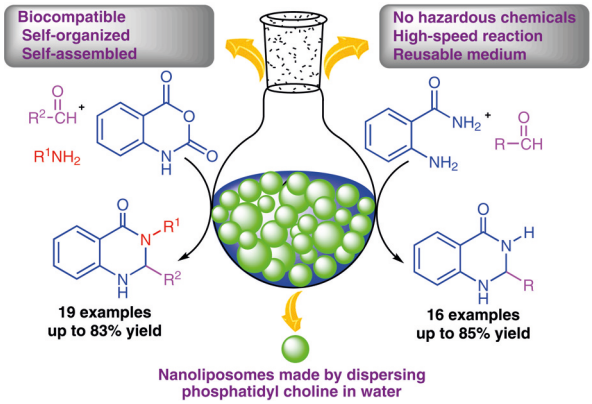
Synlett F. Tamaddon et al. Letter

Self-Assembled Nanoliposomes of Phosphatidylcholine: Bridging the Gap between Organic and Aqueous Media for a Green Synthesis of Hydroquinazolinones

Fatemeh Tamaddon*
Mohammad Taghi
Kazemi Varnamkhasti

Department of Chemistry, Yazd University, Yazd 89195-741, Iran
ftamaddon@yazduni.ac.ir



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Abstract Self-assembly of phosphatidylcholine in water creates liposomal nanoreactors for environmentally friendly synthesis of hydroquinazolinones by two- or three-component reactions, without the use of an extra catalyst or solvent. Recycling of the reaction medium and the absence of a need for other organic reagents are further advantages of this protocol.

Key words liposomes, self-assembly, nanoreactors, phosphatidylcholine, hydroquinazolinones, green chemistry

The development of chemical transformations that proceed under biocompatible water-based conditions is one of the essential goals of green chemistry.[1,2] The benefits of such water-based transformations would be accentuated if these transformations were multicomponent reactions (MCRs)[3] and subject to catalysis by nanoliposomes. Because of the high diffusion power and large surface area of nanocatalysts, various nanoscale flakes, fibers, fluids, sheets, powders, and particles[4–7] have been efficiently used to promote organic reactions.[8] However, despite well-developed techniques for preparing nanomaterials, their generation in situ by self-assembly in water remains the simplest approach. Since the discovery of liposomes by Bangham and Horne,[9] these biomimetic nanomaterials have been developed as layered microvesicles and as carriers for delivery and encapsulation of medicines, genes, cosmetics, agrichemicals, or foods.[10–12] Nanoliposomes, which consist of three-dimensional hollow vesicles, have the advantages of versatility, biocompatibility, and an adjustable chain length.[13] In water, nanoliposomes are usually formed from bilayer phospholipids with their lipophilic tails oriented to form stable uni- or multilamellar spheres with a hydrophilic shell and a water-filled cavity. The thickness of the bilayer is typically 3–6 nm, whereas the diameter of the nanoliposome is generally in the range 80–300 nm (Figure 1).[14]

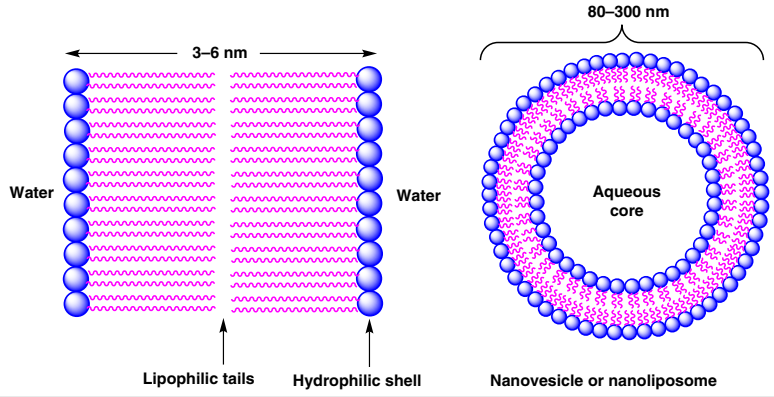


Figure 1 Bilayer phospholipids in cell membranes, nanovesicles, or nanoliposomes

Phosphatidylcholine (PC) is a phospholipid with a negatively charged phosphate group and a positively charged choline moiety in its hydrophilic head (Figure 2). In aqueous solutions, PC spontaneously forms bilayer semi-permeable micelles with a thickness of 4 nm and a diameter of 50–100 nm.[15,16] In vitro mimicking of organic reactions with biocatalysts in water can help in understanding in vivo biotransformations and in developing greener organic reactions.[17,18]

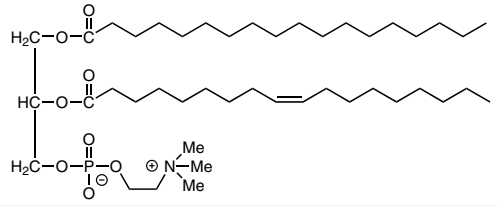


Figure 2 Phosphatidylcholine

Quinazolinones are basic fragment of natural products such as luotonin A,[19] glycosaminine,[20] and rutaecarpine,[21] and of pharmaceuticals with antimalarial, antidiabetic, anticancer, anticonvulsant, or antilipedimic properties.[22,23] As a result, various protocols for their synthesis have been developed that use a range of starting materials and acid catalysts under various reaction conditions.[24]

2-Aminobenzamide and isatoic anhydride [2*H*-3,1-benzoxazine-2,4(1*H*)-dione] are common precursors for the acid-catalyzed synthesis of hydroquinazolinones (HQs).[25,26] We recently developed a heterogeneous base-catalyzed synthesis of dihydroquinazolinones (DHQs) from 2-aminobenzonitrile in water.[27] In continuation of our recent work on water-based organic reactions,[28] we describe a synthetic protocol that uses nanoliposomes formed in vitro for the rapid synthesis of HQs from 2-aminobenzamide or isatoic anhydride in water without use of additional reagents or organic solvent (Figure 3).

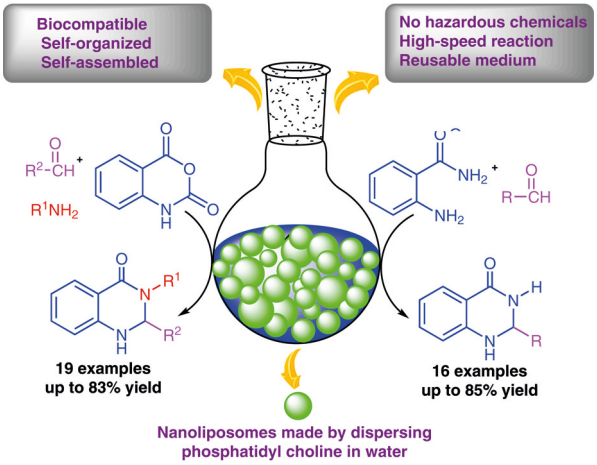
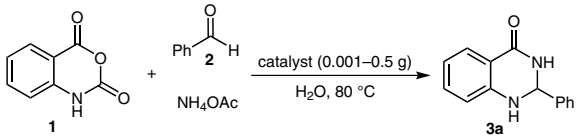


Figure 3 Synthesis of hydroquinazolinones in nanoliposomes assembled from phosphatidylcholine in water

In an initial study of the synthesis of 2-phenyl-2,3-dihydroquinazoline-4(1*H*)-one (**3a**) in a vesicular medium, we screened the one-pot three-component reaction of isatoic anhydride (**1**), ammonium acetate, and benzaldehyde (**2**) in water using various amounts of phosphatidylcholine (PC), phosphatidylethanolamine (PEA), or phosphatidylinositol (PI) (Table 1, entries 1–14).

Table 1 Optimization of the Reaction with Phospholipids as Catalysts[a]



Entry	Catalyst (g)	Solvent	Temp (°C)	Time (min)	Yield[b] (%)
1	–	H_2O	80	4800	40
2	PC (0.001)	H_2O	80	120	80
3	PC (0.002)	H_2O	80	90	81
4	PC (0.003)	H_2O	80	45	87
5	PC (0.004)	H_2O	80	25	90
6	PC (0.005)	H_2O	80	15	97
7	PC (0.005)	H_2O	70	35	92
8	PC (0.005)	H_2O	100	15	96
9	PC (0.01)	H_2O	80	15	97
10	PC (0.005)	50:50 H_2O–EtOH	80	25	91
11	PC (0.005)	EtOH	80	45	81
12	PEA (0.005)	H_2O	80	45	76
13	PI (0.005)	H_2O	80	70	72
14	PI (0.05)	H_2O	80	90	78
15	PPA[c] (0.005)	H_2O	80	50	83
16	PC[d] (0.005)	H_2O	80	20	96
17	choline chloride (0.005)	H_2O	80	180	67
18	stearic acid (0.005)	H_2O	80	180	67
19	reused reaction medium from entry 16		80	20	95

[a] Reaction conditions: isatoic anhydride (**1**; 1 mmol), PhCHO (**2**; 1 mmol), NH_4OAc (1 mmol), solvent (2 mL).
[b] Isolated yield. The pure precipitated product was isolated simply by addition of crushed ice and subsequent filtration.
[c] (2*R*)-2,3-Bis(octanoyloxy)propyl dihydrogen phosphate.
[d] The reaction was carried out at 50 mmol scale.

In the absence of PC, the reaction in water was incomplete even after an extended reaction time (Table 1, entry 1), but a maximum 97% yield of product **3** was obtained in just 15 minutes by using 0.005 g of PC in 2 mL of water (entry 5). Given that the molecular weight of PC is 768, its concentration in this experiment was 0.0025 g/L or 3.26 mM, close to the range of 5–10 mM for the critical liposome concentration of PC,[29] the appropriate concentration for the

production of liposomes with a diameter of 100 nm. The lower yield of product with smaller amounts of PC (entries 2–5) might be attributed to lower numbers of micelles. A reduction in the yield of **3** with EtOH as co-solvent can be attributed to the depression of the surface tension of the solvent and the breakup of the nanoliposomes (entry 10). The superior catalytic performance of PC to that of PEA (entry 12) or PI (entry 13) highlights the reactivity–structure relationship of the surfactants.

To clarify the catalytic role of the combination of the choline head and hydrophobic portion of PC, we compared the results shown in Table 1, entries 1 and 6 with those obtained in the presence of choline chloride (entry 17) and stearic acid (entry 18). The significantly lower yields for the reaction in water alone (Table 1, entry 1) or in the presence of choline chloride (entry 17) or stearic acid (entry 18) provide evidence for the occurrence of the reaction within the PC nanoliposomes, rather than as the result of the action of isolated hydrophobic chains or polar choline groups.

To provide evidence to support the formation of liposomes and to evaluate their morphology, we performed freeze-fracture transmittance electron microscopy studies (TEM) to obtain a high-contrast image of the self-assembled liposomes in the reaction medium (Figure 4).

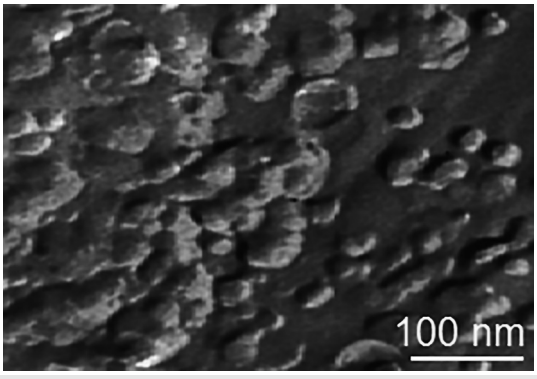


Figure 4 Transmission electron micrograph of nanoliposomes of PC in water

The scalability and reusability of the reaction were confirmed by recycling of the filtrate from the model reaction at a 50 mmol scale (Table 1, entry 16) in a subsequent run. After the completion of the first reaction, the product was extracted with EtOAc and the aqueous phase was reused in a second reaction that gave pure **3a** isolated in 95% yield in the same reaction time (entry 19).

The merits of our nanoliposomal reaction[30] are evident from a comparison with the results of the three-component model reaction with those for previously reported methods in aqueous media (Table 2).

Table 2 The Relative Catalytic Performance of PC Nanoliposomes in the Synthesis of **3a**

Entry	Catalyst (g)	Solvent (4 mL)	Temp (°C)	Time (min)	Yield[a] (%)
1	PC (0.005)	H_2O	80	15	97[b]
2	Amberlyst A26 OH (0.2)	1:1 EtOH–H_2O	50–60	180	93[27]
3	$Zn(PFO)_2$[c] (0.027)	1:3 H_2O–EtOH	reflux	360	78[31]
4	Silica sulfuric acid (0.08)	H_2O	80	180	84[32]

[a] Isolated yield.
[b] This work.
[c] PFO = perfluorooctanoate.

To examine the scope of the method and the catalytic performance of the self-assembled nanoliposomes of PC in water, three-component reactions of isatoic anhydride with various aldehydes and amines or ammonium acetate[30] were carried out under the optimized conditions (Table 3). In all cases, the reaction reached completion rapidly gave and excellent yields of the precipitated HQs, isolated by simple filtration. Even the enolizable ketones of cyclopentanone and cyclohexanone gave excellent yields of the desired products (Table 3, entries 14 and 15).

Encouraged by the catalytic superiority of the PC nanoliposomes, we extended the optimized reaction conditions to the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones from 2-aminobenzamide and a range of aldehydes. Again, the desired products **3a**–**m** were isolated in good to excellent yields (Table 4, entries 1–15). Replacement of aldehydes with cyclopentanones, cyclohexanones, and acetone gave the corresponding products **3n**–**t** in 90–93% yields (entries 14–16).

In conclusion, we have developed an environmentally benign protocol that is advantageous for the rapid and high-yielding three- or two-component syntheses of HQs in an in vitro vesicular medium, made by dispersal of PC as a biosurfactant in water. The possibility of recycling the reaction medium and the absence of a need for other organic reagents are additional advantages of this protocol.

Acknowledgment

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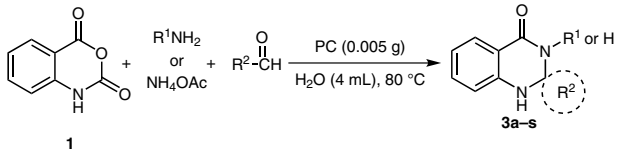
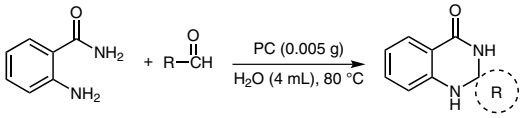
Table 3 PC-Catalyzed Synthesis of Quinazolinones in Nanoliposomal Medium[a]



Entry	R^1	R^2	Product	Time (min)	Yield[b] (%)	Mp (°C) (Lit.)
1	H[c]	Ph	**3a**	15	97	221–223 (219–222)27
2	H[c]	4-Tol	**3b**	45	96	231–233 (232–235)27
3	H[c]	4-$MeOC_6H_4$	**3c**	60	95	195–197 (194–195)27
4	H[c]	4-HOC_6H_4	**3d**	90	92	276–278 (278–282)27
5	H[c]	3,4-$(MeO)_2C_6H_3$	**3e**	75	92	213–215 (211–214)27
6	H[c]	3,5-$(MeO)_2C_6H_3$	**3f**	60	94	146–148
7	H[c]	4-*i*-PrC_6H_4	**3g**	60	97	161–163 (162–164)22
8	H[c]	4-$Me_2NC_6H_4$	**3h**	45	94	201–203 (202–204)33
9	H[c]	2-Naph	**3i**	120	83	171–173 (172–174)22
10	H[c]	4-ClC_6H_4	**3j**	45	93	205–207 (206–208)27
11	H[c]	3-BrC_6H_4	**3k**	30	91	223–225 (>220)30
12	H[c]	2-BrC_6H_4	**3l**	90	87	180–182 (183–185)33
13	H[c]	2-ClC_6H_4	**3m**	90	90	199–201 (200–202)33
14	H[c]	cyclopentanone	**3n**	120	91	257–259 (258–259)24
15	H[c]	cyclohexanone	**3o**	180	91	224–226 (225–227)27
16	Ph	4-$MeOC_6H_4$	**3p**	90	94	202–205 (204–205)33
17	4-$MeOC_6H_4$	Ph	**3q**	60	91	208–210 (209–211)33
18	4-MeC_6H_4	Ph	**3r**	75	92	196–198 (197–198)33
19	4-$PhOC_6H_4$	Ph	**3s**	90	93	208–210 (209–211)33

[a] Reaction conditions: isatoic anhydride (**1**; 2 mmol), R^2CHO (2 mmol), NH_4OAc or R^1NH_2 (2 mmol), PC (0.01 g), H_2O (4 mL), 80 °C.
[b] Isolated yield.
[c] NH_4OAc was used.

Table 4 PC-Catalyzed Synthesis of 2,3-Dihydro-4(1*H*)-quinazolinones[a]



Entry	R	Product	Time (min)	Yield[b] (%)	mp (°C) (Lit.)
1	Ph	**3a**	20	95	220–222 (219–222)27
2	4-Tol	**3b**	50	93	230–232 (232–235)27
3	4-$MeOC_6H_4$	**3c**	75	92	193–195 (194–195)32
4	4-HOC_6H_4	**3d**	60	91	277–279 (278–282)27
5	3,4-$(MeO)_2C_6H_3$	**3e**	90	95	213–215 (211–214)27
6	3,5-$(MeO)_2C_6H_3$	**3f**	80	91	144–146
7	4-*i*-PrC_6H_4	**3g**	60	98	163–165 (162–164)22
8	4-$(Me_2N)C_6H_4$	**3h**	75	94	201–203 (202–204)33
9	-2-Naph	**3i**	270	85	170–172 (172–174)22
10	4-ClC_6H_4	**3j**	75	95	205–207 (206–208)27
11	3-BrC_6H_4	**3k**	60	92	220–222 (>220)33
12	2-BrC_6H_4	**3l**	180	89	182–184 (183–185)33
13	2-ClC_6H_4	**3m**	150	91	201–203 (200–202)33
14	cyclopentanone	**3n**	210	91	255–257 (258–259)24
15	cyclohexanone	**3o**	240	90	225–227 (225–227)27
16	[acetone]	**3t**	90	93	183–184 (184–185)27

[a] Reactions were performed with 2-aminobenzamide (2 mmol), aldehyde or acetone (2 mmol), PC (0.01 g), H_2O (4 mL).
[b] Isolated yield.

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(30) **Hydroquinazolinones from Isatoic Anhydride; General Procedure**
Isatoic anhydride (**1**; 2 mmol), the appropriate aldehyde (2 mmol), and the appropriate ammonium salt (2.5 mmol) or amine (2 mmol) were added to a stirred mixture of H_2O (4 mL) and PC (0.01 g) at ~80 °C. When the reaction was complete (TLC), the product was isolated either by simple filtration or by extraction with EtOAc. In some cases, the crude product was crystallized from 70:30 EtOH–H_2O.
2,3-Dihydroquinazolinones from 2-Aminobenzamide; General Procedure
2-Aminobenzamide (2 mmol) and the appropriate aldehyde (2 mmol) were added to a stirred mixture of PC (0.01 g) and H_2O (4 mL) at ~80 °C. When the reaction was complete (TLC), the precipitated product was isolated by filtration.
Selected Analytical Data
3-(4-Phenoxyphenyl)-2-phenyl-1,2-dihydroquinazolin-4(1*H*)-one (3s)
White solid; yield (2 mmol scale): 730 mg (93%); mp 208–210 °C. FT-IR (KBr): 3273, 1637, 1609, 1506 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.27 (s, 1 H), 6.72 (t, *J* = 7.4 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.94–6.98 (m, 4 H), 7.13 (t, *J* = 7.3 Hz, 1 H), 7.25–7.33 (m, 6 H), 7.38 (m, 4 H), 7.62 (s, 1 H, NH), 7.72 (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.59, 115.64, 116.13, 118.40, 119.45, 119.48, 124.41, 127.57, 128.83, 129.07, 129.22, 129.26, 130.92, 134.62, 136.96, 141.38, 141.42, 147.50, 147.55, 155.30, 157.43, 163.23.
2-(3,4-Dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e)
Pale-yellow solid; yield (2 mmol scale): 540 mg (95%); mp 213–215 °C. FT-IR (KBr): 3331, 3297, 1654, 1611, 1512, 1484, 1232, 1263 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.35 (s, 1 H, NH), 3.76 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 5.71 (s, 1 H, CH), 6.70 (t, *J* = 7.2, 1 H), 6.77 (d, *J* = 8.4, 1 H), 6.96 (d, *J* = 8.4, 1 H), 7.01 (d, *J* = 8.4, 1 H), 7.15 (d, *J*= 2.0, 1 H), 7.26 (dt, J_1 = 7.6, J_2 = 1.6, 1 H), 7.63 (dd, J_1 = 7.6, J_2 = 1.6, 1 H), 8.20 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.9, 67.0, 111.1, 111.7, 114.9, 114.9, 115.5, 117.6, 119.7, 127.8, 133.7, 134.1, 148.6, 149.1, 149.5, 164.2.
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