

Quinazolinone Derivatives as Anti-Inflammatory Agents: A Review of Chemistry, Mechanisms and Structure Activity Relationships

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Abstract

Inflammation is a protective response of the body to injury and infection, but its persistence contributes to arthritis, cardiovascular disease and many other disorders. Non-steroidal anti-inflammatory drugs remain the most widely used therapy, yet gastrointestinal and cardiovascular adverse effects limit their long-term use, which keeps the search for safer anti-inflammatory scaffolds active. The quinazolinone nucleus, a fused benzene and pyrimidinone ring system, is regarded as a privileged scaffold in medicinal chemistry and is present in drugs and natural products with anti-inflammatory and immunomodulatory properties. In this review, published literature on quinazolinone derivatives with anti-inflammatory activity is summarised with emphasis on the chemistry of the scaffold, common synthetic approaches, molecular targets, structure activity relationships and the experimental models used for evaluation. Reported mechanisms include inhibition of cyclooxygenase-2, suppression of the nuclear factor kappa B pathway and of the downstream mediators nitric oxide, tumour necrosis factor alpha and interleukins, and inhibition of phosphodiesterase 7. Substituents at positions 2, 3, 6 and 8 are found to influence potency and selectivity, and hybridisation with nitric oxide donors is reported to improve the gastric safety profile. Current limitations, including the dependence on rodent oedema models, limited enzyme level validation and scarce toxicity data, are discussed together with future directions.

Keywords: Quinazolinone, Anti-Inflammatory Activity, Cyclooxygenase-2, Nuclear Factor Kappa B, Structure Activity Relationship, Molecular Docking

1. Introduction

Inflammation is a defensive response coordinated by tissue cells and the innate immune system to remove the cause of injury and to start tissue repair. When the response is not resolved, chronic inflammation develops and is now recognised as a contributor to rheumatoid arthritis, inflammatory bowel disease, atherosclerosis and several neurodegenerative conditions [1].

Prostaglandins formed by the cyclooxygenase (COX) enzymes are major mediators of pain, fever and swelling, and the inhibition of their synthesis is the basis of the action of aspirin-like drugs [2, 3]. Non-steroidal anti-inflammatory drugs (NSAIDs) are therefore widely prescribed, but inhibition of COX-1 is associated with gastric injury, while selective COX-2 inhibitors were found to carry cardiovascular risk

[4]. Corticosteroids are effective but are limited by metabolic and endocrine adverse effects. These limitations explain the continuing interest in new chemical scaffolds that act on COX-2 and on other inflammatory targets with improved safety.

Quinazolinones are bicyclic heterocycles in which a benzene ring is fused to a pyrimidinone ring. The scaffold is found in natural alkaloids and synthetic compounds that show anti-inflammatory, analgesic, anticonvulsant, antimicrobial, antihypertensive and anticancer activities [5, 6, 7]. Several general reviews cover the pharmacology of quinazolines and quinazolinones [5, 6, 7, 8], but the anti-inflammatory literature is scattered across medicinal chemistry journals and has expanded rapidly with recent work on nuclear factor kappa B (NF- κ B) signalling and phosphodiesterase 7 (PDE7). The present review brings together published studies on the anti-inflammatory activity of quinazolinone derivatives, with attention to chemistry, mechanisms, structure activity relationships (SAR), evaluation methods and open problems.

2. Molecular Targets in Inflammation

2.1 Cyclooxygenase Pathway

Arachidonic acid released from membrane phospholipids is converted by COX enzymes into prostaglandin H₂, which is further transformed into the prostaglandins responsible for vasodilation, oedema and pain. COX-1 is expressed constitutively and supports gastric mucosal protection, whereas COX-2 is induced at inflammatory sites and is the preferred target for anti-inflammatory therapy [3].

2.2 NF- κ B Signalling and Cytokines

NF- κ B is a central transcription factor of the inflammatory response. Stimuli such as bacterial lipopolysaccharide (LPS) act through toll-like receptor 4, leading to phosphorylation and degradation of the inhibitor of kappa B and to nuclear translocation of the p65 and p50 dimer. In the nucleus, NF- κ B drives transcription of COX-2, inducible nitric oxide synthase (iNOS), tumour necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β) and interleukin-6 (IL-6) [9]. Macrophage cell lines such as RAW 264.7 stimulated with LPS are therefore widely used to study this pathway, and nitric oxide (NO) release is used as a simple read-out of iNOS activity. The main pathways and the points at which quinazolinones interfere are summarised in Figure 1.

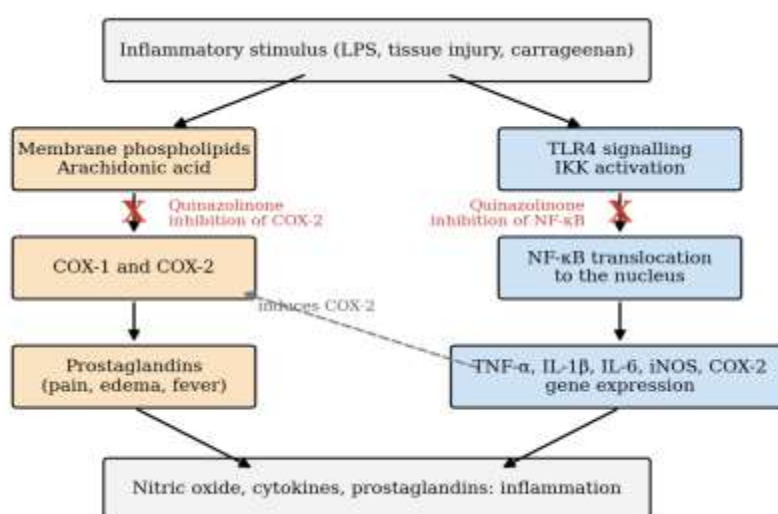


Figure 1 : Major Inflammatory Pathways and the Points of Interference by Quinazolinone Derivatives

3. Chemistry of the Quinazolinone Scaffold

3.1 Structure and Numbering

Quinazoline is a benzo-fused pyrimidine, and the introduction of a carbonyl group gives the quinazolinones. The 4(3H)-quinazolinone isomer is the most common form in the literature, while the 2(1H)-quinazolinone isomer is represented by proquazone. Positions 2 and 3 of the pyrimidinone ring are the most frequently modified, and positions 5 to 8 on the benzene ring are varied to tune lipophilicity and electronic properties (Figure 2) [5, 10]. The lactam carbonyl at position 4 and the ring nitrogen atoms can act as hydrogen bond acceptors in enzyme binding sites.

3.2 Synthetic Approaches

Classical routes to the 4(3H)-quinazolinone nucleus start from anthranilic acid. In the Niementowski reaction, anthranilic acid is heated with an amide to give the quinazolinone directly. In an alternative and widely used route, anthranilic acid is acylated and cyclised with acetic anhydride to give a 2-methyl-3,1-benzoxazin-4-one, which reacts with amines or hydrazines to give 3-substituted 2-methylquinazolin-4(3H)-ones [10]. Condensation of anthranilamide with aldehydes, reactions of isatoic anhydride in multicomponent procedures, and metal-catalysed and microwave-assisted methods have also been described [5, 10].

Functionalisation of a preformed quinazolinone is equally important for anti-inflammatory work. The ring NH of quinazolin-4(3H)-one can be alkylated at position 3 with alkyl or benzyl halides in the presence of a base, and the methyl group of 2-methylquinazolin-4(3H)-ones can be condensed with aromatic aldehydes to give 2-styryl derivatives. A recent example is the Wilgerodt-Kindler reaction of 2-methylquinazolin-4-one with amines using sulphur in dimethyl sulphoxide, which gives quinazolin-4(3H)-one-2-carbothioamides in one step [11].

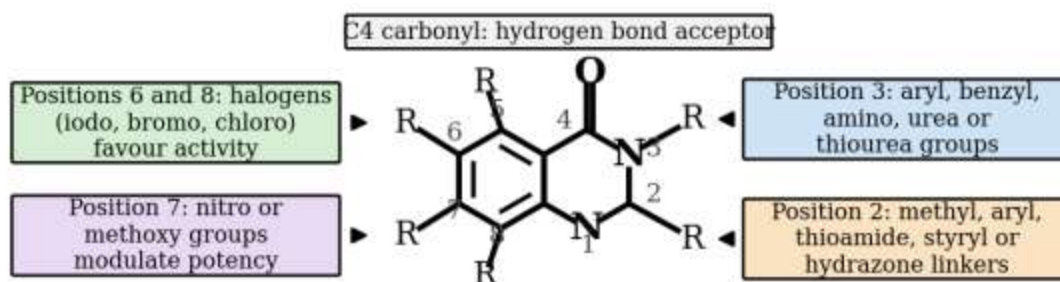


Figure 2 : Quinazolin-4(3H)-one Nucleus with Numbering and Positions Commonly Modified for Anti-Inflammatory Activity

4. Quinazolinone Drugs and Natural Products with Anti-Inflammatory Relevance

Proquazone and fluproquazone are well-known examples of quinazolinone-type NSAIDs, and the alkaloid rutaecarpine from *Evodia rutaecarpa* is reported to inhibit COX-2 with high selectivity [11]. These compounds established that the scaffold is compatible with COX inhibition and provided starting points for later design work.

Beyond COX inhibition, the quinazolin-4(3H)-one core is present in idelalisib, an inhibitor of phosphoinositide 3-kinase delta that was approved for chronic lymphocytic leukaemia [12]. Although idelalisib is not an anti-inflammatory drug, the enzyme it targets is central to immune cell signalling,

which illustrates the relevance of the scaffold to immune regulation. Halofuginone, a halogenated derivative of the quinazolinone alkaloid febrifugine, has antifibrotic activity [13] and inhibits the differentiation of pro-inflammatory Th17 cells [14].

5. Mechanisms of Anti-Inflammatory Action

5.1 Inhibition of COX-2

Chaitanya et al. (2014) synthesised 36 substituted quinazolinones and evaluated them by the carrageenan-induced paw oedema model and by in vitro COX-1 and COX-2 assays. The compounds were selective towards COX-2, and the best compound inhibited COX-2 more strongly than celecoxib; pharmacophore modelling and 3D-QSAR were used to explain the activity [15]. Farag et al. (2015) prepared 2-methylquinazolin-4(3H)-ones carrying urea, thiourea and sulphonamide groups at position 3, together with hybrids bearing nitrate ester NO-releasing groups. All compounds showed moderate to potent activity compared with meloxicam, and the nitrate esters had lower affinity for COX-1 than their parent compounds (COX-1 IC₅₀ values of 34.6 μ M for one nitrate ester and 23.76 μ M for its parent compound), which suggests a lower tendency to cause gastric ulceration [16].

Not all substitution patterns give strong COX-2 inhibition. A series of 2,3-diaryl-4(3H)-quinazolinones showed a maximum COX-2 inhibition of 27.72 percent at 22 μ M, and only mild activity in the rat oedema test at 50 mg/kg [17]. In contrast, 6-iodo-2-phenylquinazolin-4(3H)-one derivatives showed considerable activity against indomethacin as the reference drug, with a better gastrointestinal safety profile, and docking into COX-2 correlated with the biological results [18]. Styryl derivatives at position 2 of 3-(methylphenyl)quinazolin-4(3H)-ones gave four compounds with potent activity relative to diclofenac sodium, while the correlation between lipophilicity and activity was poor [19]. Spiro-fused triazino[2,3-c]quinazolines were selected by docking as potential COX-2 inhibitors and showed activity in the formalin-induced oedema model [20].

5.2 Suppression of NF- κ B and Cytokines

Kerdphon et al. (2023) examined quinazolinones in LPS-stimulated RAW 264.7 cells and reported that the compounds reduced the expression of COX-2, IL-1 β , iNOS and TNF- α genes through inhibition of NF- κ B. At 62.5 μ M, COX-2 and IL-1 β mRNA expression fell to 0.50 and 3.10 percent, respectively, and docking was used to interpret the SAR [21]. A very recent series of 3-amino-2-methylquinazolinones was designed as NF- κ B inhibitors, and docking showed a marked increase in binding of the lead compound to the NF- κ B and DNA complex, identifying it as a potential inhibitor of the canonical pathway [22].

Closely related quinazolines point in the same direction. Alkylthiourea derivatives of 4-anilinoquinazoline selectively inhibited NF- κ B activation in macrophage-like THP-1 cells with low cytotoxicity; the best compound inhibited IL-6 and TNF- α release with IC₅₀ values of 0.84 and 4.0 μ M, respectively, and blocked nuclear translocation of the NF- κ B dimer [23].

5.3 Inhibition of Nitric Oxide Production

Nguyen et al. (2025) designed sixteen quinazolin-4(3H)-one-2-carbothioamides and evaluated them by inhibition of NO production in LPS-activated RAW 264.7 cells. The most active compound showed an IC₅₀ of 13.44 μ M, comparable with dexamethasone, and docking suggested hydrophobic interactions stabilised by hydrogen bonds in the target site [11].

5.4 Inhibition of Phosphodiesterase 7

PDE7 is a high-affinity, cAMP-specific phosphodiesterase expressed in immune and pro-inflammatory cells, and its selective inhibition is considered a new route to control inflammation. Substituted 4-

hydrazinoquinazolines and fused triazoloquinazolines were evaluated against PDE7A, and four compounds showed good potency [24]. A more recent study of benzylthioquinazolinone hydrazones reported anti-inflammatory activity in the carrageenan oedema model and prioritised one compound as the leading candidate, but PDE7A involvement was inferred only computationally and was stated to require biochemical and selectivity validation [25].

6. Structure Activity Relationships

The studies discussed above allow some general trends to be drawn, although direct comparison is limited because different models, doses and reference drugs were used (Table 1). At position 2, small lipophilic groups, phenyl rings, styryl groups and thioamide linkers attached to aryl groups have all produced active compounds. In the carbothioamide series, a thioamide attached directly to a phenyl ring bearing 4-chloro, 4-bromo or 4-trifluoromethyl substituents was associated with the strongest NO inhibition [11], and quinazolinones with aliphatic substituents at position 2 were also effective in suppressing inflammatory gene expression [21].

At position 3, aryl groups gave only modest COX-2 inhibition in the 2,3-diaryl series [17], whereas amino, urea, thiourea and sulphonamide substituents were used successfully in COX-2 and NF- κ B directed designs [16, 22]. On the benzene ring, halogen substitution as in the 6-iodo series [18], and halogens on pendant aryl rings [11], is repeatedly linked with higher activity, which may reflect increased lipophilicity and halogen mediated interactions in the binding pocket. Lipophilicity alone is not a reliable predictor, as shown by the poor correlation reported for styrylquinazolinones [19].

Hybridisation is a second useful strategy. Attachment of NO-releasing nitrate esters retained anti-inflammatory activity and reduced COX-1 affinity [16], while computational approaches such as pharmacophore modelling, 3D-QSAR and docking have been used to rationalise activity in several series [15, 16, 18].

Table 1 : Representative Studies on Quinazolinone Derivatives with Anti-Inflammatory Activity

Compound Class	Model or Assay	Key Finding	Ref.
Thirty-six substituted quinazolinones	Carrageenan oedema; COX-1 and COX-2 assays; 3D-QSAR	COX-2 selective; best compound exceeded celecoxib in COX-2 inhibition	[15]
2-Methyl-3-substituted urea, thiourea and sulphonamide quinazolinones and NO-releasing hybrids	Rat oedema; COX-1 and COX-2 assays; docking	Nitrate esters showed lower COX-1 affinity than parent compounds	[16]
2,3-Diaryl-4(3H)-quinazolinones	COX inhibitor screening; carrageenan oedema	Maximum COX-2 inhibition of 27.72 percent at 22 μ M; mild in vivo activity	[17]
6-Iodo-2-phenylquinazolin-4(3H)-ones	Carrageenan oedema; COX-2 docking	Considerable activity against indomethacin with better GI safety	[18]

Compound Class	Model or Assay	Key Finding	Ref.
2-Styryl-3-(methylphenyl)quinazolin-4(3H)-ones	Carrageenan oedema	Four compounds potent relative to diclofenac sodium	[19]
Quinazolinones with varied substituents	LPS-stimulated RAW 264.7 gene expression; docking	COX-2 and IL-1 β mRNA down to 0.50 and 3.10 percent at 62.5 μ M	[21]
3-Amino-2-methylquinazolinones	NF- κ B inhibition design; docking	High predicted binding to the NF- κ B and DNA complex	[22]
Quinazolin-4(3H)-one-2-carbothioamides	NO inhibition in LPS-activated RAW 264.7 cells; docking	Best IC ₅₀ of 13.44 μ M, comparable with dexamethasone	[11]
4-Hydrazinoquinazolines and triazoloquinazolines	In vitro PDE7A inhibition	Four compounds with good potency	[24]
Benzylthioquinazolinone hydrazones	Carrageenan oedema; PDE7A docking	One lead compound; PDE7A role computationally inferred	[25]

7. Experimental Evaluation of Anti-Inflammatory Activity

7.1 In Vivo Models

The carrageenan-induced rat paw oedema test of Winter and co-workers remains the most common primary screen for quinazolinones, and activity is expressed as percent reduction in paw volume against a reference drug such as indomethacin, diclofenac or meloxicam [26]. Formalin-induced oedema has also been used [20]. These models are simple and reproducible, but they measure acute inflammation only and do not identify the molecular target.

7.2 In Vitro Assays

Inhibition of heat-induced protein denaturation is a simple screening method based on the observation that anti-inflammatory drugs protect proteins from denaturation [27], and it is often combined with proteinase inhibition assays. More informative cell-based assays use LPS-activated RAW 264.7 macrophages to measure NO release, cytokine levels and gene expression [11, 21], while enzyme assays give COX-1 and COX-2 inhibition and selectivity data [15, 16] and PDE7A assays are used for phosphodiesterase directed series [24].

7.3 In Silico Methods

Molecular docking against COX-2, NF- κ B and PDE7A has been used to rationalise activity and to select compounds for synthesis [15, 18, 22, 25]. Docking scores correlate with biological data in some series [18], but they remain predictions and should be supported by enzyme or cell-based results.

8. Challenges and Future Perspectives

Several limitations are evident in the present literature. Many reports rely on single-dose carrageenan oedema tests without COX-1 and COX-2 enzyme data, so selectivity cannot be judged. Docking is frequently the only support for a proposed target, as in the PDE7A study in which the target was

computationally inferred [25]. Toxicity, ulcerogenic index and pharmacokinetic data are reported for only a small number of compounds, and chronic models such as adjuvant arthritis are rarely used.

Future work should combine target-directed design with orthogonal validation, that is, enzyme assays, cytokine profiling and gene expression in cells, followed by chronic in vivo models and early ADME and safety assessment. Multi-target designs that join COX-2, NF- κ B or PDE7 activity in one molecule, and hybrids with NO donors [16], appear to be the most promising routes to compounds with better gastric safety. Since the scaffold is synthetically accessible by short routes from anthranilic acid [10], iterative design, synthesis and testing cycles can be carried out in academic laboratories.

9. Conclusion

Quinazolinones remain an attractive and versatile scaffold for anti-inflammatory drug discovery. The literature shows that activity can be directed to COX-2, to the NF- κ B pathway and its mediators, to NO production and to PDE7 by choosing appropriate substituents at positions 2, 3, 6 and 8. However, the evidence base is uneven, and stronger target validation, standard reference compounds and safety data are needed before any new derivative can be considered a realistic lead for development.

References

1. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008; 454(7203): 428-435.
2. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biology*. 1971; 231(25): 232-235.
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2011; 31(5): 986-1000.
4. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *Journal of Clinical Investigation*. 2006; 116(1): 4-15.
5. Khan I, Zaib S, Batool S, Abbas N, Ashraf Z, Iqbal J, Saeed A. Quinazolinones and quinazolinones as ubiquitous structural fragments in medicinal chemistry: an update on the development of synthetic methods and pharmacological diversification. *Bioorganic and Medicinal Chemistry*. 2016; 24(11): 2361-2381.
6. Alagarsamy V, Chitra K, Saravanan G, Solomon VR, Sulthana MT, Narendhar B. An overview of quinazolinones: pharmacological significance and recent developments. *European Journal of Medicinal Chemistry*. 2018; 151: 628-685.
7. Dhanawat M, Gupta S, Mujwar S. Quinazolinone: pharmacophore with endless pharmacological actions. *Current Indian Science*. 2023; 1: 1-22. <https://doi.org/10.2174/2210299X02666221125101550>
8. Parambi DGT, et al. A literature review on pharmacological aspects, docking studies, and synthetic approaches of quinazoline and quinazolinone derivatives. *Archiv der Pharmazie*. 2024. <https://doi.org/10.1002/ardp.202400057>
9. Liu T, Zhang L, Joo D, Sun SC. NF- κ B signaling in inflammation. *Signal Transduction and Targeted Therapy*. 2017; 2: 17023.
10. Connolly DJ, Cusack D, O'Sullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. *Tetrahedron*. 2005; 61(43): 10153-10202.

11. Nguyen LTH, Vu DH, Pham MQ, Ngo QA. Design, synthesis, anti-inflammatory evaluation, and molecular docking studies of novel quinazoline-4(3H)-one-2-carbothioamide derivatives. *RSC Advances*. 2025; 15(4): 2850-2861. <https://doi.org/10.1039/D4RA09094B>
12. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *New England Journal of Medicine*. 2014; 370(11): 997-1007.
13. Pines M, Spector I. Halofuginone - the multifaceted molecule. *Molecules*. 2015; 20(1): 573-594.
14. Sundrud MS, Koralov SB, Feuerer M, et al. Halofuginone inhibits TH17 cell differentiation by activating the amino acid starvation response. *Science*. 2009; 324(5932): 1334-1338.
15. Chaitanya P, Reddy GD, Varun G, Srikanth LM, Prasad VVSR, Ravindernath A. Design and synthesis of quinazolinone derivatives as anti-inflammatory agents: pharmacophore modeling and 3D QSAR studies. *Medicinal Chemistry*. 2014; 10(7): 711-723. <https://doi.org/10.2174/1573406409666131128142843>
16. Farag DB, Farag NA, Esmat A, Abuelezz SA, Abdel-Salam Ibrahim E, Abou El Ella DA. Synthesis, 3D pharmacophore, QSAR and docking studies of novel quinazoline derivatives with nitric oxide release moiety as preferential COX-2 inhibitors. *MedChemComm*. 2015; 6(2). <https://doi.org/10.1039/C4MD00392F>
17. Yadav MR, Shirude ST, Parmar A, Balaraman R, Giridhar R. Synthesis and anti-inflammatory activity of 2,3-diaryl-4(3H)-quinazolinones. *Chemistry of Heterocyclic Compounds*. 2006; 42: 1038. <https://doi.org/10.1007/s10593-006-0201-4>
18. Ibrahim M. Design, synthesis, molecular docking and biological evaluation of some novel quinazolin-4(3H)-one derivatives as anti-inflammatory agents. *Al-Azhar Journal of Pharmaceutical Sciences*. 2012; 46(2): 185-203. <https://doi.org/10.21608/ajps.2012.7145>
19. Sathish NK, Shahensha S, Ali MI, Chethan IA. Synthesis, characterisation and anti-inflammatory activity of some novel quinazolin-4-(3H)-one analogues. *Indian Journal of Pharmaceutical Education and Research*. 2012; 46(2): 185-191. <https://www.ijper.org/article/46/2/185>
20. Kolomoets O, Voskoboynik O, Antypenko O, Berest G, Nosulenko I, Palchikov V, Karpenko O, Kovalenko S. Design, synthesis and anti-inflammatory activity of derivatives 10-R-3-aryl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones of spiro-fused cyclic frameworks. *Acta Chimica Slovenica*. 2017; 64(4): 902-910. <https://doi.org/10.17344/acsi.2017.3575>
21. Kerdphon S, Khamto N, Buddhachat K, Ngoenkam J, Paensuwan P, Pongcharoen S, Singh T, Meepowpan P, Jongcharoenkamol J. Structure-activity relationship and molecular docking of quinazolinones inhibiting expression of COX-2, IL-1 β , iNOS, and TNF- α through NF- κ B pathways. *ACS Medicinal Chemistry Letters*. 2023; 14: 1167-1173. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10510524/>
22. Mikra C, Petriki V, Tsioupros E, et al. Novel 3-amino-2-methylquinazolinone NF- κ B inhibitors: synthesis and potential anti-inflammatory function. *International Journal of Molecular Sciences*. 2026; 27(14): 6431. <https://doi.org/10.3390/ijms27146431>
23. Darwish SS, Chen PJ, Hamed MM, Wagdy RA, Chen SH, Abadi AH, Abdel-Halim M, Hwang TL, Engel M. Development of (4-phenylamino)quinazoline alkylthiourea derivatives as novel NF- κ B inhibitors. *Pharmaceuticals*. 2022; 15(7): 778. <https://doi.org/10.3390/ph15070778>
24. El-Malah AA, Gineinah MM, Khayat MT, Aljahdali AS, Safar MM, Almazmumi HA, Khinkar RM. Design, synthesis, molecular docking, and molecular dynamic studies of novel quinazoline derivatives

- as phosphodiesterase 7 inhibitors. *Frontiers in Pharmacology*. 2024; 15: 1389076. <https://doi.org/10.3389/fphar.2024.1389076>
25. Alharbi M, et al. New quinazoline derivatives with anti-inflammatory activity and computationally predicted PDE7A binding: synthesis, molecular modeling, and in silico pharmacokinetic evaluation. *Frontiers in Pharmacology*. 2026; 17: 1859798. <https://doi.org/10.3389/fphar.2026.1859798>
26. Winter CA, Risley EA, Nuss GW. Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. *Proceedings of the Society for Experimental Biology and Medicine*. 1962; 111: 544-547.
27. Mizushima Y, Kobayashi M. Interaction of anti-inflammatory drugs with serum proteins, especially with some biologically active proteins. *Journal of Pharmacy and Pharmacology*. 1968; 20(3): 169-173.