

3-ARYL-[1,2,4]TRIAZOLO[4,3-*c*]QUINAZOLINE DERIVATIVES: SYNTHESIS AND MODIFICATIONS

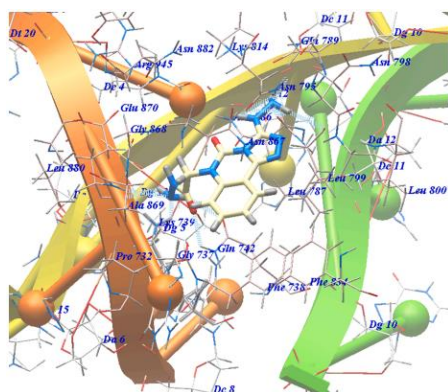
Emiliya V. Nosova, Alexandra E. Kopotilova, Tatiana N. Moshkina, Margarita D. Likhacheva

Ural Federal University named after the first President of Russia B.N.Yeltsin, Russia, 620002
Ekaterinburg, Mira st., 19, e-mail: emilia.nosova@yandex.ru



INTRODUCTION

[1,2,4]Triazolo[1,5-*a*]pyrimidine is an attractive scaffold for the design of antitumor agents, since its derivatives have proved to be tubulin inhibitors [1, 2]. Recently, the ability of 3-hydrazinyl[1,2,4]triazolo[4,3-*c*]quinazoline-5-ones to act as penetrating DNA intercalators [3] has been demonstrated.

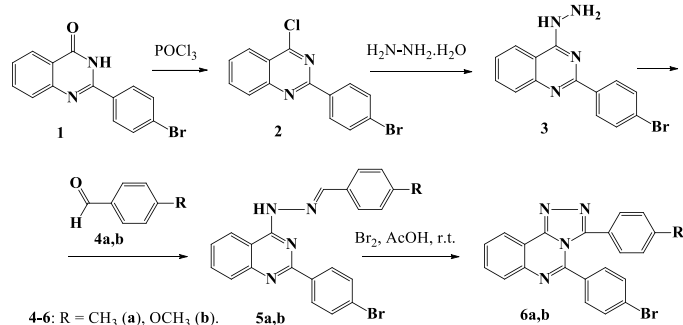


Binding mode of known triazoloquinazolines with DNA [3]

The creation of convenient methods to produce 3,5-diaryl[1,2,4]triazolo[4,3-*c*]quinazolines can open wide possibilities for varying substituents in the triazoloquinazoline core.

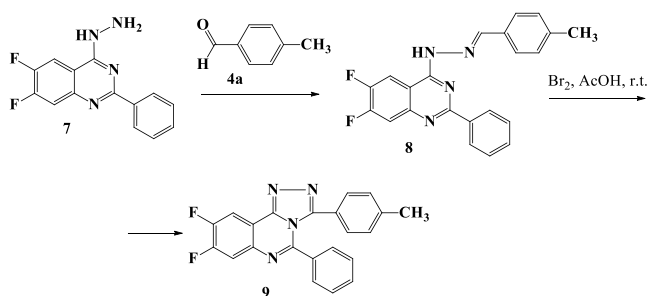
SYNTHESIS

On the basis of 2-(4-bromophenyl)quinazolin-4-one **1**, obtained from antranilamide and 4-bromobenzaldehyde following the procedure [4], we realized the synthesis of triazoloquinazolines **6a,b**; hydrazones **5a,b** underwent the cyclization under stirring with bromine in glacial acetic acid at room temperature during 3 h (Scheme 1).



Scheme 1

Synthesis of hydrazone **8** was achieved by heating of 2-phenyl-4-hydrazino-6,7-difluoroquinazoline **7** with *p*-tolylaldehyde. Preparation of **7** from 4,5-difluoroantranilic acid was described [5], triazoloquinazoline **9** was obtained by oxidative cyclization with bromine (Scheme 2).

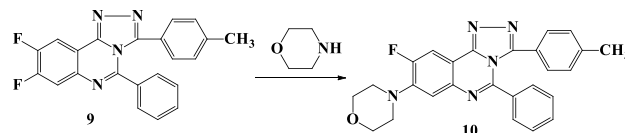


Scheme 2

MODIFICATIONS

Nucleophilic substitution of fluorine atom

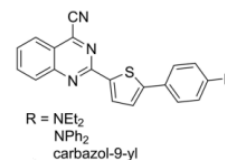
Compound **10** was obtained as a result of substitution of fluorine atom in quinazoline **9** with morpholine residue (Scheme 3). Incorporation of other cycloalkylimine residues is in progress.



Scheme 3

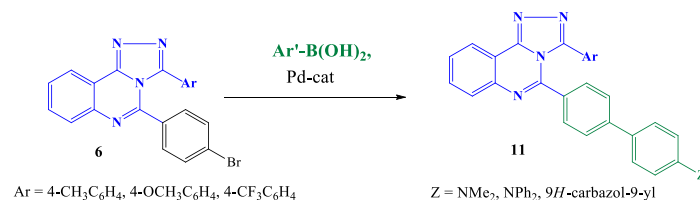
Design of luminophores

Last year we reported a series of chromophores bearing 4-cyanoquinazoline electron-acceptor (A) and 5-(4-aminophenyl)thiophen-2-yl electron-donor (D) units [6].



Annellation of triazole ring can be regarded as one more way to enhance the electron acceptor ability of quinazoline core, so triazoloquinazolines can be used for design push-pull fluorophores.

Bromophenyl derivatives **6** were subjected to the PdCl₂(PPh₃)₂-catalyzed Suzuki–Miyaura cross-coupling reaction with arylboronic acid or 4-(9H-carbazol-9-yl)phenylboronic acid pinacol ester to obtain the push-pull quinazolines **11** (Scheme 4).



Scheme 4

FUTURE PROSPECTS

We study the reaction of hydrazone **3** with aliphatic aldehyde in order to obtain 5-(4-bromophenyl)-3-alkyl[1,2,4]triazolo[4,3-*c*]quinazoline and apply it in Suzuki–Miyaura cross-coupling reaction for design 3-alkyl counterparts of compounds **11**. Moreover, we study the reaction of 4-fluorophenyl counterpart of quinazoline **6** with lithium salt of acridane and other N-nucleophiles.

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