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Synthesis of eight-membered hydroquinolines related to alkaloid skeletons via addition of 4-hydroxycoumarin or 4-hydroxypyran-2-one to quinolinium salts

Firouz Matloubi Moghaddam [a,*], Zohreh Mirjafary [a], Hamdollah Saeidian [a,b], Salman Taheri [a], Bardia Soltanzadeh [a]

[a] Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, PO Box 11155-9516 Tehran, Iran
[b] Department of Chemistry, Payame Noor University, Zanjan Branch, Zanjan, Iran

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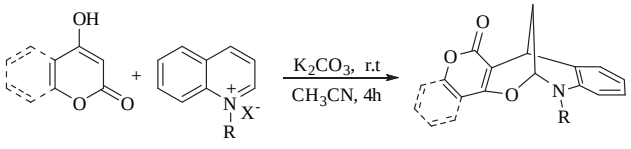
ABSTRACT

A new one-pot synthesis of hitherto unknown polyheterocyclic systems via tandem C-alkylation and intramolecular O-alkylation of 4-hydroxycoumarin or 4-hydroxypyran-2-one with quinolinium salts in excellent yields (71–89%) is reported. The present approach provides a powerful route into polycyclic structures containing nitrogen and oxygen related to alkaloids.

1. Introduction

Heterocycles have popularly been utilized as pharmacophores for preparing drugs.[1] More than half of the biologically active compounds produced by nature contain heterocyclic rings as fundamental components in their skeleton.[2] Coumarin and pyrone fused with other heterocycles are particularly interesting core structures due to their remarkable array of biological activities.[3] On the other hand, functionalized quinoline frameworks continue to play an important role in nitrogen heterocyclic chemistry, due to the fact that this moiety can be found in a variety of physiologically active compounds.[4] Also, the polycyclic frameworks lead to relatively rigid structures that might be expected to show substantial selectivity in their interaction with enzymes or receptors.[5] Development of new methodologies that afford polyheterocyclic and complex molecules from relatively simple starting materials with fewer synthetic steps, environmentally friendly and mild reaction conditions leading to high yields, are recent challenges in organic synthesis.[6] Tandem reactions (TRs), which result from the combination of multiple transformation in a one-pot are highly efficient tools for the synthesis of complex compounds. The TRs have become an increasingly active area of research, affording novel chemical scaffolds for drug discovery efforts.[7]

On the other hand, addition of nucleophilic reagents to quinolinium salts has been shown to be a useful method for the synthesis of substituted quinoline derivatives.[8,6b] We have earlier demonstrated an unusual and efficient synthesis of hitherto unknown indole-annulated pentacyclic indolyl–tetrahydroquinoline and indolyltetrahydroisoquinoline skeletons via addition of indolin-2-thiones as bifunctional nucleophiles to quinolinium and isoquinolinium salts.[9] This protocol was a very mild and simple method for construction of an eight-membered ring in fused heterocycles in a one step process. In the context of our interest in exploring convenient access to heterocyclic systems,[10] we wish to report herein our results on the reaction of 4-hydroxycoumarin and/or 4-hydroxy-6-methyl-pyran-2-one **1** with quinolinium salts **2**, which led to coumarin/pyrone-annulated heterocycles **3a–m** fused at the C-2 and C-4 positions of quinoline in 71–89% yields (Scheme 1).



1 **2** **3a-m**

X = Br, I

R = Me, Et, Bn, *p*-$BrC_6H_4CH_2$, allyl, propargyl

Scheme 1. Synthesis of coumarin/pyrone-annulated heterocycles.

2. Results and discussion

Initially we set out to investigate solvent and base effects in the reaction of *N*-methyl quinolinium salts and 4-hydroxycoumarin as simple model substrates. The results showed that the presence of a base is required to achieve the synthesis of the desired product. In the optimized conditions, CH_3CN, and K_2CO_3 were found to be the best solvent and base for higher yields and shorter reaction times.

* Corresponding author. Tel.: +98 2166165309; fax: +98 2166012983; e-mail address: matloubi@sharif.edu (F.M. Moghaddam).

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The elemental analyses, ^{1}H, ^{13}C NMR, 2 DNMR, and FT-IR spectra of the products clearly indicated the formation of **3a–m**. The IR spectra of **3a** exhibited ν_{max} at 1700 cm^{-1} for the ester carbonyl function. The ^{1}H NMR spectra of **3a** showed two peaks (δ 2.21 and 2.29) for the geminal aliphatic methylene protons, a singlet for the N–CH_3 (δ 3.28), a multiplet for the deshielded benzylic proton (δ 4.29) and a multiplet for the N–CH–O (δ 5.87). When 2-methyl quinolinium salt was used as a starting material, the signal at δ 5.87 disappeared, instead a signal at δ 2.01 for the methyl group was observed. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 19 distinct resonances in agreement with the proposed structure. ^{13}C DEPT experiment showed resonances at δ 25.9 readily recognized as the methylene carbon (C-23), at δ 27.9 (C-17), at δ 37.6 (N–Me), at δ 87.1 (C-13), at δ 162.5 (COO), eight distinct resonances for aromatic methine carbons, and six other quaternary carbons. Further evidence for the bridged structure is given by the HMBC spectrum. In the HMBC spectrum, the key correlations between the H_a at δ 5.87 and carbons at δ 159.5 (C-7), and 25.9 (C-23) implied that the connection points of the pyran ring and the tetrahydroquinoline ring were at C-13 and C-17. Some key HMBC correlations are shown in Figure 1.

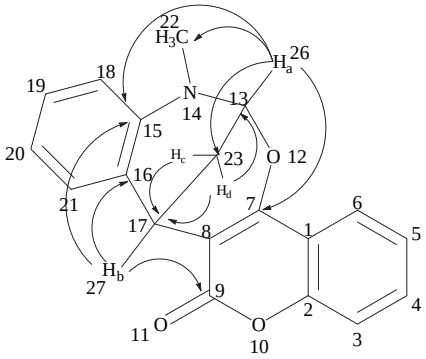
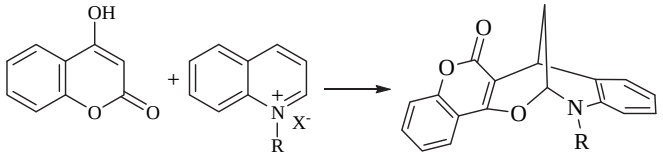


Figure 1. The key HMBC correlations of compound **3a**.

The same configuration was assumed for the other derivatives on account of their NMR spectroscopic similarities. This outcome is in agreement with the relative toxicity observed in previous nucleophilic substitutions of **2**.[9]

In view of the success of the above reaction, we explored the scope of this promising reaction by varying the structure of the *N*-alkylquinolinium salts **2** (Table 1). The reaction proceeds very cleanly under mild conditions at room temperature, and no undesirable side reactions were observed under these reaction conditions.

Table 1
Synthesis of coumarin-annulated heterocycles

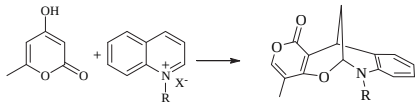


Entry	R	Product	Yield[a] (%)
1	Me	**3a**	89
2	Et	**3b**	84
3	Bn	**3c**	78
4	*p*-Br $C_6H_4CH_2$	**3d**	76
5	Allyl	**3e**	87
6	Propargyl	**3f**	73
7[b]	Me	**3g**	72

[a] Isolated yield.
[b] 2-Methylquinolinium salt as a starting material.

The applicability of this method was further extended by performing the *N*-alkylquinolinium salts **2** and 4-hydroxy-6-methylpyran-2-one. The reaction worked well and the yield of products was satisfactory (Table 2).

Table 2
Synthesis of pyrone-annulated heterocycles



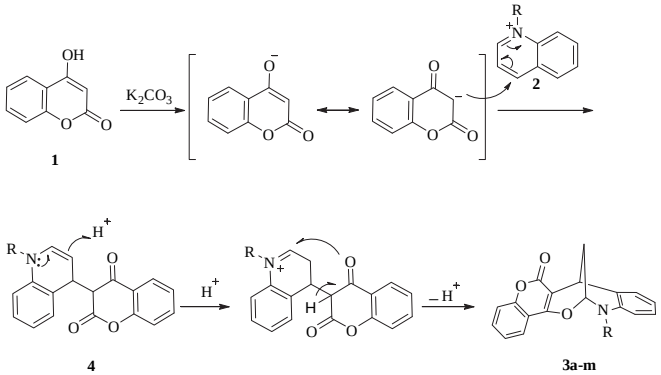
Entry	R_1	Product	Yield[a] (%)
1	Me	**3h**	86
2	Et	**3i**	83
3	Bn	**3j**	79
4	Allyl	**3k**	88
5	Propargyl	**3l**	72
6[b]	Me	**3m**	71

[a] Isolated yield.
[b] 2-Methylquinolinium salt as a starting material.

In the case of quinolinium salts with electron withdrawing groups on N, such as *N*-acetylquinolinium salt under the optimized reaction conditions, no reaction was observed and the initial quinolinium salt and 4-hydroxycoumarin were recovered without any changes.

As a next step, we investigated the scope of the reaction by using the *N*-methyl isoquinolinium salt as a starting material, but the reaction failed to produce the desired product even on heating and by using stronger base or longer reaction time.

A plausible mechanism for formation of the product is shown in Scheme 2. 4-Hydroxycoumarin **1** undergoes a C-alkylation by attack at C-4 of quinolinium salt through the carbon atom of the enolate. This would lead to the formation of an enamine in the pyridine ring of the quinoline, which could be protonated to form an iminium ion. Intramolecular nucleophilic cyclization by the oxygen atom gives the desired product. It was hoped that we could isolate intermediate **4**, but all attempted efforts failed.



Scheme 2. Proposed mechanism for the formation of **3**.

In conclusion, we have reported a novel and highly efficient method for the synthesis of coumarin/pyrone-annulated hydroquinolines. This method offers several advantages, such as high yields and high selectivity and starts from easily accessible starting materials, which makes it a useful and attractive process for the preparation of fused coumarin/pyrone-annulated hydroquinolines in a single step operation.

3. Experimental section

3.1. General

^{1}H NMR spectra were recorded on 500 MHz NMR spectrometer and ^{13}C NMR, DEPT 90 and DEPT 135 spectra were recorded on 125 MHz NMR spectrometer using $CDCl_3$ as solvent, chemical shifts have been expressed in part per million. Melting points were determined on a Buchi B540 apparatus. All the reactions were monitored by thin layer chromatography (TLC) carried out on silica gel with UV light and iodine, as detecting agents. Silica gel and petroleum ether and ethyl acetate were used for flash chromatography. Quinolinium salts **2**[11] were prepared according to the previously reported procedure.

3.2. General procedure for the synthesis of polycyclic hydroquinoline derivatives 3a–m

A mixture of a 4-hydroxycoumarin or 4-hydroxypyran-2-one **1** (1 mmol), quinolinium salt **2** (1 mmol), and K_2CO_3 (0.14 g, 1 mmol) in CH_3CN (5 mL) was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was separated by flash column chromatography on a silica gel with petroleum ether/ethyl acetate (1:1) as an eluent to obtain pure product.

3.3. Spectroscopic data of the products

*3.3.1. 9-Methyl-9,14-dihydro-1H,8H-8,14-methanochromeno [4,3-d][3,1]-benzoxazocin-1-one (**3a**).* Light yellow powder. Mp: 138–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.21 (ddd, J=13.0, 2.5, 2.4 Hz, 1H), 2.28 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 3.28 (s, 3H), 4.29–4.30 (m, 1H), 5.87–5.88 (m, 1H), 6.74 (d, J=8.1 Hz, 1H), 6.82 (t, J=7.4 Hz, 1H), 7.16 (t, J=7.4 Hz, 1H), 7.25–7.27 (m, 2H), 7.49 (t, J=7.7 Hz, 1H), 7.56 (d, J=7.4 Hz, 1H), 7.82 (d, J=8.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9 (CH_2), 27.9 (CH), 37.6 (CH_3), 87.1 (CH), 106.2 (C), 111.1 (CH), 116.2 (C), 116.9 (CH), 119.0 (CH), 123.2 (CH), 124.1 (CH), 126.2 (C), 128.2 (CH), 128.6 (CH), 131.9 (CH), 141.5 (C), 152.5 (C), 159.5 (C), 162.5 (C) ppm. IR (KBr): 1700, 1621, 1397, 1017, 755 cm^{-1}. Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.62; H, 5.17; N, 4.67.

*3.3.2. 9-Ethyl-9,14-dihydro-1H,8H-8,14-methanochromeno [4,3-d][3,1]benzoxazocin-1-one (**3b**).* Light yellow powder. Mp: 133–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (t, J=7.1 Hz, 3H), 2.17 (ddd, J=13.0, 2.5, 2.3 Hz, 1H), 2.29 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 3.54–3.61 (m, 1H), 3.86–3.93 (m, 1H), 4.27–4.28 (m, 1H), 5.91–5.92 (m, 1H), 6.77 (d, J=8.1 Hz, 1H), 6.81 (t, J=7.4 Hz, 1H), 7.16 (t, J=7.4 Hz, 1H), 7.26–7.30 (m, 2H), 7.49 (t, J=7.7 Hz, 1H), 7.56 (d, J=7.4 Hz, 1H), 7.82 (d, J=8.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6 (CH_3), 26.1 (CH_2), 28.1 (CH), 44.8 (CH_2), 86.2 (CH), 106.2 (C), 111.1 (CH), 116.3 (C), 117.0 (CH), 118.8 (CH), 123.1 (CH), 124.1 (CH), 126.4 (C), 128.1 (CH), 128.9 (CH), 131.9 (CH), 140.2 (C), 152.6 (C), 159.3 (C), 162.4 (C) ppm. IR (KBr): 1702, 1622, 1397, 1103, 965, 755 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.35; H, 5.29; N 4.42.

*3.3.3. 9-Benzyl-9,14-dihydro-1H,8H-8,14-methanochromeno[4,3-d][3,1]-benzoxazocin-1-one (**3c**).* Yellow powder. Mp: 166–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (ddd, J=13.0, 2.6, 2.2 Hz, 1H), 2.38 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 4.36–4.37 (m, 1H), 4.78 (ABd, J=17.3 Hz, 1H), 4.99 (ABd, J=17.3 Hz, 1H), 5.94–5.95 (m, 1H), 6.65 (d, J=8.1 Hz, 1H), 6.83 (t, J=7.4 Hz, 1H), 7.07 (t, J=7.5 Hz, 1H), 7.27–7.35 (m, 7H), 7.53 (t, J=7.4 Hz, 1H), 7.60 (d, J=7.5 Hz, 1H), 7.80 (d, J=7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.2 (CH_2), 28.0 (CH), 53.5 (CH_2), 85.7 (CH), 106.2 (C), 111.7 (CH), 116.1 (C), 117.0 (CH), 119.3 (CH), 123.2 (CH), 124.2 (CH), 126.1 (C), 126.7 (CH), 127.7 (CH), 128.2 (CH), 128.8 (CH), 129.3 (CH), 132.0 (CH), 138.1 (C), 141.1 (C), 152.6 (C), 159.2 (C), 162.4 (C) ppm. IR (KBr): 1706, 1495, 1396, 961, 765 cm^{-1}. Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.59; H, 5.15; N, 3.60.

*3.3.4. 9-(4-Bromobenzyl)-9,14-dihydro-1H,8H-8,14-methano chromeno[4,3-d][3,1]benzoxazocin-1-one (**3d**).* Yellow powder. Mp: 183–185 °C. ^{1}H NMR (500 MHz, DMSO): δ 2.21 (ddd, J=13.0, 2.5, 2.4 Hz, 1H), 2.34 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 4.12–4.13 (m, 1H), 4.75 (ABd, J=17.4 Hz, 1H), 5.0 (ABd, J=17.4 Hz, 1H), 6.20–6.21 (m, 1H), 6.57 (d, J=8.1 Hz, 1H), 6.69 (t, J=7.4 Hz, 1H), 6.97 (t, J=7.9 Hz, 1H), 7.18 (d, J=8.2 Hz, 2H), 7.31–7.39 (m, 5H), 7.61 (t, J=7.7 Hz, 1H), 7.70 (d, J=7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7 (CH_2), 28.1 (CH), 53.2 (CH_2), 85.9 (CH), 106.3 (C), 112.1 (CH), 115.8 (C), 117.2 (CH), 118.9 (CH), 120.7 (C), 123.4 (CH), 125.0 (CH), 126.6 (C), 128.3 (CH), 128.5 (CH), 129.6 (CH), 132.1 (CH), 132.9 (CH), 138.8 (C), 140.9 (C), 152.4 (C), 159.1 (C), 161.6 (C) ppm. IR (KBr): 1698, 1623, 1492, 1396 cm^{-1}. Anal. Calcd for $C_{25}H_{18}BrNO_3$: C, 65.23; H, 3.94; N, 3.04. Found: C, 65.40; H, 3.88; N, 3.01.

*3.3.5. 9-Allyl-9,14-dihydro-1H,8H-8,14-methanochromeno [4,3-d]-[3,1]benzoxazocin-1-one (**3e**).* Pale yellow powder. Mp: 129–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.21 (ddd, J=13.0, 2.6, 2.2 Hz, 1H), 2.32 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 4.12–4.17 (m, 1H), 4.30–4.31 (m, 1H), 4.35–4.39 (m, 1H), 5.22–5.27 (m, 2H), 5.88–5.89 (m, 1H), 5.90–5.97 (m, 1H), 6.72 (d, J=8.1 Hz, 1H), 6.82 (t, J=7.4 Hz, 1H), 7.14 (t, J=8.1 Hz, 1H), 7.26–7.30 (m, 2H), 7.50 (t, J=7.7 Hz, 1H), 7.56 (d, J=7.4 Hz, 1H), 7.82 (d, J=7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.1 (CH_2), 28.1 (CH), 52.2 (CH_2), 85.5 (CH), 106.1 (C), 111.6 (CH), 116.2 (C), 116.97 (CH), 116.99 (CH_2), 119.1 (CH), 123.1 (CH), 124.1 (CH), 126.2 (C), 128.1 (CH), 128.7 (CH), 131.9 (CH), 133.6 (CH), 140.7 (C), 152.6 (C), 159.1 (C), 162.3 (C) ppm. IR (KBr): 1709, 1620, 1491, 1390, 956, 752 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.21; H, 5.04; N, 4.30.

*3.3.6. 9-Prop-2-yn-1-yl-9,14-dihydro-1H,8H-8,14-methano chromeno[4,3-d][3,1]benzoxazocin-1-one (**3f**).* Light brown powder. Mp: 138–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (ddd, J=13.0, 2.5, 2.1 Hz, 1H), 2.22–2.23 (m, 1H), 2.33 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 4.23 (ABdd, J=18.3, 2.3 Hz, 1H), 4.28–4.29 (m, 1H), 4.48 (ABdd, J=18.3, 2.4 Hz, 1H), 6.01–6.02 (m, 1H), 6.87 (t, J=7.4 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 7.21 (t, J=7.4 Hz, 1H), 7.27–7.30 (m, 2H), 7.50 (t, J=7.7 Hz, 1H), 7.57 (d, J=7.4 Hz, 1H), 7.83 (d, J=8.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.3 (CH_2), 28.0 (CH), 39.3 (CH_2), 72.6 (CH), 79.7 (C), 85.1 (CH), 106.0 (C), 111.7 (CH), 116.1 (C), 117.0 (CH), 119.8 (CH), 123.2 (CH), 124.1 (CH), 126.8 (C), 128.2 (CH), 128.8 (CH), 132.0 (CH), 139.9 (C), 152.6 (C), 159.1 (C), 162.4 (C) ppm. IR (KBr): 1703, 1623, 1493, 1396, 1036, 751 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.34; H, 4.45; N, 4.36.

*3.3.7. 8,9-Dimethyl-9,14-dihydro-1H,8H-8,14-methano chromeno[4,3-d][3,1]benzoxazocin-1-one (**3g**).* Light yellow powder. Mp: 142–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.23–2.31 (m, 2H), 3.16 (s, 3H), 4.21–4.22 (m, 1H), 6.73 (d, J=8.1 Hz, 1H), 6.80 (t, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 7.28–7.30 (m, 2H), 7.50–7.51 (m, 2H), 7.86 (d, J=7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.0 (CH_3), 29.7 (CH_3), 32.4 (CH), 34.7 (CH_2), 95.5 (C), 105.3 (C), 112.0 (CH), 116.3 (C), 117.0 (CH), 118.8 (CH), 123.0 (CH), 124.1 (CH), 127.0 (C), 128.0 (CH), 128.1 (CH), 131.8 (CH), 143.3 (C), 152.7 (C), 159.5 (C), 162.6 (C) ppm. IR (KBr): 1705, 1623, 1389, 1038, 754 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.32; H, 5.47; N 4.31.

*3.3.8. 9-Methyl-9,14-dihydro-1H,8H-8,14-methanochromeno [4,3-d]-[3,1]benzoxazocin-1-one (**3h**).* Pale yellow powder. Mp: 123–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (ddd, J=13.0, 2.5, 2.4 Hz, 1H), 2.11 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 2.16 (s, 3H), 3.28 (s, 3H), 4.10–4.11 (m, 1H), 5.63–5.64 (m, 1H), 5.81 (s, 1H), 6.72 (d, J=8.1 Hz, 1H), 6.79 (t,

J=7.4 Hz, 1H), 7.16 (t, J=7.4 Hz, 1H), 7.48 (d, J=7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2 (CH_3), 25.9 (CH_2), 27.4 (CH), 37.5 (CH_3), 86.7 (CH), 100.6 (CH), 103.6 (C), 110.9 (CH), 118.9 (CH), 126.5 (C), 128.0 (CH), 128.4 (CH), 141.5 (C), 160.2 (C), 164.1 (C), 164.2 (C) ppm. IR (KBr): 1698, 1571, 1405, 1324, 745 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.56; H, 5.75; N, 5.13.

*3.3.9. 7-Ethyl-3-methyl-7,12-dihydro-1H,6H-6,12-methano pyrano-[4,3-d][3,1]benzoxazocin-1-one (**3i**).* Pale yellow powder. Mp: 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, J=7.1 Hz, 3H), 2.04 (ddd, J=12.9, 2.7, 2.1 Hz, 1H), 2.14 (ddd, J=12.9, 3.1, 3.0 Hz, 1H), 2.16 (s, 3H), 3.48–3.55 (m, 1H), 3.77–3.82 (m, 1H), 4.09–4.10 (m, 1H), 5.67–5.68 (m, 1H), 5.81 (s, 1H), 6.74–6.79 (m, 2H), 7.15 (t, J=7.4 Hz, 1H), 7.48 (d, J=7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5 (CH_3), 20.2 (CH_3), 26.1 (CH_2), 27.5 (CH), 44.6 (CH_2), 85.6 (CH), 100.6 (CH), 103.5 (C), 110.9 (CH), 118.5 (CH), 126.6 (C), 128.0 (CH), 128.7 (CH), 140.2 (C), 160.2 (C), 163.9 (C), 164.2 (C) ppm. IR (KBr): 1699, 1575, 1495, 1190, 922, 746, 594 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.94; H, 6.18; N, 5.06.

*3.3.10. 7-Benzyl-3-methyl-7,12-dihydro-1H,6H-6,12-methano pyrano-[4,3-d][3,1]benzoxazocin-1-one (**3j**).* Light yellow powder. Mp: 158–160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.22–2.23 (m, 2H), 4.18–4.19 (m, 1H), 4.74 (ABd, J=17.5 Hz, 1H), 4.90 (ABd, J=17.5 Hz, 1H), 5.71–5.72 (m, 1H), 5.84 (s, 1H), 6.62 (d, J=8.1 Hz, 1H), 6.80 (t, J=7.4 Hz, 1H), 7.05 (t, J=7.5 Hz, 1H), 7.26 (d, J=7.5 Hz, 2H), 7.30–7.39 (m, 3H), 7.53 (d, J=7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.2 (CH_2), 27.4 (CH), 53.3 (CH_2), 85.2 (CH), 100.5 (CH), 103.5 (C), 111.6 (CH), 119.1 (CH), 126.4 (C), 126.6 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 129.2 (CH), 138.2 (C), 141.0(C), 160.4 (C), 163.7 (C), 164.2 (C) ppm. IR (KBr): 1705, 1589, 997, 816, 733 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.39; H, 5.66; N, 4.12.

*3.3.11. 7-Allyl-3-methyl-7,12-dihydro-1H,6H-6,12-methano pyrano-[4,3-d][3,1]benzoxazocin-1-one (**3k**).* Light yellow powder. Mp: 143–145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (ddd, J=13.0, 2.6, 2.3 Hz, 1H), 2.17 (s, 3H), 2.18 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 4.08–4.12 (m, 2H), 4.25–4.30 (m, 1H), 5.19–5.24 (m, 2H), 5.64–5.65 (m, 1H), 5.81 (s, 1H), 5.88–5.95 (m, 1H), 6.69 (d, J=8.1 Hz, 1H), 6.79 (t, J=7.4 Hz, 1H), 7.13 (t, J=7.4 Hz, 1H), 7.49 (d, J=7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.1 (CH_2), 27.5 (CH), 52.0 (CH_2), 84.9 (CH), 100.5 (CH), 103.3 (C), 111.4 (CH), 116.8 (CH_2), 118.9 (CH), 126.4 (C), 127.9 (CH), 128.5 (CH), 133.6 (CH), 140.7 (C), 160.3 (C), 163.7 (C), 164.1 (C) ppm. IR (KBr): 1702, 1576, 1496, 1223, 920, 747, 597 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.04; H, 5.89; N, 4.86.

*3.3.12. 3-Methyl-7-prop-2-yn-1-yl-7,12-dihydro-1H,6H-6,12-methanopyrano[4,3-d][3,1]benzoxazocin-1-one (**3l**).* Light brown powder. Mp: 146–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07 (ddd, J=13.0, 2.5, 2.1 Hz, 1H), 2.15 (s, 3H), 2.18 (ddd, J=13.0, 3.1, 3.0 Hz, 1H), 2.28–2.29 (m, 1H), 4.09–4.10 (m, 1H), 4.18 (ABdd, J=18.3, 2.3 Hz, 1H), 4.38 (ABdd, J=18.3, 2.3 Hz, 1H), 5.76–5.77 (m, 1H), 5.81 (s, 1H), 6.84 (t, J=7.4 Hz, 1H), 6.89 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.4 Hz, 1H), 7.49 (d, J=7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.2 (CH_2), 27.3 (CH), 39.2 (CH_2), 72.5 (CH), 79.8 (C), 84.6 (CH), 100.5 (CH), 103.3 (C), 111.5 (CH), 119.6 (CH), 127.0 (C), 128.0 (CH), 128.5 (CH), 139.9 (C), 160.4 (C), 163.6 (C), 164.1 (C) ppm. IR (KBr):1700, 1578, 1396, 911, 750 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.60; H, 5.22; N, 4.59.

*3.3.13. 3,6,7-Trimethyl-7,12-dihydro-1H,6H-6,12-methano pyrano-[4,3-d][3,1]benzoxazocin-1-one (**3m**).* Pale yellow powder. Mp: 133–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.09 (dd, J=13.0, 3.4 Hz, 1H), 2.17 (s, 3H), 2.18 (dd, J=13.0, 2.7 Hz, 1H), 3.10 (s, 3H), 4.04–4.05 (m, 1H), 5.79 (s, 1H), 6.71 (d, J=8.1 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 7.44 (d, J=7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2 (CH_3), 26.0 (CH_3), 29.1 (CH_3), 32.2 (CH), 34.7 (CH_2), 89.2 (C), 100.7 (CH), 102.6 (C), 111.8 (CH), 118.6 (CH), 127.3 (C), 127.8 (CH), 127.9 (CH), 143.3 (C), 160.3 (C), 164.1 (C), 164.3 (C) ppm. IR (KBr): 1705, 1579, 1390, 984, 759 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.90; H, 6.23; N, 5.12.

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