Heck-type hydroarylations and 1,3-dipolar cycloaddition reactions of new tricyclic hydrazones

Melek Gul and Nuket Ocal

Abstract: The C–C coupling of the new tricyclic hydrazones **3–7** with aryl and heteroaryl halides gave under reductive Heck conditions the tricyclic 1-(arylideneamino)pyrolidine-2,5-diones **8–11a**, **9–11b**, **10c**, and **12**. The [3+2] cycloadditions of **3–7** with *p*-chlorophenyl nitrile oxide (**13**) yielded the bridged isoxazoline derivatives **14–18** with potential biological activity.

Key words: tricyclic hydrazone, reductive Heck reactions, C–C coupling, nitrile oxides, isoxazolines.

Résumé : Le couplage C–C des nouvelles hydrazones tricycliques **3–7** avec des halogénures d'aryles et d'hétéroaryles, dans les conditions réductrices de Heck, conduisent à la formation des 1-(arylidèneamino)pyrolidine-2,5-diones tricycles **8–11a**, **9–11b**, **10c** et **12**. Les cycloadditions [3+2] des composés **3–7** avec l'oxyde du *p*-chlorophénylnitrile (**13**) conduisent à la formation des dérivés isoxazolines pontées **14–18** qui peuvent présenter une activité biologique.

Mots-clés : hydrazone tricyclique, réactions réductrices de Heck, couplage C–C, oxydes de nitriles, isoxazolines.

[Traduit par la Rédaction]

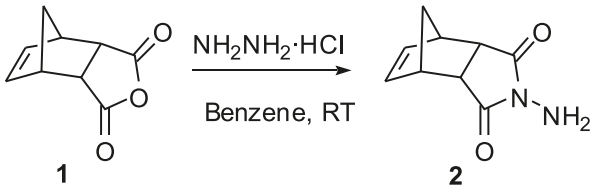
Introduction

In a collaborative effort with Kaufmann and co-workers,[1–3] we reported palladium(II) acetate catalyzed asymmetric Heck-type hydroarylations of bicyclic and tricyclic alkenes, such as epibatidine analogs, and their domino–Heck applications by treating with aryl (or heteroaryl) iodides.[4] We then focused on reductive Heck reactions of tricyclic molecules containing a strained C=C bond and an acylamino imide or hydrazide group and possessing potential biological activity.[5,6]

Hydrazones are a versatile class of ligands that have extensive applications in various fields, possessing pronounced biological and pharmaceutical activities as antitumor,[7,8] antimicrobial,[9] antituberculosis,[10] and antimalarial agents.[11] These compounds play an important role in improving the antitumor selectivity and toxicity profile of antitumor agents by forming drug-carrier systems employing suitable carrier proteins.[12] Hydrazones, such as salicylaldeyde and heteroaryl substituted aldo hydrazones, act as orally effective drugs for treatment of iron-overload diseases or genetic diseases like β-thalassemia.[13]

In addition, five-membered heterocycles such as isoxazolines represent a class of compounds of great biological importance. For instance, isoxazolines possess a broad spectrum of biological activity, such as insecticidal, antibacterial, antibiotic, antitumor, and antifungal activities.[14–16]

Scheme 1. Preparation of compound **2**.



Isoxazolines are generally synthesized by 1,3-dipolar cycloadditions of alkenes onto nitrile oxides. 1,3-Dipolar cycloaddition reactions are useful tools for the construction of biologically potent five-membered heterocycles.[17]

There are a few reports in the literature of the synthesis of tricyclic hydrazones and practically no information on their structure analyses.[18,19] Therefore, we became interested in the synthesis of possible bioactive aryl- and hetero-aryl substituted tricyclic hydrazones by reductive Heck reactions and their isoxazoline derivatives via 1,3-dipolar cycloadditions.

Results and discussion

Our synthesis started with the reaction of *endo*-bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic anhydride (**1**) and hydrazine hydrate. The reaction occurred in benzene at room temperature to give *N*-amino-bicyclo[2.2.1]hept-5-ene-2,*endo*-3-*endo*-dicarboximide (**2**) as colorless crystals in a yield of 87%[19] (Scheme 1).

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This article is dedicated to Professor Dieter E. Kaufmann on the occasion of his 62nd birthday.

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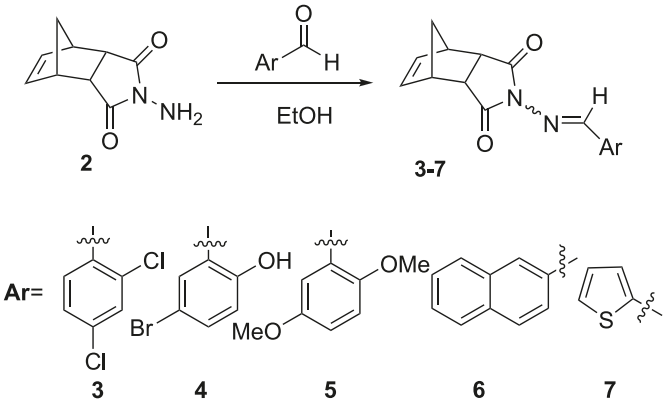
Scheme 2. Synthesis of compounds **3**–**7**.

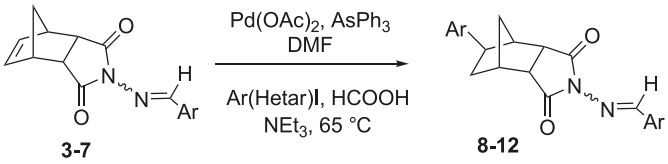


We carried out the condensation of **2** with aryl- or heteroaryl-substituted aldeyhdes in dry ethanol to obtain new tricyclic hydrazones (**3**–**7**) (Scheme 2). The structures of these synthesized compounds were elucidated using FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic methods as well as elemental analysis. ^{1}H NMR spectroscopy revealed that in $CDCl_3$ **4**–**7** exist as an inseparable mixture of *E* and *Z* isomers pertaining to the stereochemistry about the carbon=-nitrogen double bond; the major isomers were tentatively assigned the *E* configuration. In compounds **4**–**7**, varying ratios of *E*/*Z* isomers (93:7, 92:8, 78:22, 52:48, respectively) of the C=N bond were observed. The percentages of *E* and *Z* isomers were determined by integration of the H_8 protons. Assignment of the stereochemistry was based upon the consideration that in the *E* isomer, the proton attached to C=N is in proximity to the imide nitrogen, resulting in an upfield shift compared with the chemical shift of the *Z* isomer. Further evidence for these structures were obtained from the phase-sensitive NOESY measurements. The NOESY experiment confirmed the assigned stereochemistries, showing an interaction between H_2 and H_3 and the H_8. In addition to the ^{13}C NMR and FTIR spectral data and elemental analyses which were in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular ion peaks.

Treatment of **3** with 4-chloro-1-iodobenzene and 4-methoxy-1-iodobenzene under reductive Heck conditions and subsequent column chromatography on silica gel gave **8a** and **8b** as single diastereomers in isolated yields of 55%–61%. The same reductive Heck arylation conditions were successfully applied to the reaction of **4** with 4-methoxy-1-iodobenzene and 2-chloro-5-iodopyridine to give the new *exo*-arylated heterocycles **9a** and **9b** in good yields after chromatographic separation. We also synthesized **10a**, **10b**, and **10c** from **5** with 2-iodothiophene, 4-chloro-1-iodobenzene, and 2-chloro-1-iodobenzene and prepared **11a** and **11b** from **6** with 1-iodobenzene and 2-iodothiophene (all obtained as *exo*-isomers) under the same conditions. This hydroarylation reaction was also applied successfully to **7** using 4-methoxy-1-iodobenzene to give **12** containing 4-methoxyphenyl group (Table 1 and Scheme 3). All new compounds were observed as *E* forms due to the isomerization of *Z* forms during hydroarylation conditions.

The stereochemistry for each Heck product was inferred from NMR spectra including diagnostic spin–spin interactions. (Table 2). The *exo*-position of the C–5 substituent was confirmed by the fact that H_5 showed no significant interaction with H_1. The geminal protons on C–6 were identified by vicinal coupling to H_1.

Scheme 3. Synthesis of reductive Heck compounds **8**–**12**.



Additionally, ^{1}H–^{1}H COSY spectra showed cross peaks between H_2 and H_3 and between H_5 and H_6, respectively. In addition to the ^{13}C NMR, NOESY, HSQC, and FTIR spectral data and elemental analyses which were in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular ion peaks.

Norbornene and its derivatives have figured prominently in organic chemistry. The presence of a rigid bicyclic skeleton gives rise to stereoisomers with fixed spatial orientation of substitutents. The double bond in substituted norbornenes is quite reactive toward cycloaadends, in particular toward nitrile oxides in 1,3-dipolar additions. We carried out the [3+2] cycloaddition of **3**–**7** with 4-chlorophenyl nitrile oxide **13** (generated in situ from 4-chlorobenzaldehyde with NaOCl) to obtain the target compounds **14**–**18** (Scheme 4), respectively.

The ^{1}H NMR spectra of **14**–**18** are in accord with the proposed structures. To identify the configuration of the isoxazolines with tricyclic hydrazone adducts, we have studied selective ^{1}H–^{1}H COSY and NOESY spectra obtained from these compounds (Table 3).

^{1}H–^{1}H COSY spectra show the cross peaks between resonances for H_2 and H_3; H_{5n} and H_{6n}. NOESY spectra show that there are appropriate cross-peak resonances (H_1 and H_2; H_1 and H_{6n}; H_4 and H_3; H_4 and H_{5n}; H_2 and H_{6n}; H_3 and H_{5n}, respectively) verifying that the six protons are in close spatial proximity and syn. The EI-MS spectra of cycloadducts **14**–**18** showed the characteristic molecular ion peaks.

In summary, palladium(II) acetate catalyzed hydroarylation of the readily accessible tricyclic hydrazones **3**–**7**, in the presence of triphenylarsine as ligand, was shown to be a stereoselective, versatile, and high-yield approach to the synthesis of aryl and heteroaryl derivatives of tricyclic hydrazones. Our results have also demonstrated that the 1,3-dipolar cycloadditions of nitrile oxides onto bridged tricyclic hydrazone derivatives prove useful for the construction of novel heterocycles of potential pharmacological interest.

Experimental

All the reactions were carried out under nitrogen atmosphere unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC). Visualization of the developed chromatograms was performed either with UV light or $KMnO_4$ stain. Products were 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 PerkinElmer FTIR instrument, and absorption frequencies are reported in cm^{-1}. Melting points

Table 1. Hydroarylation reactions of tricyclic hydrazones, **3**–**7**.

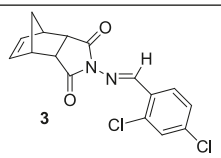
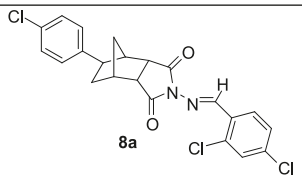
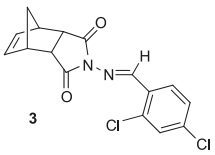
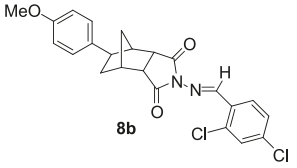
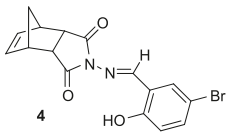
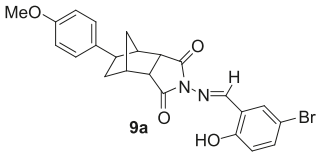
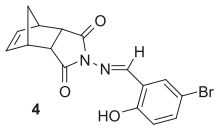
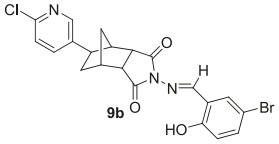
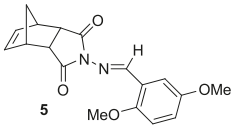
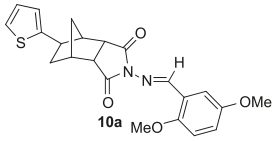
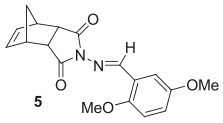
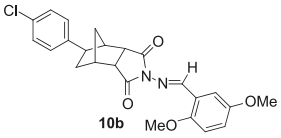
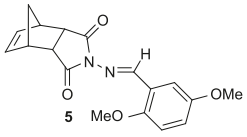
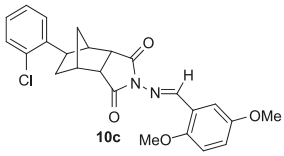
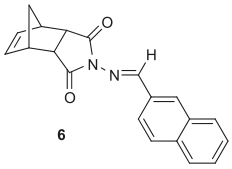
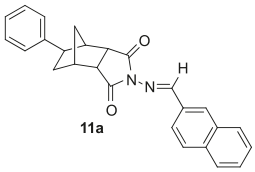
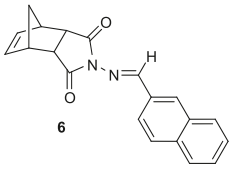
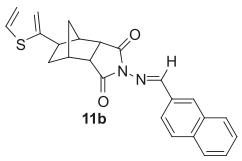
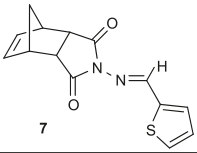
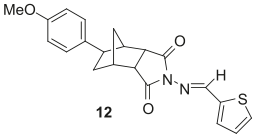
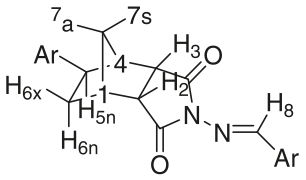
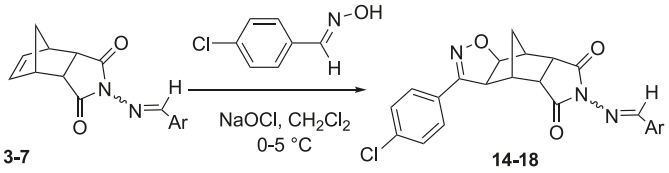
Entry	Substrate **3-7**	Product	Yield %
1	 **3**	 **8a**	55
2	 **3**	 **8b**	61
3	 **4**	 **9a**	47
4	 **4**	 **9b**	60
5	 **5**	 **10a**	65
6	 **5**	 **10b**	55
7	 **5**	 **10c**	59
8	 **6**	 **11a**	62
9	 **6**	 **11b**	62
10	 **7**	 **12**	58

Table 2. Selected ^{1}H NMR data for compounds **8**–**12**.



Entry	Compound	H_{7a}	H_4	H_{5n}	H_8
1	**8a**	1.63, d	3.02, brs	2.97–2.89, m	9.68, s
2	**8b**	1.51, d	2.91, brs	2.85–2.79, m	9.59, s
3	**9a**	1.60, d	2.95, brs	2.88–2.84, m	9.43, s
4	**9b**	1.62, d	2.98, brs	2.83, dd	9.35, s
5	**10a**	1.66, d	2.98, brs	3.29–3.19, m	9.34, s
6	**10b**	1.68–1.62, m	2.91, brs	3.16, ddd	9.27, s
7	**10c**	1.68–1.60, m	2.91, brs	3.16, ddd	9.21, s
8	**11a**	1.62, d	3.03, brs	3.03, brs	9.37, s
9	**11b**	1.67, d	3.01, brs	3.33–3.21, m	9.35, s
10	**12**	1.49, d	2.89, brs	2.85–2.82, m	9.24, s

Scheme 4. Synthesis of compounds **14**–**18**.



were determined with a Gallenkamp digital thermometer equipment. All melting points are uncorrected. NMR spectra were determined with a Bruker Ac-250 MHz NMR, Bruker Ac-400 MHz NMR, or Varian-INOVA-500 MHz instrument. 2D NMR experiments, such as COSY, 2D NOESY, HMBC, and HSQC, were performed with a Bruker Ac-400 MHz instrument. TMS (tetramethylsilane) was used as 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; and m, multiplet. Mass spectra were measured either with Agillent LC–MSD Trap SL or MS-ESI. Elemental analyses were carried out with a Thermo Flash EA 1112 Series apparatus.

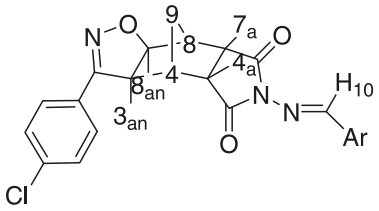
Experimental procedure for the preparation of tricylic hydrazones, 3–7

A mixture of **2** (178.85 mg, 1 mmol) and aromatic or heteroaromatic aldehyde (1.00 mmol) in ethanol (50–70 mL) was heated at reflux for 10–12 h under nitrogen. The reaction mixture was concentrated and the residue was chromatographed on silica gel with ethyl acetate/*n*-hexane.

N-*{[(2,4-dichlorophenyl)methylene]amino}-bicyclo[2.2.1]hept-5-ene*-endo-*2,*endo-*3-dicarboximide (3)*

Colorless crystals, 65% yield. Mp 170 °C. R_f = 0.60 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3010, 2995, 2941, 1732, 1710, 1618, 1582, 1471, 1380, 1183, 745, 728. ^{1}H NMR (400 MHz) δ (ppm): 9.50 (s, 1H, H_8), 8.12 (d, J = 8.5 Hz, 1H, $H_{aro.}$), 7.43 (s, 1H, $H_{aro.}$), 7.30 (d, J = 7.2 Hz, 1H, $H_{aro.}$), 6.23 (s, 2H, H_5–H_6) 3.54 (brs, 2H, H_1–H_4), 3.36 (s, 2H, H_2–H_3), 1.79 (d, J = 8.8 Hz, 1H, H_{7s}), 1.61 (d, J = 8.8, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 173.8 (2C, C=O), 156.4 (N=CH), 138.3 (C–Cl), 136.4 ($C_{subst.}$), 134.7, 129.7 (C–Cl), 129.5, 128.9, 127.6, 51.8, 45.3, 44.0. MS-ESI (EI, 70 eV): 336 [M$^+$ + 1], 335 [M$^+$], 270.96, 197.86, 166.08, 147.86, 119.95. Anal. calcd. for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.15; H, 3.44; N, 8.26.

Table 3. Selected ^{1}H NMR data for compounds **14**–**18**.



Entry	Compound	H_{3an}	H_{8an}	H_{9a}	H_{10}
1	**14**	3.61, dd	4.73, d	1.57, d	9.35, s
2	**15**	3.66, d	4.79, d	1.67, d	9.40, s
3	**16**	3.63, d	4.76, d	1.55, d	9.21, s
4	**17**	3.63, d	4.75, d	1.55, d	9.20, s
5	**18**	3.69, d	4.80, d	1.64, d	9.25, s

N-*{[(5-bromo-2-hydroxyphenyl)methylene]amino}-bicyclo[2.2.1]hept-5-ene*-endo-*2,*endo-*3-dicarboximide (4)*

Colorless crystals, 52% yield. Mp 178 °C. R_f = 0.58 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3316, 3005, 2970, 1730, 1700, 1623, 1563, 1475, 1364, 1180, 745, 728. ^{1}H NMR (400 MHz) δ (ppm): 11.12 (s, 1H, O–H, minor), 11.04 (s, 1H, O–H, major), 9.38 (s, 1H, H_8, minor), 9.24 (s, 1H, H_8, major), 7.46–7.40 (m, 2H, $H_{aro.}$), 6.89 (d, J = 8.8 Hz, 1H, $H_{aro.}$), 6.20 (s, 2H, H_5–H_6), 3.50 (s, 2H, H_1–H_4, major), 3.37 (s, 2H, H_2–H_3, major), 3.18 (brs, 2H, H_1–H_4, minor), 2.87 (brs, 2H, H_2–H_3, minor), 1.79 (d, J = 8.8 Hz, 1H, H_{7s}, major), 1.58–1.67 (m, 2H, H_{7s}minor – H_{7a}major), 1.36 (d, J = 8.8 Hz, 1H, H_{7a}, minor) (*E*/*Z*, 93:7). ^{13}C NMR (100 MHz) δ (ppm): 173.9 (2C, C=O, minor), 173.1 (2C, C=O, major), 160.4 (C–OH, minor), 160.2 (C–OH, major), 158.6 (N=CH, minor), 158.7 (N=CH, major), 136.1 (C–Br,

minor), 136.0 (C–Br, major), 134.7 ($C_{subst.}$), 134.5 (minor), 134.5 (major), 119.6 (minor), 119.5 (major), 111.0 ($C_{subst.}$, minor), 110.9 ($C_{subst.}$, major), 51.9, 46.9 (minor), 45.3 (major), 44.0 (major), 41.8 (minor). LC–MSD: 362 [M^+ + 1], 361 [M^+], 360 [M^+ – 1], 296, 266, 195, 162. Anal. calcd. for $C_{16}H_{13}BrN_2O_3$: C, 53.21; H, 3.63, N, 7.76. Found: C, 53.15; H, 3.49; N, 7.69.

N-*{[(2,5-dimethoxyphenyl)methylene]amino}-bicyclo[2.2.1]hept-5-ene*-endo-*2,*endo-*3-dicarboximide (5)*

Colorless crystals, 45% yield. Mp 141 °C. R_f = 0.47 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3005, 2970, 2950, 1762, 1712, 1596, 1577 1495, 1463, 1180, 728, 716. ^1H NMR (400 MHz) δ (ppm): 9.30 (s, 1H, H_8, minor), 9.19 (s, 1H, H_8, major), 7.64 (d, J = 3.1 Hz, 1H, $H_{aro.}$, minor), 7.58 (d, J = 3.1 Hz, $H_{aro.}$, major), 7.01 (dd, J = 3.1 and 7.7 Hz, 2H, $H_{aro.}$, major and minor), 6.86 (d, J = 8.8 Hz, 2H, $H_{aro.}$, major–minor), 6.24 (s, 2H, H_5–H_6), 3.83 (s, 12H, –OCH_3, major–minor), 3.49 (s, 2H, H_1–H_4, major), 3.34 (s, 2H, H_2–H_3, major), 3.16 (brs, 2H, H_1–H_4, minor), 2.86 (brs, 2H, H_2–H_3, minor), 1.78 (d, J = 8.8 Hz, 1H, H_{7s}, minor), 1.58 (m, 2H, H_{7a}–H_{7s}, major–minor), 1.46 (d, J = 8.8 Hz, 1H, H_{7a}, minor) (*E*/*Z*, 92:8). ^{13}C NMR (100 MHz) δ (ppm): 174.5 (2C, C=O, major), 173.8 (2C, C=O, minor), 159.6 (N=CH, major), 159.4 (N=CH, minor), 154.1 (C–OCH_3, major), 154.0 (C–OCH_3, minor), 153.6 (C–OCH_3, major), 153.5 (C–OCH_3, minor), 134.8 (minor), 134.7 (major), 121.6 ($C_{subst.}$), 121.2 (major), 121.1 (minor), 112.7 (major), 112.6 (minor), 110.0 (minor), 109.9 (major), 56.2 (minor), 55.9 (major), 51.8 (major), 51.5 (minor), 45.1 (major), 45.0 (minor), 44.5 (minor), 44.1 (major). LC–MSD: 327 [M^+ + 1], 326 [M^+], 325 [M^+ – 1], 266, 242. Anal. calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.12; H, 5.54; N, 8.55.

N-*{[2-naphthylmethylene]amino}-bicyclo [2.2.1]hept-5-ene*-endo-*2,*endo-*3-dicarboximide (6)*

Colorless crystals, 72% yield. Mp 158 °C. R_f = 0.41 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 2967, 2963, 2860, 1734, 1710, 1603, 1568 1365, 1335, 1171, 756, 746. ^1H NMR (500 MHz) δ (ppm): 9.24 (s, 1H, H_8, minor), 9.11 (s, 1H, H_8, major), 8.04 (d, J = 5.8 Hz, 1H, $H_{aro.}$), 7.99 (d, J = 8.8 Hz, 1H, $H_{aro.}$), 7.77–7.84 (m, 3H, $H_{aro.}$), 7.43–7.50 (m, 2H, $H_{aro.}$), 6.17 (s, 2H, H_5–H_6), 3.44 (s, 2H, H_2–H_3, major), 3.23 (s, 2H, H_1–H_4, major), 3.10 (brs, 2H, H_2–H_3, minor), 2.81 (brs, 2H, H_1–H_4, minor), 1.72 (d, J = 8.8 Hz, 1H $H_{7s,}$ major), 1.56 (d, J = 8.8 Hz, 1H, $H_{7s,}$ minor), 1.52 (d, J = 8.8 Hz, 1H, $H_{7a,}$ major), 1.39 (d, J = 7.8 Hz, 1H, $H_{7a,}$ minor) (*E*/*Z*, 78:22). ^{13}C NMR (100 MHz) δ (ppm): 174.3 (2C, C=O, minor), 174.1 (2C, C=O, major), 161.9 (N=CH, minor), 161.7 (N=CH, major), 135.3 (minor), 135.2 (major), 134.7, 132.9 (minor), 132.8 (major), 131.6 (minor), 131.5 (major), 130.8 (minor), 130.7 (major), 128.9 (minor), 128.8 (major), 128.7 (minor), 128.6 (major), 127.9 ($C_{subst.}$), 127.8 (minor), 127.8 (major), 126.7, 123.4 (minor), 123.3 (major), 51.8, 41.8, 39.6. LC–MSD: 339 [M^+ + Na], 317 [M^+ + 1], 316 [M^+], 282, 244. Anal. calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.81; H, 4.98; N, 8.76.

N-*{[2-thienylmethylene]amino}-bicyclo[2.2.1]-hept-5-ene*-endo-*2,*endo-*3-dicarboximide (7)*

Colorless crystals, 59% yield. Mp 122 °C. R_f = 0.49 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3104, 3011, 2972, 2935, 1764, 1738, 1696, 1589, 1427, 1373, 1180, 748, 719. ^1H NMR (250 MHz) δ (ppm): 9.12 (s, 1H, H_8, minor), 9.07 (s, 1H, H_8, major), 7.48–7.37 (m, 2H, $H_{aro.}$), **7.**05 (dd, J = 4.9 and 8.8 Hz, 1H, $H_{aro.}$), 6.14 (s, 2H, H_5–H_6), 3.41 (brs, H_3, major–minor), 3.35 (brs, 2H, H_2, major–minor), 3.06 (brs, 2H, H_4, major–minor), 2.78 (brs, 2H, H_1, major–minor), 1.71 (d, J = 7.8 Hz, 2H, H_{7s}, major–minor), 1.34 (d, J = 7.8 Hz, 2H, H_{7a}, major–minor) (*E*/*Z*, 52:48). ^{13}C NMR (62.5 MHz) δ (ppm): 173.8 (2C, C=O, minor), 173.6 (2C, C=O, major), 155.7 (N=CH, minor), 155.6 (N=CH, major), 134.6, 133.7 (minor), 133.6 (major), 131.3 (minor), 131.2 (major), 129.0 ($C_{subst.}$, minor), 128.8 ($C_{subst.}$, major), 127.7 (minor), 127.6 (major), 51.8, 46.8, 45.3, 45.2, 44.0. LC–MSD: 295 [M^+ + Na], 273 [M^+ + 1], 272 [M^+], 229, 163. Anal. calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.69; H, 4.29; N, 10.19; S, 11.88.

Experimental procedure for the preparation of 8a–11a, 8b–11b, 10c, and 12

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 to form the catalyst complex. Then, aryl iodide (306 mg, 1.5 mmol), hydrazone (**3**–**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 24–48 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, and the residue was purified by chromatography.

5-(4-Chlorophenyl)*-N-*{[(2,4-dichlorophenyl) methylene]amino}-bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (8a)

Light yellow crystals, 55% yield. Mp 157 °C. R_f = 0.39 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3068, 3025, 2963, 2875, 1789, 1714, 1616, 1582, 1491, 1469, 1416, 1384, 1098, 866, 800. ^1H NMR (400 MHz) δ (ppm): 9.68 (s, 1H, H_8), 8.20 (d, J = 8.5 Hz, 1H, $H_{aro.}$), 7.47 (d, J = 1.9 Hz, 1H, $H_{aro.}$), 7.34 (dd, J = 1.9 and 8.5 Hz, 1H, $H_{aro.}$), 7.28 (d, J = 4.0 Hz, 2H, $H_{aro.}$), 7.13 (d, J = 8.4 Hz, 2H, $H_{aro.}$) 3.33–3.23 (m, 2H, H_2–H_3), 3.02 (brs, 1H, H_4), 2.97–2.89 (m, 2H, H_1–H_{5n}), 1.96–1.88 (m, 3H, H_{7s}, H_{6x} ve H_{6n}), 1.63 (d, J = 10.7, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 174.2–174.1 (2C, C=O), 156.9 (N=CH), 142.6 ($C_{subst.}$), 138.6 ($C_{subst.}$), 136.6 (C–Cl), 132.0 (C–Cl), 129.8, 129.4 (C–Cl), 128.9, 128.5, 128.3, 127.7, 46.8, 46.3, 46.0, 41.2, 40.0, 39.0, 32.6. LC–MS: 447 [M^+], 412, 390, 258, 171. Anal. calcd. for $C_{22}H_{17}Cl_3N_2O_2$: C, 59.02; H, 3.83; N, 6.26. Found: C, 58.91; H, 3.71; N, 6.16.

5-(4-Methoxyphenyl)*-N-*{[(2,4-dichlorophenyl) methylene]amino}-bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (8b)

Colorless crystals, 61% yield. Mp 184 °C. R_f = 0.39 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3037, 3015, 2975, 2960, 1771, 1711, 1596, 1582, 1499, 1471, 1454, 1377, 1275, 1260, 1174, 878, 867. ^1H NMR (500 MHz) δ (ppm): 9.59 (s, 1H, H_8), 8.11 (d, J = 7.8 Hz, 1H, $H_{aro.}$), 7.38–7.36 (m, 1H, $H_{aro.}$), 7.26–7.24 (m, 1H, $H_{aro.}$), 7.03 (d, J = 8.8 Hz,

2H, $H_{aro.}$), 6.75 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 3.73 (s, 3H, OCH_3), 3.19–3.13 (m, 2H, H_2–H_3), 2.91 (brs, 1H, H_4), 2.85–2.79 (m, 2H, H_1–H_{5n}), 1.84–1.82 (m, 3H, H_{7s}, H_{6n}, H_{6x}), 1.51 (d, J = 10.7 Hz, 1H, H_{7a}). ^{13}C NMR (125 MHz) δ (ppm): 174.3–173.2 (2C, C=O), 155.6–154.8 (N=CH), 136.8 ($C_{subst.}$), 135.4 ($C_{subst.}$), 132.7 (C–Cl), 130.3 (C–Cl), 128.0, 127.9, 127.0, 126.7, 112.8, 54.2, 45.8, 40.8, 40.0, 39.0, 38.6, 38.0, 31.6. LC–MS: 443 [M$^+$], 374, 322, 268. Anal. calcd. for $C_{23}H_{20}Cl_2N_2O_3$: C, 62.31; H, 4.55; N, 6.32. Found: C, 62.18; H, 4.39; N, 6.37.

5-(4-Methoxyphenyl)-N-*{[(5-bromo-2-hydroxyphenyl) methylene]amino}-bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (9a)*

Light yellow crystals, 47% yield. Mp 187 °C. R_f = 0.60 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3463, 3032, 3025, 2970, 2946, 1737, 1714, 1604, 1552, 1512, 1473, 1432, 1373, 1230, 1216, 1176, 822, 799, 777, 748. ^{1}H NMR (400 MHz) δ (ppm): 11.14 (s, 1H, OH), 9.43 (s, 1H, H_8), 7.48–7.46 (m, 2H, $H_{aro.}$), 7.12 (d, J = 8.6 Hz, 2H, $H_{aro.}$), 6.95 (d, J = 9.39 Hz, 1H, $H_{aro.}$), 6.85 (d, J = 8.6 Hz, 2H, $H_{aro.}$), 3.79 (s, 3H, OCH_3), 3.32–3.19 (m, 2H, H_2–H_3), 2.95 (brs, 1H, H_4), 2.88 (d, J = 6.8 Hz, 1H, H_1), 2.88–2.84 (m, 1H, H_{5n}), 1.95–1.89 (m, 3H, $H_{7s,}$ H_{6x} ve H_{6n}), 1.60 (d, J = 9.8 Hz, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 174.5–174.4 (2C, C=O), 162.1 (N=CH), 144.3 ($C_{subst.}$), 135.3, 132.9, 131.8, 130.7 ($C_{subst.}$), 128.9, 128.7, 128.5, 127.9 (C–OCH_3), 127.1, 126.7 (C–Br), 126.2, 123.3, 47.0, 46.5, 46.0, 41.8, 40.0, 39.1, 32.5. LC–MS: 470 [M$^+$ + 1], 469 [M$^+$], 468 [M$^+$ – 1], 390, 374, 344, 296, 220, 180. Anal. calcd. for $C_{23}H_{21}BrN_2O_4$: C, 58.86; H, 4.51; N, 5.97. Found: C, 58.73; H, 4.40; N, 5.86.

5-(6-Chloro-3-pyridyl)-N-*{[(5-bromo-2-hydroxy-phenyl)methylene]amino}-bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (9b)*

Colorless crystals, 60% yield. Mp 175 °C. R_f = 0.59 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3362, 3037, 2950, 2875, 1764, 1712, 1604, 1582, 1474, 1461, 1431, 1178, 825, 789, 740. ^{1}H NMR (500 MHz) δ (ppm): 10.96 (s, 1H, OH), 9.35 (s, 1H, H_8), 8.17 (d, J = 2.9 Hz, 1H, $H_{aro.}$), 7.40–7.38 (m, 3H, $H_{aro.}$), 7.19 (d, J = 8.8 Hz, 1H, $H_{aro.}$), 6.86 (d, J = 8.8 Hz, 1H, $H_{aro.}$), 3.27 (dd, J = 5.8, 9.8 Hz, 1H, H_3), 3.20 (ddd, J = 1.9, 4.8, and 6.8 Hz, 1H, H_2), 2.98 (brs, 1H, H_4), 2.92 (d, J = 4.8 Hz, 1H, H_1), 2.83 (dd, J = 5.8 and 8.8 Hz, 1H, H_{5n}), 1.90 (ddd, J = 1.9, 8.8, and 10.7 Hz, 1H, H_{6n}), 1.82–1.76 (m, 2H, H_{7s}, H_{6x}), 1.62 (d, J = 10.7 Hz, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 172.2–172.1 (2C, C=O), 159.8 (N=CH), 157.8 (C–OH), 148.7 ($C_{subst.}$), 147.3, ($C_{subst.}$), 137.3 (C–Cl), 136.6 (C–Br), 135.4, 133.6, 123.0 118.6, 117.4, 110.1 45.7, 45.2, 44.5, 39.0, 38.2, 38.1, 31.6. LC–MS: 475 [M$^+$ + 1], 474 [M$^+$], 473 [M$^+$ – 1], 395, 345, 282, 180. Anal. calcd. for $C_{21}H_{17}BrClN_3O_3$: C, 53.13; H, 3.61; N, 8.85. Found: C, 53.03; H, 3.70; N, 8.79.

5-(2-Thienyl)-N-*{[(2,5-dimethoxyphenyl) methylene]amino}-bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (10a)*

Colorless crystals, 65% yield. Mp 167 °C. R_f = 0.42 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3119, 3058, 2964, 2881, 2837, 1759, 1698, 1613, 1595, 1494, 1467, 1455, 1421, 1384, 1224, 1195, 815, 733, 711. ^{1}H NMR (400 MHz) δ (ppm): 9.34 (s, 1H, H_8), 7.66 (d, J = 2.8 Hz, 1H, $H_{aro.}$), 7.15 (d, J = 5.2 Hz, 1H, $H_{aro.}$), 7.05 (dd, J = 3.2 and 9.2 Hz, 1H, $H_{aro.}$), 6.94 (dd, J = 3.6 and 4.8 Hz, 1H, $H_{aro.}$), 6.88 (d, J = 9.2 Hz, 1H, $H_{aro.}$), 6.83 (d, J = 3.2 Hz, 1H, $H_{aro.}$), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.29–3.19 (m, 3H, H_2–H_3 and H_{5n}), 2.98 (brs, 2H, H_1–H_4), 2.11–2.01 (m, 2H, H_{6x}–H_{6n}), 1.94–1.89 (m, 1H, H_{7s}), 1.66 (d, J = 10.7 Hz, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 174.0–173.9 (2C, C=O), 159.8 (N=CH), 154.1 (C–OCH_3), 153.6 (C–OCH_3), 149.3 ($C_{subst.}$), 126.8, 123.5, 123.4 ($C_{subst.}$), 121.5, 121.4, 112.7, 110.0, 55.9–56.2 (2C, OCH_3), 47.4, 46.6, 46.2, 39.6, 39.5, 37.9, 34.9. LC–MS: 433 [M + Na$^+$], 410 [M$^+$], 409 [M$^+$ – 1], 274, 244, 218, 138. Anal. calcd. for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82; S, 7.81. Found: C, 64.20; H, 5.29; N, 6.71; S, 7.99.

5-(4-Chlorophenyl)-{[(2,5-dimethoxyphenyl) methylene]amino}-bicyclo[2.2.1]heptane-endo-*2,*endo-*3-dicarboximide (10b)*

Colorless crystals, 55% yield. Mp 185 °C. R_f = 0.45 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3058, 2969, 2947, 2878, 2839, 1737, 1706, 1614, 1598, 1493, 1462, 1423, 1376, 1217, 1189, 810, 792, 751. ^{1}H NMR (500 MHz) δ (ppm): 9.27 (s, 1H, H_8), 7.57 (d, J = 3.8 Hz, 1H, $H_{aro.}$), 7.17 (d, J = 8.7 Hz, 2H, $H_{aro.}$), 7.05 (d, J = 8.7 Hz, 2H, $H_{aro.}$), 6.96 (dd, J = 3.8 and 8.6 Hz, 1H, $H_{aro.}$), 6.79 (d, J = 8.7 Hz, 1H, $H_{aro.}$), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.25–3.21 (m, 2H, H_2–H_3), 3.16 (ddd, J = 1.9, 8.8, and 11.7 Hz, 1H, H_{5n}), 2.98 (d, J = 4.8 Hz, 1H, H_1), 2.91 (brs, 1H, H_4), 2.08 (ddd, J = 1.9, 8.8, and 11.7 Hz, 1H, H_{6n}), 1.89 (d, J = 9.7 Hz, 1H, H_{6x}), 1.68–1.62 (m, 2H, H_{7a} ve H_{7s}). ^{13}C NMR (100 MHz) δ (ppm): 173.1–173.0 (2C, C=O), 158.6 (N=CH), 153.1 (C–OCH_3), 152.7 (C–OCH_3), 141.8 (C–Cl), 130.9 ($C_{subst.}$), 127.5, 127.4, 120.6 ($C_{subst.}$), 120.2, 111.8, 109.1, 55.3–54.9 (2C, OCH_3), 45.9, 45.2, 44.9, 40.2, 38.9, 38.0, 31.6. LC–MS: 439 [M$^+$ + 1], 438 [M$^+$], 437 [M$^+$ – 1], 378, 322, 268, 246, 139. Anal. calcd. for $C_{24}H_{23}ClN_2O_4$: C, 65.68; H, 5.28; N, 6.38. Found: C, 65.53; H, 5.21; N, 6.43.

5-(2-Chlorophenyl)-{[(2,5-dimethoxyphenyl) methylene]amino}-bicyclo[2.2.1]heptane-endo-*2,*endo-*3-dicarboximide (10c)*

Colorless crystals, 59% yield. Mp 126 °C. R_f = 0.39 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3053, 2969, 2951, 2875, 1768, 1704, 1613, 1596, 1493, 1464, 1441, 1180, 837, 812, 792. ^{1}H NMR (500 MHz) δ (ppm): 9.21 (s, 1H, H_8), 7.59 (d, J = 3.9 Hz, 1H, $H_{aro.}$), 7.29 (d, J = 7.8 Hz, 1H, $H_{aro.}$), 7.18–7.13 (m, 2H, $H_{aro.}$), 7.07 (ddd, J = 1.9, 8.8, and 14.6 Hz, 1H, $H_{aro.}$), 6.96 (dd, J = 2.9 and 8.8 Hz, 1H, $H_{aro.}$), 6.79 (d, J = 8.7 Hz, 1H, $H_{aro.}$), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.25–3.21 (m, 2H, H_2–H_3), 3.16 (ddd, J = 1.9, 8.7, and 11.7 Hz, 1H, H_{5n}), 2.98 (d, J = 4.8 Hz, 1H, H_1), 2.91 (brs, 1H, H_4), 2.08 (ddd, J = 1.9, 8.7, and 11.7 Hz, 1H, H_{6n}), 1.89 (d, J = 9.7 Hz, 1H, H_{6x}), 1.68–1.60 (m, 2H, H_{7a}–H_{7s}). ^{13}C NMR (100 MHz) δ (ppm): 173.1–172.8 (2C, C=O), 154.5 (N=CH), 156.1 (C–Cl), 154.5 ($C_{subst.}$), 140.7 (C–OCH_3), 138.1 ($C_{subst.}$), 128.8, 127.1, 120.2, 125.2, 120.6, 111.6, 110.2, 55.4–55.2 (2C, OCH_3), 46.1, 45.2, 43.6, 40.0, 39.0, 38.0, 32.2. LC–MS: 439 [M$^+$ +

1], 438 [M+], 437 [M+ – 1], 378, 322, 268, 246, 139. Anal. calcd. for $C_{24}H_{23}ClN_2O_4$: C, 65.68; H, 5.28; N, 6.38. Found: C, 65.59; H, 5.23; N, 6.45.

5-(Phenyl)*-N-*{[2-napthylmethylene]amino}bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (11a)

Light yellow crystals, 62% yield. Mp 132 °C. R_f = 0.57 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3053, 3012, 2970, 2921, 2882, 1737, 1724, 1703, 1605, 1587, 1512, 1455, 1433, 1178, 761, 738. ^{1}H NMR (400 MHz) δ (ppm): 9.37 (s, 1H, H_8), 8.20 (s, 1H, $H_{aro.}$), 8.16 (d, J = 8.7 Hz, 1H, $H_{aro.}$), 7.94–7.87 (m, 3H, $H_{aro.}$), 7.53–7.60 (m, 2H, $H_{aro.}$), 7.33–7.19 (m, 5H, $H_{aro.}$), 3.34–3.24 (m, 2H, H_2–H_3), 3.03 (brs, 3H, H_1–H_4 and H_{5n}), 2.05–1.94 (m, 3H, H_{7s}, H_{6x} ve H_{6n}), 1.62 (d, J = 9.0 Hz, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 174.5–174.4 (2C, C=O), 162.1 (N=CH), 144.3 ($C_{subst.}$), 135.3, 132.9, 131.8, 130.7, 128.9, 128.7, 128.5, 127.9, 127.0, 126.7, 126.2, 123.3, 47.0, 46.5, 46.0, 41.8, 40.0, 39.1, 32.5. LC–MS: 395 [M+ + 1], 394 [M+], 393 [M+ – 1], 332, 234, 206, 194, 167. Anal. calcd. for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.70; N, 6.99.

5-(2-Thienyl)*-N-*{[2-naphthylmethylene]amino}bicyclo-[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (11b)

Light yellow crystals, 62% yield. Mp 145 °C. R_f = 0.57 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3058, 3045, 2953, 2921, 2875, 1734, 1700, 1607, 1569, 1467, 1438, 1350, 1180, 773, 760, 741, 697. ^{1}H NMR (400 MHz) δ (ppm): 9.35 (s, 1H, H_8), 8.20 (brs, 1H, $H_{aro.}$), 8.15 (d, J = 8.8 Hz, 1H, $H_{aro.}$), 7.94–7.87 (m, 3H, $H_{aro.}$), 7.53–7.60 (m, 2H, $H_{aro.}$), 7.16 (d, J = 4.7 Hz, 1H, $H_{aro.}$), 6.95–6.92 (m, 1H, $H_{aro.}$), 6.84 (d, J = 3.4 Hz, 1H, $H_{aro.}$), 3.33–3.21 (m, 3H, H_2–H_3 and H_{5n}), 3.01 (brs, 2H, H_1–H_4), 2.18–2.03 (m, 2H, H_{6x}–H_{6n}), 1.95–1.90 (m, 1H, H_{7s}), 1.67 (d, J = 10.2 Hz, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 174.2–174.1 (2C, C=O), 162.2 (N=CH), 149.2 ($C_{subst.}$), 135.3, 132.9, 131.8, 130.6 ($C_{subst.}$), 128.9, 128.7, 127.9, 126.8, 126.7, 123.4, 123.3, 47.3, 46.6, 46.1, 39.6, 39.4, 38.0, 35.0. LC–MS: 400 [M+], 399 [M+ – 1], 370, 234, 206, 167. Anal. calcd. for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99; S, 8.01. Found: C, 71.81; H, 5.19; N, 6.81; S, 8.08.

5-(4-Methoxyphenyl)*-N-*{[2-thienylmethylene] amino}-bicyclo[2.2.1]heptane*-endo-*2,*endo-*3-dicarboximide (12)

Colorless crystals, 58% yield. Mp 177 °C. R_f= 0.49 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3082, 3032, 3068, 3053, 3012, 2955, 2886, 1764, 1713, 1609, 1581, 1511, 1464, 14434, 1373, 1247, 1170, 802, 744, 723. ^{1}H NMR (500 MHz) δ (ppm): 9.24 (s, 1H, H_8), 7.48 (d, J = 4.8 Hz, 1H, $H_{aro.}$), 7.43 (d, J = 2.9 Hz, 1H, $H_{aro.}$), 7.05–7.02 (m, 3H, $H_{aro.}$), 6.75 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 3.69 (s, 3H, OCH_3), 3.18–3.09 (m, 2H, H_2–H_3), 2.89 (brs, 1H, H_4), 2.85–2.82 (m, 2H, H_1–H_{5n}), 1.83–1.79 (m, 3H, H_{7s}, H_{6n}, H_{6x}), 1.49 (d, J = 10.7 Hz, 1H, H_{7a}). ^{13}C NMR (100 MHz) δ (ppm): 173.3–173.2 (2C, C=O), 157.0 (N=CH), 154.8 ($C_{subst.}$), 136.8 ($C_{subst.}$), 135.4, 132.7, 130.3, 127.0, 126.7, 112.8, 54.2 (C–OCH_3), 45.9, 45.4, 45.3, 40.0, 38.9, 38.0, 31.6. LC–MS: 381 [M+ + 1], 380 (M+), 379 [M+ – 1], 366, 232, 206, 167. Anal. calcd. for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36; S, 8.43. Found: C, 66.08; H, 5.33; N, 7.23; S, 8.47.

Experimental procedure for the preparation of 14–18

To a solution of 4-chlorobenzaldoxime (202.25 mg, 1.3 mmol) in dichloromethane was added tricyclic hydrazone **3–7** (1 mmol), and the solution was cooled to 0 °C. Aqueous sodium hypochloride (5.25%, 3.5 g, 2.5 mmol) was added dropwise over 30 min, and the reaction was stirred overnight (0 °C – room temperature). The reaction mixture was extracted with either dichloromethane (3 × 10 mL) or diethyl ether and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by chromatography.

4,8-Methano-3-(4-chlorophenyl)-6-(2,4-dichloromethyleneamino)-4,4a,8,*exo-*8a-tetrahydro*-exo-*3aH-isoxazolo[5,4-f]isoindole-5,7(6H,7aH)*-endo-*dione (14)

Colorless crystals, 80% yield. Mp 241 °C. R_f = 0.60 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3100, 3045, 2959, 2870, 1775, 1707, 1598, 1583, 1496, 1471, 1377, 1357, 1315, 1301, 1175, 900, 868, 827. ^{1}H NMR (400 MHz) δ (ppm): 9.35 (s, 1H, H_{10}), 8.10 (d, J = 8.8 Hz, 1H, $H_{aro.}$), 7.55 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 7.39 (d, J = 1.95 Hz, 1H, $H_{aro.}$), 7.32 (d, J = 7.8 Hz, 2H, $H_{aro.}$), 7.26 (dd, J = 1.9 and 7.8 Hz, 1H, $H_{aro.}$), 4.73 (d, J = 7.8 Hz, 1H, H_{8an}), 3.61 (dd, J = 1.4 and 7.8 Hz, 1H, H_{3an}), 3.26–3.23 (m, 2H, H_{4a}–H_{7a}), 3.22 (brs, 1H, H_8), 3.02 (brs, 1H, H_4), 1.82 (d, J = 10.7 Hz, 1H, H_{9s}), 1.57 (d, J = 9.0 Hz, 1H, H_{9a}). ^{13}C NMR (100 MHz) δ (ppm): 172.0–171.1 (2C, C=O), 156.7 ($C_{subst.}$), 154.2 (N=CH), 137.9 ($C_{subst.}$), 135.7 ($C_{subst.}$), 135.4 ($C_{subst.}$), 128.9, 128.2, 128.0, 127.9, 127.0, 126.8, 125.5, 82.8, 51.4, 44.9, 43.8, 41.5, 41.2, 34.7. LC–MS: 491 [M+ + 1], 488.75 [M+], 487 [M+ – 1]. MS-ESI (EI, 70 eV): 490 [M+], 389.38, 363.31, 334.85, 317.14, 270.92, 220.07, 202.13, 167.23. Anal. calcd. for $C_{23}H_{16}Cl_3N_3O_3$: C, 56.52; H, 3.30; N, 8.60. Found: C, 56.01; H, 3.33; N, 8.65.

4,8-Methano-3-(4-chlorophenyl)-6-(5-bromo-2-hydroxy-phenylmethyleneamino)-4,4a,8,*exo-*8a-tetrahydro*-exo-*3aH-isoxazolo[5,4-f]isoindole-5,7(6H,7aH)*-endo-*dione (15)

Colorless crystals, 78% yield. Mp 162 °C. R_f = 0.58 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3394, 3011, 2979, 2946, 1791, 1708, 1608, 1594, 1494, 1476, 1403, 1354, 1322, 1169, 741, 716. ^{1}H NMR (400 MHz) δ (ppm): 10.91 (s, 1H, O–H), 9.40 (s, 1H, H_{10}), 7.62 (d, J = 8.5 Hz, 2H, $H_{aro.}$), 7.50 (d, J = 7.8 Hz, 2H, $H_{aro.}$), 7.41 (d, J = 8.5 Hz, 2H, $H_{aro.}$), 6.95 (d, J = 9.0 Hz, 1H, $H_{aro.}$), 4.79 (d, J = 8.0 Hz, 1H, H_{8an}), 3.66 (d, J = 8.0 Hz, 1H, H_{3an}), 3.34 (d, J = 3.7 Hz, 2H, H_{4a}–H_{7a}), 3.30 (brs, 1H, H_8), 3.11 (brs, 1H, H_4), 1.92 (d, J = 11.3 Hz, 1H, H_{9s}), 1.67 (d, J = 11.3 Hz, 1H, H_{9a}). ^{13}C NMR (100 MHz) δ (ppm): 172.3–171.7 (2C, C=O), 161.5 (N=CH), 158.8 ($C_{subst.}$), 155.1 ($C_{subst.}$), 136.6 ($C_{subst.}$), 136.5 ($C_{subst.}$), 134.7, 129.3, 128.0, 126.3, 119.7, 118.1, 111.2, 83.2, 52.5, 45.8, 44.7, 42.5, 42.1, 35.7. LC–MS: 516 [M+ + 1], 515 [M+], 513 [M+ – 1]. Anal. calcd. for $C_{23}H_{17}BrClN_3O_4$: C, 53.67; H, 3.33; N, 8.16. Found: C, 53.48; H, 3.41; N, 8.19.

4,8-Methano-3-(4-chlorophenyl)-6-(2,5-dimethoxy-phenylmethyleneamino)-4,4a,8,*exo-*8a-tetrahydro*-exo-*3aH-isoxazolo[5,4-f]isoindole-5,7(6H,7aH)*-endo-*dione (16)

Colorless crystals, 69% yield. Mp 211 °C. R_f = 0.49 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3053, 3009, 2970,

2947, 1767, 1704, 1610, 1599, 1496, 1468, 1422, 1406, 1378, 1225, 1184, 920, 900, 822. ^{1}H NMR (400 MHz) δ (ppm): 9.21 (s, 1H, H_{10}), 7.57–7.56 (brs, 1H, $H_{aro.}$), 7.54 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 7.30 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 6.98 (dd, J = 2.9 and 8.8 Hz, 1H, $H_{aro.}$), 6.80 (d, J = 9.7 Hz, 1H, $H_{aro.}$), 4.76 (d, J = 8.8 Hz, 1H, H_{8an}), 3.77 (s, 3H, m-subst., OCH_3), 3.74 (s, 3H, *o*-substituted, OCH_3), 3.63 (d, J = 8.8 Hz, 1H, H_{3an}), 3.21 (d, J = 3.9 Hz, 2H, H_{4a}–H_{7a}), 3.19 (brs, 1H, H_8), 3.00 (brs, 1H, H_4), 1.80 (d, J = 11.7 Hz, 1H, H_{9s}), 1.55 (d, J = 11.7 Hz, 1H, H_{9a}). ^{13}C NMR (100 MHz) δ (ppm): 172.0–171.1 (2C, C=O), 159.5 (N=CH), 154.3 ($C_{subst.}$), 153.2 ($C_{subst.}$), 152.7 ($C_{subst.}$), 135.3 ($C_{subst.}$), 128.2, 127.0, 125.5, 120.6, 120.1, 111.8, 109.0, 82.2, 55.2, 54.9, 51.5, 44.8, 43.9, 41.7, 41.1, 34.7. LC–MS: 481 [M^+ + 1], 480 [M^+]. Anal. calcd. for $C_{25}H_{22}ClN_3O_5$: C, 62.57; H, 4.62; N, 8.76. Found: C, 62.49; H, 4.59; N, 8.81.

4,8-Methano-3-(4-chlorophenyl)-6-(2-napthylmethyleneamino)-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-f]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (17)

Colorless crystals, 85% yield. Mp 135 °C. R_f = 0.41 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3027, 3011, 2958, 2916, 2850, 1767, 1706, 1625, 1606, 1593, 1493, 1468, 1366, 1346, 1178, 798, 738, 724. ^{1}H NMR (400 MHz) δ (ppm): 9.20 (s, 1H, H_{10}), 8.01 (dd, J = 1.4 and 8.8 Hz, 1H, $H_{aro.}$), 7.82–7.77 (m, 3H, $H_{aro.}$), 7.53 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 7.50–7.43 (m, 2H, $H_{aro.}$), 7.28 (d, J = 8.8 Hz, 2H, $H_{aro.}$), 4.75 (d, J = 8.3 Hz, 1H, H_{8an}), 3.63 (d, J = 8.3 Hz, 1H, H_{3an}), 3.23 (d, J = 4.8 Hz, 2H, H_{4a}–H_{7a}), 3.20 (brs, 1H, H_8), 2.99 (brs, 1H, H_4), 1.80 (d, J = 11.2 Hz, 1H, H_{9s}), 1.55 (d, J = 11.2 Hz, 1H, H_{9a}). ^{13}C NMR (100 MHz) δ (ppm): 172.2–171.4 (2C, C=O), 161.8 ($C_{subst.}$), 154.3 (N=CH), 135.3 ($C_{subst.}$), 134.4 ($C_{subst.}$), 131.8 ($C_{subst.}$), 131.0, 129.3, 128.2, 127.9, 127.8, 127.1, 127.0, 125.8, 125.5, 122.0, 82.3, 52.4, 51.4, 44.8, 43.8, 41.6, 41.1. LC–MS: 471 [M^+ + 1], 470 [M^+], 469 [M^+ – 1]. Anal. calcd. for $C_{27}H_{20}ClN_3O_3$: C, 69.01; H, 4.29; N, 8.94. Found: C, 69.19; H, 4.26; N, 8.78.

4,8-Methano-3-(4-chlorophenyl)-6-(2-thienylmethyleneamino)-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-f]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (18)

Colorless crystals, 75% yield. Mp 169 °C. R_f = 0.47 (2:1, ethyl acetate/*n*-hexane). FTIR (cm^{-1}): 3088, 2976, 2921, 1769, 1701, 1592, 1514, 1494, 1343, 1319, 1184, 806, 728, 712. ^{1}H NMR (400 MHz) δ (ppm): 9.25 (s, 1H, H_{10}), 7.62 (d, J = 8.3 Hz, 2H, $H_{aro.}$), 7.59 (d, J = 5.0 Hz, 1H, $H_{aro.}$), 7.53 (d, J = 3.6 Hz, 1H, $H_{aro.}$), 7.38 (d, J = 8.2 Hz, 1H, $H_{aro.}$), 7.15 (d, J = 4.0 Hz, 2H, $H_{aro.}$), 4.80 (d, J = 8.3 Hz, 1H, H_{8an}), 3.69 (d, J = 8.3 Hz, 1H, H_{3an}), 3.32 (d, J = 3.7 Hz, 2H, H_{4a}–H_{7a}), 3.26 (brs, 1H, H_8), 3.07 (brs, 1H, H_4), 1.88 (d, J = 11.2 Hz, 1H, H_{9s}), 1.64 (d, J = 11.2 Hz, 1H, H_{9a}). ^{13}C NMR (100 MHz) δ (ppm): 173.0–171.3 (2C, C=O), 156.7 ($C_{subst.}$), 155.3 (N=CH), 137.2 ($C_{subst.}$), 136.3, 134.4, 131.9, 129.2, 128.1, 127.9, 126.4, 83.3, 52.4, 45.8, 44.7, 42.5, 42.1, 35.7. LC–MS: 427 [M^+ + 1], 426 [M^+], 425 [M^+ – 1]. Anal. calcd. for $C_{21}H_{16}ClN_3O_3S$: C, 59.22; H, 3.79; N, 9.87; S, 7.53. Found: C, 59.01; H, 3.67; N, 9.75; S, 7.59.

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