

The synthesis of dibenzazocines *via* tandem dinucleophilic addition of phenols to quinolinium salts

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Abstract

Dibenzazocines were prepared *via* tandem dinucleophilic addition of phenols to quinolinium salts in good yields. The procedure is efficient, simple and the substrates are easily available.

Keywords: Polycyclic heterocycles, tandem reaction, dibenzazocines, quinolinium salts, phenols

Introduction

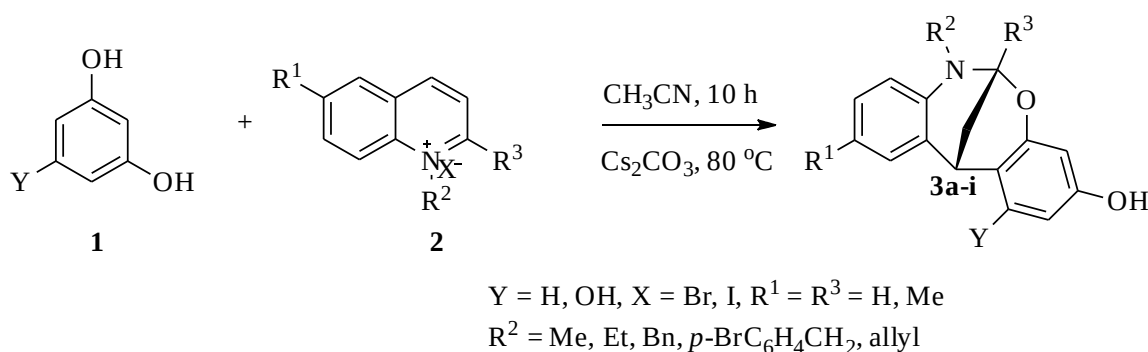
Nitrogen- and oxygen-containing heterocyclic compounds are widespread in nature and their applications for biologically active pharmaceuticals and functional materials are important. Among the large variety of heterocyclic compounds, benzoxazocines have received considerable attention because of their pharmacological properties including antidepressant, antithrombotic, antipsychotic and activities against breast cancer.¹ On the other hand, the quinoline skeleton is found in a large number of naturally occurring and synthetic biologically-active heterocyclic compounds. In particular, 1,4-dihydroquinoline derivatives act as inhibitor of the cholesterol ester transfer protein, antiallergenic, antiinflammatory, antiviral, antimalarial and antihypertensive agents.² Phenols constitute the preminent core of the biologically important natural and non-natural compounds. They are also versatile materials for synthesis of complex heterocycles.³ They can behave as 1,3-carbon, oxygen dinucleophiles in one-pot reactions. Furthermore, the construction of medium-ring heterocycles especially eight-membered rings remains a significant synthetic challenge goal in modern organic synthesis because of entropy reasons and ring strain. However, limited attention has been given to the synthesis of medium-ring heterocycles, examples include cycloadditions, ring-closing metathesis, ring expansion, Mitsunobu reactions, and metal-mediated ring cyclization.⁴ Therefore, the development of

methods to generate medium-ring systems for applications in natural product or non-natural compound synthesis is a useful aim. Tandem reactions (TRs) gained significant interest within the scientific community as an efficient, convenient, facile execution and time-saving approach to a variety of complex heterocyclic molecules. Therefore, the design of novel TRs has attracted great attention from research groups working in areas such as drug discovery, organic synthesis and materials science.⁵

Quinolinium and isoquinolinium salts represent important synthetic building blocks, which can be generated by alkylation or acylation of quinoline and isoquinoline. Addition of nucleophilic reagents to these salts proved to be a useful method for the synthesis of substituted quinoline and isoquinoline derivatives.⁶ We earlier demonstrated an efficient synthesis of a broad spectrum of dibenzazocines *via* unique tandem 1,3-dinucleophilic addition of different bifunctional nucleophiles to quinolinium and isoquinolinium salts.⁷ This protocol is a very mild and simple method for construction of eight-membered ring in fused heterocycles in one-step process.

Results and Discussion

We herein describe an unprecedented C-alkylation/ intramolecular O-alkylation tandem process for the construction of heterotetracyclic dibenzazocines. The reaction generally involves the initial addition of phenol to quinolinium salt to form enamine intermediate which can be trapped by intramolecular O-alkylation of phenol (Scheme 1). To the best of our knowledge, there has not been any report on the reaction between phenols and quinolinium salts.



Scheme 1

We started our study by examining the reaction of the *N*-methyl quinolinium salt **2a** as a test substrate with phloroglucinol, to produce corresponding dibenzazocines **3a**. We investigated the effects of solvent, base and temperature (Table 1). In the absence of base, no desired product was obtained, while good results were obtained in the presence of Cs₂CO₃ at 80 °C after 10 h. The effect of temperature was studied by carrying out the model reaction at room temperature, and

reflux temperature of solvents. It was observed that the yield was increased as the reaction temperature raised. Then we continued to optimize the model reaction by detecting the efficiency of polar and non-polar solvents. The polar solvent such as CH₃CN was much better than non-polar solvent. With considering the reaction time, amount of substrates and the yield, the best optimized condition is: Cs₂CO₃ (1 equiv.), quinolinium salt (1equiv.) and phenol (2 equiv.) in CH₃CN (5 mL) at 80 °C for 10 hours.

Table 1. Optimization of the model reaction conditions

Entry	Base	Solvent	T(°C)	Time (h)	Ratio 1/2	Yield (%)
1	K ₂ CO ₃	CH ₃ CN	rt	72	1:1	trace
2	K ₂ CO ₃	CHCl ₃	rt	72	1:1	-
3	K ₂ CO ₃	Toluene	rt	24	1:1	-
4	K ₂ CO ₃	DMF	rt	24	1:1	-
5	K ₂ CO ₃	CH ₃ CN	80	10	1:1	25
6	K ₂ CO ₃	CH ₃ OH	70	10	1:1	18
7	K ₂ CO ₃	Toluene	110	10	1:1	15
8	Cs ₂ CO ₃	CH ₃ CN	80	10	1:1	30
9	Cs ₂ CO ₃	CH ₃ CN	80	10	1:2	50
10	Cs₂CO₃	CH₃CN	80	10	2:1	73

The elemental analyses, ¹H, ¹³C NMR and 2DNMR and FT-IR spectra of the products clearly indicated the formation of **3a-i**. The IR spectrum of **3a** exhibited $\nu_{\max}$ at 3341, 3226, 1615, 1139, 1055, 817 and 746 cm⁻¹. The ¹H NMR spectra of **3a** showed two peaks (δ 1.84 and 2.00) for the geminal aliphatic methylene protons in hydroquinoline ring, a singlet for the N-CH₃ (δ 3.05), a multiplet for the deshielded benzylic proton (δ 4.05), a multiplet for the N-CH-O (δ 5.47) and two singlet resonances at δ 8.93 and 9.28 for two phenolic protons using DMSO as solvent. When 2-methylquinolinium salt **2e** was used as a starting material, the signal at δ 5.54 disappeared, instead a signal at δ 1.79 for methyl group was observed (see ¹H NMR of **3e**). The ¹H-decoupled ¹³C NMR spectrum of **3a** showed 16 distinct resonances in agreement with the proposed structure. The ¹³C DEPT experiment showed resonances at δ 26.6 readily recognized as methylene carbon (C-19), δ 27.4 (C-10), δ 37.3 (N-Me), δ 83.5 (C-9), six distinct resonances for the aromatic methine carbons and six distinct resonances for the aromatic quaternary carbons. Further evidence for the bridged structure was provided by the HMBC spectrum. The key correlations between H_a at δ 5.47 and the carbons at δ 157.1 (C-3) and 26.6 (C-19) implied that the connection points of phenol ring and the tetrahydroquinoline ring were at C-9 and C-10. Some of the key HMBC correlations are shown in Figure 1.

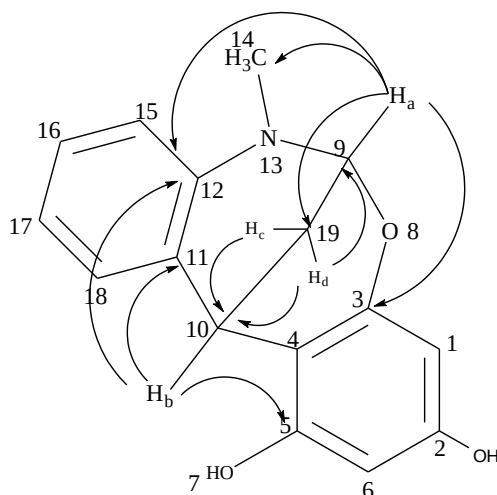


Figure 1. The key HMBC correlations in compound **3a**

To evaluate the scope of the reaction, we reacted other *N*-alkylquinolinium salts **2** and phenols **1** to give the corresponding dibenzazocines under optimized reaction conditions (Table 2). We found that in the case of resorcinol (Table 2 entries 7, 8, 9) only one product was observed and reaction proceeded with high regioselectivity.

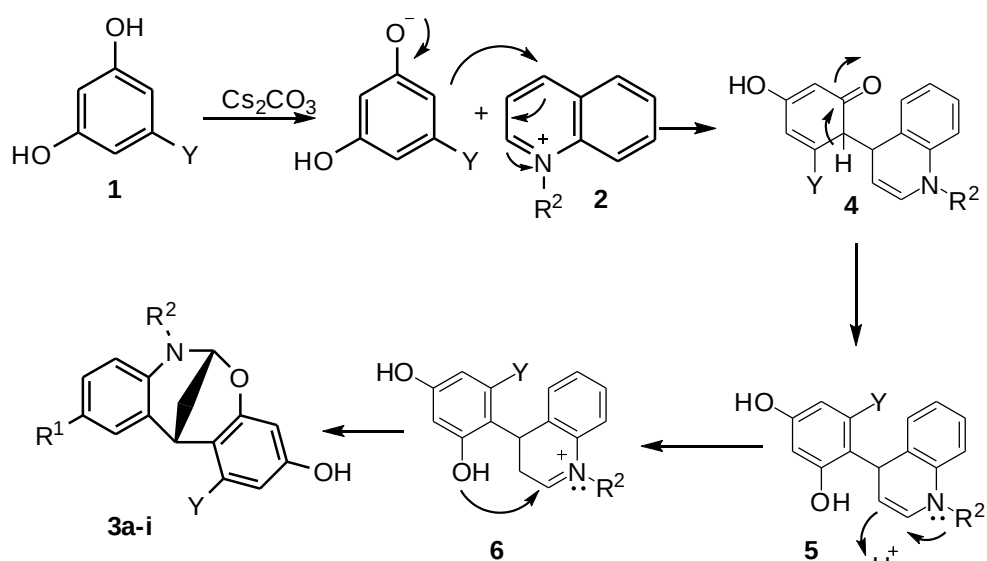
The same configuration was assumed for the other derivatives on account of their spectroscopic similarities. This outcome is in agreement with the relative toxicity observed in previous nucleophilic substitutions of **2**.^{7a}

Table 2. Efficient synthesis of dibenzazocines *via* tandem dinucleophilic addition

Entry	Y	R ¹	R ²	R ³	Product	Yield (%)
1	OH	H	Me	H	3a	73
2	OH	H	Et	H	3b	70
3	OH	H	Bn	H	3c	66
4	OH	H	<i>p</i> -BrC ₆ H ₄ CH ₂	H	3d	65
5	OH	H	Me	Me	3e	63
6	OH	Me	Me	H	3f	68
7	H	H	Me	H	3g	67
8	H	H	Bn	H	3h	65
9	H	H	allyl	H	3i	60

A possible reaction mechanism to account for the formation of dibenzazocines is proposed in Scheme 2. Phenol **1** undergoes a C-alkylation by attack at C-4 of quinolinium salt. The resulting enamine **5** can in turn be reactivated *via* iminium intermediate **6** to undergo second nucleophilic addition. Finally intramolecular nucleophilic cyclization involving the hydroxyl group gives the

desired product. The excess amount of phenol may act as a proton source for isomerization process of enamine **5** to iminium **6**.



Scheme 2

Conclusions

In conclusion, we have developed an efficient, simple and novel method for the preparation of different types of dibenzazocines which are important compounds in medicinal and industrial chemistry. Good product yield, high selectivity and low cost of the reagents are the salient features of this method. The reaction starts from easily accessible starting materials, which makes it a useful and attractive process for the preparation of benzoxazocines in a one step operation.

Experimental Section

General. All chemicals were purchased from Merck and Aldrich and were used without any further purification. NMR spectra were recorded at 500 MHz for proton and at 125 MHz for carbon nuclei in CDCl_3 and DMSO. The products were purified by column chromatography carried out on silica gel by using petroleum ether/ethyl acetate.

General procedure for the synthesis of dibenzazocines (3a-i)

A mixture of a phenol **1** (2 mmol), quinolinium salt **2** (1 mmol), and cesium carbonate (1 mmol) in CH₃CN (5 ml) was heated at 80 °C for 10 hours. 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 (2:1) as an eluent to obtain pure solid product.

7-Methyl-7,12-dihydro-6H-6,12-methanodibenzo[*d,g*][1,3]oxazocine-1,3-diol (3a). ¹H NMR (500 MHz, DMSO-*d*₆): δ 1.84 (ddd, *J* 12.6, 2.5, 2.4 Hz, 1H, H_c), 2.00 (ddd, *J* 12.6, 3.1, 3.0 Hz, 1H, H_d), 3.05 (s, 3H, N-CH₃), 4.05-4.06 (m, 1H, H_b), 5.47-5.48 (m, 1H, H_a), 5.70 (d, *J* 1.8 Hz, 1H, ArH), 5.82 (d, *J* 2.0 Hz, 1H, ArH), 6.59 (t, *J* 7.3 Hz, 1H, ArH), 6.62 (d, *J* 8.1 Hz, 1H, ArH), 6.99 (t, *J* 7.7 Hz, 1H, ArH), 7.24 (d, *J* 7.2 Hz, 1H, ArH), 8.93 (s, 1H, OH), 9.28 (s, 1H, OH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 26.6 (C-19), 27.4 (C-10), 37.3 (N-CH₃), 83.5 (C-9), 95.1 (ArCH), 95.7 (ArCH), 106.4 (ArC), 110.7 (ArCH), 117.4 (ArCH), 127.5 (ArCH), 127.8 (ArCH), 128.7 (ArC), 142.9 (ArC), 154.0 (ArC), 156.1 (ArC), 157.1 (ArC). FT-IR (KBr): 3341, 3226, 1615, 1139, 1055, 817, 746. Anal. Calcd for C₁₆H₁₅NO₃: C 71.36, H 5.61, N 5.20, Found: C 71.54, H 5.49, N 5.31.

7-Ethyl-7,12-dihydro-6H-6,12-methanodibenzo[*d,g*][1,3]oxazocine-1,3-diol (3b). ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆): δ 1.09 (t, *J* 7.0 Hz, 3H, N-CH₂CH₃), 1.78 (ddd, *J* 12.5, 2.5, 2.4 Hz, 1H, H_c), 2.04 (ddd, *J* 12.5, 3.1, 3.0 Hz, 1H, H_d), 3.31-3.35 (m, 1H, N-CHHCH₃), 3.62-3.67 (m, 1H, N-CHHCH₃), 4.11-4.12 (m, 1H, H_b), 5.34-5.35 (m, 1H, H_a), 5.77 (d, *J* 2.2 Hz, 1H, ArH), 5.82 (d, *J* 2.2 Hz, 1H, ArH), 6.49 (t, *J* 7.3 Hz, 1H, ArH), 6.52 (d, *J* 8.1 Hz, 1H, ArH), 6.90 (t, *J* 7.7 Hz, 1H, ArH), 7.27 (d, *J* 7.3 Hz, 1H, ArH), 8.24 (s, 1H, OH), 8.43 (s, 1H, OH). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆): δ 13.3 (N-CH₂CH₃), 26.6 (C-19), 27.5 (C-10), 43.9 (N-CH₂), 82.6 (C-9), 95.4 (ArCH), 95.9 (ArCH), 106.3 (ArC), 110.2 (ArCH), 116.9 (ArCH), 127.0 (ArCH), 128.0 (ArCH), 128.7 (ArC), 141.3 (ArC), 153.6 (ArC), 155.7 (ArC), 156.6 (ArC). FT-IR (KBr): 3348, 3225, 1615, 1126, 810, 594 cm⁻¹. Anal. Calcd for C₁₇H₁₇NO₃: C 72.07, H 6.05, N 4.94, Found: C 72.25, H 6.17, N 4.82.

7-Benzyl-7,12-dihydro-6H-6,12-methanodibenzo[*d,g*][1,3]oxazocine-1,3-diol (3c). ¹H NMR (500 MHz, CDCl₃): δ 2.10 (ddd, *J* 12.7, 2.5, 2.4 Hz, 1H, H_c), 2.27 (ddd, *J* 12.7, 2.9, 2.7 Hz, 1H, H_d), 4.34-4.35 (m, 1H, H_b), 4.72 (ABd, *J* 17.5 Hz, 1H, N-CHH), 4.95 (ABd, *J* 17.5 Hz, 1H, N-CHH), 5.57-5.58 (m, 1H, H_a), 5.81 (brs, 1H, OH), 5.83 (d, *J* 2.0 Hz, 1H, ArH), 5.92 (brs, 1H, OH), 6.03 (d, *J* 2.0 Hz, 1H, ArH), 6.57 (d, *J* 8.1 Hz, 1H, ArH), 6.72 (t, *J* 7.3 Hz, 1H, ArH), 6.99 (t, *J* 7.3 Hz, 1H, ArH), 7.26-7.36 (m, 5H, ArH), 7.46 (d, *J* 7.3 Hz, 1H, ArH). ¹³C NMR (125 MHz, CDCl₃): δ 26.6 (C-19), 27.7 (C-10), 52.9 (N-CH₂), 83.0 (C-9), 96.2 (ArCH), 96.6 (ArCH), 107.5 (ArC), 111.4 (ArCH), 117.9 (ArCH), 126.7 (ArCH), 127.4 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.0 (ArC), 129.1 (ArCH), 138.8 (ArC), 142.0 (ArC), 153.8 (ArC), 154.7 (ArC), 155.2 (ArC). FT-IR (KBr): 3340, 3228, 1615, 1132, 815 cm⁻¹. Anal. Calcd for C₂₂H₁₉NO₃: C 76.50, H 5.54, N 4.06, Found: C 76.36, H 5.63, N 3.95.

7-(4-Bromobenzyl)-7,12-dihydro-6H-6,12-methanodibenzo[d,g][1,3]oxazocine-1,3-diol (3d).

¹H NMR (500 MHz, CDCl₃): δ 2.07 (ddd, *J* 12.7, 2.5, 2.4 Hz, 1H, H_c), 2.24 (ddd, *J* 12.7, 2.8, 2.7 Hz, 1H, H_d), 4.32-4.33 (m, 1H, H_b), 4.61 (ABd, *J* 17.5 Hz, 1H, N-CHH), 4.88 (ABd, *J* 17.5 Hz, 1H, N-CHH), 5.52-5.53 (m, 1H, H_a), 5.72 (brs, 1H, OH), 5.84 (brs, 1H, OH), 5.92 (d, *J* 1.7 Hz, 1H, ArH), 6.01 (d, *J* 1.7 Hz, 1H, ArH), 6.47 (d, *J* 8.1 Hz, 1H, ArH), 6.70 (t, *J* 7.3 Hz, 1H, ArH), 6.96 (t, *J* 7.9 Hz, 1H, ArH), 7.11 (d, *J* 8.2 Hz, 2H, ArH), 7.43 (d, *J* 8.3 Hz, 2H, ArH), 7.44 (d, *J* 7.3 Hz, 1H, ArH). ¹³C NMR (125 MHz, CDCl₃): δ 26.6 (C-19), 27.6 (C-10), 52.7 (N-CH₂), 83.0 (C-9), 96.2 (ArCH), 96.6 (ArCH), 107.3 (ArC), 111.3 (ArCH), 118.2 (ArCH), 121.1 (ArC), 127.6 (ArCH), 127.9 (ArCH), 128.1 (ArC), 128.6 (ArCH), 132.2 (ArCH), 137.8 (ArC), 141.7 (ArC), 153.8 (ArC), 154.7 (ArC), 155.4 (ArC). FT-IR (KBr): 3338, 3233, 1616, 1137, 806, 606 cm⁻¹. Anal. Calcd for C₂₂H₁₈BrNO₃: C 62.28, H 4.28, N 3.30, Found: C 62.14, H 4.41, N 3.19.

6,7-Dimethyl-7,12-dihydro-6H-6,12-methanodibenzo[d,g][1,3]oxazocine-1,3-diol (3e).

¹H NMR (500 MHz, CDCl₃): δ 1.79 (s, 3H, CH₃), 2.05 (dd, *J* 12.7, 2.5 Hz, 1H, H_c), 2.17 (dd, *J* 12.7, 3.6 Hz, 1H, H_d), 3.05 (s, 3H, N-CH₃), 4.19-4.20 (m, 1H, H_b), 5.96 (d, *J* 2.1 Hz, 1H, ArH), 5.98 (d, *J* 2.1 Hz, 1H, ArH), 6.63-6.70 (m, 4H, ArH), 7.07 (d, *J* 7.3 Hz, 1H, ArH), 7.34 (d, *J* 7.3 Hz, 1H, ArH). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆): δ 26.4 (CH₃), 31.7 (C-10), 35.1 (C-19), 37.1 (N-CH₃), 84.9 (C-9), 95.3 (ArCH), 95.9 (ArCH), 105.1 (ArC), 111.1 (ArCH), 116.7 (ArCH), 126.8 (ArCH), 127.1 (ArCH), 129.5 (ArC), 144.3 (ArC), 154.3 (ArC), 156.7 (ArC), 155.0 (ArC). FT-IR (KBr): 3345, 3230, 1615, 1131, 1055, 813, 741 cm⁻¹. Anal. Calcd for C₁₇H₁₇NO₃: C 72.07, H 6.05, N 4.94, Found: C 72.24, H 5.81, N 5.07.

7,10-Dimethyl-7,12-dihydro-6H-6,12-methanodibenzo[d,g][1,3]oxazocine-1,3-diol (3f).

¹H NMR (500 MHz, CDCl₃): δ 1.99 (ddd, *J* 12.6, 2.5, 2.4 Hz, 1H, H_c), 2.17 (ddd, *J* 12.6, 3.1, 3.0 Hz, 1H, H_d), 2.27 (s, 3H, CH₃), 3.18 (s, 3H, N-CH₃), 4.22-4.23 (m, 1H, H_b), 5.46-5.47 (m, 1H, H_a), 5.76 (brs, 1H, OH), 5.77 (d, *J* 2.0 Hz, 1H, ArH), 5.90 (brs, 1H, OH), 5.91 (d, *J* 2.0 Hz, 1H, ArH), 6.60 (d, *J* 8.2 Hz, 1H, ArH), 6.92 (dd, *J* 8.2, 1.6 Hz, 1H, ArH), 7.23 (d, *J* 1.8 Hz, 1H, ArH). ¹³C NMR (125 MHz, CDCl₃): δ 20.8 (CH₃), 26.5 (C-19), 27.6 (C-10), 37.1 (N-CH₃), 84.5 (C-9), 95.8 (ArCH), 96.4 (ArCH), 107.7 (ArC), 110.7 (ArCH), 126.8 (ArC), 127.97 (ArCH), 128.03 (ArC), 128.4 (ArCH), 140.3 (ArC), 154.1 (ArC), 154.4 (ArC), 155.0 (ArC). FT-IR (KBr): 3340, 3226, 1615, 1129, 1043, 815 cm⁻¹. Anal. Calcd for C₁₇H₁₇NO₃: C 72.07, H 6.05, N 4.94, Found: C 71.87, H 6.14, N 5.12.

7-Methyl-7,12-dihydro-6H-6,12-methanodibenzo[d,g][1,3]oxazocin-3-ol (3g).

¹H NMR (500 MHz, CDCl₃): δ 1.93 (ddd, *J* 12.5, 2.5, 2.4 Hz, 1H, H_c), 2.17 (ddd, *J* 12.5, 3.1, 3.0 Hz, 1H, H_d), 3.07 (s, 3H, N-CH₃), 3.78-3.79 (m, 1H, H_b), 5.32 (brs, 1H, OH), 5.35-5.36 (m, 1H, H_a), 6.23 (dd, *J* 8.1, 2.3 Hz, 1H, ArH), 6.26 (d, *J* 2.3 Hz, 1H, ArH), 6.54 (d, *J* 8.1 Hz, 1H, ArH), 6.58 (t, *J* 7.3 Hz, 1H, ArH), 6.58 (d, *J* 8.1 Hz, 1H, ArH), 6.98 (t, *J* 8.2 Hz, 1H, ArH), 7.07 (d, *J* 7.3 Hz, 1H, ArH). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆): δ 26.6 (C-19), 34.3 (C-10), 37.0 (N-CH₃), 83.8 (C-9), 103.9 (ArCH), 108.6 (ArCH), 110.6 (ArCH), 117.8 (ArCH), 118.4 (ArC), 126.4 (ArCH), 127.6 (ArCH), 128.8 (ArC), 129.3 (ArCH), 142.3 (ArC), 153.1 (ArC), 157.0 (ArC). FT-IR (KBr): 3342, 1603, 1506, 1229, 1016, 752 cm⁻¹. Anal. Calcd for C₁₆H₁₅NO₂: C 75.87, H 5.97, N 5.53, Found: C 75.96, H 5.88, N 5.44.

7-Benzyl-7,12-dihydro-6H-6,12-methanodibenzo[d,g] [1,3]oxazocin-3-ol (3h). ^1H NMR (500 MHz, CDCl_3): δ 2.15 (ddd, J 12.6, 2.5, 2.4 Hz, 1H, H_c), 2.36 (ddd, J 12.6, 3.1, 3.0 Hz, 1H, H_d), 3.97-3.98 (m, 1H, H_b), 4.68 (ABd, J 17.5 Hz, 1H, N-CHH), 4.93 (ABd, J 17.5 Hz, 1H, N-CHH), 5.30 (brs, 1H, OH), 5.56-5.57 (m, 1H, H_a), 6.38 (dd, J 8.2, 2.3 Hz, 1H, ArH), 6.43 (d, J 2.3 Hz, 1H, ArH), 6.55 (d, J 8.1 Hz, 1H, ArH), 6.73 (t, J 7.2 Hz, 1H, ArH), 6.98-7.03 (m, 2H, ArH), 7.24-7.36 (m, 6H, ArH). ^{13}C NMR (125 MHz, CDCl_3): δ 26.8 (C-19), 34.4 (C-10), 53.0 (N-CH₂), 82.7 (C-9), 104.1 (ArCH), 108.8 (ArCH), 111.5 (ArCH), 118.2 (ArCH), 119.2 (ArC), 126.7 (ArCH), 126.8 (ArCH), 127.4 (ArCH), 127.9 (ArCH), 128.7 (ArC), 129.1 (ArCH), 129.8 (ArCH), 138.8 (ArC), 141.9 (ArC), 153.1 (ArC), 156.0 (ArC). FT-IR (KBr): 3387, 1602, 1506, 1106, 746 cm^{-1} . Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_2$: C 80.22, H 5.81, N 4.25, Found: C 80.08, H 5.93, N 4.34.

7-Vinyl-7,12-dihydro-6H-6,12-methanodibenzo[d,g] [1,3] oxazocin-3-ol (3i). ^1H NMR (500 MHz, CDCl_3): δ 2.03 (ddd, J 12.6, 2.5, 2.4 Hz, 1H, H_c), 2.32 (ddd, J 12.6, 3.1, 3.0 Hz, 1H, H_d), 3.93-3.94 (m, 1H, H_b), 4.04-4.08 (m, 1H, N-CHH), 4.28-4.33 (m, 1H, N-CHH), 5.17-5.21 (m, 2H, $\text{CH}=\text{CH}_2$), 5.37 (brs, 1H, OH), 5.50-5.51 (m, 1H, H_a), 5.89-5.94 (m, 1H, $\text{CH}=\text{CH}_2$), 6.34 (dd, J 7.3, 2.4 Hz, 1H, ArH), 6.37 (d, J 2.4 Hz, 1H, ArH), 6.63 (d, J 8.2 Hz, 1H, ArH), 6.72 (t, J 7.4 Hz, 1H, ArH), 6.97 (d, J 8.0 Hz, 1H, ArH), 7.08 (t, J 8.3 Hz, 1H, ArH), 7.20 (d, J 7.3 Hz, 1H, ArH). ^{13}C NMR (125 MHz, CDCl_3): δ 26.7 (C-19), 34.4 (C-10), 51.6 (N-CH₂), 82.3 (C-9), 104.1 (ArCH), 108.7 (ArCH), 111.3 (ArCH), 116.4 ($\text{CH}=\text{CH}_2$), 118.0 (ArCH), 119.1 (ArC), 126.6 (ArCH), 127.8 (ArCH), 128.7 (ArC), 129.8 (ArCH), 134.1 ($\text{CH}=\text{CH}_2$), 141.5 (ArC), 153.0 (ArC), 155.8 (ArC). FT-IR (KBr): 3406, 1603, 1499, 1106, 746 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_2$: C 77.40, H 6.13, N 5.01, Found: C 77.27, H 6.06, N 5.13.

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References

- (a) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244. (b) Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Arànega, A.; Gallo, M. Á.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547. (c) Xu, Y. J.; Liu, H.; Pan, W.; Chen, X.; Wong, W. C.; Labelle, M. *Tetrahedron Lett.* **2005**, *46*, 7523. (d) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1485. (e) Liao, Y.; Venhuis, B. J.; Rodenhuis, N.; Timmerman, W.; Wikstrom, H.; Meire, E.; Bartoszyk, G. D.; Bottcher, H.; Seyfried, C. A.; Sundell, S. *J. Med. Chem.* **1999**, *42*, 2235.

2. (a) Kumar, A.; Srivastava, S.; Gupta, G.; *Tetrahedron Lett.* **2010**, 51, 517. (b) Rano, T. A.; McMaster, E. S.; Pelton, P. D.; Yang, M., Demarest, K. T.G., Kuo, H. *Bioorg. Med. Chem. Lett.* **2009**, 19, 2456. (c) Jayagobi, M.; Poornachandran, M.; Raghunathan, R. *Tetrahedron Lett.* **2009**, 50, 648. (d) Carling, R. W.; Leeson, P. D.; Marshall, G. R.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, A. S. *Bioorg. Med. Chem. Lett.* **1993**, 3, 65.
3. (a) Skerget, M.; Kotnik, P.; Hadolin, M.; Harg, R.; Simonig, M.; Knez, Z. *Food Chem.* **2005**, 89, 191. (b) Park, K. K.; Lee, J. H.; Kim, H. E.; Kang, K. S. *J. Photochem. Photobiol. A: Chemistry.* **2003**, 159, 17 and references cited therein. (c) Weissermel, K.; Arpe, H. J. *Industrial Organic chemistry*; 3rd Ed; VCH: Weinheim, **1997**, 358. (d) Majumder, P.; Saha, S. *Phytochemistry.* **1978**, 17, 1439.
4. (a) Pflantz, R.; Sluiter, J.; Krička, M.; Saak, W.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2009**, 5431. (b) Schmidt, A.; Michalik, D.; Rotzoll, S.; Ullah, E.; Fischer, C.; Reinke, H.; Görls, H.; Langer, P. *Org. Biomol. Chem.* **2008**, 6, 2804. (c) Alamdari, M. H.; Helliwell, M.; Baradarani, M. M.; Joule, J. A. *Arkivoc* **2008**, (xiv), 166. (d) Mishra, J. K.; Panda, G. J. *Comb. Chem.* **2007**, 9, 321. (e) Pflantz, R.; Tielmann, P.; Rössle, M.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, 3227. (f) Schmidt, A.; Gütlein, J. P.; Mkrtchyan, S.; Görls, H.; Langer, P. *Synlett* **2007**, 1305. (g) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, 7, 4781. (h) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, 126, 3529. (i) Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H.; Nakada, M. *Tetrahedron Lett.* **2004**, 45, 8653. (j) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, 104, 2199.
5. (a) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Rominger, F.; Gross, J. H. *Tetrahedron Lett.* **2008**, 49, 6965. (b) Yavari, I.; Karimi, E. *Tetrahedron Lett.* **2008**, 49, 6433. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, 46, 1570. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, 107, 3180. (e) Overman, L. E.; Velthuisen, E. J. J. *Org. Chem.* **2006**, 71, 1581. (f) Tietze, L. F.; Rackelman, N. *In Multicomponent Reaction*; J. Zhu, I. Bienayme, Eds.; Wiley-VCH: Weinheim, **2005**. (g) Tietze, L. F. *Chem. Rev.* **1996**, 96, 115. (h) Ho, T. L. *Tandem Organic Reactions*; Wiley and Sons: New York, NY, **1992**.
6. (a) Shaabani, A.; Soleimani, E.; Moghimi-Rad, J. *Tetrahedron Lett.* **2008**, 49, 1277. (b) Yavari, I.; Mirzaei, A.; Moradi, L.; Hosseini, N. *Tetrahedron Lett.* **2008**, 49, 2355. (c) Paira, P.; Hazra, A.; Sahu, K. B.; Banerjee, S.; Mondal, N. B.; Sahu, N. P.; Weber, M.; Luger, P. *Tetrahedron* **2008**, 64, 4026. (d) Shaabani, A.; Soleimani, E.; Khavasi, H. R. *Tetrahedron Lett.* **2007**, 48, 4743. (e) Liu, Y.; Hu, H. Y.; Liu, Q. J.; Hu, H. W.; Xu, J. H. *Tetrahedron* **2007**, 63, 2024. (f) Yue, G.; Wan, Y.; Song, S.; Yang, G.; Chen, Z. *Bioorg. Med. Chem.* **2005**, 15, 453. (g) Schmidt, A.; Gütlein, J. P.; Preuss, A.; Albrecht, U.; Reinke, H.; Langer, P. *Synlett* **2005**, 2489. (h) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, 122, 6327.
7. (a) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Doulabi, M.; Kiamehr, M. *Tetrahedron* **2010**, 66, 134. (b) Moghaddam, F.M.; Taheri, S.; Mirjafary, Z.; Saeidian, H.;

Synlett **2010**, 123. (c) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Khodabakhshi, M. R. *Tetrahedron Lett.* **2010**, 51, 2704. (d) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Soltanzadeh, B. *Tetrahedron* **2010**, 66, 3678. (e) Moghaddam, F. M.; Moridi, F. M. *Tetrahedron Lett.* **2010**, 51, 540. (f) Moghaddam, F. M.; Kiamehr, M.; Taheri, S.; Mirjafary, Z.; *Helv. Chim. Acta* **2010**, 93, 964. (g) Moghaddam, F. M.; Saeidian, H.; Mirjafary, Z.; Taheri, S.; Kheirjou, S. *Synlett* **2009**, 1047. (h) Kiamehr, M.; Moghaddam, F. M. *Tetrahedron Lett.* **2009**, 50, 6723. (i) Enders, D.; Saeidian, H.; Mirjafary, Z.; Iffland, D.; Raabe, G.; Runsink, J. *Synlett* **2009**, 2872. (j) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Javan, M. J. *Synlett* **2008**, 892.