

# N- and / or O- Alkylation of Quinazolinone Derivatives



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## Abstract

Here we report on a strategy based on the capabilities of 2D NMR spectroscopy, which focuses on determining the exact structures of promising HDAC / VEGF-2 inhibitors and intermediate N- or O-alkylated building blocks for their construction. Due to which, in contrast to the erroneous conclusions of other studies, it has been unequivocally established that quinazolin-4-ones with alkyl halides under the classical conditions of two-phase catalysis: the solid phase (alkali metal carbonates) and liquid (aprotic solvents) are subjected to alkylation in the 3-N-position.

**Keywords:** Analgesic; Anti-inflammatory; Antibacterial; Antifungal; Antiviral; Antihistamine; Antihypertensive; Anti-cancer; Antihyperglycemic; Anti-HIV

## Introduction

The study of the regiochemistry of the alkylation process takes one of the key positions in the development of the organic synthesis methodology [1-8]. A classic synthetic problem that remains unresolved is a reaction that involves the control of N- and / or O-alkylation of ambident anions, in particular, the study of the process of N- and O-alkylation of quinazolinones. Uncertainty (inaccuracy) of whether the product(s) are N- and / or O-alkylated is common and can be an unpleasant (expensive) omission (especially in pharmacology) if the structure of the final compound is not adequately defined.

Currently, one of the promising strategies in creating new pharmaceuticals is the design and synthesis of hybrid compounds consisting of two or more different bioactive fragments and acting through the activation / blocking of several targets. The combination of two active groups in one molecule can lead to a more pronounced therapeutic effect, compared with the individual components [9-10]. Thereby, successful work appeared

on the development of hybrid molecules based on quinazoline. Quinazolinone derivatives, which contain a natural uracil fragment, exhibit a wide range of biological activity: analgesic [11], anti-inflammatory [12], antibacterial [13,14], antifungal [15], antiviral [16], antihistamine [17], antihypertensive [18], anti-cancer [19], antihyperglycemic [20] and anti-HIV [21]. Combining the foregoing fragment with other pharmacophores, there were constructed polyfunctional inhibitors containing a quinazoline cycle and hydroxamic acid acting on HDAC and other targets: vascular endothelial growth factor (VEGF-2) [21-23], tyrosine kinases (EGFR, HER2) [24-27]. The most successful compound (CUDC-101) is undergoing clinical trials as a multi-target antitumor drug [28,29].

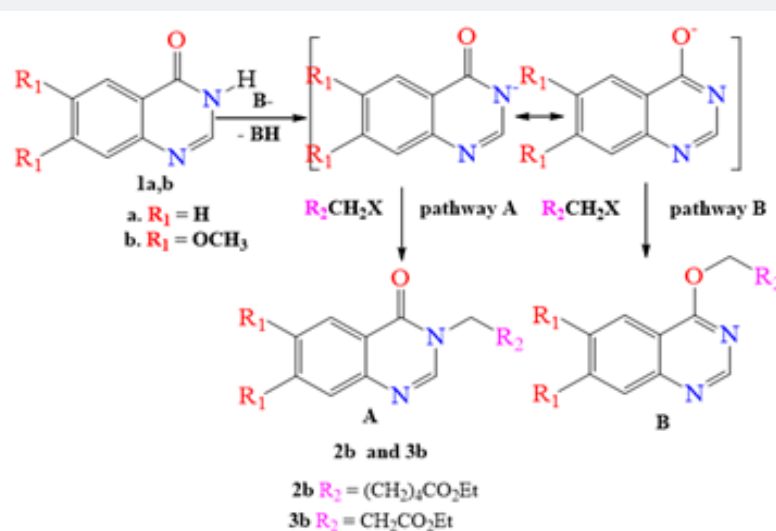
## Results

Based on the foregoing, in order to create more efficient hybrid molecules with bi-inhibitory activity of HDAC / VEGF-2,

we decided to construct a system similar to Vorinostat (Figure 1) by functionalizing it with N- and/or O-alkylation based on quinazoline derivatives (analogs of VEGF-2 inhibitors) as a "capping" group (Scheme 1).



Figure 1: Pharmacophore structure of HDACi on the example of the drug Vorinostat.



Scheme 1: General scheme of the alkylation of quinazolin-4-ones.

To see of literature sources afford that for the O-alkylation of quinazolin-4-ones, good results are obtained when carrying out processes in a two-phase system: solid phase ( $K_2CO_3$  or  $Cs_2CO_3$ ) – liquid phase (DMF, DMSO, acetone, etc. aprotic solvents) [30-31]. However, when we carried out the alkylation of quinazolin-4-one with ethyl 6-bromohexanoate in the described conditions, it was found out that, in contrast to the expected O-isomer B, the product of N-alkylation 2b ( $R_1 = OCH_3$ ,  $R_2 = (CH_2)_5CO_2CH_2CH_3$ ) was formed with 85% yield (pathway A). The structure of product 2b was established based on 2D NMR spectroscopy (HSQC/NOESY, HMBC and  $^{13}C$ )1e-f, which allow one to determine the regioselectivity of alkylation during optimization of synthetic routes. In particular, the formation of the N-alkylation product is confirmed by the correlation of the protons of the  $NCH_2$  group with the 2-H proton of the quinazolinone ring in the NOESY spectrum, as well as the chemical shift of the carbon of the  $NCH_2$  group equal to 45.57ppm (Figure 2).

This discrepancy led us to consider the process more carefully, given that studying the process of N- and O-alkylation of quinazolinones by changing the conditions of the alkylation and / or the nature of the substituents (donor-acceptor properties and steric features) in the used reagents opens up wide possibilities for obtaining from the same reagents of both 3-N-alkylquinazolinone and 4-alkoxyquinazoline. This circumstance has recently become an important tool in creating libraries of various scaffolds for SAR in the search for biologically active substances [32-34]. The urgent need was the repetition of these [30-31] studies, which contradicts the results of work [35], where instead of the O-alkylation product, the N-alkylation product was obtained in the course of reactions under almost the same conditions, which we proved using various methods of NMR spectroscopy of compounds obtained by the above methods. The alkylation of 6,7-dimethoxyquinazolin-4(3H)-one with ethyl chloroacetate under the above [30-31,35-38] conditions also led to the formation of the N-alkylation product 3b

( $R^1=OCH_3$ ,  $R^2=CH_2CO_2CH_2CH_3$ ) with 82 % yield (pathway A), which was confirmed by 2D NMR spectroscopy. The formation of the N-alkylation product is confirmed by the correlation of the protons

of the  $NCH_2$  group with the 2-H proton of the quinazolinone in the COSY spectrum, as well as the chemical shift of the carbon of the  $NCH_2$  group equal to 47.79ppm (Figure 3).

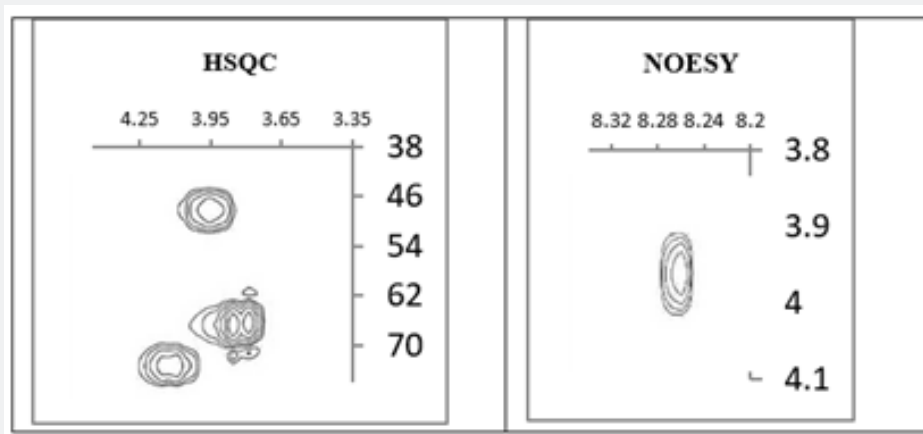


Figure 2: 2D NMR spectra of product 2b.

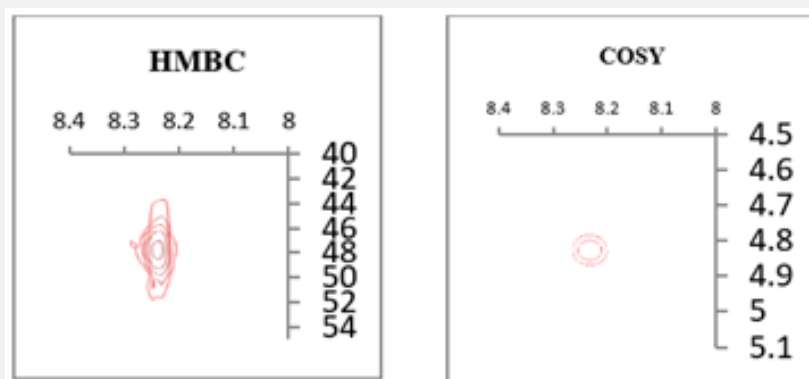


Figure 3: 2D NMR spectra of product 3b.

Alkylation of quinazolin-4(3H)-one (1a) with benzyl chloride in the presence of potassium carbonate in DMF upon heating for 3 hours at 100°C expectedly led to the product of N-alkylation 4a with a yield of 82 %. It turned out that the Regio chemistry of the process is also independent of the nature of the base (when using cesium carbonate the N-alkylation product yield is 81.0 %, and sodium hydride is 77.8 %). Here, the correlation of the 2-H proton of the quinazolinone and  $\alpha$ -methylene protons of the  $NCH_2R$  group is also observed in the COSY spectra, and the correlation of the 2-H proton of the quinazolinone and the carbon of the  $NCH_2R$  group (49.32ppm) in the HMBC spectrum (Figure 3).

This is also confirmed by the fact that the chemical shift of the protons of the benzyl group is at 5.21ppm, which coincides with the  $^1H$  NMR data [39] of compound 4a obtained by counter synthesis using benzylamine (Scheme 2). The formation of the N-alkylation product is confirmed by the correlations of the NCHN

proton of quinazolinone with the proton and carbon of the  $NCH_2R$  group shown in the two-dimensional HMBC and COSY spectra, as well as the signal of the C=O group at 160.10ppm  $^{13}C$  NMR spectrum (Figure 4).

In the case of alkylation of 6,7-dimethoxyquinazolin-4-one with benzyl chloride, potassium carbonate was replaced by cesium carbonate and the process was carried out at 70°C, which also led to the product of N-alkylation 4b with a yield of 82%. The introduction of two methoxy groups into the quinazolinone molecule did not affect the chemical shift of methylene protons of the benzyl group-5.21ppm, which is consistent with the  $^1H$  NMR spectrum of compound 4b obtained by counter synthesis according to the condensation technique [40] of 2-amino-4,5-dimethoxybenzoic acids with triethylorthoformate and benzylamine.

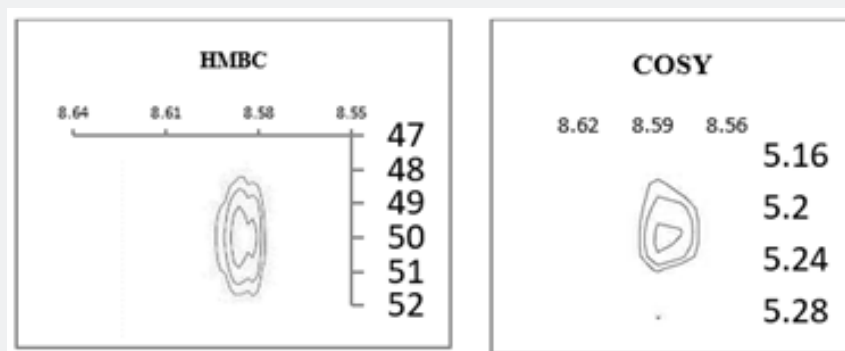
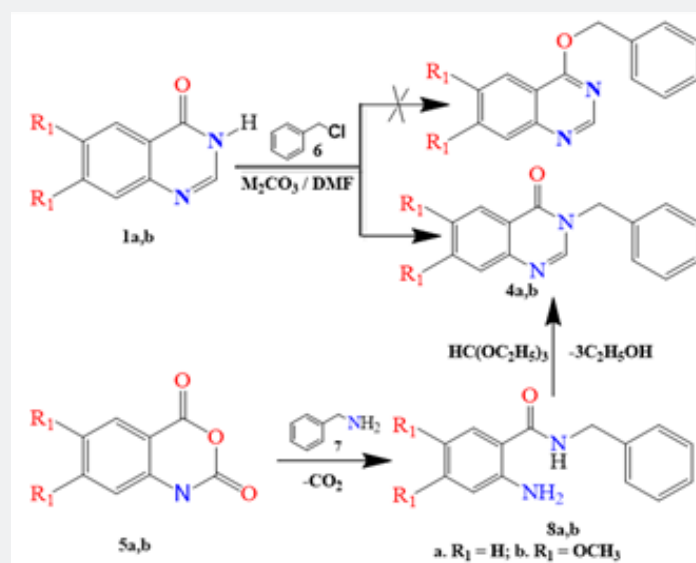


Figure 4: 2D NMR spectra of product 4a.



Scheme 2: Alkylation of quinazolin-4-ones with benzyl chloride.

A similar situation that we observed during a repeat of work [31] when quinazolinone was alkylated with epichlorohydrin. Isolation of N-alkylation product 9a (LCMS,  $m/z = 203 [M + H]^+$ ,  $t_R = 10.9$  min) with a yield of 27%, contains 13% dimer (LCMS,  $m/z = 349 [M + H]^+$ ,  $t_R = 12.2$  min). We suppose that this product was obtained by N- but not O-alkylation, and, moreover, does not contain an oxirane ring, which was hydrolyzed to give the corresponding diol, most likely when authors of work [31] isolated reaction products or used wet acetone as a solvent for alkylation process. Indeed, a comparison of the  $^1H$  NMR spectra showed the identity of the compound they obtained in the reaction of quinazolinone with epichlorohydrin and the product 10a obtained by hydrolysis of quinazolinone 9a.

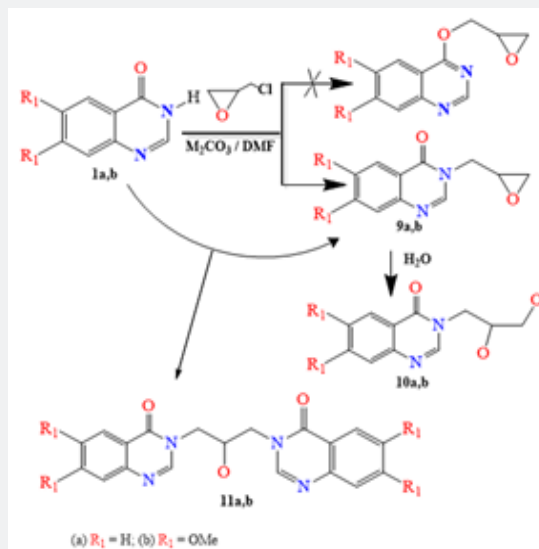
The presence of the oxirane ring in the compound 9a we obtained is confirmed by the presence of two proton groups in the PMR spectrum: the CH group in the form of a multiplet at 3.37-3.34ppm and  $CH_2$  groups in the form of a doublet of doublets at

2.58ppm with J values equal to 4.8 and 2.6 Hz. The protons of the  $NCH_2$  group, due to nonequivalence, give two groups of signals: at 4.32 and 4.08ppm in the form of a doublet of doublets with J values equal to 14.3 and 5.4 Hz (Figure 5). The formation of the N-alkylation product is confirmed with two-dimensional HMBC spectra by correlations of the NCHN proton of quinazolinone with carbon and both carbons of C-2 and C-4 quinazolinone with protons of the  $NCH_2R$  group, as well as the C = O group signal at 160.34ppm of  $^{13}C$  NMR spectra.

When carrying out the same reaction in the presence of cesium carbonate in DMF at room temperature, dimer 11a is formed (LCMS,  $m/z = 349 [M + H]^+$ ,  $t_R = 12.2$  min) with a yield of 46 % (Scheme 3). The formation of the N-alkylation product is confirmed by the presence of  $NCH_2$  group signals in the  $^1H$  NMR spectrum in the form of two groups of signals: at 4.29 and 3.83ppm in the form of a doublet of doublets with J values at 13.4 and 3.4 Hz, and at 49.73ppm in the  $^{13}C$  NMR spectrum. Also, in

the 2D NOESY spectrum, a 2-H correlation of the quinazolinone proton with the protons of the NCH<sub>2</sub>R group is observed along with the signal of the C = O group at 160.50ppm in the <sup>13</sup>C NMR spectrum. In the HMBC 2D spectrum, there are correlations of the

2-H quinazolinone proton with the carbon of the NCH<sub>2</sub>R group and both carbons of C-2 and C-4 quinazolinone with the protons of the NCH<sub>2</sub>R group (Figure 6).



Scheme 3: Alkylation of quinazolin-4-ones with epichlorohydrin.

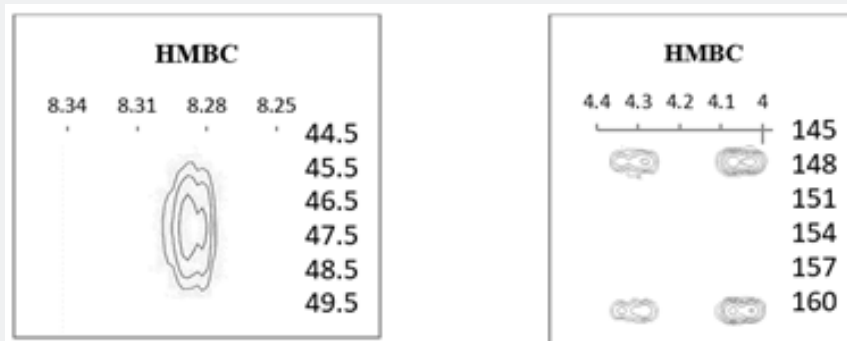


Figure 5: 2D NMR spectra of product 9a.

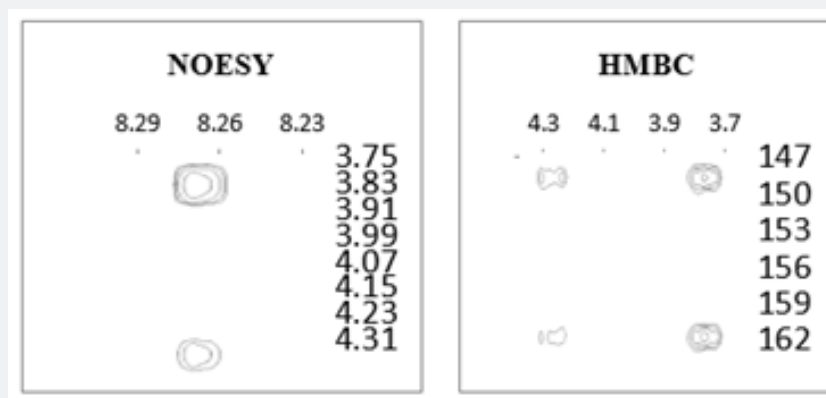
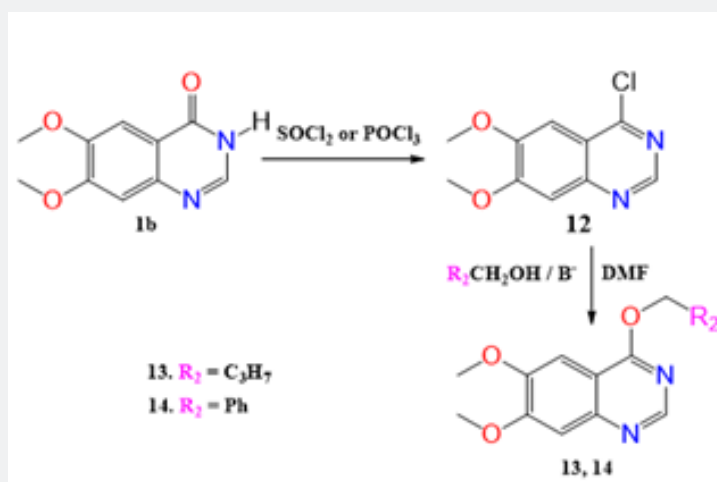


Figure 6: 2D NMR spectra of product 11a.

The results show that a different synthesis route must be used to obtain O-alkylation products. It turned out that in order to realize this, quinazolin-4-one derivatives must first be converted to the corresponding 4-chloroquinazolines by the action of thionyl chloride [41] or phosphorus oxychloride [42] followed by a stage of alcoholysis (Scheme 4). The 4-chloro-6,7-dimethoxyquinazoline (12) obtained in this way was subjected to alcoholysis with butanol and benzyl alcohol. In the case of n-butyl alcohol during the reaction in the presence of sodium hydride in DMF for 48 hours at room temperature and then heating for 3 hours at 70°C, compound 13 was obtained with a 56 % yield, and 4-O-ether 14 was formed with benzyl alcohol at reflux in dioxane at 100°C for 21 hours with 63% yield. The chemical shift of the protons of the benzyl group of the O-alkylation product 14 appears at 5.64ppm, while for the N-alkylation products 4a at 5.21ppm, 4b at 5.18ppm.

## Conclusion

Thus, the studies have shown that under classical two-phase conditions, quinazolin-4-ones to use the solid phase (alkali metal carbonates) - liquid (aprotic solvents) are regioselectively subjected to 3-N-alkylation. It is unequivocally proved by detailed analysis of two-dimensional (HSQC/NOESY, HMBC and  $^{13}\text{C}$ ) NMR spectra of the reaction products, as well as by comparing the physicochemical properties of the products we obtained with those products obtained by counter synthesis. The above is very important for us when conducting our SAR in the search for effective HDAC/VEGFR-2 bi-inhibitors, since the authors of work [29,35] performed SAR to search for VEGFR-2 inhibitors on supposedly 4-O-alkylquinazolines, whereas in reality they had products of N-alkylation (Scheme 4). This led us to develop an alternative route [37,38] for the synthesis of 4-alkoxyquinazolines.



**Scheme 4:** Synthesis of 4-alkoxyquinazolines 13, 14.

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