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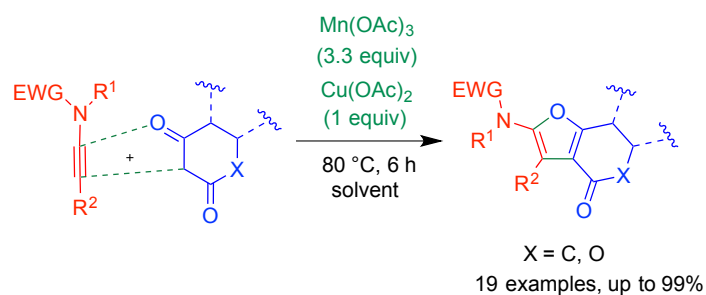


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Ynamides in radical reactions: a route to original persubstituted 2-aminofurans.

Aurélien Galibert-Guijarro, Dominique Mouysset, Liliane Mimoun, Michèle P. Bertrand* and Laurence Feray*

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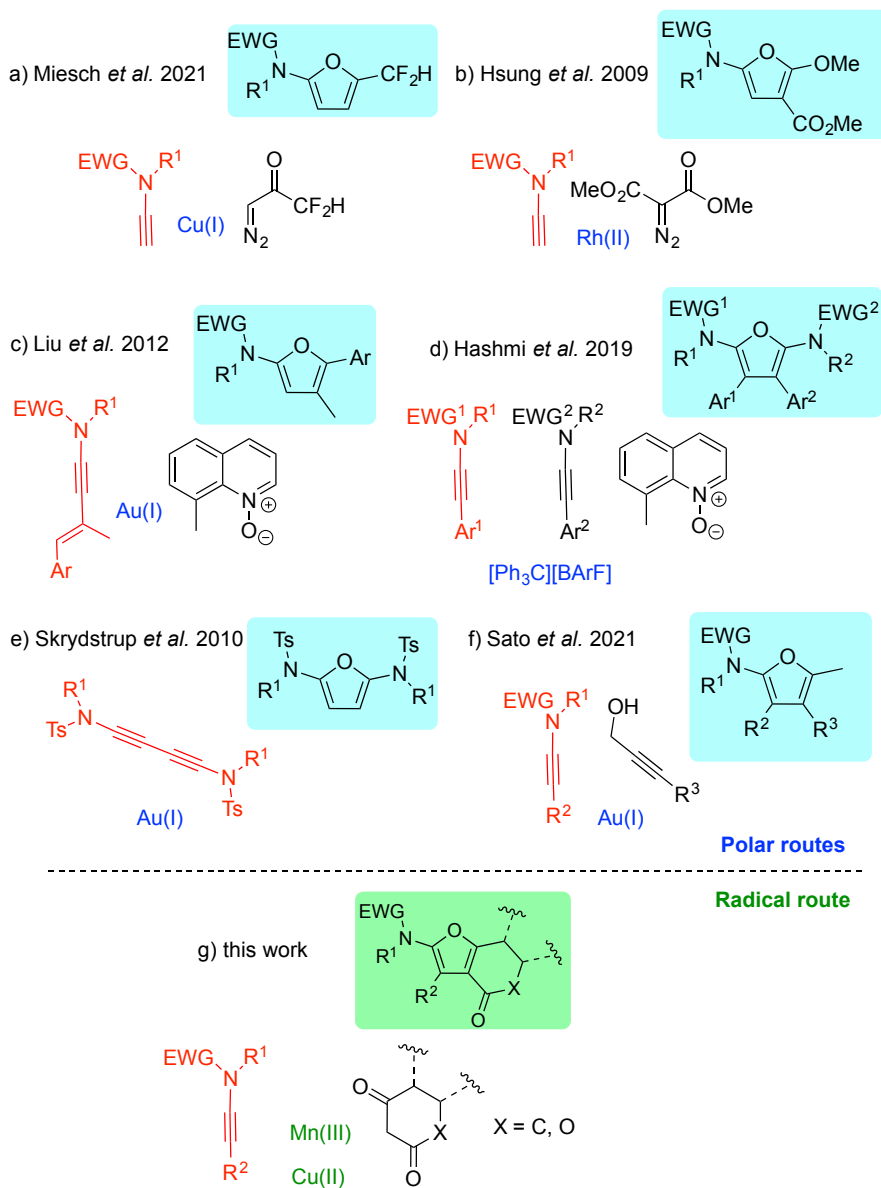


Abstract: Mn(OAc)₃/Cu(OAc)₂-mediated reaction between ynamides, derived from oxazolidone or 3-methyl indole carboxylate, and cyclic alpha-dicarbonyl radicals, led to the one-pot synthesis of 2-aminofurans. The transformation involves addition of α-dicarbonyl radical to ynamide, oxidation to ketene-iminium and polar cyclisation steps to provide original persubstituted 2-aminofurans with good to excellent yields. This work represents the first radical route for the synthesis of furans from ynamides.

Introduction. The interest in ynamides as building blocks for organic synthesis has been growing exponentially since the turn of the century.^{1,2} Due to the electron donating effect of the nitrogen atom, tempered by the nature of its electron withdrawing substituent, ynamides behave as activated polarized alkynes that have been extensively used to perform regioselective, rapid, and elegant constructions of versatile *N*-containing molecules. With respect to the direct synthesis of aminofurans, which are key structural motifs for several biologically active compounds and useful intermediates in synthetic chemistry,^{3,4} only a few reports describe the use of ynamides as substrates to reach this goal (Scheme 1). Miesch⁵ and Hsung⁶ reported that terminal ynamides react with diazo derivatives under Cu(I) (Scheme 1a) and Rh(II) (Scheme 1b) catalysis to give di- and tri-substituted 2-aminofurans. In addition, a strategy based on gold-catalyzed formal [4+1]-cycloadditions between 3-en-1-ynamides in the presence of 8-methylquinoline oxide was developed by Liu⁷ and coworkers (Scheme 1c). Hashmi⁸ reported that the same type of oxides can be used in carbocation-catalyzed oxidative [2+2+1] annulation of two molecules of ynamide to give tetrasubstituted 2-aminofurans (Scheme 1d). Finally,

Au(I)-catalyzed hydration of dimerized ynarnides and Au(I)-catalyzed cascade reaction of ynarnides with propargyl alcohols was reported by Skrydstrup⁹ and coworkers (Scheme 1e) and Oonishi and Sato¹⁰ (Scheme 1f). The synthesis of aminofurans from ynarnides through radical reaction has not been reported yet.

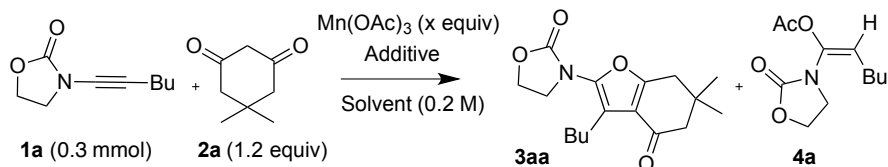
Regarding radical chemistry, ynarnides behave as electron rich radical acceptors. Indeed, the relevant literature shows that, if one excepts intramolecular radical additions devised for heterocyclic synthesis, the few reported intermolecular additions onto ynarnides essentially involve electrophilic sulfanyl radicals.¹¹ Recently, we have shown that the strategy based on atom transfer radical addition (ATRA) using ethyl α -iodoacetate, α -iodo-acetonitrile or α -iodo-*N,N*-diethyl acetamide as radical precursors is efficient to achieve this transformation. Again, the latter results point to the ability of ynarnides to react with electrophilic carbon-centered radicals.¹²



Scheme 1. One-pot synthesis of 2-aminofurans from ynarnides

Following on from our investigation of radical addition of carbon-centered radicals to ynamides and in view of the limited methods for the direct construction of 2-aminofurans from ynamides, we envisaged to use 1,3-dicarbonyl compounds, well-known precursors of alpha-dicarbonyl radicals under oxidative reaction conditions.^{13,14} We report herein the first one pot radical synthesis of original persubstituted 2-aminofurans from ynamides and cyclic 1,3-dicarbonyl compounds (Scheme 1g).

Table 1. Optimization of synthesis of furan **3aa** from ynamide **1a** and dimedone **2a**.

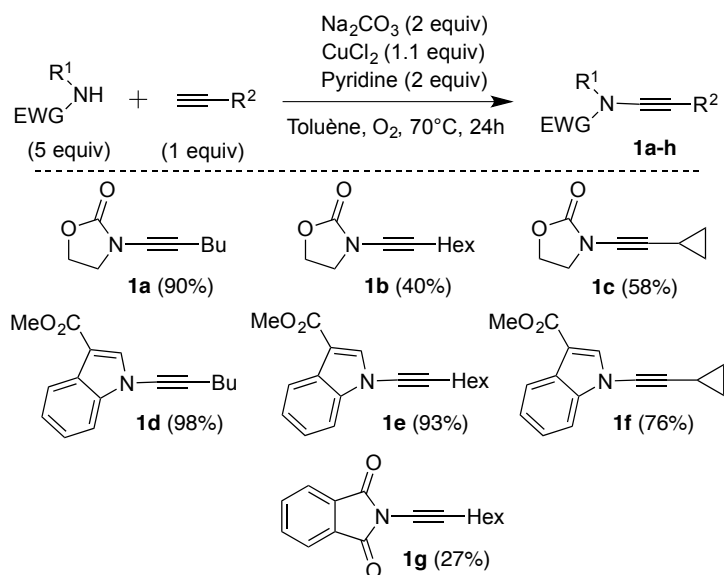


Entry	x	Additive (equiv)	Solvent	T (°C)	t (h)	1a:3aa:4a
1	2.2		AcOH	40	24	0:50:50 ^a
2	2.2		CH ₂ Cl ₂	40	48	20:80:0 ^a
3	2.2		DCE	70	24	0:70:30 ^a
4	2.2		CH ₃ CN	70	24	-
5	2.2	Cu(OAc) ₂ (1)	AcOH	40	48	0:70:30 ^a
6	2.2	Cu(OAc) ₂ (1)	CH ₂ Cl ₂	40	48	0:85:15 ^a
7	2.2		AcOH	80	24	0:14:0 ^b
8	2.2	Cu(OAc) ₂ (1)	AcOH	80	24	0:35:0 ^b
9	2.2	Cu(OAc) ₂ (1)	(Cl ₂ CH) ₂	80	24	0:73:0 ^b
10	3.3	Cu(OAc) ₂ (1)	(Cl ₂ CH) ₂	80	6	0:79:0 ^b
11	3.3		(Cl ₂ CH) ₂	80	6	0:66:0 ^b
12	3.3	Cu(OAc) ₂ (1)	(Cl ₂ CH) ₂	80	6	No reaction ^c

a) ¹H NMR ratio. b) Isolated yield in %. c) 1 equivalent of TEMPO was added

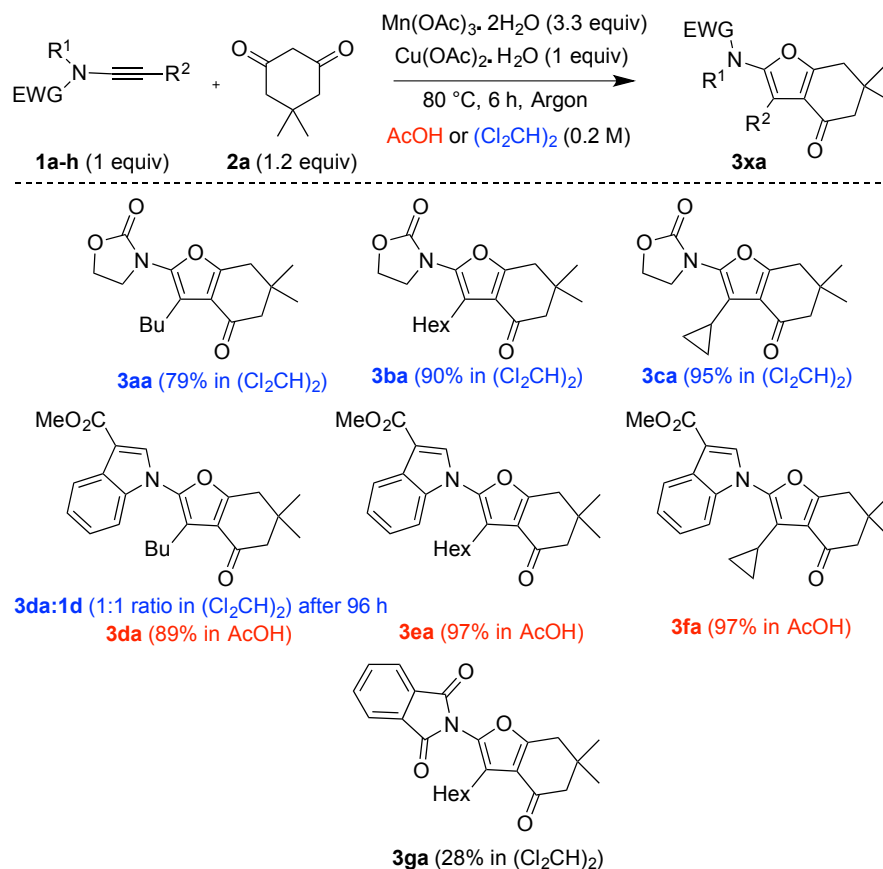
Results and discussion. We started optimizing experimental conditions selecting ynamide **1a** (0.3 mmol) as model substrate and dimedone **2a** as precursor of the alpha-dicarbonyl radical in the presence of Mn(OAc)₃·2H₂O as the oxidant (Table 1). Controlled experiments demonstrated that the use of Mn(OAc)₃ and, what's more, in degassed solvent was mandatory for the reaction to proceed. The use of 2.2 equivalents of Mn(III) in acetic acid¹⁵ at 40 °C led after 24 hours to a mixture of furan **3aa** and enamide **4a**, resulting from the addition of acetic acid to ynamide,¹⁶ in a 1:1 ratio determined from the ¹H NMR spectrum of the crude reaction mixture (entry 1). Moving from acetic acid to dichloromethane (CH₂Cl₂) aprotic medium prevented the formation of **4a** but significant amount of ynamide **1a** was recovered even after 48 hours of reaction (entry 2). To increase the temperature at 70 °C, dichloroethane (DCE) was tested as solvent leading to a 7:3 mixture of **3aa:4a** after 24 hours (entry 3). The use of acetonitrile at the same temperature provided no reaction (entry 4). Mn(OAc)₃ is not as good an oxidant as Cu(OAc)₂ with respect to carbon-centered radicals.¹⁷ We supposed that the faster oxidation of the intermediate carbon-centered radical would result in lowering the relative amount of **4a** (vide infra for mechanistic discussion). The addition of 1 equivalent of Cu(OAc)₂·H₂O increased the relative amount of **3aa** efficiency at 40 °C in both acetic acid and CH₂Cl₂ providing cleanest crude reaction mixture (entries 5,6 / entries 1,2). Nevertheless, undesired enamide **4a** was still detected under these conditions. The solubility of manganese triacetate appeared to be crucial in the process. We tried to improve the reaction in acetic acid by increasing the temperature to 80 °C. Whether Cu(II) was

added to the reaction mixture or not, undesired enamide **4a** was detected as traces amount at this temperature after 24 hours and furan **3aa** was isolated in poor yields after purification (entries 7,8). Fortunately, when the reaction was conducted in 1,1,2,2-tetrachloroethane as solvent at 80 °C in the presence of 2.2 equivalents of Mn(III) et 1 equivalent of Cu(II) neither the starting material nor enamide **4a** were detected in the crude reaction mixture after 24 hours and furan **3aa** was isolated after purification in 73% yield (entry 9). Tetrachloroethane appeared to be a solvent of choice for Mn(III) solubilisation. When the same procedure was repeated in the presence of 3.3 equivalents of Mn(III), the yield reached 79 % in only 6 hours (entry 10). The same experiment conducted without Cu(II) led after 6 hours to 66% yield of furan but from a very messy crude mixture (entry 11). Optimized reaction conditions (entry 10) were used to explore the scope of this transformation.



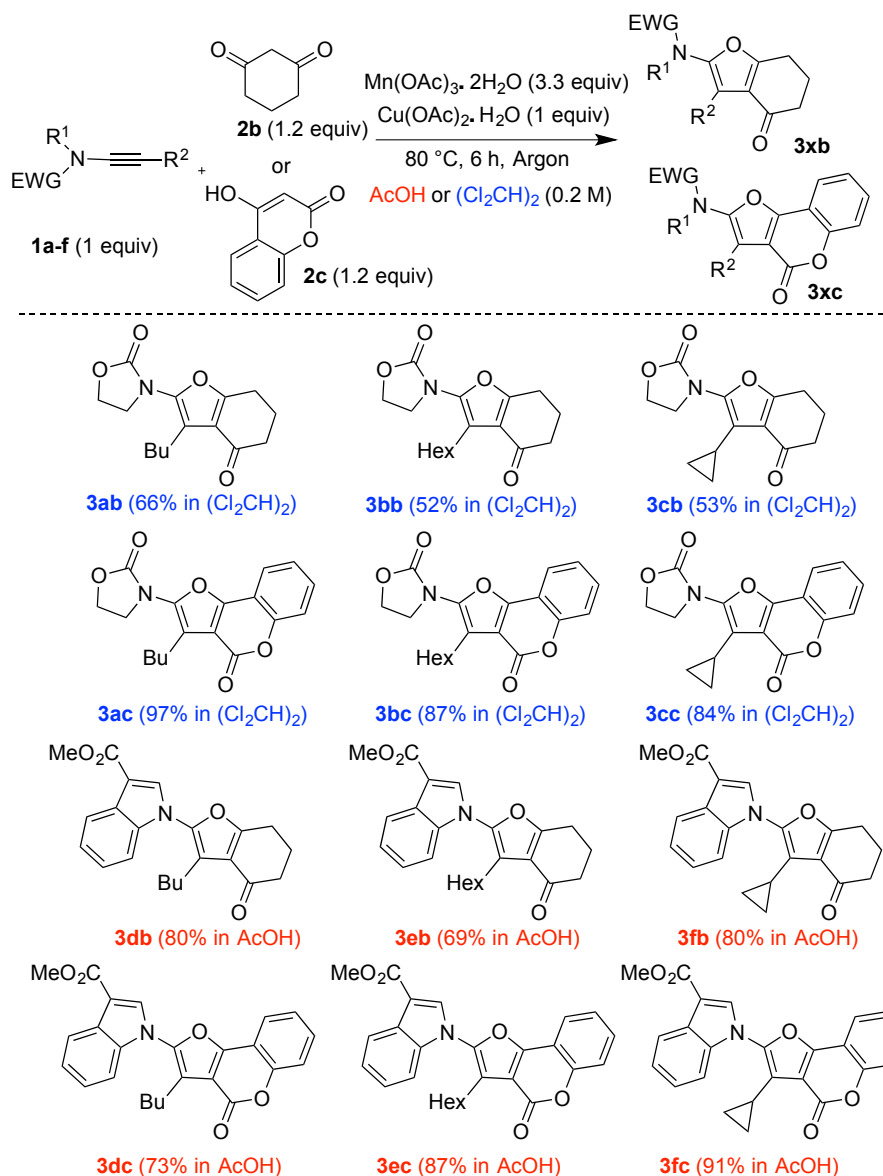
Scheme 2. Synthesis of ynamides **1a-g**

To this purpose, a selection of ynamides **1** derived from oxazolidone, 3-methyl indole carboxylate and phthalimide were prepared with moderate to good yields according to modified Stahl procedure¹⁸ (Scheme 2).



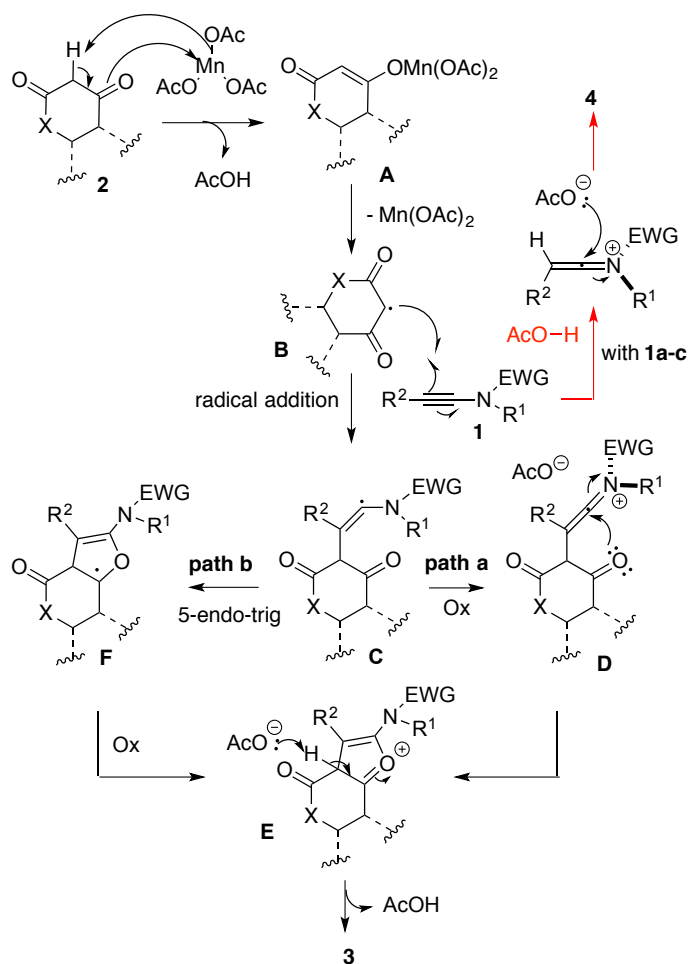
Scheme 3. Synthesis of furans **3xa** from dimedone

The results of oxidative addition experiments are reported in scheme 3. Reacting substrates **1a-c** derived from oxazolidone in tetrachloroethane led to the desired furans **3aa-ca** in good yields. Conversely, in the same experimental conditions, furan **3da** was obtained in poor yield when ynamide **1d** derived from 3-methyl indole carboxylate was used. ^1H NMR spectrum performed on the crude reaction mixture showed the presence of starting material and desired furan **3da** in a 1:1 ratio even after 96 hours reaction time. Surprisingly using acetic acid as solvent allowed the formation of furan **3da** without detection of starting material or the non-desired product resulting from the competitive addition of acetic acid to the triple bond. Using acetic acid as solvent in the case of ynamides **1d-f** led to the formation of original furans **3da-fa**, isolated in excellent yields, up to 96 %. Finally, ynamide **1g** derived from phthalimide showed poor reactivity in this process, whatever the solvent, leading to furan **3ga** in modest yield. It is to be noted that, whatever the experimental conditions, the entire process liberates 2 equivalents of acetic acid in the reaction medium (vide infra). However, no trace of product resulting from polar addition of AcOH was detected with the indole 3-methylcarboxylate- and phthalimide- derived ynamides. This event most particularly interferes when the reaction is conducted in acetic acid as the solvent. This observation is in agreement with the decrease of the electron donating effect of the nitrogen atom that lowers Bronst d basicity of these latter compared to ynamides in the oxazolidinone series.



Scheme 4. Synthesis of furans **3xb** from 1,3-cyclohexadione and furans **3xc** from 4-hydroxycoumarin

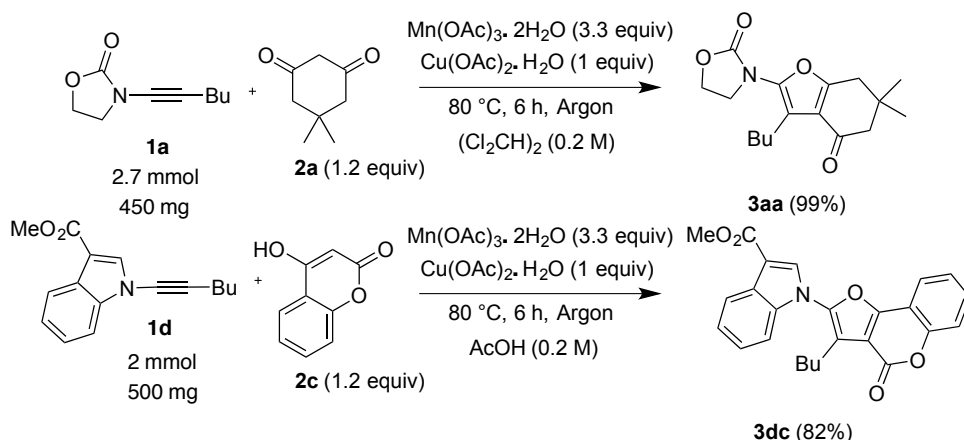
We next explored the reaction scope using 1,3-cyclohexadione **2b** and 4-hydroxycoumarin **2c** as precursors of alpha-dicarbonyl radicals (Scheme 4). Original persubstituted 2-aminofurans were prepared this way, in tetrachloroethane or acetic acid, with good to excellent yields. It is worth mentioning that this synthesis allowed for the preparation of new indole-substituted furocoumarines of type **3xc** whose potential photophysical, photochemical, and biological properties remain to be explored.¹⁹ The major limitation of this transformation resides in the use of acyclic 1,3-dicarbonyl compounds; reactions conducted with acetylacetone or ethyl acetoacetate led to complex crude mixtures. A second limitation resides in the use of ynamides derived from *N*-tosyl-amines. Indeed, reactions involving *N*-benzyl-*N*-(alkynyl)-4-methylbenzenesulfonamide as substrates follow a completely different path leading to mixture of products. Their reactivity is currently being investigated.



Scheme 5. Proposed mechanism

A plausible mechanism for the entire process is depicted in Scheme 5. This mechanism, involving radical species, takes into account the fact that the reactions necessitated the use of degassed solvent to proceed with good yields and that controlled experiment conducted on ynamide **1a** and dimedone **2a** in the presence of 1 equivalent of TEMPO led to no transformation (Table 1, entry 12). First, reaction between manganese triacetate and 1,3-dicarbonyl compounds **2** allows the formation of a manganese enolate intermediate **A** that loses manganese diacetate to produce α -dicarbonyl radical **B**. Then, regioselective radical addition of **B** to the carbon in β position to the nitrogen atom of the triple bond of ynamide **1** conducts to vinyl radical **C**.²⁰ At this stage, two pathways can be envisaged. In path a, the oxidation of vinyl radical **C** leads to ketene iminium **D**. The latter further gives furan **3** through subsequent polar cyclization via intermediate **E** and deprotonation. In path b, intermediate **E** can be formed after 5-endo-trig cyclization of vinyl radical **C** onto the double bond of the carbonyl group and oxidation of the resulting radical intermediate **F**.

Finally, this protocol was scaled up to 2.7 mmol of ynamide **1a** and 2 mmol of ynamide **1d** that were reacted in the presence of dimedone **2a** and 4-hydroxycoumarin **2c**, respectively (Scheme 6). Furans **3aa** and **3dc** were isolated in 99% and 82% yield showing the synthetic utility of the process.



Scheme 6. Scaled-up reactions

Conclusion. To conclude, we proposed a $\text{Mn}(\text{OAc})_3/\text{Cu}(\text{OAc})_2$ -mediated reaction between ynamides and cyclic 1,3-dicarbonyl compounds which provides a new access to persubstituted 2-aminofurans in good yields and with excellent regioselectivity. Tetra-chloroethane or acetic acid can be used as solvent, depending on the basicity of the substrates. By reporting the first one pot radical synthesis of original persubstituted 2-aminofurans from ynamides, this work advances both the area of ynamides radical chemistry by proposing a new reaction between ynamides and electrophilic carbon-centered radicals and the area of 2-amino furans synthesis. The photophysical, photochemical, and biological properties of these new compounds in particular furocoumarine derivatives remain to be explored and are expected to open up interesting development in the fields of photocatalysis and medicinal chemistry.

Experimental procedures

General. Commercially available solvents and reagents were used as purchased. CH_2Cl_2 (GC grade) and DMF were stored on molecular sieves. Analytical thin layer chromatography was performed on pre-coated silica gel plates. NMR spectra were recorded at 300, 400 (^1H) and 75, 100 MHz (^{13}C) using CDCl_3 as the solvent. Chemical shifts (δ) are reported in ppm. Signals due to residual protonated solvent or to the deuterated solvent served as the internal standards to calibrate the spectra (^1H NMR, CHCl_3 , 7.26 ppm; ^{13}C NMR, CDCl_3 , 77.16 ppm). Multiplicity is indicated by one or more of the following descriptors: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). The J values are given in Hz.

General procedure for ynamides synthesis. In a two-neck round-bottom flask equipped with a stir-bar, CuCl₂ (1.1 equiv), oxazolidin-2-one (5.0 equiv), Na₂CO₃ (2.0 equiv) and dry toluene were combined. The reaction flask was purged with oxygen for 15 minutes. A solution of pyridine (2 equiv) in dry toluene was added to the reaction flask via a syringe at room temperature. A balloon filled with oxygen was connected on the top of the refrigerator via a needle. The flask was placed in an oil-bath and heated at 70°C. A solution of alkyne (1 equiv) in dry toluene was added over 6h by using a syringe pump. After the addition was completed, the reaction mixture was stirred at 70°C for 18h, and then cooled to room temperature. The crude mixture was concentrated under vacuum and the residue was purified by flash chromatography on silica gel.

3-(Hex-1-yn-1-yl)oxazolidin-2-one (1a). (known compound)²¹ The reaction was conducted according to the general procedure in presence of CuCl₂ (4.4 mmol, 592 mg), oxazolidin-2-one (20 mmol, 1.74 g), and Na₂CO₃ (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. 1-Hexyne (4 mmol, 0.45 mL) was added in dry toluene (20 mL). Purification by flash chromatography on silica gel (pentane/ethyl acetate (95/05 to 80/20)) led to ynamide **1a** (600 mg, 3.59 mmol, 90% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 4.40 (pseudo t, *J* = 7.9, 2H), 3.86 (pseudo t, *J* = 8.1, 2H), 2.29 (t, *J* = 7.0, 2H), 1.49 (quint, *J* = 7.1, 2H), 1.39 (sext, *J* = 7.2, 2H), 0.91 (t, *J* = 7.3, 3H).

3-(Oct-1-yn-1-yl)oxazolidin-2-one (1b). The reaction was conducted according to the general procedure in presence of CuCl₂ (4.4 mmol, 592 mg), oxazolidin-2-one (20 mmol, 1.74 g), and Na₂CO₃ (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. 1-Octyne (4 mmol, 0.54 mL) was added in dry toluene (20 mL). Purification by flash chromatography on silica gel (pentane/ethyl acetate (90/10 to 80/20)) led to ynamide **1b** (305 mg, 1.56 mmol, 40% yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ: 4.40 (pseudo t, *J* = 7.8, 2H), 3.86 (pseudo t, *J* = 8.1, 2H), 2.29 (t, *J* = 7.1, 2H), 1.49-1.52 (m, 2H), 1.30-1.47 (m, 2H), 1.25-1.30 (m, 4H), 0.89 (t, *J* = 6.8, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 156.6 (C=O), 71.2 (≡C), 70.0 (≡C), 62.7 (CH₂), 47.2 (CH₂), 31.4 (CH₂), 28.9 (CH₂), 28.4 (CH₂), 22.5 (CH₂), 18.4 (CH₂), 14.1 (CH₃). HRMS (ESI): *m/z* for [M+Na⁺] C₁₁H₁₇NO₂Na: calcd: 218.1152, found: 218.1154.

3-(Cyclopropylethynyl)oxazolidin-2-one (1c). (known compound)²² The reaction was conducted according to the general procedure in presence of CuCl₂ (4.4 mmol, 592 mg), oxazolidin-2-one (20 mmol, 1.74 g), and Na₂CO₃ (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. Ethynylcyclopropane (4 mmol, 0.34 mL) was added in dry toluene (20 mL). Purification by flash chromatography on silica gel (pentane/ethyl acetate (90/10 to 60/40)) led to ynamide **1c** (349 mg, 2.30 mmol, 58% yield) as a colourless solid. ¹H NMR (400 MHz, CDCl₃) δ: 4.30 (pseudo t, *J* = 7.8, 2H), 3.75 (pseudo t, *J* = 8.2, 2H), 1.23 (tt, *J* = 8.2 and 4.9, 1H), 0.62-0.74 (m, 2H), 0.52-0.60 (m, 2H). ¹³C{¹H} NMR (100 MHz,

CDCl_3) δ : 156.6 (C=O), 74.6 ($\equiv\text{C}$), 65.4 ($\equiv\text{C}$), 62.7 (CH_2), 46.8 (CH_2), 8.3 ($2\times\text{CH}_2$), -1.3 (CH). HRMS (ESI): m/z : for $[\text{M}+\text{NH}_4^+]$ $\text{C}_8\text{H}_{13}\text{N}_2\text{O}_2$ calcd: 169.0972; found: 169.0974.

Methyl 1-(hex-1-yn-1-yl)-1H-indole-3-carboxylate (1d). The reaction was conducted according to the general procedure in presence of CuCl_2 (4.4 mmol, 592 mg), methyl-indole-3-carboxylate (20 mmol, 3.50 g), and Na_2CO_3 (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. 1-Hexyne (4 mmol, 0.45 mL) was added in dry toluene (20 mL). Purification by flash chromatography on silica gel (pentane/ethyl acetate (97/03 to 80/20)) led to ynamide **1d** (990 mg, 3.9 mmol, 98% yield) as a brown oil. ^1H NMR (300 MHz, CDCl_3) δ : 8.10-8.17 (pseudo d, $J = 7.9$, 1H), 7.88 (s, 1H), 7.50-7.54 (pseudo d, $J = 8.2$, 1H), 7.30-7.40 (m, 2H), 3.92 (s, 3H), 2.48 (t, $J = 6.9$, 2H), 1.59-1.65 (m, 2H), 1.48-1.53 (m, 2H), 0.98 (t, $J = 7.3$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 164.4 (C=O), 138.5 ($=\text{C}$), 135.2 ($=\text{CH}$), 125.2 ($=\text{C}$), 124.2 ($=\text{CH}$), 123.3 ($=\text{CH}$), 121.8 ($=\text{CH}$), 111.4 ($=\text{CH}$), 109.9 ($=\text{C}$), 71.8 ($\equiv\text{C}$), 70.6 ($\equiv\text{C}$), 51.2 (CH_3), 30.8 (CH_2), 22.0 (CH_2), 18.0 (CH_2), 13.6 (CH_3). HRMS (ESI): m/z : for $[\text{M}+\text{Na}^+]$ $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{Na}$ calcd: 278.1152, found: 278.1158.

Methyl 1-(oct-1-yn-1-yl)-1H-indole-3-carboxylate (1e). The reaction was conducted according to the general procedure in presence of CuCl_2 (4.4 mmol, 592 mg), methyl-indole-3-carboxylate (20 mmol, 3.50 g), and Na_2CO_3 (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. 1-Octyne (4 mmol, 0.6 mL) was added in dry toluene (20 mL). Purification by flash chromatography on silica gel (pentane/ethyl acetate 97/03) led to ynamide **1e** (1.06 g, 3.74 mmol, 93% yield) as a pink solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.10-8.16 (pseudo d, $J = 7.2$, 1H), 7.88 (s, 1H), 7.49-7.54 (pseudo d, $J = 7.4$, 1H), 7.28-7.35 (m, 2H), 3.92 (s, 3H), 2.48 (t, $J = 7.0$, 2H), 1.60-1.65 (m, 2H), 1.49-1.53 (m, 3H), 1.30-1.35 (m, 3H), 0.92 (t, $J = 7.0$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 164.5 (C=O), 138.6 ($=\text{C}$), 135.3 ($=\text{CH}$), 125.2 ($=\text{C}$), 124.2 ($=\text{CH}$), 123.3 ($=\text{CH}$), 121.8 ($=\text{CH}$), 111.4 ($=\text{CH}$), 109.9 ($=\text{C}$), 71.9 ($\equiv\text{C}$), 70.6 ($\equiv\text{C}$), 51.3 (CH_3), 31.3 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 18.4 (CH_2), 14.0 (CH_3). HRMS (ESI): m/z : for $[\text{M}+\text{Na}^+]$ $\text{C}_{18}\text{H}_{21}\text{NO}_2\text{Na}$, calcd: 306.1465, found: 306.1468.

Methyl 1-(cyclopropylethynyl)-1H-indole-3-carboxylate (1f). The reaction was conducted according to the general procedure in presence of CuCl_2 (4.4 mmol, 592 mg), methyl-indole-3-carboxylate (20 mmol, 3.50 g), and Na_2CO_3 (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. Ethynylcyclopropane (4 mmol, 0.34 mL) was added in dry toluene (20 mL). Purification by flash chromatography on silica gel (pentane/ethyl acetate 90/10) led to ynamide **1f** (0.7 g, 3.05 mmol, 76% yield) as a pink solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.10-8.18 (pseudo d, $J = 8.0$, 1H), 7.86 (s, 1H), 7.51-7.54 (pseudo d, $J = 7.5$, 1H), 7.28-7.35 (m, 2H), 3.92 (s, 3H), 1.48-1.54 (m, 1H), 0.89-0.95 (m, 2H), 0.80-0.87 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 164.4 (C=O), 138.6 ($=\text{C}$), 135.4 ($=\text{CH}$), 125.2 ($=\text{C}$), 124.2 ($=\text{CH}$), 123.4 ($=\text{CH}$), 121.9

(=CH), 111.3 (=CH), 109.9 (=C), 75.7 (\equiv C), 65.9 (\equiv C), 51.2 (CH₃), 8.9 (2xCH₂), -0.9 (CH). HRMS (ESI): m/z: for [M+H⁺] C₁₅H₁₄NO₂ calcd: 240.1019, found: 240.1020.

2-(Oct-1-yn-1-yl)isoindoline-1,3-dione (1g). The reaction was conducted according to the general procedure in presence of CuCl₂ (4.4 mmol, 592 mg), isoindoline-1,3-dione (20 mmol, 2.95 g), and Na₂CO₃ (8 mmol, 848 mg) in dry toluene (20 mL). Then, a solution of pyridine (8 mmol, 0.64 mL) in dry toluene (20 mL) was added. 1-Octyne (4 mmol, 0.6 mL) was added in dry toluene (20 mL). Purification by flash chromatography on neutral alumina gel (pentane/ethyl acetate (90/10 to 85/15)) led to ynamide **1g** (290 mg, 1.13 mmol, 27% yield) as a yellow powder. ¹H NMR (400 MHz, CDCl₃) δ : 7.87-7.93 (m, 2H), 7.75-7.79 (m, 2H), 2.46 (t, *J* = 7.2, 2H), 1.52-1.63 (m, 2H), 1.46-1.49 (m, 2H), 1.31-1.40 (m, 4H), 0.89 (t, *J* = 7.0, 3H). ¹³C {¹H} NMR (100 MHz, CDCl₃) δ : 165.6 (2xC=O), 134.9 (2x=CH), 131.3 (2x=C), 124.0 (2x=CH), 80.3 (\equiv C), 63.9 (\equiv C), 31.3 (CH₂), 29.6 (CH₂), 28.5 (CH₂), 22.5 (CH₂), 18.6 (CH₂), 14.0 (CH₃). HRMS (ESI): m/z: for [M+Na⁺] C₁₆H₁₇NO₂Na calcd: 278.1152, found: 278.1157.

General procedure for furan synthesis. In a round-bottom flask equipped with a stir-bar and a refrigerant, ynamide **1** (1 equiv), dimedone **2a** (1.2 equiv), Mn(OAc)₃·2H₂O (3.3 equiv), Cu(OAc)₂·H₂O (1 equiv) were combined under argon atmosphere. The solvent (0.2 M), previously degassed by bubbling argon for 30 minutes, was added to the reaction flask at room temperature. A balloon filled with argon was connected on the top of the refrigerant via a needle. The flask was placed in an oil-bath and heated at 80 °C for 6 h and then cooled to room temperature and evaporated under reduce pressure. The residue was filtered on neutral alumina solid face with pentane (200 mL, Fraction 1) and ethyl acetate (600 mL, Fraction 2). The F₂ fraction was partially evaporated under vacuum. Water was added and the layers were separated. Aqueous layer was extracted with AcOEt (3 x 15 ml). The combined organic phases were washed with water (20 mL), and dried over MgSO₄. The mixture was filtered and concentrated under vacuum. The crude residue was purified by flash chromatography on neutral alumina solid face if necessary.

3-(3-Butyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)oxazolidin-2-one (3aa) and 1-(2-oxooxazolidin-3-yl)hex-1-en-1-yl acetate (4a). The reaction was conducted according to the general procedure in presence of ynamide **1a** (0.30 mmol, 50 mg), dimedone **2a** (0.36 mmol, 50 mg), manganese triacetate (0.66 mmol, 177 mg), copper diacetate (0.30 mmol, 60 mg) in CH₂Cl₂ (1.5 mL) at 40°C for 48 h. ¹H NMR spectrum of the crude residue showed the presence of furan **3aa** in admixture with acetic acid adduct **4a** in a 85:15 ratio. Pure **4a** (0.15 mmol, 42 mg) was isolated after reacting ynamide **1a** (38 mg, 0.23 mmol) for 24h in acetic acid (2 mL) at 40 °C. (**4a**) ¹H NMR (400 MHz, CDCl₃) δ : 5.25 (t, *J* = 7.5, 1H), 4.33 (pseudo t, *J* = 7.8, 2H), 3.74 (pseudo t, *J* = 8.2, 2H), 2.09 (s, 3H), 2.00 (q, *J* = 7.2, 2H), 1.31-1.39 (m, 2H), 1.24-1.30 (m, 2H), 0.83 (t, *J* = 7.2, 3H). ¹³C {¹H} NMR (100 MHz, CDCl₃) δ : 169.5 (=C), 155.5 (C=O), 136.0 (=C), 118.7 (=CH), 62.6 (CH₂), 45.4 (CH₂), 30.9 (CH₂), 25.7 (CH₂), 22.2 (CH₂), 20.4 (CH₃), 13.7 (CH₃). HRMS (ESI): m/z: for [M+Na⁺] C₁₁H₁₇NO₄Na calcd: 250.1050; found: 250.1049.

The reaction was conducted according to the general procedure in presence of ynamide **1a** (0.30 mmol, 50 mg), dimedone **2a** (0.36 mmol, 50 mg), manganese triacetate (0.99 mmol, 266 mg), copper diacetate (0.30 mmol, 60 mg) in 1,1,2,2-tetrachloroethane (1.5 mL) at 80°C for 6 h. This procedure led to furan **3aa** (72 mg, 0.237 mmol, 79% yield) isolated as a yellow powder. (**3aa**) ¹H NMR (400 MHz, CDCl₃) δ: 4.45 (pseudo t, *J* = 7.8, 2H), 3.90 (pseudo t, *J* = 8.1, 2H), 2.65 (s, 2H), 2.53 (t, *J* = 7.7, 2H), 2.32 (s, 2H), 1.49-1.52 (m, 2H), 1.25-1.30 (m, 2H), 1.04 (s, 6H), 0.90 (t, *J* = 7.3, 3H). ¹³C{¹H} (100 MHz, CDCl₃) δ: 193.7 (C=O), 163.5 (=C), 156.1 (C=O), 139.7 (=C), 119.7 (=C), 118.6 (=C), 62.7 (CH₂), 52.5 (CH₂), 46.9 (CH₂), 37.2 (CH₂), 34.7 (C), 31.3 (CH₂), 28.6 (2xCH₃), 23.2 (CH₂), 22.6 (CH₂), 13.7 (CH₃). HRMS (ESI): *m/z*: for [M+H]⁺ C₁₇H₂₄NO₄ calcd: 306.1700; found: 306.1702.

A scale-up was realized with ynamide **1a** (2.7 mmol, 450 mg), dimedone **2a** (3.2 mmol, 454 mg), manganese triacetate (8.9 mmol, 2.38 g), copper diacetate (2.7 mmol, 540 mg) in 1,1,2,2-tetrachloroethane (13.5 mL) at 80°C for 6 h. This procedure led to furan **3aa** (812 mg, 2.66 mmol, 99% yield) isolated as a yellow powder.

3-(3-Butyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)oxazolidin-2-one (3ab). The reaction was conducted according to the general procedure in presence of ynamide **1a** (0.30 mmol, 50 mg), cyclohexane-1,3-dione **2b** (0.36 mmol, 40 mg), manganese triacetate (0.99 mmol, 266 mg), copper diacetate (0.30 mmol, 60 mg) in 1,1,2,2-tetrachloroethane (1.5 mL) at 80°C for 6 h. This procedure led to furan **3ab** (55 mg, 0.2 mmol, 66% yield) isolated as a colourless powder. ¹H NMR (300 MHz, CDCl₃) δ: 4.53 (t, *J* = 7.7, 2H), 3.92 (t, *J* = 8.2, 2H), 2.80 (t, *J* = 6.3, 2H), 2.50-2.65 (m, 2H), 2.35-2.50 (m, 2H), 2.15 (pseudo quint, *J* = 6.3, 2H), 1.48-1.68 (m, 2H), 1.28-1.43 (m, 2H), 0.91 (t, *J* = 7.3, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 194.3 (C=O), 164.6 (=C), 156.2 (C=O), 139.4 (=C), 120.8 (=C), 118.9 (=C), 62.7 (CH₂), 46.9 (CH₂), 38.2 (CH₂), 31.3 (CH₂), 23.5 (CH₂), 23.2 (CH₂), 22.6 (CH₂), 22.2 (CH₂), 13.8 (CH₃). HRMS (ESI): *m/z*: for [M+H]⁺ C₁₅H₂₀NO₄ calcd: 278.1387; found: 278.1383.

3-(3-Butyl-4-oxo-4H-furo[3,2-c]chromen-2-yl)oxazolidin-2-one (3ac). The reaction was conducted according to the general procedure in presence of ynamide **1a** (0.30 mmol, 50 mg), 4-hydroxycoumarin **2c** (0.36 mmol, 58 mg), manganese triacetate (0.99 mmol, 266 mg), copper diacetate (0.30 mmol, 60 mg) in 1,1,2,2-tetrachloroethane (1.5 mL) at 80°C for 6 h. This procedure led to furan **3ac** (95 mg, 0.29 mmol, 97% yield) isolated as a colourless powder. ¹H NMR (400 MHz, CDCl₃) δ: 7.73-7.80 (m, 1H), 7.46-7.54 (m, 1H), 7.36-7.44 (m, 1H), 7.28-7.36 (m, 1H), 4.61 (pseudo t, *J* = 7.8, 2H), 4.00-4.16 (m, 2H), 2.71 (t, *J* = 6.6, 2H), 1.59-1.76 (m, 2H), 1.33-1.48 (m, 2H), 0.93 (t, *J* = 7.3, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 157.5 (=C), 155.7 (C=O), 154.9 (C=O), 152.9 (=C), 141.8 (=C), 130.8 (=CH), 124.4 (=CH), 120.8 (=CH), 119.9 (=C), 117.3 (=CH), 112.3 (=C), 110.7 (=C), 62.9 (CH₂), 46.8 (CH₂), 31.2 (CH₂), 23.0 (CH₂), 22.5 (CH₂), 13.8 (CH₃). HRMS (ESI): *m/z*: for [M+H]⁺ C₁₈H₁₈NO₅ calcd: 328.1179; found: 328.1177.

3-(3-Hexyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)oxazolidin-2-one (3ba). The reaction was conducted according to the general procedure in presence of ynamide **1b** (0.24 mmol, 50 mg), dimedone **2a** (0.29 mmol, 40 mg), manganese triacetate (0.79 mmol, 212 mg), copper diacetate (0.24 mmol, 48 mg) in 1,1,2,2-tetrachloroethane (1.2 mL) at 80°C for 6 h. This procedure led to furan **3ba** (75 mg, 0.216 mmol, 90% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 4.52 (pseudo t, *J* = 7.8, 2H), 3.92 (pseudo t, *J* = 8.2, 2H), 2.66 (s, 2H), 2.53 (pseudo t, *J* = 7.7, 2H), 2.33 (s, 2H), 1.50-1.59 (m, 2H), 1.21-1.39 (m, 6H), 1.13 (s, 6H), 0.86 (distorted t, *J* = 6.7, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 193.9 (C=O), 163.6 (=C), 156.2 (C=O), 139.5 (=C), 119.6 (=C), 118.7 (=C), 62.6 (CH₂), 52.5 (CH₂), 46.9 (CH₂), 37.3 (CH₂), 34.8 (C), 31.6 (CH₂), 29.6 (CH₂), 29.1 (CH₂), 28.6 (2xCH₃), 23.4 (CH₂), 22.7 (CH₂), 14.1 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₁₉H₂₈NO₄ calcd: 334.2013; found: 334.2017.

3-(3-Hexyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)oxazolidin-2-one (3bb). The reaction was conducted according to the general procedure in presence of ynamide **1b** (0.24 mmol, 50 mg), cyclohexane-1,3-dione **2b** (0.29 mmol, 32 mg), manganese triacetate (0.79 mmol, 212 mg), copper diacetate (0.24 mmol, 48 mg) in 1,1,2,2-tetrachloroethane (1.2 mL) at 80°C for 6 h. This procedure led to furan **3bb** (40 mg, 0.125 mmol, 52% yield) isolated as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ: 4.53 (pseudo t, *J* = 7.8, 2H), 3.92 (pseudo t, *J* = 8.2, 2H), 2.80 (t, *J* = 6.3, 2H), 2.50-2.65 (m, 2H), 2.35-2.50 (m, 2H), 2.15 (quint, *J* = 6.3, 2H), 1.50-1.56 (m, 2H), 1.25-1.30 (m, 6H), 0.87 (distorted t, *J* = 6.5, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 194.3 (C=O), 164.6 (=C), 156.1 (C=O), 139.4 (=C), 120.8 (=C), 118.9 (=C), 62.8 (CH₂), 46.9 (CH₂), 38.2 (CH₂), 31.5 (CH₂), 29.4 (CH₂), 29.1 (CH₂), 23.5 (CH₂), 23.4 (CH₂), 22.6 (CH₂), 22.3 (CH₂), 14.0 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₁₇H₂₄NO₄ calcd: 306.1700; found: 306.1700.

3-(3-Hexyl-4-oxo-4H-furo[3,2-c]chromen-2-yl)oxazolidin-2-one (3bc). The reaction was conducted according to the general procedure in presence of ynamide **1b** (0.24 mmol, 50 mg), 4-hydroxycoumarin **2c** (0.29 mmol, 47 mg), manganese triacetate (0.79 mmol, 212 mg), copper diacetate (0.24 mmol, 48 mg) in 1,1,2,2-tetrachloroethane (1.2 mL) at 80°C for 6 h. This procedure led to furan **3bc** (77 mg, 0.21 mmol, 87% yield) isolated as a colourless powder. ¹H NMR (300 MHz, CDCl₃) δ: 7.74-7.84 (m, 1H), 7.47-7.56 (m, 1H), 7.39-7.46 (m, 1H), 7.30-7.37 (m, 1H), 4.62 (t, *J* = 7.7, 2H), 4.06 (t, *J* = 8.2, 2H), 2.71 (t, *J* = 7.6, 2H), 1.70 (quint, *J* = 6.7, 2H), 1.20-1.40 (m, 6H), 0.88 (pseudo t, *J* = 6.7, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 157.5 (=C), 155.7 (C=O), 155.0 (C=O), 152.9 (=C), 141.8 (=C), 130.9 (=CH), 124.5 (=CH), 120.8 (=CH), 120.0 (=C), 117.3 (=CH), 112.5 (=C), 110.9 (=C), 62.9 (CH₂), 46.8 (CH₂), 31.5 (CH₂), 29.7 (CH₂), 29.1 (CH₂), 23.3 (CH₂), 22.6 (CH₂), 14.0 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₂₀H₂₂NO₅ calcd: 356.1492; found: 356.1492.

3-(3-Cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)oxazolidin-2-one (3ca). The reaction was conducted according to the general procedure in presence of ynamide **1c** (0.33 mmol, 50 mg), dimedone **2a** (0.4 mmol, 56 mg), manganese

triacetate (1.09 mmol, 292 mg), copper diacetate (0.33 mmol, 66 mg) in 1,1,2,2-tetrachloroethane (1.7 mL) at 80°C for 6 h. This procedure led to furan **3ca** (92 mg, 0.317 mmol, 95% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 4.51 (pseudo t, *J* = 7.8, 2H), 3.93 (pseudo t, *J* = 8.2, 2H), 2.64 (s, 2H), 2.32 (s, 2H), 1.84 (tt, *J* = 8.5 and 5.9, 1H), 1.12 (s, 6H), 0.55-0.75 (m, 2H), 0.50-0.54 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 193.3 (C=O), 163.4 (=C), 156.2 (C=O), 139.5 (=C), 120.2 (=C), 120.0 (=C), 62.7 (CH₂), 52.6 (CH₂), 47.0 (CH₂), 37.3 (CH₂), 34.7 (C), 28.6 (2xCH₃), 6.3 (2xCH₂), 5.5 (CH). HRMS (ESI): *m/z*: for [M+H⁺] C₁₆H₂₀NO₄ calcd: 290.1387; found: 290.1387.

3-(3-Cyclopropyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)oxazolidin-2-one (3cb). The reaction was conducted according to the general procedure in presence of ynamide **3c** (0.33 mmol, 50 mg), cyclohexane-1,3-dione **2b** (0.40 mmol, 45 mg), manganese triacetate (1.089 mmol, 292 mg), copper diacetate (0.33 mmol, 66 mg) in 1,1,2,2-tetrachloroethane (1.7 mL) at 80°C for 6 h. This procedure led to furan **3cb** (45 mg, 0.17 mmol, 53% yield) isolated as a colourless powder. ¹H NMR (400 MHz, CDCl₃) δ: 4.55 (pseudo t, *J* = 7.8, 2H), 3.95 (pseudo t, *J* = 8.3, 2H), 2.81 (t, *J* = 6.3, 2H), 2.49 (pseudo t, *J* = 6.0, 2H), 2.16 (pseudo quint, *J* = 6.4, 2H), 1.90 (tt, *J* = 8.6 and 5.5, 1H), 0.55-0.75 (m, 2H), 0.49-0.55 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 194.0 (C=O), 164.6 (=C), 156.1 (C=O), 139.2 (=C), 121.5 (=C), 120.4 (=C), 62.7 (CH₂), 47.1 (CH₂), 38.4 (CH₂), 23.5 (CH₂), 22.1 (CH₂), 6.5 (2xCH₂), 5.4 (CH). HRMS (ESI): *m/z*: for [M+H⁺] C₁₄H₁₆NO₄ calcd: 262.1074; found: 262.1074.

3-(3-Cyclopropyl-4-oxo-4H-furo[3,2-c]chromen-2-yl)oxazolidin-2-one (3cc). The reaction was conducted according to the general procedure in presence of ynamide **1c** (0.33 mmol, 50 mg), 4-hydroxycoumarin **2c** (0.40 mmol, 65 mg), manganese triacetate (1.089 mmol, 292 mg), copper diacetate (0.33 mmol, 66 mg) in 1,1,2,2-tetrachloroethane (1.7 mL) at 80°C for 6 h. This procedure led to furan **3cc** (85 mg, 0.27 mmol, 84% yield) as a colourless powder. ¹H NMR (400 MHz, CDCl₃) δ: 7.75-7.82 (dd, *J* = 7.8 and 1.4, 1H), 7.47-7.55 (t, *J* = 7.3, 1H), 7.38-7.44 (d, *J* = 7.8, 1H), 7.29-7.35 (tt, *J* = 8.2 and 1.0, 1H), 4.63 (pseudo t, *J* = 7.7, 2H), 4.10 (pseudo t, *J* = 8.1, 2H), 1.97 (tt, *J* = 8.2 and 5.7, 1H), 0.99-1.05 (m, 2H), 0.94-0.99 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 157.1 (=C), 155.9 (C=O), 155.0 (C=O), 152.9 (=C), 141.6 (=C), 131.0 (=CH), 124.5 (=CH), 121.4 (=C), 120.9 (=CH), 117.3 (=CH), 112.2 (=C), 110.8 (=C), 63.3 (CH₂), 47.0 (CH₂), 6.6 (2xCH₂), 5.3 (CH). HRMS (ESI): *m/z*: for [M+H⁺] C₁₇H₁₄NO₅ calcd: 312.0866; found: 312.0866.

Methyl-1-(3-butyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)-1H-indole-2-carboxylate (3da). The reaction was conducted according to the general procedure in presence of ynamide **1d** (0.2 mmol, 50 mg), dimedone **2a** (0.24 mmol, 24 mg), manganese triacetate (0.66 mmol, 177 mg), copper diacetate (0.2 mmol, 40 mg) in AcOH (1 mL) at 80°C for 6 h. This procedure led to furan **3da** (70 mg, 0.18 mmol, 89% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.23 (d, *J* = 7.5, 1H), 7.85 (s, 1H), 7.26-7.37 (m, 2H), 7.22 (d, *J* = 8.0, 1H), 3.94 (s, 3H), 2.76 (s, 2H), 2.50 (pseudo t, *J* = 7.5, 2H), 2.44 (s, 2H), 1.44-1.51 (m,

2H), 1.25 (superimposed s, 6H), 1.20-1.24 (m, 2H), 0.74 (t, $J = 7.3$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 194.0 (C=O), 165.1 (C=O), 164.0 (=C), 140.3 (=C), 138.2 (=C), 134.8 (=CH), 126.1 (=C), 124.1 (=CH), 123.1 (=CH), 121.9 (=CH), 120.0 (=C), 118.0 (=C), 110.9 (=CH), 110.6 (=C), 52.8 (CH_2), 51.4 (CH_3), 37.4 (CH_2), 35.2 (C), 31.5 (CH_2), 28.7 ($2\times\text{CH}_3$), 23.0 (CH_2), 22.5 (CH_2), 13.4 (CH_3). HRMS (ESI): m/z : for $[\text{M}+\text{H}^+]$ $\text{C}_{24}\text{H}_{28}\text{NO}_4$ calcd: 394.2013; found: 394.2004.

Methyl 1-(3-butyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)-1H-indole-3-carboxylate (3db). The reaction was conducted according to the general procedure in presence of ynamide **1d** (0.2 mmol, 50 mg), cyclohexane-1,3-dione **2b** (0.24 mmol, 27 mg), manganese triacetate (0.66 mmol, 177 mg), copper diacetate (0.2 mmol, 40 mg) in AcOH (1 mL) at 80°C for 6 h. This procedure led to furan **3db** (59 mg, 0.16 mmol, 80% yield) isolated as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.22 (d, $J = 7.5$, 1H), 7.84 (s, 1H), 7.25-7.40 (2 superimposed t, $J = 7.5$, 2H), 7.2 (d, $J = 7.4$, 1H), 3.95 (s, 3H), 2.90 (t, $J = 6.0$, 2H), 2.57 (t, $J = 6.5$, 2H), 2.50 (t, $J = 7.4$, 2H), 2.25 (pseudo t, $J = 6.3$, 2H), 1.49 (quint, $J = 7.4$, 2H), 1.17-1.23 (m, 2H), 0.76 (t, $J = 7.3$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 194.4 (C=O), 165.0 (C=O), 164.7 (=C), 140.2 (=C), 138.1 (=C), 134.7 (=CH), 125.9 (=C), 124.1 (=CH), 123.1 (=CH), 122.0 (=CH), 120.9 (=C), 118.1 (=C), 111.0 (=CH), 110.5 (=C), 51.3 (CH_3), 38.3 (CH_2), 31.6 (CH_2), 30.0 (CH_2), 23.4 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 13.6 (CH_3). HRMS (ESI): m/z : for $[\text{M}+\text{H}^+]$ $\text{C}_{22}\text{H}_{24}\text{NO}_4$ calcd: 366.1700; found: 366.1696.

Methyl 1-(3-butyl-4-oxo-4H-furo[3,2-c]chromen-2-yl)-1H-indole-3-carboxylate (3dc). The reaction was conducted according to the general procedure in presence of ynamide **1d** (0.20 mmol, 50 mg), 4-hydroxycoumarin **2c** (0.24 mmol, 39 mg), manganese triacetate (0.66 mmol, 177 mg), copper diacetate (0.2 mmol, 40 mg) in AcOH (1 mL) at 80°C for 6 h. This procedure led to furan **3dc** (60 mg, 0.14 mmol, 73% yield) isolated as a colourless powder. ^1H NMR (400 MHz, CDCl_3) δ : 8.27 (d, $J = 7.3$, 1H), 7.95 (s, 1H), 7.81 (dd, $J = 7.9$ and 1.3, 1H), 7.53-7.58 (m, 1H), 7.46-7.50 (m, 1H), 7.33-7.42 (m, 3H), 7.27-7.30 (m, 1H), 3.98 (s, 3H), 2.69 (pseudo t, $J = 7.6$, 2H), 1.58 (quint, $J = 7.4$, 2H), 1.28 (sext, $J = 7.5$, 2H), 0.79 (t, $J = 7.3$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 164.8 (C=O), 157.4 (=C), 155.4 (C=O), 153.1 (=C), 142.1 (=C), 138.1 (=C), 134.3 (=CH), 131.4 (=CH), 126.2 (=C), 124.7 (=CH), 124.6 (=CH), 123.4 (=CH), 122.2 (=CH), 121.1 (=CH), 119.2 (=C), 117.5 (=CH), 112.3 (=C), 111.5 (=C), 110.9 (=CH), 110.8 (=C), 51.4 (CH_3), 31.4 (CH_2), 22.8 (CH_2), 22.2 (CH_2), 13.6 (CH_3). HRMS (ESI): m/z : for $[\text{M}+\text{H}^+]$ $\text{C}_{25}\text{H}_{22}\text{NO}_5$ calcd: 416.1492; found: 416.1490.

A scale up was realized with ynamide **1d** (2 mmol, 500 mg), 4-hydroxycoumarin **2c** (2.4 mmol, 390 mg), manganese triacetate (6.6 mmol, 1.78 g), copper diacetate (2.0 mmol, 400 mg) in AcOH (10 mL) at 80°C for 6 h. This procedure led to furan **3dc** (681 mg, 1.64 mmol, 82% yield) isolated as a yellow powder.

Methyl-1-(3-hexyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)-1H-indole-3-carboxylate (3ea). The reaction was conducted according to the general procedure in presence of ynamide **1e** (0.18 mmol, 53 mg), dimedone **2a** (0.22 mmol, 31 mg),

manganese triacetate (0.6 mmol, 161 mg), copper diacetate (0.18 mmol, 36 mg) in AcOH (0.9 mL) at 80°C for 6 h. This procedure led to furan **3ea** (75 mg, 0.17 mmol, 97% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.23 (d, *J* = 7.2, 1H), 7.85 (s, 1H), 7.32-7.38 (2 superimposed td, *J* = 7.1 and 1.2, 2H), 7.22 (d, *J* = 7.3, 1H), 3.94 (s, 3H), 2.76 (s, 2H), 2.50 (pseudo t, *J* = 7.5, 2H), 2.44 (s, 2H), 1.51 (quint, *J* = 7.5, 2H), 1.26-1.29 (m, 2H), 1.20 (s, 6H), 1.14-1.20 (m, 4H), 0.77 (t, *J* = 6.7, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 193.9 (C=O), 165.0 (C=O), 163.7 (=C), 140.3 (=C), 138.2 (=C), 134.8 (=CH), 126.1 (=C), 124.1 (=CH), 123.1 (=CH), 121.9 (=CH), 119.7 (=C), 118.0 (=C), 111.0 (=CH), 110.6 (=C), 52.6 (CH₂), 51.3 (CH₃), 37.2 (CH₂), 35.1 (C), 31.2 (CH₂), 29.2 (CH₂), 28.8 (CH₂), 28.6 (2xCH₃), 23.2 (CH₂), 22.5 (CH₂), 14.0 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₂₆H₃₂NO₄ calcd: 422.2326; found: 422.2317.

Methyl 1-(3-hexyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)-1H-indole-3-carboxylate (3eb). The reaction was conducted according to the general procedure in presence of ynamide **1e** (0.18 mmol, 53 mg), cyclohexane-1,3-dione **2b** (0.22 mmol, 25 mg), manganese triacetate (0.60 mmol, 161 mg), copper diacetate (0.18 mmol, 36 mg) in AcOH (0.9 mL) at 80°C for 6 h. This procedure led to furan **3eb** (50 mg, 0.13 mmol, 69% yield) isolated as a colourless powder. ¹H NMR (400 MHz, CDCl₃) δ: 8.22 (dd, *J* = 7.3 and 1.1, 1H), 7.83 (s, 1H), 7.28-7.40 (2 superimposed td, *J* = 7.1 and 1.3, 2H), 7.22 (d, *J* = 7.1, 1H), 3.94 (s, 3H), 2.90 (t, *J* = 6.3, 2H), 2.57 (pseudo t, *J* = 6.0, 2H), 2.49 (pseudo t, *J* = 6.5, 2H), 2.25 (quint, *J* = 6.5, 2H), 1.48 (quint, *J* = 7.5, 2H), 1.07-1.18 (m, 6H), 0.77 (t, *J* = 6.8, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 194.4 (C=O), 164.9 (C=O), 164.7 (=C), 140.1 (=C), 138.2 (=C), 134.7 (=CH), 126.1 (=C), 124.1 (=CH), 123.1 (=CH), 121.9 (=CH), 121.0 (=C), 118.1 (=C), 111.0 (=CH), 110.7 (=C), 51.3 (CH₃), 38.3 (CH₂), 31.2 (CH₂), 29.2 (CH₂), 28.9 (CH₂), 23.3 (CH₂), 23.2 (CH₂), 22.5 (CH₂), 22.4 (CH₂), 14.0 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₂₄H₂₈NO₄ calcd: 394.2013; found: 394.2011.

Methyl 1-(3-hexyl-4-oxo-4H-furo[3,2-c]chromen-2-yl)-1H-indole-3-carboxylate (3ec). The reaction was conducted according to the general procedure in presence of ynamide **1e** (0.18 mmol, 53 mg), 4-hydroxycoumarin **2c** (0.22 mmol, 36 mg), manganese triacetate (0.60 mmol, 161 mg), copper diacetate (0.18 mmol, 36 mg) in AcOH (0.9 mL) at 80°C. This procedure led to furan **3ec** (70 mg, 0.16 mmol, 87% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.19 (*J* = 7.2 and 1.1, 1H), 7.87 (s, 1H), 7.74 (dd, *J* = 7.9 and 1.3, 1H), 7.46-7.50 (m, 1H), 7.39 (dd, *J* = 7.1 and 1.6, 1H), 7.26-7.33 (3H), 7.20-7.23 (m, 1H), 3.90 (s, 3H), 2.60 (pseudo t, *J* = 7.5, 2H), 1.54 (quint, *J* = 7.3, 2H), 1.14-1.21 (m, 6H), 0.70 (t, *J* = 6.7, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 164.8 (C=O), 157.5 (=C), 155.4 (C=O), 153.1 (=C), 142.2 (=C), 138.1 (=C), 134.4 (=CH), 131.3 (=CH), 126.2 (=C), 124.7 (=CH), 124.5 (=CH), 123.5 (=CH), 122.1 (=CH), 121.0 (=CH), 119.2 (=C), 117.5 (=CH), 112.3 (=C), 111.5 (=C), 110.9 (=CH), 110.8 (=C), 51.4 (CH₃), 31.2 (CH₂), 29.2 (CH₂), 28.8 (CH₂), 23.0 (CH₂), 22.4 (CH₂), 13.9 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₂₇H₂₆NO₅ calcd: 444.1805; found: 444.1804.

Methyl 1-(3-cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)-1H-indole-3-carboxylate (3fa). The reaction was conducted according to the general procedure in presence of ynamide **1f** (0.21 mmol, 50 mg), dimesone **2a** (0.26 mmol, 37 mg), manganese triacetate (0.7 mmol, 188 mg), copper diacetate (0.21 mmol, 42 mg) in AcOH (1.1 mL) at 80°C for 6 h. This procedure led to furan **3fa** (76 mg, 0.2 mmol, 97% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.22 (dd, *J* = 6.8 and 2.1, 1H), 7.90 (s, 1H), 7.24-7.38 (m, 3H), 3.95 (s, 3H), 2.74 (s, 2H), 2.44 (s, 2H), 1.81 (tt, *J* = 8.6 and 5.4, 1H), 1.19 (s, 6H), 0.67-0.74 (m, 2H), 0.48-0.52 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 193.4 (C=O), 165.0 (C=O), 163.6 (=C), 139.9 (=C), 138.2 (=CH), 135.1 (=CH), 126.0 (=C), 124.2 (=CH), 123.1 (=CH), 121.8 (=C), 120.3 (=C), 119.0 (=C), 111.5 (=CH), 110.7 (=C), 52.7 (CH₂), 51.3 (CH₃), 37.3 (CH₂), 29.9 (C), 28.4 (2xCH₃), 6.6 (2xCH₂), 5.6 (CH). HRMS (ESI): *m/z*: for [M+H⁺] C₂₃H₂₄NO₄ calcd: 378.1700; found: 378.1696.

Methyl 1-(3-cyclopropyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)-1H-indole-3-carboxylate (3fb). The reaction was conducted according to the general procedure in presence of ynamide **1f** (0.21 mmol, 50 mg), cyclohexane-1,3-dione **2b** (0.26 mmol, 29 mg), manganese triacetate (0.7 mmol, 188 mg), copper diacetate (0.21 mmol, 42 mg) in AcOH (1.1 mL) at 80°C for 6 h. This procedure led to furan **3fb** (59 mg, 0.17 mmol, 80% yield) isolated as a colourless powder. ¹H NMR (400 MHz, CDCl₃) δ: 8.22 (dd, *J* = 6.3 and 1.5, 1H), 7.88 (s, 1H), 7.27-7.39 (m, 3H), 3.95 (s, 3H), 2.86 (pseudo t, *J* = 6.3, 2H), 2.59 (pseudo t, *J* = 7.0, 2H), 2.24 (pseudo quint, *J* = 6.3, 2H), 1.84 (tt, *J* = 6.2 and 3.1, 1H), 0.66-0.77 (m, 2H), 0.39-0.52 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 193.9 (C=O), 164.9 (C=O), 164.5 (=C), 139.7 (=C), 138.2 (=C), 134.9 (=CH), 126.0 (=C), 124.1 (=CH), 123.1 (=CH), 121.9 (=CH), 121.5 (=C), 119.0 (=C), 111.2 (=CH), 110.7 (=C), 51.3 (CH₃), 38.4 (CH₂), 23.5 (CH₂), 22.3 (CH₂), 6.5 (2xCH₂), 5.7 (CH). HRMS (ESI): *m/z*: for [M+Na] C₂₁H₁₉NO₄Na calcd: 372.1206; found: 372.1205.

Methyl 1-(3-cyclopropyl-4-oxo-4H-furo[3,2-c]chromen-2-yl)-1H-indole-3-carboxylate (3fc). The reaction was conducted according to the general procedure in presence of ynamide **1f** (0.21 mmol, 50 mg), 4-hydroxycoumarin **2c** (0.24 mmol, 41 mg), manganese triacetate (0.7 mmol, 188 mg), copper diacetate (0.21 mmol, 42 mg) in AcOH (1.1 mL) at 80°C for 6 h. This procedure led to furan **3fc** (75 mg, 0.187 mmol, 91% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.24-8.31 (m, 1H), 8.01 (s, 1H), 7.81 (dd, *J* = 7.9, *J* = 1.3, 1H), 7.53-7.60 (m, 1H), 7.43-7.51 (m, 1H), 7.33-7.43 (m, 4H), 3.98 (s, 3H), 1.93 (tt, *J* = 8.6 and 5.4, 1H), 0.80-0.92 (m, 2H), 0.68-0.77 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 164.8 (C=O), 157.1 (=C), 155.2 (C=O), 153.1 (=C), 141.9 (=C), 138.1 (=C), 134.6 (=CH), 131.3 (=CH), 126.0 (=C), 124.7 (=CH), 124.5 (=CH), 123.6 (=CH), 122.0 (=CH), 121.0 (=CH), 120.1 (=C), 117.5 (=CH), 112.1 (=C), 111.5 (=C), 111.0 (=CH), 110.9 (=C), 51.5 (CH₃), 7.0 (2xCH₂), 5.7 (CH). HRMS (ESI): *m/z*: for [M+H⁺] C₂₄H₁₈NO₅ calcd: 400.1179; found: 400.1175.

2-(3-hexyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-yl)isoindoline-1,3-dione (3ga). The reaction was conducted according to the general procedure in presence of ynamide **1g** (0.20 mmol, 54 mg), dimedone **2a** (0.24 mmol, 34 mg), manganese triacetate (0.66 mmol, 177 mg), copper diacetate (0.20 mmol, 40 mg) in tetrachloroethane (1 mL) at 80°C for 6 h. This procedure led to furan **3ga** (22 mg, 0.056 mmol, 28% yield) isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.94-8.02 (m, 2H), 7.80-7.88 (m, 2H), 2.74 (s, 2H), 2.44-2.53 (m, 2H), 2.39 (s, 2H), 1.54 (quint, *J* = 7.1, 2H), 1.20-1.14 (m, 6H), 1.1 (s, 6H), 0.79 (t, *J* = 6.7, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 193.7 (C=O), 166.4 (=C), 165.0 (2xC=O), 134.9 (2x=CH), 133.6 (=C), 131.8 (=C), 124.3 (2x=CH), 122.1 (=C), 119.9 (=C), 52.5 (CH₂), 37.3 (CH₂), 34.8 (C), 31.4 (CH₂), 29.6 (CH₂), 29.0 (CH₂), 28.7 (2xCH₃), 23.5 (CH₂), 22.5 (CH₂), 14.0 (CH₃). HRMS (ESI): *m/z*: for [M+H⁺] C₂₄H₂₈NO₄ calcd: 394.2013, found: 394.2010.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

¹H and ¹³C{¹H} NMR spectra for all new compounds. This material is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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