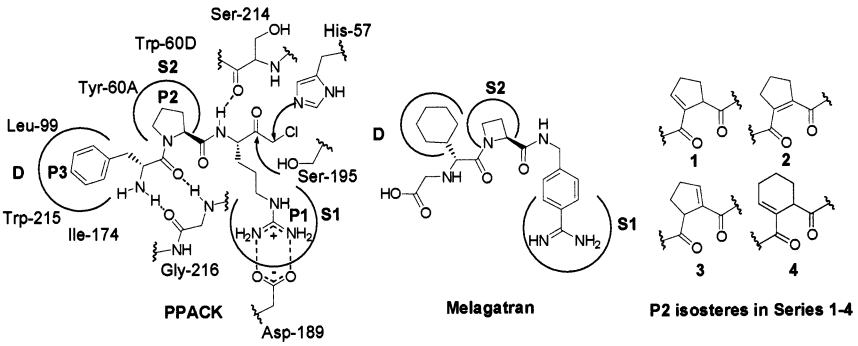
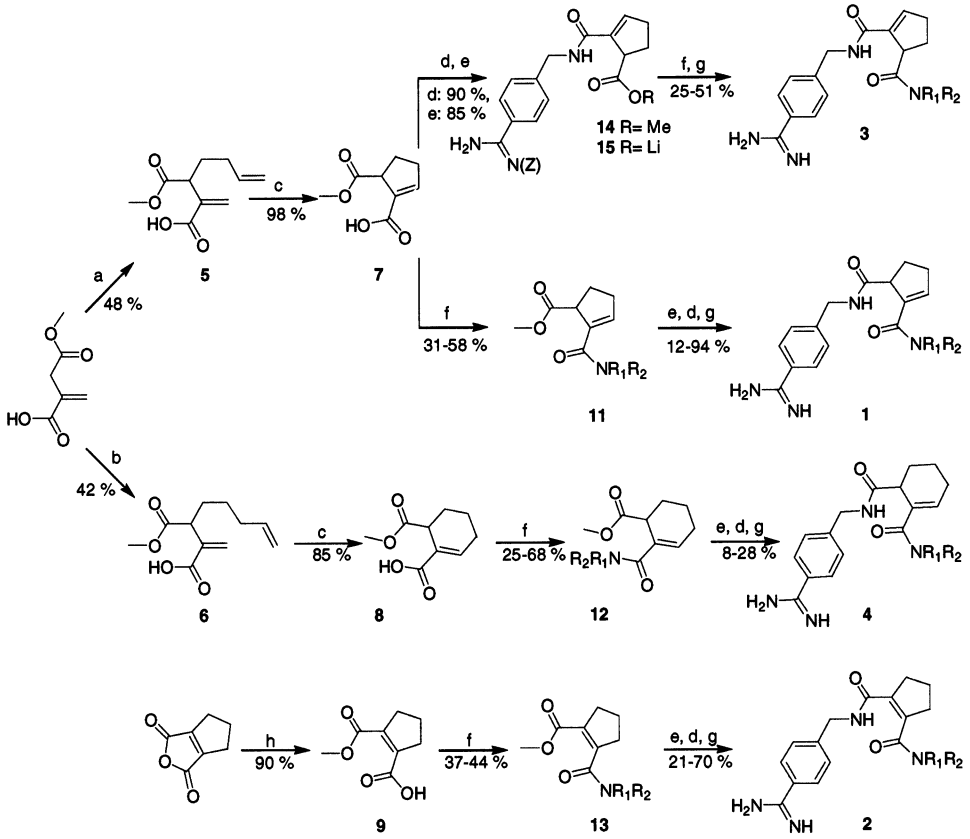


Figure 1. (Left) PPACK (IC_{50} = 0.017 nM) interactions with thrombin; (middle) melagatran (IC_{50} = 4.7 nM); (right) P2 isosteres used in the target compounds in series **1**−**4**.

Scheme 1. Synthesis of the Target Compounds in Series **1**−**4**[a]

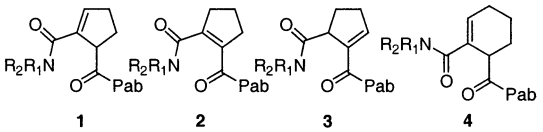


[a] Reagents: (a) 4-bromobutene, LDA, LiI, DMPU/THF, 1:1, −85 °C; (b) 5-bromopentene, LDA, LiI, DMPU/THF, 1:1, −85 °C; (c) second-generation Grubbs' catalyst ($C_{46}H_{65}Cl_2N_2PRu$), DCM, 40 °C; (d) DCC−HOBt, Pab(Z), DIPEA, THF (50 °C); (e) LiOH, dioxane/H_2O (1:1); (f) BOP-Cl, DIPEA, various HNR_1R_2 from chemset **10**, DMF; (g) TFMSA, anisole, DCM; (h) $ZnCl_2$, methanol.

using lithium hydroxide in dioxane/water (1:1). After coevaporation with methanol/toluene (1:1), the resulting lithium carboxylates were coupled with *p*-(*N*-benzyloxycarbonyl)amidinobenzylamine dihydrochloride (Pab(Z)·2HCl)[11] using dicyclohexylcarbodiimide(1-hydroxybenzotriazol) (DCC-HOBt) and diisopropylethylamine (DIPEA) in THF (50° C). Use of other coupling reagents (BOP-Cl, HATU, PyBOP) in DMF failed to improve yields. The Z protecting group and the *tert*-butyl protecting group in library members derivatized with **11**{*7*} were simultaneously hydrolyzed using TFMSA in DCM at 0 °C, yielding the target compounds in series **1**, **2**, and **4**. Coupling of the acid **7** with Pab(Z)·2HCl using DCC-HOBt and DIPEA gave the benzamidine(Z) methyl ester **14** in 90% yield. Saponification with lithium hydroxide in dioxane/water gave the lithium salt **15**, which was coevaporated several times with toluene/DCM (1:1) to afford water-free crystals and then dissolved in DMF (50 °C) and coupled with various amines from reagent chemset **10** using BOP-Cl as coupling reagent. The Z group was cleaved using TFMSA and anisole in DCM to yield the target compounds in series **3**.

The *N*-ethyl- and *N*-cyclohexyl-substituted anilines in reagent chemset **10** (Scheme 2, Table 2) were synthesized from acetaldehyde or cyclohexanone and various anilines, forming the corresponding imines that were reduced to the corresponding amines using borane−pyridine and 4 Å molecular sieves as drying agent in methanol.[12] Compound **10**{*7*} was synthesized using *o*-toluidine, *tert*-butyl bromoacetate, and potassium carbonate in DMF at 80 °C.

Table 1. Activities of Target Compounds in Series **1**−**4**



compd	IC_{50} (μM)	compd	IC_{50} (μM)	compd	IC_{50} (μM)	compd	IC_{50} (μM)
1{*1*}	0.24	**2**{*1*}	24	**3**{*1*}	7.8		
1{*2*}	4.6	**2**{*2*}	>130	**3**{*2*}	22		
1{*3*}	0.68	**2**{*3*}	33	**3**{*3*}	19	**4**{*3*}	4.6
1{*4*}	0.97[a]	**2**{*4*}	28	**3**{*4*}	16	**4**{*4*}	3.8
1{*5*}	0.35			**3**{*5*}	93		
1{*6*}	0.25						
1{*7*}	1.3	**2**{*7*}	120				
1{*8*}	1.5[a]	**2**{*8*}	19			**4**{*8*}	>130
1{*9*}	0.39						
1{*10*}	0.63						
1{*11*}	0.21						
1{*12*}	0.94						
1{*13*}	3.4						
1{*14*}	0.22	**2**{*14*}	23				
		2{*15*}	58				
1{*16*}	6.0[a]					**4**{*16*}	38
1{*17*}	4.9[a]					**4**{*17*}	130
1{*18*}	11.2[a]					**4**{*18*}	109
1{*19*}	0.27						
1{*20*}	0.073						
1{*21*}	0.26						
1{*22*}	0.049						
(*S*)**1**{*1*}	2.1						
(*R*)**1**{*1*}	0.12						

[a] Only the *R* enantiomer. Data are taken from ref 6.

Structure−Activity Relationship

In the D-Phe-Pro-Arg motif, the directional vectors of the P2-pyrrolidine ring are $sp^3 \Rightarrow$ P1 and $sp^2 \Rightarrow$ P3. It can clearly be seen from an activity comparison of the compounds **1**{*1*−*4*}, **2**{*1*−*4*}, and **3**{*1*−*4*} (Table 1) that reversing the hybridization of the directional vectors of the P2-cyclopentene in **3**{*1*−*4*} compared to **1**{*1*−*4*} has a detrimental effect on the activity against thrombin. The activity drops on average 20 times in series **3** compared to the compounds in series **1** with the same P3 moiety. The same is valid for the compounds in series **2**, where the change from $sp^3 \Rightarrow$ P1 to $sp^2 \Rightarrow$ P1 results in an average 50-fold decrease in activity. Thus, it may safely be concluded that within the series of P2-cyclopentenedicarboxylic derivatives, the motif with $sp^3 \Rightarrow$ P1 and $sp^2 \Rightarrow$ P3 directional vectors results in the best interactions with thrombin. The slightly increased flexibility of the cyclohexene ring in series **4** does not result in improved interactions with the enzyme, and the activity drops on average 10 times compared to the corresponding analogues in series **1**.

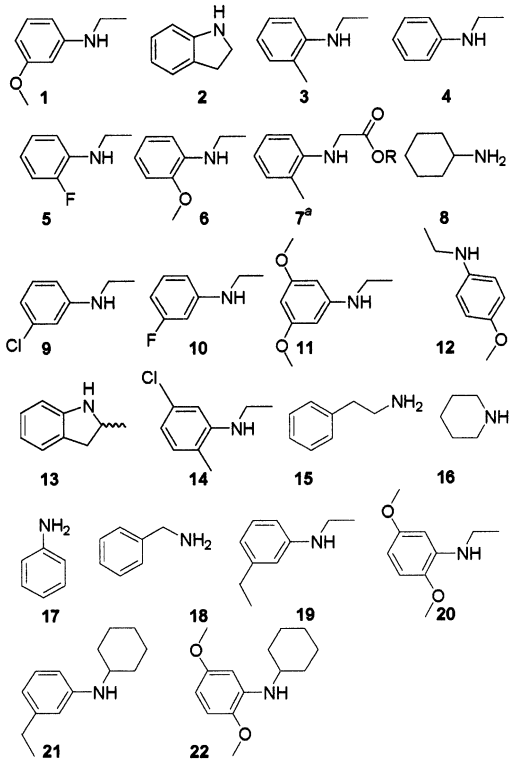
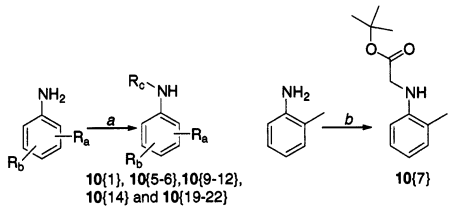


Figure 2. Amines (HNR_1R_2) in reagent chemset **10**. R = H in **1**{*7*} and in **2**{*7*}. R = t-Bu in **10**{*7*}, **11**{*7*}, and **13**{*7*}.

Scheme 2. Synthesis of the Commercially Unavailable Amines in Chemset **10**[a]



[a] Reagents: (a) acetaldehyde or cyclohexanone, 4 Å molecular sieves, borane−pyridine, methanol; (b) *tert*-butyl bromoacetate, K_2CO_3, DMF (80 °C).

To fully understand the interactions between the enzyme and the ligands in series **1**, the racemate of compound **1**{*14*}, which at that time was the most potent compound, was cocrystallized with α-thrombin. The alignment of the X-ray structure of the α-thrombin−**1**{*14*} complex and the thrombin−PPACK is shown in

Table 2. Yield for Compounds[a]

compd	yield (%)	compd	yield (%)	compd	yield (%)	compd	yield (%)	compd	yield (%)	compd	yield (%)	compd	yield (%)
1{*1*}	65	**1**{*14*}	60	**3**{*1*}	44	**10**{*5*}	22	**11**{*1*}	58	**11**{*19*}	54	**11**{*9*}	31
(*S*)-**1**{*1*}	51[g]	**1**{*19*}	55	**3**{*2*}	51	**10**{*6*}	63	**11**{*2*}	75[c]	**11**{*20*}	43[f]	**13**{*4*}	70
(*R*)-**1**{*1*}	90[g]	**1**{*20*}	67	**3**{*3*}	25	**10**{*7*}	64	**11**{*3*}	16[a]	**11**{*21*}	24	**13**{*7*}	65[b]
1{*2*}	94	**1**{*21*}	25	**3**{*4*}	47	**10**{*9*}	75	**11**{*5*}	42	**11**{*22*}	22[f]	**13**{*8*}	37
1{*3*}	31[a]	**1**{*22*}	52	**3**{*5*}	40	**10**{*10*}	80	**11**{*6*}	51[b]	**12**{*3*}	40	**13**{*14*}	44[c]
1{*5*}	64	**2**{*1*}	7[e]	**4**{*3*}	8	**10**{*11*}	77	**11**{*7*}	52[b]	**12**{*4*}	25	**13**{*15*}	65
1{*6*}	59	**2**{*2*}	41	**4**{*4*}	28	**10**{*12*}	41	**11**{*9*}	31	**12**{*8*}	56		
1{*7*}	23	**2**{*3*}	59	**4**{*8*}	9	**10**{*14*}	52	**11**{*10*}	50	**12**{*16*}	68		
1{*9*}	72	**2**{*4*}	70	**4**{*16*}	10	**10**{*19*}	56	**11**{*11*}	32	**12**{*17*}	51		
1{*10*}	44	**2**{*7*}	29	**4**{*17*}	12	**10**{*20*}	79	**11**{*12*}	56	**12**{*18*}	65		
1{*11*}	50	**2**{*14*}	21	**4**{*18*}	11	**10**{*21*}	42	**11**{*13*}	81[c]	**13**{*1*}	23[d]		
1{*12*}	67	**2**{*15*}	65	**10**{*1*}	75	**10**{*22*}	19	**11**{*14*}	50	**13**{*2*}	41		

[a] HATU, DIPEA, DMF (room temp). [b] BOP-Cl, DIPEA, DMF (90 °C). [c] DCC-HOBt, THF (reflux). [d] BOP-Cl, DIPEA, THF (room temp). [e] BOP-Cl, DIPEA, THF (50 °C). [f] BOP-Cl, DIPEA, DMF (65 °C). [g] BOP-Cl, DMF, 0° C.

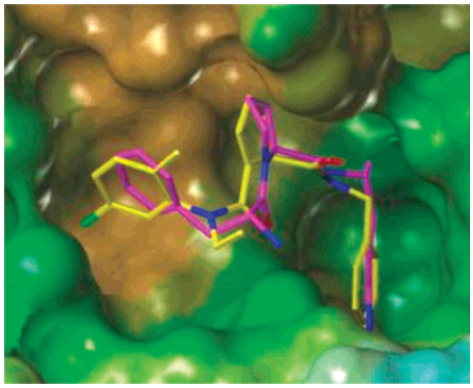


Figure 3. Connolly surface map of the X-ray structure of the α-thrombin−**1**{*14*} complex (yellow) at 1.9 Å resolution superimposed on the X-ray structure of the α-thrombin−PPACK complex (magenta).

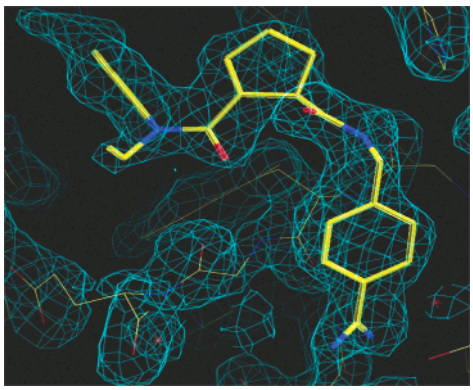


Figure 4. Electron density map of **1**{*14*} showing the well-defined region of the P1-bensamidino in the S1 cavity.

Figure 3. Clearly, a direct comparison with PPACK regarding the affinity may not seem relevant, since PPACK through its chloromethyl and aldehyde groups is covalently bonded to His-57 and Ser-195. However, it has been shown that noncovalent inhibitors such as melagatran[3] can achieve high affinity toward thrombin and can interact in a similar way forming an extensive hydrogen bond network with Ser-214 and Gly-216 (Figure 1). The overall alignment of the *R* enantiomer of **1**{*14*} in complex with thrombin compares well with that of PPACK. The *S* form fits less well into electron density, and we may safely conclude that the *R* form is the binding enantiomer in series **1**. This was further verified by the enantiospecific synthesis of (*R*)-**1**{*1*} and (*S*)-**1**{*1*}. (*R*)-**1**{*1*} (120 nM) was almost 20 times as potent as (*S*)-**1**{*1*} (2100 nM). The benzamidine group fits nicely into the S1 pocket, exhibiting very strong electrostatic interactions between the amidine group and the carboxylate of Asp-189, with N−O distances of 2.45 and 2.71 Å. The shortest distance is shorter than what is normally observed, but the electron density for the inhibitor is well defined in this region (Figure 4) and similar N−O distances involved in hydrogen bonds have been reported in the Cambridge Crystallographic Databank.[13]

The cyclopentene ring of **1**{*14*} fits nicely into the hydrophobic proximal pocket (S2) of thrombin in a way that closely resembles that of PPACK. The N−H of the P1−P2 amide group of **1**{*14*} makes a slightly weaker hydrogen bond (N−O distance 3.21 Å) with the carbonyl group of Ser- 214 compared to that of PPACK (2.87 Å), and also the N−O distance of the carbonyl oxygen of the amide group connecting the P2 and P3 groups and N−H of Gly-216 (N−O distance 3.35 Å) is slightly longer compared to the corresponding distance in the PPACK−thrombin complex (3.11 Å). The orientation of the P1−P2 amide group of **1**{*14*}, almost perpendicular to the cyclopentene ring, provides a rationale for the dramatic drop in activity of series **2** and **3**. To fit the S1 and proximal cavities, the P1−P2 carbamoyl group of series **2** and **3** is forced to move out of planarity and break the conjugation with the endocyclic double bond, an energy penalty that obviously is not compensated by other favorable interactions. The P3−*N*-phenyl ring occupies the distal pocket (D pocket), whereas the P3−*N*-ethyl group merely points toward the surrounding water. Thus, the importance of the *N*-ethyl group is to favor the cis orientation of the P3−phenyl group around the P3−P2 amide bond, thereby providing adequate orientation for interaction with the D pocket. This results in an 11-fold increase in activity going from the P3−*N*-phenyl analogue (*R*)-**1**{*17*} to the P3−*N*-ethyl−*N*-phenyl analogue (*R*)-**1**{*4*}. We reasoned that by replacement of the *N*-ethyl group with the *N*-acetic acid group the unfavorable interactions between the *N*-ethyl group and the surrounding water would be avoided. In contrast, this replacement results in a 6-fold drop in potency going from **1**{*4*} to **1**{*7*}. Obviously, the solvation for the *N*-ethyl group of **1**{*4*} does not change going from the free ligand to the bound state and will not affect the affinity, whereas the partial desolvation of the *N*-acetic acid group of **1**{*7*} in the bound state results in reduced potency. Eventually, the reduced potency is a consequence of less favorable ligand binding conformations of **1**{*7*} compared to the conformations of **1**{*4*}. It is also of interest to compare the difference in binding affinity of **1**{*14*} (210 nM) with the noncovalently bond inhibitor melagatran (4.7 nM). The latter has, except for the lack of covalent bonds to His-57 and Ser-195, a similar binding mode as PPACK with α-thrombin.[14] The 50-fold loss in potency for **1**{*14*} compared to that of melagatran is probably the result of the absence of a hydrogen bond of **1**{*14*} to the backbone carbonyl of Gly-216 and the penalty to be paid for the strong deviation from planarity of the P2−P3 amide bond (36°) of **1**{*14*} in complex with α-thrombin. A similar deviation in planarity was also observed in the X-ray crystallography results of **1**{*4*}.[6]

The P3−phenyl ring substitution results in improved potency for ortho and meta substitution in general, whereas the only para-substituted analogue **1**{*12*} has a negligible effect on the activity. The meta substitution on the P3−phenyl group results in increased affinity for the enzyme in **1**{*1*}, **1**{*9*−*11*}, **1**{*19*}, and **1**{*21*}, with almost the same effect for the methoxy, ethyl, and the chloro substituents and slightly lower for the fluoro substituent. The D pocket is essentially hydrophobic in this interior region, and the current trend indicates that slightly larger hydrophobic groups may increase potency further. Even more interesting is the gain in potency observed for the compounds having an ortho substituent, **1**{*3*} and **1**{*5*,*6*}. In the X-ray structure of the **1**{*14*}−thrombin complex, the electron density of the P3-5-chloro-2-methylphenyl is slightly broken toward the D pocket, and this indicates that both conformations are

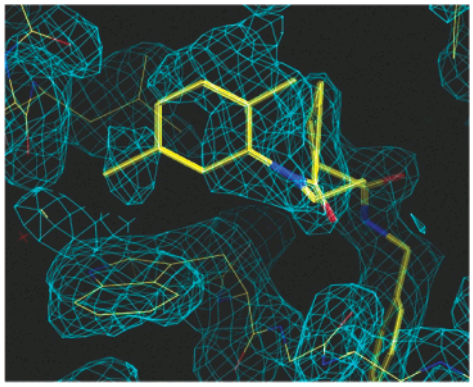


Figure 5. Electron density of the P3 group and the fitted structure of **1**{*14*} showing the slightly broken electron density in the D pocket.

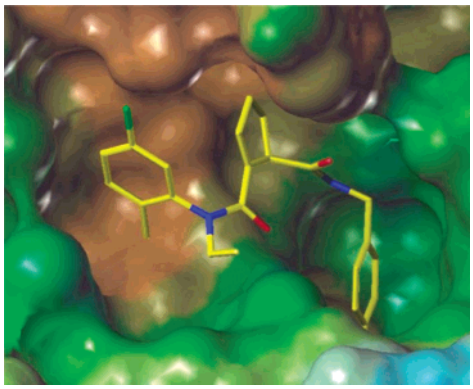


Figure 6. Possible orientation of the P3−phenyl group that would lower the energy of the ligand binding conformation.

populated where the 2-methyl or the 5-chloro substituent is directed toward the interior of the D pocket (Figure 5) This is in line with almost similar effects on the activity having the same substituent in either the ortho or the meta position. This is also corroborated by modeling studies of **1**{*14*} that propose both conformations of almost similar rank, whereas modeling of monosubstituted analogues in either the ortho or the meta position almost exclusive favors a conformation where the substituent is oriented toward the D pocket. An alternative explanation is that the ortho group is oriented toward surface as shown in the X-ray structure of the **1**{*14*}−thrombin complex and that the presence of the ortho group lowers the energy of the ligand binding conformation (Figure 6). Rigidifying the P3 group as in **1**{*2*} and **1**{*13*} results in a 10-fold loss in activity, which evidently is a result of a less favorable orientation of the phenyl group both with respect to the amide bond and with respect to its possibility to orient along the N−phenyl bond.

In light of now better understanding the ligand interactions with thrombin for this series, we were intrigued to explore if we could further improve the potency of this series of compounds. Docking studies, using the Glide modeling program,[15] of the **1** motif with different P3-(*N*,*N*-disubstituted phenyl)alkylamines resulted in a selection of four additional compounds **1**{*19*−*22*}. Gratifyingly, this provided an additional increase in potency. The introduction of a second methoxy group as in **1**{*20*} improved the potency 3-fold compared to that of the monomethoxy-substituted **1**{*6*} and **1**{*1*}. This probably indicates that the P3−phenyl ring adopts two conformers, where the 2- or the 5-methoxy group is interacting with the D cavity. The increased size of the *N*-cyclohexyl group compared to *N*-ethyl group shifts the cis−trans equilibrium around the P2−P3 amide linker, thereby further favoring the desired cis conformer of the *N*-phenyl ring, which results in an increase in potency going from **1**{*20*} (73nM) to **1**{*22*} (49nM). Surprisingly, no significant gain in activity was observed going from *N*-ethyl-**1**{*19*} (270 nM) to *N*-cyclohexyl-**1**{*21*} (260 nM).

The potency of the *N*-3-ethylphenyl analogue **1**{*19*} is almost the same as that of the corresponding *N*-(3-methoxyphenyl) analogue **1**{*1*}, indicating that no further gain in activity is obtained for the slightly more hydrophobic ethyl group.

Conclusions

By use of ring-closing metathesis chemistry, cyclopentene- and cyclohexenedicarboxylic acids have been synthesized and evaluated as P2 motifs in thrombin inhibitors. Low-nanomolar thrombin inhibitors, e.g., compound **1**{*22*} with an IC_{50} of 49 nM, have been discovered guided by structure-based drug design and X-ray crystallography data. From the SAR obtained for this series of thrombin inhibitors, we believe there are still opportunities to further increase the potency of series **1**, since modeling studies have indicated that several other variations of the P3 group could create additional favorable interactions with the D pocket.

Experiment

Thrombin Inhibition Measurements. The thrombin inhibitor potency was measured with a chromogenic substrate method in a Plato 3300 robotic microplate processor (Rosys AG, CH-8634 Hombrechtikon, Switzerland), using 96-well, half-volume microtiter plates (Costar, Cambridge, MA, catalog no. 3690). Stock solutions of test substance in DMSO (72 μL), 10 mmol/L, were diluted serially 1:3 (24 + 48 μL) with DMSO to obtain 10 different concentrations, which were analyzed as samples in the assay, together with controls and blanks. The dilutions of each test substance were analyzed consecutively, row-wise on the microtiter plate, with wash cycles between substances to avoid cross-contamination. An amount of 2 μL of test sample was diluted with 124 μL of assay buffer (0.05 mol/L Tris-HCl, pH 7.4, ionic strength of 0.15 adjusted with NaCl, BSA, 1 g/L) and 12 μL of chromogenic substrate solution (S-2366, Chromogenix, Mölndal, Sweden). Finally, 12 μL of α-thrombin solution (human α-thrombin from Haematologic Technologies, Inc., Essex, VT; catalog no. HCT-0020) in buffer was added and the samples were mixed. The final assay concentrations were the following: test substance, 0.00068−13.3 μmol/L; S-2366, 0.30 mmol/L; α-thrombin, 0.020 NIHU/mL. The linear absorbance increase during a 40 min incubation at 37 °C was used for calculation of the percent inhibition of the test samples compared to blanks without inhibitor. The IC_{50} value, corresponding to the inhibitor concentration that caused 50% inhibition of the thrombin activity, was calculated from a log dose vs inhibition curve.

X-ray Crystallography. Human α-thrombin was purchased from Enzyme Research Laboratories, Inc., South Bend, IN, and hirugen was purchased from American Diagnostica, Inc., Greenwich, CT. The hirugen−thrombin complex was prepared according to the method of Skrzypczak−Jankun et al. The crystallization was done as described previously. The X-ray diffraction data were collected on a MAR-II imaging plate system, MAR Research, Hamburg, Germany, using Cu Kα radiation from a rotating anode. The data were reduced and scaled using DENZO and SCALEPACK programs. The hirugen−α-thrombin structure previously examined in our

Table 3. Parameters and Statistics for X-ray Crystallography Data Collection and Refinement

parameter	data
no. of measurements	103 729
no. of unique reflections	14 826
data completeness (%)	94.5
R_{merge} [a]	0.062
no. of atoms in refined model	2538
no. of atmos in protein	2239
no. of atmos in cofactor (hirugen)	90
no. of atmos in inhibitor	32
no. of atmos in solvent	177
resolution range in refinement (Å)	25−2.30
rmsd for bond length (Å)	0.006
rmsd for angles (deg)	1.35
R_{cryst} [b]	0.201
R_{free}	0.238

[a] $R_{merge} = S_h S_i(|I(h,i) - \langle I(h)\rangle|)/[S_h S_i I(h,i)]$ where $I(h,i)$ is the intensity value of the ith measurement of h and where $\langle I(h)\rangle$ is the corresponding mean value of h for all i measurements of h. [b] $R_{cryst} = S_{hkl}(|F_o - F_c|)/[S_{hkl}|F_o|$. $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes, respectively.

laboratory was used in the refinement of the **1**{*14*} structure. The refinement was performed using REFMAC (CCP4 package) with subsequent runs of CNX. Statistics for X-ray data collection and refinement are presented in Table 3

General Methods. NMR spectra were recorded on a Varian 300 instrument using $CDCl_3$ or methanol-d_4 with TMS as an internal standard. NMR measurements on the benzamidine target products were performed on the trifluoroacetic acid salts. Prior elemental analyses of compounds incorporating the 4-aminobenzamidine moiety have not been satisfactionary.[16] Thus, high-resolution mass spectrometry was performed instead. HRMS was performed using a Finnigan MAT900 equipped with an electrospray ion source. Samples were infused at 1 μL/min. Preparative HPLC was performed on a Gynkotek (pump, P580; detector, UVD 170S; software, Chromeleon) using a Kromasil 100-10-C18 (250 mm × 20 mm) column. Chiral HPLC was performed using the Chiralpak AD (250 mm × 20 mm) column. TLC was carried out on Merck precoated 60 F_{254} plates using UV light and charring with ethanol/sulfuric acid/acetic acid/*p*-aninsaldehyde (90:3:1:2). Concentrations were performed under diminished pressure (1−2 kPa) at a bath temperature of 40 °C. All low-temperature reactions were accomplished by submerging the reaction vessels into an ethanol bath that had been cooled by additions of liquid nitrogen. All degassing of solvents was achieved using ultrasonification (Ultrasonik 104X) for at least 2 h. Optical rotation was performed on a Perkin-Elmer 141. Drying of solvents and reagents were as follows. THF was refluxed over sodium/benzophenone and distilled onto 4 Å MS. DMPU was dried over 3 Å molecular sieves. 4-Bromobutene was dried over 3 Å molecular sieves. Filtration was achieved using filter paper from Munktell, which was of OOH quality.

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl(3-methoxyphenyl)amide] (1{*1*}). Compound **1**{*1*} (52 mg, 65%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*1*} (45 mg, 0.15 mmol) instead of **11**{*2*}. Compounds (*S*)-**1**{*1*} (20 mg, 51%) and (*R*)-**1**{*1*} (36 mg, 90%) were collected as white powders according to the method for preparing **1**{*2*} using 0 °C DMF and BOP-Cl (instead of 50 °C THF and DCC/HOBt) and (*S*)-**11**{1} (27 mg, 0.090 mmol) and (*R*)-**1**{*1*} (28 mg, 0.092 mmol), respectively, instead of **11**{*2*}. $[\alpha]^{22}_D$ −36.9 (*c* 1.6, MeOH) for (*S*)-**1**{*1*}. $[\alpha]^{22}_D$ +37.7 (*c* 1.2, MeOH) for (*R*)-**1**{*1*}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.02−1.10 (m, 3H), 1.78−1.83 (m, 1H), 2.05−2.21 (m, 1H), 2.22−2.37 (m, 2H), 3.57−3.74 (m, 2H), 3.79 (s, 3H), 3.86−4.03 (m, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.58 (d, J = 16.0 Hz, 1H), 5.63−5.76 (m, 1H), 6.80−6.94 (m, 3H), 7.22−7.33 (m, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 11.9, 28.1, 32.6, 42.4, 45.1, 53.1, 54.8, 113.3, 113.9, 120.0, 126.9, 127.9, 128.1, 128.9, 129.8, 137.8, 142.5, 144.0, 146.2, 160.1, 167.1, 175.8. HRMS *m*/*z*: 421.2239 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_3^+$, 421.2240].

2-(1-(2,3-Dihydroindol-1-yl)methanoyl)cyclopent-2-enecarboxylic Acid 4-Carbamimidoylbenzylamide (1{*2*}). To a solution of compound **11**{*2*} (65 mg, 0.24 mmol) in dioxane/water (1:1, 3.5 mL) was added LiOH (5.8 mg, 0.24 mmol) at 0 °C. After hydrolysis (ca. 5 h), the lithium salt of the carboxylic acid was collected through coevaporation with methanol/toluene (1:3). The salt was dissolved in warm THF (3 mL, 50 °C), and dicyclohexylcarbodiimide (DCC) (0.052 g, 0.25 mmol), 1-hydroxybenzotriazol (HOBt) (0.25 mL, 1 M solution, 0.25 mmol), diisopropylethylamine (DIPEA) (0.22 mL, 1.3 mmol), and Pab(Z)·2HCl (89 mg, 0.25 mmol) were added. The mixture was stirred for 2 h. Thereafter it was concentrated and applied to a short column of silica and eluted with ethyl acetate. The combined ethyl acetate fractions were evaporated and redissolved in dichloromethane (5 mL). A mixture of trifluromethanesulfonic acid, anisole, and DCM (4.6 mmol, 0.46 mmol, 5 mL) was added. After 30 min, the solution was neutralized with triethylamine, concentrated, and redissolved in methanol/water/trifluoroacetic acid (7:3:0.1, 3 mL). The milky water/methanol solution was filtered. The precipitate was analyzed with MALDI-TOF MS, which indicated no product. The clear filtrate was subjected to preparative HPLC (Kromasil C-18; methanol/water, 1:1, + 0.1% TFA). The purified TFA salt of **1**{*2*} was dissolved in 15 mL of dioxane/water (1:1), frozen with liquid nitrogen, lyophilized, and collected as a white powder (0.11 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01−2.12 (m, 1H), 2.25−2.41 (m, 1H), 2.52−2.81 (m, 2H), 2.95−3.10 (m, 3H), 3.97−4.08 (m, 1H), 4.09−4.42 (m, 3H), 4.52−4.60 (d, J = 16.0 Hz, 1H), 7.03−7.08 (m, 1H), 7.14−7.11 (m, 2H), 7.40−7.51 (m, 4H), 7.98−8.06 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.5, 27.9, 33.1, 42.4, 50.4, 53.5, 117.5, 124.4, 124.7, 126.9, 127.8, 128.0, 128.8, 133.3, 137.9, 138.6, 142.6, 146.0, 166.3, 167.0, 175.6. HRMS *m*/*z*: 389.1981 [(M + H)$^+$ calcd for $C_{23}H_{25}N_4O_2^+$, 389.1977].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) (2-Ethyl-*o*-tolylamide) (1{*3*}). To a solution of compound **11**{*3*} (0.20 g, 0.68 mmol) in *tert*-butyl alcohol/water (1:1, 9 mL) was added LiOH (0.032 g, 1.35 mmol) at 0 °C. The mixture was stirred for 5 h, acidified to pH 2 with 1 M hydrochloric acid, and extracted several times with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The crude carboxylic acid was redissolved in DMF (4 mL), and HATU (0.310 g, 0.82 mmol) and DIPEA (diisopropylethylamine) (0.59 mL, 3.4 mmol) were added. After 15 min, 4-aminomethylbenzamidine dihydrochloride (0.291, 0.82 mmol) was added. The mixture was stirred for 6 h and extracted thrice with toluene/acid water (AcOH). The combined organic phases were dried, filtered, concentrated, applied to a short column of silica, and eluted with ethyl acetate. The combined ethyl acetate fractions were evaporated and redissolved in dichloromethane (30 mL). A mixture of trifluromethanesulfonic acid, anisole, and DCM (10:3:100) was added until the solution was red (∼1 mL). After 15 min, the solution was extracted several times with water. The water phase was concentrated to a volume of ∼4 mL and was subjected to preparative HPLC (Kromasil C-18; methanol/water, 3:1, + 0.1% TEA). The purified **1**{*3*} was dissolved in dioxane/water (1:1, 5 mL), lyophilized, and collected as slightly brown-white flakes (0.11 g, 31%). ^{1}H NMR (250 MHz, CD_3OD): δ 1.05−1.18 (m, 3H), 1.70−1.82 (m, 1H), 1.98−2.36 (m, 6H), [3.15−3.25 and 3.43−3.52 (m, 1H)],[18] [3.54−3.62 and 3.64−3.75 (m, 1H)],[18] [3.88−4.03 and 4.09−4.22 (m, 1H)],[18] 4.38−4.62 (m, 2H), [5.31 and 5.45 (s, 1H)],[18] 7.16−7.33 (m, 4H), 7.57 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H). ^{13}C NMR (62.9 MHz, CD_3OD) [12.4 and 13.0],[18] [17.8 and 18.1],[18] [29.0 and 29.4],[18] 34.0, 43.6, [45.2 and 46.0],[18] [48.3 and 48.6],[18] 128.0, 129.1, 129.2, 129.4, 131.1, 132.4, 136.5, 137.5, 139.3, 141.8, 142.7, 147.3, 167.7, 168.3, 177.6. HRMS *m*/*z*: 405.2289 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_2^+$, 405.2291].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl(2-fluorophenyl)amide]

(1{*5*}). Compound **1**{*5*} (28 mg, 64%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*5*} (24 mg, 0.084 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.04−1.17 (t, J = 7.1 Hz, 3H), 1.76−2.00 (m, 1H), 2.05−2.44 (m, 3H), 3.47−3.80 (m, 2H), 3.81−4.01 (m, 1H), 4.38−4.62 (m, 2H), 5.45−5.82 (m, 1H), 7.18−7.24 (m, 2H), 7.30−7.35 (m, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD):[17] δ 11.6, 28.0, 32.6, 42.5, 42.3, 53.1, 116.2, 116.4, 124.8, 126.9, 127.9, 128.0, 128.2, 129.0, 129.8, 131.1, 137.3, 140.3, 146.2, 156.4, 159.9, 160.5, 167.1, 176.2. HRMS *m*/*z*: 409.2032 [(M + H)$^+$ calcd for $C_{23}H_{26}FN_4O_2^+$, 409.2040].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl-(2-methoxyphenyl)amide] (1{*6*}). Compound **1**{*6*} (37 mg, 59%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*6*} (36 mg, 0.12 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.01−1.18 (m, 3H), 1.76−1.82 (m, 1H), 1.83−2.20 (m, 3H), 3.40−3.58 (m, 1H), 3.60−3.70 (m, 1H), 3.82 (s, 3H), 3.86−4.01 (m, 1H), 4.40−4.61 (m, 2H), 5.50−5.63 (m, 1H), 6.90−7.21 (m, 3H), 7.22−7.40 (m, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 28.1, 32.5, 42.5, 43.5, 53.1, 54.9, 111.8, 120.7, 126.8, 127.9, 127.9, 128.0, 128.7, 129.3, 130.3, 139.7, 146.3, 157.6, 168.7, 175.4. HRMS *m*/*z*: 421.2247 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_3^+$, 421.2240].

{**[5-(4-Carbamimidoylbenzylcarbamoyl)cyclopent-1-enecarbonyl]-*o*-tolylamino}acetic Acid (1{*7*}).** Compound **1**{*7*} (0.034 g, 23%) was prepared from **11**{*7*} (0.10 g, 0.27 mmol) according to the method for the preparation of **1**{*3*} but using DCC (0.062 g, 0.30 mmol) and HOBt (0.30 mL, 1 M solution, 0.30 mmol) in warm THF (50 °C) instead of HATU in DMF. Purification was achieved using preparative HPLC (Kromasil C-18; methanol/water, 1:1, + 0.1% TFA). **1**{*7*} was produced as a white powder. ^{1}H NMR (250 MHz, CD_3OD): δ 1.81−1.96 (m, 1H), 2.0−2.12 (m, 1H), 2.38−2.43, (m, 5H), 3.60−3.79 (m, 1H), 3.81−3.87 (d, J = 16.8 Hz, 0.5H),[18] 3.90−3.97 (d, J = 16.8 Hz, 0.5 H), 4.39−4.60 (m, 2H), 4.58−4.64 (d, J = 16.8 Hz, 0.5H),[18] 4.70−4.76 (d, J = 16.8 Hz, 0.5H),[18] 5.41−5.08 (m, 1H), 7.12−7.35 (m, 3H), 7.39−7.48 (m, 1H), 7.52−7.78 (m, 4 H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 16.1, 27.3 (d), 32.9 (d), 42.5 (d), 51.2 (d), 53.0 (d), 126.9, 127.0, 127.8, 128.0, 128.5, 128.6, 128.8, 129.7, 131.2, 131.5, 142.4, 142.5, 163.7, 174.6, 176.8, 180.4. HRMS *m*/*z*: 435.2037 [(M + H)$^+$ calcd for $C_{24}H_{27}N_4O_4^+$, 435.2032].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[(3-Chlorophenyl)ethylamide] (1{*9*}). Compound **1**{*9*} (65 mg, 72%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*9*} (51 mg, 0.12 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.10 (t, J = 7.1 Hz, 3H), 1.78−1.83 (m, 1H), 2.17−2.21 (m, 1H), 2.25−2.30 (m, 2H), 3.57−3.63 (m, 1H), 3.77−3.81 (m, 1H), 3.97−4.03 (m, 1H), 4.44 (d, J = 15.1 Hz, 1H), 4.60 (d, J = 15.1 Hz, 1H), 5.62−5.65 (m, 1H), 7.22−7.42 (m, 4H), 7.58 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9, 28.1, 32.7, 42.5, 45.1, 53.2, 126.6, 127.5, 127.9, 128.0, 128.2, 130.3, 134.5, 137.7, 141.0, 144.4, 146.2, 160.2, 167.1, 169.2, 175.7. HRMS *m*/*z*: 425.1751 [(M + H)$^+$ calcd for $C_{23}H_{26}ClN_4O_2^+$, 425.1744].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl(3-fluorophenyl)amide] (1{*10*}). Compound **1**{*10*} (27 mg, 44%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*10*} (34 mg, 0.11 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.10 (t, J = 7.1 Hz, 3H), 1.78−1.82 (m, 1H), 2.18−2.21 (m, 1H), 2.35−3.39 (m, 2H), 3.58−3.65 (m, 1H), 3.76−3.81 (m, 1H), 3.97−4.03 (m, 1H), 4.44 (d, J = 16.1 Hz, 1H), 4.60 (d, J = 16.1 Hz, 1H), 5.61−5.64 (m, 1H), 7.01−7.10 (m, 1H), 7.16−7.21 (m, 2H), 7.37−7.43 (m, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$):[17] δ 11.8, 28.0, 32.7, 42.5, 45.1, 53.1, 114.0, 114.3, 115.5, 124.0, 127.9, 130.4, 130.5, 140.9, 146.2, 164.5, 175.0. HRMS *m*/*z*: 409.2032 [(M + H)$^+$ calcd for $C_{23}H_{26}FN_4O_2^+$, 409.2040].

Cyclopent-2-ene-1,2-dicarboxylic Acid 2-(4-Carbamimidoylbenzylamide) 1-[(3,5-Dimethoxyphenyl)ethylamide] (1{*11*}). Compound **1**{*11*} (21 mg, 50%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*11*} (25 mg, 0.074 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.10 (t, J = 7.1 Hz, 3H), 1.80−1.90 (m, 1H), 2.17−2.20 (m, 1H), 2.23−2.39 (m, 2H), 3.55−3.66 (m, 1H), 3.88−4.05 (m, 1H), 4.45 (d, J = 16.1 Hz, 1H), 4.60 (d, J = 16.1 Hz, 1H), 6.76−7.79 (m, 1H), 6.42−6.47 (m, 1H), 6.52−6.56 (m, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 32.6, 42.4, 45.0, 46.8, 53.1, 54.9, 99.5, 106.3, 127.0, 127.9, 128.0, 137.9, 140.4, 144.6, 146.3, 161.5, 168.5, 175.7. HRMS *m*/*z*: 451.2342 [(M + H)$^+$ calcd for $C_{25}H_{31}N_4O_4^+$, 451.2345].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl(4-methoxyphenyl)amide] (1{12}). Compound **1**{*12*} (47 mg, 67%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*12*} (40 mg, 0.13 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.14 (t, J = 7.1 Hz, 3H), 1.78−1.82 (m, 1H), 2.05−2.20 (m, 1H), 2.21−2.30 (m, 2H), 3.58−3.70 (m, 2H), 3.93−4.01 (m, 1H), 4.42 (d, J = 15.9 Hz, 1H), 4.58 (d, J = 15.9 Hz, 1H), 5.78−5.82 (m, 1H), 7.10 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9, 28.0, 32.6, 42.4, 45.3, 53.2, 54.7, 114.3, 127.4, 127.9, 128.0, 129.2, 135.6, 137.9, 141.9, 146.2, 159.3, 167.8, 175.8. HRMS *m*/*z*: 421.2244 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_3^+$, 421.2240].

2-[1-(2-Methyl-2,3-dihydroindol-1-yl)methanoyl]cyclopent-2-enecarboxylic Acid 4-Carbamimidoylbenzylamide (1{*13*}). Compound **1**{*13*} (4.5 mg, 12%) was prepared from **11**{*13*} (0.18 g, 0.62 mmol) according to the method for the preparation of **1**{*7*}. **1**{*13*} was produced as a white powder. ^{1}H NMR on diastereomers (300 MHz, $CDCl_3$): δ 1.18−1.25 (m, 3H), 2.05−2.20 (m, 1H), 2.21−2.39 (m, 1H), 2.43−2.78 (m, 3H), 2.97−3.07 (m, 1H), 3.95−4.04 (m, 1H), 4.21−4.38 (m, 1H), 4.53−4.61 (m, 1H), 4.70−4.82 (m, 1H), 6.30−6.47 (m, 1H), 7.02−7.17 (m, 1H), 7.19−7.25 (m, 2H), 7.40 (s, 2H), 7.49−7.60 (m, 2H), 7.90−8.04 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7, [27.3 and 27.6],[18] [32.8 and 32.9],[18] 35.8, 42.4, 53.5, [56.9 and 57.7],[18] 117.5, 124.3, 125.2, 125.3, 126.7, 127.0, 127.5, 127.7, 127.8, 127.9, 138.2, 144.3, 166.4, 166.7, 178.5. HRMS *m*/*z*: 403.2131 [(M + H)$^+$ calcd for $C_{24}H_{27}N_4O_2^+$, 403.2133].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[(5-Chloro-2-methylphenyl)-ethylamide (1{*14*}). Compound **1**{*14*} (38 mg, 60%) was collected as a white powder according to the method for preparing **1**{*2*} using **11**{*14*} (37 mg, 0.11 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.02−1.19 (m, 3H), 1.78−1.93 (m, 1H), 1.98−2.43 (m, 6H), 3.18−3.23 (m, 1H), [3.43−3.52 and 4.62−3.75 (m, 1H)],[18] [3.82−3.98 and 4.05−4.19 (m, 1H),[18] 4.38−4.62 (m, 2H), [5.38−5.44 and 5.54−5.62 (m, 1H)],[18] 7.22−7.40 (m, 3H), 7.45−7.60 (m, 2H), 7.72−7.82 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 11.2, 16.2, 28.0, 32.9, 42.4, 43.9, 53.4, 124.3, 126.8, 127.8, 127.9, 128.0, 128.2, 128.7, 129.9, 132.4, 140.4, 145.5, 150.1, 162.0, 165.2, 175.9. HRMS *m*/*z*: 439.1885 [(M + H)$^+$ calcd for $C_{24}H_{28}ClN_4O_2^+$, 439.1901].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl-(3-ethylphenyl)amide] (1{*19*}). Compound **1**{*19*} (50 mg, 60%) was collected as a white powder according to the method for preparing **1**{*2*} using 0 °C DMF and BOP-Cl instead of 50 °C THF and DCC/HOBt and using **11**{*19*} (53 mg, 0.17 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H), 1.78−1−92 (m, 1H), 2.02−2.38 (m, 3H), 2.58−2.67 (q, J = 7.6 Hz, 2H), 3.58−3.70 (m, 2H), 3.93−4.02 (m, 1H), 4.43 (d, J = 16.1 Hz, 1H), 4.60 (d, J = 16.1 Hz, 1H), 5.58−5.62 (m, 1H), 7.02−7.10 (m, 3H), 7.12−7−16 (m 1H), 8.60 (d, J = 8.2 Hz, 2H), 8.78 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9, 15.0, 28.1, 28.4, 32.6, 42.6, 45.0, 53.2, 125.1, 126.9, 127.0, 127.7, 127.9, 128.0, 129.1, 137.9, 140.7, 142.9, 146.0, 146.2, 160.1, 167.1, 175.7. HRMS *m*/*z*: 419.2443 [(M + H)$^+$ calcd for $C_{25}H_{31}N_4O_2^+$, 419.2447].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[(2,5-Dimethoxyphenyl)ethylamide] (1{*20*}). Compound **1**{*20*} (86 mg, 67%) was collected as a white powder according to the method for preparing **1**{*2*} using 0 °C DMF and BOP-Cl instead of 50 °C THF and DCC/HOBt and using **11**{*20*} (76 mg, 0.23 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02−1.18 (m, 3H), 1.90−2.00 (m, 1H), 2.01−2.45 (m, 3H), 3.43−3.60 (m, 1H), 3.60−3.81 (m, 7H), 3.90−4.01(m, 1H), 4.40−4.62 (m, 2H), 5.58−5.82 (m, 1H), 6.78−7.02 (m, 3H), 7.58 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.5, 28.1, 32.5, 42.5, 43.6, 53.1, 55.1, 112.5, 113.8, 114.1, 116.2, 126.9, 127.9, 137.5, 139.5, 146.3, 149.2, 153.9, 164.7, 167.1, 170.5, 175.7. HRMS *m*/*z*: 451.2349 [(M + H)$^+$ calcd for $C_{25}H_{31}N_4O_4^+$, 451.2345].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Cyclohexyl(3-ethylphenyl)amide] (1{*21*}). Compound **1**{*21*} (13 mg, 25%) was collected as a white powder according to the method for preparing **1**{*2*} using 0 °C DMF and BOP-Cl instead of 50 °C THF and DCC/HOBt and using **11**{*21*} (32 mg, 0.090 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84−1.05 (m, 2H), 1.21−1.43 (m, 7H), 1.50−1.95 (m, 5H), 2.00−2.38 (m, 3H), 2.64 (q, J = 7.1 Hz, 2H), 3.18−3.23 (m, 1H), 3.58−3.65 (m, 1H), 4.38−4.60 (m, 2H), 5.37−5.55 (m, 1H), 6.95−7.05 (m, 2H), 7.20−7.30 (m, 2H), 7.60 (d, J = 8.4 Hz, 2H), 8.80 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 25.4, 25.9, 27.9, 28.4, 31.0, 31.9, 32.6, 42.4, 53.6, 127.6, 127.9, 128.0, 128.6, 138.3, 142.4, 146.3, 164.2, 175.2, 175.7. HRMS *m*/*z*: 473.2925 [(M + H)$^+$ calcd for $C_{29}H_{37}N_4O_2^+$, 473.2917].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Cyclohexyl(2,5-dimethoxyphenyl)amide] (1{*22*}). Compound **1**{*22*} (27 mg, 52%) was collected as a white powder according to the method for preparing **1**{*2*} using 0 °C DMF and BOP-Cl instead of 50 °C THF and DCC/HOBt and using **11**{*22*} (32 mg, 0.083 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82−1.16 (m, 2H), 1.22−1.42 (m, 3H), 1.50−2.02 (m, 7H), 2.03−2.42 (m, 2H), 3.41−3.50 (m, 1H), 3.63−3.80 (m, 7H), 4.44−4.60 (m, 2H), 5.45−5.80 (m, 1H), 7.67−7.77 (m, 1H), 6.83−7.01 (m, 2H), 7.55−7.64 (m, 2H), 7.78−7.83 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.5, 25.8, 28.0, 29.7, 31.5, 32.5, 42.5, 53.5, 54.9, 55.1, 112.0, 114.1, 117.7, 127.7, 127.9, 128.0, 138.5, 154.1, 161.2, 166.3, 166.6, 173.9, 174.6. HRMS *m*/*z*: 505.2813 [(M + H)$^+$ calcd for $C_{29}H_{37}N_4O_4^+$, 505.2815].

Cyclopent-1-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[Ethyl(3-methoxyphenyl)amide] (2{*1*}). Compound **2**{*1*} (4.4 mg, 6.8%) was collected as a white powder according to the method for preparing **1**{*2*} using **13**{*1*} (37 mg, 0.12 mmol) instead of **11**{*2*} and using BOP-Cl (54 mg, 024 mmol) instead of DCC/HOBt as coupling reagent. ^{1}H NMR (300 MHz, CD_3OD): δ 1.10−1.19 (m, 3H), 1.63−1.80 (m, 2H), 2.32−2.48 (m, 4H), 3.69 (s, 3H), 3.75−3.83 (m, 2H), 4.52 (s, 2H), 6.79−6.97 (m, 3H), 7.19−7.30 (m, 1H), 7.50−7.62 (m, 2H), 7.74−7.83 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 12.8, 21.9, 32.8, 37.2, 43.5, 44.4, 56.0, 114.3, 114.9, 120.7, 128.1, 129.1, 129.2, 130.7, 140.8, 147.1, 161.7, 164.1, 166.2, 168.1. HRMS *m*/*z*: 421.2244 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_3^+$, 421.2240].

2-(1-(2,3-Dihydroindol-1-yl)methanoyl)cyclopent-1-enecarboxylic Acid 4-Carbamimidoylbenzylamide (2{*2*}). Compound **2**{*2*} (87 mg, 41%) was collected as a white powder according to the method for preparing **1**{*2*} using **13**{*2*} (0.11 g, 0.42 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3OD): δ 2.03−2.24 (m, 2H), 2.71−2.90 (m, 4H), 3.05−3.19 (m, 2H), 3.85−4.02 (m, 2H), 4.37−57 (m, 2H), 7.00−7.25 (m, 3H), 7.37−7.50 (m, 2H), 7.60−7.69 (m, 2H), 8.05−8.14 (m, 1H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 22.8, 27.6, 32.1, 35.3, 42.4, 47.0, 114.3, 117.0, 124.5, 125.1, 127.0, 127.9, 128.8, 132.8, 134.6, 142.2, 145.8, 146.5, 160.6, 165.2, 168.3. HRMS *m*/*z*: 389.1980 [(M + H)$^+$ calcd for $C_{23}H_{25}N_4O_2^+$, 389.1978].

Cyclopent-1-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-(Ethyl-*o*-tolylamide) (2{*3*}). Compound **2**{*3*} (25 mg, 59%) was collected as a white powder according to the method for preparing **1**{*2*} using **13**{*3*} (23.4 mg, 0.081 mmol) instead of **13**{*2*}. ^{1}H NMR (250 MHz, CD_3OD): δ 1.13−1.20 (m, 3H), [1.50−1.63 and 1.69−1.82 (m, 1H)],[18] 2.03−2.52 (m, 6H), 2.74−2.87 (m, 2H), [3.10−3.22 and 3.28−3.34 (m, 1H)],[18] [3.55−3.65 and 4.15−4.30 (m, 1H)],[18] 4.53−4.62 (m, 2H), 7.10−7.28 (m, 4H), 7.55 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 10.3, 12.4, 17.8, [24.0 and 24.2],[18] 33.4, 36.4, [43.5 and 44.0],[18] 124.4, 128.4, 129.1, 129.3, 129.9, 132.0, 132.3, 136.9, 137.4, 140.5, 147.1, 147.4, 166.6, 168.2, 171.3. HRMS *m*/*z*: 405.2284 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_2^+$ 405.2291].

Cyclopent-1-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-(Ethylphenylamide) (2{*4*}). Compound **2**{*4*} (0.12 g, 70%) was prepared from **13**{*4*} (0.18 g, 0.35 mmol) according to the method for the preparation of **1**{*7*}. **2**{*4*} was produced as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02−1.20 (t, J = 7.2 Hz, 3H), 1.63−1.80 (m, 2H), 2.38−2.44 (m, 4H), 3.74−3.86 (q, J = 7.2 Hz, 2H), 4.48 (s, 2H), 7.18−7.37 (m, 5H), 7.50−7.60 (d, J = 8.4 Hz, 2H), 7.80−7.91 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.7, 22.7, 31.9, 36.1, 41.3, 43.5, 126.8, 127.0, 127.8, 127.9, 128.1, 128.2, 128.7, 129.0, 146.1, 146.6. HRMS *m*/*z*: 391.2132 [(M + H)$^+$ calcd for $C_{23}H_{27}N_4O_2^+$, 391.2133].

({1-[2-(4-Carbamimidoylbenzylcarbamoyl)cyclopent-1-enyl]methanoyl}-*o*-tolylamino)acetic Acid (2{*7*}). Compound **2**{*7*} (66 mg, 29%) was collected as a white powder according to the method for preparing **1**{*2*} using **13**{*7*} (0.15 g, 0.42 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.51−1.78 (m, 2H), 2.24 (s, 3H), 2.32−2.59 (m, 4H), 3.89−4.00 (m, 2H), 4.38−4.77 (m, 2H), 7.09−7.82 (m, 8H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 16.8, 22.4, 33.1, 35.9, 42.6, 50.3, 126.5, 127.6, 127.9, 128.0, 128.2, 129.0, 129.2, 131.3, 135.7, 138.3, 140.2, 143.5, 159.8, 160.5, 165.4, 170.6. HRMS *m*/*z*: 435.2067 [(M + H)$^+$ calcd for $C_{24}H_{27}N_4O_4^+$, 435.2032].

Cyclopent-1-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-Cyclohexylamide (2{*8*}). Compound **2**{*8*} (8.0 mg, 11%) was collected as a white powder according to the method for preparing **1**{*2*} using **13**{*8*} (49 mg, 0.19 mmol) instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.09−1.44 (m, 6H), 1.68−1.89 (m, 4H), 1.89−2.01 (m, 2H), 2.70−2.83 (m, 4H), 3.58−3.74 (m, 1H), 4.54 (s, 2H), 7.52−7.61 (m, 2H), 7.72−7.81 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 13.3, 20.6, 21.5, 25.4, 35.5, 42.5, 60.4, 67.0, 125.1, 128.0, 128.1, 128.7, 137.7, 145.9, 166.1, 167.3, 171.9. HRMS *m*/*z*: 369.2295 [(M + H)$^+$ calcd for $C_{21}H_{29}N_4O_2^+$, 369.2291].

Cyclopent-1-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-[(5-Chloro-2-methylphenyl)-ethylamide] (2{*14*}). Compound **2**{*14*} (44 mg, 21%) was collected as a white powder according to the method for preparing **1**{*2*} using **13**{*14*} (0.13 mg, 0.39 mmol instead of **11**{*2*}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.10−1.38 (m, 3H), 1.52−1.91 (m, 2H), 2.19 (s, 3H), 2.24−2.60 (m, 4H), 2.72−2.91 (m, 2H), 4.48−4.63 (m, 2H), 7.22−7.82 (m, 7H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 8.0, 11.2, 16.2, 22.9, 31.9, 35.3, 42.4, 128.0, 128.7, 129.6, 131.3, 132.4, 134.7, 136.2, 140.5, 146.0, 146.5, 165.2, 167.0, 170.0. HRMS *m*/*z*: 439.1885 [(M + H)$^+$ calcd for $C_{24}H_{28}ClN_4O_2^+$, 439.1901].

Cyclopent-1-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-(Phenethylamide) (2{*15*}). Compound **2**{*15*} (0.092 g, 65%) was prepared from **13**{*15*} (0.15 g, 0.28 mmol) according to the method for the preparation of **1**{*7*}. **2**{*15*} was produced as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92−2.00 (q, J = 7.8 Hz, 2H), 2.83−2.91 (m, 6H), 3.43−3.51 (t, J = 7.8 Hz), 4.55 (s, 2H), 7.08−7.28 (m, 5H), 7.58−7.62 (d, J = 7.8 Hz, 2H), 7.78−7.82 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5, 35.2, 35.5, 41.0, 42.5, 126.2, 128.0, 128.1, 128.3, 128.6, 138.2, 139.2, 140.8, 140.9, 145.9, 166.2, 175.2. HRMS *m*/*z*: 391.2139 [(M + H)$^+$ calcd for $C_{23}H_{27}N_4O_2^+$, 391.2133].

Cyclopent-2-ene-1,2-dicarboxylic Acid 2-(4-Carbamimidoylbenzylamide) 1-[Ethyl(3-methoxyphenyl)amide] (3{*1*}). Compound **3**{*1*} (24.7 mg, 44%) was synthesized from **15** (45.6 mg, 0.11 mmol) according to the method for preparing **3**{*3*} using ethyl(3-methoxyphenyl)amine (23.8 mg, 0.16 mmol) instead of ethyl-*o*-tolylamine. **3**{*1*} was produced as a white

powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.02−1.17 (m, 3H), 1.82−2.01 (m, 2H), 2.30−2.42 (m, 2H), 2.55−2.74 (m, 2H), 3.19−3.23 (m, 1H), 3.74−3.90 (m, 3H), 4.42 (d, J = 16.1 Hz, 1H), 4.60 (d, J = 16.1 Hz, 1H), 6.57−6.61 (m, 1H), 6.93−7.05 (m, 3H), 7.38−7.41 (m, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 8.0, 12.0, 28.9, 32.4, 42.2, 44.2, 54.8, 113.9, 114.2, 120.6, 125.3, 127.7, 127.8, 127.9, 130.2, 138.4, 139.8, 143.4, 146.4, 161.0, 166.4, 175.2. HRMS *m/z*: 421.2248 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_3^+$, 421.2240].

5-(1-(2,3-Dihydroindol-1-yl)methanoyl)cyclopent-1-enecarboxylic Acid 4-Carbamimidoylbenzylamide (3{*2*}). Compound **3**{*2*} (34.5 mg, 51%) was synthesized from **15** (60.0 mg, 0.13 mmol) according to the method for preparing **3**{*3*} using indoline (24.1 mg, 0.20 mmol) instead of ethyl-*o*-tolylamine. **3**{*2*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.94−2.10 (m, 1H), 2.40−2.57 (m, 1H), 2.60−2.78 (m, 2H), 3.16−3.22 (m, 2H), 4.16−4.37 (m, 2H), 4.39−4.60 (m, 2H), 6.74−6.80 (m, 1H), 6.98−7.08 (m, 1H), 7.08−7.33 (m, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 27.6, 27.9, 32.7, 42.3, 48.5, 50.4, 117.0, 124.0, 124.6, 126.9, 127.8, 128.0, 128.7, 132.5, 139.2, 139.3, 142.5, 146.2, 166.4, 168.2, 174.2. HRMS *m/z*: 389.1975 [(M + H)$^+$ calcd for $C_{23}H_{25}N_4O_2^+$, 389.1978].

Cyclopent-2-ene-1,2-dicarboxylic Acid 2-(4-Carbamimidoylbenzylamide) 1-(Ethyl-*o*-tolylamide) (3{*3*}). The lithium salt **15** (40 mg, 0.094 mmol) was dissolved in warm DMF (50 °C), and BOP-Cl (25.4 mg, 0. 10 mmol) was added. The pH was adjusted to ∼8 with DIPEA (8.7 μL, 0.05 mmol), and ethyl-*o*-tolylamine (13.5 mg, 0.10 mmol) was added. After the mixture was stirred for 8 h, the reaction mixture was concentrated and dissolved in ethyl acetate/methanol (9:1), applied to a short silica column, and eluted with ethyl acetate. The collected fractions were evaporated and dissolved in DCM (5 mL), and a TFMSA/anisole solution was added (1.88 mmol, 0.19 mmol). After 30 min, the reaction mixture was neutralized with TEA. The clear DCM solution was concentrated and dissolved in methanol/water/TFA (7:3:0.1, 3 mL). The milky water/methanol solution was filtered. The precipitate was analyzed with MALDI-TOF MS, which indicated no product. The clear filtrate was subjected to preparative HPLC (Kromasil C-18; methanol/water, 1:1, + 0.1% TFA). The purified TFA salt of **3**{*3*} (12.2 mg, 25%) was dissolved in 15 mL of dioxane/water (1:1), frozen with liquid nitrogen, lyophilized, and collected as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.05−1.17 (m, 3H), 1.83−1.99 (m, 2H), 2.22−2.42 (m, 4H), 2.50−2.64 (m, 1H), 3.01−3.20 (m, 1H), [3.40−3.50 and 3.63−3.75, (m, 1H)],[18] 4.05−4.21 (m, 1H), 4.40−4.65 (m, 2H), 6.52−6.60 (m, 1H), 7.11−7.42 (m, 4H), 7.49−7.60 (m, 2H), 7.76−7.80 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ [11.6 and 11.8],[18] [16.6 and 16.9],[18] [28.2 and 29.1],[18] [32.2 and 32.6],[18] [42.2 and 42.2],[18] [43.1 and 43.4],[18] 49.6, 126.6, 126.9, 127.8, 127.9, 128.5, 128.7, 129.7, 130.1, 131.2, 131.6, 138.2, 146.4, 164.4, 165.6, 176.4. HRMS *m/z*: 405.2289 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_2^+$, 405.2291].

Cyclopent-2-ene-1,2-dicarboxylic Acid 2-(4-Carbamimidoylbenzylamide) 1-(Ethylphenylamide) (3{*4*}). Compound **3**{*4*} (25.3 mg, 47%) was synthesized from **15** (45.6 mg, 0.11 mmol) according to the method for preparing **3**{*3*} using ethylphenylamine (14.2 mg, 0.12 mmol) instead of ethyl-*o*-tolylamine. **3**{*4*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.05−1.18 (t, J = 7.1 Hz, 3H), 1.82−1.99 (m, 2H), 2.36−2.45 (m, 1H), 2.56−2.3.63 (m, 1H), 3.63−3.80 (m, 3H), 4.45 (d, J = 16.2 Hz, 1H), 4.60 (d, J = 16.3 Hz, 1H), 7.57−7.64 (m, 1H), 7.38−7.53 (m, 5H), 7.58 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 11.9, 28.7, 32.4, 42.2, 44.3, 49.0, 126.8, 127.8, 127.9, 128.2, 128.6, 129.6, 138.4, 137.7, 142.4, 146.4, 166.4, 167.4, 175.3. HRMS *m/z*: 391.2148 [(M + H)$^+$ calcd for $C_{23}H_{27}N_4O_2^+$, 391.2134].

Cyclopent-2-ene-1,2-dicarboxylic Acid 2-(4-Carbamimidoylbenzylamide) 1-[Ethyl(2-fluorophenyl)amide] (3{*5*}). Compound **3**{*5*} (28.2 mg, 40%) was synthesized from **15** (60.0 mg, 0.13 mmol) according to the method for preparing **3**{*3*} using ethyl(2-fluorophenyl)amine (28.1 mg, 0.20 mmol) instead of ethyl-*o*-tolylamine. **3**{*5*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.03−1.20 (m, 3H), 1.88−2.03 (m, 2H), 2.36−2.41 (m, 1H), 2.51−2.72 (m, 1H), 3.57−3.82 (m, 3H), 4.42−4.62 (m, 2H), 6.58−6.61 (m, 1H), 7.20−7.49 (m, 4H), 7.50−7.60 (m, 2H), 7.62−7.80 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD):[17] δ 8.0, 11.8, 28.0, 32.6, 42.2, 65.4, 118.2, 123.2, 125.3, 127.8, 127.9, 128.1, 128.4, 130.5, 131.4, 133.4, 138.6, 146.4, 158.6, 158.8, 164.2, 164.7, 176.3. HRMS *m/z*: 409.2040 [(M + H)$^+$ calcd for $C_{23}H_{26}FN_4O_2^+$, 409.2040].

Cyclohex-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-(Ethyl-*o*-tolylamide) (4{*3*}). Compound **4**{*3*} (4.8 mg, 8%) was prepared from **12**{*3*} (33 mg, 0.114 mmol) according to the method for the preparation of **1**{*7*}. **4**{*3*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 0.98−1.17 (m, 3H), 1.20−2.15 (m, 6H), 2.20 (s, 1.5 H), 2.25 (s, 1.5H), 3.02−3.23 (m, 1H), 3.40−3.62 (m, 1H), 4.16−4.25 (m, 1H), 4.38−61 (m, 2H), 5.62−5.72 (m, 1H), 7.02−7.37 (m, 4H), 7.65−7.93 (m, 5H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 13.5, 20.3, 22.1, 28.2, 29.2, 46.9, 49.7, 55.9, 128.4, 129.3, 129.4, 129.7, 130.4, 130.5, 130.8, 133.4, 139.6, 146.1, 149.0, 169.9, 175.6, 179.0. HRMS *m/z*: 419.2441 [(M + H)$^+$ calcd for $C_{25}H_{31}N_4O_2^+$, 419.2447].

Cyclohex-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-(Ethylphenylamide) (4{*4*}). Compound **4**{*4*} (10.6 mg, 28%) was prepared from **12**{*4*} (20 mg, 0.072 mmol) according to the method for the preparation of **1**{*7*}. **4**{*4*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.02−1.15 (m, 3H), 1.25−1.48 (m, 1H), 1.63−1.78 (m, 2H), 1.80−1.98 (m, 3H), 3.23−3.30 (m, 1H), 3.55−3.65 (m, 1H), 3.95−4.05 (m, 1H), 4.38−4.46 (d, J = 15.9 Hz, 1H), 4.53−4.62 (d, J = 15.9 Hz, 1H), 6.85−6.93 (m, 1H), 7.22−7.30 (m, 1H), 7.36−7.44 (m, 4H), 7.54−7.60 (d, J = 8.6 Hz, 2H), 7.74−7.79 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 14.6, 22.7, 27.2, 29.9, 45.1, 46.7, 48.0, 129.5, 130.4, 130.5, 130.6 130.7, 131.7, 134.8, 139.6, 146.1, 149.0, 169.8, 174.3, 178.6. HRMS *m/z*: 405.2289 [(M + H)$^+$ calcd for $C_{24}H_{29}N_4O_2^+$, 405.2290].

Cyclohex-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-Cyclohexylamide (4{*8*}). Compound **4**{*8*} (10.0 mg, 9%) was prepared from **12**{*8*} (58 mg, 0.22 mmol) according to the method for the preparation of **1**{*7*}. **4**{*8*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.09−1.40 (m, 6H), 1.52−2.00 (m, 8H), 2.19−2.40 (m, 2H), 3.38−3.44 (m, 1H), 3.50−3.63 (m, 1H), 4.40−4.50 (d, J = 15.9 Hz, 1H), 4.52−4.60 (d, J = 15.9 Hz, 1H), 7.65−7.70 (m, 1H), 7.48−7.54 (d, J = 8.8 Hz, 2H), 7.63−7.78 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 19.6, 21.2 (d), 24.9 (d), 25.5, 26.0, 26.2, 27.3, 32.5 (d), 42.3 (d), 127.8, 127.9, 133.2, 135.1, 146.5, 164.3, 172.4, 173.4, 174.9. HRMS *m/z*: 383.2454 [(M + H)$^+$ calcd for $C_{22}H_{31}N_4O_2^+$, 383.2447].

2-(1-Piperidin-1-ylmethanoyl)cyclohex-2-enecarboxylic Acid 4-Carbamimidoylbenzylamide (4{*16*}). Compound **4**{*16*} (20 mg, 10%) was prepared from **12**{*16*} (99 mg, 0.39 mmol) according to the method for the preparation of **1**{*7*}. **4**{*16*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.42−1.65 (m, 6H), 1.76−1.90 (m, 3H), 1.92−2.08 (m, 1H), 2.10−2.34 (m, 2H), 3.40−3.64 (m, 5H), 4.31−4.40 (d, J = 15.9 Hz, 1H), 4.48−4.52 (m, J = 15.9 Hz, 1H), 6.01−6.06 (m, 1H), 7.45−7.50 (d, J = 8.4 Hz, 2H), 7.21−7.26 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 20.4, 24.2, 24.4, 25.9, 26.0, 27.0, 42.4, 43.9, 127.9, 131.6, 131.9, 146.2, 159.4, 159.9, 171.5, 175.5, 180.7. HRMS *m/z*: 369.2291 [(M + H)$^+$ calcd for $C_{21}H_{29}N_4O_2^+$, 369.229].

Cyclohex-2-ene-1,2-dicarboxylic Acid 1-(4-Carbamimidoylbenzylamide) 2-Phenylamide (4{*17*}). Compound **4**{*17*} (14.0 mg, 12%) was prepared from **12**{*17*} (63 mg, 0.24 mmol) according to the method for the preparation of **1**{*7*}. **4**{*17*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.60−1.70 (m, 1H), 1.72−2.10 (m, 3H), 2.2−2.39 (m, 2H), 3.60−3.67 (m, 1H), 4.39−4.58 (d, J = 15.9 Hz, 1H), 4.53−4.61 (d, J = 15.9 Hz, 1H), 6.74−6.78 (m, 1H), 7.02−7.10 (m, 1H), 7.22−7.30 (m, 2H), 7.46−7.54 (m, 4H), 7.62−7.68 (m, 2H). ^{13}C NMR

(75.5 MHz, CD_3OD): δ 19.6, 25.0, 27.2, 42.4, 43.2, 120.1, 123.8, 127.7, 127.8, 128.1, 128.5, 133.1, 135.3, 138.2, 146.4, 161.2, 170.4, 174.4. HRMS *m/z*: 377.1975 [$(M + H)^+$ calcd for $C_{22}H_{25}N_4O_2^+$, 377.1977].

Cyclohex-2-ene-1,2-dicarboxylic Acid 2-Benzylamide 1-(4-Carbamimidoylbenzylamide (4{*18*}). Compound **4**{*18*} (20 mg, 11%) was prepared from **12**{*18*} (97 mg, 36 mmol) according to the method for the preparation of **1**{*7*}. **4**{*18*} was produced as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 1.55−1.63 (m, 1H), 1.77−2.05 (m, 3H), 2.20−2.28 (m, 2H), 3.44−3.60 (1H), 4.34 (s, 2H), 4.38−4.44 (d, J = 15.9 Hz, 1H), 4.52−4.60 (d, J = 15.9 Hz, 1H), 6.70−6.74 (m, 1H), 7.18−7.25 (m, 5H), 7.46−7.54 (d, J = 8.7 Hz, 2H), 7.66−7.73 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 19.6, 21.2, 25.0, 27.3, 42.3, 42.9, 126.7, 126.8, 127.1, 127.7, 127.8, 128.1, 128.3, 129.1, 135.2, 140.6, 165.4, 170.6, 172.2. HRMS *m/z*: 391.2138 [$(M + H)^+$ calcd for $C_{23}H_{27}N_4O_2^+$, 391.2133].

2-But-3-enyl-3-methylenesuccinic Acid 1-Methyl Ester (5). 4-Methyl itaconate (2.88 g, 20 mmol) was dissolved in 20 mL of dry THF and 20 mL of DMPU in a 6 in. long-necked 100 mL round flask, and the mixture was cooled (−85 °C). After 20 min at −85 °C, 21 mL of 2 M LDA (42 mmol) was added portionwise. After 30 min of enolate generation, a 5 mL THF solution of 4-bromobutene (2.8 mL, 28 mmol) and oven-dried (130 °C) LiI (1.07 g, 8 mmol) was added portionwise. More liquid nitrogen was added to keep the temperature at −85 °C during the following 2 h. Then was it allowed to reach room temperature overnight. After 20 h, the reaction was quenched with saturated ammonium chloride (40 mL). The resulting mixture was then extracted thrice with toluene and 10% acetic acid. The combined organic phases were dried, filtered, and evaporated. The crude product was purified by flash column chromatography (toluene/EtOAc, 9:1, 1% AcOH), and **5** (1.90 g, 48%) was collected as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.70−1.90 (m, 1H), 1.95−2.12 (m, 3H), 3.45−3.54 (m, 1H), 3.70 (s, 3H), 4.92−5.11 (m, 2H), 5.70−5.89 (m, 1H), 5.90 (s, 1H), 6.52 (s, 1H), 9.90−10.43 (bs, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 30.1, 31.4, 45.6, 52.2, 115.6, 129.5, 137.3, 137.6, 171.5, 173.5. HRMS *m/z*: 197.0808 [$(M - H)^-$ calcd for $C_{10}H_{13}O_4^-$, 197.0814].

2-Methylene-3-pent-4-enylsuccinic Acid 4-Methyl Ester (6). Compound **6** (1.78 g, 42%) was prepared from 4-methyl itaconate (2.88 g, 20 mmol) according to the method for the preparation of **4** using 5-bromobutene instead of 4-bromobutene. **6** was produced as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33−1.44 (m, 2 H), 1.62−1.74 (m, 1H), 1.84−1.96 (m, 1H), 2.02−2.10 (m, 2H), 3.47−3.52 (t, J = 7.4 Hz, 1H), 3.67 (s, 3H), 4.91−5.04 (m, 2H), 5.68−5.82 (m, 1H), 5.86 (s, 1H), 6.50 (s, 1H), 10.92−11.34 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.9, 30.9, 33.5, 46.3, 52.3, 115.1, 129.5, 137.9, 138.3, 171.8, 173.8. HRMS *m/z*: 211.097 [$(M - H)^-$ calcd for $C_{11}H_{15}O_4^-$, 211.097].

Cyclopent-2-ene-1,2-dicarboxylic Acid 1-Methyl Ester (7). A degassed DCM solution of **5** (1.68 g, 8.48 mmol, 0.01 M) was heated to reflux, and tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]-ruthenium(IV) dichloride (0.265 g, 0.312 mmol) was added. The reaction mixture was stirred for 20 h for completion. The catalyst was chelated by the addition of lead tetraacetate (0.28 g, 0.64 mmol), and the reaction mixture was stirred for an additional 20 h. The evaporated, crude product was purified by flash column chromatography (toluene/EtOAc, 9:1, 1% AcOH), and **7** (1.41 g, 98%) was collected as white crystals: mp 70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97−2.10 (m, 1H), 2.19−2.38 (m, 1H), 2.42−2.65 (m, 2H), (m, 1H), 3.58 (s, 3H), 3.70 (s, 1H), 6.95 (s, 1H), 10.20−10.60 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.6, 32.5, 48.9, 51.9, 134.9, 148.5, 169.0, 174.9. HRMS *m/z*: 169.0493 [$(M - H)^-$ calcd for $C_8H_9O_4^-$, 169.0501].

Cyclohex-2-ene-1,2-dicarboxylic Acid 1-Methyl Ester (8). Compound **8** (1.22 g, 85%) was prepared from **6** (1.65 g, 7.78 mmol) according to the method for the preparation of **7**. **8** was produced as a white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55−1.63 (m, 2H), 1.75−2.00 (m, 2H), 2.11−2.34 (m, 2H), 3.44 (s, 1H), 3.64 (s, 3H), 7.21 (s, 1H), 9.60−10.25 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.0, 25.9, 26.2, 40.3, 52.3, 128.5, 144.1, 172.0, 175.0. HRMS *m/z*: 183.0657 [$(M - H)^-$ calcd for $C_9H_{11}O_4^-$, 183.0657].

Cyclopent-1-ene-1,2-dicarboxylic Acid Monomethyl Ester (9). 1,2-Dicarboxylic anhydride (0.98 g, 7.10 mmol) was dissolved in 40 mL of methanol, and 3 mol % $ZnCl_2$ (0.4 mL (0.5 M $ZnCl_2$ in THF, 0.2 mmol)) was added as catalyst. After 3 h, the reaction mixture was evaporated and applied on a silica column (toluene/ethyl acetate, 1:1, + 1% AcOH). **9** (1.08 g, 90%) was collected as a slightly yellow syrup. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.78−1.98 (m, 2H), 2.76−2.90 (m, 4H), 3.9 (s, 3H), 8.78−8.90 (bs, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.3, 35.6, 36.7, 53.6, 139.1, 148.0, 164.4, 168.7. HRMS *m/z*: 171.0647 [$(M + H)^+$ calcd for $C_8H_{11}O_4^+$, 171.0657].

***N*-Ethyl-3-methoxyaniline (10{*1*}).** Compound **10**{*1*} (1.2 g, 75%) was prepared according to the method for preparing **10**{*14*} using *m*-anisidine (1.3 g, 11 mmol) instead of 5-chloro-*o*-toluidine. **10**{*1*} was produced as a slightly yellow oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.30 (t, J = 7.1 Hz, 3H), 3.20 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 6.20−6.38 (m, 3H), 7.05−7.20 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.1, 38.7, 55.3, 99.0, 105.6, 106.3, 130.2, 150.2, 161.2. HRMS *m/z*: 152.1078 [$(M + H)^+$ calcd for $C_9H_{14}NO^+$, 152.1075].

***N*-Ethyl-2-fluoroaniline (10{*5*}).** Compound **10**{*5*} (0.28 g, 22%) was prepared according to the method for preparing **10**{*14*} using 2-fluoroaniline (1.0 g, 9.0 mmol) instead of 5-chloro-*o*-toluidine. **10**{*5*} was produced as a colorless oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.37 (t, J = 7.1 Hz, 3H), 3.20 (q, J = 7.1 Hz, 2H), 3.92 (bs, 1H), 6.62−6.90 (m, 2H), 6.98−7.15 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 38.4, 112.3, [114.5 and 114.7],[19] [116.6 and 116.7],[19] 124.9, [128.1 and 129.0],[19] [150.0 and 154.0].[19]

***N*-Ethyl-2-methoxyaniline (10{*6*}).** Compound **10**{*6*} (0.86 g, 63%) was prepared according to the method for preparing **10**{*14*} using 2-methoxyaniline (1.1 g, 0.0 mmol) instead of 5-chloro-*o*-toluidine. **10**{*6*} was produced as a yellow oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.37 (t, J = 7.1 Hz, 3H), 3.27 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 6.62−6.78 (m, 2H), 7.80−7.84 (m, 1H), 6.90−7.01 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 45.2, 38.4, 55.6, [109.7 and 110.1],[18] 116.5, 121.7, 125.6, [138.4 and 139.0],[18] [147.1 and 148.0].[18] HRMS *m/z*: 152.1078 [$(M + H)^+$ calcd for $C_9H_{14}NO^+$, 152.1075].

2-Tolylaminoacetic Acid *tert*-Butyl Ester (10{*7*}). To a heated (80 °C) DMF solution (25 mL) toluidine (1.1 mL, 11 mmol), potassium carbonate (3.8 g, 27.1 mmol), and *tert*-butyl bromoacetate (1.8 mL, 11 mmol) were added. After being stirred overnight (14 h), the solution was cooled and filtered. To the clear solution 30 mL of water was added, and the mixture was extracted (3 × 30 mL, ethyl acetate). The combined organic phases were dried and concentrated, and purification was achieved using flash column chromatography (toluene/EtOAc, 18:1). The secondary aniline **10**{*7*} (1.5 g, 64%) was collected as white crystals: mp 30 °C. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.52 (s, 9H), 2.22 (s, 3H), 3.85 (s, 2H), 6.48 (d, J = 8.0 Hz, 1H), 6.63−6.73 (m, 1H), 7.05−7.26 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.5, 28.3, 46.8, 82.2, 110.1, 117.8, 122.6, 127.3, 130.4, 145.4, 170.6. HRMS *m/z*: 222.1486 [$(M + H)^+$ calcd for $C_{13}H_2ONO_2^+$, 222.1494].

***N*-Ethyl-3-chloroaniline (10{*9*}).** Compound **10**{*9*} (1.0 g, 75%) was prepared according to the method for preparing **10**{*14*} using 2-fluoroaniline (1.0 mL, 9.0 mmol) instead of 5-chloro-*o*-toluidine. **10**{*9*} was produced as a slighly yellow oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.23 (t, J = 7.1 Hz, 3H), 3.10 (q, J = 7.1 Hz, 2H), 3.60 (bs, 1H), 6.43−6.67 (m, 3H), 7.08 (t, J = 8.0 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 38.6, 111.3, 112.4, 117.2, 130.3, 135.2, 149.8. HRMS *m/z*: 156.0589 [$(M + H)^+$ calcd for $C_8H_{11}ClN^+$, 156.058].

***N*-Ethyl-3-fluoroaniline (10{*10*}).** Compound **10**{*10*} (1.0 g, 80%) was prepared according to the method for preparing **10**{*14*} using 3-fluoroaniline (1.2 mL, 9.0 mmol) instead of 5-chloro-*o*-toluidine. **10**{10} was produced as a colorless oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.32 (t, J = 7.0 Hz, 3H), 3.17 (q, J = 7.0 Hz, 3H), 3.70 (bs, 1H), 6.34−6.50 (m, 3H), 7.06−

7.20 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.8, 38.6, [99.3 and 99.7]f,[23] [103.5 and 103.8],[19] 108.9, [130.4 and 130.5],[19] [150.5 and 150.6],[19] [152.9 and 166.1][19]

***N*-Ethyl 3,5-dimethoxyaniline (10{*11*}).** Compound **10**{*11*} (1.1 g, 77%) was prepared according to the method for preparing **10**{*14*} using 2-fluoroaniline (1.2 g, 8.1 mmol) instead of 5-chloro-*o*-toluidine. **10**{*11*} was produced as a yellow-brown oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.21 (t, J = 7.1 Hz, 3H), 3.17 (q, J = 7.1 Hz, 2H), 3.75 (s, 6H), 5.78−5.82 (m, 2H), 5.92−5.96 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 38.6, 55.3, 89.8, 91.8, 125.6, 147.6, 150.8, 162.0. HRMS *m*/*z*: 182.1184 [(M + H)$^+$ calcd for $C_{10}H_{16}NO_2^+$, 182.1184].

***N*-Ethyl-4-methoxyaniline (10{*12*}).** Compound **10**{*12*} (0.57 g, 41%) was prepared according to the method for preparing **10**{*14*} using 4-methoxyaniline (1.1 g, 9.0 mmol) instead of 5-chloro-*o*-toluidine. **10**{*5*} was produced as a yellow-brown oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.24 (t, J = 7.1 Hz, 3H), 3.07 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 6.77−6.83 (m, 2H), 6.85−6.94 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.2, 39.6, 56.0, 114.2, 115.1, 129.2, 152.2. HRMS *m*/*z*: 152.1123 [(M + H)$^+$ calcd for $C_9H_{14}NO^+$, 152.1075].

***N*-Ethyl-5-chloro-2-chlorotoluidine (10{*14*}).** To a methanol (40 mL) solution containing powdered 4 Å molecular sieves (0.79 g) acetaldehyde (0.50 mL, 9 mmol), 5-chloro-*o*-toluidine (1.3 g, 9 0.0 mmol), and pyridine−borane (0.76 mL, 7.5 mmol) were sequentially added. After being stirred overnight (14 h), the solution was filtered through a small pad of Celite 545 and concentrated. Purification was achieved using flash column chromatography (toluene), and the secondary aniline **10**{*14*} (0.79 g, 52%) was collected as a yellow oil. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.37 (t, J = 7.1 Hz, 3H), 2.18 (s, 3H), 3.21 (q, J = 7.1 Hz, 2H), 3.45 (bs, 1H), 6.65−6.74 (m, 2H), 7.0−7.08 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.1, 17.2, 38.6, 109.8, 116.5, 120.3, 129.4, 131.0, 148.0. HRMS *m*/*z*: 170.0766 [(M + H)$^+$ calcd for $C_9H_{13}ClN^+$, 170.0737].

Ethyl(3-ethylphenyl)amine (10{*19*}). Compound **10**{*19*}-(0.92 g, 56%) was prepared according to the method for preparing **10**{*14*} using 3-ethylaniline (1.3 g, 11 mmol) instead of 5-chloro-*o*-toluidine. **10**{19} was produced as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 1.58 (t, J = 7.6 Hz, 3H), 2.82 (q, J = 7.56, 2H), 3.34 (q, J = 7.1 Hz, 2H), 3.62 (bs, 1H), 6.60−6.65 (m, 2H), 6.80 (d, J = 7.4 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.3, 16.0, 29.6, 38.9, 110.6, 112.9, 117.4, 129.6, 145.7, 149.0. HRMS *m*/*z*: 150.1284 [(M + H)$^+$ calcd for $C_{10}H_{16}N^+$, 150.1283].

(2,5-Dimethoxyphenyl)ethylamine (10{*20*}). Compound **10**{*20*} (1.6 g, 79%) was prepared according to the method for preparing **10**{*14*} using 2,5-dimethoxyaniline (1.7 g, 11 mmol) instead of 5-chloro-*o*-toluidine. **10**{*20*} was produced as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 7.0 Hz, 3H), 3.20 (q, J = 7.0 Hz, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 4.22 (bs, 1H), 6.19−6.23 (m, 1H), 6.25−6.27 (m, 1H), 7.70−7.74 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 38.3, 55.6, 56.1, 98.3, 98.7, 110.1, 139.8, 141.8, 155.3. HRMS *m*/*z*: 182.1184 [(M + H)$^+$ calcd for $C_{10}H_{16}NO_2^+$, 182.1181].

Cyclohexyl(3-ethylphenyl)amine (10{*21*}). To a methanol (50 mL) solution containing powdered 4 Å molecular sieves (1.2 g) cyclohexanone (1.1 mL, 11 mmol), 3-ethylaniline (1.3 g, 11 mmol), and pyridine−borane (0.92 mL, 9.1 mmol) were sequentially added. After being stirred overnight (14 h), the solution was filtered through a small pad of Celite 545 and concentrated. Purification was achieved using flash column chromatography (toluene), and the secondary aniline **10**{*21*} (0.94 g, 42%) was collected as a yellow-brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21−1.62 (m, 8H), 1.78−1.90 (m, 1H), 1.91−2.01 (m, 2H), 2.18−2.30 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 3.38−3.44 (m, 1H), 3.60 (bs, 1H), 6.58−6.62 (m, 2H), 6.72 (d, J = 7.6 Hz, 1H), 7.26 (q, J = 7.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.0, 25.5, 26.4, 29.5, 34.0, 52.1, 110.9, 113.3, 117.0, 129.6, 145.7, 147.9. HRMS *m*/*z*: 204.1754 [(M + H)$^+$ calcd for $C_{14}H_{22}N^+$, 204.1752].

Cyclohexyl(2,5-dimethoxyphenyl)amine (10{*22*}). Compound **10**{*22*} (0.40 g, 19%) was prepared according to the method for preparing **10**{*21*} using 2,5-dimethoxyaniline (1.7 g, 11 mmol) instead of 3-ethylaniline. **10**{22} was produced as a brown syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17−1.50 (m, 5H), 1.62−1.71 (m, 1H), 1.73−1.85 (m, 2H), 2.05−2.15 (m, 2H), 3.19−3.30 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 4.20 (bs, 1H), 6.15 (dd, J = 2.74, 8.5 Hz, 1H), 6.28 (d, J = 2.7 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.3, 26.2, 33.6, 51.6, 55.7, 56.2, 98.1, 98.7, 110.2, 138.6, 141.8, 155.1. HRMS *m*/*z*: 236.1649 [(M + H)$^+$ calcd for $C_{14}H_{22}NO_2^+$, 236.1651].

2-[Ethyl(3-methoxyphenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*1*}). To a DMF solution of the acid **7** (0.11 g, 0.65 mmol) *N*-ethyl-3-methoxyaniline (0.13 g, 0.84 mmol), DIPEA (0.28 mL, 1.62 mmol), and BOP-Cl (0.33 g, 1.29 mmol) were added. The reaction mixture was stirred for 16 h, concentrated, and subjected to flash column chromatography (toluene/ethyl acetate, 3:1) to yield **11**{*1*} (0.11 g, 58%) as a slightly yellow syrup. **11**{*1*} (60 mg) was subjected to chiral HPLC (heptane/isopropyl alcohol, 9:1), and (*S*)-**11**{*1*} (27.4 mg) and (*R*)-**11**{*1*} (27.8 mg) were separated. $[\alpha]^{22}_D$ +49.6 (*c* 0.55, $CHCl_3$) for (*R*)-**11**{*1*}. $[\alpha]^{22}_D$ -47.8 (*c* 0.55, $CHCl_3$) for (*S*)-**11**{*1*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, J = 7.1 Hz, 3H), 1.90−1.96 (m, 1H), 2.05−2.38 (m, 3H), 3.62 (dd, J = 7.1, 13.4 Hz, 1H), 3.65−3.69 (m, 4H), 3.76 (s, 3H), 3.94 (dd, J = 7.1, 13.4 Hz, 1H), 5.55−5.60 (m, 1H), 6.78−6.84 (m, 3H), 7.17−7.25 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.1, 27.5, 33.0, 45.1, 51.5, 52.0, 55.6, 113.1, 114.1, 120.4, 130.0, 137.5, 140.1, 144.5, 160.3, 166.0, 175.1. HRMS *m*/*z*: 304.1550 [(M + H)$^+$ calcd for $C_{17}H_{22}NO_4^+$, 304.1549].

2-(1-(2,3-Dihydroindol-1-yl)methanoyl)cyclopent-2-enecarboxylic Acid Methyl Ester (11{*2*}). Compound **11**{*2*} (0.15 g, 74%) was prepared from **7** (0.124 g, 0.729 mmol) according to the method for the preparation of **11**{*13*} using indoline instead of 4-methylindoline. **11**{*2*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02−2.16 (m, 1H), 2.30−2.41 (m, 1H), 2.49−2.74 (m, 2H), 3.0−3.26 (m, 2H), 3.64 (s, 3H), 4.05−4.18 (m, 2H), 4.22−4.34 (m, 1H), 6.21−6.28 (m, 1H), 6.95−7.08 (m, 1H), 7.15−7.21 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.6, 28.5, 33.2, 50.6, 51.7, 52.2, 117.6, 124.1, 124.9, 127.5, 137.1, 165.5, 175.1. HRMS *m*/*z*: 272.1286 [(M + H)$^+$ calcd for $C_{16}H_{18}NO_3^+$, 272.1287].

2-(Ethyl-*o*-tolylcarbamoyl)cyclopent-2-enecarboxylic Acid Methyl Ester (11{*3*}). The carboxylic acid **7** (0.77, 4.51 mmol) was dissolved in DMF, and *N*-ethyl-*o*-toluidine (0.78 mL, 5.4 mmol), DIPEA (2.5 mL, 14.4 mmol), and HATU (2.1 g, 5.4 mmol) were added. After being stirred for 10 h, the reaction mixture was extracted twice with toluene/basic water (10% TEA) and twice with toluene/acidic water (10% AcOH). The combined organic phases were evaporated, and the brown oil was subjected to flash column chromatography (toluene/ethyl acetate, 3:1). The purified **11**{*3*} (0.21 g, 16%) was collected as yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.05−1.21 (m, 3H), 1.77−1.84 (m, 1H), 2.02−2.18 (m, 1H), 2.20−2.38 (m, 5H), [3.10−3.21 and 3.42−3.53 (m, 1H)],[18] 3.58−3.77 (m, 4H), [3.91−4.08 and 4.10−4.29 (m, 1H)],[18] [5.23−5.30 and 5.32−5.39 (m, 1H)],[18] 7.05−7.32 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ [12.1 and 12.7],[18] 17.7, [27.1 and 27.3],[18] [33.0 and 33.1],[18] 43.7, 44.6, 51.5, 127.9, 128.2, 129.0, 130.0, 131.1, 131.6, 139.1, 140.1, 164.6, 168.3.

2-[Ethyl-(2-fluorophenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*5*}). Compound **11**{*5*} (0.078 g, 42%) was prepared from **7** (0.11 g, 0.65 mmol) according to the method for preparing **11**{*1*} using ethyl(2-fluorophenyl)amine (0.14 g, 0.84 mmol) instead of ethyl(3-methoxyphenyl)amine. **11**{*5*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08−1.14 (m, 3H), 1.78−2.45 (m, 4H), 3.50−4.01 (m, 6H), 5.45−5.70 (m, 1H), 7.08−7.19 (m, 2H), 7.24−7.37 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$):[17] δ 12.6, 28.8, 33.2, 44.2, 49.1, 52.4, 116.6, 116.8, 124.8, 129.5, 121.4, 135.4, 137.1, 139.5, 151.5, 151.6, 163.0, 174.5. HRMS *m*/*z*: 292.1311 [(M + H)$^+$ calcd for $C_{16}H_{19}FNO_3^+$, 292.1349].

2-[Ethyl(2-methoxyphenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*6*}). Compound **11**{*6*} (54 mg, 51%) was prepared from **7** (60 mg, 0.35 mmol) according to the method for the preparation of **11**{*7*} using

2-methoxyaniline (64 mg, 0.42 mmol) instead of 2-tolylaminoacetic acid *tert*-butyl ester. **11**{*6*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.10 (t, J = 7.1 Hz, 3H), 2.04−2.20 (m, 2H), 2.21−2.40 (m, 2H), 3.38−2.44 (m, 1H), 3.65−3.75 (m, 4H), 3.80 (s, 3H), 3.88−4.03 (m, 1H), 5.43−5.60 (m, 1H), 6.82−6.90 (m, 2H), 7.01−7.18 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.6, 28.9, 33.0, 43.5, 49.3, 52.3, 55.6, 111.7, 120.9, 129.0, 130.8, 134.5, 138.5, 149.0, 151.5, 158.0, 174.4. HRMS *m*/*z*: 304.1583 [(M + H)$^+$ calcd for $C_{17}H_{22}NO_4^+$, 304.1549].

2-(*tert*-Butoxycarbonylmethyl-*o*-tolylcarbamoyl)cyclopent-2-enecarboxylic Acid Methyl Ester (11{*7*}). To a 90 °C DMF solution of **7** (0.087 g, 0.51 mmol) was added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) (0.26 g, 1.02 mmol) portionwise over 15 min. Five minutes after the last BOP-Cl addition, *o*-tolylaminoacetic acid *tert*-butyl ester (0.15 g, 0.67 mmol) and triethylamine (0.178 mL, 1.28 mmol) were added. After 7 h, the reaction mixture was extracted twice with ethyl acetate/water and the combined organic phases were dried, filtered, and evaporated. The crude product was purified with flash column chromatography (toluene/ethyl acetate, 3:1), and **11**{*7*} was collected as a yellow oil (0.10 g, 52%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.78−1.97 (m, 1H), 2.02−2.19 (m, 1H), 2.22−2.38 (m, 2H), 2.25 (s, 3H), 3.58−3.63 (d, J = 16.8 Hz, 0.5H),[18] 3.68−3.76 (m, 4.5 H), 4.55−4.60 (d, J = 16.8 Hz, 0.5H),[18] 4.75−4.80 (d, J = 16.8 Hz, 0.5H),[18] 5.30−5.32 (m, 0.5H),[18] 5.43−5.45 (m, 0.5H),[18] 7.15−7.33 (m, 3H), 7.40−7.54 (m, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 18.1, 33.1, [33.7 and 34.0],[18] [38.0 and 38.1],[18] [52.0 and 52.2][18] , [52.6 and 52.8],[18] [52.9 and 60.0],[18] 81.8, 125.3, 129.0, 130.7, 134.4, 134.6, 138.9, 142.1, 142.2, 165.0, 169.0, 178.2. HRMS *m*/*z*: 374.1969 [(M + H)$^+$ calcd for $C_{21}H_{28}NO_5^+$, 374.1967].

2-[(3-Chlorophenyl)ethylcarbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*9*}). Compound **11**{*9*} (34 mg, 31%) was prepared from **7** (60 mg, 0.35 mmol) according to the method for preparing **11**{*1*} using *N*-ethyl-3-chloroaniline (66 mg, 0.42 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*9*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.18 (t, J = 7.1 Hz, 3H), 1.82−1.97 (m, 1H), 2.05−2.20 (m, 1H), 2.22−2.38 (m, 2H), 3.57−3.67 (m, 1H), 3.70−3.92 (m, 4H), 3.88−4.09 (m, 1H), 5.53−5.59 (m, 1H), 7.12−7.19 (m, 1H), 7.24−7.30 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.0, 27.4, 33.0, 45.2, 51.5, 52.1, 126.6, 127.6, 128.3, 130.3, 134.8, 137.3, 140.5, 144.7, 166.0, 175.0.

2-[Ethyl(3-fluorophenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*10*}). Compound **11**{*10*} (51 mg, 50%) was prepared from **7** (60 mg, 0.35 mmol) according to the method for preparing **11**{*1*} using *N*-ethyl-3-fluoroaniline (59 mg, 0.42 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{10} was produced as a yellow syrup. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.16 (t, J = 7.1 Hz, 3H), 2.04−2.20 (m, 2H), 2.21−2.44 (m, 2H), 3.61−3.78 (m, 4H), 3.79−3.85 (m, 1H), 3.98−4.08 (m, 1H), 5.55−5.59 (m, 1H), 6.95.7.10 (m, 2H), 7.12−7.13 (m, 1H), 7.25−7.35 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$):[17] δ 13.0, 28.9, 33.1, 49.1, 50.5, 52.3, 114.3, 114.6, 115.4, 115.7, 130.3, 130.5, 134.5, 140.4, 145.5, 151.4, 159.3, 174.4.

2-[(3,5-Dimethoxyphenyl)ethylcarbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*11*}). Compound **11**{*11*} (37 mg, 32%) was prepared from **7** (60 mg, 0.35 mmol) according to the method for preparing **11**{*1*} using *N*-ethyl-3−5-dimetoxyaniline (77 mg, 0.42 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*11*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.18 (t, J = 7.1 Hz, 3H), 1.82−1.96 (m, 1H), 2.10−2.20 (m, 1H), 2.25−2.38 (m, 2H), 3.57−3.63 (m, 1H), 3.65−3.70 (m, 4H), 3.77 (s, 6H), 3.89−4.00 (m, 1H), 5.53.5.56 (m, 1H), 6.37−6.40 (m, 1H), 6.41−6.44 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.1, 27.6, 33.0, 45.1, 51.5, 52.0, 55.7, 99.55, 106.6, 125.5, 128.4, 129.2, 139.9, 161.2, 175.0. HRMS *m*/*z*: 334.1645 [(M + H)$^+$ calcd for $C_{18}H_{24}NO_5^+$, 334.1654].

2-[Ethyl(4-methoxyphenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*12*}). Compound **11**{*12*} (59 mg, 56%) was prepared from **7** (60 mg, 0.35 mmol) according to the method for preparing **11**{*1*} using *N*-ethyl-4-methoxyaniline (64 mg, 0.42 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*12*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, CD_3Cl_3): δ 1.05 (t, J = 7.1 Hz, 3H), 1.80−1.90 (m, 1H), 2.01−2.16 (m, 1H), 2.20−2.28 (m, 2H), 3.55−3.62 (m, 1H), 3.63−3.73 (m, 4H), 3.80 (s, 3H), 3.85−4.01 (m, 1H), 5.45−5.52 (m, 1H), 7.78−7.82 (m, 2H), 7.05−7.17 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.0, 27.4, 33.0, 45.2, 51.7, 52.0, 55.6, 114.5, 129.4, 137.7, 140.0, 158.8, 175.2.

2-[1-(2-Methyl-2,3-dihydroindol-1-yl)methanoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*13*}). The carboxylic acid **7** (0.15 g, 0.89 mmol) was dissolved in refluxing THF (10 mL), and DCC (0.20 g, 0.98 mmol), HOBt (0.13 g, 0.98 mmol), DIPEA (0.17 mL, 0.98 mmol), and 4-methylindoline (0.13 g, 0.98 mmol) were added. After 2 h, the reaction mixture was evaporated and subjected to flash column chromatography (toluene/EtOAc, 3:1). **11**{*13*} (0.21 g, 81%) was collected as a colorless syrup. ^{1}H NMR on diastereomers (300 MHz, $CDCl_3$): δ 1.25−1.38 (m, 3H), 2.15−2.40 (m, 2H), 2.42−2.80 (m, 3H), 3.30−3.42 (m, 1H), 3.62−3.75 (m, 3H), 4.02−4.18 (m, 1H), 4.72−4.83 (m, 1H), 6.29−6.38 (m, 1H), 6.98−7.20 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.6, 27.4, 33.1, 36.5, 51.9, 52.1, 56.7, 117.5, 123.9, 125.3, 127.6, 137.4, 165.4, 175.0. HRMS *m*/*z*: 286.1443 [(M + H)$^+$ calcd for $C_{17}H_{20}NO_3^+$, 286.1443].

2-[(5-Chloro-2-methylphenyl)ethylcarbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*14*}). Compound **11**{*14*} (0.11 g, 50%) was prepared from **7** (0.11 g, 0.65 mmol) according to the method for preparing **11**{*1*} using (5-chloro-2-methylphenyl)ethylamine (0.14 g, 0.84 mmol) instead of *N*-ethyl-3methoxyaniline. **11**{*14*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09−1.17 (m, 3H), 1.76−1.95 (m, 1H), 2.01−2.42 (m, 6H), [3.08−3.22 and 3.41−3.55 (m, 1H)],[18] 3.57−3.83 (m, 4H), [3.83−3.97 and 4.08−4.21 (m, 1H)],[18] [5.27−5.38 and 5.40−5.44 (m, 1H)],[18] 7.08−7.25 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ [12.3 and 13.0],[18] [17.4 and 17.5],[18] [27.3 and 27.6],[18] [33.2 and 33.4],[18] [44.0 and 45.0],[18] 49.1, [51.7 and 52.0],[18] 128.2, 129.2, 130.1, 132.3, 132.7, 139.4, 141.0, 151.5, 168.5, 174.3. HRMS *m*/*z*: 322.1205 [(M + H)$^+$ calcd for $C_{17}H_{21}ClNO_3^+$, 322.1210].

2-[Ethyl(3-ethylphenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*19*}). Compound **11**{*19*} (53 mg, 54%) was prepared from **7** (55 mg, 0.32 mmol) according to the method for preparing **11**{*1*} using ethyl(3-ethylphenyl)amine (63 mg, 0.42 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*19*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.6 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.82−1.91 (m, 1H), 2.03−2.40 (m, 3H), 2.62 (q, J = 7.6 Hz, 1H), 3.60−3.70 (m, 5H), 3.95−4.01 (m, 1H), 5.44−5.50 (m, 1H), 7.02−7.08 (m, 3H), 7.15−7.19 8 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.1, 16.8, 27.5, 28.8, 32.9, 45.1, 51.5, 52.0, 125.3, 127.0, 127.8, 129.2, 137.7, 140.0, 143.3, 145.7, 151.5, 175.1. HRMS *m*/*z*: 302.1756 [(M + H)$^+$ calcd for $C_{18}H_{24}NO_3^+$, 302.1756].

2-[(2,5-Dimethoxyphenyl)ethylcarbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*20*}). Compound **11**{*20*} (76 mg, 43%) was prepared from **7** (90 mg, 0.53 mmol) according to the method for preparing **11**{*1*} at 65 °C instead of at room temperature and using (2,5-dimethoxyphenyl)-ethylamine (0.12 g, 0.68 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*20*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, J = 7.1 Hz, 3H), 1.80−2.42 (m, 4H), 3.38−3.44 (m, 1H), 3.65−3.91 (m, 10H), 3.93−3.99 (m, 1H), 5.41−5.65 (m, 1H), 6.80−7.05 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.6, 27.7, [28.9 and 29.0],[18] 32.9, 43.5, [49.1 and 49.3],[18] 52.0, 56.0, 112.4, 113.8, 116.6, 134.5, 138.4, 151.4, 151.5, 153.6, 174.4, 175.2. HRMS *m*/*z*: 334.1667 [(M + H)$^+$ calcd for $C_{18}H_{24}NO_5^+$, 334.1654].

2-[Cyclohexyl(3-ethylphenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*21*}). Compound **11**{*21*} (32 mg, 24%) was prepared from **7** (65 mg, 0.38 mmol) according to the method for preparing **11**{*1*} using cyclohexyl-(3-ethylphenyl)amine (0.10 g, 0.50 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*21*} was produced as a yellow syrup. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 0.95−1.05 (m, 1H), 1.10−1.40 (m, 4H), 1.45−2.02 (m, 6H), 2.04−2.45 (m, 4H), 2.50−2.80 (m, 4H), 3.55−3.61 (m, 1H), 3.65−3.77 (m, 3H), 4.45−4.61 (m, 1H), 5.38−5.42 (m, 1H), 6.86−6.90 (m, 2H), 7.05−7.12 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.8, 25.7, 26.0, 27.3, 28.9, 31.3, 33.0, 33.1, 49.1, 52.0, 52.4, 55.2, 127.6, 128.6, 134.5, 138.2, 139.1, 139.9, 151.4, 159.2, 174.4, 175.1. HRMS *m/z*: 356.2276 [$(M + H)^+$ calcd for $C_{22}H_{30}NO_3^+$, 356.2226].

2-[Cyclohexyl(2,5-dimethoxyphenyl)carbamoyl]cyclopent-2-enecarboxylic Acid Methyl Ester (11{*22*}). Compound **11**{*22*} (32 mg, 22%) was prepared from **7** (63 mg, 0.37 mmol) according to the method for preparing **11**{*1*} at 65 °C instead of at room temperature and using cyclohexyl(2,5-dimethoxyphenyl)amine (0.11 g, 0.48 mmol) instead of *N*-ethyl-3-methoxyaniline. **11**{*22*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91−1.00 (m, 1H), 1.20−1.38 (m, 2H), 1.45−1.98 (m, 5H), 2.05−2.20 (m, 2H), 2.23−2.31 (m, 2H), 2.55−2.90 (m, 2H), 3.64−3.92 (m, 10H), 4.40−4.50 (m, 1H), 5.45−5.62 (m, 1H), 6.61−6.65 (m 1H), 6.70−6.80 (m, 1H), 7.03−7.08 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.8, 26.2, 27.7, 28.9, 29.7, 31.9, 33.1, 49.1, 52.0, 52.4, 55.7, 56.0, 111.8, 113.7, 117.7, 134.5, 137.2, 137.8, 151.5, 159.2, 174.4, 175.1. HRMS *m/z*: 388.2127 [$(M + H)^+$ calcd for $C_{22}H_{30}NO_5^+$, 388.2124].

2-(Ethyl-*o*-tolylcarbamoyl)cyclohex-2-enecarboxylic Acid Methyl Ester (12{*3*}). Compound **12**{*3*} (33 mg, 40%) was prepared from **8** (51 mg, 0.28 mmol) according to the method for the preparation of **11**{*1*} using *N*-ethyl-*o*-toluidine instead of *N*-ethyl-3-methoxyaniline. **12**{*3*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02−1.17 (t, J = 6.9 Hz, 3H), 1.24−1.97 (m, 6H), 2.20 (s, 1.2H), 2.25 (s, 1.8H), 3.0−3.18 (m, 1H), 3.44−3.60 (m, 1H), 3.70 (s, 3H), 4.18−4.23 (m, 1H), 5.58−5.64 (m, 1H), 7.02−7.30 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 18.1, 19.7, 25.1, 26.0, 41.7, 44.2, 52.0 (d), 126.5, 127.9, 126.8, 127.6, 130.2, 131.3, 135.8, 136.0, 164.5, 174.9. HRMS *m/z*: 183.0657 [$(M - H)^-$ calcd for $C_9H_{11}O_4^-$, 183.0657].

2-(Ethylphenylcarbamoyl)cyclohex-2-enecarboxylic Acid Methyl Ester (12{*4*}). Compound **12**{*4*} (20 mg, 25%) was prepared from **8** (51 mg, 0.28 mmol) according to the method for the preparation of **11**{*1*} using *N*-ethylaniline instead of *N*-ethyl-3-methoxyaniline. **12**{*4*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05−1.18 (t, J = 6.9 Hz, 3H), 1.38−1.65 (m, 2H), 1.77−1.95 (m, 4H), 3.44−3.52 (m, 1H), 3.54−3.68 (1H), 3.72 (s, 3H), 4.00−4.12 (1H, m), 5.79−5.82 (m, 1H), 7.19−7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.0, 20.0, 25.1, 26.1, 41.8, 45.6, 52.0, 100.4, 126.7, 127.7, 129.2, 137.6, 136.8, 163.2, 178.1.

2-Cyclohexylcarbamoylcyclohex-2-enecarboxylic Acid Methyl Ester (12{*8*}). Compound **12**{*8*} (0.092 g, 56%) was prepared from **6** (0.11 g, 0.61 mmol) according to the method for the preparation of **11**{*1*} using cyclohexylamine instead of *N*-ethyl-3-methoxyaniline. **12**{*8*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02−1.19 (m, 3H), 1.21−1.40 (m, 2H), 1.55−1.98 (m, 9H), 2.05−2.10 (m, 2H), 3.58−71 (m, 4H), 4.88−4.93 (m, 1H), 5.60−5.80 (bs, 1H), 6.40−6.48 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.5, 25.0, 25.2, 25.8, 25.9, 33.3, 40.5, 48.3, 58.2, 133.1, 133.6, 134.5, 176.8. HRMS *m/z*: 266.1758 [$(M + H)^+$ calcd for $C_{15}H_{24}NO_3^+$, 266.1756].

2-(1-Piperidin-1-ylmethanoyl)cyclohex-2-enecarboxylic Acid Methyl Ester (12{*16*}). Compound **12**{*16*} (0.10 g, 68%) was prepared from **8** (0.11 g, 0.61 mmol) according to the method for the preparation of **11**{*1*} using piperidine instead of *N*-ethyl-3-methoxyaniline. **12**{*16*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48−1.69 (m, 8H), 1.77.1.87 (m, 1H), 1.93−2.20 (m, 3H), 3.44−3.74 (m, 8H), 6.88−6.91 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.4 (d), 24.8 (d), 25.3 (d), 25.8 (d), 40.39, 41.4 (d), 44.1, 52.1 (d), 130.8, 131.4, 134.4, 174.5. HRMS *m/z*: 252.1593 [$(M + H)^+$ calcd for $C_{14}H_{22}NO_3^+$, 252.1599].

2-Phenylcarbamoylcyclohex-2-enecarboxylic Acid Methyl Ester (12{*17*}). Compound **12**{*17*} 0080 g, 51%) was prepared from **8** (0.11 g, 0.61 mmol) according to the method for the preparation of **11**{*1*} using aniline instead of *N*-ethyl-3-methoxyaniline. **12**{*17*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60−1.72 (m, 2H), 1.80−1.91 (m, 1H), 2.0−2.12 (m, 1H), 2.18−2.33 (m, 2H), 3.69 (s, 3H), 3.71−76 (m, 1H), 6.62−6.71 (m, 1H), 7.02−10 (m, 1H), 7.23−7.36 (m, 2H), 7.50−7.58 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.4, 25.4, 25.9, 40.5, 52.4, 120.2, 124.3, 129.1, 134.0, 134.7, 138.1, 163.5, 174.9. HRMS *m/z*: 260.1286 [$(M + H)^+$ calcd for $C_{15}H_{18}NO_3^+$, 260.1287].

2-Benzylcarbamoylcyclohex-2-enecarboxylic Acid Methyl Ester (12{*18*}). Compound **12**{*18*} (0.11, 65%) was prepared from **6** (0.11 g, 0.61 mmol) according to the method for the preparation of **11**{*1*} using benzylamine instead of *N*-ethyl-3-methoxyaniline. **12**{*18*} was produced as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56−1.66 (m, 2H), 1.72−1.86 (m, 1H), 1.94−2.08 (m, 1 H), 2.10−2.20 (m, 2H), 3.58−3.68 (m, 1H), 3.62 (s, 3H), 4.44−4.49 (d, J = 5.8 Hz, 2H), 6.20−6.31 (bs, 1H), 6.45−6.54 (m, 1H), 7.20−7.37 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.4 (d), 25.3, 25.9 (d), 40.4 (d), 43.8 (d), 52.2, 127.6, 127.9, 128.8, 133.9, 134.6, 139.5, 168.9, 174.8. HRMS *m/z*: 274.1456 [$(M + H)^+$ calcd for $C_{16}H_{20}NO_3^+$, 274.1443].

2-[Ethyl(3-methoxyphenyl)carbamoyl]cyclopent-1-enecarboxylic Acid Methyl Ester (13{*1*}). Carboxylic acid **9** (90 mg, 0.52 mmol) was dissolved in 3 mL of THF, and BOP-Cl (0.15 g, 0.57 mmol), *N*-ethyl-3-methoxyaniline (86 mg, 0.57 mmol), and DIPEA (0.10 mL, 0.57 mmol) were added. After 23 h, the reaction mixture was diluted with toluene and extracted twice with 10% AcOH followed by two washes with diluted Na_2CO_3 solution. The combined organic phases were dried, filtered, evaporated, and applied to a silica column (toluene/ethyl acetate, 3:1, + 1% AcOH) to give **13**{*1*} (37 mg, 23%) as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12−1.23 (m, 3H), 1.59−1.78 (m, 2H), 2.38−2.57 (m, 4H), 3.70−3.74 (m, 6H), 3.75−3.91 (m, 2H), 6.71−6.98 (m, 1H), 7.12−7.30 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.0, 22.5, 32.6, 37.2, 43.8, 51.7, 55.4, 113.8, 113.9, 120.1, 129.9, 132.2, 142.2, 150.8, 160.0, 164.3, 165.8. HRMS *m/z*: 304.1532 [$(M + H)^+$ calcd for $C_{17}H_{22}NO_4^+$, 304.1549].

2-(1-(2,3-Dihydroindol-1-yl)methanoyl)cyclopent-1-enecarboxylic Acid Methyl Ester (13{*2*}). Compound **13**{*2*} (0.11 g, 48%) was prepared from **9** (0.15 g, 0.88 mmol) according to the method for the preparation of **13**{*4*} using indoline instead of *N*-ethylaniline. **13**{*2*} was produced as a white crystals: mp 102.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99−2.20 (m, 2H), 2.65−2.91 (m, 4H), 3.03−3.22 (m, 2H), 3.64 (s, 3H), 3.82−4.00 (m, 2H), 6.93−7.37 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.6, 28.3, 32.9, 36.6, 48.3, 52.1, 117.4, 124.4, 124.8, 127.9, 131.9, 132.0, 142.2, 150.3, 164.6, 166.2. HRMS *m/z*: 272.1306 [$(M + H)^+$ calcd for $C_{16}H_{18}NO_3^+$, 272.1287].

2-(Ethyl-*o*-tolylcarbamoyl)cyclopent-1-enecarboxylic Acid Methyl Ester (13{*3*}). Compound **13**{*3*} (0.048 g, 54%) was prepared from **9** (0.050 g, 0.29 mmol) according to the method for the preparation of **13**{*4*} using *N*-ethyl-2-toluidine (59 μL, 0.32 mmol). **13**{*3*} was produced as a white powder. ^{1}H NMR (250 MHz, CD_3OD): δ 1.10−1.31 (m, 3H), 1.44−1.75 (m, 2H), 1.85−2.10 (m, 2H), 2.20−2.31 (m, 3H), 2.41−2.54 (m, 2H), 2.90−3.08 (m, 1H), 3.77 (s, 3H), 4.36−4.50 (m, 1H), 7.08−7.30 (m, 4H). ^{13}C NMR (62.9 MHz, CD_3OD): δ 12.3, 17.6, 22.2, 25.0, 35.8, 42.4, 51.7, 126.4, 128.6, 129.8, 131.0, 135.6, 138.5, 150.0, 150.7, 164.7, 168.2.

2-(Ethylphenylcarbamoyl)cyclopent-1-enecarboxylic Acid Methyl Ester (13{*4*}). Compound **9** (0.17 g, 0.99 mmol) was dissolved in 5 mL of warm THF (50 °C), and DCC (0.23 g, 1.10 mmol) and HOBt (1.10 mL, 1 M HOBt in NMP, 1.10 mmol) were added. Afterward, the THF solution was slightly milky and *N*-ethylaniline (0.13 g, 1.10 mmol) was added. After 2 h, the reaction mixture was diluted with toluene and extracted twice with 10% AcOH followed by two washes with diluted Na_2CO_3(aq) solution. The combined organic phases were dried, filtered, and evaporated. The crude product was purified with flash column chromatography (toluene/ethyl acetate, 3:1), and **13**{*4*} (9.16 g, 60%) was collected as a slightly yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04−1.20 (m, 3H), 1.43−1.74 (m, 2H), 2.22−2.39 (m, 4H), 3.70 (s, 3H), 3.78−

3.94 (m, 2H), 7.02−7.30 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.0, 22.5, 32.5, 37.2, 43.6, 51.7, 127.9, 128.0, 128.3, 129.2, 141.4, 150.8, 164.6, 168.0. HRMS *m/z*: 274.1463 [(M + H)$^+$ calcd for $C_{16}H_{20}NO_3^+$, 274.1443].

2-(*tert*-Butoxycarbonylmethyl-*o*-tolylcarbamoyl)cyclopent-1-enecarboxylic Acid Methyl Ester (13{*7*}). Compound **13**{*7*} (0.21 g, 65%) was prepared from **9** (0.15 g, 0.88 mmol according to the method for the preparation of **1**{*7*} using 2-tolylaminoacetic acid *tert*-butyl ester (0.20 g, 0.97 mmol). **13**{*7*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.51−1.73 (m, 2H), 2.24 (s, 3H), 2.25−2.61 (m, 4H), 3.62−3.78 (m, 2H), 3.79 (s, 3H), 7.07−7.27 (m, 3H), 7.43−7.52 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.8, 22.9, 28.1, 32.6, 36.7, 50.7, 51.9, 81.9, 125.4, 126.5, 128.3, 128.8, 129.0, 130.1, 133.8, 135.5, 164.6, 167.4, 168.9. HRMS *m/z*: 374.1963 [(M + H)$^+$ calcd for $C_{21}H_{28}NO_5^+$, 374.1967].

2-Cyclohexylcarbamoylcyclopent-1-enecarboxylic Acid Methyl Ester (13{*8*}). Compound **13**{*8*} (59 mg, 37%) was prepared from **9** (0.11 g, 0.63 mmol) according to the method for preparing **11**{*1*} using cyclohexylamine (0.080 mL, 0.69 mmol) instead of *N*-ethyl-3-methoxyaniline. **13**{*8*} was produced as a white crystals: mp 98.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10−1.44 (m, 6H), 1.51−1.74 (m, 4H), 1.74−1.89 (m, 2H), 2.67−2.88 (m, 4H), 3.72 (s, 3H), 3.76−3.88 (m, 1H), 7.98−8.17 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1, 24.9, 25.8, 33.0, 35.9, 37.3, 48.3, 52.3, 133.2, 150.1, 163.9, 167.0. HRMS *m/z*: 252.1603 [(M + H)$^+$ calcd for $C_{14}H_{22}NO_3^+$, 252.1600].

2-[(5-Chloro-2-methylphenyl)ethylcarbamoyl]cyclopent-1-enecarboxylic Acid Methyl Ester (13{*14*}). Compound **13**{*14*} (0.13 g, 44%) was prepared from **9** (0.15 g, 0.88 mmol) according to the method for preparing **11**{*1*} using 5-chloro-2-methylphenyl)ethylamine (0.16 mg, 0.97 mmol) instead of *N*-ethyl-3-methoxyaniline. **13**{*14*} was produced as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13−1.21 (m, 3H), 1.80−1.91 (m, 2H), 2.29 (s, 3H), 2.75−2.88 (m, 4H), 2.96−3.11 (m, 1H), 3.72 (s, 3H), 4.21−4.38 (m, 1H), 7.03−7.22 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.5, 13.9, 17.3, 22.7, 32.5, 36.1, 51.8, 125.5, 128.4, 128.9, 129.2, 129.9, 131.9, 132.2, 150.2, 164.8, 168.4. HRMS *m/z*: 322.1206 [(M + H)$^+$ calcd for $C_{17}H_{21}ClNO_3^+$, 322.1210].

2-Phenethylcarbamoylcyclopent-1-enecarboxylic Acid Methyl Ester (13{*15*}). Compound **13**{*15*} (0.20 g, 60%) was prepared from **9** (0.21 g, 1.25 mmol) according to the method for the preparation **13**{*4*} using phenethylamine instead of *N*-ethylaniline. **13**{*15*} was produced as a slightly yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88−1.94 (m, 2H), 2.65−2.97 (m, 6H), 3.50−3.60 (m 2H), 3.72 (s, 3H), 7.05−7.38 (m, 5H), 8.25 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.9, 35.9, 36.0, 37.0, 41.1, 52.2, 126.3, 128.2, 128.5, 139.3, 149.5, 164.8, 166.7, 168.6. HRMS *m/z*: 274.1460 [(M + H)$^+$ calcd for $C_{16}H_{20}NO_3^+$, 274.1443].

2-[4-(1-Amino-1-benzyloxycarbonyliminomethyl)-benzylcarbamoyl]cyclopent-2-enecarboxylic Acid Methyl (14). To a solution of **7** (0.47 g, 2.76 mmol) in THF (14 mL) were added DCC (0.63 g, 3.0 mmol), HOBt (3.0 mL of a 1 M solution, 3 mmol), and DIPEA (2.4 mL, 14 mmol). After 15 min, *p*-(*N*-benzyloxycarbonyl)amidinobenzylamine dihydrochloride (1.1 g, 3.0 mmol) was added and the reaction mixture was stirred for 3 h. Concentration in a vacuum gave a yellow oil that was purified using flash chromatography (100% ethyl acetate) to yield the title compound **14** (1.08 g, 90%) as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00−2.23 (m, 2H), 2.31−2.62 (m, 2H), 3.58 (s, 3H), 3.75−3.81 (m, 1H), 4.22−4.40 (m, 2H), 5.18 (s, 2H), 6.61−6.65 (m, 1H), 7.00 (d, J = 8.4 Hz, 2H), 7.05−7.36 (m, 3H), 7.38 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.6, 32.7, 42.9, 50.0, 52.3, 67.3, 127.3, 128.0, 128.2, 128.4, 128.7, 133.3, 136.9, 138.0, 140.9, 143.1, 164.2, 165.1, 169.2, 175.3. HRMS *m/z*: 436.1877 [(M + H)$^+$ calcd for $C_{24}H_{26}N_3O_5^+$, 436.1872].

Lithium 2-[4-(1-Amino-1-benzyloxycarbonyliminomethyl)benzylcarbamoyl]cyclopent-2-enecarboxylate (15). The methyl ester **14** (0.59 g, 1.36 mmol) was hydrolyzed using LiOH (34.2 mg, 1.42 mmol) in dioxane/water (1:1, 40 mL). Evaporation of the reaction mixture yielded a syrup, which was dissolved in toluene/DCM (1:1, 40 mL) and evaporated. The lithium salt was dissolved in THF (50 mL), dried with MgSO (without the drying procedure, the subsequent coupling step did not work), filtered, evaporated, and dissolved in THF/toluene (1:1, 25 mL). Coevaporation of the THF/toluene mixture yielded the slightly yellow lithium salt **15** (0.49 g, 85%) as a white, fine powder. ^{1}H NMR (300 MHz, CD_3OD): δ 2.15−2.27 (m, 1H), 2.33−2.42 (m, 2H), 2.57−2.70 (m, 1H), 3.58−3.78 (m, 2H), 4.38−4.60 (m, 3H), 6.72−6.77 (m, 1H), 7.30−7.45 (m, 5H), 7.68−7.77 (m, 2H), 7.91−7.97 (m, 2H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 29.3, 31.6, 42.5, 53.1, 70.3, 126.7, 127.2, 127.3, 127.7, 128.0, 132.2, 139.7, 141.2, 141.3, 141.8, 143.2, 167.1, 167.2, 180.9. HRMS *m/z*: 422.1713 [(M + H)$^+$ calcd for $C_{23}H_{24}N_3O_5^+$, 422.1716].

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(18) Rotameric pattern.
(19) Two peaks were due to $^{13}C-^{19}F$ couplings.

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