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Synthesis of Cyclopentadiene-Fused Chromanones via One-Pot Multicomponent Reactions

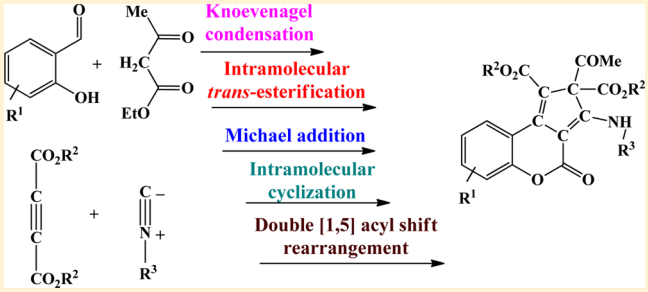
Mehdi Ghandi,[†,*] Ali-Tabatabaei Ghomi,[†] and Maciej Kubicki[‡]

[†]School of Chemistry, College of Science, University of Tehran, P.O. Box 14155, Tehran 6455, Iran

[‡]Faculty of Chemistry, Adam Mickiewicz University in Poznan, Umultowska 89b, 61-614 Poznan, Poland

Supporting Information

ABSTRACT: We have developed one-pot method for the synthesis of functionalized novel cyclopentadiene-fused chromanone scaffolds. A variety of 4-oxo-2,4-dihydrocyclopenta[*c*]chromene-1,2-dicarboxylates were obtained in moderate to good yields via condensation of 2-hydroxybenzaldehydes and ethyl acetoacetate with 1:1 acetylenecarboxylate−isocyanides in toluene. These reactions presumably proceed via reaction of the in situ generated 3-acetyl-2*H*-chromen-2-ones with acetylenecarboxylate−isocyanide zwitterionic intermediates through Michael addition/intramolecular cyclization and double [1,5] acyl shift rearrangement cascade.



INTRODUCTION

The so-called multicomponent reactions (MCRs) are one-pot processes in which at least three or more different simple substrates react for the preparation of target materials.[1] These reactions, which have gained much attention during the past years, are frequently occurring not through a single-step procedure but rather by several sequential steps or multicomponent cascade or domino reactions.[2] Simplicity, greater efficiency, and atom economy with generation of molecular complexity and diversity in the one-pot transformation are some of the advantages of these reactions. As an important subclass of MCRs, the isocyanide-based multicomponent reactions (IMCRs) are processes in which an isocyanide is used as one of the starting materials in order to obtain new compounds.[3] The pioneering work of Ugi describes the most popular IMCR in which a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in a one-pot manner to afford an *N*-substituted acyl aminoamide containing four independently varying groups.[4]

The reaction of isocyanides and acetylene compounds, first described by Winterfeld in 1969, is perhaps the founding basis for a large class of new, accessible scaffolds.[5] This reaction initially affords a zwitterionic adduct, which might undergo cycloaddition to activated alkenes, leading to a variety of novel highly substituted cyclopentadienoid systems.[6]

The abundance of naturally occurring chromene and chromane derivatives, and their interesting physiological properties have gained a vital place in the field of heterocyclic chemistry.[7] The chromanones are heterocycles with medicinal properties.[8] Chromone and coumarin derivatives have been found to exhibit a broad range of biological activities such as antiviral,[9] antimicrobial,[10] and antitumor ones.[11] The 3,4-dihydrocoumarin system is widely distributed in nature, and some derivatives have been shown to exhibit pharmacological activity.[12] On the other hand, the hebertane sesquiterpene hebertenolide, which contains a cyclopentane-fused chromanone, is a biologically active compound.[13]

In continuation of our investigation in searching for MCRs,[14] we decided to explore the idea that trapping of acetylenecarboxylate−isocyanide zwitterionic intermediates with 3-acetyl-2*H*-chromen-2-ones might be hopeful in gaining access to new types of chromanones, annulated-cyclopentadiene moieties, via a three-component reaction. In addition, it seemed intriguing to involve a domino process in this IMCR by increasing the number of reactants if we could carry out the in situ generation of 3-acetyl-2*H*-chromen-2-ones in the same pot. Herein, we report the synthesis of novel 4-oxo-2,4-dihydrocyclopenta[*c*]chromene-1,2-dicarboxylates via a one-pot, four-component reaction of a variety of 2-hydroxybenzaldehydes with ethyl acetoacetate, acetylenedicarboxylates, and cyclohexyl or *tert*-butyl isocyanides in toluene.

RESULTS AND DISCUSSION

3-Acetyl-2*H*-chromen-2-one (**1a**) served for our early exploration. Indeed, **2a** was isolated as the sole reaction product upon treatment of **1a** with an equimolar amount of dimethyl acetylenedicaboxylate (DMAD) and *tert*-butyl isocyanide within 2 h, in refluxing toluene (Scheme 1).

Our later studies revealed that **2a** could be synthesized in a one-pot reaction if **1a** prepared in situ from piperidine-catalyzed condensation of salicylaldehyde (**3a**) with ethyl

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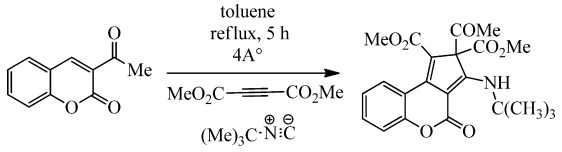
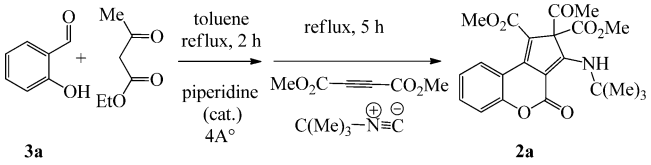
Scheme 1. Formation of 2a from Reaction of 1a with DMAD and *tert*-Butyl Isocyanide



1a **2a**

acetoacetate at reflux within 2 h was treated with equimolar amounts of DMAD and *tert*-butyl isocyanide within 3 h under reflux conditions (Scheme 2). Therefore, the implication of 3-acetyl-2*H*-chromen-2-one (**1a**) in the initial reaction is confirmed.

Scheme 2. One-Pot Synthesis of 2a

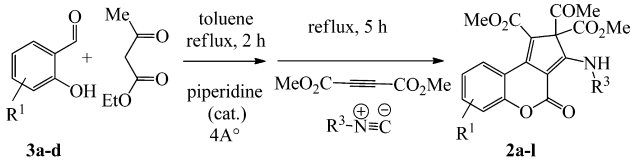


3a **2a**

(73%)

Encouraged by this result, this new method was then applied to a range of 2-hydroxybenzaldehydes **3a–d**, *tert*-butyl, cyclohexyl, or 1,1,3,3-tetramethylbutyl isocyanides and DMAD (Table 1) or diethyl acetylenedicarboxylate (DEAD)

Table 1. Products 2a–l Obtained via One-Pot Reaction of 3a–d with DMAD and Isocyanides



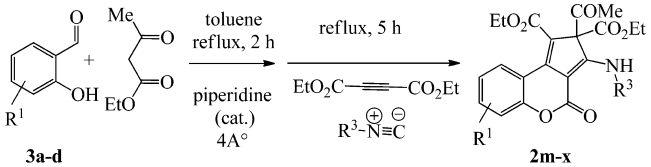
3a-d **2a-l**

(52 to 75%)

entry	R^1	R^3	product	yield (%)
1	H	*tert*-butyl	**2a**	73
2	H	cyclohexyl	**2b**	75
3	H	tetramethylbutyl	**2c**	65
4	5-Br	*tert*-butyl	**2d**	74
5	5-Br	cyclohexyl	**2e**	75
6	5-Br	tetramethylbutyl	**2f**	64
7	5-NO_2	*tert*-butyl	**2g**	58
8	5-NO_2	cyclohexyl	**2h**	54
9	5-NO_2	tetramethylbutyl	**2i**	52
10	3-OMe	*tert*-butyl	**2j**	59
11	3-OMe	cyclohexyl	**2k**	63
12	3-OMe	tetramethylbutyl	**2l**	53

(Table 2) . The structures of **2a–p** were deduced by elemental analysis, MS, IR, and ^{1}H and ^{13}C NMR spectroscopy. For example, part of the ^{1}H NMR spectrum of dimethyl 2-acetyl-8-bromo-3-(cyclohexylamino)-4-oxo-2,4-dihydrocyclopenta[*c*]-chromene-1,2-dicarboxylate (**2e**) exhibited four singlets at δ 2.75 (3H), 3.74 (3H), 3.77 (3H), and 9.61 (1H) due to MeCO, MeOCO, MeOCO, and NH, respectively. The ^{1}H-decoupled ^{13}C NMR revealed three characteristic signals at δ 195.7, 167.1, and 165.0 due to three carbonyl groups. Unambiguous evidence

Table 2. Products 2m–x Obtained via One-Pot Reaction of 3a–d with DEAD and Isocyanides



3a-d **2m-x**

(50 to 77%)

entry	R^1	R^3	product	yield (%)
1	H	*tert*-butyl	**2m**	72
2	H	cyclohexyl	**2n**	73
3	H	tetramethylbutyl	**2o**	50
4	5-Br	*tert*-butyl	**2p**	77
5	5-Br	cyclohexyl	**2q**	72
6	5-Br	tetramethylbutyl	**2r**	62
7	5-NO_2	*tert*-butyl	**2s**	55
8	5-NO_2	cyclohexyl	**2t**	56
9	5-NO_2	tetramethylbutyl	**2u**	50
10	3-OMe	*tert*-butyl	**2v**	55
11	3-OMe	cyclohexyl	**2w**	57
12	3-OMe	tetramethylbutyl	**2x**	54

for the proposed structure of **2q** was finally obtained by single-crystal X-ray-diffraction analysis (Figure 1).

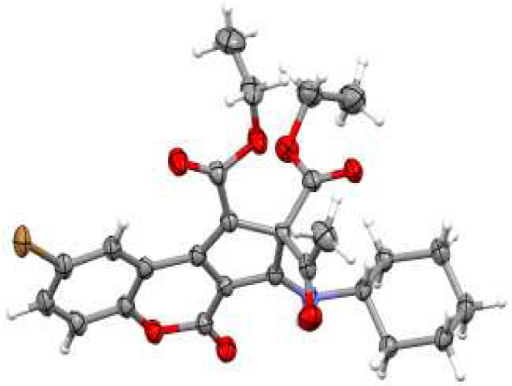


Figure 1. X-ray crystal structure of compound **2q**.[16]

Although the precise mechanism is not known, a mechanistic postulate as shown in Scheme 3 may be invoked to rationalize the formation of **2a**. It is conceivable that the zwitterionic intermediate **I**, formed by the 1:1 interaction between the isocyanide and acetylenedicarboxylate,[15] attacks preferentially the C-4 of 3-acetyl-2*H*-chromen-2-one (**1a**) leading to 1,7- or 1,5-dipolar intermediates **II** and **III**. The subsequently generated **IV** upon ring closure is transformed into **V** via an allowed [1,5] H shift. It is finally transformed into **2a**, presumably through two consecutive allowed [1,5] acyl shifts. Generation of an extra conjugation between cyclopentadiene ring and six-membered C=O group seems to be the driving force for these rearrangements.

As indicated in Tables 1 and 2, whereas unsubstituted aldehydes (entries 1 to 3) or substituted with a modest electron-withdrawing group (EWG) (entries 4–6) afford products **2a–f** and **2m–r** in higher yields, those bearing a strong EWG (entries 7–9) or a strong electron-donating group (EDG) (entries 10–12) produce the corresponding products **2g–l** and **2s–x** in lower yields. This behavior is the result of a

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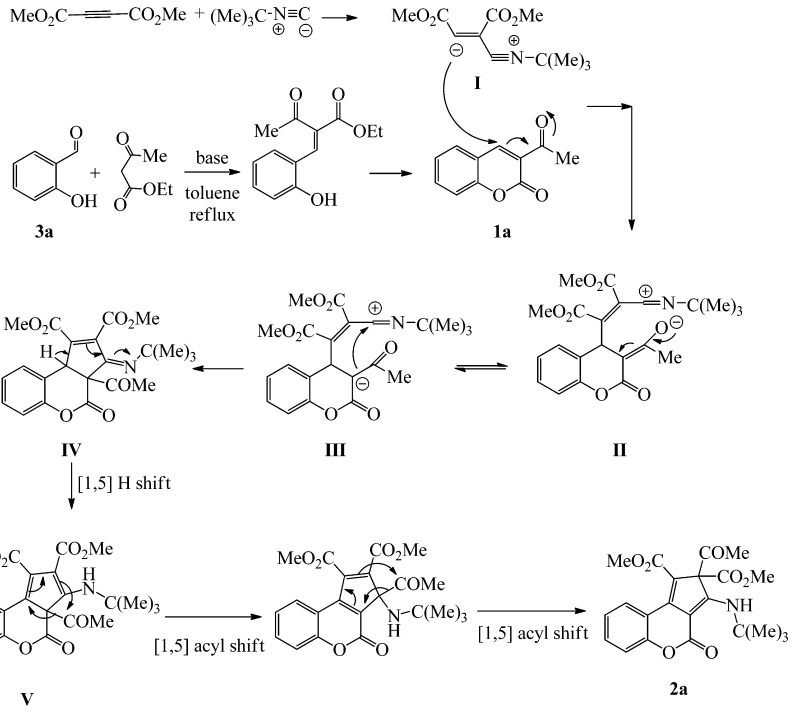
Scheme 3. Mechanistic Rationalization for the Formation of Compound 2a



multistep reaction in which one step may be rate determining for EWGs, but a different step may become rate limiting for ERG substituents.[17] Although substituted aldehyde with EWG facilitates the formation rate of intermediates **II** and **III** via the addition of zwitterionic intermediate **I** to the double bond of **1a**, the subsequent cyclization step to iminocyclopentene **IV** (Schemes 3) becomes rate limiting for this substitutent. In contrast, the first step is expected to be rate limiting for aldehyde bearing EDG. Therefore, obtaining lower yields of **2g–l** and **2s–x** in comparison to other products indicated in Tables 1 and 2 is anticipated. On the other hand, the products **2m–x** (Table 2) have generally been formed in lower yields in comparison to those of **2a–l** (Table 2), perhaps due to larger steric effect of DEAD.

Overall, novel 4-oxo-2,4-dihydrocyclopenta[*c*]chromene-1,2-dicarboxylates were obtained as the major products in moderate to good yields. More importantly, doing the experiment in one-pot reaction with four different simple substrates is of fundamental importance due to the simplicity, greater efficiency and atom economy with generation of molecular complexity and diversity.

In conclusion, a number of 2-hydroxybenzaldehydes, ethyl acetoacetate, acetylenecarboxylates, and isocyanides underwent one-pot multicomponent reactions in toluene, affording the desired products. These reactions were designed to obtain a variety of biologically interesting cyclopentadiene-fused chromanones. These new structures broaden the scaffolds that are accessible through Knoevenagel condensation–trans esterification–Michael addition–intramolecular cyclization–acyl shift rearrangement cascade and many of them may represent interesting pharmacophores.

EXPERIMENTAL SECTION

General Information. ^{1}HNMR, ^{13}C NMR, MS, and elemental analysis were measured with conventional spectrometers. All solvents were purified and dried by following standard procedures unless otherwise stated.

Synthesis of Dimethyl 3-(*tert*-Butylamino)-2-acetyl-5-oxacyclopenta[*a*]naphthalen-4(2*H*)-one-1,2-dicarboxylate Derivatives 2a–x. *General Procedure.* To a stirring solution of piperidine (0.17 g, 20 mol %) in toluene (20 mL) containing molecular sieves 4 Å was added 2-hydroxybenzaldehyde derivatives (**3a–d**) (1.0 mmol) and ethyl acetoacetate (1.0 mmol), and the mixture was heated at reflux for 2 h. Acetylenedicarboxylate (1.0 mmol) and isocyanide (1.0 mmol) were then added, and the mixture was heated at reflux for another 5 h. After completion as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, eluent: 1:3 *n*-hexane/EtOAc) to afford the products **2a–x**.

*Dimethyl 3-(tert-butylamino)-2-acetyl-5-oxacyclopenta[a]-naphthalen-4(2H)-one-1,2-dicarboxylate (**2a**):* yellow solid (301 mg, 73%); mp 140–142 °C; IR (KBr) ν_{max} 3402, 1711, 1688, 1647, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.66 (9H, s), 2.74 (3H, s), 3.74 (3H, s), 3.77(3H, s), 7.35–7.43 (2H, m), 7.66–7.89 (2H, m), 9.53 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.9, 30.6, 51.3, 52.3, 52.4, 96.2, 107.5, 121.5, 121.8, 125.4, 126.1, 128.7, 129.1, 146.0, 150.1, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 413 (17, M$^+$), 385 (25), 371 (60), 315 (100), 56 (55). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.79; H, 5.58; N, 3.33.

*Dimethyl 2-acetyl-3-(cyclohexylamino)-5-oxacyclopenta[a]-naphthalen-4(2H)-one-1,2-dicarboxylate (**2b**):* orange solid (329 mg, 75%); mp 150–152 °C; IR (KBr) ν_{max} 3408, 1711, 1673, 1638, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43–2.27 (10H, m), 2.75 (3H, s), 3.49–3.59 (1H, m), 3.74 (3H, s), 3.77 (3H, s), 7.35–7.43 (2H, m), 7.66–7.89 (2H, m), 9.63 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 23.7, 25.2, 26.3, 26.4, 30.0, 30.1, 51.4, 52.3, 52.4, 96.3, 107.5, 121.5, 121.8, 125.4, 126.1, 128.7, 129.1, 146.0, 150.1, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 440 (15, M$^+$ + 1), 411 (35), 397 (60), 315 (100), 56 (50). Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.48; H, 5.78; N, 3.13.

*Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2c**):* orange solid (304 mg, 65%); mp 151–152 °C; IR (KBr) ν_{max} 3448, 1711, 1688, 1647, 1610 cm^{-1};δ_H (400 MHz, $CDCl_3$) 1.06 (9H, S), 1.65 (6H, s), 1.78 (2H, s), 2.64 (3H), 3.74 (3H, s), 3.77 (3H, s), 7.35–7.43 (2H, m), 7.66–7.89 (2H, m), 9.53 (1H, s) ppm; δ_C (100

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MHz, $CDCl_3$) 25.9, 27.9, 31.0, 31.6, 31.7, 41.4, 52.3, 52.4, 53.4, 96.7, 107.5, 121.5, 121.8, 125.4, 126.1, 128.7, 129.1, 146.0, 150.1, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 469 (12, M^+),441 (32), 427 (55), 315 (100), 56 (55). Anal.Calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.65; N, 2.98. Found: C, 66.48; H, 6.58; N, 3.03.

*Dimethyl 3-(tert-butylamino)-2-acetyl-8-bromo-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2d**):* orange solid (364 mg, 74%); mp 148−150 °C; IR (KBr) ν_{max} 3412, 1712, 1701, 1688, 1623 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.66 (9H, s), 2.74 (3H, s), 3.74(3H, s), 3.77 (3H, s), 7.31 (1H, d, *J* 8.4 Hz), 7.70 (1H, dd, *J* = 8.4, 2.4 Hz), 8.01 (1H, d, *J* = 2.4 Hz), 9.60 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.9, 30.6, 53.4, 55.3, 59.1, 96.2, 107.5, 118.1, 118.7, 121.1(C_1), 128.4, 129.1, 132.2, 146.0, 150.1, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 494 (M^+ + 2 [^{81}Br], 8), 492(M^+ [^{79}Br], 8),463 (15), 394 (33), 363 (66), 57 (100). Anal. Calcd for $C_{22}H_{22}BrNO_7$: C, 53.67; H, 4.50; N, 2.85. Found: C, 53.58; H, 4.48; N, 2.83.

*Dimethyl 2-acetyl-8-bromo-3-(cyclohexylamino)-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2e**):* orange solid (388 mg, 75%); mp 153−155 °C; IR (KBr) ν_{max} 3428, 1722, 1711, 1688, 1638 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43−2.27 (10H, m), 2.75 (3H, s), 3.55 (1H, m), 3.74 (3H, s), 3.77 (3H, s),7.31 (1H, d, *J* 8.4 Hz), 7.70 (1H, dd, *J* = 8.4, 2.4 Hz), 8.01 (1H, d, *J* = 2.4 Hz),9.61 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 23.8, 25.2, 26.3, 26.4, 30.0, 30.1, 53.2, 55.3, 57.2, 96.3, 107.5, 118.1, 118.7, 121.1, 128.4, 129.1, 132.2, 146.0, 150.1, 155.3, 160.6, 165.0, 167.0, 195.6 ppm; *m*/*z* (EI, 70 eV) 519 (M^+ + 2 [^{81}Br], 8), 517(M^+ [^{79}Br], 8),489 (19), 475 (23), 392(65),57 (100). Anal. Calcd for $C_{24}H_{24}BrNO_7$: C, 55.61; H, 4.67; N, 2.70. Found: C, 55.58; H, 4.68; N, 2.74.

*Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-8-bromo-5-oxacyclopenta[a]naphthalene-4(2H)-one-1,2-dicarboxylate (**2f**):* orange solid (350 mg, 64%); mp 160−162 °C; IR (KBr) ν_{max} 3458, 1732, 1721, 1688, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s), 1.65 (6H, s), 1.78 (2H, s), 2.64 (3H, s), 3.84 (3H, s), 3.90(3H, s),7.32 (1H, d, *J* 8.4 Hz), 7.70 (1H, dd, *J* = 8.4, 2.4 Hz), 8.01 (1H, d, *J* = 2.4 Hz), 9.60 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.8, 27.9, 31.0, 31.6, 31.7, 42.4, 51.2, 53.5, 55.4, 96.4, 107.5, 118.1, 118.7, 121.1, 128.4, 129.1, 132.2, 146.1, 150.0, 155.3, 160.6, 165.0, 167.2, 195.5 ppm; *m*/*z* (EI, 70 eV) 549 (M^+ + 2 [^{81}Br], 11), 547 (M^+ [^{79}Br], 11), 519 (22), 505 (53), 392(65), 57 (100). Anal. Calcd for $C_{26}H_{30}BrNO_7$: C, 56.94; H, 5.51; N, 2.55. Found: C, 56.97; H, 5.48; N, 2.54.

*Dimethyl 3-(tert-butylamino)-2-acetyl-8-nitro-5-oxa-cyclopenta-[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2g**):* yellow solid (265 mg, 58%); mp 158−160 °C; IR (KBr) ν_{max} 3402, 1706, 1688,1622, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.66 (9H, s), 2.64 (3H, s), 4.04 (3H, s), 4.07 (3H, s),7.55 (1H, d, *J* 9.6 Hz), 8.52−8.61 (2H, m), 10.22 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.9, 30.6, 53.4, 55.4, 59.1, 96.2, 107.5, 118.7, 121.1, 121.9, 125.4, 128.1, 144.0, 146.0, 153.1, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 458(17, M^+), 430 (25), 416 (55), 360 (100), 56 (100). Anal. Calcd for $C_{22}H_{22}N_2O_9$: C, 57.64; H, 4.84; N, 6.11. Found: C, 57.67; H, 4.82; N, 6.12.

*Dimethyl 2-acetyl-3-(cyclohexylamino)-8-nitro-5-oxacyclopenta-[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**3h**):* yellow solid (261 mg, 54%); mp 165−167 °C; IR (KBr) ν_{max} 3418, 1711, 1701, 1638, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43−2.27 (10H, m), 2.75 (3H, s), 3.53 (1H, m), 4.04 (3H, s),4.07 (3H, s), 7.55(1H, d, *J* 9.6 Hz), 8.52−8.61 (2H, m), 10.22 (1H, s), ppm; δ_C (100 MHz, $CDCl_3$) 23.8, 25.2, 26.3, 26.4, 30.0, 30.1, 53.2, 55.3, 57.3, 93.2, 107.5, 118.7, 121.1, 121.9, 125.4, 128.1, 144.1, 146.1, 153.1, 155.3, 160.6, 165.1, 167.2, 195.5 ppm; *m*/*z* (EI, 70 eV) 484 (15, M^+), 456 (28), 442 (55), 360 (100), 56 (59). Anal. Calcd for $C_{24}H_{24}N_2O_9$: C, 59.50; H, 4.99; N, 5.78. Found: C, 59.48; H, 4.96; N, 5.75.

*Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-8-nitro-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2i**):* yellow solid (267 mg, 52%); mp 166−168 °C; IR (KBr) ν_{max} 3428, 1721, 1706, 1647, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s), 1.65 (6H, s), 1.78 (2H, s), 2.64 (3H), 4.04 (3H, s), 4.07 (3H, s), 7.55(1H, d, *J* 9.6 Hz), 8.52−8.61 (2H, m), 10.22 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.9, 27.9, 31.0, 31.6, 31.7, 43.4, 51.2, 53.5, 55.4, 96.9.2, 107.6, 118.7, 121.1, 121.9, 125.4, 128.1, 144.1, 146.1, 153.1, 155.3, 160.6, 165.1, 167.2, 195.4 ppm; *m*/*z* (EI, 70 eV) 514 (18, M^+), 486 (45), 472 (65), 416 (100), 56 (55). Anal. Calcd for $C_{26}H_{30}N_2O_9$: C, 60.69; H, 5.88; N, 5.44; N, 5.78. Found: C, 60.65; H, 5.86; N, 5.48.

*Dimethyl 3-(tert-butylamino)-2-acetyl-6-methoxy-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2j**):* yellow solid (261 mg, 59%); mp 151 °C; IR (KBr) ν_{max} 3402, 1711, 1701, 1647, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.66 (9H, s), 2.64 (3H, s),3.74 (3H, s) 3.77 (3H, s), 4.00 (3H, s), 7.28 (1H, d, *J* 8.4 Hz), 7.71 (1H, dd, *J* = 8.4, 2.4 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 9.28 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.9, 30.6, 52.3,52.7, 55.7, 59.1, 97.5, 107.5, 113.5, 119.1, 120.1, 125.4, 128.1, 142.1, 147.6, 148.0, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 443 (14, M^+), 401 (66), 371 (100), 315 (80),56 (55). Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; N, 3.16. Found: C, 62.27; H, 5.65; N, 3.13.

*Dimethyl 2-acetyl-3-(cyclohexylamino)-6-methoxy-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2k**):* yellow solid (295 mg, 63%); mp 149 °C; IR (KBr) ν_{max} 3418, 1711, 1706, 1647, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43−2.27 (10H, m), 2.75 (3H, s), 3.53 (1H, m) 3.74(3H, s) 3.77 (3H, s), 4.02(3H, s), 7.27 (1H, d, *J* 8.4 Hz), 7.71 (1H, dd, *J* = 8.4, 2.4 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 9.26 (1H, s) ppm, δ_C (100 MHz, $CDCl_3$) 23.7, 25.2, 26.3, 26.4, 30.0, 30.1, 52.3, 52.7, 55.7, 57.7, 97.2, 107.4, 113.5, 119.1, 120.1, 125.5, 128.1, 142.1, 147.0, 148.0, 155.4, 160.6, 165.1, 167.1, 195.1 ppm; *m*/*z* (EI, 70 eV) 469 (15, M^+), 427 (50), 397 (100), 315 (90), 55 (55). Anal. Calcd for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98%. Found: C, 63.89; H, 5.75; N, 3.02.

*Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-6-methoxy-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2l**):* yellow solid (295 mg, 63%); mp 147−148 °C.IR (KBr) ν_{max} 3428, 1712, 1706, 1647, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s), 1.65 (6H, s), 1.78 (2H, s), 2.64 (3H, s), 3.74(3H, s), 3.74 (3H, s), 4.03(3H, s), 7.27 (1H, d, *J* 8.4 Hz), 7.71 (1H, dd, *J* = 8.4, 2.4 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 9.26 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 25.8, 27.8, 31.0, 31.6, 31.7, 45.0, 52.7, 53.5, 55.4, 54.7, 97.1, 107.4, 113.5, 119.2, 120.1, 125.5, 128.2, 142.2, 147.0, 148.0, 155.3, 160.6, 165.1, 167.2, 195.3 ppm; *m*/*z* (EI, 70 eV) 499 (15, M^+), 471 (40), 427 (35), 315 (100), 57 (95). Anal. Calcd for $C_{27}H_{33}NO_8$: C, 64.92; H, 6.66; N, 2.80. Found: C, 64.86; H, 6.68; N, 2.82.

*Diethyl 3-(tert-butylamino)-2-acetyl-5-oxacyclopenta[a]-naphthalen-4(2H)-one-1,2-dicarboxylate (**2m**):* orange solid (317 mg, 72%); mp 145−147 °C; IR (KBr) ν_{max} 3403, 1712, 1688, 1647, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.66 (9H, s), 2.74 (3H, s), 4.13−4.26 (4H, m), 7.35−7.43 (2H, m), 7.66−7.89 (2H, m), 9.60 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 30.6, 51.3, 59.2, 61.4, 95.3, 107.3, 121.1, 121.6, 125.4, 126.1, 128.7, 129.1, 146.0, 150.1, 155.3, 160.6, 165.0, 167.1, 195.3 ppm; *m*/*z* (EI, 70 eV) 441 (17, M^+), 385 (21), 371 (40), 315 (100), 56 (55). Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.27; H, 6.12; N, 3.19.

*Diethyl 2-acetyl-3-(cyclohexylamino)-5-oxacyclopenta[a]-naphthalen-4(2H)-one-1,2-dicarboxylate (**2n**):* orange solid (340 mg, 73%); mp148−150 °C; IR (KBr) ν_{max} 3418, 1713, 1688, 1648, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.43−2.27 (10H, m), 2.75 (3H, s), 3.49−3.59 (1H, m, CHN) 4.13−4.23 (4H, m), 7.35−7.43 (2H, m), 7.66−7.89 (2H, m), 9.60 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 23.7, 25.2, 26.3, 26.4, 30.0, 30.1, 51.4 (CHN, 59.2, 61.4, 95.1, 107.3, 121.1, 121.6, 125.4, 126.1, 128.7, 129.1, 146.1, 150.3, 155.1, 160.0, 165.1, 167.7, 195.1 ppm; *m*/*z* (EI, 70 eV) 467 (15, M^+), 411 (28), 397 (65), 315 (100), 56 (55). Anal. Calcd for $C_{26}H_{29}NO_7$: C, 66.80; H, 6.20; N, 3.00. Found: C, 66.72; H, 6.23; N, 3.02.

*Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2O**):* orange solid (248 mg, 50%); mp153−154 °C; IR (KBr) ν_{max} 3449, 1710, 1700, 1647, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s), 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.65 (6H, s), 1.78 (2H, s), 2.74 (3H), 7.35−7.43 (2H, m), 7.66−7.89 (2H, m), 9.59 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9,14.6, 25.9, 27.9, 31.0, 31.6, 31.7, 41.5, 53.4, 59.2, 61.4, 95.2, 107.6, 121.1, 121.6, 125.4, 126.1, 128.7, 129.1, 146.8, 150.3, 155.2, 160.0, 165.2, 167.6, 195.2 ppm; *m*/*z* (EI, 70 eV) 498 (12,

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M^+ + 1), 427 (15), 343 (50), 315 (100), 57 (57). Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09; N, 2.81. Found: C, 67.64; H, 7.02; N, 2.82.

*Diethyl 3-(tert-butylamino)-2-acetyl-8-bromo-5-oxacyclopenta-[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2P**):* orange solid (400 mg, 77%); mp 153−155 °C; IR (KBr) ν_{max} 3413, 1712, 1701, 1688, 1633 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.66 (9H, s), 2.74 (3H, s), 4.13−4.26 (4H, m), 7.32 (1H, d, *J* 8.4 Hz), 7.70 (1H, dd, *J* = 8.4, 2.4 Hz), 8.01 (1H, d, *J* = 2.4 Hz), 9.60 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 30.6, 51.3, 59.3, 61.4, 95.5, 107.4, 118.1, 118.7, 121.1, 128.5, 129.1, 132.2, 146.0, 150.0, 155.6, 160.3, 165.0, 167.1, 195.5 ppm; *m*/*z* (EI, 70 eV) 521 (M^+ + 2 [81Br], 14), 519 (M + [79Br], 8), 505 (30), 433 (100), 417 (60), 55 (90). Anal. Calcd for $C_{24}H_{26}BrNO_7$: C, 55.39; H, 5.04; N, 2.69. Found: C, 55.43; H, 5.02; N, 2.72.

*Diethyl 2-acetyl-8-bromo-3-(cyclohexylamino)-5-oxacyclopenta-[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2q**):* orange solid (393 mg, 72%); mp 152−153 °C; IR (KBr) ν_{max} 3429, 1724, 1712, 1688, 1647 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.43−2.27 (10H, m), 2.75 (3H, s), 3.49−3.56 (1H, m), 4.13−4.23 (4H, m), 7.31 (1H, d, *J* 8.4 Hz), 7.70 (1H, dd, *J* = 8.4, 2.4 Hz), 9.60 (1H, d, *J* = 2.4 Hz), 8.44 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 23.7, 25.1, 26.3, 26.4, 30.0, 30.1, 51.4, 59.2, 61.4, 95.0, 107.4, 118.1, 118.7, 121.1, 128.4, 129.1, 132.2, 146.1, 150.0, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 547 (M^+ + 2 [81Br], 13), 545 (M^+ [79Br], 13), 505 (25), 475 (63), 459 (100), 56 (55). Anal. Calcd for $C_{26}H_{28}BrNO_7$: C, 57.15; H, 5.17; N, 2.56. Found: C, 57.13; H, 5.12; N, 2.54.

*Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-8-bromo-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2r**):* orange solid (357 mg, 62%); mp 161−163 °C; IR (KBr) ν_{max} 3459, 1742, 1721, 1688, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s), 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.65 (6H, s), 1.78 (2H, s), 2.74 (3H, s), 7.32 (1H, d, *J* 8.4 Hz), 7.70 (1H, dd, *J* = 8.4, 2.4 Hz), 9.59 (1H, d, *J* = 2.4 Hz), 8.45 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 27.9, 31.0, 31.6, 31.7, 41.4, 51.2, 59.2, 61.4, 95.3, 107.4, 118.1, 118.7, 121.1, 128.4, 129.1, 132.2, 146.1, 150.0, 155.3, 160.6, 165.0, 167.1, 195.3 ppm; *m*/*z* (EI, 70 eV) 577 (M^+ + 2 [81Br], 16), 575 (M^+ [79Br], 16), 505 (57), 475 (48), 388(100), 56 (45). Anal. Calcd for $C_{28}H_{34}BrNO_7$: C, 58.34; H, 5.94; N, 2.43. Found: C, 58.36; H, 5.96; N, 2.43.

*Diethyl 3-(tert-butylamino)-2-acetyl-8-nitro-5-oxacyclopenta[a]-naphthalen-4(2H)-one-1,2-dicarboxylate (**2s**):* yellow solid (267 mg, 55%); mp 165 °C; IR (KBr) ν_{max} 3404, 1710, 1698,1632, 1603 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.66 (9H, s), 2.74 (3H, s), 4.13−4.26(4H, m), 7.55(1H, d, *J* 9.6 Hz), 8.52−8.61 (2H, m), 10.38 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 30.6, 51.1, 61.2, 63.3, 96.2, 107.5, 118.7, 121.1, 121.9, 125.4, 128.1, 144.0, 146.0, 153.1, 155.6, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 486 (19, M^+), 444 (49), 416 (55), 384 (100), 56 (50). Anal. Calcd for $C_{24}H_{26}N_2O_9$: C, 59.25; H, 5.39; N, 5.76. Found: C, 59.29; H, 5.36; N, 5.75%.

*Diethyl 2-acetyl-3-(cyclohexylamino)-8-nitro-5-oxacyclopenta-[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**3t**):* yellow solid (286 mg, 56%); mp 173−175 °C; IR (KBr) ν_{max} 3420, 1712, 1701, 1638, 1603 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.43−2.27 (10H, m), 2.75 (3H, s), 3.49−3.56 (1H, m) 4.13−4.23 (4H, m), 7.55 (1H, d, *J* = 9.6 Hz), 8.52−8.61 (2H, m) 10.39 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 23.7, 25.1, 26.3, 26.4, 30.0, 30.1, 51.4, 61.3, 63.3, 96.2, 107.5, 118.7, 121.1, 121.9, 125.4, 128.1, 144.1, 146.1, 153.1, 155.3, 160.6, 165.1, 167.1, 195.6 ppm; *m*/*z* (EI, 70 eV) 486 (12, M^+), 442 (38), 410 (57), 313 (100), 56 (49). Anal. Calcd for $C_{26}H_{28}N_2O_9$: C, 60.93; H, 5.51; N, 5.47. Found: C, 60.86; H, 5.50; N, 5.48.

*Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-8-nitro-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2u**):* yellow solid (271 mg, 50%); mp 163−165 °C; IR (KBr) ν_{max} 3429, 1722, 1710, 1647, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s), 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.65 (6H, s), 1.78 (2H, s), 2.74 (3H, s), 4.13−4.26 (4H, m), 7.55(1H, d, *J* 9.6 Hz), 8.52−8.61 (2H, m), 10.39 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 27.9, 31.0, 31.6, 31.7, 43.4, 51.2, 61.4, 63.3, 96.9, 107.6, 118.7, 121.1, 121.9, 125.4, 128.1, 144.1, 146.1, 153.1, 155.3, 160.6, 165.1, 167.1, 195.4 ppm; *m*/*z* (EI, 70 eV) 542 (11, M^+), 472 (35), 440 (65), 313 (100), 56 (55). Anal. Calcd for $C_{28}H_{34}N_2O_9$: C, 61.98; H, 6.32; N, 5.19. Found: C, 62.02; H, 6.36; N, 5.15.

*Diethyl 3-(tert-butylamino)-2-acetyl-6-methoxy-5-oxacyclo-penta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2v**):* yellow solid (259 mg, 55%); mp 153−155 °C; IR (KBr) ν_{max} 3404, 1712, 1701, 1648, 1610 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.66 (9H, s), 2.74 (3H, s), 3.93 (3H, s), 4.13−4.26 (4H, m), 7.27 (1H, d, *J* 8.4 Hz), 7.71 (1H, dd, *J* = 8.4, 2.4 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 9.28 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 30.6, 55.7, 59.1, 61.4, 63.3, 97.5, 107.5, 113.5, 119.1, 120.1, 125.4, 128.1, 142.1, 147.0, 148.0, 155.3, 160.6, 165.0, 167.0, 195.0 ppm; *m*/*z* (EI, 70 eV) 471 (20, M+), 457 (56), 355 (67), 268 (100), 56 (55). Anal. Calcd for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.75; H, 6.20; N, 3.02.

*Diethyl 2-acetyl-3-(cyclohexylamino)-6-methoxy-5-oxacyclo-penta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2w**):* yellow solid (283 mg, 57%); mp 158−160 °C; IR (KBr) ν_{max} 3420, 1712, 1706, 1657, 1610 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.43−2.27 (10H, m), 2.75 (3H, s), 3.49−3.56 (1H, m), 3.93 (3H, s), 4.13−4.26 (4H, m), 7.27 (1H, d, *J* 8.4 Hz), 7.71 (1H, dd, *J* = 8.4, 2.4 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 9.28 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 23.7, 25.1, 26.3, 26.4, 30.0, 30.1, 51.7, 55.7, 61.4, 63.3, 97.1, 107.4, 113.5, 119.1, 120.1, 125.5, 128.1, 142.1, 147.0, 148.0, 155.4, 160.6, 165.1, 167.1, 195.3 ppm; *m*/*z* (EI, 70 eV) 497 (17, M^+), 483 (50), 453 (25), 268 (100), 56 (55). Anal. Calcd for $C_{27}H_{31}NO_8$: C, 65.18; H, 6.28; N, 2.82. Found: C, 65.27; H, 6.27; N, 2.84.

*Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-2-acetyl-6-methoxy-5-oxacyclopenta[a]naphthalen-4(2H)-one-1,2-dicarboxylate (**2x**):* yellow solid (284 mg, 54%); mp 149−151 °C; IR (KBr) ν_{max} 3429, 1714, 1705, 1648, 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s), 1.17 (3H, t, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.65 (6H, s), 1.78 (2H, s), 2.74 (3H, s), 3.93 (3H, s), 4.13−4.26 (4H, m), 7.27 (1H, d, *J* 8.4 Hz), 7.71 (1H, dd, *J* = 8.4, 2.4 Hz), 8.63 (1H, d, *J* = 2.4 Hz), 9.27 (1H, s) ppm; δ_C (100 MHz, $CDCl_3$) 13.9, 14.6, 25.9, 27.9, 31.0, 31.6, 31.7, 45.0, 51.7, 55.7, 61.4, 63.3, 97.1, 107.4, 113.4, 119.2, 120.1, 125.5, 128.1, 142.2, 147.0, 148.0, 155.3, 160.2, 165.1, 167.3, 195.2 ppm; *m*/*z* (EI, 70 eV) 527 (19, M^+), 513 (34), 499 (45), 268 (100), 56 (55). Anal. Calcd for $C_{29}H_{37}NO_8$: C, 66.02; H, 7.07; N, 2.65. Found: C, 66.31; H, 7.15; N, 2.58.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of all compounds; X-ray data for compound **2q** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ghandi@khayam.ut.ac.ir.

Notes

The authors declare no competing financial interest.

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