Recent Advancement in Quinazoline Moieties with Biological Potentials: A Comprehensive Review

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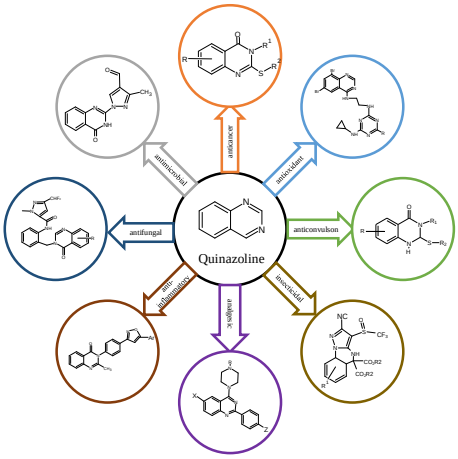
Abstract

Quinazoline derivatives have emerged as a flexible and promising category of substances, showcasing a diverse array of pharmacological significance like antitumor, antimicrobial, anti-inflammatory and antihypertensive properties. In recent decades, considerable research work has been attentive on investigating structural diversity & synthesis methods of these heterocyclic compounds, with the goal of enhancing their pharmacological effectiveness. This review provides an in-depth overview of the recent advancements in the creation and evaluation of quinazoline derivatives, emphasizing their considerable effectiveness across various therapeutic fields. The discussion showcases innovative techniques, encompassing both traditional and eco-friendly chemistry methods that have enabled the effective construction of quinazoline frameworks. This article aims to offer important insights for the development of new quinazoline-based drugs by summarizing key structural characteristics and their impact on biological effectiveness. This detailed analysis not only highlights the significance of quinazoline derivatives in medicinal chemistry but also paves the way for forthcoming research and clinical applications.

Keywords: antitumor, antimicrobial, anti-inflammatory, antihypertensive properties.

Graphical Abstract



1. Introduction:

Compounds that contain heterocycles encompass most significant class in the area of medicinal chemistry for treating sicknesses and contaminations, with quinazoline being a prominent example from this category[1] **(Fig.1)**. Quinazoline is type of heterocyclic substance formed by fusion by two aromatic 6-membered rings[2]; one of these rings having two nitrogen and is known as a pyrimidine ring, while the other is a benzene ring[3,4]. As a result, quinazoline can be classified as a phenyl pyrimidine compound.

Quinazolines exhibit a wide-ranging of medicinal characteristics. They are utilized across various fields, such as anticancer[5-7], antioxidant[8,9] and antidiabetic[10-12], anticonvulsant[13,14], antituberculosis[15-17], pain relief[18-20], antihypertensive[21,22], anti-inflammatory[23-25], antimalarial[26-28], antibacterial[29-31], and many other uses.

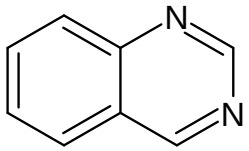
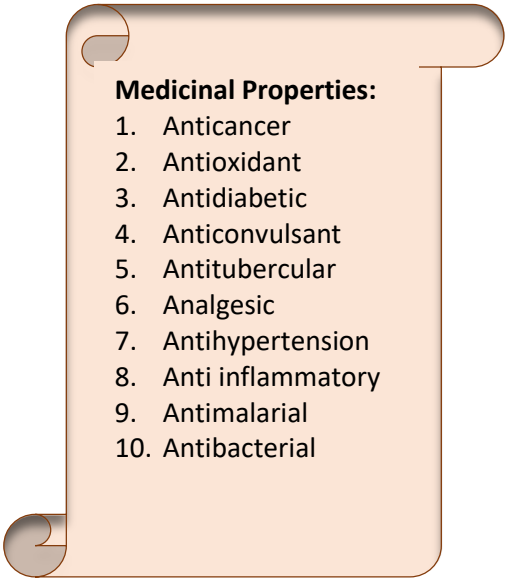


Fig. 1 Quinazoline

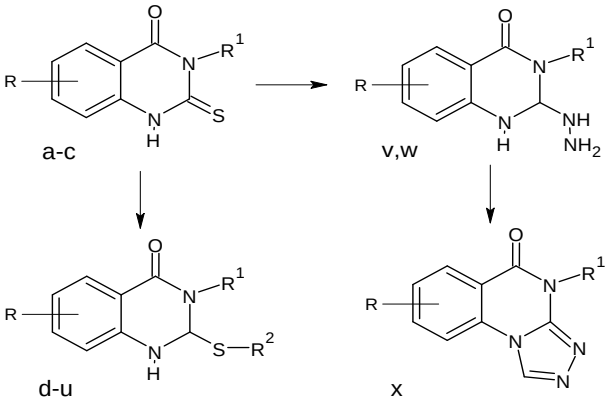


The production of quinazoline derivatives has progressed notably, with numerous methods improving their structural variety and biological effectiveness. Established synthetic approaches have been enhanced by contemporary techniques such as microwave-assisted synthesis[32-35], metal-mediated reactions[36-38], and ultrasound-initiated reactions[39,40]. These

innovations have optimized the creation of quinazoline compounds, making it easier to investigate their pharmacological properties.[41]

This review aims to provide a comprehensive overview on recent advancements in synthesis of quinazoline derivatives and their notable biological activities. By exploring different synthetic methods and their associated bioactivities, we aim to emphasize the therapeutic potential of these compounds and their importance in medicinal chemistry.

2. Synthetic pathways of Quinazoline derivatives

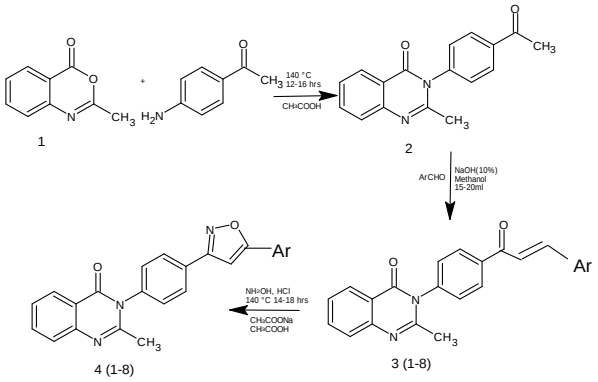


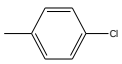
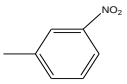
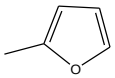
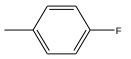
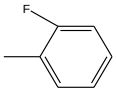
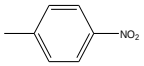
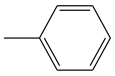
Compounds	R	R^1	R^2
a	$-CH_3$	-Ph	-
b	$-OCH_3$	-Ph	-
c	$-CH_3$	$-C_4H_9$	-
d	$-CH_3$	$-C_4H_9$	-ethyl
e	$-CH_3$	$-C_4H_9$	-allyl
f	$-CH_3$	$-C_4H_9$	-2-methyl-benzyl
g	$-CH_3$	$-C_4H_9$	-3-methyl-benzyl
h	$-CH_3$	$-C_4H_9$	-4-cl-benzyl
i	$-CH_3$	$-C_4H_9$	$-4-NO_2$-benzyl
j	$-CH_3$	$-C_4H_9$	-2-cyno-benzyl
k	$-CH_3$	$-C_4H_9$	-3-cyno-benzyl
l	$-CH_3$	$-C_4H_9$	-4-cyno-benzyl
m	$-CH_3$	$-C_4H_9$	-3-methoxy-benzyl
n	$-CH_3$	$-C_4H_9$	-(1H-benzoimidazole-2-yl) methyl
o	$-CH_3$	$-C_4H_9$	-morphilinoethyl
p	$-CH_3$	-Ph	-4-cyno-benzyl
q	$-CH_3$	-Ph	-2-methyl-benzyl
r	$-CH_3$	-Ph	$-4-NO_2$-benzyl
s	$-CH_3$	-Ph	$-7-NO_2$-benzoxadiazole
t	$-OCH_3$	-Ph	-3-(Phthalimido-2-yl) propyl
u	$-OCH_3$	-Ph	-morphilinoethyl
v	$-CH_3$	$-C_4H_9$	-hydrazine
w	$-CH_3$	-Ph	-hydrazine
x	$-CH_3$	-Ph	-

Scheme 1: Synthetic pathways of quinazoline (anticonvulsant activity)

The compounds demonstrated anticonvulsant efficacy between 17% and 100% in the scPTZ assay doses varying, from 0.204 to 0.376 mmol/kg. Among tested compounds **h, m**, and **s** exhibited the highest levels of potency showing effectiveness at doses 0.248, 0.239, and 0.338 mmol/kg, respectively. Their activity was approximately 3 to 4 times greater than that of ethosuximide (1.06 mmol/kg), though they remained less potent compared to phenobarbital.

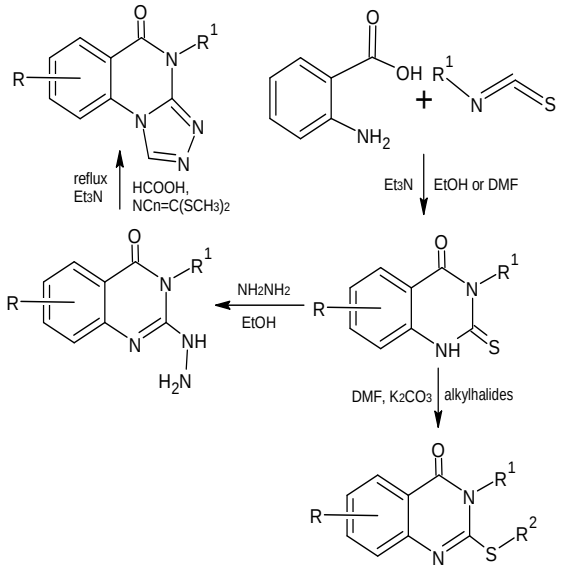
Inclusion of a -C_4H_9 group on site 3 is essential for enhancing anticonvulsant activity and preventing the spread of seizures, as observed in compounds h and m. Furthermore, adding a benzodiazoxazole part at site 2 increases the antiepileptic effectiveness of phenyl-substituted derivatives at site 3, although this change seems to slightly reduce their capacity to completely avert seizures, as seen with compound s. It is noteworthy that the quinazoline ring with a methyl substitution demonstrated more effective anticonvulsant properties than its methoxy-substituted equivalent. Molecular docking studies indicates the impressive efficacy of the synthesized quinazolines primarily results from their stable ligand-enzyme interactions, which are marked by the lowest binding energy, numerous H bonds & robust a A.A interactions at potent site of hCA-II. [42]



Compounds	Ar	Compounds	Ar
1		5	
2		6	
3		7	
4		8	

Scheme 2: Quinazoline-4-3H-one derivatives (anti-convulsant and anti-inflammatory

The reaction between 2-Methylbenzoxazinone (1) & p-aminoacetophenone led to the formation of 3-(p-acetylphenyl)-2-methylquinazolin-4(3H)-one (2). Subsequent Claisen-Schmidt condensation of compound 2 with a range of aromatic and heterocyclic aldehydes resulted in the synthesis of diverse quinazolyl chalcones 3(1-8). Refluxing these chalcones with Hydroxyammonium chloride produced 3-[4-(5-(3-substitutedphenyl) isoxazol-3-yl) phenyl]-2-methylquinazolin-4(3H)-one. 4(1-8) in good yields. Biological evaluation revealed that compounds 4(1), 4(2), and 4(6) displayed significant anti-convulsant activity, while 4(3) and 4(6) exhibited noteworthy anti-inflammatory effects. [43]

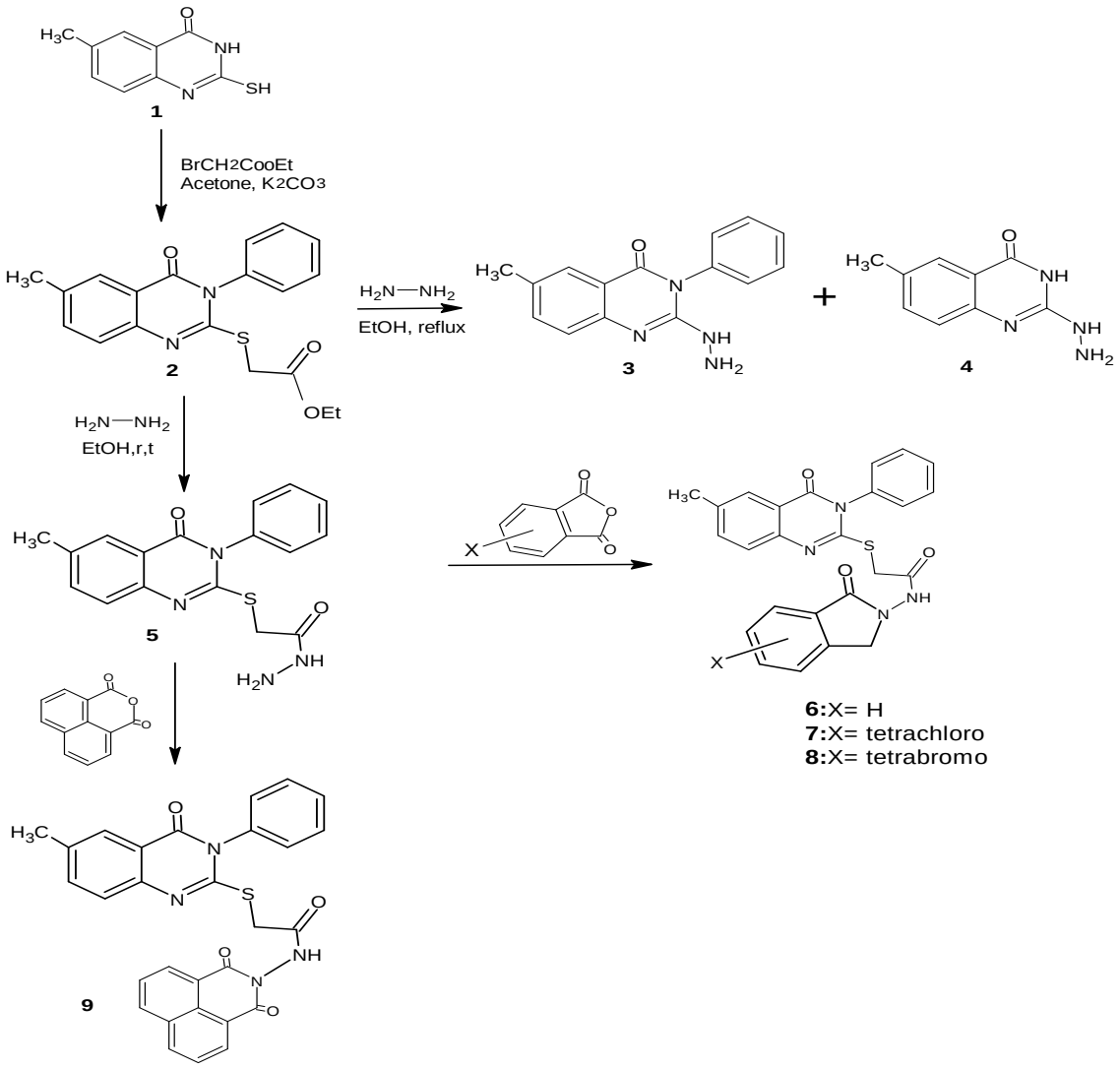


Compound	R	R^1	R^2
1	-CH_3	-Ph	-
2	-OCH_3	-Ph	-
3	-CH_3	-C_4H_9	-
4	-CH_3	-C_4H_9	-C_2H_5
5	-CH_3	-C_4H_9	allyl
6	-CH_3	-C_4H_9	2-methyl-benzyl
7	-CH_3	-C_4H_9	3-methyl-benzyl
8	-CH_3	-C_4H_9	4-chloro-benzyl
9	-CH_3	-C_4H_9	4-nitro-benzyl
10	-CH_3	-C_4H_9	2-cyano-benzyl
11	-CH_3	-C_4H_9	3-cyano-benzyl
12	-CH_3	-C_4H_9	4-cyano-benzyl
13	-CH_3	-C_4H_9	3-methoxy-benzyl
14	-CH_3	-C_4H_9	(1H-benzimidazole-2-yl) methyl
15	-CH_3	-C_4H_9	morpholinoethyl
16	-CH_3	-C_4H_9	3-(phthalimido-2-yl) propyl
17	-CH_3	-Ph	ethyl
18	-CH_3	-Ph	allyl
19	-CH_3	-Ph	2-methyl-benzyl
20	-CH_3	-Ph	3-methyl-benzyl
21	-CH_3	-Ph	4-chloro-benzyl
22	-OCH_3	-Ph	4-nitro-benzyl
23	-OCH_3	-Ph	morpholinoethyl
24	-CH_3	-C_4H_9	-hydrazine
25	-CH_3	-Ph	-hydrazine
26	-CH_3	-C_4H_9	-

Scheme 3: Synthesis of compounds (anticancer activity)

A novel sequence of quinazoline compounds (3 to 26) were created & analyzed using various physicochemical and spectral techniques. The synthesis began with a reaction between 2-amino-m-Methylbenzoic acid and Butyl mustard oil, resulting in the production of 4-Hydroxy-2-thioxoquinazoline (3). Following this, chemical modifications such as alkylation & hydrazinolysis of thioxo group in compounds (1–3) led to the generation of the correlate thioethers (4–23) & **–NH-NH₂** derivatives (24 and 25). Furthermore, a cyclocondensation reaction involving compound 24 resulted in the formation of a tricyclic derivative, 26. derivatives 1 & 2, was previously synthesized, are already recognized for their anticancer properties. The cytotoxic effects of all the newly produced compounds were identify *in vitro* counter to HeLa and MDA-MB231 tumors cell-lines. For comparison, compounds 1 and 2 were included in the testing alongside the new derivatives. Cell viability was assessed through the MTT assay, with treatments administered at concentrations of 0, 1, 5, 10, 25, and 50 µM. The cells were stand for 24 hours in the presence of 50% DMSO. The IC50 values for each compound were determined, with gefitinib acting as the standard reference medication.

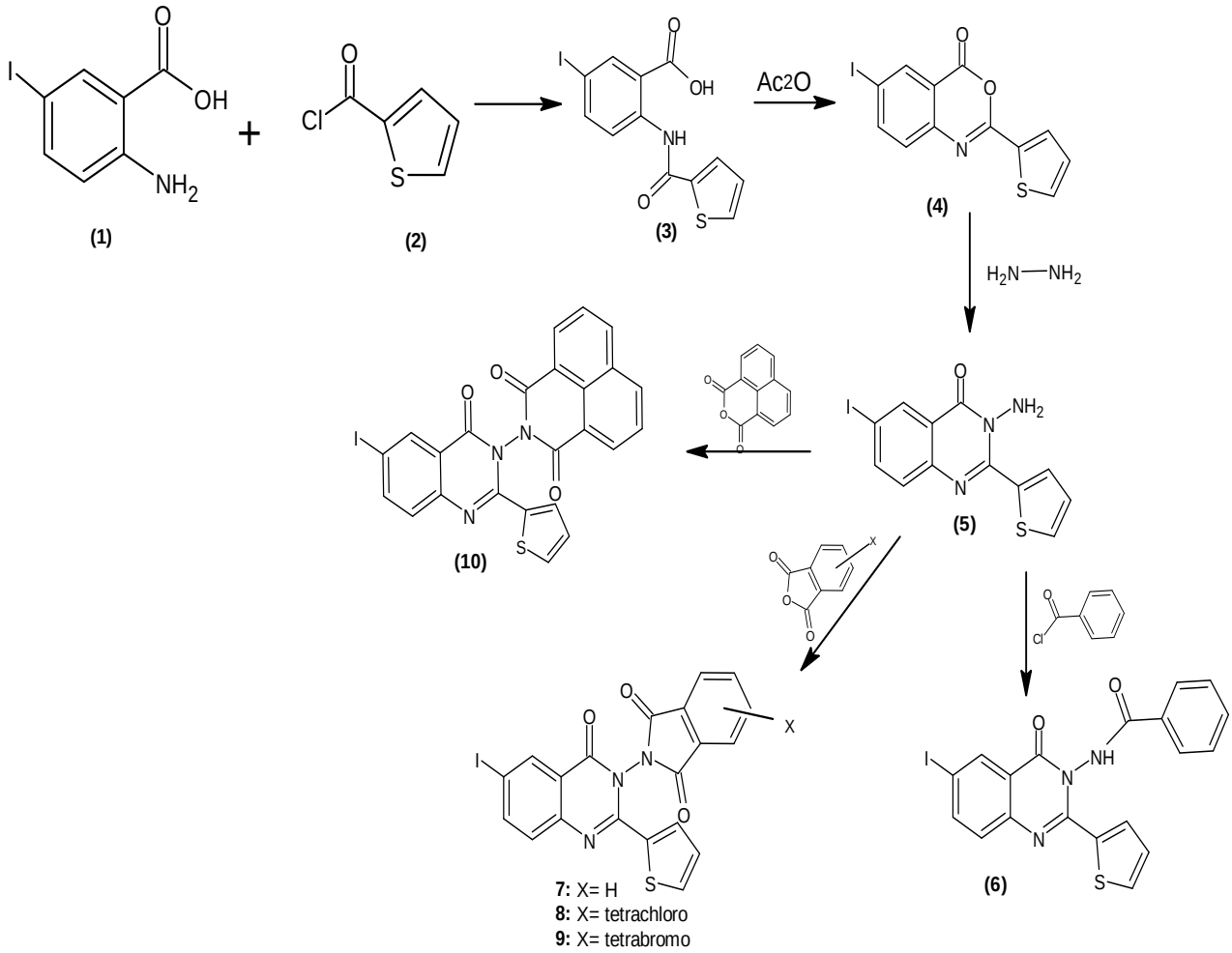
The findings show that all examined derivatives produced significant cell death against both cancer cell lines. While derivatives 1–3 produced moderate effectiveness, derivatives 21–23 demonstrated greater potency in comparison to gefitinib. In particular, these compounds had IC_{50} ideals from 1.85 to 2.81 µM, which are considerably lower than those of gefitinib. Therefore, compounds 21–23 appear to be promising candidates for further exploration as anticancer agents. [44]



Scheme 4: Synthesis for target compounds 6-9 (70% efficiency)

A variety of quinazoline derivatives stood developed, produced, and determined of their antiepileptic effects. derivatives 1 and 7 demonstrated 70–100% protection against seizures induced by PTZ by work as agonists of the $GABA_A$ receptor.

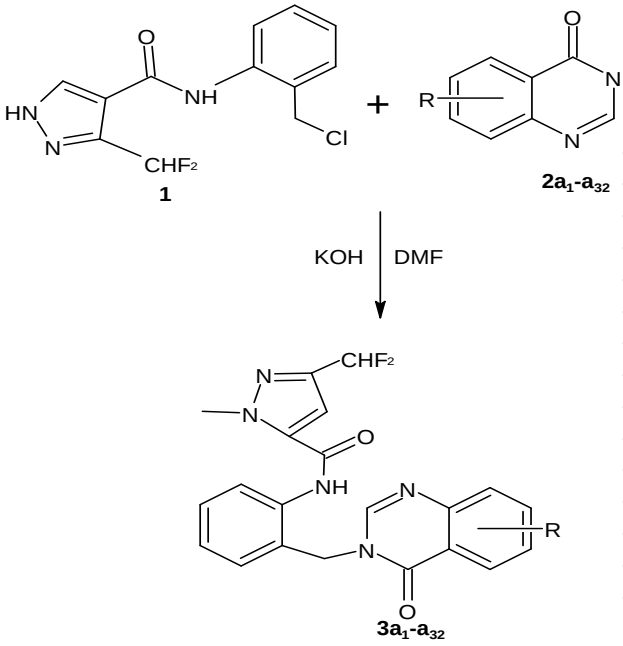
The compound (7) exhibited moderate anticonvulsant activity. Structural analysis and structure-activity relationship (SAR) insights suggested that the anticonvulsant effects are attributed to the synthesized quinazoline derivatives. Notably, the parent derivative, (1), provided 70% protection against seizures caused by pentylenetetrazol (PTZ). This indicates the potential of quinazoline-based compounds in anticonvulsant therapy.



Scheme 5: Synthetic of target compounds 6-10 (100% activity and 6 &7 are most active)

A novel quinazoline derivatives was considered, produced, & estimated antiepileptic potential. Among these, derivatives 5, 6, and 7 displayed significant protection (70–100%) against seizures induced by PTZ, work as GABAA receptor agonists. Notably, derivative produced more activity with ED_{50}. Interestingly, compound 38 demonstrated nearly double the anticonvulsant action related to the sodium valproate.

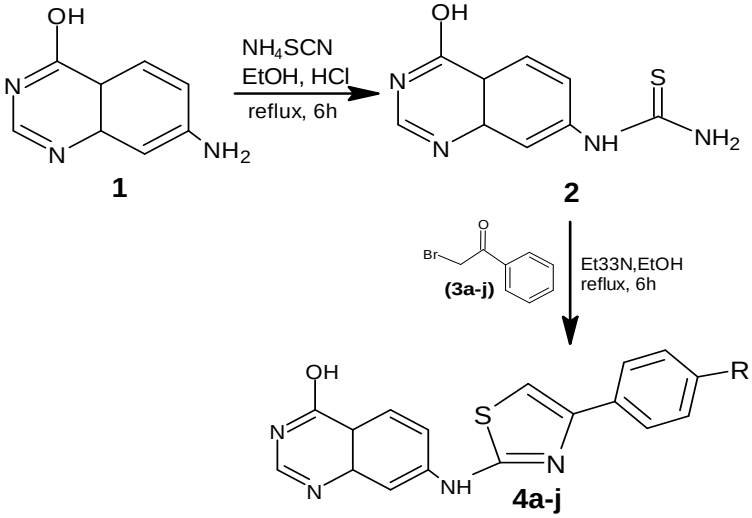
Within the 6-iodo-2-thienoquinazoline series, derivatives 5, 6, and 7 stood out as the most potent anticonvulsants. Compound 5, a 3-amino derivative, achieved complete protection against PTZ-induced convulsions. Its benzoylation produced compound 6, a benzamido derivative that retained strong anticonvulsant activity. Further modification with a phthalimido group at position 3 resulted in compound 7, which also conferred 100% protection. These findings highlight the promising role of quinazoline derivatives in anticonvulsant therapy. [45]



Compounds (3)	R	Compounds (3)	R
a1	H	a17	6-Cl-8-Me
a2	5-Me	a18	5-Br
a3	6-Me	a19	6-Br
a4	7-Me	a20	7-Br
a5	8-Me	a21	8-Br
a6	7,8-diMe	a22	6,8-diBr
a7	5-F	a23	5-OMe
a8	6-F	a24	6-OMe
a9	7-F	a25	7-OMe
a10	8-F	a26	8-OMe
a11	6,7-diF	a27	6,7-diOMe
a12	5-Cl	a28	5-NO_2
a13	6-Cl	a29	6- NO_2
a14	7-Cl	a30	7- NO_2
a15	8-Cl	a31	8- NO_2

Scheme 6: Synthesis of target compounds 3 a_1-a_{32} (anti-fungal)

To identify a new fungicide targeting *Rhizoctonia solani* and 32 novel pyrazole carbamide derivatives featuring a quinazolinone framework were conceptualized & developed. The structure of the target derivatives identified through single-crystal XRD **(a_{11})**. The *in vitro* fungal properties of aimed derivatives in contradiction of *R. solani* were determined a concentration of 100 μg/mL. The SAR study exhibited antimycotic properties peaked at site 6 with a substitution. Moreover, the effectiveness of the antifungal properties was affected by site and the amount of chlorine molecule present. Through *in vitro* bio-assays, it was found that a16 displayed greater antimycotic potency counter to *R. solani* likened to fluconazole, yet it was not as effective as bixafen. The results indicated that the strategy of developing antifungal agents through molecular hybridization was successful. Meanwhile, compounds incorporating a quinazolinone component within pyrazole carbamide showed promising antifungal activity against *R. solani.*

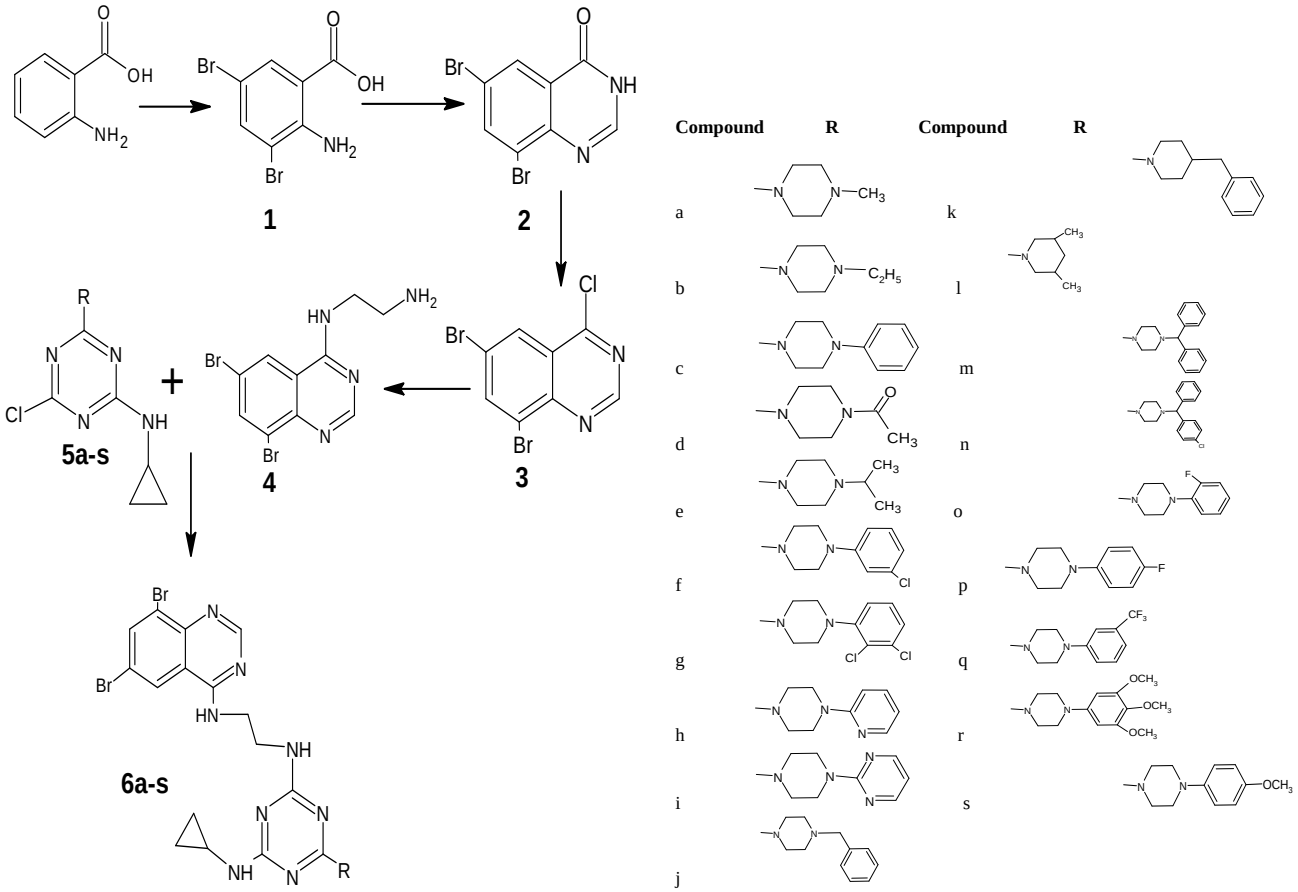


Compound	R
4_a	-H
4_b	-CH_3
4_c	-OH
4_d	-OCH_3
4_e	-NH_2
4_f	-F
4_g	-Cl
4_h	-Br
4_i	-CF_3
4_j	-NO_2

Scheme 7: Quinazoline compounds

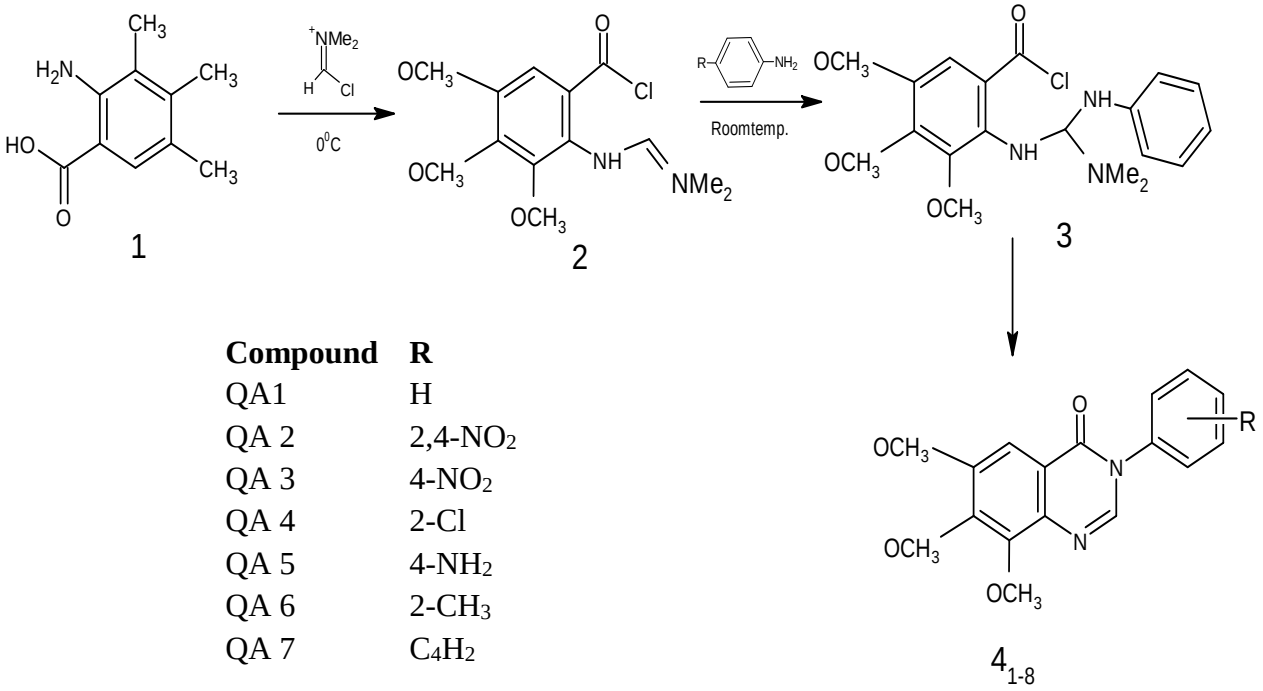
A novel series of thiazole compounds derived from quinazoline (4a-j) was created and identify through in vitro anticancer efficacy on the MCF-7 and HepG2 tumor cell lines, along with A549. In comparison to the control group, erlotinib, as well as derivatives 4g, 4i, and 4j, display marked inhibition of tumor. The inhibition properties of every derivative were evaluated against wild-type as well as altered EGFR kinases.

The IC_{50} ideals for wholly derivatives 4a-j in nanomolar series, indicating robust activity. Identifying revealed derivatives 4i and 4j had extra potent EGFR-kinase inhibitory properties than developed treatments staurosporine, brigatinib, and osimertinib. Among the various compounds, 4i emerged as one of the most potential candidates, displaying IC_{50} ideals of 2.17, 2.81, & 3.62 nm inhibition properties of wild-type, mutant EGFR kinases, respectively.



Scheme 8: Quinazoline compounds (anti-oxidant)

Summary of synthetic approach for creating (7a–7s). New derivatives for quinazolines and their mixed heterocycles have been developed, leading to the finding that some compounds inhibited aldehyde oxidase by over 98 %. [46]

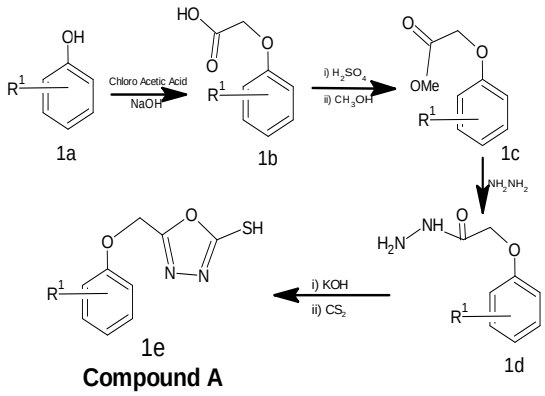


Compound	R
QA1	H
QA 2	2,4-NO_2
QA 3	4-NO_2
QA 4	2-Cl
QA 5	4-NH_2
QA 6	2-CH_3
QA 7	C_4H_2

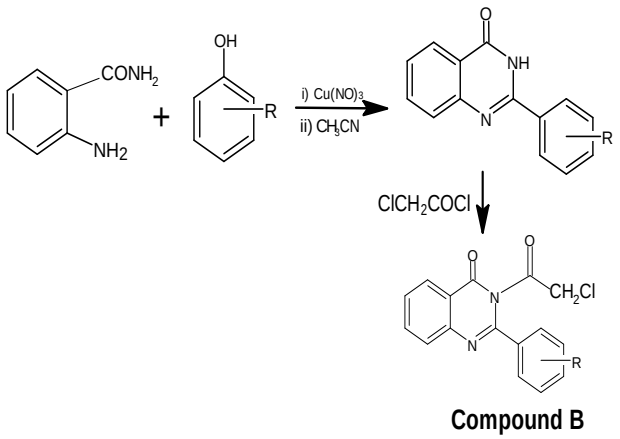
Scheme 9: Synthesis of compounds (Anti-inflammatory)

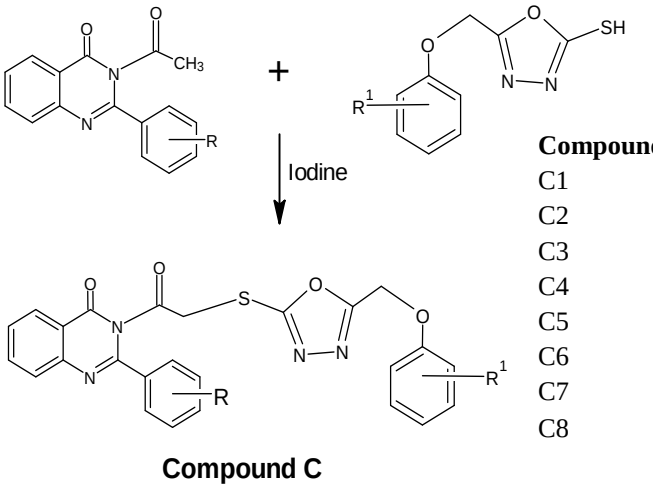
A range of new quinazolinone derivatives (QA-1 to QA-8) has been produced through the reaction of 3,4,5-trimethoxy-2-aminobenzoic acid with Valmeyer reagent. Spectroscopic procedures were employed to illustrate & confirm physical properties of all synthesized molecules. NSAIDs properties, were identified using an *in vivo* model of rat paw edema. The outcomes produced that derivatives QA-2 and QA-6 display considerable anti-inflammatory properties, while QA-1, QA-4, and QA-7 display moderate effects. Conversely, derivatives QA-3, QA-5, and QA-8 showed the lowest levels of anti-inflammatory activity among those that were synthesized. [47]

PART I



PART II

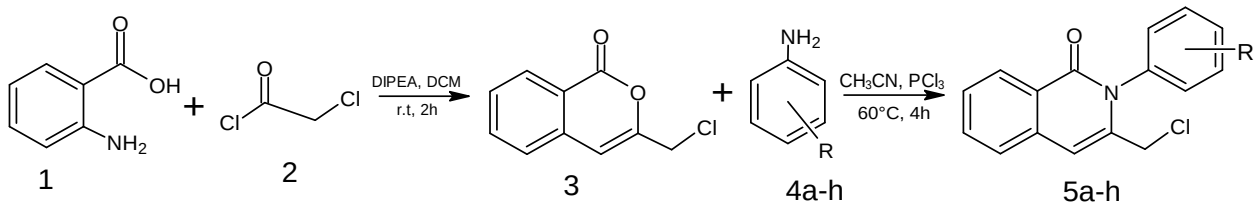


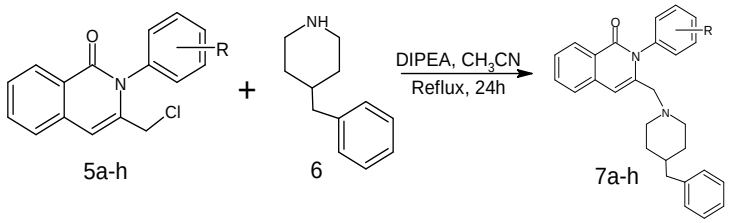


Compound	R	R1	Compound	R	R1
C1	2-Cl	H	C9	H	H
C2	3-Cl	H	C10	2-OH	H
C3	4-Cl	H	C11	4-OH	H
C4	H	2-cl	C12	4-CH_3	H
C5	H	3-cl	C13	3-CH_3	H
C6	H	4-cl	C14	2-CH_3	H
C7	2-NO_2	H	C15	2-OCH_3	H
C8	4-NO_2	H			

Scheme10: Various compounds

A novel set of Quinazoline-oxadiazole derivatives was conceptualized, synthesized, & determine their anticonvulsant effects compared to chemically-induced seizures, in comparison to the ideal medication valproate. The composites C4, C8, C10, and C11 showed an effectiveness of 70-100% in preventing seizures induced by PTZ. Derivatives C4, C8, C10, & C11 showed greatest binding affinities and displayed the most potent anticonvulsant effects in mice. The findings suggested that many of the active compounds have potential for further development, alteration, and research focused on creating more effective analogues. [48]



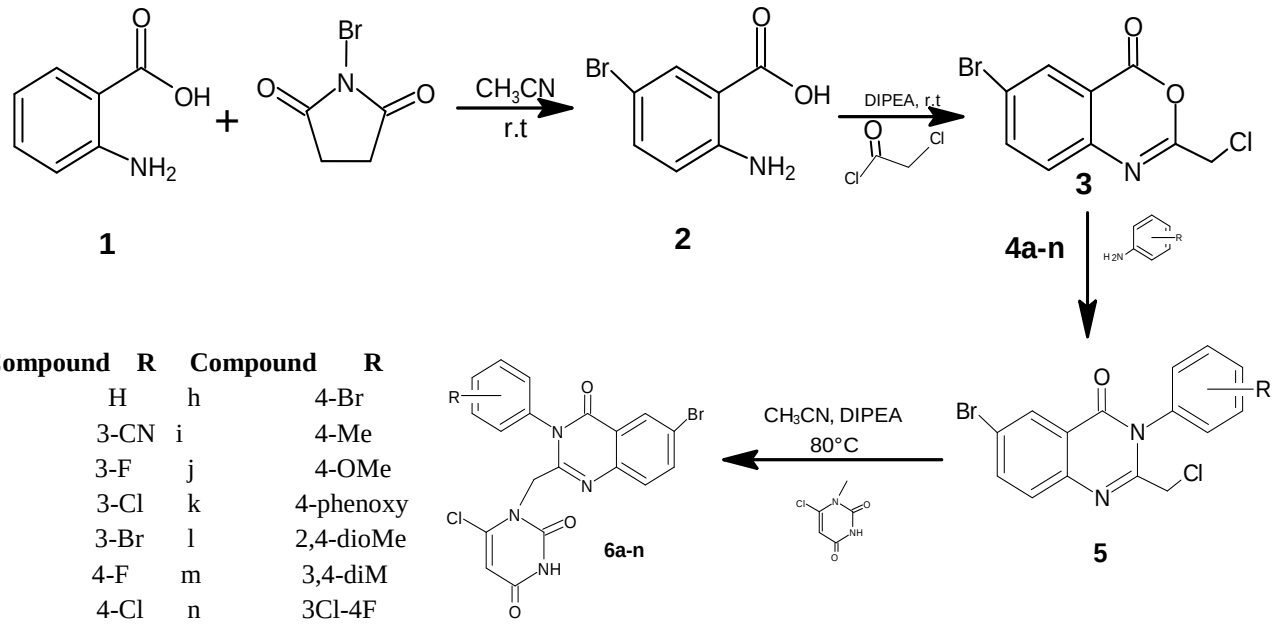


Compound	R
4,7a	3-Cl
4,7b	3-Br
4,7c	2,4 diOMe
4,7d	3-CF_3
4,7e	4-F
4,7f	4-Cl

Scheme 11: Synthetic path of designed quinazoline (7a-h)

Quinazolinone derivatives (7a–7h) were created as potential agents to inhibit cell growth. The synthesized compounds generally display moderate effectiveness opposite 3 cell lines studied. They also showed a positive preference for tumorigenic cell lines over non-tumorigenic ones. In the quest identify new antiproliferative derivatives, a series of quinazolinone-benzyl piperidine compounds was developed and assessed. The effectiveness of the derivatives was

determine using three cancer cell lines (MCF-7, A549, and 5637), while their selectivity was also examined opposite both carcinogenic and non- carcinogenic cell lines. Several these derivatives, particularly 7b, 7e, & 7f, produced moderate effectiveness against the cancer cell lines analyzed, whereas assessments on normal cell lines revealed lower toxicity. [49]



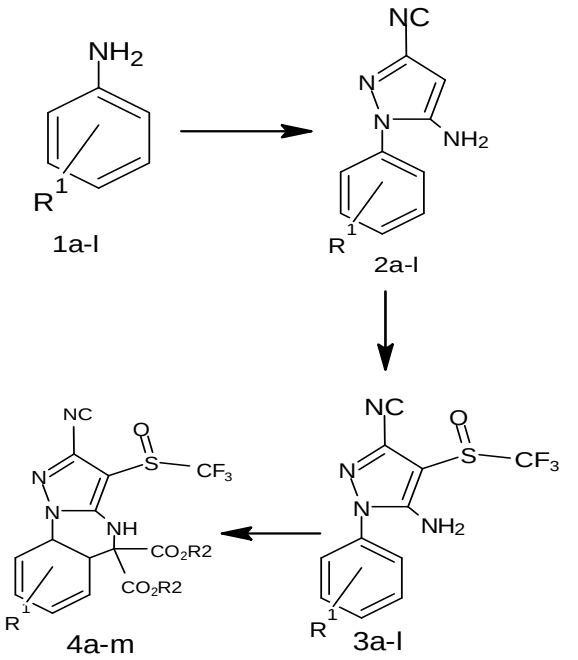
Compound	R	Compound	R
a	H	h	4-Br
b	3-CN	i	4-Me
c	3-F	j	4-OMe
d	3-Cl	k	4-phenoxy
e	3-Br	l	2,4-dioMe
f	4-F	m	3,4-diM
g	4-Cl	n	3Cl-4F

Scheme 12: Synthetic compound (6a-n)

Quinazoline derivatives represent a crucial class of heterocyclic derivatives that have attracted substantial attention in the development & progress novel pharmaceuticals because of their varied pharmacological properties. Furthermore, various studies have shown the promise of pyrimidine analogs as agents against cancer. As a result, this research focused on creating novel compounds with cytotoxic effects by emphasizing different hybrids of quinazolinone and pyrimidine.

A novel sequence of quinazoline-pyrimidine (6a-6n) was synthesized & tested for inhibiting cell proliferation. The newly developed compounds' effects on cell proliferation were determine against 3 human tumor cell lines. The compounds showed noteworthy potential, exhibiting IC50 in the evaluated cell-lines.

Derivative 6n demonstrated strongest antimetabolite effects, showing IC_{50} ideals of 5.9 ± 1.69 μm, 2.3 ± 5.91 μm, & 5.65 ± 2.33. These consequences show 6n might trigger caspase-mediated cell death in the A549 cell-line in a dose-dependent way & cause a halt in S phase of cell cycle. To identify precise attachment patterns that produced derivatives with EGFR, docking investigations were also carried out. [50]

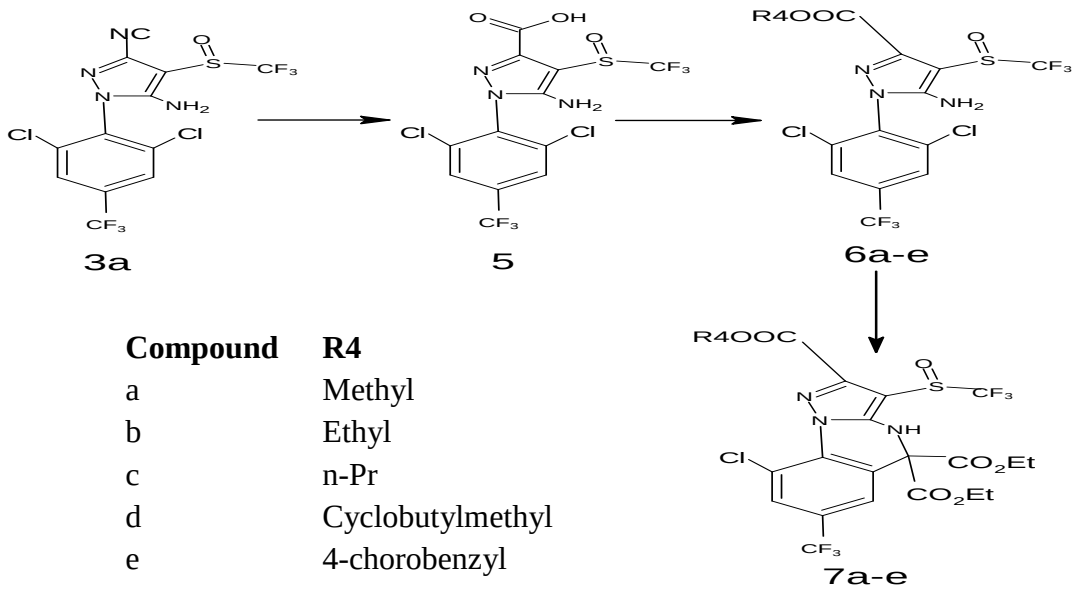


3a-l	R1	4a-m	R1	R2
3a	2,6-di-Cl, 4-CF_3	4a	4-CF_3,6-Cl	Et
3b	2,6-di-Cl, 4-NO_2	4b	4-NO_2, 6-Cl	Et
3c	2,6-di-Cl, 4-CN	4c	4-CN, 6-Cl	Et
3d	2,4,6-tri-Cl	4d	4,6-Cl	Et
3e	2,6-di-Cl, 4-Br	4e	4-Br, 6-Cl	Et
3f	2-Cl, 4-CF_3	4f	4-CF_3	Et
3g	2,6-di-Br, 4-NO_2	4g	4-NO_2,6-Br	Et
3h	2,6-dibromo, 4-cyanophenyl	4h	4-CN, 6-Cl	Et
3i	2,6-dibromo, 4-chlorophenyl	4i	4-Cl, ,6—Br	Et
3j	2,4,6-tri-Br	4j	4,6-Br	Et
3k	2,6-dibromo-4-fluoro	4k	4-F, 6-Br	Et
3l	2,6-di-Br, 4-OCF_3	4l	4-OCF_3,6-Br	Et
		4m	4-CF_3,6-Cl	Me

Scheme 13: Synthesis of compound 4a-m (insecticidal activity)

Compounds 4a–4m and their control (positive), indoxacarb and fipronil were evaluated for their insect-killing properties against *P. xylostella* larvae in their third instar. In general, most of the substances showed good insecticidal effects (>50% mortality) to outstanding ones (100% mortality). Five of the 13 target compounds had a substantial mortality rate at 100 mg/L that was more than 50%. These compounds' LC50 values (4a, 4f, 4j, 4l, and 4m) against *P. xylostella* larvae in their third instar were then determined. The results shows that derivate 4m had highest activity; its LC50 value in contrast to *P. xylostella* was higher than fipronil, but it was comparable to indoxacarb, commonly used commercial pesticide for *P. xylostella* control. Additionally, compounds 4a and 4f showed comparably significant insecticidal activity (LC50 = 4.80 and 5.10 mg/L).

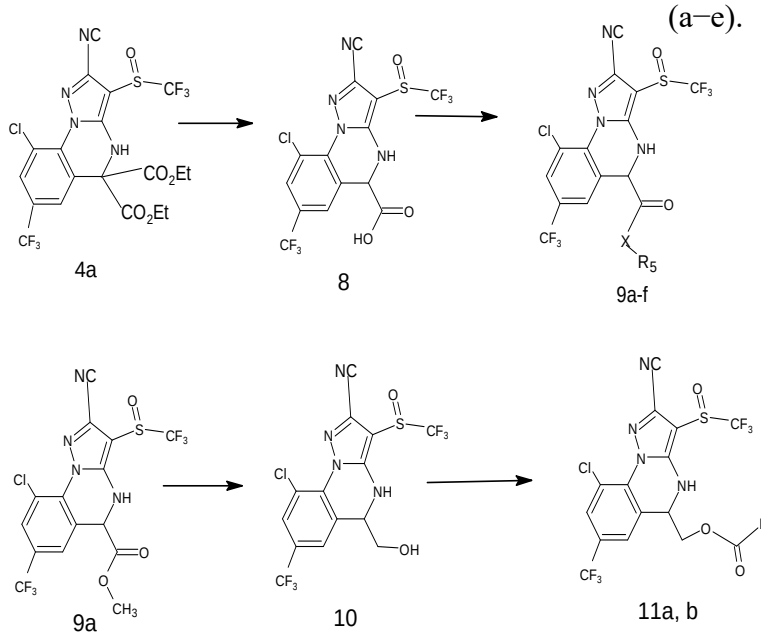
The other drugs (4j, 4l) had LC50 values ranging from 9.42 to 24.35 mg/L against *P. xylostella*. According to the results, the cyano group on the pyrazole ring and the 4-CF_3 group on phenyl moiety are essential for the synthetic 4,5-dihydropyrazolo[1,5-a] quinazolines to achieve efficient acaricidal effects (over 50% mortality). These characteristics match the chemical structure of fipronil and are shared by three compounds with greater activity (4a, 4f, and 4m). For example, there were significant decreases in insecticidal effectiveness when the 4-CF3 group on the phenyl ring (moiety A) of 4a was substituted by alternative electron-withdrawing groups like: −NO2 (4b), −cyno (4c), −chlorine (4d) or −bromine (4j).



Compound	R4
a	Methyl
b	Ethyl
c	n-Pr
d	Cyclobutylmethyl
e	4-chorobenzyl

Scheme 14: Synthesis of the target compounds **(7a-e)**

Compounds a–e was evaluated for their insecticidal efficacy by testing positive controls (indoxacarb and fipronil) against *P. xylostella* larvae in their third instar. In general, the majority of the compounds exhibited insecticidal qualities that ranged from good (over 50% mortality) to exceptional (100% mortality). Dosage 100 mg/L, one of the five target compounds showed a substantial death rate of more than 50%. Bioactivity was likewise decreased or eliminated when esters were used to replace the -CN group on the pyrazole ring (moiety B) (a–e).



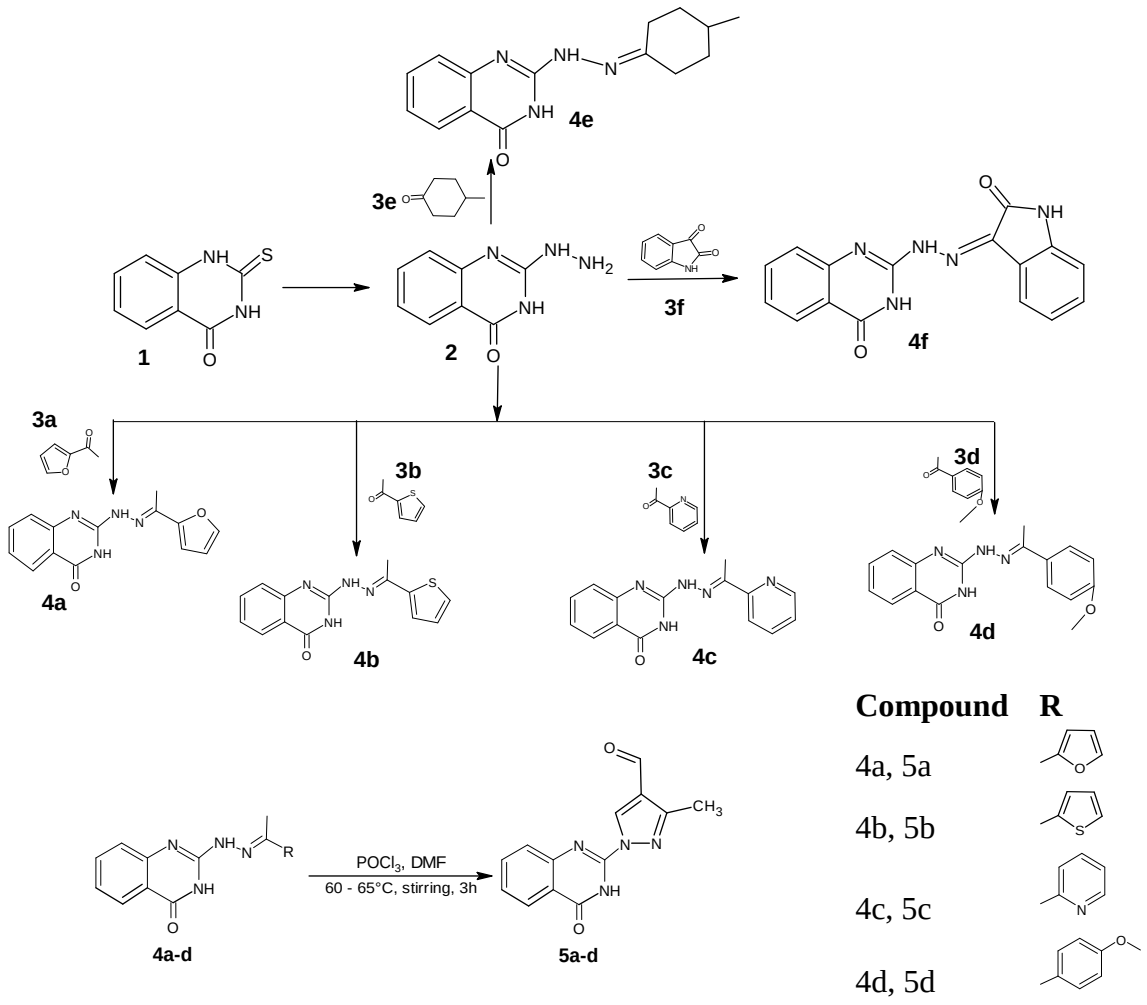
Compound	X	R5
9a	O	Me
9b	O	Et
9c	NH	$-CH_2CF_3$
9d	NH	2,4-dimethylphenyl
9e	NH	2-chloro-5-methylthiazole
9f	NH	2-chloro-5-methylpyridine

Compound	R6
11a	2-methylthiophene
11b	2,6-difluorophenyl

Scheme 15: Synthesis of compounds 9a-9f, 10, 11a & b

The insecticidal efficacy of 9a−9f, 10, and 11a−b, as well as the standard drugs (fipronil and indoxacarb), was evaluated for *P. xylostella*. Overall, the majority of the compounds showed a

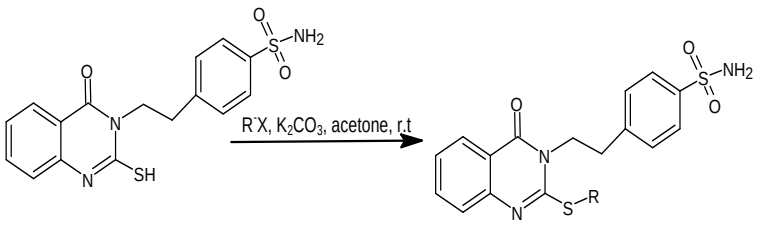
significant (>50% mortality) to very good (100% mortality) insects killing effect. The nine compounds resulted in a mortality rate greater than 50% at a concentration of 25 mg/L. The LC50 values for derivates mentioned (9a, 9d, 9e and 10) were determined for *P. xylostella.* The side chain at 5-position, of the quinazoline (moiety C) did not significantly affect the insect killing potency 9−11, that displayed comparable strong biological activity. Among these compounds, 9d and 9e demonstrated the highest levels of bioactivity (LC50 = 9.42 and 10.95 mg/l). The LC50 for the remaining (9a, 9d, 9e, and 10) counter to *P. xylostella*. [51]

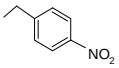


Scheme 16: Synthesis of new derivatives relating 4-formyl-pyrazoles **(5a-d)** (antimicrobial activity)

A sequence of novels featuring quinazolin-4(3H)-one derivatives (4a–f and 5a–d) was developed to explore their effectiveness as microbicides. Initial compound 2-Hydrazino-4(3H)-quinazolinone (2), remained produced then reacted by different C=O groups to produce hydrazone (4a–f). Additionally, the hydrazone compounds 4a–d was subjected to treatment of dimethylformamide and POCl3, resulting in formation of the formyl-pyrazole by-products 5a–d. All synthesized derivates were examined for their microbicidal effects against bacterial and fungal strains. The most of confirmed substance exhibited notable antimicrobials action in comparison to standard antibiotics. Compound 5a displayed the greatest effectiveness, with

minimum inhibitory concentration values ranging between 1 to 16 µg/ml. Moreover, the compounds that displayed the highest efficacy in contradiction of *E. coli* were estimated for their capacity. Derivatives 4a, 5a, 5c and 5d showed the furthermost pronounced inhibitory effects. [52]

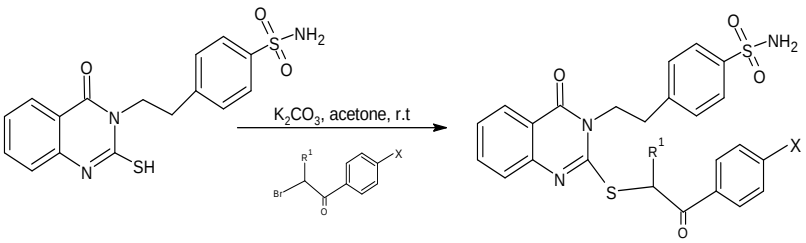


Compound	R
1	-CH_3
2	-C_2H_5
3	
4	
5	
6	
7	
8	

Scheme 17: Synthesis pathway of 1-9 derivatives

A study assessed a one dosage of 10 µm using comprehensive NCI 59-cell line panel evaluate for a range of 2-(R)-mercaptoquinazoline derivatives 1-8. The cell death properties observed in the verified cell lines were significantly more pronounced in composites that included a 2-thiol group, particularly those featuring a 2-ethylmercapto fragment. (2). To examine the mechanisms underlying the antineoplastic properties of compounds, the repressive effects of the greatest effective mediators, particularly 2 and 3, were examined on EGFR, HER2, and CDK9 kinases, along with the Cyclooxygenase 2 enzyme.

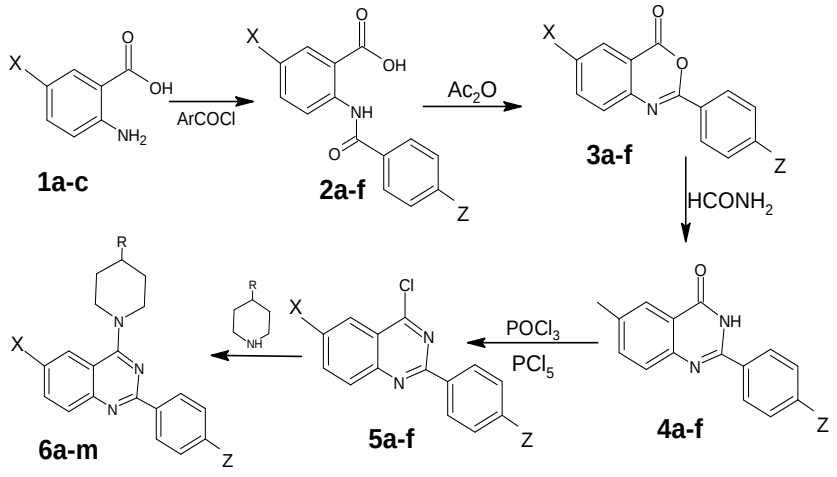
Derivatives 3 and 8, featuring 2-benzylmercapto sections, showed efficacy as inhibitors. Additionally, compound 3, which includes a 2-benzylmercapto segment, displayed a level of potency comparable to that of the established CDK9 kinase inhibitor dinaciclib, whereas compound 2, incorporating a 2-ethylmercapto portion, remained known as maximum effective cyclooxygenase-2 inhibitor when compared to standard medicine celecoxib. This research presented that analysis of cell cycle for derivative 8 led to a reduction in cell growing through G2/M phase, resulting in pre-G1 programmed cell death in the MCF-7 cell-line. Molecular docking analyses of byproducts 2 and 3 offered valuable information on how these compounds interact with receptors. The findings from this research will beneficial for upcoming endeavors in lead optimization, aiding researchers to plan and justify the development of new, more effective inhibitors.



Compound	X	R^1
1	-H	-Hydrogen
2	-Br	-Hydrogen
3	-Cl	-Hydrogen
4	-F	-Hydrogen
5	-CH3	-Hydrogen
6	-H	-Methyl group

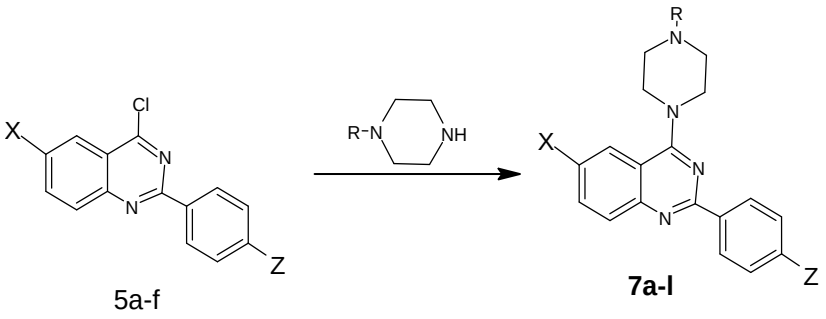
Scheme 18: Synthetic pathway for 1 to 6

The present investigation reveals results from one a concentration of 10 μm assessed via a comprehensive NCI 59-cell line panel for various derivatives. of 2-(substitute mercapto)-quinazoline, designated as 1 – 6. The antitumor effects seen in evaluated cell lines, particularly significant for compounds featuring a 2-thiol group (1). Conversely, the inclusion of 2-phenacylmercapto groups (1 – 6) seemed to diminish both potency and cytotoxicity, with the exception of compound 6. The study aimed to uncover the mode of action behind the antineoplastic properties of these derivatives via evaluation of blocking response of the more effective chemicals, especially product 1, on EGFR, HER2 and CDK9 kinases, as well as the cyclooxygenase-2 enzyme. Compound 1, which contains the phenacylmercapto fragment, exhibited significant inhibition of ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2) when compared with reference medications gefitinib and erlotinib. Molecular docking studies of the derivatives offered understanding of the interactions between this group of compounds and the binding sites of EGFR and CDK9 kinases, as well as the COX-2 enzyme. The knowledge obtained from this investigation will be beneficial for upcoming lead optimization efforts, assisting researchers in the development and strategic design of improved inhibitors. [53]



Compounds	Z	X	R
6(a)	H	H	Me
6(b)	H	H	Ph
6(c)	H	Br	Me
6(d)	H	Br	Ph
6(e)	H	I	Me
6(f)	H	I	Ph
6(g)	Cl	H	Me
6(h)	Cl	H	Ph
6(i)	Cl	Br	Me

Scheme 19: Compound synthesis quinazoline (analgesic and anti-inflammatory)



Compounds	Z	X	R
7a	H	H	Methyl
7b	H	H	Phenyl
7c	H	Br	Methyl
7d	H	Br	Phenyl
7e	H	I	Methyl
7f	H	I	Phenyl
7g	Cl	H	Methyl
7h	Cl	H	Phenyl
7i	Cl	Br	Methyl

Scheme 20: Compound synthesis quinazoline (analgesic and anti-inflammatory)

Scheme 19 and 20: The pathway of quinazoline derivatives 6a-m and 7a-l was carried out following Schemes 19 and 20. In brief, suitable acid chloride was combined by the chosen derivative of anthranilic acid in dichloromethane, using triethylamine as a catalyst, which led to the generation of compounds 2a-f. The synthesis of benzoazone derivatives 3a-f was achieved by heating compounds 2a-f with acetic anhydride. Characterization of compounds 3a through 3f was performed using methods of analysis and spectroscopy. Both the I.R and 1H-NMR analyses showed the lack of -NH and -OH functional moieties. Following this, benzoxazone analogues 3a-f were heated via formamide, resulting in formation of the equivalent 3H-quinazolin-4-one product 4a-f.

The halozination process for these by-products was carried out via combining phosphorus oxychloride with phosphorus pentachloride for fusion, resulting in formation of para-chloro derivates 5a-f. Then I.R Spectral for derivatives 5a-f showed lack of amino group (NH) and cyclic ketone group from the original compounds, and no -NH signals were detected in the 1H-Nuclear Magnetic Resonance spectral. The relevant piperidine or piperazine derivatives treated via p-chloro compound in acetone, using potassium carbonate (anhydrous), which resulted in formation of the desired 4-substituted derivation 6a-m and 7a-l. These structures were confirmed through spectral analysis. Generally, unique methyl group protons associated with piperidine and piperazine frameworks, along with their respective carbons, were detected in 1H-NMR and 13-C spectra. Derivatives 6b, 6f, 6j, and 7b showed higher activity compared by standard drug.

The analgesic activity of derivate 6b was atleast 1.5 times greater than indomethacin. Derivative 6m demonstrated a potency similar to that of the reference drug. In general, compounds containing piperidine were usually more effective than those including piperazine. Among the piperidine derivatives, compounds without halogens typically demonstrated greater activity compared to those with halogens. Compounds 6a, 6b, and 6m showed notably higher activity than 6i-l, while 7a and 7b exhibited considerable analgesic properties, and the compounds 7c-l did not exhibit any analgesic effects. The inclusion of a halogen at the 6-position of the quinazoline structure exhibited an effect on activity similar to that phenyl ring attached at 2-position. [54]

3. Conclusion

In summary, quinazoline derivatives have emerged as a crucial category of compounds in medicinal chemistry, showcasing a broad variety of pharmacological functions with significant therapeutic promise. The flexibility of quinazoline structures has facilitated the creation of various effective agents, especially in anticancer, antimicrobial, anti-inflammatory, and analgesic treatments. Utilizing a wide range of synthetic techniques, from conventional methods to contemporary innovations such as microwave-assisted and metal-catalyzed reactions, researchers have successfully modified the quinazoline framework, resulting in improved bioactivity and selectivity.

An in-depth investigation of these compounds underscores their vital contribution not only to drug discovery but also to elucidating biological processes at the molecular level. As scientific advancements progress, further exploration of structure-activity relationships and targeted drug development will certainly reveal new therapeutic possibilities.
This review emphasizes the necessity of combining natural and synthetic strategies to enhance quinazoline derivatives, ensuring they align with the growing requirements of modern medicine. Future inquiries should aim at addressing pharmacokinetic hurdles, improving drug effectiveness, and reducing adverse effects. By promoting interdisciplinary collaboration, the full capabilities of quinazoline-based therapies can be achieved, making substantial contributions to global health and well-being.

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