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Design and synthesis of 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-ones by Huisgen 1,3-dipolar cycloaddition with PI3Kγ isoform selective activity

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ABSTRACT

A strategy for construction of medicinally important 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-ones has been devised and presented here. The compounds have been synthesized using one-pot multi-component strategy under microwave assisted conditions. Triazolyl-quinazolinone based D-ring modified analogs are designed based on IC87114 scaffold, which is first known isoform selective inhibitor of PI3Kδ. Herein, we identified two triazolyl-quinazolinone compounds (**5a** and **5l**) based on same scaffold with PI3Kγ specific inhibitory potential, the selectivity towards this isoform is well supported by *in silico* results, wherein, these compounds show better interaction and affinity and inhibitory activity for PI3Kγ rather than PI3Kδ. This repositioning of scaffold from PI3Kδ to PI3Kγ isoform can be very useful from medicinal chemistry and drug discovery perspective to unravel molecular interactions of this new scaffold in different cellular pathways.

1,2,3-Triazoles are widely used in different ways, like peptide bond mimetics[1–7] and they can act as an option for double bond in the chemical structures, which is an important feature from the perspective of medicinal chemistry and drug discovery.[8,9] Moreover, triazoles can also be used as furan substitutes as well.[10] Therefore, they are of great importance from structural point of view and provide fast access to construct five-membered heterocyclic ring. They attribute to important and wide range of applications in biological and pharmacological activities.[11–14]

Triazole based structures are exhaustively exploited in many applications in organic, organometallic and material chemistry.[15] The synthesis of 1,4-substituted 1,2,3-triazoles from halides, azides, and acetylenes in the presence of copper (I) salt in one pot is well known reaction.[16–22] Mostly, these 1,2,3-triazole moieties are constructed using click chemistry approach by using Huisgen 1,3-dipolar cycloadditions of azides and alkynes.[15,23,24] Microwave assisted methods for the synthesis of 1,2,3-triazoles are also reported.[25–28] The increased interest of chemist in the 1,2,3-triazole remains continued due to their non-toxic properties, benign nature and their structural rigidity as well as high stability. Triazoles are particularly interesting for medicinal use because of their water solubility compared to other hetero-aromatic compounds, and they are stable in biological systems.[29]

We recently published a protocol for the synthesis of purine-quinazolinone and some other scaffolds that have been designed on the basis of their biological importance in PI3K isoform selective inhibitory activity for cancer.[30–32] In one of our ongoing study, we aimed to design analogs based on quinazolinone scaffold by medicinal chemistry of clinical candidates for developing anticancer agents and isoform specific inhibitors of PI3K-δ. In this direction, we chose to work on medicinal chemistry of purine quinazolinone IC87114 molecule, the first isoform-selective PI3K-δ inhibitor reported and patented by ICOS in 2001.[33–36] This compound exhibited nanomolar inhibition against PI3K-δ isoform (IC_{50} = 130 nM) and a 100- to 1000-fold selectivity against the other class I PI3K's. Subsequently, several molecules based on quinazolinone scaffold started appearing in preclinical and clinical investigation stages and one of the most promising PI3K-δ isoform-selective inhibitors to date is GS1101/CAL-101 by Gilead with IC_{50} of 2.5 nM named as

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Idelalisib, which has been approved recently by US-FDA as monotherapy for B-cell malignancies and in combination with rituximab as second-line drug for chronic lymphocytic leukemia (CLL) cases.[37–40]

PI3K-δ and PI3K-γ isoforms are preferentially expressed in leukocytes, where they have distinct and non-overlapping roles in immune cell function.[41–43] Class IA PI3Ks contain, p110α, p110β and p110δ as catalytic subunits, and these are activated in tyrosine kinase receptor signaling. Class IB PI3Ks contain only p110γ as a catalytic subunit, which is mostly activated by seven-transmembrane G-protein-coupled receptors (GPCRs) via its regulatory subunit p101 and G-protein γ subunits. While PI3Kα and PI3Kβ are ubiquitously expressed, however, PI3Kγ and PI3Kδ expression is mainly restricted to the hematopoietic system.[44] The p110α and p110β isoforms are known to stimulate cell proliferation and invasive cell growth,[45] p110δ controls proliferation in acute myeloid leukemia[46] and migration of breast cancer cells,[47] whereas, a role has been suggested for p110γ in tumor angiogenesis[48] and drug resistance of chronic myeloid leukemia cells.[49]

In continuation of our interest in medicinal chemistry of quinazolinone scaffold for discovery of PI3K isoform specific inhibitors,[30–32] we now designed a new triazole based quinazolinone structures (Fig. 1); as triazole based scaffold, in particular 1,2,4-triazoles are also reported for PI3K inhibitory activity.[50] In this endeavor, we report a protocol for the synthesis of 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-one scaffold under microwave assisted conditions using one-pot multicomponent strategy along with their PI3Kγ specific activity.

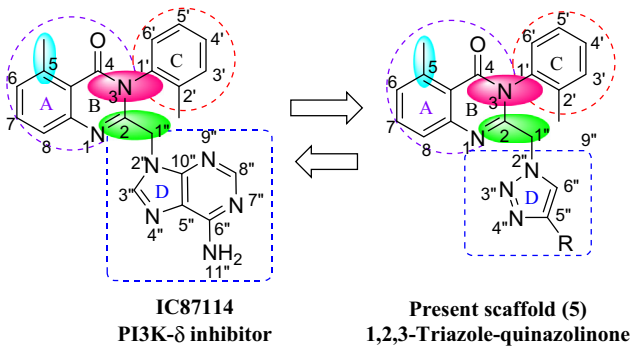


Fig. 1. Structural features and similarities in IC87114 and the designer 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-one scaffold.

Table 1
Solvent optimization for the synthesis of 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-ones.

S. No.	Catalyst (10 mol%)	Solvent	Time (Min)	Yield of **5a** (%)[a]
1	CuI	H_2O	3	–
2	CuI	THF	3	–
3	CuI	DCM	3	–
4	CuI	DMSO	3	5
5	CuI	CAN	3	10
6	CuI	MeOH	3	65
7	CuI	Acetone	3	70
8	CuI	DMF	3	80

[a] Isolated yield.

As an extension of our earlier work, we initiated our studies to generate functionalized derivatives and analogs of quinazolinone based structure as PI3K inhibitors. In an effort to optimize reaction conditions for the synthesis of 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-ones, we opted to use a procedure similar to one, which has been reported by our group recently for purine quinazolinones synthesis.[30] In this study, similar procedure was used to synthesize and obtain intermediate **3**. Further, we reacted, intermediate **3** with alkyne, in this we used one-pot strategy and typically phenylacetylene (**4**) was taken for optimization under microwave irradiation using established conditions of purine quinazolinone, and the reaction was carried in neat conditions. This has not given any product; we switched to conduct reactions using solvents to observe the solvent effect. Different solvents were screened as mentioned in table 1. Here, in case of dimethyl formamide (DMF), the product formation was observed, reaction in DMF has given highest about 80% yields and reaction in dimethyl sulfoxide, acetonitrile, methanol and acetone gave 5%, 10%, 65% and 70% yield of product **5a** respectively. In case of reaction in water, tetrahydrofuran and dichloromethane, the reaction did not proceed. Therefore, all the future optimization reactions were performed using the condition mentioned in entry 8 of table 1.

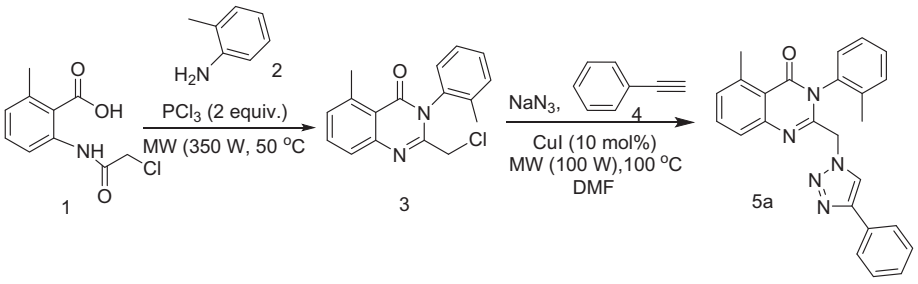
The intermediate **3** was prepared using reported method, this was used for synthesizing 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-one analogs (Scheme 1).

The reaction conditions for microwave protocol was optimized as mentioned in Table 2, where the best conversion was observed

Table 2
Optimization of microwave irradiation conditions for the synthesis of 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-ones.

Entry	Microwave Power (Watts)	Temp. (°C)	Time (Min.)	Yield of **5a** (%)[a]
1	80	100	3	75
2	100	100	3	80

[a] Series of 1,4-substituted 1*H*-1,2,3-triazolo-quinazolin-4(3*H*)-one compounds were prepared using optimized protocol (Table 3). Variety of alkynes viz. substituted aryl acetylenes; -*N* and *O*-propargylated substituted aryls, and also substituted *N*-propargyl arylsulphonamides were used to bring the diversity in the scaffold. Different kind of substitutions were chosen in acetylenes; electron donating as well as electron withdrawing groups have been accommodated for preparation of diverse triazole analogs of quinazolinone. Moreover, various substitutions on aryl rings of quinazolinone and *N*-aryl compounds were also synthesized. The observed yields were in the range of 70–80% using optimized conditions.



Scheme 1. Synthesis of 5-methyl-2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-3-(*O*-tolyl)quinazolin-4(3*H*)-one using cyclo-addition reaction approach.