SYNTHESIS OF (2-ARYLQUINAZOLIN-4-YL)HYDRAZONES OF 2-HYDROXYBENZALDEHYDES AS POTENTIAL PHOSPHOINOSITIDE 3-KINASE δ (IP3Kδ) AND CASEIN KINASE 2 (CK2) INHIBITORS

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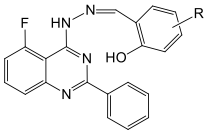
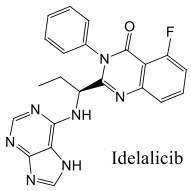
INTRODUCTION

Phosphoinositide-3-kinase and casein kinase 2 are favorable targets for the design of antitumor agents. Idelalisib (Zydelig) - a fluorine-containing derivative of quinazoline, is used as a drug for the treatment of certain types of blood cancer, the molecule acts as a P110δ inhibitor, a delta isoform of the enzyme phosphoinositide 3-kinase [1]. Protein kinase CK2 is an ubiquitous, highly conserved and constitutively active serine/threonine protein kinase; overexpression and hyperactivation of CK2 has been observed in a wide variety of cancers, including breast, lung, prostate, colorectal, and renal [2].

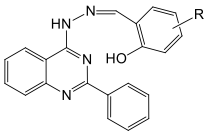
(2-Phenylquinazolin-4-yl)hydrazones of 2-hydroxybenzaldehydes **1a-c, 2a-c, 3a,b** were previously considered as N,N,O-ligands for fluorescent zinc(II) complexes [3].



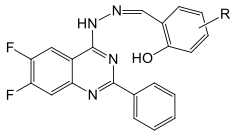
1: R = H (**a**), 4-OH (**b**), 3,5-diBr (**c**).



Idelalicib



2: R = H (**a**), 4-OH (**b**), 3,5-diBr (**c**).

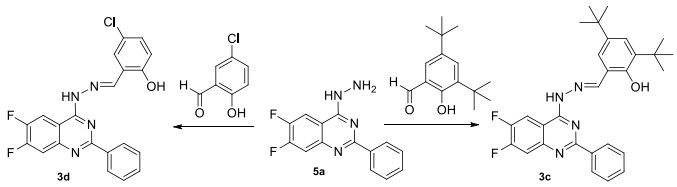


3: R = H (**a**), 5-NO_2 (**b**).

We developed the synthetic approach to series of new 2-arylquinazolines **3c,d, 4a,b** bearing salicylidenehydrazono group at position 4 and estimated their interactions with two targets of anticancer drugs (IP3Kδ and CK2) using molecular docking analysis.

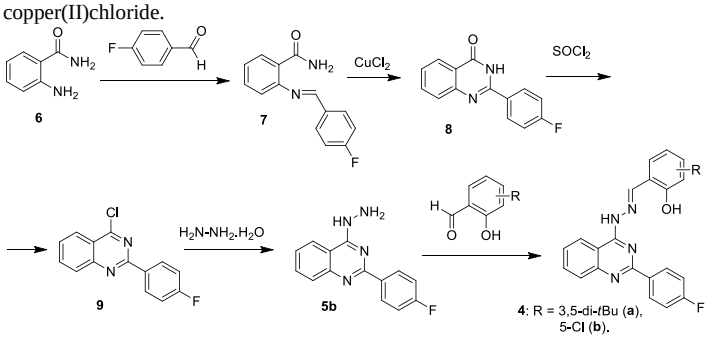
SYNTHESIS

2-Phenyl-6,7-difluoro derivatives **3c,d** were obtained from 4,5-difluoroantranilic acid by condensation with benzoyl chloride, 3,1-benzoxazin-4-one ring transformation under the heating with ammonium acetate, chloro-desoxygenation in quinazolin-4-one, substitution of chlorine atom with hydrazino group and reaction with the corresponding salicylic aldehyde.



Scheme 1

We developed the synthetic approach to 2-(4-fluorophenyl)derivatives 1k,l based on condensation of anthranilamide with 4-fluorobenzaldehyde and oxidative cyclization of imine into quinazolin-4-one under the heating with copper(II)chloride.

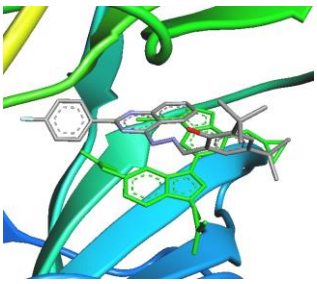


Scheme 2

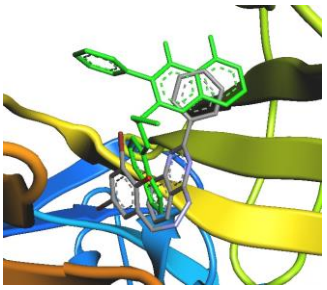
MOLECULAR DOCKING

Compound	Binding with IP3Kδ ΔG, kcal/mol	Binding with CK2 ΔG, kcal/mol
1a	-11,98	-12,33
1b	-12.56	-13,16
1c	**-13.83**	-12,20
2a	-12,05	-11,84
2b	-12,25	-12,77
2c	**-14,38**	-13,10
3a	-12,83	**-13,91**
3b	-12,80	-12,47
3c	-13,10	-11,33
3d	**-13,81**	-12,69
4a	-11,70	**-14,16**
4b	-12,27	-12,70
Idelalicib (IC50 = 19 nM)	-9,88	–
CHEMBL2062585 (IC50 = 3nM)	–	-10,67

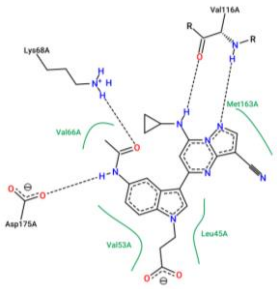
BINDING MODES

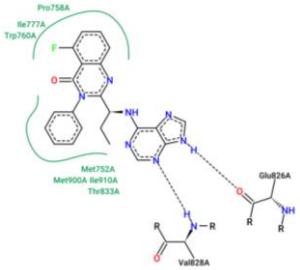


4a in the active center of CK2

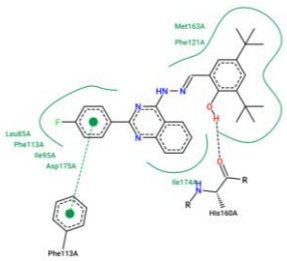


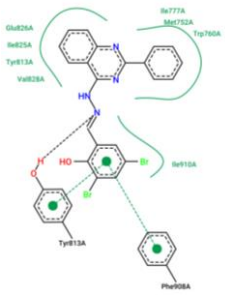
2c in the active center of PI3Kdelta





Interaction of CHEMBL2062585 with CK2 / Interaction of Idelalisib with PI3Kdelta





Interaction of quinazoline 4a with CK2 **Interaction of quinazoline 2c with PI3Kdelta**

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1. R.R. Furman, J.P. Sharman, S. E. Coutre et al. *The New England Journal of Medicine*. **2014**, *370*, 997-1007.
2. M. Haddach, F. Pierre, C. F. Regan et al. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 45–48.
3. T.V. Trashakhova, E.V. Nosova, P.A. Slepukhin, M.S. Valova, G.N. Lipunova, V.N. Charushin. *Russ. Chem. Bull*. **2011**, *60*, 2347–2353.