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ORIGINAL ARTICLE

Insilico Docking Analysis of Some Novel Quinazoline Derivatives as Potent Antimicrobial Agent

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Abstract:
Heterocyclic compounds have been utilised as therapeutic agents in the field of study for a significant period. The Quinazoline heterocyclic nucleus is a highly important class for the development of novel drugs. Molecular docking is a technique used in Computer Aided Drug Designing to examine the interaction between a ligand and a protein. The primary objective of this study is to conduct an initial screening using SAR studies, OSIRIS molecular property explorer, PASS Prediction Activity spectra, and Rule of Five. The aim is to assess the potential activity of the proposed quinazoline compounds as anti-microbial agents through Docking studies with Escherichia coli strain (PDB ID 1AB4) using the docking tool PyRX Vina wizard. The compound 4c is named (E)-3-(4-hydroxybenzylideneamino)-6-bromo. The compound is named as 2-methyl quinazolin-4(3H). The binding energy of -one was notably higher at -7.1 kcal/Mol compared to the reference (ciprofloxacin at -9.2 Kcal/mol), and it also had the lowest RMSD value. Compound 4c exhibited Vander Waals' interactions with the amino acids Asp, Tyr, Phe, and Ala.
Keywords: Quinazoline, Heterocyclic compounds, Antimicrobial, Docking simulation

Introduction

Medicinal chemistry is a chemical discipline that includes elements of biological science, medicine and medicine. It involves the development, exploration, production, discovery and creation of biologically active substances. This field is also involved in studying how these substances are metabolized, understanding their mechanism of action at the molecular level, and building activity-activity relationships (SARs). to examine the relationship between chemical structure and pharmacological effects in a compound. (Lemke & Williams, 2008; Valentina P).

Quinazoline is a heterocyclic molecule that plays a crucial function in synthetic pharmaceutical chemistry. Quinazoline synthetic compounds are employed as therapeutic agents to address various pathological disorders. (He et al., 2017) The compound quinazoline was initially synthesised through the condensation of anthranilic acid and amides using the Niementowski quinazolinone synthesis method. Anthranilic acid is primarily used as a starting material to produce quinazolinone molecules. Quinazolinone and its derivatives are a significant group of biologically active compounds that have a wide range of therapeutic effects. (Yu et al., 2022) These effects include being anti-HIV, antifungal, anticancer, antibacterial, anticoccidial, anti-mutagenic, anticonvulsant, anti-inflammatory, anti-malarial, antioxidant, antidepressant, and anti-leukemic. (Chen et al., 2006) Quinazolinone derivatives have recently gained significant attention from researchers in the fields of organic and medicinal chemistry because of their notable biological activity.

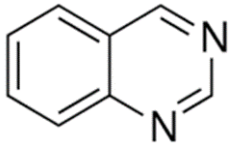


Figure 1 Structure of Quinazoline

Objective of the study - The present work comprises of studying, Docking simulation of (E)-3-(Substituted benzylidineamio)-6-bromo-2-methyl quinazolin-4(3H)-one derivatives as potent antimicrobial agent.

Methodology -

Docking Studies

Software used - Python language was downloaded from www.python.com, Chemdraw, Marvin sketch, OSIRIS Molecular property explorer, PASS Prediction was used for preliminary screening of proposed derivatives and BIOVIA **2.**

drug discovery, PYRX docking software was used for this research study.

In silico analysis is frequently employed to evaluate a compound's physical and chemical characteristics.

Pre-validation of compound – before docking simulation pre-screening was performed in four phases as:

1. **Structure Activity Relationships (SAR)** – Form the literature survey, main structural requirement are discussed in **Figure 2**. (Jha et al., 2020)

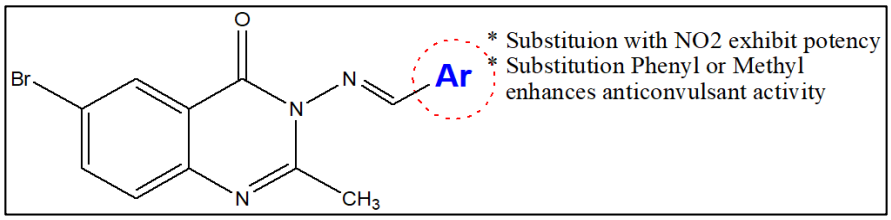


Figure 2. Structure of Quinazoline derivative

3. **OSIRIS Molecular Property Explorer** - It Java-based web application estimates molecules characteristics and allows to draw the structure and calculates drug-relevant properties like cLogP, Drug Likeness, Polar surface area (PSA), and risk factors like mutagenicity or intestinal absorption (Sander et al., 2009), shown in red, yellow, and green color**. Table 1** covered all results.
4. **PASS Predication** - PASS predicts substance activity spectrum This online programme evaluates the biological activity of drug-like molecules (Lagunin et al., 2000). The result computed using "Pa (probability of activeness) and Pi (probability of inactivity)". All potential carboline derivatives' Pa & Pi are shown in **Table 2**, addressed all outcomes.
5. **Rule of Five' or 'Lipinski Rule'** - The "Rule of Five" or "Lipinski rule," developed by Lipinski in 1995, is used for in-silico studies. This rule establishes the physical characteristics of any molecule, including log P (Partition Coefficient). The molecular weight, hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), and total polar surface area (PSA) are essential factors for achieving selectivity with proteins. The source cited is Lipinski (2004). Molecules that adhere to Lipinski's criteria are considered orally bioavailable. The values were calculated using Chem Draw and Marvin Sketch 5.0 software. **Table 3** provides a summary of the limits for each of the proposed compounds based on the standard values of the Lipinski "Rule of Five".

Docking Simulation of proposed Quinazoline derivatives -

Docking simulation technique is frequently used in computer aided drug design and discovery, to predict the molecular interaction between the Escherichia coli (PDB ID 1AB4) (Cabral et al., 1997) and the proposed quinazoline derivatives. docking simulation is a trustworthy computational method employed to forecast the interaction energy between two molecules, often a protein

and ligand. (Madeswaran et al., 2012). This current objective of this study is to screen the in-silico docking simulation between 59KDA fragment of DNA gyrase from E. coli (PDB ID 1AB4) and proposed quinazoline derivatives. The PyRx Autodock VINA wizard was used to perform docking simulation. PyRx is a software designed for computational drug discovery. It allows for the screening of chemical databases versus possible drug targets via Virtual Screening. (Coumar, 2021)

Method – The Protein structure of Escherichia coli (PDB ID 1AB4) was downloaded from RSCB protein data bank complexed with ligand 59KDA. The structure has 2.80 Å (single chain) as displayed in figure 4. The water molecules, heteroatoms and unwanted ligands were eliminated from the protein structure of E. coli (1AB4) using discovery studio. Polar hydrogen was added into the protein structure of E. coli and to stabilize the charge and PDB file is converted into PDBQT format. All proposed quinazoline derivatives are drawn in Marvin sketch and saved as PDB format and converted to PDBQT The grid box was set at the centre and X = 59.77 Å. Y = 82.40 Å, Z = 62.62 Å as shown in **Figure 3** which covers all amino acid residue such as Ser 165, Val236, Thr237, Met233, Glu 108 etc. Then run the PyRx vina wizard to obtain the docking score in terms of binding energies in kcal/mol and Root Mean Square Deviation (RMSD) and bond length measured in Å. All results were displayed in **Table 4** and two dimensional and three-dimensional interaction between protein and ligand were generated by using BIOVIA discovery studio and shown in Figure .

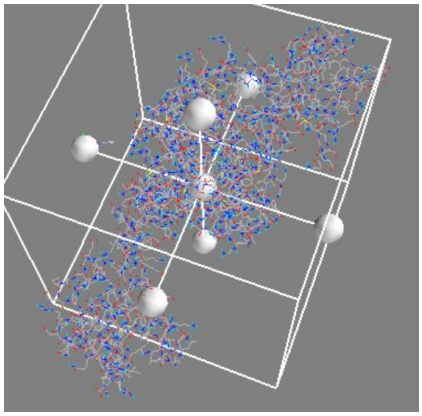


Figure 3. Grid Box setting of Ligand and Protein

Result & Discussion

The present research involves the synthesis of novel quinazoline derivatives, conducting docking simulation and synthesis, and analysing their antibacterial effectiveness. Quinazoline is a versatile pharmacophore that exhibits a range of antimicrobial actions.

Computational approaches enable the rapid and cost-effective development of novel drugs. Virtual screening, in silico antimicrobial activity and toxicology prediction, and protein-ligand interaction detection are three crucial computational tasks in the field of drug development. Next, the drug-likeness is confirmed with Pre ADMET. The idea of drug-likeness was created to offer helpful guidance in the initial phases of drug development, with the aim of enhancing the probability of a chemical successfully entering and completing clinical trials. The unique characteristics of medications are determined by the combined molecular physicochemical qualities. (Khedkar S A, 2006).

The Present work comprises for pre-screening by SAR studies, OSIRIS Molecular Property explorer. PASS Prediction and Rule of five was calculated. Then docking simulation were performed on all quinazoline derivatives.

Docking Studies

The lead chemical was optimised by utilising computed drug-like properties. The compounds underwent pre-validation through SAR studies, molecular property prediction utilising the OSIRIS property explorer, Prediction of Activity Spectra for Substances (PASS), and Lipinski's rule.

1. **Structure Activity Relationships –** SAR of quinazoline was derived from the literature review as - [28 – 32] (Jha et al., 2020).

- Isoquinoline ring is essential for activity for binding with Tyrosine, histidine, Glycine amino acid. (Jha et al., 2020)
- Substitution with nitro group exhibit potency. (Jha et al., 2020)
- Substitution with aromatic compounds. (Jha et al., 2020)
- Lactone moiety act as electron donor.

All essential features of structure is discussed in Figure 3. which may be required for binding with protein or enzyme.

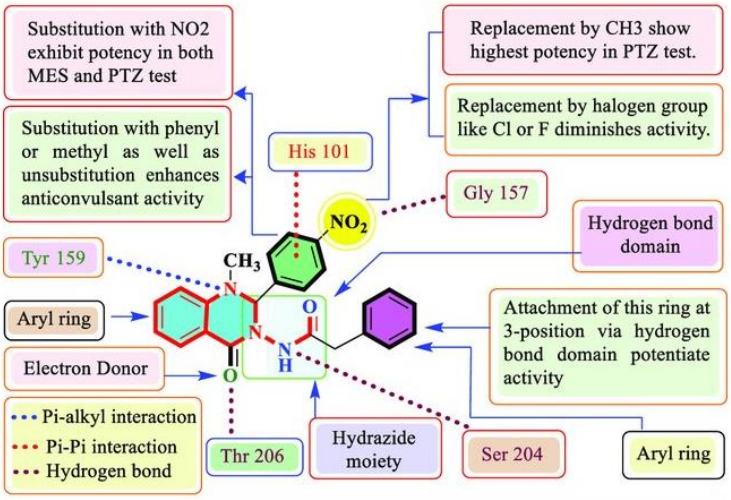


Figure 4. Structure activity relationship of Quinazoline moiety (Jha et al., 2020).

2. **OSIRIS Molecular Property Explorer** – It is an interactive website can be used to verify the integrity of a structure and compute attributes associated with pharmaceutical substances. The **Table 1** provides descriptions of the drug score, drug-likeness, solubility, and toxicity tests for all quinazoline derivatives. The results are presented in Table 1, indicating that the values for Drug Score for compound **4a** was found at 0.68, compound **4b** at 0.56, compound **4c** at 0.72 and compound **4d** drug score was found at 0.42. Drug Likeness of all quinazoline derivatives found within the range 2.73 to 3.17. Solubilty of all derivative fall between the range of 4.17 to 5.20. All compounds are at No Risk except compound **4d** showed reproductive toxicity. From Table 1 it was noted that **compound 4c** ((E)-3-(4-hydroxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one) showed best potential. (Sander et al., 2009),
3. **PASS Prediction** – PASS prediction [Prediction of Activity Spectra for Substances], is a software application specifically developed to assess the overall biological potential of an organic drug-like compound. It utilises the chemical structure of molecules to give predictions for different forms of biological activity. The predicted values for each component in **Table 1** are converted into antimicrobial activity, which is indicated by the "Probability of being active (Pa)" being higher than the "probability of being inactive (Pi)". (Filimonov DA et.al, 1995). It was observed from Table 2 that 'Pa' is more than 'Pi' of all compounds. Compound 4c possess the highest 'Pa' 0.388 and lowest 'Pi' as 0.033.
4. **Lipinski's 'Rule of Five'** – Predictive parameters such as log P, molecular weight, hydrogen bond donor (HBA), hydrogen bond acceptor (HBA), and polar surface area (PSA) were determined using ChemDraw and Marvin Sketch software. The logarithmic range of log P (2.73 to 3.20) indicates that compounds possess exceptionally high permeability through the cell membrane. The Polar surface area of all compounds was found to be less than 140 Ao, indicating their high affinity for binding to the receptor or enzyme.

Every compound possesses a molecular weight that is less than 500. Additionally, these compounds have no more than five hydrogen donors (the combined total of OH and NH groups) and no more than ten hydrogen bond acceptors (the combined total of O and N atoms). (Lipinski, 2004).

Table 1 provides a summary of these characteristics, and all compounds adhere to the Lipinski Rule of Five.

Docking Simulation

Molecular docking is a widely employed technique in computer-aided drug design that operates based on the "*Lock and key*" model. The word pertains to an optimisation activity that seeks to ascertain the most efficient confirmation and interaction between a ligand and a protein. (Madeswaran et al. 2012). Molecular docking use computational techniques to predict the binding affinity and interaction between macromolecules and a smaller ligand. Pre-synthetic evaluation involves assessing the potential pharmacological effects of a chemical. To comprehend intermolecular interactions, one must grasp the concept of binding affinity (Coumar, 2021).

The 1AB4 (E. coli) protein was chosen for the investigation. The binding affinity quantifies the intensity of the binding association. Therefore, the measure of binding affinity, reported in kcal/mol, is utilised to classify the results of virtual screening (Coumar, 2021). To compare the binding affinities depicted in **Figures 5,** the ligand (Ciprofloxacin), was used as a reference drug.

Table 1. Docking score between E. coli (1AB4) and Ligands (Quinazoline derivatives)

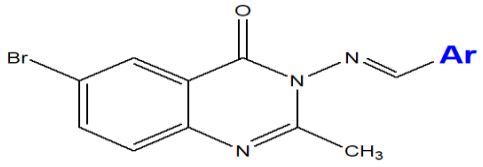
S. No.	Compound Name (ID)	Binding affinity (kcal/mol)	RMSD	Interacting amino acid
1.	(E)-3-(benzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4a)	-6.4	7.759	VAL54, GLU139, LYS154, GLU149, PHE145
2.	(E)-3-(2-chlorobenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4b)	-5.5	7.270	PHE513, TRP59, LYS129
3.	(E)-3-(4-hydroxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4c)	-7.1	2.312	PHE513, ILE130, GLN512, LYS129
4.	(E)-3-(2-hydroxy-4-methoxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4d)	-5.2	9.510	LYS129, TRP59, ALA128, ASP104, PHE513
5.	Standard (Ciprofloxacin)	-9.2	0.000	GLU133, GLN512, PHE513, LYS129, ASN53, ALA136

The best possible interaction was achieved by reducing the docking energy. Table 2 presents the quantitative measure of the strength of binding, the Root Mean Square Deviation (RMSD), and the amino acids involved in the interaction. Figures 11 in Discovery Studio examined the interactions between E. coli protein (PDB ID: 1AB4) and several ligands (ciprofloxacin and quinazoline derivatives). This work involved the investigation of hydrogen bonds and the lengths of these bonds. The diagrams depict the typical sites of attachment between the protein and ligand, with dashed lines denoting the interactions. The hydrogen bonding contacts are depicted as green dashed lines, whereas light pink indicates alkyl interactions, and pink and magenta represent Pi interactions. The presence of a red dashed line indicates an unnamed hydrogen donor. All interaction were displayed in **Table** 2.

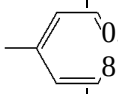
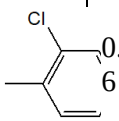
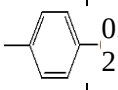
Quinazoline derivatives is basic heterocyclic moiety that is responsible for hydrophobic interaction. Compound 4a (E)-3-(benzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one interacted with Pi-Pi bond with phenylalanine (Phe) and Vander waals forces interaction with Leu, Gly and Tyr. 4a compound produced binding affinities at -6.4 Kcal/mol. Compound 4b (E)-3-(2-chlorobenzylideneamino)-

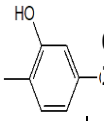
6-bromo-2-methylquinazolin-4(3H)-one) showed Vander Waal's interaction with Tyr, Asp, Ala and Arg while Pi – Pi interaction Trp and Phe. Binding affinities of Compound 4b was found at -5.5 Kcal/mol. Compound 4c, (E)-3-(4-hydroxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one had a significantly higher binding energy of -7.1 kcal/Mol and lowest RMSD value as compared to standard (ciprofloxacin at -9.2 Kcal/mol), Compound 4c showed Vander Waals' interaction with Asp, Tyr, Phe and Ala while it also shows an unfavourable hydrogen acceptor bond. Compound 4d ((E)-3-(2-hydroxy-4-methoxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one) binds Pi-Pi interaction with Trp, Phe and Ala, Binding affinities of compound 4d was found at -5.2 Kcal/mol. All 2D and 3D interaction displayed in Figure 5.

Table 2. OSIRIS molecular property, PASS Prediction result and Lipinski rule of 5 of proposed compounds.



(*E*)-3-(substitued benzylideneamino)-6-bromo-2-methylquinazolin-4(3*H*)-one (4 a - d)

S. No.	Compound Name	Ar	OSIRIS (Molecular Property Explorer)						PASS Prediction		Lipinski Parameters						
									Antimicrobial								
			rug Score	C log P	rug Likeness	Solubility	TPSA	Toxicity Risk	Pa	Pi	Mol. Weight (dalton)	BA	BD	SA A2)	log P	R (m3/ ol)	Obey Lipinski rule
1.	(E)-3-(benzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4a)		0.68	3.43	2.73	4.46	45.03	No Risk	0,347	0,044	342.19	4	1	45.03	3.66	88.11	Yes
2.	(E)-3-(2-chlorobenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4b)		0.56	4.03	3.17	5.20	45.03	No Risk	0,287	0,,065	376.64	4	1	45.03	4.29	92.82	Yes
3.	(E)-3-(4-hydroxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4c)		0.72	3.08	2.97	4.17	65.26	No Risk	0,388	0,033	358.19	5	1	65.26	3.36	90.09	Yes

4.	(E)-3-(2-hydroxy-4-methoxybenzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (4d)		0.42	3.01	2.96	4.19	74.49	Reproductive effect	0,380	0,035	388.22	6	1	74.49	3.22	96.56	Yes

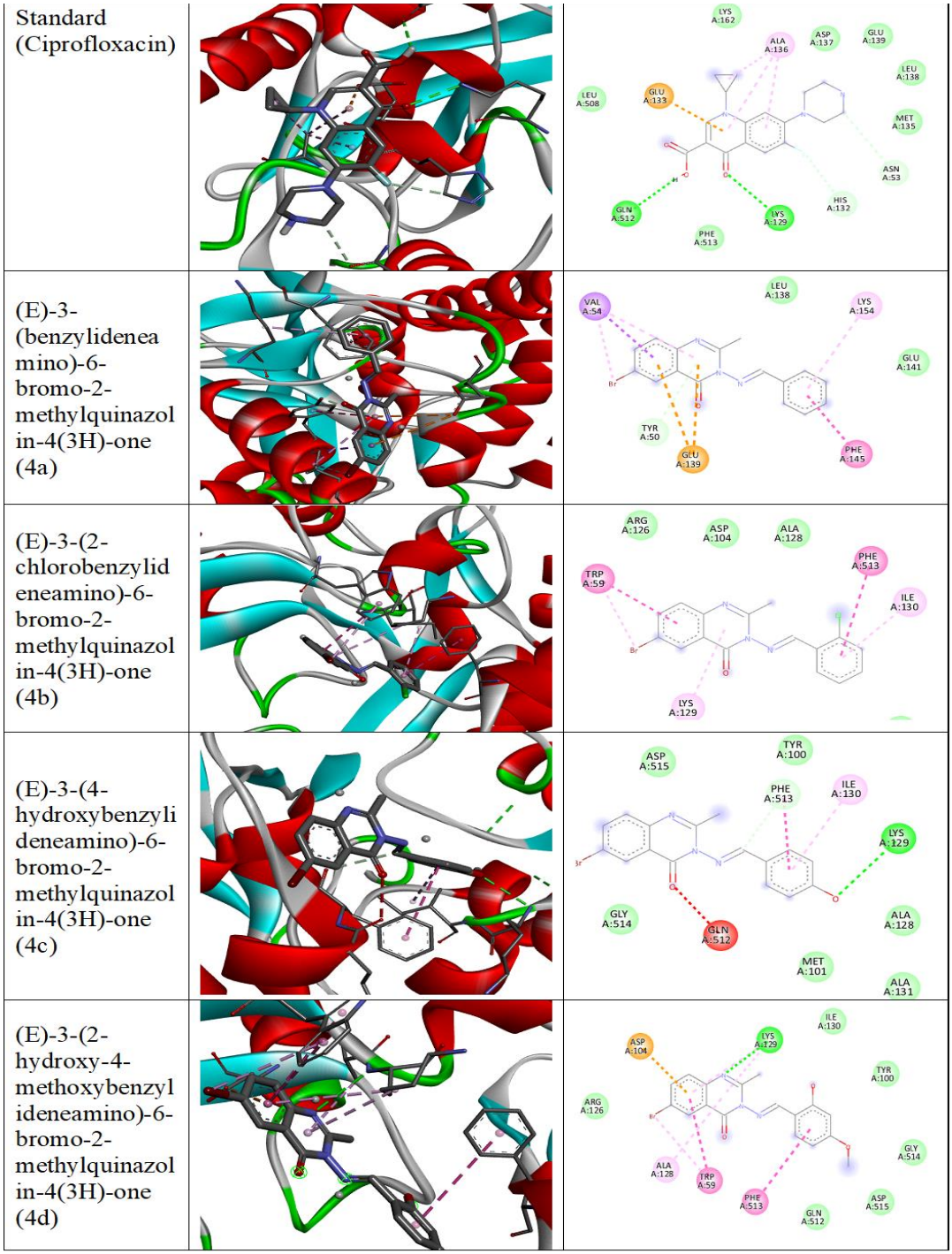


Figure 5. 2D & 3D Interaction between E. coli (PDB ID 1AB4) and ligands (standard & quinazoline derivatives).

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