# SYNTHESIS AND PREDICTION OF ANTITUMOR ACTIVITY OF SUBSTITUTED QUINAZOLINE-4(3*H*)-ONES

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**Introduction.** Nitrogen-containing heterocycles are broadly dispersed in nature and are basic to life, assuming an indispensable job in the digestion of every single living cell. 4(3H)-Quinazolinones have risen as a significant class of nitrogen containing heterocycles that have pulled in critical manufactured intrigue on account of their pharmacological and remedial properties. Among this class of compounds, 3-substituted 4(3*H*)-quinazolinones are notable since they are available in an enormous group of items with expansive organic molecules. Hence, their union has gotten impressive consideration. A few customary arrangement strategies required refluxed temperature and long response time (3 days). Recently, new improvements for the blend of 3-substituted 4(3*H*)-quinazolinones by a three-segment, one-pot buildup of anthranilic corrosive, amines, and ortho esters within the sight of different impetuses. Some novel 3-substituted 4-(2*H*)-quinazolinones have been integrated from anthranilic acid, amine and orthoester. In this communication, we report a novel protocol for the selective synthesis of 3-substituted quinazolin-4(3*H*)-ones by using $Bi(OTf)_3$ as effective catalyst.

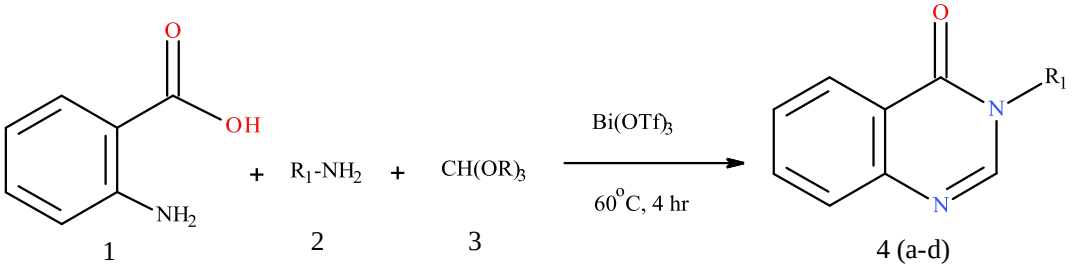
**Aim.** Synthesis and prediction of antitumor activity of substituted quinazoline-4(3*H*)-ones.

**Materials and methods.** Compounds were observed for their purity by TLC on silica gel G plates with spots checked by iodine vapors. The NMR spectra were recorded by using a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz and spectra ($^1$H NMR and $^{13}$C NMR) were recorded by using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6.

For receptor-oriented flexible docking, the Autodock 4.2 software package was used. Ligands were prepared using the MGL Tools 1.5.6 program. The Ligand optimization was performed using the Avogadro program. To perform calculations in the Autodock 4.2 program the output formats of the receptor and ligand data were converted to a special PDBQT format. The active macromolecule centers of the tyrosine kinase receptor EGFR (PDB ID: 4HJO, 1M17) and human cytochrome P450 CYP1A1 (PDB ID: 6DWM) from the Protein Data Bank (PDB) were used as a biological targets for docking. The receptor maps were made in MGL Tools and AutoGrid programs. Water molecules, ions, and the ligand were removed from the PDB file ID: 6DWM, 4HJO, 1M17.

**Results and discussion.** It was discovered that the reaction could be done under extremely basic response conditions within the sight of $Bi(OTf)_3$ which gives the ideal 3-substituted quinazolinone derivatives in great yield. $Bi(OTf)_3$ can productively catalyze a one-pot cyclisation of 3-substituted quinazolinones through a three-part buildup of anthranilic acid, amine and orthoester (Scheme 1).

**Scheme 1**




1 2 3 4 (a-d)

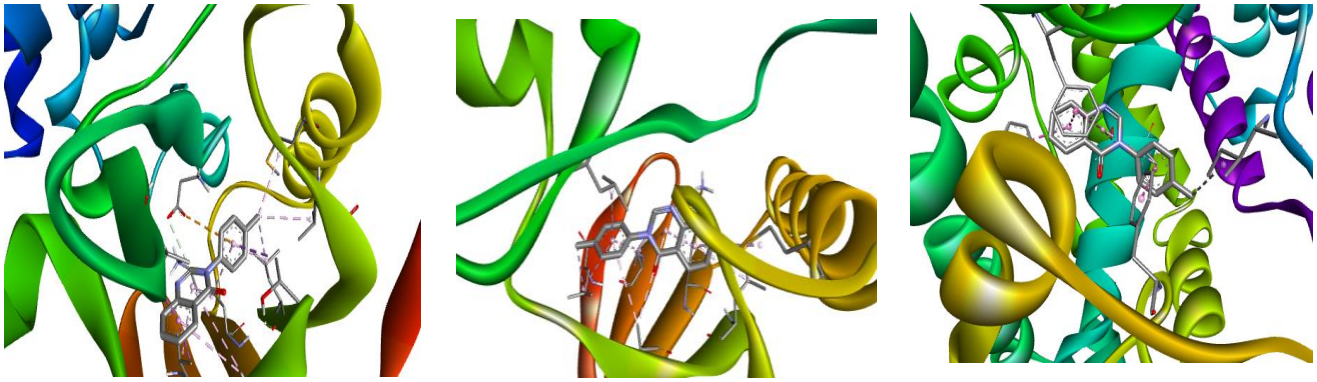
4a $R_1 = C_6H_5$, 4b $R_1$ = 4-$OCH_3$-$C_6H_5$, 4c $R_1$ = 4-$CH_3$-$C_6H_5$ , 4d $R_1$ = 4-$CF_3$-$C_6H_5$

For the synthesized compounds, a computer prediction of antitumor activity was carried out. Thus, it can be assumed that the inhibitory activity of the molecules tested relative to the receptors PDB ID: 4HJO, 1M17, 6DWM can be actualized by forming complexes between them; their stability is provided mainly due to the energy favorable geometric location of ligands in the active center of this acceptor, the formation of hydrogen bonds between them, intermolecular electrostatic and donor-acceptor interactions. As a consequence, the thermodynamic probability of such binding is confirmed by negative values of the scoring function (Affinity DG, kcal/mol), calculated values of the free energy of binding EDoc (kcal/mol), and binding constants Ki (mM/ μM)

Taking into account the detailed analysis of the location of the molecules tested in the active site of receptors, the formation of a number of intermolecular interactions between them, negative values of scoring functions and calculated values of binding constants it can be concluded that the tested molecules have an affinity for these specified biological target targets (fig. 1).

(a) (b) (c)

Fig 1. The Ligand 4c superposition in the complex with the biotargets PDB ID: 4HJO (a),



1M17 (b), 6DWM (c)

**Conclusion.** The current work infers that $Bi(OTf)_3$ has been utilized as a novel and productive impetus for the synthesis of 3-substituted quinazolinone derivatives. The remarkable highlights of this technique are mild reaction conditions, great yield, improved rates and straightforwardness in activity, which make it a valuable and alluring procedure for the synthesis of 3-substituted quinazolinone derivatives.

*In silico* prediction showed that these compounds are promising due to their inhibitory activity towards antitumor targets PDB ID: 4HJO, 1M17, 6DWM. The inhibitory activity of the tested molecules can be realized by forming complexes between them; their stability is provided mainly due to the energetically favorable geometric arrangement of the ligands in the active centers of these acceptors, the formation of hydrogen bonds between them, and intermolecular electrostatic and donor-acceptor interactions. As a consequence, the thermodynamic probability of such binding is confirmed by negative values of the evaluation function (Affinity DG, kcal / mol), calculated values of the free binding energy EDoc (kcal / mol), and binding constants Ki (mM / mol). μM). The data obtained can be used in planning experimental screening for antitumor activity.