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Synthesis of novel 2-alkyl triazole-3-alkyl substituted quinoline derivatives and their cytotoxic activity

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ABSTRACT

The propargyl alcohol on reaction with alkylazides under Sharpless conditions through click chemistry concept gave exclusively 1,4-disubstituted triazoles **2**. The compounds **2** were oxidized to aldehydes **3** followed by reaction with aniline resulted Schiff's bases **4**. The compounds **4** was further reacted with various aldehydes having α-hydrogen using molecular iodine as a catalyst and obtained 2-alkyl triazole-3-alkyl substituted quinoline derivatives **5**. All the final compounds were screened against four human cancer cell lines (THP-1, Colo205, U937 & HeLa) and promising compounds have been identified.

Quinoline nucleus present in many biologically active molecules and their derivatives play an important role as versatile building blocks for the synthesis of complex natural products.[1–5] Quinoline based compounds with specific substituent at an appropriate position known to have wide range of activity. In particular, 2-aryl quinolines were reported as antimalarial and antitumor agents.[6] Recently, 6-fluoroquinolones are considered as potential antibacterial agents and some of the promising fluoro quinolones are namely Norfloxacine, Ciprofloxacine, Ofloxacine and so on. The classic methods for the synthesis of quinolines include Beller et al.,[7] Charmantray et al.,[8] Demeunynck et al.,[9] Igarashi et al.[10] and so on. Recent efforts on synthesis of quinoline derivatives is mainly by intermolecular [4+2] cycloaddition,[11] Baylis–Hillman approach,[12] C–C coupling[13–17] and use of iodine as a catalyst.[18] Alternatively, the 1,2,3-triazoles due to their unique chemical and structural properties, received much attention over the past decades and found wide application in medicinal chemistry.[19–23] In order to construct 1,2,3-triazole ring system, several synthetic methods have been developed.[24] Recently Fokin and Sharpless reported Cu(I) catalyzed regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles.[25,26] However, synthesis of 2,3-disubstituted quinoline derivatives were not been extensively studied.

Based on the importance of both the scaffolds that is, Quinoline, 1,2,3-triazole and in continuation of our efforts on synthesis of potential molecules,[27–29] we have developed an efficient method for the synthesis of novel 2-alkyl triazole-3-alkyl substituted quinoline derivatives using molecular iodine as a catalyst and reporting here for the first time.

The propargyl alcohol was reacted with alkyl azide **1** in *t*-butanol in the presence of $Cu(OAc)_2$ under Sharpless conditions and obtained exclusively (1-alkyl substituted-1*H*-1,2,3-triazol-4yl) methanol **2**. The alcohol **2** was further oxidized into an aldehyde **3** by using Jones reagent followed by the reaction of aniline in acetonitrile at room temparature furnished Schiff's base **4**. Compounds **4** were further reacted with aliphatic aldehydes in the presence of I_2 in THF obtained 2-alkyl triazole-3-alkyl substituted quinoline derivatives **5** in high yields. The sequence of reaction is mainly the iodine complexes with imine followed by attack of active methylene of enolised aldehyde and cyclised to give quinoline derivatives. All the products **5** were screened for cytotoxic activity and promising compounds have been identified. The details of reactions outlined in Scheme 1 and products were tabulated in Table 1. The 2-alkyl triazole substituted quinoline derivatives **5a–o** were tested for in vitro cytotoxic activity against THP-1, Colo205, U937 & HeLa human cancer cell lines by MTT assay method.[30] IC_{50} values of the test compounds for 24 h on THP-1, Colo205, U937 and HeLa cell lines was calculated and presented in Table 2. It is evident from the results that, most of the compounds have shown significant decrease in cell viability in all the test cell lines on concentration dependent manner. Compounds activity is more specific to U937 cell lines compared to other three cell lines (THP-1, Colo205 and HeLa). Among the derivatives, compound **5b** and **5e** exhibited significant activity on U937 cells at IC_{50} <20 μg/ml and other derivatives also

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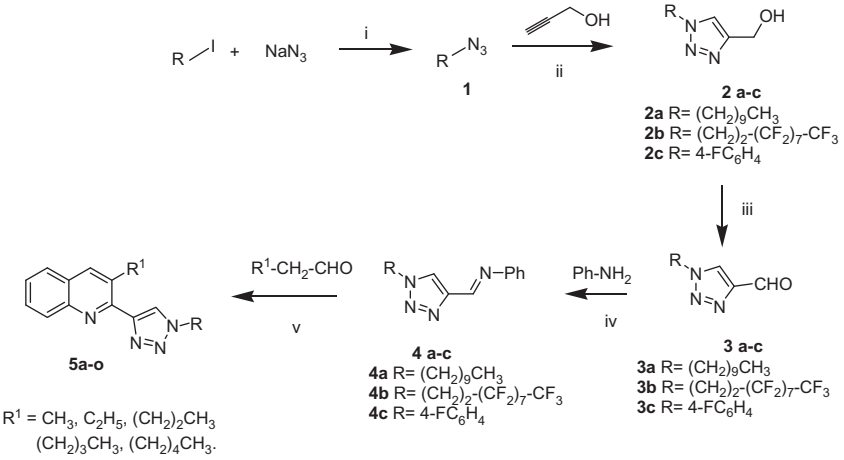

Scheme 1. (i) Acetone:water (3:1), reflux, 8 h; (ii) $Cu(OAc)_2$, *t*-BuOH, rt, 18 h; (iii) Jones reagent, acetone, 0 °C, 30 min; (iv) Ph-NH_2, CH_3CN, rt, 6 h; (v) I_2, THF, reflux, 4–5 h.

Table 1
Preparation of compounds **5a–o**

S. No	Compound	R	R^1	Yield (%)	mp (°C)
1	**5a**	$(CH_2)_9CH_3$	CH_3	81	61–62
2	**5b**	$(CH_2)_9CH_3$	C_2H_5	83	67–69
3	**5c**	$(CH_2)_9CH_3$	$(CH_2)_2CH_3$	85	68–70
4	**5d**	$(CH_2)_9CH_3$	$(CH_2)_3CH_3$	86	73–74
5	**5e**	$(CH_2)_9CH_3$	$(CH_2)_4CH_3$	88	78–80
6	**5f**	$(CH_2)_2$-$(CF_2)_7$-CF_3	CH_3	85	108–109
7	**5g**	$(CH_2)_2$-$(CF_2)_7$-CF_3	C_2H_5	86	110–112
8	**5h**	$(CH_2)_2$-$(CF_2)_7$-CF_3	$(CH_2)_2CH_3$	88	118–120
9	**5i**	$(CH_2)_2$-$(CF_2)_7$-CF_3	$(CH_2)_3CH_3$	89	124–126
10	**5j**	$(CH_2)_2$-$(CF_2)_7$-CF_3	$(CH_2)_4CH_3$	90	131–133
11	**5k**	4-FC_6H_4	CH_3	89	96–98
12	**5l**	4-FC_6H_4	C_2H_5	91	106–108
13	**5m**	4-FC_6H_4	$(CH_2)_2CH_3$	92	98–100
14	**5n**	4-FC_6H_4	$(CH_2)_3CH_3$	94	95–97
15	**5o**	4-FC_6H_4	$(CH_2)_4CH_3$	94	106–108

shown good activity on U937 cell line at <70 μg/ml. However, the compounds **5a** & **5i** had shown potent cytotoxicity on two cell lines (colo205 & HeLa) at <50 μg/ml, and **5b** & **5e** on THP-1 and U937 at <90 μg/ml. The compound **5h** showed moderate activity on only one cell line (HeLa). The structure verses activity studies reveal that the increase in aliphatic chain length on C-3 position has no additional advantage in improving the activity, however the increase in length of aliphatic chain on triazole ring found to promote activity.

Compounds **5f–j** having perfluoroalkyl chain on triazole ring do not contribute to improve the activity inspite of increasing the aliphatic chain length on C-3 position which is in consistent with the earlier statement. Based on the relative activity among the cell lines the order of sensitivity is U937 > HeLa > THP-1 > Colo205. Though, these derivatives are comparatively less potent than the commercially available drug molecule, 5-fluorouracil (positive control); nevertheless slight structural modification of these active derivatives may yield as prospective anticancer drugs.

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Table 2
In vitro cytotoxicity of 2-alkyl triazole-3-alkyl substituted quinoline derivatives against THP-1, Colo205, U937 & HeLa human cancer cells by MTT assay

S. No.	Compound	THP-1	Colo205	U937	HeLa
		IC_{50}[a] (μg/ml)			
1	**5a**	—	44.46 ± 3.69	—	28.17 ± 2.91
2	**5b**	34.28 ± 2.61	—	12.72 ± 3.21	—
3	**5c**	—	—	26.57 ± 1.47	—
4	**5d**	—	—	25.24 ± 2.2	—
5	**5e**	87.97 ± 1.29	—	18.19 ± 3.74	—
6	**5f**	—	75.83 ± 2.98	56.57 ± 1.5	—
7	**5g**	—	95.21 ± 4.24	55.93 ± 0.97	—
8	**5h**	—	—	—	37.79 ± 3.12
9	**5i**	—	—	59.11 ± 1.92	32.8 ± 3.19
10	**5j**	—	—	—	—
11	**5k**	—	—	65.58 ± 3.3	—
12	**5l**	—	—	—	—
13	**5m**	—	—	67.43 ± 2.14	—
14	**5n**	78.32 ± 2.52	—	66.16 ± 1.4	—
15	**5o**	—	—	67.49 ± 2.34	—
Control	5-Fluorouracil[b]	0.54 ± 0.13	4.03 ± 0.84	0.87 ± 0.21	1.28 ± 0.73

Exponentially growing cells were treated with different concentrations of 2-alkyl triazole-3-alkyl substituted quinoline derivatives for 24 h and cell growth inhibition was analyzed through MTT assay.

[a] IC_{50} is defined as the concentration, which results in a 50% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis. The values represent the mean ± SE of three individual observations.

[b] 5-Fluorouracil was employed as positive control, — indicates IC_{50} value >100 μg/ml.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.01.021.

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