

Divergent Pd(II) and Au(III) mediated nitroalkynol cycloisomerizations†

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A new cycloisomerization reaction comprising the simultaneous addition of nitro and alcohol groups across C≡C leading to skeletally diverse small molecules is documented.

Introduction

Domino reactions characterized by several bond formations through sequential intramolecular transformations address both molecular complexity and synthetic efficiency.¹ This demands integration of novel reactions and innovative substrate design. Herein we report a simple domino process comprising an unprecedented nitroalkynol cycloisomerization. Fig. 1 describes the general concept and the originating pyridine mediated photochemical isotogen synthesis (eq.1).² The reaction mechanism involves pyridinium betaine intermediate **B** formation followed by its spontaneous conversion to isotogen **II**. We speculated that if such a transient betaine **C** is generated by an intramolecular nucleophilic addition across the alkyne (eq.2),³ it should undergo post irradiation transformations similar to those of the isotogen synthesis leading finally either to a *N*-hydroxy-spiroindolinone derivative **IV** or a spirobenzoxazinone derivative **V**, depending upon the preference of approach of the nucleophile for either the N or the O of nitroso group (eq. 2) in a stepwise or synchronous manner⁴ (1,5- or 1,6- electrocyclizations).

Results and discussion

With this concept in mind, the nitroalkynols **1aa**^{5b,5c} and **1ba**^{5b,5c} were prepared under standard Sonogashira^{5a} conditions. The feasibility of the proposed cycloisomerization was examined by screening various Pd(II), Au(III) and Pt(II) complexes.^{6–8} The cycloisomerization of **1aa** with the majority of the Pd(II) complexes resulted in the formation of two distinguishable products (Table 1). Amongst these complexes, the reaction with Pd(CH₃CN)₂Cl₂ was found to be clean, with a complete conversion of **1aa** within 6 h at room temperature. The reaction gave the anticipated spirobenzoxazinone derivative **3aa** along with the spiroindolinone derivative **2aa**^{9a,9c} resulting from the reduction of the anticipated *N*-hydroxy indolin-3-one derivative. The breakdown of the N–O

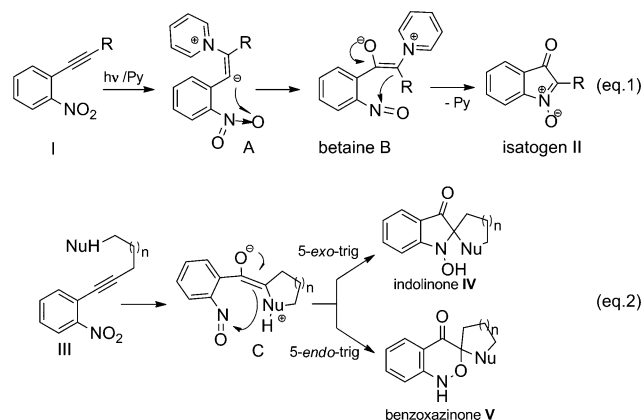


Fig. 1 Huisgen's mechanism for photochemical isotogen synthesis and the projected nitroalkynol cycloisomerizations.

bond with electrophilic Pd(II)-complexes is a rare example, but it is not unprecedented.¹⁰

The exposure of pentynol **1aa** to AuCl₃ or AuBr₃ led to the formation of a polar mixture, the composition of which could not be determined. A similar set of catalysts were employed for the cycloisomerization of the hexynol derivative **1ba** (Table 2). The

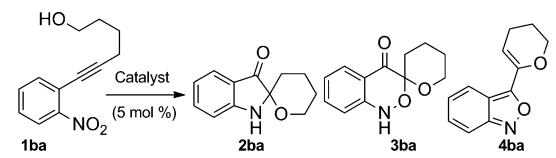
Table 1 Catalysts screened for the nitroalkynol cycloisomerization of **1aa**

Entry	Catalyst	Product(s) (2aa : 3aa) ^a
1	PdCl ₂	1 : 1
2	PdBr ₂	1 : 1
3	PdI ₂	No reaction
4	Pd(OAc) ₂	No reaction
5	Pd(CH ₃ CN) ₂ Cl ₂	1.1 : 1
6	Pd(PhCN) ₂ Cl ₂	No reaction
7	<i>cis</i> -Pt(CH ₃ CN) ₂ Cl ₂	No reaction
8	<i>cis</i> -Pt(PhCN) ₂ Cl ₂	No reaction
9	AuCl ₃	Complex mixture ^b
10	AuBr ₃	Complex mixture ^b

^a All the ratios are given on the basis of the NMR of the crude product. ^b In dichloromethane also, the starting material decomposed within 5 min.

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† Electronic supplementary information (ESI) available: ¹H, ¹³C NMR and ESI-MS spectra of all the cycloisomerization products. CCDC reference numbers 795522, 836106 and 836107. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00858c

Table 2 Catalysts screened for the nitroalkynol cycloisomerization of **1ba**


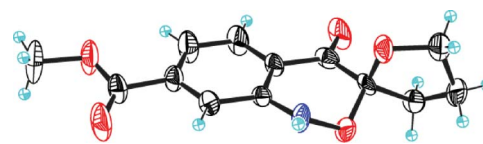
Entry	Catalyst	Product(s) (2ba : 3ba : 4ba) ^a
1	PdCl ₂	5 : 1 : 0
2	PdBr ₂	5 : 1 : 0
3	^b PdI ₂	No reaction
4	Pd(NO ₂) ₂	No reaction
5	Pd(OAc) ₂	No reaction
6	Pd(CH ₃ CN) ₂ NO ₂ Cl	slow reaction
7	Pd(CH ₃ CN) ₂ Cl ₂	1 : 0 : 0
8	Pd(PhCN) ₂ Cl ₂	No reaction
9	<i>cis</i> -Pt(CH ₃ CN) ₂ Cl ₂	No reaction
10	<i>cis</i> -Pt(PhCN) ₂ Cl ₂	No reaction
11	AuCl ₃	Complex mixture
12	^c AuCl ₃	0 : 4 : 3
13	HAuCl ₄	Complex Mixture
14	^c HAuCl ₄	0 : 5 : 6
15	AuBr ₃	0 : 3.6 : 1
16	^c AuBr ₃	0 : 4 : 3
17	(PPh ₃) ₃ (O)Au ₃ BF ₄	Complex mixture
18	^c (PPh ₃) ₃ (O)Au ₃ BF ₄	0 : 1.5 : 1

^a All the ratios are given on the basis of the NMR of crude product. ^b PdI₂ is sparingly soluble in majority of the solvents used and in DMSO it has good solubility. However, the attempted cycloisomerization with Pd(II)I₂ in this solvent gave an intractable complex mixture ^c Dichloromethane was used as a solvent.

cycloisomerization of **1ba** with Pd(CH₃CN)₂Cl₂ gave exclusively the spiroindolinone **2ba**^{9b,9c} in good yield. With the three Au(III) salts, the outcome of the reaction was solvent dependent. Whilst the cycloisomerization of **1ba** with AuBr₃ in acetonitrile gave predominantly the spirobenzoxazinone **3ba** and anthranil **4ba** as a minor product, the reactions with AuCl₃ and HAuCl₄ in acetonitrile resulted in immediate disappearance of alkynol and gave untractable polar mixtures. When the solvent was changed to CH₂Cl₂, a mixture of spirobenzoxazinone **3ba** and anthranil **4ba** were obtained in moderate yields with AuCl₃ and HAuCl₄. After a preliminary screening of various metal complexes, further generalization of this novel reaction has been carried out using Pd(CH₃CN)₂Cl₂ and AuBr₃ in acetonitrile. Table 3 provides the scope and the product divergence of the Pd(II) and Au(III) mediated nitroalkynol cycloisomerization. With the pentynols **1aa** (α = a–d), the palladium catalyzed cycloisomerizations in general gave a ~1 : 1 mixture of **2aa** and **3aa**. The constitution of one of the benzoxazinones **3ad** was confirmed with the help of single crystal X-ray structural analysis (Fig. 2). With all the hexynols **1ba** (α = a–d), as well as with the propargyl glycol derivatives **1ca** (α = a–d), the indolin-3-one derivatives were isolated exclusively in good to excellent yields. Formation of substantial amounts of anthranil derivatives **4ba** along with the benzoxazinones **3ba** was noticed in the reactions of hexynols **1ba** with AuBr₃. The AuBr₃ catalyzed cyclization of propargyl glycol derivatives **1ca** afforded exclusively the benzoxazinone derivatives **3ca**.

Mechanism

A plausible mechanism for the palladium- and gold-mediated cyclizations is given in Fig. 3. Primarily, two competing pathways exist—(a) the alkynol cycloisomerization and (b) the internal

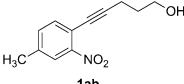
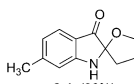
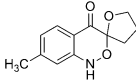
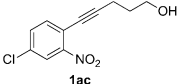
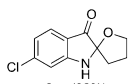
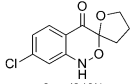
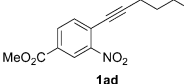
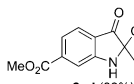
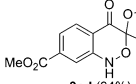
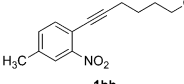
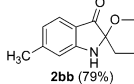
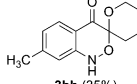
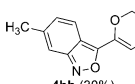
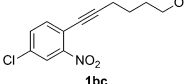
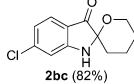
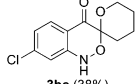
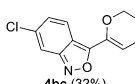
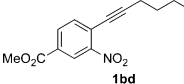
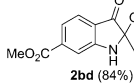
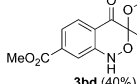
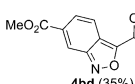
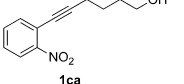
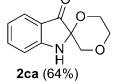
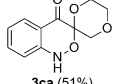
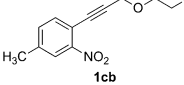
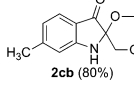
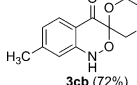
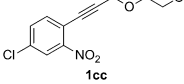
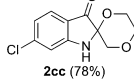
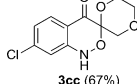
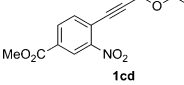
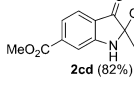
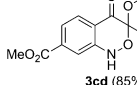
**Fig. 2** ORTEP diagram of **3ad**.

redox *via* nitroalkyne cycloisomerization. With the alkynol cycloisomerization, the formation of proto demetallated intermediates such as *exo*-glycols as side products is expected.¹³ However, no such side products are observed and we speculate that the reactions are proceeding with the initial internal nitroalkyne redox. Next, the internal N–O bond redox could occur either by the 5-*exo*-dig or 6-*endo*-dig^{14–16} mode of nitroalkyne cycloisomerization depending upon substrate and the metal complex employed.

In the first case, which we extend for the Pd(II)-mediated cyclization,^{11,12} a 5-*exo*-dig nitroalkyne cyclization giving **D** which upon internal N–O bond redox, leads to the intermediate metal carbene **F** (Fig. 3, eq.3). This metal carbene **F** could undergo a nucleophilic addition either by the nitrogen of the nitroso-group or by the oxygen of the –OH group. With the pentynol substrates, where both these additions lead to 5-membered heterocycles, it seems to be that both the cyclizations are competing equally leading to two different products. The addition of the nitrogen to the metal carbene (Fig. 3, *path a*) leads to the isatogens **II** which subsequently undergo an intramolecular addition of the –OH group to the imine carbon proceeded or preceded by the N–O bond reduction and thus give the indolinone **2**. Whereas the addition of –OH to the metal carbene followed by the proto-depalladation (Fig. 3, *path b*) leads to the enol **L**, which subsequently undergoes a 6*n*-electrocyclization resulting in benzoxazinone **3** (Fig. 3, eq.4). When the addition of the –OH forms a 6-membered ring, which is the case with hexynols and propargyl glycols, the cyclization is energetically more demanding, and the addition of nitrogen of the nitroso-group to the metal carbene is the exclusive path thus providing the indolinones only.

Next, considering the available information, for the cyclizations with the Au(III)-complex, we extend a 6-*endo*-dig mode of nitroalkyne cycloisomerization and the formation of the alkenyl-Au(III) species **E**. The intermediate **E** can undergo either an internal redox forming the regiomer metal carbene **G** (Fig. 3, *path c*) or a protodemetalation giving nitronate **H** (Fig. 3, *path d*). The intermediate **H** upon hydration gives the *nitroso-ene-diol* **I**. This path is in parallel to the mechanism that has been extended by Yamamoto for nitroalkyne cycloisomerizations leading to isatogens and/or anthranils.⁷ The resulting ene-diol **I** could be trapped by the internal OH nucleophile to provide the intermediate **L**. The intermediate **L** should undergo a 6*n*-electrocyclization to give the benzoxazinone **3** (Fig. 3, eq.6). The formation of benzoxazinones either as the major or as exclusive products indicates that with AuBr₃, the protodemetalation seems to be more facile than the metalcarbene formation. The formation of anthranil side products could be explained by the internal addition of oxygen of nitroso group to the metal carbene **M** (formed *via* the dehydration of the metal carbene **G**) resulting in **N**, which upon protodemetalation followed by deprotonation forms the anthranil **4** (Fig. 3, eq.5). As a control, the benzoxazinone **3bc** was exposed to AuBr₃ (5 mol%, CH₃CN, rt, 3 h) and found to be intact. This

Table 3 Product divergence in Pd(II) and Au(III) mediated nitroalkynol cycloisomerizations

Entry	Nitroalkynol	Products (Yield %)		
		$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, CH_3CN , rt	AuBr_3 , CH_3CN , rt	
1 ^a	 1ab	 2ab (36%)	 3ab (34%)	NA
2	 1ac	 2ac (32%)	 3ac (31%)	NA
3	 1ad	 2ad (38%)	 3ad (34%)	Complex mixture
4	 1bb	 2bb (79%)	 3bb (35%)	 4bb (30%)
6	 1bc	 2bc (82%)	 3bc (38%)	 4bc (32%)
7	 1bd	 2bd (84%)	 3bd (40%)	 4bd (35%)
8	 1ca	 2ca (64%)	 3ca (51%)	
9	 1cb	 2cb (80%)	 3cb (72%)	
10	 1cc	 2cc (78%)	 3cc (67%)	
11	 1cd	 2cd (82%)	 3cd (85%)	

^a **1ab** was slowly converting to the cycloisomerization products on standing in CDCl₃ which might be due to traces of [Pd]-present.

control experiment indicated that both the benzoxazinone and anthranil are formed independently.

Conclusions

In summary, the intramolecular addition of nitro and alcohol units across the alkyne leading to spiro-indolin-3-one and spiro-benzoxazin-4-one derivatives was revealed by employing palladium and gold catalysts. Whilst the former units can be found

in a variety of natural products,^{17,18} the latter 2,3-benzoxazinone unit is rare and present in important antitumor, antibiotic natural products FR900482¹⁹ and FR66979²⁰ (structurally related to the anticancer drug mitomycin C, with more potent DNA cross-linking activity and decreased toxicity). The present transformation therefore can find an important application in the synthesis of related small molecule libraries. Further investigations dealing with the details of the mechanism and the scope of these reactions are in progress.

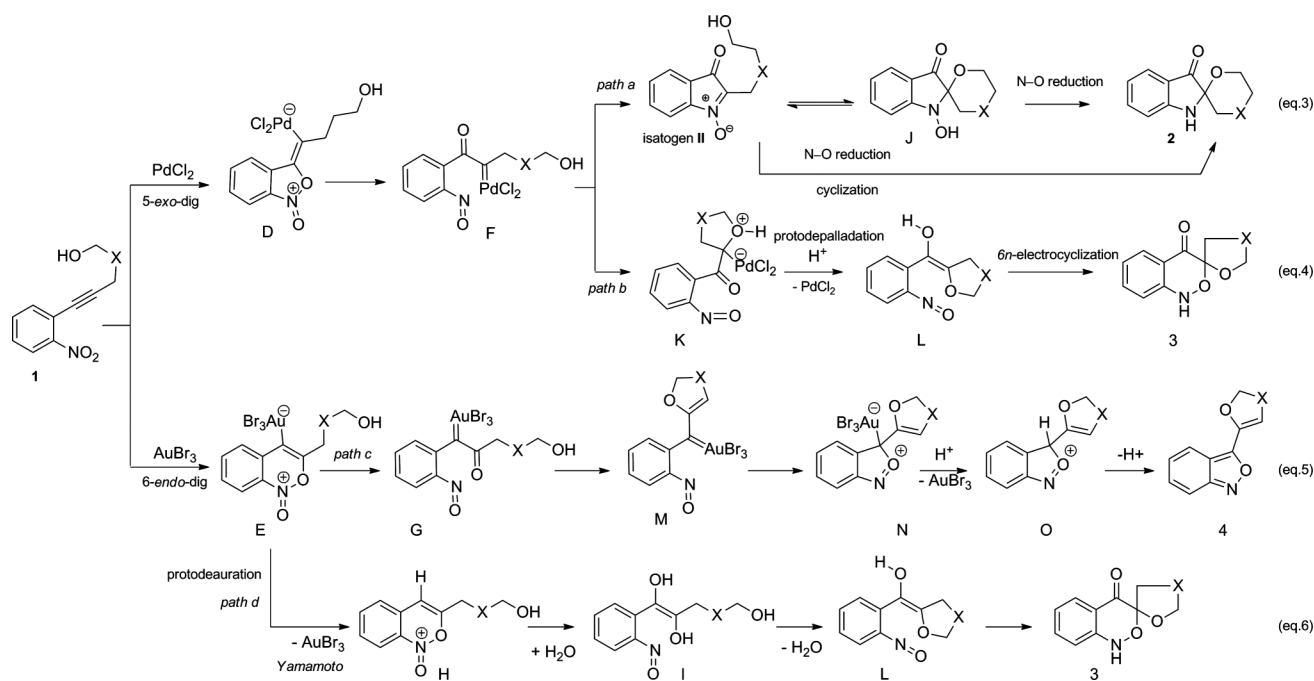


Fig. 3 The possible modes of cyclization and possible mechanism for the product divergence with Pd(II) and Au(III)-mediated nitroalkynol cycloisomerization (for clarity of the figures the acetonitrile ligands on the Pd(II)-complex have not been shown).

Experimental

General procedure for cycloisomerization with Pd[CH₃CN]₂Cl₂ or AuBr₃

To a degassed solution of alkyne **1** (0.5 mmol) in CH₃CN (15 mL) was added Pd[CH₃CN]₂Cl₂ or AuBr₃ (5 mol%) and the contents stirred under argon for 4 h or 6 h at rt. The reaction mixture was concentrated and the residue obtained was purified by column chromatography (ethyl acetate in petroleum ether) to afford **2/3** or **3/4**.

Compound 2aa. Yellow liquid, 29% yield. IR (CHCl₃): ν 3022, 2926, 1717, 1608, 1526, 1469, 1348, 1235, 1048 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.93–2.16 (m, 2H), 2.21–2.32 (m, 2H), 4.02–4.18 (m, 2H), 4.83 (br s, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H), 7.41 (ddd, J = 1.3, 7.3, 8.4 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), ppm. ¹³C NMR (50 MHz, CDCl₃): δ 25.7 (t), 33.9 (t), 69.2 (t), 95.0 (s), 112.1 (d), 119.0 (s), 119.6 (d), 125.0 (d), 137.8 (d), 159.6 (s), 200.9 (s) ppm. ESI-MS: m/z 190.2 (100%, [M+H]⁺). HRMS: Found: 190.0856 ([M+H]⁺); Calcd.: 190.0868 ([M+H]⁺). Anal. Calcd for C₁₁H₁₁NO₂: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.67; H, 5.82; N, 7.35.

Compound 2ab. Yellow colour solid, Mp. 133 °C, 36% yield. IR (CHCl₃): ν 3017, 2915, 2888, 1712, 1616, 1587, 1459, 1324, 1216, 1111, 1021, 755 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.91–2.12 (m, 2H), 2.20–2.34 (m, 2H), 2.28 (s, 3H), 4.05–4.13 (m, 2H), 4.91 (br s, 1H), 6.51 (s, 1H), 6.60 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 22.3 (q), 25.6 (t), 33.9 (t), 69.1 (t), 95.2 (s), 112.3 (d), 116.6 (s), 121.0 (d), 124.6 (d), 149.5 (s), 160.1 (s), 200.1 (s) ppm. ESI-MS: m/z 202.1 (100%, [M – H]⁺), 204.1 (50%, [M+H]⁺). HRMS: Found: 204.1039 ([M+H]⁺), Calcd.: 204.1025 ([M+H]⁺). Anal. Calcd for

C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.85; H, 6.33; N, 6.67.

Compound 2ac. Yellow solid, Mp. 136 °C, 32% yield. IR (CHCl₃): ν 3019, 2985, 1714, 1610, 1580, 1454, 1316, 1215, 1066, 928, 755 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.96–2.09 (m, 2H), 2.21–2.31 (m, 2H), 4.00–4.15 (m, 2H), 5.06 (br s, 1H), 6.69 (d, J = 1.6 Hz, 1H), 6.75 (dd, J = 1.6, 8.1 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 25.6 (t), 33.9 (t), 69.3 (t), 95.3 (s), 112.0 (d), 117.3 (s), 120.2 (d), 126.0 (d), 144.3 (s), 160.0 (s), 199.5 (s) ppm. ESI-MS: m/z 246.2 (100%, [M+Na]⁺). HRMS: Found: 222.0321 ([M – H]⁺), Calcd.: 222.0322 ([M – H]⁺). Anal. Calcd for C₁₁H₁₀ClNO₂: C, 59.07; H, 4.51; Cl, 15.85; N, 6.26. Found: C, 59.20; H, 4.63; Cl, 15.69; N, 6.09.

Compound 2ad. Yellow liquid, 38% yield. IR (CHCl₃): ν 3012, 2998, 1715, 1702, 1608, 1568, 1508, 1474, 1466, 1316, 1263, cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.99–2.14 (m, 2H), 2.23–2.33 (m, 2H), 3.91 (s, 3H), 4.05–4.15 (m, 2H), 4.93 (br s, 1H), 7.39 (br s, 1H), 7.46 (dd, J = 1.3, 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 25.7 (t), 33.9 (t), 52.5 (q), 69.3 (t), 95.3 (s), 113.1 (d), 120.5 (d), 122.1 (s), 124.9 (d), 138.1 (s), 159.1 (s), 166.3 (s), 200.7 (s) ppm. ESI-MS: m/z 270.1 (100%, [M+Na]⁺). HRMS: Found: 246.0317 ([M – H]⁺), Calcd.: 246.0202 ([M – H]⁺). Anal. Calcd for C₁₃H₁₃NO₄: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.01; H, 5.17; N, 5.52.

Compound 2ba. Yellow solid, Mp. 112 °C, 55% yield. IR (CHCl₃): ν 2985, 2924, 1713, 1625, 1489, 1455, 1307, 1268, 1118, 1077 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.50–1.85 (m, 4H), 1.94–2.11 (m, 2H), 3.74–3.86 (m, 1H), 4.05–4.15 (m, 1H), 5.13 (br s, 1H), 6.08–6.87 (m, 2H), 7.44 (dt, J = 1.22, 8.2 Hz, 1H), 7.59 (dd, J = 1.1, 7.9 Hz, 1H), ppm. ¹³C NMR (50 MHz, CDCl₃): δ 19.2 (t), 24.7 (t), 30.5 (t), 63.7 (t), 87.5 (s), 112.7 (d), 119.8 (s), 120.0 (d),

125.4 (d), 137.8 (d), 159.4 (s), 198.9 (s) ppm. ESI-MS: m/z 226.3 (100%, $[M+Na]^+$). HRMS: Found: 226.0904 ($[M+Na]^+$), Calcd.: 226.0844 ($[M+Na]^+$). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.77; H, 6.39; N, 6.72.

Compound 2bb. Brown colour solid, Mp. 128 °C, 79% yield. IR (CHCl₃): ν 3015, 1711, 1616, 1570, 1459, 1323, 1289, 1021, 756 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.47–1.83 (m, 4H), 1.93–2.11 (m, 2H), 2.32 (s, 3H), 3.72–3.84 (m, 1H), 4.03–4.13 (m, 1H), 5.12 (br s, 1H), 6.62 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), ppm. ¹³C NMR (50 MHz, CDCl₃): δ 19.2 (t), 22.4 (q), 24.7 (t), 30.6 (t), 63.7 (t), 87.8 (s), 112.8 (d), 117.4 (s), 121.5 (d), 125.1 (d), 149.5 (s), 159.9 (s), 198.2 (s) ppm. ESI-MS: m/z 218.2 (100%, $[M+Na]^+$). HRMS: Found: 218.1168 ($[M+H]^+$), Calcd.: 218.1181 ($[M+H]^+$). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.79; H, 6.82; N, 6.33.

Compound 2bc. Low melting solid, 82% yield. IR (CHCl₃): ν 3018, 3945, 1718, 1604, 1457, 1314, 1215, 1045 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.50–1.85 (m, 4H), 1.94–2.16 (m, 2H), 3.71–3.83 (m, 1H), 4.06–4.16 (m, 1H), 5.20 (br s, 1H), 6.79 (dd, J = 1.6, 8.2 Hz, 1H), 6.82 (s, 1H), 7.51 (dd, J = 1.6, 7.2 Hz, 1H), ppm. ¹³C NMR (50 MHz, CDCl₃): δ 19.1 (t), 24.6 (t), 30.5 (t), 63.8 (t), 87.7 (s), 112.5 (d), 118.1 (s), 120.6 (d), 126.4 (d), 144.1 (s), 159.7 (s), 197.4 (s) ppm. ESI-MS: m/z 240.3 (100%, $[M+Na]^+$). HRMS: Found: 260.0871 ($[M+Na]^+$), Calcd.: 260.0454 ($[M+Na]^+$). Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; Cl, 14.92; N, 5.89. Found: C, 60.58; H, 5.20; Cl, 14.77; N, 5.71.

Compound 2bd. Yellow solid, Mp. 162 °C, 84% yield. IR (CHCl₃): ν 3032, 2945, 1715, 1702, 1615, 1568, 1527, 1480, 1466, 1345, 1210, 1018 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.52–1.84 (m, 4H), 1.94–2.17 (m, 2H), 3.73–3.85 (m, 1H), 3.90 (s, 3H), 4.05–4.15 (m, 1H), 5.30 (br s, 1H), 7.44–7.48 (m, 2H), 7.62 (d, J = 8.3 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 19.0 (t), 24.6 (t), 30.4 (t), 52.5 (q), 63.7 (t), 87.7 (s), 113.7 (d), 120.5 (d), 122.7 (s), 125.2 (d), 138.0 (s), 158.9 (s), 166.2 (s), 198.73 (s) ppm. ESI-MS: m/z 284.2 (100%, $[M+Na]^+$). HRMS: Found: 284.3364 ($[M+Na]^+$), Calcd.: 284.0899 ($[M+Na]^+$). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.22; H, 5.58; N, 5.29.

Compound 2ca. Yellow liquid, 64% yield. IR (CHCl₃): ν 3016, 2964, 2925, 1709, 1619, 1486, 1471, 1321, 1234, 1121, 1081 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 3.61 (d, J = 11.5 Hz, 1H), 3.78–3.99 (m, 3H), 3.89 (d, J = 11.5 Hz, 1H), 4.03–4.16 (m, 1H), 5.53 (br s, 1H), 6.85–6.92 (m, 2H), 7.50 (dt, J = 1.3, 7.2 Hz, 1H), 7.6 (d, J = 7.7 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 62.4 (t), 66.5 (t), 71.0 (t), 86.6 (s), 113.2 (d), 120.2 (s), 120.6 (d), 125.4 (d), 138.2 (d), 159.6 (s), 195.9 (s) ppm. ESI-MS: m/z 228.1 (100%, $[M+Na]^+$). HRMS: Found: 228.0598 ($[M+Na]^+$), Calcd.: 228.0637 ($[M+Na]^+$). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.21; H, 5.29; N, 6.71.

Compound 2cb. Yellow liquid, 80% yield. IR (CHCl₃): ν 3018, 2947, 1718, 1611, 1581, 1452, 1314, 1215, 1066 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 2.36 (s, 3H), 3.59 (d, J = 11.5 Hz, 1H), 3.83–3.98 (m, 3H), 3.88 (d, J = 11.5 Hz, 1H), 4.01–4.15 (m, 1H), 5.48 (br s, 1H), 6.69 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 22.5 (q), 62.4 (t), 66.4 (t), 71.1 (t), 86.9 (s), 113.3 (d), 118.0 (s), 122.2 (d), 125.1 (d), 150.2 (s), 160.1 (s), 195.1 (s) ppm. ESI-MS: m/z 242.1 (100%,

$[M+Na]^+$). HRMS: Found: 242.2808 ($[M+Na]^+$), Calcd.: 242.0793 ($[M+Na]^+$). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 5.78; N, 6.22.

Compound 2cc. Yellow liquid, 78% yield. IR (CHCl₃): ν 2946, 2895, 1718, 1604, 1550, 1439, 1314, 1212, 1067 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 3.60 (d, J = 11.5 Hz, 1H), 3.80–3.97 (m, 3H), 3.87 (d, J = 11.5 Hz, 1H), 3.99–4.11 (m, 1H), 5.74 (br s, 1H), 6.84 (dd, J = 1.6, 8.2 Hz, 1H), 6.88 (d, J = 1.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 62.4 (t), 66.4 (t), 70.8 (t), 86.8 (s), 113.1 (d), 118.4 (s), 121.2 (d), 126.4 (d), 144.7 (s), 159.9 (s), 194.5 (s) ppm. ESI-MS: m/z 262.2 (100%, $[M+Na]^+$). HRMS: Found: 240.0542 ($[M+H]^+$), Calcd.: 240.0427 ($[M+H]^+$). Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; Cl, 14.79; N, 5.84. Found: C, 55.23; H, 4.18; Cl, 14.57; N, 5.71.

Compound 2cd. Yellow colour solid, Mp. 171 °C, 82% yield. IR (CHCl₃): ν 3018, 2951, 1727, 1715, 1624, 1587, 1495, 1454, 1322, 1263, 1161, 1002 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 3.61 (d, J = 11.5 Hz, 1H), 3.84–3.98 (m, 3H), 3.89 (d, J = 11.5 Hz, 1H), 3.93 (s, 3H), 4.02–4.15 (m, 1H), 5.66 (br s, 1H), 7.52 (dd, J = 1.2, 8.7 Hz, 1H), 7.56 (s, 1H), 7.65 (d, J = 8.7 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 52.6 (q), 62.4 (t), 66.4 (t), 70.7 (t), 86.7 (s), 114.2 (d), 121.2 (d), 123.1 (s), 125.3 (d), 138.5 (s), 159.1 (s), 166.1 (s), 195.8 (s) ppm. ESI-MS: m/z 279.4 (100%, $[M+Na]^+$). HRMS: Found: 263.1181 ($[M]^+$), Calcd.: 263.0794 ($[M]^+$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.20; H, 4.85; N, 5.23.

Compound 3aa. Yellow liquid, 27% yield. IR (CHCl₃): ν 3019, 1695, 1645, 1599, 1448, 1215, 1078 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.93–2.19 (m, 3H), 2.70–2.85 (m, 1H), 4.05–4.24 (m, 2H), 6.85 (d, J = 8.2 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.43 (ddd, J = 1.4, 7.3, 8.3 Hz, 1H), 7.94 (dd, J = 1.4, 7.9 Hz, 1H) ppm (The N–H proton is missing in the spectrum). ¹³C NMR (50 MHz, CDCl₃): δ 24.7 (t), 31.2 (t), 71.0 (t), 107.5 (s), 114.7 (d), 117.7 (s), 122.4 (d), 127.7 (d), 134.8 (d), 150.4 (s), 185.1 (s) ppm. ESI-MS: m/z 228.2 (100%, $[M+Na]^+$). HRMS: Found: 228.0597 ($[M+Na]^+$), Calcd.: 228.0637 ($[M+Na]^+$). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.31; N, 6.72.

Compound 3ab. Brown colour solid, Mp. 118 °C, 34% yield. IR (CHCl₃): ν 3012, 2981, 1685, 1613, 1459, 1340, 1294, 1019 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.92–2.17 (m, 3H), 2.32 (s, 3H), 2.69–2.83 (m, 1H), 4.04–4.22 (m, 2H), 6.63 (s, 1H), 6.85 (dd, J = 0.7, 8.1 Hz, 1H), 7.41 (br s, 1H), 7.82 (d, J = 8.1 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 22.0 (q), 24.7 (t), 31.2 (t), 71.0 (t), 107.6 (s), 114.6 (d), 115.6 (s), 123.9 (d), 127.7 (d), 146.2 (s), 150.5 (s), 184.9 (s) ppm. ESI-MS: m/z 242.2 (100%, $[M+Na]^+$). HRMS: Found: 220.0960 ($[M+H]^+$), Calcd.: 220.0974 ($[M+H]^+$). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.79; H, 5.79; N, 6.27.

Compound 3ac. Yellow colour solid, Mp. 118 °C, 31% yield. IR (CHCl₃): ν 2923, 1682, 1613, 1452, 1313, 1270, 1056 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.92–2.23 (m, 3H), 2.68–2.83 (m, 1H), 4.04–4.23 (m, 2H), 6.85 (d, J = 1.8 Hz, 1H), 6.99 (dd, J = 1.8, 8.6 Hz, 1H), 7.55 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 24.6 (t), 31.1 (t), 71.1 (t), 107.5 (s), 114.3 (d), 115.9 (s), 122.9 (d), 129.3 (d), 141.0 (s), 151.1 (s), 184.2 (s) ppm. ESI-MS: m/z 240.2 (100%, $[M+H]^+$). HRMS: Found:

240.0420 ($[M+H]^+$), Calcd.: 240.0427 ($[M+H]^+$). Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; Cl, 14.79; N, 5.84. Found: C, 55.01; H, 4.09; Cl, 14.58; N, 5.79.

Compound 3ad. Yellow colour solid, Mp. 123 °C. 34% yield. IR ($CHCl_3$): ν 3020, 1729, 1684, 1618, 1590, 1435, 1301, 1215, 1090 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 1.99–2.05 (m, 1H), 2.10–2.21 (m, 2H), 2.73–2.81 (m, 1H), 3.91 (s, 3H), 4.08–4.14 (m, 1H), 4.16–4.22 (m, 1H), 7.55 (s, 1H), 7.57 (br s, 1H), 7.65 (dd, $J = 1.4, 8.1$ Hz, 1H), 7.98 (d, $J = 8.1$ Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7 (t), 31.2 (t), 52.6 (q), 71.3 (t), 107.4 (s), 116.4 (d), 120.3 (s), 122.6 (d), 128.1 (d), 135.3 (s), 150.2 (s), 165.8 (s), 184.6 (s) ppm. ESI-MS: m/z 270.1 (100%, $[M+Na]^+$). HRMS: Found: 263.0849 ($[M]^+$), Calcd.: 263.0794 ($[M]^+$). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.27; H, 4.89; N, 5.22.

X-Ray crystallographic data²¹. X-ray intensity data of compound **3ad**[†] was collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo-K α = 0.71073 Å) radiation at room temperature. Data were collected with ω scan width of 0.3° and with four different settings of ϕ (0°, 90°, 180° and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2 θ) fixed at –28°. The X-ray data collection was monitored by SMART program (Bruker, 2003).^{22a} All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs.^{22a} SHELX-97^{22b} was used for structure solution and full-matrix least-squares refinement on F^2 . Hydrogen atoms were included in the refinement as per the riding model. The overall quality of the diffraction data was very poor due to the poor quality of the crystals which is reflected in its high R-value.

Crystal data for **3ad** ($C_{13}H_{13}NO_5$): $M = 263.24$, crystal dimensions $0.22 \times 0.16 \times 0.06$ mm³, monoclinic, space group $P2_1/n$, $a = 14.478(8)$, $b = 5.258(3)$, $c = 17.353(10)$ Å, $V = 1315.8(13)$ Å³, $Z = 4$; $\rho_{calcd} = 1.329$ g cm^{–3}, $\mu(Mo-K\alpha) = 0.103$ mm^{–1}, $F(000) = 552$, $2\theta_{max} = 50.00^\circ$, 7556 reflections collected, 1815 unique, 1346 observed ($I > 2\sigma(I)$) reflections, 173 refined parameters, R value 0.1249, $wR_2 = 0.3022$ (all data $R = 0.1520$, $wR_2 = 0.3159$), $S = 1.241$, minimum and maximum transmission 0.9780 and 0.9934 respectively, maximum and minimum residual electron densities +0.495 and –0.374 e Å^{–3}.

Compound 3ba. Yellow solid, Mp. 121 °C, 57% yield. IR ($CHCl_3$): ν 3020, 2930, 1725, 1605, 1550, 1461, 1302, 1217, 1108, 1080, 756 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 1.61–1.75 (m, 2H), 1.80–1.87 (m, 3H), 2.33–2.42 (m, 1H), 3.87–3.97 (m, 2H), 6.86 (d, $J = 8.2$ Hz, 1H), 7.04 (ddd, $J = 1.0, 7.3, 8.0$ Hz, 1H), 7.27 (s, 1H), 7.43 (ddd, $J = 1.5, 7.3, 8.5$ Hz, 1H), 7.95 (dd, $J = 1.0, 8.0$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9 (t), 24.4 (t), 25.6 (t), 63.5 (t), 98.8 (s), 114.0 (d), 116.9 (s), 122.2 (d), 128.1 (d), 134.5 (d), 150.5 (s), 185.2 (s) ppm. ESI-MS: m/z 242.2 (100%, $[M+Na]^+$). HRMS: Found: 220.1017 ($[M+H]^+$), Calcd.: 220.0974 ($[M+H]^+$). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.85; H, 5.76; N, 6.25.

Compound 3bb. Sticky liquid, 35% yield. IR ($CHCl_3$): ν 3019, 2948, 2855, 1686, 1614, 1580, 1454, 1310, 1270, 1215, 1045 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 1.58–1.74 (m, 2H), 1.76–1.84 (m, 3H), 2.28–2.51 (m, 1H), 2.33 (s, 3H), 3.88–3.94 (m, 2H), 6.64 (s, 1H), 6.85 (dd, $J = 0.8, 8.1$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9 (t), 22.0 (q), 24.5 (t), 25.6 (t),

63.5 (t), 98.7 (s), 114.0 (d), 114.9 (s), 123.7 (d), 128.1 (d), 145.9 (s), 150.6 (s), 185.0 (s) ppm. ESI-MS: m/z 256.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.74; H, 6.32; N, 5.87.

Compound 3bc. Low melting solid, 38% yield. IR ($CHCl_3$): ν 3020, 1683, 1614, 1453, 1314, 1216, 1058, 919 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 1.62–1.73 (m, 2H), 1.78–1.86 (m, 3H), 2.27–2.43 (m, 1H), 3.88–3.92 (m, 2H), 6.87 (d, $J = 1.8$ Hz, 1H), 6.99 (dd, $J = 1.8, 8.5$ Hz, 1H), 7.26 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.8 (t), 24.4 (t), 25.4 (t), 63.6 (t), 98.8 (s), 113.76 (d), 115.2 (s), 122.7 (d), 129.7 (d), 140.8 (s), 151.1 (s), 184.2 (s) ppm. ESI-MS: m/z 276.1 (100%, $[M+H]^+$). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; Cl, 13.98; N, 5.52. Found: C, 56.99; H, 4.71; Cl, 13.75; N, 5.41.

Compound 3bd. Yellow solid, Mp. 153 °C, 40% yield. IR ($CHCl_3$): ν 2951, 1727, 1703, 1615, 1580, 1438, 1286, 1229, 1092, 752 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 1.62–1.86 (m, 5H), 2.27–2.43 (m, 1H), 3.90–4.00 (m, 2H), 3.91 (s, 3H), 7.36 (br s, 1H), 7.54 (d, $J = 1.3$ Hz, 1H), 7.63 (dd, $J = 1.3, 8.2$ Hz, 1H), 7.99 (d, $J = 8.2$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9 (t), 24.4 (t), 25.4 (t), 52.6 (q), 63.6 (t), 98.7 (s), 115.6 (d), 119.5 (s), 122.3 (d), 128.4 (d), 135.0 (s), 150.2 (s), 165.9 (s), 184.6 (s) ppm. ESI-MS: m/z 278.2 (100%, $[M+H]^+$). HRMS: Found: 278.1007 ($[M+H]^+$), Calcd.: 278.1028 ($[M+H]^+$). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.52; H, 5.28; N, 4.88.

Compound 3ca. Yellow liquid, 51% yield. IR ($CHCl_3$): ν 2927, 2857, 1682, 1605, 1478, 1348, 1086, 1057, 918, 752 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 3.72 (d, $J = 11.1$ Hz, 1H), 3.81–3.87 (m, 2H), 3.84 (d, $J = 12.6$ Hz, 1H), 4.18–4.36 (m, 1H), 4.30 (d, $J = 12.6$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 6.98–7.06 (m, 1H), 7.44 (ddd, $J = 1.5, 7.2, 8.3$ Hz, 1H), 7.61 (br s, 1H), 7.91 (dd, $J = 1.5, 7.9$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 61.3 (t), 65.6 (t, 2C), 95.4 (s), 113.6 (d), 116.5 (s), 122.1 (d), 127.9 (d), 135.0 (d), 150.5 (s), 183.7 (s) ppm. ESI-MS: m/z 244.3 (100%, $[M+Na]^+$). HRMS: Found: 221.0753 ($[M]^+$), Calcd.: 221.0688 ($[M]^+$). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.59; H, 4.95; N, 6.19.

Compound 3cb. Yellow liquid, 72% yield. IR ($CHCl_3$): ν 3019, 2980, 2928, 1687, 1615, 1453, 1381, 1321, 1215, 1115, 1068 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.69 (d, $J = 11.2$ Hz, 1H), 3.79–3.90 (m, 2H), 3.83 (d, $J = 12.6$ Hz, 1H), 4.16–4.34 (m, 1H), 4.27 (d, $J = 12.6$ Hz, 1H), 6.62 (s, 1H), 6.81 (dd, $J = 0.7, 8.1$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0 (q), 61.2 (t), 65.6 (t, 2C), 95.3 (s), 113.3 (d), 114.2 (s), 123.5 (d), 127.7 (d), 146.5 (s), 150.6 (s), 183.5 (s) ppm. ESI-MS: m/z 236.2 (100%, $[M+H]^+$). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.30; H, 5.41; N, 5.76.

Compound 3cc. Yellow liquid, 67% yield. IR ($CHCl_3$): ν 3019, 2927, 2855, 1694, 1600, 1442, 1215, 1045, 758, 668 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$): δ 3.72 (d, $J = 11.1$ Hz, 1H), 3.80–3.87 (m, 2H), 3.84 (d, $J = 12.7$ Hz, 1H), 4.16–4.37 (m, 1H), 4.29 (d, $J = 12.7$ Hz, 1H), 6.88 (d, $J = 1.6$ Hz, 1H), 6.99 (dd, $J = 1.6, 8.5$ Hz, 1H), 7.62 (br s, 1H), 7.84 (d, $J = 8.5$ Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 61.3 (t), 65.4 (t), 65.6 (t), 95.3 (s), 113.3 (d), 114.8 (s), 122.7 (d), 129.5 (d), 141.4 (s), 151.0 (s), 182.8 (s) ppm. ESI-MS: m/z 256.3 (100%, $[M+H]^+$). HRMS: Found:

256.0373 ([M+H]⁺), Calcd.: 256.0377 ([M+H]⁺). Anal. Calcd for C₁₁H₁₀ClNO₄: C, 51.68; H, 3.94; Cl, 13.87; N, 5.48. Found: C, 51.55; H, 3.89; Cl, 13.62; N, 5.39.

Compound 3cd. Yellow colour solid, Mp. 168 °C, 85% yield. IR (CHCl₃): ν 2924, 1726, 1693, 1619, 1506, 1438, 1298, 1228, 1094, 1055, 918, 752 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 3.69 (d, *J* = 10.9 Hz, 1H), 3.81–3.97 (m, 2H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.92 (s, 3H), 4.17–4.36 (m, 1H), 4.31 (d, *J* = 12.7 Hz, 1H), 7.58 (d, *J* = 1.4 Hz, 1H), 7.62 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.84 (br s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 52.7 (q), 61.3 (t), 65.4 (t), 65.6 (t), 95.2 (s), 115.3 (d), 119.0 (s), 122.2 (d), 128.2 (d), 135.5 (s), 150.2 (s), 165.8 (s), 183.2 (s) ppm. ESI-MS: *m/z* 279.4 (100%, [M]⁺). HRMS: Found: 279.0936 ([M]⁺), Calcd.: 279.0743 ([M]⁺). Anal. Calcd for C₁₃H₁₃NO₆: C, 55.91; H, 4.69; N, 5.02. Found: C, 55.85; H, 4.73; N, 5.12.

Compound 4bb. Yellow liquid, 30% yield. IR (CHCl₃): ν 3019, 2927, 2855, 1729, 1626, 1557, 1440, 1300, 1215, 1045, 759 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.96–2.00 (m, 2H), 2.28–2.32 (m, 2H), 2.35 (s, 3H), 4.24 (t, *J* = 5.1 Hz, 2H), 5.88 (t, *J* = 4.3 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 1H), 7.20 (s, 1H), 7.65 (d, *J* = 9.1 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 20.4 (t), 22.0 (t), 22.4 (q), 66.6 (t), 104.7 (d), 112.1 (d), 113.1 (s), 121.4 (d), 127.2 (d), 141.2 (s), 144.4 (s), 158.0 (s), 159.8 (s) ppm. ESI-MS: *m/z* 216.2 (100%, [M+H]⁺). HRMS: Found: 216.1022 ([M+H]⁺), Calcd. 216.1025 ([M+H]⁺). Anal. Calcd for C₁₃H₁₃NO₂: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.59; H, 6.23; N, 6.45.

Compound 4bc. Colourless liquid, 32% yield. IR (CHCl₃): ν 3018, 2926, 1723, 1609, 1506, 1461, 1323, 1217, 1117, 756, 666 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.93–2.04 (m, 2H), 2.27–2.36 (m, 2H), 4.25 (t, *J* = 5.1 Hz, 2H), 5.95 (t, *J* = 4.3 Hz, 1H), 6.85 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.49 (dd, *J* = 0.9, 1.6 Hz, 1H), 7.74 (dd, *J* = 0.9, 9.2 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 20.4 (t), 21.9 (t), 66.7 (t), 105.8 (d), 112.8 (s), 113.2 (d), 123.7 (d), 125.6 (d), 137.3 (s), 144.1 (s), 157.5 (s), 161.1 (s) ppm. ESI-MS: *m/z* 236.0 (100%, [M+H]⁺). HRMS: Found: 236.0461 ([M+H]⁺), Calcd. 236.0478 ([M+H]⁺). Anal. Calcd for C₁₂H₁₀ClNO₂: C, 61.16; H, 4.28; Cl, 15.04; N, 5.94. Found: C, 61.21; H, 4.19; Cl, 14.94; N, 5.77.

Compound 4bd. Off white solid, Mp. 131 °C 35% yield. IR (CHCl₃): ν 3022, 2958, 2922, 1710, 1695, 1608, 1568, 1527, 1480, 1466, 1345, 1216 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.94–2.05 (m, 2H), 2.28–2.37 (m, 2H), 3.94 (s, 3H), 4.27 (t, *J* = 5.1 Hz, 2H), 5.97 (t, *J* = 4.3 Hz, 1H), 7.49 (dd, *J* = 1.1, 9.1 Hz, 1H), 7.83 (dd, *J* = 1.1, 9.1 Hz, 1H), 8.28 (t, *J* = 1.1 Hz, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ 20.4 (t), 22.0 (t), 52.6 (q), 66.7 (t), 105.7 (d), 115.2 (s), 118.7 (d), 122.6 (d), 122.8 (d), 132.8 (s), 144.2 (s), 157.1 (s), 161.2 (s), 166.3 (s) ppm. ESI-MS: *m/z* 282.3 (100%, [M+H]⁺). Found: 260.0508 ([M+H]⁺), Calcd. 260.0923 ([M+H]⁺). Anal. Calcd for C₁₄H₁₃NO₄: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.72; H, 5.19; N, 5.29.

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