Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 64 (2008) 4026–4036
www.elsevier.com/locate/tet

Facile synthesis of seven to nine-membered-fused tricyclic quinolones and quinolinium salts under phase transfer catalyzed conditions

Priyankar Paira [a], Abhijit Hazra [a], Krishnendu B. Sahu [a], Sukdeb Banerjee [a], Nirup B. Mondal [a,*], Niranjan P. Sahu [a], Manuela Weber [b], Peter Luger [b]

[a] *Steroid and Terpenoid Chemistry Division, Indian Institute of Chemical Biology, 4 Raja S C Mullick Road, Jadavpur, Kolkata 700 032, India*
[b] *Freie Universitat Berlin, Institut fur Chemie and Biochemie/Kristallographie, Fabeckstr, 36a D-14195 Berlin, Germany*

Received 28 September 2007; received in revised form 30 January 2008; accepted 14 February 2008
Available online 20 February 2008

Abstract

Phase transfer catalyzed one-pot syntheses of fused oxazepino, oxazocino, and oxazonino quinolinium cations and quinolones were achieved from 8-hydroxy quinoline derivatives with 1,ω-dihaloalkanes. Structures of all the products were elucidated by spectroscopic analysis. Single crystal X-ray crystallographic analysis of three compounds and graphical superposition of the structures indicate that products having seven-membered ring are less planar compared to the product having eight-membered ring.

Keywords: 8-Hydroxy quinoline; PTC; Quinolinium cations; Quinolones

1. Introduction

More than half of the biologically active compounds produced by nature contain heterocyclic rings as fundamental components in their skeleton.[1] These compounds and their modified products have popularly been utilized as pharmacophores for preparing drugs.[2] Great efforts have therefore been made to discover and optimize new reactions to facilitate the construction of heterocycles.[3,4] Recent challenges in organic synthesis include the development of (i) new methodologies that afford products of greater structural complexity with fewer synthetic steps,[5] (ii) complex molecules from relatively simple starting materials via tandem reactions,[6–17] and (iii) environment friendly, mild reaction conditions producing high yields with operational simplicity.[18] Preparation and testing of analogues or enantiomers of the drugs that are known to exert their pharmacological action via specific enzymes or receptors[19] are considered to be the core objective of these endeavors. In a previous communication,[20] we have demonstrated for the first time a facile methodology for the synthesis of fused tricyclic oxazinoquinolones from the easily available 8-hydroxy quinolines and 1,2-dichloroethane under phase transfer catalyzed conditions. Analogues of seven-membered heteroatomic molecules like dibenzoxepines,[21–24] benzazepines, and benzothiepines[25–27] have gained much attention as potent mCPP and CCR5 antagonists, respectively, and have been considered as potential anxiolytic/antidepressants[28–30] and oral HIV-1 candidates.[31–34] Moreover, moieties containing *N*-heteroaromatic cations have shown high affinity for DNA.[35] We therefore contemplated the synthesis of expanded ring system analogues of oxazinoquinolines like oxazepins, oxazocines, and oxazonines. Following our earlier report,[20] the synthesis of molecules containing a seven/eight-membered 1,4-oxa-aza-quinolinium-ring system appeared to be possible if higher homologues of dihaloalkanes were used. The extended ring systems of 1,4-oxa-aza-quinoliniums of choice could be conveniently prepared by proper selection of the reagent and regulating the reaction conditions. We therefore wished to investigate a methodology involving a one-pot reaction, wherein 8-hydroxy quinoline (**1**) and its different derivatives, e.g., 2-methyl (**2**), 5-chloro (**3**), and 5,7-dibromo (**4**) are used as model substrates and homologues of 1, ω-dihalo (chloro and bromo) derivatives of ethane (**5**),

* Corresponding author. Tel.: +91 33 2473 3491; fax: +91 33 2473 5197.
E-mail address: nirup@iicb.res.in (N.B. Mondal).

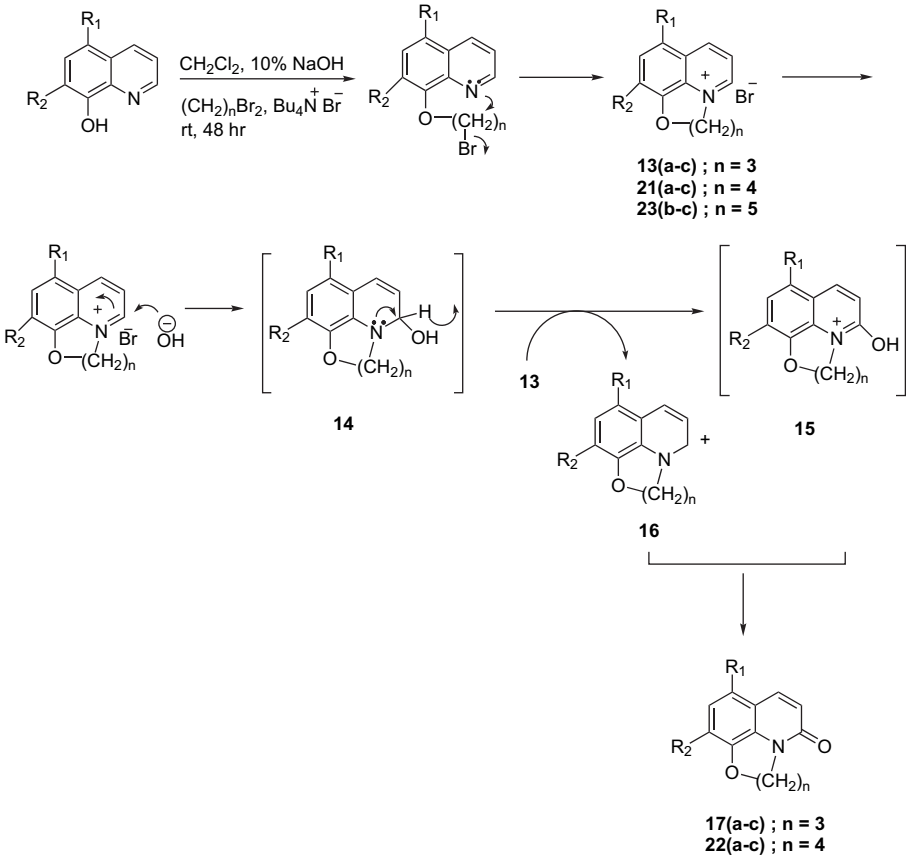
0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.02.048

propane (**6**), butane (**7**), and pentane (**8**) are employed as the alkylating agents. The reactions were carried out using catalytic amounts of commercially available quaternary ammonium halides as a phase transfer catalyst (PTC) in the presence of an inorganic base. The course of the reaction was expected to follow the mechanistic path as proposed in the formation of oxazinoquinolones.[20] But to our surprise a new class of fused tricyclic oxa-aza-quinolinium cations were also isolated along with the expected product 1,4-oxazepino quinolones. Further studies furnished new classes of fused tricyclic oxa-aza-quinolinium cations. The generality of the reaction system and the plausible mechanism of this tandem reaction are the subject of this paper. Finally, the methodology has been further developed via the use of a co-oxidizing agent in this biphasic system to isolate the tricyclic quinolone derivatives in high yield. We feel that our approach for the fused tricyclic compounds has both generality and preparative simplicity, and will yield subsets of heterocycles having the potentiality to serve as templates for new biologically active molecules.

2. Results and discussion

Initially, the reaction of 2-methyl-8-hydroxy quinoline (**2**) with 1,3-dichloropropane (**6**) in 1:1.5 mole ratio was carried out at ambient temperature using catalytic amounts of tetrabutylammonium bromide as PTC in the presence of aq NaOH for 48 h, which afforded two products, one major (40%) and the other minor (<10%). On mass spectral analysis, the products appeared to be the di-ether, 1,3-bis[(2-methyl-8-quinolyl)oxy]-propane (**9**), and the mono-ether, 1-chloro-3-(2-methyl-8-quinolyl)oxy propane (**10**). The use of excess (2–3 equiv) of the alkylating agent for ~72 h neither increased the yield nor afforded the expected cyclic product. The yields of the products were virtually unaffected even after increasing the reaction temperature (50 °C). Similar results were obtained with 1,4-dichlorobutane (**7**) and 1,5-dichloropentane (**8**), resulting in the formation of 1,4-bis-[(2-methyl-8-quinolyl)oxy]butane (**11**) and 1,5-bis-[(2-methyl-8-quinolyl)oxy]pentane (**12**), respectively, in 35–40% yield besides trace amounts of the corresponding mono-ethers. Contemplating similar outcome, the other substrates were not reacted with dichloroalkanes. We then opted for dibromoalkanes as bromine is a better leaving group than chlorine, but the reactions took an altogether different course.

Following similar experimental protocol, the reaction of 5,7-dibromo-8-hydroxy quinoline (**4**) with 1,3-dibromopropane (**6**) for about 48 h indeed yielded a solid product characterized (Scheme 1) as 1,4-oxazepino-5,7-dibromoquinolinium (**13a**) from its mass, ^{1}H, and ^{13}C NMR spectral analyses. The molecular ion peak in positive mode (ESI) was displayed as M^{+} characteristic of a cation rather than a protonated or sodiated ion. Two other products were isolated and characterized as 1,4-oxazepino-5,7-dibromo quinolone (**17a**), and a trace



Scheme 1. Possible reaction pathway leading to fused quinolone analogues.

amount of the di-ether. Employment of 2–3 molar equiv of **6** enhanced the yields of both **13a** and **17a**; no bis-ether product could be isolated. Similar products identified as **13b/17b**, **18/17b**, and **13c/17c** were obtained from the substrates **1**–**3**, respectively, when subjected to reaction with **6**. The structures were determined on the basis of their MS, ^{1}H, and ^{13}C NMR data, and elemental analysis. Besides, the molecular structures of **13a** and **17a** were unambiguously determined by single crystal X-ray analysis. ORTEP representations[36] of the molecular structures showing the atomic numbering schemes are shown in Figure 1. Thereafter, we turned our attention to the synthesis of eight-membered-fused quinolones, the oxazocino quinolone analogues. Following similar reaction parameters, reaction of 5,7-dibromo-8-hydroxy quinoline (**4**) with 1,4-dibromobutane (**7**) furnished the oxazocino quinolinium (**21a**) and the corresponding quinolone (**22a**) as expected. The structure of oxazocino quinolinium **21a** was confirmed by both spectral analysis and single crystal X-ray analysis (Fig. 1). The quinolinium cation was recognizable by the shortening of the bond N5–C6, which is 1.335(6) and 1.326(7) Å for **21a** and **13a**, respectively, compared to 1.388(3) Å for **17a**. Similarly, we could isolate differently substituted eight-membered quinolinium cations and the corresponding quinolones **21b/22b** and **21c/22c** from the substrates **1** and **3**, respectively, when subjected to reaction with 1,4 dibromobutane (**7**). The percentage yield of all the analogues is summarized in Table 1. Finally, the reactions of **1** and **3** were performed with 1,5-dibromopentane (**8**) as the alkylating agent to isolate only a small amount (~5%) of oxazonino quinoliniums **23b** and **23c**. However, the corresponding quinolones could not be isolated probably due to the very low yield of the quinoliniums.

As proposed in Schemes 1 and 2, the reaction may proceed through the intermediate quinolinium salts (**13**, **18**, **21**, and **23**), the key intermediates for this unusual ring formation. Isolation and characterization of the intermediate quinolinium salts clearly indicate that the formation of the quinolone derivatives has occurred in a stepwise manner and not in a synchronized fashion, as was suggested previously,[20] where nucleophilic addition of OH^{-} occurred following the intramolecular nucleophilic substitution. The present observation of fused quinolinium cation formation in the case of extended ring systems (seven, eight, and nine-membered) prompted us to revisit our previous work[20] to see whether any six-membered-fused quinolinium cation formation had occurred and remained undetected. Indeed, here also we were able to isolate a trace amount of six-membered-fused quinolinium salt after 30 h. However, with an increase in the reaction time the yield of oxazinoquinolinium salt decreases and finally after 48 h no salt could be isolated, as it has been converted into its corresponding quinolone.

The major factors influencing the yields of six to nine-membered quinoliniums and the corresponding quinolone products are the leaving group aptitude (Table 2) and length of the alkyl chain of the dihaloalkanes. As the quinolinium intermediates are aromatic stabilized, the described reaction proceeds through this intermediate. In the published systems, the equilibrium tends to be driven by destabilizing effects on the heteroaromatic cation, which enhances its oxidizing power.[5,37,38] Several driving forces can explain the efficiency of this redox reaction. First, the positive charge on quaternary ammonium salt in **13**, **18**, **21**, and **23** is neutralized by the nucleophilic addition of the hydroxide ion to the C-2 position of this quinolinium intermediate. Secondly, the aromaticity of intermediate **14** is being lost, whereas the central heterocycle in intermediate **15** regains the aromatic character during oxidation. Finally, tautomerization of intermediate **15** takes place leading to isolated quinolones. The formation of **16a** in the same reaction process indicated that the oxidation process occurred through hydride transfer of the intermediate **14** to **13a**. It was demonstrated from the spectral analysis of the product that was produced by carrying out the reaction of an aqueous solution of **13a** with sodium borohydride for about 15 min under nitrogen atmosphere. The ^{1}H NMR spectrum of the product is in full agreement with the structure of **16a**. But the presence of a doublet at δ 91.5 along with some additional peaks in its ^{13}C NMR spectra clearly indicates its partial transformation toward **14a**. The lability of **16a** became obvious when the same reaction was carried out without a nitrogen atmosphere for about 1 h, not a trace of it could be isolated, rather the quinolone **17a** was isolated in good yields indicating that the conversion of **16a** to **17a** was facile and it must have proceeded through aerial oxidation (Scheme 3).

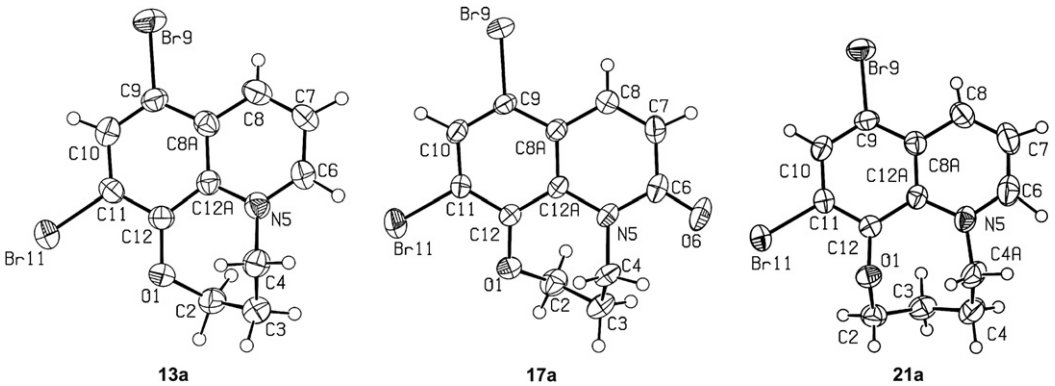
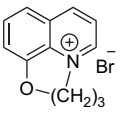
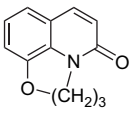
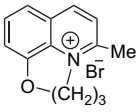
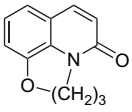
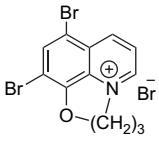
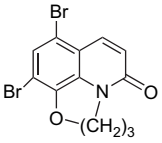
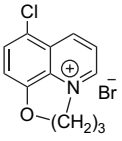
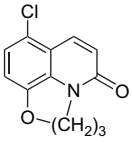
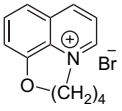
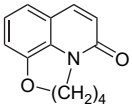
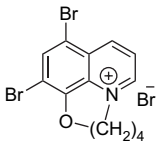
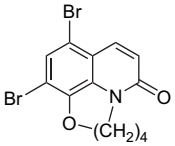
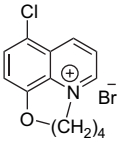
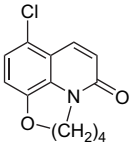
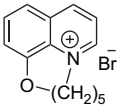
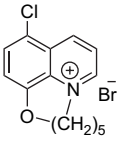


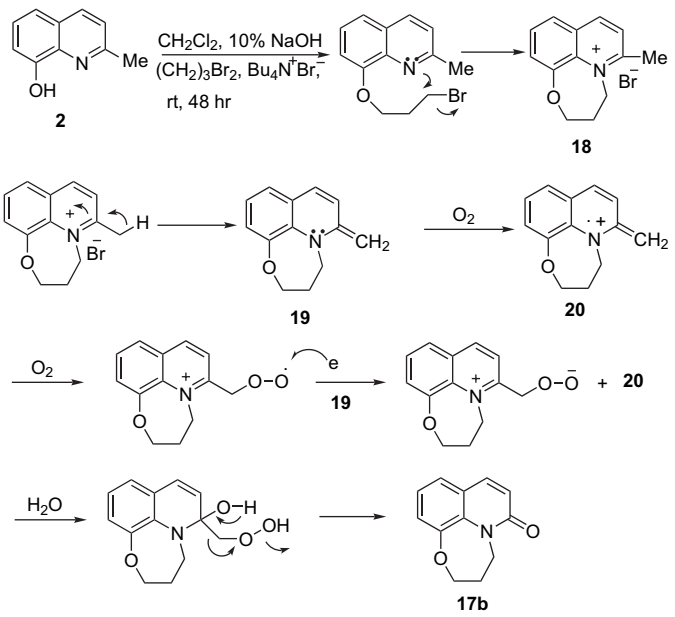
Figure 1. ORTEP representations of **13a**, **17a**, and **21a**, the displacement ellipsoids are drawn at a probability of 50%.

Table 1
Fused tricyclic quinolinium and quinolone frameworks obtained via this described method

Substrate	Alkylating agent (**6**–**8**)	Time (h)	Structure of products		Yield of products (%)	
			Quinolinium	Quinolone	Quinolinium	Quinolone
1	$(CH_2)_3Br_2$	48	 **13b**	 **17b**	40	30
2	$(CH_2)_3Br_2$	48	 **18**	 **17b**	40	35
4	$(CH_2)_3Br_2$	48	 **13a**	 **17a**	45	45
3	$(CH_2)_3Br_2$	48	 **13c**	 **17c**	45	40
1	$(CH_2)_4Br_2$	48	 **21b**	 **22b**	35	30
4	$(CH_2)_4Br_2$	48	 **21a**	 **22a**	40	40
3	$(CH_2)_4Br_2$	48	 **21c**	 **22c**	40	35
1	$(CH_2)_5Br_2$	72	 **23b**	—	5	NI
3	$(CH_2)_5Br_2$	72	 **23c**	—	2	NI

NI=not isolated.

We also tried the reaction with the quinolinium cation (**13a**) itself for transforming it into the corresponding quinolone in the presence of 10% NaOH. The conversion of the quinolinium to the corresponding quinolone was, however, incomplete. The double bond of the heterocycle moiety of **14** is more labile, as it does not belong to an aromatic system. We presume that the intermediate **14** disproportionates (Scheme 4) in the organic layer leading to the oxidation



Scheme 2. Possible reaction pathway leading to fused quinolone from **2**.

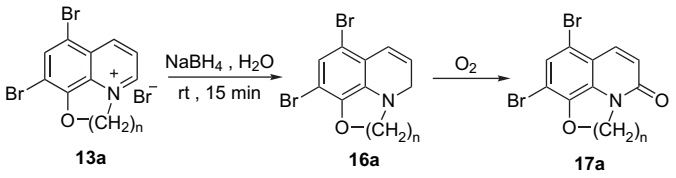
Table 2
Yield of quinolinium (**13b**, **21b**, and **23b**) and the corresponding quinolone (**17b** and **22b**) in the presence of different alkylating agent with progress of time via the described method

Alkylating agent $(CH_2)_nX_2$	Time (h)	Yield of quinolinium (%)			Yield of quinolone (%)		
		n=3	n=4	n=5	n=3	n=4	n=5
$(CH_2)_nCl_2$	12	0	0	0	0	0	0
$(CH_2)_nCl_2$	48	ND	ND	ND	<5	ND	ND
$(CH_2)_nCl_2$	72	ND	ND	ND	<5	ND	ND
$(CH_2)_nBr_2$	12	20	15	ND	0	0	ND
$(CH_2)_nBr_2$	24	40	35	ND	10	10	ND
$(CH_2)_nBr_2$	48	45	40	ND	45	40	ND
$(CH_2)_nBr_2$	72	30	35	5	60	50	ND
$(CH_2)_nI_2$	48	25	25	5	60	55	ND

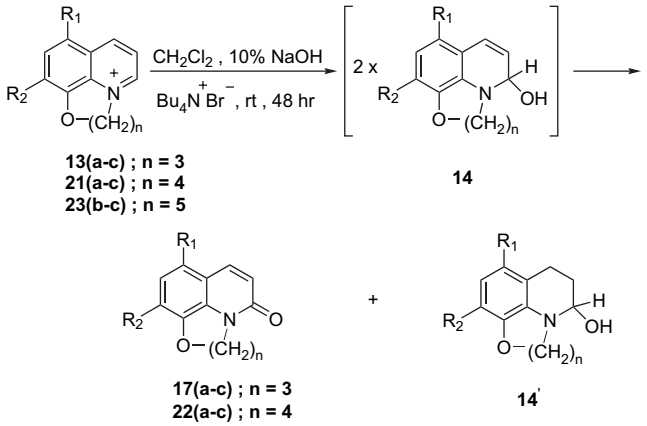
ND=Not detected.

product **17a** and the reduction product **14′**, which was in accord with the similar experiments carried out by Parenty et al.,[5] though the reduced product could not be isolated. However, when the same reaction was carried out in the presence of either 50% NaOH or oxidizing agents like DDQ or NBS, almost complete conversion of quinoliniums to quinolones (Scheme 5) was observed. This observation intrigued us to perform the reaction of 5,7-dibromo-8-hydroxy quinoline (**4**) with 1,3-dibromopropane (**6**) in the presence of 50% NaOH along with DDQ, which yielded only quinolone.

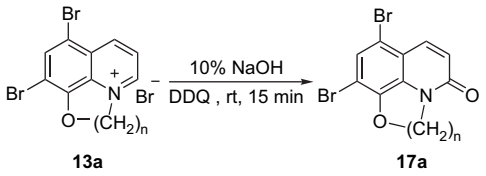
In the formation of 1,4-fused tricyclic ring system (oxazino to oxazonino), the length of the alkyl chain $(-CH_2-)_n$ is also



Scheme 3. Sodium borohydride reduction of quinolinium derivative **13a**.



Scheme 4. Disproportionation of quinolinium derivatives during the proposed method.



Scheme 5. Modified method, using DDQ on quinolinium derivative (**13a**).

a factor. The presence of seven-membered rings in **13a** and **17a** instead of the eight-membered ring in **21a** causes noticeable strain for the quinoline ring system, which is less planar for **13a** and **17a**. This is indicated by the rms deviations of fitted atoms from least squares planes, which are 0.08 Å for both **13a** and **17a** but 0.01 Å for **21a**. Moreover, the atoms directly bonded to the quinoline system deviated considerably from the least square planes up to 0.56 Å and 0.48 Å for C4 in **17a** and **13a**, respectively. The corresponding maximum deviation for **21a** is only 0.05 Å found for O1. The graphical superposition of the molecular structures of **13a**, **17a**, and **21a** (Fig. 2) displayed that the molecules are rather alike except for some minor differences as discussed above. This holds not only for the two seven-membered ring compounds with very comparable ring conformations, but also for seven atoms of the eight-membered ring in **21a**, which occupy almost the same positions as the atoms in the seven-membered rings in **13a** and **17a**. Only the additional atom (C2) differs noticeably in position. While no close intermolecular interactions are seen in the crystal lattices of **17a** and **21a** (Fig. 3), an interesting hydrogen-bonding pattern was observed for **13a**. The water molecule is a donor for two O–H···Br hydrogen bonds, which generate via a crystallographic inversion center a closed eight-membered ring cycle, which is further related to weak C6–H6···O1W bond. The differences in planarity of seven and eight-membered ring systems appear to influence their respective yields.

3. Conclusion

In summary, we have shown a novel, general, and effective method for the synthesis of the expanded ring system of fused tricyclic oxa-aza-quinolinium cations or their corresponding

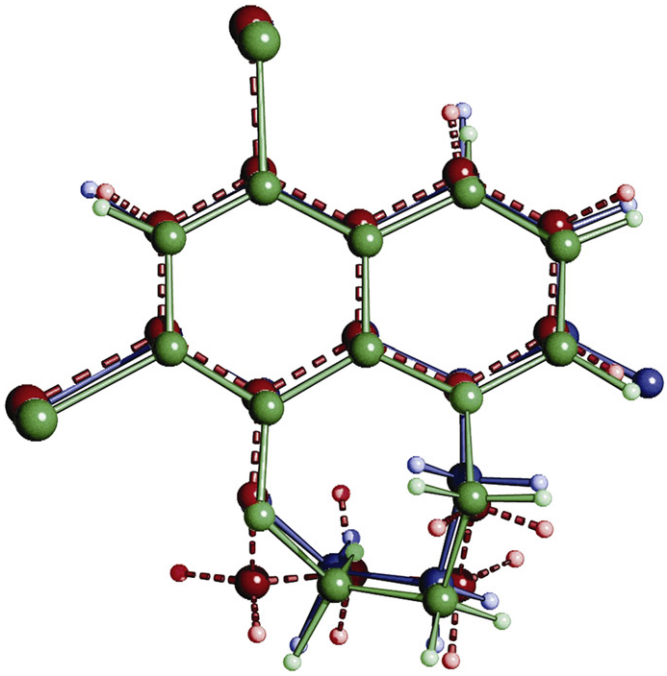


Figure 2. Graphical superposition of **13a** (in green), **17a** (in blue), and **21a** (in red, dashed), SCHAKAL99 drawing.[39]

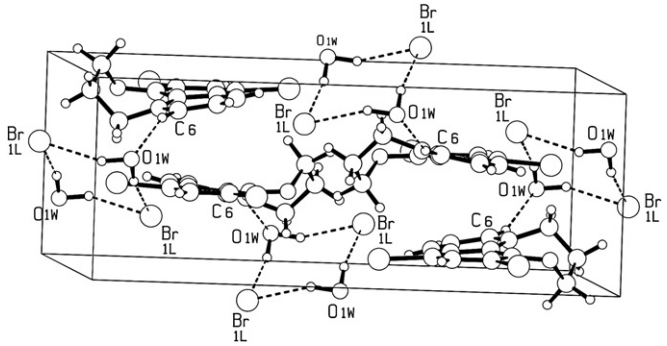


Figure 3. Packing interactions of **13a**, projection of the lattice onto the *x*–*z*-plane, SCHAKAL99 drawing.[39]

quinolones in a one-pot sequence. The mechanism of the reaction is fully understood in the case of quinolinium and quinolone derivatives and has allowed the development of a biphasic protocol in both the cases. This procedure allows a great deal of synthetic flexibility and offers the possibility of synthesizing newer heteroaromatic systems having potential biological activity. The salient features of this methodology are that it works with inexpensive and easily available reactants operating in an environment friendly, mild reaction condition with operational simplicity.

4. Experimental section

4.1. General

Melting points were determined with a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FTIR (model 410) in KBr pellets. ESI-MS (positive) was conducted using LC-ESI-Q-TOF micro mass spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker 300 MHz DPX spectrometer at 300 and 74.99 MHz, respectively, with tetramethylsilane as an internal standard and the chemical shifts are reported in δ units. 8-Hydroxy quinoline derivatives, 1,ω-dihaloalkanes, and PTC (tetra butyl ammonium bromide) were purchased from Aldrich Chemical Ltd (USA). Organic solvents used for the chemical synthesis and for chromatography acquired from E. Merck (India) were of analytical grade. All chromatographic purification was performed with silica gel (60–120 mesh) and was obtained from SRL (India). Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} aluminum sheets (E. Merck, Germany) using the solvent system 1–6% MeOH in $CHCl_3$ and spots were developed using Liebermann–Burchard solution.

4.2. General procedure for the synthesis of molecules 9–12

2-Methyl-8-hydroxy quinoline (**2**) (1.25 mmol) was dissolved in 25 mL of dichloromethane in a 250 mL RB flask placed on a magnetic stirrer. Aqueous NaOH solution (2.5 g, 62.5 mmol, 10% in 25 ml H_2O) was added to the solution at ambient temperature. Then, dichloroalkanes (**6–8**) (1.87 mmol) were added successively to the solution followed by addition of catalytic amount of tetra butyl ammonium bromide (322.4 mg, 1 mmol). The mixture was stirred continuously for 48 h. After completion of the reaction (monitored by TLC), the contents were transferred to a separating funnel and the organic layer was separated. The aqueous layer was extracted 2–3 times with 20–25 mL of dichloromethane. Then, all the dichloromethane extracts were mixed, washed thoroughly with water until free from alkali, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure using a rotary evaporator. The residue was chromatographed over silica gel (60–120 mesh) using petroleum ether (60–80 °C) and chloroform in different ratios yielded the dimer in 70–80% along with a very low amount of monomer.

4.2.1. 1,3-Bis-[(2-methyl-8-quinolyl)oxy]propane (9)

The product **9** was obtained from **2** (1.25 mmol) and 1,3-dichloropropane (1.87 mmol). Purification of the crude product by chromatography (eluant: petrol–chloroform 1:3) and subsequent crystallization from dichloromethane–hexane gave **9** as fine needles (yield 40%). Mp 122–124 °C; R_f (25% pet. ether–$CHCl_3$) 0.45; IR (KBr, ν_{max}) 3365, 3126, 2526, 1864, 1530, 1383 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (m, 2H, $-O-CH_2-CH_2-CH_2$), 2.77 (s, 6H, $2\times CH_3$), 4.56 (t, 4H, J=6.3 Hz, $2\times O-CH_2$), 7.15 (m, 2H, H-7, 7′), 7.31 (m, 6H, H-3, 3′, 5, 5′, 6, 6′), 7.97 (d, 2H, J=8.4 Hz, H-4, 4′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.0 (q, $2\times CH_3$), 29.8 (t, $-O-CH_2-CH_2-CH_2-O-$), 66.5 (t, $2\times -O-CH_2$), 110.2 (d, C-7, 7′), 120.0 (d, C-5, 5′), 122.8 (d, C-3, 3′), 126.1 (d, C-6, 6′), 128.1 (s, C-4a, 4′a), 136.4 (d, C-4, 4′), 140.4 (s, C-8a, 8′a), 154.5 (s, C-8, 8′), 158.4 (s, C-2, 2′); MS [ESI]: *m/z* 359 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{23}H_{23}N_2O_2$: $[M+H]^+$ 359.1760; found: 359.1745.

*4.2.2. 1-Chloro-3-(2-methyl-8-quinolyl)oxy propane (**10**)*

A mixture of **2** (1.25 mmol) was allowed to react with 1,3-dichloropropane (1.87 mmol) following the general procedure to afford **10**. Purification of the residue by chromatography (eluant: petrol–chloroform 4:1) and subsequent crystallization from chloroform–hexane gave **10** as white needles in 10% yield. Mp 134–135 °C; R_f (80% pet. ether–$CHCl_3$) 0.55; IR (KBr, ν_{max}) 3165, 2826, 1580, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.58 (q, 2H, J=6.3 Hz, $-O-CH_2-CH_2-$), 2.78 (s, 3H, $-CH_3$), 4.38 (t, 2H, J=6.3 Hz, $-OCH_2-$), 3.74 (t, 2H, J=6.3 Hz, $-CH_2Cl$), 7.09 (d, 2H, J=6.6 Hz, H-7), 7.30 (d, 1H, J=8.4 Hz, H-3), 7.35 (m, 2H, H-5 and 6), 8.02 (d, 1H, J=8.4 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.9 (q, $-CH_3$), 30.8 (t, $-CH_2$), 32.6 (t, $-CH_2Br$), 110.3 (d, C-7), 120.3 (d, C-5), 122.9 (d, C-3), 126.1 (d, C-6), 128.2 (s, C-4a), 136.6 (d, C-4), 140.2 (s, C-8a), 154.4 (s, C-8). HRMS (ESI) *m/z* calcd for $C_{13}H_{15}ClNO$: $[M+H]^+$ 236.0842; found: 236.0860.

*4.2.3. 1,4-Bis-[(2-methyl-8-quinolyl)oxy]butane (**11**)*

The product **8** was obtained from **2** (1.4 mmol) and 1,4-dichlorobutane (2.1 mmol) following the general procedure. The residue was purified by chromatography (eluant: petrol–chloroform 1:3) and subsequent crystallization from acetonitrile–hexane gave **11** as white needles (yield 35%). Mp 172–174 °C; R_f (25% pet. ether–$CHCl_3$) 0.48; IR (KBr, ν_{max}): 3463, 3046, 2925, 1602, 1564, 1503, 1430, 1383, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.30 (m, 4H, $-CH_2-CH_2-$), 2.71 (s, 6H, 2×CH_3), 4.40 (m, 4H, 2×$-O-CH_2$), 7.08 (dd, J=2.1, 6.3 Hz, 2H, H-7, 7′), 7.33 (m, 6H, H-3, 3′, 5, 5′, 6, 6′), 7.99 (d, J=8.4 Hz, 2H, H-4, 4′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.1 (q, 2×CH_3), 26.3 (t, $-CH_2-CH_2-$), 69.3 (t, 2×$-OCH_2$), 109.6 (d, C-7, 7′), 119.7 (d, C-5, 5′), 122.8 (d, C-3, 3′), 126.1 (d, C-6, 6′), 128.1 (s, C-4a, 4′a), 136.4 (d, C-4, 4′), 140.3 (s, C-8a, 8′a), 154.6 (s, C-8, 8′), 158.4 (s, C-2, 2′); MS [ESI]: *m/z* 373 $[M+H]^+$, 395 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{25}N_2O_2$: $[M+H]^+$ 373.1916; found: 373.1902.

*4.2.4. 1,5-Bis-[(2-methyl-8-quinolyl)oxy]pentane (**12**)*

A mixture of **2** (1.3 mmol) was allowed to react with 1,5-dichloropentane (1.95 mmol) following the general procedure to afford **12**. Purification of the residue by chromatography (eluant: petrol–chloroform 1:3) and subsequent crystallization from acetonitrile–hexane gave **12** as needles (yield 40%). Mp 178–180 °C; R_f (25% pet. ether–$CHCl_3$) 0.47; IR (KBr, ν_{max}): 3508, 3050, 2946, 1606, 1563, 1261, 1106, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.80 (m, 2H, $-CH_2-$), 2.17 (m, 4H, 2×$-O-CH_2-CH_2-$), 2.78 (s, 6H, 2×CH_3), 4.29 (t, 4H, J=6.9 Hz, 2×$-OCH_2$), 7.05 (m, 2H, H-7, 7′), 7.34 (m, 6H, H-3, 3′, 5, 5′, 6, 6′), 8.01 (d, J=8.4 Hz, 2H, H-4, 4′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1 (t, $-CH_2-$), 25.9 (q, 2×CH_3), 29.1 (t, 2×$-CH_2-$), 69.4 (t, 2×$-OCH_2$), 109.7 (d, C-7, 7′), 119.7 (d, C-5, 5′), 122.9 (d, C-3, 3′), 126.3 (d, C-6, 6′), 128.1 (s, C-4a, 4a′), 136.8 (d, C-4, 4′), 139.9 (s, C-8a, 8′a), 154.5 (s, C-8, 8′), 158.5 (s, C-2, 2′); MS [ESI]: *m/z* 387 $[M+H]^+$, 409 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{25}H_{27}N_2O_2$: $[M+H]^+$ 387.2073; found: 387.2064.

*4.3. General biphasic procedure for the synthesis of molecules **13(a–c)**, **17(a–c)**, **18**, **21(a–c)**, **22(a–c)**, and **23(b–c)***

The necessary 8-hydroxy quinoline derivative (**1**, **2**, **3**, or **4**) (3.3 mmol) was dissolved in 30 mL of dichloromethane in a 250-mLRB flask followed by the addition of 30 mL of 10% aqueous NaOH (3 g, 75 mmol) solution, and was stirred at room temperature for about 30 min. 1,ω-Dibromoalkane (**5**, **6**, **7**, or **8**) (10 mmol, 1:3 ratio with respect to the substrate) was added successively to the stirred solution and stirring continued for 10 min. Finally, a catalytic amount of tetra butyl ammonium bromide (Phase Transfer Catalyst) was added to the solution and the reaction mixture was stirred at ambient temperature for 48 h. During the course of reaction, TLC was performed after every 5–6 h to monitor the course of the reaction. After completion of the reaction, the contents of the reaction mixture were poured to a separating funnel; the organic layer was separated followed by extraction of the aqueous layer thrice with 20–25 mL of dichloromethane. The entire aqueous layer was further extracted with *n*-butanol for collecting the rest amount of compounds. Then, all the organic layers were mixed together, washed thoroughly with water until free from alkali, dried over sodium sulfate, and evaporated to dryness in a rotary evaporator under reduced pressure. The residue was chromatographed over silica gel (60–120 mesh), eluting with a mixture of petroleum ether–chloroform and chloroform–methanol in different ratios yielded the respective fused quinolinium cation and its corresponding quinolone with 45–50% in both.

*4.3.1. 1,3-Dibromo-8,9-dihydro-7H-10-oxa-6a-azonia-cyclohepta[de]naphthalene; bromide (**13a**)*

Bromide **13a** was obtained from the column, eluted with 1% methanol–chloroform, and was crystallized from a chloroform–benzene mixture to give the corresponding quinolinium cation as deep yellow needles in 45% yield. Mp 206–208 °C; R_f (1% MeOH–$CHCl_3$) 0.37; IR (KBr, ν_{max}): 1374, 1397, 3438 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.66 (2H, t, J=6 Hz, $-CH_2-CH_2N-$), 4.53 (t, 2H, J=7.2 Hz, $-CH_2-CH_2N-$), 5.23 (t, 2H, J=5.1 Hz, $-O-CH_2-CH_2-$), 8.26 (dd, 1H, J=5.7, 8.7 Hz, H-5), 8.69 (s, 1H, H-2), 9.26 (d, 1H, J=8.7 Hz, H-4), 9.58 (d, 1H, J=5.7 Hz, H-6); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 28.6 (CH_2), 60.3 (CH_2), 72.8 (CH_2), 117.8 (C), 122.5 (C), 124.9 (CH), 130.5 (C), 135.9 (C), 137.5 (CH), 147.0 (CH), 152.6 (CH); MS (ESI): *m/z* 344 $[M-Br]^+$, 346 $[M+2-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{10}NOBr_2$: $[M-Br]^+$ 341.9129; found: 341.9104.

*4.3.2. 1,3-Dibromo-8,9-dihydro-7H-10-oxa-6a-aza-cyclohepta[de]naphthalen-6-one (**17a**)*

Quinolone **17a** was obtained from the 30% chloroform–petroleum ether fraction and was crystallized from chloroform–petroleum ether mixture to give quinolone as a brownish needle crystal in 45% yield. Mp 170–172 °C; R_f (70% pet. ether–$CHCl_3$) 0.54; IR (KBr, ν_{max}): 1438, 1558, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.36 (q, 2H, J=6.9 Hz, $-OCH_2-CH_2-$), 4.38 (t, 2H, J=6 Hz, $-CH_2-CH_2N$), 4.61

(t, 2H, J=6 Hz, −OCH_2), 6.75 (d, 1H, J=9 Hz, H-5), 7.63 (s, 1H, H-2), 7.98 (d, 1H, J=9.9 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.9 (CH_2), 42.8 (CH_2), 71.8 (CH_2), 116.7 (C), 118.2 (C), 121.2 (C), 123.5 (CH), 130.5 (CH), 135.9 (C), 138.2 (CH), 145.8 (C), 162.4 (−CO); MS [ESI]: *m/z* 360 $[M+H]^+$, 362 $[M+2+H]^+$, 382 $[M+Na]^+$, 384 $[M+2+Na]^+$, 386 $[M+4+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{10}Br_2NO_2$: $[M+H]^+$ 357.9078; found: 357.9069.

4.3.3. 8,9-Dihydro-7H-10-oxa-6a-azonia-cyclohepta-[de]naphthalene; bromide (**13b**)

Bromide **13b** was obtained from the column, eluted with 5% methanol−chloroform, and was crystallized from a chloroform−benzene mixture to give the corresponding quinolinium cation as a white needles in a 40% yield. Mp 246−248 °C; R_f (5% MeOH−$CHCl_3$) 0.38; IR (KBr, ν_{max}): 1409, 1535, 3449 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz): δ 2.63 (m, 2H, CH_2−CH_2N), 4.39 (t, 2H, J=7.5 Hz, −OCH_2−CH_2), 5.16 (t, 2H, J=5.4 Hz, −OCH_2), 7.62 (d, 1H, J=6.9 Hz, H-1), 7.70 (t, 1H, J=7.8 Hz, H-5), 7.88 (m, 2H, H-2, 3), 8.93 (d, 1H, J=8.4 Hz, H-4), 9.07 (d, 1H, J=5.7 Hz, H-6); ^{13}C NMR (D_2O, 75 MHz): δ 28.9 (CH_2), 59.8 (CH_2), 72.4 (CH_2), 122.4 (CH), 126.3 (CH), 127.4 (CH), 131.2 (CH), 132.3 (C), 134.0 (C), 148.0 (CH), 149.7(CH), 150.9 (C); MS [ESI]: *m/z* 186 $[M-Br]^+$. Anal. Calcd for $C_{12}H_{12}NOBr$: C, 54.16; H, 4.54; N, 5.26. Found: C, 54.18; H, 4.47; N, 5.66.

4.3.4. 8,9-Dihydro-7H-10-oxa-6a-aza-cyclohepta-[de]naphthalen-6-one (**17b**)

Compound **17b** was obtained from the 50% chloroform−petroleum ether fraction and was crystallized from chloroform−petroleum ether mixture to give quinolone as yellow needles in 30% yield. Mp 182−184 °C; R_f (50% pet. ether−$CHCl_3$) 0.51; IR (KBr, ν_{max}): 1452, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (m, 2H, −OCH_2−CH_2), 4.30 (t, 2H, J=7.2 Hz, CH_2−CH_2N), 4.63 (t, 2H, J=5.7 Hz, −OCH_2), 6.66 (d, 1H, J=9.6 Hz, H-5), 7.13 (m, 3H, H-1, 2, 3), 7.59 (d, 1H, J=9.3 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3 (CH_2), 42.0 (CH_2), 71.5 (CH_2), 122.3 (CH), 122.8 (C), 122.8 (CH), 123.4 (CH), 123.7 (CH), 133.9 (C), 139.5 (CH), 149.6 (C), 162.8 (CO); MS [ESI]: *m/z* 202 $[M+H]^+$, 224 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{12}NO_2$: $[M+H]^+$ 202.0868; found: 202.0877.

4.3.5. 3-Chloro-8,9-dihydro-7H-10-oxa-6a-azonia-cyclohepta[de]naphthalene; bromide (**13c**)

Molecule **13c** was obtained from the column, eluted with 2% methanol−chloroform, and was crystallized from a chloroform−benzene mixture to give the corresponding quinolinium cation as yellowish brown needles in a 45% yield. Mp 218−220 °C; R_f (2% MeOH−$CHCl_3$) 0.40; IR (KBr, ν_{max}): 1289, 1525, 3432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.95 (t, 2H, J=5.7 Hz, CH_2−CH_2N), 4.52 (m, 2H, −OCH_2−CH_2), 5.66 (t, 2H, J=5.1 Hz, −OCH_2), 7.66 (d, 1H, J=8.4 Hz, H-1), 7.87 (d, 1H, J=8.7 Hz, H-2), 8.32 (m, 1H, H-5), 9.23 (d, 1H, J=8.7 Hz, H-4), 10.64 (d, 1H, J=5.1 Hz, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.2 (CH_2), 60.0 (CH_2), 72.7 (CH_2), 124.4 (CH), 127.0 (CH), 128.6 (C), 129.6 (C), 131.0 (CH), 134.6 (C), 143.7 (CH), 151.4 (C), 152.8 (CH); MS [ESI]: *m/z* 220 $[M-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{11}NOCl$: $[M-Br]^+$ 220.0529; found: 220.0569.

4.3.6. 3-Chloro-8,9-dihydro-7H-10-oxa-6a-aza-cyclohepta-[de]naphthalen-6-one (**17c**)

Molecule **17c** was obtained from the 40% chloroform−petroleum ether fraction and was crystallized from chloroform−petroleum ether mixture to give quinolone as white powder in 30% yield. Mp 163−165 °C; R_f (60% pet. ether−$CHCl_3$) 0.55; IR (KBr, ν_{max}): 1450, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (q, 2H, J=6.9 Hz, -OCH_2−CH_2), 4.29 (d, 2H, J=6.9 Hz, CH_2−CH_2N), 4.61 (d, 2H, J=6 Hz, -OCH_2), 6.74 (d, 1H, J=9.9 Hz, H-5), 7.09 (dd, 2H, J=8.55 and 21.75 Hz, H-1, 2), 8.04 (d, 1H, J=9.9 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.2 (CH_2), 42.3 (CH_2), 71.5 (CH_2), 120.5 (C), 122.9 (CH), 123.2 (CH), 123.8 (CH), 127.0 (C), 135.2 (C), 135.8 (CH), 148.5 (C), 162.3 (-CO); MS [ESI]: *m/z* 236 $[M+H]^+$, 238 $[M+2+H]^+$, 258 $[M+Na]^+$, 260 $[M+2+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{10}ClNO_2Na$: $[M+Na]^+$ 258.0298; found: 258.0321.

4.3.7. 6-Methyl-8,9-dihydro-7H-10-oxa-6a-azonia-cyclohepta[de]naphthalene; bromide (**18**)

Molecule **18** was obtained from the column, eluted with 1% methanol−chloroform, and was crystallized from a chloroform−benzene mixture to give the corresponding quinolinium cation as greenish needles in 40% yield. Mp 184−186 °C; R_f (1% MeOH−$CHCl_3$) 0.38; IR (KBr, ν_{max}): 1289, 1435, 1518, 3432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.82 (t, 2H, J=6.6 Hz, CH_2−CH_2N), 3.36 (s, 3H, CH_3), 4.5 (m, 2H, −OCH_2−CH_2), 5.17 (t, 2H, J=6 Hz, −OCH_2), 7.63 (d, 1H, J=6.6 Hz, H-1), 7.71 (t, 1H, J=8.1 Hz, H-2), 7.93 (d, 1H, J= 8.1 Hz, H-3), 8.06 (d, 1H, J=8.7 Hz, H-5), 8.93 (d, 1H, J=8.7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.5 (CH_3), 28.0 (CH_2), 54.0 (CH_2), 71.8 (CH_2), 125.4 (CH), 126.5 (CH), 126.7 (CH), 130.4 (CH), 130.8 (C), 134.6 (C), 146.5 (CH), 161.8 (C); MS [ESI]: *m/z* 200 $[M-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}NO$: $[M-Br]^+$ 200.1075; found: 200.1089.

4.3.8. 1,3-Dibromo-7,8,9,10-tetrahydro-11-oxa-6a-azonia-cycloocta[de]naphthalene; bromide (**21a**)

Molecule **21a** was obtained from the column, eluted with 2% methanol−chloroform, and was crystallized from a chloroform−benzene mixture to give the corresponding quinolinium cation as yellowish brown needles in 40% yield. Mp 182−184 °C; R_f (2% MeOH−$CHCl_3$) 0.37; IR (KBr, ν_{max}): 1223, 1510, 3447 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.29 (m, 2H, CH_2−CH_2N), 4.29 (m, 2H, CH_2−CH_2N), 4.63 (m, 2H, −OCH_2−CH_2), 4.99 (m, 2H, −OCH_2), 8.32 (dd, 1H, J=6 and 8.7 Hz, H-5), 8.78 (s, 1H, H-2), 9.35 (d, 1H, J=8.7 Hz, H-4), 9.64 (d, 1H, J=5.7 Hz, H-6); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.8 (CH_2), 28.6 (CH_2), 62.7 (CH_2), 75.5 (CH_2), 120.2 (C), 126.7 (C), 125.2 (CH), 130.2 (C), 138.1 (CH), 138.3 (C), 147.6 (CH), 154.3 (CH); MS [ESI]:

m/z 358 $[M-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{12}NOBr_2$: $[M-Br]^+$ 355.9286; found: 355.9235.

*4.3.9. 1,3-Dibromo-7,8,9,10-tetrahydro-11-oxa-6a-aza-cycloocta[de]naphthalene-6-one (**22a**)*

Compound **22a** was obtained from the 30% chloroform–petroleum ether fraction and was crystallized from chloroform–petroleum ether mixture to give quinolone as white powder in 40% yield. Mp 178–180 °C; R_f (70% pet. ether–$CHCl_3$) 0.52; IR (KBr, ν_{max}): 1440, 1555, 1657 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.55 (m, 2H, CH_2–CH_2N), 1.98 (m, 2H, OCH_2–CH_2), 4.10 (br s, 2H, CH_2–CH_2N), 4.71 (br s, 2H, –OCH_2), 6.79 (d, 1H, *J*=9.9 Hz, H-5), 7.90 (s, 1H, H-2), 8.06 (d, 1H, *J*=9.9 Hz, H-4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.5 (CH_2), 27.0 (CH_2), 44.7 (CH_2), 76.5 (CH_2), 119.0 (C), 120.5 (C), 122.6 (C), 124.0 (CH), 138.5 (CH), 139.2 (C), 141.9 (C), 161.9 (–CO); MS [ESI]: *m/z* 374 $[M+H]^+$, 396 $[M+Na]^+$, 398 $[M+2+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{11}Br_2NO_2Na$: $[M+Na]^+$ 393.9054; found: 393.9021.

*4.3.10. 7,8,9,10-Tetrahydro-11-oxa-6a-azonia-cycloocta-[de]naphthalene; bromide (**21b**)*

Molecule **21b** was obtained from the column, eluted with 1% methanol–chloroform, and was crystallized from a chloroform–benzene mixture to give the corresponding quinolinium cation as yellow powder in 35% yield. Mp 204–206 °C; R_f (2% MeOH–chloroform) 0.32; IR (KBr, ν_{max}): 1291, 1531, 3414 cm^{-1}; ^1H NMR (D_2O, 300 MHz): δ 2.03 (m, 2H, CH_2–CH_2N), 2.20 (m, 2H, CH_2–CH_2N), 4.47 (m, 2H, –OCH_2–CH_2), 5.47 (s, 2H, –OCH_2), 7.47 (d, 1H, *J*=6.6 Hz, H-1), 7.70 (m, 2H, H-2, 3), 7.87 (t, 1H, *J*=8.1 Hz, H-5), 8.90 (d, 1H, *J*=8.1 Hz, H-4), 9.06 (m, 1H, H-6); MS [ESI]: *m/z* 200$[M-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}NO$: $[M-Br]^+$ 200.1075; found: 200.1046.

*4.3.11. 7,8,9,10-Tetrahydro-11-oxa-6a-aza-cycloocta-[de]naphthalene-6-one (**22b**)*

Molecule **22b** was obtained from the 40% chloroform–petroleum ether fraction and was crystallized from chloroform–petroleum ether mixture to give quinolone as white powders in 30% yield. Mp 100–102 °C; R_f (60% pet. ether–$CHCl_3$) 0.54; IR (KBr, ν_{max}): 1452, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56 (m, 2H, CH_2–CH_2N), 2.09 (m, 2H, OCH_2–CH_2), 4.24 (m, 2H, CH_2–CH_2N), 4.93 (m, 2H, –OCH_2), 6.71 (d, 1H, *J*=8.4 Hz, H-5), 7.13 (t, 1H, *J*=7.5 Hz, H-2), 7.23 (d, 1H, *J*=6.3 Hz, H-3), 7.31 (d, 1H, *J*=7.8 Hz, H-1), 7.64 (d, 1H, *J*=9.3 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5 (CH_2), 27.0 (CH_2), 44.0 (CH_2), 78.2 (CH_2), 122.2 (CH), 122.7 (C), 123.4 (CH), 125.7 (CH), 126.9 (CH), 137.0 (C), 139.7 (CH), 145.4 (C), 162.9 (–CO); MS [ESI]: *m/z* 216 $[M+H]^+$, 238 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}NO_2$: $[M+H]^+$ 216.1025; found: 216.1069.

*4.3.12. 3-Chloro-7,8,9,10-tetrahydro-11-oxa-6a-azonia-cycloocta[de]naphthalene; bromide (**21c**)*

Compound **21c** was obtained from the column, eluted with 1% methanol–chloroform, and was crystallized from a chloroform–benzene mixture to give the corresponding quinolinium cation as yellow crystalline solid in 40% yield. Mp 190–192 °C; R_f (1% MeOH–$CHCl_3$) 0.32; IR (KBr, ν_{max}): 1265, 1526, 3383 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.74 (m, 2H, CH_2–CH_2N), 4.73 (t, 2H, *J*=11.7 Hz, CH_2–CH_2N), 5.63 (m, 2H, –OCH_2–CH_2), 6.13 (t, 2H, *J*=9.9 Hz, –OCH_2), 7.84 (d, 1H, *J*=8.1 Hz, H-1), 8.04 (d, 1H, *J*=8.4 Hz, H-2), 8.44 (dd, 1H, *J*=5.7 and 8.7 Hz, H-5), 9.39 (d, 1H, *J*=8.7 Hz, H-4), 10.63 (d, 1H, *J*=5.4 Hz, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8 (CH_2), 28.1 (CH_2), 62.4 (CH_2), 78.1 (CH_2), 124.8 (CH), 129.1 (C), 130.3 (C), 130.8 (CH), 131.7 (CH), 137.2 (C), 144.2 (CH), 147.6 (CH), 154.2 (CH); MS [ESI]: *m/z* 235 $[M-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{13}NOCl$: $[M-Br]^+$ 234.0686; found: 234.0677.

*4.3.13. 3-Chloro-7,8,9,10-tetrahydro-11-oxa-6a-aza-cyclo-octa[de]naphthalene-6-one (**22c**)*

Compound **22c** was obtained from the 30% chloroform–petroleum ether fraction and was crystallized from chloroform–petroleum ether mixture to give quinolone as white crystalline solid in 35% yield. Mp 104–106 °C; R_f (70% pet. ether–$CHCl_3$) 0.56; IR (KBr, ν_{max}): 1247, 1449, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.57 (m, 2H, CH_2–CH_2N), 2.09 (m, 2H, OCH_2–CH_2), 4.01 (br s, 2H, CH_2–CH_2N), 4.91 (m, 2H, –OCH_2), 6.78 (d, 1H, *J*=9.9 Hz, H-5), 7.18 (m, 2H, H-1, 2), 8.13 (d, 1H, *J*=9.9 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5 (CH_2), 26.7 (CH_2), 44.4 (CH_2), 78.4 (CH_2), 119.9 (C), 123.2 (CH), 124.0 (CH), 127.0 (CH), 129.1 (C), 135.8 (CH), 138.3 (C), 144.5 (C), 162.5 (–CO); MS [ESI]: *m/z* 250 $[M+H]^+$, 252 $[M+2+H]^+$, 273 $[M+Na]^+$, 275 $[M+2+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{12}ClNO_2Na$: $[M+Na]^+$ 272.0454; found: 272.0453.

*4.3.14. 8,9,10,11-Tetrahydro-7H-12-oxa-6a-azonia-cyclo-nona[de]naphthalene; bromide (**23b**)*

Compound **23b** was obtained from the column, eluted with 5% methanol–chloroform, and was crystallized from a chloroform–benzene mixture to give the corresponding quinolinium cation as yellow powder in 5% yield. Mp 234–236 °C; R_f (5% MeOH–$CHCl_3$) 0.34; IR (KBr, ν_{max}): 1112, 1266, 3384 cm^{-1}; ^1H NMR (D_2O, 300 MHz): δ 1.74 (m, 2H, CH_2–CH_2–CH_2N), 1.96 (m, 2H, CH_2–CH_2–CH_2N), 2.16 (br s, 2H, –OCH_2–CH_2), 4.26 (m, 2H, –CH_2N), 5.15 (m, 2H, –OCH_2), 7.60 (d, 1H, *J*=7.5 Hz, H-1), 7.71 (m, 2H, H-2, 3), 7.85(t, 1H, *J*=8.1 Hz, H-5), 8.86 (d, 1H, *J*=8.4 Hz, H-4), 8.99 (d, 1H, *J*=5.7 Hz, H-6); MS [ESI]: *m/z* 214 $[M-Br]^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{16}NO$: $[M-Br]^+$ 214.1232; found: 214.1214.

*4.3.15. 3-Chloro-8,9,10,11-tetrahydro-7H-12-oxa-6a-azonia-cyclononа[de]naphthalene; bromide (**23c**)*

Compound **23c** was obtained from the column, eluted with 5% methanol–chloroform, and was crystallized from a chloroform–benzene mixture to give the corresponding quinolinium cation as yellow powder in 2% yield. Mp 210–212 °C; R_f (5% MeOH–$CHCl_3$) 0.35; MS [ESI]: *m/z* 248$[M-Br]^+$.

4.4. General procedure for the synthesis of molecule **16a** from **13a**

Compound **13a** (0.6 mmol) was dissolved in 20 mL of water in a 50 mL RB flask under a nitrogen atmosphere. Then, it was stirred followed by the addition of a small amount of sodium borohydride and stirring continued for about 15 min. Product **16a** was obtained by simple filtration of the reaction mixture cautiously avoiding aerial oxidation and it was kept under vacuum.

4.4.1. 1,3-Dibromo-8,9-dihydro-6H,7H,10-oxa-6a-aza-cyclohepta[de]naphthalene (**16a**)

Compound **16a** was obtained as white powdered solid in 30% yield. Mp 138–140 °C; R_f (80% pet. ether–$CHCl_3$) 0.55; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.12 (q, 2H, J=5.7 Hz, CH_2–CH_2N), 3.46 (t, 2H, J=5.2 Hz, CH_2–CH_2N), 3.97 (d, 2H, J=4.2 Hz, H-6), 4.23 (t, 2H, J=6.6 Hz, –OCH_2), 5.82 (m, 1H, H-5), 6.63 (d, 1H, J=9.9 Hz, H-4), 7.07 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.8 (CH_2), 52.2 (CH_2), 53.1 (CH_2), 71.6 (CH_2), 115.9 (C), 116.2 (C), 123.4 (CH), 124.4 (C), 126.4 (CH), 128.9 (CH), 135.7 (C), 145.5 (C); MS [ESI]: m/z 346 $[M+H]^+$. HRMS (ESI) m/z calcd for $C_{12}H_{12}Br_2NO$: $[M+H]^+$ 343.9286; found: 343.9244.

4.5. X-ray experiments, structural determination, and refinements

For all three compounds, the X-ray structural determination followed the same procedure. X-ray data were measured at room temperature with Mo Kα radiation (graphite monochromator, λ=0.7107 Å) on a Huber four circle diffractometer (type 512) equipped with a Bruker-APEX area detector. For data collection and integration SMART and SAINT routines[40] were used. Data reduction and absorption correction were carried out using SADABS and XPREP.[40]

Structural solution and refinement (programs SHELXS-97[41] and SHELXL-97[42]) ran routinely. In each of the crystal lattices of **13a** and **21a**, one water solvent molecule was identified; the lattice of **17a** is free of solvent. C, N, O, and Br atoms were refined anisotropically and isotropic displacement parameters were assigned to the hydrogens, which could all be located from difference syntheses, except for the water hydrogens in **21a**, which were not found.

4.5.1. Crystal data for **13a**

$C_{12}H_{10}ONBr_2\times Br\cdot H_2O$, M_r=3441.96, colorless small plate shaped crystals were grown from chloroform–hexane. Dimensions of the specimen used for X-ray experiments 0.34×0.22×0.08 mm. Space group monoclinic $P2_1/c$. Lattice constants (Å): a=10.527(16), b=97.243(8), c=18.75(3), β=101.40(4)°, cell volume V=1401(3) Å^3, formula units/cell Z=4, X-ray density ρ_x=2.095 g cm^{-3}, $2\theta_{max}$=46.49°. Number of independent reflections 1920, unobserved ($F_o<4\sigma(F_o)$) 351, linear absorption coeff. μ=86.3 cm^{-1}, T_{min}/T_{max}=0.38. After convergence R_1=0.037, wR_2=0.090, Gof=1.07.

4.5.2. Crystal data for **17a**

$C_{12}H_9O_2NBr_2$, M_r=359.02, light yellow rod shaped crystals were grown from ethylacetate–hexane. Dimensions of the specimen used for X-ray experiments 0.70×0.40×0.30 mm. Space group triclinic P1bar. Lattice constants (Å): a=7.8242(3), b=9.2246(3), c=9.4567(3), α=60.709(1)°, β=87.430(1)°, γ=83.099(1)°, cell volume V=590.88(4) Å^3, formula units/cell Z=2, X-ray density ρ_x=2.018 g cm^{-3}, $2\theta_{max}$=61.96°. Number of independent reflections 3502, unobserved ($F_o<4\sigma(F_o)$) 445, linear absorption coeff. μ=68.5 cm^{-1}, T_{min}/T_{max}=0.60. After convergence of refinements R_1=0.028, R_w=0.070, GoF=1.06.

4.5.3. Crystal data for **21a**

$C_{12}H_{12}ONBr_2\times Br\cdot H_2O$, M_r=454.97, dark yellow small plate shaped crystals were grown from chloroform–hexane. Dimensions of the specimen used for X-ray experiments 0.52×0.34×0.16 mm. Space group orthorhombic $Pcab$. Lattice constants (Å): a=7.5286(3), b=13.4705(5), c=29.0126(10), cell volume V=2942.28(19) Å^3, formula units/cell Z=8, X-ray density ρ_x=2.054 g cm^{-3}, $2\theta_{max}$=62.09°. Number of independent reflections 4590, unobserved ($F_o<4\sigma(F_o)$) 795, linear absorption coeff. μ=82.2 cm^{-1}, T_{min}/T_{max}=0.49. After convergence of refinements R_1=0.057, R_w=0.120, GoF=1.12.

Acknowledgements

Our thanks are due to Dr. Basudeb Achari, Emeritus Scientist, CSIR, for his helpful suggestions and encouragement. N.P.S. is indebted to CSIR for the award of Emeritus Scientist. P.P., A.H., and K.B.S. are also thankful to the CSIR for fellowships respectively. N.B.M. and S.B. are thankful to DBT for financial assistance.

Supplementary data

^{1}H and ^{13}C NMR spectra for all the new compounds associated with this article can be found in the online version. Crystallographic data in CIF format are available free of charge via the Internet at CCDC (CCDC Nos. 650773–650775). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.048.

References and notes

1. Katritzky, A. K.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheeseman, G. W. H., Eds.; pergamon: New York, NY, 1984; pp 1–38.
2. Gadamasetti, K. G. *Process Chemistry in the Pharmaceutical Industry*; Marcel Dekker: New York, NY, 1999.
3. Nicolaou, K. C.; Huang, X.; Giuseppone, N.; Rao, P. B.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4705–4709.
4. Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239–2329.

5. Parenty, A. D. C.; Smith, L. V.; Pickering, A. L.; Long, D. L.; Cronin, L. *J. Org. Chem.* **2004**, *69*, 5934–5946.
6. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
7. Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–165.
8. Winker, J. D. *Chem. Rev.* **1996**, *96*, 167–176.
9. Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194.
10. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206.
11. Wang, K. K. *Chem. Rev.* **1996**, *96*, 207–222.
12. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269.
13. Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306.
14. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338.
15. Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163.
16. Ho, T.-L. *Tandem Organic Reactions*; Wiley and Sons: New York, NY, 1992.
17. Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581–1587.
18. Arai, S.; Nakayama, K.; Hatano, K.; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 9572–9575.
19. Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853–3874.
20. Dutta, R.; Mandal, D.; Panda, N.; Mondal, N. B.; Banerjee, S.; Kumer, S.; Weber, M.; Lugar, P.; Sahu, N. P. *Tetrahedron Lett.* **2004**, *45*, 9361–9364.
21. Trabanco, A. A.; Alonso, J. M.; Andres, J. I.; Cid, J. M.; Fernandez, J.; Iturrino, l.; Megens, A. *Chem. Pharm. Bull.* **2004**, *52*, 262–265.
22. Andres, J. I.; Alonso, J. M.; Diaz, A.; Fernandez, J.; Iturrino, L.; Martinez, P.; Meert, T. F.; Sipido, V. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3573–3577.
23. Gil-Lopetegui, P.; Fernandez-Gadea, F. J.; Meert, T. F; Janseen Pharmaceutica N.V. Patent Application PCT/EP97/01829; WO 97/38991, 23 October, 1997.
24. Andres-Gil, J. I.; Farnandez-Gadea, F. J.; Gil-Lopetegui, P.; Diaz-Martinez, A.; Janseen Pharmaceutica N.V. Patent Application PCT/EP98/06352; WO 99/19317, 22 April, 1999.
25. Aramaki, Y.; Seto, M.; Okawa, T.; Oda, T.; Kanzaki, N.; Shiraishi, M. *Chem. Pharm. Bull.* **2004**, *52*, 254–258.
26. Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; fujino, M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5698–5703.
27. Shiraishi, M.; Aramaki, Y.; Seto, M.; Imoto, H.; Nishikawa, Y.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Nishimura, O.; Baba, M.; Fujino, M. *J. Med. Chem.* **2000**, *43*, 2049–2063.
28. Bromidge, S. M.; Dabbs, S.; Davis, D. T.; Duckworth, D. M.; Forbes, I. T.; Gaster, L. M.; Ham, P.; Jones, G. E.; King, F. D.; Mulholland, K. R.; Saunders, D. V.; Wyman, P. A.; Blany, F. E.; Clarke, S. E.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Lightowler, S.; Middlemiss, D. N.; Trail, B.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **2000**, *43*, 1123–1134.
29. Di Matteo, V.; Di Giovanni, G.; Esposito, E. *CNS Drug Rev.* **2000**, *6*, 195–205.
30. Meert, T. F.; Melis, W.; Aerts, N.; Clincke, G. *Behav. Pharmacol.* **1997**, *8*, 353–363.
31. Feng, Y.; Broder, C. C.; Kennedy, P. E.; Berger, E. A. *Science* **1996**, *272*, 872–877.
32. Alkhatib, G.; Combadiere, C.; Broder, C. C.; Feng, Y.; Keneddy, P. E.; Murphy, P. M.; Berger, E. A. *Science* **1996**, *272*, 1955–1958.
33. Deng, H.; Liu, R.; Ellmeier, W.; Choe, S.; Unutmaz, D.; Burkhart, M.; Marzio, P. D.; Marmon, S.; Sutton, R. E.; Hill, C. M.; Davis, C. B.; Peiper, S. C.; Schall, T. J.; Litman, D. R.; Landau, N. R. *Nature (London)* **1996**, *381*, 661–666.
34. Dragic, T.; Litwin, V.; Allaway, G. P.; Martin, S. R.; Huang, Y.; Nagas, A.; Cayanan, C.; Maddon, P. J.; Koup, R. A.; Moore, J. P.; Paxton, W. A. *Nature (London)* **1996**, *381*, 667–673.
35. Brana, M. F.; Cacho, M.; Gradillas, A.; de Pascual-Teresa, B.; Ramos, A. *Curr. Pharm. Des.* **2001**, *7*, 1745–1780.
36. Burnett, M. N.; Johnson, C. K. *ORTEP III, Oak Ridge Thermal Ellipsoid Plot program fir Crystal Structure Illustration*; Oak Ridge National Laboratory: Oak Ridge, Tennessee, USA, 1996; Report ORNL-6895.
37. Lee, I. S. H.; Chow, K. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 7755–7761.
38. Lee, I. S. H.; Jeoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 7492–7496.
39. Keller, E. *SCHAKAL99. A Fortran Program for the graphical Representation of Molecular and Crystallographic Models*; University of Freiburg: Germany, 1999.
40. *SMART and SAINT-Plus (SADABS, XPREP). Data Collection and Processing Software for the SMART System*; Bruker AXS: Madison, Wisconsin, USA, 1995–2005.
41. Sheldrick, G. M. *SHELXS-97. A Program for Crystal Structure Solution. Technical report*; University of Göttingen: Göttingen, Germany, 1997.
42. Sheldrick, G. M. *SHELXL-97. A Program for Refinement Structure. Technical report*; University of Göttingen: Göttingen, Germany, 1997.