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Intramolecular Nitrofuran Diels-Alder reactions: extremely substituent-tolerant cycloadditions via asynchronous transition states

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Abstract: Nitrofurans undergo intramolecular Diels-Alder reactions with tethered electron-poor dienophiles more rapidly and in higher yield than non-nitrated furans. Computational studies indicate that increased stabilization of a partial positive charge on the nitro-substituted carbon in both transition state and product is the driving force for these reactions. Frontier molecular orbital energy differences indicate a switch from normal to inverse electron demand upon nitration. There does not appear to be a contribution from any differences in aromatic stabilization energy between furans and nitrofurans. Calculations show that the nitrofuran reactions proceed via a highly asynchronous transition state allowing easier bond formation between two sterically hindered carbons.

Introduction

The Diels-Alder reaction remains one of the most widely–used and powerful reactions in organic chemistry.¹ The use of furan as both a diene and a dienophile has been
studied extensively, with many applications in target synthesis.\textsuperscript{2,3} For the majority of Diels-Alder reactions employing non-aromatic dienes, frontier orbital energies and coefficients are readily used to explain reactivity and selectivity.\textsuperscript{1} In contrast, a number of experimental and computational reports\textsuperscript{4} on intramolecular Diels-Alder reaction of furan (IMDAF) indicate that other factors, including tether substitution can override frontier orbital considerations in certain cases. Padwa and Houk first identified positive charge stabilization as being a kinetic and thermodynamic driving force in reactions of halofurans.\textsuperscript{5} We identified a dipolar interaction term (Scheme 1) as an additional factor in halofuran/haloalkene IMDAF reactions.\textsuperscript{6} We also discovered a correlation between transition state structure and energy that was consistent with the late transition state indicated in previous reports.\textsuperscript{7} We now report the results of our investigations in intramolecular nitrofuran cycloadditions.

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=circle,fill=black,inner sep=1pt] (a) at (0,0) {a) Unfavorable and b) favorable dipolar interactions affecting IMDAF transition states in haloalkene IMDAF reactions\textsuperscript{6}};
  \node[draw,shape=circle,fill=black,inner sep=1pt] (b) at (2,0) {Scheme 1};
\end{tikzpicture}
\end{center}

There have been a number of reports of the use of nitrofurans in intramolecular Diels-Alder reactions,\textsuperscript{8} but dienophile substitution has not been widely studied and the reactions have not been fully analyzed by modern computational methods. Furthermore, the relative reactivity of nitrofurans and their non-nitratated counterparts is yet to be analysed in any detail.\textsuperscript{9} The variables affecting the IMDAF reaction are more complex than those involving non-aromatic dienes, but there is much evidence indicating that furan most often behaves as an electron-rich diene,\textsuperscript{2,10} reacting with electron-poor dienophiles most rapidly. Intuitively, one might therefore expect that incorporation of a nitro-substituent would retard or prevent the reaction entirely.
Indeed, to the best of our knowledge there are no reports of intermolecular Diels-Alder reactions involving nitrofurans as dienes.\textsuperscript{11} Our results indicate, however, that this intuition is incorrect for the substrates studied herein.

**Results and discussion**

A series of IMDAF precursors 1a-n and 2a-n were synthesised starting from either furfural or 5-nitrofurfural to afford the required nitrated and non-nitrated IMDAF substrates (see supporting information for details). The IMDAF precursors were heated in toluene at reflux and conversions to adducts 3a-n and 4a-n given at the times indicated in Tables 1 and 2 (as measured by $^1$H NMR spectroscopy). Isolated yields are in parentheses.\textsuperscript{12}
1a $X = \text{H}$ 3 h, 33% conversion;
24 h 93%,\textsuperscript{a} (70% isolated yield)
3a $X = \text{H}$ 3 h, 33%;
24 h 93% (70% isolated yield)
4a $X = \text{NO}_2$ 3 h, 49%;
24 h, 100% (quant.)

1b $X = \text{H}$
2b $X = \text{NO}_2$
3b $X = \text{H}$ 5 h, 9% conversion;
48 h, 28% (18)\textsuperscript{a}
4b $\text{NO}_2$ 5 h, 29% conversion;
48 h, 90% (67)\textsuperscript{a}

1c $X = \text{H}$
2c $X = \text{NO}_2$
3c $X = \text{H}$ 2 h, 16% conversion
48 h, 60%; (54)\textsuperscript{b}
4c $X = \text{NO}_2$ 2 h, 74% conversion
24 h, 100% (78)

1d $X = \text{H}$
2d $X = \text{NO}_2$
3d $X = \text{H}$ 2 h, not observed;
45 h <10% (not isolated)
4d $X = \text{NO}_2$ 2 h, 40 % conversion;
26 h, 78% (43)\textsuperscript{a}

1e $X = \text{H}$
2e $X = \text{NO}_2$
3e $X = \text{H}$ 2 h, not observed;
27 h, not observed
4e $X = \text{NO}_2$ 2 h ~5% conversion;
27 h, 30% (27)\textsuperscript{a}
Table 1 Effect of alkyl substitution on nitrofuran and simple furan IMDAF reactions (all reactions conducted in toluene at reflux)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Conditions</th>
<th>Conversion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1f X = H</td>
<td><img src="image1" alt="Structure" /></td>
<td>1 h, not detected; 24 h, ~7% (not isolated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2f X = NO₂</td>
<td><img src="image2" alt="Structure" /></td>
<td>1 h, 27% conversion; 24 h, 44% (32)³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3g X = H</td>
<td><img src="image3" alt="Structure" /></td>
<td>3 h, 16% conversion; 22 h, 46% (41)²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4g X = NO₂</td>
<td><img src="image4" alt="Structure" /></td>
<td>3 h, 71% conversion; 22 h, 100% (93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1h X = H</td>
<td><img src="image5" alt="Structure" /></td>
<td>5 h, not detected; 48 h not detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2h X = NO₂</td>
<td><img src="image6" alt="Structure" /></td>
<td>5 h, 20% conversion; 48 h, 60% (55)³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3i X = H</td>
<td><img src="image7" alt="Structure" /></td>
<td>2 h, not detected; 48 h, &lt;5% (not isolated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4i X = NO₂</td>
<td><img src="image8" alt="Structure" /></td>
<td>2 h, 21% conversion; 26 h, 27% (20)²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

³ Significant decomposition after any longer reaction time
² Equilibrium reached, no further conversion

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In all cases the nitro-substituted precursors reacted faster than their non-nitro analogues, as shown by the conversions at the early time points (recorded before equilibrium was reached). We noted that it was not always possible to determine if the reactions had reached equilibrium, because of significant decomposition (footnote a in tables 1 and 2) concurrent with cycloaddition. However, in those cases where the equilibrium position could be confirmed (where extended reaction time did not result in decomposition, footnote b in tables 1 and 2), the equilibrium favored the adduct to a greater extent in the nitrated cases (substrates 3c/4c, 3g/4g, 3i/4i, 3j/4j, 3k/4k, 3l/4l). These effects are most striking in more substituted systems, despite the fact that the nitrated adducts contain a fully substituted carbon adjacent to the carbon bearing the substituents on the acrylic or cinnamic acid derivatives. Indeed, the non-nitrated substrates do not tolerate simple alkyl substitution (Table 1) at all well, with conversions less than 50% in most cases. By contrast, the nitro substrates are capable of reacting to give very densely functionalized products. In the most extreme case, nitrated substrate 2i even reacts to give partial conversion to the adduct 4i, which possesses four contiguous fully substituted carbons. By contrast the non-nitro substrate 1i was unreactive. Similarly, aryl substitution was tolerated far better in the nitrated systems than the non-nitro ones (Table 2), although the reactions were more sluggish.
1j $X = H$
2j $X = \text{NO}_2$

3j $X = H$ 1 h, 6% conversion; 24 h, 9% (8)$^b$

4j $X = \text{NO}_2$ 1 h, 17% conversion; 5 h, 28% (23)$^b$

1k $X = H$
2k $X = \text{NO}_2$

3k $X = H$ 1 h, not detected; 24 h, <5% (not isolated)

4k $X = \text{NO}_2$ 1 h, 17% conversion; 24 h, 22% (17)$^b$

1l $X = H$
2l $X = \text{NO}_2$

3l $X = H$ 3 h, not detected; 72 h, not detected

4l $X = \text{NO}_2$ 3 h, 25% conversion; 72 h, 36% (32)$^b$

1m $X = H$
2m $X = \text{NO}_2$

3m $X = H$ 120 h, not detected

4m $X = \text{NO}_2$ ~5% conversion, 120 h (not isolated)

$^b$ Equilibrium reached, no further conversion nor noticeable decomposition
Table 2 Effect of aryl substitution on nitrofuran and simple furan IMDAF reactions

We were particularly intrigued by these results, and set out to discover why the nitrated systems reacted more rapidly and more favorably than their non-nitrated analogues and were also more tolerant of substitution. We examined a number of possibilities using advanced computation: 1) that positive charge stabilization is greater for nitrated systems in the cycloadduct than the starting material, as identified by Houk, providing an additional driving force for the reaction in those cases; 2) that nitro substitution leads to an increased loss of aromatic stabilization energy, making the nitrofuran IMDAF reaction more favourable; 3) that nitration had induced a favourable change in frontier molecular orbital energies. Although a number of methods are available for estimating these quantities, it would appear that, to date, none has ever been applied to nitrofurans.

We first calculated the energetics of the isodesmic equations shown in Scheme 2. It is clear from these results that there is a significant kinetic and thermodynamic benefit in having the nitro group attached to a fully substituted sp³ carbon (as in the cycloadducts 4a-n) rather than an sp² centre (as in the starting materials 2a-n). This is consistent with analogous results in the halofuran series. Padwa and Houk ascribed the effect as being due to hyperconjugative stabilization of partial positive charge on the halogen-bearing carbon. The size of the effect for the nitro group is intermediate in magnitude between those calculated for Br and Cl.
Scheme 2 Isodesmic equations allowing quantification of cation stabilization effects ($\Delta H_r$ in kcal mol$^{-1}$)

The aromatic stabilization energy of nitrofuran was next probed using a standard method, using the homodesmotic equations in Scheme 3, as previously outlined by von Schleyer for 5-membered heterocycles.$^{13}$ The calculations suggest that there is a greater aromatic stabilization in 2-nitrofuran than in furan itself (Equations 5 and 6). This is therefore not likely to be a source of the increased reactivity we observe for nitrated systems.

$$\begin{align*}
H_3C-NO_2 + H_3C-CH_3 & \rightarrow CH_4 + H_3C-C^{'NO_2}H -4.8 \text{ (Eq 1)} \\
H_3C-NO_2 + H_3C-C^{'H}CH_3 & \rightarrow CH_4 + H_3C-C^{'NO_2}H -8.2 \text{ (Eq 2)} \\
H_3C-NO_2 + H_3C-C^{'H}CH_3 & \rightarrow CH_4 + H_3C-C^{'NO_2}H -9.5 \text{ (Eq 3)} \\
H_3C-NO_2 + H_2C=CH & \rightarrow CH_4 + H_3C-C^{'NO_2}H -4.4 \text{ (Eq 4)} 
\end{align*}$$

Scheme 3 Homodesmotic equations comparing aromatic stabilization for furan and 2-nitrofuran ($\Delta H_r$ in kcal mol$^{-1}$).

$$\begin{align*}
\text{O}_2\text{N} & + 2 \text{Fur} + \text{Fur} -12.2 \text{ (Eq 5)} \\
\text{O}_2\text{N} & + 2 \text{Fur} + \text{Fur} -15.1 \text{ (Eq 6)} 
\end{align*}$$
Computational Details.

All electronic structure computations were using Gaussian 09 (Revision D.01).\textsuperscript{14} Preliminary geometries were obtained by means of density based models, B3LYP\textsuperscript{15,16} functional with a split-valence double-zeta basis, 6-31G. All optimized structures were subject to a subsequent frequency calculation, to validate the nature of the stationary point. The thermochemical pathway, based on the conversion of 1\textit{a}, 2\textit{a}, 1\textit{d}, 2\textit{d}, 1\textit{n} and 2\textit{n} to the corresponding cycloadduct, was probed at both 298.15 K and 383.00 K using a highly accurate complete basis set (CBS) model.\textsuperscript{17,18,19,20} The particular extrapolation procedure utilized was CBS-QB3,\textsuperscript{19} a variant of the original CBS-Q\textsuperscript{18} model. The frontier molecular orbital (FMO) energies were obtained from the B3LYP\textsuperscript{15,16} functional with a split-valence triple-zeta basis, 6-311G(2d,d,p). The HOMO (LUMO) orbitals relating to the dienophile were selected rationally; the highest occupied (lowest unoccupied) orbital demonstrating significant amplitude of in-phase (out-of-phase) overlap of appropriate locally out-of-plane p-orbitals located on the ethylenic carbon atoms. The identification of the HOMO (LUMO) relating to the diene segment was straightforward, although the presence of the nitro substituent gave rise to a distinct difference in the observed LUMOs, with an extra nodal point at position three of the nitrofuran system when compared to the non-nitrated counterpart.

Electronic structure calculations were performed for substrates 1\textit{a}, 2\textit{a}, 1\textit{d} and 2\textit{d}. Key energetic reaction parameters and FMO energies were calculated (Table 3). The effect of nitration is substantial. Reaction of substrates 1\textit{a} and 1\textit{d} occurs via a normal electron-demand process, but their nitrated analogues 2\textit{a} and 2\textit{d} react via an inverse electron-demand process. Intuitively, 2\textit{a} might be expected to be a polarity-mismatched IMDAF substrate and hence undergo slower reaction. The calculations indicate that the switch in polarity results in a smaller FMO energy difference, which presumably makes a contribution to increasing the reaction rate.
Table 3 Theoretically calculated reaction energetics at 383.00K and associated FMO energies expressed in terms of kcal mol\(^{-1}\) and electron volts, respectively.\(^{21}\)

In order to explain why the nitro systems are more tolerant of steric hindrance, the calculated transition states for the reaction of these four representative substrates were examined in more detail. All four pericyclic processes were found to be asynchronous, with a significant difference in length between the partially-formed ring fusion bond marked a (Fig. 1) than for the partially-formed bond marked b, between the nitro-bearing/H-bearing carbon and the alkene terminus. The difference increases with alkene substitution and the effect is much more marked for the nitro-substituted cases. This is consistent with a more asynchronous pericyclic process in the nitro cases, and indicates a greater degree of charge separation in the transition state. One might expect that transfer of electron density from dienophile to diene would lead to a stabilization of the positive charge at the nitro-bearing carbon. This is then likely to be responsible for the longer interatomic distance b in the transition state, which would in turn suggest that the reactions of nitro substrates are likely to be less susceptible to steric effects at the alkene terminus than the non-nitro analogues.
Figure 1 Illustrating the asynchronicity of nitrofuran IMDA reactions

There is less reason to expect a similar electron density transfer in the non-nitrated substrates, and the interatomic distances between the atoms involved in formation of the two new σ-bonds are calculated to be much more equal, indicating a more synchronous process. The activation barriers and observed rates for each of the reactions (Table 3) are consistent with this analysis.

The only exception to the nitration effect we have observed is seen in substrates 1n and 2n (Scheme 4 and table 4), derived from the use of monoethyl fumaryl chloride as acylating agent, leading to the formation of 3n and 4n. These precursors contain extremely electron-deficient dienophiles. In this case, IMDA product 3n was isolated directly upon work-up of the acylation reaction. Nitro substrate 4n required heating for 1 h to achieve complete conversion, but that reaction is still faster than all the others. In this unusual case, it appears that nitration does indeed produce a polarity
mismatched, although still favorable, IMDA reaction. We performed calculations on the N-Phenyl analogues 1o and 2o of these substrates as model compounds. The calculated activation barriers are consistent with more rapid reactions, in accord with experiment. The calculated FMO energies indicate a switch to a normal-demand cycloaddition in these particular cases.

![Scheme 4 Fumarate cycloadditions](image)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>ΔH‡ (kcal/mol)</th>
<th>ΔG‡ (kcal/mol)</th>
<th>ΔrH° (kcal/mol)</th>
<th>ΔrG° (kcal/mol)</th>
<th>FMO ΔE(Normal) (eV)</th>
<th>FMO ΔE(inverse) (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1o</td>
<td>11.9</td>
<td>17.9</td>
<td>-15.7</td>
<td>-9.0</td>
<td>4.5</td>
<td>8.3</td>
</tr>
<tr>
<td>2o</td>
<td>11.7</td>
<td>17.9</td>
<td>-17.8</td>
<td>-11.0</td>
<td>5.1</td>
<td>5.9</td>
</tr>
</tbody>
</table>

**Table 4** Theoretically calculated reaction energetics for substrates 1o and 2o at 383.00K and associated FMO energies expressed in terms of kcal mol\(^{-1}\) and electron volts, respectively.\(^{22}\)

**Conclusion**

The effect of nitro-substitution of furan on the intramolecular furan Diels-Alder cycloaddition has been investigated. In all but one case the cycloaddition was faster.
and more favorable for the nitrated substrates. This was found to be due largely to an extreme example of positive charge stabilization in the transition state and cycloaducts, rather than any major changes to the aromaticity of the heterocycle. Given the ready availability of nitrofuran substrates, it is likely that their use will lead to synthetically useful yields of highly functionalized cycloaducts that are unavailable from non-nitrated cycloadition precursors. More general consideration of asynchronicity is likely to lead to more effective design of substrates for very sterically demanding intramolecular cycloadditions.

EXPERIMENTAL

General Information

Melting points were obtained in open capillary tubes and are uncorrected. $^1$H NMR spectra were recorded on Bruker AV 300, DPX 400 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. $^{13}$C NMR spectrum were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks (CDCl$_3$ at δH 7.26). J values are given in Hz and s, d, dd, ddd, t, dt, q, m, br and app. abbreviations correspond to singlet, doublet, doublet of doublet, doublet of doublet of doublet, triplet, triplet of doublet, quartet, multiplet, broad and apparent respectively. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate.

Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) and stained by the use of aqueous acidic KMnO$_4$. Anhydrous dichloromethane (DCM) was obtained from a solvent drying system (MB-SPS-800). Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was flame-dried under a stream of dry argon.
N-(Furan-2-ylmethyl)aniline\(^{23}\):

To a solution of furfural (1.66 mL, 20.0 mmol) in 1,2-dichloroethane (70 mL) under nitrogen was added aniline (1.82 mL, 20.0 mmol) followed by sodium triacetoxyl borohydride (6.0 g, 28 mmol) in one portion. The solution stirred at room temperature for 3 hours where the reaction was quenched with the addition of NaHCO\(_3\) (100 mL). The solution was extracted with chloroform (3 x 50 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as a red oil (4.2 g) which was chromatographed on silica gel (EtOAc/Pet. Ether ~5%) to provide N-(furan-2-ylmethyl)aniline as a yellow oil (3.0 g, 87%).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.43\) (m, 1H), 7.20 (m, 2H), 6.87 (m, 1H), 6.79 (m, 1H), 6.39 (m, 1H), 6.30 (m, 1H), 4.37 (s, 2H), 4.07 (s, br, 1H).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 152.9, 147.7, 142.0, 129.3, 118.1, 113.2, 110.4, 107.1, 41.5\). IR (cm\(^{-1}\)): 3409, 3051, 1729, 1601, 1503, 1460, 1431, 1316, 1252, 1180, 1145, 1011, 883, 806.

N-((5-Nitrofuran-2-yl)methyl)aniline:\(^{24}\)

To a solution of 5-nitrofuran-2-carbaldehyde (1.41 mg, 10.0 mmol) in dichloromethane (35 mL) under nitrogen was added aniline (0.92 mL, 10.0 mmol) and the solution stirred at room temperature for 2 hours. Following the stirring to the solution was added sodium borohydride (490 mg, 13 mmol) in one portion followed by acetic acid (1.0 mL) to effervescence. The solution stirred at room temperature overnight where the reaction was quenched with the addition of water (100 mL). The solution was extracted with chloroform (3 x 50 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as a red oil (2.4 g) which was chromatographed on silica gel (EtOAc/Pet. Ether ~10%) to provide N-((5-nitrofuran-2-yl)methyl)aniline as a red crystals (2.0 g, 93%). M. p.: 55-57 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.30\) (m, 1H), 6.87 (m, 1H), 6.73 (dd, \(J = 8.6, 1.1\) Hz, 1H), 6.54 (d, \(J = 3.7\) Hz, 1H), 4.52 (s, 1H), 4.29 (s, br, 1H).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 157.4, 146.6, 129.5, 118.8, 113.2, 112.9, 110.6, 41.5\). IR (cm\(^{-1}\)): 3390, 3142, 3116, 1598, 1582, 1506, 1444, 1361, 1314, 1253, 1169, 1153, 1115, 1096, 979, 815.

N-(Furan-2-ylmethyl)-N-phenylacrylamide (1a):\(^6\)

Acryloyl chloride (125 mg, 1.3 mmol) was added at -20 °C carefully to a solution of N-(furan-2-ylmethyl)aniline (200 mg, 1.15 mmol), triethylamine (0.243 mL, 1.7 mmol) and DMAP in dry dichloromethane (5.00 mL) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with
dichloromethane (10 mL) and water (10 mL) was added. The mixture was further extracted with dichloromethane (2 × 10 mL) and the combined organic phase dried (Na₂SO₄). Purification by column chromatography (1:1.5 ethyl acetate/ petroleum ether) afforded the title compound: (147 mg, 52%) as an orange oil. 

**1H-NMR (300 MHz, CDCl₃):** δ = 7.46 – 7.29 (m, 4H), 7.17 – 6.98 (m, 2H), 6.44 (dd, J = 16.8, 2.0 Hz, 1H), 6.30 (dd, J = 3.2, 1.9 Hz, 1H), 6.21 (dq, J = 3.2, 0.7 Hz, 1H), 6.03 (dd, J = 16.8, 10.2 Hz, 1H), 5.56 (dd, J = 10.3, 2.0 Hz, 1H), 4.97 (s, 2H).

**N-((5-Nitrofuran-2-yl)methyl)-N-phenylacrylamide (2a):**

![Chemical Structure](image)

Acryloyl chloride (415 mg, 4.60 mmol) was added carefully to a solution of N-((5-nitrofuran-2-yl)methyl)aniline (1.00 g, 4.60 mmol), triethylamine (0.23 mL, 9.60 mmol) and DMAP (13 mg, 0.11 mmol) in dry dichloromethane (5.00 mL) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 mL) and water (10 mL) was added. The mixture was further extracted with dichloromethane (2 × 10 mL) and the combined organic phase dried (Na₂SO₄). Purification by column chromatography (1:4 ethyl acetate/ petroleum ether) afforded the title compound: Wt 647 mg; 52%; brown/orange oil.

**1H-NMR (300 MHz, CDCl₃):** δ = 7.47 – 7.34 (m, 3H), 7.24 (d, J = 3.6 Hz, 1H, H₄), 7.21 – 7.16 (m, 2H), 6.55 (d, J = 3.6 Hz, 1H), 6.42 (dd, J = 16.8, 1.9 Hz, 1H), 6.04 (dd, J = 16.8, 10.3 Hz, 1H), 5.59 (dd, J = 10.3, 1.9 Hz, 1H), 4.98 (s, 2H).

**13C-NMR (75 MHz, CDCl₃):** δ = 165.7, 154.6, 151.5, 141.3, 123.0, 129.0, 128.6, 127.9, 127.7, 112.6, 112.1, 46.5. **IR (cm⁻¹):** 3134, 3064, 3040, 2928, 1656, 1593, 1528, 1489, 1352, 1255, 1230, 1170, 1018. **HRMS (ESI-ion trap) m/z:** [M + Na]+ Calcd for C₁₄H₁₁N₂O₄Na 295.0689; **found:** 295.0681 (δ ppm = 1.0).

**((E)-N-(Furan-2-ylmethyl)-N-phenylhex-2-enamide (1b):**

![Chemical Structure](image)

(E)-Hex-2-enoxy chloride was prepared by the addition of oxalyl chloride (1.3 mL, 15 mmol) to a solution of trans-2-hexenoic acid (1.0 g, 9.2 mmol). The solution was stirred at 80 °C for 1 hour. The crude solution was concentrated to yield pure 3-methylbut-2-enoxy chloride as a yellow oil. To a solution of N-((1H-furan-2-yl)methyl)aniline (159 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-hex-2-enoxy chloride (145 mg, 1.1 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to
yield the crude product as oil (264 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to afford (E)-N-(furan-2-ylmethyl)-N-phenylhex-2-enamide as a yellow oil (177 mg, 72%).

\[ ^1H\text{-NMR (300 MHz, CDCl}_3\text{): } \delta = 7.39 \sim 7.27 \text{ (m, 4H), 7.09 \sim 7.03 \text{ (m, 2H), 6.94 \text{ (dt, } J = 15.1, 7.1 \text{ Hz, 1H), 6.26 \sim 6.14 \text{ (m, 2H), 5.64 \text{ (d, } J = 15.1 \text{ Hz, 1H), 4.92 \text{ (s, 2H), 2.00 \text{ (dd, } J = 7.3, 1.5 \text{ Hz, 2H), 1.34 \text{ (h, } J = 7.3 \text{ Hz, 2H), 0.82 \text{ (t, } J = 7.4 \text{ Hz, 3H).} \]

\[ ^13C\text{-NMR (75 MHz, CDCl}_3\text{): } \delta = 166.0, 151.0, 146.8, 142.1, 129.4, 128.4, 127.8, 121.5, 110.4, 108.9, 45.8, 34.4, 21.6, 13.7. \]

\[ \text{IR (cm}^{-1}\text{): 2958, 2930, 2872, 1661, 1628, 1593, 1287, 1178, 1016, 975, 935, 730, 639.} \]

\[ \text{HRMS (ESI-ion trap) m/z: } [M + H]^+ \text{ Calcd for C}_{17}\text{H}_{20}\text{NO}_2 270.1489; \text{ Found 270.1487 (δ ppm = -0.6).} \]

(E)-N-((5-Nitrofuran-2-yl)methyl)-N-phenylhex-2-enamide (2b):

(E)-Hex-2-enoyl chloride was prepared by the addition of oxalyl chloride (1.3 mL, 15 mmol) to a solution of trans-2-hexenoic acid (1.0 g, 9.2 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure 3-methylbut-2-enoyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (200 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-hex-2-enoyl chloride (145 mg, 1.1 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (290 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to afford compound 2b as an orange oil (227 mg, 78%).

\[ ^1H\text{-NMR (300 MHz, CDCl}_3\text{): } \delta = 7.49 \sim 7.30 \text{ (m, 3H), 7.23 \text{ (d, } J = 3.7 \text{ Hz, 1H), 7.20 \sim 7.15 \text{ (m, 2H), 6.95 \text{ (dt, } J = 15.1, 7.1 \text{ Hz, 1H), 6.53 \text{ (dt, } J = 3.7, 0.7 \text{ Hz, 1H), 5.68 \text{ (dt, } J = 15.2, 1.5 \text{ Hz, 1H), 4.96 \text{ (s, 2H), 2.02 \text{ (qd, } J = 7.3, 1.5 \text{ Hz, 2H), 1.35 \text{ (h, } J = 7.4 \text{ Hz, 2H), 0.83 \text{ (t, } J = 7.4 \text{ Hz, 3H).} \]

\[ ^13C\text{-NMR (75 MHz, CDCl}_3\text{): } \delta = 166.3, 155.1, 147.9, 141.8, 129.9, 128.4, 128.1, 120.8, 112.7, 112.1, 46.5, 34.4, 21.5, 13.7. \]

\[ \text{IR (cm}^{-1}\text{): 2959, 2931, 2872, 1661, 1628, 1593, 1287, 1178, 1016, 975, 935, 730, 639.} \]

\[ \text{HRMS (ASAP+ - TOF) m/z: } [M + H]^+ \text{ Calcd for C}_{17}\text{H}_{19}\text{N}_2\text{O}_4 315.1345; \text{ Found 315.1342 (δ ppm = -1.0).} \]

(E)-N-(Furan-2-ylmethyl)-2-methyl-N-phenylbut-2-enamide (1c):

(E)-2-Methylbut-2-enoyl chloride was prepared by the addition of oxalyl chloride (1.3 mL, 15 mmol) to tiglic acid (1.0 g, 10 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure (E)-2-methylbut-2-enoyl chloride as a yellow oil. To a solution of N-((1H-furan-2-yl)methyl)aniline (159 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4
mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-2-methylbut-2-enoyl chloride (140 mg, 1.10 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (253 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to afford compound 1c as a yellow oil (217 mg, 93%). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.33 ~ 7.13 (m, 4H), 7.07 ~ 6.96 (m, 2H), 6.25 (dd, $J$ = 3.2, 1.9 Hz, 1H), 6.16 (dd, $J$ = 3.3, 0.9 Hz, 1H), 5.75 (dd, $J$ = 6.9, 1.5 Hz, 1H), 4.90 (s, 2H), 1.55 ~ 1.53 (m, 3H), 1.44 (dd, $J$ = 6.9, 1.2 Hz, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 173.0, 151.2, 143.6, 142.0, 132.5, 131.0, 129.0, 127.3, 126.8, 110.4, 108.7, 46.4, 14.1, 13.4. IR (cm$^{-1}$): 3038, 2920, 1736, 1658, 1635, 1594, 1584, 1493, 1454, 1365, 1196, 1164, 1014, 933, 813, 735. HRMS (ESI-ion trap) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{18}$NO$_2$ 256.1332; Found 256.1333 ($\delta$ ppm = 0.4).

(E)-2-Methyl-N-((5-nitrofuran-2-yl)methyl)-N-phenylbut-2-enamide (2c):

(E)-2-Methylbut-2-enoyl chloride was prepared by the addition of oxalyl chloride (1.3 mL, 15 mmol) to tiglic acid (1.0 g, 10 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure (E)-2-methylbut-2-enoyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (200 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-2-methylbut-2-enoyl chloride (140 mg, 1.10 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (283 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to afford compound 2c as an orange oil (236 mg, 85%). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.51 ~ 7.43 (m, 2H), 7.42 ~ 7.35 (m, 2H), 7.28 ~ 7.23 (m, 2H), 6.66 (dt, $J$ = 3.7, 0.8 Hz, 1H), 5.97 (dd, $J$ = 6.9, 1.5 Hz, 1H), 5.11 (s, 2H), 1.70 ~ 1.67 (m, 3H), 1.62 (dd, $J$ = 6.9, 1.2 Hz, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 173.1, 155.2, 143.3, 132.5, 131.9, 129.5, 127.3, 126.9, 112.8, 111.9, 47.1, 13.9, 13.6. IR (cm$^{-1}$): 2921, 2247, 1634, 1564, 1529, 1492, 1353, 1297, 1278, 1232, 1159, 1018, 909, 810, 771. HRMS (APSI+ - TOF) m/z: [M]$^+$ Calcd for C$_{16}$H$_{15}$N$_2$O$_4$ 299.1032; Found 299.1029 ($\delta$ ppm = 0.4).

N-(Furan-2-ylmethyl)-3-methyl-N-phenylbut-2-enamide (1d):
3-Methylbut-2-enoyl chloride was prepared by the addition of oxalyl chloride (2.8 mL, 33 mmol) to a solution of 3-methyl crotonic acid (3.0 g, 30 mmol) in dichloromethane (25 mL). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure 3-methylbut-2-enoyl chloride as a yellow oil. To a solution of N-((1H-furan-2-yl)methyl)aniline (317 mg, 1.83 mmol) and pyridine (0.22 mL, 2.75 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of 3-methylbut-2-enoyl chloride (260 mg, 2.20 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (465 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to afford compound 3d as a yellow oil (407 mg, 87%).

**1H-NMR (300 MHz, CDCl₃):** δ = 7.38 ~ 7.18 (m, 4H), 7.05 ~ 6.98 (m, 2H), 6.21 (dd, J = 3.2, 1.8 Hz, 1H), 6.11 (dd, J = 3.2, 0.9 Hz, 1H), 5.37 (s, 1H), 4.84 (s, 2H), 2.09 (d, J = 1.3 Hz, 3H), 1.61 (s, 3H).

**13C-NMR (75 MHz, CDCl₃):** δ = 166.9, 151.5, 151.4, 142.7, 142.0, 129.3, 128.1, 127.52 117.5, 110.4, 108.7, 45.4, 27.4, 20.4. **IR (cm⁻¹):** 2912, 1712, 1650, 1632, 1593, 1494, 1447, 1393, 1364, 1263, 1170, 1146, 1016, 934, 843, 747. **HRMS (ESI-ion trap) m/z:** [M + H]⁺ Calcd for C₁₆H₁₈NO₂ 256.1332; Found 256.1330 (δ ppm =-0.8).

3-Methyl-N-((5-nitrofuran-2-yl)methyl)-N-phenylbut-2-enamide (2d):

3-methylbut-2-enoyl chloride was prepared by the addition of oxalyl chloride (2.8 mL, 33 mmol) to a solution of 3-methyl crotonic acid (3.0 g, 30 mmol) in dichloromethane (25 mL). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure 3-methylbut-2-enoyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (400 mg, 1.83 mmol) and pyridine (0.22 mL, 2.75 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of 3-methylbut-2-enoyl chloride (260 mg, 2.20 mmol) in dichloromethane (2 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (638 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide 3-methyl-N-((5-nitrofuran-2-yl)methyl)-N-phenylbut-2-enamide as a yellow oil (503 mg, 92%).

**1H-NMR (300 MHz, CDCl₃):** δ = 7.44 ~ 7.28 (m, 3H), 7.23 (d, J = 3.6 Hz, 1H), 7.19 ~ 7.13 (m, 2H), 6.52 (dd, J = 3.7, 0.8 Hz, 1H), 5.43 (s, 1H), 4.93 (s, 2H), 2.14 (s, 3H), 1.69 (s, 3H). **13C-NMR (75 MHz, CDCl₃):** δ = 167.0, 155.5, 153.3, 142.4, 129.8, 128.1, 127.9, 116.7, 112.8, 111.8, 46.3, 27.5, 20.4. **IR (cm⁻¹):** 2913, 1711, 1650, 1632, 1593, 1494, 1447, 1393, 1364, 1263, 1170, 1146, 1016, 934, 843, 747.
1492, 1447, 1399, 1353, 1265, 1221, 1163, 1019, 969, 955, 843, 809, 752. **HRMS (ASAP+ - TOF) m/z:** [M]\(^+\) Calcd for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_4\) 301.1188; **Found** 301.1186 (δ ppm = 0.7).

2-Cyclopentylidene-N-(furan-2-ylmethyl)-N-phenylacetamide (1e):

Cyclopent-1-ene-1-carbonyl chloride was prepared by the addition of oxalyl chloride (66.4 µL, 0.77 mmol) to 2-cyclopentylideneacetic acid (110 mg, 0.64 mmol) The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure the corresponding acyl chloride as a yellow oil. To a solution of N-(furan-2-ylmethyl)aniline (134 mg, 0.77 mmol) and pyridine (78 µL, 0.97 mmol) in dichloromethane (1.4 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (1.4 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 1e (138 mg, 76%) as a pale yellow solid. **M. p.:** 72-75 °C. **^1H-NMR (300 MHz, CDCl\(_3\))**: δ = 7.31 – 7.17 (m, 4H), 7.03 – 6.96 (m, 2H), 6.17 (dd, J = 3.2, 1.9 Hz, 1H), 6.08 (dq, J = 3.2, 0.8 Hz, 1H), 5.51 (s, 1H), 4.82 (s, 2H), 3.04 – 2.61 (m, 2H), 2.31 – 2.01 (m, 3H), 1.72 – 1.56 (m, 2H), 1.55 – 1.40 (m, 2H). **^13C-NMR (75 MHz, CDCl\(_3\))**: δ = 166.5, 165.6, 151.4, 142.7, 141.9, 129.3, 128.3, 127.4, 111.8, 110.3, 108.5, 45.3, 36.0, 32.5, 26.6, 25.4. **IR (cm\(^-1\))**: 1655, 1626, 1594, 1493, 1393, 1384, 1257, 1247, 1230, 1218, 1178, 1154, 1142, 1130, 855, 755, 744, 732, 663, 643, 599, 566. **HRMS (ESI-ion trap) m/z:** [M + H]^+ Calcd for C\(_{18}\)H\(_{20}\)NO\(_2\) 282.1489; **Found** 282.1488 (δ ppm = 0.2).

2-Cyclopentylidene-N-((5-nitrofuran-2-yl)methyl)-N-phenylacetamide (2e):

Cyclopent-1-ene-1-carbonyl chloride was prepared by the addition of oxalyl chloride (78 µL, 0.91 mmol) to 2-cyclopentylideneacetic acid (130 mg, 0.76 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure the corresponding acyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (200 mg, 0.91 mmol) and pyridine (93 µL, 1.14 mmol) in dichloromethane (1.7 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (1.7 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 5:1 to 3:1) to provide compound 2e (185 mg, 0.567 mmol, 74%) as a yellow oil. **^1H-NMR (300 MHz, CDCl\(_3\))**: δ = 7.43 – 7.27
(m, 3H), 7.21 (d, J = 3.7 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.51 (dd, J = 3.7, 0.8 Hz, 1H), 5.61 (t, J = 2.3 Hz, 1H), 4.92 (s, 2H), 2.92 – 2.73 (m, 2H), 2.29 – 2.16 (m, 2H), 1.77 – 1.62 (m, 2H), 1.61 – 1.45 (m, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 167.2, 166.7, 155.6, 142.4, 129.8, 128.0, 127.9, 117.1, 111.1, 46.2, 36.2, 32.6, 26.5, 25.3. IR (cm$^{-1}$): 1655, 1493, 1348, 1254, 1228, 1018, 809, 736, 666. HRMS (ESI-ion trap) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{19}$N$_2$O$_4$ 327.1339; Found 327.1340 (δ ppm 0.2).

2-Cyclohexylidene-N-(furan-2-ylmethyl)-N-phenylacetamide (1f):

2-Cyclohexylideneacetyl chloride was prepared by the addition of thionyl chloride (4.9 mL) to a solution of 2-cyclohexylideneacetic acid (561 mg, 4.0 mmol). The solution was stirred at room temperature for 3 hour. The crude solution was concentrated to yield 2-cyclohexylideneacetyl chloride as a yellow oil (80% purity). To a solution of N-((1H-furan-2-yl)methyl)aniline (159 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of 2-Cyclohexylideneacetyl chloride (221 mg, 1.4 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (418 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to compound 1f as a yellow oil (175 mg, 64%). $^1$H-NMR (300 MHz, CDCl$_3$): δ = 7.39 ~ 7.26 (m, 4H), 7.13 ~ 7.03 (m, 2H), 6.26 (dd, J = 3.2, 1.9 Hz, 1H), 6.16 (dd, J = 3.2, 0.8 Hz, 1H), 5.35 (s, 1H), 4.90 (s, 2H), 2.80 ~ 2.66 (m, 2H), 1.94 (t, J = 5.7 Hz, 2H), 1.64 ~ 1.45 (m, 6H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 167.7, 157.6, 151.4, 142.8, 142.0, 129.3, 128.2, 127.5, 115.1, 110.4, 108.7, 45.5, 37.9, 30.2, 28.6, 27.9, 26.5. IR (cm$^{-1}$): 2927, 2852, 1650, 1594, 1494, 1446, 1420, 1398, 1355, 1228, 1255, 1173, 1042, 982, 847, 732, 666. HRMS (ESI-ion trap) m/z: [M + H]$^+$ Calcd for C$_{19}$H$_{22}$NO$_2$ 296.1656; Found 296.1649 (δ ppm -2.4).

2-Cyclohexylidene-N-((5-nitrofuran-2-yl)methyl)-N-phenylacetamide (2f):

2-Cyclohexylideneacetyl chloride was prepared by the addition of thionyl chloride (4.9 mL) to a solution of 2-cyclohexylideneacetic acid (561 mg, 4.0 mmol). The solution was stirred at room temperature for 3 hour. The crude solution was concentrated to yield 2-cyclohexylideneacetyl chloride as a yellow oil (80% purity).

To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (200 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of 2-Cyclohexylideneacetyl chloride (221 mg, 1.4 mmol) in dichloromethane (2 mL). The solution...
stirred at room temperature for 16 hours where the reaction was quenched with the addition
of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The
combined organic layers were dried with sodium sulfate and concentrated to yield the crude
product as oil (489 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to
provide compound 2f as a red oil (192 mg, 61%). 1H-NMR (300 MHz, CDCl₃): δ = 7.43 ~
7.28 (m, 3H), 7.24 (d, J = 3.6 Hz, 1H), 7.21 ~ 7.16 (m, 2H), 6.53 (d, J = 3.6 Hz, 1H), 5.38 (s,
1H), 4.94 (s, 2H), 2.81 ~ 2.65 (m, 2H), 1.97 (t, J = 5.5 Hz, 2H), 1.71 ~ 1.44 (m, 6H). 13C-
NMR (75 MHz, CDCl₃): δ = 167.3, 159.5, 155.5, 142.5, 129.8, 128.1, 127.9, 114.2, 112.8,
111.9, 46.3, 31.1, 30.3, 28.7, 27.9, 26.4. IR (cm⁻¹): 2928, 2853, 1650, 1593, 1528, 1492,
1447, 1401, 1350, 1275, 1223, 1166, 1019, 984, 969, 848, 809, 737, 668. HRMS (ASAP+ -
TOF) m/z: [M+H]^+ Calcd for C₁₉H₂₁N₂O₄ 341.1501; Found 341.1502 (δ ppm 0.3).

N-(Furan-2-ylmethyl)-N-phenylcyclopent-1-ene-1-carboxamide (1g):
The acyl chloride was prepared by the addition of thionyl chloride (1.2
mL, 16.07 mmol) to cyclopent-1-ene-1-carboxylic acid (106 mg, 0.94
mmol) The solution was stirred at room temperature for 1 hour. The
crude solution was concentrated to yield pure the corresponding acyl
chloride as a yellow oil. To a solution of N-(furan-2-ylmethyl)aniline (196 mg, 1.13 mmol) and
pyridine (115 µL, 1.42 mmol) in dichloromethane (2.05 mL) under nitrogen was added, a
solution of acyl chloride in dichloromethane (2.05 mL). The solution stirred at room
temperature for 16 hours where the reaction was quenched with the addition of dilute HCl
(10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined
organic layers were dried with sodium sulfate and concentrated to yield the crude product
which was chromatographed on silica gel (Pet. Ether/EtOAc 7:1) to provide compound 1g
(212 mg, 84% yield) as a pale yellow solid. M. p. = 48 – 50 ºC. 1H-NMR (300 MHz, CDCl₃):
δ = 7.37 ~ 7.25 (m, 4H), 7.11 ~ 7.04 (m, 2H), 6.29 (ddd, J = 3.0, 1.8, 1.0 Hz, 1H), 6.20 (dt, J
= 3.2, 0.8 Hz, 1H), 5.88 ~ 5.84 (m, 1H), 4.95 (s, 2H), 2.27 ~ 2.15 (m, 4H), 1.79 ~ 1.60 (m,
2H). 13C-NMR (75 MHz, CDCl₃): δ = 168.0, 151.0, 143.1, 142.1, 139.3, 139.1, 129.1, 127.9,
127.4, 110.4, 108.9, 46.4, 33.7, 33.1, 23.3. IR (cm⁻¹): 2949, 2844, 1710, 1638, 1615, 1592,
1493, 1374, 1301, 1275, 1182, 1074, 1008, 949, 884, 735. HRMS (ASAP+ - TOF) m/z:
[M+H]^+ Calcd for C₁₇H₁₈N₂O₂ 268.1332; Found 268.1332 (δ ppm = 0.0).

N-((5-Nitrofuran-2-yl)methyl)-N-phenylcyclopent-1-ene-1-carboxamide (2g)
The acyl chloride was prepared by the addition of thionyl chloride
(1.2 mL, 17.4 mmol) to cyclopent-1-ene-1-carboxylic acid (115 mg,
1.0 mmol). The solution was stirred at room temperature for 1 hour.
The crude solution was concentrated to yield pure the corresponding acyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (269 mg, 1.23 mmol) and pyridine (124 µL, 1.54 mmol) in dichloromethane (2.2 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (2.2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 3:1) to provide compound 2g (210 mg, 66%) as an orange oil. ¹H-NMR (300 MHz, CDCl₃): δ = 7.40 – 7.27 (m, 3H), 7.24 (d, J = 3.7 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.54 (dt, J = 3.7, 0.7 Hz, 1H), 5.93 – 5.82 (m, 1H), 4.96 (t, J = 0.6 Hz, 2H), 2.28 – 2.13 (m, 4H), 1.77 – 1.62 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ = 167.9, 154.9, 151.4, 142.6, 140.3, 138.4, 129.4, 127.8, 127.4, 112.7, 111.9, 47.0, 33.4, 33.0, 23.1. IR (cm⁻¹): 1641, 1593, 1529, 1491, 1451, 1398, 1303, 1276, 1233, 1173, 1075, 1019, 980, 950, 908, 810, 772, 734, 698, 682, 589, 560. HRMS (ASAP+ - TOF) m/z: [M+H]⁺ Calcd for C₁₇H₁₇N₂O₄ 313.1183; Found 313.1183 (δ ppm = 0.1).

N-(Furan-2-ylmethyl)-N-phenylcyclohex-1-ene-1-carboxamide (1h):

Cyclohex-1-ene-1-carbonyl chloride was prepared by the addition of thionyl chloride (4.9 mL) to 1-cyclohexene-1-carboxylic acid (505 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure cyclohex-1-ene-1-carbonyl chloride as a yellow oil. To a solution of N-((1H-furan-2-yl)methyl)aniline (159 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of cyclohex-1-ene-1-carbonyl chloride (160 mg, 1.10 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (465 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 1h as a yellow oil (189 mg, 73%). ¹H-NMR (300 MHz, CDCl₃): δ = 7.33 ~ 7.16 (m, 4H), 7.07 ~ 7.00 (m, 2H), 6.26 (dd, J = 3.2, 1.9 Hz, 1H), 6.17 (dd, J = 3.2, 0.8 Hz, 1H), 5.85 (tt, J = 3.7, 1.7 Hz, 1H), 4.92 (s, 2H), 2.03 ~ 1.91 (m, 2H), 1.91 ~ 1.81 (m, 2H), 1.54 ~ 1.31 (m, 4H). ¹³C-NMR (75 MHz, CDCl₃): δ = 172.4, 151.2, 143.7, 142.0, 134.5, 133.2, 129.0, 127.3, 126.9, 110.4, 108.7, 46.3, 26.1, 25.1, 22.1, 21.5. IR (cm⁻¹): 2929, 2857, 1633, 1594, 1493, 1493, 1384, 1294, 127.8, 127.4, 112.7, 111.9, 47.0, 33.4, 33.0, 23.1. HRMS (ESI – ion trap) m/z: [M+H]⁺ Calcd for C₁₈H₂₀NO₂ 282.1500; Found 282.1492 (δ ppm = -2.7).
**N-((5-Nitrofuran-2-yl)methyl)-N-phenylcyclohex-1-ene-1-carboxamide (2h):**

Cyclohex-1-ene-1-carbonyl chloride was prepared by the addition of thionyl chloride (4.9 mL) to 1-cyclohexene-1-carboxylic acid (505 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure cyclohex-1-ene-1-carbonyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (200 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of cyclohex-1-ene-1-carbonyl chloride (160 mg, 1.10 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (465 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 2h as a red oil (275 mg, 92%).

**1H-NMR (300 MHz, CDCl$_3$):** δ = 7.38 ~ 7.27 (m, 3H), 7.25 ~ 7.22 (m, 1H), 7.16 ~ 7.10 (m, 2H), 6.53 (dt, $J = 3.7$, 0.6 Hz, 1H), 5.93 (tt, $J = 3.7$, 1.7 Hz, 1H), 4.97 (s, 2H), 2.00 ~ 1.83 (m, 4H), 1.54 ~ 1.34 (m, 4H).

**13C-NMR (75 MHz, CDCl$_3$):** δ = 172.5, 155.2, 143.4, 134.7, 133.9, 129.5, 127.5, 127.0, 112.8, 111.9, 47.1, 25.9, 25.2, 22.1, 21.5. **IR (cm$^{-1}$):** 2931, 1734, 1633, 1594, 1528, 1491, 1454, 1399, 1352, 1279, 1232, 1173, 1045, 1017, 968, 920, 854, 809, 697. **HRMS (ASAP+ - TOF) m/z:** [M+H]$^+$ Calcd for C$_{18}$H$_{19}$N$_2$O$_4$ 327.1345; Found 327.1338 (δ ppm = -2.1).

**2-Cyclohexylidene-N-(furan-2-ylmethyl)-N-phenylpropanamide (1i):**

The acyl chloride was prepared by the addition of oxalyl chloride (54.5 µL, 0.63 mmol) to 2-cyclohexylideneopropanoic acid (86 mg, 0.56 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure the corresponding acyl chloride as a yellow oil. To a solution of N-(furan-2-ylmethyl)aniline (88 mg, 0.51 mmol) and pyridine (49.3 µL, 0.61 mmol) in dichloromethane (0.5 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (0.5 mL). The solution stirred at 70 ºC for 16 hours where the reaction was quenched with the addition of dilute HCl (10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 6:1 to 4:1) to provide compound 1i as a colourless oil.

**1H-NMR (300 MHz, CDCl$_3$):** δ = 7.39 – 7.24 (m, 4H), 7.11 – 7.01 (m, 2H), 6.29 (dd, $J = 3.2$, 1.7 Hz, 1H), 6.21 (d, $J = 3.2$ Hz, 1H), 4.97 (s, 2H), 2.13 (s, 2H), 1.90 (d, $J = 7.8$ Hz, 2H), 1.62 (s, 3H), 1.54 – 1.30.
(m, 6H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 173.2, 151.0, 142.1, 141.9, 138.3, 128.6, 127.4, 127.4, 122.7, 110.4, 108.8, 45.2, 32.4, 29.1, 27.0, 26.9, 26.3, 15.9. IR (cm$^{-1}$): 1634, 1594, 1494, 1372, 1012, 728, 698, 599. HRMS (ESI – ion trap) m/z: [M+H]$^+$ Calcd for C$_{20}$H$_{24}$NO$_2$ 310.1800; Found 310.1802 ($\delta$ ppm = -0.5).

2-Cyclohexylidene-$N$-((5-nitrofuran-2-yl)methyl)-$N$-phenylpropanamide (2i):

The acyl chloride was prepared by the addition of oxalyl chloride (93 µL, 1.09 mmol) to 2-cyclohexylidene propanoic acid (148 mg, 0.96 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure the corresponding acyl chloride as a yellow oil. To a solution of $N$-((5-nitrofuran-2-yl)methyl)aniline (190 mg, 0.87 mmol) and pyridine (85 µL, 1.04 mmol) in dichloromethane (0.9 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (0.9 mL). The solution was stirred at 70 ºC for 16 hours where the reaction was quenched with the addition of dilute HCl (10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 4: 1) to provide compound 2i (196 mg, 63% yield) as a yellow oil. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.42 – 7.25$ (m, 4H), 7.19 – 7.16 (m, 2H), 6.55 (d, $J = 3.7$ Hz, 1H), 5.03 (s, 2H), 2.14 (s, 2H), 1.93 (t, $J = 6.0$ Hz, 2H), 1.62 (s, 3H), 1.55 – 1.34 (m, 6H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 173.5, 155.0, 141.9, 139.7, 129.1, 127.8, 127.0, 121.9, 112.6, 111.6, 105.0, 46.0, 32.5, 29.2, 27.1, 26.8, 26.2, 15.8. IR (cm$^{-1}$): 1640, 1597, 1529, 1493, 1353, 1300, 1227, 1017, 810, 738, 698. HRMS (ASAP+ - TOF) m/z: [M+H]$^+$ Calcd for C$_{20}$H$_{23}$N$_2$O$_4$ 355.1652; Found 355.1653 ($\delta$ ppm = 0.2).

$N$-(Furan-2-ylmethyl)-$N$-phenylcinnamamide (1j):

Cinnamoyl chloride (231 mg, 1.3 mmol) was added at -20 ºC carefully to a solution of $N$-(furan-2-ylmethyl)aniline (200 mg, 1.15 mmol), triethylamine (0.243 mL, 1.7 mmol) and DMAP in dry dichloromethane (5.00 mL) at 0 ºC with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 mL) and water (10 mL) was added. The mixture was further extracted with dichloromethane (2 x 10 mL) and the combined organic phase dried (Na$_2$SO$_4$). Purification by column chromatography (1:1.5 Et$_2$O/ petroleum ether) afforded the title compound: (279 mg, 80%) as a white solid. M. p.: 75-76 ºC. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.65$ (d, $J = 15.5$ Hz, 1H), 7.42 – 7.27 (m, 3H), 7.27 –
7.13 (m, 6H), 7.13 – 7.00 (m, 2H), 6.30 – 6.16 (m, 2H), 6.13 (dd, J = 3.2, 0.8 Hz, 1H), 4.92 (s, 2H).  
**13C-NMR (75 MHz, CDCl₃):** δ = 165.8, 150.9, 142.4, 142.1, 141.9, 135.2, 129.6, 129.5, 128.7, 128.0, 127.9, 118.7, 110.4, 109.0, 45.9.  
**IR (cm⁻¹):** 3042, 1978, 1646, 1605, 706.  
**HRMS (ESI – ion trap) m/z:** [M+H]⁺ Calcd for C₂₀H₁₈NO₃ 304.1338; Found 304.1332 (δ ppm = 0.3).

**N-((5-Nitrofuran-2-yl)methyl)-N-phenylcinnamamide (2j):**

Cinnamoyl chloride (458 mg, 2.5 mmol) was added at -20 °C carefully to a solution of N-((5-nitrofuran-2-yl)methyl)aniline (500 mg, 2.3 mmol), triethylamine (0.48 mL, 3.4 mmol) and DMAP in dry dichloromethane (5.00 mL) at 0 °C with stirring. The reaction mixture was allowed to rise to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 mL) and water (10 mL) was added. The mixture was further extracted with dichloromethane (2 × 10 mL) and the combined organic phase dried (Na₂SO₄). Purification by column chromatography (1:1 Et₂O/ petroleum ether) afforded the title compound: (676 mg, 85%) as a dark orange oil.  
**1H-NMR (300 MHz, CDCl₃):** δ = 7.75 (d, J = 15.6 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.48 – 7.39 (m, 2H), 7.39 – 7.20 (m, 8H), 6.61 (dd, J = 3.7, 0.8 Hz, 1H), 6.35 (d, J = 15.6 Hz, 1H), 5.07 (s, 2H).  
**13C-NMR (75 MHz, CDCl₃):** δ = 166.2, 154.8, 143.3, 141.6, 134.8, 130.0, 129.9, 128.8, 128.5, 128.0, 117.8, 112.6, 112.1, 46.6.  
**IR (cm⁻¹):** 2975, 2867, 1704, 1655, 1492, 1353, 751, 698.  
**HRMS (ASAP+ - TOF) m/z:** [M+H]⁺ Calcd for C₂₀H₁₇N₂O₄ 349.1183; Found 349.1185 (δ ppm = 0.1).

**((E)-N-(furan-2-ylmethyl)-3-(4-methoxyphenyl)-N-phenylacrylamide (1k):**

(E)-3-(4-methoxyphenyl)acryloyl chloride was prepared by the addition of thionyl chloride (5.0 mL) to (E)-3-(4-methoxyphenyl)acrylic acid (712 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure (E)-3-(4-methoxyphenyl)acryloyl chloride as a yellow oil. To a solution of N-((furan-2-yl)methyl)aniline (161 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-3-(4-methoxyphenyl)acryloyl chloride (275 mg, 1.4 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the
crude product as oil (462 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to yield compound 1k as a yellow oil (168 mg, 54%). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta =$ 7.71 (d, $J = 15.5$ Hz, 1H), 7.47 – 7.35 (m, 4H), 7.29 – 7.13 (m, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.36 – 6.29 (m, 1H), 6.23 (dd, $J = 3.2$, 0.8 Hz, 1H), 5.02 (s, 2H), 3.81 (s, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta =$ 166.3, 160.9, 151.1, 142.2, 142.2, 129.6, 128.5, 128.0, 127.9, 116.4, 114.2, 110.5, 109.0, 55.4, 46.0. IR (cm$^{-1}$): 2932, 1651, 1593, 1574, 1511, 1492, 1455, 1422, 1373, 1303, 1177, 1077, 1030, 1017, 980, 937, 860, 824, 750, 699, 638, 599, 584, 554. HRMS (ESI – ion trap) m/z: [M+H]$^+$ Calcd for C$_{21}$H$_{20}$NO$_3$ 334.1438; Found 334.1438 ($\delta$ ppm 0.1).

(E)-3-(4-methoxyphenyl)-N-((5-nitrofuran-2-yl)methyl)-N-phenylacrylamide (2k):

Cyclopent-1-ene-1-carboxylic acid was prepared by the addition of oxalyl dichloride (75 µL, 0.875 mmol) to (E)-3-(4-methoxyphenyl)acrylic acid (130 mg, 0.730 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure the corresponding N-[(5-nitrofuran-2-yl)methyl]aniline (191 mg, 0.875 mmol) and pyridine (89 µL, 1.094 mmol) in dichloromethane (1.5 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (1.5 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (10 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 2k (239 mg, 87%) as a yellow oil. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta =$ 7.67 (d, $J = 15.5$ Hz, 1H), 7.55 – 7.36 (m, 3H), 7.32 – 7.22 (m, 5H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.58 (d, $J = 3.7$ Hz, 1H), 6.18 (d, $J = 15.5$ Hz, 1H), 5.13 – 4.94 (m, 2H), 3.79 (s, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta =$ 166.6, 161.2, 155.1, 142.1, 144.8, 130.1, 130.0, 129.7, 128.5, 128.1, 127.6, 115.3, 114.3, 112.8, 112.1, 55.4, 46.7. IR (cm$^{-1}$): 2912, 1712, 1650, 1632, 1593, 1494, 1447, 1393, 1364, 1263, 1170, 1146, 1016, 934, 843, 747. HRMS (ESI – ion trap) m/z: [M+H]$^+$ Calcd for C$_{27}$H$_{19}$N$_2$O$_5$ 379.1288; Found 379.1283 ($\delta$ ppm -1.4).

(E)-N-(furan-2-ylmethyl)-3-(4-nitrophenyl)-N-phenylacrylamide (1l):

(E)-3-(4-nitrophenyl)acryloyl chloride was prepared by the addition of thionyl chloride (5.0 mL) to (E)-3-(4-nitrophenyl)acrylic acid (773 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure (E)-3-(4-nitrophenyl)acryloyl
chloride as a yellow oil. To a solution of \( N-((\text{furan-2-yl})\text{methyl})\text{aniline} \) (159 mg, 0.9 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of \((E)-3-(4\text{-nitrophenyl})\text{acryloyl chloride} \) (296 mg, 1.4 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (462 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to yield compound 1 as a white crystals (141 mg, 44\%). M. p.: 136-138 °C. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta = 8.12 \) (d, \( J = 8.8 \) Hz, 2H), 7.74 (d, \( J = 15.6 \) Hz, 1H), 7.47 ~ 7.38 (m, 5H), 7.34 (dd, \( J = 1.8, 0.8 \) Hz, 1H), 7.19 ~ 7.09 (m, 2H), 6.40 (d, \( J = 15.6 \) Hz, 1H), 6.29 (dd, \( J = 3.2, 1.9 \) Hz, 1H), 6.21 (dd, \( J = 3.2, 0.8 \) Hz, 1H), 5.00 (s, 2H). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta = 164.9, 150.5, 148.1, 142.3, 141.5, 141.4, 139.6, 129.8, 128.5, 128.4, 128.3, 124.1, 122.9, 110.5, 109.3, 46.1. \) IR (cm\(^{-1}\)): 3075, 2936, 1651, 1614, 1592, 1511, 1503, 1413, 1392, 1338, 1281, 1191, 1077, 1033, 980, 884. HRMS (ESI – ion trap) m/z: [M+H]\(^+\) Calcd for C\(_{20}\)H\(_{17}\)N\(_2\)O\(_4\) 349.1183; Found 349.1186 (\( \delta \) ppm =0.9).

\((E)-N-((5\text{-nitrofuran-2-yl})\text{methyl})-3-(4\text{-nitrophenyl})-N\text{-phenylacrylamide} \) (22):

\((E)-3-(4\text{-nitrophenyl})\text{acryloyl chloride} \) was prepared by the addition of thionyl chloride (5.0 mL) to \((E)-3-(4\text{-nitrophenyl})\text{acrylic acid} \) (773 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure \((E)-3-(4\text{-nitrophenyl})\text{acryloyl chloride} \) as a yellow oil. To a solution of \( N-((5\text{-nitrofuran-2-yl})\text{methyl})\text{aniline} \) (119 mg, 0.55 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of \((E)-3-(4\text{-nitrophenyl})\text{acryloyl chloride} \) (296 mg, 1.4 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (462 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to yield compound 22 as beige crystals (195 mg, 90\%). M. p.: 152-154 °C. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta = 8.15 \) (d, \( J = 8.8 \) Hz, 2H), 7.74 (d, \( J = 15.6 \) Hz, 1H), 7.54 ~ 7.39 (m, 5H), 7.27 (d, \( J = 2.1 \) Hz, 1H), 7.26 (d, \( J = 3.7 \) Hz, 2H), 6.58 (d, \( J = 3.7 \) Hz, 1H), 6.43 (d, \( J = 15.6 \) Hz, 1H), 5.05 (s, 2H). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta = 165.3, 154.3, 148.4, 141.3, 141.0, 140.5, 130.3, 129.0, 128.7, 128.1, 124.2, 122.0, 112.6, 112.4, 46.8 IR (cm\(^{-1}\)): 3140, 1657, 1620, 1530, 1523, 1497, 1483, 1297, 1191, 1077, 1033, 980, 884.
1504, 1374, 1339, 1240, 1169, 1109, 1017, 979, 867, 735. **HRMS (ESI – ion trap) m/z:**

[M+H]⁺ Calcd for C₂₀H₁₆N₃O₆ 394.1039; **Found** 394.1040 (δ ppm 0.3).

**(E)-N-(furan-2-ylmethyl)-N,3-diphenylbut-2-enamide (1m):**

(E)-3-phenylbut-2-enoyl chloride was prepared by the addition of thionyl chloride (5.7 mL) to (E)-3-phenylbut-2-enolic acid (650 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure (E)-3-phenylbut-2-enolic acid as a yellow oil. To a solution of N-((1H-furan-2-yl)methyl)aniline (159 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-3-phenylbut-2-enoyl chloride (253 mg, 1.4 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (398 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to yield compound 1m as a yellow oil (255 mg, 87%). **¹H-NMR (300 MHz, CDCl₃):** δ = 7.42 ~ 7.28 (m, 4H), 7.23 (d, J = 3.3 Hz, 2H), 7.16-7.12 (m, 4H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 6.22 (dd, J = 3.3, 0.9 Hz, 1H), 5.89 (s, 1H), 4.97 (s, 2H), 2.52 (s, 3H). **¹³C-NMR (75 MHz, CDCl₃):** δ = 167.0, 151.2, 150.0, 142.9, 142.6, 142.1, 129.5, 128.4, 128.3, 128.1, 127.8, 126.2, 119.6, 110.5, 108.9, 45.5, 18.2. **IR (cm⁻¹):** 3058, 1654, 1615, 1593, 1493, 1446, 1366, 1277, 1176, 114, 1075, 1016, 927, 883, 755. **HRMS (ESI – ion trap) m/z:** [M+H]⁺ Calcd for C₂₁H₂₀N₂O₂ 318.1489; **Found** 318.1492 (δ ppm 1.1).

**(E)-N-((5-nitrofuran-2-yl)methyl)-N,3-diphenylbut-2-enamide (2m):**

(E)-3-phenylbut-2-enoyl chloride was prepared by the addition of thionyl chloride (5.7 mL) to (E)-3-phenylbut-2-enolic acid (650 mg, 4.0 mmol). The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure (E)-3-phenylbut-2-enolic acid as a yellow oil. To a solution of N-((5-(nitrofuran-2-yl)methyl)aniline (200 mg, 0.92 mmol) and pyridine (0.11 mL, 1.4 mmol) in dichloromethane (2 mL) under nitrogen was added, a solution of (E)-3-phenylbut-2-enoyl chloride (253 mg, 1.4 mmol) in dichloromethane (2 mL). The solution stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product as oil (462 mg) which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to
yield compound 2m as a red oil (287 mg, 86%). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.49 - 7.33\) (m, 3H), 7.29 - 7.23 (m, 5H), 7.20 - 7.14 (m, 2H), 6.59 (d, \(J = 3.7\) Hz, 1H), 5.93 (s, 1H), 5.02 (s, 2H), 2.53 (d, \(J = 1.3\) Hz, 3H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 167.2, 155.2, 151.7, 142.6, 142.3, 129.9, 128.7, 128.5, 128.3, 127.8, 126.2, 118.5, 112.8, 112.0, 46.4, 18.3\). IR (cm\textsuperscript{-1}): 3057, 1704, 1645, 1594, 1557, 1530, 1493, 1145, 1354, 1266, 1227, 1170, 1075, 1020, 916, 862, 811, 761, 734, 596, 577, 562. HRMS (ASAP+ - TOF) m/z: [M+H]\textsuperscript{+} Calcd for C\textsubscript{21}H\textsubscript{19}N\textsubscript{2}O\textsubscript{4} 363.1345; Found 363.1351 (δ ppm 1.7).

Ethyl (E)-4-(((5-nitrofuran-2-yl)methyl)(phenyl)amino)-4-oxobut-2-enoate (2n):

The acyl chloride was prepared by the addition of thionyl chloride (1.63 mL, 22.4 mmol) to (E)-4-ethoxy-4-oxobut-2-enoic acid (190 mg, 1.3 mmol) The solution was stirred at room temperature for 1 hour. The crude solution was concentrated to yield pure the corresponding acyl chloride as a yellow oil. To a solution of N-((5-nitrofuran-2-yl)methyl)aniline (345 mg, 1.58 mmol) and pyridine (0.160 mL, 1.98 mmol) in dichloromethane (2.87 mL) under nitrogen was added, a solution of acyl chloride in dichloromethane (2.87 mL). The solution was stirred at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (5 mL). The solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1 to 2:1) to provide compound 2n (240 mg, 53%) as a colorless oil. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.50 - 7.39\) (m, 3H), 7.24 (d, \(J = 3.7\) Hz, 1H), 7.21 – 7.15 (m, 2H), 6.89 (d, \(J = 15.3\) Hz, 1H), 6.79 (d, \(J = 15.4\) Hz, 1H), 6.54 (dd, \(J = 3.7, 0.7\) Hz, 1H), 5.00 (s, 2H), 4.16 (q, \(J = 7.1\) Hz, 2H), 1.24 (t, \(J = 7.2\) Hz, 3H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 165.2, 164.1, 153.8, 140.5, 133.1, 132.3, 130.2, 129.1, 129.00, 127.7, 112.5, 112.3, 61.1, 46.6, 14.0\). IR (cm\textsuperscript{-1}): 1720, 1662, 1493, 1359, 1296, 1265, 1250, 1223, 1160, 1020, 971, 810, 758, 717, 699, 690. HRMS (ESI – ion trap) m/z: [M+H]\textsuperscript{+} Calcd for C\textsubscript{17}H\textsubscript{17}N\textsubscript{2}O\textsubscript{6} 345.1081; Found 345.1083 (δ ppm = 0.5).

General Procedure for the intramolecular Diels-Alder reaction.

A solution of the corresponding furan in Toluene (0.046 M) under nitrogen was heated to reflux and stirred for the time indicated in each case. Then, the toluene was removed under vacuum and the crude was purified by column chromatography with the eluent indicated in each case.

(3aRS,6RS)-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (3a).\textsuperscript{7}
A solution of N-(furan-2-ylmethyl)-N-phenylacrylamide (145 mg, 23.5 mmol) in toluene (13.9 mL) was heated to reflux with stirring for 24 hours under nitrogen. Toluene was then removed in vacuo to afford the crude product. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel (Pet. Ether/EtOAc 1:1) to provide compound 3a as an orange solid (102 mg, 70%). M. p.: 139 - 140 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.64 – 7.47 (m, 2H), 7.42 – 7.16 (m, 2H), 7.07 (ddt, J = 7.8, 1.1 Hz, 1H), 6.50 – 6.28 (m, 2H), 5.02 (dd, J = 4.6, 1.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 4.05 (d, J = 11.5 Hz, 1H), 2.55 (dd, J = 8.8, 3.4 Hz, 1H), 2.23 (ddd, J = 8.8, 3.4 Hz, 1H). 13C-NMR (75 MHz, CDCl3): δ = 173.4, 139.4, 137.5, 133.0, 128.9, 124.7, 120.3, 88.1, 79.3, 50.9, 48.8, 28.9. IR (cm⁻¹): 3002.1, 2976.9, 2946.2, 1683.0, 1601.5, 1500.0, 687.4.

(3aRS,6SR)-6-nitro-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (4a).

A solution of N-(furan-2-ylmethyl)-N-phenylacrylamide (64.0 mg, 23.5 mmol) in toluene (2.50 mL) was heated to reflux with stirring for 24 hours under nitrogen. Toluene was then removed in vacuo to afford the pure title compound: Wt 64 mg; 100% as a beige solid. M. p.: 165 - 166 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.66 – 7.54 (m, 2H), 7.46 – 7.33 (m, 2H), 7.24 – 7.16 (m, 1H), 6.79 (s, 2H), 4.50 (d, J = 12.0 Hz, 1H), 4.30 (d, J = 12.0 Hz, 1H), 2.95 (dd, J = 8.7, 3.6 Hz, 1H), 2.71 (dd, J = 11.7, 3.6 Hz, 1H), 2.44 (dd, J = 11.7, 8.7 Hz, 1H). 13C-NMR (75 MHz, CDCl3): δ = 170.5, 138.6, 135.9, 135.0, 129.1, 125.5, 120.4, 111.7, 87.8, 50.8, 50.4, 34.0. IR (cm⁻¹): 3117, 3098, 3067, 2992, 1688, 1552, 1500, 1489, 1472, 1358, 1292, 1156, 1116, 1055. HRMS (ESI – ion trap) m/z: [M+H]+ Calcd for C14H13N2O4 273.0870; Found 273.0869 (δ ppm = -0.1).

(3aRS,6RS)-2-Phenyl-7-propyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (3b):

A solution of (E)-N-(furan-2-ylmethyl)-N-phenylhex-2-enamide (122 mg, 0.45 mmol) in toluene (10 mL) under nitrogen was heated to reflux and stirred for 48 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 3b as white crystals (22 mg, 18%, 50% BRSM). M. p.: 106-108 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.69 ~ 7.60 (m, 2H), 7.42 ~ 7.31 (m, 2H), 7.18 ~ 7.10 (m, 1H), 6.56 (d, J = 5.8 Hz, 1H), 6.43 (dd, J = 5.9, 1.7 Hz, 1H), 4.98 (dd, J = 4.4, 1.7 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.09 (d, J = 11.5 Hz, 1H), 2.64 (tt, J = 8.0, 4.1 Hz, 1H), 2.19 (d, J = 3.8 Hz, 1H), 1.53 ~ 1.40 (m, 2H), 1.28 ~ 1.19 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). 13C-NMR (75 MHz, CDCl3): δ = 173.5, 139.6, 135.7, 134.3, 129.0, 124.7, 120.2, 88.6, 82.1, 55.4, 51.1, 43.6, 35.0, 22.0, 14.2. IR (cm⁻¹): 2985, 2968, 2922, 2850, 1682, 1597, 1470, 1397, 1355,
1244, 1190, 1075, 1038, 987, 881, 757. HRMS (ESI – ion trap) m/z: [M+H]^+ Calcd for C_{17}H_{20}NO_2 270.1489; Found 270.1489 (δ ppm = 0.2).

(3aRS,6RS)-6-Nitro-2-phenyl-7-propyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (4b):

A solution of (E)-N-((5-nitrofuran-2-yl)methyl)-N-phenylhex-2-enamide (100 mg, 0.33 mmol) in toluene (10 mL) under nitrogen was heated to reflux and stirred for 48 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 4b as white crystals (110 mg, 67%). M. p.: 194-196 °C. 1H-NMR (300 MHz, CDCl_3): δ = 7.66 ~ 7.59 (m, 2H), 7.45 ~ 7.34 (m, 2H), 7.22 ~ 7.14 (m, 1H), 6.79 (d, J = 1.2 Hz, 2H), 4.43 (d, J = 12.0 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 2.89 (dt, J = 11.5, 3.9 Hz, 1H), 2.51 (d, J = 3.9 Hz, 1H), 1.90 ~ 1.74 (m, 1H), 1.58 ~ 1.40 (m, 2H), 1.14 ~ 1.00 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). 13C-NMR (75 MHz, CDCl_3): δ = 170.5, 138.7, 136.4, 132.9, 129.0, 125.2, 120.1, 105.0, 87.2, 56.9, 50.4, 48.6, 33.2, 21.1, 13. 8. IR (cm⁻¹): 3144, 3112, 2961, 2925, 2870, 2358, 1704, 1594, 1505, 1464, 1356, 1331, 1294, 1235, 1189, 1130, 1016, 980, 913. HRMS (ASAP+ – TOF) m/z: [M+H]^+ Calcd for C_{17}H_{19}N_2O_4 315.1345; Found 315.1349 (δ ppm = 1.3).

(3aRS,6RS)-7,7a-Dimethyl-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (3c):

A solution of (Z)-N-(furan-2-ylmethyl)-2-methyl-N-phenylbut-2-enamide (100 mg, 0.33 mmol) in toluene (10 mL) under nitrogen was heated to reflux and stirred for 48 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 3c (54 mg, 54%). M. p.: 116-118 °C. 1H-NMR (300 MHz, CDCl_3): δ = 7.62 ~ 7.54 (m, 2H), 7.35 ~ 7.25 (m, 2H), 7.07 (ddt, J = 7.7, 6.9, 1.1 Hz, 1H), 6.45 (d, J = 1.4 Hz, 2H), 4.83 ~ 4.80 (m, 1H), 4.26 (d, J = 11.4 Hz, 1H), 4.00 (d, J = 11.4 Hz, 1H), 2.71 (qd, J = 7.4, 4.5 Hz, 1H), 0.92 (s, 3H), 0.80 (d, J = 7.4 Hz, 3H). 13C-NMR (75 MHz, CDCl_3): δ = 178.0, 139.8, 137.0, 133.2, 129.0, 124.5, 120.0, 91.2, 82.9, 55.5, 49.8, 39.9, 15.7, 13.1. IR (cm⁻¹): 2960, 2929, 2874, 1692, 1597, 1493, 1353, 1293, 1220, 1095, 1008, 893, 758. HRMS (ESI – ion trap) m/z: [M+H]^+ Calcd for C_{16}H_{16}NO_2 256.1332; Found 256.1333 (δ ppm = 0.4).

(3aRS,6RS)-7,7a-Dimethyl-6-nitro-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (4c):
A solution of 3-methyl-N-((5-nitro-1H-pyrrol-2-yl)methyl)-N-phenylbut-2-enamide (160 mg, 0.53 mmol) in toluene (10 mL) under nitrogen was heated to reflux and stirred for 24 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 4c as white crystals (124 mg, 78%). M. p.: 126-128 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.68 ~ 7.58 (m, 2H), 7.44 ~ 7.35 (m, 1H), 6.82 (d, J = 5.8 Hz, 1H), 6.75 (d, J = 5.8 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 3.05 (q, J = 7.3 Hz, 1H), 1.10 (d, J = 7.4 Hz, 3H), 1.08 (s, 3H). 13C-NMR (75 MHz, CDCl3): δ = 175.4, 139.1, 136.0, 133.6, 129.2, 125.2, 120.2, 114.4, 90.1, 58.2, 49.1, 45.6, 15.6, 12.3. IR (cm⁻¹): 2971, 1693, 1641, 1599, 1548, 1493, 1354, 1331, 1306, 1217, 1175, 1069, 1024, 877, 809, 706. HRMS (ASAP+ – TOF) m/z: [M+H]+ Calcd for C16H17N2O4 301.1188; Found 301.1185 (δ ppm = -1.0).

(3aRS,6RS)-7,7-Dimethyl-6-nitro-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (4d).

A solution of 3-methyl-N-((5-nitro-1H-pyrrol-2-yl)methyl)-N-phenylbut-2-enamide (100 mg, 0.33 mmol) in toluene (10 mL) under nitrogen was heated to reflux and stirred for 48 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1) to provide compound 4d as white crystals (43 mg, 43%). M. p.: 175-178 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.60 ~ 7.52 (m, 2H), 7.39 (dd, J = 8.5, 7.5 Hz, 2H), 7.23 ~ 7.14 (m, 1H), 6.75 (s, 2H), 4.36 (d, J = 12.0 Hz, 1H), 4.19 (d, J = 12.0 Hz, 1H), 2.47 (s, 1H), 1.38 (s, 3H), 1.35 (s, 3H). 13C-NMR (75 MHz, CDCl3): δ = 169.5, 138.6, 135.9, 134.4, 129.1, 125.5, 120.6, 116.2, 86.3, 58.1, 50.1, 47.4, 25.8, 19.9. IR (cm⁻¹): 3073, 2981, 2359, 2340, 1677, 1597, 1555, 1493, 1454, 1345, 1396, 1361, 1296, 1212, 1159, 1073, 997. HRMS (ASAP+ – TOF) m/z: [M+H]+ Calcd for C15H17N2O4 301.1188; Found 301.1185 (δ ppm = -1.0).

(3a'R,S,6'R,S)-6'-Nitro-2'-phenyl-2',3'-dihydro-6'H-spiro[cyclopentane-1,7']-[3a,6']epoxyisoindol-1'(7a'H)-one (4e):

A solution of 2-cyclopentylidene-N-((5-nitrofuran-2-yl)methyl)-N-phenylacetamide (90 mg, 0.276 mmol) in Toluene (6 mL) under nitrogen was heated to reflux and stirred for 27 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Petroleum Ether/EtOAc (7:1) to provide compound 4e (21 mg, 23%) as a white solid. M. p.: 210-212 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.66 ~ 7.58 (m, 2H), 7.47 ~ 7.38 (m, 2H), 7.27 ~ 7.19 (m, 1H), 6.87 (d, J = 5.6 Hz, 1H), 6.80 (d, J = 5.6 Hz, 1H), 4.41 (d, J = 12.0
Hz, 1H), 4.27 (d, J = 12.0 Hz, 1H), 2.61 (s, 1H), 2.34 (ddd, J = 13.2, 8.1, 4.7 Hz, 1H), 2.24 – 2.03 (m, 2H), 1.91 – 1.57 (m, 3H), 1.49 (dd, J = 7.6, 5.5 Hz, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 169.5, 138.6, 136.5, 134.8, 129.0, 125.4, 120.6, 115.8, 86.2, 61.8, 57.9, 49.9, 37.4, 29.5, 25.2, 24.8. IR (cm$^{-1}$): 1676, 1554, 1492, 1409, 1209, 1145, 833, 771, 690. HRMS (ASAP+ – TOF) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{19}$N$_2$O$_4$ 327.1339; Found 327.1340 (δ ppm = 0.2).

(3a′R,S,6′R,S)-6′-Nitro-2′-phenyl-2′,3′-dihydro-6′H-spiro[cyclohexane-1,7′-[3a,6]epoxyisoindol]-1′(7a′H)-one (4f)

A solution of 3-vinyl-N-v((5-vinyl-1H-pyrrolyl)methyl)-N-phenylbut-2-enamide (109 mg, 0.32 mmol) in toluene (7 mL) under nitrogen was heated to reflux and stirred for 48 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel as eluent Petroleum Ether/EtOAc (4:1) to provide compound 4f as white crystals (35 mg, 32%). M. p.: 183-185 °C. $^{1}$H-NMR (300 MHz, CDCl$_3$): δ = 7.62 ~ 7.53 (m, 2H), 7.42 ~ 7.33 (m, 2H), 7.22 ~ 7.14 (m, 1H), 6.78 (d, J = 5.6 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 4.33 (d, J = 11.9 Hz, 1H), 4.21 (d, J = 11.9 Hz, 1H), 2.50 (s, 1H), 2.52 ~ 2.37 (m, 1H), 2.05 ~ 1.02 (m, 10H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 169.4, 138.6, 135.3, 135.2, 129.0, 125.4, 120.8, 117.1, 86.6, 58.1, 52.8, 49.9, 35.3, 28.5, 24.7, 23.6, 22.6. IR (cm$^{-1}$): 2932, 2855, 1677, 1597, 1570, 1550, 1492, 1356, 1289, 1243, 1138, 1076, 1043, 976, 917, 844, 731, 697. HRMS (ASAP+–TOF) m/z: [M+H]$^+$ Calcd for C$_{19}$H$_{21}$N$_2$O$_4$ 341.1501; Found 341.1497 (δ ppm = -1.2).

(3aR,S,6R,S,9aSR)-2-Phenyl-2,3,6a,7,8,9-hexahydro-1H,6H-3a,6-epoxycyclopenta[d]isoindol-1-one (3g):

A solution of N-(furan-2-ylmethyl)-N-phenylcyclopent-1-ene-1-carboxamide (94 mg, 0.352 mmol) in Toluene (7.6 mL) under nitrogen was heated to reflux and stirred for 22 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Pet. Ether/EtOAc (4:1) to provide compound 3g (48 mg, 41 % yield) as a white solid. M. p.: 41-43 °C. $^{1}$H-NMR (300 MHz, CDCl$_3$): δ = 7.72 – 7.59 (m, 2H), 7.44 – 7.29 (m, 2H), 7.20 – 7.08 (m, 1H), 6.62 – 6.51 (m, 2H), 4.95 (dd, J = 5.0, 1.4 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.05 (d, J = 11.5 Hz, 1H), 3.27 (ddd, J = 8.9, 5.3, 3.3 Hz, 1H), 1.92 – 1.74 (m, 3H), 1.71 – 1.45 (m, 2H), 1.37 – 1.22 (m, 1H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 177.4, 139.6, 138.1, 133.5, 128.9, 124.4, 120.0, 90.6, 82.0, 67.3, 52.7, 50.3, 30.9, 28.5, 17.1. IR (cm$^{-1}$): 2951, 1687, 1599, 1556, 1493, 1464, 1446, 1396, 1354, 1311, 1294, 1279, 1217, 1202, 1181, 1149, 1132, 1100, 1060, 1012, 998, 976, 962, 904, 856, 823, 787, 708, 688, 614, 575, 560. HRMS (ESI – ion trap) m/z: [M+H]$^+$ Calcd for C$_{17}$H$_{18}$NO$_2$ 268.1332; Found 268.1332 (δ ppm = 0.0).
(3aRS,6RS)-6-Nitro-2-phenyl-2,3,6a,7,8,9-hexahydro-1H,6H-3a,6-epoxycyclopenta[d]isoindol-1-one (4g)

A solution of N-((5-nitrofuran-2-yl)methyl)-N-phenylcyclopent-1-ene-1-carboxamide (119 mg, 0.38 mmol) in Toluene (8.3 mL) under nitrogen was heated to reflux and stirred for 22 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Pet. Ether/EtOAc (4:1) to provide compound 4g (111 mg, 93% yield) as a pale yellow solid. M. p.: 198-201 °C. 

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.72 – 7.57 (m, 2H), 7.46 – 7.33 (m, 2H), 7.24 – 7.13 (m, 1H), 6.85 (d, $J$ = 5.8 Hz, 1H), 6.79 (d, $J$ = 5.7 Hz, 1H), 4.39 (d, $J$ = 12.0 Hz, 1H), 4.21 (dd, $J$ = 11.9, 1.3 Hz, 1H), 3.49 (dd, $J$ = 8.8, 2.5 Hz, 1H), 2.07 – 1.55 (m, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 174.7, 138.8, 136.2, 134.9, 129.0, 125.1, 120.1, 113.3, 89.6, 69.7, 57.8, 49.6, 30.9, 28.1, 27.0. IR (cm$^{-1}$): 2952, 2860, 1686, 1599, 1556, 1489, 1464, 1446, 1407, 1356, 1294, 1279, 1217, 1185, 1150, 1101, 1062, 1034, 1010, 970, 937, 907, 899, 854, 819, 794, 726, 688, 643, 619, 590, 577, 560. HRMS (ASAP+ – TOF) m/z: [M+H]$^+$ Calcd for C$_{17}$H$_{17}$N$_2$O$_4$ 313.1183; Found 313.1183 (δ ppm = 0.1).

(3aRS,6RS,6aSR,10aSR)-6-Nitro-2-phenyl-2,3,6,6a,7,8,9,10-octahydro-1H-3a,6-epoxybenzo[d]isoindol-1-one (4h)

A solution of N-((5-nitrofuran-2-yl)methyl)-N-phenylcyclohex-1-ene-1-carboxamide (215 mg, 0.66 mmol) in toluene (10 mL) under nitrogen was heated to reflux and stirred for 48 hours. The solution was concentrated to yield the crude product as crystals which was chromatographed on silica gel using as eluent Pet. Ether/EtOAc (4:1) to provide compound 4h as a white solid (119 mg, 55%). M. p.: 178-180 °C. 

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.66 - 7.60 (m, 2H), 7.44 - 7.33 (m, 2H), 7.17 (ddt, $J$ = 8.0, 7.1, 1.2 Hz, 1H), 6.82 (d, $J$ = 5.7 Hz, 1H), 6.75 (d, $J$ = 5.7 Hz, 1H), 4.38 (d, $J$ = 11.9 Hz, 1H), 4.22 (d, $J$ = 11.9 Hz, 1H), 2.85 (dd, $J$ = 12.6, 6.1 Hz, 1H), 2.16 - 0.81 (m, 8H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 174.4, 139.2, 136.1, 134.0, 129.1, 125.1, 120.0, 114.0, 90.2, 57.4, 49.1, 47.5, 25.1, 22.1, 18.4, 16.2. IR (cm$^{-1}$): 3114, 2947, 2869, 1685, 1598, 1552, 1491, 1459, 1357, 1305, 1294, 1126, 1093, 937, 851, 758, 627. HRMS (ESI – ion trap) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{19}$N$_2$O$_4$ 327.1339; Found 327.1342 (δ ppm = 0.8).
(3a'RS,6'RS)-7a'-Methyl-6'-nitro-2'-phenyl-2',3'-dihydro-6'H-spiro[cyclohexane-1,7'-
[3a,6]epoxyisoindol]-1'(7a'H)-one (4i):
A solution of 2-cyclohexylidene-N-((5-nitrofuran-2-yl)methyl)-N-
phenylpropanamide (110 mg, 0.310 mmol) in Toluene (6.7 mL) under
nitrogen was heated to reflux and stirred for 26 h. The solution was
concentrated to yield the crude product which was chromatographed on
silica gel using as eluent Pet. Ether/EtOAc (6:1) to provide compound 4i (22 mg, 20% yield)
as a white solid. M. p.: 166-169 ºC. 1H-NMR (300 MHz, CDCl3): δ = 7.63 – 7.52 (m, 2H), 7.46 – 7.32 (m, 2H), 6.84 (d, J = 5.7 Hz, 1H), 6.65 (d, J = 5.7 Hz, 1H), 4.26 (d, J = 11.8 Hz, 1H), 4.17 (d, J = 11.8 Hz, 1H), 2.37 – 2.10 (m, 2H), 1.85 (ddd, J = 15.3, 11.6, 3.8 Hz, 1H), 1.77 – 1.41 (m, 6H), 1.34 (ddd, J = 14.0, 10.3, 3.6 Hz, 1H), 1.24 (s, 3H). 13C-NMR (75 MHz, CDCl3): δ = 173.6, 138.8, 135.7, 134.7, 129.0, 125.2, 120.6, 117.2, 89.0, 60.2, 54.1, 48.2, 30.7, 30.3, 24.9, 23.4, 23.1, 17.8. IR (cm⁻¹): 2948, 1694, 1549, 1490, 1471, 1452, 1404, 1371, 1351, 1289, 1228, 1215, 1165, 1098, 1087, 1063, 1039, 1021, 979, 886, 866, 848, 818, 801, 763, 686, 661, 591, 566. HRMS (ASAP+ – TOF) m/z: [M+H]+ Calcd for C20H23N2O4 355.1652; Found 355.1654 (δ ppm = 0.5).

(3aRS,6SR)-2,7-diphenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (3j):
A solution of N-(furan-2-ylmethyl)-N-phenylcinnamamide (207 mg, 0.68 mmol) in Toluene (14.8 mL) under nitrogen was heated to reflux
and stirred for 24 h. The solution was concentrated to yield the crude
product which was chromatographed on Petroleum Ether/EtOAc (4:1) to provide compound 3j as a white solid (16 mg, 8 %). M. p.: 132-132 ºC. 1H-NMR (300 MHz, CDCl3): δ = 7.73 – 7.63 (m, 2H), 7.39 (dd, J = 8.9, 7.2 Hz, 2H), 7.29-7.27 (m, 4H), 6.66 (d, J = 5.8 Hz, 1H), 6.37 (dd, J = 5.8, 1.7 Hz, 1H), 5.27 (dd, J = 4.5, 1.7 Hz, 1H), 4.50 (d, J = 1.6 Hz, 1H), 4.19 (d, J = 11.6 Hz, 1H), 3.97 (t, J = 4.3 Hz, 1H), 2.94 (d, J = 4.2 Hz, 1H). 13C-NMR (75 MHz, CDCl3): δ = 172.8, 139.5, 139.1, 136.4, 134.1, 128.9, 128.4, 127.9, 126.8, 124.7, 120.2, 89.3, 82.9, 56.5, 51.0, 48.1. IR (cm⁻¹): 3063, 1692, 1599, 1498, 1401, 1352, 1316, 1188, 1124, 1082, 988, 968, 888, 862, 753, 692. HRMS (ESI – ion trap) m/z: [M+H]^+ Calcd for C20H18N2O2 304.1332; Found 304.1333 (δ ppm = 0.5).
(3aRS,6RS)-6-nitro-2,7-diphenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (4j).

A solution of N-((5-nitrofuran-2-yl)methyl)-N-phenylcinnamamide (150 mg, 0.15 mmol) in Toluene (9.3 mL) under nitrogen was heated to reflux and stirred for 5 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Petroleum Ether/EtOAc (1:1.5) to provide compound 4j as an orange solid (35 mg, 23 %). M. p.: 170-171 °C. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.68 – 7.49\) (m, 2H), 7.40 – 7.29 (m, 2H), 7.25 (ddt, \(J = 5.7\), 4.0, 2.4 Hz, 3H), 7.18 – 7.03 (m, 3H), 6.91 (d, \(J = 5.7\) Hz, 1H), 6.60 (d, \(J = 5.7\) Hz, 1H), 4.47 (d, \(J = 12.1\) Hz, 1H), 4.25 (d, \(J = 12.1\) Hz, 1H), 4.12 (d, \(J = 4.2\) Hz, 1H). \(^13\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 170.2, 138.9, 136.9, 136.2, 133.3, 129.1, 128.7, 128.6, 128.1, 125.4, 120.3, 114.7, 88.4, 59.1, 52.7, 50.4\.)

IR (cm\(^{-1}\)): 2923.6, 1691.6, 1552.6, 740.0, 699.7, 689.7. HRMS (ESI – ion trap) m/z: [M+H]\(^+\) Calcd for C\(_{20}\)H\(_{17}\)N\(_2\)O\(_4\) 349.1183; Found 349.1179 (\(\delta\) ppm = 0.4).

(3aRS,6RS)-6-Nitro-7-(4-nitrophenyl)-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (4k):

A solution of (E)-N-((5-nitrofuran-2-yl)methyl)-3-(4-nitrophenyl)-N-phenylacrylamide (59 mg, 0.150 mmol) in Toluene (3.26 mL) under nitrogen was heated to reflux and stirred for 72 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Petroleum Ether/EtOAc (4:1) to provide compound 4k (19 mg, 32.2 % yield) as a white solid. M. p.: 105-108 °C. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.26 – 8.15\) (m, 2H), 7.68 – 7.57 (m, 2H), 7.42 (t, \(J = 7.8\) Hz, 2H), 7.38 – 7.31 (m, 2H), 7.22 (d, \(J = 7.3\) Hz, 1H), 7.07 (d, \(J = 5.7\) Hz, 1H), 6.68 (d, \(J = 5.7\) Hz, 1H), 4.57 (d, \(J = 12.2\) Hz, 1H), 4.35 (d, \(J = 12.2\) Hz, 1H), 4.27 (d, \(J = 4.2\) Hz, 1H), 3.24 (d, \(J = 4.2\) Hz, 1H). \(^13\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 169.4, 148.0, 141.7, 138.4, 137.2, 132.9, 129.2, 129.2, 125.7, 123.9, 120.4, 114.1, 88.4, 76.6, 59.4, 52.1, 50.4\.) IR (cm\(^{-1}\)): 2922, 2852, 1688, 1600, 1553, 1520, 1491, 1465, 1403, 1346, 1298, 1271, 1240, 1226, 1204, 1150, 1125, 1108, 1048, 1005, 912, 844, 808, 758, 691, 671, 649, 597, 561. HRMS (ESI – ion trap) m/z: [M+H]\(^+\) Calcd for C\(_{20}\)H\(_{16}\)N\(_2\)O\(_6\) 394.1034; Found 394.1032 (\(\delta\) ppm = -0.4).
(3aRS,6RS)-7-(4-Methoxyphenyl)-6-nitro-2-phenyl-2,3,7,7a-tetrahydro-3a,6-epoxisoindol-1(6H)-one (4l):

A solution of (E)-3-(4-methoxyphenyl)-N-((5-nitrofuran-2-yl)methyl)-N-phenylacrylamide (109 mg, 0.29 mmol) in Toluene (6.26 mL) under nitrogen was heated to reflux and stirred for 24 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Petroleum Ether/EtOAc (5:1) to provide compound 4l (19 mg, 17%) as a white solid. M. p.: 97-101 °C. ¹H-NMR (300 MHz, CDCl₃): δ = 7.64 (dt, J = 8.0, 1.1 Hz, 2H), 7.48 – 7.36 (m, 2H), 7.21 (s, 1H), 7.05 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 5.7 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 5.7 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.31 (d, J = 12.0 Hz, 1H), 4.13 (d, J = 4.2 Hz, 1H), 3.80 (s, 3H), 3.19 (d, J = 4.2 Hz, 1H). ¹³C-NMR (75 MHz, CDCl₃): δ = 170.2, 159.8, 138.7, 136.0, 133.3, 129.3, 129.1, 125.4, 120.3, 114.7, 114.1, 105.0, 88.3, 59.2, 55.3, 52.2, 50.4.

Ethyl (3aRS,6RS)-1-oxo-2-phenyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxisoindole-7-carboxylate (3n): To a solution of (E)-4-ethoxy-4-oxobut-2-enolic acid (159 mg, 1.10 mmol) was added thionyl chloride (1.4 mL). The solution was stirred at 80 °C for 1 hour. The crude solution was concentrated to yield the acyl chloride as a yellow oil. To a solution of N-(furan-2-ylmethyl)aniline (191 mg, 1.1 mmol) and triethylamine (303 µL, 2.20 mmol) in dichloromethane (3.8 mL) under nitrogen was added, a solution of the acyl chloride in dichloromethane (3.8 mL) at room temperature for 16 hours where the reaction was quenched with the addition of dilute HCl (20 mL). The solution was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with sodium sulfate and concentrated to yield the crude product which was chromatographed on silica gel (Pet. Ether/EtOAc 4:1 to 2:1) to provide compound 3n (186 mg, 63%) as a white solid. M. p.: 115-117 °C. ¹H-NMR (300 MHz, CDCl₃): δ = 7.70 – 7.57 (m, 2H), 7.46 – 7.31 (m, 2H), 7.17 (dt, J = 6.9, 1.0 Hz, 1H), 6.63 (d, J = 5.8 Hz, 1H), 6.38 (dd, J = 5.8, 1.6 Hz, 1H), 5.30 (dd, J = 4.8, 1.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 4.25 – 4.07 (m, 3H), 3.59 (dd, J = 4.8, 3.5 Hz, 1H), 3.13 (d, J = 3.5 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ = 171.8, 170.3, 139.2, 135.3, 134.9, 129.0, 124.9, 120.2, 89.4, 80.6, 61.3, 52.6, 50.8, 47.5, 14.2. IR (cm⁻¹): 1725, 1681, 1401, 1361, 1342, 1267, 1203, 1024, 1007, 950, 872, 848, 707, 687. HRMS (ESI – ion trap) m/z: [M+H]⁺ Calcd for C₁₇H₁₈NO₄ 300.1230; Found 300.1231 (δ ppm = 0.2).
(3aRS,6RS)-6-Nitro-1-oxo-2-phenyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylate (4n):

A solution of ethyl (E)-4-(((5-nitrofuran-2-yl)methyl)(phenyl)amino)-4-oxobut-2-enoate (90 mg, 0.26 mmol) in Toluene (5.7 mL) under nitrogen was heated to reflux and stirred for 1 h. The solution was concentrated to yield the crude product which was chromatographed on silica gel using as eluent Petroleum Ether/EtOAc (2:1) to provide compound 4n (81 mg, 90%) as a white solid.

M. p.: 196-198 °C. 1H-NMR (300 MHz, CDCl3): δ = 7.65 – 7.58 (m, 2H), 7.47 – 7.36 (m, 2H), 7.25 – 7.18 (m, 1H), 6.89 (d, J = 5.7 Hz, 1H), 6.77 (d, J = 5.7 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.34 – 4.14 (m, 3H), 3.97 (d, J = 3.7 Hz, 1H), 3.34 (d, J = 3.7 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H). 13C-NMR (75 MHz, CDCl3): δ = 169.3, 167.8, 138.5, 137.0, 132.5, 129.1, 125.6, 120.4, 112.6, 88.8, 62.3, 55.6, 50.9, 50.3, 14.0. IR (cm⁻¹): 2947, 1749, 1649, 1556, 1503, 1467, 1363, 1264, 1251, 1196, 1026, 1015, 911, 803, 689, 674. HRMS (ESI – ion trap) m/z: [M+H]^+ Calcd for C_{17}H_{17}N_{2}O_{6} 345.1081; Found 345.1082 (δ ppm = 0.3).
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Supporting information. $^1$H and $^{13}$C NMR spectra for all new compounds. Full details of calculated data and images of relevant frontier orbitals.

References and notes


9. The early Japanese work was focused on substrate activation by use of metal-chelating substituents rather than direct comparison of nitrated and non-nitrated substrates; see references 8a and 8b.

10. A SciFinder Scholar™ search for such reactions generated no hits.


12. Some decomposition was observed (NMR) in those reactions where the conversion and yield do not match closely. Reactions to give products 3c/4c, 3g/4g, 3i/4i, 3j/4j, 3k/4k, 3l/4l appeared to have reached equilibrium and in these cases, the expected amount of starting material was recovered in high yield.


21. For analogous data calculated at 298.15 K, see S-88 in the supporting information.

22. For a table detailing these values, see Table S-88 in the supporting information.

