Hydroarylation reactions of *N*-acylaminosubstituted tricyclic imides

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The palladium-catalysed hydroarylation of unsaturated *N*-acylamino-substituted tricyclic imides provided a new stereoselective synthesis of *exo*-aryl(heteroaryl)-substituted tricyclic *N*-acylamino imides.

Keywords: tricyclic imides, C–C coupling, heterocycles

Organopalladium-catalysed C–C bond formation has become one of the most efficient approaches to the synthesis of organic molecules. The Heck reaction, is widely used as an important method to build biologically active compounds in synthetic chemistry and the pharmaceutical industry.[1,2] As an extension of the Heck reaction, the Pd-catalysed hydroarylation of alkynes and alkenes continues to attract attention in simple coupling processes and cyclisation reactions.[3,4]

In the presence of triphenylarsine as a ligand,[5,6] palladium-catalysed hydroarylation (Fig. 1) of easily accessible unsaturated tricyclic *N*-substituted imides has been proven to be a stereoselective, versatile and high-yield approach to the synthesis of the corresponding aryl and heteroaryl derivatives.[7–11] We reported palladium(II) acetate catalysed asymmetric Heck-type hydroarylations of bicyclic and tricyclic alkenes such as epibatidine analogues, and their domino-Heck applications by treating them with aryl (or heteroaryl) iodides.[12,13] The products were evaluated for their antioxidant and radical scavenging activities.[14]

N-Substituted imides, such as maleimides,[15] isohematinic acids,[16] and especially bicyclic and tricyclic derivatives such as tandospirone derivatives[17,18] are known for their broad spectrum of pharmacological properties, showing antibiotic, fungicidal, analgesic, anxiolytic and cytostatic effects. The imide moiety is an integral structural part of various important bioactive molecules such as fumaramidemycin, granulatimide, isogranulatimide and rebeccamycin which are reported to exhibit antitumour, anti-inflammatory and antimicrobial activities.[19,20]

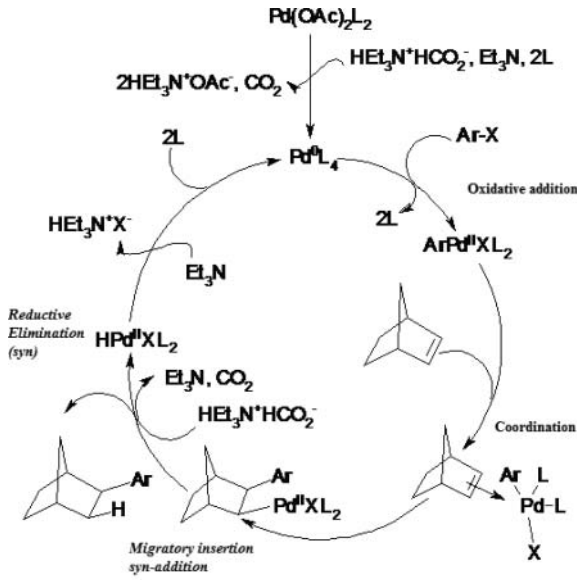

Fig. 1 The reductive Heck reactions cycle.

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Here, we focus on reductive Heck reactions of tricyclic imide molecules containing a strained C=C bond and having an acylamino group which might possess potential biological activity.

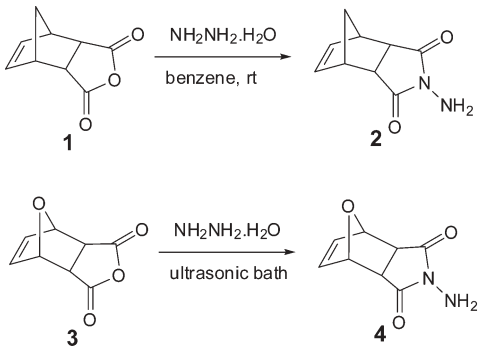
Results and discussion

Our synthesis started with the Diels–Alder reaction of cyclopentadiene or furan with maleic anhydride. Hydrazinolysis of anhydride **1** was carried out with hydrazine hydrate in benzene for 4 h to give *N*-aminobicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboximide **2**. We also synthesised *N*-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboximide (**4**) from **3** by a different method using an ultrasonic bath without any solvent (Scheme 1).

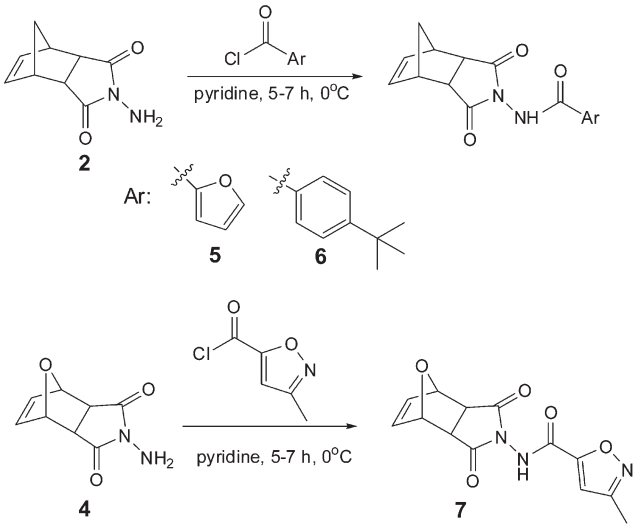
Tricyclic imide **2** reacted with 2-furoyl chloride in pyridine as a base to afford *N*-(2-furoylamino)bicyclo[2.2.1]hept-5-ene-2-*endo*-3-*endo*-dicarboximide (**5**). The same reaction was performed with p-ter*t*-butylbenzoyl chloride to give *N*-(4-*tert*-*butyl*benzoyl)aminobicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboximide (**6**). The tricyclic imide **4** also reacted with 3-methylisoxazole-5-carbonyl chloride to give *N*-(3-methylisoxazole-5-carbonyl)amino-7-oxabicyclo[2.2.1]-hept-5-ene-2-*exo*,3-*exo*-dicarboximide (**7**) (Scheme 2).

The presence of a strained C=C bond in the *N*-substituted aminoimides **5**, **6** and **7** provided the possibility for carrying out reductive Heck reactions with aryl(heteroaryl) iodides, in the presence of triphenylarsine ($AsPh_3$) as a ligand and palladium(II) acetate. Reaction of **5** and **6** with iodobenzene, 1-iodo-4-methoxybenzene, 2-chloro-5-iodopyridine and 2-iodothiophene under reductive Heck conditions gave the new compounds **8a–d** and **9a–d** as 5-*exo* products after chromatographic separation. We also synthesised **10a–f** as new 5-*exo* compounds from **7** with iodobenzene, 1-iodo-4-methoxybenzene, 2-chloro-5-iodopyridine, 2-iodothiophene, 4-chloro-1-iodobenzene and 5-iodo-3-methylisoxazole respectively, under the hydroarylation conditions (Scheme 3).

We selected 5-iodo-3-methylisoxazole and 2-chloro-5-iodopyridine as the arylation reagents because of the structural similarity of the products with epibatidine and epiboxidine[22,23] which are known to behave as a potent α4β2 nicotinic receptors.



Scheme 1 Preparations of **2** and **4**.



Scheme 2 Synthesis of tricyclic imides, **5**, **6** and **7**.

The configuration of the new compounds was inferred from their ^{1}H NMR and ^{1}H,^{1}H-COSY data. Due to the symmetry of **5**, **6** and **7**, after column chromatographic separation, we obtained single diastereoisomers. The *exo*-stereochemistry for each Heck product was inferred from ^{1}H NMR spectra including diagnostic spin–spin interactions. The *exo*-position of the C-5 substituent was confirmed by the fact that H_{5n} showed no significant interaction with H_1. The geminal protons on C-6 were identified by vicinal coupling to H_1. Therefore H_1 was observed as a doublet and H_4 observed as a singlet in the expected region. The NOESY spectra of **9b** is clearly showed cross peak between N–H and H_{5n} (Scheme 4). This is proof that they are in the same plane.

Additionally, ^{1}H–^{1}H-COSY spectra showed cross peaks between H_2–H_3 and H_5–H_6, respectively. In addition to the ^{13}C NMR and HSQC spectral data which were in agreement with the proposed structures and the mass spectra of all new compounds showed the expected molecular ion peaks (Table 1). Scheme 5 shows LCMS spectra of **10b** compounds.

Conclusions

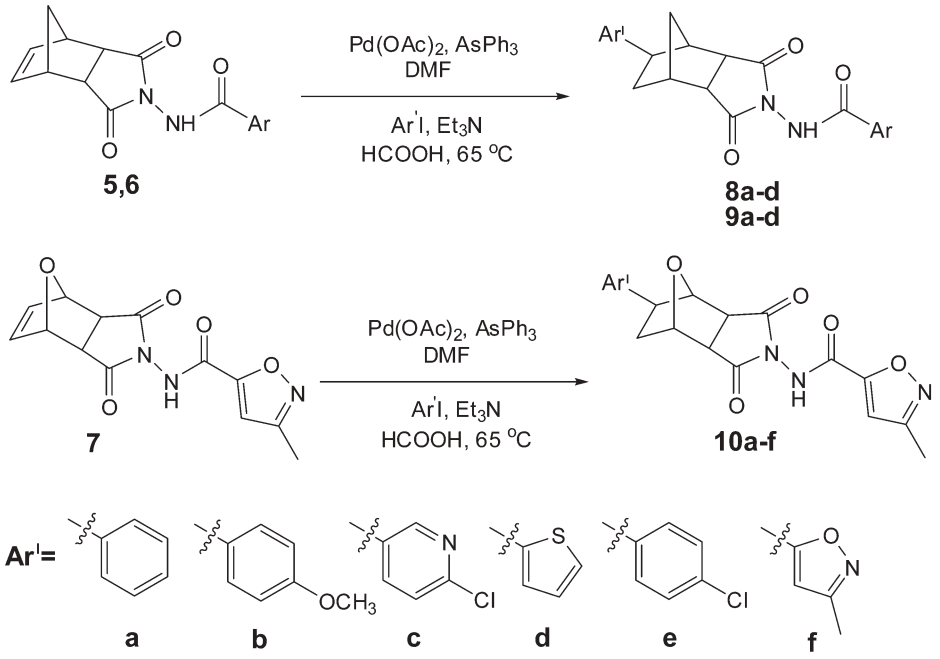
In summary, the [$Pd(OAc)_2$]-catalysed hydroarylation of the easily accessible tricyclic unsaturated *N*-(acylamino)-imides **5**, **6** and **7** in the presence of $AsPh_3$ as a ligand, proved to be a stereoselective, versatile and high-yield approach for the synthesis of the aryl and heteroaryl derivatives of imides. Moreover, Heck type hydroarylation reactions of the tricyclic unsaturated *N*-(acylamino)-imides (**5**, **6** and **7**) with aryl(hetaryl) iodides provide selectively the aryl and hetaryl derivatives of imides which could be a good candidate for the synthesis of potential biological active compounds. Our results showed that the different stereochemical functionality of starting compounds (*endo* or *exo tricyclic systems*) have yielded only *exo* coupling compounds due to Pd(II) acetate as catalytic.

Experimental

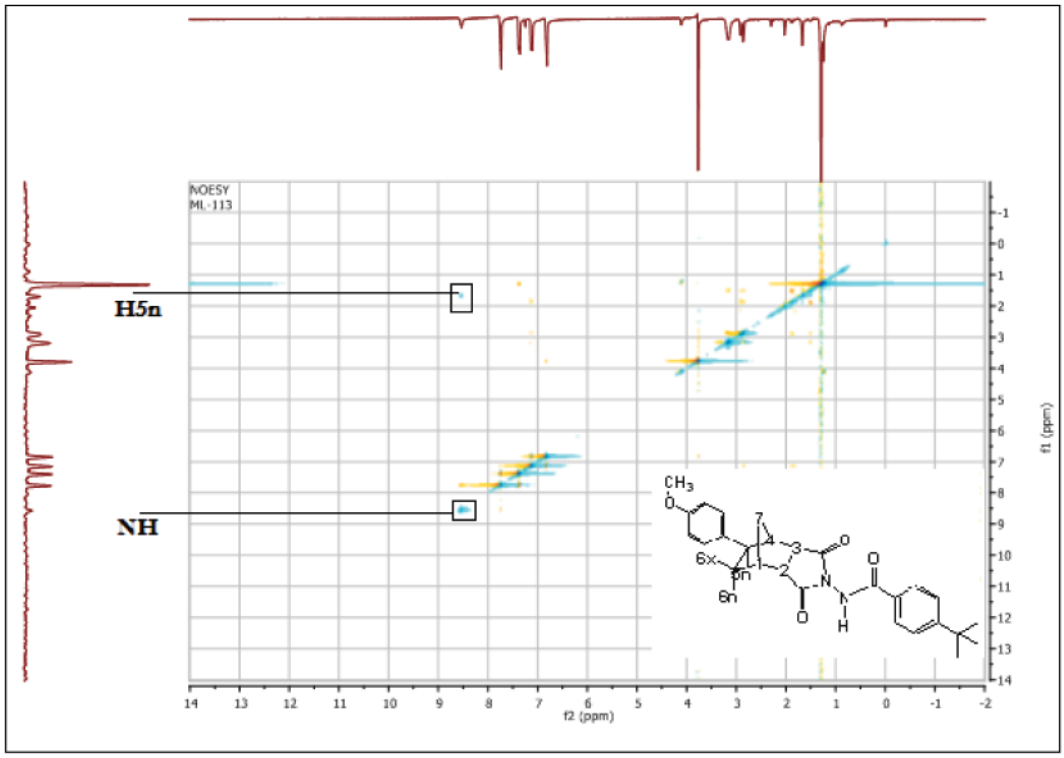
All the reactions were carried out under nitrogen atmosphere unless otherwise indicated. Reactions were monitored using TLC. Resulting residue was purified by silica gel chromatography with a solvent gradient of 2:1 (ethyl acetate/n-hexane) to afford the title compounds. IR spectra were obtained with a Perkin Elmer, FT-IR system and are reported in terms of frequency of absorption (cm^{-1}). Melting points were determined with a Gallenkamp digital thermometer equipment. All melting points are uncorrected. NMR spectra were determined with a "Bruker Ac-400 MHz NMR", and "Varian-INOVA-500 MHz NMR". NMR 2D experimental studies such as COSY, 2D-NOESY, HMBC, HSQC were measured with a Bruker Ac-400 MHz NMR. TMS (tetramethylsilane) was used an internal standard and $CDCl_3$ was used as the solvent. Signal multiplicities in the NMR spectra are reported as follows: s-singlet, brs-broad singlet, d-doublet, dd-doublet of doublets, m-multiplet. Mass spectra were measured with Agilent 6890N GC-System-5973 IMSD or Agilent LC-MSD Trap SL.

Synthesis of bicyclic carboximides **5–7***; typical procedure*

A mixture of **2** or **4** (1.00 mmol) and acyl chloride (1.00 mmol) (furan-2-carbonyl chloride, 4-*tert*-butyl-benzoyl chloride or 3-methylisoxazole-5-carbonyl chloride) in pyridine (5 mL), was stirring in an



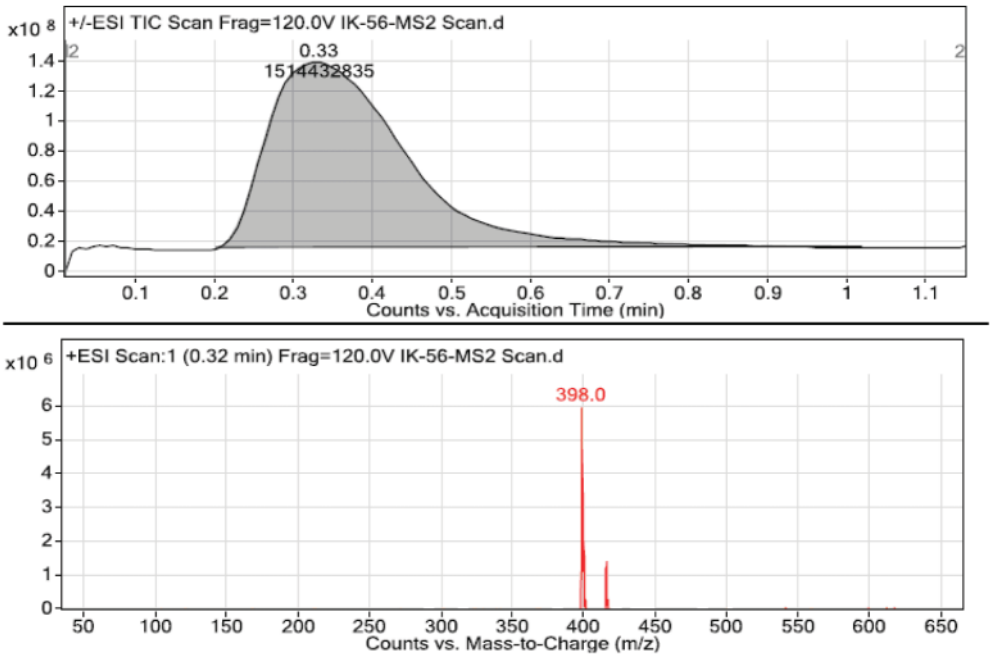
Scheme 3 Synthesis of new hydroarylation compounds.



Scheme 4 **9b** compound NOESY spectra.

Table 1 Some compounds ^{1}H NMR details

H_n	8d	9c	10e
H_{6x}	1.54, d, J = 9.8 Hz	1.63, d, J = 10.5 Hz	1.95, dt, J = 5.0; 10.4 Hz
H_{6n}	1.94, d, J = 9.8 Hz	1.83, d, J = 10.5 Hz	2.28, dd, J = 9.1; 12.9 Hz
H_{5n}	1.82 dt, J = 3.9, 13.6 Hz	1.77–1.73, m	3.05, dd, J = 5.0; 9.1 Hz
H_3 - H_2	3.12–3.17, m	3.24, dt, J = 8.5, 22.5 Hz	3.22, d, J = 7.2 Hz
H_1	2.22, d, J = 4.7 Hz	2.92, d, J = 4.8 Hz	5.10, d, J = 5.0 Hz
H_4	2.31, brs	2.97, brs	4.84, s



Scheme 5 **10b** compound LCMS spectra.

ice-bath for 5–7h under the nitrogen. The solvent was removed, the residue was treated with a mixture of chloroform with water, 1:1, the organic layer was washed in succession with water solution of hydrochloric acid, with saturated solution of sodium hydrogen carbonate, and with water. The organic layer was separated, dried with calcined magnesium sulfate, and the solvent was removed. The reaction product was recrystallised from 2-propanol.

N-(2-Furoylamino)bicyclo[2.2.1]hept-5-ene-2-endo,3-endo-dicarboximide (**5**): Colourless crystals, 65% yield; m.p. 138–141 °C; R_f = 0.42 (7:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3231, 3010, 2970, 2886, 1720, 1687, 1587, 1567, 1468, 1374, 1283, 1241, 1172, 754, 723 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.49 (d, *J* = 8.7 Hz, 1H, H_{7a}), 1.69 (d, *J* = 8.78 Hz, 1H, H_{7s}), 3.33 (bs, 2H, H_1 and H_4), 3.38 (bs, 2H, H_2 and H_3), 6.12 (s, 2H, H_5 and H_6), 6.41 (dd, *J* = 1.96; 5.37 Hz, 1H, H_{aro}), 7.10 (m, 1H, H_{aro}), 7.38 (d, *J* = 7.81 Hz, 1H, H_{aro}), 8.47 (s, 1H, NH, major), 8.71 (s, 1H, NH, minor) ppm; ^{13}C NMR (100 MHz) δ 44.3, 45.1, 51.8, 112.4, 115.6, 117.1, 134.8, 136.4 ($C_{subst.}$), 156.4 (C=O), 173.8 (2C, C=O) ppm; GC-MS for $C_{14}H_{12}N_2O_4$: 272 (M^+), 207, 95, 66; Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.56; H, 4.56; N, 10.39%.

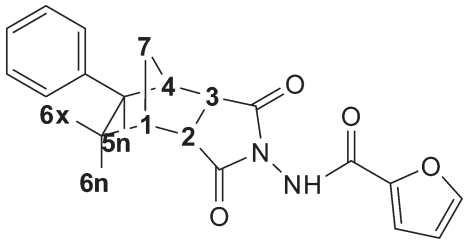
N-[(4-tert-Butyl)benzoylamino]bicyclo[2.2.1]hept-5-ene-2-endo,3-endo-dicarboximide (**6**): Colourless crystals, 65% yield; m.p. 137–142 °C; R_f=0.48 (7:1 ethyl acetate/*n*-hexane); FTIR(ATR): ν 3264, 3010, 2964, 2096, 2871, 1719, 1682,1671, 1609, 1525, 1493, 1463, 1406 νe 1365, 1273, 1189, 843 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.23 (s, 9H, *t*-butyl), 1.49 (d, *J* = 8.7 Hz, 1H, H_{7a}), 1.69 (d, *J* = 8.7 Hz, 1H, H_{7s}), 3.30 (bs, 2H, H_1 and H_4), 3.36 (bs, 2H, H_2 and H_3), 6.12 (s, 2H, H_5 and H_6), 7.32 (d, *J* = 8.7 Hz, 2H, H_{aro}), 7.65 (d, *J* = 8.7 Hz, 2H, H_{aro}), 8.20 (s, 1H, NH, major), 8.45 (s, 1H, NH, minor) ppm; ^{13}C NMR (100 MHz) δ 31.2, 35.1, 44.3, 44.9, 51.8, 125.6, 126.3, 127.8, 127.8 and 134.8 (2C, $C_{subst.}$), 156.4 (C=O), 174.2 (2C, C=O) ppm; GC-MS for $C_{20}H_{22}N_2O_3$: 338(M^+), 281, 207, 179, 161, 73; Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.22; H, 6.38; N, 8.49%.

N-[(3-Methylisoxazole-5-carbonyl)amino]-7-oxabicyclo[2.2.1]hept-5-ene-2-exo,3-exo-dicarboximide (**7**): Colourless crystals, 52% yield; m.p. 176 °C; R_f = 0.20 (2:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3307, 3169, 3009, 2960, 2916, 2849, 1798, 1733, 1706 1683, 1616, 1505, 1443, 1411, 1212, 1203, 1190, 1158 cm^{-1}; ^{1}H NMR (500 MHz) δ 2.13 (s, 3H, CH_3), 3.14 (s, 2H, H_2 and H_3), 5.44 (brs, 3H, H_1, H_4 and =CH), 6.38 (s, 2H, H_5 and H_6), 6.96 (brs, 1H, NH) ppm; ^{13}C NMR (125 MHz) δ 11.4, 46.6, 80.9, 109.9 (=CH), 131.8 and 134.2 (2C, C-sbst), 136.3, 153.7 (1C, C=O), 160.8 (1C, C=O), 172.1 (1C, C=O) ppm; GC-MS for $C_{13}H_{11}N_3O_5$: 289 (M^+), 264, 253, 246, 235, 223, 180, 166, 152, 137, 123, 110, 97, 83, 69, 55, 41; Anal. Calcd for $C_{12}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 54.06; H, 3.70; N, 14.24%.

Synthesis of arylated bicyclic carboximides; typical procedure

A solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and $AsPh_3$ (33.7 mg, 0.11 mmol) in dry DMF (3 mL) was stirred in a Schlenk flask under nitrogen at 65 °C for 15 min in order to form the catalyst complex. Then aryl or hetaryl iodides (1.5 mmol) and **5** (**6** or **7**) (1.00 mmol), triethylamine (354 mg, 3.5 mmol) and formic acid (138 mg, 3.0 mmol) were added. The mixture was heated to 65 °C for 28 h. After cooling down to rt, brine (50 mL) was added, the reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated, the residue purified by chromatography.

N-(2-Furoylamino)-5-exo-phenylbicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**8a**): Colourless crystals, 67% yield; m.p. 127 °C; R_f = 0.63 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3228, 3002, 2969, 2888, 1722, 1688, 1587, 1567, 1469, 1404, 1381, 1281, 1179, 757 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.17–1.21 (m, 1H, H_{7a}), 1.53 (d, *J* = 10.4 Hz, 1H, H_{7s}), 1.85–1.90 (m, 2H, H_{6x} and H_{5n}), 2.05 (d, *J* = 9.7 Hz, 1H, H_{6n}), 2.90–2.93 (m, 2H, H_1 and H_4) 3.21–3.28 (m, 2H, H_2 and H_3), 6.42 (dd, *J* = 5.2, 3.8 Hz, 1H, H_{aro}), 7.13 (d, *J* = 3.8 Hz, 1H, H_{aro}), 7.16–7.18 (m, 1H, H_{aro}), 7.21 (d, *J* = 8.7 Hz, 2H, H_{aro}), 7.27–7.30 (m, 1H, H_{aro}), 7.41 (d, *J* = 8.7 Hz, 2H, H_{aro}), 9.30 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 32.6, 39.2, 39.9, 41.6, 45.7, 46.4, 47.1, 112.3, 116.9, 126.1, 127.3, 127.1, 128.4, 144.9 and 145.6 (2C, C-sbst), 175.1 (1C, C=O), 175.4 (2C, C=O) ppm; GC-MS for $C_{20}H_{18}N_2O_4$: 350 (M^+), 270, 171, 95; Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.39; H, 5.39; N, 8.16%.



N-(2-Furoylamino)-5-exo-(4-methoxyphenyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**8b**): Colourless crystals, 69% yield; m.p. 125 °C; R_f = 0.60 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3239, 2965, 2932, 2885, 1720, 1688, 1587, 1567, 1467, 1405, 1282, 1178, 758 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.92–0.96 (m, 1H, H_{7a}), 1.24–1.27 (m, 1H, H_{7s}), 1.56 (d, *J* = 10.6 Hz, 1H, H_{6x}), 1.84 (dt, *J* = 13.5; 5.9 Hz 1H, H_{5n}), 1.91 (d, *J* = 10.7 Hz, 1H, H_{6n}), 2.90 (d, *J* = 4.7 Hz, 2H, H_1), 2.96 (brs, 1H, H_4), 3.28–3.30 (m, 2H, H_2 and H_3), 3.78 (s, 3H, OCH_3), 6.83 (d, *J* = 8.8 Hz, 2H, H_{aro}), 7.13 (d, *J* = 8.7 Hz, 2H, H_{aro}), 7.20 (d, *J* = 3.5 Hz, 2H, H_{aro}), 7.48 (s, 1H, H_{aro}), 8.64 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 38.9, 39.3, 39.9, 42.2, 46.4, 46.9, 55.32, 112.6, 113.8, 125.8, 127.9, 129.1, 148.3 and 156.1 (2C, C-sbst), 164.3 (C–OCH_3), 174.5 (1C, C=O), 174.8 (2C, C=O) ppm; GC-MS for $C_{21}H_{20}N_2O_5$: 380(M^+), 285, 270, 172, 95; Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.14; H, 5.59; N, 7.29%.

N-(2-Furoylamino)-5-exo-(6-chloro-3-pyridyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**8c**): Colourless crystals, 63% yield; m.p. 119 °C; R_f = 0.64 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3227, 3000, 2964, 2884, 1724, 1680, 1587, 1565, 1465, 1403, 1284, 1182, 758 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.96–1.12 (m, 1H, H_{7a}), 1.28–1.30 (m, 1H, H_{7s}), 1.67 (d, *J* = 10.5 Hz, 1H, H_{6x}), 1.79–1.82 (m, 1H, H_{5n}), 1.89 (d, *J* = 10.5 Hz, 1H, H_{6n}), 2.96–2.99 (m, 2H, H_4 and H_1) 3.48–3.63 (m, 2H, H_2 and H_3), 6.56 (d, *J* = 1.8 Hz, 1H, H_{aro}), 7.24–7.28 (m, 2H, H_{aro}), 7.54 (m, 2H, H_{aro}), 8.22 (s, 1H, H_{aro}), 8.65 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 32.3, 38.9, 39.3, 39.9, 45.2, 46.2, 46.9, 112.6, 117.5, 117.6, 117.8, 123.9, 138.1, 145.5 (C–Cl), 148.3 and 156.1 (2C, C-sbst), 174.3 (1C, C=O), 174.5 (2C, C=O) ppm; GC-MS for $C_{19}H_{16}ClN_3O_4$: 385 (M^+), 271, 172, 95; Anal. Calcd for $C_{19}H_{16}ClN_3O_4$: C, 59.15; H, 4.18; N, 10.89. Found: C, 58.97; H, 4.24; N, 10.78%.

N-(2-Furoylamino)-5-exo-(2-thienyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**8d**): Colourless crystals, 69% yield; m.p. 127 °C; R_f = 0.63 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3228, 3002, 2969, 2888, 1722, 1688, 1587, 1567, 1469, 1404, 1381, 1281, 1179, 757 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.11–1.19 (m, 2H, H_{7a} and H_{7s}), 1.54 (d, *J* = 9.8 Hz, 1H, H_{6x}), 1.82 (dt, *J* = 3.9, 13.6 Hz, 1H, H_{5n}), 1.94 (d, *J* = 9.8 Hz, 1H, H_{6n}), 2.22 (d, *J* = 4.7 Hz, 1H, H_1), 2.31 (brs, 1H, H_4), 3.12–3.17 (m, 2H, H_2 and H_3), 6.44 (dd, *J* = 1.9, 3.2 Hz, 1H, H_{aro}), 6.74 (d, *J* = 3.4 Hz, 1H, H_{aro}), 6.84 (dd, *J* = 3.4; 5.2 Hz, 1H, H_{aro}), 7.05 (dd, *J* = 0.9; 5.2 Hz, 1H, H_{aro}), 7.14 (d, *J* = 3.2 Hz, 1H, H_{aro}), 7.41–7.42 (m, 1H, H_{aro}), 8.43 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 34.8, 37.8, 39.5, 39.9, 46.2, 46.6, 47.4, 112.5, 117.5, 123.3, 123.6, 126.7, 127.3, 149.5 and 155.8 (2C, C-sbst), 174.4 (1C, C=O), 174.5 (2C, C=O) ppm; GC-MS for $C_{18}H_{16}N_2O_4S$: 356 (M^+), 261, 145, 95, 66; Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found: C, 60.52; H, 4.66; N, 7.99%.

N-[(4-tert-Butyl)benzoylamino]-5-exo-phenylbicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**9a**): Colourless crystals, 72% yield; m.p. 127–132 °C; R_f = 0.56 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3277, 3010, 2963, 2901, 2870, 1720, 1691, 1608, 1524, 1493, 1405, 1365, 1302, 1273, 1182, 848 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.13–1.16 (m, 1H, H_{7a}), 1.19–1.23 (m, 10H, H_{7s} and *t*-butyl), 1.47 (d, *J* = 10.1 Hz, 1H, H_{6x}), 1.79–1.82 (m, 1H, H_{5n}), 1.84 (d, *J* = 10.2 Hz, 1H, H_{6n}), 2.84–2.87 (m, 2H, H_1 and H_4), 3.08–3.13 (m, 2H, H_2 and H_3), 7.08–7.11 (m, 1H, H_{aro}), 7.14 (d, *J* = 8.1 Hz, 2H, H_{aro}), 7.18–7.23 (m, 2H, H_{aro}), 7.29 (d, *J* = 8.7 Hz, 2H, H_{aro}), 7.66 (d, *J* = 8.7 Hz, 2H, H_{aro}), 8.59 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 31.1, 35.2, 39.2, 39.9, 41.6, 45.8, 46.5, 47.1, 124.8, 125.6, 126.2, 127.0, 128.4, 151.1 and 156.4 (2C, $C_{subst.}$), 165.1 (C=O), 175.4 (2C, C=O) ppm; GC-MS for $C_{26}H_{28}N_2O_3$: 416(M^+), 161, 146, 73; Anal. Calcd for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73. Found: C, 74.78; H, 6.94; N, 6.90%.

N-[(4-tert-Butyl)benzoylamino]-5-exo-(4-methoxyphenyl)bicyclo[2.2.1]-heptane-2-endo,3-endo-dicarboximide (**9b**): Colourless crystals, 65% yield; m.p. 127 °C; R_f = 0.63 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3251, 2968, 2907, 2885, 1722, 1691, 1609, 1523, 1453,

1408, 1369, 1274, 1187, 832 cm^{-1}; ^1H NMR (400 MHz) δ 1.26 (d, J = 3.6 1H, H_{7a}), 1.31 (s, 9H, *t*-butyl), 1.52 (d, J = 10.4 1H, H_{7s}), 1.687 (brs, 1H, H_{5n}), 1.82–1.87 (m, 1H, H_{6x}), 1.90 (d, J = 10.4 Hz, 1H, H_{6n}), 2.86–2.87 (m, 1H, H_1), 2.98 (brs, 1H, H_4), 3.15–3.19(m, 2H, H_2 and H_3), 3.78 (s, 3H, OCH_3), 6.82 (d, J = 8.2 Hz, 2H, H_{aro}), 7.13 (d, J = 8.5 Hz, 2H, H_{aro}), 7.38 (d, J = 8.7 Hz, 2H, H_{aro}), 7.75(d, J = 8.7 Hz, 2H, H_{aro}), 8.54 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 31.9, 35.0, 39.2, 39.8, 40.9, 46.2, 47.1, 55.30, 113.8, 125.7, 127.6, 128.1, 137.15 (C-*t*-butyl), 156.3 and 157.8 (2C, C-sbst), 165.1 (C–OCH_3), 175.2 (1C, C=O), 175.6 (2C, C=O) ppm; GC-MS for $C_{27}H_{30}N_2O_4$: 446 (M^+), 340, 161; Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.48; H, 6.93; N, 6.21%.

N-[(4-tert-Butyl)benzoylamino]-5-exo-(6-chloro-3-pyridyl)bicyclo[2.2.1]-heptane-2-endo,3-endo-dicarboximide (**9c**): Colourless crystals, 65% yield; m.p. 127 °C; R_f = 0.63 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3249, 2962, 2906, 2875, 1725, 1690, 1611, 1525, 1457, 1412, 1364, 1275, 1189, 824 cm^{-1}; ^1H NMR (400 MHz) δ 1.16–1.28 (m, 1H, H_{7a}), 1.32–1.47 (m, 10H, H_{7s} and *t*-butyl), 1.63 (d, J = 10.5 Hz, 1H, H_{6x}), 1.77–1.73 (m, 1H, H_{5n}), 1.83 (d, J = 10.5 Hz, 1H, H_{6n}), 2.92 (d, J = 4.8 Hz, 1H, H_1), 2.97 (brs, 1H, H_4), 3.24 (dt, J = 8.5, 22.5 Hz, 2H, H_2 and H_3), 7.23 (d, J = 8.2 Hz, 1H, H_{aro}), 7.42 (d, J = 8.5 Hz, 2H, H_{aro}), 7.48–7.51 (m, 1H, H_{aro}), 7.80 (d, J = 8.5 Hz, 2H, H_{aro}), 8.23 (s, 1H, H_{aro}), 8.96 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 31.0, 35.1, 38.9, 39.3, 39.9, 45.2, 46.2, 46.9, 123.9, 125.7, 127.6, 134.7, 138.1, 148.2 (C-*t*-butyl), 148.3 and 149.1 (2C, $C_{subst.}$), 156.5 (C–Cl), 165.5 (1C, C=O), 174.7 (2C, C=O), ppm; GC-MS for $C_{25}H_{26}ClN_3O_3$: 452 (M^+), 340, 161,73; Anal. Calcd for $C_{25}H_{26}ClN_3O_3$: C, 66.44; H, 5.80; N, 9.30. Found: C, 66.52; H, 5.64; N, 9.10%.

N-[(4-tert-Butyl)benzoylamino]-5-exo-(2-thienyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**9d**): Colourless crystals, 68% yield; m.p. 134 °C; R_f = 0.61 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3254, 2964, 2908, 2873, 1725, 1688, 1609, 1526, 1456, 1404, 1364, 1273, 1183, 829 cm^{-1}; ^1H NMR (400 MHz) δ 1.09–1.18 (m, 1H, H_{7a}), 1.22–1.26 (m, 10H, H_{7s} and *t*-butyl), 1.50 (d, J = 9.7 Hz, 1H, H_{6x}), 1.79 (dt, J = 3.9, 13.6 Hz, 1H, H_{5n}), 1.90 (d, J = 9.7 Hz, 1H, H_{6n}), 2.81–2.84 (m, 2H, H_1 and H_4), 3.07–3.10 (m, 2H, H_2 and H_3), 6.73 (d, J = 3.9 Hz, 1H, H_{aro}), 6.83 (dd, J = 3.9, 8.7 Hz, 1H, H_{aro}), 7.05 (d, J = 3.9 Hz, 1H, H_{aro}), 7.27 (d, J = 8.7 Hz, 2H, H_{aro}), 7.64 (d, J = 8.7 Hz, 2H, H_{aro}), 8.69 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz) δ 31.3, 35.1, 35.3, 38.1, 39.7, 44.6, 46.5, 46.8, 123.4, 123.6, 125.8, 127.0, 127.7, 138.7, 149.8 and 156.6 (3C, $C_{subst.}$), 165.3 (C=O), 175.4 (2C, C=O) ppm; GC-MS for $C_{24}H_{26}N_2O_3S$: 422 (M^+), 340, 161, 73; Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63. Found: C, 68.31; H, 6.24; N, 5.94%.

N-[(3-Methylisoxazole-5-carbonyl)amino]-5-exo-phenyl-7-oxabicyclo-[2.2.1]heptane-2-exo,3-exo-dicarboximide (**10a**): Colourless crystals, 77% yield; m.p. 205–207 °C; R_f = 0.48 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3213, 3130, 3009, 2980, 1798, 1728, 1607, 1590, 1508, 1495, 1446, 1412, 1296, 1265, 1193, 748, 700 cm^{-1}; ^1H NMR (500 MHz) δ 1.86–1.90 (dt, J = 5.0;10.4 Hz, 1H, H_{6x}), 2.16–2.22 (m, 1H, H_{6n}), 2.29 (s, 3H, CH_3), 2.96–2.98 (dd, J = 5.0; 9.1 Hz, 1H, H_{5n}), 3.07–3.13 (dd, J = 7.2; 23.9 Hz, 2H, H_2 and H_3), 4.78 (s, 1H, H_4), 4.99 (d, J = 5.0 Hz, 1H, H_1), 6.76 (s, 1H, =CH), 7.10–7.12 (m, 3H, H_{aro}), 7.17–7.20 (m, 2H, H_{aro}), 9.19 (brs, 1H, –NH) ppm; ^{13}C NMR (125 MHz) δ 11.4, 40.1, 47.2, 48.3, 48.7, 79.2, 84.7, 109.8 (=CH), 126.9, 127.0, 128.7, 143.6, 153.6 and 160.4 (3C, C-subst) 160.8 (1C, C=O) 172.4 (1C, C=O), 172.7 (1C, C=O) ppm; GC-MS for $C_{19}H_{17}N_3O_5$: 354 (M-CH_3), 121, 103, 95, 79, 55; Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 61.12; H, 4.66; N, 11.44. Found: C, 61.35; H, 4.49; N, 11.65%.

N-[(3-Methylisoxazole-5-carbonyl)amino]-5-exo-(4-methoxyphenyl)-7-oxabicyclo[2.2.1] heptane-2-exo,3-exo-dicarboximide (**10b**): Colourless crystals, 56% yield; m.p. 118–119 °C; R_f = 0.58 (4:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3215, 3126, 3009, 2956, 2928, 1796, 1728, 1702, 1611, 1586, 1511, 1463, 1444, 1412, 1294, 1246, 1194, 1177, 824, 783 cm^{-1}; ^1H NMR (500 MHz) δ 1.87–1.91 (dt, J = 5.0; 10.4 Hz, 1H, H_{6x}), 2.17–2.22 (m, 1H, H_{6n}), 2.32 (s, 3H, CH_3), 2.95–2.97 (dd, J = 5.0; 9.1 Hz, 1H, H_{5n}), 3.09–3.15 (dd, J = 7.2; 24.5 Hz, 2H, H_2 and H_3), 3.71(s, 3H, CH_3), 4.76 (s, 1H, H_4), 5.01 (d, J = 5.0 Hz, 1H, H_1), 6.74 (d, J = 8.8 Hz, 2H, H_{aro}), 6.80 (s, 1H, =CH), 7.07 (d, J = 8.8 Hz, 2H, H_{aro}), 8.68 (brs, 1H, –NH) ppm; ^{13}C NMR (125 MHz) δ 11.4, 40.1, 46.5, 48.3, 48.7, 55.2 (OCH_3), 79.2, 84.9, 109.8 (=CH), 114.0, 128.1, 135.8, 153.5, 158.5, 160.3, 160.8 (1C, C=O), 172.3 (1C, C=O), 172.6 (1C, C=O) ppm. LC-MSD *m/z* (relative intensity): 398 (M^+, 100); Anal. Calcd for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.57. Found: C, 60.42; H, 4.99; N, 10.38%.

N-[(3-Methylisoxazole-5-carbonyl)amino]-5-exo-(6-chloropyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-exo,3-exo-dicarboximide (**10c**): Colourless crystals, 25% yield; m.p. 234 °C; R_f = 0.27 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3202, 3009, 2960, 2929, 1795, 1730, 1702, 1611, 1587, 1512, 1457, 1411, 1292, 1268, 1212, 1196, 1181, 826, 795 cm^{-1}; ^1H NMR (500 MHz) δ 1.90–1.95 (dt, J = 5.0; 10.4 Hz, 1H, H_{6x}), 2.37 (s, 3H, CH_3), 2.47–2.52 (dd, J = 9.1; 12.9 Hz, 1H, H_{6n}), 3.43–3.47 (m, 2H, H_2 and H_3), 3.50–3.51 (m, 1H, H_{5n}), 4.71 (s, 1H, H_4), 5.04 (d, J = 5.3 Hz, 1H, H_1), 7.05 (s, 1H, =CH), 7.40 (d, J = 8.1 Hz, 1H, H_{aro}), 7.28–7.29 (dd, J = 2.5; 8.1 Hz, 1H, H_{aro}), 8.34 (d, J = 2.5 Hz, 1H, H_{aro}), 10.55 (brs, 1H, –NH) ppm; ^{13}C NMR (125 MHz) δ 11.2, 40.3, 44.5, 48.9, 49.1, 80.1, 85.4, 109.8 (=CH), 124.9, 138.9, 149.8, 158.0, 161.6, 161.7, 162.0, 173.4 (1C, C=O), 173.7 (1C, C=O), 176.0 (1C, C=O) ppm; GC-MS for $C_{18}H_{15}ClN_4O_5$: 402(M^+), 387, 348, 292, 257, 207, 161, 98, 68); Anal. Calcd for $C_{18}H_{15}ClN_4O_5$: C, 53.67; H, 3.75; N, 13.91. Found: C, 53.74; H, 3.61; N, 14.11%.

N-[(3-Methylisoxazole-5-carbonyl)amino]-5-exo-(2-thienyl)-7-oxabicyclo[2.2.1]heptane-2-exo,3-exo-dicarboximide (**10d**): Colourless crystals, 64% yield; m.p. 194–195 °C; R_f = 0.58 (3:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3279, 3105, 3009, 2977, 2949, 1796, 1720, 1695, 1611, 1586, 1504, 1471, 1441, 1421, 1409, 1294, 1267, 1205, 1195, 1177, 822, 804 cm^{-1}; ^1H NMR (500 MHz) δ 1.95–2.00 (dt, J = 5.0; 10.4 Hz, 1H, H_{6x}), 2.36 (s, 3H, CH_3), 2.44–2.49 (dd, J = 9.1; 12.9 Hz, 1H, H_{6n}), 3.38 (d, J = 7.2, 1H, H_2), 3.48 (d, J = 7.2, 1H, H_3), 3.68–3.71 (dd, J = 4.4; 9.1 Hz, 1H, H_{5n}), 4.64 (s, 1H, H_4), 4.98 (d, J = 5.3 Hz, 1H, H_1), 6.93–6.96 (m, 2H, H_{aro}), 7.04 (s, 1H, =CH), 7.28–7.29 (dd, J = 0.9; 4.7 Hz, 1H, H_{aro}), 8.74 (brs, 1H, –NH) ppm; ^{13}C NMR (125 MHz) δ 11.2, 41.0, 43.3, 48.7, 48.7, 79.9, 86.0, 109.8 (=CH), 124.9, 127.4, 139.1, 153.5, 158.5, 160.3, 161.7 (1C, C=O), 173.5 (1C, C=O), 173.7 (1C, C=O) ppm; GC-MS for $C_{17}H_{15}N_3O_5S$: 373(M^+), 359, 349, 319, 303, 249, 236, 207, 179, 150, 123, 98, 68; Anal. Calcd for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25. Found: C, 54.52; H, 4.21; N, 11.01%.

N-[(3-Methylisoxazole-5-carbonyl)amino]-5-exo-(4-chlorophenyl)-7-oxabicyclo[2.2.1]heptane-2-exo,3-exo-dicarboximide (**10e**): Colourless crystals, 36% yield; m.p. 222–223 °C; R_f = 0.60 (3:1 ethyl acetate/*n*-hexane); FTIR(ATR): ν 3249, 3126, 3009, 2958, 2932, 1795, 1728, 1700, 1617, 1591, 1506, 1463, 1438, 1412, 1298, 1267, 1194, 1179, 820, 812 cm^{-1}; ^1H NMR (500 MHz) δ 1.93–1.97 (dt, J = 5.0; 10.4 Hz, 1H, H_{6x}), 2.28–2.32 (dd, J = 9.1; 12.9 Hz, 1H, H_{6n}), 2.39 (s, 3H, CH_3), 3.04–3.07 (dd, J = 5.0; 9.1 Hz, 1H, H_{5n}), 3.17 (d, J = 7.2 Hz, 1H, H_2), 3.22 (d, J = 7.2 Hz, 1H, H_3), 4.84 (s, 1H, H_4), 5.10 (d, J = 5.0 Hz, 1H, H_1), 6.87 (s, 1H, =CH), 7.16 (d, J = 8.1 Hz, 2H, H_{aro}), 7.25–7.27 (t, J = 3.7; 8.1 Hz, 2H, H_{aro}), 8.74 (brs, 1H, –NH) ppm; ^{13}C NMR (125 MHz) δ 11.2, 40.5, 47.0, 48.9, 49.3, 80.0, 85.6, 109.8 (=CH), 129.3, 129.9, 132.6, 144.9, 161.7 (C=O), 173.5 (C=O), 173.8 (C=O) ppm.; GC-MS for $C_{19}H_{16}ClN_3O_5$: 401 (M^+), 362, 292, 277, 233, 220, 207, 191, 167, 127, 98, 68; Anal. Calcd for $C_{19}H_{16}ClN_3O_5$: C, 56.80; H, 4.01; N, 10.46. Found: C, 56.93; H, 3.94; N, 10.37%.

*N-[(3-Methylisoxazole-5-carbonyl)amino]-5-exo-(*3-methylisoxazol-5-yl*)-7-oxabicyclo[2.2.1]heptane-2-exo,3-exo-dicarboximide* (**10f**): Colourless crystals, 42% yield; m.p. 200 °C(decomp); R_f = 0.45 (5:1 ethyl acetate/*n*-hexane); FTIR (ATR): ν 3182, 3130, 3009, 2968, 2931, 1797, 1733, 1699, 1604, 1512, 1497, 144, 1416, 1267, 1218, 1198, 1179, 836, 794 cm^{-1}; ^1H NMR (500 MHz) δ 2.06–2.08 (m, 1H, H_{6x}), 2.21 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.39–2.44 (dd, J = 9.1; 12.9 Hz, 1H, H_{6n}), 3.42–3.43 (m, 1H, H_{5n}), 3.53–3.57 (m, 2H, H_2 and H_3), 4.87 (s, 1H, H_4), 4.98 (d, J = 5.3 Hz, 1H, H_1), 6.14 (s, 1H, =CH), 7.05 (s, 1H, =CH), 10.55 (brs, 1H, –NH) ppm; ^{13}C NMR (125 MHz) δ 11.2, 11.2, 36.6, 40.3, 48.7, 48.7, 80.0, 83.4, 102.2 (=CH), 109.8 (=CH), 146.9, 146.3, 160.4, 161.1, 161.7 (1C, C=O), 174.4 (1C, C=O), 175.1 (1C, C=O) ppm. GC-MS for $C_{17}H_{16}N_4O_6$: 372 (M^+), 264, 248, 177, 163, 149, 123, 97, 58; Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 54.78; H, 4.49; N, 14.94%.

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