Scientific paper

# 1,3-Dipolar Cycloaddition Reactions of *N*-Methyl-Substituted Tricyclic Imides

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## Abstract

The [3+2] cycloadditions of *N*-methyl derivatives of unsaturated imides with various nitrile oxides to yield new bridged isoxazoline derivatives with potential biological activity is described.

**Keywords:** Alkenes, cycloadditions, heterocycles, triyclic imides, cantharidin analogues

## 1. Introduction

Cycloaddition reactions are among the most powerful methods for the construction of rings.[1] The 1,3-dipolar cycloaddition of nitrile oxides to alkenes is a widely used, efficient method for the synthesis of isoxazolines.[2] Isoxazolines are versatile intermediates for the synthesis of a variety of bioactive compounds and possess a broad spectrum of biological activity such as insecticidal, antibacterial, antibiotic, antitumor and antifungal.[3–5] The isoxazoline ring has been revealed to be a latent precursor for a variety of difunctional compounds, like γ-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles and unsaturated oximes, therefore this heterocycle has been utilized for construction of natural products having such functionalities.[6,7]

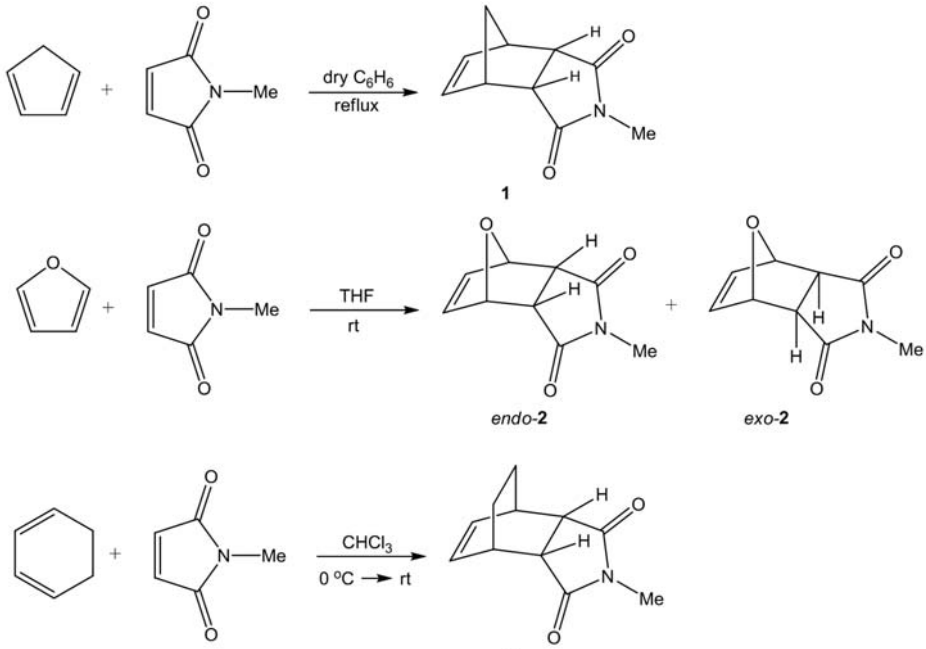
In addition, *N*-substituted imides, such as maleimides,[8] isohematinic acids[9] and especially bicyclic and tricyclic derivatives such as tandospirone derivatives[10,11] are known for their broad spectrum of pharmacological properties, thus showing antibiotic, fungicidal, analgesic, anxiolytic and cytostatic effects. The imide moiety is an integral structural part of various important bioactive molecules such as fumaramidmycin, granulatimide, isogranulatimide and rebeccamycin. These molecules are reported to exhibit antitumor, anti-inflammatory and antimicrobial activities.[12,13] A literature search reveals that certain compounds with antitumor activity, and in particular molecules able to interact with DNA, are characterized by the presence of both an extended π-system and an imide function. Apart from biological activities, imide derivatives are useful in the reactions involving condensations, alkylations, acylations and cyclocondensations.

On the other hand, the intramolecular cycloaddition is useful synthetic strategy to yield bicyclic and tricyclic compounds, often proceeding with high regio- and stereoselectivity. Derivatives of the tricyclic anhydride *exo*-5,6-dehydronorcantharidin are also pharmacologically active. Hu and Deng had studied the reactions of 5,6-dehydronorcantharidin derivatives with three types of nitrile oxides and found that they are active against HL60 cells, but only in high concentration.[14] Recently, we were interested in the intramolecular cycloaddition of aryl and heteroaryl substituted tricyclic hydrazones with nitrile oxides because of possible bioactive compounds.[15] In this paper, we describe the synthesis of various tetracyclic isoxazolines (via 1,3-dipolar cycloaddition) as new representatives of 5,6-dehydronorcantharidin derivatives.

## 2. Results and Discussion

Our synthesis started with the Diels–Alder reaction of cyclopentadiene and *N*-methylmaleimide. The reaction occurred in dry benzene under reflux to give *N*-methylbicyclo[2.2.1]hept-8-ene-3,*endo*-5-*endo*-dicarboximide (**1**) as colorless crystals (yield 93%).[16] The same reaction was successfully applied to the reaction of furan with *N*-methylmaleimide to give both diastereomers, the *N*-methyl-10-oxabicyclo[2.2.1]hept-8-ene-3,*endo*-5-*endo*-

dicarboximide (*endo*-**2**) and *N*-methyl-10-oxabicyclo[2.2.1]hept-8-ene-3,*exo*-5-*exo*-dicarboximide (*exo*-**2**) in good yields after chromatographic separation.[17] We also synthesized **3** from 1,3-cyclohexadiene with *N*-methylmaleimide under the similar conditions (Scheme 1).[16]




**Scheme 1.** Synthesis of compounds **1**–**3**

Norbornene and its derivatives have figured prominently in organic chemistry. The presence of a rigid bicyclic skeleton gives rise to stereoisomers with fixed spatial orientation of substitutents. The double bond in substituted norbornenes is quite reactive toward cycloadends, in particular toward nitrile oxides in 1,3-dipolar cycloadditions. We carried out the [3+2] cycloaddition of **1** and *exo*-**2** with 2-chlorophenyl nitrile oxide (generated in situ from 2-chlorobenzaldehyde oxime with NaOCl), to obtain the target compounds **4** and **13**. The same conditions were successfully applied to the reactions of *endo*-**2** and **3** with 4-chlorobenzaldeyde oxime to give the new heterocycles **7** and **10** in good yields after chromatographic separation. Analogously, compounds **8**, **11** and **14** were obtained from *endo*-**2**, *exo*-**2** and **3** with 2,5-dimethoxybenzaldehyde oxime, respectively, and compound **5** was prepared from **1** with 2,4-dimethylbenzaldehyde oxime (Scheme 2).

We also synthesized **6**, **9**, **12** and **15** from **1**–**3** with 2-thiophencarbaldehyde oxime prepared as new isoxazolines under the 1,3-dipolar cycloaddition conditions (Scheme 2).

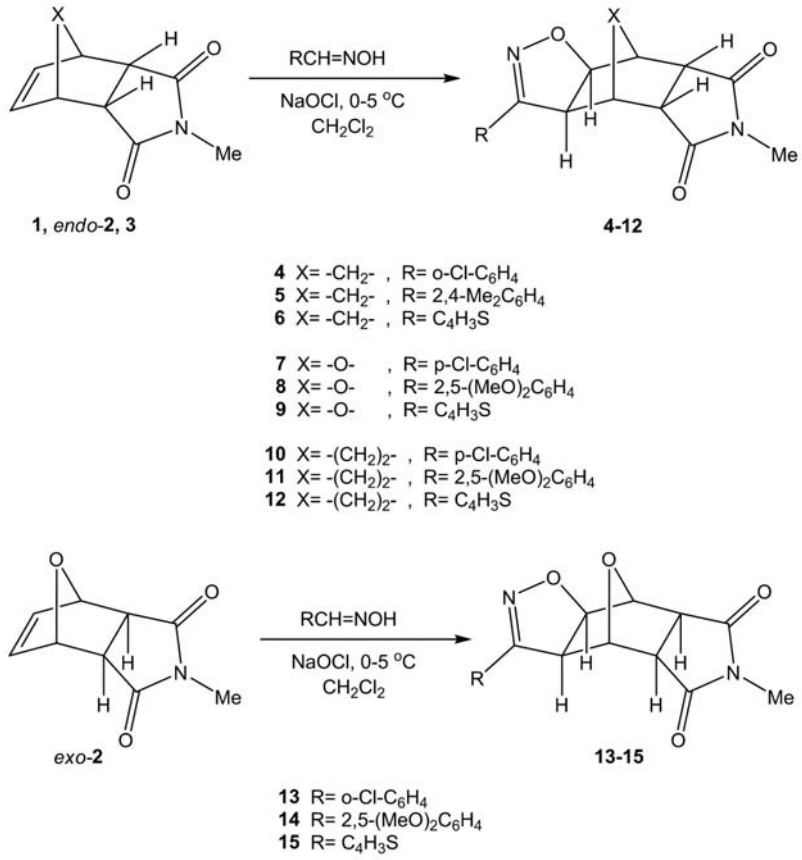
The $^1$H NMR spectra of **4**–**15** are in accord with the proposed structures. In order to identify the configuration of the isoxazolines with tricyclic imide adducts we have studied selective $^1$H-$^1$H-COSY spectra obtained from these compounds. $^1$H-$^1$H-COSY spectra show the cross peaks between resonances for $H_{4a}$ and $H_{7a}$; $H_{3an}$ and $H_{8an}$. The MS/EI spectra of cycloadducts **4**–**15** showed the characteristic molecular ion peaks.

# 3. Experimental

Reactions were monitored by thin-layer chromatography (TLC). Visualization of the developed chromatograms was performed either with UV light or $KMnO_4$ stain. Products were purified by silica gel chromatography with a solvent gradient of ethyl acetate/*n*-hexane to afford the title compounds. IR spectra were obtained with a Perkin Elmer, FT-IR instrument and absorption frequencies are reported in $cm^{-1}$. Melting points were determined with a Gallenkamp digital thermometer. All NMR spectra were determined with a Varian-INOVA-500 spectrometer. TMS (tetramethylsilane) was used as internal standard and $CDCl_3$ as the solvent. Mass spectra were measured with Agilent 6890N GC-System-5973 IMSD and Agilent 6460-A model LC-Triple Quadrupole MS/MS system (Jet Stream Electro spray ionization source).

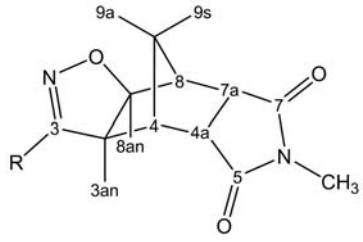
## 3. 1. General Procedure for Preparing Isoxazolines 4–15

Olefin (1 mmol) and aldoxime (1 mmol) were dissolved in $CH_2Cl_2$ and the solution was cooled to 0 °C. NaOCl (10–13%) was added dropwise to the stirring solution. The biphasic mixture was allowed to warm to room temperature and was stirred for 8 h. An additional volume of water was added and the layers were separa-




**Scheme 2**. General synthesis of compounds **4-15**

ted. The aqueous layer was extracted two to three additional times with $CH_2Cl_2$, and the combined organic layers were dried with $MgSO_4$, evaporated under vacuum and purified by column chromatography to give the product.




**4,8-Methano-3-(2-chlorophenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (4).** Colorless solid, yield 92%, mp 200–204 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.54 (d, $J$ = 11.1 Hz, 1H, H-9s), 1.82 (d, $J$ = 11.1 Hz, 1H, H-9a), 2.69 (brs, 1H, H-4), 2.94 (s, 3H, $N$-$CH_3$), 3.08 (brs, 1H, H-8), 3.10–3.12 (m, 2H, H-4a and H-7a), 3.82 (d, $J$ = 8.4 Hz, 1H, H-3an), 4.56 (d, $J$ = 8.4 Hz, 1H, H-8an), 7.22 (dd, $J_1$ = $J_2$ = 8.7 Hz, 1H, ArH), 7.29 (dd, $J_1$ = $J_2$ = 8.7 Hz, 1H, ArH), 7.37 (d, $J$ = 8.7 Hz, 1H, ArH), 7.42 (d, $J$ = 8.7 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 24.74 ($N$-$CH_3$), 36.04 (C-9), 41.32 (C-4), 44.65 (C-8), 45.57 (C-4a), 46.73 (C-7a), 54.63 (C-3a), 83.08 (C-8a), 127.09 (ArC), 127.38 (ArC), 130.86 (ArC), 130.90 (ArC), 131.11 (ArC), 132.92 (ArC), 156.09 (C-3), 176.10 (C-7), 176.51 (C-5). IR (ATR) ν 2992, 2959, 1765 (C=O), 1690 (C=O), 1591, 1462, 1427, 1374, 1347, 1276, 1133, 1113, 977, 905, 867, 771 cm$^{-1}$. GC-MS (EI, 70 eV) $m/z$ 330 ($M^+$), 295, 206, 192, 178, 111, 66.

**4,8-Methano-3-(2,4-dimethylphenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (5).** Colorless solid, yield 53%, mp 165–169 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.58 (d, $J$ = 11.1 Hz, 1H, H-9s), 1.86 (d, $J$ = 11.1 Hz, 1H, H-9a), 2.36 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 2.90–2.92 (m, 1H, H-4), 3.05 (s, 3H, $N$-$CH_3$), 3.16–3.19 (m, 1H, H-8), 3.20–3.23 (m, 2H, H-4a and H-7a), 3.64 (d, $J$ = 8.3 Hz, 1H, H-3an), 4.53 (d, $J$ = 8.3 Hz, 1H, H-8an), 7.07–7.12 (m, 2H, ArH), 7.25 (d, $J$ = 7.7 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 21.21 ($CH_3$), 23.36 ($CH_3$), 24.74 ($N$-$CH_3$), 36.09 (C-9), 41.83 (C-4), 44.59 (C-8), 45.80 (C-4a), 46.89 (C-7a), 54.89 (C-3a), 81.54 (C-8a), 124.12 (ArC), 126.84 (ArC), 128.91 (ArC), 132.75 (ArC), 138.48 (ArC), 139.77 (ArC), 157.04 (C-3), 176.27 (C-7), 177.00 (C-5). IR (ATR) ν 2976, 2942, 1770 (C=O), 1696

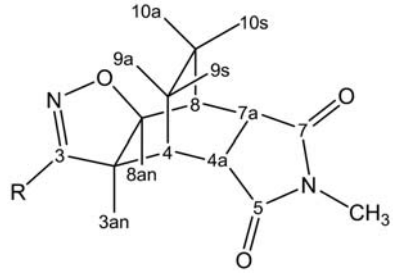
(C=O), 1585, 1431, 1380, 1276, 1130, 1037, 983, 942, 921, 896, 869, 816 $cm^{-1}$; GC-MS (EI, 70 eV) *m/z* 324 ($M^+$), 309, 295, 281, 236, 191, 66.

**4,8-Methano-3-(2-thienyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (6).** Colorless solid, yield 60%, mp 245–248 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.55 (d, *J* = 10.7 Hz, 1H, H-9s), 1.81 (d, *J* = 10.7 Hz, 1H, H-9a), 2.94 (s, 3H, *N*-$CH_3$), 3.03 (brd, *J* = 4.8 Hz, 1H, H-4), 3.09 (brd, *J* = 4.8 Hz, 1H, H-8), 3.12–3.19 (m, 2H, H-4a and H-7a), 3.41 (d, *J* = 6.8 Hz, 1H, H-3an), 4.53 (d, *J* = 6.8 Hz, 1H, H-8an), 6.99 (dd, $J_1$ = 4.2 Hz, $J_2$ = 5.6 Hz, 1H, ArH), 7.18 (dd, $J_1$ = 0.9 Hz, $J_2$ = 3.9 Hz, 1H, ArH), 7.32 (dd, $J_1$ = 0.9 Hz, $J_2$ = 3.9 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 24.92 (*N*-$CH_3$), 36.32 (C-9), 42.40 (C-4), 44.62 (C-8), 45.64 (C-4a), 47.08 (C-7a), 53.95 (C-3a), 83.62 (C-8a), 127.71 (ArC), 128.77 (ArC), 128.86 (ArC), 130.92 (ArC), 152.42 (C-3), 176.22 (C-7), 176.98 (C-5). IR (ATR) ν 3103, 2976, 1769, 1676, 1429, 1377, 1357, 1274, 1130, 1120, 1077, 981, 916, 837, 808 $cm^{-1}$; GC-MS (EI, 70 eV) *m/z* 302 ($M^+$), 163, 66.

**4,8-Epoxy-3-(4-chlorophenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (7).** Colorless solid, yield 65%, mp 267–269 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.97 (s, 3H, *N*-$CH_3$), 3.47–3.53 (m, 2H, H-4a and H-7a), 3.79 (d, *J* = 7.8 Hz, 1H, H-3an), 4.80 (d, *J* = 7.8 Hz, 1H, H-8an), 4.89 (d, *J* = 5.8 Hz, 1H, H-4), 5.08 (d, *J* = 5.8 Hz, 1H, H-8), 7.34 (d, *J* = 8.7 Hz, 2H, ArH), 7.50 (d, *J* = 8.7 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 25.38 (*N*-$CH_3$), 47.76 (C-4a), 50.13 (C-7a), 55.10 (C-3a), 79.38 (C-8a), 83.48 (C-4), 83.77 (C-8), 126.42 (ArC), 128.22 (ArC), 129.65 (ArC), 136.89 (ArC), 153.76 (C-3), 173.68 (C-7), 174.63 (C-5). IR (ATR) ν 3063, 2925, 2850, 1769 (C=O), 1693 (C=O), 1595, 1493, 1435, 1379, 1354, 1277, 1136, 1092, 994, 890, 831, 819 $cm^{-1}$; GC-MS (EI, 70 eV) *m/z* 332 ($M^+$), 178, 153, 137, 111, 68.

**4,8-Epoxy-3-(2,5-dimethoxyphenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (8).** Colorless solid, yield 60%, mp 221–222 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.95 (s, 3H, *N*-$CH_3$), 3.43–3.45 (m, 2H, H-4a and H-7a), 3.70 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 4.14 (d, *J* = 8.7 Hz, 1H, H-3an), 4.72 (d, *J* = 8.7 Hz, 1H, H-8an), 4.82 (brd, *J* = 3.9 Hz, 1H, H-4), 5.01 (brd, *J* = 3.9 Hz, 1H, H-8), 6.82 (d, *J* = 8.7 Hz, 1H, ArH), 6.89 (dd, $J_1$ = 2.9 Hz, $J_2$ = 8.7 Hz, 1H, ArH), 7.40 (d, *J* = 2.9 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 25.24 (*N*-$CH_3$), 48.00 (C-4a), 50.11 (C-7a), 55.93 (C-3a), 56.00 ($OCH_3$), 57.41 ($OCH_3$), 80.38 (C-8a), 83.01 (C-4), 83.57 (C-8), 112.90 (ArC), 113.20 (ArC), 116.65 (ArC), 119.32 (ArC), 151.53 (ArC), 153.84 (ArC), 153.93 (C-3), 174.13 (C-7), 174.32 (C-5). IR (ATR) ν 3020, 2957, 2835, 1781 (C=O), 1692 (C=O), 1563, 1491, 1462, 1445, 1427, 1376, 1337, 1294, 1268, 1213, 1186, 1129, 1041, 1011, 921, 893, 796 $cm^{-1}$; GC-MS (EI, 70 eV) *m/z* 358 ($M^+$), 329, 301, 190, 176, 163, 148, 68.

**4,8-Epoxy-3-(2-thienyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (9).** Colorless solid, yield 50%, mp 267–269 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.96 (s, 3H, *N*-$CH_3$), 3.46–3.53 (m, 2H, H-4a and H-7a), 3.78 (d, *J* = 7.8 Hz, 1H, H-3an), 4.78 (d, *J* = 7.8 Hz, 1H, H-8an), 5.03 (d, *J* = 5.8 Hz, 1H, H-4), 5.08 (d, *J* = 5.8 Hz, 1H, H-8), 7.02 (dd, $J_1$ = 3.4 Hz, $J_2$ = 4.8 Hz, 1H, ArH), 7.16 (dd, $J_1$ = 0.9 Hz, $J_2$ = 3.4 Hz, 1H, ArH), 7.35 (dd, $J_1$ = 0.9 Hz, $J_2$ = 4.8 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 24.13 (*N*-$CH_3$), 46.47 (C-4a), 48.85 (C-7a), 55.05 (C-3a), 78.38 (C-8a), 82.15 (C-4), 82.46 (C-8), 126.51 (ArC), 127.35 (ArC), 128.05 (ArC), 129.31 (ArC), 149.35 (C-3), 172.47 (C-7), 173.25 (C-5). IR (ATR) ν 3104, 2981, 1776 (C=O), 1691 (C=O), 1585, 1436, 1423, 1337, 1276, 1226, 1132, 1060, 1034, 997, 921, 734 $cm^{-1}$; GC-MS (EI, 70 eV) *m/z* 304 ($M^+$), 275, 247, 164, 136, 109, 84, 68.




**4,8-Ethano-3-(4-chlorophenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*endo*-dione (10).** Colorless solid, yield 57%, mp 240 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.30–1.41 (m, 3H, H-10s, H-9a and H-9s), 1.94–2.03 (m, 1H, H-10a), 2.57–2.60 (m, 1H, H-4), 2.63–2.65 (m, 1H, H-8), 2.91 (dd, $J_1$ = 3.9 Hz, $J_2$ = 9.2 Hz, 1H, H-4a), 2.97 (dd, $J_1$ = 3.9 Hz, $J_2$ = 9.2 Hz, 1H, H-7a), 3.00 (s, 3H, *N*-$CH_3$), 3.43 (ddd, $J_1$ = 1.4 Hz, $J_2$ = 3.4 Hz, $J_3$ =11.7 Hz, 1H, H-3an), 4.55 (dd, $J_1$ = 3.4 Hz, $J_2$ = 11.7 Hz, 1H, H-8an), 7.31 (d, *J* = 8.7 Hz, 2H, ArH), 7.49 (d, *J* = 8.7 Hz, 2H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.45 (C-9), 20.33 (C-10), 25.17 (*N*-$CH_3$), 27.48 (C-4), 29.53 (C-8), 40.90 (C-4a), 42.46 (C-7a), 46.73 (C-3a), 78.53 (C-8a), 127.29 (ArC), 128.15 (ArC), 129.52 (ArC), 136.56 (ArC), 156.18 (C-3), 178.19 (C-7), 178.82 (C-5). IR (ATR) ν 3053, 2954, 2926, 1764 (C=O), 1675 (C=O), 1591, 1492, 1436, 1387, 1282, 1129, 1092, 1014, 974, 917, 891, 826 $cm^{-1}$; GC-MS (EI, 70 eV) *m/z* 344 ($M^+$), 327, 232, 178, 113, 96, 79.

**4,8-Ethano-3-(2,5-dimethoxyphenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-**

**5,7(6*H*,7a*H*)-*endo*-dione (11).** Colorless solid, yield 63%, mp 175–177 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.23–1.33 (m, 2H, H-10s and H-9s), 1.37–1.43 (m, 1H, H-9a), 1.96–2.02 (m, 1H, H-10a), 2.37–2.40 (m, 1H, H-4), 2.57–2.61 (m, 1H, H-8), 2.82 (dd, 1H, $J_1$ = 3.9 Hz, $J_2$ = 9.2 Hz, H-4a), 2.92 (dd, 1H, $J_1$ = 3.9 Hz, $J_2$ = 9.2 Hz, H-7a), 2.98 (s, 3H, *N*-$CH_3$), 3.72 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.82 (brd, 1H, *J* = 12.2 Hz, H-3an), 4.50 (dd, 1H, $J_1$ = 3.9 Hz, $J_2$ = 12.2 Hz, H-8an), 6.87 (dd, 1H, $J_1$ = 2.9 Hz, $J_2$ = 8.7 Hz, ArH), 6.79 (d, 1H, *J* = 8.7 Hz, ArH), 7.27 (d, 1H, *J* = 2.9 Hz, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.45 (C-9), 20.84 (C-10), 25.06 (*N*-$CH_3$), 27.51 (C-4), 29.79 (C-8), 41.42 (C-4a), 42.79 (C-7a), 48.35 (C-3a), 56.06 ($OCH_3$), 56.07 ($OCH_3$), 78.28 (C-8a), 113.07 (ArC), 113.79 (ArC), 118.20 (ArC), 123.60 (ArC), 151.86 (ArC), 153.84 (ArC), 157.15 (C-3), 178.55 (C-7), 178.81 (C-5). IR (ATR) ν 3012, 2951, 2918, 2876, 1774 (C=O), 1690 (C=O), 1557, 1493, 1428, 1377, 1275, 1223, 1123, 1043, 1014, 907, 817 cm$^{-1}$; GC-MS (EI, 70 eV) *m/z* 370 ($M^+$), 339, 190, 176, 148, 79.

**4,8-Ethano-3-(2-thienyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*, 7a*H*)-*endo*-dione (12).** Pale yellow solid, yield 45%, mp 166–170 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.33–1.37 (m, 2H, H-9s and H-10s), 1.45–1.53 (m, 1H, H-9a), 1.98–2.03 (m, 1H, H-10a), 2.62–2.64 (m, 1H, H-4), 2.70–2.72 (m, 1H, H-8), 2.92 (dd, $J_1$ = 3.9 Hz, $J_2$ = 9.2 Hz, 1H, H-4a), 2.97 (dd, $J_1$ = 3.9 Hz, $J_2$ = 9.2 Hz, 1H, H-7a), 2.98 (s, 3H, *N*-$CH_3$), 3.40 (brd, *J* = 11.7 Hz, 1H, H-3an), 4.53 (dd, $J_1$ = 3.9 Hz, $J_2$ = 11.7 Hz, 1H, H-8an), 6.98 (dd, $J_1$ = 3.9 Hz, $J_2$ = 4.8 Hz, 1H, ArH), 7.14 (d, *J* = 3.9 Hz, 1H, ArH), 7.31 (d, *J* = 4.8 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.46 (C-9), 20.34 (C-10), 25.17 (*N*-$CH_3$), 28.06 (C-4), 29.50 (C-8), 40.91 (C-4a), 42.45 (C-7a), 47.99 (C-3a), 78.56 (C-8a), 127.71 (ArC), 128.19 (ArC), 128.57 (ArC), 131.21 (ArC), 152.93 (C-3), 178.24 (C-7), 178.80 (C-5). IR (ATR) ν 3096, 2948, 2922, 2877, 1767 (C=O), 1690 (C=O), 1520, 1432, 1377, 1278, 1215, 1129, 1091, 972, 911, 838 cm$^{-1}$; GC-MS (EI, 70 eV) *m/z* 316 ($M^+$), 151, 113, 96, 79.

**4,8-Epoxy-3-(2-chlorophenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*, 7a*H*)-*exo*-dione (13).** Colorless solid, yield 75%, mp 125–128 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.96 (s, 3H, *N*-$CH_3$), 3.01 (d, *J* = 6.9 Hz, 1H, H-4a), 3.05 (d, *J* = 6.9 Hz, 1H, H-7a), 4.46 (d, *J* = 8.2 Hz, 1H, H-3an), 4.70 (s, 1H, H-4), 5.05 (d, *J* = 8.2 Hz, 1H, H-8an), 5.10 (s, 1H, H-8), 7.33 (dd, $J_1$ = $J_2$ = 8.7 Hz, 1H, ArH), 7.42 (dd, $J_1$ = $J_2$ = 8.7 Hz, 1H, ArH), 7.47 (d, *J* = 8.7 Hz, 1H, ArH), 7.52 (d, *J* = 8.7 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 25.42 (*N*-$CH_3$), 44.99 (C-4a), 48.22 (C-7a), 59.51 (C-3a), 79.56 (C-8a), 84.52 (C-4), 85.63 (C-8), 127.18 (ArC), 127.42 (ArC), 130.54 (ArC), 131.55 (ArC), 131.57 (ArC), 132.49 (ArC), 154.35 (C-3), 175.67 (C-7), 177.59 (C-5). IR (ATR) ν 3077, 1771 (C=O), 1689 (C=O), 1474, 1430, 1380, 1345, 1287, 1174, 1134, 1082, 1040, 1018, 906, 877, 846, 822, 756 cm$^{-1}$; GC-MS (EI, 70 eV) *m/z* 332 ($M^+$), 303, 275, 241, 193, 178, 111, 68.

**4,8-Epoxy-3-(2,5-dimethoxyphenyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*,7a*H*)-*exo*-dione (14).** Colorless solid, yield 64%, mp 186–188 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.87 (d, *J* = 6.8 Hz, 1H, H-4a), 2.89 (s, 3H, *N*-$CH_3$), 2.93 (d, *J* = 6.8 Hz, 1H, H-7a), 3.69 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 4.24 (d, *J* = 8.3 Hz, 1H, H-3an), 4.76 (s, 1H, H-4), 4.86 (d, *J* = 8.3 Hz, 1H, H-8an), 4.98 (s, 1H, H-8), 6.84 (d, *J* = 8.7 Hz, 1H, ArH), 6.90 (dd, $J_1$ = 2.9 Hz, $J_2$ = 8.7 Hz, 1H, ArH), 7.24 (d, *J* = 2.9 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 25.54 (*N*-$CH_3$), 45.38 (C-4a), 48.79 (C-7a), 56.03 (C-3a), 56.40 ($OCH_3$), 60.16 ($OCH_3$), 80.79 (C-8a), 84.51 (C-4), 85.62 (C-8), 113.29 (ArC), 113.82 (ArC), 117.21 (ArC), 118.79 (ArC), 151.51 (ArC), 153.98 (ArC), 154.00 (C-3), 175.75 (C-7), 175.94 (C-5). IR (ATR) ν 3012, 2949, 2832, 1771 (C=O), 1694 (C=O), 1558, 1496, 1465, 1436, 1421, 1386, 1345, 1262, 1224, 1140, 1062, 1021, 992, 910, 847, 807 cm$^{-1}$; GC-MS (EI, 70 eV) *m/z* 358 ($M^+$), 329, 207, 179, 163, 148, 68.

**4,8-Epoxy-3-(2-thienyl)-6-methyl-4,4a,8,*exo*-8a-tetrahydro-*exo*-3a*H*-isoxazolo[5,4-*f*]isoindole-5,7(6*H*, 7a*H*)-*exo*-dione (15).** Pale yellow solid, yield 48%, mp 205–210 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.88 (d, *J* = 6.8 Hz, 1H, H-4a), 2.91 (s, 3H, *N*-$CH_3$), 3.02 (d, *J* = 6.8 Hz, 1H, H-7a), 3.90 (d, *J* = 8.0 Hz, 1H, H-3an), 4.93 (d, *J* = 8.0 Hz, 1H, H-8an), 5.02 (s, 1H, H-4), 5.05 (s, 1H, H-8), 7.04 (dd, $J_1$ = 3.6 Hz, $J_2$ = 4.9 Hz, 1H, ArH), 7.24 (d, *J* = 3.6 Hz, 1H, ArH), 7.37 (d, *J* = 4.9 Hz, 1H, ArH). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 25.65 (*N*-$CH_3$), 45.15 (C-4a), 48.76 (C-7a), 58.17 (C-3a), 80.11 (C-8a), 84.72 (C-4), 86.05 (C-8), 127.72 (ArC), 128.32 (ArC), 128.65 (ArC), 131.11 (ArC), 153.57 (C-3), 175.38 (C-5), 175.69 (C-7). IR (ATR) ν 3080, 2924, 2854, 1777 (C=O), 1695 (C=O), 1434, 1385, 1286, 1215, 1132, 1031, 1007, 901, 875, 842 cm$^{-1}$; GC-MS (EI, 70eV) *m/z* 304 ($M^+$), 221, 191, 163, 136, 109, 68.

## 4. Conclusion

We first synthesized *N*-methylsubstituted adducts **1–3** of the unsaturated imides by a hydroarylation procedure to check the effect on both, the reactivity of the starting materials as well as the bioactivity of the products as Cantharidin analogues.[18] In this work, our results have also demonstrated that the 1,3-dipolar cycloadditions of nitrile oxides onto bridged cyclic imide derivatives prove useful for the construction of novel heterocycles of potential pharmacological interest.

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## Povzetek

Opisana je [3+2] cikloadicija *N*-metilnih derivatov nesubstituiranih imidov z različnimi nitril oksidi, pri čemer nastanejo novi premosteni izoksazolinski derivati, ki so potencialno biološki aktivni.