Pd-Catalyzed Synthesis and Anticancer Evaluation of Novel 1-Isobutyl-N-Phenyl-1*H*-Imidazo[4,5-C] Quinolin-4-Amine Derivatives

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***Abstract*—In this study, a series of 1-isobutyl-N-phenyl-1*H*-imidazo[4,5-c] quinolin-4-amine derivatives were synthesized via a Pd-catalyzed amination protocol employing Pd_2dba_3 and Xantphos ligands. Synthetic optimization of catalyst loading, solvents, and bases led to isolated yields ranging from 61% to 81%. The structures of target molecules were confirmed by NMR, FTIR, and mass spectrometry. Selected compounds were evaluated for anticancer activity against Human Lung Cancer Cell Line Hop-62 using the SRB assay, with cytotoxicity determined by LC_{50}, TGI, and GI_{50} values. The findings reveal promising cytotoxic profiles for several derivatives, highlighting the potential of imidazoquinoline scaffolds in drug discovery. This work demonstrates an efficient synthetic protocol while highlighting the need for facile and fundamental work for advancing the pharmacological importance of these heterocycles.**

***Index Terms*—Imidazoquinolines, Palladium-catalyzed amination, Anticancer activity, Breast cancer cell lines, Heterocyclic synthesis, Medicinal chemistry.**

I. INTRODUCTION

The discovery of novel library ofmolecules from promising heterocyclic scaffolds continues to push innovation pipeline in medicinal chemistry, particularly for lead candidates that address diverse challenges of cancer. The imidazoquinoline class, characterized by its fused imidazole and quinoline core, has established itself as a privileged structure for modulating immune responses and exerting direct anticancer effects. Recent reviews (2018–2025) highlight the development of numerous substituted imidazoquinoline derivatives, spanning synthetic advances and biological evaluations [1-2]. These scaffolds are potent Toll-like receptor (TLR) 7/8 agonists, capable of stimulating cytokine production and providing a foundation for both immune adjuvants and anti-tumor agents [3-6].

Notably, tailored imidazoquinoline derivatives have demonstrated promising preclinical activity by simultaneously inhibiting key inflammatory and pro-survival pathways, such as JAK/STAT and NF-κB, with strong anti-inflammatory and cytotoxic effects *in vivo* [7]. Strategic substitution patterns—including isobutyl, phenyl, and related aryl/alkyl groups—have shown marked effects on biological performance (IC_{50} values in the low nanomolar to micromolar range) and pharmacokinetic profiles, as demonstrated by recent structure–activity relationship studies [8-13].

Efforts to expand this chemotype rely on efficient and sustainable synthetic methodologies are well recognised need of the time. And in this endeavour, palladium-catalyzed C–N and C–C bond-forming reactions, including amination and arylation, have become central to the construction and diversification of nitrogen-rich heterocycles [14-18]. Advances in catalyst selection (e.g., Pd_2dba_3, NHC ligands), solvent optimization, and green chemistry approaches have enabled higher yields and broader substrate compatibility, increasing the molecular diversity accessible for biological screening.

In light of these developments, the present study describes the synthesis of novel 1-isobutyl-N-phenyl-

1*H*-imidazo[4,5-c] quinolin-4-amine derivatives using a Pd-catalyzed protocol and explores their cytotoxic potential against Human Lung Cancer Cell Line Hop-62. This work addresses the imperative need for new tumor-selective agents and contributes to an expanding library of lead-like heterocycles built on modern synthetic innovation.

II. EXPERIMENTAL SECTION

2.1 Chemicals and Solvents

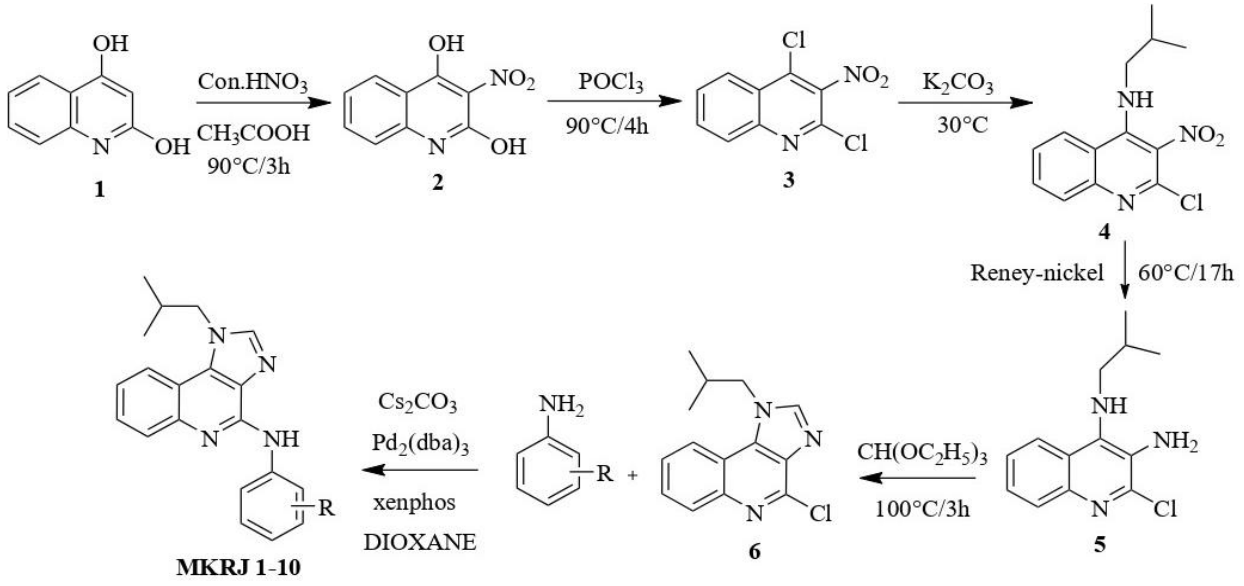
All chemicals and solvents were procured from Sigma Aldrich Chemical Co., Merck Chemicals, Finar, and Spectrochem Ltd. and were used as received without further purification unless otherwise stated. Thin-layer chromatography (TLC) was performed on precoated silica gel G60 F254 plates (0.2 mm thickness) from Merck. Spots were visualized under UV light at 254 and 365 nm or by iodine vapor staining. The anticancer activity was evaluated at the Anti-Cancer Drug Screening Facility (ACDSF), Research & Education in Cancer, Tata Memorial Centre, Mumbai, India. The cell lines used in this study were made available and maintained by ACDSF, Tata Memorial Centre, India.

2.2 Instrumentation

FTIR spectra were recorded on a Shimadzu FTIR-8400 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AVANCE-II 400 and 600 MHz spectrometers using $CDCl_3$or DMSO-d_6 as solvents with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a GC-MS QP-2010 mass spectrophotometer using the direct probe method. Melting points were measured by Labronics digital melting point apparatus. Products were purified by column chromatography and isolated using a BUCHI rotary evaporator.

2.3 Synthetic Procedures

A general procedure for the synthesis of 1-isobutyl-N-phenyl-1*H*-imidazo[4,5-c] quinolin-4-amine derivatives (MKRJ 01-10) is shown in Scheme 1. Typically, 0.5 g (0.002 mol) of 4-chloro-1-isobutyl-1*H*-imidazo[4,5-c] quinoline and 0.002 mol of the substituted aniline were dissolved in 1,4-dioxane (10 mL). $Pd_2(dba)_3$ (0.16 g, 8.5 mol%) and Xantphos (0.22 g, 17 mol%) were added under nitrogen atmosphere. The mixture was heated at 110 °C for 2 hours, cooled, filtered, and purified by column chromatography using 7:3hexane-ethyl acetate system.



Scheme 1. General sequence for the synthesis of 1-isobutyl-N-phenyl-1*H*-imidazo[4,5-c] quinolin-4-amine derivatives (MKRJ 01-10)

2.4 Optimization of Conditions

Catalyst loading, solvent, and base were optimized as shown in Table 1, with $Pd_2(dba)_3$ 8.5 mol%, Xantphos 17 mol%, 1,4-dioxane, and Cs_2CO_3 providing most favourable reaction conditions.

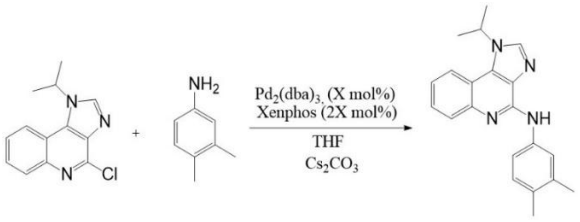


Table 1. Optimization of catalystloading

Entry	$Pd_2(dba)_3$	Xanphos	Yield (%) (Isolated)
1	3 mol %	6 mol %	11
2	5 mol %	10 mol %	32
3	8 mol %	16 mol %	44
4	8.5 mol %	17mol %	59
5	9 mol %	18mol %	55
6	10 mol %	20 mol %	51

Building on the promising preliminary results with optimized catalyst loading, we systematically evaluated a variety of solvents and bases to further improve the reaction efficiency. Among the solvents tested, 1,4-dioxane provided the highest yield, reaching 67%. Using these conditions, we next screened several inorganic bases including Cs_2CO_3, Na_2CO_3, and K_2CO_3. As summarized in Table 2, none of the alternative base and solvent combinations matched the performance observed with Cs_2CO_3 in 1,4-dioxane, which remained the optimal pairing for maximal yield.

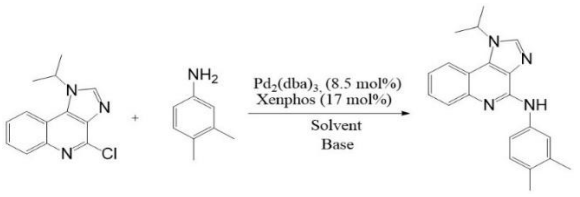
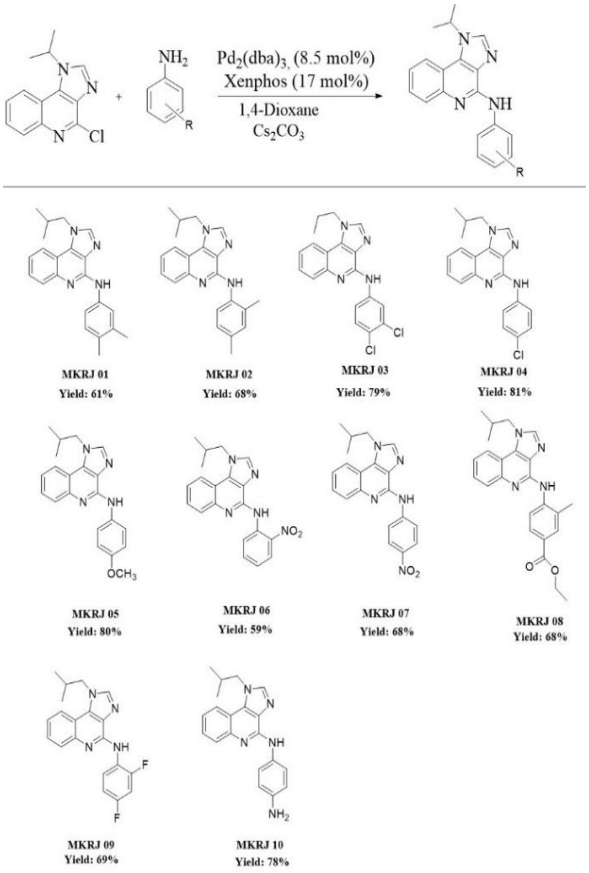


Table 2. Optimization of solvent and base

Entry	Solvent	Base	Yield (%)
1	THF	CS_2CO_3	51
2	1,4-dioxane	CS_2CO_3	67
3	DMSO	CS_2CO_3	57
4	Methanol	CS_2CO_3	14
5	1,4-dioxane	Na_2CO_3	55
6	1,4-dioxane	K_2CO_3	58

Using the in situ generated catalytic complex of $Pd_2(dba)_3$ (8.5 mol%) and Xantphos (17 mol%) in 1,4-dioxane with Cs_2CO_3 as base, we established the optimal reaction conditions. Employing this catalytic system, a series of substituted aniline derivatives was successfully coupled with 4-chloro-1-isobutyl-1*H*-imidazo[4,5-c] quinoline (Scheme 2). This approach afforded the desired products with isolated yields ranging from 59 to 81%, demonstrating broad substrate scope and efficiency.



Scheme 2. Substrate scope for 1-Isobutyl-N-phenyl-1*H*-imidazo[4,5-c] quinolin-4-amine derivatives

2.5 Biological Assay

Selected compounds were tested against Human Lung Cancer Cell Line Hop-62 by SRB assay in 96-well plates at 10, 20, 40, 80 μM concentrations, with adriamycin as control. Experiments were performed in triplicate and LC_{50}, TGI, and GI_{50}calculated.

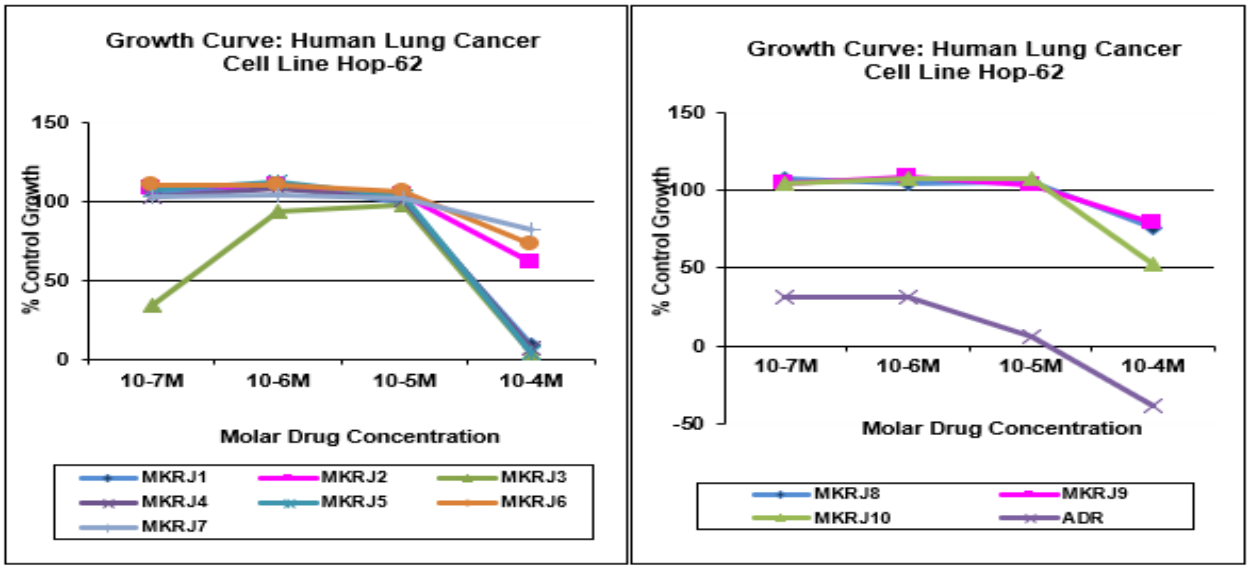


Figure 1 (A-B). Growth Curve: Human lung cancer cell line Hop-62

Table-3: Results of biological evaluation/ cytotoxicity evaluation

	Human Lung Cancer Cell Line Hop-62															
	% Control Growth															
	Molar Drug Concentrations															
	Experiment 1				Experiment 2				Experiment 3				Average Values			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
MKRJ1	114.2	123.0	99.1	8.1	105.7	108.7	97.6	7.5	94.3	101.2	99.1	10.5	104.7	111.0	98.6	8.7
MKRJ2	116.9	119.8	109.7	59.9	107.6	110.4	100.4	59.3	101.3	101.5	102.8	65.3	108.6	110.5	104.3	61.5
MKRJ3	42.5	107.5	100.4	3.3	31.3	91.4	94.5	3.9	28.6	81.2	99.0	5.5	34.1	93.4	98.0	4.2
MKRJ4	120.4	120.4	109.5	6.8	97.6	103.0	95.5	3.8	92.5	102.0	98.2	12.2	103.5	108.5	101.1	7.6
MKRJ5	116.3	124.8	110.2	5.2	106.1	108.2	98.8	3.3	100.7	105.9	101.1	4.7	107.7	112.9	103.4	4.4
MKRJ6	117.9	118.8	111.0	73.8	108.7	111.2	104.7	71.6	103.9	102.7	103.1	73.6	110.2	110.9	106.3	73.0
MKRJ7	102.6	105.4	102.2	84.0	106.3	104.6	98.6	82.8	100.3	101.5	104.1	79.5	103.1	103.8	101.6	82.1
MKRJ8	103.6	94.3	96.0	75.3	99.1	98.0	101.0	72.9	119.7	120.6	117.9	77.6	107.5	104.3	104.9	75.2
MKRJ9	105.0	99.3	95.3	81.6	98.6	97.6	96.8	77.2	109.7	127.0	116.1	76.4	104.5	107.9	102.7	78.4
MKRJ10	106.5	102.5	104.8	54.1	97.1	96.4	98.3	50.8	109.4	121.8	119.8	52.8	104.3	106.9	107.6	52.6
ADR	60.9	31.5	6.8	-31.1	26.9	29.1	3.9	-42.1	6.2	31.5	5.5	-42.8	31.3	30.7	5.4	-38.7

III. RESULTS AND DISCUSSION

3.1 Catalyst and Condition Optimization

Optimal catalyst loadings and solvent/base pairs were established with $Pd_2(dba)_3$ (8.5 mol%) and Xantphos (17 mol%) in 1,4-dioxane using Cs_2CO_3(Tables 1 & 2). Yields ranged 59–81%.

3.2 Substrate Scope

The approach delivered 10 derivatives (MKRJ 01–10) efficiently from various anilines (Scheme 2).

3.3 Structural Confirmation

Characterization by FTIR, NMR, and mass spectrometry confirmed the expected structures; detailed spectral data provided in supplementary information.

3.4 Spectral data of compounds

3.4.1.4-chloro-1-isobutyl-1H-imidazo[4,5-c] quinolone (6).

Yellow solid; 0.68 (7:3 hexane-EtOAc); mp138-140 °C, ^{1}H NMR 400Hz DMSC D_6, δ 1.04 (s,3H), 1.06 (s,3H), 2.32-2.39 (m,1H), 4.37 (d, 2H, *J*=7.6 *Hz*), 7.63-7.63 (m,1H), 7.68-7.73 (m,1H), 7.94 (s,1H), 8.08 (dd,1H, *J*=8.4 *Hz*& 1.2 *Hz*), 8.19 (dd, 1H, *J*=8.0 *Hz* & 1.6 *Hz*) MS(*m/z*): 259.74, Elemental analysis for $C_{14}H_{14}ClN_3$, Found: C, 64.74; H, 5.43; Cl, 13.65; N, 16.18.

3.4.2.N-(3,4-dimethylphenyl)-1-isobutyl-1*H*-imidazo[4,5-c] quinolin-4-amine (MKRJ 01).

Yellow solid; 0.62 (7:3 hexane-EtOAc); mp122-124°C, ^{1}H NMR 400Hz DMSC D_6, δ 1.02 (s,6H), 2.25(s,3H), 2.31(s,3H) 2.32(s,1H) 7.51(d,1H,*J*=8.4 *Hz*) 7.33(td,1H, *J*=7.2 *Hz*& 1.2 *Hz*) 7.53 (td,1H,*J*=8.4 *Hz*& 1.2 *Hz*) 7.74 (s,2H) 7.80 (d, 1H, *J*=81.6 *Hz*) 7.84 (dd,1H,*J*=8.2 *Hz*& 2.4 *Hz*) 7.87 (d,1H,*J*=8.0 *Hz*) 8.02 (dd, 1H, *J*=8.4 *Hz*& 0.8 *Hz*): ^{13}CNMR (100Hz,$CDCl_3$), 19.18, 19.84, 20.20, 28.82, 55.13, 76.73,77.05,77.36,115.74,116.61,119.74,120.43, 122.63, 127.23, 128.58, 129.16, 129.93, 130.23, 132.02, 136.95, 138.04, 141.92, 145.05, 147.80: MS(*m/z*): 344.45, Elemental analysis for $C_{22}H_{24}N_4$, Found: C, 76.71; H, 7.02; N, 16.27.

3.4.3.N-(2,4-dimethylphenyl)-1-isobutyl-1*H*-imidazo[4,5-c] quinolin-4-amine (MKRJ02).

Yellow solid; 0.64 (7:3 hexane-EtOAc); mp-130-132°C ^{1}H NMR 400Hz DMSC D_6, δ 0.95 (d,6H,*J*=6.8 *Hz*), 1.71-2.33 (m,4H), 3.63 (s,1H), 4.22 (d,2H,*J*=7.2 *Hz*) 6.98 (s,1H), 7.05 (d,1H,*J*=8.4 *Hz*), 7.26 (td,1H,*J*=8.0 *Hz*& 1.2 *Hz*), 7.44 (td,1H, *J*=5.6 *Hz*& 1.6 *Hz*), 7.54 (s,1H), 7.69 (s,1H), 7.82 (dd,1H,*J*=8.0 *Hz*& 0.8 *Hz*), 7.89 (dd,1H,*J*=8.4 *Hz*& 0.8 *Hz*), 8.52 (d,1H,*J*=84.0 *Hz*): ^{13}C NMR (100Hz,$CDCl_3$),18.00, 19.84, 20.89, 28.83, 55.12, 76.74, 77.05, 77.37, 115.79, 119.74, 120.79, 122.61, 127.17, 127.19, 127.34, 128.62, 129.40, 131.04,1 31.99, 132.03, 135.63, 142.01, 145.04,147.98: MS(*m/z*): 344.45, Elemental analysis for $C_{22}H_{24}N_4$, Found: C, 76.71; H, 7.02; N, 16.27.

3.4.4.N-(3,4-dichlorophenyl)-1-isobutyl-1*H*-imidazo[4,5-c] quinolin-4-amine (MKRJ 03).

Yellow solid; 0.65 (7:3 hexane-EtOAc); mp128-130°C ^{1}H NMR 400Hz DMSC $D_6\delta$ 0.95 (d,5H,*J*=6.8 *Hz*), 1.17 (s,2H), 1.96-2.30 (m,1H), 4.2 (d, 2H, *J*=7.2 *Hz*), 7.23-7.34 (m, 2H), 7.48-7.52 (m,1H), 7.67 (dd,1H, *J*=8.4 *Hz*& 3.4 *Hz*), 7.81 (d,1H,*J*=8.0 *Hz*), 7.87 (s,1H), 7.96 (d,1H,*J*=8.4*Hz*) 8.42 (d,1H, *J*=2.4 *Hz*) MS(*m/z*): 385.29, Elemental analysis for $C_{20}H_{18}N_4Cl_2$, Found: C, 62.35; H, 4.71; Cl, 18.40; N, 14.54

3.4.5.N-(4-chlorophenyl)-1-isobutyl-1*H*-imidazo[4,5-c] quinolin-4-amine (MKRJ 04).

Yellow solid;0.63 (7:3 hexane-EtOAc);mp128-130°C ^{1}H NMR 400Hz DMSC D_6, δ 0.96 (d,6H,*J*=6.8 *Hz*), 1.97 (s,1H), 2.26-2.33(m,1H), 4.22 (t,2H,*J*=7.2 *Hz*), 7.27 (d,2H,*J*=8.8 *Hz*), 7.32 (t,1H,*J*=7.2 *Hz*), 7.5 (t,1H,*J*=8.0 *Hz*), 7.71 (s,1H), 7.82 (d,1H,*J*=8.8 *Hz*), δ 7.96 (t,1H,*J*=8.8 *Hz*): MS(*m/z*): 350.84, Elemental analysis for $C_{20}H_{19}ClN_4$, Found: C, 68.47; H, 5.46; Cl, 10.10; N, 15.97

3.4.6.Ethyl 4-((1-isobutyl-1*H*-imidazo[4,5-c] quinolin-4-yl) amino)-3-methylbenzoate (MKRJ 08).

Yellow solid;0.67 (7:3 hexane-EtOAc);mp120-122°C ^{1}H NMR 400Hz DMSC D_6, δ 0.98 (d,6H,*J*=6.8 *Hz*), 1.17-2.34(m,1H), 2.45 (s,3H), 3.84 (s,3H), 4.26 (d,2H,*J*=8.0 *Hz*), 7.35 (td,1H,*J*=8.4 *Hz*& 1.2 *Hz*), 7.52 (td,1H,*J*=8.4 *Hz*&1.2 *Hz*), 7.7 (s,1H) 7.85(d,1H,*J*=1.2 *Hz*), 7.88 (dd, 1H, *J*=8.4 *Hz*& 0.4 *Hz*), 7.39 (s,1H), 7.97 (dd,1H,*J*=8.8 *Hz*& 2.0 *Hz*) 8.01 (dd,1H,*J*=8.4

Hz& 0.8 *Hz*), 9.16 (d,1H,*J*=8.8 *Hz*). ^{13}CNMR (100Hz, $CDCl_3$),17.75, 19.82, 28.86, 51.84, 55.18, 76.72, 77.04, 77.36, 116.07, 117.90, 119.83, 122.64, 123.55, 124.85, 127.48, 128.94, 129.08, 129.54, 131.63, 132.29, 142.31, 142.92, 144.50, 147.06, 160.08, 167.30: MS(*m/z*): 402.5, Elemental analysis for $C_{24}H_{26}N_4O_2$, Found: C, 71.62; H, 6.51; N, 13.92; O, 7.95

3.4.7.N-(2,4-difluorophenyl)-1-isobutyl-1*H*-imidazo[4,5-c] quinolin-4-amine (MKRJ 09).
Yellow solid;0.65 (7:3 hexane-EtOAc);mp116-118°C ^{1}H NMR 400Hz DMSC D_6, δ 0.98 (d,6H,*J*=6.8 *Hz*), 2.3 (t,1H,*J*=6.8 *Hz*), 4.25 (d,2H,*J*=7.2 *Hz*), 6.80-6.9 (m,2H), 7.33 (td,1H,*J*=8.4 *Hz*& 1.2 *Hz*), 7.50 (td,1H,*J*=5.6 *Hz*& 1.6 *Hz*), 7.73 (s,1H), 7.87 (dd,2H,*J*=8.0 *Hz*& 01.2 *Hz*), 7.95 (dd,1H,*J*=1.2 *Hz*& 0.4 *Hz*), 9.11 (td,1H,*J*=9.2 *Hz*& 6.0 *Hz*):MS(*m/z*): 352.39, Elemental analysis for $C_{20}H_{18}N_4F_2$, Found: C, 68.17; H, 5.15; F, 10.78; N, 15.

3.4 Biological Activity
The compounds showed promising growth inhibition of Human Lung Cancer Cell Line Hop-62 with several exceeding adriamycin activity (Table 2).

3.5 Discussion
Results suggest substituent electronic and steric factors significantly affect cytotoxic activity, corroborating literature [3,7]. Pd-catalyzed amination is effective for heterocycle diversification and drug lead generation.

IV. CONCLUSION

This study demonstrates an efficient Pd-catalyzed synthetic method to diversify 1-isobutyl-N-phenyl-1*H*-imidazo[4,5-c] quinolin-4-amine derivatives with promising anticancer activity against Human Lung Cancer Cell Line Hop-62. The findings promise the expansion of pharmacologically important heterocycles for drug discovery efforts, especially towards combating the cancer.

Author contributions. The research scheme was designed by YN and MS. PA and MS wrote the main manuscript. TM and SH supported in the characterization and prepared supporting material file. All authors reviewed the manuscript.

Data Availability Statement:
The authors declare that the data supporting the findings of this study are available within the paper. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request.

V. DECLARATIONS

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Consent to Publish declaration: not applicable

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