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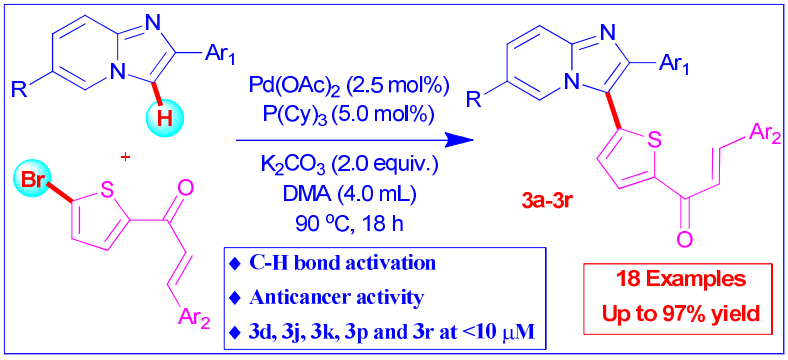
Graphical Abstract



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ARTICLE TYPE

Palladium(0)-Catalyzed Direct C-H Hetero-Arylation of 2-Arylimadazo [1,2-*a*]pyridines with (*E*)-1-(5-Bromothiophen-2-yl)-3-arylprop-2-en-1-ones and Their Anticancer Activity

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An efficient palladium (0)-catalyzed direct hetero-arylation of imidazo[1,2-*a*]pyridines at the C-3 position of imidazole ring has been described. All synthesized compounds 3a-3r were evaluated for their anticancer activity against a panel of four human cancer cell lines and among all the compounds, 3d, 3j, 3k, 3p and 3r showed promising activity at <10 µM.

Cancer is a multifaceted disease that represents one of the leading causes of mortality in developed countries. The occurrence and humanity of cancer patients have become one of the very important issues discussed worldwide.[1] Unfortunately, development of resistance to chemotherapeutic agents is a common impediment in the treatment of different types of cancers. Among the different type of cancers, lung cancer, cervical cancer, breast cancer and prostate cancer are the most common cancers in humans, other than skin cancer, and the second leading cause of cancer death in men and women.[2] In the history of twenty years, there have been several improvements in the war against cancer. More and more anticancer drugs and vaccines have been developed. There are about 79 FDA approved anticancer drugs and vaccines since past twenty years. Among them, 39 synthetic anticancer drugs received FDA approval.[3] Imidazo[1,2-*a*]pyridine derivatives have attracted considerable interest due to their diverse biological activities and therapeutic properties.[4] For instance, this heterocyclic system has received

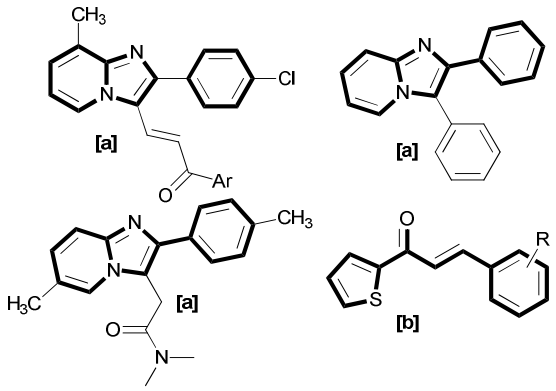


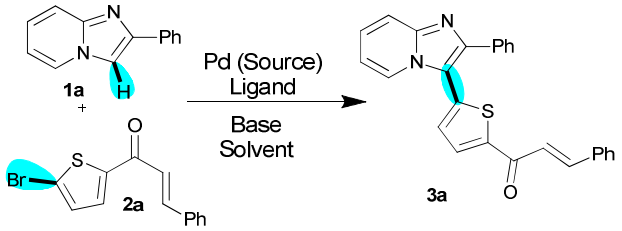
Fig.1 Pharmaceutically important [a] imidazo[1,2-*a*]pyridine core and [b] (*E*)-3-aryl-1-(thiophen-2-yl)prop-2-en-1-one core containing scaffolds

therapeutic importance acting as anticancer,[5] antimicrobial,[6] antiprotozoal,[7] antiherpetic,[8] anti-HIV,[9] antiviral,[10] and anti-inflammatory[11] agents. Several imidazo[1,2-*a*]pyridines are already available in the market including zolimidine (an antiulcer drug), zolpidem (a hypnotic drug), and alpidem (a nonsedative anxiolytic).[12] Similarly, chalcone derivatives occupy an elite place in the field of medicinal chemistry due to a wide range of biological activities exhibited by them; the heterocycle-derived chalcone derivatives have wide variety of pharmacological activities like antimalarial, anti-inflammatory, cytotoxic, anticancer, and antioxidant properties.[13] Recently, the antitumor agents,[14] antimicrobial agents,[15] breast cancer inhibitors,[16] were also reported. The pharmaceutically active imidazole and thiophene chalcone cores are depicted in Fig.1.[17] The imidazopyridine core and analogues of chalcone derivative possess many anti-infective properties including anticancer, antibacterial,[18] antiviral,[19] antiprotozoal,[20] $MCHR_1$ antagonist,[21] and antihelmintic[22] activities.

In the past few years, much more interest has been made to the synthesis of 3-aryl/heteroarylimidazo[1,2-a]pyridine derivatives by transition-metal-catalyzed direct C-3 (hetero) arylation.[23-24] This field has thus undergone rapid development. Although direct arylation of heterocycles has been successful, direct C3-arylation of free imidazo[1,2-a]pyridines still has opportunity for further development. The palladium(0)-catalyzed C-H arylation of imidazo[1,2-*a*]pyridines at the C-3 position of imidazole ring with aryl/heteroaryl halides is one of the direct strategies to generate 3-aryl/hetero-arylimidazo[1,2-a]pyridine derivatives.[23] In 2006, B. Raboin et al. developed 5 mol % of $Pd(OAc)_2$ and 10 mol % of PPh_3 for the C3-arylation of imidazo[1,2-a]pyridines[23b] and recently, Doucet and co-workers revealed a phosphine free Pd-catalyzed direct C-3 arylation of imidazo[1,2-a]-pyridines with aryl bromides at low catalyst loading.[23c-d] However, aryl bromides were the only appropriate electrophiles. In 2014, Zhan et al. developed an efficient synthesis of 3-arylimidazo[1,2a] pyridines through oxidative coupling reaction[23k] and H. M. Lee et al. reported the Pd(0)-catalysed decarboxylative arylation of imidazo[1,2-a]pyridine-3-carboxylic acid with aryl halides.[23l] The Suzuki coupling between 3-haloimidazo[1,2-a]pyridines and arylboronic acids is another direct strategies to generate 3-arylimidazo[1,2-a]pyridine derivatives.[24] Herein we describe, the

palladium(0)-catalyzed direct C-H hetero-arylation at C-3 position of imidazole ring of 2-arylimidazo[1,2-*a*]pyridine with (*E*)-1-(5-bromothiophen-2-yl)-3-arylprop-2-en-1-one (heteroaryl) as starting materials and their cytotoxic evaluation against four human cancer lines (A549, MCF7, HeLa and DU145).

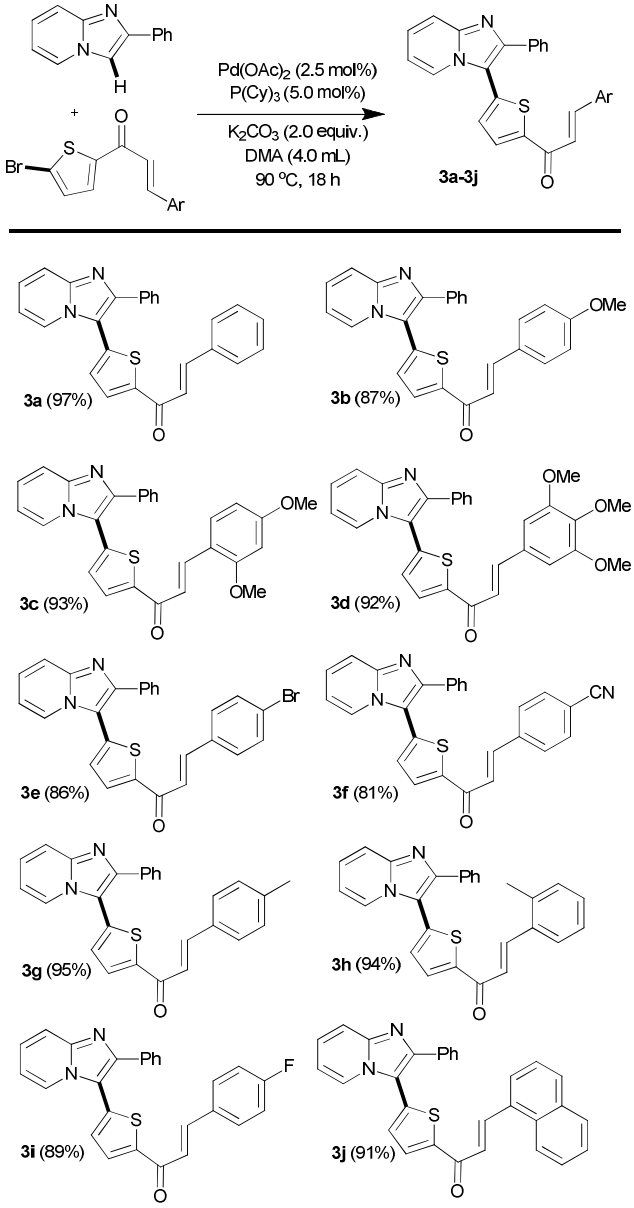
Table 1 Optimization of the reaction conditions [a]



Entry	Pd Source	Ligand	Base	Solvent	Yield of **3a**(%)[b]
1	$Pd(OAc)_2$	TPP[c]	K_2CO_3	DMF	73
2	$Pd(OAc)_2$	TPP	K_2CO_3	Toluene	78
3	$Pd(OAc)_2$	TPP	K_2CO_3	DMSO	81
4	$Pd(OAc)_2$	TPP	K_2CO_3	DCE	71
5	$Pd(OAc)_2$	TPP	K_2CO_3	DMA	84
6	**$Pd(OAc)_2$**	**$P(Cy)_3$[c]**	**K_2CO_3**	**DMA**	**97**
7	$Pd(OAc)_2$	$P(Cy)_3$	*t*-BuOK	DMA	94
8	$Pd(OAc)_2$	$P(Cy)_3$	Cs_2CO_3	DMA	93
9	$Pd(TFA)_2$	$P(Cy)_3$	K_2CO_3	DMA	79
10	$Pd(PPh_3)_4$	TPP	K_2CO_3	DMA	82
11	$Pd_2(dba)_3$	TPP	K_2CO_3	DMA	88
12	$PdCl_2(dppp)$[c]	TPP	K_2CO_3	DMA	69
13	$Pd(OAc)_2$	DPPP[c]	K_2CO_3	DMA	72
14	$Pd(OAc)_2$	X-Phos[c]	K_2CO_3	DMA	68
15	$Pd(OAc)_2$	TPTP[c]	K_2CO_3	DMA	79

[a] Unless specified, the reaction was carried out with **1a** (0.5 mmol), **2a** (0.6 mmol), Pd (0.025 equiv.), ligand (0.05 equiv.), base (2.0 equiv.) under N_2 atm. at 100 °C in a solvent (4.0 mL) for 18.0 h. [b] Isolated yield (average of two runs). [c] TPP = Triphenyl phosphine, $P(Cy)_3$ = Tricyclohexcyl phosphine, DPPP = 1,3-Bis(diphenylphosphino)propane, X-Phos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, TPTP = Tri(*p*-tolyl)phosphine, $PdCl_2(dppp)$ = (1,3-Bis(diphenylphosphino)propane)palladium(II)chloride.

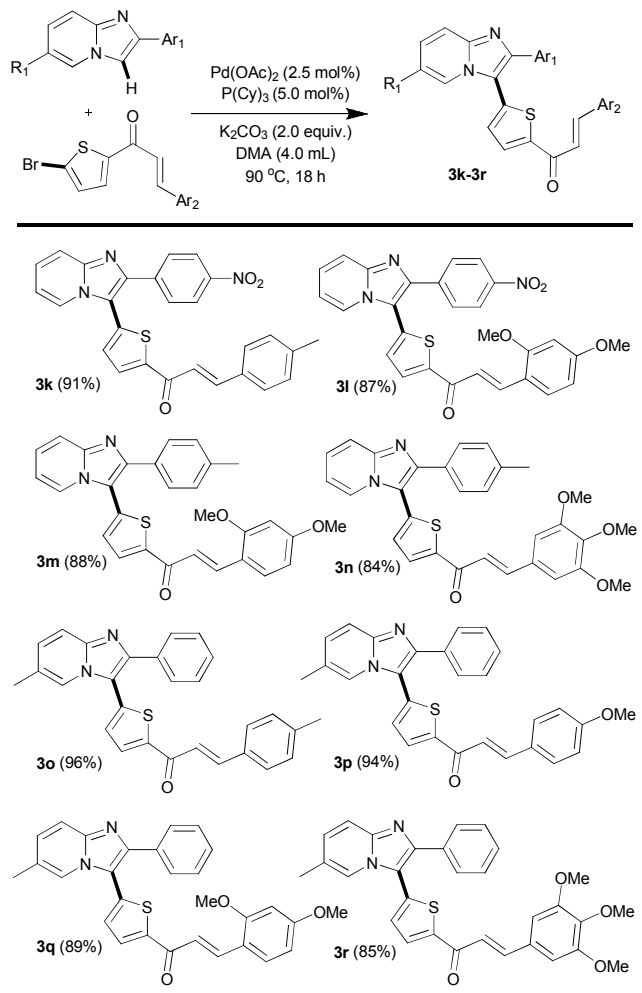
At the outset of our study, the required starting materials, 2-arylimidazo[1,2-*a*]pyridine, and (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one derivatives were synthesized according to literature procedure.[25] The direct cross-coupling between 2-arylimidazo[1,2-*a*]pyridine (**1a**) with (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one (**2a**) as a model substrate (Table 1). Initially, the reaction was performed with 2 mol% $Pd(OAc)_2$, TPP (3 mol%) and potassium carbonate (2 equiv.) with DMF as a solvent the reaction gave moderate yield (entry 1). By changing the solvent like toluene, DMSO, DCE, and DMA, the reaction gave moderate to good yields (entries 2-5). The effect of ligand addition was also noted, good to excellent yields was observed by replacing TPP with PCy_3 (entry 6). The addition of different bases did not affect the outcome of the reaction yields (entries 7 and 8). The reaction product yields did not increase with the change of $Pd(OAc)_2$ with different palladium sources like $Pd(TFA)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $PdCl_2(dppp)$ (entries 9-12). The reaction outcome did not improve by the addition of different phosphine ligands like Dppp, X-Phos and TPTP (entries 13-15).



Scheme 1 Synthetic scope of (*E*)-1-(5-bromothiophen-2-yl)-3-arylprop-2-en-1-one derivatives [a].

Under the optimized reaction conditions (Table 1, entry 6), the various (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one derivatives were examined with 2-arylimidazo[1,2-*a*]pyridine derivatives and results to this regard are summarized in Scheme 1 and 2. It was observed that (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one with electron-donating groups (methyl, methoxy) and electron withdrawing group (cyano) were well tolerated and gave the corresponding cross coupling product with good to excellent yields (Scheme 1, entries **3a-3g**). The halogen bearing (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one derivatives was well tolerated and the corresponding coupling product was obtained in excellent yields (entries **3h** and **3i**). The deactivated fused ring system bearing (*E*)-1-(5-bromothiophen-2-yl)-3-(naphthalen-1-yl)prop-2-en-1-one derivative also underwent smooth coupling (**3j**). The electron donating and electron

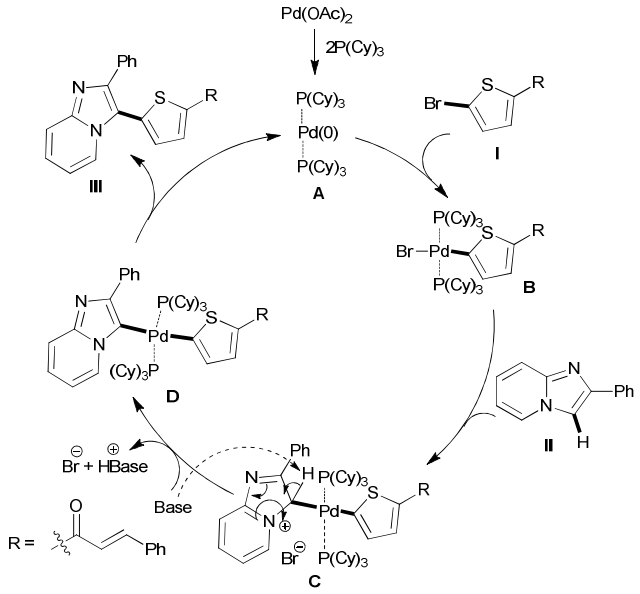
withdrawing group bearing 2-arylimidazo[1,2-*a*]pyridine derivatives underwent smooth coupling with electron donating and electron withdrawing group bearing (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one derivatives (Scheme 2, **3k-3r**).



Scheme 2 Synthetic scope of 2-arylimidazo[1,2-*a*]pyridine derivatives [a].

Based on the previous reports a plausible mechanism is illustrated in scheme 3.[23] The first step, which involves the activation of $Pd(OAc)_2$ using tricyclohexcyl phosphine (PCy_3) to form the active Pd(0) complex (**A**). The Pd(0) complex (**A**) undergoes the oxidative addition of (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one (**I**) to form complex (**B**). The complex **B** undergoes electrophilic attack with 2-phenylimidazo [1,2-*a*]pyridine (**II**) to get complex **C.**[23j,p] In complex **C,** the C-H hydrogen (at C3 position) was abstracted by base to get complex **D**. The complex **D** undergoes the reductive elimination to give the desired product (**III**) and Pd(0) complex (**A**) and initiating the new catalytic cycle.

The *in vitro* cytotoxic activity of synthesized compounds **3a-3r** were evaluated using standard MTT assay[26] against four human cancer cell lines, lung cancer (A549), breast cancer (MCF7), cervical cancer (HeLa), and prostate cancer (DU145) cell lines, respectively. The *in vitro* cytotoxic activity was expressed as IC_{50} (μM) values and doxorubicin was used as a positive control. The results to this regard are depicted in Table 2.



Scheme 3 Proposed mechanism for Pd(0)-catalyzed C-H Hetero-arylation.

Table 2 Anticancer activity of compounds **3a-3r** against four human cancer cell lines

Compound	IC_{50} values in (μM)			
	A549 [a]	MCF7 [a]	HeLa [a]	DU145 [a]
3a	78.6 ± 0.42	58.8 ± 0.48	71.4 ± 0.54	66.9 ± 0.33
3b	31.2 ± 0.33	22.8 ± 0.14	21.3 ± 0.22	28.9 ± 0.29
3c	–[b]	–	–	–
3d	**8.4 ± 0.24**	**6.4 ± 0.12**	**5.2 ± 0.16**	**7.9 ± 0.18**
3e	205.0 ± 0.42	–	–	112.1 ± 0.58
3f	–	–	–	–
3g	32.9 ± 0.48	33.3 ± 0.28	41.1 ± 0.24	32.9 ± 0.36
3h	26.5 ± 0.13	26.4 ± 0.18	29.9 ± 0.28	31.2 ± 0.32
3i	16.9 ± 0.14	15.8 ± 0.16	15.4 ± 0.22	14.2 ± 0.24
3j	11.8 ± 0.21	**9.8 ± 0.12**	**10.8 ± 0.36**	11.2 ± 0.22
3k	**9.0 ± 0.16**	**7.2 ± 0.24**	**8.8 ± 0.12**	**8.1 ± 0.22**
3l	–	–	–	–
3m	17.9 ± 0.16	15.9 ± 0.26	18.2 ± 0.24	19.1 ± 0.22
3n	14.3 ± 0.32	11.4 ± 0.14	12.5 ± 0.16	18.4 ± 0.18
3o	50.8 ± 0.46	48.9 ± 0.26	49.2 ± 0.33	30.8 ± 0.26
3p	**11.2 ± 0.33**	**9.7 ± 0.32**	**10.4 ± 0.15**	**9.8 ± 0.22**
3q	24.3 ± 0.12	22.3 ± 0.11	19.8 ± 0.24	18.4 ± 0.32
3r	**6.5 ± 0.11**	**5.4 ± 0.22**	**5.1 ± 0.16**	**6.1 ± 0.08**
Dox [c]	0.7 ± 0.09	0.8 ± 0.08	0.7 ± 0.11	0.6 ± 0.09

[a] A549 = Lung cancer (CCL-185); MCF7 = Breast cancer (HTB-22); DU145 = Prostate cancer (HTB-81); HeLa = Cervical cancer (CCL-2). [b] – = No activity. [c] Dox = Doxorubicine.

The cytotoxicity results revealed that (*E*)-3-aryl-1-(5-(2-arylimidazo[1,2-*a*]pyridin-3-yl)thiophen-2-yl)prop-2-en-1-one derivatives **3d, 3k, 3p** and **3r** bearing methoxy, methyl substituted (*E*)-1-(5-bromothiophen-2-yl)-3-phenylprop-2-en-1-one derivatives with methyl, nitro substituted 2-arylimidazo[1,2-*a*]pyridine derivatives showed most promising inhibition (IC_{50} <10 μM) against all four human cancer cell lines (A549, MCF7, HeLa and DU145) with as compared to the standard doxorubicin. Whereas, the (*E*)-3-aryl-1-(5-(2-arylimidazo[1,2-*a*]pyridin-3-yl)thiophen-2-yl)prop-2-en-1-one derivatives **3i, 3j, 3m** and **3n** bearing naphthyl and methoxy substituted (*E*)-1-(5-

bromothiophen-2-yl)-3-phenylprop-2-en-1-one derivatives with phenyl and methyl substituted 2-arylimidazo[1,2-*a*]pyridine derivatives exhibited good inhibition (IC_{50} <20 μM) against all four human cancer cell lines with as compared to the standard doxorubicin.

The cytotoxicity of the lead compounds (**3d, 3j. 3k, 3p** and **3r**) was also evaluated against IMR-90 (normal human lung cell line, ATCC no. CCL-186). The selectivity index (SI) = IC_{50} of pure compound in a normal cell line / IC_{50} of the same pure compound in cancer cell line, where IC_{50} is the concentration required to inhibit 50% of the cell population was also calculated and has been included in Table 3. High SI value (>2) of a compound gives a selective toxicity towards cancer cells, while the compound with SI value <2 is considered to give general toxicity in which it also can cause cytotoxicity in normal cells.[27] We have compared our results of the lead compounds along with doxorubicin with literature data and the results to this regard are presented in Table 4.[28-32]

Table 3 Cytotoxicity results of the lead compounds and their calculated selectivity index (SI) values

	IC_{50} values in (μM)								
Compound	A549	SI [a]	MCF7	SI	HeLa	SI	DU145	SI	IMR-90 [a]
3d	8.4 ± 0.24	**9.5**	6.4 ± 0.12	**12.5**	5.2 ± 0.16	**15.4**	7.9 ± 0.18	**10.2**	80.2 ± 0.24
3j	11.8 ± 0.21	**7.5**	9.8 ± 0.12	**9.1**	10.8 ± 0.36	**8.2**	11.2 ± 0.22	**7.9**	88.9 ± 0.42
3k	9.0 ± 0.16	**9.0**	7.2 ± 0.24	**11.3**	8.8 ± 0.12	**9.2**	8.1 ± 0.22	**10.0**	81.2 ± 0.32
3p	11.2 ± 0.33	**8.5**	9.7 ± 0.32	**9.8**	10.4 ± 0.15	**9.2**	9.8 ± 0.22	**9.7**	95.2 ± 0.33
3r	6.5 ± 0.11	**11.8**	5.4 ± 0.22	**14.2**	5.1 ± 0.16	**15.0**	6.1 ± 0.08	**12.6**	76.9 ± 0.28
Doxorubicin	0.7 ± 0.09	37.7	0.8 ± 0.08	33.0	0.7 ± 0.11	37.7	0.6 ± 0.09	44.0	26.4 ± 0 .12

[a] Selectivity index (SI) = IC_{50} of pure compound in a normal cell line / IC_{50} of the same pure compound in cancer cell line, where IC_{50} is the concentration required to inhibit 50% of the cell population; IMR-90 (normal human lung cell line, ATCC no. CCL-186).

Table 4 Doxorubicin was positive controls: a comparison

Compound	IC_{50} values in (μM)				
Tested	A549	MCF7	HeLa	DU145	Ref.
Doxo	**0.7**	**0.8**	**0.7**	**0.6**	Present study
3d	8.4	6.4	5.2	7.9	”
3j	11.8	9.8	10.8	11.2	”
3k	9.0	7.2	8.8	8.1	”
3p	11.2	9.7	10.4	9.8	”
3r	6.5	5.4	5.1	6.1	”
Doxo	**0.8**	**0.7**	**0.6**	**0.8**	28
5h	5.2	9.8	11.1	12.3	”
Doxo	**0.7**	-	**0.71**	-	29
7b	4.5	-	7.0	-	”
9b	1.0	-	2.0	-	”
Doxo	**1.21**	**1.05**	**0.45**	-	30
5b	-	0.58	-	-	”
Doxo	-	**0.75**	**1.17**	-	31
19	-	3.6	36.6	-	”
Doxo	**3.4**	**-**	**6.0**	-	32
4j	8.9	-	6.5	-	”

Conclusions

In conclusion, a new and efficient palladium-catalyzed direct hetero-arylation at the C-3 position of imidazole ring of 2-arylimidazo[1,2-*a*]pyridines has been described. This mild condition allowed the tolerance of the wide range of functionalities. The cytotoxicity results revealed that (*E*)-3-aryl-1-(5-(2-arylimidazo[1,2-a]pyridin-3-yl)thiophen-2-yl)prop-2-en-1-one, **3d, 3k, 3p** and **3r,** showed promising inhibitory activity against all four human cell lines whereas the compounds **3i, 3j, 3m** and **3n** derivatives exhibited good inhibition against all the four human cancer cell lines (A549, MCF7, HeLa and DU145). Further, scope and SAR studies are under progress.

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Notes and references

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