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Identification of novel 7-amino-5-methyl-1,6-naphthyridin-2(1*H*)-one derivatives as potent PI3K/mTOR dual inhibitors

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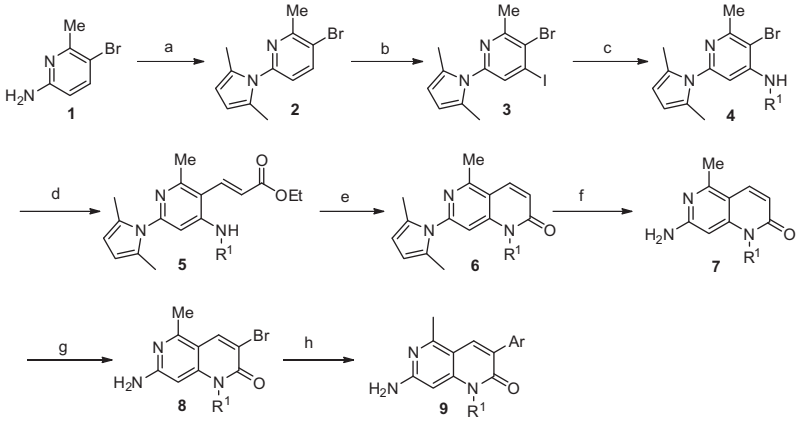
ABSTRACT

Inhibition of the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway is one of the most intensively studied approaches to cancer therapy. Rational design led to the identification of novel 7-amino-5-methyl-1,6-naphthyridin-2(1*H*)-one derivatives as potent PI3K/mTOR dual inhibitors. Design, synthesis and structure activity relationship are reported.

The phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway is a critical regulator of many essential cellular functions including cell growth and proliferation and is perhaps the most commonly activated signaling pathway in human cancer.[1,2] Inhibition of this pathway by targeting PI3K, AKT and mTOR with small molecules individually or jointly is expected to have a substantial therapeutic effect and has therefore become one of the most intensively studied approaches to cancer therapy.[3] Notably along this pathway, mTOR is in the PI3K superfamily and bears considerable structural



Scheme 1. Synthesis of compounds **9**. Reagents and conditions: (a) 2,5-Hexanedione, TsOH, PhMe, reflux; (b) LDA, I_2, −78 °C; (c) R^1NH_2, DIEA, NMP, 160 °C; (d) ethyl acrylate, $Pd(PPh_3)_4$, TEA, 130 °C; (e) *t*-BuOK, DBU, DMA, 150 °C; (f) NH_2OH–HCl, EtOH/H_2O, reflux; (g) NBS, DMF, rt; (h) aryl borate or boronic acid, Palladium catalyst, K_2CO_3, DMF/H_2O, 100 °C.

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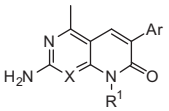
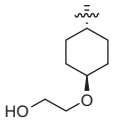
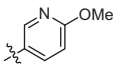
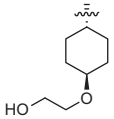
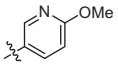
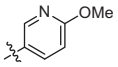
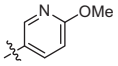
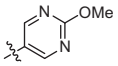
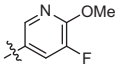
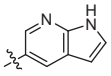
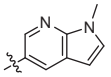
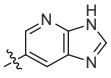
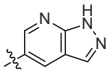
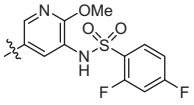
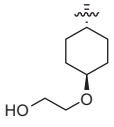
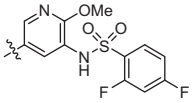
Table 1
PI3K/mTOR inhibiting activities of **9a–k**



9a-k

Compound	X	R^1	Ar	PI3Kα IC_{50} (nM)[15]	mTOR IC_{50} (nM)[16]
PF-04691502	N			8.33	7.90
9a	C			35.41	11.19
9b	N			2.80	30.09
9c	C			13.60	39.04
9d	C			6.45	36.54
9e	C			5.95	159.96
9f	C			2.45	12.25
9g	C			15.20	82.12
9h	C			2.90	13.91
9i	C			6.00	171.72
9j	C			12.03	33.92
9k	C			2.42	8.55

similarity to class I PI3Ks.[2,4,5] This similarity presents an opportunity to generate dual-specificity compounds, targeting PI3K/mTOR simultaneously in one pathway. These dual inhibitors could, in principle, effectively block the signal transduction and overcome feedback loops.[6] Another advantage derived from dual inhibitors is anticipated to be the largely reduced possibility of drug resistance. In recent years, a number of dual PI3K/mTOR inhibitors have crowded into the clinical trials to generate clinical efficacy and are on the way towards regulatory approvals.[7–13]

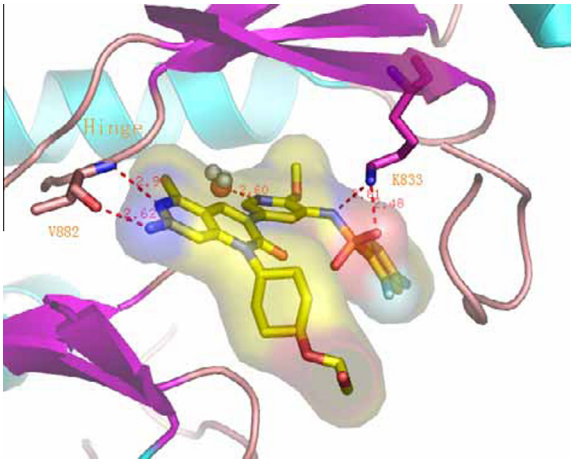
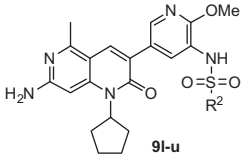
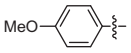
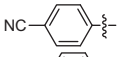
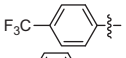
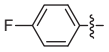
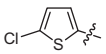


Figure 1. Predicted binding mode for **9k** (yellow) with PI3Kγ (PDB ID: 3ML9). Hydrogen bonding interactions are shown in red dashed lines to the hinge region (Val 882) and the catalytic lysine (Lys833). Images generated using PyMol.

Table 2
PI3K/mTOR inhibiting activities of **9l–u**



9l-u

Compound	R^2	PI3Kα IC_{50} (nM)[15]	mTOR IC_{50} (nM)[16]
9l	Me	23.14	62.64
9m		69.11	140.9
9n		116.75	19.2
9o		174.28	65.64
9p		14.27	24.69
9q		174.88	78.20
9r		72.59	35.02
9s		60.51	13.88
9t		37.33	ND[a]
9u		31.16	8.49

[a] ND = not determined.

4-Methylpyridopyrimidinone (MPP) has proven to be a potent chemical scaffold for dual PI3K/mTOR inhibitors, demonstrating excellent anti-tumor activities in both cell proliferation assays and xenograft models.[8,9] PF-04691502, with such a scaffold, entered into Phase I/II clinical trials in patients with early breast cancer, further elucidating its anti-tumor effectiveness.[14]

The key interactions between MPP and PI3K have been validated through determination of co-crystal structure of PF-04691502 bound in PI3Kγ (PDB ID: 3ML9). The NH_2 functionality together with the N atom adjacent to the methyl group at the 4