chemengineering

MDPI

Review

Medicinal Chemistry of Quinazolines as Analgesic and Anti-Inflammatory Agents

Mohamed F. Zayed [1,2]

[1] Pharmaceutical Sciences Department, Fakeeh College for Medical Sciences, Jeddah 21461, Saudi Arabia; mfzayed@fcms.edu.sa; Tel.: +966-59-803-5201
[2] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo 11884, Egypt

Abstract: Quinazoline is an essential scaffold, known to be linked with various biological activities. Some of the prominent biological activities of this system are analgesic, anti-inflammatory, anti-hypertensive, anti-bacterial, anti-diabetic, anti-malarial, sedative–hypnotic, anti-histaminic, anti-cancer, anti-convulsant, anti-tubercular, and anti-viral activities. This diversity in the pharmacological response of the quinazoline system has encouraged medicinal chemists to study and discover this system and its multitude of potential against several biological activities. Many of these studies have successfully investigated the structure–activity relationship to explore the specific structural features of their biological targets. The developing understanding of quinazoline derivatives and their biological targets presents opportunities for the discovery of novel therapeutics. This review represents different aspects of medicinal chemistry, including drug design, structure–activity relationship, and the mode of action of some analgesic and anti-inflammatory quinazoline compounds. It pays comprehensive attention to the analgesic and anti-inflammatory activities of quinazolines from the viewpoint of drug discovery and its development.

Keywords: quinazoline; development; discovery; design; synthesis; structure–activity relationship

Citation: Zayed, M.F. Medicinal Chemistry of Quinazolines as Analgesic and Anti-Inflammatory Agents. *ChemEngineering* **2022**, *6*, 94. https://doi.org/10.3390/chemengineering6060094

Academic Editor: Dmitry Yu. Murzin

Received: 4 October 2022
Accepted: 15 November 2022
Published: 2 December 2022

1. Introduction

Quinazoline is a double-ring heterocyclic system with two nitrogen heteroatoms in the six-membered aromatic ring fused to the benzene ring [1–4]. Quinazoline is formed from the pyrimidine ring fused to the benzene ring at two adjacent carbon atoms (Figure 1). It is classified as phenyl pyrimidine [5–7]. The first quinazoline derivative was synthesized by Griess et al. in 1869 through a condensation reaction [8]. It was also prepared from 2-carboxylate derivatives by a decarboxylation reaction [9–12]. Several quinazoline derivatives were synthesized and studied for their physical and chemical properties in 1903 by Gabriel and Colman [8]. The quinazoline system may contain an oxo group (=O) at C-2 to form the carbonyl group (C=O), named quinazoline-2(1H)-one (2-quinazolinone) 1 (Figure 1), or at C-4 and named quinazoline-4(3H)-one (4-quinazolinone) 2 (Figure 1). Otherwise, it may contain two oxo groups at C-2 and C-4 to form quinazoline-2,4-dione 3 (quinazolinedione) (Figure 1) [13–16]. Quinazolines are a group of versatile derivatives with a wide range of pharmacological activities [17–20]. They are used as analgesic, anti-hypertensive, anti-inflammatory, anti-bacterial, anti-diabetic, sedative–hypnotic, anti-histaminic, anti-cancer, anti-convulsant, anti-tubercular, and anti-viral agents, as well as having many other uses [21–25]. The aim of this review was to collect the literature reported by researchers on quinazoline derivatives, their pharmacological activities, and their structure–activity relationship as analgesic anti-inflammatory therapeutic agents.

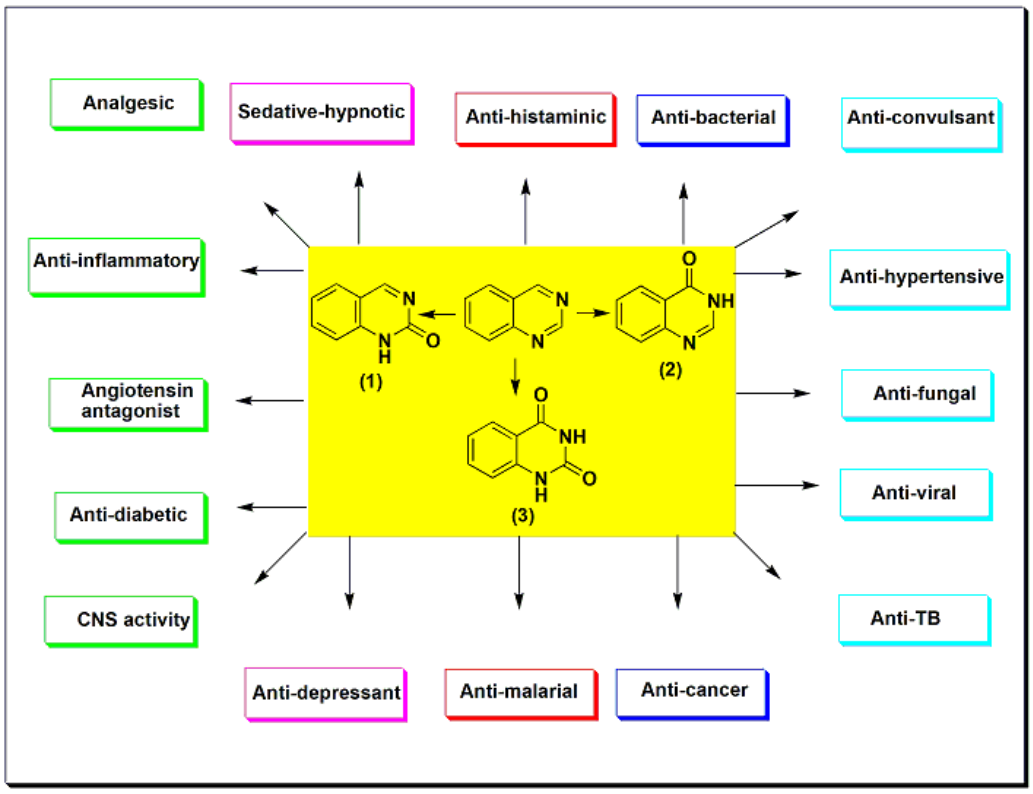


Figure 1. The quinazolines and some of their pharmacological activities.

2. Physicochemical Characters of Quinazolines

Figure 2 shows the molecular structures of quinazoline, 4-quinazolinone, 2-quinazolinone, and 2,4-quinazolinedione, represented by ball-and-line mode [26]. Table 1 shows the physicochemical characters of quinazoline, 2-quinazolinone, 4-quinazolinone, and 2,4-quinazolinedione [27]. Figures 3 and 4 show the lipophilic and the electrostatic potentials of these quinazolines [26].

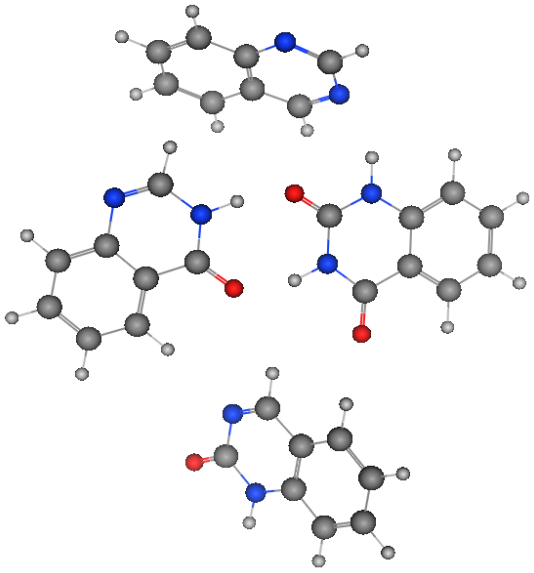


Figure 2. Molecular structure of quinazoline, 2-quinazolinone, 4-quinazolinone, and 2,4-quinazolinedione, represented by ball-and-line mode.

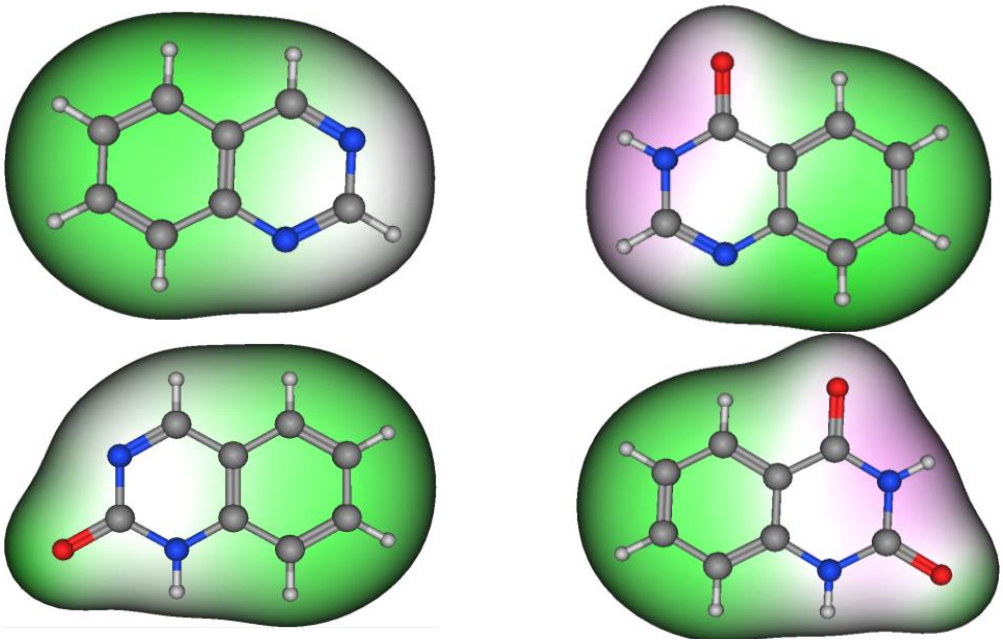


Figure 3. Lipophilic potential of quinazoline, 4-quinazolinone, 2-quinazolinone, and 2,4-quinazolinedione. Green color represents lipophilic area, white color represents neutral area, and pink color represents hydrophilic area.

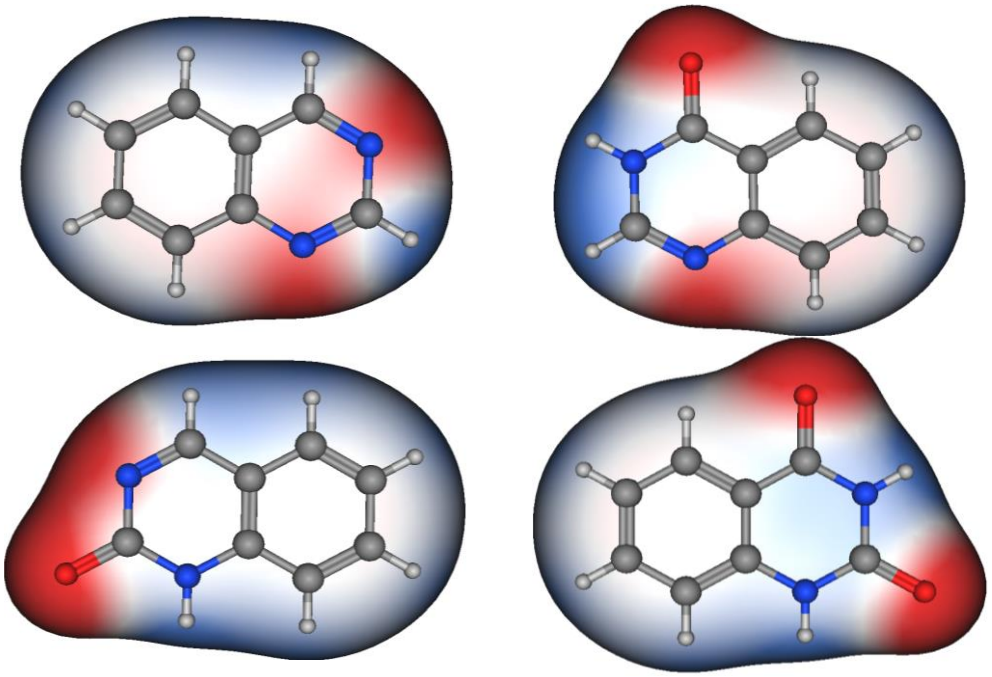


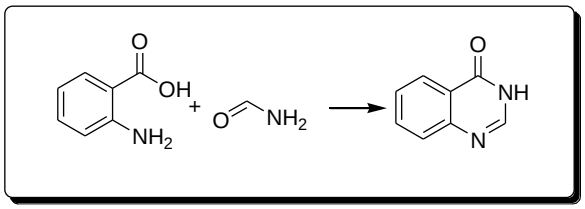
Figure 4. Electrostatic potential of quinazoline, 4-quinazolinone, 2-quinazolinone, and 2,4-quinazoline dione. Red color represents high polarity, white color represents neutral polarity, and blue color represents mild polarity.

Table 1. The physicochemical characters of quinazoline, 2-quinazolinone, 4-quinazolinone, and 2,4-quinazolinedione.

Character	2-Quinazolinone	4-Quinazolinone	2,4-Quinazolinedione
Molecular formula	$C_8H_6N_2$	$C_8H_6N_2O$	$C_8H_6N_2O_2$
Molecular weight	130.15 g/mol	146.15 g/mol	162.15 g/mol
Number of heavy atoms	10	11	12
Number of aromatic heavy atoms	10	10	10
Fraction Csp3	0	0	0
Number of rotatable bonds	0	0	0
Number of H-bond acceptors	2	2	2
Number of H-bond donors	0	1	2
Molar refractivity	39.54	42.36	45.19
Tropological polar surface area	25.78 A2	45.75 A2	65.72
Lipophilicity	1.46	1.14	1.04
Water solubility	Soluble	Soluble	Soluble
GI absorption	High	High	High
BBB permeation	Yes	Yes	No
Bioavailability score	0.55	0.55	0.55
Lipinski	Yes	Yes	Yes
Synthetic accessibility	Very easy	Very easy	Very easy

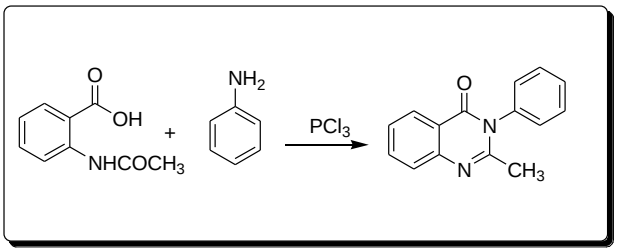
3. Methods of Preparation of Quinazolines

1. The Niemetowski method (Scheme 1) is based on the reaction of anthranilic acid and formamide under high temperature to yield 4-(3H)-quinazolinone [25,28].



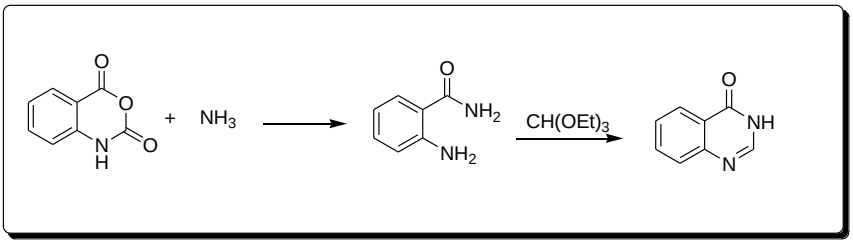
Scheme 1. Synthesis of 4-quinazolinone by Niemetowski method.

2. Morgan's method for the synthesis of quinazoline (Scheme 2) uses the reaction between 2-acetamidobenzoic acid and an amine in the presence of phosphorous trichloride to yield 2-methyl-3-phenylquinazolin-4(3H)-one [25,28]



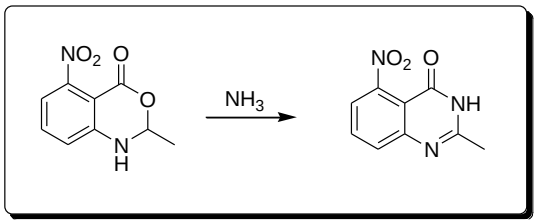
Scheme 2. Synthesis of 4-quinazolineone by Morgan's method.

3. The reaction between isatoic anhydride and an amine, followed by refluxing with ethyl orthoformate (Scheme 3) produces 4-(3H)-quinazolinone [25,29].



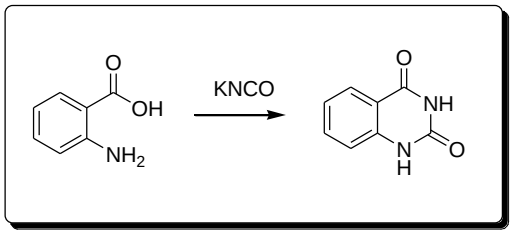
Scheme 3. Synthesis of 4-quinazolinone.

4. The reaction of amines 2-methyl-4-nitro-bezoxazine-4-one derivatives produces 2-methyl-4-nitro-quinazolin-4-one derivatives (Scheme 4) [28].



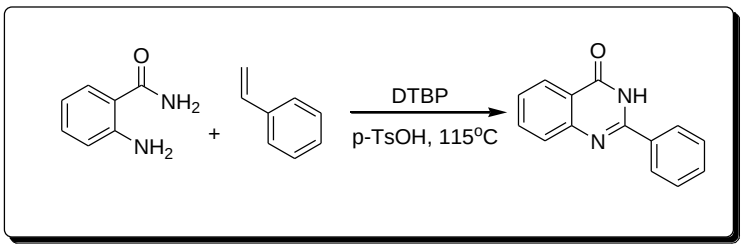
Scheme 4. Synthesis of 4-quinazolinone by amination reaction.

5. Anthranilic acid and potassium cyanate react together (Scheme 5) to produce 2,4-quinazolinedione derivatives [29,30].



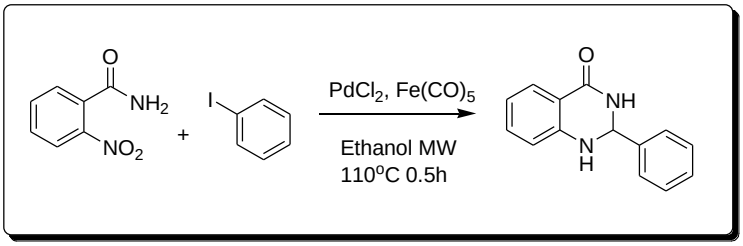
Scheme 5. Synthesis of 2,4-quinazolindione.

6. The reaction of 2-aminobenzamide and styrene in the presence of Di-tertiary-butyl peroxide (DTBP) and P-toluene sulfonic acid (p-TsOH) produces 2-phenylquinazoline-4(3H)-one derivatives (Scheme 6) [29,30].



Scheme 6. Synthesis of 4-quinazolinone.

7. Transition metals are catalyzed by the synthesis of quinazoline (Scheme 7) [30]. This method is based on the catalytic reduction in the nitro benzamide derivative using palladium chloride ($PdCl_2$) and iron pentacarbonyl $Fe(CO)_5$.



Scheme 7. Synthesis of 4-quinazolinone by transition-metal-catalyzed method.

4. Analgesic Activity

Many quinazolines have been synthesized and evaluated for their analgesic and anti-inflammatory activities [31–38]. 2-Phenyl quinazolinone **4** (Figure 5) was synthesized by Alagarsamy et al. in 2002 [39]. It was biologically evaluated as an analgesic agent. The

structure–activity relationship study explained that the highest activity was obtained by the compound with diethyl substitution, while aromatic and alicyclic amine substitution decreased analgesic activity. This activity was 58 ± 0.45% at 2 h and at 20 mg/kg compared to that of standard diclofenac sodium, which is 53 ± 0.35% at 2 h at 20 mg/kg. The modification of compound **4** to thiourea-substituted 2-methyl quinazolinone derivatives **5** produced more active compounds. The most active one was the compound which had the pyrrolidine ring at C-3 (Figure 5) [40]. The activity of this compound was 65 ± 0.79% at 2 h at 20 mg/kg. The activity of standard diclofenac during this experiment was 60 ± 0.54% at 1 h at 20 mg/kg. Further modification to thiourea-substituted 2-methylthio quinazolinone **6** yielded higher activity, i.e., 67 ± 1.18% at 2 h at 20 mg/kg [41]. Increasing lipophilicity at C-2 by placing the butyl group instead of the methyl group yielded a more active compound **7** with 73 ± 1.49% analgesic activity at 2 h at 20 mg/kg. Standard diclofenac produced 62 ± 1.49% analgesic activity at 2 h at 20 mg/kg. Placing the benzylamino group at C-2 produced active compound **8** with 55 ± 0.36% analgesic activity at 2 h at 20 mg/kg [42]. This activity was the same as standard diclofenac. Methylamino substituted 2-phenylquinazolinones **9** were synthesized and evaluated for analgesic activity [43]. They yielded 43 ± 0.51 to 61 ± 1.08% analgesic activity at 2 h at 20 mg/kg.

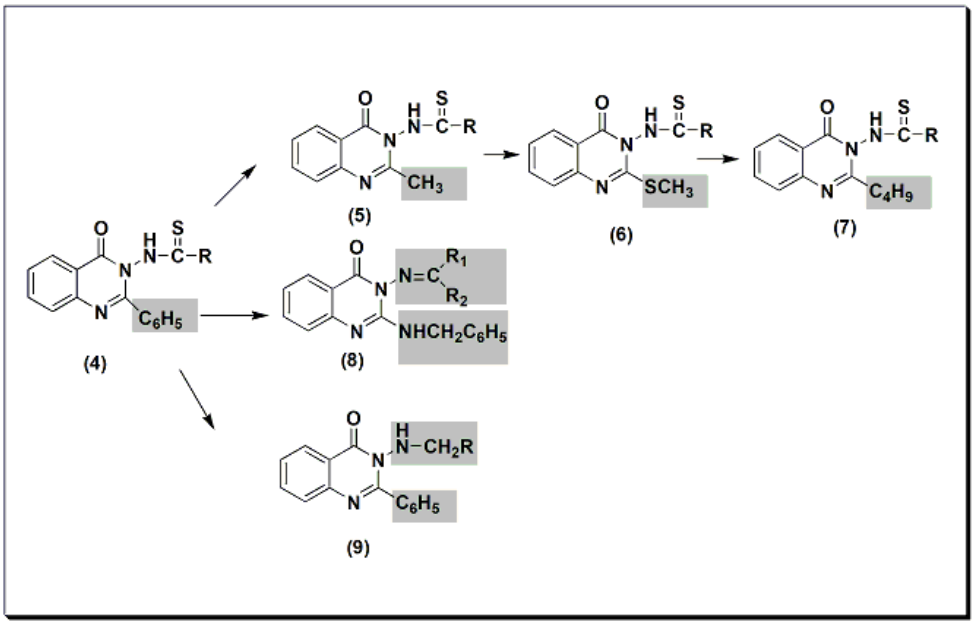


Figure 5. The analgesic quinazolines **4**, **5**, **6**, **7**, **8**, and **9**.

A series of 2-amino-substituted 3-(4-methoxy phenyl) quinazolinones **10** (Figure 6) was tested for analgesic activity. It produced 64 ± 1.19% analgesic activity at 2 h at 20 mg/kg for the compound with methylpropylidene, while the compound with ethylpropylidene yielded higher activity, i.e., 73 ± 1.94% analgesic activity at 2 h at 20 mg/kg [44]. Placing cycloalkyl chain at C-2 decreased the activity (55 ± 1.38 to 57 ± 1.36% analgesic activity at 2 h at 20 mg/kg). The electron-withdrawing group at the N-3 aryl group decreased the activity (44 ± 1.15 to 54 ± 1.25% analgesic activity at 2 h at 20 mg/kg) compared to standard diclofenac (62 ± 1.49% at 2 h at 20 mg/kg). Another series **11** of amino-substituted 3-phenylquinazolinone was synthesized by replacing the 4-substituted aryl group in **10** by the phenyl ring, resulting in less analgesic activity [45]. The cyclization reaction of C-2 and N-3 produced (1,3,4)-thiadiazol quinazolinones **12** (Figure 6) [46,47]. The cyclic derivative bearing alkyl moiety showed more analgesic activity than the cyclic derivative with aryl moiety. The analgesic activity of the cyclic derivative was less than the open derivative (39 ± 1.32 to 48 ± 1.40% analgesic activity at 2 h at 20 mg/kg).

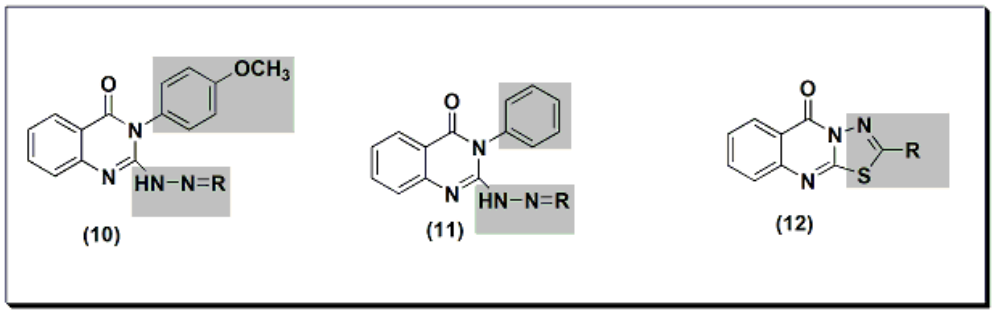


Figure 6. The analgesic quinazolines **10**, **11**, and **12**.

Other derivatives of 2-chloroacetonyl-3-substituted quinazolinones 13 (Figure 7) were synthesized and evaluated for their analgesic activity by Kumar et al. [48]. They displayed mild-to-moderate analgesic activity. The first series 13 yielded moderate activity, hydrazino derivative 14 of this series yielded poor activity, while pyrazoline derivatives 15 yielded good activity with cyclooxygenase inhibitory activity [48].

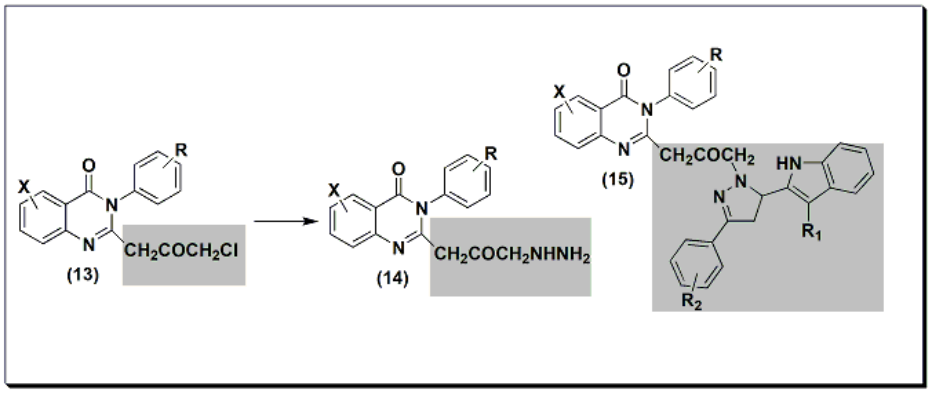


Figure 7. The analgesic quinazolines 13, 14, and 15.

A series of pyrazole-substituted quinazolinones 16 (Figure 8) was synthesized [49]. The 2-phenyl derivative of this series yielded 65% inhibition, the 2-ethyl derivative yielded 44% inhibition, and the 2-methyl derivative yielded 48%, compared to standard phenylbutazone (25% inhibition) and acetyl salicylic acid (20% inhibition). Further modification of these derivatives to improve their pharmacokinetic characteristics produced other derivatives of pyrazole-substituted quinazolinones 17 [50]. These derivatives were examined for their analgesic activity. The structure activity relationship (SAR) study showed that 8-methyl, 6-Cl, and 7-Cl did not increase analgesic activity. However, the 6-chloro-2-phenylquinazoline derivative displayed 43% inhibition in acetic acid peritonitis, compared to standard phenylbutazone (11% inhibition) and indomethacin (66% inhibition) at a 10 mg/kg dose. The high dose 300 mg/kg of compound 17 displayed a less harmful effect (ulcer index 60) than standard phenylbutazone (ulcer index 75) and indomethacin (ulcer index 300).

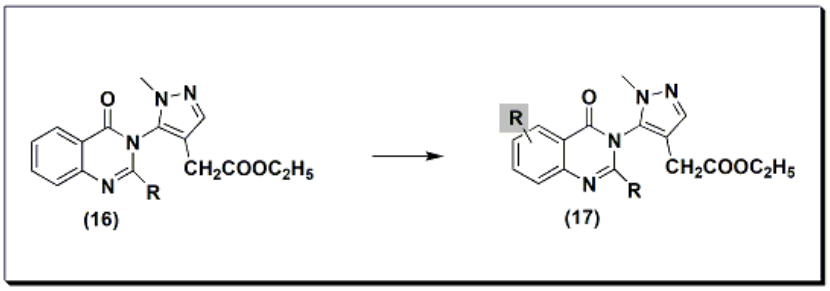


Figure 8. The analgesic quinazolines 16 and 17.

Several bicyclic heteroaromatic systems (Figure 9) were synthesized and tested for the in vitro inhibition of the capsaicin activation of novel transient receptor potential vanilloid 1 (TRPV1) [51]. The order of activity of these different systems is as follows: 5-isoquinoline < 8-quinoline = 8-quinazoline < 8-isoquinoline ≥ cinnoline ≈ Phthalazine ≈ quinoxaline ≈ 5-quinoline. The study showed that two substituted quinazoline derivatives, 18 and 19 (Figure 9), substantially lowered pain and had good activity in animal models of visceral and inflammatory pain. One of these two derivatives containing 4-trifluromethyl substitution 18 showed good analgesic activity (IC_{50} = 42 nM). Meanwhile, another one, containing 4-bromo substitution 19, showed analgesic activity with 170 nM.

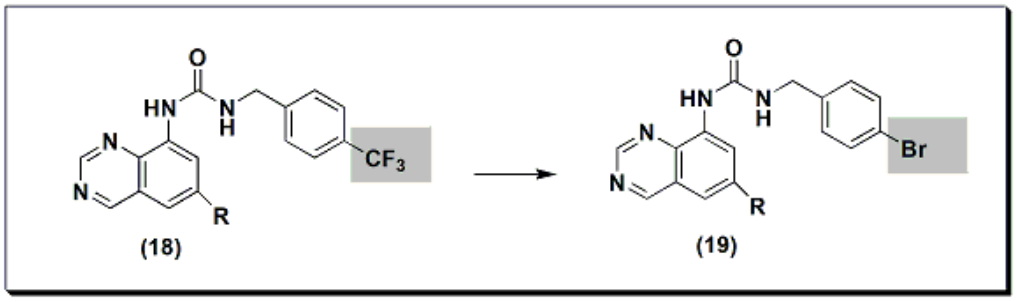


Figure 9. The analgesic quinazolines 18 and 19.

Hybrid derivatives of isatin-substituted quinazolinones (Figure 10) were examined for their analgesic activity [52]. Out of these derivatives, 7-methyl isatin joined with 2-phenylquinazolinone 20 was the most active one. The introduction of 2-aminophenyl at N-1 of quinazolinone 20 did not increase the activity [53].

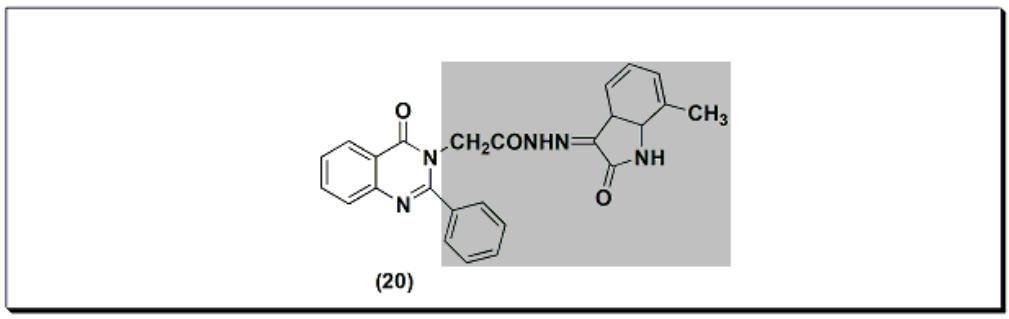


Figure 10. The analgesic quinazoline 20.

In 2019, Sakr et al. [54] prepared some novel quinazoline benzamide derivatives (Figure 11). These derivatives were evaluated for their analgesic, anti-inflammatory, and anti-COX-1/2 activities. The analgesic activity of the new derivatives was assessed by the acetic-acid-generated writhing test using the reference drugs indomethacin, diclofenac sodium, and celecoxib as positive controls. Out of these derivatives, two compounds showed potent analgesic activity. This activity was 4–21-fold more potent than the references, namely indomethacin and diclofenac sodium. SAR studies showed that compounds with a substitution on two phenyl rings, 21 and 22, produced higher activity than the unsubstituted derivatives. This may be due to an increase in lipophilic characters.

In 2021, Saravanan et al. [55] synthesized a novel series of hybrid quinazoline derivatives of isoxazole moiety, joined with substituted quinazolinone 23 (Figure 12). These derivatives were evaluated for their analgesic and anti-inflammatory activities. Analgesic activity was tested via the tail-flick technique using diclofenac sodium as a reference. Additionally, they were examined for their antimicrobial and ulcerogenic activities. They displayed mild-to-strong analgesic activity and low-to-moderate ulcerogenic activity. An SAR study showed that the compounds with a substitution at 4-position of the attached phenyl ring produced higher analgesic activity than the compounds containing substitution

at 3-posiyion of the attached phenyl ring. The electron-withdrawing groups yielded higher activity than the electron-donating groups. The trifluoro methyl derivative 23 showed the highest activity among these derivatives.

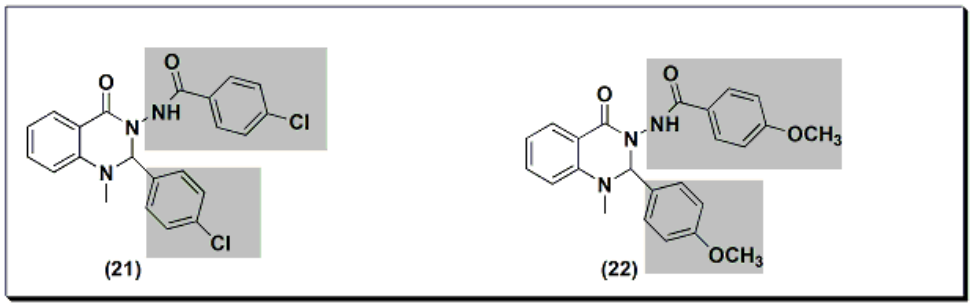


Figure 11. The analgesic quinazolines 21 and 22.

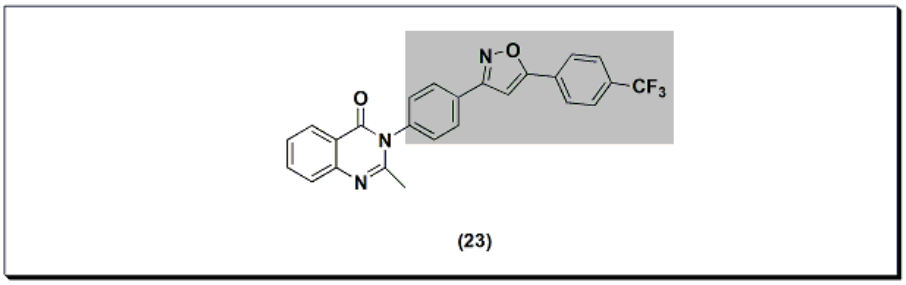


Figure 12. The analgesic quinazoline 23.

5. Anti-Inflammatory Activity

The previously discussed compounds (4–23) were evaluated for their anti-inflammatory activity. All these derivatives showed anti-inflammatory activity except the compound 20. It showed low anti-inflammatory activity when it was unsubstituted, while substitution with Cl at C-6 and CH_3 at C-8 showed good activity.

Two new derivatives of quinazolines, 25 and 26 (Figure 13), were designed, synthesized, and evaluated for their anti-inflammatory activity [56]. These derivatives were substituted isoquino-quinazolinone 25 and substituted quinazolino-quinazolinone 26. They were compared to the potent substituted 2-phenyl-quinazoline compound 24, but both were less active than compound 24.

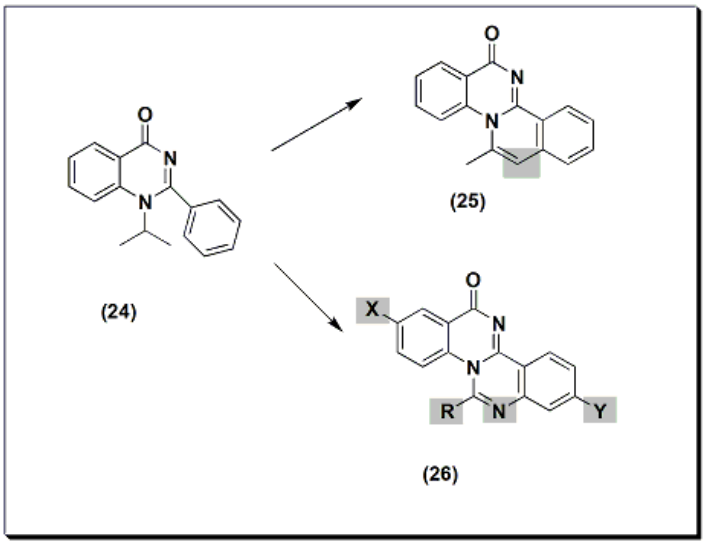


Figure 13. The anti-inflammatory quinazolines 24, 25, and 26.

Other derivatives of compound 27 (Figure 14) were tested for their anti-inflammatory activity at 8 mg/kg using standard piroxicam at 4 mg/kg [57]. An SAR study showed that unsubstituted, 4-methyl, and 3-nitro derivatives of compound 27 yielded better activity than standard piroxicam. Using a 4 mg/kg dose yielded lower activity than piroxicam or diclofenac for the three derivatives. A structural modification was conducted by the introduction of the nicotinyl thiadiazole group at C-3 of 28 to improve the anti-inflammatory activity [58]. Nicotinyl-5-pyridyl thiadiazole of substituted 2-phenylquinazolinone yielded the highest activity, equivalent to standard ibuprofen. Substituted quino-quinazolinedione derivatives 29 and 30 showed an activity range of 12.7–58.2%. SAR studies showed that 10-iodosubstitution resulted in a significant increase in anti-inflammatory activity. Additionally, 4-phenylaminomethyl and 6-methoxyphenylaminomethyl substitution enhanced anti-inflammatory activity [59].

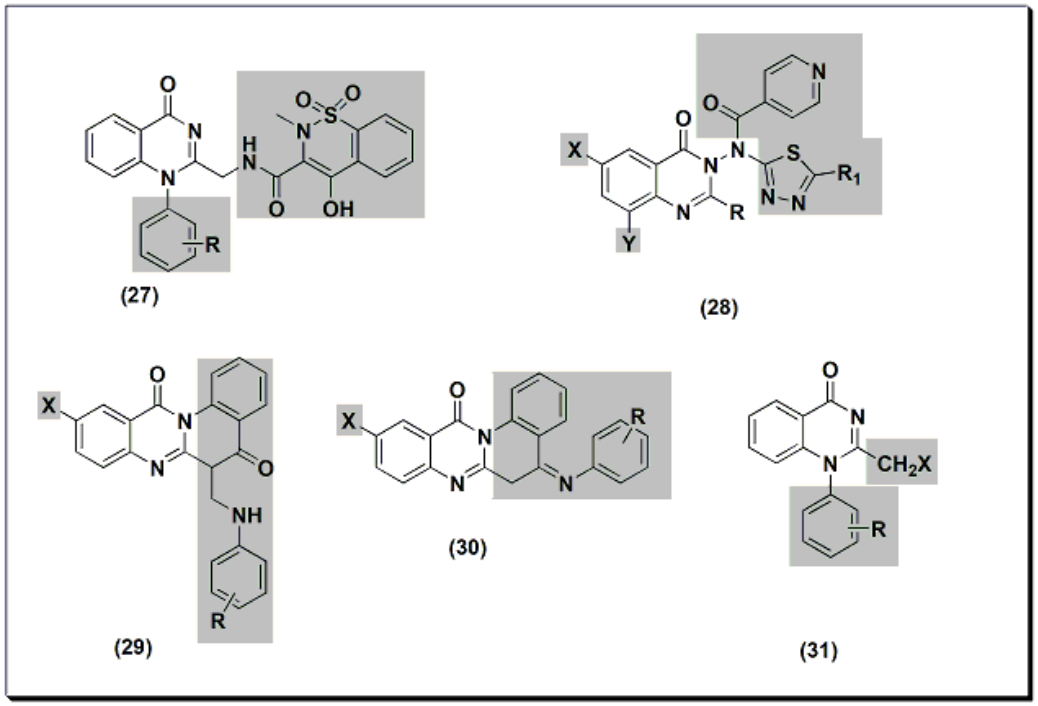


Figure 14. The anti-inflammatory quinazolines 27, 28, 29, 30, and 31.

A series of 1-phenyl quinazolinone derivative 31 was synthesized to be evaluated as anti-inflammatory agents. Among these derivatives, 2-piperidenomethyl was the most active compound followed by 2-methlyl and then the 2-dimethylaminomethyl derivative. The 2-chloromethyl substituents showed least activity [60].

2,3,6-trisubstituted quinazolinone derivatives 32–36 (Figure 15) were designed, synthesized, and tested as anti-inflammatory agents [61]. These derivatives showed a variable activity range of 10.28–53.33%. Compounds with o-methoxyphenyl substituents at C-3 and p-dimethylaminophenyl at C-2 showed activity higher than standard phenylbutazone. In addition, these derivatives were tested for their ulcerogenic activity. The highly active anti-inflammatory derivatives were less ulcerogenic compared to standard phenylbutazone.

Some novel derivatives of benzothiazole-substituted 2-phenyl quinazolinone derivatives 37, 38 (Figure 16) were tested for their anti-inflammatory activity using indomethacin as a reference drug [62]. All the derivatives showed less activity (21.3–77.5% protection) than indomethacin (80.9% protection). The brominated substituted derivatives 38 showed lower activity (21.3–27% protection) than the unsubstituted derivatives (30–77.5% protection). An SAR study explained that compounds with electron-withdrawing groups, such as 4-nitro and halogen, yielded less activity than those with electron-releasing groups, such as 4-alkyl and alkoxy. Moreover, when these derivatives were tested for their COX-I- and COX-II-inhibitory activity, they showed weak activity against COX-I, and strong activity against

COX-II. The activity was IC_{50} = 98–100 μM for COX-I and 0.39–1.87 μM for COX-II. While standard indomethacin showed 0.22 μM for COX-I and 2.64 for COX-II. Additionally, the active derivative showed a good GI safety profile at a 100 mg/kg/day oral dose without ulceration, compared to 100% ulceration which was the result from indomethacin at the same dose.

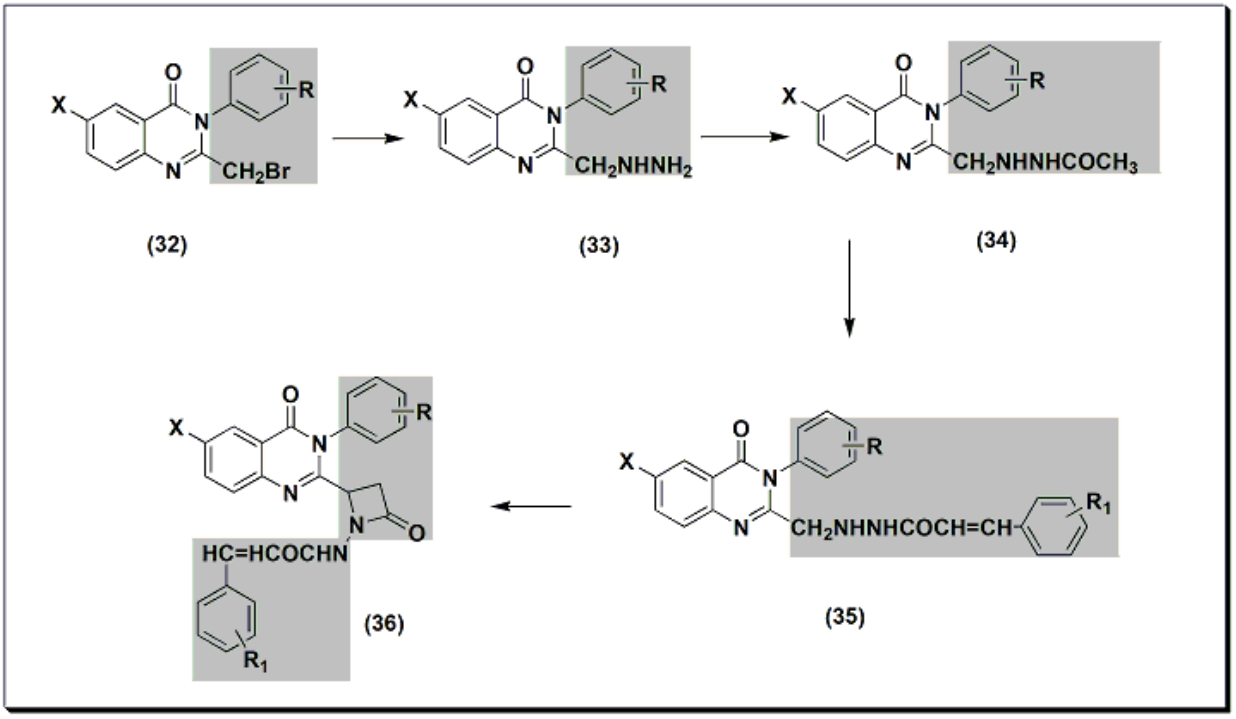


Figure 15. The anti-inflammatory quinazolines 32, 33, 34, 35, and 36.

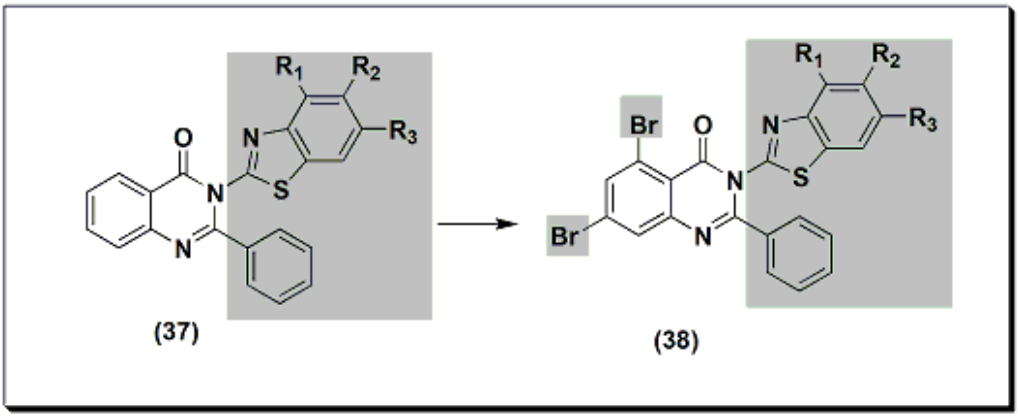


Figure 16. The anti-inflammatory quinazolines 37 and 38.

New derivatives of quinazolinones 39 (Figure 17) displayed significant activity at a 200 mg/kg dose, comparable to standard ibuprofen [63]. The most active derivatives were 4-nitrostyryl-substituted quinazolinone, and 4-hydroxystyryl-substituted quinazolinone. They showed an activity range of 62.2–80.7% reduction in the edema volume. The 3-naphtalene-substituted quinazolinone derivatives 40 (Figure 17) were tested for their anti-inflammatory activity at 50 mg/kg. They yielded 19.69–59.61% inhibition, with a good GI safety profile (30–70% ulcerogenic activity). Among these derivatives, 6-bromo-substituted-quinazolinone was the most potent derivative. The anti-inflammatory activity of standard phenylbutazone was 38.9% with 50% ulcerogenic activity [64].

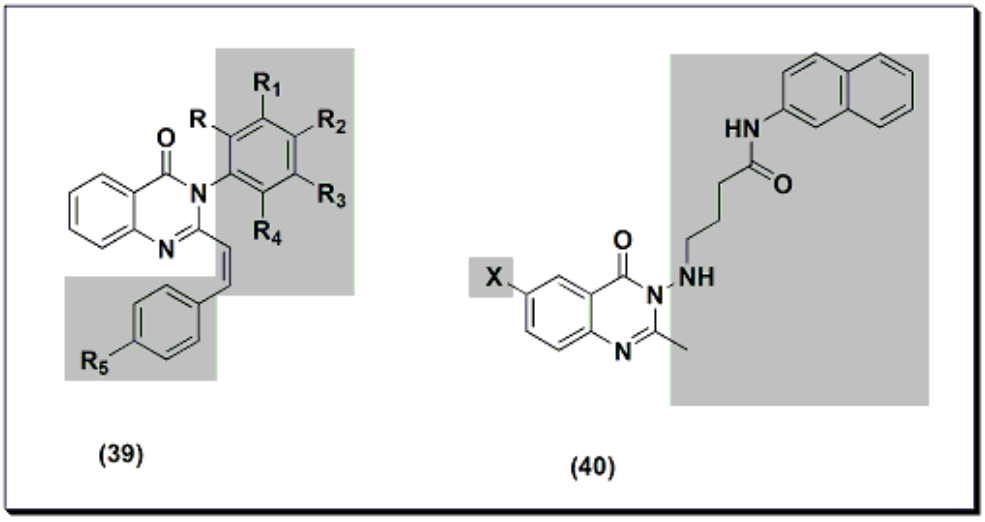


Figure 17. The anti-inflammatory quinazolines 39 and 40.

The placing of thiazolidindione and azetidinone at C-3 of quinazolinone produced novel derivatives 41–43 (Figure 18). These derivatives were evaluated for their anti-inflammatory activity [65]. They yielded comparable activity (16.3–36.3%) to standard phenylbutazone at a 50 mg/kg dose. The cyclization reaction of arylidene in compound 41 resulted in azetidinone derivative 42 and thiazolidinone derivative 43. The series thiazolidinone derivatives showed superior anti-inflammatory activity compared to the series of azetidinone derivatives.

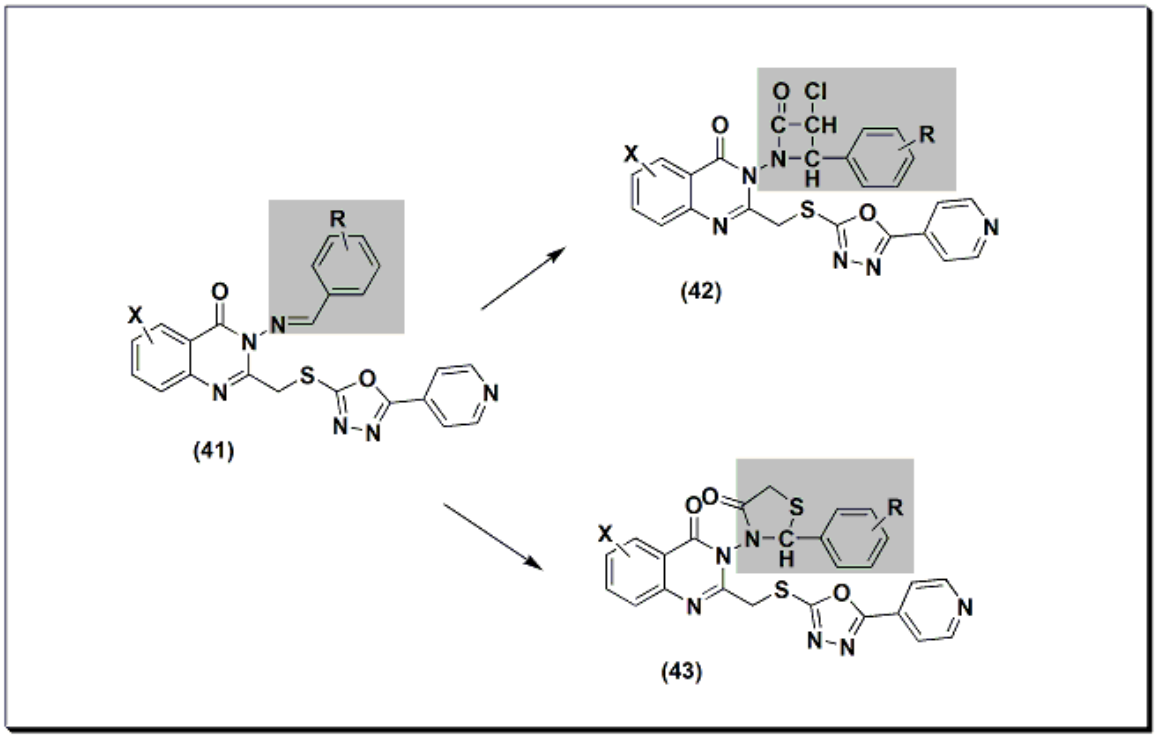


Figure 18. The anti-inflammatory quinazolines 41, 42, and 43.

The 5-chloro-2-substituted-triazoloquinazoline derivative 44 (Figure 19) was reported to be an anti-inflammatory agent, which had activity ranging from more potent to equipotent to the reference ketoprofen [66]. Another series of substituted triazolo-quinazoline derivatives 45 (Figure 19) were designed, synthesized, and evaluated for the anti-inflammatory activity

through the carrageenin-induced paw edema test. The results showed comparable activity to the reference indomethacin [66].

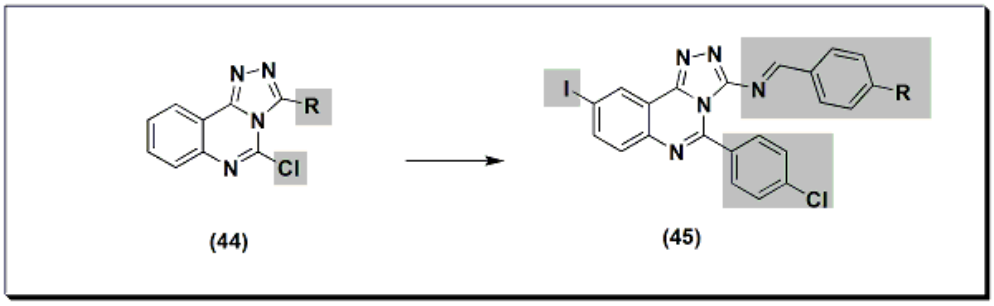


Figure 19. The anti-inflammatory quinazolines 44 and 45.

Other derivatives of the piperidinyl-substituted quinazolinone 46 (Figure 20) was evaluated as an anti-inflammatory agent for the treatment of inflammatory diseases, including rheumatoid arthritis, autoimmune diseases, and ulcerative colitis [66]. It showed potent anti-inflammatory activity. The reported 5-chloro-2-methylsulfonyl-triazoloquiazoline 47 (Figure 20) was reported to be a potent anti-inflammatory agent against different types of inflammatory mediators, such as nitric oxide (NO), tumor necrotic factor α (TNF-α), prostaglandin (PGE-2), and bacterial lipopolysaccharide (LPS)-stimulated macrophages.

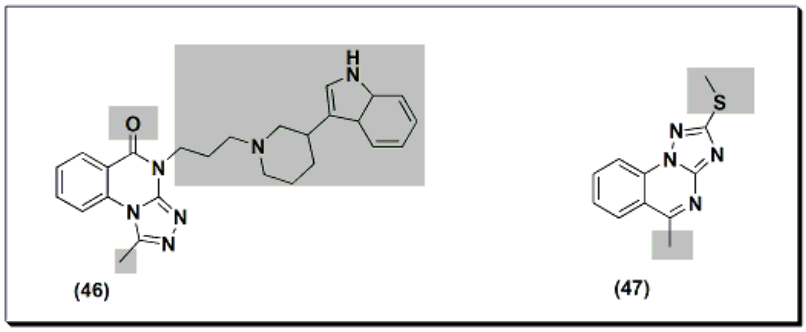


Figure 20. The anti-inflammatory quinazolines 46 and 47.

Leniolisib 49 (Figure 21) [67] is a quinazoline-based selective phosphoinositol-3-kinase δ (PI3Kδ) inhibitor. It has been designed as an anti-inflammatory immunomodulator agent [67]. It shows potent inhibitory activity (IC_{50} = 9 nM). It inhibits a wide spectrum of immune-cell functions for neutrophils, basophils, mast cells, monocytes, plasmacytoid, and dendritic cells. It is currently under clinical research for treating Sjogren's syndrome and APDS/PASLI, which is a disease caused by a gain of function mutations of PI3Kδ.

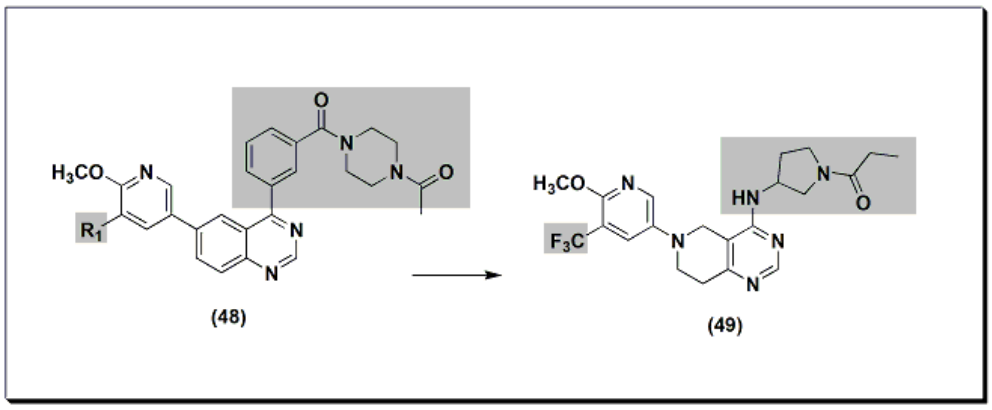


Figure 21. The anti-inflammatory quinazolines 48 and 49.

6. Analgesic and Anti-Inflammatory Quinazolines Marketed Drugs

The marketed drug proquazone 50 (Figure 22) [68] is a quinazoline-based non-steroidal anti-inflammatory agent (NSAI). It is a 4-aryl-1-alkyl-quinazolinone derivative [68]. It is the first effective anti-inflammatory drug of a non-acidic nature. It is used in the treatment of rheumatoid arthritis and osteoarthritis. The dose of 300 to 900 mg/day is as effective as aspirin and diclofenac in the patients with osteoarthritis. Earliest studies have proved the efficacy of proquazone in acute inflammatory disorders and revealed that it offers useful analgesic support in acute pain conditions, such as dysmenorrhea and headache.

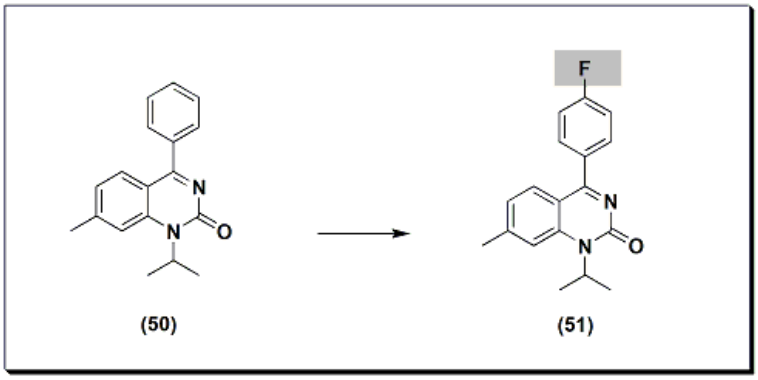


Figure 22. The molecular structure of proquazone and fluproquazone.

Fluproquazone 51 (Figure 22) is a fluoro-substituent derivative of proquazone. Additionally, it is a non-steroidal anti-inflammatory drug (NSAID) with potent activity.

The marketed quinazoline anti-inflammatory agent NSC127213 (Figure 23) [68] is a derivative of tetrazolo quinazoline [68]. NSC127213 works by inhibiting the histamine-1 receptor (H1R) and the histamine-4 receptor (H4R) for the treatment and prevention of inflammatory, autoimmune, and allergic diseases. The molecular structure of these marketed drugs was based on previous studies on analgesic anti-inflammatory quinazolines (Table 2).

Table 2. Molecular formula, generic names, chemical names, and uses of marketed analgesic and anti-inflammatory quinazolines [68].

Molecular Formula	Generic Names	Chemical Name	Uses
$C_{18}H_{18}N_2O$	Proquazone Proquazonum RU 43715 SaH 43-715 Sandoz 43-715 UNII-42VPJ2980S	2(1H)-Quinazolinone, 1-isopropyl-7-methyl-4-phenyl	Analgesic Anti-inflammatory Antirheumatic Cyclooxygenase Inhibitors
$C_{18}H_{17}FN_2O$	Fluproquazone Fluproquazonum Fluproquazona RF 46-790 SaH 46-790 Tormosyl UNII-U4K85O58HD BRN 089183	2(1H)-Quinazolinone, 4-(4-fluorophenyl)-7-methyl-1-(1-methylethyl)	Analgesic Anti-inflammatory Antirheumatic
$C_8H_5N_5$	NSC127213 UNII-7UWV5UYI5C	Tetrazolo(1,5-c)quinazoline	Anti-inflammatory

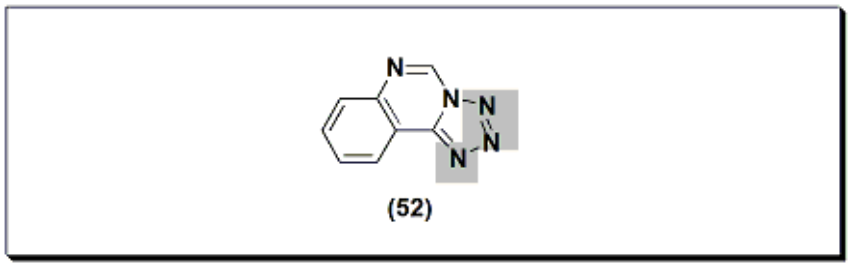


Figure 23. The molecular structure of NSC127213.

7. Summary of SAR Studies of Analgesic and Anti-Inflammatory Quinazolines

1. A strong analgesic activity was noted when N-3 was an aliphatic substituent in quinazolinone moiety. Changing the aliphatic group to an aryl group enhanced the analgesic activity. Generally, electron-withdrawing groups at N-3 decreased the activity. The cyclization of C-2 and C-3 in quinazolinone moiety resulted in decreased analgesic potency. The molecular hybridization of quinazolinone moiety with another heterocyclic system, such as thiazolidinone, thiazole, and azetidinone, improved the analgesic activity
2. The anti-inflammatory effect was increased by the presence of electron-withdrawing groups in C-1, C-6, and C-7 of the quinazolinone system. The introduction of the phenyl ring at N-1 position decreased the anti-inflammatory activity. The molecular hybridization of quinazolinone moiety with another heterocyclic system, such as thiazolidinone, thiazole, and azetidinone, improved the anti-inflammatory activity.

8. Conclusions

As mentioned above, the quinazoline system has a wide range of biological activities, such as being analgesic, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, anti-hypertensive, anti-bacterial, anti-fungal, anti-viral, anti-malarial, anti-convulsant, anti-cancer, anti-depressant, and anti-tubercular agents, as well as other activities. Therefore, it has great therapeutic potential for the treatment of different types of diseases and infections. The study of the structural–activity relationship (SAR) is the key for the improvement of efficient quinazoline therapeutic agents. Optimized quinazoline derivatives will be produced via an SAR-based study. Structural modifications can be performed by different techniques, such as the molecular hybridization or bioisosteric replacement techniques. Based on that, it is very possible that improved quinazolines having great potency and low side effects will go on to be created.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The author would like to extend his thanks to the Department of Pharmaceutical Sciences, Fakeeh College for Medical Sciences, Jeddah, Saudi Arabia for providing valuable suggestions and moral support.

Conflicts of Interest: The author declares no conflict of interest, financial or otherwise.

References

1. El-Zahabia, M.A.; Bamanie, H.F.; Ghareeb, S.; Alshaeri, K.H.; Alasmari, M.M.; Muostafa, M.; Al-Marzoki, Z.; Zayed, M.F. Design, Synthesis, Molecular Modeling andAnti-Hyperglycemic Evaluation of Quinazoline-Sulfonylurea Hybrids as Peroxisome Proliferator-Activated Receptor Gamma (PPAR) and Sulfonylurea Receptor (SUR) Agonists. *Int. J. Mol. Sci.* **2022**, *23*, 9605. [CrossRef] [PubMed]
2. Zayed, M.F.; Ibrahim, S.; Habib, E.E.; Hassan, M.H.; Ahmed, S.; Rateb, H.S. Design, synthesis, antimicrobial and anti-biofilm evaluation, and molecular docking of new substituted fluoroquinazolinones. *J. Med. Chem.* **2019**, *15*, 657–673.

3. Zhang, J.; Liu, J.; Ma, Y.; Ren, D.; Cheng, P.; Zhao, J.; Zhang, F.; Yao, Y. One-pot synthesis and antifungal activity against plant pathogens of quinazolinone derivatives containing an amide moiety. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2273–2277. [CrossRef] [PubMed]
4. Zayed, M.F.; Rateb, H.; Ahmed, S.; Khaled, O.; Ibrahim, S. Quinazolinone-amino acid hybrids as Dual Inhibitors of EGFR Kinase and Tubulin Polymerization. *Molecules* **2018**, *23*, 1699. [CrossRef]
5. Santos-Ballardo, L.; García-Páez, F.; Picos-Corrales, L.A.; Ochoa-Terán, A.; Bastidas, P.; Calderón-Zamora, L.; Rendón-Maldonado, G.; Osuna-Martínez, U.; Sarmiento-Sánchez, J.I. Synthesis, biological evaluation and molecular docking of 3-substituted quinazoline-2,4(1H, 3H)-diones. *J. Chem. Sci.* **2020**, *132*, 100. [CrossRef]
6. Zayed, M.F.; Ahmed, S.; Ihmaid, S.; Ahmed, H.E.; Rateb, H.; Ibrahim, S. Design, Synthesis, Cytotoxic Evaluation and Molecular Docking of New Fluoroquinazolinones as Potent Anticancer Agents with Dual EGFR Kinase and Tubulin Polymerization Inhibitory Effects. *Int. J. Mol. Sci.* **2018**, *19*, 1731. [CrossRef] [PubMed]
7. Jain, R.K.; Kashaw, V. Design, synthesis and evaluation of novel 2,3-disubstituted-4-(3H) quinazolinone derivatives. *Asian J. Pharm. Pharmacol.* **2018**, *4*, 644–656. [CrossRef]
8. Alagarsamy, V.; Chitra, K.; Saravanan, G.; Solomon, V.R.; Sulthana, M.T.; Narendhar, B. An overview of quinazolines: Pharmacological significance and recent developments. *Eur. J. Med. Chem.* **2018**, *151*, 628–685. [CrossRef] [PubMed]
9. Zayed, M.F.; Ahmed, H.E.A.; Ihmaid, S.; El-Adl, K.; Asiri, A.; Omar, A.M. Modelling and Anticonvulsant Studies of New Quinazolines Showing Three Highly Active Compounds with Low Toxicity and High Affinity to the GABA-A Receptor. *Molecules* **2017**, *22*, 188. [CrossRef]
10. Hricoviniova, J.; Hricoviniova, Z.; Kozica, K. Antioxidant, Cytotoxic, Genotoxic, and DNA Protective Potential of 2,3-Substituted Quinazolinones: Structure—Activity Relationship Study. *Int. J. Mol. Sci.* **2021**, *22*, 610. [CrossRef]
11. Zayed, M.F.; Ahmed, H.E.A.; Ihmaid, S.K.; Omar, A.M.; Abdelrahim, A.S. Synthesis and screening of some new fluorinated quinazolinone–sulphonamide hybrids as anticancer agents. *J. Taibah Univ. Sci.* **2015**, *10*, 333–339. [CrossRef]
12. Sunil Kumar, A.; Kudva, J.; Lahtinen, M.; Peuronen, A.; Sadashiva, R.; Naral, D. Synthesis, characterization, crystal structures and biological screening of 4-amino quinazoline sulfonamide derivatives. *J. Mol. Struct.* **2019**, *1190*, 29–36. [CrossRef]
13. Zayed, M.F. New fluorinated quinazolinone derivatives as anticonvulsant agents. *J. Taibah Univ. Sci.* **2014**, *9*, 104–109. [CrossRef]
14. Ghorab, M.M.; Abdel-Kader, M.S.; Alqahtani, A.S.; Soliman, A.M. Synthesis of some quinazolinones inspired from the natural alkaloid L-norephedrine as EGFR inhibitors and radiosensitizers. *J. Enzym. Inhib. Med. Chem.* **2021**, *36*, 218–237. [CrossRef] [PubMed]
15. Zayed, M.F.; Hassan, M.H. Synthesis and biological evaluation studies of novel quinazolinone derivatives as antibacterial and anti-inflammatory agents. *Saudi Pharm. J.* **2014**, *22*, 157–162. [CrossRef]
16. Zayed, M.F.; Hassan, M.H. Design, Synthesis and Biological Evaluation Studies of Novel Quinazoline Derivatives as Cytotoxic Agents. *Drug Res.* **2013**, *63*, 210–215. [CrossRef]
17. Zayed, M.F.; Ahmed, E.A.; Omar, A.M.; Abdelrahim, A.S.; El-Adl, K. Design, synthesis, and biological evaluation studies of novel quinazolinone derivatives as anticonvulsant agents. *Med. Chem. Res.* **2013**, *22*, 5823–5831. [CrossRef]
18. Alam, M.J.; Alam, O.; Naim, M.J.; Alam, P. A review: Recent investigations on quinazoline scaffold. *Int. J. Adv. Res.* **2015**, *3*, 1656–1664.
19. Connolly, D.J.; Cusack, D.; O'Sullivan, T.P.; Guiry, P.J. Synthesis of quinazolinones and quinazolines. *Tetrahedron* **2005**, *61*, 10153–10202. [CrossRef]
20. Meyer, J.F.; Wagner, E.C. The Niementowski reaction. The use of methyl anthranilate or isatoic anhydride with substituted amides or amidines in the formation of 3-substituted-4-keto-3,4-dihydroquinazolines. The course of the reaction. *J. Org. Chem.* **1943**, *8*, 239–252. [CrossRef]
21. Asif, M. Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives. *Int. J. Med. Chem.* **2014**, *2014*, 395637. [CrossRef]
22. Hameed, A.; Al-Rashida, M.; Uroos, M.; Ali, S.A.; Arshia; Ishtiaq, M.; Khan, K.M. Quinazoline and quinazolinone as important medicinal scaffolds: A comparative patent review (2011–2016). *Expert Opin. Ther. Pat.* **2018**, *28*, 281–297. [CrossRef]
23. Auti, P.S.; George, G.; Paul, A.T. Recent advances in the pharmacological diversification of quinazoline/quinazolinone hybrids. *RSC Adv.* **2020**, *10*, 41353–41392. [CrossRef]
24. Gupta, T.; Rohilla, A.; Pathak, A.; Akhtar, M.J.; Haider, M.R.; Yar, M.S. Current perspectives on quinazolines with potent biological activities: A review. *Synth. Commun.* **2018**, *48*, 1099–1127. [CrossRef]
25. Bisht, A.S.; Negi, J.S.; Sharma, D.K. Chemistry and activity of quinazoline moiety: A systematic review study. *Int. J. Pharm. Chem. Anal.* **2020**, *7*, 61–65. [CrossRef]
26. Molecular Operating Environment (MOE). Chemical Computing Group. Available online: http://www.chemcomp.com (accessed on 10 May 2019).
27. Swiss Institute of Bioinformatics (SwissADME). Available online: http://www.swissADME.ch (accessed on 10 March 2022).
28. Wang, D.; Gao, F. Quinazoline derivatives: Synthesis and bioactivities. *Chem. Cent. J.* **2013**, *7*, 95. [CrossRef] [PubMed]
29. Agrawal, G.; Khan, N.; Dwivedi, S.; Patel, R.; Singh, G. Synthesis, Characterization and Anti-Microbial Evaluation of a Series of Quinazoline analogs. *J. Adv. Sci. Res.* **2021**, *12*, 123–130. [CrossRef]
30. Reddy, M.M.; Sivaramakrishna, A. Remarkably flexible quinazolinones—Synthesis and biological applications. *J. Heterocycl. Chem.* **2020**, *57*, 942–954. [CrossRef]

31. Kumar, A.; Sharma, S.; Bajaj, K.; Sharma, S.; Panwar, H.; Singh, T.; Srivastava, V.K. Some new 2,3,6-trisubstituted quinazolinones as potent anti-inflammatory, analgesic, and COX-II inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 5293–5299. [CrossRef]
32. Kumar, A.; Singh, R.C.; Kumar, B.S. Synthesis of 3-[4′-(p-chlorophenyl)-thiazol-2′-yl]-2-[(substitutedazetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones as anti-inflammatory agent. *Bioorg. Med. Chem.* **2007**, *15*, 3089–3096. [CrossRef]
33. Pannerselvam, P.; Pradeepchandran, R.V.; Sridhar, S.K. Synthesis, characterization and biological activities of novel 2-methylquinazolin-4(3H)-ones. *Indian J. Pharm. Sci.* **2003**, *65*, 268–273.
34. Gomtsyan, A.; Bayburt, E.K.; Schmidt, R.G.; Zheng, G.Z.; Perner, R.J.; Didomenico, S.; Koenig, J.R.; Turner, S.; Jinkerson, T.; Drizin, I.; et al. Novel transient receptor potential vanilloid 1 receptor antagonists for the treatment of pain: Structure activity relationships for ureas with quinoline, isoquinoline, quinazoline, phthalazine, quinoxaline, and cinnoline moieties. *J. Med. Chem.* **2005**, *48*, 744–752. [CrossRef] [PubMed]
35. Rakesh, K.P.; Manukumar, H.M.; Gowda, D.C. Schiff's bases of quinazolinone derivatives: Synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1072–1077. [CrossRef]
36. Pu, Y.; Cao, D.; Xie, C.; Pei, H.; Li, D.; Tang, M.; Lijuan, C. Anti-arthritis effect of a novel quinazoline derivative through inhibiting production of TNF-α mediated by TNF-α converting enzyme in murine collagen-induced arthritis model. *Biochem. Biophys. Res. Commun.* **2015**, *462*, 288–293. [CrossRef]
37. Hu, J.; Zhang, Y.; Dong, L.; Wang, Z.; Chen, L.; Liang, D.; Shi, D.; Shan, X.; Liang, G. Design, synthesis, and biological evaluation of novel quinazoline derivatives as anti-inflammatory agents against lipopolysaccharide-induced acute lung injury in rats. *Chem. Biol. Drug. Des.* **2015**, *85*, 672–684. [CrossRef] [PubMed]
38. Alagarsamy, V.; Solomon, V.R.; Vanikavitha, G.; Paluchamy, V.; Chandran, M.R.; Sujin, A.A.; Thangathiruppathy, A.; Amuthalakshmi, S.; Revathi, R. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-phenyl-3-substituted quinazolin-4(3H)-ones. *Biol. Pharm. Bull.* **2002**, *25*, 1432–1435. [CrossRef] [PubMed]
39. Alagarsamy, V.; Murugananthan, G.; Venkateshaperumal, R. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-methyl-3-substituted quinazolin-4(3H)-ones. *Biol. Pharm. Bull.* **2003**, *26*, 1711–1714. [CrossRef] [PubMed]
40. Alagarsamy, V.; Rajesh, R.; Ramaseshu, M.; Vijaykumar, S.; Ramseshu, K.V.; Duraianandakumar, T. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-methylthio-3-substitutedquinazolin-4(3H)-one. *Biol. Pharm. Bull.* **2004**, *27*, 652–656. [CrossRef]
41. Alagarsamy, V.; Solomon, V.R.; Meena, R.; Ramseshu, K.V. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-butyl-3-substituted quinazolin-4(3H)-ones. *Biol. Pharm. Bull.* **2005**, *28*, 1091–1094. [CrossRef]
42. Alagarsamy, V.; Muthukumar, V.; Pavalarani, N.; Vasanthanathan, P.; Revathi, R. Synthesis, analgesic, and anti-inflammatory activities of some novel 2,3-disubstituted quinazolin-4(3H)-ones. *Biol. Pharm. Bull.* **2003**, *26*, 557–559. [CrossRef]
43. Alagarsamy, V.; Revathi, S.; Kalaiselvi, R. Analgesic, anti-inflammatory and antibacterial activity of some novel 2-phenyl-3-(substitutedmethylamino) quinazolin- 4(3H)-ones. *Indian J. Pharm. Sci.* **2003**, *65*, 534–537.
44. Alagarsamy, V.; Murugesan, S. Synthesis and pharmacological evaluation of some 3-(4-methoxyphenyl)-2-substitutedamino-quinazolin-4(3H)-ones as analgesic and anti-inflammatory agents. *Chem. Pharm. Bull.* **2007**, *55*, 76–80. [CrossRef] [PubMed]
45. Alagarsamy, V.; Solomon, V.R.; Dhanabal, K. Synthesis, and pharmacological evaluation of some 3-phenyl-2-substituted-3H-quinazolin-4-one as analgesic, anti-inflammatory agents. *Bio. Med. Chem.* **2007**, *15*, 235–241. [CrossRef] [PubMed]
46. Alagarsamy, V.; Thangathirupathi, A.; Mandal, S.C. Pharmacological evaluation of 2- substituted-(1,3,4)-thiadiazoloquinazolines. *Indian J. Pharm. Sci.* **2006**, *68*, 108–111. [CrossRef]
47. Alagarsamy, V.; Shankar, D.; Solomon, V.R. Synthesis of some novel 2-mercapto-3-(substitutedamino)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-ones as analgesic and anti-inflammatory agents. *Arkivoc* **2006**, *XVI*, 149–159.
48. Kumar, A.; Sharma, S.; Bajaj, K. Synthesis and anti-inflammatory, analgesic, ulcerogenic and cyclooxygenase activities of novel quinazolinyl-Δ2-pyrazolines. *Indian J. Chem.* **2003**, *42B*, 1979–1984.
49. Daidone, G.; Maggio, B.; Raffa, D.; Plescia, S.; Bajardi, M.L.; Caruso, A.; Cutuli, V.M.C.; Amico-Roxas, M. Synthesis and pharmacological study of ethyl 1-methyl-5-[2-substituted-4-oxo-3(4H)-quinazolinyl]-1H-pyrazole-4-acetates. *Eur. J. Med. Chem.* **1994**, *29*, 707–711. [CrossRef]
50. Maggio, B.; Daidone, G.; Raffa, D.; Plescia, S.; Mantione, L.; Cutuli, V.M.C.; Mangano, N.G.; Caruso, A. Synthesis and pharmacological study of ethyl 1-methyl-5-(substituted-3,4-dihydro-4-oxoquinazolin-3-yl)-1H-pyrazole-4-acetates. *Eur. J. Med. Chem.* **2001**, *36*, 737–742. [CrossRef]
51. Bonacorso, H.G.; Rosa, W.C.; Oliveira, S.M.; Brusco, I.; Pozza, C.C.D.; Nogara, P.A.; Wiethan, C.W.; Rodrigues, M.B.; Frizzo, C.P.; Zanatta, N. Synthesis and antinociceptive activity of new 2-substituted 4-(trifluoromethyl)-5,6- dihydrobenzo[h]quinazolines. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4808–4814. [CrossRef]
52. Sarangapani, M.; Reddy, A.N.; Jayamma, Y.; Reddy, V.M. Synthesis and pharmacological activities of new isatin hydrazones. *Indian Drugs* **1998**, *35*, 336–343.
53. Reddy, P.S.; Venugopala, K.N.; Rao, G.K.; Pai, P.N.S. Synthesis of some substituted quinazolinones as analgesic and anti-inflammatory agents. *Indian J. Hetero. Chem.* **2007**, *16*, 243–246.
54. Sakr, A.; Kothayer, H.; Ibrahim, S.M.; Baraka, M.M.; Rezq, S. 1,4-Dihydroquinazolin-3(2H)-yl benzamide derivatives as anti-inflammatory and analgesic agents with an improved gastric profile: Design, synthesis, COX-1/2 inhibitory activity and molecular docking study. *Bioorg. Chem.* **2019**, *84*, 76–86. [CrossRef]

55. Saravanan, G.; Alagarsamy, V.; Dineshkumar, P. Synthesis, analgesic, anti-inflammatory and in vitro antimicrobial activities of some novel isoxazole coupled quinazolin-4(3H)-one derivatives. *Arch. Pharm. Res.* **2021**, *44*, 1–11. [CrossRef] [PubMed]
56. Ozaki, K.I.; Yamada, Y.; Oine, T. Studies on 4(1H)-quinazolinones. IV: Convenient syntheses of 12-methyl-6H-isoquino[2,1-a]quinazolin-6-one and 6-methyl-13Hquinazolino[3,4-a]quinazolin-13-one. *Chem. Pharm. Bull.* **1984**, *32*, 2160–2164. [CrossRef]
57. Bothara, K.G.; Kadam, S.S.; Shivram, V.S. Synthesis, and pharmacological screening of novel anti-inflammatory agents. *Indian Drugs* **1998**, *35*, 372–376.
58. Sarma, G.V.S.R.; Thomas, J.; Murugan, V.; Elango, K. Nicotinyl incorporated quinazolinonyl thiadiazoles as possible NSAIDs. *Indian J. Heterocycl. Chem.* **1999**, *9*, 151–152.
59. Saxena, S.; Verma, M.; Saxena, A.K. Synthesis and biological activity of quino(2,1-b)-quinazolinones. *Indian J. Chem.* **1991**, *30B*, 453–456.
60. Gangwal, N.A.; Narasimhan, B.; Mourya, V.K.; Dhake, A.S. Synthesis and QSAR studies of substituted-4(1H)-quinazolinones. *Indian J. Heterocycl. Chem.* **2003**, *12*, 201–204.
61. Rani, P.; Archana; Srivastava, V.K.; Kumar, A. Synthesis and anti-inflammatory activity of some new 2,3-disubstituted 6-monosubstitutedquinazolin-4(3H)-ones. *Indian J. Chem.* **2002**, *41B*, 2642–2646.
62. Sachin, S.L.; Sudhir, G.W.; Sharad, K.M. Studies on some biologically active substituted 4(3H)-quinazolinones. Part 1: Synthesis, characterization and antiinflammatory, anti-microbial activity of 6,8-disubstituted-2-phenyl-3 [substitutedbenzothiazol-2-yl]-4(3H)-quinazolinones. *Arkivoc* **2006**, *11*, 1–20.
63. Jessy, E.M.; Sambantham, A.T.; Alex, J. Synthesis, and biological evaluation of some novel quinazolones. *Indian J. Pharm. Sci.* **2007**, *69*, 476–478. [CrossRef]
64. Bansal, E.; Srivastava, V.K.; Kumar, A. Synthesis, and anti-inflammatory activity of 1-acetyl-5-substitutedaryl-3-(β-aminonaphthyl)-2-pyrazolines and β-(substitutedaminoethyl) amidonaphthalenes. *Eur J. Med. Chem.* **2001**, *36*, 81–92. [CrossRef] [PubMed]
65. Kumar, A.; Rajput, C.S. Synthesis, and anti-inflammatory activity of newer quinazolin-4-one derivatives. *Eur. J. Med. Chem.* **2007**, *44*, 83–90. [CrossRef] [PubMed]
66. Abuelizz, H.A.; Rashad, A. An overview of triazoloquinazolines: Pharmacological significance and recent developments. *Bioorg. Chem.* **2021**, *115*, 105263. [CrossRef] [PubMed]
67. Hoegenauer, K.; Soldermann, N.; Zécri, F.; Strang, R.S.; Graveleau, N.; Wolf, R.M.; Cooke, N.G.; Smith, A.B.; Hollingworth, G.J.; Blanz, J.; et al. Discovery of CDZ173 (Leniolisib), representing a structurally novel class of PI3K delta-selective inhibitors. *ACS Med. Chem. Lett.* **2017**, *8*, 975–980. [CrossRef]
68. Drug Information Portal. Available online: https://druginfo.nlm.nih.gov/drugportal/ (accessed on 25 September 2022).