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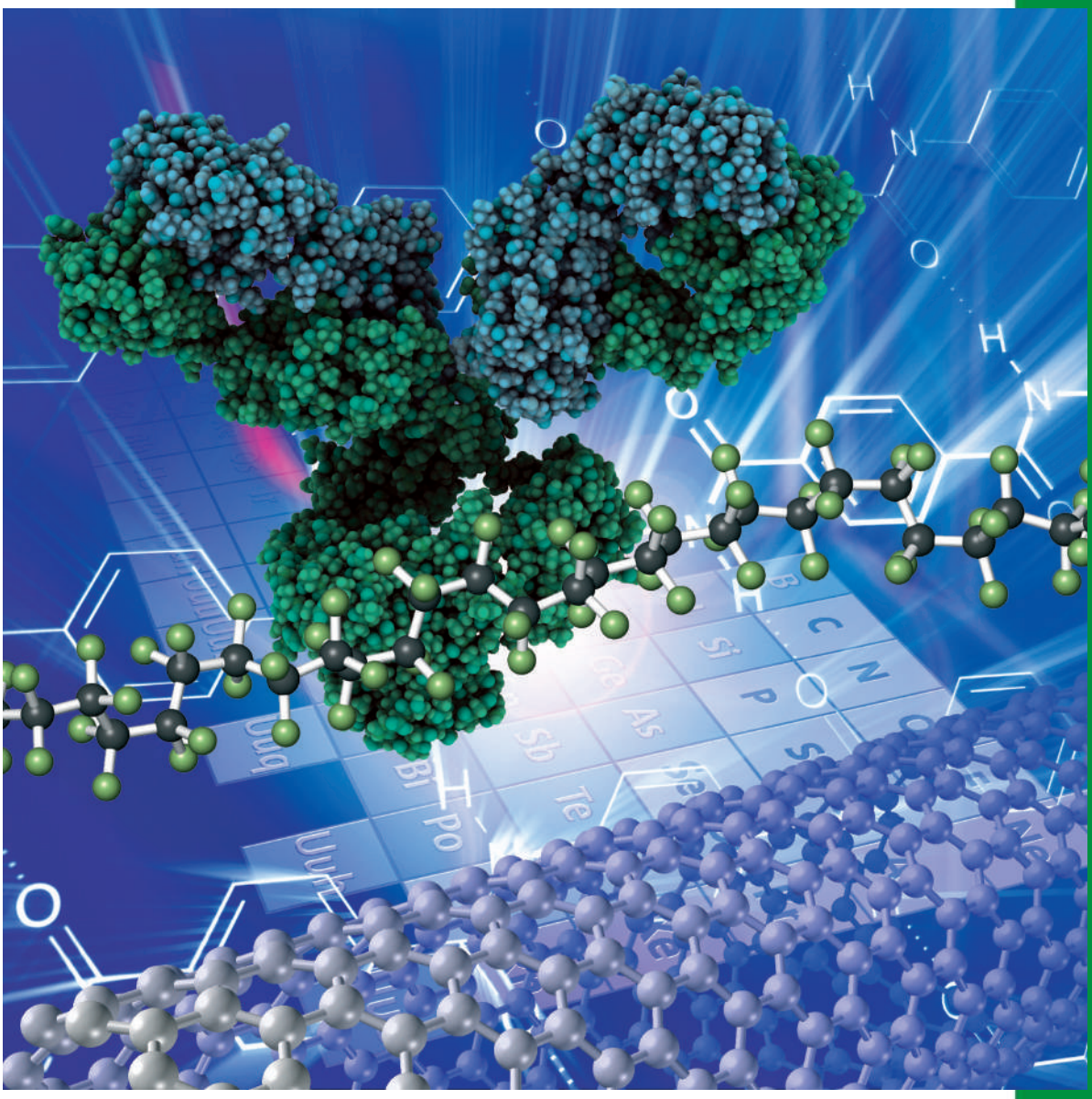

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Chemistry SELECT Full Papers

Medicinal Chemistry & Drug Discovery

"Quinoline Consists of 1*H*-1,2,3-Triazole Hybrids: Design, Synthesis and Anticancer Evaluation"

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A series of novel 8-bromo-1*H*-1,2,3-triazol-4-yl-2-methylquinoline derivatives and their Suzuki coupling products were synthesized *via* Copper catalyzed azide-alkyne cycloaddition (CuAAC) strategy followed by microwave assisted Suzuki coupling for the development of new series of anticancer agents. The *invitro* anticancer activity of the synthesized compounds were screened against human breast cancer (MDA-MB-231) and melanoma cell lines (B16F10). Among these, compounds **5c** (Azetidine), **5e** (Nitro benzoate), **5f** (fluorobenzyl)-1*H*-pyrazole), **5g** (Boc piperidine), **6a** (cyclo propyl), **6c** (5-fluoro-6-methoxypyridin-3-yl)and **6d** (2-methoxypyridin-3-yl) were showed anticancer activity ranging from 13.44 μM to 38.2 μM. The cellular toxicity of the novel compounds was also evaluated using normal human embryonic kidney (HEK) cell lines.

Introduction

Nitrogen-containing heterocyclic compounds are fundamental constituents in abundant biologically active compounds. Quinoline and its derivatives establish the extreme significant family of compounds among these heterocycles, and there has been substantial interest in developing efficient methods for their synthesis. Quinoline containing triazoles symbolize an important class of organic molecules that have attracted great deal of attention from synthetic as well as medicinal chemists due to their presence in various natural products, exhibiting a wide range of physiological activities.[1a–f] An assemblage of quinoline-triazole in a diverse molecular entity obtained a new outline that has been used for the generation of a small library of molecules as probable anticancer agents. Moreover, the main core of Quinoline linked to triazole moieties are often a criterion for biological activity and can thus heavily influence the pharmacokinetics, drug targeting and mechanism of action. These are the subject of considerable research, mainly due to their usefulness in synthetic organic chemistry and also due to their variety of interesting biological activities such as antibacterial,[2] antimicrobial,[3] antituberculosis,[4] anticancer,[5] antiviral,[6] Acetylcholine-sterase Inhibitors,[7] Cytotoxic,[8] anti-inflammatory,[9] and Antioxidant activity.[10] The importance of the Quinoline containing triazoles has been well established as explained by the large number of patents utilizing such species as Anticancer agents. As a result, new drugs with divergent, unique structure and also with mechanism of action possibly different from that of existing drugs are urgently required. In the field of Medicinal chemistry, researchers are constantly seeking for new molecules and construct that exhibit specific properties of molecules.Although this novel philosophy for drug discovery is very appealing, the medicinal chemists in this field seem to be nervous.

Encouraged by the biological profile of 1,2,3- triazole derivatives and quinoline analogues, and their collective importance in Pharmaceutical and Biological Evaluations, and also in continuation of our work on the synthesis of biologically active heterocyclic compounds, it was thought meaningful to commence the synthesis of biheterocyclic systems having Quinoline consists of 1*H*-1,2,3- triazole. To the best of our knowledge there is less number of reports on the synthesis of title compounds. We herein report the utility of strategic starting material, 2-amino-3-bromo-5-iodobenzaldehyde **1** for the synthesis of target compounds.

Results and Discussion

Chemistry

Our synthetic approach for key alkyne intermeidate **3** is illustrated in Scheme 1. The synthesis of 2-amino-3-bromo-5-((trimethylsilyl) ethynyl)benzaldehyde **2** commenced from 2-amino-3-bromo-5-iodobenzaldehyde **1**.[11] Sonagashira coupling of **1** was carried out under TMS acetylene, CuI, Et_3N in THF conditions at ambient temperature for 16 h provided **2** in 77% yield. Next, base mediated Quinoline formation and deprotec-

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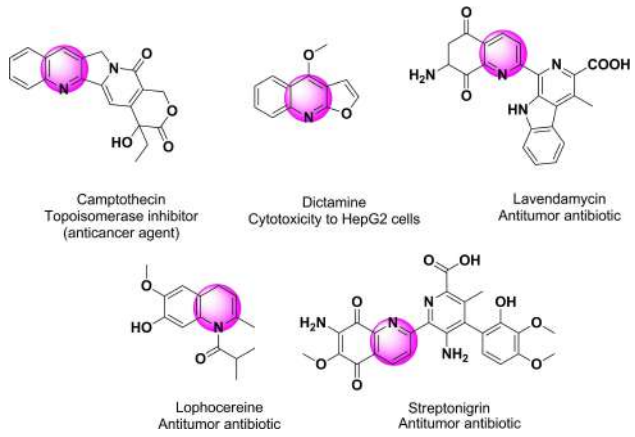


Figure 1. Representative Examples of Quinoline drugs having anticancer activity.

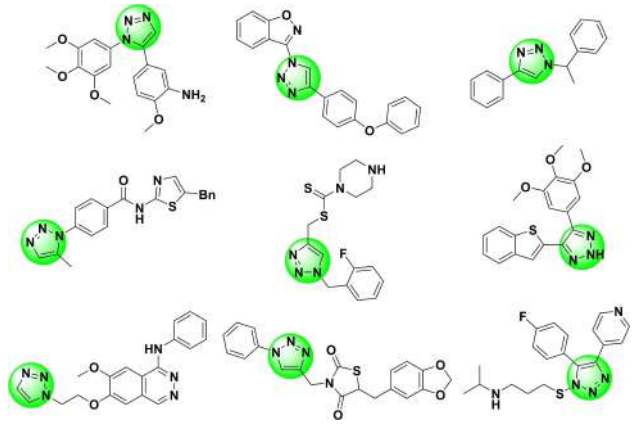
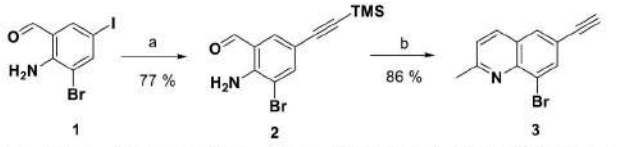


Figure 2. 1,2,3-triazole containing anticancer drugs.



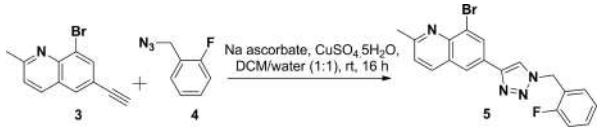
Conditions: a) Trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 16 h; b) Acetone:EtOH (1:2), KOH, rt, 1 h;

Scheme 1. Synthesis of alkyne intrmediate **3**.

tion of silyl group was accomplished by using KOH in Acetone: EtOH solvent at room temperature[11] for 1 h to generate a 8-bromo-6-ethynyl-2-methylquinoline **3** in excellent yield.

After synthesized alkyne **3**, Initially we attempted the Click reaction of alkyne **3** with azide **4** in the presence of sodium ascorbate (0.1 eq) and $CuSO_4.5H_2O$ (0.05 eq) in *t*-BuOH:water at ambient temperature for 30 h to prepare the desired **5** (Table 1). The reaction went smoothly and afforded the **5** in 49% yield. In order to improving the yield of the product, various solvents were investigated (Table 1). Further optimization was improved the yield from 49% to 81%. We investigated

Table 1. Optimized conditions for click reaction.



Entry	Azide **4** [equiv.]	$CuSO_4$	Sodium ascorbate	Solvent	Conditions	Yield
1	1.0	0.05	0.1	*t*-BuOH/H_2O	rt, 30 h	49 %
2	1.5	0.1	0.2	THF/water	rt, 48 h	39 %
3	1.2	0.05	0.1	EtOH/water	rt, 36 h	42 %
4	1.2	0.05	0.1	DMF/water	rt, 30 h	42 %
5	**1.2**	**0.2**	**0.4**	**DCM/water**	**rt, 16 h**	**81 %**

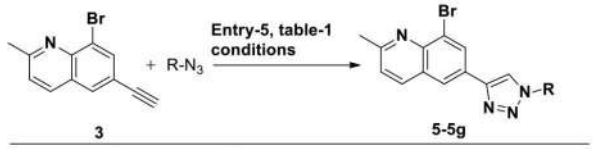
the effect of solvents on reaction rate as well as on yields of products. It showed us with various solvents screened such as *t*-BuOH, THF, EtOH and DMF, however **5** was obtained in moderate yield (Table 1). After several experimental optimizations, we found the best conditions are sodium ascorbate (0.4 eq) and $CuSO_4.5H_2O$ (0.2 eq) in CH_2Cl_2:water at room temperature for 16 hours provided target molecule in 81% yield. (entry-5, Table 1).

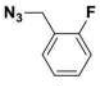
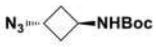
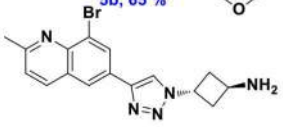
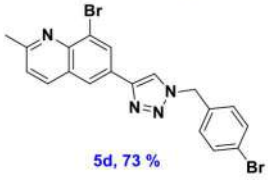
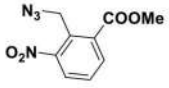
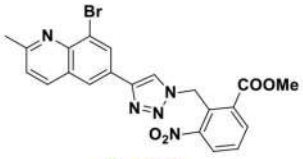
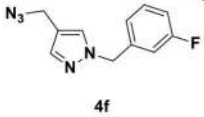
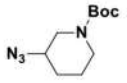
With optimized reaction conditions in our hand, we extended this method to other azides such as **4a** to **4g**. In all cases, the corresponding 8-bromo-6-(1-(2-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)-2-methylquinoline derivatives were obtained in good yields (Table 2).The corresponding azides **4a-g** were prepared from their respective bromides and mesylates using known procedures from the available literature[12a–e] except for **4c** and **4f**. Where as for **4c** was prepared from mesylate using NaN_3 at 60 °C for 2 h in DMF as a solvent conditionsand **4f** prepared from alcohol using, DPPA, DBU in THF at room temperature conditions. All the azides in this investigations were used directly with out further purification.

Next, we aimed at synthesizing the corresponding Suzuki coupling products of key intermediate **5**.[13a–f] Initially we attempted coupling of **5** with (4-methoxyphenyl)boronic acid in the presence of $Pd(PPh_3)_4$ (0.05 eq), Cs_2CO_3 (3 eq) in THF: water at 65 °C for 16 h afforded **6b** in 32% yield. Although the reaction proceeds at 65 °C, it required a prolonged reaction time with low yield. In order to achieve high conversion we switched to microwave conditions. The rate of reaction was enhanced remarkably by increasing the temperature from 60 °C to 100 °C and by increasing the loading of Pd catalyst from 0.05 eq to 0.1 eq under microwave conditions. Various bases such as K_3PO_4, Na_2CO_3, KF and K_2CO_3 have also been screened of these Cs_2CO_3 found to be more effective.

Further, we investigated the effect of solvents on rate of reaction as well as on yields of products. Of these solvent combination EtOH:THF:water provided the best results. After several experimental optimizations, the best optimization conditions were $Pd(PPh_3)_4$ (0.1 eq), Cs_2CO_3 (3 eq) in EtOH:THF:

Table 2. Synthesis of different triazoles.



Entry	Azide moiety (R)	Product
1		
	4	5, 81 %
2		
	4a	5a, 70 %
3		
	4b	5b, 65 %
4		
	4c	5c, 55 %, two steps
5		
	4d	5d, 73 %
6		
	4e	5e, 76 %
7		
	4f	5f, 63 %
8		
	4g	5g, 76 %

water (10:6:2) at 100^0 C in microwave for 1 h provided in 77% Yield (Table 3). With optimized conditions in hand, the methodology has been extended to other boronic acids. In all cases, the corresponding Suzuki coupling products were obtained in good to excellent yields.

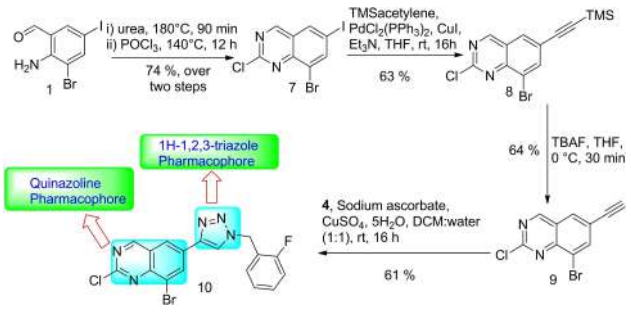
The above results provided a gateway to extend this process to other substrates like Quinazoline. The synthesis of the **10** was commenced with 2-amino-3-bromo-5-iodobenzaldehyde **1**, which was cyclized to quinazoline using urea at 180 ^{0} C for 90 min followed by chlorination with $POCl_3$ at 140 °C for 12 h provided 8-bromo-2-chloro-6-iodoquinazoline **7** in 75% over two steps. Sonagashira coupling of **7** by using TMSacetylene, $PdCl_2(PPh_3)_2$, CuI and Et_3N in THF for 16 h at ambient temparature afforded **8** in 63% yield with traces of di-TMS product. Trimethy silyl deprotection was carriedout under TBAF conditions generated **9** in 64% yield. Next click reaction of **9** under sodium ascorbateand $CuSO_4.5H_2O$ in DCM/water (1:1) for 16 h at ambient temperature afforded **10** in 61% yield. (Scheme 2).

Biology: Anticancer Activity Determination by MTT Assay

The *in vitro* anticancer activity of the synthesized compounds were determined against two different cancer cell lines. The cellular toxicity of the novel compounds was also evaluated using normal human embryonic kidney (HEK) cell lines.

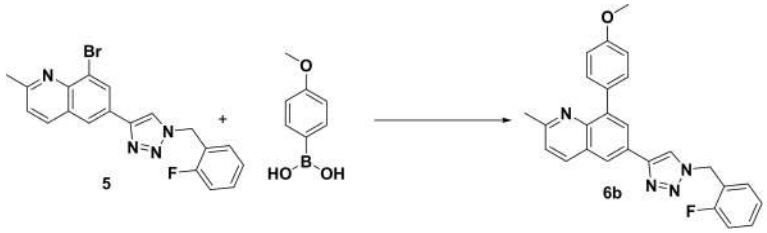
For the purpose, MTT assay was carried out on murine skin melanoma cell line (B16F10) and human breast cancer (MDA-MB-231) cells as cancer cell lines. All the cell lines were cultured in DMEM (high glucose media: AL007 S, Dulbecco's modified eagle medium) with 10% fetal bovine serum (FBS) and 1% antibiotic (Pen strep: A001), incubated at 37 °C and 5% CO_2 atmosphere. MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide], a yellow dye was used for the assay.[14] All reagents were purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India.

As per the protocol, 96 well plate was seeded with 100 µL/well cell suspension with the cell density of 1×10^4 per well and were incubated overnight. Subsequently, the medium was aspirated and the cells were treated with the compounds at a concentration of 100 µM and 10 µM in 150 µL DMEM complete medium in duplicate for 48 hours. The mini through put assay was used to find out the comparable potency of all the compounds using two different doses in duplicate. The culture medium was aspirated and subsequently, 50 µl of 5 mg/mL concentrated solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) in phenol red free DMEM media was prepared and added into each well and incubated for



Scheme 2. Synthesis of quinazoline analogue (**10**).

Table 3. Suzuki optimization conditions; (C: conventional heating; MWI: microwave irradiation).



Entry	Pd Catalyst/Ligand	Base	Solvent	Temp and Time	Yield (%)	Method
1	$Pd(PPh_3)_4$	Cs_2CO_3	THF/water	65 °C, 16 h	32	C
2	$Pd(OAc)_2/P(O\text{-}tol)_3$	K_2CO_3	EtOH/PhMe	85 °C, 12 h	26	C
3	$PdCl_2(dppf)$	KF	Dioxane/water	100 °C, 12 h	29	C
4	$PdCl_2(dppf)$	K_3PO_4	THF/water	70 °C, 12 h	33	C
5	$PdCl_2(dppf)DCM$	Na_2CO_3	EtOH/PhMe/H_2O	85 °C, 12 h	35	C
6	$Pd_2(dba)_3/P(tBu)_3$	Cs_2CO_3	Doxane	100 °C, 8 h	42	C
7	$Pd_2(dba)_3/P(tBu)_3$	K_3PO_4	Toluene	100 °C, 8 h	39	C
8	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**EtOH:THF:Water**	**100 °C, 1 h**	**77**	**MWI**
9	$Pd(PPh_3)_4$	2M Na_2CO_3	Dioxane	150 °C, 2 h	62	MWI
10	$Pd_2(tBu)_2P$	2M Na_2CO_3	THF/EtOH	80 °C, 2 h	53	MWI

3 hours to allow the formation of formazan crystals that are formed as a result of cellular enzymatic activity. 50 μL of DMSO was added into each well to dissolve the formed formazan crystals and the absorbance was measured using multi-well plate reader Spectramax (Molecular Devices, USA) at two different wavelengths of 570 nm and 650 nm. The % cell viability was calculated as a fraction of absorbance obtained from the treated cells from the absorbance of DMSO vehicle treated control cells. The same procedure was followed for all the cell lines.

The seven most promising compounds from the series were tested for further screening to determine their IC_{50} values from the dose response curve. The DMSO solutions of the selected compounds were prepared and they were further diluted to 200 μM, 100 μM, 50 μM, 25 μM, 12.5 μM, 6.25 μM, 3.125 μM, 1.562 μM and 0.781 μM with the DMEM complete media for the determination of IC_{50} values along with a blank control containing equivalent amount of DMSO in medium and BG45 was used as positive control in all the cell based experiment which actually validate the assay procedure as well.[15] The cells were incubated with the compounds for 48 hrs. The experiment was repeated with different a batch of cells following the same protocol for all the cell lines and the cell viability was assayed by MTT assay as discussed.[15]

Results and Discussion

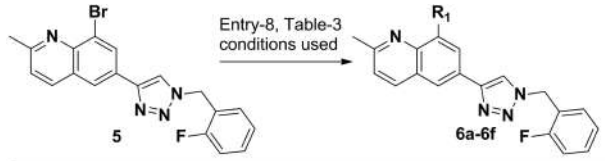
The results obtained from biological screening experiments were depicted in the following figures.

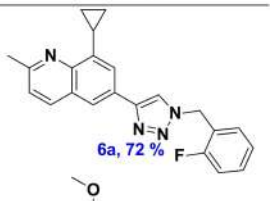
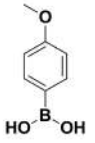
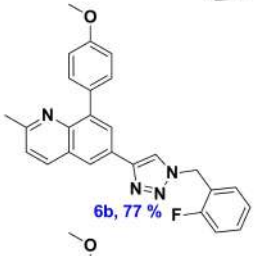
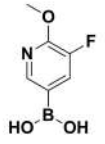
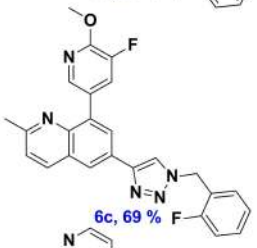
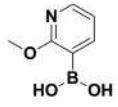
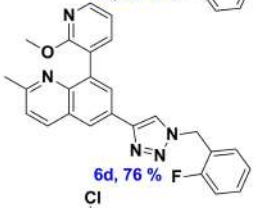
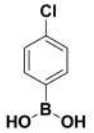
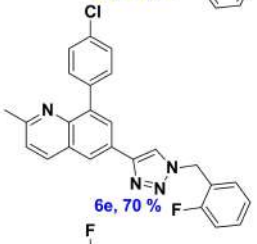
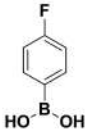
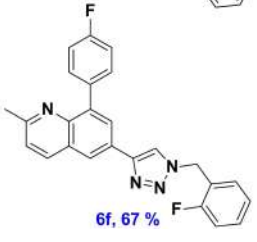
Figure 3 and Figure 4 showed the % cell viability of the given compounds at 100 μM and 10 μM in MDA-MB-231 and B16F10 cell lines.

Figure 6 showed the cytotoxicity profile of the compounds against HEK cell lines at 100 μM and 10 μM respectively. Compounds 5c, 5e, 5f, 5 g, 6a, 6c and 6d were showed better anticancer activity, hence they were further selected for screening of their IC_{50} value determination with a wider range of concentrations on MDA-MB-231, B16F10 cell lines for the determination their anti-cancer activity more accurately (Figure 5).

The IC_{50} values of cellular toxicity of the same selected promising compounds were determined against HEK cells following the same protocol with concentration range from 3.5 μM to 1000 μM (Figure 7). The determined IC50 values of

Table 4. Synthesis of various suzuki coupling products.



Entry	Boronic acid (R_1)	Product
1		 6a, 72 %
2		 6b, 77 %
3		 6c, 69 %
4		 6d, 76 %
5		 6e, 70 %
6		 6f, 67 %

the compounds against cancer cell lines and normal cells lines delineated some selectivity of the compounds for cancer cell lines over normal lines. The selectivity of the compounds for cancer cell line over normal cell line with their corresponding IC50 values represented in Table 5.

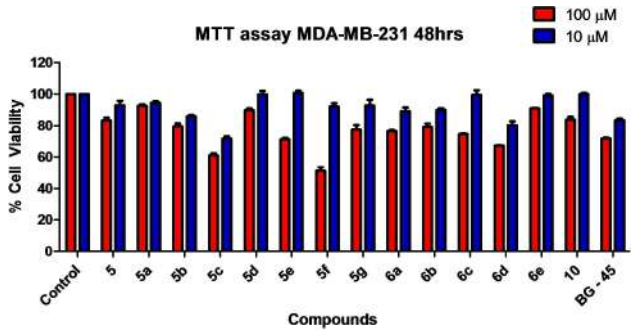


Figure 3. Anticancer activity of novel compounds by MTT assay on human breast cancer (MDA-MB-231) cell line. Cells were treated with all compounds at two; 100 µM and 10 µM in duplicate. Data represents mean ± SD (n = 2).

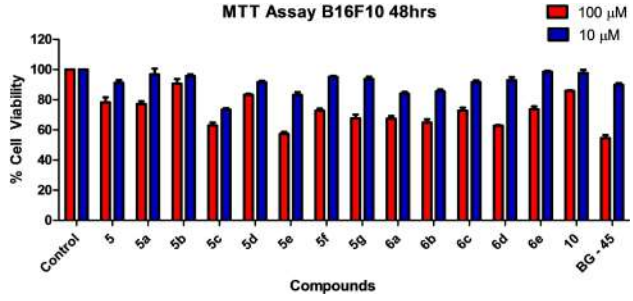


Figure 4. Anticancer activity of novel compounds by MTT assay on murine skin melanoma cell line (B16F10) cell line. Cells were treated with all compounds at two doses; 100 µM and 10 µM in duplicate. Data represents mean ± SD (n = 2).

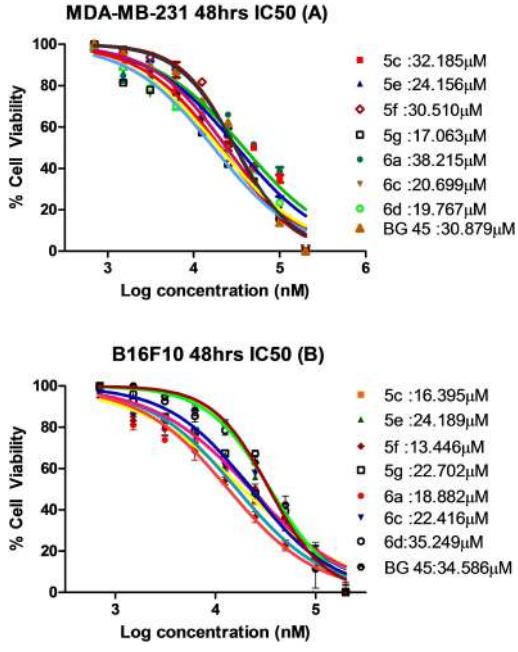


Figure 5. IC_{50} results of the selected seven compounds (**5c**, **5e**, **5f**, **5g**, **6a**, **6c** and **6d** with BG-45 as positive control) by MTT assay. MDA-MB-231 (**A**) and B16F10 (**B**) cell lines were treated with the compounds at concentration range of 0.781 µM - 200 µM (n = 2) for 48 hours. Data represents mean ± SD.

Table 5. The IC50 values and their selectivity profile of the selected compounds for cancer cell lines over normal cell line.

		IC50 in μM			Selectivity for Cancer cells	
S.No	Compound No.	MDA-MB-231	B16F10	HEK	MDA-MB-231	B16F10
1	5c	32.185	16.395	275.5	8.56	16.80
2	5f	30.510	13.446	126.9	4.16	9.43
3	5g	17.063	22.702	116.3	6.82	5.12
4	5e	24.156	24.189	160.7	6.65	6.64
5	6a	38.215	18.882	219.7	5.75	11.64
6	6c	20.699	22.416	137.2	6.63	6.12
7	6d	19.767	35.249	203.2	10.28	5.76

Cellular Toxicity Data of the Compounds Against Normal Cell Line

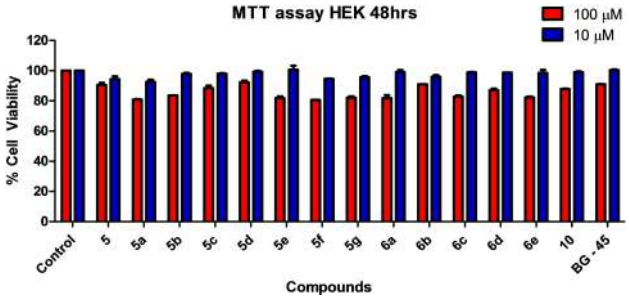


Figure 6. Cytotoxicity profile of the compounds against human embryonic kidney cell line (HEK). Cells were treated with all the compounds at two doses; 100 μM and 10 μM in duplicate. Data represents mean ± SD (n = 2). BG-45 is used as positive control.

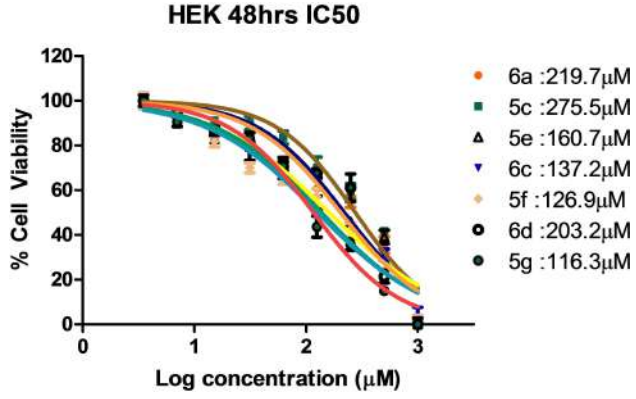


Figure 7. IC_{50} results of the selected seven compounds (**5c**, **5e**, **5f**, **5g**, **6a**, **6c** and **6d**) by MTT assay. HEK cell lines were treated with the compounds at concentration range of 3.5 μM - 1000 μM (n = 2) for 48 hours. Data represents mean ± SD.

Conclusions

A novel hybrid template designed by linking two pharmacophoric groups quinoline and triazole moieties have been used for the generation of a library of molecules as potential anticancer agents. Synthesis of these compounds were carried out by using a strategy that involved Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) followed by microwave assisted Suzuki coupling as a key steps. The *invitro* anticancer activity of the synthesized compounds has been screened against human breast cancer (MDA-MB-231) and melanoma cell lines (B16F10). Among them, compounds 5c, 5e, 5f, 5 g, 6a,6cand 6d were showed better anticancer activity ranging from 13.44 μM to 38.2 μM. The cellular toxicity of the novel compounds was also evaluated using normal human embryonic kidney (HEK) cell lines. Thus, these results deserve the need for further synthesis of similar libraries with other substituents to ascertain the trend described in this work. In this contest we have already extended our work to quinazoline derivatives.

Supporting Information Summary

Detailed information about the experimental procedure, spectral Characterization data such as ^{1}H NMR, ^{13}C NMR, FT-IR and LC–MS spectra of all synthesized products are provided.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Anticancer Evaluation · CuAAC strategy · Quinoline · Suzuki coupling · triazoles

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