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Discovery of 1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-ones based novel, potent and PI3Kδ selective inhibitors[#]

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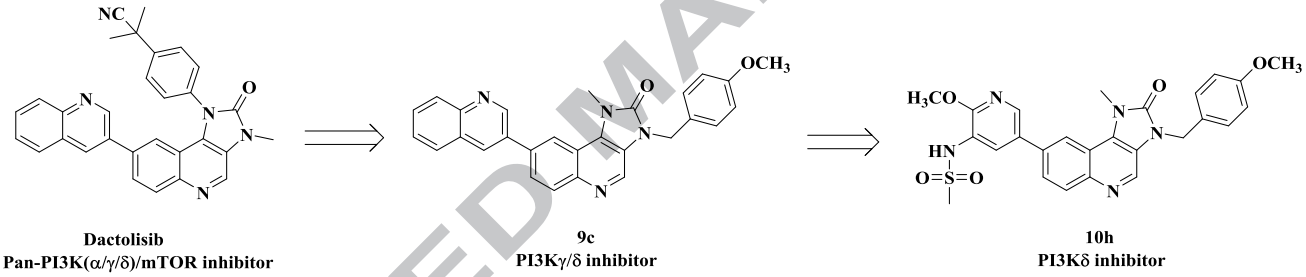

ABSTRACT:

PI3Kδ is implicated in various inflammatory and autoimmune diseases. For the effective treatment of chronic immunological disorders such as rheumatoid arthritis, it is essential to develop isoform selective PI3Kδ inhibitors. Structure guided optimization of an imidazo-quinolinones based pan-PI3K/*m*-TOR inhibitor (Dactolisib) led to the discovery of a potent and orally bioavailable PI3K*δ* isoform selective inhibitor (**10h**), with an improved efficacy in the animal models.

#ZRC communication No: 587 *(Part of PhD thesis work of Mr. B. Dave).*

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Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovitis and joint destruction. Treatment with biologic agents such as tumor necrosis factor (TNF) inhibitors has improved outcomes, but in general, biologics are expensive, injectable and many patients have inadequate responses. Thus, orally bioavailable small molecule inhibitors that target signal transduction and regulate innate and adaptive immune responses in RA have emerged as potential alternatives to expensive biologics.[1]

Phosphoinositide-3-kinases (PI3Ks) constitute central signaling hub that mediates diverse and crucial cell functions, including cell growth, proliferation, differentiation and survival.[2,3] PI3Ks have been classified into three classes (I, II and III) based on substrate specificity, sequence homology and regulatory subunits. The class I PI3Ks consists of four kinases (PI3K-*α*, *β*, *δ* and *γ)* and further grouped into two sub-classes: class IA and class IB. The class IA comprises three closely related kinases, PI3K-*α*, *β* and *δ*, while the class IB contains only one member PI3K-*γ*.[4] The PI3Kα and β are expressed in a wide variety of tissues and organs. PI3Kγ is found mainly in leukocytes, while expression of PI3Kδ is restricted to spleen, thymus, hematopoietic cells and peripheral blood leukocytes.[5] PI3Kγ and PI3Kδ are mainly expressed in rheumatoid arthritis (RA) synovium and regulate innate and adaptive immune responses.[6]

Inhibition of PI3Ks is considered as one of the most interesting targets. Earlier attempts were mainly focused on developing the broad-spectrum (pan) inhibitors of the PI3K (*α*, *β*, *γ* and *δ*) isoforms, as potential oncology therapeutics.[7,8,9] Knowing the potential side effects associated with PI3K*α* and *β* isoforms inhibition (due to universal expression), recently, efforts are directed towards the development of PI3K*δ* selective inhibitors, for the effective treatment of hematological malignancy and inflammatory disorders. [10,11,12]

Over the past decades, several structurally diverse PI3K inhibitors were identified containing quinolines and imidazoquinolinones as promising scaffold (Figure 1). The Omipalisib[13,14] and Dactolisib[14], discovered by GlaxoSmithKline and Novartis respectively, as dual PI3K and mTOR inhibitors are under clinical trials. PI3Kδ selective inhibitors, Idelalisib[15] (ZYDELIG®, Gilead Sciences, in 2014) is available for the treatment of hematologic malignancies. Recently, US-FDA approved Duvelisib[16,17] (COPIKTRA®, Verastem, Inc) for the treatment of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). There is still requirement to develop safe and highly potent PI3Kδ selective inhibitors, for the effective management of

chronic inflammatory and autoimmune disorders, such as rheumatoid arthritis (RA) and hematological malignancy.

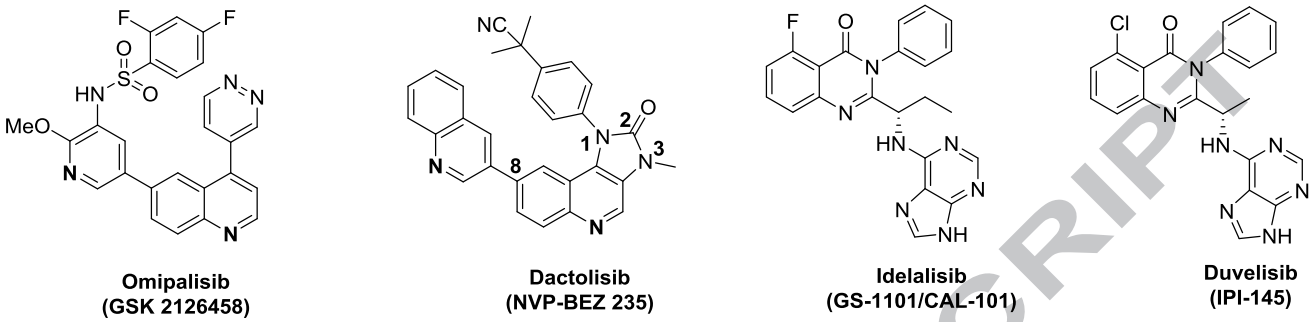


Figure 1. The structures of quinoline and imidazoquinolinone-based PI3K inhibitors.

We aim to discover novel, potent and orally bioavailable PI3K*δ* selective inhibitors, mainly by favoring the suitable accommodation of designed molecules, in the specificity pocket, to achieve PI3Kδ selectivity.[18] Considering imidazoquinolinone moiety as a starting point, appropriate structural modifications were carried out in the Dactolisib (pan-PI3K/mTOR inhibitor), to improve PI3Kδ selectivity. Two set of compounds were designed (as listed in Table 1 and 2). Initial modifications on imidazole ring (of Dactolisib), involves positional changes of methyl (N1 to N3) and phenyl (N3 to N1) groups and introduction of a carbon spacer (phenyl to benzyl) at N3 position. Further modifications were carried out at the *p*-position of benzyl ring (Set-1, Table 1) to obtain the single digit nM potency (**9c**). Compound **9c** was found to be potent but showed moderate isoform selectivity (Table 3). In the second set (Set-2, Table 2), changes were carried out on the 8th position of **9c** to improve isoform selectivity and in vivo efficacy.

Herein, we report, design, synthesis and biological evaluation of novel 1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-ones based PI3K*δ* selective inhibitors. Test compounds were screened in vitro for PI3Kδ inhibitory activity and most potent compounds from each set were tested for in vitro PI3K isoform selectivity (α, β & γ) and mTOR inhibitory activity. Based on the in vitro results, highly potent and selective compound **10h** was selected for in vivo PK and PD (anticancer and anti-inflammatory activities) studies.

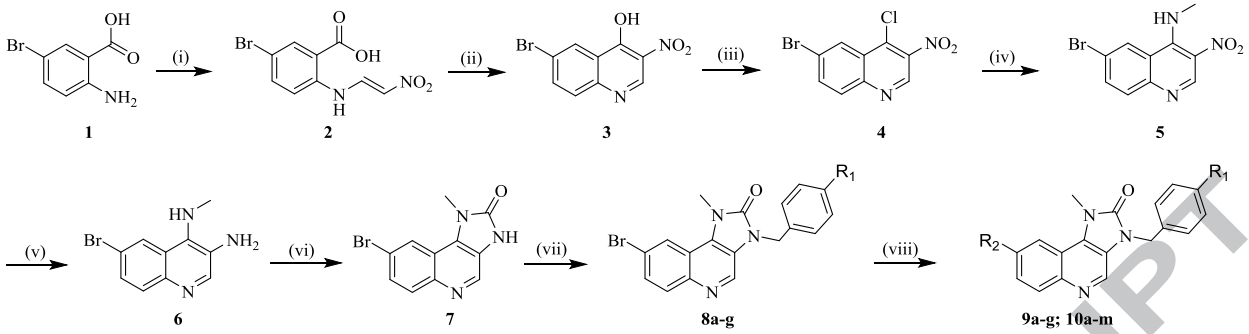
Synthesis of 1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one derivatives (**9a-g** and **10a-m**) was carried out as depicted in Scheme 1, following the modified literature procedure.[20] Treatment of

bromo anthranilic acid (**1**) with nitro methane gives nitro vinyl anthranilic acid (**2**), which was cyclized using potassium acetate in acetic anhydride to get the bromo nitro quinolinol (**3**). Compound **3** was converted to reactive chloro derivate (**4**) using $POCl_3$, followed by nucleophilic substitution with methylamine to get the compound **5**. Nitro group of **5** was reduced, using $SnCl_2$ to get the compound **6,** which was cyclized using diphosgene in the presence of base, to obtain the imidazoquinoline (**7**). Alkylation of **7** using strong base and aryl halides furnished compounds **8a-g**, which were converted to **9a-g** and **10a-m**, using $PdCl_2(PPh_3)_2$, potassium bicarbonate and aryl or heteroaryl boronic acids.

Overall, 20 compounds (**9a-g** and **10a-m**) were prepared in good yield (60 to 80%), under the mild reaction condition. Spectral data of compounds were found to be in conformity with the structures assigned, which ensure the formation of the compounds **9a-g** and **10a-m** (see supporting information for analytical and spectral data).

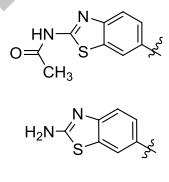
For in vitro PI3Kδ inhibitory activities, Idelalisib and Dactolisib were used as a positive control. In Set-1 (Table 1), 4-substituted-(benzyl)-8-quinolinyl-imidazo[4,5-*c*]quinolinone (**9a-g**) analogues displayed varying degree of PI3Kδ inhibitory activities at 100 nM concentration. Compound **9a** (2-methyl-propanenitrile substitution on a benzyl ring) showed moderate PI3Kδ inhibitory activity (56% PI3Kδ inhibition at 100 nM), while replacement of the nitrile group (Compound **9b**: 73% inhibition) exhibited enhanced PI3Kδ inhibitory activity (IC_{50}: 28.3 nM). Replacement of isopropyl (**9b**) with methoxy (**9c**, IC_{50}: 9.5 nM) and methyl (**9d**, IC_{50}: 18.4 nM) demonstrated higher PI3Kδ inhibitory activity, whereas replacement with an electron withdrawing NO_2 (**9e**, 62% inhibition), electronegative F (**9f**: 51% inhibition) and the unsubstituted compound **9g** (22% inhibition) displayed weak PI3Kδ activity.

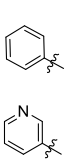
Scheme 1: Synthesis of compounds **9a**-**g** and **10a**-**l**.

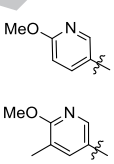


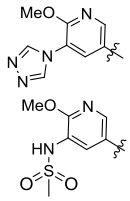
Compound	R_1
8a	$-C(CH_3)_2CN$
8b	$-CH(CH_3)_2$
8c	OCH_3
8d	CH_3
8e	NO_2
8f	F
8g	H

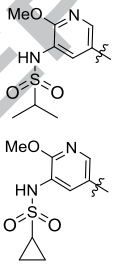
Compound	R_1	R_2
9a	$-C(CH_3)_2CN$	
9b	$-CH(CH_3)_2$	
9c	OCH_3	
9d	CH_3	
9e	NO_2	
9f	F	
9g	H	

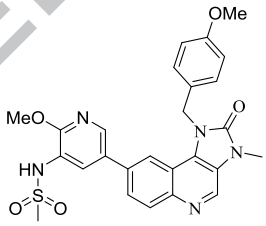
Compound	R_1	R_2
10a	OCH_3	
10b		

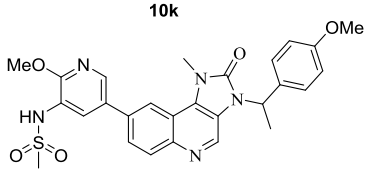
Compound	R_1	R_2
10c	OCH_3	
10d		

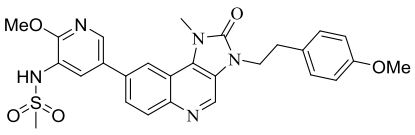
Compound	R_1	R_2
10e	OCH_3	
10f		

Compound	R_1	R_2
10g	OCH_3	
10h		

Compound	R_1	R_2
10i	OCH_3	
10j		


10k

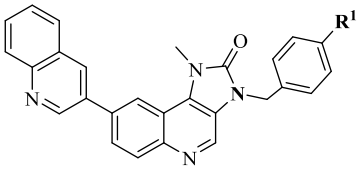

10l


10m

Reagents and conditions: i) conc. HCl, water, 26°C,6 h, then nitro methane, NaOH, water, Conc. HCl, 26 °C,16 h, 95%; ii) KOAc, acetic anhydride, 120-125 °C,4h, 60%; iii) $POCl_3$, 120 °C, 4h, 80%; iv) Me-NH_2, TEA, DCM, 26°C, 12h, 94%; v) $SnCl_2.2(H_2O)_2$, EtOAc, 26 °C , 60%; vi) Diphosgene, TEA, DCM, 0-26°C, 65%; vii) R_1-Ar-CH_2-X (Cl or Br), NaH, THF, 0-26 °C, 65 – 75 %; viii) R_2-$B(OH)_2$,$PdCl_2(PPh_3)_2$, $KHCO_3$, DMF, H_2O, 90-95 °C, 1.5 h, 60 - 80%.

In Set-1, compound **9c** (methoxy) showed most potent PI3Kδ inhibitory activity, which was found to be similar to Dactolisib (IC_{50}: 8 nM; Table 1) and 4.5 fold less potent compared to Idelalisib (IC_{50}: 2.1 nM). Thus, in the Set-1, positional changes of methyl (N1 to N3) and phenyl (N3 to N1) groups and introduction of a carbon spacer (phenyl to benzyl) at N3 position, followed by substitution on *p*-position of benzyl ring led to the single digit nM potent compound (**9c**) with moderate isoform selectivity (Table 3).

Table 1: PI3K*δ* inhibitory activity of 4-substituted-(benzyl)-8-quinolinyl-imidazo[4,5-*c*]quinolinone (**9a-g**)



9a-g

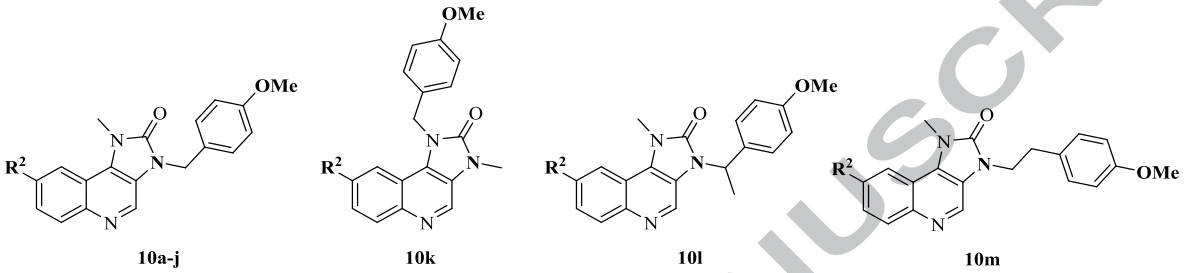
Comp.	R^1	PI3Kδ inhibition (%)[a,b]	PI3Kδ IC_{50} (nM)[c]
9a		56	ND
9b		73	28.3
9c		98	9.5
9d	$-CH_3$	80	18.4
9e	$-NO_2$	62	ND
9f	-F	51	ND
9g	-H	22	ND
Dactolisib	-	92	8
Idelalisib	-	96	2.1

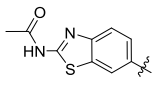
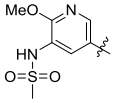
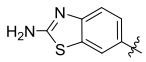
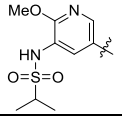
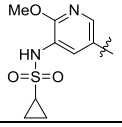
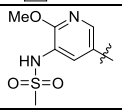
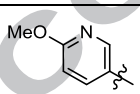
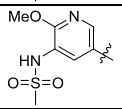
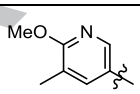
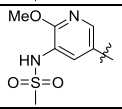
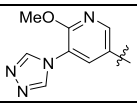
[a]All the data are shown as the mean for at least two experiments. [b]PI3Kδ inhibition at the concentration of 100 nM using PI3K Kinase Activity/Inhibitor assay Kit from Millipore. [c]The IC_{50} values for PI3Kδ inhibition.ND: not detected.

To improve PI3Kδ isoform selectivity, modifications were carried out in **9c** as a primary lead. In the second set (Table 2), we found that the PI3K*δ* inhibitory activity was retained by doing modifications at 8th position of quinoline in **9c**. As listed in Table 2 (Compounds **10a-m**), replacement of quinoline moiety in **9c** with benzothiazole (**10a** and **10b** (acylated **10a**)) showed 50% PI3Kδ inhibition at 100 nM. Phenyl derivative (**10c**) was found to be less potent (PI3K*δ* IC_{50}: 29.4 nM) compared to **9c**, while Pyridyl derivatives (**10d**) showed some improvement in the potency (IC_{50}: 20 nM). Introduction of methoxy (**10e**) and 3-methyl-2-methoxy substituents

(**10f**) were found to be equipotent (IC_{50}: ~11 nM). Triazole motif (**10g**) showed less activity compared to **9c**, while *m*-methanesulfonamide derivative (**10h**) was found to be the most potent (IC_{50}: 1.9 nM) among all. Replacement of methyl group in **10h**, with iso-propyl (**10i**) and cyclo-propyl (**10j**) showed three fold less activity compared to **10h**.

Table 2: Influence of modification of C8 position of Quinoline moiety on PI3K*δ* isoform selectivity and mTOR selectivity.



Comp.	R^2	PI3Kδ inhibition (%)[a,b]	PI3Kδ IC_{50} (nM)[c]	Comp.	R^2	PI3Kδ inhibition (%)[a,b]	PI3Kδ IC_{50} (nM)[c]
10a		52	ND	**10h**		99	1.9
10b		58	ND	**10i**		91	6.2
10c		72	29.4	**10j**		93	5.9
10d		81	20	**10k**		98	4.1
10e		87	11.4	**10l**		60	ND
10f		88	11.1	**10m**		56	ND
10g		62	ND	**Idelalisib**		96	2.1

[a]All the data are shown as the mean for at least two experiments. [b]PI3Kδ inhibition at the concentration of 100 nM using PI3K Kinase Activity/Inhibitor assay Kit from Millipore. [c]The IC_{50} values for PI3Kδ inhibition.ND: not detected.

Compound **10K**, a regioisomer of **10h**, wherein benzyl and methyl groups are interchanged on imidazole ring showed two fold less active compared to **10h**. Similarly, racemic compound **10l**, and **10m** (one carbon homologs at N3 with respect to **10h**) were found to be less active.

Most potent compounds (**9c**, **10h** and **10k**) were evaluated for their selectivity against PI3K isoforms (α, β and γ) and mTOR. As shown in the Table 3, initial hits (**9c** and **10k**) showed moderate selectivity against PI3K isoforms and mTOR over PI3Kδ. Compound **10h** (IC_{50}: 1.9 nM) demonstrated 469, 310, and 59-fold selectivity over PI3Kα, β and γ respectively. Moreover, it was noted that selectivity of **10h** against all the three isoforms was higher than standard compounds. In general, it was observed that the potency and selectivity of imidazoquinolinone-based PI3Kδ inhibitors can be modulated using suitable substituents at R^1 and R^2 positions.

Table 3: Isoform selectivity of compounds against PI3K (α,β,γ, and δ) and mTOR activities.

Comp.	Biochemical IC_{50} [nM][a]				
	PI3Kα[b]	PI3Kβ[b]	PI3Kγ[b]	PI3Kδ[b]	mTOR[b] (p70S6K)
9c	421	342	38	9.5	676
10h	891	589	112	1.9	>1000
10k	289	241	42	4.1	580
Dactolisib	5	79	6	8	14
Idelalisib	831	571	92	2.1	>1000

[a]The IC_{50} values are shown as the mean for at least two experiments. [b]PI3K inhibitory activity assay Kit (Millipore) was used to screen the test compounds.

In vitro kinase profiling study of **10h** was carried out @ 1μM concentration, against 140 kinases and % inhibition was found to be < 20% at 1μM concentration. Compound **10h** was tested for its anti-proliferative activities against TMD-8 cell lines[21] with Idelalisib as a reference compound. In anti-proliferative in vitro assay, **10h** and Idelalisib exhibited potent anti-proliferative activity with an IC_{50} value of 340 and 795 nM respectively. Additional profiling studies of compound **10h** was carried out and it was found to be devoid of CYP[22] (<10% CYP inhibition at 10 μM

concentration, for CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2C19 and CYP3A4) and hERG liabilities (IC_{50}: > 30 μM), while Idelalisib showed moderate CYP3A4 inhibition. [23]

A comparative single dose (3 mg/kg, po and 1 mg/kg, iv) PK profile of compounds **9h**, **10h** and Dactolisib was evaluated in male C57BL/6J mice (n =6) and the various PK parameters (Tmax, Cmax, $t_{1/2}$, Cl, AUC and %F) were recorded (Table 4). In PK study, **9c** showed moderate AUC and clearance, which resulted into overall low bioavailability (~15%). Compound **10h** showed rapid Tmax, higher AUC (~5 fold, compared to standard), extended $t_{1/2}$ (~3.5 hr) and good oral bioavailability (%F ~69 over standard, 38%). Compound **10h** showed extended $t_{1/2}$ and higher AUC, which could be due to its low clearance compared to standard (8.24 vs 72.5 ml/min/kg, iv).

Table 4: Pharmacokinetic study parameters[a] of **9c**, **10h** and Dactolisib in C57 mice

Compd	Tmax (h)	Cmax (μg/ml)	$t_{1/2}$ (h)	Cl (ml/min/kg), iv	AUC (0-α) h μg/ml	%F*
9c	0.38	127.61	2.31	22.9	329.08	14.77
10h	0.25	1278.49	3.48	8.24	3831.48	68.91
Dactolisib	0.21	273.83	1.88	72.5	243.64	37.82

[a]In male C57BL/6J mice (n=6), compounds were administered orally (p.o) at 3 mg/kg dose and plasma concentration was analyzed by LC-MS, values indicate Mean ± SD.

* Oral bioavailability (%F) was calculated wrt to iv AUC. Compounds **9c**, **10h** and Dactolisib administered at 1 mg/kg dose, iv AUC: 742.56, 1852.95 and 215.14 respectively.

Considering low bioavailability of **9c**, in PD models, only **10h** was evaluated. Collagen Induced Arthritis (CIA) mice model was used to check anti-arthritic efficacy of test compounds.[17] Arthritis was developed in male DBA1j mice, using collagen mixture and mice were recruited for the study once clinical signs were visible. Eight animals were assigned in each of the four groups [vehicle, positive control (Dactolisib, 60 mg/kg dose was selected considering low oral bioavailability, compared to **10h**) and two doses of test compound **10h** (10 and 30 mg/kg) was selected considering 89% plasma protein binding and $t_{1/2}$ of ~3.5 h]. Treatment was continued for four weeks and percentage inhibition in clinical score was recorded.

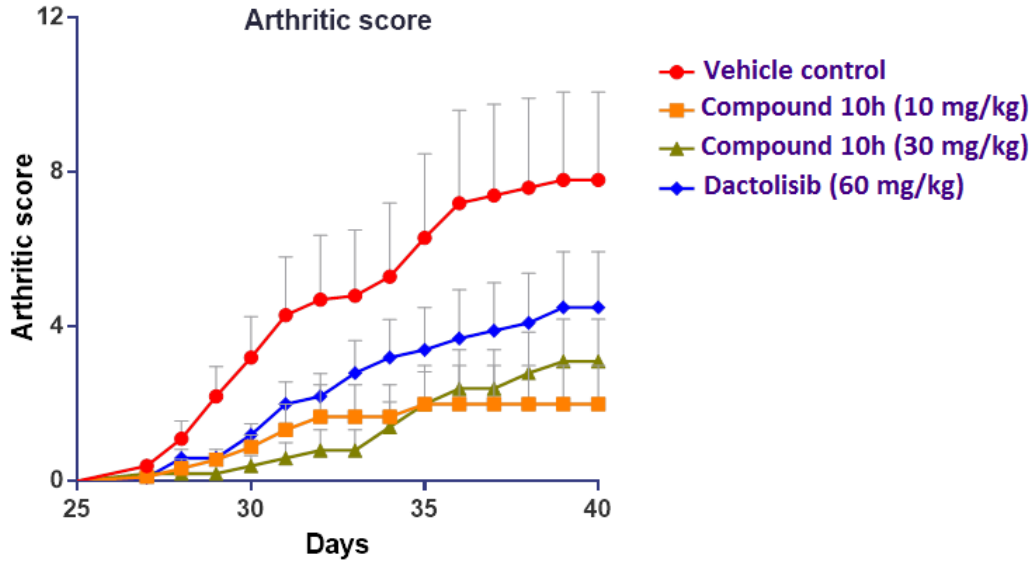


Figure 2a: Effect of Compound **10h** and **Dactolisib** in CIA mice model.

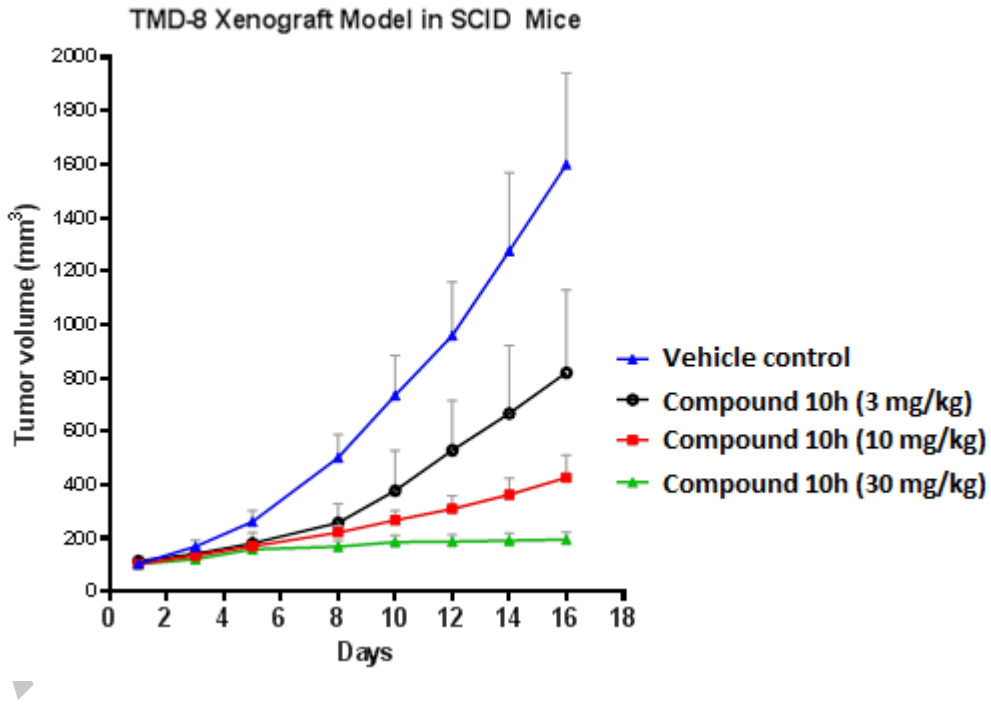


Figure 2b: In vivo anti-tumor activity of Compound **10h** in SCID mice xenograft model.

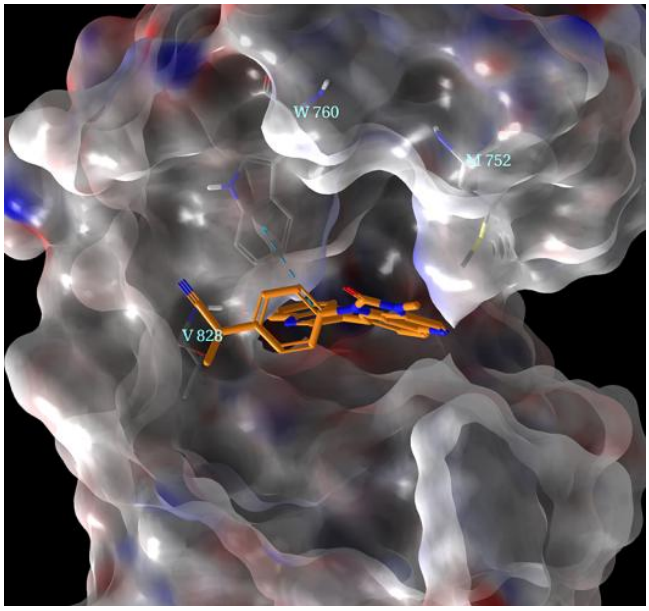
As shown in the Figure 2a, standard and **10h** showed good reduction in the arthritic score, compared to vehicle control (untreated group). Two fold higher dose of a standard compound was used, considering two fold difference in the mice oral bioavailability. At 30 mg/kg dose, compound **10h** showed superior activity compared to standard compound (dose 60 mg/kg). Body weights of the animals were also recorded 3 times a week as a measure of treatment related side effect and **10h** showed no significant reduction in the body weight, even at 30 mg/kg dose, while Dactolisib exhibited reduction in body weight.

Additionally, in vivo anti-tumor activity of **10h** was checked in male SCID mice xenograft model (inoculated with TMD-8 cells). Inhibition of tumor volume compared to vehicle control (untreated group) was considered as efficacy end point. As shown in Figure 2b, three doses (3, 10 and 30 mg/kg/day, orally) of **10h** were administered and it showed dose dependent reduction in the tumor volume. At 30 mg/kg dose, **10h** showed complete inhibition of tumor volume compared to vehicle control. Body weights of the animals were also recorded and **10h** showed no significant reduction in the body weight, even at 30 mg/kg dose. Thus improved PK of **10h** justifies its potent in vivo activity in both the animal models.

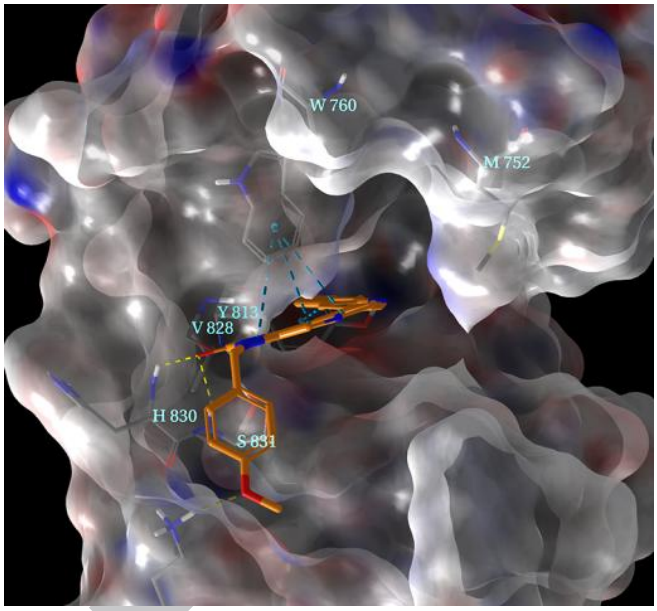
The structure of mPI3Kδ co-crystallised with Idelalisib (PDB ID: 4XE0)[18] was prepared using protein preparation wizard of Schrodinger Suite 2018 at pH 7.4, which was used for generating the docking grid. The Glide docking was performed using Glide SP with default parameters. Ligand molecules (Idelalisib, Dactolisib, **9c**, **10h** and **10k**) were prepared using LigPrep module of Schrodinger Suite 2018. [24]

The results of docking has been summarized in Figure 3 where it is clear from the docking poses of the docked ligands that specificity pocket was fully occupied by **10h** and **10k**, however in case of Dactolisib and **9c**, the specificity pocket was not occupied and this explains why **10h** and **10k** were more selective towards PI3Kδ.

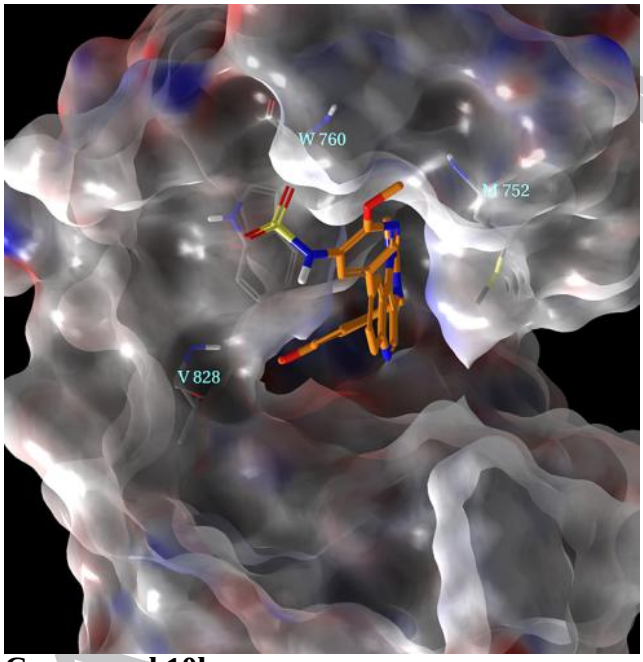
A



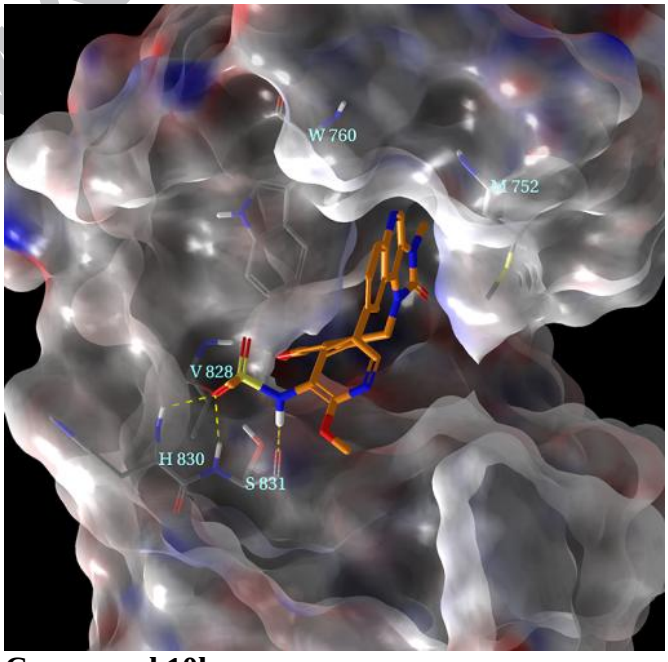
Dactolisib



Compound 9c



Compound 10h



Compound 10k

Figure 3: The Glide docking studies of Compounds **9c, 10h**, **10k** and **Dactolisib** into the site of PI3Kδ (PDB ID: 4XE0). Compounds are shown as sticks. Hydrogen bonds are shown as yellow dashed lines.

In conclusion, we have synthesized and evaluated two sets of novel series of 1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one derivatives as selective PI3Kδ inhibitors. In first set, appropriate modifications were carried out in the imidazoquinoline ring, which led to an identification of a single digit nM potent PI3Kδ inhibitor (**9c**), with moderate isoform selectivity. In set 2, further structure-activity relationship (SAR) studies on the 8th position of **9c** resulted in to the discovery of *N*-(2-methoxy-5-(3-(4-methoxybenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-*c*]quinolin-8-yl)pyridin-3-yl)methanesulfonamide (**10h**) that showed improved isoform selectivity, PK profile and good efficacy in a CIA and xenograft animal models. The results of docking study showed that specificity pocket was fully occupied by **10h**, which explains its more selective towards PI3Kδ. Overall pre-clinical data suggest that the development of a potent and selective PI3Kδ inhibitor could be viable therapeutic option for the effective management of rheumatoid arthritis.

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Notes

The authors declare no competing financial interest.

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