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RESEARCH ARTICLE

Prediction of antitumor activity of 3-substituted quinazolinone derivatives synthesized in one-pot method catalyzed by $Bi(OTf)_3$

L. Perekhoda[2], M. Hari Krishna[1], T. Sekhar[1], A. Venkateswarlu[1], P. Thriveni[1], M. Suleiman[2], A. Semenets[2], A. Fedosov[2], L. Grinevich[2], N. Kobzar[2], V. Yaremenko[2]

[1]Department of Chemistry, Vikrama Simhapuri University, Nellore-524001, Andhra Pradesh, India.
[2]Department of Medicinal Chemistry, National University of Pharmacy,
Pushkinska 53, 61002, Kharkiv, Ukraine.
*Corresponding Author E-mail: **suleiman.nfau@outlook.com**

ABSTRACT:

A series of 3-substituted guinazolinone derivatives have been synthesized in good to excellent yields and high selectivity by one-pot reaction using anthranilic acid, amine and orthoester in ethanol under mild conditions, respectively. The reaction was efficiently promoted by $Bi(OTf)_3$ and the catalyst could be recovered easily after the reactions and reused without evident loss of reactivity. Docking studies have shown that the tested molecules have an affinity for anticancer targets. The data obtained can be used in planning experimental screening for antitumor activity.

KEYWORDS: Synthesis, $Bi(OTf)_3$, anthranilic acid, orthoester, one-pot union, amine, quinazolinone derivatives, molecular docking, antitumor activity.

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, for example, antibacterial, antifungal, antimalarial, antihypertensive, anticonvulsant, for treatment Parkinsonism, antihistaminic and nearby sedative, pain relieving, mitigating antiviral and anticancer activities [1-10]. Few quinazolinones have been accounted for as strong chemotherapeutic operators in the treatment of tuberculosis. For instance, 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones and 3-arylquinazoline-2,4(1H,3H)-diones were recommended as antimycobacterial agents[11] and as antitubercular agents [12].

The antihyperlipidemic activities of these molecules were also investigated[13]. A new series of 3-[(dialkylamino) methyl]-2-substituted-4(3H)-quinazolinones were screened for anti-inflammatory activity and were showed their significant anti-inflammatory activity is higher that of standard[14]. A series of 6-substituted 2-ethyl-3-[substituted benzothiazol-2-yl]-4(3H)-quinazolinones have been showed most prominent anticonvulsant activity with low side effects compared with the reference drug Phenytoin sodium in MES test and Diazepam in scPTZ test.[15]

The easy generation of complex molecular diversity through broadly applicable, cost-effective, practical and sustainable synthetic methods in a straightforward fashion along with the importance of these motifs in medicinal chemistry, received significant attention from researchers engaged in drug design and heterocyclic methodology development. There are a few strategies for the cyclisation on basis of 4(3*H*)-quinazolinones[16-17]. Nitrogen-containing heterocycles are the most bountiful and vital frameworks that happen pervasively in an assortment of engineered drugs, bioactive characteristic items, pharmaceuticals and agrochemicals[18-20]. The nearness of N-heterocycles as a basic auxiliary theme in

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an assortment of naturally dynamic substances has invigorated the improvement of new methodologies and advances for their blend. Quinazolinone is part of about 200 commonly found alkaloids that belong to various groups of plants and microorganisms. The first quinazoline alkaloid isolated was vazicine (peganin 1) in 1888 [21]. The first quinazolinone synthesized in the late 1860s from anthranilic corrosive and cyanogens to give 2-cyanoquinazolinone [22]. Some of biologically active compounds containing 4-(2*H*)-quinazolinones moiety were shown in below (fig.1).

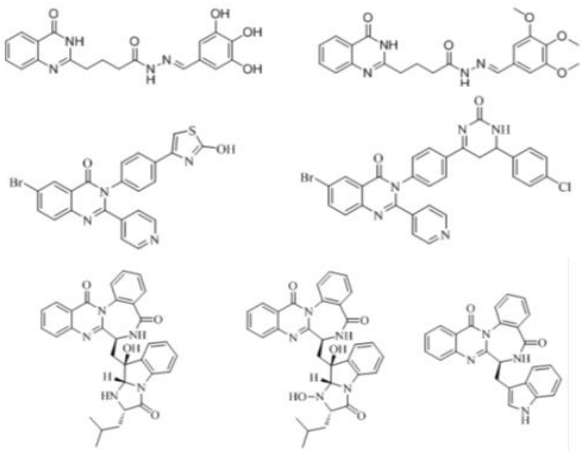


Fig.1: Biologically active compounds containing 4-(2*H*)-quinazolinone moiety

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) [23]. 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, for example, $NaHSO_4$ or Amberlyst-15 [24], Yb(III)-resin [25], $Yb(OTf)_3$ [26], $Bi(TFA)_3$-[nbp]$FeCl_4$] ionic liquid[27], $La(NO_3)_3$. $6H_2O$ p-toluenesulfonic acid[28], Keggin-type heteropolyacid under microwave irradiation[29], $SnCl_4.4H_2O$ [30], and SiO_2-$FeCl_3$ [31] have been accounted for. Be that as it may, a portion of these techniques are related with specific downsides, for example, long response times, low yields, cruel response conditions, troublesome work-up and utilization of earth poisonous reagents or media. Be that as it may, these conventional and microwave procedures are related with different downsides, similar to the reaction conditions, accessibility of reagents and chemical hazards.

The aim of our work is to optimize the production method using a new catalyst.

To achieve this aim, new series of 3-substituted 4-(2H)-quinazolinones were synthesized from anthranilic acid, amine and orthoester and physical and chemical properties were investigated using modern methods. 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. $Bi(OTf)_3$ can be considered as a new and efficient Lewis-acid-type catalyst for a number of reactions involving various Lewis bases as substrates. The relatively low cost and high catalytic efficiency of $Bi(OTf)_3$ makes it similar to rare-earth triflates. The small number of publications reporting catalysis by $Bi(OTf)_3$ compared to that of rare-earth triflates indicates that the dawn of the use of $Bi(OTf)_3$ in organic synthesis has just begun. There is no doubt that $Bi(OTf)_3$ will emerge as a new, powerful and environmentally friendly Lewis acid catalyst for synthetic methodologies needed for green chemistry.

MATERIALS AND METHODS:

All solvents were purified before use. Compounds were observed for their purity by thin-layer chromatography (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 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm and ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm). Chemical shifts are reported in ppm units use of δ scale.

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. In previous studies, a similar software package was used [32-35]. 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.

The choice of crystallographic models of PDB ID: 4HJO and tyrosine kinase PDB ID: 1M17 (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-

anilinoquinazoline inhibitor erlotinib) as a biological target for the study of the possible antitumor activity is due to the existing crystallographic model co-crystallized with a derivative of 4-anilinoquinazoline. Erlotinib, tyrosine kinase inhibitors [36-37] used to block EGFR (epidermal growth factor receptor) signalling in cancer, are thought to bind only the active conformation of the EGFR-TKD (tyrosine kinase domain). Computational and crystallographic studies have shown that a crystallographic model with erlotinib (PDB ID: 4HJO) indicates binding to active and inactive EGFR-TKD conformations, which has the potential for use in mutated EGFR forms of cancer [38]. The crystal structure of the epidermal growth factor kinase domain EGFRK (PDB ID: 1M17) assumes a conformation that is similar to the phosphorylated active form of the kinase domain, which leads to significant intermolecular contacts[39].

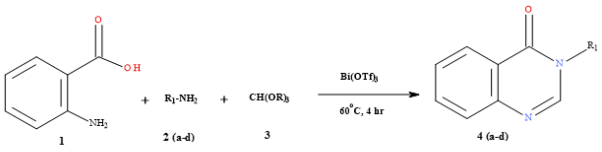
Human cytochrome P450 1A1 (CYP1A1) is an extrahepatic enzyme involved in the monooxygenation of structurally diverse compounds ranging from natural products to drugs and protoxins. Because CYP1A1 has a role in human carcinogenesis, inhibiting its activity may potentially aid in cancer chemoprevention, whereas utilizing CYP1A1's oxidative activity could help selectively activate anticancer prodrugs. Such potential therapeutic purposes require detailed knowledge of CYP1A1's interactions with potential ligands. Known CYP1A1 ligands also vary substantially in size, and it has not been apparent from a single existing CYP1A1 structure how larger, structurally diverse ligands are accommodated within the enclosed active site. Here, two new X-ray structures with the natural product furanocoumarin bergamottin (at 2.85 Å resolution) and the lung cancer drug erlotinib (3.0 Å) revealed binding orientations consistent with the formation of innocuous metabolites and of toxic metabolites, respectively [40].

The following docking parameters were determined: the maximum RMS tolerance for the conformational cluster analysis – 2 Å; the free energy coefficient for torsional degrees of freedom – 0.2983; the cluster tolerance – 2 Å; the external grid energy – 1000; the maximum initial energy – 0; the maximum number of retries – 10 000; the number of individuals in the population – 150; the maximum number of energy evaluations – 2500000; the maximum number of generations – 27000; the number of top individuals to survive to the next generation – 1; the rate of gene mutation – 0.02; the rate of crossover – 0.8; the crossover mode – arithmetic; the α-parameter of Gauss distribution – 0; the β-parameter of Gauss distribution – 1. The visual analysis of complexes of substances in the active center of the tyrosine kinase receptor (PDB ID: 6DWM, 4HJO, 1M17) was performed using the Discovery Studio Visualizer program.

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. Bismuth (III) triflate can productively catalyze a one-pot cyclisation of 3-substituted quinazolinones through a three-part buildup of anthranilic acid, amine and orthoester. Synthesis was carried according Scheme 1:

Scheme 1



3 R = CH_3, 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

We discovered that the high yields of the target compounds were achieved by introducing the equimolar amounts of the reagents at temperature 60 °without solvent.

All the products were identified by spectral (^{1}H NMR, ^{13}C NMR) and analytical data.

For the synthesized compounds, a computer prediction of antitumor activity was carried out. Based on the results of molecular docking the following data were calculated: the scoring function indicating the enthalpy contribution to the value of the free energy of binding (Affinity DG) for the best conformational positions (Table. 1); the values of the free energy of binding and binding constants (EDoc kcal/mol and Ki mM (millimolar)) for a specific conformational position of the ligand; they allow assessing the stability of complexes formed between ligands and the corresponding receptor (Table. 2).

Table 1: Affinity DG values for best conformational positions of the test compounds in combination with the biotargets (PDB ID: 4HJO, 1M17, 6DWM)

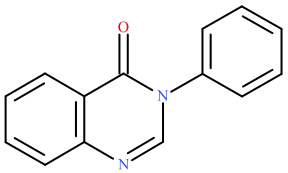
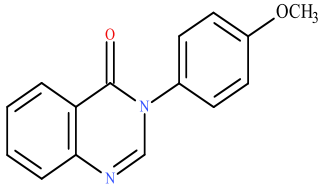
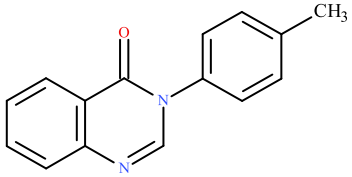
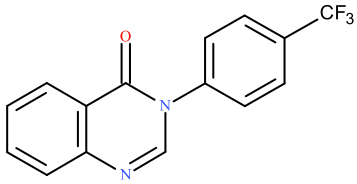
Ligand	Afinity DG, kcal/mol		
	4HJO	**1M17**	**6DWM**
 **4 a**	-8,2	-8,3	-9,3
 **4 b**	-8,5	-7,8	-10,4
 **4 c**	-8,7	-8,1	-10,6
 **4 d**	-8,1	-7,9	-10,3

Table 2: Values of the free energy of binding and binding coefficients of the test antitumor agents in combination with the biotargets (PDB ID: 4HJO, 1M17, 6DWM)

Ligand	4HJO		1M17		6DWM	
	EDoc kcal/mol	Ki uM micromolar	EDoc kcal/mol	Ki uM micromolar	EDoc kcal/mol	Ki uM micromolar
4 a	-6.06	36.37 uM	-5.73	63.60 uM	-6.24	26.87 uM
4 b	-5.51	91.70 uM	-5.72	63.74 uM	-6.13	32.04 uM
4 c	-5.80	56.33 uM	-6.11	33.04 uM	-6.35	22.31 uM
4 d	-5.40	89.60 uM	-5.71	63.53 uM	-6.09	32.24 uM

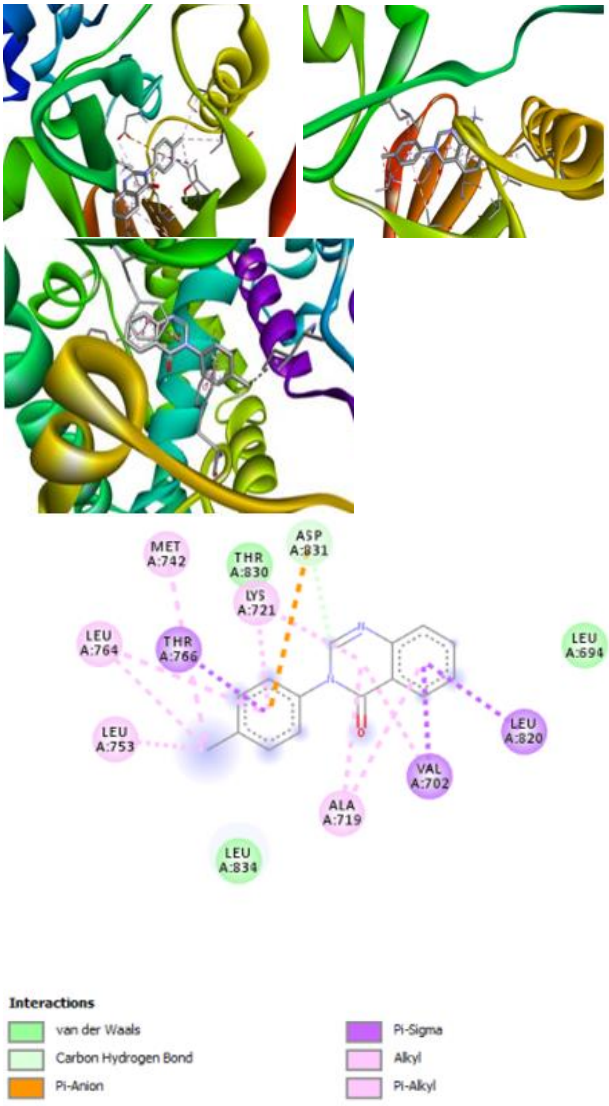
Thus, it can be assumed that the inhibitory activity of the molecules tested relative to the receptors PDB ID: 4HJO, 1M17, 6DWM can be actualized by forming complexes between them; their stability is provided mainly due to the energy favorable geometric location of ligands in the active center of this 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) (Table. 2).

In order to understand how the affinity of the drugs studied to the target occurred a detailed analysis of the geometric location of the active molecule 4 c (PDB ID: 4HJO Afinity DG = -8,7 kcal/mol, EDoc = -5.80 kcal/mol, Ki = 56.33 uM; PDB ID: 1M17 Afinity DG = -8,1 kcal/mol, EDoc = -6.11 kcal/mol, Ki = 33.04 uM; PDB ID: 6DWM Afinity DG = -10,6 kcal/mol, EDoc = -6.35 kcal/mol, Ki = 22.31 uM) in the active site of the receptors was conducted.

The values of interatomic distances, categories and types of intermolecular interactions of the molecule 4 c in the active sites of the biotargets (PDB ID: 4HJO, 1M17, 6DWM) are given in Tab. 3.

Table 3: Values of interatomic distances, categories and types of intermolecular interactions of the molecule 4 c in the active sites of the biotargets (PDB ID: 4HJO, 1M17, 6DWM)

4HJO			1M17			6DWM		
Distance, Å	**Category**	**Types**	**Distance, Å**	**Category**	**Types**	**Distance, Å**	**Category**	**Types**
3,54	**Hydrogen Bond**	**Carbon Hydrogen Bond**	**4,57**	**Electrostatic**	**Pi-Cation**	**3,68**	**Hydrophobic**	**Pi-Sigma**
4,76	Electrostatic	Pi-Anion	4,21	Hydrophobic	Alkyl	3,83	Hydrophobic	Pi-Pi Stacked
3,66	Hydrophobic	Pi-Sigma	4,11	Hydrophobic	Pi-Alkyl	3,67	Hydrophobic	Pi-Pi Stacked
3,93	Hydrophobic	Pi-Sigma	5,48	Hydrophobic	Pi-Alkyl	4,89	Hydrophobic	Pi-Pi T-shaped
3,94	Hydrophobic	Pi-Sigma	5,30	Hydrophobic	Pi-Alkyl	4,73	Hydrophobic	Pi-Pi T-shaped
4,61	Hydrophobic	Alkyl	5,36	Hydrophobic	Pi-Alkyl	3,50	Hydrophobic	Amide-Pi Stacked
4,04	Hydrophobic	Alkyl	5,37	Hydrophobic	Pi-Alkyl	5,18	Hydrophobic	Alkyl
3,87	Hydrophobic	Alkyl	5,12	Hydrophobic	Pi-Alkyl	5,18	Hydrophobic	Pi-Alkyl
4,87	Hydrophobic	Pi-Alkyl	5,47	Hydrophobic	Pi-Alkyl			
4,21	Hydrophobic	Pi-Alkyl	4,88	Hydrophobic	Pi-Alkyl			
5,36	Hydrophobic	Pi-Alkyl	4,81	Hydrophobic	Pi-Alkyl			
5,20	Hydrophobic	Pi-Alkyl	4,73	Hydrophobic	Pi-Alkyl			
4,78	Hydrophobic	Pi-Alkyl						
5,19	Hydrophobic	Pi-Alkyl						



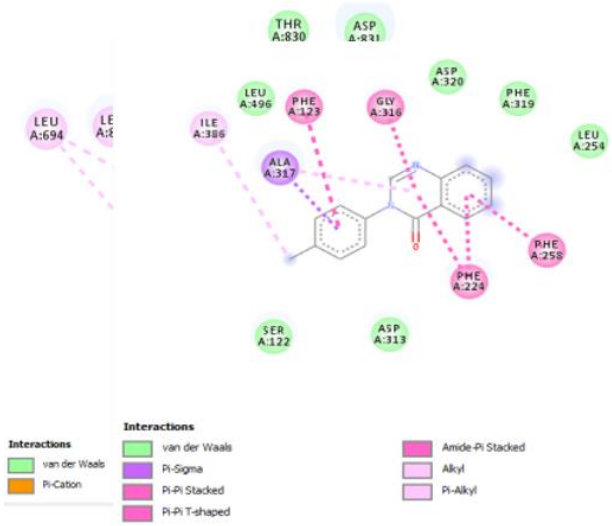


Fig 2. The Ligand 4 c superposition and the diagram of intermolecular interactions in the complex with the biotargets PDB ID: 4HJO (a), 1M17 (b), 6DWM (c)

Molecule 4 c forms a chelate complex with the tyrosine kinase receptor (PDB ID: 4HJO) due to the carbon bond and the π-anionic interaction between the quinazoline ring and the phenyl moiety and the Asp831 residue. (Fig. 2).The Chelate 3 complex is facilitated by π-σ bonds between aromatic components and residues and Thr766, Val702, Leu820. The complex 4 c with tyrosine kinase (PDB ID: 1M17) is formed due to the π-cation interaction with the lysine residue Lys721. Stabilization of complexes is stimulated by π-Alk and Alk intermolecular interactions with amino acid residues Leu820, Leu764, Leu694, Lys721, Ala719, Val702, Met742.

Molecule 4 c forms a chelate complex with the enzyme system CYP1A1 (PDB ID: 6DWM) due to π-σ, π-π, π-amide, π-Alk and Alk intermolecular interactions

between the components of the molecule and amino acid residues Gly316, Phe224, Phe258, P , Ile386 (Fig. 2).

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. The obtained data can be used in planning experimental screening for antitumor activity.

General Procedure for the synthesis of 3-Substituted Quinazolinone derivatives 4(a-d):

$Bi(OTf)_3$ (0.05 mmol, 1 mol %) was added to a solution of anthranilic acid 1 (10 mmol), amine 2 (12 mmol) and orthoester 3 (12 mmol) in ethanol (10mL). The mixture was stirred at 60°C for 4 hrs, the progress of the reaction was checked by TLC. After completion, the reaction mixture was allowed to cool to room temperature and water (20 mL) was added. The solid product 4 was obtained through simple filtering. The resulting precipitates were dried and recrystallized from ethanol. Target compounds ***4.a-c*** were crystallized from organic solvents and obtained with the yields of 79-90%.

Spectral data for selected compounds:

3-Phenylquinazolin-4(3*H*)-one: (4a) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (ddd, J = 8.0, 1.5, 0.7 Hz, 1H), 8.14 (s, 1H), 7.89 –7.73 (m, 2H), 7.61–7.48 (m, 4H),7.47-7.38(m, 2H). ^{13}C NMR (100 MHz, CDCl3): δ 160.63, 147.76, 145.98, 137.38, 134.47 129.53, 129.02 127.54, 127.36 127.06, 126.91 122.32.

3-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (4b): ^{1}H NMR (400 MHz, CDCl3): δ 8.37 (dd, J1 = 0.4 Hz, J2 = 8.0 Hz, 1H), 8.11(s, 1H), 7.80-7.77 (m, 2H), 7.55 (t, J = 6.4 Hz, 1H), 7.34 (d, J = 9.1Hz, 2H), 7.06(d, J = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.02148.00, 147.45, 146.58 134.66, 131.26 128.27, 127.72, 127.65, 127.29, 122.47, 114.96, 55.74.

3-p-Tolylquinazolin-4(3*H*)-one (4c): ^{1}H NMR (400 MHz, CDCl3): δ 8.37 (d, J = 8.0 Hz, 1H), 8.12(s, 1H), 7.82-7.49 (m, 2H), 7.59(t, J = 7.2 Hz, 1H), 7.36-7.28 (m, 4H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.02, 148.04, 146.42, 139.37, 135.05, 134.63, 130.37, 127.68 127.31, 126.85 122.54, 21.35.

3-(4-(Trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (4d): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35(ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 8.11(s, 1H), 7.87 –7.71(m, 4H), 7.64–7.51 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.27, 147.62 145.07, 140.35 134.85, 131.19, 128, 127.65 127.47, 127.13 126.77, 123.50, 122.07.

CONCLUSION:

New compounds 3-substituted quinazolinone derivatives were synthesized using a catalyst $Bi(OTf)_3$. The remarkable highlights of this synthetic technique are mild reaction conditions, great yields, improved rates, which make it a valuable procedure for the synthesis of 3-substituted quinazolinone derivatives. For the synthesized compounds, a computer prediction of antitumor activity was carried out. 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.

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CONFLICT OF INTEREST:

The authors have declared no conflict of interest.

REFERENCES:

1. Shaheda Sultana Sk, Parveen P, Usha P, Vasu Naik V, Rajesh Ak, Gayatri Ramya M. Pharmacological Evaluation of Synthesized Test Compounds of Quinazolinones and Pyrazolinones. Asian J Research Chem. 2014; 7(1): 33-40.
2. Niraimathi V, Vamsadhara C. Analgesic Activity of 2-Hetero Substituted -4-Quinazolinones. Research J Pharm and Tech. 2010; 3 (4): 1093-1095.
3. Girija K, Sathiyaraj S,. Rajendiran V, Hemalatha K. 2, 3-Disubstituted Quinazolinones: Study of its Anti-microbial Activity. Research J Pharm and Tech. 2017; 10(4): 1020-1024. doi: 10.5958/0974-360X.2017.00184.6.
4. Hemalatha K, Selvin J,. Girija K. Synthesis, In silico Molecular Docking Study and Anti-bacterial Evaluation of some Novel 4-Anilino Quinazolines. Asian J Pharm Res. 2018; 8(3): 125-132. doi: 10.5958/2231-5691.2018.00022.9.
5. Battin SN, Manikshete AH,. Sarasamkar SK, Asabe MR, Sathe DJ. Synthesis, Spectral, Antibacterial, Antifungal and Anticancer activity Studies of Schiff bases Derived from O-Vanillin and Aminoquinolines. Asian J Research Chem. 2017; 10(5): 660-668. doi: 10.5958/0974-

4150.2017.00112.2.
6. Rishipathak DD, Kokate AB, Madhawai KS. Activity of Quinazoline Derivatives: A Review. Asian J. Res. Pharm. Sci. 2017; 7(4):209-211. doi: 10.5958/2231-5659.2017.00032.7
7. Virupakshi Prabhakar, Venkateswarlu B, Punagani Bhargavi, Sura Jagadeesh. Design, Synthesis and Activity of Novel Quinazoline Derivatives Linked with various Sulphonamides. Asian J. Research Chem. 2016; 9(10):485-504. doi: 10.5958/0974-4150.2016.00073.0
8. Dinesh D Rishipathak, Trupti A Jadhav, Sonal P Tathe, Pavan B Udavant. Microwave Assisted Synthesis and Pharmacological Evaluation of Few 4-Quinazolinone Derivatives. Asian J. Pharm. Res. 2019; 9(3):147-154. doi: 10.5958/2231-5691.2019.00023.6
9. Dahikar G. D., Yeole P.G., Ganjiwale R.O., Rahangdale V.T.. The Preparation and Biological Evaluation of Some New 6-Iodo-2-Ethyl-4(3H)-3 (5-Substituted Benzothiazole-2'-Yl) Quinazolinone Derivatives as an Anticonvulsant. Asian J. Research Chem. 3(3): July-Sept. 2010; Page 555-557.
10. Kavitha K, Nehla Yahoob, Vijayakumar B, Reshma Fathima K. Synthesis and Evaluation of Quinazolinone Derivatives. Asian J. Research Chem. 2017; 10(4):577-581. doi: 10.5958/0974-4150.2017.00096.7.
11. Waisser K, Gregor J, Dostal H, Kunes J, Kubicova L, Klimesova V. Influence of the replacement of the oxo function with the thioxo group on the antimycobacterial activity of 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones and 3-arylquinazoline-2,4(1H,3H)-diones. J Farmaco. 2001; 566: 803-807. doi: 10.1016/s0014-827x(01)01134-x.
12. Kunesˇ J, Bazant J, Pour M, Waisser K, losarek S, Janota M., Quinazoline derivatives with antitubercular activity. J Farmaco. 2000; 55: 725-729. doi: 10.1016/s0014-827x(00)00100-2.
13. Refaie FM, Esmat AY, Abdel-Gawad SM, Ibrahim AM, Mohamed MA. The antihyperlipidemic activities of 4(3H) quinazolinone and two halogenated derivatives in rats. Lipids Health Dis. 2005; 4: 22. doi: 10.1186/1476-511X-4-22.
14. Ganesh Akula, Rangu Nirmala, Shanthipriya CH, Rohini Reddy S, Jaswanth A. Synthesis of novel 3-[(dialkyl/aryl amino) methyl]-2-substituted-4(3H)-Quinazolinones and evaluation of their Anti-inflammatory activity. Asian J Pharm Res. 2017; 7(2): 60-62. doi: 10.5958/2231-5691.2017.00010.7.
15. Vinod GU, Sudhir GW, Chandrabhan T. Chopde. Design, Development and Screening of Some Novel Quinazolinones for Anticonvulsant Activity. Asian J Research Chem. 2011; 4(11): 1717-1721.
16. Khan I, Ibrar A, Ahmed W, Saeed A, et al. Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: the advances continue. Eur J Med Chem. 2015; 90: 124-169.
17. Khan I, Ibrar A, Abbas N, Saeed A. Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: synthetic approaches and multifarious applications. Eur J Med Chem. 2014; 76: 193-244.
18. Hrast M, Rozman K, Jukic M, Patin D, Gobec S, Sova M. Synthesis and structure eactivity relationship study of novel quinazolinone based inhibitors of Mur A. Bioorg Med Chem Lett. 2017; 27: 3529-3533.
19. Ighachane H, Sedra MH, Lazrek H, Synthesis and evaluation of antifungal activities of (3H)-quinazolin-4-one derivatives against tree plant fungi. J Mater Environ Sci. 2017; 8: 134-143.
20. Alaa AM, Abou-Zeid LA, ElTahir KEH, Ayyad RR, Magda AA, El-Azab AS. Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4 (3H)-quinazolinones. Eur J Med Chem. 2016; 121: 410-421.
21. Santosh Mhaske B, Narshinha Argade P. Concise and Efficient Synthesis of Bioactive Natural Products Pegamine, Deoxyvasicinone, and (-)-Vasicinone. J Org Chem. 2001; 66: 9038-9040. DOI: 10.1021/jo010727l.
22. Venkataramireddy V, Tejeswararao A, Jayashree A, Ravi Varala. Synthesis and biological evaluation of functionalized quinoxaline derivatives. Der Pharma Chemica. 2014; 6(6): 73-78.
23. Szczepankiewicz Suwinski W. One-pot synthesis of 3-(2-cyanophenyl)-quinazolin-4(3H)-one. J Chem Heterocycl Compd. 2000; 36: 809-10.
24. Das B. Banerjee. Silica-Supported Sodium Hydrogen Sulfate and Amberlyst-15: Two Efficient Heterogeneous Catalysts for Single-Step Synthesis of 4(3H)-Quinazolinones from Anthranilic Acid, Orthoesters, and Amines under Solvent-Free Conditions. J Chem Lett. 2004; 33: 960-61.
25. Jiang ZD, Chen RF. Synthesis of 3,4-Dihydropyrimidine-2(1H)-thiones and Quinazolin-4(3H)-ones over Yb(III)-Resin Catalyst Under Solvent-free Conditions. Synth Commun. 2005; 35: 503-9. https://doi.org/10.1081/SCC-200049766.
26. Wang LM, Xia JJ, Qin F, Qian CT, Sun J. Yb(OTf)3-catalyzed one-pot synthesis of quinazolin-4(3H)-ones from anthranilic acid, amines, and ortho esters (or formic acid) in solvent-free conditions. Synthesis. 2003; 1241.
27. Khosropour AR, Mohammadpoor-Baltork I, Ghorbankhani H. Bi(TFA)3- [nbp]FeCl4: A new, efficient, and reusable promoter system for the synthesis of 4(3H)- quinazolinone derivatives. Tetrahedron Lett. 2006; 47: 3561.
28. Narasimhulu M, Mahesh KC, Reddy TS, Rajesh K, Venkateswarlu Y. Lanthanum(III) nitrate hexahydrate or p-toluenesulfonic acid–catalyzed one-pot synthesis of 4(3H)-quinazolinones under solvent-free conditions. Tetrahedron Lett. 2006; 47: 4381.
29. Ighilahriz K, Boutemeur B, Chami F, Rabia C, Hamdi M, Hamdi SM. A microwave-assisted and heteropolyacids-catalysed cyclocondensation reaction for the synthesis of 4(3H)-quinazolinones. Molecules. 2008; 13: 779.
30. Oskooie HA, Baghernezhad B, Heravi MM. $SnCl_4$ $4H_2O$ as an efficient catalyst for the synthesis of 4(3H)-quinazolinone derivatives. Indian J Heterocycl Chem. 2007; 17: 95.
31. Chari MA, Mukkanti DSK. Silica gel=$FeCl_3$: An efficient and recyclable heterogenous catalyst for one-step synthesis of 4(3H)-quinazolinones under solvent-free conditions. Catal Commun. 2006; 7: 787.
32. Drapak I, Suleiman M, Protopopov M, Yeromina H, Sych I, Ieromina Z, Sych I, Perekhoda L. The use of the docking studies with the purpose of searching potential antihypertensive drugs. Research Journal of Pharmacy and Technology. 2019; 12(10): 4889-4894. doi: 10.5958/0974-360X.2019.00846.1.
33. Hemalatha K, Girija K. Evaluation of Drug Candidature of some Benzimidazole Derivatives as Biotin Carboxylase Inhibitors: Molecular docking and Insilico studies. Asian J. Res. Pharm. Sci. 6(1): Jan.-Mar., 2016; Page 15-20. doi: 10.5958/2231-5659.2016.00002.3
34. Sindhu TJ, Arathi K N, Akhila Devi, Aswathi TA, Noushida M, Midhun M, Sajil Saju Kuttiyil. Synthesis, Molecular Docking and Antibacterial Studies of Novel Azole derivatives as Enoyl ACP Reductase Inhibitor in Escherichia coli. Asian J. Res. Pharm. Sci. 2019; 9(3): 174-180. doi: 10.5958/2231-5659.2019.00027.4
35. Radhika Chelamalla, Ajitha Makula. Molecular docking studies and ADMET Predictions of Pyrimidine Coumarin Scaffolds as Potential IDO Inhibitors. Asian J. Research Chem. 2017; 10(3):331-340. doi: 10.5958/0974-4150.2017.00056.6
36. Sandip S Kshirsager, Dr. Siraj N Shaikh, Narendra B Patil, Ketan B Patil. Novel Molecule of Protein Tyrosine Kinase Enzyme Inhibitor in Treatment of Breast Cancer: Neratinib Maleate. Asian J. Res. Pharm. Sci. 2020; 10(2):100-102. doi: 10.5958/2231-5659.2020.00019.3
37. Sravani M, Duganath N, Deepak Reddy Gade, Sandeep Reddy CH. Insilico Analysis and Docking of Imatinib Derivatives Targeting BCR-ABL Oncoprotein for Chronic Myeloid Leukemia. Asian J. Research Chem. 5(1): January 2012; Page 153-158.
38. Park JH, Liu Y, Lemmon MA, Radhakrishnan R. Erlotinib binds both inactive and active conformations of the EGFR tyrosine kinase domain. Biochem J. 2012; 448: 417-423.
39. Stamos J, Sliwkowski MX, Eigenbrot C. Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor. J Biol Chem. 2002; 277: 46265-46272.
40. Bart AG, Scott EE. Structures of human cytochrome P450 1A1 with bergamottin and erlotinib reveal active-site modifications for binding of diverse ligands. J Biol Chem. 2018; 293: 19201-192.