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Short communication

# Synthesis of 7-cycloalkylimino substituted 3-amino-6-fluoro-2-methyl-3H-quinazolin-4-ones

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ABSTRACT

A versatile pathway for the synthesis of 7-cycloalkylimino substituted 3-amino-6-fluoro-2-methyl-3H-quinazolin-4-ones from 4,5-difluoroanthranylic acid has been advanced. Nucleophilic amination–defluorination reaction of the 6,7-difluoro derivative of 3-amino-2-methyl-3H-quinazolin-4-one has been established to occur at position 7, as shown by X-ray crystallographic analysis.



## 1. Introduction

3-Amino-7-cycloalkylimino substituted 6-fluoroquinazolin-2,4-diones have recently been identified as high effective inhibitors of the bacterial type-2 topoisomerase [1]. Nucleophilic displacement of fluorine atoms proved to be a versatile synthetic tool for structural modifications of fluorinated quinazolin-4-ones [2], however the available data on the synthesis of biologically active compounds through amination–defluorination of difluoroquinazolines are limited with a few publications [3], dealing mainly with substitution of a fluorine atom in the benzene ring [4]. Meanwhile, quinazolines, bearing a fluorine atom and a cycloalkylimino moiety in the benzene ring, are of interest due to a profound antitumor activity exhibited by 2-aryl-7-fluoro-6-(4-methylpiperazin-1-yl)-4(3H)-quinazolin-4-one, obtained in 5 steps from 4-fluoro-2-nitro-5-(4-methylpiperazin-1-yl)aniline [5]. It should be noted that hydrazination-defluorination at C(7)-F in 3-amino-6,7,8-trifluoro-2-methylquinazolin-4-one was described earlier [6], although no data on substitution of F(7) in 6,7-difluoro-2-methylquinazolin-4-one are available in the literature. Here we report a simple synthetic approach toward new fluorinated quinazolines.

## 2. Results and discussion

Heating of difluorobenzoxazinone **1** with hydrazine hydrate for a short time did not result in displacement of fluorine atom at 7-position with the hydrazino moiety, as shown earlier [6]. The optimal conditions for preparation of difluoroquinazolonone **2** proved to be reflux of **1** with 1.5 equiv. of hydrazine hydrate in ethanol for 1 h. Also the compound **3** was obtained in a high yield when benzoxazinone **1** was allowed to be kept on reflux in ethanol with 4 equiv. of hydrazine hydrate for 10 h in order to transform the oxazine ring into the pyrimidine one, as well as to cause substitution of fluorine atom at 7-position with hydrazine. The structure of hydrazine compound **3** is evidenced by $^1$H NMR spectra, showing the presence of $NHNH_2$ group signals in addition to doublets of H(5) and H(8) protons (scheme).

The fluorine atom at position 7 of 3-amino-6,7-difluoro-2-methyl-3*H*-quinazolin-4-one (**2**) was shown to be displaced smoothly by action cycloalkylimines to give compounds **4** in high yields on heating under reflux with 1-methylpiperazine, 3-methylpiperidine, morpholine or 1-ethoxycarbonylpiperazine in DMSO for 9 h (Scheme 1).

The structure of fluoroquinazolines **4a–d** was substantiated with $^1$H NMR, $^{19}$F NMR and mass spectrometry data. The $^1$H NMR spectra of **4a–d** reveal two doublets of H(5) and H(8) protons with the characteristic values of coupling constants $^3J$[H(5), F(6)] and $^4J$[H(8), F(6)] in the ranges of 12.8–13.1 and 7.9–8.1 Hz correspondingly.

Since displacement of F(6) atom would also give a rise to two doublets in $^1$H NMR with close values of $^3J$[H(8), F(7)] and

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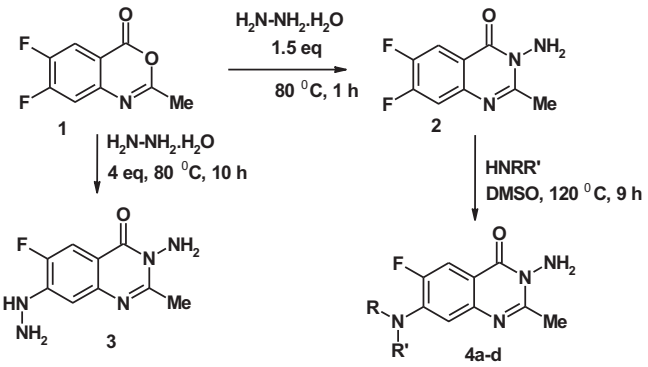


**Scheme 1.** Compounds **4**: NRR′ = 4-methylpiperazin-1-yl (**a**), 3-methylpiperidin-1-yl (**b**), morpholin-4-yl (**c**), 4-ethoxycarbonylpiperazin-1-yl (**d**).

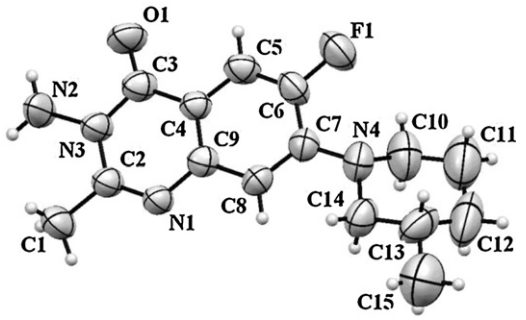


**Fig. 1.** Molecular structure for quinazolinone **4b**.

$^4J$[H(5), F (7)], the $^1$H and $^{19}$F spectral data aren't not sufficient for the proof of products **4a–d** structure. Convincing arguments for displacement of F(7), but not F(6), have been obtained by the X-ray crystallography analysis performed for compound **4b** (Fig. 1).

According to the X-ray data compound **4b** is crystallized in centrosymmetric space group of monoclinic system. General geometry of the compound (bond length and angles) does not exhibit any significant deviations from standard values. Molecular packing is formed by layers of molecules oriented on axe 0b. Interactions in layers is realized by H-bonds between NH2-group and nitrogen of pyrimidine: with d(N2···N1[$-x+3/2$, $y+1/2$, $-z+1/2$]) = 3.061 Å. Hydrogen atoms at N(2) were added in calculated positions and refined in the riding model.

The multiplete character of signals of F(6) in the $^{19}$F NMR spectra of quinazolinones **3** and **4a–d** indicates that F(6) is coupled with not only H(5) and H(8) protons of the benzene ring, but also with $CH_2$-protones of the cycloalkylimino group in case of compounds **4**, or with NH-proton of the hydrazine group in case of compound **3**. It is worth noting that spin–spin couplings of F(6) with protons of the cycloalkylimino fragments at position 7 of [*i*,*j*]-annelated fluoroquinolones have also been described in the paper [7].

## 3. Conclusion

A versatile synthetic route to the family of 7-substituted 6-fluoroquinazolinones **4** has been developed. Presently, the antibacterial and antifungal properties of these compounds are under investigation. The corresponding results will be reported elsewhere in due course.

## 4. Experimental

### 4.1. General

X-ray structural analyses of compound 4b was accomplished with using "Xcalibur S" diffractometer with CCD (λ(Mo Kα) = 0.71073 Å, $T$ = 295(2) K, ω-scans with 1.0° steps in $\omega$ and 20 s per frame exposure) for prismatic light brown crystal 0.25 mm × 0.20 mm × 0.15 mm. Absorption correction not performed ($\mu$ = 0.092 mm$^{-1}$). Crystal is monoclinic, $a$ = 11.1363(16) Å, $b$ = 12.3042(10) Å, $c$ = 11.7801(17) Å, $\beta$ = 111.457(13), space group $P2_1/n$. In limits $3.16° < \theta < 28.29°$ 7879 reflections were collected, 3478 independent reflections ($R_{int}$ = 0.0409), 1042 reflections with $I > 2\sigma(I)$. Completeness for $\theta$ = 26.00° 95.7%. The structure was solved by direct method and refined by full-matrix least-squares technique against on $F^2$ in anisotropic (isotropic for H-atoms) approximation. Hydrogen atoms were located from Fourier synthesis and refined in riding model. All calculations were performed using SHELXTL [8]. Results of refinement: $R_1$ = 0.0630, $wR_2$ = 0.1585 (for $I > 2\sigma(I)$), $R_1$ = 0.1720, $wR_2$ = 0.1714 (for all data), $S$ = 1.005. $\Delta\rho_{\bar{e}} = 0.552/-0.200$ ēÅ$^{-3}$.

The X-ray diffraction data for structure **4b** have been deposited with the Cambridge Crystallographic Data Center (CCDC No. 885182). These data are free and can be made available upon request at www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of compound **2** from 4,5-difluoroanthranylic acid was reported in [6], the reaction time for transformation **1**–**2** was diminished to 1 h.

NMR, MS and analytical data for compound obtained are presented in Supporting Information.

### 4.2. Synthesis of 3-amino-6-fluoro-7-hydrazino-2-methyl-3H-quinazolin-4-one (*3*)

Hydrazine hydrate (98%) (0.4 mL, 8 mmol) was added to a solution of benzoxazinone **1** (0.4 g, 2 mmol) in 10 mL of ethanol. The reaction mixture was kept at 80 °C reflux for 10 h. After the mixture was cooled, the precipitate formed was collected by filtration and washed with water (15 mL) to give 0.45 g (92%) of **3**, mp 238–240 °C.

### 4.3. Typical procedure for the synthesis of 3-amino-7-cycloalkylimino-6-fluoro-2-methyl-3H-quinazolin-4-ones *4a-d*

The 1-methylpiperazine **1a** (0.4 g, 4 mmol) was added to a solution of difluoroquinazolinone (**2**) (0.3 g, 1.5 mmol) in 2 mL of DMSO. The reaction mixture was heated at 120 °C for 9 h. After the mixture was cooled the precipitate formed was collected by filtration, washed with hot ethanol (5 mL) and recrystallized from DMSO to give 0.36 g (82%) of **4a**.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.10.003.

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