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Synthesis of novel 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives and their cytotoxic activity

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ABSTRACT

The propargyl alcohol on reaction with aldoxime and NaOCl in DCM gave exclusively (3-arylisoxazol-5-yl) methanol **1**. The compound **1** was oxidized to an aldehyde **2** followed by reaction with aniline resulted in Schiff's base **3**. The compounds **3** were further reacted with various aldehydes having α-hydrogen using molecular iodine as catalyst and which yielded 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives **4**. All the final compounds **4** were screened against four human cancer cell lines (A549, COLO 205, MDA-MB 231 and PC-3) and among these compounds **4n** showed potent cytotoxicity against all the cell lines at IC_{50} values of <12 μM.

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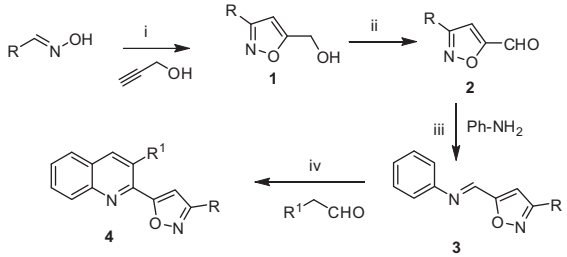
Quinoline and their derivatives, which usually possess diverse biological activities, play an important role as versatile building blocks for the synthesis of natural products and as therapeutic agents.[1] In particular, 2-arylquinolines are biologically active and occur in number of antimalarial[2] and antitumor agents.[3] Therefore, the synthesis of quinolines have attracted much attention in organic synthesis. The classic methods for the synthesis of quinolines include Skraup,[4] Doebner–von Miller,[5] Conrad–Limbach,[6] Combes,[7] Pfitzinger[8] and a number of general synthetic methods have also been reported.[9] However, some of these methods suffer from several disadvantages such as harsh reaction conditions, multi step, a large amount of promoters and long reaction times. Therefore, the development of new synthetic approaches using mild reaction conditions remains an active research area. Alternatively, the isoxazole due to their unique chemical and structural properties, received much attention over the past decade and found wide application in medicinal chemistry.[10–12] In order to construct isoxazole ring system, several synthetic methods have been developed.[13,14] Based on the importance of both the scaffolds that is, quinoline, isoxazole and in continuation of our efforts[15–17] to develop new synthetic routes for promising molecules, herein we report a mild and efficient molecular iodine-catalyzed synthesis of 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives from imines and enolizable aldehydes.

The propargyl alcohol was reacted with aldoxime and NaOCl in DCM at room temperature obtained exclusively (3-aryl isoxazol-5yl) methanol **1**. The methanol **1** was further oxidized to an aldehyde **2** by using Jones reagent at 0 °C and further reacted with aniline in acetonitrile at room temperature furnishing Schiff's base **3**. All the Schiff's bases **3** were further reacted with various aldehydes having α-hydrogen in THF using molecular iodine as a catalyst and obtained 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives **4** in high yield. The sequence of reaction involves imine complexes with iodine followed by attack of active methylene of enolized aldehyde and cyclized to give quinoline derivatives **4**.



Scheme 1. Synthesis of 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives Reagents and conditions: (i) NaOCl, DCM, rt, 8 h. (ii) Jones reagent, acetone, 0 °C, 30 min. (iii) CH_3CN, rt, 6 h. (iv) I_2, THF reflux, 3-4 h.

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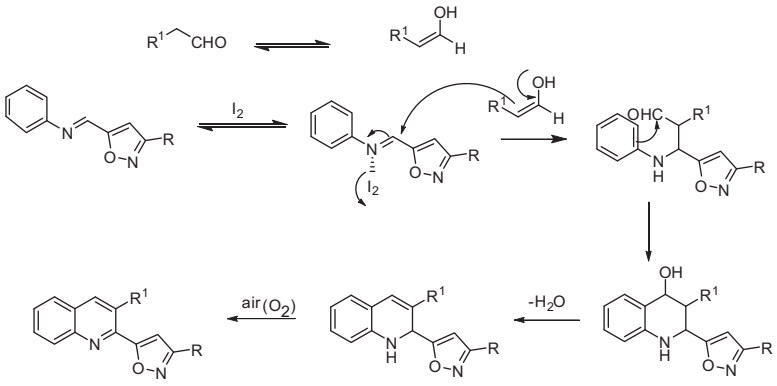

Scheme 2. Mechanism of 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives.

Table 1
Preparation of compounds **3a–d** and **4a–o**

S. No.	Compd	R	R^1	Yield[a] (%)	mp (°C)
1	**3a**	C_6H_5	–	82	112–114
2	**3b**	4-FC_6H_4	–	79	115–117
3	**3c**	4-$CH_3C_6H_4$	–	74	118–120
4	**3d**	4-$CF_3C_6H_4$	–	78	126–128
5	**4a**	C_6H_5	CH_2CH_3	81	72-74
6	**4b**	C_6H_5	$(CH_2)_2CH_3$	78	74–76
7	**4c**	C_6H_5	$(CH_2)_3CH_3$	74	75–76
8	**4d**	C_6H_5	$(CH_2)_4CH_3$	69	78–80
9	**4e**	4-FC_6H_4	CH_2CH_3	76	102–104
10	**4f**	4-FC_6H_4	$(CH_2)_2CH_3$	72	98–100
11	**4g**	4-FC_6H_4	$(CH_2)_3CH_3$	69	106–108
12	**4h**	4-$CH_3C_6H_4$	$(CH_2CH_3$	81	88–90
13	**4i**	4-$CH_3C_6H_4$	$(CH_2)_2CH_3$	79	89–90
14	**4j**	4-$CH_3C_6H_4$	$(CH_2)_3CH_3$	78	87–89
15	**4k**	4-$CH_3C_6H_4$	$(CH_2)_4CH_3$	72	91–93
16	**4l**	4-$CF_3C_6H_4$	CH_2CH_3	73	118–120
17	**4m**	4-$CF_3C_6H_4$	$(CH_2)_2CH_3$	72	122–124
18	**4n**	4-$CF_3C_6H_4$	$(CH_2)_3CH_3$	69	126–127
19	**4o**	4-$CF_3C_6H_4$	$(CH_2)_4CH_3$	64	128–130

[a] Isolated yields

All the products **3** and **4** were screened for cytotoxicity against A549, COLO 205, MDA-MB 231 and PC-3 human cancer cell lines by MTT assay method and compounds which showed promising activity at micro molar concentration have been identified. The details of reactions outlined in Schemes 1 and 2 and products were tabulated in Table 1.

The *N*-((3-arylisoxazol-5-yl)methylene)aniline (**3a–d**) and 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives (**4a–o**) were tested for in vitro cytotoxicity against A549, COLO 205, MDA-MB 231 and PC-3 human cancer cell lines by MTT assay. IC_{50} values of the test compounds for 24 h on A549, COLO 205, MDA-MB 231 and PC-3 cell lines was calculated and presented in Table 2. It is evident from the results that, most of the compounds showed significant decrease in cell viability in all the tested cell lines in a concentration-dependent manner. Compounds **3b**, **3c**, **3d**, **4b**, **4f**, **4g**, **4m**, **4n** and **4o** exhibited significant activity against all the cell lines (A549, COLO 205, MDA-MB 231 and PC-3) at $IC_{50} < 50$ μM. The structure–activity relationship revealed that fluorine or trifluoromethyl group at fourth position of phenyl in isoxazole ring was found to promote the activity while the hydrogen or methyl group had no additional advantage in improving the activity. Among all the derivatives, compound **4n** showed potent cytotoxicity against all the tested cell lines (A549, COLO 205, MDA-MB 231 and PC-3) at $IC_{50} < 12$ μM. Doxorubicin was used as a positive control. Slight structural modification of these active derivatives may yield prospective anticancer drugs.

Table 2
In vitro cytotoxicity of compounds **3a–d** and **4a–o**[a]

S. No.	Compd	[b]IC_{50} values (in μM)			
		A549	COLO205	MDA-MB-231	PC-3
1	**3a**	48.1 ± 0.22	89.1 ± 0.41	–	–
2	**3b**	34.5 ± 0.42	33.1 ± 0.36	41.2 ± 0.09	36.5 ± 0.12
3	**3c**	32.0 ± 0.11	28.9 ± 0.23	29.4 ± 0.22	31.6 ± 0.24
4	**3d**	38.9 ± 0.44	41.3 ± 0.51	37.4 ± 0.08	35.7 ± 0.36
5	**4a**	–	–	–	–
6	**4b**	52.5 ± 0.21	48.9 ± 0.42	47.2 ± 0.12	51.3 ± 0.26
7	**4c**	–	–	–	–
8	**4d**	92.3 ± 0.23	–	–	–
9	**4e**	–	–	–	–
10	**4f**	51.3 ± 0.26	50.3 ± 0.14	48.4 ± 0.36	42.2 ± 0.27
11	**4g**	27.5 ± 0.22	25.3 ± 0.33	24.2 ± 0.44	26.3 ± 0.35
12	**4h**	–	–	–	–
13	**4i**	–	–	–	–
14	**4j**	–	–	–	–
15	**4k**	–	–	–	–
16	**4l**	–	–	–	–
17	**4m**	43.9 ± 0.33	42.2 ± 0.24	36.5 ± 0.28	33.8 ± 0.18
18	**4n**	9.4 ± 0.34	11.9 ± 0.22	10.4 ± 0.11	10.8 ± 0.35
19	**4o**	28.3 ± 0.41	24.5 ± 0.42	22.1 ± 0.12	30.2 ± 0.17
20	Dox[c]	0.8 ± 0.22	0.7 ± 0.42	0.8 ± 0.44	0.6 ± 0.28

[a] Exponentially growing cells were treated with different concentrations of *N*-((3-arylisoxazol-5-yl)methylene)aniline derivatives **3a–d** and 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives **4a–o** for 24 h and cell growth inhibition was analyzed through MTT assay[18].

[b] 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. The values represent the mean ± SE of three individual observations.

[c] Dox—Doxorubicin was employed as positive control, – indicates IC_{50} value >100 μM.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.01.038.

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