Synthesis of 4-oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione derivatives as lead scaffolds for neuroprotective agents

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Abstract

Neurodegenerative disorders are characterised by progressive loss of neuronal functions. Of the proposed mechanisms, excitotoxicity, mediated by prolonged glutamate activation and calcium overload, is prominent. NGP1-01, a polycyclic cage amine, and tricyclo[6.2.1.0^2,7]undec-9-ene-3,6-dione have been shown to display calcium-modulating properties. In this study, we synthesised structurally-related 4-oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione as the base scaffold, and incorporated various functional moieties through aminolysis, to afford a series of imide derivatives. All final compounds were obtained in yields between 47-97% and their structures were confirmed by NMR, IR and MS. These structurally-related derivatives could potentially act as neuroprotective agents. Additionally, their synthetic versatilities could make them precursors, as lead compounds, to potential pharmacologically-active agents.

Keywords: 4-Oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione, cycloaddition reactions, aminolysis, norbornenes, norbornene scaffolds, neurodegenerative disorders

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Introduction

Neurodegenerative disorders are diseases characterised by persistent and progressive loss of neuronal function that eventually lead to neuronal death and reduction of sensory, motor, cognition and memory functions.\textsuperscript{1,2} These disorders include Parkinson’s disease (PD), Alzheimer’s disease (AD), progressive supranuclear palsy, amyotrophic lateral sclerosis (ALS) and Huntington disease.\textsuperscript{3} These multifactorial diseases not only share many common features, such as a late appearance in life, neuronal loss and synaptic abnormalities, but also share common molecular mechanisms that include excitotoxicity, mitochondrial dysfunction, apoptosis, oxidative stress and impaired protein homeostasis.\textsuperscript{4} Of the proposed mechanisms, the influence of excitotoxicity is prominent. In excitotoxicity, extracellular glutamate levels are elevated to such an extent that they over-activate ionotropic receptors, \textit{N}-methyl-\textit{D}-aspartate (NMDA) receptors, and associated voltage-gated calcium channels (VGCC) in particular. This results in the increase of intracellular calcium ions, thus disrupting calcium homeostasis.\textsuperscript{5-9} Due to the sensitivity of neurons towards intracellular calcium-ion concentration, disruption of calcium homeostasis can lead to destructive consequences, such as damage to cell dendrites or neuronal cell death, in part, by activating calpain, a cysteine protease, that degrades a variety of substrates, such as cytoskeletal proteins, membrane receptors and metabolic enzymes.\textsuperscript{10-13} Therefore, molecules capable of modulating calcium influx \textit{via} the NMDA receptor and/or VGCC could provide protection against calcium overload mediated by prolonged glutamate activity. MK-801 has been shown to uncompetitively block NMDA receptors, but is marked by undesirable psychotomimetic side effects such as hallucination, psychosis, dysphoria and amnesia. This makes it unsuitable for therapeutic purpose.\textsuperscript{14}

To date, no drug is available to stop the neurodegenerative process. Adamatanes such as amantadine and memantine (Figure 1), however, have been shown to offer symptomatic relief in patients with PD and AD, respectively, and have subsequently been approved by the FDA for these purposes.

![Figure 1. Polycyclic cage-like uncompetitive NMDA receptor antagonists.](image)

The activities and clinical tolerabilities of the adamantanes are attributed to their ability to uncompetitively block NMDA receptors while displaying minimal adverse effects.\textsuperscript{15-18} Over the past few decades, a number of structurally-related polycyclic cage amines have been synthesised.\textsuperscript{19-26} A very good example is NGP1-01, a multifunctional neuroprotective agent that displayed dual attenuation of calcium entry in neuronal cells by blocking NMDA receptors and VGCCs. It exhibits neuroprotective properties and a good safety profile as demonstrated by several studies.\textsuperscript{27-31} The need for more structurally-related scaffolds with similar effects and good safety profiles, that could potentially halt the degenerative process of neuronal cells, is thus, clear.

A series of tricycloundecene derivatives that exhibit calcium-inhibitory effects \textit{via} the NMDA receptor and VGCC have been reported (Figure 2).\textsuperscript{26}
The significant activity observed for tricyclo[6.2.1.0^2,7]undec-9-ene-3,6-dione (1) was attributed to its structural similarities to MK-801 and the adamantanes (Figure 1). In the synthesis of 1, the cycloaddition reaction between p-benzoquinone and monomerised cyclopentadiene yielded an intermediate, which was subsequently selectively reduced by zinc to afford the desired compound in fair yield (Figure 3).^25,26

Cycloaddition reactions are common, and found to be useful in the formation of most norbornene-derived molecules, particularly the polycyclic-cage scaffolds. These molecules are prominent scaffolds in improving the pharmacokinetic and pharmacological properties of active pharmaceutical substances. Moreover, they display wide reactivity as substrates for various functional moieties, and, as such, are very useful and highly desirable synthetic intermediates in the field of organic and organometallic chemistry. The desire to continuously expand on existing lead molecules with neuroprotective potential justify the need for additional structurally-related analogues.

In the present study, we explored similar cycloaddition reactions to synthesise 4-oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione (2), which was used as the base scaffold. To this base structure, a number of aliphatic, heterocyclic or aromatic functionalities were incorporated through aminolysis to synthesise a series of 4-oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione derivatives (3-13, Figure 4).

This series of compounds are structurally related to NGP1-01, MK-801, the adamantanes and 1, and we hypothesise that these derivatives would exhibit similar or improved calcium-modulating effects and significant neuroprotective properties. They may also serve as lead scaffolds in the development of neuroprotective agents.
**Results and Discussion**

**Synthesis and structural elucidation**

Under reflux conditions, the Diels-Alder reaction between maleic anhydride and cyclopentadiene afforded compound 2, an open cage-like 4-oxatricyclo[5.2.1.0²6]dec-8-ene-3,5-dione molecule, which was used to obtain compounds 3-13 in moderate-to-high yields (see Figure 4). The aminolysis of 2 with benzylamine afforded compound 3 and the byproduct 4 (dibenzylamide moiety; Figure 5) in yields of 83% and 6%, respectively.

The presence of the norbornene scaffold in compound 4 justifies its inclusion in the series. Moreover, the replacement of the furandione moiety with a dibenzylamine moiety provides scope for additional structure-activity relationships within this series. Compounds 9 and 10 were obtained under similar reaction conditions involving compound 2 and ethylenediamine; however, they differed in their work-up. Extraction using ethyl acetate afforded 9 in a yield of 90%, while precipitation from ice-cold methanol produced compound 10 (10%; Figure 5). Compound 10 was included in the series due to its bis-4-oxatricyclo[5.2.1.0²6]dec-8-ene-3,5-dione structure. Amongst the diamines (9-13), the reaction of compound 2 and N,N-dimethylethylene diamine
produced the highest yield, 96% (13). This was due to the dimethyl substitution of one of the amines which limited byproduct formation.

The structures of compounds 2-13 were characterised by their respective $^1$H, $^{13}$C, IR and HRMS spectra. In the IR spectra, the characteristic C=O signals were observed in the 1654-1766 cm$^{-1}$ region for all the compounds (2-13). The appearance of absorption bands at around 1654 cm$^{-1}$ (C=O) and 3304 cm$^{-1}$ (N-H) confirms the amide moieties observed in 4. The presence of characteristic medium and broad signals for aliphatic primary amines in the 3372-3386 cm$^{-1}$ region indicate mono-substitution of the diamines, which correspond to the structure of compound 9, 11 and 12. The appearance of a strong, sharp absorption band at 3265 cm$^{-1}$ supported the presence of an aliphatic alkyne in the structure of 6. In the $^1$H NMR spectra, the bridge protons resonate in the $\delta = 1.55-1.81$ and $\delta = 1.45-1.59$ ppm range for all compounds. The aromatic protons of 3 and 4 were identified as multiplets in the $\delta = 7.18-7.31$ ppm region with integrations of five and ten hydrogens, respectively. The aromatic protons of 8 were observed as a doublet of doubles (δ = 7.20-7.24 ppm; J 15.9, 7.6 Hz), a triplet (δ = 6.93-6.97 ppm; J 7.4 Hz) and a doublet (δ = 6.75-6.76 ppm; J 7.7 Hz). The piperidinyl protons of 5 were observed as a triplet (δ = 3.07-3.10 ppm; 4H) and two multiplets (δ = 1.61-1.67 ppm, 4H; δ = 1.37-1.43 ppm, 2H). In compound 6, the doublet (δ 4.09 ppm; J 2.5 Hz; 2H) and triplet (δ 2.13 ppm; J 2.5 Hz; 1H) signals were assigned to the CH$_2$ and CH groups of the propargyl conjugate. The appearance of multiplet (δ = 1.41-1.51 ppm; 2H) and triplet (δ = 0.84-0.87 ppm; J 7.4 Hz; 3H) signals in the spectra of 7 indicates the presence of a propyl moiety. The presence of a triplet at δ = 2.72-2.75 ppm (J 6.4 Hz; 2H), and a doublet at δ = 3.40 ppm (J 6.4 Hz; 2H), confirms the successful incorporation of the diamine conjugate (9). The disappearance of signals in the 2.00-3.00 ppm region suggest dissubstitution of the diamine to afford 10. Due to the symmetrical nature of the carbons adjacent to the nitrogen groups, the CH$_2$ protons were observed downfield as a multiplet (δ = 3.64 ppm; 4H). In comparison to 9, the appearance of a singlet (δ = 2.20 ppm; 6H) indicates the presence of the dimethyl substituent as observed in 13. The appearance of a doublet of triplet signal and a doublet of doublet signal at δ = 1.59-1.64 ppm (J 6.7, 4.8 Hz; 1H) and δ = 1.65-1.71 ppm (J 13.7, 5.1 Hz; 1H), respectively, indicates the presence of an additional CH$_2$ group when compared to compound 9, thus, confirming the formation of the diaminopropane conjugate (11). In comparison to 11, the additional CH$_2$ group of 12 was observed as a multiplet at δ = 1.34-1.41 ppm with an integration of two protons, thus, confirming the presence of a diaminobutane conjugate. In general, all of the protons of compounds 9-13 were accounted for, and assigned according to their respective spectra. In the $^{13}$C NMR spectra, the characteristic signals for carbonyl and aromatic moieties were observed in the δ = 171-178 ppm and δ = 115-138 ppm regions, respectively. The carbon signals in the spectra of all compounds (2-13) were identified, and they corresponded to their proposed structures. The HRMS showed the respective molecular ion peaks that correspond to the empirical formula of each compound.

Reaction conditions that led to the formation of 2 and 3 afforded the respective endo-isomers. The physical characteristics of these isomers correspond to those reported in the literature.$^{43-46}$ Similar reaction conditions were used in the synthesis of the remaining compounds (5-13), and their respective isomers were derived in a similar manner.

NMDA and VGCC studies

The abilities of compounds 2-13 to block calcium influx via the NMDA receptor and VGCCs were evaluated using neuroblastoma cells, and the fluorescent ratiometric calcium indicator FURA-2AM, as previously described in detail by our group.$^{21,22,26}$ The compounds were found to exhibit calcium modulating abilities at the NMDA receptor and VGCC within a similar activity range as NGP1-01 and 1 at a 10 µM concentration.
These initial promising biological findings have now led to the further exploration of their calcium modulating effect, neuroprotective abilities and toxicity profiles.

Conclusions

4-Oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione derivatives (2-13) were successfully synthesised and characterised. All compounds, except the byproducts 4 (6.3%) and 10 (12.3%), were obtained in considerable yields of 47-96%. We established that the derivatives (2-13) have significant calcium-modulating effect and could potentially act as neuroprotective agents. Additionally, they could serve as versatile synthetic precursors for potential neuroprotective agents or pharmaceutically-active scaffolds.

Experimental Section

General. Unless otherwise specified, all reagents were obtained from Merck (St Louis, MO, USA) and Sigma-Aldrich® (Darmstadt, Germany) and used without further purification unless specified. Solvents used for reactions and chromatography were purchased from various commercial sources and dried using standard methods. The structures of the desired compounds were characterised and confirmed by means of nuclear magnetic resonance (NMR), Fourier transform infrared (FT-IR) and mass spectrometry (MS) techniques. In the NMR spectroscopy, $^1$H, $^{13}$C and distortionless enhancement of polarisation transfer (DEPT) analysis were performed for structural elucidation. Using a Bruker Avance III HD spectrometer, the $^1$H spectra were obtained at 400 MHz while the $^{13}$C spectra were obtained at 100 MHz. Tetramethylsilane (TMS) and deuterated solvent peaks were used as internal standards. The multiplicities of NMR signals are expressed as: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; m, multiplet. High-resolution mass spectra (HRMS) were recorded on a Waters API Q-TOF Ultima spectrometer using the electrospray ionization technique. Infrared spectra were obtained on a Perkin Elmer Spectrum 400 FT-IR/FT-NIR spectrometer, fitted with a diamond attenuated total reflectance (ATR) attachment. The melting points were determined using a Stuart SMP-300 melting point apparatus and capillary tubes.

Chemistry

(1R,2S,6R,7S)-4-Oxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione (2). To a solution of maleic anhydride (10 g, 100 mmol) in toluene (100 ml), monomerised cyclopentadiene (7 g, 105.90 mmol) was slowly added and refluxed. After 1.5 hours, the mixture was allowed to cool to room temperature and concentrated in vacuo to form a crude white product. The product was purified by re-crystallisation in methanol to afford a white crystalline material (8.04 g, 49%). The NMR data and melting point of compound 2 correspond to those reported in the literature. Physical characteristics: mp 163-165 °C (Lit. 164 °C). FT-IR (ATR): $\nu_{max}$ (cm$^{-1}$) = 1840, 1766, 1229, 1088, 901, 733. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 6.31 (t, $J$ 1.6 Hz, 2H), 3.58-3.57 (dd, $J$ 3.0, 1.7 Hz, 2H), 3.51-3.50 (dd, $J$ 3.0, 1.7 Hz, 2H), 1.80-1.77 (dt, $J$ 9.0 Hz, 1H). $^1$H-NMR (400 MHz, CDCl$_3$) and DEPT-135: $\delta$ 171.29 (C=O), 135.55 (C=C), 52.76 (CH$_2$), 47.08 (CH), 46.13 (CH).

The appropriate amine ((benzylamine (3, 1 mmol), 1-aminopiperidine (5, 1 mmol), propargylamine (6, 2.6 mmol), propylamine (7, 3.9 mmol), phenylhydrazine (8, 4 mmol), ethylenediamine (9, 2.7 mmol), 1,3-
diaminopropane (11, 1.4 mmol), 1,4-diaminobutane (12, 3 mmol) or N,N-dimethylethylenediamine (13, 2.5 mmol) were reacted with compound 2 (1 mmol) in toluene (100 ml) under reflux conditions for 10-24 hours to afford compounds 3-13, respectively.

(1R,2S,6R,7S)-4-Benzyl-4-azatricyclo[5.2.1.02,6]deca-8-ene-3,5-dione (3) and N,N'-dibenzylbicyclo[2.2.1]-hepta-5-ene-2,3-dicarboxamide (4). The crude yellow oil formed was purified using silica gel column chromatography with 25% hexane in ethyl acetate as mobile phase to afford 3 and impurity 4 as white powders (3: 1.28 g, 83%; 4: 0.13 g, 6%). The NMR data of compound 3 correspond to those reported in the literature. Physical characteristics (3): mp 87-89 °C. FT-IR (ATR): νmax (cm⁻¹) = 2875, 1689, 1391, 1336, 1169, 901, 702. ¹H-NMR (400 MHz, CDCl₃): δ 7.31-7.22 (m, 5H), 5.89 (t, J 1.6 Hz, 2H), 4.48 (s, 2H), 3.37-3.36 (dd, J 2.7, 1.6 Hz, 2H), 3.25-3.24 (dd, J 2.8, 1.5 Hz, 2H), 1.70-1.67 (dt, J 8.8, 1.4 Hz, 1H), 1.50-1.52 (d, J 8.8 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃) and DEPT-135: δ 177.44 (C=O), 136.03 (Ar-C), 134.34 (C=C), 128.92 (Ar-C), 128.39 (Ar-C), 127.76 (Ar-C), 52.14 (CH₂), 45.76 (CH), 45.02 (CH), 42.03 (CH₂). HRMS (ESI/TOF) m/z: [M+H]+ calcd. for C₁₆H₁₅NO₂ 254.1176; Found 254.1177. Physical characteristics (4): mp 141-143 °C. FT-IR (ATR): νmax (cm⁻¹) = 3304, 2977, 1654, 1532, 1454, 1227, 1028, 908, 698. ¹H-NMR (400 MHz, CDCl₃): δ 7.31-7.18 (m, 10H), 6.33 (m, 2H), 4.25-4.14 (m, 4H), 3.23 (m, 2H), 3.10 (m, 2H), 1.44 (d, J 8.5, 1H), 1.24 (d, J 9.2 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃) and DEPT-135: δ 172.80 (C=O), 138.21 (Ar-C), 135.76 (C=C), 128.62 (Ar-C), 127.73 (Ar-C), 127.34 (Ar-C), 52.04 (CH), 49.98 (CH₂), 47.35 (CH), 45.32 (CH₂). HRMS (ESI/TOF) m/z: [M+H]+ calcd. for C₂₃H₂₄N₂O₂ 361.1910; Found 361.1913.

(1R,2S,6R,7S)-4-(1-Piperidyl)-4-azatricyclo[5.2.1.02,6]deca-8-ene-3,5-dione (5). After evaporating the solvent in vacuo, the final product was crystallized from methanol as white crystals (0.70 g, 47%). Physical characteristics: mp 163-166 °C. FT-IR (ATR): νmax (cm⁻¹) = 2996, 2938, 1708, 1452, 1339, 1285, 1185, 845, 718. ¹H-NMR (400 MHz, CDCl₃): δ 6.12-6.11 (t, J 1.6 Hz, 2H), 3.39 (m, 2H), 3.12-3.11 (dd, J 2.8, 1.5 Hz, 2H), 3.10-3.07 (t, J 5.4 Hz, 4H), 1.70-1.67 (dt, J 8.8, 1.6 Hz, 1H), 1.67-1.61 (m, 4H), 1.48-1.45 (d, J 8.8 Hz, 1H), 1.43-1.37 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) and DEPT-135: δ 172.80 (C=O), 138.21 (Ar-C), 135.76 (C=C), 128.62 (Ar-C), 127.73 (Ar-C), 127.34 (Ar-C), 52.04 (CH), 49.98 (CH₂), 47.35 (CH), 45.32 (CH₂). HRMS (ESI/TOF) m/z: [M+H]+ calcd. for C₁₆H₁₃N₂O₂ 247.1441; Found 247.1446.

(1R,2S,6R,7S)-4-Prop-2-ynyl-4-azatricyclo[5.2.1.02,6]deca-8-ene-3,5-dione (6). The crude yellow oil formed was purified by recrystallization in a mixture of hexane and ethyl acetate to afford yellow crystals (0.93 g, 76%). Physical characteristics: mp 99-101 °C. FT-IR (ATR): νmax (cm⁻¹) = 3265, 1759, 1703, 1530, 1423, 1383, 1323, 1175, 1120, 1090, 951, 906, 845, 715, 668. ¹H-NMR (400 MHz, CDCl₃): δ 6.11-6.10 (t, J 1.6 Hz, 2H), 4.09-4.08 (d, J 2.5 Hz, 2H), 3.42 (m, 2H), 3.30-3.29 (dd, J 2.8, 1.5 Hz, 2H), 2.14-2.12 (t, J 2.5 Hz, 1H), 1.75-1.72 (dt, J 8.8,1.5 Hz, 1H), 1.55-1.53 (d, J 8.8 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃) and DEPT-135: δ 176.38 (C=O), 134.46 (C=C), 70.97 (C), 52.14 (CH₂), 45.86 (CH), 45.17 (CH), 27.21 (CH₂). HRMS (ESI/TOF) m/z: [M+H]+ calcd. for C₁₂H₁₁N₂O₂ 202.0863; Found 202.0866.

(1R,2S,6R,7S)-4-propyl-4-azatricyclo[5.2.1.02,6]deca-8-ene-3,5-dione (7). The crude residue was purified by crystallization from hexane to afford the final product as white crystals (1.19 g, 95%). Physical characteristics: mp 70-72 °C. FT-IR (ATR): νmax (cm⁻¹) = 3267, 2965, 1763, 1683, 1550, 1467, 1337, 1301, 1198, 1138, 1015, 874, 737, 666. ¹H-NMR (400 MHz, CDCl₃): δ 6.10 (t, J 1.5 Hz, 2H), 3.39 (m, 2H), 3.31-3.28 (t, J 7.4 Hz, 2H), 3.25-3.24 (dd, J 2.8, 1.5 Hz, 2H), 1.74-1.72 (dt, J 8.7, 1.5 Hz, 1H), 1.55-1.53 (d, J 8.8 Hz, 1H), 1.51-1.41 (m, 2H), 0.87-0.84 (t, J 7.4 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) and DEPT-135: δ 177.84 (C=O), 134.43 (C=C), 52.23 (CH₂), 45.73 (CH), 44.90 (CH), 40.05 (CH₂), 21.16 (CH₂), 11.38 (CH₃). HRMS (ESI/TOF) m/z: [M+H]+ calcd. for C₁₂H₁₅NO₂ 206.1176; Found 206.1179.

(1R,2S,6R,7S)-4-Anilino-4-azatricyclo[5.2.1.02,6]deca-8-ene-3,5-dione (8). The crude white powder was purified by precipitation from ice-cold methanol to produce a white powder (0.76 g, 49%). Physical characteristics: mp 191-194 °C. FT-IR (ATR): νmax (cm⁻¹) = 3282, 2955, 1767, 1703, 1601, 1497, 1381, 1295, 1184, 1138, 1056, 980,
[1R,2S,5R,7S]-4-(2-Aminoethyl)-4-azatricyclo[5.2.1.0\(^2.6\)]dodec-8-ene-3,5-dione (9) and 3,5-dioxo-4-azatricyclo[5.2.1.0\(^2.6\)]dodec-8-ene-4-yl]ethyl-4-azatricyclo[5.2.1.0\(^2.6\)]dodec-8-ene-3,5-dione (10). The crude mixture was stirred in ethyl acetate (100 ml) at room temperature for 30 minutes and filtered. The filtrate was concentrated in vacuo to afford a yellow oil that solidified at room temperature rendering compound 9 (1.13 g, 90%). The precipitate formed was isolated and re-crystallised from ice-cold methanol to afford 10 as white crystals (0.21 g, 10%). Physical characteristics (9): FT-IR (ATR): \(\nu_{\text{max}} (\text{cm}^{-1}) = 3379, 2946, 1762, 1687, 1549, 1490, 1440, 1400, 1335, 1156, 1051, 842, 778, 724. 1^H-NMR (400 MHz, CDCl\(_3\)): \(\delta 6.12-6.11 \) (t, \(J 1.7 \text{ Hz}, 2\text{H}), 3.40 \) (d, \(J 6.4 \text{ Hz}, 2\text{H}), 3.38 \) (m, 2\text{H}), 3.27-3.26 (dd, \(J 2.8, 1.5 \text{ Hz}, 2\text{H}), 2.75-2.72 \) (t, \(J 6.4 \text{ Hz}, 2\text{H}) 1.75-1.72 \) (dt, \(J 8.8, 1.5 \text{ Hz}, 1\text{H}), 1.55-1.53 \) (d, \(J 8.8 \text{ Hz}, 1\text{H}). 13C-NMR (100 MHz, CDCl\(_3\)) and DEPT-135: \(\delta 177.98 \) (C=O), 134.57 (C=C), 52.31 (CH\(_2\)), 45.81 (CH), 44.92 (CH), 41.67 (CH\(_2\)), 40.11 (CH\(_2\)). HRMS (ESI/TOF) \(m/z\): [M+H]^+ calcd. for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_2\) 255.1128; Found 255.1133.

[1R,2S,5R,7S]-4-(3-Aminopropyl)-4-azatricyclo[5.2.1.0\(^2.6\)]dodec-8-ene-3,5-dione (11). The crude yellow mixture formed was purified using silica gel column chromatography with 90% ethyl acetate in methanol as mobile phase to afford a light-yellow oil (0.68 g, 51%). Physical characteristics: FT-IR (ATR): \(\nu_{\text{max}} (\text{cm}^{-1}) = 3372, 2944, 2868, 1729, 1658, 1474, 1406, 1339, 1299, 1251, 1193, 1127, 977, 918, 840, 747, 717. 1^H-NMR (400 MHz, CDCl_3): \(\delta 6.03-6.01 \) (dd, \(J 5.6, 2.7 \text{ Hz}, 1\text{H}), 5.99-5.97 \) (dd, \(J 5.6, 2.7 \text{ Hz}, 1\text{H}), 3.33-3.30 (m, 2\text{H}), 0.25-2.36 (m, \(J 3.2, 1.6 \text{ Hz}, 2\text{H}), 3.17-3.16 (m, 1\text{H}), 3.15-3.12 (dd, \(J 7.8, 4.6 \text{ Hz}, 1\text{H}), 1.71-1.65 \) (dd, \(J 13.7, 5.1 \text{ Hz}, 1\text{H}), 1.64-1.59 (dt, \(J 6.7, 4.8 \text{ Hz}, 1\text{H}), 1.58-1.55 (dt, \(J 8.6, 1.6 \text{ Hz}, 1\text{H}), 1.49-1.47 \) (d, \(J 8.6 \text{ Hz}, 1\text{H}). 13C-NMR (100 MHz, CDCl\(_3\)) and DEPT-135: \(\delta 176.90 \) (C=O), 134.45 (C=C), 52.14 (CH\(_2\)), 45.96 (CH), 44.67 (CH), 36.37 (CH\(_2\)). HRMS (ESI/TOF) \(m/z\): [M+H]^+ calcd. for C\(_{22}\)H\(_{20}\)N\(_2\)O\(_4\) 353.1496; Found 353.1497.

[1R,2S,5R,7S]-4-(4-Aminobutyl)-4-azatricyclo[5.2.1.0\(^2.6\)]dodec-8-ene-3,5-dione (12). The crude yellow product formed was purified using silica gel column chromatography with ethyl acetate/ammonia/methanol (69:1:30) as mobile phase to afford a light-yellow oil (0.80 g, 56%). Physical characteristics: FT-IR (ATR): \(\nu_{\text{max}} (\text{cm}^{-1}) = 3387, 2941, 2869, 1760, 1684, 1567, 1436, 1337, 1217, 1146, 1024, 896, 843, 723. 1^H-NMR (400 MHz, CDCl\(_3\)): \(\delta 6.08 \) (t, \(J 1.6 \text{ Hz}, 2\text{H}), 3.37 \) (m, 2\text{H}), 3.34-3.30 (t, \(J 7.1 \text{ Hz}, 2\text{H}), 3.23-3.22 \) (dd, \(J 2.7, 1.4 \text{ Hz}, 2\text{H}), 2.68-2.65 (t, \(J 6.9 \text{ Hz}, 2\text{H}), 1.73-1.70 \) (dt, \(J 8.8, 1.4 \text{ Hz}, 1\text{H}), 1.53-1.51 (d, \(J 8.0 \text{ Hz}, 1\text{H}), 1.48-1.42 \) (m, 2\text{H}), 1.41-1.34 \) (m, 2\text{H}). 13C-NMR (100 MHz, CDCl\(_3\)) and DEPT-135: \(\delta 177.76 \) (C=O), 134.23 (C=C), 52.24 (CH\(_2\)), 45.74 (CH), 44.90 (CH), 41.61 (CH\(_2\)), 38.15 (CH\(_2\)), 30.88 (CH\(_2\)), 25.14 (CH\(_2\)). HRMS (ESI/TOF) \(m/z\): [M+H]^+ calcd. for C\(_{13}\)H\(_{16}\)N\(_2\)O\(_2\) 235.1441; Found 235.1443.

[1R,2S,5R,7S]-4-[2-(Dimethylamino)ethyl]-4-azatricyclo[5.2.1.0\(^2.6\)]dodec-8-ene-3,5-dione (13). The crude residue was purified using silica gel column chromatography with 90% ethyl acetate as mobile phase to afford a white oil that solidified at room temperature to give the final product as a white powder (1.39 g, 97%). Physical characteristics: mp 83-85 °C. FT-IR (ATR): \(\nu_{\text{max}} (\text{cm}^{-1}) = 3456, 2971, 2789, 1739, 1687, 1355, 1229, 1152, 1046, 1001, 950, 914, 843, 778, 722. 1^H-NMR (400 MHz, CDCl\(_3\)): \(\delta 6.06 \) (t, \(J 1.6 \text{ Hz}, 2\text{H}), 3.44-3.41 \) (t, \(J 6.9 \text{ Hz}, 2\text{H}).
Hz, 2H), 3.35 (m, 2H), 3.24-3.23 (dd, J=2.8, 1.5 Hz, 2H), 2.32-2.29 (t, J=6.9 Hz, 2H), 2.20 (s, 6H), 1.71-1.69 (dt, J=8.7, 1.4 Hz, 1H), 1.52-1.50 (d, J=8.7 Hz, 2H). 13C-NMR (100 MHz, CDCl3) and DEPT-135: δ 177.70 (C=O), 134.37 (C=C), 56.26 (CH2), 52.09 (CH2), 45.77 (CH), 45.37 (CH3), 44.85 (CH), 36.19 (CH2). HRMS (ESI/TOF) m/z: [M+H]+ calcd. for C13H18N2O2 235.1441; Found 235.1442.

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### Supplementary Material

Electronic Supplementary Information available in the online version: copies of the 1H, 13C and DEPT NMR-, IR- and HRMS spectra for all new compounds.

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