Heterocyclic compounds with quinoline subunits are among several compounds of interest due to their pharmacological properties as evidenced by the occurrence in alkaloids molecules. So far 15 approved anticancer drugs include the quinoline core. The triple bond functional group has a special place in the synthesis of different heterocyclic compounds. Extensive efforts have been devoted to develop synthetic routes to incorporate triple bond transformations into complex heterocyclic compounds. Over the past years, metal-catalyzed Sonogashira coupling reaction of terminal alkynes, which is a synthetic tool for C-C bond formation, has been widely studied. Several reports starting from alkynylation of 2-chloroquinolines resulted in poly-heterocycles such as: benzo[b]pyrazolo[5,1-f][1,6]naphthyridines, 3-phenylbenzo[b][1,6]naphthyridines, pyranoquinolinones, benzo[b]oxazolo[2,3-f][1,6]naphthyridine, 1,2-dihydrobenzo[1,6]naphthyridines, and quino[2,3-b]carbazoles.

In this context, Gao groups have developed a practical strategy for the construction of natural products containing indolinizone or quinolinizone scaffolds and their analogs, which proceeded via a cascade exo hydroamination followed by spontaneous lactamization. They applied this method to the synthesis of camptothecin, 22-hydroxyacuminatine, oxypalmatine, norketoyobyrine, naucleficine and nauclefine. Verma and coworkers have established an iodine-catalyzed reaction regarding to the synthesize of 4-iodo-pyrano[4,3-b]quinolines and ortho-alkynyl esters from ortho-alkynyl aldehydes. Interestingly, Samala et al. have disclosed that four, five and six membered cyclic amino acids reacted with 2-alkynyl aryl aldehyde to yield the corresponding 1H-benzo[g]indoles, tetrahydrobenzo[h]quinolines, and naphtho[1,2-b]azepines. In contrast condensation of 2-alkynyl pyridine/quinoline aldehydes with proline furnished the corresponding hexahydropyrrolo[2,1-b]oxazoles.

Choosing a versatile starting material can provide access for the synthesis of various useful molecules. During the past two decades 2-chloroquinoline-3-carboxaldehydes have gained more...
attraction as starting material to synthetic chemists to construct the diverse quinoline-based molecules.\textsuperscript{14}

In our further research on quinolines chemistry,\textsuperscript{15} herein we wish to report palladium catalyzed Sonogashira reaction followed by a subsequent dimerization of 2-chloro-3-((chloromethyl)-quinolines 1.

Results and discussion

We prepared 2-chloro-3-((chloromethyl)-quinolines 1 as starting material from acetanilides with different substituents as outlined in Scheme 1.\textsuperscript{16}

A series of experiments were performed with 2-chloro-3-((chloromethyl)-8-methylquinoline 1a and phenylacetylene 2a as the model reaction. Pleasingly, this reaction in the presence of PdCl\textsubscript{2}, PPh\textsubscript{3} and TEA in toluene, gave 3a instead of the expected simple Sonogashira coupling product 3'a (Scheme 2).

Thus, we chose to optimize the model reactions with different palladium sources, ligands, bases, solvents, and temperatures. The reaction with PdCl\textsubscript{2}, PPh\textsubscript{3}, TEA in CH\textsubscript{3}CN under air atmosphere gave no product but under N\textsubscript{2} atmosphere, even at room temperature, produced 3a in 70% yield (Table 1, entries 1-3). Elevating the temperature to 80°C in CH\textsubscript{3}CN increased the yield to 88% (Table 1, entry 4). Screening of solvents revealed that CH\textsubscript{3}CN is the optimal choice yielding a high yield within a short reaction time (Table 1, entries 5-8). This may be due to the fair interaction of lone pair of nitrogen in acetonitrile with Pd. Using alternative catalytic systems such as: Pd(OAc)\textsubscript{2}, Pd(OAc)\textsubscript{2}/CuI or PdCl\textsubscript{2}/CuI showed no significant difference with PdCl\textsubscript{2} (Table 1, 9-11). Application of P(CycHex)\textsubscript{3}, TMEDA, or L-proline as ligands considerably diminished the yields of the desired product 3a (Table 1, entries 12-14). TEA as organic base was more efficient than the inorganic bases evaluated (Table 1, entries 15-18).

Overall, the best yield was achieved by performing the reaction with PdCl\textsubscript{2}, PPh\textsubscript{3}, and Et\textsubscript{3}N in CH\textsubscript{3}CN at 80°C under nitrogen atmosphere for 3 h (Table 1, entry 4). Our next task was to

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Scheme 1. Synthesis of starting materials 2-chloro-3-((chloromethyl)-quinolines 1.

Scheme 2. Sonogashira coupling of 1a and 2a and then dimerization.
evaluate the scope of this optimized methodology for a range of 2-chloro-3-(chloromethyl)quino-
lines 1 and terminal acetylenes (Table 2). Quinoline 1 containing methyl, methoxy, chlorine and 
bromine substituents reacted properly with phenylacetylene to furnish corresponding dimers 3a-f 
(Table 2, entries 1-6). Furthermore, aliphatic acetylenes were also well tolerated in the synthesis 
of corresponding salts 3g-l in good to high yields (Table 2, entries 7-12). The scope of the

### Table 1. Optimization of the reaction condition.

| Entry | Solvent | Base   | Catalyst/ Ligand | Time(h) | Yield a,b (%) |
|-------|---------|--------|------------------|---------|---------------|
| 1     | CH3CN   | TEA    | PdCl2            | 24c, d  | –             |
| 2     | CH3CN   | TEA    | PdCl2/ PPh3      | 24c, d  | –             |
| 3     | CH3CN   | TEA    | PdCl2/ PPh3      | 24c, d  | 70c           |
| 4     | CH3CN   | TEA    | PdCl2/ PPh3      | 3       | 88            |
| 5     | DMF     | TEA    | PdCl2/ PPh3      | 6       | 70            |
| 6     | DMSO    | TEA    | PdCl2/ PPh3      | 9       | 66            |
| 7     | Toluene | TEA    | PdCl2/ PPh3      | 12      | 30            |
| 8     | CH3Cl2  | TEA    | PdCl2/ PPh3      | 15      | 30            |
| 9     | CH3CN   | TEA    | PdCl2/ Cu/ PPh3  | 8       | 35            |
| 10    | CH3CN   | TEA    | Pd(OAc)2/ PPh3   | 5       | 76            |
| 11    | CH3CN   | TEA    | Pd(OAc)2/ Cu/ PPh3 | 8  | 65            |
| 12    | CH3CN   | TEA    | PdCl2/ P(Cy)3    | 8       | 27            |
| 13    | CH3CN   | TEA    | PdCl2/ TMEDA     | 10      | 20            |
| 14    | CH3CN   | TEA    | PdCl2/ L-proline | 10      | 30            |
| 15    | CH3CN   | K2CO3  | PdCl2/ PPh3      | 10      | 50            |
| 16    | CH3CN   | Cs2CO3 | PdCl2/ PPh3      | 9       | 45            |
| 17    | CH3CN   | t-BuOK | PdCl2/ PPh3      | 24      | 23            |
| 18    | CH3CN   | t-BuONa | PdCl2/ PPh3     | 24      | 27            |

aAll reactions were carried out using 1a (1 mmol), 2a (1.2 mmol), catalyst (4 mol%), ligand (8 mol%), base (2 mmol), and solvent (2.0 mL) and stirred under N2 atm., at 80 °C unless otherwise noted.
bIsolated yields.
cAt room temperature.
dAir atmosphere.

### Table 2. Synthesis of various derivatives of dimer 3a-3n.

| Entry | R1   | R2 | R3       | Product | Yield a (%) |
|-------|------|----|----------|---------|-------------|
| 1     | H    | Me | Ph       | 3a      | 88          |
| 2     | Me   | H  | Ph       | 3b      | 86          |
| 3     | Cl   | H  | Ph       | 3c      | 75          |
| 4     | H    | H  | Ph       | 3d      | 85          |
| 5     | OMe  | H  | Ph       | 3e      | 83          |
| 6     | Br   | H  | Ph       | 3f      | 80          |
| 7     | Me   | H  | PhOCH2-  | 3g      | 78          |
| 8     | H    | H  | PhOCH2-  | 3h      | 84          |
| 9     | H    | Me | PhOCH2-  | 3i      | 85          |
| 10    | H    | H  | 4-Me-PHOCH2- | 3j | 79          |
| 11    | Me   | H  | 4-Me-PHOCH2- | 3k | 85          |
| 12    | H    | H  | 4-Br-PHOCH2- | 3l | 86          |
| 13    | H    | H  | 3m, 87%  |         |             |
| 14    | Me   | H  | 3n, 81%  |         |             |

[Diagram of dimer 3a-3n]
reaction was also expanded to include 2-chloro-3-(chloromethyl)benzo[h]quinoline as a coupling partner; this produced compounds 3m and 3n in 81%–87% yields respectively with phenylacetylene and propargyl phenoxide (Table 2).

Investigating the conversion of the produced salts 3 into more complicated quinoline derivatives was performed by the reacting 3b with phenol and thiophenol under basic conditions which afforded the corresponding ether 4a and thioether 4b (Scheme 3).

The proposed mechanism for the reaction is shown in Scheme 4. The general mechanism starts from the in-situ generation of the Pd(0) complex with PPh₃, followed by the oxidative addition of the Ar-Cl bond of the quinoline heterocycle to form I. Addition of terminal acetylene to intermediate I assisted by Et₃N generated the complex II which, by reductive elimination, led to compound III. Finally, dimerization of III via nucleophilic substitution of nitrogen of one molecule to Csp³-Cl of another one formed the salt 3 (Scheme 4).

With regards to investigating the mechanism described above, reactions in Scheme 5 were performed. Treatment of 2-chloro-3-chloromethylquinoline with Et₃N in refluxing CH₂CN did not yield product even after 24 h (Scheme 5). This may be due to the existence of an electron withdrawing Cl in the 2 position of quinoline which reduced activation of nitrogen toward nucleophilic substitution. In addition, 3-(chloromethyl)-2-(phenylethynyl)quinoline (B), which has alkyne as electron releasing group, in the presence of Et₃N tended to dimerize to 4d. Notably increasing the temperature to reflux converted B to unidentified polymer.
Conclusions

In summary, because of the importance of quinoline core and the ability of 2-chloro-3-(chloro-methyl)quinolines to expand into more complex compounds, the primary materials of 1 were subject of reaction with terminal alkynes in a Sonogashira reaction. Surprisingly, in addition to the Sonogashira coupling, the corresponding adducts were dimerized in-situ to afford novel attractive molecules 3. Interestingly, the product 3b reacted efficiently with phenoxide and thio-phenoxide to yield the corresponding ether and thioether respectively.

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