Int. J. Sci. R. Tech., 2025 2(4)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Insilico Studies and Synthesis of New 2-Cycloproply Quinazoline Derivatives as Potential Anticancer Agents

Soheila Azim Patrawala*[1], Dr. Bhavini Gharia[1], Amankumar Vaghasiya[2]

[1]*Department of Pharmaceutical Chemistry, Bhagwan Mahavir College of Pharmacy, Bhagwan Mahavir University, Surat, Gujarat 395007*
[2]*Department of Pharmaceutical Chemistry, Shree Dhanvantri Pharmacy College, Kim 394110*

ABSTRACT

The quinazoline scaffold is of significant importance in medicinal chemistry due to the diverse pharmacological activities of its derivatives, particularly their prominent role in cancer chemotherapy. In our continuous pursuit of novel anticancer pharmacophores, we aimed to synthesize a series of substituted quinazolines fused with substituted benzothiazoles and assess their in vitro anticancer potential. We commenced this endeavor by reacting anthranilic acid with cyclopropyl carbonyl chloride in the presence of 2,6-lutidine to yield an oxazine intermediate, which was subsequently converted into the targeted quinazoline derivatives. The subsequent reaction of these quinazolines with substituted isothiocyanatobenzene produced a series of novel compounds designed as potential inhibitors of EGF receptor tyrosine kinase. With a focus on the C-3 position of the quinazoline ring, we synthesized eleven diverse derivatives. These compounds underwent characterization and confirmation using IR, 1H NMR, 13C NMR, and mass spectrometry. All eleven synthesized compounds were submitted to the National Cancer Institute (NCI), USA, for in vitro anticancer screening, and seven of these were selected by the NCI for further evaluation against the full NCI 60 cell panel at a single high dose (10-5 M).

Keywords: Insilico Studies, Synthesis, Cycloproply Quinazoline Derivatives, Anticancer Agents

INTRODUCTION

The past decade has witnessed the ascendancy of heterocycle synthesis as a pivotal domain within synthetic organic chemistry, driven by the diverse applications of these compounds in medicinal and pharmaceutical contexts. The utilization of heterocycles as privileged structures in drug discovery represents a central focus within medicinal chemistry. These privileged structures, characterized by their capacity to act as ligands for a spectrum of biological receptors with high binding affinities, offer a strategic approach for the expedited discovery of novel bioactive compounds across a broad spectrum of therapeutic areas. Consequently, contemporary research in heterocyclic chemistry emphasizes the synthesis of biheterocyclic architectures, including conjugated tri- or tetracyclic molecules incorporating multiple privileged structural motifs. [1-3]

1.1 CANCER

Cancer encompasses a diverse group of diseases characterized by dysregulated cellular proliferation and differentiation. This uncontrolled growth manifests as tumors, except in leukemias, where abnormal cell division disrupts blood function. Malignancy arises from cellular abnormalities, stemming from inherited genetic mutations or environmental exposures like chemicals, radiation, or infectious agents. Tumors can disrupt vital physiological systems, including digestive, nervous, and circulatory functions, and secrete hormones that alter bodily processes. Benign tumors exhibit localized growth, whereas malignant tumors invade surrounding tissues and metastasize through angiogenesis and lymphatic/hematogenous dissemination. Cancer treatment modalities include surgery, radiation, immunotherapy, chemotherapy, and chemoprevention. Ideally, anticancer drugs would selectively eradicate malignant cells without harming healthy tissues. However, current

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

chemotherapeutic agents, often targeting DNA replication and transcription, exhibit significant toxicities, necessitating a careful assessment of the therapeutic index. Cellular growth and division are tightly regulated processes, governed by a balance between growth-promoting and growth-suppressing genes. Cancer emerges when these regulatory mechanisms are disrupted, leading to unchecked cell proliferation. Genetic mutations, arising from external factors or errors during cell division, can accumulate, enabling cells to evade normal control mechanisms and proliferate uncontrollably. The body possesses error-correction mechanisms, but cancer cells can circumvent these, fostering further genetic instability and tumor progression.

1.2 TARGET FOR ANTICANCER DRUGS

Contemporary oncology therapeutics frequently target cell surface receptors or intracellular phosphoproteins and kinases within key signaling pathways. Elucidating the phosphorylation status of pivotal signaling molecules in tumor cells provides crucial insights into the tumor's type, stage, and dynamic state. This information is paramount for accurate diagnosis, precise prognostication, and the formulation of personalized treatment strategies. [4,5]

1.2.1 Epidermal Growth Factor Receptor

The ErbB, or epidermal growth factor receptor (EGFR), family comprises four structurally related receptor tyrosine kinases. The nomenclature, ErbB, originates from its homology to the erythroblastic leukemia viral oncogene. Inadequate ErbB signaling in humans correlates with the pathogenesis of neurodegenerative disorders, including multiple sclerosis and Alzheimer's disease. Conversely, in murine models, ablation of signaling from any ErbB family member results in embryonic lethality, accompanied by developmental defects in vital organs such as the lungs, skin, heart, and brain. Furthermore, aberrant ErbB signaling is implicated in the development of a broad spectrum of solid tumors. Notably, ErbB-1 and ErbB-2 are frequently overexpressed in human malignancies, and their amplified signaling pathways are considered critical drivers of tumorigenesis and malignant progression.

Structure of EGFR

The epidermal growth factor receptor belongs to the ErbB family of receptor tyrocine kinases (RTK). There are four members of the EGFR family20:

a) ErbB-1, also named epidermal growth factor receptor (EGFR)
b) ErbB-2, also named HER2 in humans and in rodents
c) ErbB-3, also named HER3
d) ErbB-4, also named HER4
e) V-ErbBs are homologous to EGFR, but lack sequences within the ligand binding ectodomain.

The epidermal growth factor receptor is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands composed of extracellular domain, a hydrophobic transmembrane domain and intracellular domain. [6,7]

Role of EGFR in Kinase Activation

The ErbB protein family, comprising four members, exhibits the capacity to form homo- and heterodimers, and potentially higher-order oligomers, upon activation by a subset of eleven distinct growth factor ligands. The ligand-receptor interaction specificity is characterized by differential activation capabilities, as delineated in the provided table. In the absence of ligand binding, ErbB-1, -3, and -4 adopt a 'tethered' conformation, wherein a 10-amino-acid dimerization arm is sterically hindered, precluding monomer-monomer interactions. Conversely, ligand binding to ErbB-1, or the intrinsic conformational state of unliganded ErbB-2, results in the untethering and exposure of the dimerization arm, facilitating receptor dimerization. Ectodomain dimerization engenders the spatial juxtaposition of cytoplasmic domains, enabling transphosphorylation of specific tyrosine, serine, and threonine residues within each ErbB subunit. For ErbB-1, at least ten tyrosine, seven serine, and two threonine phosphorylation sites have been identified, with some sites, such as Tyr 992, subject to dephosphorylation upon receptor dimerization. Despite the multiplicity of potential phosphorylation sites, typically only one, or rarely two, sites are phosphorylated concurrently following dimerization, indicating a tightly regulated phosphorylation cascade. [8-11]

Role of EGFR in Cancer

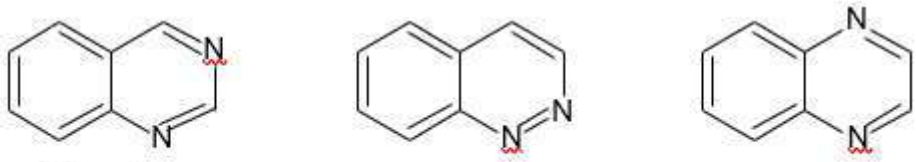
The receptor tyrosine kinases ErbB-1 (EGFR) and ErbB-2 (HER-2) are critical regulators of cellular proliferation and differentiation. Aberrant overexpression and/or hyperactivation of these receptors are frequently observed across diverse tumor types. EGFR plays a pivotal role in the pathogenesis and progression of various carcinomas, including those of the breast, lung, ovary, prostate, and head and neck. In human carcinomas, EGFR and its cognate EGF-like peptide ligands are often overexpressed, and both in vivo and in vitro studies have demonstrated their capacity to induce cellular transformation. Consequently, inhibitors targeting the EGFR protein tyrosine kinase (PTK) hold significant therapeutic promise for the treatment of both malignant and non-malignant epithelial disorders. [12-17]

Inhibitors of EGFR

The concept of targeting EGFR for cancer therapy emerged in the 1980s, yielding diverse therapeutic strategies. These include monoclonal antibodies (mAbs), such as cetuximab (Erbitux), which target the extracellular domain of EGFR, and small molecule tyrosine kinase inhibitors (TKIs), like gefitinib (Iressa) and erlotinib (Tarceva), that inhibit receptor signaling by targeting the catalytic kinase domain. Cetuximab, a chimeric mAb, has been extensively studied and clinically approved for specific EGFR inhibition. A complementary approach involves TKIs that disrupt EGFR tyrosine kinase (TK) domain activation. These agents competitively inhibit ATP binding to the TK domain, thereby selectively blocking EGFR autophosphorylation. TKIs are synthetic, predominantly quinazoline-derived, low-molecular-weight compounds that interact with the intracellular TK domain of EGFR and other receptors. They impede ligand-induced receptor phosphorylation through competitive bidding at the intracellular Mg-ATP-binding site. [18-22]

1.3 Quinazoline

The interest in this heterocycle prompted us to set up a short and efficient route toward quinazoline nucleus. The quinazoline nucleus is a very attractive and useful scaffold in medicinal chemistry: it can be found as a pharmacophore in a wide variety of biologically active compounds, such as antitumorals, antibacterials, antivirals, and many other therapeutic agents. The name quinazoline (1) was first proposed for this compound by Weddige, on observing that this was isomeric with the compounds cinnoline (2) and quinoxaline (3). Paal and Bush 34 suggested the numbering of quinazoline ring system, which is currentlyused. The other less commonly used na,es for this ring system are ‘phenmiazine’ and 5,6-benzopyrimidine. However, the name quinazoline is now universally accepted.

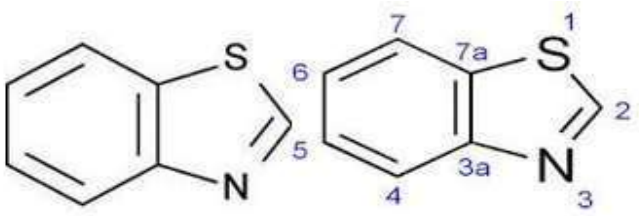


Quinazoline Cinnoline Quinoxaline

1 2 3

There are many derivatives of quinazoline system known so far, among which keto- quinazolines also called as quinazolinones, are the most important compounds. Depending upon the position of the keto or oxo group, these compounds may be classified inti two types: 2-(1H) quinazolinones or 1,2dihydro-2-oxoquinazolines and 4(3H)-quinazolines or 3,4-dihydro-oxoquinazolines. These systems exhibit lactam- lactim tautomerism and undergo hydroxyl group replacement reactions. 2-Cyano- 4(3H)-quinazolinone was the first quinazolinone derivative to be synthesized. [23,24]

1.4 Benzothiazole:



Chemistry of Benzothiazole: - There is only one way in which the benzene ring can be fused to each of 1,3-thiazoles generating benzothiazole ring having the molecular formula C7H5NS. Biological activities of Benzothiazole: - Being a heterocyclic benzothiazoles finds used in research as a starting material for synthesis of larger, usually in compounds involved in research aimed at evaluatings new products possessing interesting biological activities such as antitumor, anthelmintic, antimicrobial, antileshmanial, antidiabetic and antitubercular activity. In addition, they have been reported to selectively inhibit several therapeutic receptors and enzymes, extending their applications in modern drug design. [25-27]

MATERIALS AND METHODS

The identification and characterization of the compound were carried out by the following procedures to ascertain that all prepared compounds were of different chemical nature, than the respective parent compound.

1. Melting point
2. Solubility
3. Thin layer chromatography
4. Infrared spectroscopy
5. Proton nuclear magnetic resonance
6. Mass spectroscopy

The chemicals employed in the synthetic work i.e. anthranilic acid and cyclopropyl carbonyl chloride was purchased from Sigma-Aldrich. All the solvents were used after distillation. Most of the solvents and chemicals used were of LR grade. The purity of the compounds was confirmed by thin layer chromatography using precoated TLC plates and solvent systems of Chloroform:Methanol (9:1). The spots were visualized under ultraviolet lamp. Melting points were determined in one end open capillary tubes on a liquid paraffin bath. Infrared (IR) and 1H nuclear magnetic resonance (1H NMR) spectra were recorded for the compounds on Perkin Elmer IR 4000-400 (ν max in cm-1) Spectrophotometer in KBr pellets and Bruker Model Advance II 400 (400 MHz, 1H NMR) instrument, respectively. Chemical shifts are reported as δ parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. [28-31]

Docking studies: Docking studies played a pivotal role in the experimentation, simulating ligand-protein interactions to predict binding affinity and orientation. This computational approach enables virtual screening of compound libraries, accelerating the identification of potential drug candidates. It also facilitates lead optimization by predicting how structural modifications impact binding, guiding the refinement of promising compounds. Furthermore, docking studies elucidate the molecular mechanisms underlying drug efficacy, providing crucial insights into ligand-protein interactions. By offering a rapid and cost-effective means of assessing molecular interactions, docking studies significantly contribute to the efficiency and success of drug discovery and development. In our present study, we used computational approach to identify the potent and selective EGFR inhibitors. Three-dimensional (3D) pharmacophore models were generated using the known set of EGFR inhibitors, to reveal the chemical features required for its activity. Best pharmacophore is validated with docking and structure based pharmacophore studies. These models were used to rapidly screen compounds from database, for the identification of a series of novel and highly potent EGFR inhibitors. Molecules were selected from virtual screening using pharmacophore as query and these molecules are selected for synthesis and in vitro screening studies based on the docking scores, predicted binding location and their drug like properties. [32,33]

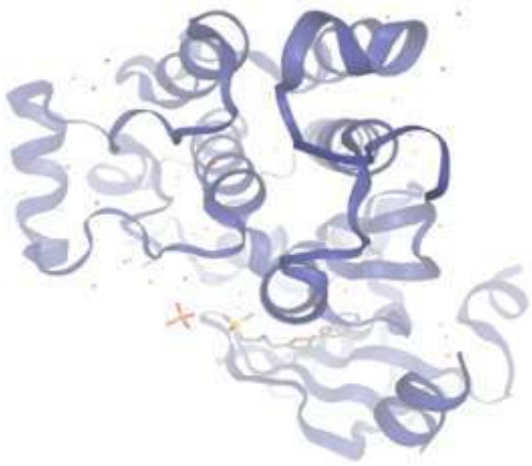


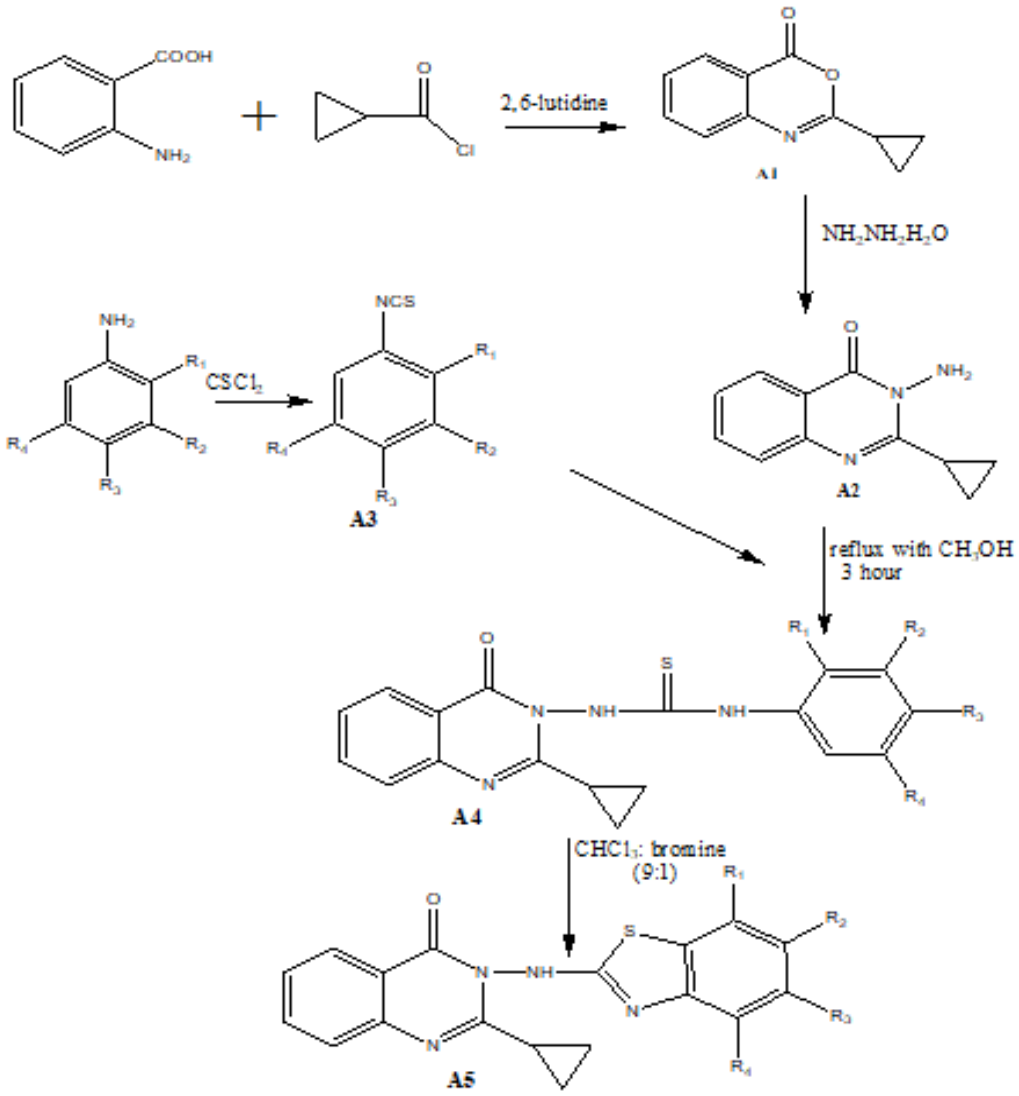
Fig2. Docking structure of EGFR inhibitor (PDB structure 1XKK)

2.1 Reaction Schemes

The experimental work comprises of scheme:

1. Synthesis of oxazin derivative (A1)
2.Synthesis of 2-cyclopropyl-4H benzo[d] [1,3] oxazin-4-one derivative (A2)
3.Synthesis of optically active substituted isothiocyanates(A3) (a-g)
4. Synthesis of 1-(2-cyclopropyl-4-oxoquinazolin-3(4H)-yl)-3-phenylthiourea (A4) (a-g)
5.Synthesis of 3-(benzo) [d]thiazole-2-ylamino)-2-cyclopropylquinazoline-4(3H)- one (A5) (a-g)

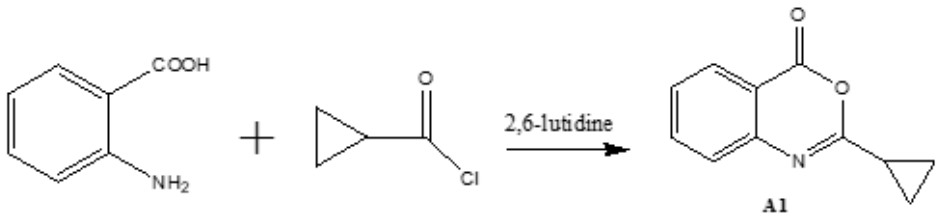
Scheme I



Compound	R_1	R_2	R_3	R_4
A4 (A)	OCH_3	H	H	OCH_3
A4 (B)	Cl	H	H	H
A4 (C)	F	H	H	H
A4 (D)	Cl	H	H	Cl
A4 (E)	OCH_3	H	H	H
A4 (F)	Cl	H	CH_3	H

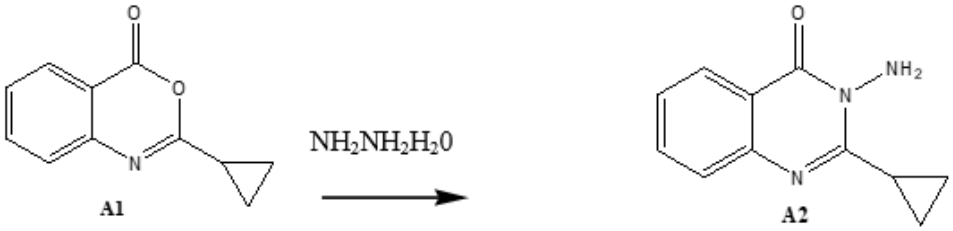
a) Scheme

Step-1 Preparation Of 2-Cycloproyl-4h-Benzo[D] [1,3] Oxazin-4-One (A1)



A solution of cyclopropane carbonyl chloride (1 g, 4.62mmol) was added to a stirred solution of Anthranilc acid (1 g, 4.62 mmol) in 2, 6-Lutidine (10 V) at 0 oC for 30 min, reaction mixture was allowed to rt and maintained 2h. Reaction mixture was poured in to ice cold water and filtered the solid, washed with water. Crude compound was used for next step without any further purification. [34-38]

Step-2 Synthesis of 3-amino-2-cyclopropylquinazolin-4(3H)-one (A2)



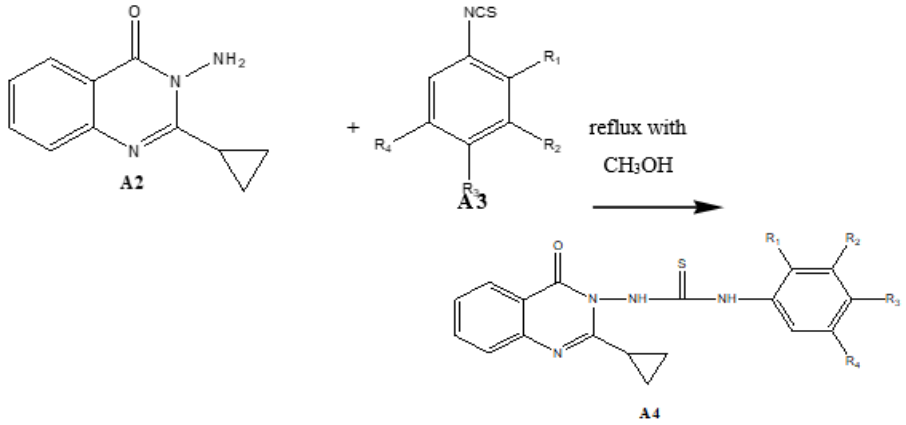
To this cyclopropyl oxazin(0.1)mol add hydrazine hydrate sufficient quantity which dissolve oxazin. Heat it in oil bath for 2000 c for 1 hour. Mixture is cooled and add methanol to this mixture. The separated solid was collected by filteration , washed with methanol, dried and crystallized from ethanol.[39,40]

Step-3 Synthesis of optically active substituted isothiocyanates (A3) (a-f)

To the solution of thiophosgene (0.01 mol) in dichloromethane (100 ml), optically active substituted primary amine (0.01 mol) was added quickly at room temperature under stirring. Then a 25 ml saturated solution of NaHCO3 was added slowly and stirred for 3 h. The CH2Cl2 layer was dried over anhydrous

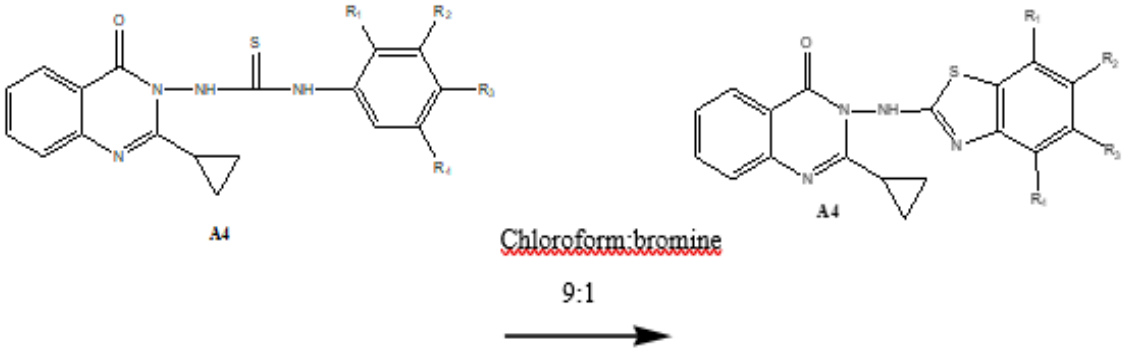
sodium sulphate and removed under reduced pressure. [41-45]

Step-4 Synthesis of 1-(2-cyclopropyl-4-oxoquinazolin-3(4H)-yl)-3-phenylthiourea (A4) (a-f)



To a solution of optically active substituted isothiocyanates (0.01 mol) in dry MeOH (10 ml), an equimolar quantity of 2-Cycloproyl-4h-Benzo[D][1,3]Oxazin-4-One (0.01 mol) was added with stirring.The reaction mixture was heated on a steam bath at 70°C for about 2-3 h and then the solvent was distilled off. The solid residue that separated was washed with water and dried at 40 °C and recrystallized by methanol.

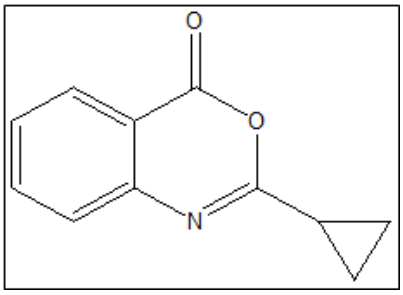
Step-5 Synthesis of 3-(benzo) [d]thiazole-2-ylamino)-2-cyclopropylquinazoline-4(3H)-one (A5) (a-f)



Optically active substituted thiourea (0.01 mol) were dissolved in chloroform (15 ml), the reaction mixture was cooled in an ice bath and then bromine: chloroform acid (1:9) mixture was added drop wise. The reaction was monitored by TLC and after an hour, was poured on to crushed ice. The solid that separated was filtered, dried in each case and recrystallized by methanol. [46-50]

RESULT AND DISCUSSION

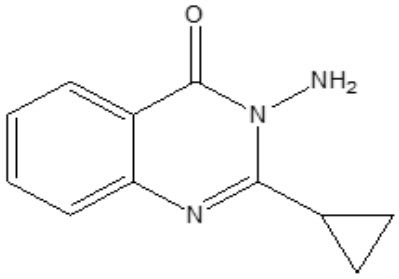
Characterization of Scheme Compound 2-Cyclopropyl Benzo Oxazin 4 One(A1)



Sr. No.	Observed Parameters	Result
1	Melting Point	215-220 ^{0}C
2	Molecular formula	$C_{11}H_{12}N_2O_2$
3	Molecular weight	204.23
4	R_f Value	0.66

IR(KBr cm^{-1})	Functional Group
1685	-C=O
1635	-C=N

3-Amino-2-Cyclopropyl Quinazolin-4(3h)-One (A2)



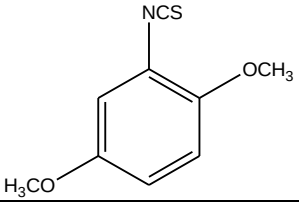
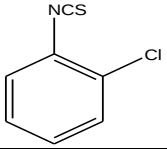
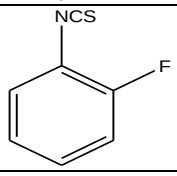
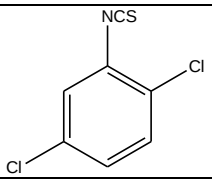
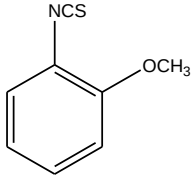
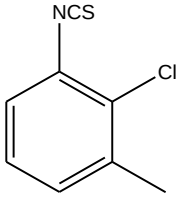
Sr. No.	Observed Parameters	Result
1	Melting Point	215-220 ^{0}C
2	Molecular formula	$C_{11}H_{11}N_3O$
3	Molecular weight	201.22
4	R_f Value	0.56

IR (KBr, cm^{-1})	Functional group
1325.14	-N-NH_2
1712.85	-C=O
3243	-NH_2
1628.94	-C=N

Physical characteristics of substituted isothiocyanate derivatives:-(A3) (a-f)

Compounds	Compound Name	Mol. Formula	Mol. Weight(gm)	M.P. (◦C)	R_f value
a.	2-isothiocyanato-1,4-dimethoxy benzene	$C_9H_9NO_2S$	195.24	80-82	0.76
b.	2-isothiocyanato-1-chloro benzene	C_7H_4ClNS	169.63	83-85	0.27
c.	1, fluro-2-isothiocyanato benzene	C_7H_4FNS	153.18	90-92	0.48
d.	2,4-dichloro-2-isothiocyanato benzene	$C_7H_3Cl_2NS$	204.08	110-112	0.40
e.	2-methoxy-1-isothiocyanato benzene	C_8H_7NOS	165.21	75-77	0.35
f.	1-chloro-2-methyl-3-isothiocyanato benzene	C_8H_6ClNS	183.66	90-92	0.33

g.	2,4-difluoro-1-isothiocyanato benzene	$C_7H_3F_2NS$	171.17	38-42	0.42
h.	1,4 dimethyl-2-isothiocyanato benzene	C_9H_9NS	163.24	205-207	0.76
i.	2-isothiocyanato-1,4-dichloro benzene	$C_7H_3Cl_2N_2S$	204.08	125-130	0.47

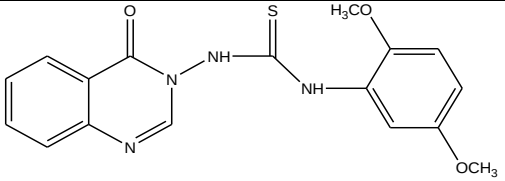
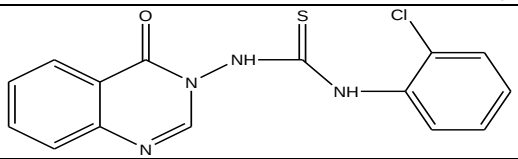
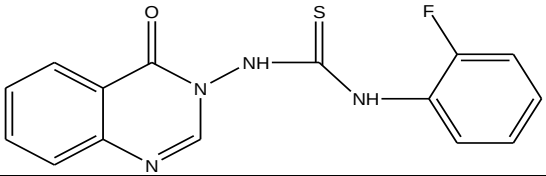
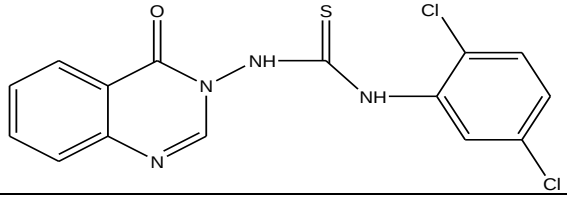
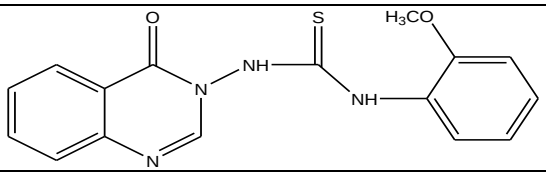
Sr. no.	Molecular structure	Chemical name	IR with KBr (cm^{-1})	
A.		2-isothiocyanato-1,4-dimethoxy benzene	(N=C=S)	2095
			(-CH_2)	2921
B.		2-isothiocyanato-1-chloro benzene	(N=C=S)	2005
			(C-F)	855
C.		1, fluro-2-isothiocyanato benzene	(N=C=S)	2054
			(C-F)	779
D.		1,4-dichloro-2-isothiocyanatobenzene	(N=C=S)	2088
			(C-Cl)	740
E.		2-methoxy-1-isothiocyanato benzene	(N=C=S)	2047
			(C-Cl)	750
F.		1-chloro-2-methyl-3-isothiocyanato benzene	(N=C=S)	2055
			(C-F)	779

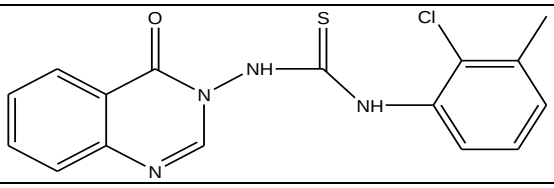
Physical characteristics of substituted thiourea derivatives:-(A4) (a-f)

Compound	Name	Mol. Formula	Mol. Weight (gm)	M.P. (◦C)	R_f value
a.	1-(2,5-dimethoxyphenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{17}H_{16}N4O_3S$	365.4	118-120	0.55
b.	1-(2-chlorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{15}H_{11}ClN_4OS$	330.79	113-115	0.87

c.	1-(2-fluorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{15}H_{11}FN_4OS$	314.34	140-142	0.32
d.	1-(2,5-dichlorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{15}H_{10}Cl_2N_4OS$	365.24	130-132	0.5
e.	1-(2-methoxyphenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{16}H_{14}N_4O_2S$	326.37	110-112	0.44
f.	1-(2-chloro-3-methylphenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{16}H_{13}ClN_4OS$	344.82	115-117	0.28
g.	1-(2-chlorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{15}H_{11}ClN_4OS$	330.79	83-85	0.27
h.	1-(2,5-dimethylphenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{17}H_{16}N_4OS$	324.4	205-207	0.76
i.	1-(2,4-difluorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea	$C_{15}H_{10}F_2N_4OS$	332.33	142-145	0.48

Physical characteristics of substituted thiourea derivatives:-(A4) (a-f)

Sr. no.	Chemical name	Molecular structure	IR with KBr (cm^{-1})	
A.	1-(2,5-dimethoxyphenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea		C=S C=O 2^0 NH	1145 1712.85 3201
B.	1-(2-chlorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea		C-Cl C=S C=O 2^0 NH	810 1145 1712 3201.9
C.	1-(2-fluorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea		C-F C=S C=O 2^0 NH	780 1145 1720 3201
D.	1-(2,5-dichlorophenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea		C-Cl C=S C=O 2^0 NH	810 1145 1712 3201.9
E.	1-(2-methoxyphenyl)-3-(4-oxoquinazolin-3(4H)-yl) thiourea		C-Cl C=S C=O 2^0 NH	750 1172 1680 3301
F.	1-(2-chloro-3-methylphenyl)-3-(4-		C-Cl C=S -CH_2	767 1172 2995

	oxoquinazolin-3(4H)-yl) thiourea		2^0 NH	3301

Cluster number	Cluster member	AC Score	SwissParam Score
0	1	253.658297	-7.0395
1	1	255.019438	-6.6801
2	1	255.435875	-6.8012
3	1	255.764576	-6.7433
4	1	255.931249	-6.3650
5	1	256.806882	-6.4846
6	1	257.547787	-6.1704
7	1	257.568391	-6.4733
8	1	258.619526	-6.1044
9	1	258.686582	-6.5975

Table. The docking score with other details

Ligand	CC1=C(C)C(C)=C(C)C2=C1SC(NN1C(=O) C3=C(C=CC=C3)N=C1C1CC1)=N2
Target	1xkk.pdb
Method	Attracting Cavities 2.0
Date	March 12, 2025, 5:01 am UTC

Parameters:

Box center:	21 - 41 - 35	Sampling exhaustivity:	medium	Number of RIC:	1
Box size:	20 - 20 - 20	Cavity prioritization:	buried		

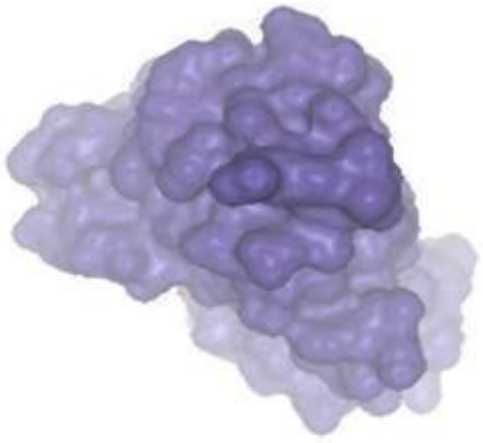


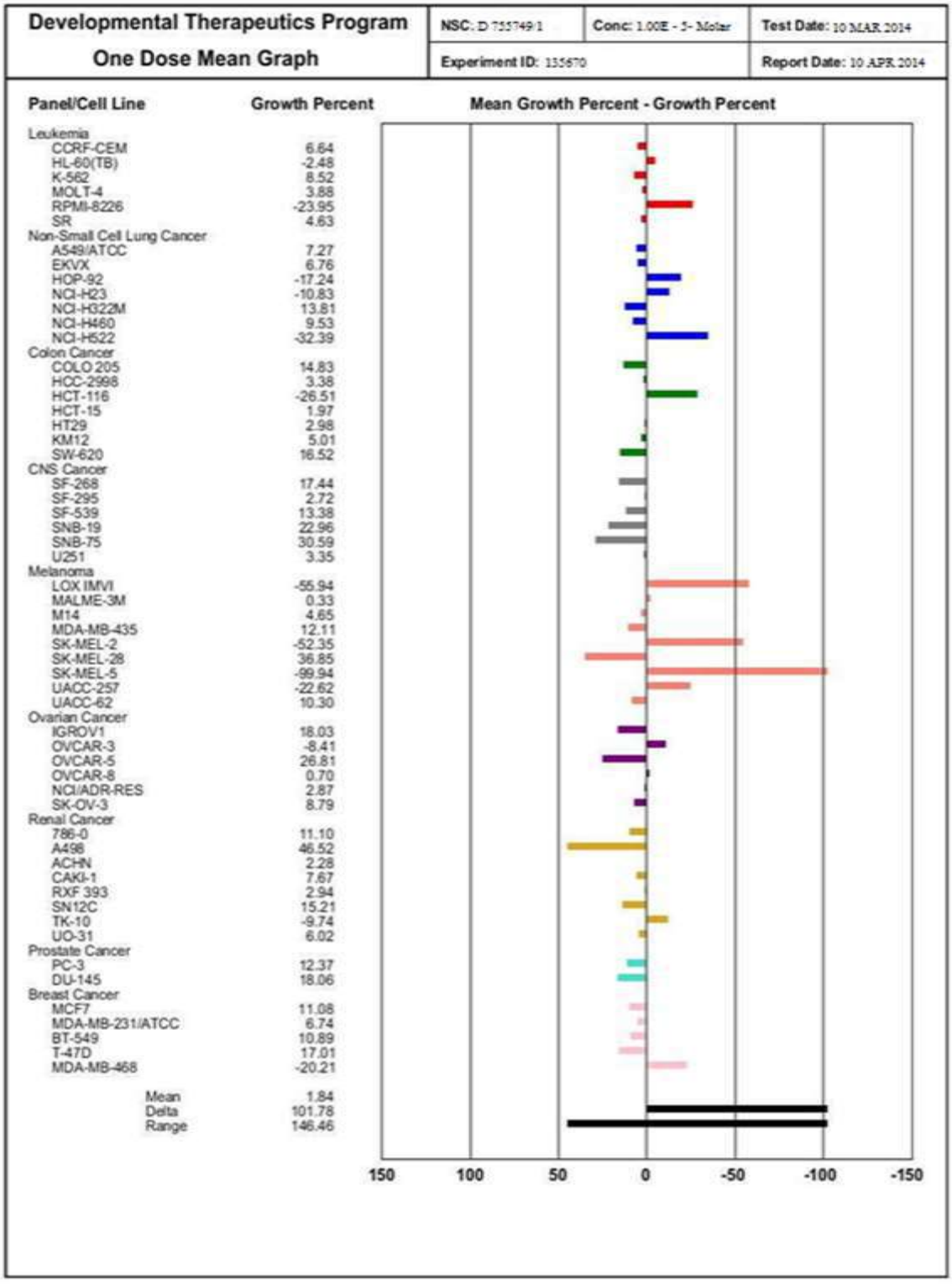
Fig3. Docked EGFR protein surface

4. ANTICANCER ACTIVITY DATA

The tumor growth inhibition properties of the compound A5(B) with the NCI code T ID-127927 respectively selected by the National Cancer Institute

(NCI), USA, under the drug discovery program of the NCI in a primary one dose anti cancer assay and was performed in full NCI 60 cell panel representing leukemia, melanoma and cancers of lung, colon, brain, breast, ovary, kidney and prostate in accordance with the protocol of the NCI, USA. Among the synthesized compounds, 15 compounds were uploaded for anticancer activity in NCI; U.S.A. Among which 11 compounds were screened for in-vitro anticancer activity against 60 cell lines at NCI; U.S.A. Result of Compound has been obtained. Compound A5 (B) has shown good anticancer activity. The output from the one dose screen is reported as a mean graph and is available for analysis by the COMPARE program as in table below.

Anticancer Activity Data of compound A5 (B)



CONCLUSION

In summary, a series of quinazoline derivatives were synthesized with satisfactory yields and evaluated for their anticancer potential. Specifically, 2-cyclopropyl quinazoline derivatives were successfully generated from cyclopropyl carbonyl, adhering to the established reaction scheme. The synthesized quinazoline derivatives exhibited yields ranging from 40% to 60%. Thin-layer chromatography revealed distinct Rf values for each compound, confirming their individual identities. Melting point determination and spectral analyses, including IR, NMR, and mass spectrometry, further characterized the synthesized compounds, with detailed spectral data provided in the appendix. Among the synthesized compounds, one selected derivative was submitted to the National Cancer Institute (NCI), U.S.A., for in vitro anticancer screening against a panel of 60 cell lines. Preliminary results indicated promising anticancer activity, leading to the selection of this compound for a five-dose assay, the results of which are pending. This compound demonstrated significant anticancer activity

REFERENCE

1. of the P53 tumor suppressor gene, N. Engl. J. Med. 329, 1993, 1318-1327.
2. www.medicalnewstoday.com/info/cancer-oncology.
3. L. A. Liott, P. S. Steeg, W. G. Steller-Stevenson, Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation, Cell 64, 1991, 327-336.
4. P. Mignatti, D. B. Rifkin, Biology and biochemistry of proteinases in tumor invasion, Physiol. Rev. 73, 1993, 161-165.
5. S. D. Auerbuch, B. A. Chabner, J. M. Collins (Eds.), Cancer Chemotherapy: Principles and Practice, Lippincott, Philadelphia, 1990, pp. 314-328.
6. Cancer prevention: 7 steps to reduce your risk", Mayo Clinic, 27 September 2008. Retrieved 30 January 2010.
7. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M "Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors". Lancet 366 ,9499, 2005 1784–93.
8. "Cancer". World Health Organization. Retrieved 9 January 2011.
9. Wicki A, Hagmann, J September 2011, "Diet and cancer", Swiss medical weekly, 141: 13250.
10. Cappellani A, Di Vita M, Zanghi A, Cavallaro A, Piccolo G, Veroux M, (2012). "Diet, obesity and breast cancer: an update". Front Biosci Schol Ed 4, 90–108.
11. Key TJ (January 2011). "Fruit and vegetables and cancer risk". Br. J. Cancer 104.
12. Rostom A, Dube C, Lewin G, Tsertsvadze A, "Nonsteroidal anti- inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force". Ann. Intern. Med. 146, 5, 2007, 376–89.
13. Thomsen A, Kolesar JM "Chemoprevention of breast cancer". Am J Health Syst Pharm 65 ,23, 2008, 2221–8.
14. Deng, Z., Li, J., Zhu, P., Wang, J., Kong, Y., Hu, Y., ... & Dong, C. (2025). Quinazolinones as Potential Anticancer Agents: Synthesis and Action Mechanisms. Biomolecules, 15(2), 210.
15. . Abdulwahab, M. K., Sidek, F. N. E. M., Daker, M., Marzuki, M., Keflee, R. D., Tan, Y. S., ... & Ariffin, A. (2025). Anticancer activity of fused quinazoline-quinazolinone: Synthesis, biological evaluations, and computational studies. Journal of Molecular Structure, 1326, 141065.
16. Lin, R. J., Xie, L., Gao, T. Y., Yang, Y. Z., Huang, L., Cheng, K., & Chen, Z. P. (2025). Design, synthesis and anti-tumor evaluation of novel pyrimidine and quinazoline analogues. European Journal of Medicinal Chemistry, 282, 117057.
17. Resta, S., & Resta, G. (2025). Quinazolinones as Novel Antitumor Agents. International Journal of Recent Advances in Multidisciplinary.
18. Manhas, N., Kumar, G., Dhawan, S., Makhanya, T., & Singh, P. A Systematic Review of Synthetic and Anticancer and Antimicrobial Activity of Quinazoline/Quinazolin-4-one Analogues. ChemistryOpen, e202400439.
19. Nafie, M. S., Fahmy, S. A., Kahwash, S. H., Diab, M. K., Dawood, K. M., & Abbas, A. A. (2025). Recent advances on anticancer activity of benzodiazine heterocycles through kinase inhibition. RSC advances, 15(7), 5597-5638.

20. Devi, M., Kumari, A., Yadav, A., Kumar, A., Dwivedi, J., & Kaur, N. (2025). Synthesis of Quinazoline Derivatives. Current Organic Chemistry.
21. Liu, C. S., Tong, J. P., Fang, Z. Y., Guo, X. M., Shi, T. T., Liu, S. R., & Sun, J. (2025). Molecular modeling aided design, synthesis and biological evaluation of quinazoline derivatives for the treatment of human cancer. Molecular Diversity, 1-16.
22. Singh, S., Kumar, R., Tripathi, S., Salahuddin, Mazumder, A., & Singh, N. (2025). Fused and Substituted Piperazines as Anticancer Agents: A Review. Chemical Biology & Drug Design, 105(3), e70077.
23. Reddy, A. B., Allaka, T. R., Avuthu, V. S. R., Chepuri, K., Ahmed, M. Z., & Nagarajaiah, H. (2025). New Quinazolinone-1, 2, 4-Triazole Analogues: Synthesis, Anticancer Evaluation, Molecular Docking, and In Silico ADMET Prediction. Journal of Molecular Structure, 141850.
24. Shourkaei, F. A., Ranjbar, P. R., Foroumadi, A., & Shams, F. (2024). Design and synthesis of BMH-21-like quinazolinone derivatives as potential anti-cancer agents. Journal of Molecular Structure, 1308, 138083.
25. Naim, M. J. Advancements in Quinazoline Derivatives as Targeted Anticancer Agents: A Review on its Synthesis, Mechanisms, and Therapeutic Potential.
26. Haggag, H. S., Aboukhatwa, S. M., Nafie, M. S., Paul, A., Sharafeldin, N., Oliver, A. W., & El-Hamamsy, M. H. (2024). Design and synthesis of quinazolin-4-one derivatives as potential anticancer agents and investigation of their interaction with RecQ helicases. Bioorganic Chemistry, 144, 107086.
27. El-Malah, A., Malebari, A. M., Khayyat, A. N., Mohammad, K. A., Gineinah, M. M., & Mahmoud, Z. (2024). Design, synthesis, and antiproliferative activities of novel substitutedhydrazone/triazolo-linked quinazoline derivatives. Journal of Molecular Structure, 1306, 137822.
28. Zayed, M. F., & Zayed, M. (2024). Quinazoline Derivatives as Targeted Chemotherapeutic Agents. Cureus, 16(5).
29. Lin, R. J., Xie, L., Gao, T. Y., Yang, Y. Z., Huang, L., Cheng, K., & Chen, Z. P. (2025). Design, synthesis and anti-tumor evaluation of novel pyrimidine and quinazoline analogues. European Journal of Medicinal Chemistry, 282, 117057.
30. Mansour, M. A., AboulMagd, A. M., Abbas, S. H., Abdel-Aziz, M., & Abdel-Rahman, H. M. (2024). Quinazoline-chalcone hybrids as HDAC/EGFR dual inhibitors: Design, synthesis, mechanistic, and in-silico studies of potential anticancer activity against multiple myeloma. Archiv der Pharmazie, 357(5), 2300626.
31. Syam, Y. M., Abd El-Karim, S. S., & Abdel-Mohsen, H. T. (2024). Quinazoline-oxindole hybrids as angiokinase inhibitors and anticancer agents: Design, synthesis, biological evaluation, and molecular docking studies. Archiv der Pharmazie, 357(10), e2300682.
32. Kumar, G., Kumar, P., Soni, A., Sharma, V., & Nemiwal, M. (2024). Efficient synthesis and molecular docking analysis of quinazoline and azole hybrid derivatives as promising agents for anti-cancer and anti-tuberculosis activities. Journal of Molecular Structure, 138289.
33. Shourkaei, F. A., Ranjbar, P. R., Foroumadi, A., & Shams, F. (2024). Design and synthesis of BMH-21-like quinazolinone derivatives as potential anti-cancer agents. Journal of Molecular Structure, 1308, 138083.
34. Wdowiak, P., Matysiak, J., Kuszta, P., Czarnek, K., Niezabitowska, E., & Baj, T. (2021). Quinazoline derivatives as potential therapeutic agents in urinary bladder cancer therapy. Frontiers in Chemistry, 9, 765552.
35. Mansour, M., Abbas, S. H., AboulMagd, A., Abdel-Rahman, H., & Osman, M. (2024). The significance of quinazoline derivatives as potential multi-target anti-cancer agents. Journal of advanced Biomedical and Pharmaceutical Sciences, 7(1), 1-17.
36. Ataollahi, E., Behrouz, M., Mardaneh, P., Emami, M., Zafarian, H., Khabnadideh, S., & Emami, L. (2024). Novel quinazolinone derivatives as anticancer agents: Design, synthesis, biological evaluation and computational studies. Journal of Molecular Structure, 1295, 136622.
37. Deng, Z., Li, J., Zhu, P., Wang, J., Kong, Y., Hu, Y., ... & Dong, C. (2025). Quinazolinones as

Potential Anticancer Agents: Synthesis and Action Mechanisms. Biomolecules, 15(2), 210.

38. ElZahabi, H. S., Nafie, M. S., Osman, D., Elghazawy, N. H., Soliman, D. H., El-Helby, A. A. H., & Arafa, R. K. (2021). Design, synthesis and evaluation of new quinazolin-4-one derivatives as apoptotic enhancers and autophagy inhibitors with potent antitumor activity. European Journal of Medicinal Chemistry, 222, 113609.
39. Zahran, S. S., Ragab, F. A., El-Gazzar, M. G., Soliman, A. M., Mahmoud, W. R., & Ghorab, M. M. (2023). Antiproliferative, antiangiogenic and apoptotic effect of new hybrids of quinazoline-4 (3H)-ones and sulfachloropyridazine. European Journal of Medicinal Chemistry, 245, 114912.
40. Zayed, M. F. (2023). Medicinal chemistry of quinazolines as anticancer agents targeting tyrosine kinases. Scientia Pharmaceutica, 91(2), 18.
41. Ghoneim, M. M., Abdelgawad, M. A., Elkanzi, N. A., Parambi, D. G. T., Alsalahat, I., Farouk, A., & Bakr, R. B. (2024). A literature review on pharmacological aspects, docking studies, and synthetic approaches of quinazoline and quinazolinone derivatives. Archiv der Pharmazie, 357(8), 2400057.
42. Yousefbeyk, F., & Ghasemi, S. (2024). A Review of Quinazoline-Based EGFR/VEGFR-2 Dual Inhibitors as Potent Anticancer Agents: Structure-Activity Relationship and Docking Studies. Pharmaceutical Sciences, 31(1), 43-64.
43. Kumar, A., Narang, R. K., & Bhatia, R. K. (2024). Impact of epidermal growth factor receptors as a key clinical target against cancer. In Current Molecular Targets of Heterocyclic Compounds for Cancer Therapy (pp. 139-159). Academic Press.
44. Ostlund, T. R. (2023). Design, Synthesis, and Biological Evaluation of Novel Steroidal Analogs: Potential Anticancer Agents. South Dakota State University.
45. Shihab, W. A., Kubba, A. A. R., Tahtamouni, L. H., Saleh, K. M., AlSakhen, M. F., Kanaan, S. I., ... & Yasin, S. R. (2024). Synthesis, In Silico Prediction, and In Vitro Evaluation of Anti-tumor Activities of Novel 4'-Hydroxybiphenyl-4-carboxylic Acid Derivatives as EGFR Allosteric Site Inhibitors. Current Medicinal Chemistry, 31(38), 6336-6356.
46. JALIL, N. A. S., & ABD HAMID, S. H. A. F. I. D. A. (2023). Molecular Docking Analysis on the Designed Benzimidazole Derivatives as EGFR Inhibitors: Comparison between EGFR Wild-Type (EGFR. Sains Malaysiana, 52(4), 1203-1215.
47. Maack, E. E. (2021). Design, synthesis, and evaluation of quinazoline-2, 4-dione topoisomerase inhibitors for increased cellular accumulation and evasion of efflux (Doctoral dissertation, The University of Iowa).
48. Shihab, W. A., Kubba, A. A. R., Tahtamouni, L. H., Saleh, K. M., AlSakhen, M. F., Kanaan, S. I., ... & Yasin, S. R. (2024). Synthesis, In Silico Prediction, and In Vitro Evaluation of Anti-tumor Activities of Novel 4'-Hydroxybiphenyl-4-carboxylic Acid Derivatives as EGFR Allosteric Site Inhibitors. Current Medicinal Chemistry, 31(38), 6336-6356.
49. Basu, D., Pal, R., Sarkar, M., Barma, S., Halder, S., Roy, H., ... & Samadder, A. (2023). To investigate growth factor receptor targets and generate cancer targeting inhibitors. Current Topics in Medicinal Chemistry, 23(30), 2877-2972.
50. Dodlapati, V. R., Ramya Sucharitha, E., Palabindela, R., Kapavarapu, R., Kavela, S., & Narsimha, S. (2024). Organocatalytic [3+ 2] Cycloaddition: Synthesis of Quinazoline Containing Sulfonyl 1, 2, 3-Triazoles as Potent EGFR Targeting Anti-Breast Cancer Agents. Journal of Heterocyclic Chemistry, 61(11), 1762-1776.

HOW TO CITE: Soheila Azim Patrawala*, Dr. Bhavini Gharia, Amankumar Vaghasiya, Insilico Studies and Synthesis of New 2-Cycloproply Quinazoline Derivatives as Potential Anticancer Agents, Int. J. Sci. R. Tech., 2025, 2 (4), 306-320. https://doi.org/10.5281/zenodo.15212322