A novel class of pyrazole analogues as aurora kinase A inhibitor: design, synthesis, and anticancer evaluation. PI3Kδ and mTOR dual inhibitors: design, synthesis and anticancer evaluation of 3-substituted aminomethylquinoline analogues

Digambar Yevale[a] and Chetan B. Sangania,[a,b]

[a]Department of Chemistry, Shri M.M Patel Institute of Sciences and Research, Kadi Sarva Vishwavidyalaya, Gandhinagar- 382016, Gujarat, India.

[b]Department of Chemistry, Government Science College Gandhinagar-382016, Gujarat University, Gujarat, India. E-mail: yevaledb@gmail.com

Introduction

The PI3K/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR, PAM) pathway has drawn significant pharmacological investment in the search for inhibitors to treat human cancers. Phosphoinositide 3 kinases (PI3Ks) are a lipid kinase family that includes PI3K1, PI3K2, and PI3K3. PI3K1 is a well-studied PI3K that consists of a catalytic subunit (p110α, p110β, p110γ, and p110δ)

PI3Kδ, one of these four PI3K isoforms, is predominantly expressed in B-cells and catalyzes the phosphorylation of phosphatidylinositol-4,5-biphosphate to phosphatidylinositol 3,4,5-triphosphate *via* the PI3K/Akt signaling downstream, making it essential for B-cell proliferation, development, and survival. As a result, PI3Kδ inhibition is thought to be therapeutically advantageous for hematological malignancies.

On the other hand, mTOR, the downstream signaling effector in the PI3K/Akt/mTOR cascades, is a kinase that belongs to the phosphatidylinositol 3-kinase family. Phosphorylation of PI3K causes phosphorylation of various downstream effectors, including mTOR and protein kinase B (PKB/Akt), resulting in cell cycle progression, proliferation, survival, and migration. Several PI3K/mTOR dual inhibitors have moved into clinical trials, including BGT226, GSK1059615, dactolisib, omipalisib, and others .

Abstract

A new family of quinoline analogues was designed, developed, and evaluated as dual inhibitors of PI3Kδ/mTOR. The preliminary biological activity analysis led to the discovery of the lead compounds **5h** and **5e**. Compounds **5h** and **5e** exhibited excellent anti-tumor potency with IC_{50} of 0.26 μM and 0.34 μM against Ramos cells, respectively. Importantly, based on the enzymatic activity assay results, compounds **5h** and **5e** were identified as dual inhibitors of PI3Kδ and mTOR, with IC_{50} values of 0.042 μM and 0.056 μM for PI3Kδ and 0.059 μM and 0.073 μM for mTOR, respectively.

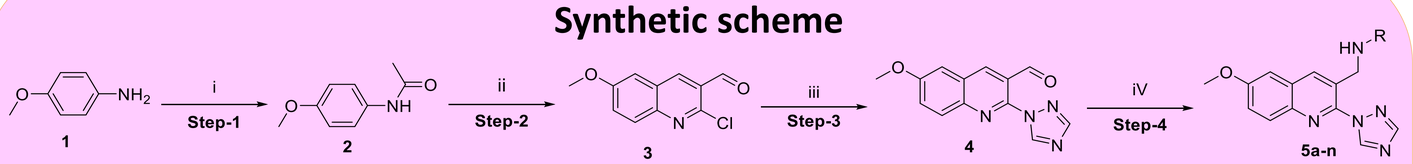
Anticancer activity

6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinoline-3-carbaldehyde was modified with substituted phenylamines and benzylamines to produce N-((6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinolin-3-yl)methyl)aniline **(5a-e)** and N-benzyl-1-(6-methoxy-2-(1H-1,2,4-triazol-1-yl)quinolin-3-yl)methanamine **(5f-n)** analogues. It was then linked to cytotoxicity and PI3Kδ inhibition. Parent compounds **(5a, 5f)** with unsubstituted phenylamine and benzylamine rings performed poorly in both assays. Except for **5g** (3-fluoro-4-methyl), electron-donating and withdrawing groups, such as **5e** (3-bromo-4-methoxy) and **5h** (4-chloro-3-methyl), conferred the greatest cytotoxicity and kinase activity**.** These studies showed that larger atoms like chloro and bromo contributed more to high activity than fluorine. The incorporation of two electron-donating groups, such as **5i** (3,4-dimethyl) and **5j** (2,3-dimethyl), displayed moderate activity in both assays. Adding two electron-withdrawing groups to **5b** (3,5-difluoro), **5k** (3-chloro-4-fluoro), and **5l** (2,6-difluoro), on the other hand, caused weak to equivalent inhibition in both tests. The bulky groups, containing compounds such as **5m** (n-butyl) and **5n** (isobutyl), were more cytotoxic than the smaller **5c** (isopropyl) and **5d** (methyl). These compounds inhibited kinase to a low to moderate extent. These studies assessed that bi-substitution in the third and fourth with electron-donating and withdrawing groups boosted activity. The substitution of two electron-donating or withdrawing groups provoked modest activity. Also, aromatic replacements enhanced activity more than aliphatic substituents. Furthermore, compounds **(5f-n)** were more active than **(5a-e)**, confirming the rationale for inserting the bulky amine side chain on the C-3 of quinoline.

Table 1. Cytotoxic activity of aminomethylquinoline analogues.

Compound	R	Ramos IC_{50} (μM)	Compound	R	Ramos IC_{50} (μM)
5a		9.26±0.57	5i		1.76±0.014
5b		0.71±0.066	5j		2.12±0.05
5c		2.46±0.39	5k		0.69±0.019
5d		4.69±0.62	5l		7.68±0.58
5e		0.34±0.012	5m		0.58±0.027
5f		8.73±1.02	5n		0.81±0.015
5g		3.05±0.67	Dactolisib	-	0.76±0.08
5h		0.26±0.054			

Synthetic scheme



5	R	5	R	5	R
a	Ph	f	CH_2Ph	k	3-Cl, 4-F-CH_2Ph
b	3,5-F-Ph	g	4-CH_3, 5-F-CH_2Ph	l	2, 6-F-CH_2Ph
c	$CH(CH_3)_2$	h	4-Cl, 6-CH_3-CH_2Ph	m	$(CH_2)_3CH_3$
d	CH_3	i	3, 4-CH_3-CH_2Ph	n	$CH_2CH(CH_3)_2$
e	4-OCH_3, 5-Br-Ph	j	2, 3-CH_3-CH_2Ph		

Scheme 1. Reagents and conditions: (i) Ac_2O, AcOH, 100 °C, 16 h (ii) phosphorus oxychloride, DMF, 80 °C, 1 h (iii) 1,2,4-triazole, NaH (60%), DMF, 80 °C, 2 h, (iv) alkylamines,, substituted phenylamines and benzylamines, $NaBH_3CN$, MeOH, AcOH, 25 °C, 16 h.

Conclusion

Current work has developed new substituted aminomethylquinoline analogues by substituting quinoline at the C-3 position. Compounds **5h** and **5e** showed promising cytotoxicity against Ramos cells, with IC_{50s} of 0.26 μM and 0.34 μM, respectively. Both **5h** and **5e** significantly inhibited PI3Kδ/mTOR, with IC_{50s} of (0.042 μM and 0.056 μM) and (0.059 μM and 0.073 μM), respectively.

References

- Bioorganic Chemistry 147 (2024) 207-323.
- WO 2008/118468 A1-Heterocyclic compounds and their uses.

International Conference on
Composite Materials for Environment Protection & Remediation
(ICCMEPR - 2024) 02-03 July, 2024