PR-15

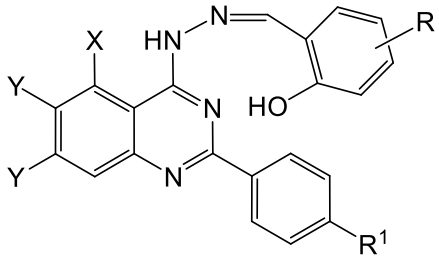
SYNTHESIS OF (2-ARYLQUINAZOLIN-4-YL)HYDRAZONES OF 2-HYDROXYBENZALDEHYDES AS POTENTIAL PHOSPHOINOSITIDE 3-KINASE (IP3Kδ) AND CASEIN KINASE 2 (CK2) INHIBITORS

Nosova E. V. *, Butorin I. I., Kopotilova A. E., Likhacheva M. D.
Chemical Technology Institute, UrFU, 620002 Ekaterinburg, 19 Mira St.
*E-mail: emilia.nosova@yandex.ru

Abstract. Phosphoinositide 3-kinase and casein kinase 2 are propitious targets for designing anticancer drugs. Idelalisib (Zydelig), fluorine-containing quinazoline derivative, is used as a medication to treat certain blood cancers, the molecule acts as inhibitor of P110δ, the delta isoform of the enzyme phosphoinositide 3-kinase.[1]

(2-Phenylquinazolin-4-yl)hydrazones of 2-hydroxybenzaldehydes was previously considered as N,N,O-ligands for fluorescent zinc(II) complexes.[2] We developed the synthetic approach to series of new 2-arylquinazolines **1** bearing salicylidenehydrazono group at position 4 and estimated their interactions with two targets of anticancer drugs (IP3Kδ and CK2) using molecular docking analysis.

2-Phenyl-6,7-difluoro derivatives **1g-j** 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. 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.



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1: X = F, Y = R^1 = H, R = H (**a**), 4-OH (**b**), 3,5-diBr (**c**);
X = Y = R^1 = H, R = H (**d**), 4-OH (**e**), 3,5-diBr (**f**);
X = R^1 = H, Y = F, R = H (**g**), 5-NO_2 (**h**), 3,5-di-*t*Bu (**i**), 5-Cl (**j**);
X = Y = H, R^1 = F, R = 3,5-di-*t*Bu (**k**), 5-Cl (**l**).

Quinazoline **1c** demonstrated better affinity to IP3Kδ (ΔG = -13.83 kcal/mol) than Idelalisib (ΔG = -9.92 kcal/mol). Salicilidenehydrazono quinazolines **1i** and **1l** showed the best affinity to casein kinase 2 ((ΔG = -11.31 kcal/mol and -12.70 kcal/mol, correspondently).

References

1. Furman R.R., Sharman J.P., Coutre S. E. et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. The New England Journal of Medicine. 2014, vol. 370, pp. 997–1007.

2. Trashakhova T. V., Nosova E. V., Slepukhin P. A. et al. 2-Hydroxybenzaldehyde (2-phenylquinazolin-4-yl)hydrazones and their Zn II complexes: Synthesis and photophysical properties. Russ. Chem. Bull. 2011, vol. 60, pp. 2347–2353.

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