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Microwave-assisted synthesis of 4,6-disubstituted isoindoline-1,3-diones by Diels-Alder reactions

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ABSTRACT

The synthesis of 4,6-disubstituted isoindoline-1,3-diones through microwave-assisted Diels-Alder (DA) reactions is reported. Chromones bearing an α,β-unsaturated carbonyl system at C-3 were used as dienes and a scope of maleimides as dienophiles was investigated. The proposed mechanism involves a DA reaction of 3-benzoylvinylchromones with different maleimides, followed by chromanone ring opening and *in situ* oxidation. The observed aromatization of DA adducts was accomplished without employment of any oxidizing agent and can be explained by the presence of several acidic protons due to the electron-withdrawing groups (carbonyl groups), affording the 4,6-disubstituted isoindoline-1,3-diones in 15-59% yield. Among tested maleimides, *N*-phenylmaleimide revealed to be the most reactive dienophile, yielding the corresponding 2-phenylisoindoline-1,3-dione in 59% yield.

1. Introduction

Isoindoline-1,3-diones, so-called phthalimides (Fig. 1), as well as their *N*-substituted analogues, are vital pharmacophoric units, often found in both natural and synthetic compounds with a myriad of biological activities [1–6]. The particular interest of isoindoline-1,3-diones came not only from their wide structural diversity, but also from their general structure -CO-N(R)-CO-, so that they are hydrophobic and neutral, having the ability to cross biological membranes *in vivo* [7]. Concerning the cancer therapy, one can find the isoindoline-1,3-dione core in many examples of anticancer agents, with some of them highlighted in Fig. 1, presenting anti-prostate cancer activity (**A**) [8], inhibitory activity against cyclin-dependent kinases (CDKs) (**B**) [9], and on tumour necrosis factor α (TNF-α) (**C**) [10], as well as antiproliferative capacity against A549 and HepG2 cell lines (**D**) [6].

The utility of isoindoline-1,3-diones has prompted the development of various synthetic procedures for their synthesis. The most common approach to isoindoline-1,3-diones involves the condensation of phthalic acids or anhydrides with amines [11–13]. Nevertheless, other alternative strategies have been developed such as Ru-catalysed reaction of 1,2-benzenedimethanol with amines [14], multicomponent reaction of arynes with isocyanides and CO_2 [15], metal-catalysed cyclocarbonylation of aromatic amides [16], or Pd-catalysed oxidative carbonylation reactions *via in situ* condensation of aldehydes and amines [17]. More recently, leading strategies for the synthesis of isoindoline-1,3-diones based on transition-metal-catalysed benzannulation reactions have also been reported, with seminal examples of Pd-catalysed annulation of vinylarenes with maleimides [18], and Cu-catalysed cycloaddition of oximes with maleimides [19]. Despite these transition-metal-catalysed methods being able to deliver isoindoline-1,3-diones in a broad scope of structural diversity, more environmentally benign and atom economical protocols are still highly desired in modern green chemistry. As so, alternative methodologies involving atom economical Diels-Alder (DA) reactions are themselves particularly interesting and frequently employed in target orientated syntheses, as well as in total synthesis endeavours [20–22].

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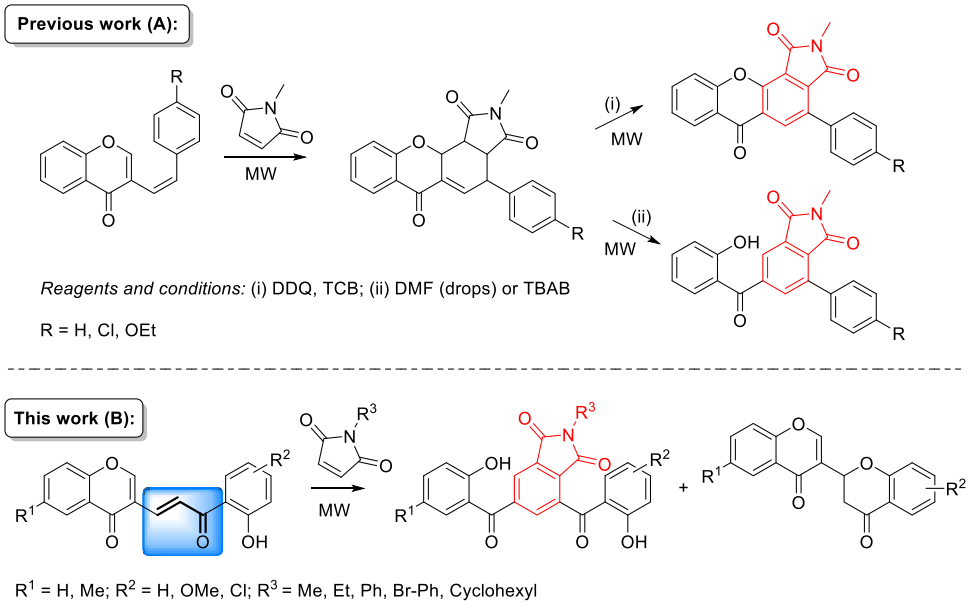


Scheme 1. MW-assisted DA reactions of 3-substituted chromone derivatives with maleimides.

Following the long-lasting interest of our research group in both inter- and intramolecular DA reactions to produce a variety of isoindoline-1,3-diones, with a range of different substitution patterns, some synthetic methods were developed, using chromone derivatives as dienes and maleimides as privileged dienophiles [23–27]. Previous work from Pinto *et al.* [24] discloses the synthesis of both fused and di-substituted isoindoline-1,3-diones from (*Z*)-3-styrylchromone derivatives as dienes and *N*-methylmaleimide (NMM) as dienophile, through microwave (MW)-promoted DA reactions (Scheme 1, **A**). This stepwise approach produces the tetrahydro-1*H*-isoindole-1,3-dione, which requires the addition of an oxidizing agent [2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)] to complete the aromatization into the corresponding isoindoline-1,3-dione (Scheme 1, **A**). As a further effort to develop a one-pot method to prepare isoindoline-1,3-diones expanding their structural diversity, the present work discloses the synthesis of bis(2-hydroxyacetophenone)-substituted isoindoline-1,3-diones, starting from chromones bearing an α,β-unsaturated carbonyl system at C-3 (highlighted in blue) (Scheme 1, **B**).

2. Materials and methods

2.1. General remarks

Melting points were measured with a Büchi Melting Point B-540 apparatus and are uncorrected. MW-assisted syntheses were carried out using a monomode microwave CEM Discover SP instrument. NMR spectra were recorded with a Bruker Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer, in $CDCl_3$ as solvent. Chemical shifts are reported in ppm and coupling constants (*J*) in Hz; the internal standard was tetramethylsilane (TMS). Unequivocal ^{13}C assignments were made with the aid of 2D *g*HSQC and *g*HMBC (delays for one-bond and long-range *J* C/H couplings were optimized for 145 and 7 Hz, respectively) experiments. Positive and negative ESI mass spectra were acquired with an LTQ Orbitrap XL or a QTOF 2 spectrometers. Preparative thin layer chromatography (TLC) was performed with Macherey–Nagel silica gel G/UV254. Column chromatography was performed with Acros Organics silica gel 60 Å (0.060–0.200 mm). All chemicals and solvents were obtained from commercial sources and used as received or dried by standard procedures.

2.2. General procedure for the synthesis of compounds 4a-d and 6-11

The appropriate (*E*)-3-[3-(2-hydroxyphenyl)-3-oxoprop-1-enyl]-4*H*-chromen-4-one **3a-d** (0.171 mmol) and the appropriate dienophile (5 equiv) were mixed in DMF (few drops) in a closed glass microwave reactor. The reaction mixture was heated under MW irradiation for 20 min at 200 °C. The reaction crude was dissolved in EtOH and the solvent was subsequently removed under reduced pressure. Then, it was purified by preparative TLC using DCM/Hex (9:1) as eluent. Michael adducts **5a-d** were also obtained as by-products during the reaction [28].

*4,6-Bis(2-hydroxybenzoyl)-2-methylisoindoline-1,3-dione (**4a**):* yellow solid (33.6 mg, 49% yield, mp 223-225 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.19 (s, 3H, N-C*H*$_3$), 6.84 (ddd, *J* 1.1, 7.2, 8.2 Hz, 1H, H-5'), 6.94 (ddd, *J* 1.1, 7.3, 8.2 Hz, 1H, H-5''), 7.10-7.13 (m, 2H, H-3',3''), 7.19 (dd, *J* 1.6, 8.0 Hz, 1H, H-6'), 7.47 (dd, *J* 1.6, 8.1 Hz, 1H, H-6''), 7.53-7.62 (m, 2H, H-4',4''), 7.95 (d, *J* 1.4 Hz, 1H, H-5), 8.25 (d, *J* 1.4 Hz, 1H, H-7), 11.64 (s, 1H, 2''-O*H*), 11.70 (s, 1H, 2'-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4 (N-*C*H$_3$), 118.3 (C-1''), 118.8 and 119.1 (C-3',3''), 119.3,* 119.4 and 119.5 (C-5',5''), 124.7 (C-7), 131.1 (C-3a), 132.7,* 132.75 and 132.77 (C-6',6''), 133.0 (C-5), 135.5,* 137.7 and 137.9 (C-4',4''), 143.3,* 163.2 (C-2'), 163.5 (C-2''), 165.6 (C-3), 166.5 (C-1), 197.8 (4-*C*=O), 198.3 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{23}H_{15}NO_6+Na]^+$: 424.0797, found: 424.0790.

*6-(2-Hydroxy-5-methylbenzoyl)-4-(2-hydroxybenzoyl)-2-methylisoindoline-1,3-dione (**4b**):* yellow solid (24.2 mg, 34% yield, mp 212-214 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, 5''-C*H*$_3$), 3.20 (s, 3H, N-C*H*$_3$), 6.85 (ddd, *J* 1.1, 7.2, 8.2 Hz, 1H, H-5'), 7.02 (d, *J* 8.6 Hz, 1H, H-3''), 7.12 (dd, *J* 1.1, 8.6 Hz, 1H, H-3'), 7.19-7.23 (m, 2H, H-6',6''), 7.40 (dd, *J* 2.2, 8.6 Hz, 1H, H-4''), 7.56 (ddd, *J* 1.7, 7.2, 8.6 Hz, 1H, H-4'), 7.93 (d, *J* 1.4 Hz, 1H, H-5), 8.23 (d, *J* 1.4 Hz, 1H, H-7), 11.47 (s, 1H, 2''-O*H*), 11.72 (s, 1H, 2'-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6 (5''-*C*H$_3$), 24.4 (N-*C*H$_3$), 118.0 (C-1''), 118.8 (C-3',3''), 119.30,* 119.33 (C-5'), 124.5 (C-7), 128.7 (C-5''), 131.1 (C-3a), 132.2 (C-6''), 132.5 (C-5), 132.7 (C-6'), 133.0,* 135.4,* 137.9 (C-4'), 138.9 (C-4''), 143.5,* 161.6 (C-2''), 163.2 (C-2'), 165.7 (C-3),

166.6 (C-1), 197.8 (4-*C*=O), 198.3 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{24}H_{17}NO_6+Na]^+$: 438.0954, found: 438.0947.

*4-(2-Hydroxy-4-methoxybenzoyl)-6-(2-hydroxybenzoyl)-2-methylisoindoline-1,3-dione (**4c**):* yellow solid (11.1 mg, 15% yield, mp 211-213 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.19 (s, 3H, N-C*H*$_3$), 3.87 (s, 3H, 4'-OC*H*$_3$), 6.37 (dd, *J* 2.4, 8.9 Hz, 1H, H-5'), 6.54 (d, *J* 2.4 Hz, 1H, H-3'), 6.93 (ddd, *J* 1.1, 7.2, 8.2 Hz, 1H, H-5''), 7.07 (d, *J* 8.9 Hz, 1H, H-6'), 7.12 (dd, *J* 1.1, 8.6 Hz, 1H, H-3''), 7.47 (dd, *J* 1.7, 8.2 Hz, 1H, H-6''), 7.58 (ddd, *J* 1.7, 7.2, 8.6 Hz, 1H, H-4''), 7.93 (d, *J* 1.4 Hz, 1H, H-5), 8.23 (d, *J* 1.4 Hz, 1H, H-7), 11.66 (s, 1H, 2'-O*H*), 12.21 (s, 1H, 2''-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4 (N-*C*H$_3$), 55.8 (4'-OC*H*$_3$), 101.1 (C-3'), 108.7 (C-5'), 113.5 (C-1'), 118.3 (C-1''), 119.0 (C-3''), 119.5 (C-5''), 124.4 (C-7), 131.0 (C-3a), 132.8 (C-6''), 133.0 (C-5), 134.3 (C-6'), 135.7,* 137.7 (C-4''), 143.2,* 163.5 (C-2''), 165.7 (C-3), 166.3 (C-2'), 166.6 (C-1), 167.4 (C-4'), 195.4 (4-*C*=O), 198.4 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{24}H_{17}NO_7+H]^+$: 432.1083, found: 432.1096.

*4-(5-Chloro-2-hydroxybenzoyl)-6-(2-hydroxybenzoyl)-2-methylisoindoline-1,3-dione (**4d**):* yellow solid (25.3 mg, 34% yield, mp 214-216 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (s, 3H, N-C*H*$_3$), 6.96 (ddd, *J* 1.1, 7.3, 8.2 Hz, 1H, H-5''), 7.09 (d, *J* 9.0 Hz, 1H, H-3'), 7.13 (dd, *J* 1.1, 8.6 Hz, 1H, H-3''), 7.13 (d, *J* 2.6 Hz, 1H, H-6'), 7.46-7.52 (m, 2H, H-4',6''), 7.60 (ddd, *J* 1.6, 7.3, 8.6 Hz, 1H, H-4''), 7.94 (d, *J* 1.3 Hz, 1H, H-5), 8.29 (d, *J* 1.3 Hz, 1H, H-7), 11.62 (s, 1H, 2'-O*H*), 11.62 (s, 1H, 2''-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5 (N-*C*H$_3$), 118.2 (C-1''), 119.1 (C-3''), 119.5 (C-5''), 119.9,* 120.6 (C-3'), 124.0 (C-5'), 125.1 (C-7), 131.3 (C-3a), 131.3 (C-6'), 132.5 (C-5), 132.7 (C-6''), 133.1,* 134.6,* 137.77 and 137.81 (C-4',4''), 143.4,* 161.6 (C-2'), 163.6 (C-2''), 165.6 (C-3), 166.3 (C-1), 197.1 (4-*C*=O), 198.0 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{23}H_{14}ClNO_6+Na]^+$: 458.0407, found: 458.0422.

*2-Ethyl-4,6-bis(2-hydroxybenzoyl)isoindoline-1,3-dione (**6**):* yellow solid (31.3 mg, 44% yield, mp 213-215 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, *J* 7.2 Hz, 3H, N-CH$_2$C*H*$_3$), 3.75 (q, *J* 7.2 Hz, 2H, N-C*H*$_2$CH$_3$), 6.84 (ddd, *J* 1.1, 7.2, 8.2 Hz, 1H, H-5'), 6.93 (ddd, *J* 1.1, 7.2, 8.2 Hz, 1H, H-5''), 7.10-7.14 (m, 2H, H-3',3''), 7.20 (dd, *J* 1.6, 8.0 Hz, 1H, H-6'), 7.48 (dd, *J* 1.6, 8.1 Hz, 1H, H-6''), 7.53-7.62 (m, 2H, H-4',4''), 7.95 (d, *J* 1.4 Hz, 1H, H-5), 8.24 (d, *J* 1.4 Hz, 1H, H-7), 11.66 (s, 1H, 2''-O*H*), 11.72 (s, 1H, 2'-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (N-CH$_2$CH$_3$), 33.6 (N-*C*H$_2$CH$_3$), 118.3 (C-1''), 118.8 and 119.1 (C-3',3''), 119.3,* 119.4 and 119.5 (C-5',5''), 124.6 (C-7), 131.3 (C-3a), 131.6,* 132.6 (C-5), 132.8 (C-6',6''), 135.5,* 137.7 and 137.9 (C-4',4''), 143.2,* 163.2 (C-2'), 163.6 (C-2''), 165.4 (C-3), 166.3 (C-1), 197.9 (4-*C*=O), 198.3 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{24}H_{17}NO_6+H]^+$: 416.1134, found: 416.1130.

*4,6-Bis(2-hydroxybenzoyl)-2-phenylisoindoline-1,3-dione (**7**):* yellow solid (46.8 mg, 59% yield, mp 179-181 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (ddd, *J* 1.1, 7.3, 8.2, Hz, 1H, H-5'), 6.96 (ddd, *J* 1.1, 7.3, 8.2 Hz, 1H, H-5''), 7.09-7.15 (m, 2H, H-3',3''), 7.23-7.26 (m, 1H, H-6'), 7.38-7.63 (m, 8H, H-4',4'',6'',2''',3''',4''',5''',6'''), 8.03 (d, *J* 1.3 Hz, 1H, H-5), 8.36 (d, *J* 1.3 Hz, 1H, H-7), 11.66 (s, 1H, 2''-O*H*), 11.69 (s, 1H, 2'-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.3 (C-1''), 118.9 and 119.1 (C-3',3''), 119.3,* 119.4 and 119.5 (C-5',5''), 125.2 (C-7), 126.3, 128.6 and 129.2 (C-2''',3''',4''',5''',6'''), 130.7 (C-3a), 130.9 (C-1'''), 132.5,* 132.7 and 132.8 (C-6',6''), 133.0 (C-5), 136.0,* 137.8 and 137.9 (C-4',4''), 143.7,* 163.2 (C-2'), 163.6 (C-2''), 164.5 (C-3), 165.4 (C-1), 197.8 (4-*C*=O), 198.2 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{28}H_{17}NO_6+H]^+$: 464.1134, found: 464.1130.

*2-(4-Bromophenyl)-4,6-bis(2-hydroxybenzoyl)isoindoline-1,3-dione (**8**):* yellow solid (16.7 mg, 18% yield, mp 191-193 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (ddd, *J* 1.0, 7.3, 8.1 Hz, 1H, H-5'), 6.95 (ddd, *J* 1.1, 7.3, 8.2 Hz, 1H, H-5''), 7.10-7.15 (m, 2H, H-3',3''), 7.23 (dd, *J* 1.8, 8.3 Hz, 1H, H-6'), 7.33 (d, *J* 8.8 Hz, 2H, H-2''',6'''), 7.49 (dd, *J* 1.6, 8.1 Hz, 1H, H-6''), 7.53-7.63 (m, 2H, H-4',4''), 7.62 (d, *J* 8.8 Hz, 2H, H-3''',5'''), 8.03 (d, *J* 1.3 Hz, 1H, H-5), 8.35 (d, *J* 1.3 Hz, 1H, H-7), 11.64 (s, 1H, 2''-O*H*), 11.67 (s, 1H, 2'-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.2 (C-1''), 118.9 and 119.1 (C-3',3''), 119.2,* 119.4 and 119.5 (C-5',5''), 122.4 (C-4'''), 125.2 (C-7), 127.6 (C-2''',6'''), 130.0 (C-1'''), 130.5 (C-3a), 132.3,* 132.38 (C-3''',5'''), 132.67 and 132.71 (C-6',6''), 133.1 (C-5), 136.1,* 137.8 (C-4''), 138.0 (C-4'), 143.9,* 163.2 (C-2'), 163.6 (C-2''), 164.2 (C-3), 165.0 (C-1), 197.6 (4-*C*=O), 198.0 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{28}H_{16}{}^{79}BrNO_6+H]^+$: 542.02396, found: 542.24542; $[C_{28}H_{16}{}^{81}BrNO_6+H]^+$: 544.02191, found: 544.19861.

*2-Cyclohexyl-4,6-bis(2-hydroxybenzoyl)isoindoline-1,3-dione (**9**):* yellowish oil (12.0 mg, 15% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19-2.22 (m, 5H, H-2''',3''',4''',5''',6'''), 4.10 (tt, *J* 3.8, 12.3 Hz, 1H, H-1'''), 6.84 (ddd, *J* 1.0, 7.2, 8.1 Hz, 1H, H-5'), 6.93 (ddd, *J* 1.0, 7.2, 8.2 Hz, 1H, H-5''), 7.10-7.13 (m, 2H, H-3',3''), 7.21 (dd, *J* 1.6, 8.0 Hz, 1H, H-6'), 7.47 (dd, *J* 1.5, 8.1 Hz, 1H, H-6''), 7.53-7.61 (m, 2H, H-4',4''), 7.92 (d, *J* 1.3 Hz, 1H, H-5), 8.21 (d, *J* 1.3 Hz, 1H, H-7), 11.67 (s, 1H, 2''-O*H*), 11.73 (s, 1H, 2'-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 25.9 and 29.7 (C-2''',3''',4''',5''',6'''), 51.7 (C-1'''), 118.3 (C-1''), 118.8 and 119.0 (C-3',3''), 119.3,* 119.3 and 119.4 (C-5',5''), 124.5 (C-7), 131.1 (C-3a), 132.4 (C-5), 132.8 (C-6',6''), 132.9,* 135.3,* 137.7 and 137.9 (C-4',4''), 143.1,* 163.2 (C-2'), 163.6 (C-2''), 165.7 (C-3), 166.5 (C-1), 198.1 (4-*C*=O), 198.4 (6-*C*=O) ppm. *C-1', C-4, C-6 or C-7a. HRMS-ESI *m/z* calcd. for $[C_{28}H_{23}NO_6+H]^+$: 470.16036, found: 470.16182.

*Dimethyl 3,5-bis(2-hydroxybenzoyl)phthalate (**10**):* yellowish oil (14.9 mg, 20% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 and 3.96 (2 s, 6H, 1,2-CO$_2$C*H*$_3$), 6.85-6.95 (m, 2H, H-5',5''), 7.06-7.12 (m, 2H, H-3',3''), 7.33 (dd, *J* 1.6, 8.0 Hz, 1H, H-6'), 7.48 (dd, *J* 1.5, 8.1 Hz, 1H, H-6''), 7.52-7.59 (m, 2H, H-4',4''), 7.88 (d, *J* 1.6 Hz, 1H, H-3), 8.34 (d, *J* 1.6 Hz, 1H, H-5), 11.57 (s, 1H, 2'-O*H*), 11.68 (s, 1H, 2''-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.2 and 53.3 (1,2-CO$_2$*C*H$_3$), 118.4 (C-1'), 118.6 (C-3'), 118.8 (C-1''), 118.9 (C-3''), 119.3 (C-5''), 119.4 (C-5'), 131.3 (C-2), 131.6 (C-3), 131.9 (C-5), 132.9 (C-6''), 133.0 (C-6'), 136,2 (C-4), 137.5 and 137.6 (C-4',4''), 138.1 (C-1), 138.7 (C-6), 163.2 (C-2'), 163.4 (C-2''), 165.2 and 166.7 (1,2-*C*O$_2$CH$_3$), 198.5 (4-*C*=O), 199.3 (6-*C*=O) ppm. HRMS-ESI *m/z* calcd. for $[C_{24}H_{18}O_8-H]^-$: 433.09234, found: 433.09468.

*Diethyl 3,5-bis(2-hydroxybenzoyl)phthalate (**11**):* yellowish oil (19.0 mg, 24% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 and 1.39 (2 t, *J* 7.1 Hz, 6H, 1,2-CO$_2$CH$_2$C*H*$_3$), 4.22 and 4.41 (2 q, *J* 7.2 Hz, 4H, 1,2-CO$_2$C*H*$_2$CH$_3$), 6.85-6.95 (m, 2H, H-5',5''), 7.05-7.12 (m, 2H, H-3',3''), 7.32 (dd, *J* 1.6, 8.0 Hz, 1H, H-6'), 7.49 (dd, *J* 1.6, 8.1 Hz, 1H, H-6''), 7.51-7.59 (m, 2H, H-4',4''), 7.85 (d, *J* 1.7 Hz, 1H, H-4), 8.30 (d, *J* 1.7 Hz, 1H, H-2), 11.63 (s, 1H, 2'-O*H*), 11.71 (s, 1H, 2''-O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 and 14.1 (1,2-CO$_2$CH$_2$*C*H$_3$), 62.5 (1,2-CO$_2$*C*H$_2$CH$_3$), 118.4 (C-1'), 118,6 (C-3'), 118.9 (C-3''), 119.0 (C-1''), 119.3 (C-5''), 119.3 (C-5'), 131.0 (C-3), 131.6 (C-5), 131.9 (C-2), 132.9 (C-6''), 133.1 (C-6'), 135.9 (C-4), 137.4 (C-4''), 137.5 (C-4''), 138.2 (C-1), 138.9 (C-6), 163.1 (C-2'), 163.4 (C-2''), 165.1 and 165.7 (1,2-*C*O$_2$CH$_2$CH$_3$), 198.6 (4-*C*=O), 199.6 (6-*C*=O) ppm. HRMS-ESI *m/z* calcd. for $[C_{26}H_{22}O_8-H]^-$: 461.12364, found: 461.12624.

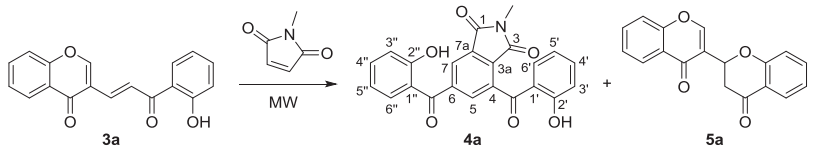
3. Results and discussion

3.1. DA reactions of (E)*-3-(3-(2-hydroxyphenyl)-3-oxoprop-1-en-1-yl)-4*H*-chromen-4-ones*

To begin with, the required 3-benzoylvinylchromones **3a-d** were prepared in fair to very good yields (32-89%) through base-promoted aldol condensation reactions of 3-formylchromones **1a,b** with 2'-hydroxyacetophenones **2a-c**, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base (Scheme 2).

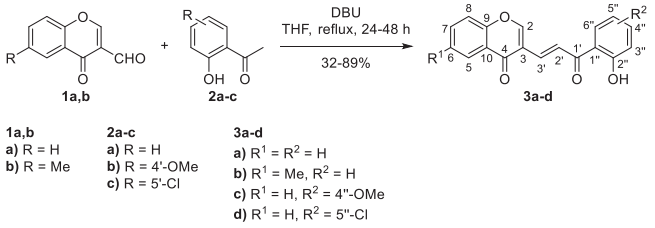
Subsequently, the synthesized chromones **3a-d** were used as dienes in MW-assisted DA reactions. The reaction conditions were primarily optimized using NMM as model dienophile (Table 1).

Table 1
Optimization of the DA reaction of 3-benzoylvinylchromone **3a** with NMM under MW irradiation.



Entry	NMM (equiv)	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]		Recovery of **3a** (%)
					4a	**5a**	
1	2	DMF	160	40	27	15	Traces
2	5	DMF	160	40	27	18	14
3	5	DMF	160	60	35	4	Traces
4	5	DMF	200	60	52	8	Traces
5	5	DMF	200	20	49	9	Traces
6[b]	5	DMF	200	20	42	12	11
7[b]	5	DMF	200	40	44	6	Traces
8	5	TCB[c]	200	20	35	19	Traces
9	5	TCB[c]	220	20	39	12	Traces

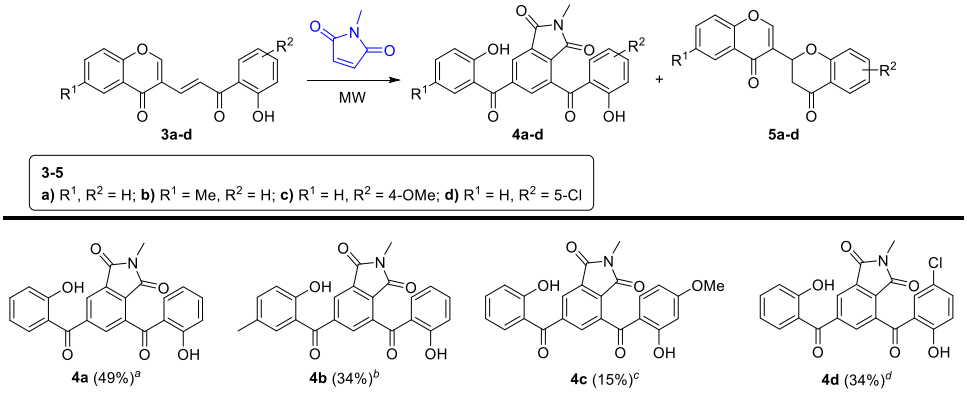
[a] Isolated yields.
[b] Reactions performed in the presence of 10 mol% of $Sc(OTf)_3$.
[c] TCB = 1,2,4-Trichlorobenzene.



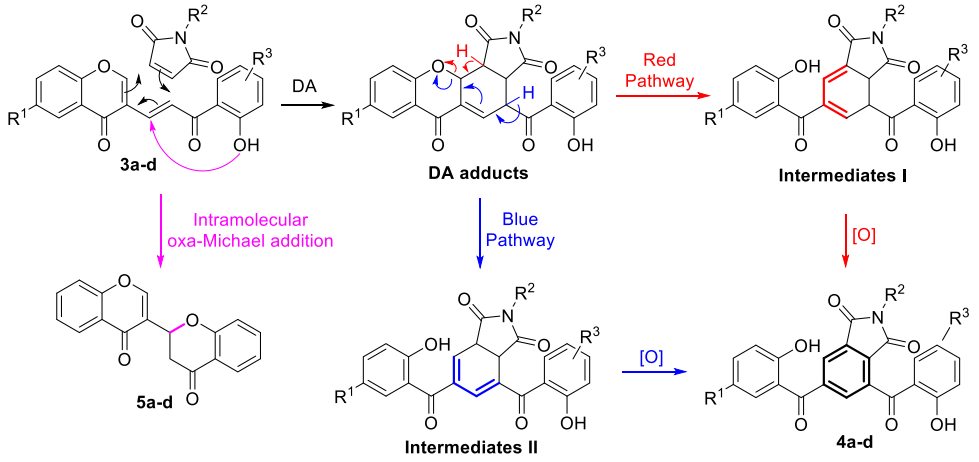
Scheme 2. Synthesis of the starting 3-benzoylvinylchromones **3a-d**.

The initial experiments involved the DA reaction of chromone **3a** with 2 or 5 equiv of NMM in dimethylformamide (DMF) at 160 °C for 40 min under MW irradiation, affording the isoindoline-1,3-dione **4a** as main product (27% yield), together with the by-product **5a** (15-18% yield) and recovering 9-14% of the starting chromone **3a** (Table 1, entries 1 and 2). In order to improve the isolated yield of compound **4a** by hindering the formation of by-product **5a** and promoting the full consumption of the starting chromone **3a**, other experiments were carried out. There was a slight improvement in compound **4a** yield (35% yield) when the reaction time was increased (Table 1, entry 3). However, it was the rise of the reaction temperature to 200 °C (Table 1, entries 4 and 5) that led to the major improvement in compound **4a** yield (49-52% yield). On the other hand, by changing the solvent to 1,2,4-trichlorobenzene (TCB) revealed to be unfavourable since a decrease in compound **4a** yield (35-39% yield) was observed (Table 1, entries 8 and 9). Further employment of $Sc(OTf)_3$ as Lewis acid (LA) catalyst was also attempted (Table 1, entries 6 and 7). Under the classical theory of the normal and inverse electron demand in DA reactions, in this particular case, the use of LA catalyst does not make sense since we are in the presence of electron-poor diene and dienophile. However, recent investigations on LA-catalysed DA reactions demonstrated that LAs accelerate DA reactions by a diminished Pauli repulsion between the π-electron systems of the diene and dienophile [29,30]. It turns out though that the presence of $Sc(OTf)_3$ had no significant effect in the isolated yield of compound **4a** (42-44% yield) (Table 1, entries 6 and 7). Finally, the best results were accomplished in the presence of 5 equiv of NMM, in DMF, at 200 °C during 20 min under MW irradiation (Table 1, entry 5). The desired compound **4a** was obtained in 49% yield together with by-product **5a** in 9% yield, recovering only 8% of the starting chromone **3a**.

Next, the reaction scope was expanded to additional chromones **3b-d**, applying the optimized DA reaction conditions for the model substrate **3a**, and using NMM as dienophile (Scheme 3). The presence of an electron-donating substituent (methoxy group) had a major impact in the reactivity of chromone **3c** (Scheme 3), since the corresponding isoindoline-1,3-diones **4c** was obtained in poor



Scheme 3. DA reaction scope of chromones **3a-d** with NMM. Reaction conditions: 5 equiv of NMM in DMF, at 200 °C for 20 min under MW irradiation. Isolated yields between brackets. [a] **5a** (9%); [b] **5b** (15%), 10% of **3b** recovered from crude reaction; [c] **5c** (10%), 40% of **3c** recovered from crude reaction; [d] **5d** (30%).

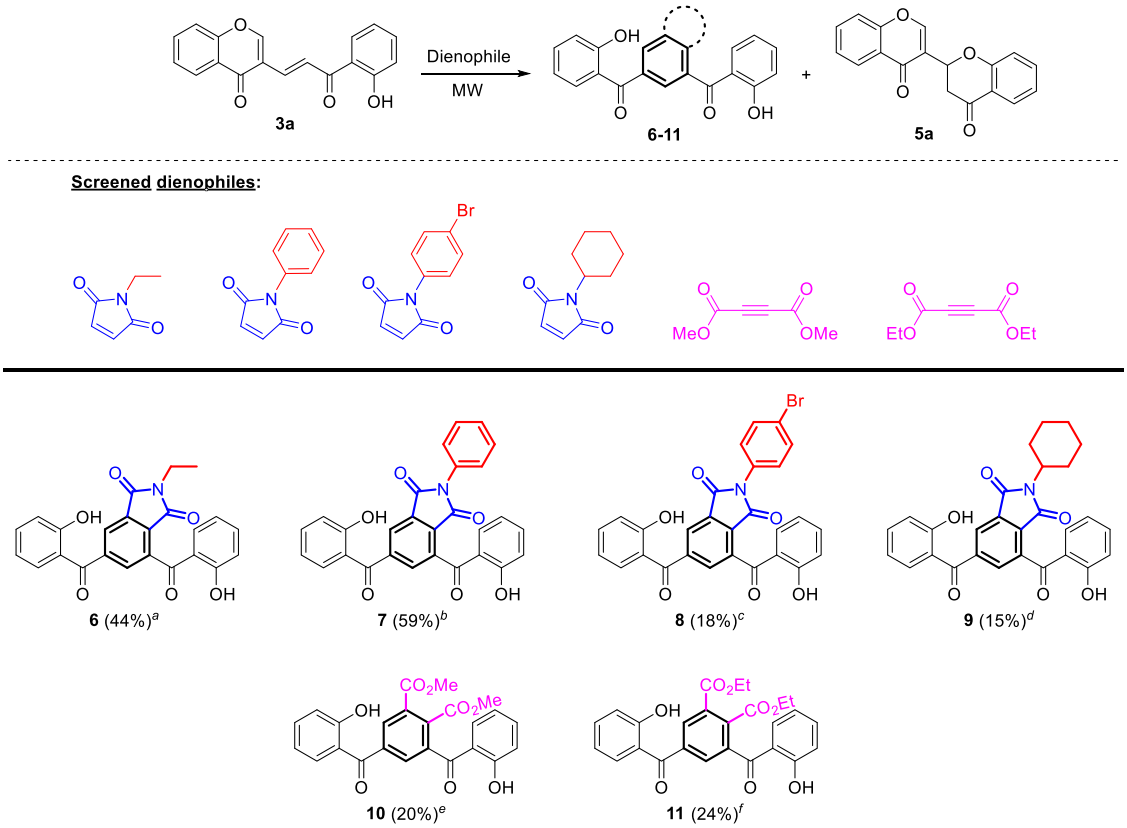


Scheme 4. Plausible mechanisms for the formation of isoindoline-1,3-diones **4a-d** and Michael adducts **5a-d**.

yield (15%), much lower than the other derivatives (Scheme 3). On the other hand, the other isoindoline-1,3-diones **4a,b,d** were synthesized in moderate yields (34-49%), indicating that the DA reaction of chromones **3a,b,d** with poorly electron-donating groups are more suitable substrates (Scheme 3).

It is worth nothing that isoindoline-1,3-diones **4a-d** were obtained in moderate yields, possibly as consequence of the multistep sequence involved in their formation (Scheme 4, blue and red pathways), as well as the intramolecular oxa-Michael addition competing reaction to give the by-products **5a-d** (9-30%) (Scheme 4, pink pathway) [28]. A plausible mechanism for the formation of 2-methylindoline-1,3-diones **4a-d** would involve: (i) the DA reaction of NMM with chromones **3a-d** leading to DA adducts; followed by (ii) chromanone ring opening by at least two possible pathways which lead to intermediates **I** and **II** and (iii) *in situ* oxidation to give the final compounds **4a-d**. In addition, the starting chromones **3a-d** represent electron-deficient dienes against electron-deficient dienophiles with consequent unfavourable conditions for normal- and inverse-demand DA reactions. This was also supported by the recovery of appreciable amounts of the starting chromones (7-40%).

With the diene scope of the reaction already established, the dienophile scope was also screened as illustrated Scheme 5. Dienophiles such as *N*-ethyl, *N*-phenyl, *N*-(4-bromophenyl) and *N*-cyclohexylmaleimides were employed as well as two acyclic dienophiles (dimethyl and diethyl acetylene-dicarboxylates).



Scheme 5. Dienophile scope for chromone **3a**. Reaction conditions: 5 equiv of dienophile in DMF, at 200 °C for 20 min under MW irradiation. Isolated yields between brackets. [a] **5a** (15%); [b] **5a** (21%); [c] **5a** (37%), 42% of **3a** recovered; [d] **5a** (20%), 62% of **3a** recovered; [e] **5a** (28%), 26% of **3a** recovered; [f] **5a** (31%), 34% of **3a** recovered.

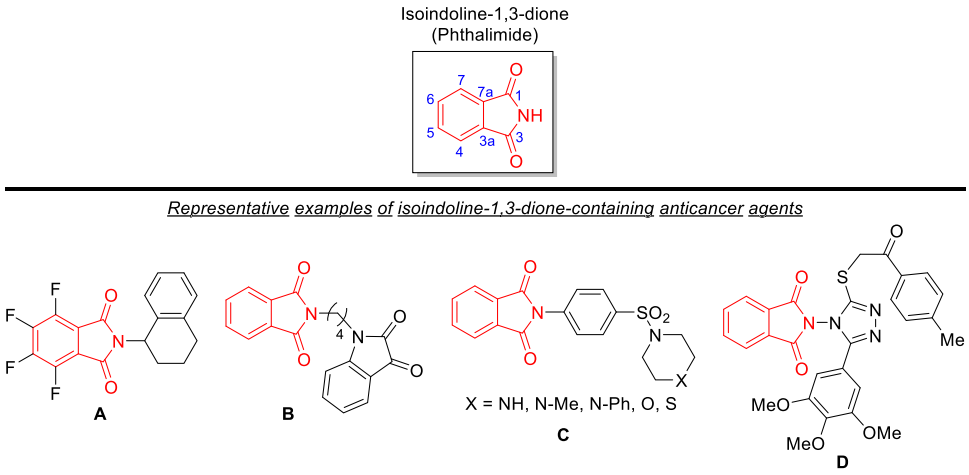


Fig. 1. Isoindoline-1,3-dione structure and representative examples of anticancer agents **A-D**.

N-Phenylmaleimide emerged as the most reactive dienophile towards the diene **3a**, giving the corresponding 2-phenylisoindoline-1,3-dione **7** in 59% yield (Scheme 5). *N*-Ethylmaleimide presented lower reactivity than its *N*-phenyl analogue, with consequent decrease in the isolated yield of 2-ethylisoindoline-1,3-dione **6** (44%) (Scheme 5). The remaining compounds **8-11** were obtained in low yields (15-24%), indicating the very poor reactivity of their corresponding dienophiles (Scheme 5). Once again, the competition of the intramolecular oxa-Michael addition was observed, affording the respective Michael adduct **5a** in appreciable amounts (15-37%) (Scheme 5).

3.2. Structural characterization of 2-methylisoindoline-1,3-diones 4a-d

The structure of the 2-methylisoindoline-1,3-diones **4a-d** was established by detailed spectral studies including ^{1}H and ^{13}C NMR, and 2D NMR, together with single-crystal X-ray diffraction.

Comparing the ^{1}H NMR spectra of compounds **4a-d** with those of their precursors **3a-d**, the occurrence of the proposed reaction cascade with NMM can be easily confirmed by: (i) the absence of two doublets ($J_{\alpha\text{-}\beta} \approx 16$ Hz) of both vinylic protons H-α and H-β as well as the absence of the singlet corresponding to H-2; (ii) the presence of two singlets at δ 7.93-7.95 and 8.23-8.29 ppm, corresponding to H-5 and H-7, respectively, belonging to isoindoline-1,3-dione aromatic moiety (see SI for NMR spectra). The chromanone ring opening was confirmed by the presence of an additional singlet at δ 11.62-11.70 ppm, corresponding to 2''-O*H* (see SI for NMR spectra). These features were also found in compounds **6-11**, indicating that all of them share the same mechanistic path with compounds **4a-d** (see SI for NMR spectra).

Compound **4a** crystallizes in the centrosymmetric space group *P*2/c, with the asymmetric unit being composed of a whole molecular unit as depicted in Fig. 2. Although the molecule contains

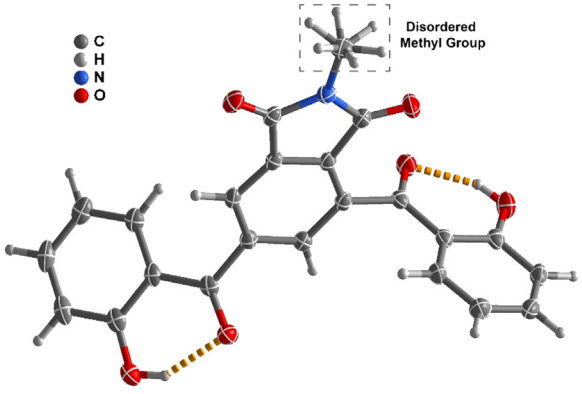


Fig. 2. Schematic representation of the molecular unit present in compound **4a**. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as small spheres with arbitrary radii. Intramolecular hydrogen bonding interactions are depicted in dashed orange lines.

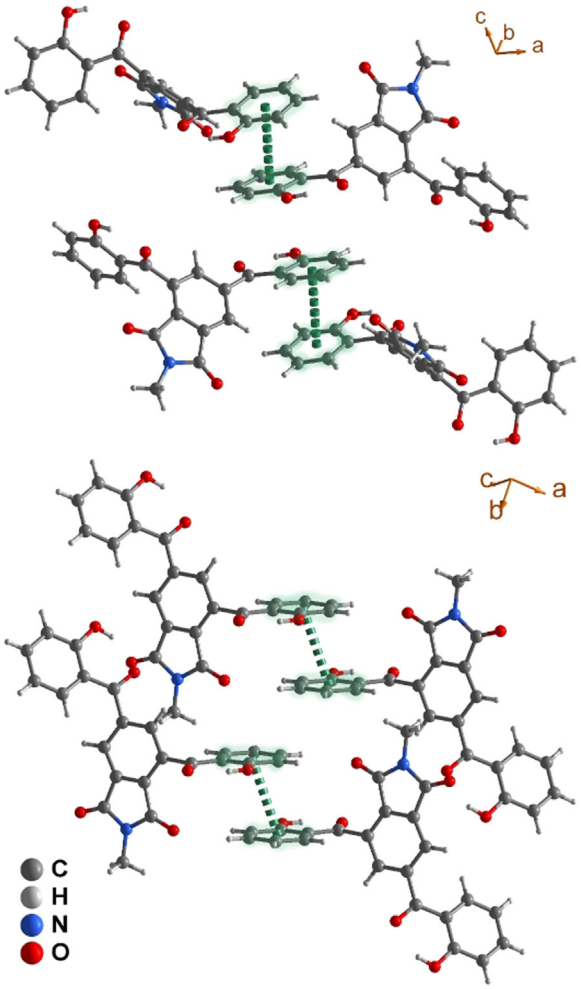


Fig. 3. Schematic representation of the π-π interactions between phenol rings of neighbouring molecular units in the crystal structure of compound **4a**.

several possible donor and acceptor atoms to establish hydrogen bonding interactions, the crystal packing is mainly mediated by the need to fill the available space helped by several weak C–H···O intermolecular interactions (from one oxygen present in the 2-methylisoindoline-1,3-dione, [$d_{C\cdots O}$ = 3.2309(17) Å with <(CHO) interaction angle of 140° – *not shown*]). Several intermolecular interactions are present between the phenolic aromatic rings of neighbouring molecules by way of π-π interactions as shown in Fig. 3: intercentroid $d_{\pi\cdots\pi}$ distances in the 3.5394(8)-3.7251(8) Å) range. One notes the existence of two intramolecular hydrogen bonding interactions between the phenol rings and the neighbouring oxygen atoms (Fig. 2, represented as dashed orange lines with $d_{O\cdots O}$ distances in the 2.5794(14)-2.5868(14) Å range, and with <(CHO) interaction angles between 145° and 146°).

4. Conclusions

To sum up, a new synthetic methodology to prepare 4,6-disubstituted isoindoline-1,3-diones was developed by MW-assisted DA reactions of chromones bearing an α,β-unsaturated carbonyl system as dienes and different maleimides as dienophiles. The obtained yields ranged from 15 to 59%. Among tested dienes, the one containing a highly electron-donating substituent (methoxy group) showed lower reactivity in DA reaction with NMM (15% yield). In addition, among dienophiles, *N*-phenylmaleimide was the most reactive towards simple 3-substituted chromone (59% yield). It is noteworthy that the reaction cascade, which follows a DA reaction, chromanone ring opening and *in situ* oxidation, do not involve any oxidizing agent. Finally, this procedure allows the high functionalization of the interesting scaffold of isoindole-1,3-dione, which might be a crucial point to modulate its biological properties.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Fatiha Nouali: Investigation. **Joana L.C. Sousa:** Conceptualization, Writing – review & editing, Supervision. **Hélio M.T. Albuquerque:** Writing – review & editing. **Ricardo F. Mendes:** Investigation, Writing – original draft. **Filipe A. Almeida Paz:** Investigation, Writing – original draft. **Liza Saher:** Writing – original draft. **Zahira Kibou:** Supervision. **Nouredine Choukchou-Braham:** Supervision. **Oualid Talhi:** Conceptualization, Supervision. **Artur M.S. Silva:** Conceptualization, Supervision, Project administration.

Data availability

Data will be made available on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2022.134608.

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