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TETRAHEDRON

Manganese(III) acetate mediated radical reactions leading to araliopsine and related quinoline alkaloids

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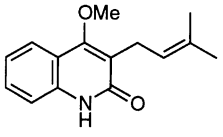
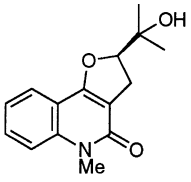
Abstract—Tricyclic quinoline alkaloids, including araliopsine **2**, can be prepared in 'one-pot' by reaction of 4-hydroxy-1-methyl-2(1*H*)-quinoline **5** or 2,4-quinolinediol **31** with manganese(III) acetate in the presence of a variety of electron-rich alkenes. The reaction mechanism involves an initial intermolecular radical addition reaction followed by radical oxidation and cyclisation steps. Both angular and linear tricyclic alkaloids can be formed and the regioselectivity of the cyclisation is shown to depend on whether alkyl or aryl groups are attached to the alkene.

1. Introduction

A considerable number of medicinally important quinoline alkaloids have been isolated from the *Rutaceae* family of plants.[1] Representative examples of this class of compound include atanine **1**, the angular alkaloid araliopsine **2** and the linear alkaloid isoplatydesmine **3**. These types of compounds have been shown to exhibit a variety of biological properties including antibacterial, antifungal and antiviral activities, and so their synthesis is of considerable importance.[2] In nature, these alkaloids are believed to be formed from *C*-prenylation of 4-hydroxyquinolone **4**, which is derived from anthranilic acid. This potentially straightforward and flexible approach has been investigated in the laboratory and, for example, the *C*-alkylation of quinolone **5** has been attempted by reaction with base and prenyl bromide. Unfortunately, this biomimetic approach proceeds in very low yields because of competitive dialkylation and *O*-alkylation reactions.[3] The unselective nature of this ionic alkylation reaction attracted our attention and led us to investigate the formation of these types of alkaloids using a radical alkylation reaction mediated by manganese(III) acetate.[4]



1



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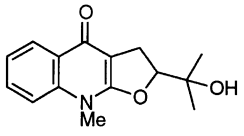

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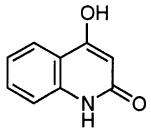

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2. Results and discussion

Our preliminary reactions centred on the alkylation of commercially available 4-hydroxy-1-methyl-2(1*H*)-quinolone **5** using 1-octene (Scheme 1). When **5** was added to 1 equiv. of 1-octene and 2 equiv. of manganese(III) acetate in acetic acid, and the solution stirred at 60°C, only starting material was recovered. This was thought to be due to the low solubility of **5** in acetic acid and so the same reaction was carried out in an ultrasonic bath (300 W, 30–40 kHz) at 60°C.[5] Gratifyingly, this reaction led to the alkylation of **5** and the formation of tricycle **6** in 28% yield. Although attempts to increase the yield of **6** by adding the co-oxidant copper(II) acetate were unsuccessful, the yield of **6** was improved to 50% when the number of equivalents of 1-octene was increased from 1 to 10. Interestingly, the reaction could also be carried out using less than 1 equiv. of manganese(III) acetate when potassium permanganate was added. Hence, reaction of **5** with 10 equiv. of 1-octene, 0.3 equiv. of manganese(III) acetate and 0.6 equiv. of potassium permanganate (added portionwise over 3 h) gave **6** in 58% yield. Potassium permanganate can, therefore, be used to selectively oxidise manganese(II) back to manganese(III) in the reaction mixture.[6]

The formation of **6** is expected to involve initial oxidation of **5** to form radical **7**. Although **7** could be formed in one of several possible ways, the involvement of an intermediate

Keywords: alkaloids; manganese and compounds; quinolines; radicals and radical reactions.

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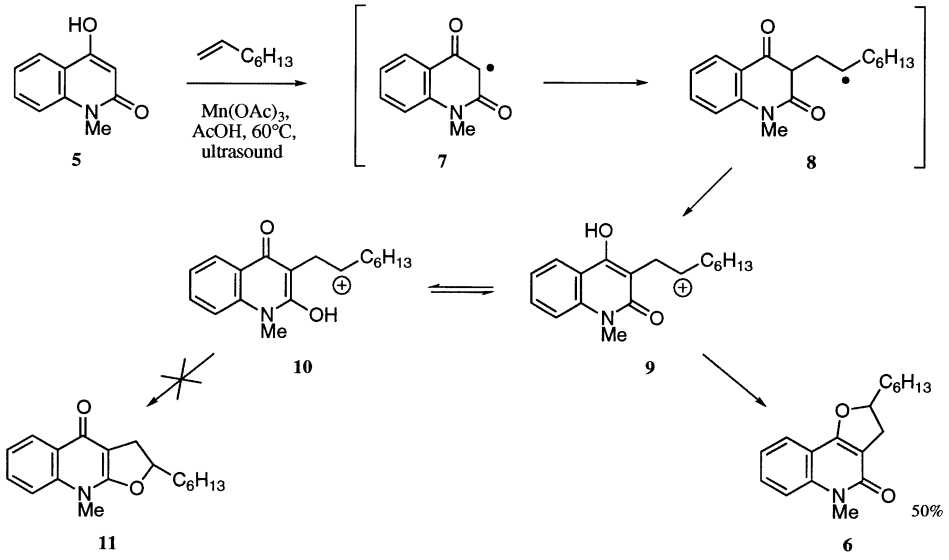


Scheme 1.

manganese(III) enolate is thought to be likely for these reactions.[7] Radical **7** is then expected to add regioselectively (on steric and electronic grounds) to the electron-rich double bond of 1-octene to form secondary radical **8**. Oxidation by a second equivalent of manganese(III) acetate will form secondary cation **9**, which could react with the nucleophilic hydroxyl group of the enol to form the five-membered ring in **6**. It is of interest to note that only the angular alkaloid was isolated from this reaction; none of the linear regioisomer **11**, derived from cyclisation of enol **10**, was observed.

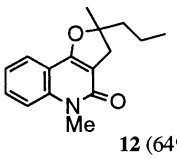
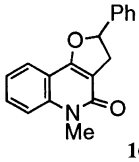
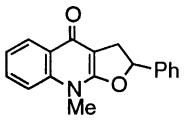
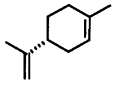
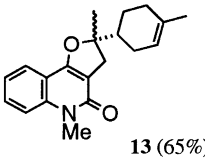
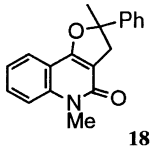
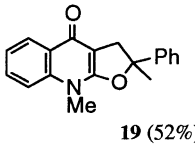
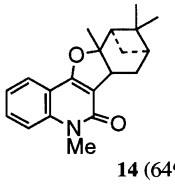
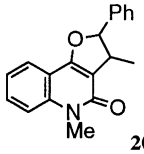
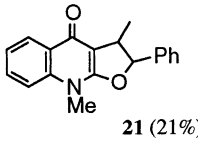
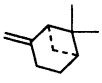
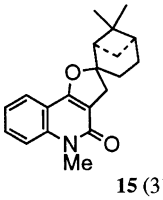
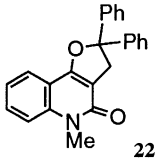
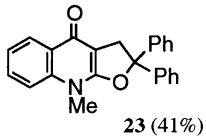
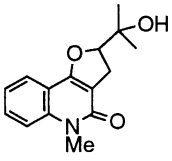
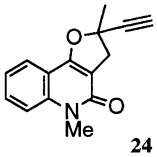
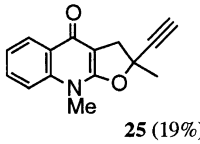
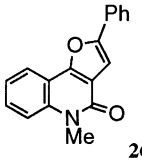
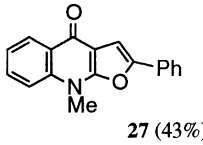
Reaction of **5** with electron-poor alkenes, including methyl methacrylate, was also briefly investigated. However, these reactions gave only unreacted starting material or a mixture of products in very low yield and this could be explained by radical polarity. Thus electrophilic radical **7** is expected to add much more slowly to electron-poor double bonds to give radical adducts, which, because of the adjacent electron-withdrawing groups, will be extremely difficult to oxidise to cations. All subsequent reactions were therefore carried out using electron-rich alkenes.

A range of substituted alkenes were then reacted with **5** as outlined in Table 1. Hence reaction of **5** with 2-methyl-1-pentene, (*R*)- (+)-limonene or (1*S*)- (−)-α-pinene produced the angular quinolines **12**–**14** in 64–65% yield, respectively, while reaction with (1*S*)- (−)-β-pinene gave **15** in 31% yield (entries 1–4). A similar reaction was observed when using 2-methyl-3-buten-2-ol to give (±)-araliopsine **2** in 40% yield (entry 5). This reaction could also be carried out using 0.3 equiv. of manganese(III) acetate when 0.7 equiv. of potassium permanganate was added to the reaction; this produced (±)-araliopsine **2** in 35% yield. Attempts to improve the yield of **2** by varying the reaction temperature and the number of equivalents of starting material was unsuccessful, presumably due to competitive protonation/elimination of the tertiary alcohol. Interestingly, when **5** was reacted with related alkenes, namely allyl alcohol or 2-methyl-1,3-butadiene (isoprene), in the presence of 2 equiv. of manganese(III) acetate, the yields of the angular quinolones were much lower (i.e. 6 and 18%, respectively). These lower yields may be explained by the propensity of, for example, 2-methyl-1,3-butadiene to undergo radical polymerisation.

In contrast to the above reactions, when **5** was reacted with styrene, α-methylstyrene, *trans*-β-methylstyrene, 1,1-diphenylethene, 2-methyl-1-buten-3-yne or phenylacetylene, a mixture of angular and linear quinolines **16**–**27** were isolated (entries 6–11). The introduction of substituents on the alkene, which can help to stabilise radical/cation intermediates, therefore, promotes the formation of linear isomers in similar yields to the angular isomers. Thus, reaction of **5** with styrene, α-methylstyrene or 1,1-diphenylethene is expected to produce intermediate benzylic radicals/cations while reaction with phenylacetylene is expected to produce an intermediate α-styryl radical/cation, which can be stabilised by delocalisation over the benzene ring.[8,9] It should be noted that α-styryl radicals (of the type $PhC^{\cdot}{=}CR_2$) are unusual in that vinyl radicals are generally σ-radicals (rather than π-radicals), which are very unstable and extremely difficult to oxidise. Indeed, when **5** was reacted with terminal alkynes bearing an alkyl rather than an aryl substituent, a number of products were isolated in low yield and this presumably reflects the high reactivity/high oxidation potential of the intermediate vinyl radicals.

The explanation for why both linear and angular isomers are formed when using alkenes bearing radical/cation stabilising groups is unclear. Molecular orbital calculations (AM1 or PM3) suggest that the linear isomers are thermodynamically less stable than the angular isomers and this was supported by the slow isomerisation of **23** to **22** on heating in acetic acid. Surprisingly, therefore, the introduction of radical/cation stabilising groups promotes the formation of the thermodynamically less stable regioisomer. One possible explanation could stem from the different rates of cyclisation of the enol on to the intermediate carbocation. Thus, an enol is expected to attack a benzylic cation more slowly than an alkyl cation (because of electronic and steric effects). The slower rate of cyclisation could allow

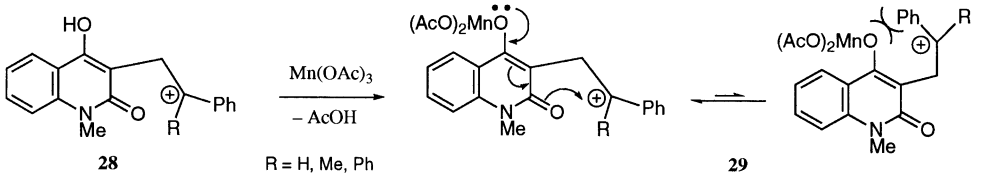
Table 1.

Entry	Alkene	Product (Yield)	Entry	Alkene	Product (Yield)
1		 **12** (64%)	6		 **16** (28%)  **17** (25%)
2		 **13** (65%)	7		 **18** (34%)  **19** (52%)
3		 **14** (64%)	8		 **20** (16%)  **21** (21%)
4		 **15** (31%)	9		 **22** (39%)  **23** (41%)
5		 (±)-**2** (40%)	10		 **24** (16%)  **25** (19%)
			11		 **26** (17%)  **27** (43%)

time for cations of type **28** to react with manganese(III) acetate to form a second manganese enolate **29** (Scheme 2). This enolate may well undergo preferential cyclisation so as to form the linear, rather than the angular isomer, because of steric interactions between the benzene ring(s) and the bulky manganese(III) substituent.

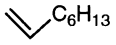
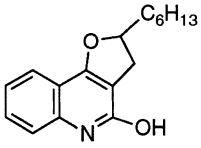
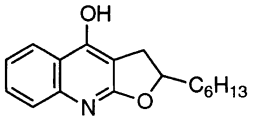
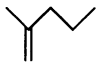
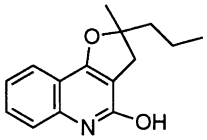
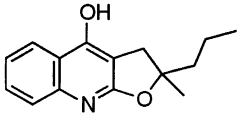
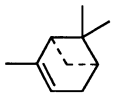
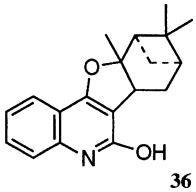
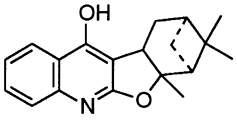
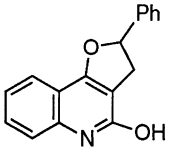
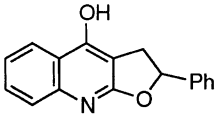
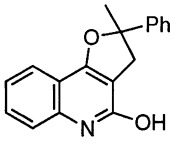
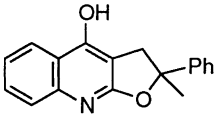
The formation of an intermediate manganese(III) enolate is also consistent with the results of related reactions mediated by silver(I)/celite.[10] These reactions involved the alkylation of various *N*-protected quinolones with electron-rich double bonds to give products derived from an analogous radical addition/radical oxidation mechanism to that shown in Scheme 1. However, these reactions only afforded the angular tricyclic products. Hence, when **5** was reacted with α-methylstyrene and Ag_2CO_3/celite, only the angular isomer **18** was formed in 43% yield.

The reaction of **5** with enol ethers was also briefly investigated. Unfortunately, the yields of tricyclic quinolone adducts were generally low; for example, the reaction of **5** with *n*-butyl vinyl ether gave tricycle **30** in only 18% yield. The low yield of **30** is likely to be a consequence of (competitive) enol ether hydrolysis under the (acidic) reaction

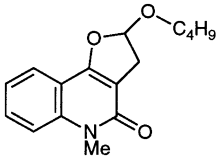


Scheme 2.

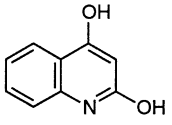
Table 2.

Entry	Alkene	Product (Yield)	
1		 **32** (41%)	 **33** (4%)
2		 **34** (71%)	 **35** (8%)
3		 **36** (64%)	 **37** (4%)
4		 **38** (41%)	 **39** (29%)
5		 **40** (41%)	 **41** (34%)

conditions. It is interesting to note, however, that only the angular isomer was isolated despite the formation of an intermediate (and relatively stable) oxonium ion.

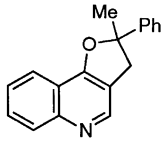


30

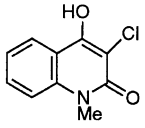


31

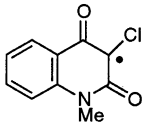
Investigations then turned to alkylation of the related quinoline, 2,4-quinolinediol **31**, using a variety of electron-rich alkenes (Table 2). It was of interest to investigate, for example, how the ratio of angular to linear compounds would change when using a diol precursor. Hence, reaction of **31** with 2.1 equiv. of manganese(III) acetate and 10 equiv. of 1-octene gave the angular and linear quinolines **32** and **33**, in 41 and 4% yield, respectively (entry 1). A similar result was observed when the same reaction was carried out at room temperature in acidic ethanol (pH 4–5 by addition of concentrated H_2SO_4); **32** and **33** were isolated in 35 and 10% yield, respectively. As for the alkylation of **5**, when alkene acceptors with phenyl substituents were employed, reasonable yields of the linear regioisomers, **39** (29%) and **41** (34%), were isolated. The presence of the hydroxy group at the 4-position of **31** is crucial for these alkylations as 2-hydroxyquinoline did not react with 1-octene (in acetic acid under sonolysis at 60°C). However, the 2-hydroxy group of **31** was also shown to be important as reaction of 4-hydroxyquinoline with α-methylstyrene and manganese(III) acetate gave the angular quinoline **42** in only 20% yield. In addition, the presence of a quinolone ring system is crucial for the alkylations as reaction of 2,4-dihydroxypyridine with manganese(III) acetate and 1-octene was unsuccessful and only unreacted starting material was recovered.



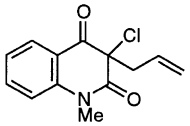
42



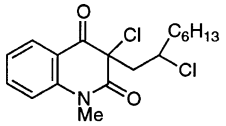
43



44



45



46

All of the above alkylation reactions have resulted in the formation of tricyclic quinolone products. With a view to

developing an approach to *C*-alkylated bicyclic quinolones, such as atanine **1**, the reaction of α-chloroquinolone **43** with manganese(III) acetate and electron-rich alkenes was investigated. The α-chloro substituent was expected to increase the electrophilicity of the initial radical **44** and, most importantly, prevent enolisation and cyclisation of the intermediate carbocation. Surprisingly, when **43** was reacted with manganese(III) acetate and, for example, 2-methyl-3-buten-2-ol (under the same conditions as for the reaction with **5**) only low yields (≤10%) of quinolone dimers were isolated. No products resulting from addition of radical **44** to the alkene could be recovered. An explanation might be that **44** is simply too stable to add to an alkene, as the chlorine atom is expected to reduce the reactivity of this radical due to electronic and steric factors. However, radical **44** can add to a double bond albeit reversibly as supported by the reaction of **43** with allyl *t*-butyl sulfide (*t*-$BuSCH_2CH{=}CH_2$), which gave the allyl derivative **45** in 40% yield.

An alternative strategy to *C*-alkylated bicyclic quinolones involves a 'one-pot' chlorination/alkylation reaction mediated by manganese(III). Although previous work has shown that β-ketoesters can be chlorinated and alkylated using $LiCl/Mn(OAc)_3$ in the presence of, for example, 1-hexene,[11] use of **5** under the same conditions proved ineffective. When **5** was reacted with 2-methyl-3-buten-2-ol (under these conditions) a number of products were formed in very low yield. However, this transformation does occur when HCl gas is bubbled into a solution of **5**, 1-octene and manganese(III) acetate in ethanol. This novel alkylation procedure resulted in the formation of dichloride **46** as a 1:1 mixture of diastereoisomers in 27% yield.

This work has demonstrated that biologically important quinolone alkaloids, including araliopsine **2**, can be prepared from reaction of quinolones **5** and **31** with electron-rich alkenes in the presence of manganese(III) acetate. A variety of linear and/or angular tricyclic alkaloids can be prepared using this one-pot reaction and the regioselectivity of the cyclisation step has been shown to depend on the alkene substituents. The formation of linear products may be explained by the cyclisation of an intermediate manganese(III) enolate of type **29** as, for example, related silver(I)/celite reactions[10] have been shown to produce only angular products. These combined intermolecular addition–cyclisation reactions offer a quick, economical and flexible approach to quinolone alkaloids and the use of manganese(III) acetate compares favourably with that of cerium(IV) ammonium nitrate (CAN) in similar alkylation reactions. Thus, for example, when **5** was reacted with CAN and 2-methyl-3-buten-2-ol (2–20 equiv.) in methanol only dimeric products derived from homo-coupling of quinolone radical **7** were formed. Although previous work has shown[12] that **5** can be dimerised by CAN in the absence of alkenes, it is unclear why radical **7** does not add to alkenes in the manganese(III)-mediated reactions. It may be that CAN forms a complex with two molecules of **5** to promote the dimerisation reaction and this will be the subject of further investigations.

3. Experimental

IR spectra were recorded on an ATI Mattson Genesis FT IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Jeol Ex 270 or Brüker AMX 500 spectrometer. The carbon spectra were assigned using DEPT experiments. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5 Hz. Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec Spectrometer system. Thin layer chromatography (TLC) was performed on Merck aluminium-backed silica gel plates. Compounds were visualised under a UV lamp, using alkaline potassium permanganate solution and/or iodine. All alkylations employed a Clifton DU-4 ultrasonic bath (300 W, 30–40 kHz). Column chromatography was performed using silica gel (Matrix Silica 60, 70–200 μm Fisons or ICN flash silica 60, 32–63 μm). Petroleum ether refers to the fraction with bp 40–60°C. The numbering of ring systems follows IUPAC nomenclature.

3.1. General procedure for manganese(III)-mediated oxidative cyclisations

To quinolone **5** or quinolinediol **31** (0.1 g, 0.57–0.62 mmol) in degassed acetic acid (10 cm^3) was added the alkene (5.7–6.2 mmol, 10 equiv.) followed by manganese(III) acetate dihydrate (1.2–1.3 mmol, 2.1 equiv.) in degassed acetic acid (40 cm^3). The solution was heated at 60°C in an ultrasonic bath until the solution changed from brown to yellow in colouration (typically within 4 h). Saturated aqueous $NaHCO_3$ (100 cm^3) was then added and the mixture extracted with dichloromethane (2×20 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo to afford crude products which were purified using column chromatography (silica) to give alkylated products, usually as oils.

3.2. General procedure for manganese(III)-mediated oxidative cyclisations in the presence of potassium permanganate

To quinolone **5** (0.1 g, 0.57 mmol) in degassed acetic acid (30 cm^3) was added 1-octene or 2-methyl-3-buten-2-ol (5.7 mmol, 10 equiv.) followed by manganese(III) acetate dihydrate (0.046 g, 0.17 mmol, 0.3 equiv.) in degassed acetic acid (20 cm^3). The solution was heated at 60°C in an ultrasonic bath and potassium permanganate (approximately 0.054–0.063 g, 0.34–0.40 mmol, 0.6–0.7 equiv.) was added portionwise over 3 h to keep the solution brown in colouration. Saturated aqueous $NaHCO_3$ (100 cm^3) was then added and the mixture extracted with dichloromethane (2×20 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$), evaporated and purified using column chromatography (silica) to give **2** (0.052 g, 35%) or **6** (0.094 g, 58%).

3.2.1. (±)-Araliopsine 2.[13,14] 40% (35% using $KMnO_4$); solid; mp 136°C; R_f 0.05 (diethyl ether); ν_{max} ($CHCl_3$) 3003 (s, br), 1660 (s), 1629 (s), 1597 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.75 (1H, dd, *J*=7.8 and 1.5 Hz, H9), 7.65–7.55 (1H, m, aromatic), 7.40–7.20 (2H, m, aromatic), 4.90 (1H, br t, *J*=10.0 Hz, H2), 3.70 (3H, s, NCH_3), 3.22 (1H, dd, *J*=15.8 and 10.0 Hz, H3), 3.14 (1H, dd *J*=15.8 and 10.0 Hz, H3), 2.00 (1H, br s, COH), 1.40 (3H, s, CCH_3), 1.30 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 162.1 (C9b), 162.3 (C4), 140.5 (C5a), 131.0 (C7), 122.9 (C8), 121.6 (C9), 114.6

(C6), 112.3 (C3a), 108.6 (C9a), 91.9 (C2), 71.9 (CMe$_2$), 29.1 (C3 and NCH_3), 25.4 (CCH_3), 23.8 (CCH_3); *m/z* (CI, NH_3) 260 ($M+H^+$, 100%); found: $M+H^+$, 260.1287. $C_{15}H_{17}NO_3$ requires for $M+H^+$, 260.1286.

3.2.2. 2-Hexyl-5-methyl-3,5-dihydro-2*H*-furo-[3,2-*c*]-quinoline-4-one 6. 50% (58% using $KMnO_4$); oil; R_f 0.3 (diethyl ether); ν_{max} ($CHCl_3$) 2932 (m), 2860 (m), 1655 (s), 1627 (s), 1595 (s), 1571 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.80–7.70, 7.55–7.51 and 7.36–7.17 (4H, m, aromatics), 5.05 (1H, m, H2), 3.70 (3H, s, NCH_3), 3.31 (1H, dd, *J*=15.3 and 9.7 Hz, H3), 2.86 (1H, dd, *J*=15.3 and 7.3 Hz, H3), 2.00–1.40 (10H, m, 5×CH_2), 0.80 (3H, t, *J*=5.4 Hz, CCH_3); δ_c (67.5 MHz, $CDCl_3$) 162.2 (C9b), 161.5 (C4), 140.5 (C5a), 130.7 (C7), 123.0 (C8), 121.4 (C9), 114.4 (C6), 112.7 (C3a), 107.9 (C9a), 86.3 (C2), 36.2 (C3), 33.4 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 28.9 (CH_3N), 24.9 (CH_2), 22.5 (CH_2), 14.0 (CCH_3); *m/z* (CI, NH_3) 286 ($M+H^+$, 100%); found: $M+H^+$, 286.1810. $C_{18}H_{23}NO_2$ requires for $M+H^+$, 286.1807.

3.2.3. 2-Methyl-2-*n*-propyl-5-methyl-3,5-dihydro-3*H*-furo-[3,2-*c*]-quinoline-4-one 12. 64%; oil; R_f 0.35 (4:1, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 3000 (m, br), 2964 (m, br), 1654 (s), 1626 (s), 1595 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.73 (1H, dd, *J*=8 and 1.5 Hz, H9), 7.60–7.50 (1H, m, aromatic), 7.35–7.15 (2H, m, aromatics), 3.69 (3H, s, NCH_3), 3.12 (1H, d, *J*=15.3 Hz, H3), 2.92 (1H, d, *J*=15.3 Hz, H3), 1.77 (2H, t, *J*=8.3 Hz, CCH_2), 1.50–1.38 (5H, m, CH_2 and $OCCH_3$), 0.93 (3H, t, *J*=7 Hz, CCH_3); δ_c (67.5 MHz, $CDCl_3$) 161.4 (C9b and C4), 140.5 (C5a), 130.6 (C7), 123.1 (C8), 121.3 (C9), 114.4 (C6), 112.8 (C3a), 107.5 (C9a), 93.0 (C2), 43.5 (C3), 39.0 (propyl CH_2), 28.9 (NCH_3), 26.7 (CCH_3), 17.1 (propyl CH_2), 14.3 (CH_2CH_3); *m/z* (CI, NH_3) 258 ($M+H^+$, 100%); found: $M+H^+$, 258.1486. $C_{16}H_{19}NO_2$ requires for $M+H^+$, 258.1494.

3.2.4. 2-Methyl-2-(4-methyl-3-cyclohexenyl)-5-methyl-3,5-dihydro-3*H*-furo-[3,2-*c*]-quinoline-4-one 13. 1:1 mixture of diastereoisomers as indicated by the ^{13}C NMR spectrum; 65%; oil; R_f 0.5 (7:3, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 3002 (s, br), 2930 (s, br), 1655 (s), 1595 (s), 1571 (s), 1423 (m), 1359 (m), 1245 (m, br) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.80–7.70 (1H, m, H9), 7.58–7.48 (1H, m, aromatic), 7.40–7.10 (2H, m, aromatic), 5.35 (1H, br, s, C=CH), 3.66 (3H, s, NCH_3), 3.14 (1H, d, *J*=7 Hz, cyclohexenyl CH), 2.84 (1H, d, *J*=7.5 Hz, H3), 2.79 (1H, d, *J*=7.5 Hz, H3), 2.30–1.70 (6H, m, 3×cyclohexenyl CH_2), 1.62 (3H, s, $OCCH_3$), 1.44 (3H, d, *J*=3.2 Hz, CH_3C=C); δ_C (67.5 MHz, $CDCl_3$) 161.4 (C9b), 161.3 (C4), 140.4 (C5a), 133.9, 133.0 (2×CH_3–C=CH), 130.6 (C7), 123.0 (C8), 121.3 (C9), 119.7 (CH_3–C=CH), 114.3 (C6), 112.7 (C3a), 107.4 (C9a), 95.3, 95.1 (2×C2), 43.3, 43.1 (cyclohexenyl C), 37.3 (C3), 36.6 (cyclohexenyl CH_2), 30.3, 30.2 (cyclohexenyl CH_2), 28.9 (NCH_3), 26.3, 26.0 (cyclohexenyl CH_2), 24.6, 24.4 (CH_3–C=CH), 23.4, 23.2 ($OCCH_3$); *m/z* (CI, NH_3) 310 ($M+H^+$, 100%); found: $M+H^+$, 310.1802. $C_{20}H_{23}NO_2$ requires for $M+H^+$, 310.1807.

3.2.5. 5,9,9,10a-Tetramethyl-8,10-methano-6b,7,8,9,10,10a-hexahydro[1]benzofuro[3,2-*c*]quinolin-6(5*H*)-one 14. A single diastereoisomer as indicated by the ^{13}C NMR spectrum; 65%; oil; R_f 0.5 (7:3, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 2993 (s, br), 2928 (s, br), 1654 (s), 1624 (s), 1594 (s), 1421 (m), 1359 (m), 1102 (m, br) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.73 (1H, dd, *J*=8 and 1.5 Hz, H1), 7.56–7.48 (1H, m, aromatic), 7.40–7.10 (2H, m, aromatic), 3.67 (3H, s, NCH_3), 3.39 (1H, dd, *J*=3.6 and 10.2 Hz, CHCCH$_3$), 2.50–2.00 (5H, m, H7, bridge, H10 or H8), 1.45 (3H, s, CH_3-C9 or CH_3-C10a), 1.28 (3H, s, CH_3-C9 or CH_3-C10a), 1.10–1.00 (1H, m, H10 or H8), 0.97 (3H, s, CH_3-C9 or CH_3-C10a); δ_C (67.5 MHz, $CDCl_3$) 161.3 (C11a), 160.2 (C6), 140.3 (C4a), 130.5 (C3), 123.3 (C2), 121.2 (C1), 114.5 (C11b), 114.3 (C4), 112.7 (C6a), 97.1 (C10a), 97.1 (C10a), 50.8 (C8 or C10), 40.1 (C6b), 39.3 (C8 or C10), 38.0 (C9), 32.1 (C7 or CH_2 bridge), 28.7 (NCH_3), 27.4, 27.0, 23.0 (3×CH_3), 26.0 (C7 or CH_2 bridge); *m/z* (CI, NH_3) 310 ($M+H^+$, 100%); found: $M+H^+$, 310.1793. $C_{20}H_{23}NO_2$ requires for $M+H^+$, 310.1807.

3.2.6. 2-(Spiro-1-pinanyl)-5-methyl-3,5-dihydro-3*H*-furo-[3,2-*c*]-quinoline-4-one 15. A single diastereoisomer as indicated by the ^{13}C NMR spectrum; 31%; oil; R_f 0.5 (7:3, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 2993 (s, br), 2953 (s, br), 1655 (s), 1595 (s), 1625 (s), 1594 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.75 (1H, dd, *J*=8 and 1.5 Hz, H9), 7.58–7.48 (1H, m, aromatic), 7.40–7.30 (2H, m, aromatic), 3.68 (3H, s, NCH_3), 3.16 (1H, d, *J*=15.7 Hz, H3), 3.08 (1H, d, *J*=15.7 Hz, H3), 2.60–1.60 (8H, m, OCCHCCHCH_2CH_2 and OCCHCH_2CH), 1.25 (3H, s, CCH_3), 1.10 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 161.4 (C9b), 160.3 (C4), 140.5 (C5a), 130.6 (C7), 123.2 (C8), 121.3 (C9), 114.4 (C6), 112.8 (C3a), 107.6 (C9a), 98.0 (C2), 51.5 (OCCHCCH), 42.8 (C3), 40.0 (OCCHCCH), 38.2 (OCCHCCH), 32.0 (OCCH_2CH_2CH), 28.9 (NCH_3), 26.8 (CCH$_3$), 26.6 (OCCHCH_2CH), 24.3 (OCCH$_2C$H$_2$CH), 22.9 (CCH$_3$); *m/z* (CI, NH_3) 310 ($M+H^+$, 100%), 180 (40); found: $M+H^+$, 310.1809. $C_{20}H_{23}NO_2$ requires for $M+H^+$, 310.1807.

3.2.7. 2-Phenyl-5-methyl-3,5-dihydro-2*H*-furo-[3,2-*c*]-quinoline-4-one 16. 28%; oil; R_f 0.4 (diethyl ether); ν_{max} ($CHCl_3$) 3005 (m, br), 1657 (s), 1629 (s), 1596 (s), 1571 (w), 1422 (m), 1410 (w), 1287 (m), 1247 (m), 1118 (m), 797 (m, br) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.82 (1H, dd, *J*=1.5 and 8.0 Hz. H9), 7.70–7.20 (8H, m, aromatic), 6.03 (1H, dd, *J*=7.7 and 10.4 Hz, H2), 3.72 (3H, s, NCH_3), 3.70 (1H, dd, *J*=10.4 and 15.8 Hz, H3), 3.28 (1H, dd, *J*=7.7 and 15.8 Hz, H3); δ_C (67.5 MHz, $CDCl_3$) 163.0 (C9b), 160 (C4), 141.0 (C phenyl), 140.9 (C5a), 131.0 (C7), 128.8 (CH phenyl), 128.5 (CH phenyl), 125.9 (CH phenyl), 123.2 (C8), 121.6 (C9), 114.5 (C6), 112.4 (C3a), 107.7 (C9a), 86.5 (C2), 36.3 (C3), 29.1 (CH_3N); *m/z* (CI, NH_3) 278 ($M+H^+$, 100%); found $M+H^+$, 278.1177. $C_{18}H_{15}NO_2$ requires for $M+H^+$, 278.1181.

3.2.8. 2-Phenyl-9-methyl-3,9-dihydro-2*H*-furo-[2,3-*b*]-quinoline-4-one 17. 25%; solid; mp 163°C; R_f 0.05 (diethyl ether); ν_{max} ($CHCl_3$) 2986 (m, br), 1626 (s), 1590 (s), 1550 (s), 1518 (s), 806 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.48 (1H, dd, *J*=8 and 1.7 Hz, H5), 7.60–7.50 (1H, m, aromatic), 7.45–7.25 (7H, m, aromatics), 5.93 (1H, dd, *J*=9.8 and 7.8 Hz, H2), 3.71 (1H, dd, *J*=14.6 and 9.7 Hz, H3), 3.71 (3H, s, NCH_3), 3.33 (1H, dd, *J*=14.6 and 7.8 Hz, H3); δ_C (67.5 MHz, $CDCl_3$) 173.0 (C4), 167.0 (C9a), 139.7

(C phenyl), 138.7 (C8a), 131.0 (C7), 128.9 (CH phenyl), 128.8 (CH phenyl), 126.5 (C6), 126.4 (C4a), 126.1 (CH phenyl), 123.2 (C5), 114.2 (C8), 98.6 (C3a), 86.6 (C2), 34.7 (C3), 31.3 (NCH_3); *m/z* (CI, NH_3) 278 ($M+H^+$, 100%); found: $M+H^+$, 278.1177. $C_{18}H_{15}NO_2$ requires for $M+H^+$, 278.1181.

3.2.9. 2,5-Dimethyl-2-phenyl-3,5-dihydro-3*H*-furo-[3,2-*c*]-quinoline-4-one 18. 34%; oil; R_f 0.3 (diethyl ether); ν_{max} ($CHCl_3$) 3026 (s, br), 1657 (s), 1629 (s), 1596 (m), 1571 (w), 1423 (w), 1409 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.90 (1H, dd, *J*=8 and 1.5 Hz, H9), 7.65–7.55 (1H, m, aromatic), 7.40–7.20 (7H, m, aromatics), 3.70 (3H, s, NCH_3), 3.49 (1H, d, *J*=15.3 Hz, H3), 3.41 (1H, d, *J*=15.3 Hz, H3), 1.87 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 161.6 (C9b), 161.5 (C4), 146.5 (C phenyl), 140.9 (C5a), 131.2 (C7), 128.8 (CH phenyl), 127.8 (CH phenyl), 124.6 (CH phenyl), 123.4 (C8), 121.8 (C9), 114.8 (C6), 113.0 (C3a), 107.8 (C9a), 93.1 (C2), 43.1 (C3), 29.8, 29.4 ($OCCH_3$ and NCH_3); *m/z* (CI, NH_3) 292 ($M+H^+$, 100%), 176 (10); found: $M+H^+$, 292.1333. $C_{19}H_{17}NO_2$ requires for $M+H^+$, 292.1337.

3.2.10. 2,9-Dimethyl-2-phenyl-3,9-dihydro-3*H*-furo-[2,3-*b*]-quinoline-4-one 19. 52%; oil; R_f 0.06 (diethyl ether); ν_{max} ($CHCl_3$) 3026 (m), 2982 (s, br), 1625 (s), 1589 (s), 1546 (s), 1517 (s), 1281 (m), 909 (m), 799 (m), 700 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.40 (1H, dd, *J*=1.5 and 8 Hz, H5), 7.65–7.55 (1H, m aromatic), 7.50–7.25 (7H, m, aromatic), 3.80 (3H, s, NCH_3), 3.56 (1H, d, *J*=14.3 Hz, H3), 3.46 (1H, d, *J*=14.4 Hz, H3), 1.85 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 173.8 (C4), 160.2 (C9a), 144.5 (C phenyl), 138.7 (C8a), 131.0 (C7), 128.6 (CH phenyl), 127.7 (CH phenyl), 126.3 (C6), 126.2 (C4a), 124.2 (CH phenyl), 123.1 (C5), 114.1 (C8), 96.6 (C3a), 93.5 (C2), 41.1 (C3), 31.3 (CCH_3), 29.6 (NCH_3); *m/z* (CI, NH_3), 292 ($M+H^+$, 100%); found: $M+H^+$, 292.1329. $C_{19}H_{17}NO_2$ requires for $M+H^+$, 292.1337.

3.2.11. 2-Phenyl-3-methyl-5-methyl-3,5-dihydro-2*H*-furo-[3,2-*c*]-quinoline-4-one 20. A single diastereoisomer as indicated by the ^{13}C NMR spectrum; 16%; oil; R_f 0.06 (4:1, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 3026 (m, br), 1656 (s), 1628 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.85 (1H, d, *J*=7.7 Hz, H9), 7.65–7.58 (1H, m, aromatic), 7.43–7.20 (7H, m, aromatics), 5.44 (1H, d, *J*=6.6 Hz, H2), 3.73 (3H, s, NCH_3), 3.65 (1H, m, H3), 1.59 (3H, d, *J*=6.6 Hz, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 162.2 (C9b), 161.7 (C4), 141.0 (C5a), 140.9 (C phenyl), 131.5 (C7), 129.2 (CH phenyl), 128.9 (CH phenyl), 126.1 (CH phenyl), 123.7 (C8), 122.0 (C9), 114.9 (C6), 113.0 (C3a), 112.4 (C9a), 94.5 (C2), 45.5 (C3), 29.3 (NCH_3), 19.2 (CCH_3); *m/z* (CI, NH_3) 292 ($M+H^+$, 100%); found: $M+H^+$, 292.1340. $C_{19}H_{17}NO_2$ requires for $M+H^+$, 292.1337.

3.2.12. 2-Phenyl-3-methyl-9-methyl-3,9-dihydro-2*H*-furo-[2,3-*b*]-quinoline-4-one 21. A single diastereoisomer as indicated by the ^{13}C NMR spectrum; 21%; oil; R_f 0.2 (4:1, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 2986 (w, br), 1625 (m), 1590 (s), 1545 (s), 1517 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.47 (1H, dd, *J*=1.4 and 8 Hz, H5), 7.65–7.60 (1H, m, aromatic), 7.45–7.35 (7H, m, aromatic), 5.35 (1H, d, *J*=6.7 Hz, H2), 3.77 (1H, quin, *J*=6.7 Hz, H3), 3.73 (3H, s, NCH_3), 1.61 (3H, d, *J*=6.7 Hz, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 174.5 (C4), 161.2 (C9a), 140.1 (C phenyl), 139.3 (C8a), 131.5 (C7), 129.4 (CH phenyl), 129.3 (CH phenyl), 127.4 (C4a), 126.9 (C6), 126.5 (CH phenyl), 123.7 (C5), 114.7 (C8), 103.6 (C3a), 94.4 (C2), 44.1 (C3), 31.6 (NCH_3), 19.3 (CCH_3); *m/z* (CI, NH_3) 292 ($M+H^+$, 100%); found: $M+H^+$, 292.1329. $C_{19}H_{17}NO_2$ requires for $M+H^+$, 292.1337.

3.2.13. 2,2-Diphenyl-5-methyl-3,5-dihydro-3*H*-furo-[3,2-*c*]-quinoline-4-one 22. 39%; oil; R_f 0.6 (ethyl acetate); ν_{max} ($CHCl_3$) 3026 (m, br), 1661 (s), 1629 (s), 1608 (s), 793 (m, br) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.00 (1H, dd, *J*=8 and 1.5 Hz, H9), 7.70–7.25 (13H, m, aromatics), 3.99 (2H, s, H3), 3.70 (3H, s, NCH_3); δ_C (67.5 MHz, $CDCl_3$) 161.4 (C4), 160.9 (C9b), 144.4 (2×C phenyl), 140.6 (C5a), 131.0 (C7), 128.3 (4×CH phenyl), 127.7 (2×CH phenyl), 125.7 (4×CH phenyl), 123.5 (C8), 121.6 (C9), 114.5 (C6), 112.4 (C3a), 107.6 (C9a), 95.7 (C2), 42.6 (C3), 29.0 (NCH_3); *m/z* (CI, NH_3) 354 ($M+H^+$, 100%); found: $M+H^+$, 354.1491. $C_{24}H_{19}NO_2$ requires for $M+H^+$, 354.1494.

3.2.14. 2,2-Diphenyl-9-methyl-3,9-dihydro-3*H*-furo-[2,3-*b*]-quinoline-4-one 23. 41%; oil; R_f 0.35 (ethyl acetate); ν_{max} ($CHCl_3$) 3026 (m, br), 1627 (m), 1589 (s), 1546 (s), 1517 (s), 669 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.43 (1H, dd, *J*=8 and 1.5 Hz, H5), 7.70–7.25 (13H, m, aromatics), 4.04 (2H, s, H3), 3.83 (3H, s, NCH_3); δ_C (67.5 MHz, $CDCl_3$) 173.5 (C9a), 160.1 (C4), 143.4 (2×C phenyl), 138.5 (C8a), 131.2 (C7), 128.5 (4×CH phenyl), 128.1 (2×CH phenyl), 126.4 (C6), 126.1 (C4a), 125.8 (4×CH phenyl), 123.4 (C5), 114.2 (C8), 99.0 (C3a), 96.3 (C2), 40.9 (C3), 29.0 (NCH_3); *m/z* (CI, NH_3) 354 ($M+H^+$, 100%), 176 (15); found: $M+H^+$, 354.1491. $C_{24}H_{19}NO_2$ requires for $M+H^+$, 354.1494.

3.2.15. 2-Ethynyl-2-methyl-5-methyl-3,5-dihydro-3*H*-furo-[3,2-*c*]-quinoline-4-one 24. 16%; oil; R_f 0.4 (4:1, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 3305 (m), 3004 (m, br), 1657 (s), 1630 (s), 690 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.78 (1H, dd, *J*=8 and 1.5 Hz, H9), 7.65–7.55 (1H, m, aromatic), 7.40–7.20 (2H, m, aromatic), 3.70 (3H, s, NCH_3), 3.58 (1H, d, *J*=15.5 Hz, H3), 3.26 (1H, d, *J*=15.5 Hz, H3), 2.69 (1H, s, C≡CH), 1.82 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 161.5 (C9b), 161.1 (C4), 141.1 (C5a), 131.5 (C7), 123.7 (C8), 122.1 (C9), 114.9 (C6), 112.9 (C3a), 107.5 (C9a), 85.0 (C2), 83.7 (*C*≡CH), 74.5 (C≡*C*H), 43.2 (C3), 29.5 (NCH_3), 29.1 (CCH_3); *m/z* (CI, NH_3) 240 ($M+H^+$, 100%); found: $M+H^+$, 240.1022. $C_{15}H_{13}NO_2$ requires for $M+H^+$, 240.1024.

3.2.16. 2-Ethynyl-2-methyl-9-methyl-3,9-dihydro-3*H*-furo-[2,3-*b*]-quinoline-4-one 25. 19%; oil; R_f 0.1 (4:1, diethyl ether–dichloromethane); ν_{max} ($CHCl_3$) 3305 (w), 2989 (w, br), 1625 (m), 1591 (s), 1517 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.42 (1H, ddd, *J*=8, 1.5 and 0.5 Hz, H5), 7.65–7.55 (1H, m, aromatic), 7.42–7.20 (2H, m, aromatic), 3.69 (3H, s, NCH_3), 3.61 (1H, d, *J*=14.3 Hz, H3), 3.30 (1H, d, *J*=15.3 Hz, H3), 2.72 (1H, s, C≡CH), 1.82 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 174.3 (C4), 160.1 (C9a), 139.2 (C8a), 131.6 (C7), 126.9 (C6), 126.8 (C4a), 123.8 (C5), 114.7 (C8), 98.4 (C3a), 84.3 (C2), 84.1 (*C*≡CH), 75.1 (C≡*C*H), 41.7 (C3), 31.8 (NCH_3), 29.2

(CCH_3); *m/z* (CI, NH_3) 240 ($M+H^+$, 100%); found: $M+H^+$, 240.1023. $C_{15}H_{13}NO_2$ requires for $M+H^+$, 240.1024.

3.2.17. 2-Phenyl-5-methyl-5-hydro-furo-[3,2-*c*]-quinoline-4-one 26. 17%; solid; mp 187–188°C; R_f 0.65 (diethyl ether); δ_H (270 MHz, $CDCl_3$) 8.10 (1H, dd, *J*=1.5 and 8.0 Hz, H9), 7.62–7.22 (9H, m, aromatics and OCCH), 3.80 (3H, s, NCH_3); *m/z* (CI, NH_3) 276 ($M+H^+$, 100%); found: $M+H^+$, 276.1018. $C_{18}H_{13}NO_2$ requires for $M+H^+$, 276.1024.

3.2.18. 2-Phenyl-9-methyl-9-hydro-furo-[2,3-*b*]-quinoline-4-one 27. 43%; solid; mp 193–195°C; R_f 0.3 (diethyl ether); δ_H (270 MHz, $CDCl_3$) 8.47 (1H, dd, *J*=8 and 1.5 Hz, H5), 7.43–7.15 (9H, m, aromatics and OCCH), 3.87 (3H, s, NCH_3); δ_C (67.5 MHz, $CDCl_3$) 155.0 (C9a), 149.3 (C2), 138.3 (C8a), 131.7 (C7), 128.9 (CH phenyl), 128.7 (C phenyl), 127.9 (CH phenyl), 127.0 (C6), 126.5 (C4a), 123.5 (C5), 122.5 (CH phenyl), 114.1 (C8), 108.0 (C3), 101.8 (C3a), 31.3 (NCH_3), (C4 not observed); *m/z* (CI, NH_3) 275 ($M+H^+$ 100%), 260 (10), 232 (12), 105 (16), 84 (32), 77 (25), 55 (14), 49 (42); found: $M+H^+$, 275.0948. $C_{18}H_{13}NO_2$ requires for $M+H^+$, 275.0946.

3.2.19. 2-*n*-Butoxy-5-methyl-3,5-dihydro-2*H*-furo-[3,2-*c*]-quinoline-4-one 30. 18%; oil; R_f 0.4 (diethyl ether); ν_{max} ($CHCl_3$) 3026 (s), 2961 (s), 2967 (s), 2874 (w), 1657 (s), 1630 (s), 1596 (s), 1572 (m), 1462 (w), 1359 (m), 1094 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.75 (1H, dd, *J*=7.5 and 1.5 Hz, H9), 7.62–7.52 (1H, m, aromatic), 7.40–7.10 (2H, m, aromatics), 5.90 (1H, dd, *J*=7.1 and 2.9 Hz, H2), 3.96 (1H, dt, *J*=9.5 and 6.6 Hz, OCH_2CH_2), 3.69 (3H, s, NCH_3), 3.65 (1H, dt, *J*=9.5 and 6.6 Hz, OCH_2CH_2), 3.35 (1H, dd, *J*=16.7 and 7.1 Hz, H3), 3.10 (1H, dd, *J*=16.7 and 3.2 Hz, H3), 1.70–1.30 (4H, m, 2×CH_2), 0.91 (3H, t, *J*=7.3 Hz, CCH_3); *m/z* (CI, NH_3) 274 ($M+H^+$, 100%); found: $M+H^+$, 274.1443. $C_{16}H_{19}NO_3$ requires for $M+H^+$, 274.1443.

3.2.20. 2-Hexyl-2,3-dihydrofuro[3,2-*c*]quinolin-4-ol 32. 41%; oil; R_f 0.5 (ethyl acetate); ν_{max} ($CHCl_3$) 3042 (m), 2933 (w), 1676 (s), 1223 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.71 (1H, d, *J*=7.8 Hz, H9), 7.56–7.42 (2H, m, aromatic), 7.23–7.12 (1H, m, aromatic), 5.14–5.00 (1H, m, H2), 3.34 (1H, dd, *J*=15.3 and 9.9 Hz, H3), 2.90 (1H, dd, *J*=15.3 and 7.5 Hz, H3), 2.00–1.20 (10H, m, 5×CH_2), 0.80 (3H, t, *J*=6.3 Hz, CH_2CH_3); δ_C (67.5 MHz, $CDCl_3$) 165.1 (C9b), 164.1 (C4), 140.1 (C5a), 131.2 (C7), 122.8 (C8), 122.4 (C9), 117.0 (C6), 112.4 (C3a), 108.4 (C9a), 87.3 (C2), 36.8 (C3), 33.3 (CH_2), 32.3 (CH_2), 29.7 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 14.6 (CH_2CH_3); *m/z* (CI, NH_3) 272 ($M+NH_4^+$, 100%), found: $M+NH_4^+$, 272.1652. $C_{17}H_{21}NO_2$ requires for $M+NH_4^+$, 272.1651.

3.2.21. 2-Hexyl-2,3-dihydrofuro[2,3-*b*]quinolin-4-ol 33. 4%; oil; R_f 0.4 (ethyl acetate); ν_{max} ($CHCl_3$) 3025 (m), 1229 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.39 (1H, dd, *J*=1.3 and 8 Hz, H5), 7.70–7.45 (2H, m, aromatic), 7.40–7.20 (1H, m, aromatic), 5.10–4.85 (1H, m, H2), 3.37 (1H, dd, *J*=9.2 and 14.5 Hz, H3), 2.93 (1H, dd, *J*=7.0 and 14.5 Hz, H3), 2.00–1.20 (10H, m, 5×CH_2), 0.80 (3H, t, *J*=7 Hz, CH_2CH_3); *m/z* (CI, NH_3) 272 ($M+NH_4^+$, 100%); found: $M+NH_4^+$, 272.1652. $C_{17}H_{21}NO_2$ requires for $M+NH_4^+$, 272.1651.

3.2.22. 2-Methyl-2-propyl-2,3-dihydrofuro[3,2-*c*]quinolin-4-ol 34. 71%; oil; R_f 0.45 (ethyl acetate); ν_{max} ($CHCl_3$) 2966 (m, br), 1653 (s), 1621 (s), 1512 (w), 1377 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.68 (1H, d, *J*=7.8 Hz, H9), 7.55–7.40 (2H, m, aromatic), 7.21–7.12 (1H, m, aromatic), 3.14 (1H, d, *J*=15.3 Hz, H3), 2.98 (1H, d, *J*=15.3 Hz, H3), 1.80 (2H, t, *J*=8.0 Hz, propyl CH_2), 1.51–1.45 (5H, m, propyl CH_2CH_3 and CCH_3), 0.95 (3H, t, *J*=7.3 Hz, propyl CH_2CH_3); δ_C (67.5 MHz, $CDCl_3$) 163.7 (C9b), 163.6 (C4), 139.6 (C5a), 130.5 (C7), 122.3 (C8), 121.7 (C9), 116.4 (C6), 111.9 (C3a), 107.4 (C9a), 93.4 (C2), 43.5 (C3), 38.3 (CH_2), 26.7 (CH_3), 17.1 (CH_2), 14.3 (CH_3); *m/z* (CI, NH_3) 244 ($M+H^+$, 100%); found: $M+H^+$, 244.1333. $C_{15}H_{17}NO_2$ requires for $M+H^+$, 244.1337.

3.2.23. 2-Methyl-2-propyl-2,3-dihydrofuro[2,3-*b*]quinolin-4-ol 35. 8%; oil; R_f 0.2 (ethyl acetate); ν_{max} ($CHCl_3$) 2964 (w, br), 1626 (w), 1572 (m), 663 (m, br) cm^{-1}; δ_H (270 MHz, $CDCl_3$), 8.39 (1H, dd, *J*=1.3, 8 Hz, H5), 7.70–7.41 (2H, m, aromatic), 3.13 (1H, d, *J*=14.5 Hz, H3), 2.96 (1H, d, *J*=14.5 Hz, H3), 1.70 (2H, t, *J*=8 Hz, propyl CH_2), 1.55–1.35 (5H, m, propyl CH_2 and CCH_3), 0.88 (3H, t, *J*=7.3 Hz, propyl CH_2CH_3); *m/z* (CI, NH_3) 244 ($M+H^+$, 100%); found: $M+H^+$, 244.1332. $C_{15}H_{17}NO_2$ requires for $M+H^+$, 244.1337.

3.2.24. 8,10-Methano-9,9,10a-trimethyl-6b,7,8,9,10,10a-hexahydro[1]benzofuro[3,2-*c*]quinolin-6-ol 36. A single diastereoisomer as indicated by the ^{13}C NMR spectrum; 64%; oil; R_f 0.45 (ethyl acetate); ν_{max} ($CHCl_3$) 3047 (m, br), 1692 (m), 1634 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.69 (1H, d, *J*=7.8 Hz, H1), 7.54–7.43 (2H, m, aromatic), 7.20–7.10 (1H, m, aromatic), 3.45 (1H, dd, *J*=3.4 and 10.2 Hz, H6b), 2.60–1.90 (6H, m, CH-7, CH_2-8, CH-10, CH_2 bridge), 1.50 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.01 (3H, s, CH_3); δ_C (67.5 MHz, $CDCl_3$) 163.5 (C11a), 162.5 (C6), 139.4 (C4a), 130.4 (C3), 122.5 (C2), 121.7 (C1), 116.2 (C4), 114.6 (C11b), 111.8 (C6a), 97.6 (C10a), 50.9 (C10), 39.5 (C8), 39.4 (C6b), 38.1 (C9), 32.3 (C7), 27.5 (CH_3-C10a), 27.1 (CH_3-C9), 26.0 (CH_2 bridge), 23.0 (CH_3-C9); *m/z* (CI, NH_3) 296 ($M+H^+$, 100%); found: $M+H^+$, 296.1656. $C_{19}H_{21}NO_2$ requires for $M+H^+$, 296.1651.

3.2.25. 2,4-Methano-3,3,4a-trimethyl-1,2,3,4,4a,11b-hexahydro[1]benzofuro[3,2-*b*]quinolin-11-ol 37. A single diastereoisomer as indicated by the ^1H NMR spectrum; 4%; oil; R_f 0.3 (ethyl acetate); ν_{max} ($CHCl_3$) 3041 (w, br), 1256 (m), 816 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.39 (1H, d, *J*=8 Hz, H10), 7.52–7.49 (2H, m, aromatic), 7.35–7.10 (1H, m, aromatic), 3.48 (1H, dd, *J*=3.4 and 10.0 Hz, H11b), 2.60–1.90 (6H, m, OCC*H*CC*H*CH_2 and OCCHCH_2CH), 1.46 (3H, s, CCH_3), 1.28 (3H, s, CCH_3), 0.95 (3H, s, CCH_3); *m/z* (CI, NH_3) 296 ($M+H^+$, 100%); found: $M+H^+$, 296.1645 $C_{19}H_{21}NO_2$ requires for $M+H^+$, 296.1651.

3.2.26. 2-Phenyl-2,3-dihydrofuro[3,2-*c*]quinolin-4-ol 38. 41%; oil; R_f 0.45 (ethyl acetate); ν_{max} ($CHCl_3$) 3026 (w), 1658 (m), 807 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 12.0 (1H, br s, COH), 7.76 (1H, d, *J*=7.5 Hz, H9), 7.65–7.00 (8H, m, aromatic), 6.10–6.00 (1H, dd, *J*=10.2 and 8.0 Hz, H2), 3.75 (1H, dd, *J*=15.5 and 10.2 Hz, H3), 3.31 (1H, dd, *J*=15.5 and 8.0 Hz, H3); δ_C (67.5 MHz, $CDCl_3$) 162.3 (C9b), 160.7

(C4), 141.1 (phenyl C), 139.7 (C5a), 130.8 (C7), 128.7 (phenyl CH), 128.3 (phenyl CH), 125.9 (phenyl CH), 121.9 (C8), 121.5 (C9), 115.5 (C6), 110.6 (C3a), 107.8 (C9a), 85.7 (C2), 35.5 (C3); *m/z* (CI, NH_3) 264 ($M+H^+$, 100%); found: $M+H^+$, 264.1031. $C_{17}H_{13}NO_2$ requires for $M+H^+$, 264.1024.

3.2.27. 2-Phenyl-2,3-dihydrofuro[2,3-*b*]quinolin-4-ol 39. 29%; oil; R_f 0.40 (ethyl acetate); ν_{max} ($CHCl_3$) 3014 (m), 1210 (m), 791 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.78 (1H, dd, *J*=1.5 and 8 Hz, H5), 7.59–7.17 (8H, m, aromatic), 6.05 (1H, dd, *J*=10.7 and 8.0 Hz, H2), 3.72 (1H, dd, *J*=15.5 and 10.7 Hz, H3), 3.29 (1H, dd, *J*=15.5 and 8.0 Hz, H3); *m/z* (CI, NH_3) 264 ($M+H^+$, 100%); found: $M+H^+$, 264.1026. $C_{17}H_{13}NO_2$ requires for $M+H^+$, 264.1024.

3.2.28. 2-Methyl-2-phenyl-2,3-dihydrofuro[3,2-*c*]quinolin-4-ol 40. 41%; oil; R_f 0.45 (ethyl acetate); ν_{max} ($CHCl_3$) 3004 (m, br), 1656 (m), 1321 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.85 (1H, d, *J*=7.8 Hz, H9), 7.65–7.15 (8H, m, aromatic), 3.54 and 3.46 (2H, 2×d, *J*=15.3 Hz, H3), 1.90 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 163.4 (C9b), 163.3 (C4), 145.7 (phenyl C), 139.6 (C5a), 130.8 (C7), 128.5 (phenyl CH), 127.5 (phenyl CH), 124.3 (phenyl CH), 122.3 (C8), 122.0 (C9), 116.4 (C6), 111.8 (C3a), 107.4 (C9a), 93.1 (C2), 42.1 (C3), 29.5 (CCH_3); *m/z* (CI, NH_3) 278 ($M+H^+$, 100%); found: $M+H^+$, 278.1183. $C_{18}H_{15}NO_2$ requires for $M+H^+$, 278.1181.

3.2.29. 2-Methyl-2-phenyl-2,3-dihydrofuro[2,3-*b*]quinolin-4-ol 41. 34%; oil; R_f 0.40 (ethyl acetate); ν_{max} ($CHCl_3$) 3005 (m, br), 1657 (m), 1227 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.44 (1H, dd, *J*=8.0 and 1.3 Hz, H5), 7.85–7.15 (8H m, aromatic), 3.52 (1H, d, *J*=14.5 Hz, H3), 3.44 (1H, d, *J*=14.5 Hz, H3), 1.64 (3H, s, CCH_3); *m/z* (CI, NH_3) 278 ($M+H^+$, 100%); found: $M+H^+$, 278.1183. $C_{18}H_{15}NO_2$ requires for $M+H^+$, 278.1181.

3.2.30. 2-Methyl-2-phenyl-3-hydro-3*H*-furo-[3,2-*c*]-quinoline 42. 20%; oil; R_f 0.4 (ethyl acetate); ν_{max} ($CHCl_3$) 3026 (w, br), 2958 (w, br), 1568 (m), 1403 (w), 1310 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.66 (1H, s, H4), 8.15–8.05 (2H, m, aromatic), 7.70–7.60 (1H, m, aromatic), 7.50–7.20 (6H, m, aromatic), 3.65 (1H, d, *J*=15.2 Hz, H3), 3.57 (1H, d, *J*=15.2 Hz, H3), 1.91 (3H, s, CCH_3); δ_C (67.5 MHz, $CDCl_3$) 162.5 (C9b), 148.6 (C5a), 147.9 (C4), 147.7 (phenyl C), 130.1 (C7), 129.8 (C8), 129.2 (phenyl CH), 128.2 (phenyl CH), 126.3 (C6), 125.0 (phenyl CH), 122.2 (C9), 117.2 (C9a), 116.4 (C3a), 93.4 (C2), 43.7 (C3), 30.0 (CCH_3); *m/z* (CI, NH_3) 262 ($M+H^+$, 100%); found: $M+H^+$, 262.1233. $C_{18}H_{15}NO$ requires for $M+H^+$, 262.1231.

3.2.31. 3-Chloro-4-hydroxy-1 (2H)-methyl-quinolone 43. 4-Hydroxy-1(2H)-methyl-quinolone **5** (0.5 g, 2.85 mmol) and *N*-chlorosuccinimide (0.42 g, 3.14 mmol) was heated for 3 h in chloroform (100 cm^3). The crude product was adsorbed onto silica and column chromatography (silica, ethyl acetate) gave the title compound **43** (0.49 g, 82%) as a pale yellow solid. R_f 0.5 (4:1, ethyl acetate); ν_{max} ($CHCl_3$) 3495 (w, br), 1599 (s, br), 1233 (w, br), 728 (s, br) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.10 (1H, *J*=1.5 and 8 Hz, H5), 7.69–7.60 (1H, m, aromatic), 7.42–7.23 (2H, m, aromatic), 6.45 (1H, s, OH), 3.77 (3H, s, NCH_3); *m/z* (CI, NH_3) 210 ($M+H^+$, 100%); found: $M+H^+$, 210.0324. $C_{20}H_{23}NO_2$ requires for $M+H^+$, 210.0321.

3.2.32. 3-Allyl-3-chloro-1-methyl-quinolone-2,4-dione 45. To a solution of chloroquinolone **43** (0.1 g, 0.48 mmol) and allyl *t*-butyl sulfide (0.62 g, 4.8 mmol, 10 equiv.) in degassed acetic acid (20 cm^3), under nitrogen, was added manganese(III) acetate dihydrate (0.26 g, 1.0 mmol, 2.1 equiv.) in acetic acid (30 cm^3). The solution was heated at 60°C in an ultrasonic bath until the solution changed from brown to yellow in coloration (2 h). Saturated aqueous $NaHCO_3$ (100 cm^3) was added and the mixture extracted with dichloromethane (2×20 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford crude product. This was purified by column chromatography (silica, ethyl acetate) to give **45** (23 mg, 40%) as an oil. R_f 0.6 (ethyl acetate); ν_{max} ($CHCl_3$) 3027 (m), 1672 (m), 1603 (s), 1473 (s), 700 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.05 (1H, *J*=8.0 and 1.5 Hz, H5), 7.70–7.64 (1H, m, aromatic), 7.26–7.16 (2H, m, aromatic), 5.69–5.53 (1H, m, CH_2CH=CH), 5.21–5.13 (1H, m, CH=CH_2), 5.11–5.06 (1H, m, CH=CH_2), 3.50 (3H, s, NCH_3), 3.20 (2H, dt, *J*=1.0 and 7.0 Hz, CH_2CH=CH_2); δ_C (67.5 MHz, $CDCl_3$) 188.0 (C4), 166.8 (C2), 142.2 (C8a), 136.7 (*C*H=CH_2), 130.3 (C7), 129.0 (C6), 123.7 (C8), 121.6 (C4a), 119.4 (CH=*C*H_2), 115.1 (C5), 65.1 (C3), 40.4 (*C*H_2CH=CH_2), 29.5 (NCH_3); *m/z* (CI, NH_3) 250 ($M+H^+$, 20%), 214 ($M+H^+-Cl$, 100); found: $M+H^+$, 250.0631. $C_{13}H_{12}ClNO_2$ requires for $M+H^+$, 250.0634.

3.2.33. 3-Chloro-3-(2-chlorooctyl)-1-methylquinoline-2,4-(1H,3H)dione 46. To a solution of quinolone **5** (0.1 g, 0.57 mmol), manganese(III) acetate dihydrate (0.32 g, 1.2 mmol, 2.1 equiv.) and 1-octene (0.64 g, 10 equiv.) in degassed ethanol (50 cm^3) is bubbled HCl gas,[15] while stirring, until a solution is formed. After stirring for a further 0.5 h the solution changed from brown to yellow in coloration, the solvent is removed under reduced pressure and saturated aqueous $NaHCO_3$ (10 cm^3) is added. The mixture is extracted with dichloromethane (3×20 cm^3), washed with brine, dried ($MgSO_4$) and evaporated to afford crude product. This was purified using column chromatography (silica) to give **16** (55 mg, 27%) as a 1:1 mixture of diastereoisomers (as indicated by the ^{13}C NMR spectrum as an oil). ν_{max} ($CHCl_3$) 2931 (m, br), 2859 (w, br), 1703 (s), 1668 (s), 1604 (s), 1473 (s), 1364 (s), 908 (m) cm^{-1}; *m/z* (CI, NH_3) 356 ($M+H^+$, 35%), 320 ($M+H^+-Cl$, 35), 286 ($M+H^+-2Cl$, 100); found: $M+H^+$, 356.1183. $C_{18}H_{23}Cl_2NO_2$ requires for $M+H^+$, 356.1184. *Diastereoisomer 1*: R_f 0.23 (petroleum ether–diethyl ether, 6:4); δ_H (270 MHz, $CDCl_3$) 8.16 (1H, dd, *J*=7 and 1.5 Hz, H5), 7.74–7.65 (1H, m, aromatic), 7.30–7.18 (2H, m, aromatic), 4.31–4.19 (1H, br m, CH_2CHCl), 3.56 (3H, s, NCH_3), 3.29 (1H, dd, *J*=12.5 and 10.0 Hz, CH_2CHCl), 2.89 (1H, dd, *J*=12.5 and 4.0 Hz, CH_2CHCl), 1.90–1.70 (2H, m, octyl CH_2), 1.27 (8H, br s, 4×octyl CH_2), 0.88 (3H, t, *J*=6.2 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 187.7 (C4), 167.1 (C2), 142.4 (C8a), 137.4 (C7), 130.0 (C5), 124.2 (C6), 118.9 (C8), 115.6 (C4a), 62.6 (C3), 59.6 (CHCl), 43.5, 39.1 (2×*C*H_2CHCl), 32.0 (octyl CH_2), 31.1 (NCH_3), 29.1, 26.6, 22.9 (3×octyl CH_2), 14.4 (octyl CH_3). *Diastereoisomer 2*: R_f 0.16 (petroleum ether–diethyl ether, 6:4); δ_H (270 MHz,

$CDCl_3$) 8.17 (1H, J=7 and 1.5 Hz, H5), 7.75–7.65 (1H, m, aromatic), 7.30–7.18 (2H, m, aromatic), 4.15–4.10 (1H, br m, CH_2CHCl), 3.54 (3H, s, NCH_3), 3.29 (1H, dd, J=14.0 and 10.0 Hz, CH_2CHCl), 2.87 (1H, dd, J=14.0 and 4.5 Hz, CH_2CHCl), 1.76–1.27 (10H, m, 5×octyl CH_2), 0.87 (3H, t, J=6.0 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 188.2 (C4), 168.1 (C2), 143.0 (C8a), 137.0 (C7), 129.7 (C5), 124.0 (C6), 119.0 (C8), 115.6 (C4a), 62.6 (C3), 59.4 (CHCl), 43.9, 39.2 (2×CH_2CHCl), 32.0 (octyl CH_2), 30.8 (NCH_3), 29.1, 26.5, 22.9 (3×octyl CH_2), 14.4 (octyl CH_3).

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