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Synthesis of new *N*-norbornylimide substituted amide derivatives, their reductive Heck and domino Heck reactions

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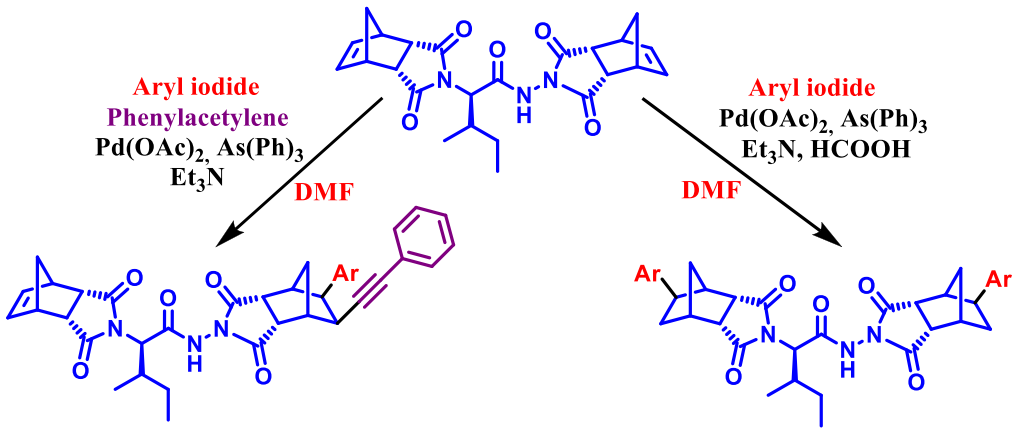
Abstract

Palladium-catalyzed, regioselective hydroarylation reactions of *N*-norbornenylimide substituted amides were studied to synthesize pentanamide derivatives containing *exo*-aryl-substituted norbornyl imide groups in excellent yields. All newly synthesized derivatives have been characterized by FTIR, ^{1}H, ^{13}C NMR, GC/MS and TOF/Qtof analyses.

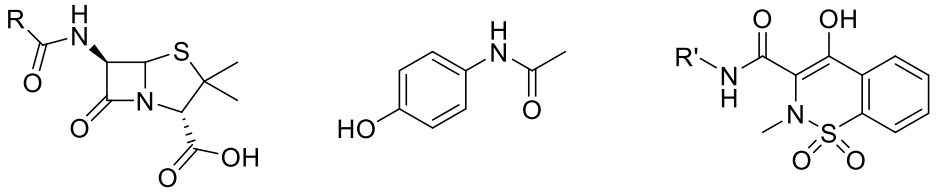


Keywords: Amides, hydrazides, microbiological activity, palladium catalyst, reductive Heck and domino Heck reactions, regioselectivity

Introduction

Carboxamide functions are widely found in various molecules such as drugs, polymers, pharmaceutical agents, peptides, natural molecules, proteins, alkaloids, etc.[1] Compounds containing an amide bond play an important role in biological processes such as enzymatic catalysis, transportation and immune protection. Amide bonds have been a main topic of scientific interest to medicinal and organic chemists for a long period due to their biological properties of amides.[2]

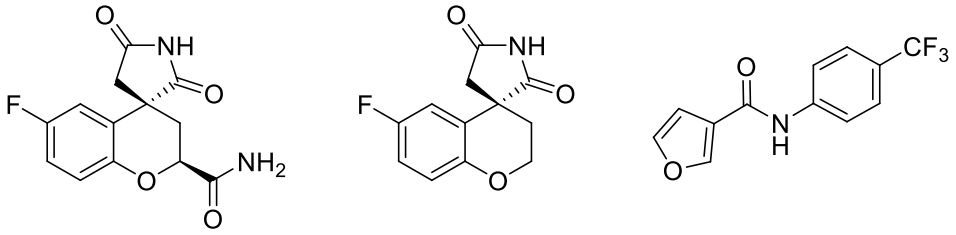
Functional groups, especially carboxamides, are important for the activity and pharmacokinetic properties of a drug. There are many drugs containing amide groups and they are still widely used today, e.g. Penicilins **1**, Paracetamol **2** and Oxicams **3** (Scheme 1). Penicilin was the first broadspectrum antibiotic to be used against many bacterial infections[3], Paracetamol is a widely used pharmaceutical to treat fever and pain[4], and Oxicams are anti-inflammatory drugs.[5] All of these important drugs contain an amide group and have a large share in the worldwide pharmaceutical market.



1 Penicilin **2** Paracetamol **3** Oxicam

Scheme 1. Some drugs including an amide group.

Additionally, anti-cancer agents containing amides have become a focus in the improvement of new treatments of cancer. An increasing number of amide antitumor agents is now becoming effective; for example, Fidarestat **4** (Scheme 2) and Sorbinil **5** are anti-cancer and anti-diabetic agents[6], and Leflunomide **6** is also a well-known anti-cancer agent.[7]



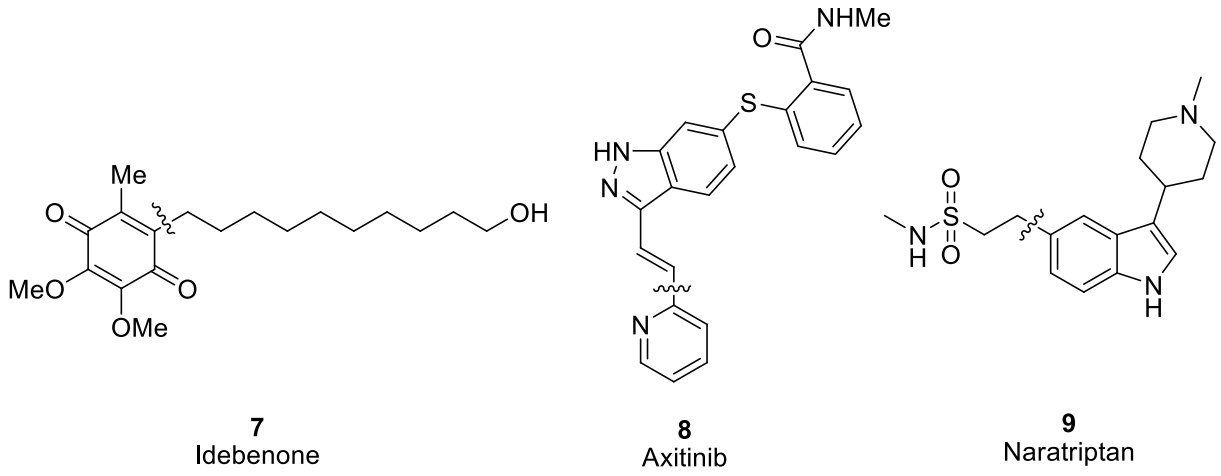
4 Fidarestat **5** Sorbinil **6** Leflunomide

Scheme 2. Some anti-cancer drugs containing an amide group.

The carbon-carbon bond formation is a crucial transformation in synthetic organic chemistry. Among the palladium-catalyzed transformations, the Heck and domino-Heck reactions are significant synthetic methods to obtain biologically active compounds in the pharmaceutical industry.[8-10] *N*-Substituted tricyclic imides are

reported for their biological effects such as antitumor, anti-inflammatory, and antimicrobial activities.[11-12] Likewise, bi- and tricyclic imides are widely used in biomedical applications due to their biological properties.[13]

Reductive Heck and domino-Heck reactions of unsaturated *N*-substituted tricyclic imides having feasible biological activities, were reported previously.[14-20] There are many additional examples of Heck reactions being used worldwide in industrial syntheses. As an example, in 2011 an Idebenone **7** total synthesis was based on a Heck reaction. This compound was initially designed for the treatment of Alzheimer's and Parkinson's diseases.[21] Another example of an application of the Heck reaction is the synthesis of Axitinib **8**. Recently, Pfizer researchers designed this compound for vascular endothelial growth factor (VEGF) inhibition.[22] Naratriptan **9** (Scheme 3), a 5-HT_1 agonist for treatment of migraine headaches from GlaxoSmithKline, was synthesized utilizing the Heck arylation.[23]



7 Idebenone **8** Axitinib **9** Naratriptan

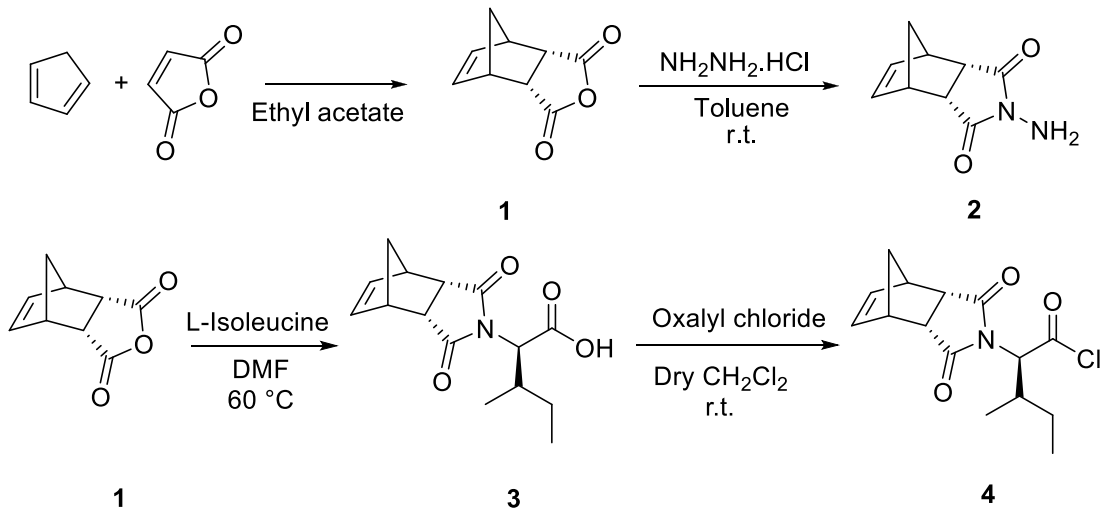
Scheme 3. Application of the Heck reaction on some drugs' total synthesis.

The Kaufmann reductive Heck procedure could allow the palladium-catalyzed, stereoselective transformation of *N*-substituted tricyclic imides thus providing a new access to *exo*-aryl(hetaryl)-substituted tricyclic imides in the presence of triphenylarsine as a ligand.[24-26]

Having this information in mind, we focused on the synthesis of a new class of compounds including *exo*-aryl(hetaryl)-substituted norbornylimide derivatives of *N*-4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl-2-(4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide (**5**).

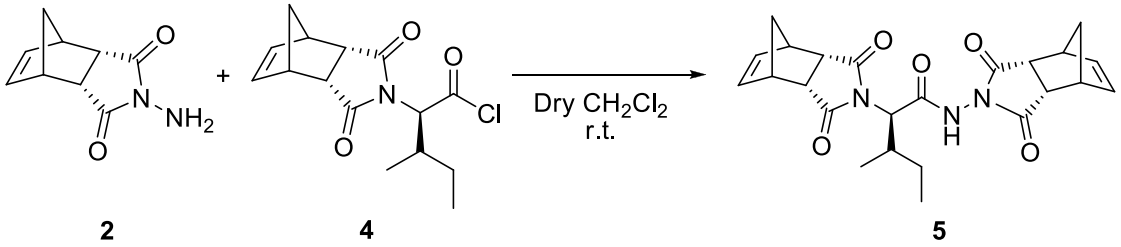
Results and Discussion

Initially, we prepared the endocyclic anhydride **1** using freshly distilled cyclopentadiene and maleic anhydride in ethyl acetate at 0 °C using a known procedure.[27] Thereafter, compound **2** was obtained from the reaction of hydrazonium chloride and compound **1** in toluene at room temperature.[28] We continued to prepare the optically active norbornenylimide substituted acid **3** from **1** using Amos' procedure.[29] As the last step of this part, we synthesized a new norbornenylimide acyl chloride derivative **4** from **3** in an excellent yield. (Scheme 4).



Scheme 4. Preparation of compunds **1** – **4**.

As the second step of our starting material preparation, we synthesized the new amide **5** from **2** and **4** in dry dichloromethane at room temperature in a good yield (Scheme 5).



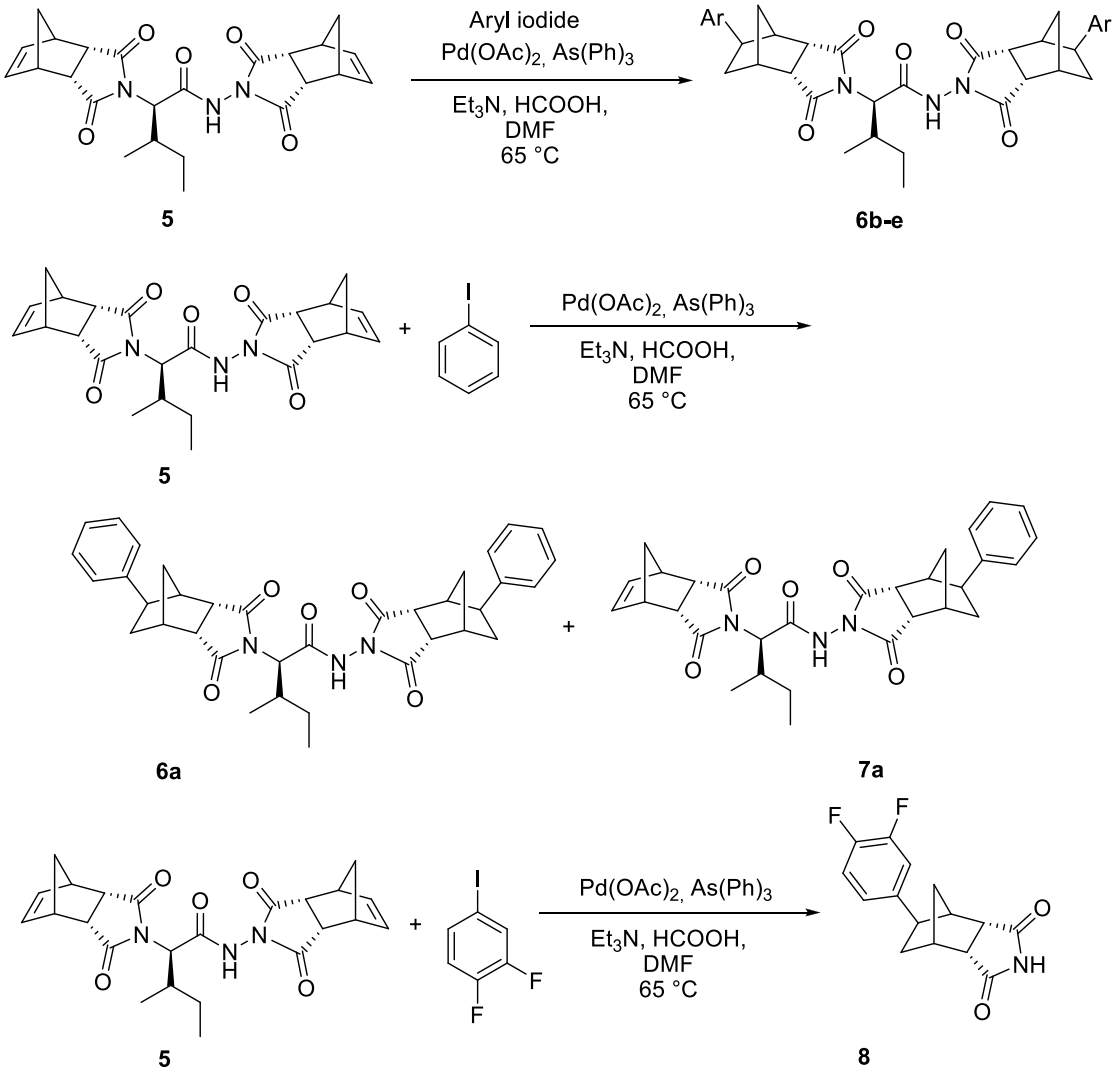
Scheme 5. Synthesis of compound **5**.

Compound **5** was then reacted with various aryl iodides (Table 1) under reductive Heck reaction conditions to afford newly synthesized amide derivatives (**6a** – **e**, **7a** and **8**) in good yields (Scheme 6). Table 1 shows the angles of specific rotation for all new products we obtained.

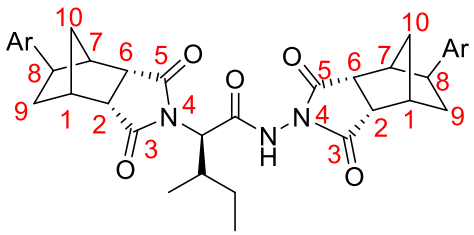
It was expected that during the reaction a mixture of diastereomers would be formed as **5** has two alkene subunits (Scheme 6). In each case an excess of the arylating agent was used. From the results presented in Scheme 6 it is apparent that the more reactive alkene is the one in the norbornene system proximal to the *N*,*N*-succinoylhydrazide functionality since the product composition **6a** and **7a** indicates that the bis-arylation succeeds the mono-arylation at the more reactive double bond. At this time, and without computational work, it would be speculative to assess the relative reactivities at the two double bonds. However, the origin is most likely an electronic one, i.e., it would not be unreasonable to argue that the norbornene system carrying the *N*,*N*-succinoylhydrazide moiety is somewhat more electron-rich than the other nornbornene double bond. Computational modeling studies are under way to address this interesting aspect of regioselectivity. The structure of the N-N-cleavage product **8,** which was obtained during the course of the attempted hydroarylation reaction of **5** with difluoroiodobenzene, helped us to determine where the first aryl group was located (Scheme 6). A structural proof by X-ray crystallography was not yet possible due to a missing single crystal.

Table 1. Bistricyclic amide derivatives **4, 5** and **6a** – **9b** produced via hydroarylation reaction

Compound	Aryl iodide	Yield %	Specific Optical Rotation $[\alpha]^{22}_{D}$ (CH_2Cl_2)	Appearance
4	-	94	-7.5° (c: 0.013 g/mL)	creamy solid
5	-	80	+12.2° (c: 0.009 g/mL)	creamy solid
6a	1-iodobenzene	85	+13.8° (c: 0.010 g/mL)	colorless oil
6b	4-chloro-1-iodobenzene	75	+25.0° (c: 0.026 g/mL)	white oil
6c	4-morpholino-1-iodobenzene	85	+15.0° (c: 0.010 g/mL)	white solid
6d	2-iodothiophene	85	+11.0° (c: 0.010 g/mL)	brown oil
6e	3-bromomethyl-1-iodobenzene	70	+11.4° (c: 0.010 g/mL)	colorless oil
7a	1-iodobenzene	85	+14.6° (c: 0.012 g/mL)	colorless oil
8	3,4-difluoro-1-iodobenzene	80	+4.0° (c: 0.010 g/mL)	yellow oil
9a	1-iodobenzene	75	+25.0° (c: 0.003 g/mL)	yellow oil
9b	4-chloro-1-iodobenzene	75	+23.0° (c: 0.010 g/mL)	yellow oil



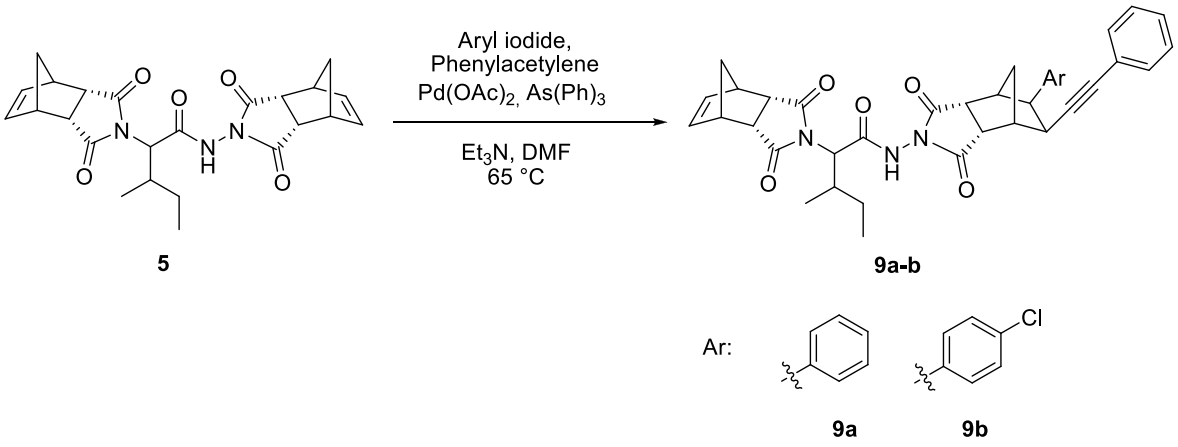
Scheme 6. Synthesis of compounds **6a-e, 7a** and **8**.



Scheme 7. Numbering of title compounds.

The *exo*-stereochemistry for each hydroarylation product was inferred from the ^{1}H NMR spectra including diagnostic spin-spin interactions. The *exo*-position of the C-8 substituent was confirmed by the fact that H_{8n} showed no significant interaction with H_1. The geminal protons on C-9 were identified by vicinal coupling to H_1. Additionally, ^{1}H–^{1}H-COSY spectra showed cross peaks between H_2 and H_6 and between H_8 and H_9, respectively. The presence of alkenic hydrogens in the ^{1}H NMR spectrum of compound **7a** shows that it undergoes hydroarylation on one side. In addition to the ^{13}C NMR and FTIR spectral data which were in agreement with the proposed structures, LC-MSMS (Qtof) results of all new compounds showed the expected accurate mass with hydrogen additions.

Domino-Heck arylation conditions were also successfully applied to the reaction of **5** with 1-iodobenzene and 4-chloro-1-iodobenzene together with phenylacetylene to give the new *exo*-alkynylated norbornyl substituted amide derivatives (**9a** and **9b**) in good yields, respectively (Scheme 8). The reactions were repeated many times, obtaining the same results. It was determined that during the determination of structures of these products, the arylation reagents were attached from the single alkenic side as compound **7a**. The absence of H_{9x} hydrogens in the proton NMR spectrum of the compounds indicates that phenyl acetylene is also bound from the *exo*-position. In addition, the structures are confirmed with the observation of alkyne carbons in the carbon NMR spectrum at the expected site.



Scheme 8. Synthesis of compounds **9a, b**.

Conclusions

New bistricyclic amide derivatives (**5, 6a** – **e, 7a)** and acyl chloride derivative **4** have been synthesized and extensively characterized by the use of spectroscopic studies such as FTIR, ^{1}H NMR, ^{13}C NMR, GC-MS and LC-MSMS/QTOF analyses. Regioselective (Domino) Heck reactions of compound **5** were also studied, leading to

the two new alkyne substituted derivatives **9a** and **9b**. These compounds should have the potential to show various microbiological activities due to their substructures aryl groups, the leucine chain, amide and imide groups.

Experimental Section

General. The solvents were dried by standard procedures. Reactions were monitored using TLC. Visualizations of the chromatograms were performed with UV light, $KMnO_4$ or Vanillin stain. All melting points are uncorrected and were determined on a Gallenkamp digital thermometer. IR spectra were obtained with a Perkin Elmer FT-IR system and are reported in terms of the frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III-500 MHz NMR spectrometer relative to tetramethylsilane, with coupling constant (*J*) values in Hertz (Hz). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; br, broad; p, pentet; and hept, heptet. Mass spectra were measured on an Agilent 6890N/5973 GC/IMSD system. High-resolution mass spectra were acquired in the positive ion mode using an Agilent G6530B TOF/Qtof Mass spectrometer. Optical rotations were measured with Bellingham Stanley ADP-410 Polarimeter. All crude compound mixtures were purified with Teledyne Isco CombiFlash Rf 200 system and RediSep Rf Gold Silica columns (4 g).

2-(4-Azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methyl pentanoyl chloride (**4**)**.** A solution of oxalyl chloride (507 mg, 4.00 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise 2-(4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanoic acid (**3**) (454 mg, 2.00 mmol) in dry CH_2Cl_2 (5 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight. The organic phase was concentrated and washed with diethyl ether. The compound **4** was obtained as a crème solid, yield 472.8 mg (94%), mp 50-52 °C, $[\alpha]_D^{22}$ -7.5° (*c* 0.013, CH_2Cl_2), R_f: 0.17 (ethyl acetate/*n*-hexane 4:1), FTIR (ATR) *v* 2967, 2936, 2876, 1747 (C=O), 1674 (C=O), 1463, 1384, 1336, 1185, 1120, 1048; ^1H NMR ($CDCl_3$, 500 MHz) *δ* 0.76 (t, *J* 7.25 Hz, 3H, CH_3), 0.88 (p, *J* 7.25 Hz, 1H, CH_2), 0.94 (d, *J* 6.62 Hz, 3H, CH_3), 1.32-1.37 (m, 1H, CH_2), 1.50 (d, *J* 8.51 Hz, 1H, H_{10a}), 1.69 (d, *J* 8.82 Hz, 1H, H_{10s}), 2.19-2.23 (m, 1H, CH), 3.27 (brs, 2H, H_1, H_7), 3.35 (brs, 2H, H_2, H_6), 4.33 (d, *J* 7.88 Hz, 1H, CH), 6.06 (brs, 2H, =CH); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 9.8 (CH_3), 15.5 (CH_3), 24.6 (CH_2), 32.8 (CH), 44.0 (CH), 44.2 (CH), 44.8 (CH), 44.9 (CH), 51.5 (CH_2), 56.3 (CH), 133.4 (=CH), 133.9 (=CH), 171.8 (C=O), 176.3 (C=O), 176.4 (C=O); GC-MS (EI, 70 eV) calculated for [$C_{15}H_{18}ClNO_3$] *m/z* 295.5 $(M)^+$, found 295 $(M)^+$, 261 (M^+-Cl), 245 ($C_{14}H_{15}NO_3$), 203 ($C_{11}H_9NO_3$), 91 (C_7H_8), 66 (C_5H_6), 54 (C_4H_6).

***N*-4-Azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl-2-(4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**5**)**.** A solution of *N*-aminobicyclo[2.2.1]hept-8-ene-2-*endo*, 6-*endo*-carboxiimide (**2**) (356 mg, 2.00 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to 2-(4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanoyl chloride (**4**) (591 mg, 2.00 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight. The organic phase was concentrated and the oily residue was washed with diethyl ether. The compound **5** was obtained as a crème yellow solid, yield 699.2 mg (80%), mp 193-195 °C, $[\alpha]_D^{22}$ +12.2° (*c* 0.009, CH_2Cl_2), R_f: 0.42 (ethyl acetate/*n*-hexane 5:1), FTIR (ATR) *v* 3328 (NH), 2972, 2950, 1765, 1716 (C=O), 1686 (C=O), 1401, 1384, 1336, 1196; ^1H NMR ($CDCl_3$, 500 MHz) *δ* 0.82 (t, *J* 7.25 Hz, 3H, CH_3), 0.97 (p, *J* 7.25 Hz, 1H, CH_2), 1.07 (d, *J* 6.93 Hz, 3H, CH_3), 1.27-1.31 (m, 1H, CH_2), 1.55 (d, *J* 7.88 Hz, 2H, H_{10a}), 1.77 (d, *J* 8.82 Hz, 2H, H_{10s}), 2.53-2.60 (m, 1H, CH), 3.34 (d, *J* 12.9 Hz, 4H, H_2 and H_6), 3.42 (s, 4H, H_1 and H_7), 4.34 (d, *J*

11.98 Hz, 1H, CH), 6.17 (dd, *J* 2.20;5.67 Hz, 1H, =CH), 6.19 (s, 2H, =CH), 6.34 (dd, *J* 2.20;5.67 Hz, 1H, =CH), 8.87 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.8 (CH_3), 15.1 (CH_3), 25.1 (CH_2), 32.0 (CH), 44.2 (CH), 44.3 (CH), 44.9 (2×CH), 45.2 (CH), 45.4 (CH), 45.6 (CH), 45.7 (CH), 51.8 (CH_2), 52.2 (CH_2), 60.8 (CH), 134.4 (=CH), 134.7 (=CH), 134.8 (=CH), 135.2 (=CH), 166.4 (C=O), 173.4 (2×C=O), 177.8 (C=O), 179.0 (C=O); HRMS (ESI): calcd for [$C_{24}H_{27}N_3O_5$] ([M]$^+$): *m/z* 437.4883, found 438.2022 [M+H]$^+$.

General procedure for the synthesis of compounds 6a-e, 7a and 8. A solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Ph_3As (67.5 mg, 0.22 mmol) in dry DMF (3 mL) was stirred in a Schlenk flask under nitrogen atmosphere at 65 °C for 15 min to form the catalyst complex. Then, aryl iodide (3.00 mmol), compound **5** (437 mg, 1.00 mmol), Et_3N (708 mg, 7.00 mmol), and HCOOH (0.226 mL, 6.00 mmol) were added. The mixture was heated to 65 °C for 24–48 h. After cooling to room temperature, brine (50 mL) was added, and the mixture was extracted with AcOEt. The aqueous layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography or flash chromatography.

***N*-[8-Phenyl-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl] 2-(8-phenyl-4-azabicyclo[2.2.1]-heptane-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**6a**)**.** Colorless oil, yield 504 mg (85%), $[\alpha]_D^{22}$ +13.8° (*c* 0.010, CH_2Cl_2), R_f: 0.32 (ethyl acetate/*n*-hexane 1:1), FTIR (ATR) *v* 3283 (NH), 3003, 2968, 2966, 2950, 1728 (C=O), 1704 (C=O), 1494, 1454, 1381, 1136 1076; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, *J* 7.25 Hz, 3H, CH_3), 1.03 (p, *J* 7.25 Hz, 1H, CH_2), 1.10 (d, *J* 6.62 Hz, 3H, CH_3), 1.28-1.35 (m, 1H, CH_2), 1.56 (d, *J* 10.08 Hz, 2H, H_{10a}), 1.69-1.78 (m, 2H, CH_2), 1.87 (d, *J* 10.08 Hz, 2H, H_{10s}), 2.08-2.19 (m, 1H, CH_2), 2.67-2.73 (m, 1H, CH_2), 2.82 (brs, 1H, H_1), 2.86 (brs, 3H, H_1 and H_7), 2.92-2.95 (m, 2H, H_{8n}), 3.08-3.12 (m, 1H, CH), 3.16-3.19 (m, 3H, H_2), 3.24-3.28 (m, 1H, H_6), 4.54 (d, *J* 11.98 Hz, 1H, CH), 7.09-7.14 (m, 5H, H_{ar}), 7.17-7.22 (m, 5H, H_{ar}), 9.08 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.0 (CH_3), 14.3 (CH_3), 24.4 (CH_2), 28.7 (CH_2), 31.0 (CH), 31.2 (CH), 31.8 (CH_2), 32.6 (CH_2), 38.3 (CH_2), 38.8 (CH), 39.1 (CH), 40.7 (CH), 44.2 (CH), 45.3 (CH), 46.0 (CH), 47.0 (CH), 47.2 (CH), 47.6 (CH), 60.1 (CH), 124.8 (C_{ar}), 125.0 (C_{ar}), 125.8 (C_{ar}), 125.9 (C_{ar}), 126.0 (C_{ar}), 126.1 (2×C_{ar}), 127.4 (C_{ar}), 127.4 (C_{ar}), 127.5 (C_{ar}), 143.5 (C_q), 143.7 (C_q), 165.8 (C=O), 165.9 (C=O), 166.1 (C=O), 172.9 (C=O), 173.0 (C=O); HRMS (ESI): calcd for [$C_{36}H_{39}N_3O_5$] ([M]$^+$): *m/z* 593.7120, found 594.2964 [M+H]$^+$.

***N*-[8-(4-Chlorophenyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl]-2-(8-(4-chlorophenyl-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**6b**)**.** White oil, yield 496.5 mg (75%), $[\alpha]_D^{22}$ +25.0° (*c* 0.026, CH_2Cl_2), R_f: 0.42 (ethyl acetate/*n*-hexane 3:1), FTIR (ATR) *v* 3328 (NH), 3003 , 2971, 2879, 1730, 1705 (C=O), 1694 (C=O), 1493, 1402, 1337, 1190, 1135; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.79 (t, *J* 7.25 Hz, 3H, CH_3), 0.94 (p, *J* 7.25 Hz, 1H, CH_2), 1.08 (d, *J* 6.62 Hz, 3H, CH_3), 1.24-1.30 (m, 1H, CH_2), 1.46 (d, *J* = 10.08 Hz, 2H, H_{10a}), 1.61-1.70 (m, 2H, CH_2), 1.78 (d, *J* 10.08 Hz, 2H, H_{10s}), 1.97-2.12 (m, 1H, CH_2), 2.61-2.67 (m, 1H, CH_2), 2.68 (brs, 1H, H_1), 2.77 (brs, 3H, H_1, H_7), 2.84-2.92 (m, 2H, H_{8n}), 2.98-3.04 (m, 1H, CH), 3.06-3.16 (m, 3H, H_2), 3.22-3.24 (m, 1H, H_6), 4.47 (d, *J* 11.98 Hz, 1H, CH), 6.95-7.05 (m, 4H, H_{ar}), 7.09-7.15 (m, 4H, H_{ar}), 9.05 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.0 (CH_3), 15.3 (CH_3), 25.3 (CH_2), 32.1 (CH), 33.5 (CH_2), 39.2 (CH_2), 39.4 (CH_2), 39.8 (CH), 39.9 (CH_2), 40.1 (CH), 41.1 (CH), 44.9 (CH), 45.4 (CH), 46.3 (CH), 46.9 (CH), 47.8 (CH), 48.1 (CH), 48.4 (CH), 61.0 (CH), 128.2 (C_{ar}), 128.3 (C_{ar}), 128.4 (2×C_{ar}), 128.5 (2×C_{ar}), 128.6 (2×C_{ar}), 131.7 (2×C_q), 143.2 (2×C_q), 166.9 (C=O), 167.0 (C=O), 173.7 (C=O), 173.8 (C=O), 174.0 (C=O); HRMS (ESI): calcd for [$C_{36}H_{37}Cl_2N_3O_5$] ([M]$^+$): *m/z* 662.6021, found 662.2189 [M+H]$^+$.

***N*-[8-Morpholino-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl]-2-(8-morpholino-4-aza-bicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**6c**)**.** White solid, yield 648.5 mg (85%), mp 191-193 °C, $[\alpha]_D^{22}$ +15.0° (*c* 0.010, CH_2Cl_2), R_f: 0.49 (ethyl acetate/*n*-hexane 6:1), FTIR (ATR) *v* 3200 (NH), 3010, 2967, 2880, 1727 (C=O), 1699 (C=O), 1494, 1470, 1439, 1381, 1182, 1137; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, *J* 7.25 Hz, 3H, CH_3), 1.08-1.14 (p, *J* 7.25 Hz, 1H, CH_2), 1.18 (d, *J* 6.62 Hz, 3H, CH_3), 1.37-1.43 (m, 1H, CH_2), 1.54 (d, *J* 9.14 Hz, 1H, H_{10a}), 1.61 (d, *J* 10.08 Hz, 1H, H_{10a}), 1.76- 1.86 (m, 2H, CH_2), 1.90-1.97 (m,

2H, H_{10s}), 2.12-2.30 (m, 2H, CH_2), 2.75-2.79 (m, 1H, CH), 2.80-2.84 (m, 1H, H_{8n}), 2.89-2.98 (m, 5H, H_1, H_7, H_{8n}), 3.13 (brd, *J* 4.72 Hz, 8H, CH_2), 3.22-3.26 (m, 3H, H_2, H_6), 3.31-,3.34 (m, 1H, H_6), 3.87 (brd, *J* 4.09 Hz, 8H, CH_2), 4.60 (d, *J* 11.98 Hz, 1H, CH), 6.83-6.86 (m, 4H, H_{ar}), 7.10-7.15 (m, 4H, H_{ar}), 9.29 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 10.1 (CH_3), 15.3 (CH_3), 25.4 (CH_2), 32.0 (CH), 32.3 (CH), 33.1 (CH_2), 33.4 (CH_2), 39.5 (CH_2), 39.8 (CH), 39.9 (CH_2), 40.6 (CH), 41.0 (CH), 45.4 (CH), 46.5 (CH), 47.0 (CH), 48.1 (CH), 48.2 (CH), 48.7 (CH), 49.6 (4×CH_2), 61.2 (CH), 66.9 (4×CH_2), 115.7 (4×C_{ar}), 127.8 (4×C_{ar}), 136.4 (2×C_q), 149.4 (2×C_q), 166.9 (C=O), 167.0 (C=O), 167.1 (C=O), 174.0 (C=O), 174.1 (C=O); HRMS (ESI): calcd for [$C_{44}H_{53}N_5O_7$] ([M]$^+$): *m/z* 763.9209, found 764.4006 [M+H]$^+$.

***N*-[8-(2-Thienyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl]-2-(8-(2-thienyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**6d**)**.** Brown oil, yield 514.8 mg (85%), [α]$_D^{22}$ +11.0° (*c* 0.010, CH_2Cl_2), R_f: 0.43 (ethyl acetate/*n*-hexane 1:1), FTIR (ATR) *v* 3282 (N-H), 3010, 2967, 2880, 1727 (C=O), 1699 (C=O), 1494, 1470, 1430, 1381, 1182, 1137; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.91 (t, *J* 7.25 Hz, 3H, CH_3), 1.10 (p, *J* 7.25 Hz, 1H, CH_2), 1.18 (d, *J* 6.93 Hz, 3H, CH_3), 1.35-1.41 (m, 1H, CH_2), 1.60 (d, *J* 8.82 Hz, 1H, H_a), 1.67 (d, *J* 10.4 Hz, 1H, H_a), 1.82-1.91 (m, 2H, CH_2), 1.98-2.05 (m, 2H, CH_2), 2.06-2.09 (m, 1H, H_s), 2.18-2.26 (m, 1H, H_s), 2.75-2.80 (m, 1H, CH), 2.91-2.99 (m, 4H, H_1 and H_7), 3.06-3.10 (m, 1H, H_{8n}), 3.18-3.19 (m, 1H, H_{8n}), 3.21-3.28 (m, 3H, H_2 and H_6), 3.30-3.34 (m, 1H, H_6), 4.58 (d, *J* 11.98 Hz, 1H, CH), 6.77-6.81 (m, 1H, H_{ar}), 6.84-6.86 (m, 1H, H_{ar}), 6.89-6.93 (m, 2H, H_{ar}), 7.11-7.15 (m, 2H, H_{ar}), 9.23 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.9 (CH_3), 15.3 (CH_3), 20.7 (CH), 25.4 (CH_2), 32.1 (CH), 34.9 (CH_2), 35.5 (CH_2), 37.7 (CH), 38.1 (CH), 39.5 (CH), 39.6 (CH_2), 39.8 (CH), 40.3 (CH_2), 46.2 (CH), 46.6 (CH), 46.9 (CH), 47.9 (CH), 48.3 (CH), 60.9 (CH), 123.1 (C_{ar}), 123.2 (C_{ar}), 123.6 (C_{ar}), 123.7 (C_{ar}), 126.7 (C_{ar}), 126.8 (C_{ar}), 149.3 (C_q), 149.5 (C_q), 166.9 (C=O), 167.0 (C=O), 173.7 (C=O), 173.9 (C=O), 176.3 (C=O); HRMS (ESI): calcd for [$C_{32}H_{35}N_3O_5S_2$] ([M]$^+$): *m/z* 605.7674, found 606.2095 [M+H]$^+$.

***N*-[8-(3-Bromomethylphenyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl] 2-(8-(3-bromomethylphenyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**6e**)**.** Colorless oil, yield 545.3 mg (70%), [α]$_D^{22}$ +11.4° (*c* 0.010, CH_2Cl_2), R_f: 0.70 (ethyl acetate/*n*-hexane 1:1), FTIR (ATR) *v* 3270 (NH), 3056, 2964, 2878, 1704 (C=O), 1607, 1588, 1514, 1455, 1438, 1379, 1182, 1042; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.83 (t, *J* 7.25 Hz, 3H, CH_3), 1.00 (p, *J* 7.25 Hz, 1H, CH_2), 1.18 (d, *J* 7.25 Hz, 3H, CH_3), 1.29-1.35 (m, 1H, CH_2), 1.48-1.57 (m, 2H, H_{10a}), 1.69-1.75 (m, 2H, H_{10s}), 1.80-1.91 (m, 3H, H_9), 2.09-2.18 (m, 1H, H_9), 2.66-2.74 (m, 1H, CH), 2.77-2.82 (m, 1H, H_{8n}), 2.86 (brs, 2H, H_1), 2.91-2.94 (m, 2H, H_7), 3.08-3.11 (m, 1H, H_{8n}), 3.14-3.18 (m, 2H, H_2), 3.23-3.27 (m, 2H, H_6), 4.51 (d, *J* 11.98 Hz, 1H, CH), 5.09 (d, *J* 7.25 Hz, 4H, CH_2), 7.09-7.11 (m, 4H, H_{ar}), 7.16-7.19 (m, 2H, H_{ar}), 8.04 (d, *J* 4.04 Hz, 2H, H_{ar}), 9.12 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 10.0 (CH_3), 15.3 (CH_3), 25.4 (CH_2), 32.0 (CH), 32.9 (CH), 39.4 (CH_2), 39.8 (CH), 40.0 (CH_2), 40.1 (CH), 41.2 (CH), 41.4 (CH), 44.9 (CH), 45.2 (CH), 46.3 (CH), 46.9 (CH), 47.0 (CH), 48.1 (CH), 48.6 (CH), 61.0 (CH), 65.7 (CH_2), 65.8 (CH_2), 124.7 (C_{ar}), 126.0 (C_{ar}), 126.8 (C_{ar}), 127.0 (C_{ar}), 127.1 (C_{ar}), 127.3 (C_{ar}), 128.7 (C_{ar}), 128.8 (C_{ar}), 135.2 (C_q), 145.3 (C_q), 145.4 (C_q), 160.7 (C_q), 166.9 (C=O), 167.0 (C=O), 173.8 (C=O), 173.9 (C=O), 174.1 (C=O); HRMS (ESI): calcd for [$C_{38}H_{41}Br_2N_3O_5$] ([M]$^+$): *m/z* 779.1319, 780.1599 found [M+H]$^+$.

***N*-[8-Phenyl-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl]-2-(4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**7a**)**.** Colorless oil, yield 438.26 mg (85%), [α]$_D^{22}$ +14.6° (*c* 0.012, CH_2Cl_2), R_f: 0.30 (ethyl acetate/*n*-hexane 1:1), FTIR (ATR) *v* 3283 (N-H), 3010, 2968, 2810, 1727 (C=O), 1703 (C=O), 1494, 1383, 1184, 1136; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (t, *J* 7.25 Hz, 3H, CH_3), 0.90 (p, *J* 6.62 Hz, 1H, CH_2), 1.03 (d, *J* 6.62 Hz, 3H, CH_3), 1.21-1.27 (m, 1H, CH_2), 1.49 (d, *J* 8.82 Hz, 2H, H_{10a}), 1.57-1.64 (m, 1H, CH_2), 1.69 (d, *J* 8.82 Hz, 1H, H_{10s}), 1.74-1.75 (m, 1H, CH_2), 1.85 (d, *J* 10.4 Hz, 1H, H_{10s}), 2.51-2.57 (m, 1H, CH), 2.84 (brd, *J* 4.41 Hz, 1H, H_1), 2.88 (brd, *J* 5.67 Hz, 1H, H_1), 3.08-3.10 (m, 1H, H_7), 3.14-3.16 (m, 1H, H_7), 3.21-3.24 (m, 1H, H_{8n}), 3.29- 3.30 (m, 2H, H_2), 3.35-3.37 (m, 2H, H_6), 4.32 (d, *J* 11.98 Hz, 1H, CH), 6.13 (dd, *J*

2.83; 5.67 Hz, 1H, =CH), 6.30 (brs, 1H, =CH), 7.07-7.13 (m, 2H, H_{ar}), 7.27-7.30 (m, 3H, H_{ar}), 9.01 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.8 (CH_3), 15.2 (CH_3), 25.2 (CH_2), 32.2 (CH), 33.2 (CH_2), 39.4 (CH_2), 39.9 (CH), 41.3 (CH), 45.2 (CH), 45.4 (CH), 45.6 (CH), 45.8 (CH), 46.5 (CH), 47.0 (CH), 47.1 (CH), 52.3 (CH_2), 60.9 (CH), 125.9 (C_{ar}), 127.0 (2×C_{ar}), 128.4 (2×C_{ar}), 134.5 (=CH), 135.3 (=CH), 144.7 (C_q), 166.9 (C=O), 174.2 (C=O), 174.3 (C=O), 177.9 (C=O), 179.1 (C=O); HRMS (ESI): calcd for [$C_{30}H_{33}N_3O_5$] ([M]$^+$): *m/z* 515.6000, found 516.2484 [M+H]$^+$.

8-(3,4-Difluorophenyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide (**8**)**.** Yellow oil, yield 220.8 mg (80%), $[\alpha]_D^{22}$ +4.0° (*c* 0.010, CH_2Cl_2), R_f: 0.36 (ethyl acetate/*n*-hexane 5:1), FTIR (ATR) *v* 3305 (N-H), 2972, 1704 (C=O), 1665 (C=O), 1609, 1519, 1477, 1179, 1125 (C-N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 (d, *J* 9.14 Hz, 1H, H_{10a}), 1.69-1.72 (m, 2H, H_{9n} and $H9_x$), 1.76 (d, *J* 10.4 Hz, 1H, H_{10s}), 2.65 (dt, *J* 6.93 Hz, 1H, H_{8n}), 2.79 (d, *J* 5.04, 1H, H_1), 2.86 (brs, 1H, H_7), 3.09 (dd, *J* 1.87; 5.04 Hz, 1H, H_2), 3.14 (dd, *J* 5.35; 9.45 Hz, 1H, H_6), 4.19 (brs, 1H, NH), 6.79-6.82 (m, 1H, H_{ar}), 6.90 (ddt, *J* 2.20; 7.56; 9.77 Hz, 1H, H_{ar}), 6.99 (dd, *J* 8.19; 10.08 Hz, 1H, H_{ar}); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.9 (CH_2), 39.1 (CH_2), 39.4 (CH), 41.1 (CH), 45.3 (CH), 46.5 (CH), 47.1 (CH), 115.9 (C_{ar}), 117.2 (C_{ar}), 122.9 (C_{ar}), 141.3 (C_q), 147.7 (C_q), 149.7 (C_q), 174.8 (C=O), 174.9 (C=O); GC-MS (EI, 70 eV) calculated for [$C_{15}H_{13}F_2NO_2$] *m/z* 276 (M)$^+$, found 276 (M$^+$), 206 ($C_{13}H_{14}F_2$), 164 (M$^+$-$C_6H_4F_2$), 114 ($C_6H_4F_2$).

General procedure for the synthesis of compound 9a and 9b. A solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Ph_3As (67.5 mg, 0.22 mmol) in dry DMF (3 mL) was stirred in a Schlenk flask under nitrogen atmosphere at 65 °C for 15 min to form the catalyst complex. Then, aryl iodide (3.00 mmol), compound **5** (437 mg, 1.00 mmol), phenylacetylene (612 mg, 6.00 mmol), and Et_3N (708 mg, 7.00 mmol) were added. The mixture was heated to 65 °C for 24–48 h. After cooling to room temperature, brine (50 mL) was added, and the mixture was extracted with AcOEt. The aqueous layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography or flash chromatography.

***N*-[9-Phenylethynl-8-phenyl-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl]-2-(4-azabicyclo-[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**9a**). Yellow oil, yield 461.7 mg (75%), $[\alpha]_D^{22}$ +25.0° (*c* 0.003, CH_2Cl_2), R_f: 0.28 (ethyl acetate/*n*-hexane 1:1), FTIR (ATR) *v* 3200 (NH), 3010, 2968, 2900, 2861, 1726 (C=O), 1700 (C=O), 1512 (C=C), 1470, 1440, 1381, 1183, 1137; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (t, *J* 7.25 Hz, 3H, CH_3), 0.92 (p, *J* 7.25 Hz, 1H, CH_2), 1.04 (d, *J* 6.62 Hz, 3H, CH_3), 1.23-1.27 (m, 1H, CH_2), 1.48-1.53 (m, 2H, H_{10a}), 1.68-1.72 (m, 2H, H_{10s}), 2.45 (d, *J* 10.71 Hz, 1H, H_8), 2.52-2.58 (m, 1H, CH), 2.99 (d, *J* 5.67 Hz, 1H, H_9), 3.11-3.19 (m, 4H, H_1, H_7), 3.29-3.31 (m, 2H, H_2, H_6), 3.36-3.40 (m, 2H, H_2, H_6), 4.38 (d, *J* 11.98 Hz, 1H, CH), 6.12 (dd, *J* 3.15;5.67 Hz, 1H, =CH), 6.29-6.32 (m, 1H, =CH), 6.72 (d, *J* 6.62 Hz, 2H, H_{ar}), 7.02-7.07 (m, 3H, H_{ar}), 7.12 (t, *J* 6.93 Hz, 1H, H_{ar}), 7.16-7.18 (m, 2H, H_{ar}), 7.21 (d, *J* 7.25 Hz, 2H, H_{ar}), 9.07 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.8 (CH_3), 15.2 (CH_3), 25.2 (CH_2), 32.2 (CH), 38.1 (CH), 40.2 (CH_2), 43.5 (CH), 45.2 (CH), 45.4 (CH), 45.6 (CH), 45.7 (CH), 45.8 (CH), 46.4 (CH), 47.3 (CH), 47.4 (CH), 52.3 (CH_2), 60.8 (CH), 85.4 (C≡C), 89.7 (C≡C), 126.1 (C_{ar}), 127.4 (C_{ar}), 127.9 (4×C_{ar}), 128.3 (2×C_{ar}), 131.3 (2×C_{ar}), 134.5 (=CH), 135.3 (=CH), 140.9 (C_q), 141.1 (C_q), 167.0 (2×C=O), 167.1 (2×C=O), 173.6 (C=O); HRMS (ESI): calcd for [$C_{38}H_{37}N_3O_5$] ([M]$^+$): *m/z* 615.7175, found 616.2804 [M+H]$^+$.

***N*-[9-Phenylethynl-8-(4-chlorophenyl)-4-azabicyclo[2.2.1]heptane-3-*endo*,5-*endo*-dicarboximide-4-yl]-2-(4-azabicyclo[2.2.1]hept-8-ene-3-*endo*,5-*endo*-dicarboximide-4-yl)-3-methylpentanamide** (**9b**)**.** Yellow oil, yield 486.9 mg (75%), $[\alpha]_D^{22}$ +23.0° (*c* 0.010, CH_2Cl_2), R_f: 0.31 (ethyl acetate/*n*-hexane 1:1), FTIR (ATR) *v* 3275 (NH), 3010, 2967, 2880, 1727 (C=O), 1699 (C=O), 1494 (C=C), 1470, 1439, 1381, 1183 (C-O), 1043 (C-N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (t, *J* 7.56 Hz, 3H, CH_3), 0.86 (p, *J* 7.56 Hz, 1H, CH_2), 1.04 (d, *J* 6.93 Hz, 3H, CH_3), 1.10-1.14 (m, 1H, CH_2), 1.47-1.50 (m, 1H, H_{10a}), 1.67-1.70 (m, 2H, H_{10a}, H_{10s}), 1.74-1.79 (m, 1H, H_{10s}), 2.42 (d, *J* 10.71 Hz, 1H, H_{9n}), 2.97-3.01 (m, 1H, CH), 3.10-3.12 (m, 1H, H_{8n}), 3.16-3.19 (m, 2H, H_7), 3.24-3.27 (m, 2H, H_1), 3.28-3.31 (m, 2H, H_2), 3.35-3.37 (m, 2H, H_6), 4.36 (d, *J* 11.98 Hz, 1H, CH), 6.10-6.13 (m, 1H, =CH), 6.29-6.31 (m, 1H,

CH), 6.71 (d, *J* 6.62 Hz, 2H, H_{ar}), 7.02-7.07 (m, 3H, H_{ar}), 7.16-7.23 (m, 4H, H_{ar}), 9.07 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.7 (CH_3), 15.2 (CH_3), 20.6 (CH), 25.1 (CH_2), 32.1 (CH), 36.6 (CH), 38.0 (CH), 40.0 (CH_2), 43.4 (CH), 44.2 (CH), 44.9 (CH), 45.2 (CH), 45.6 (CH), 46.3 (CH), 47.1 (CH), 53.2 (CH_2), 60.7 (CH), 85.7 (C≡C), 89.0 (C≡C), 123.2 (C_q), 127.6 (C_{ar}), 127.9 (C_{ar}), 128.0 (C_{ar}), 129.6 (C_{ar}), 129.7 (C_{ar}), 131.2 (C_{ar}), 131.3 (C_{ar}), 132.0 (C_q), 134.4 (C_{ar}), 134.5 (C_{ar}), 134.8 (C_{ar}), 135.2 (C_{ar}), 139.5 (C_q), 167.1 (C=O), 173.4 (C=O), 173.5 (2xC=O), 175.4 (C=O); HRMS (ESI): calcd for [$C_{38}H_{36}ClN_3O_5$] ([M]$^+$): *m/z* 649.2343, found 650.2632 [M+H]$^+$.

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Supplementary Material

^{1}H NMR, ^{13}C NMR, IR, and MS data of all new compounds are available with the article through the journal Web site

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