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Onium salt supported organic synthesis in water: application to Grieco's multicomponent reaction

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Abstract

By using an ammonium chloride salt as water solubilizing moiety, our onium salt supported organic synthesis strategy was extended to water as a solvent. This method allows for high loading capacities both of the supports and their solutions owing to low molecular weight of the onium salts and simplified purification steps as well.
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1. Introduction

Recently was developed a new strategy for supported organic synthesis, the Onium Salt Supported Organic Synthesis (OSSOS).[1,2] This strategy relies on the use of the physical properties of onium salts which confer a molecule virtually with no vapor pressure.[3] Subsequently, this onium salt moiety could be used as a template for supported organic synthesis.[4] Indeed, this scaffold could be thought as the homogenous non polymeric analog of a classical resin used since 1963's Merrifield solid phase peptide supported synthesis.[5] Purifications were simplified to the extreme as easy filtration and washes usually afforded the product in pure form. If this feature was rather common for supported organic synthesis, several advantages were brought by the OSSOS. First, reaction conditions and yields were almost identical to those published under classical homogenous phase. This was probably attributable to both the tunable solubility of onium salts and their high loading capacities. As a matter of fact, the use of soluble support such as PolyEthyleneGlycols, i.e., PEGs, is allowing for performing reactions under homogeneous conditions, but owing to their high molecular weight (5000 typically), loading capacities are small (0.02 mmol g^{-1}) and enforce performing reaction under high dilution conditions.[6] On the contrary, onium salts' molecular weights are smaller (300–500 typically) and all experiments are carried out under standard 0.1–1 M concentration. Their structural simplicity is also allowing for using routine analysis techniques such as NMR, HPLC, and MS. Finally and more importantly, their nature is easily tunable according to which properties are essential for good reactivity. As an example, for reactions requiring strictly anhydrous conditions, a good choice would certainly be the use of an onium triflimide salt that can be dried easily and be lipophilic enough to dissolve organic reagents and mix with molecular organic solvent. This methodology has been successfully applied to a large number of reactions including peptide synthesis,[7] multicomponent reactions,[8–10] transition metal catalyzed reactions,[4] even radical addition.[11] The last example clearly demonstrated how the nature of the support could largely influences the outcome of the process.[3,4] Indeed, radical reactions are very sensitive to relative kinetics, and diffusion problem associated with the use of a resin often limited resin supported radical steps to polymerization reactions. However, when using a triflimide ammonium salt as a support, results are almost identical to those reported for classical conditions except that all the purification steps are eliminated.[11]

This point was critical when we tackled multicomponent reactions.[12] Often, non-supported versions are handicapped by side reactions leading to separation difficulties. Indeed, by supporting one reactant and therefore getting supported products, purification and removal of traces of impurities were largely improved. Nevertheless examples were scarce

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due to kinetic limitations in heterogeneous medium.[13,14,10] Grieco synthesis is a one pot multicomponent reaction between anilines, aldehydes, and electron rich alkenes providing tetrahydroquinolines in high yields under acid catalysis.[15] Mild catalytic conditions (often using lanthanide triflates)[16] could be used and were compatible with a wide range of aldehydes and anilines, therefore easily providing tetrahydroquinolines with large diversity. Armstrong and Carranco have already shown that Grieco's tetrahydroquinolines' synthesis was efficient on both Wang and Merrifield type resin. In the first case, after an $SnCl_2$ catalyzed reaction, products were released from support using 15% TFA with good yields.[17] More recently, another application using scandium triflates with supported glyoxylic acid, anilines, and dihydropyridines provided tricycles in good yields.[16] We have already shown that this reaction could be supported on onium salts using triflimide counter anion.[18,8]

Here we would like to report the use of ammonium chloride salts as soluble support for Grieco's multicomponent reaction performed in pure water. Indeed, by adding a halide counteranion to any of the three components supported on an onium salt, we were able to confer a good water solubility to the reactant thus allowing to perform the reaction in water. Adducts were then obtained under pure form via very simple purification steps. Water is now widely recognized as a good, cheap, and environmentally friendly solvent for organic synthesis.[19–22] It offers numerous advantages in terms of reactivity and selectivity and therefore has been used for almost all kind of reactions. Grieco's multicomponent reaction is one of them, and like several other multicomponent reactions, it has been shown that water has no detrimental effect on reactivity, and often increased yield and selectivity.[23] As an example, using heterogeneous phase supported acids (Montmorillonite or Bentonite),[24] water turned out to be the optimal solvent. Additionally, combining solid phase and organo aqueous medium allowed better yields and selectivities.[16]

2. Results

2.1. Support synthesis

In our case, we decided to support on onium salts two of the three possible partners, namely the aniline and the benzaldehyde. Starting from trimethyl-3-hydroxypropylammonium chloride **1** both supported reagents were prepared in a couple of single pot high yielding steps. Supported aniline **2** was synthesized by coupling 4-nitrobenzoic acid with alcohol **1** followed by hydrogenation of the nitro function to the corresponding aniline. Onium salt supported benzaldehyde **3** was simply synthesized through an esterification of the corresponding benzoic acid with the same alcohol **1**. Alternatively, the ether linked benzaldehyde could be prepared following a two steps protocol involving a Williamson alkylation of 4-hydroxybenzaldehyde using 1-bromo-3-chloropropane followed by quaternization of trimethylamine with the obtained alkylchloride (Scheme 1).

Noteworthy, these supported reactants can be obtained in large scale in analytically pure form by simple washes with diethyl ether or acetone.

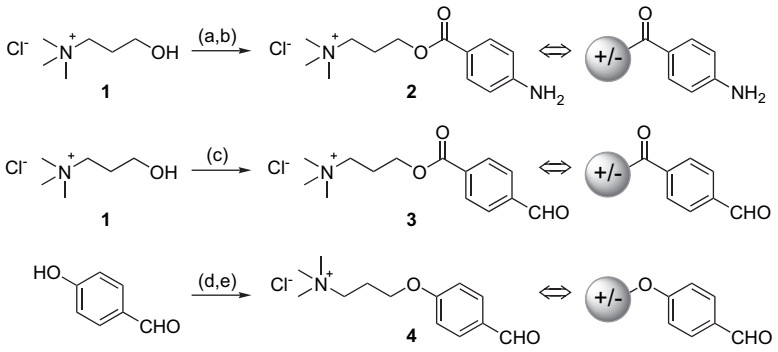
2.2. Tetrahydroquinolines' synthesis

We decided next to tackle the core of the project, namely Grieco's multicomponent reaction. To our delight, reactions proceeded extremely well under standard conditions in water. It demonstrated once again how flexible and reliable this OSSOS strategy is. In the presence of a catalytic amount of TFA, products were isolated in good yield after several hours at room temperature (Scheme 2). Using ammonium chloride supported benzaldehyde **3** (Table 1, entries 1–6), reaction proceeded smoothly with cyclopentadiene (entries 1–4) and anilines. Namely, aniline (entry 1), 4-chloroaniline (entry 2), 4-nitroaniline (entry 3), 4-toluidine (entry 4) reacted equally well affording supported Grieco's adducts in 86%, 90%, 85%, and 90%, respectively. Reaction with indene was also efficient albeit slower, in these cases (entries 5 and 6) reaction with 4-chloro and 4-nitro anilines led to the expected tetrahydroquinolines in 84% and 80% yield, respectively. Concerning the use of supported aniline **2** (Table 1, entries 7–10), the same conditions were applied to the three components system and analogous adducts were obtained in good yields. Indeed reactions between **2**, cyclopentadiene, and parasubstituted benzaldehydes were efficiently producing expected heterocycles regardless of substitution (fluorine, entry 7, 78%; chlorine, entry 8, 92%; nitro, entry 9, 77%). Like mentioned previously, reaction with indene was slightly slower but afforded expected product in 85% yield (entry 10). Noteworthy, these products were obtained with only a simple purification procedure by side product extraction from the salt using diethyl ether.

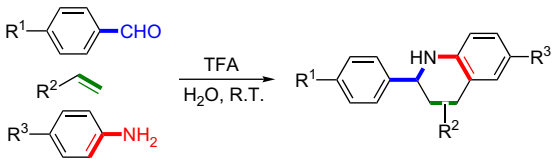
As an illustration of OSSOS simplicity for supported synthesis, standard ^{1}H NMR experiments are sufficient for monitoring reactions. In addition to these promising results, we noticed that when reaction time was extended unnecessarily, a supported side product appeared in moderate quantity (up to 10%) resulting from the oxidation of expected products into quinolines. We decided to take advantage of this opportunity to develop an alternative procedure favoring this product.

2.3. Quinolines' synthesis

Indeed, we investigated for other catalyst and found that the use of tetrafluoroboric acid as catalyst afforded quinolines in good yields after several hours. If this reaction usually needs a second oxidation step using DDQ[25] or potassium permanganate,[26] in that case oxidation is probably linked to oxygen together with apparent hydrogen transfer from the transient imine resulting in the formation of the benzyl amine in a average 20% proportion. Due to its higher water solubility, this side product is easily eliminated by a simple washing. Both supported aldehydes reacted equally well. In a few hours, reaction between supported benzaldehydes **3** and **4**, indene, and various anilines afforded quinolines in good yields



Scheme 1. Preparation of ammonium chloride supported aniline and benzaldehyde. (a) 4-$NO_2C_4H_6CO_2H$, DCC, DMAP, CH_3CN, rt; (b) Pd/C, H_2 (5 bar), H_2O, rt, 92% (over two steps); (c) 4-$CHOC_4H_6CO_2H$, DCC, DMAP, CH_3CN, rt (96%); (d) $Br(CH_2)_3Cl$, K_2CO_3, acetone, Δ, 87%; (e) NMe_3 (50% aqueous), CH_3CN, 70 °C, 18 h, 98%.



Scheme 2. Grieco's tetrahydroquinolines synthesis.

(Table 2). Halide substituted anilines (entries 4, 5, 7, and 8) yielded the expected products and no differences in reactivities were observed between electron donating and withdrawing substituted aromatic amines (entries 3 and 6). Same behavior was observed between ether (entry 2) and ester (entry 9) linkage although ester appeared slightly sensitive to hydrolysis.

3. Conclusion

Indeed, the Onium Salt Supported Organic Synthesis methodology turned out to be perfectly suitable for multicomponent reactions, a key feature for parallel synthesis. When an ester linkage is used heterocycles release from the support is performed under previously described conditions[8,1,2] (NH_3, MeOH). Additionally, both reagents (aniline and aldehyde) can be grafted and reactions are performed hereafter with equal efficiency and ease. Moreover, taking advantages of the flexibility of the onium salt part of the molecule, we managed to confer the assembly a good water solubility enabling the possibility to perform many type of reactions in pure water. This has been highlighted in this manuscript by Grieco's multicomponent condensation and a new quinolines' one-step synthesis. This broadens the use of water as a reaction solvent which is often restricted by poor substrate solubility.

4. Experimental

4.1. General methods

All reactions were carried out using standard Schlenk techniques under argon. All other standard chemicals were purchased from ACROS chemicals or Aldrich Chemical Co. and used without further purification. Reactions were monitored by gas chromatography (GC–MS) (GC system: HP 6890 series, Mass selective detector HP 5973) using a capillary column DB-5MS. Melting points were determined on an electrothermal IA9300 digital melting point instrument. NMR spectra were recorded on a Bruker ARX 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz) or AC 300 (^{1}H: 300.13 MHz), ^{1}H chemical shifts (δ) are given in parts per million relative to TMS as internal standard, J values in hertz, ^{13}C chemical shifts are given relative to the central signal of $CDCl_3$ at 77.0 ppm. High resolution mass spectra measurements were performed at the Centre Regional de Mesures Physiques de l'Ouest (C.R.M.P.O, University of Rennes 1) using a Micromass ZABSpec TOF with EBE OA TOF geometry with LSIMS Ionization (Liquid Secondary Ion Mass Spectrometry) at 8 kV with Cs^+ gun in *m*-nitrobenzyl alcohol (*m*NBA).

4.1.1. General procedure for Grieco condensation with supported aniline **2** (procedure A)

To a solution of amine (100 mg, 0.36 mmol) **2** in 0.2 mL of H_2O were successively added the benzaldehyde (1.1 equiv), the olefin (10 equiv), and TFA (1.2 equiv). After 2 h at room temperature, volatiles were removed under reduced pressure. Upon addition of Et_2O, residue crystallized. Crystals were filtered off and washed with 3×2 mL of Et_2O to afford product **6** in pure form.

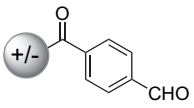
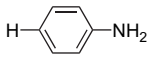
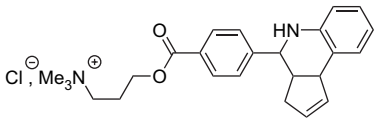
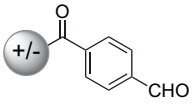
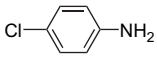
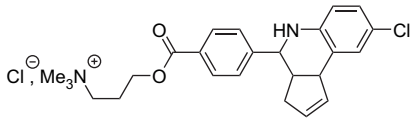
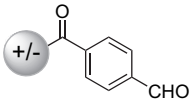
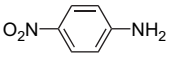
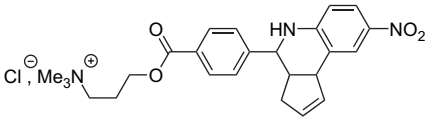
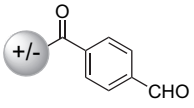
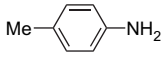
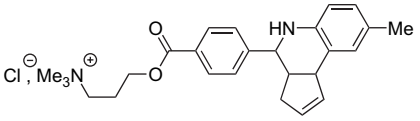
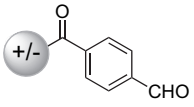
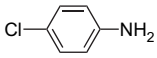
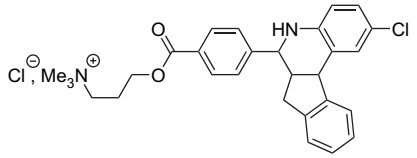
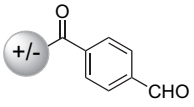
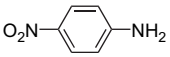
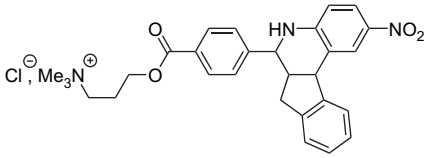
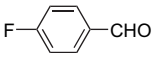
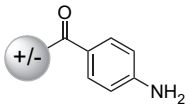
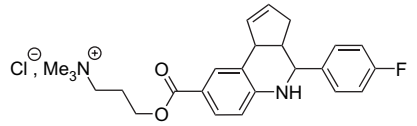
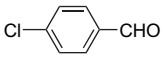
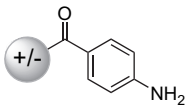
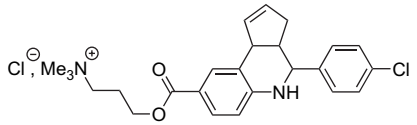
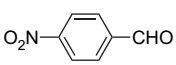
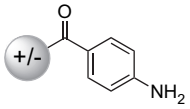
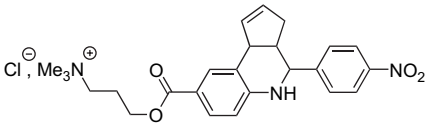
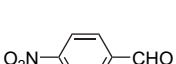
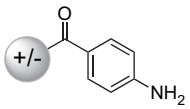
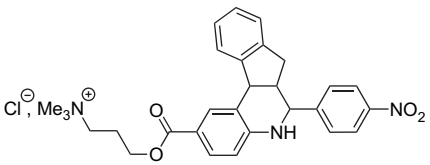
4.1.2. General procedure for Grieco condensation with supported benzaldehyde **3** (procedure B)

To a solution of aldehyde (100 mg, 0.35 mmol) **3** in 0.2 mL of H_2O were successively added aniline (1.1 equiv), olefin (10 equiv), and TFA (1.2 equiv). After 2 h at room temperature, solvent was removed under reduced pressure. Upon addition of Et_2O, residue crystallized. Crystals were filtered off and washed with 3×2 mL of Et_2O to afford product **5** in pure form.

4.1.3. General procedure for quinolines' synthesis (procedure C)

To a solution of supported aldehyde **4** (or respectively **3**) (100 mg, 0.38 mmol) in 0.2 mL of H_2O were successively added aniline (1.1 equiv), olefin (10 equiv), and HBF_4 (1.2 equiv). After 24 h at room temperature, solvent and volatiles were removed under reduced pressure. Upon addition of Et_2O, residue crystallized. After filtration, recrystallization in acetone afforded product **7** (respectively **8**) in pure form.

Table 1
Grieco's three components reaction using supported benzaldehyde **3** and aniline **2**

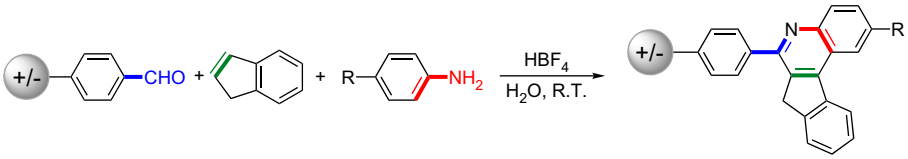
Entry	Aldehyde	Aniline	Olefin	Product		Yield %
1					**5a**	86
2					**5b**	90
3					**5c**	85
4					**5d**	90
5					**5e**	84
6					**5f**	80
7					**6a**	78
8					**6b**	92
9					**6c**	77
10					**6d**	85

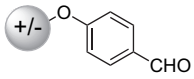
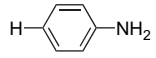
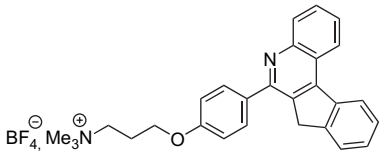
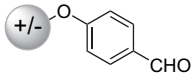
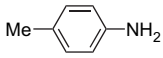
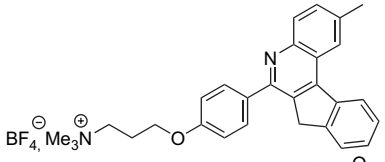
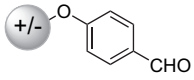
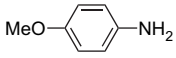
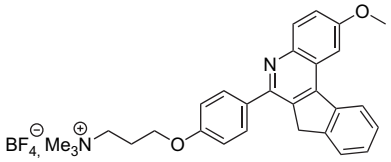
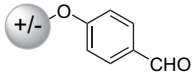
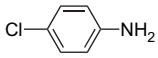
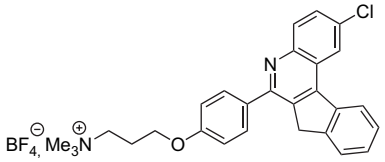
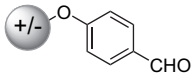
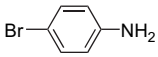
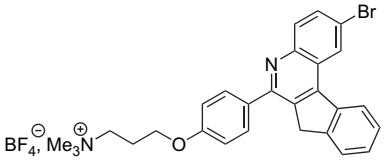
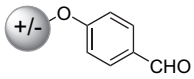
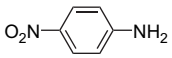
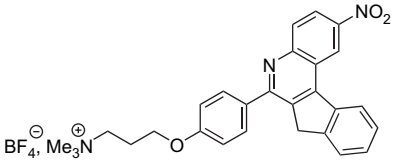
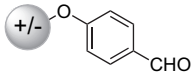
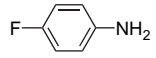
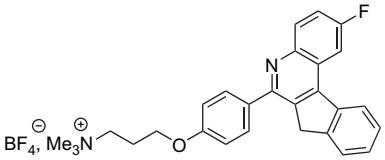
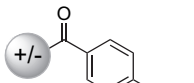
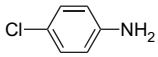
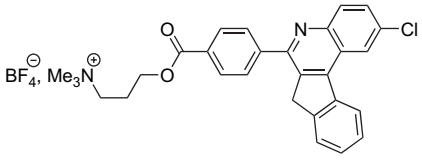
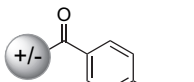
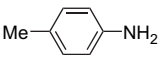
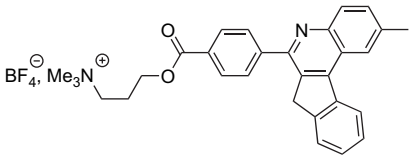
4.2. Support synthesis

4.2.1. [3-(4-Aminobenzoyloxy)propyl]trimethylammonium chloride **2**

To a mixture of alcohol **1** (5.00 g, 32.57 mmol) in 100 mL of dry acetonitrile were added DCC (48.5 mmol, 1.5 equiv), 4-nitrobenzoic acid (48.5 mmol, 1.5 equiv), and DMAP (6.52 mmol, 0.2 equiv). After 4 h at room temperature, solvents were removed under vacuum and product was extracted with 3×30 mL of Et_2O to afford an oil used without further purification in the next step. ^{1}H NMR (200 MHz, D_2O): 2.18–2.43 (m, 2H), 3.15 (s, 9H), 3.38–3.60 (m, 2H), 4.43 (t, 2H, J=5.8 Hz), 8.02 (dd, 2H, J_1=1.9 Hz, J_2=7.1 Hz), 8.18 (dd, 2H, J_1=2.1 Hz, J_2=6.9 Hz), ^{13}C NMR (50 MHz,

Table 2
Quinolines synthesis from supported benzaldehydes **3** and **4**, indene, and anilines using a three component reaction



Entry	Aldehyde	Aniline	Olefin	Product		Yield %
1					**7a**	60
2					**7b**	62
3					**7c**	60
4					**7d**	57
5					**7e**	56
6					**7f**	50
7					**7g**	62
8					**8a**	60
9					**8b**	59

D_2O): 22.6, 53.5 (t, J_{C-N}=4.0 Hz), 63.4, 64.1, 123.8, 130.9, 134.94, 150.3, 166.0. To a solution of [3-(4-nitrobenzoyloxy)-propyl]trimethylammonium chloride (8.5 g, *y* mmol) in 100 mL of water was added *x* mg of 5% Pd/C (1 mol %). The mixture was stirred under a hydrogen atmosphere (5 bar) for 48 h. After filtration and concentration under reduced pressure, 6.95 g of a white solid were obtained (90% yield, two steps). Mp 120–122 °C. ^{1}H NMR (300 MHz, D_2O): 2.10–2.25 (m, 2H), 3.09 (s, 9H), 3.32–3.45 (m, 2H), 4.48 (t, 2H, *J*=6.1 Hz), 6.75 (d, 2H, *J*=7.8 Hz), 7.72 (d, 2H, *J*=7.8 Hz), ^{13}C NMR (75 MHz, D_2O): 22.6, 53.47 (t, J_{C-N}=4.1 Hz), 61.9, 64.2, 114.9, 118.2, 132.0, 153.0, 168.8. HRMS (FAB) $C_{13}H_{21}N_2O_2$: calculated 237.1603, found: 237.1603.

4.2.2. [3-(4-Formylbenzoyloxy)propyl]trimethylammonium chloride **3**

To a solution of **1** (2 g, 13 mmol) in 100 mL of CH_3CN were added DCC (19.5 mmol, 1.5 equiv), 4-formylbenzoic acid (19.5 mmol, 1.5 equiv), and DMAP (2.6 mmol, 0.2 equiv). After 2 h at room temperature, solvent was removed and the residue was extracted with 3×30 mL of H_2O. Aqueous phase was washed with 3×30 mL of Et_2O and concentrated under reduced pressure to afford a yellow solid (yield 96%). Mp 120–122 °C. ^{1}H NMR (300 MHz, D_2O): 2.18–2.31 (m, 2H), 3.09 (s, 9H), 3.42–3.48 (m, 2H), 4.37 (t, 2H, *J*=5.8 Hz), 7.91 (d, 2H, *J*=8.2 Hz), 8.06 (d, 2H, *J*=8.2 Hz), 9.91 (s, 1H), ^{13}C NMR (75 MHz, D_2O): 22.1, 53.0 (t, J_{C-N}=4 Hz), 62.6, 63.7, 129.6, 129.91, 134.0, 138.6, 166.6, 195.1. HRMS (FAB) $C_{14}H_{20}NO_3Cl$: calculated 250.1443, found: 250.1451 (C^+).

4.2.3. 3-{(4-Formylphenoxy)propyl}trimethylammonium chloride **4**

To a solution of 4-hydroxybenzaldehyde (10.0 g, 82 mmol) in 125 mL of acetone were added 1-bromo-4-chloro-propane (164 mmol, 2 equiv, 16.2 mL) and K_2CO_3 (11.3 g, 82 mmol, 1 equiv). After 18 h under refluxing conditions, solvent was removed and the residue purified by distillation on a Kügelrohr apparatus (*T*=60 °C, *P*=0.1 mmHg) yielding 16.2 g of a colorless oil (yield 87%) corresponding to 4-(3-chloropropoxy)benzaldehyde. ^{1}H NMR (300 MHz, acetone-d_6): 2.25–2.40 (m, 2H), 3.81 (t, 2H, *J*=6.2 Hz), 4.25 (t, 2H, *J*=6.2 Hz), 7.03 (d, 2H, *J*=8.7 Hz), 7.88 (d, 2H, *J*=8.7 Hz), 9.90 (s, 1H), ^{13}C NMR (75 MHz, acetone-d_6): 32.0, 41.3, 64.8, 114.8, 130.4, 131.6, 163.7, 190.3. To a solution of 10.0 g (50.4 mmol) of this oil in acetonitrile (20 mL) was added in a schlenk tube 13.8 mL of an aqueous solution of trimethylamine (50%). After 18 h at 70 °C, the reacting mixture was concentrated under reduced pressure. The obtained residue was washed with acetone (3×10 mL) then dried under high vacuum to afford the expected product in 98% as a yellow solid. Mp 82–84 °C. ^{1}H NMR (300 MHz, D_2O): 2.21–2.32 (m, 2H), 3.11 (s, 9H), 3.42–3.58 (m, 2H), 4.19 (t, 2H, *J*=5.4 Hz), 7.03 (d, 2H, *J*=8.6 Hz), 7.85 (d, 2H, *J*=8.6 Hz), 9.71 (s, 1H), ^{13}C NMR (75 MHz, D_2O): 22.5, 52.9 (t, *J*=4.0 Hz), 63.8, 64.9, 115.0, 129.3, 132.7, 163.7, 194.8. HRMS (FAB) $C_{13}H_{20}NO_2Cl$: calculated 222.1494, found: 222.1494 (C^+).

4.3. Tetrahydroquinolines

4.3.1. {3-[4-(3a,4,5,9b-Tetrahydro-3H-cyclopenta[c]-quinolin-4-yl)benzoyloxy]propyl}trimethylammonium chloride **5a**

Following procedure A using aniline and cyclopentadiene, a light brown solid was obtained in 86% yield. Mp 128–130 °C. ^{1}H NMR (300 MHz, acetone-d_6): 1.61–1.74 (m, 1H), 2.26–2.43 (m, 2H), 2.48–2.63 (m, 1H), 2.98–3.11 (m, 1H), 3.21 (s, 9H), 3.54–3.61 (m, 2H), 4.10–4.13 (m, 1H), 4.46 (t, 2H, *J*=5.9 Hz), 4.68–4.69 (m, 1H), 5.56–5.63 (m, 1H), 5.83–5.92 (m, 1H), 6.67–6.75 (m, 2H), 6.91–6.96 (m, 1H), 7.03 (d, 1H, *J*=7.6 Hz), 7.63 (d, 2H, *J*=8.3 Hz), 8.08 (d, 2H, *J*=8.3 Hz), ^{13}C NMR (75 MHz, acetonitrile-d_3): 23.5, 31.1, 46.1, 46.6, 52.4 (t, J_{C-N}=4.0 Hz), 57.5, 61.3, 63.7, 116.0, 118.8, 122.0, 125.8, 126.5, 128.5, 129.1, 129.4, 129.8, 134.2, 145.4, 148.9, 166.3. HRMS (FAB) [$C_{25}H_{31}N_2O_2$][Cl]: calculated 391.2385, found: 391.2388 (C^+).

4.3.2. {3-[4-(8-Chloro)-3a,4,5,9b-tetrahydro-3H-cyclopenta-[c]quinolin-4-yl-benzoyloxy]propyl}trimethylammonium chloride **5b**

Following procedure A using 4-chloroaniline and cyclopentadiene, a light brown solid was obtained in 90% yield. Mp 148–150 °C. ^{1}H NMR (300 MHz, acetone-d_6): 1.58–1.70 (m, 1H), 2.22–2.42 (m, 2H), 2.45–3.61 (m, 1H), 2.93–3.09 (m, 1H), 3.21 (s, 9H), 3.56–3.61 (m, 2H), 4.03–4.16 (m, 1H), 4.46 (t, 2H, *J*=5.9 Hz), 4.66–4.47 (m, 1H), 5.69–5.72 (m, 1H), 5.81–6.93 (m, 1H), 6.71 (d, 1H, *J*=8.5 Hz), 6.89 (dd, 1H, J_1=2.1 Hz, J_2=8.5 Hz), 7.02 (s, 1H), 7.61 (d, 2H, *J*=8.2 Hz), 8.05 (d, 2H, *J*=8.2 Hz), ^{13}C NMR (75 MHz, methanol-d_4): 23.8, 32.5, 47.0, 47.6, 53.6 (t, J_{C-N}=4 Hz), 58.9, 62.7, 65.1, 117.3, 120.1, 127.2, 127.9, 129.3, 129.6, 130.1, 130.4, 130.8, 135.6, 146.9, 150.3, 166.3. HRMS (FAB) [$C_{25}H_{30}N_2O_2Cl$][Cl]: calculated 425.1995, found: 425.2000 (C^+).

4.3.3. {3-[4-(8-Nitro)-3a,4,5,9b-tetrahydro-3H-cyclopenta-[c]quinolin-4-yl-benzoyloxy]propyl}trimethylammonium chloride **5c**

Following procedure A using 4-nitroaniline and cyclopentadiene, a light brown solid was obtained in 85% yield. Mp 144–146 °C. ^{1}H NMR (300 MHz, methanol-d_4): 1.63–1.79 (m, 1H), 2.23–2.37 (m, 2H), 2.39–2.56 (m, 1H), 3.11–3.25 (m, 1H), 3.47 (s, 9H), 3.90–3.96 (m, 2H), 4.09–4.16 (m, 1H), 4.49 (t, 2H, *J*=5.8 Hz), 4.78–4.84 (m, 1H), 5.63–5.73 (m, 1H), 5.88–5.98 (m, 1H), 6.76 (d, 1H, *J*=8.6 Hz), 7.66–7.78 (m, 4H), 8.26 (d, 2H, *J*=8.6 Hz), ^{13}C NMR (75 MHz, methanol-d_4): 24.0, 32.5, 46.7, 47.7, 53.7 (t, J_{C-N}=4 Hz), 57.7, 62.2, 65.3, 116.5, 120.1, 124.5, 125.9, 128.7, 129.5, 130.9, 132.2, 135.3, 148.3, 151.3, 152.1, 168.2. HRMS (FAB) [$C_{25}H_{30}N_3O_4$][Cl]: calculated 436.2236, found: 436.2239 (C^+).

4.3.4. {3-[4-(8-Methyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta-[c]quinolin-4-yl-benzoyloxy]propyl}trimethylammonium chloride ***5d***

Following procedure A using 4-methylaniline and cyclopentadiene, a light brown solid was obtained in 90% yield. Mp 130–132 °C. ^{1}H NMR (300 MHz, acetone-d_6): 1.70–1.85 (m, 1H), 2.26 (s, 3H), 2.28–2.36 (m, 2H), 2.46–2.63 (m, 1H), 3.04–3.13 (m, 1H), 3.21 (s, 9H), 3.52–3.66 (m, 2H), 4.07–4.19 (m, 1H), 4.46 (t, 2H, J=5.9 Hz), 4.71–4.82 (m, 1H), 5.57–5.68 (m, 1H), 5.83–5.93 (m, 1H), 6.87 (d, 1H, J=8.3 Hz), 6.98 (s, 1H), 7.32 (d, 1H, J=8.3 Hz), 7.60 (d, 2H, J=8.3 Hz), 8.09 (d, 2H, J=8.3 Hz), ^{13}C NMR (75 MHz, acetone-d_6): 20.8, 23.9, 32.5, 45.2, 47.6, 53.6 (t, J_{C-N}=4 Hz), 60.0, 62.8, 65.1, 119.5, 123.8, 127.8, 128.3, 130.2, 130.6, 130.8, 130.9, 131.7, 135.1, 140.6, 147.8, 167.4. HRMS (FAB) [$C_{26}H_{33}N_2O_2$][Cl]: calculated 405.2542, found: 405.2536 (C^+).

4.3.5. {3-[4-(2-Chloro)-6,6a,7,11b-tetrahydro-6H-indeno-[2,1-c]quinolin-6-yl-benzoyloxy]propyl}trimethylammonium chloride ***5e***

Following procedure A using 4-chloroaniline and indene, a yellow solid was obtained in 84% yield. Mp 198–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 2.15–2.36 (m, 3H), 2.98–3.05 (m, 1H), 3.13 (s, 9H), 3.45–4.61 (m, 2H), 4.35 (t, 2H, J=5.6 Hz), 4.52 (d, 1H, J=7.5 Hz), 4.73 (s, 1H), 6.74 (d, 1H, J=8.6 Hz), 6.94 (dd, 1H, J_1=2.2 Hz, J_2=8.5 Hz), 7.01–7.21 (m, 3H), 7.26 (s, 1H), 7.61–7.71 (m, 3H), 8.05 (d, 2H, J=8.3 Hz), ^{13}C NMR (75 MHz, DMSO-d_{64}): 22.1, 37.1, 45.0, 46.7, 52.5 (t, J_{C-N}=4.0 Hz), 55.6, 61.7, 62.7, 114.9, 121.6, 123.8, 125.2, 125.4, 126.5, 127.2, 127.4, 127.6, 129.0, 129.9, 137.3, 142.0, 145.9, 147.3, 152.6, 165.9. HRMS (APCI) [$C_{29}H_{32}N_2O_2Cl$][Cl]: calculated 475.2152, found: 475.2159 (C^+).

4.3.6. {3-[4-(2-Nitro)-6,6a,7,11b-tetrahydro-6H-indeno-[2,1-c]quinolin-6-yl-benzoyloxy]propyl}trimethylammonium chloride ***5f***

Following procedure A using 4-nitroaniline and indene, a yellow solid was obtained in 80% yield. Mp 184–186 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 2.07–2.28 (m, 3H), 2.78–2.94 (m, 1H), 3.10 (s, 9H), 3.44–3.56 (m, 2H), 4.37 (t, 2H, J=5.6 Hz), 4.58 (d, 1H, J=7.5 Hz), 4.84 (s, 1H), 6.82 (d, 1H, J=8.9 Hz), 7.02–7.14 (m, 2H), 7.22 (t, 1H, J=7.2 Hz), 7.61–7.74 (m, 4H), 7.84 (dd, 1H, J_1=2.3 Hz, J_2=8.9 Hz), 8.06 (d, 2H, J=8.5 Hz), ^{13}C NMR (75 MHz, DMSO-d_6): 22.1, 30.8, 44.2, 46.0, 52.2 (t, J_{C-N}=4.0 Hz), 54.9, 61.8, 62.7, 114.4, 121.1, 123.3, 124.7, 124.9, 126.0, 126.3, 126.9, 127.1, 128.5, 129.4, 136.8, 141.5, 145.4, 146.8, 152.1, 165.9. HRMS (APCI) [$C_{29}H_{32}N_3O_4$][Cl]: calculated 486.2392, found: 486.2384 (C^+).

4.3.7. {3-[4-(4-Fluorophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carbonyloxy]propyl}-trimethylammonium chloride ***6a***

Following procedure B using 4-fluorobenzaldehyde and cyclopentadiene, a light brown solid was obtained in 78% yield. Mp 112–114 °C. ^{1}H NMR (300 MHz, acetone-d_6): 1.65–1.80 (m, 1H), 2.33–2.54 (m, 3H), 2.92–3.11 (m, 1H), 3.45 (s, 9H), 3.76–3.87 (m, 2H), 4.07–4.13 (m, 1H), 4.39 (t, 2H, J=5.9 Hz), 4.77 (s, 1H), 5.59–5.68 (m, 1H), 5.90–6.01 (m, 1H), 6.86 (d, 1H, J=8.5 Hz), 7.09–7.23 (d, 2H, J=8.6 Hz), 7.46–7.55 (m, 2H), 7.62 (dd, 1H, J_1=1.8 Hz, J_2=8.5 Hz), 7.72 (s, 1H), ^{13}C NMR (75 MHz, methanol-d_4): 23.3, 32.5, 46.7, 47.3, 53.6 (t, J_{C-N}=4.0 Hz), 57.5, 62.1, 65.2, 115.9, 116.1, 119.6, 125.9, 129.3, 129.4, 131.0, 132.2, 135.3, 139.5, 152.6, 163.3 (t, J_{C-F}=244 Hz), 168.3. HRMS (FAB) [$C_{25}H_{30}N_2O_2F$][Cl]: calculated 409.2291, found: 409.2296 (C^+).

4.3.8. {3-[4-(4-Chlorophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carbonyloxy]propyl}-trimethylammonium chloride ***6b***

Following procedure B using 4-chlorobenzaldehyde and cyclopentadiene, a pale greenish solid was obtained in 80% yield. Mp 166–168 °C. ^{1}H NMR (300 MHz, acetone-d_6): 1.60–1.78 (m, 1H), 2.32–2.54 (m, 3H), 2.93–3.14 (m, 1H), 3.45 (s, 9H), 3.74–3.96 (m, 2H), 4.07–4.20 (m, 1H), 4.39 (t, 2H, J=5.8 Hz), 4.78 (s, 1H), 5.54–5.67 (m, 1H), 5.72–5.80 (m, 1H), 5.87–6.03 (m, 1H), 6.87 (d, 1H, J=8.3 Hz), 7.42 (d, 2H, J=8.5 Hz), 7.51 (d, 2H, J=8.5 Hz), 7.63 (dd, 1H, J_1=1.4 Hz, J_2=8.3 Hz), 7.73 (s, 1H), ^{13}C NMR (75 MHz, methanol-d_4): 22.6, 31.1, 45.3, 45.7, 52.3 (t, J_{C-N}=4 Hz), 56.1, 60.7, 63.8, 114.8, 118.3, 124.5, 127.8, 128.0, 128.1, 129.6, 130.8, 132.4, 133.9, 140.9, 151.1, 166.8. HRMS (FAB) [$C_{25}H_{30}N_2O_2Cl$][Cl]: calculated 425.1995, found: 425.2000 (C^+).

4.3.9. {3-[4-(4-Nitrophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carbonyloxy]propyl}-trimethylammonium chloride ***6c***

Following procedure B using 4-nitrobenzaldehyde and cyclopentadiene, a light brown solid was obtained in 77% yield. Mp 120–122 °C. ^{1}H NMR (300 MHz, acetone-d_6): 1.61–1.82 (m, 1H), 2.39–2.63 (m, 3H), 3.11–3.29 (m, 1H), 3.47 (s, 9H), 3.86–4.07 (m, 2H), 4.49 (t, 2H, J=5.8 Hz), 4.69–4.76 (m, 1H), 4.81 (s, 1H), 5.53–5.60 (m, 1H), 5.63–5.72 (m, 1H), 5.83–5.98 (m, 1H), 7.16–7.21 (m, 2H), 7.66 (dd, 2H, J_1=2.2 Hz, J_2=8.5 Hz), 8.09 (dd, 2H, J_1=2.2 Hz, J_2=8.5 Hz), ^{13}C NMR (75 MHz, methanol-d_4): 21.4, 30.0, 42.3, 44.7, 51.2 (t, J_{C-N}=4.0 Hz), 55.4, 60.3, 62.8, 112.8, 118.8, 119.0, 125.3, 125.4, 127.5, 128.4, 129.9, 130.4, 130.5, 147.0, 147.1, 165.2. HRMS (FAB) [$C_{25}H_{30}N_3O_4$][Cl]: calculated 436.2236, found: 436.2239 (C^+).

4.3.10. {3-[6-(4-Nitrophenyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline-2-carbonyloxy]propyl}-trimethylammonium chloride ***6d***

Following procedure B using 4-nitrobenzaldehyde and indene, a yellow solid was obtained in 85% yield. Mp 180–182 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 2.23–2.38 (m, 1H), 2.40–2.54 (m, 2H), 3.05–3.38 (m, 2H), 3.45 (s, 9H), 3.78–3.90 (m, 2H), 4.30–4.54 (m, 2H), 4.60 (d, 1H, J=7.5 Hz), 5.04–5.12 (m, 1H), 6.15–6.20 (m, 1H), 6.83 (d, 1H, J=8.3 Hz), 7.02–7.13 (m, 3H), 7.60–7.70 (m, 2H), 7.85 (d, 2H, J=9.1 Hz), 7.95–8.01 (m, 1H), 8.30 (d, 2H, J=9.1 Hz), ^{13}C NMR (75 MHz, DMSO-d_6): 22.6, 31.3, 44.7, 46.5, 52.7 (t, J_{C-N}=4 Hz), 55.4, 62.3, 63.2, 114.9, 121.6,

123.8, 125.2, 125.5, 126.5, 127.1, 127.4, 127.6, 129.0, 129.9, 137.3, 142.0, 145.9, 147.3, 152.6, 165.9. HRMS (FAB) $[C_{29}H_{32}N_3O_4][Cl]$: calculated 486.2392, found: 486.2384 (C^+).

4.4. Quinolines

4.4.1. {3-[4-(7H-Indeno[2,1-c]quinolin-6-yl)phenoxy]-propyl}trimethylammonium tetrafluoroborate **7a**

Following procedure C using **4**, aniline, and indene, a pale greenish solid was obtained in 60% yield. Mp 220–222 °C. ^{1}H NMR (300 MHz, acetonitrile-d_3): 2.24–2.34 (m, 2H), 3.09 (s, 9H), 3.47–3.59 (m, 2H), 4.21 (t, 2H, J=5.7 Hz), 4.36 (s, 2H), 7.19 (d, 2H, J=8.7 Hz), 7.71–7.80 (m, 2H), 7.88 (dd, 1H, J_1=3.4 Hz, J_2=8.2 Hz), 8.00–8.09 (m, 3H), 8.14 (t, 1H, J=8.3 Hz), 8.75–8.78 (m, 1H), 8.83 (d, 1H, J=8.5 Hz), 9.09 (d, 1H, J=8.7 Hz), ^{13}C NMR (75 MHz, DMSO-d_6): 22.5, 38.6, 52.6 (t, J=4.0 Hz), 63.5, 64.6, 115.0, 121.2, 122.5, 123.6, 124.5, 125.4, 125.8, 128.0, 129.0, 131.2, 131.3, 133.2, 134.9, 137.6, 138.7, 147.8, 150.9, 153.4, 161.1. HRMS (FAB) $[C_{28}H_{29}N_2O][BF_4]$: calculated 409.2279, found: 409.2265 (C^+).

4.4.2. {3-[4-(2-Methyl-7H-indeno[2,1-c]quinolin-6-yl)-phenoxy]propyl}trimethylammonium tetrafluoroborate **7b**

Following procedure C using **4**, 4-methylaniline, and indene, a yellow solid was obtained in 62% yield. Mp 208–210 °C. ^{1}H NMR (300 MHz, acetone-d_6): 2.36–2.52 (m, 2H), 2.78 (s, 3H), 3.25 (s, 9H), 3.58–3.74 (m, 2H), 4.32 (t, 2H, J=5.7 Hz), 4.37 (s, 2H), 7.34 (d, 2H, J=8.6 Hz), 7.69–7.79 (m, 2H), 7.84–7.82 (m, 1H), 8.01 (m, 3H), 8.26 (d, 1H, J=8.7 Hz), 8.82 (d, 1H, J=8.7 Hz), 8.89 (s, 1H), ^{13}C NMR (75 MHz, acetonitrile-d_3): 20.6, 22.5, 38.5, 52.6 (t, J=4.0 Hz), 63.5, 64.6, 115.0, 120.6, 122.7, 123.2, 123.4, 125.4, 126.1, 128.0, 131.2, 135.3, 137.0, 137.6, 140.2, 147.7, 149.8, 153.0, 161.1. HRMS (FAB) $[C_{29}H_{31}N_2O][BF_4]$: calculated 423.2436, found: 423.2436 (C^+).

4.4.3. {3-[4-(2-Methoxy-7H-indeno[2,1-c]quinolin-6-yl)-phenoxy]propyl}trimethylammonium tetrafluoroborate **7c**

Following procedure C using **4**, 4-methoxyaniline, and indene, a yellow solid was obtained in 60% yield. Mp 198–200 °C. ^{1}H NMR (300 MHz, acetone-d_6): 2.42–2.61 (m, 2H), 3.51 (s, 9H), 3.84–3.95 (m, 2H), 4.18 (s, 3H), 4.28–4.41 (m, 4H), 7.18 (d, 2H, J=8.7 Hz), 7.47–7.68 (m, 3H), 7.87 (d, 1H, J=7.2 Hz), 8.05–8.21 (m, 4H), 8.62 (d, 1H, J=7.2 Hz), ^{13}C NMR (75 MHz, acetonitrile-d_3): 24.0, 38.3, 53.6 (t, J=4.0 Hz), 56.1, 64.9, 65.7, 102.8, 115.3, 122.5, 125.1, 125.2, 126.0, 128.3, 129.4, 131.0, 131.3, 132.4, 135.4, 140.7, 143.1, 146.2, 146.3, 152.5, 159.3, 160.3. HRMS (FAB) $[C_{29}H_{31}N_2O_2][BF_4]$: calculated 439.2385, found: 439.2375 (C^+).

4.4.4. {3-[4-(2-Chloro-7H-indeno[2,1-c]quinolin-6-yl)-phenoxy]propyl}trimethylammonium tetrafluoroborate **7d**

Following procedure C using **4**, 4-chloroaniline, and indene, a yellow solid was obtained in 57% yield. Mp 224–226 °C. ^{1}H NMR (300 MHz, acetone-d_6): 2.30–2.51 (m, 2H), 3.25 (s, 9H), 3.59–3.73 (m, 2H), 4.24–4.35 (m, 4H), 7.28 (d, 2H, J=8.7 Hz), 7.64–7.72 (m, 2H), 7.82 (dd, 1H, J_1=2.0 Hz, J_2=6.4 Hz), 7.99 (d, 2H, J=8.7 Hz), 8.27 (d, 2H, J=8.9 Hz), 8.64 (d, 1H, J=8.2 Hz), 8.96 (s, 1H), ^{13}C NMR (75 MHz, acetonitrile-d_3): 22.5, 38.4, 52.6 (t, J=4.0 Hz), 63.5, 64.5, 114.8, 123.2, 125.1, 125.3, 125.4, 127.8, 130.8, 131.1, 132.4, 133.8, 135.8, 137.6, 139.4, 147.1, 150.6, 152.1, 160.8. HRMS (FAB) $[C_{29}H_{28}N_2OCl][BF_4]$: calculated 443.1890, found: 443.1892 (C^+).

4.4.5. {3-[4-(2-Bromo-7H-indeno[2,1-c]quinolin-6-yl)-phenoxy]propyl}trimethylammonium tetrafluoroborate **7e**

Following procedure C using **4**, 4-bromoaniline, and indene, a yellow solid was obtained in 56% yield. Mp 258–260 °C. ^{1}H NMR (300 MHz, acetone-d_6): 2.56–2.63 (m, 2H), 3.43 (s, 9H), 3.85–3.93 (m, 2H), 4.36 (t, 2H, J=5.7 Hz), 4.37 (s, 2H), 7.28 (d, 2H, J=8.7 Hz), 7.64–7.72 (m, 2H), 7.82 (dd, 1H, J_1=2.0 Hz, J_2=6.4 Hz), 7.99 (d, 2H, J=8.6 Hz), 8.27 (d, 2H, J=8.9 Hz), 8.64 (d, 1H, J=8.2 Hz), 8.96 (s, 1H), ^{13}C NMR (75 MHz, acetonitrile-d_3): 23.8, 38.6, 53.8 (t, J=4.0 Hz), 64.9, 66.2, 115.8, 122.0, 125.0, 125.6, 126.4, 126.9, 128.8, 129.7, 129.9, 130.8, 131.8, 134.6, 136.6, 139.5, 144.2, 147.1, 148.4, 155.2, 161.1. HRMS (FAB) $[C_{29}H_{28}N_2OBr][BF_4]$: calculated 487.1385, found: 487.1382 (C^+).

4.4.6. {3-[4-(2-Nitro-7H-indeno[2,1-c]quinolin-6-yl)-phenoxy]propyl}trimethylammonium tetrafluoroborate **7f**

Following procedure C using **4**, 4-nitroaniline, and indene, a yellow solid was obtained in 50% yield. Mp 258–260 °C. ^{1}H NMR (300 MHz, methanol-d_4): 2.36–2.50 (m, 2H), 3.27 (s, 9H), 3.64–3.75 (m, 2H), 4.35 (t, 2H, J=5.6 Hz), 4.50 (s, 2H), 7.38 (d, 2H, J=8.6 Hz), 7.76–7.86 (m, 2H), 7.89–7.99 (m, 1H), 8.14 (d, 2H, J=8.6 Hz), 8.57 (d, 1H, J=9.4 Hz), 8.72–8.80 (m, 1H), 8.86 (d, 1H, J=9.4 Hz), 9.89 (s, 1H), ^{13}C NMR (75 MHz, methanol-d_4): 22.3, 53.7 (t, J=4.0 Hz), 65.4, 66.2, 116.2, 121.8, 123.1, 125.5, 126.1, 126.8, 127.2, 128.1, 128.7, 129.4, 132.1, 132.6, 137.7, 139.3, 146.6, 147.1, 148.5, 157.4, 162.6. HRMS (FAB) $[C_{29}H_{28}N_3O_3][BF_4]$: calculated 454.2130, found: 454.2135 (C^+).

4.4.7. {3-[4-(2-Fluoro-7H-indeno[2,1-c]quinolin-6-yl)-phenoxy]propyl}trimethylammonium tetrafluoroborate **7g**

Following procedure C using **4**, 4-fluoroaniline, and indene, a brown solid was obtained in 62% yield. Mp 218–220 °C. ^{1}H NMR (300 MHz, acetonitrile-d_3): 2.25–2.41 (m, 2H), 3.14 (s, 9H), 3.49–3.63 (m, 2H), 4.27 (t, 2H, J=5.7 Hz), 4.37 (s, 2H), 7.28 (d, 2H, J=8.7 Hz), 7.69–7.80 (m, 2H), 7.84–7.91 (m, 1H), 7.97 (d, 1H, J=8.6 Hz), 8.01 (d, 2H, J=8.8 Hz), 8.42 (d, 1H, J=5.4 Hz), 8.67 (m, 2H), ^{13}C NMR (75 MHz, acetone-d_6): 23.7, 38.4, 53.8 (t, J=4.0 Hz), 64.8, 65.9, 109.7, 116.3, 123.3, 123.7, 124.5, 125.7, 126.3, 126.6, 126.8, 129.2, 132.2, 132.4, 136.8, 138.4, 138.7, 148.4, 152.7, 162.3 (d, J=250 Hz), 162.1. HRMS (FAB) $[C_{29}H_{28}N_2OF][BF_4]$: calculated 427.2185, found: 427.2191 (C^+).

4.4.8. {3-[4-(2-Chloro-7H-indeno[2,1-c]quinolin-6-yl)-benzoloxy]propyl}trimethylammonium tetrafluoroborate **8a**

Following procedure C using **3**, 4-chloroaniline, and indene, a yellow solid was obtained in 60% yield. Mp

>260 °C. ^{1}H NMR (300 MHz, acetonitrile-d_3): 2.20–2.41 (m, 2H), 3.12 (s, 9H), 3.43–3.56 (m, 2H), 4.09 (s, 2H), 4.45 (t, 2H, J=5.8 Hz), 7.53–7.56 (m, 2H), 7.68 (d, 1H, J=8.5 Hz), 7.78 (d, 1H, J=8.5 Hz), 8.02 (d, 2H, J=8.3 Hz), 8.15 (d, 1H, J=8.7 Hz), 8.23 (d, 2H, J=8.3 Hz), 8.41 (d, 1H, J=8.7 Hz), 8.68 (s, 1H), ^{13}C NMR (75 MHz, acetonitrile-d_3): 22.0, 38.4, 52.6 (t, J=4.0 Hz), 61.5, 63.5, 122.4, 123.8, 124.1, 125.0, 127.3, 128.8, 128.9, 129.4, 129.9, 129.9, 130.5, 132.5, 135.4, 138.7, 142.9, 144.9, 145.1, 154.3, 165.9. HRMS (FAB) $[C_{29}H_{28}N_2O_2Cl][BF_4]$: calculated 427.2185, found: 427.2191 (C^+).

*4.4.9. {3-[4-(2-Methyl-7H-indeno[2,1-c]quinolin-6-yl)-benzoloxy]propyl}trimethylammonium tetrafluoroborate **8b***

Following procedure C using **3**, 4-methylaniline, and indene, a yellow solid was obtained in 59% yield. Mp 200–202 °C. ^{1}H NMR (300 MHz, acetonitrile-d_3): 2.35–2.48 (m, 2H), 2.81 (s, 3H), 3.21 (s, 9H), 3.58–3.67 (m, 2H), 4.36 (s, 2H), 4.54 (t, 2H, J=5.8 Hz), 7.74–7.83 (m, 2H), 7.89 (d, 1H, J=8.7 Hz), 8.07 (d, 1H, J=8.4 Hz), 8.17 (d, 2H, J=8.3 Hz), 8.32 (d, 1H, J=8.7 Hz), 8.42 (d, 2H, J=8.3 Hz), 8.89 (d, 1H, J=8.4 Hz), 8.97 (s, 1H), ^{13}C NMR (75 MHz, acetonitrile-d_3): 20.7, 22.1, 52.6 (t, J=4.0 Hz), 61.3, 63.5, 122.4, 123.3, 123.5, 125.0, 125.1, 128.4, 129.1, 129.5, 129.7, 131.0, 133.2, 134.6, 135.0, 139.0, 141.0, 142.2, 149.7, 152.0, 153.5, 165.8. HRMS (FAB) $[C_{30}H_{31}N_2O_2][BF_4]$: calculated 471.1839, found: 471.1835 (C^+).

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