An ionic liquid {[^{sec}bmim]$^{+}$ Br^{-}} as a "dual reagent catalyst" for the multicomponent synthesis of (quinolinyl- and isoquinolinyl- amino) alkylnaphthols, their bis- analogs and a facile route to naphthoxazines

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Abstract

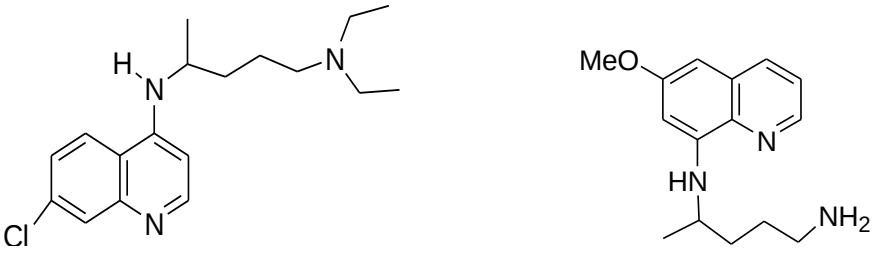
An atom-economic methodology has been developed for the multi- component one–pot synthesis of (quinolinyl- and isoquinolinyl- amino) alkyl naphthols and their bis- analogs employing the ionic liquid {[^{sec}bmim]$^{+}$ Br^{-}} as a "dual reagent catalysis" at 25 ºC. The present approach possesses several advantages such as excellent yields, lower reaction times, mild reaction conditions, recyclability and very easy purification processes. The methodology has been further extended towards the facile synthesis of naphthoxazines in very good yields employing formaldehyde in place of aromatic aldehydes.

Keywords: Ionic liquid, {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^{+}$ Br^{-}}, atom-economy, multi-component reaction, (quinolinyl- and isoquinolinyl- amino)- alkyl naphthols, naphthoxazines

Introduction

The (quinolinyl- and isoquinolinyl- amino) alkyl naphthols belong to the category of 1,3-amino-oxygenated functional group compounds which comprise varieties of biologically important natural products and potent drugs.[1] Two very important such compounds are ritonavir and lopinavir being HIV protease inhibitors of great significance.[2] The 1-aminoalkyl naphthols also exhibit biological activities like hypotensive and bradycardiac effect.[3] In addition, such 1-aminoalkyl alcohol type ligands have been utilized for asymmetric synthesis where it acts as a catalyst.[4] Therefore, the high importance of 1-aminoalkyl naphthols prompted us to undertake their synthesis, at the same time employing a one-pot multi-component methodology.

Another important point that needs mentioning is that since we have utilized amino-quinolines as one of the components in many of our reactions, the three-component coupling products are amino-quinoline derivatives. The presence of the amino-quinoline moiety is an integral part of many important drugs, two of them being chloroquine and primaquine,[5] both being used for the treatment of malaria (Figure 1).



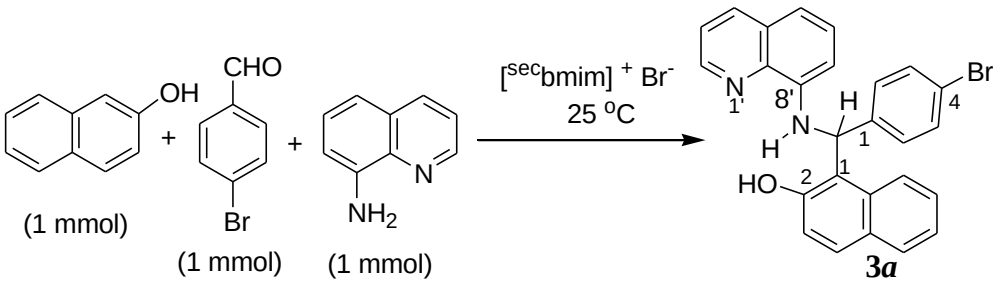
Chloroquine Primaquine

Figure 1. Important drugs with amino-quinoline moiety.

Multi-component reactions (MCRs) prove a very elegant and economic way to build up complex structures in a single synthetic operation from very simple starting materials, most of the time in one-pot.[6a-f] Such reactions show high atom economy, high selectivity and methodological simplicity due to the formation of carbon-carbon and carbon-heteroatom bonds in a single step.[7a] MCRs are generally very high yielding being a one-pot procedure and are fundamentally quite different from two-component reactions.[7b] Since several transformations are carried out in a single step, the procedure definitely approaches a step-economic condition.

During recent years, ionic liquids (ILs) have attracted increasing interest in the area of organic synthesis particularly by producing an alternative green reaction medium[8a]. Recently, the ionic liquids have been found to possess a significant role as catalyst[8a-b]. They can be also used as solvents due to their unique physical and chemical properties such as non-volatility, non-flammability, thermal stability and controlled miscibility. A number of ionic liquids have been developed and successfully applied as efficient catalysts in aldol condensation reactions[8c] or Mannich reactions.[8d] Therefore, ionic liquids have been the subject of considerable interest because they are much more advantageous in terms of catalytic efficiency and recycling of the ionic liquid compared to the inorganic salts when used as catalysts.

With this view in mind, we utilized the ionic liquid {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^{+}$ Br^{-}} both as a catalyst and as a solvent for the synthesis of the (quinolinyl- and isoquinolinyl-) amino alkylnaphthols via the one-pot three-component condensation of quinoline or isoquinoline amines, aromatic aldehydes and β- or α-naphthols at 25 ºC. All the synthesized compounds are new as this is the first report of aminoalkylation of such compounds. Below is shown Scheme 1 for a standard reaction:



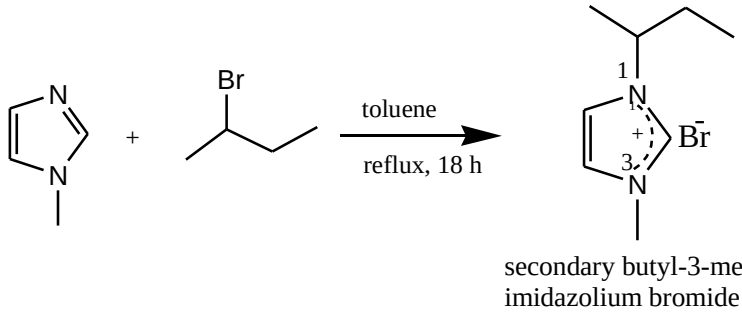
Scheme 1. Synthesis of a quinolinyl aminoalkyl naphthol in the ionic liquid {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^{+}$ Br^{-}}.

In order to choose the best catalyst, we compared the results of the reaction with our prepared IL, {[^{sec}bmim]$^{+}$ Br^{-}} and other organic and inorganic compounds (Table 1). It was observed that the prepared IL proved to be the best catalyst for this reaction (Table 1, entry 8).

Table 1. Choice of catalyst for the synthesis of 1-[(4-Bromophenyl)-(quinolin-8-ylamino)-methyl]-naphthalene-2-ol

Entry	Catalyst	Yield (%) (isolated)
1	triethylamine (1 mL)	30
2	piperidine (1 mL)	40
3	N-methylpiperazine (1 mL)	45
4	pyrrolidine (1 mL)	35
5	DABCO (20 mg)	50
6	{[bmim]$^{+}$ Br^{-}} (1 g)	80
7	{[^{sec}bmim]$^{+}$ Br^{-}} (1 g)	85

The synthetic strategy for the preparation of ionic liquid (IL) is shown below in Scheme 2.



Scheme 2. Synthesis of sec- butyl-3-methyl-imidazolium bromide {[^{sec}bmim]$^{+}$Br^{-}}(IL).

In order to optimize the reaction conditions for the above transformation, we investigated the reaction of 4-bromobenzaldehyde, 8-aminoquinoline and β-naphthol using various amounts of

the ionic liquid secondarybutyl-3-methyl-imidazolium bromide {[^{sec}bmim]$^{+}$Br^{-}} at 25 ºC and the results are given below in Table 2.

Table 2. Optimization of the amount of [^{sec}bmim]$^{+}$ Br^{-} towards the synthesis of 1-[(4-bromophenyl)-(quinolin-8-ylamino)-methyl]-naphthalene-2-ol

Entry	Amount of [^{sec}bmim]$^{+}$ Br^{-} (mg)	Yield (%) (isolated)
1	1	10
2	2	50
3	10	85
4	20	85
5	30	85
6	1g	85

On examination of Table 1 we find that, 10 mg (Table 1, entry 3) of {[^{sec}bmim]$^{+}$ Br^{-}} was the optimum amount to get maximum yield of the product. When the amount of IL was gradually increased to 1g (Table 1, entry 6), the isolated yield remained the same. So the IL acts as "dual reagent catalysis" for this reaction. It was necessary to use the IL as a solvent (dilution effect) because the product charred in some cases with lower amounts of IL and also, we did not want to use any other solvent for this reaction other than IL.

To explore the generality of the reaction, we extended our study with different aromatic aldehydes, quinoline- / isoquinoline- amines and α- and β-naphthols to prepare a series of (quinolinyl- and isoquinolinyl- amino) alkyl naphthols and the results are depicted in Table 3. It is found that almost all entries yielded products in good to excellent yields. Aromatic aldehydes possessing halogen or cyano substituents at para positions reacted to a much greater extent than electron-donating methoxy substituents at para positions or other ortho substituents. Both α- and β-naphthols reacted equally well and various quinoline amines reacted to a greater extent than isoquinoline amines. However, aliphatic aldehydes failed to produce the desired products in good yields and only trace amount of product was obtained in such cases which could not be purified further.

Table 3. Synthesis of (quinolinyl and isoquinolinyl amino) alkyl naphthols with the ionic liquid {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^+$ Br$^-$} (1g) at 25 ºC

Entry	Starting materials			Products (**3*a*-3*v***)	Time(h)	Yield (%) isolated
	Amines (Q=quinoline: IQ=isoquinoline)	aldehydes	Naphthols (2- or 1-)			
1	8-amino-Q	4-bromobenzaldehyde	2-	**3*a***	2	85
2	3-amino-Q	4-bromobenzaldehyde	2-	**3*b***	2	85
3	3-amino-Q	4-nitrobenzaldehyde	2-	**3*c***	3	80
4	3-amino-Q	4-cyanobenzaldehyde	2-	**3*d***	3	75
5	3-amino-Q	3,4-dimethoxybenzaldehyde	2-	**3*e***	3	71
6	3-amino-Q	2-nitrobenzaldehyde	2-	**3*f***	3	75
7	8-amino-Q	4-chlorobenzaldehyde	2-	**3*g***	3	85
8	3-amino-Q	4-chlorobenzaldehyde	2-	**3h**	2	82
9	8-amino-Q	3,4-dimethoxybenzaldehyde	2-	**3*i***	3	70
10	8-amino-Q	3-nitrobenzaldehyde	2-	**3*j***	3	78
11	8-amino-Q	3-bromobenzaldehyde	2-	**3*k***	3	76
12	6-amino-Q	4-chlorobenzaldehyde	2-	**3*l***	2	80
13	6-amino-Q	4-cyanobenzaldehyde	2-	**3*m***	3	82
14	6-amino-Q	4-nitrobenzaldehyde	2-	**3*n***	3	76
15	6-amino-Q	3,4-dimethoxybenzaldehyde	2-	**3*o***	3	68
16	6-amino-Q	2-nitrobenzaldehyde	2-	**3*p***	3	70
17	8-amino-Q	4-chlorobenzaldehyde	1-	**3*q***	3	85
18	8-amino-Q	4-bromobenzaldehyde	1-	**3*r***	3	83
19	5-amino-IQ	4-chlorobenzaldehyde	2-	**3*s***	2	70
20	5-amino-IQ	4-bromobenzaldehyde	2-	**3*t***	2	72
21	3-amino-Q	Pyridine-4-aldehyde	2-	**3*u***	3	74
22	8-amino-Q	Pyridine-4-aldehyde	2-	**3*v***	3	71

The main advantages of this procedure are the eco-friendly methodology, and simplicity in work-up and purification processes. The crude reaction product was diluted with ethyl acetate (5 mL) and washed with 2 mL water for dissolution of the ionic liquid. The aqueous filtrate containing the basic ionic liquid was subjected to rotary evaporation at 100 ºC under reduced pressure for 1h to afford the recovered ionic liquid (~1g) to be reused several times (Table 5). The organic layer after removal of the solvent could be directly crystallized out from ethyl acetate-petroleum without the need for column chromatography. All the synthesized compounds were previously unknown as this is the first report of synthesis of (quinolinyl- and isoquinolinyl-amino)- alkyl naphthols. Satisfactory spectral data were obtained for all the prepared compounds. The final structure was confirmed by an X-ray structural analysis of a single crystal of the product 1-[(4a-bromophenyl)-(quinoline-8'-ylamino)-methyl]-naphthalene-2-ol (Table 3, entry 1). The X-ray crystal structure (Figure II) shows the presence of two hydrogen bonds in the system; one between the N- of quinoline and amine NH and another between the β-naphthol- OH and amine- N. Hence, this could be called a *pseudo spiro* system containing a nitrogen atom.

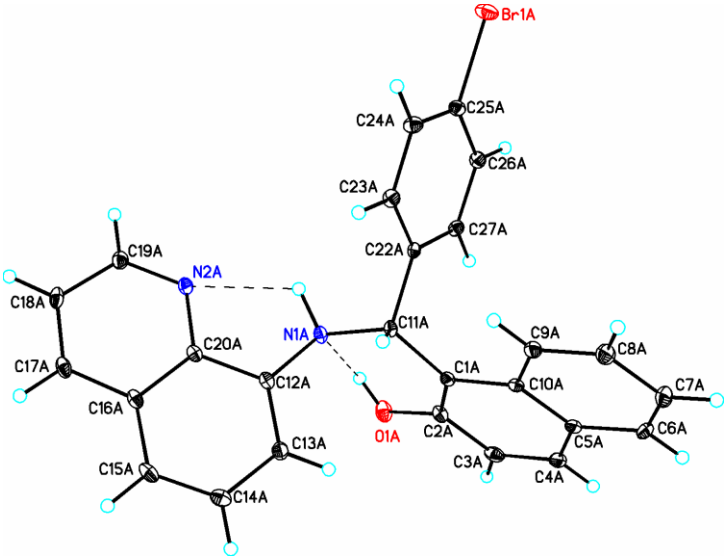
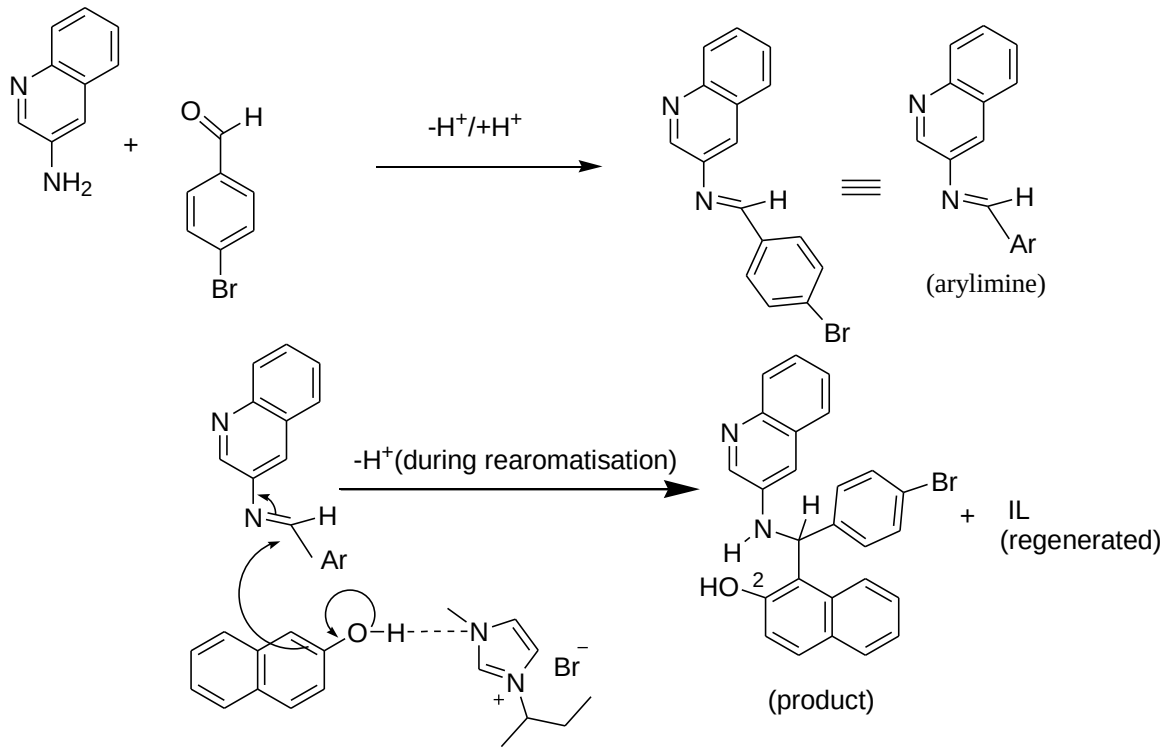


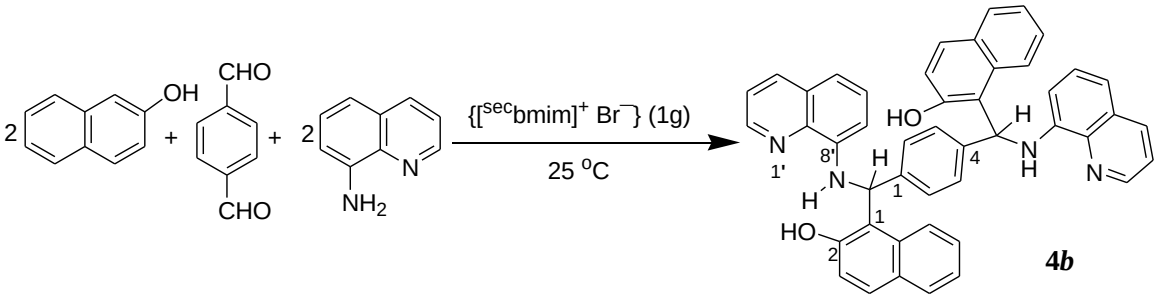
Figure 2. X-ray structural analysis of a single crystal of 1-[(4-Bromophenyl)-(quinolin-8-ylamino)-methyl]-naphthalene-2-ol (Table 3, entry 1) showing the crystallographic numbering (CCDC 760647).

A mechanistic rationale exhibiting the probable sequence of events is given in Scheme 2. Initially, the formation of the arylimine takes place which then condenses at the C_1-carbon of β-naphthol by its nucleophilic attack. The nucleophilicity of β-naphthol increases in the presence of the IL. The isolation of the following imine after 30 minutes of the reaction proves the mechanism shown in Scheme 3. Moreover, this isolated imine, on reaction with β-naphthol in the presence of the IL produces the desired product in excellent yield which further justifies the given mechanism. The spectral and analytical data for the isolated imine is given in the Supplementary Material.



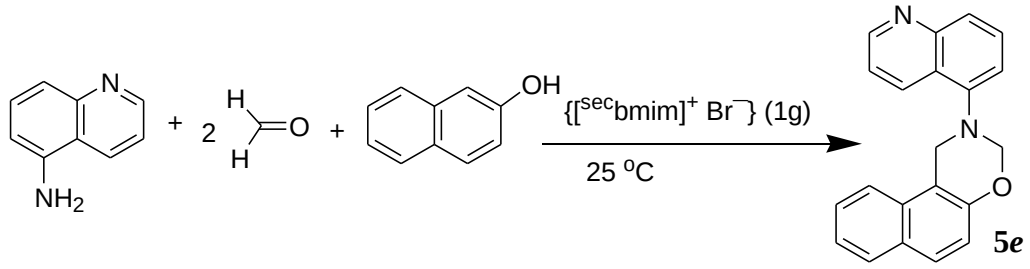
Scheme 3. Probable mechanism of (quinolinyl- amino) alkyl- naphthol formation with the ionic liquid {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^+$ Br$^-$}.

After obtaining satisfactory results for the formation of (quinolinyl- and isoquinolinyl-amino) alkyl naphthol formation, we extended our multi- component methodology in the IL (1g) towards the synthesis of the corresponding bis- analogs (Scheme 4). The products were obtained in good to excellent yields as shown in Table 3 mostly as a single diastereoisomer and in only one case (entry 1) as a diastereoisomeric mixture (dr = 84 : 16 , by crude ^{1}H NMR spectrum).



Scheme 4. Synthesis of bis-(quinolinylamino) alkyl naphthol with the IL {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^+$ Br$^-$} at 25 ºC.

With the great success of the above reactions using the ionic liquid {[^{sec}bmim]$^+$ Br$^-$}, we next thought of looking at the reaction product by using formaldehyde instead of aromatic aldehydes employing the same IL catalyst and we found that instead of (quinolinyl- and isoquinolinyl-amino) alkyl-naphthols, amino-alkylation followed by cyclization took place to yield naphthoxazines in excellent yields (Scheme 5).



Scheme 5. Synthesis of a naphthoxazine with the ionic liquid {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^+$ Br$^-$} at 25 ºC.

The 1,3-oxazines are very important in biological systems because of their potential as antibiotics,[9-12] analgesics,[13,14] antitumour[15-17] agents, and anticonvulsants.[18] This moiety has generated great interest as anti-psychotic agents and as probable effectors for dopamine and serotonin receptors.[19] Moreover, benzo- 1,3-oxazines are biologically active as anti-malarial,[20] anti-anginal,[21] anti-hypertensive[22] and potent anti-rheumatic[23] agents. Keeping in mind such high importance of these 1,3-oxazines, a number of naphtho-1, 3-oxazines were synthesized and the results are depicted in Table 4.

Table 4. Synthesis of bis- analogs of (quinolinyl- amino) alkyl naphthols with the IL {[(secondary butyl) methyl] imidazolium bromide} {[^{sec}bmim]$^+$ Br$^-$} at 25 ºC

Entry	Starting materials			Products (**4*a*-4*d***)	Time(h)	Yield (%) isolated
	Amines (Q=quinoline)	aldehyde	naphthols			
1	6-amino-Q	Benzene-1,4-dialdehyde	2-	**4*a***	6	80
2	8-amino-Q	Benzene-1,4-dialdehyde	2-	**4*b***	5	82
3	8-amino-Q	Benzene-1,4-dialdehyde	1-	**4*c***	5	78
4	3-amino-Q	Benzene-1,4-dialdehyde	2-	**4*d***	6	84

Table 5. Synthesis of naphthoxazines with the ionic liquid {[^{sec}bmim]$^+$ Br$^-$} (1g) at 25 ºC

Entry	Starting materials			Products (**5*a*-5*g***)	Time(h)	Yield (%) isolated
	Amines (Q=quinoline: IQ=isoquinoline)	aldehyde	Naphthols (2- or 1-)			
1	3-amino-Q	formaldehyde	2-	**5*a***	3	85
2	3-amino-Q	formaldehyde	1-	**5*b***	3	82
3	6-amino-Q	formaldehyde	2-	**5*c***	3	78
4	6-amino-Q	formaldehyde	1-	**5*d***	3	80
5	5-amino-Q	formaldehyde	2-	**5*e***	3	82
6	5-amino-Q	formaldehyde	1-	**5*f***	3	80
7	5-amino-IQ	formaldehyde	2-	**5*g***	3	78

The probable mechanism of naphthoxazine formation goes in the same fashion as shown in Scheme 3. The nucleophilic attack from the C_1-position of β-naphthol towards the initially formed formaldimine takes place to produce the quinolinyl-amino alkyl naphthol. Further attack by the amine lone pair to formaldehyde followed by elimination of water generates the final naphthoxazine. With aromatic aldehydes, the reaction stops at the quinolinyl- / isoquinolinyl-amino alkyl naphthol formation stage and further attack by the nitrogen lone pair onto the aldehydic carbonyl carbon does not take place. The increased reactivity of formaldehyde is responsible for the last step of amino-alkylation followed by cyclization to naphthoxazines. The most important aspect of this methodology is its very mild reaction conditions being carried out at room temperature. Also, the ionic liquid is the specific catalyst for this reaction yielding products in excellent yields. The ionic liquid could be recovered from the reaction medium in exactly the same fashion as that for the amino- alkyl naphthols. All the naphthoxazines showed satisfactory spectral data (Supplementary Section).The final structure of the naphthoxazines was confirmed by the X-ray crystallography of a single crystal of product **5g** (Table 4, entry 7) and is given below in Figure III.

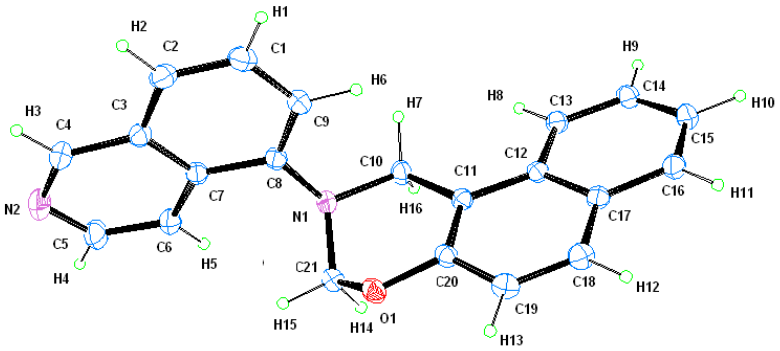
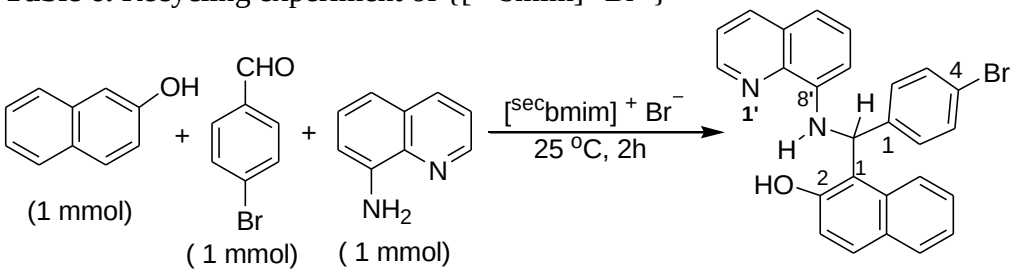


Figure 3. Ortep plot of a single crystal of the naphthoxazine **5g** (Table 5, entry 7) (CCDC 771990) showing the crystallographic numbering.

Recycling of {[^{sec}bmim]$^{+}$ Br^{-}}. A series of catalyst cycles were run to investigate the consistency of the catalytic activity. In each cycle, the catalyst was separated and then used for the next experiment directly and the results are listed in Table 6. The data showed that the IL could be reusable for at least six times with slight decrease in the yield of the product. To compensate the loss of IL during washing, 0.5 mg of IL was added after six runs.

Table 6. Recycling experiment of {[^{sec}bmim]$^{+}$ Br^{-}}



Cycles	1	2	3	4	5	6
Yield (%) (isolated)	82	82	82	80	80	80

Conclusions

We have developed an atom-efficient, high-yielding novel multi-component protocol for the synthesis of quinolinyl- / isoquinolinyl- amino alkyl naphthols, their corresponding bis- analogs and naphthoxazines with the ionic liquid {[^{sec}bmim]$^{+}$ Br^{-}}. The reaction takes place simply by mixing the ingredients in the presence of the IL and stirring at 25 ºC for the specified time. The excellent yields, mild reaction conditions, very easy purification processes without the need for column chromatography and recyclability of the catalyst makes this methodology highly attractive towards the synthesis of the amino- alkyl naphthols and naphthoxazines in both academia and industry.

Experimental Section

General. Ethanol, ethyl acetate, methanol and petroleum ether (60-80 ºC) were distilled before use. All the chemicals were purchased from Aldrich Chemical Company and Spectrochem, Pvt. Ltd. (Mumbai, India). Silica Gel G with binder from Spectrochem, Pvt. Ltd. Mumbai, India, was used for thin layer chromatography. ^{1}H and ^{13}C NMR spectra were obtained on Bruker 300 MHz instrument at 300 and 75 MHz respectively. $CDCl_3$ and DMSO-d_6 were purchased from Aldrich Chemical Company. Melting points were determined on an electrical melting point apparatus with an open capillary. IR spectra were recorded on a Perkin Elmer Spectrophotometer RX / FT-

IR system. The C-H-N-analyses were carried out on a 2400 Series II CHNS Analyzer, Perkin Elmer USA, while the HRMS data were recorded on a Qtof Micro YA 263 mass instrument.

Preparation of the new ionic liquid: {[^{sec}bmim]$^{+}$Br^{-}}[(secondary butyl)-3-methyl] imidazolium bromide)

In a 50 ml round bottomed flask fitted with a reflux condenser and a magnetic bar inside 2.46 gm (30 mmol) of 1-methylimidazole and 4.11 (30 mmol) gm of 2-bromobutane were added. To the solution, 10 ml of anhydrous toluene was added as a solvent. The resulting mixture was then refluxed for 18 hours on a magnetic stirrer. After the completion of the reaction, toluene was pumped out by rotary evaporation under reduced pressure. The product was obtained as a colorless viscous liquid. The characterization data of the ionic liquid is given below.

Secondary- butyl-3-methylimidazolium bromide, {[^{sec}bmim]$^{+}$ Br^{-}}:IR (neat): 3430, 3096, 1633, 1568, 1394, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.02 (s, 1H, C_2-H), 7.57 (d, *J*=1.5 Hz, 1H, C_4-H / C_5-H), 7.43 (d, *J*=1.5Hz, 1H, C_5-H/C_4-H), 4.49-4.42 (m, 1H, $C_{2'}$-H), 3.97 (s, 3H, N-CH_3), 1.80-1.70 (m, 2H, $C_{3'}$-H), 1.43 (d, *J*=6.9 Hz, 3H, $C_{1'}$-H), 0.73(t, *J*=7.5 Hz, 3H, C_4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9 (C_2), 123.6 (C_4 / C_5), 119.9 (C_5 / C_4), 58.5 (N-CH_3), 36.3 ($C_{2'}$), 29.6 ($C_{3'}$), 20.5 ($C_{1'}$), 9.9 ($C_{4'}$).

General experimental procedure for quinolinyl- / isoquinolinyl- amino-alkyl- naphthol formation

A mixture of quinoline- / isoquinoline- amine (1 mmol), aromatic aldehyde (1 mmol), and the naphthol (1 mmol) was stirred in the presence of ionic liquid (1 g) at room temperature (25 °C) for 2-3 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the crude reaction product was diluted with ethyl acetate (5 mL) and washed with 2 mL water for dissolution of the ionic liquid. The aqueous filtrate containing the ionic liquid was subjected to rotary evaporation at 100 ºC under reduced pressure for 1h to afford the recovered ionic liquid (~1 g) to be reused several times (Table 6). The organic layer after removal of the solvent, could be directly recrystallized from ethyl acetate-petroleum ether (60-80 ºC) to yield the pure products without the need for column chromatography. The spectral and analytical data of one unknown compound is given below. The data for all the other compounds are given in the Supplementary Section.

1-[(4-Bromophenyl)-(quinolin-8′-ylamino)-methyl]-naphthalene-2-ol (3a). (Table 3, entry 1): The titled compound was obtained as a white solid (387 mg, 85 %). Anal. Found: C: 68.79; H, 4.17; N, 6.11. Calcd. for $C_{26}H_{19}BrN_2O$, C: 68.58, H: 4.21, Br: 17.55, N: 6.15, O: 3.51 %. R_f (20% EtOAc / petroleum): 0.53. Mp: 158-160 ºC (EtOAc). ν_{max} (KBr): 3310, 3028, 2931, 1615, 1589, 1505, 1469, 1408, 1374, 1319, 1268, 1231, 1157 and 1102 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.31 (s, 1H, O-H), 8.30 (s, 1H, N-H), 8.69 (d, ^{3}J =3.0 Hz, 1H, $C_{2'}$-H), 8.18 (dd, ^{3}J =8.5 Hz and ^{4}J = 1.5 Hz, 1H, $C_{4'}$-H), 7.81-7.73 (m, 3H, C_4-H, C_5-H and C_8-H), 7.48-7.24 (m, 8H, C_{2a}-H, C_{3a}-H, C_{5a}-H, C_{6a}-H, C_6-H, C_7-H, C_3-H and $C_{6'}$-H), 7.19 (d, ^{3}J =9.0 Hz, 1H, C_3-H), 7.06 (d, ^{3}J =7.8 Hz, 1H, $C_{5'}$-H), 6.84 (s, 1H, C-H), 6.76 (d, ^{3}J =8.4 Hz, 1H, $C_{7'}$-H); ^{13}C NMR (75

MHz, DMSO-d_6) and DEPT-135 δc: 152.9 (C_2), 147.4 ($C_{2'}$), 143.8 ($C_{8'}$), 142.5 (C_{1a}), 137.6 ($C_{9'}$ and C_9), 136.2 ($C_{4'}$), 131.1 (C_{3a} and C_{5a}), 129.6 (C_4), 128.9 (C_5), 128.7 (C_{2a} and C_{6a}), 128.4 ($C_{10'}$ and C_{10}), 127.8 ($C_{6'}$ and C_7), 123.0 (C_6), 122.8 ($C_{3'}$), 121.9 (C_8), 119.4 (C_{4a}), 119.4 (C_1), 118.6 (C_3), 114.1 ($C_{5'}$), 105.3 ($C_{7'}$), 52.1 (C-H). HRMS (M^+) 454.0686; $C_{26}H_{19}ClN_2O$ requires 454.0681.

General experimental procedure for *bis*-(quinolinyl- / isoquinolinyl amino-) alkyl naphthol formation

A solution of the quinoline amine (2 mmol), the naphthol (2 mmol) and benzene-1,4-dicarboxaldehyde (1 mmol) was stirred in the presence of ionic liquid (1 g) at room temperature (25 °C) for 5-6 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the crude reaction product was diluted with ethyl acetate (7 mL) and washed with 2 mL water for dissolution of the ionic liquid. The aqueous filtrate containing the ionic liquid was subjected to rotary evaporation at 100 ºC under reduced pressure for 1h to afford the recovered ionic liquid (~1 g) to be reused several times (Table 6). The organic layer after removal of the solvent, could be directly recrystallized from ethyl acetate-petroleum ether (60-80 ºC) to yield the pure products without the need for column chromatography. The spectral and analytical data of one unknown compound is given below. The data for all the other compounds are given in the Supplementary Section.

1,4-Bis-[1-{(quinolin-6′-ylamino)-methyl}-2-hydroxy naphthyl]-benzene (4a). (Table 4, entry 1). The title compound was obtained as a yellowish solid (540 mg, 80 %). Found: C, 81.98; H, 5.18; N, 8.21. $C_{46}H_{34}N_4O_2$ requires C: 81.88, H: 5.08, N: 8.30, O: 4.74 %. R_f (80 % EtOAc / petroleum): 0.34. Mp: 158-160ºC (EtOAc). ν_{max} (KBr): 3370, 3050, 1622, 1510, 1440, 1376, 1314, 1239, 1164 and 1057 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_H 10.20 (s, 1H, O-H), 8.40 (s, 1H, $C_{2'}$-H), 8.10 (s, 1H, $C_{4'}$-H), 7.79-7.20 (m, 11H, C_{2a}-H, C_{6a}-H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, $C_{3'}$-H, $C_{5'}$-H, $C_{7'}$-H and C-H), 6.93 (s, 1H, C_3-H), 6.82-6.60 (m, 2H, N-H and $C_{8'}$-H); ^{13}C NMR (75 MHz, DMSO-d_6) and DEPT-135 δc 153.0 (C_2), 146.6 ($C_{6'}$), 145.3 ($C_{2'}$), 142.4 ($C_{9'}$), 140.5 (C_{1a}), 133.2 ($C_{4'}$), 132.3 (C_9), 129.6 ($C_{8'}$), 129.7 ($C_{10'}$), 129.3 (C_4), 128.9 (C_{10}), 128.6 (C_5), 126.7 (C_{2a} and C_{6a}), 126.0 (C_7), 122.4 (C_6 and C_8), 122.0 ($C_{3'}$), 121.3 ($C_{7'}$), 118.9 (C_1), 118.3 (C_3), 102.6 ($C_{5'}$), 52.9 (C-H); HRMS (M^+) 674.2685; $C_{46}H_{34}N_4O_2$ requires 674.2682.

General experimental procedure for naphthoxazine formation

To a mixture of quinoline- / isoquinoline- amine (1 mmol) and naphthol (1 mmol) in IL (1 g), aqueous formaldehyde (2 mmol) (37-41 % w/v) was added dropwise. The resulting mixture was then stirred for 3 hours at room temperature (25 °C). After the completion of the reaction (monitored by TLC), the crude reaction product was diluted with ethyl acetate (5 mL) and washed with 2 mL water for dissolution of the ionic liquid. The aqueous filtrate containing the ionic liquid was subjected to rotary evaporation at 100 ºC under reduced pressure for 1h to afford the recovered ionic liquid (~1 g) to be reused several times (Table 6). The organic layer after removal of the solvent, could be directly recrystallized from ethyl acetate-petroleum ether (60-

80ºC) to yield the pure products without the need for column chromatography. The spectral and analytical data of one unknown compound is given below. The data for all the other compounds are given in the Supplementary Material.

2-Quinolin-3-yl-2,3-dihydro-1*H*-naphtho-[1,2-e][1,3]- oxazine (5a). (Table 5, entry 1): The titled compound was obtained as an off-white solid (265 mg, 85 %). Found: C, 80.91; H, 5.09; N, 8.89 %. $C_{21}H_{16}N_2O$ requires C: 80.75, H: 5.16, N: 8.97, O: 5.12 %]. R_f (30% EtOAc / petroleum): 0.53. Mp: 140-142 ºC (MeOH); ν_{max} (KBr) : 3046, 1597, 1467, 1426, 1392, 1224, 1145, 951, 810 and 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.93 (d, ^3J =2.4 Hz, 1H, $C_{2'}$-H), 7.98 (d, ^3J =8.1 Hz, 1H, C_8-H), 7.74 (d, ^3J =7.8 Hz, 1H, $C_{8'}$-H), 7.68-7.54 (m, 4H,), 7.49 (t, ^3J =7.5 Hz, 2H, C_6-H and C_7-H), 7.38 (t, ^3J =9.0 Hz, 2H, $C_{6'}$-H and $C_{7'}$-H), 7.03 (d, ^3J =8.7 Hz, 1H, C_3-H), 5.44 (s, 2H, N-C$\underline{H}_2$-O), 4.98 (s, 2H, N-C$\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) and DEPT-135 C- NMR 151.9 (C_2), 145.7 ($C_{2'}$), 143.8 ($C_{3'}$), 142.0 ($C_{9'}$**),** 131.0 (C_9), 129.0 ($C_{10'}$**),** 128.8 (C_4), 128.7 (C_5), 128.5 ($C_{8'}$), 128.3 (C_{10}), 127.2 ($C_{6'}$), 126.9 ($C_{7'}$), 126.8 ($C_{5'}$), 126.77 (C_7), 123.8 (C_6), 120.7 ($C_{4'}$), 120.4 (C_8), 118.5 (C_3), 111.7 (C_1), 79.0 (N-$\underline{C}H_2$-O), 48.2 (N- $\underline{C}H_2$). HRMS (M^+): 312.1260; $C_{21}H_{16}N_2O$ requires 312.1263.

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