



– A REVIEW

QUINAZOLINE DERIVATIVES WITH POTENT ANTI-INFLAMMATORY AND ANTI-ALLERGIC ACTIVITIES

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ABSTRACT

The biosynthesis modulation of pro-inflammatory cytokines (PICs) has become an important strategy for pharmacological intervention in a variety of inflammatory and fibrotic disease states. Thus, inhibition of PICs will provide the basis for an effective choice of treatment in inflammatory disorders like rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), asthma, psoriasis, chronic bronchitis and cystic fibrosis. In this review, basic attention is directed towards the simple and fused substituted quinazolines with proven potencies whose quantitative data are consolidated from literature, which are possessing remarkable anti-inflammatory activity as nitric oxide synthase-II (NOS-II) inhibitors, nuclear factor kappa B (NFkB) inhibitors, tumor necrosis factor-alpha (TNF- α) inhibitors, interleukin-6 (IL-6) inhibitors and combined type 3 and 4 phosphodiesterase (PDE) inhibitors with both bronchodilatory and anti-inflammatory properties.

Key words: Inflammation mediators, Substituted quinazolines, Phosphodiesterase inhibitors, Carrageenin-induced paw oedema, Percent inhibition, Adenosine antagonists, Cyclooxygenase inhibitors.

INTRODUCTION

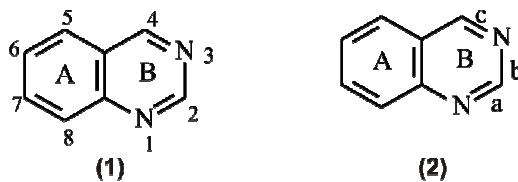
The aim of this review is to highlight the wide range of developments displayed by

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quinazolines in the treatment of inflammatory diseases and particular emphasis on potency specified in the screening assays over the last three decades. A growing interest and an absolute need for the discovery of new, selective and promising inhibitors with an improved safety and efficacy profile has stimulated us to present an attractive approach towards design and development of new anti-inflammatory and anti-allergic agents. The inflammation is a biological response to a series of biochemical reactions whose major function is protection of the body from infection and resolution of tissue damage caused by injury. The inflammation being a complex mechanism, different investigators screened their compounds with a variety of methods in different animal models. The numbers of methods employed were found to be unbelievably large. With proven pharmacological significance, quinazolines have become a favourite field for many investigators and their efforts are quite significant in literature. A couple of reviews in the past appeared in the literature giving a broader perspective of the pharmacological activities of quinazoline derivatives^{1,2}.

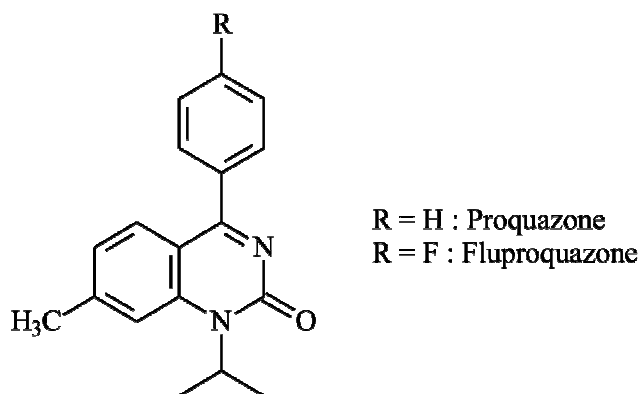
Interestingly, a large number of quinazoline derivatives are patented and there are enough indicators to suggest that several of them are potentially useful medicinal agents i. e., in various stages of development. If the current trend is any pointer, there could well be a good number of derivatives in clinical trials in near future. A large number of reports on quinazoline derivatives being as potential anti-inflammatory and anti-allergic agents, it was thought worthwhile to review them. This review is an effort to incorporate literature citations appeared during the past three decades i. e., between 1975-2005 and chemical abstracts of few patents have also been cited for reference. However, an effort has been made to include all the citations in this review but there can still be some more, which might have escaped our attention and the authors cannot rule out the doubt of its comprehensiveness. Only the compounds with proven potencies and whose quantitative data are profoundly reported in literature are included in the descriptive part of this review.

In order to format the review, the quinazoline compounds are classified based on the substituents present on different positions. The basic skeleton of quinazoline ring system **(1)** and the face of the fusion on hetero ring in quinazoline ring **(2)** as cited below.



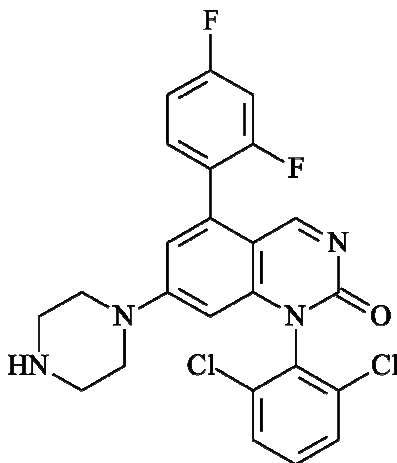
Quinazoline

Earlier in this century, first generation non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (ASA) became well established in the treatment of pain and inflammation. Continued research in this area led to a second generation of NSAIDs, such as phenylbutazone. Though this was considered as a significant improvement over the first generation, still it was felt that it is falling short of the desired activities. As a consequence, the third generation NSAIDs emerged and on an average, these agents are superior to the second generation in both; safety and efficacy. Examples of these new agents are 4-aryl-1-alkyl-2(1H)-quinazolinones³, particularly proquazone (1-isopropyl-7-methyl-4-phenyl quinazolin-2(1H)-one) and fluproquazone (4-(4-fluorophenyl)-1-isopropyl-7-methyl quinazolin-2(1H)-one)⁴. The overall anti-inflammatory profile of proquazone is comparable with that of indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid). It is very remarkable that proquazone is the first potent anti-inflammatory drug of a non-acidic nature, which is a potent prostaglandin synthesis inhibitor and a collagen-induced platelet aggregation inhibitor. Proquazone is also shown to be a highly effective and well - tolerated drug for the treatment of gout and RA.



Mitogen activated protein kinases (MAPK) are important signaling molecules that are activated by a number of extracellular stress stimuli. The events that are regulated by p38 MAPK lead to the production of cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β). The TNF- α and IL-1 β are pro-inflammatory cytokines produced in response to infection and other sources of cellular stress. TNF- α inhibition has represented a fundamental role in the control of chronic inflammatory diseases such as RA. Recently, research groups at Merck, Vertex and Glaxo-Smithkline have made efforts to develop new lead compounds to selectively inhibit p38 MAPK, represented by one of the compounds DQO-501 (1-(2, 6-dichlorophenyl)-4-(2, 4-difluorophenyl)-7-(piperazin-1-

yl) quinazolin-2 (1H)-one)⁵.



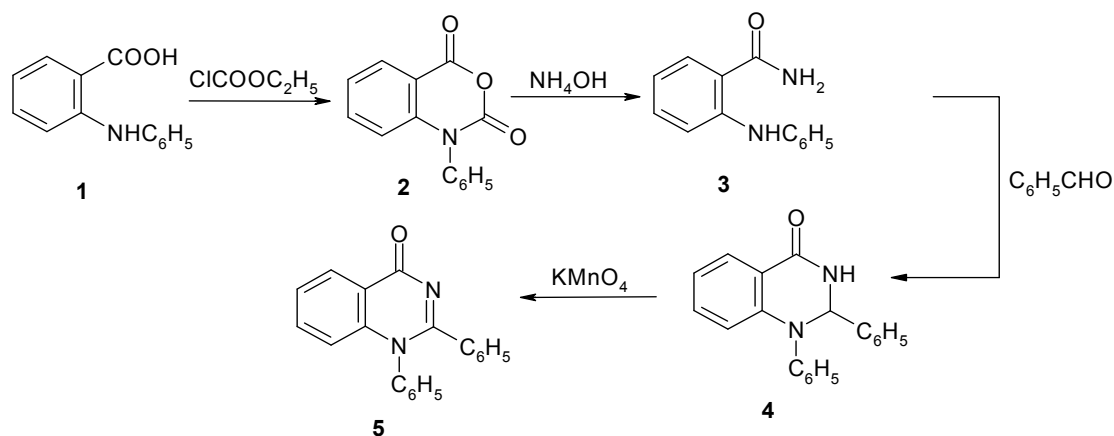
DQO-501

Chemistry

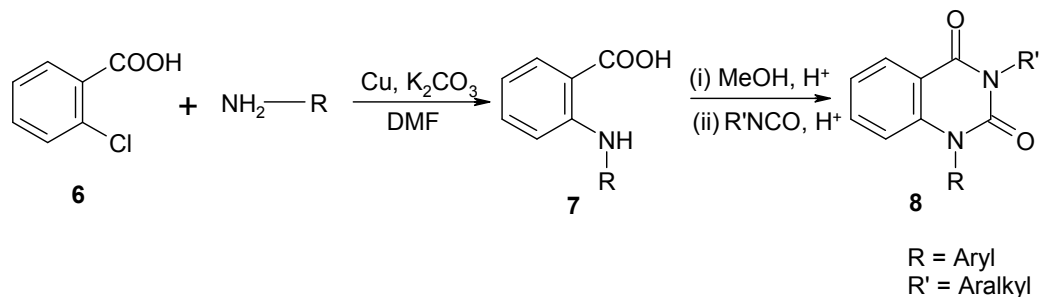
Quinazolone derivatives are synthesized mainly starting from anthranilic acid with appropriate substituent in order to have a specific substituent in three to four steps. Thus, several analogues of quinazolones have been synthesized and subjected to screening for anti-inflammatory activity using various animal models. Based on the substitution pattern in different positions of quinazolone derivatives, they are classified as (a) di-substituted, (b) tri-substituted, (c) tetra-substituted, (d) 1, 2-fused, (e) 2, 3-fused and (f) 3, 4-fused derivatives. Among all substituted quinazolone derivatives, several reports on 2, 3-disubstituted and 2, 3, 6-trisubstituted are available in literature. More specifically disubstituted quinazolone derivatives are (1, 2), (1, 3), (1, 6), (2, 3), (2, 4) and (3, 6). Trisubstituted quinazolone derivatives include (1, 2, 7), (1, 3, 7), (1, 4, 7), (1, 5, 7), (2, 3, 6), (2, 3, 7), (3, 6, 7) and (4, 6, 7). Tetrasubstituted quinazolone derivatives include (2, 3, 6, 8), (2, 4, 6, 7) and (4, 6, 7, 8). Similarly 1, 2-fused quinazolone derivatives include (1, 2, 7) and (1, 2, 4). 2, 3-fused quinazolone derivatives include (2, 3, 6, 7), (1, 2, 3) (2, 3, 6) and (2, 3, 6, 8). 3, 4-fused quinazolone derivatives include (2, 3, 4) and (2, 3, 4, 6). Several reports of synthesis being disubstituted quinazolone derivatives, representative examples have been outlined below.

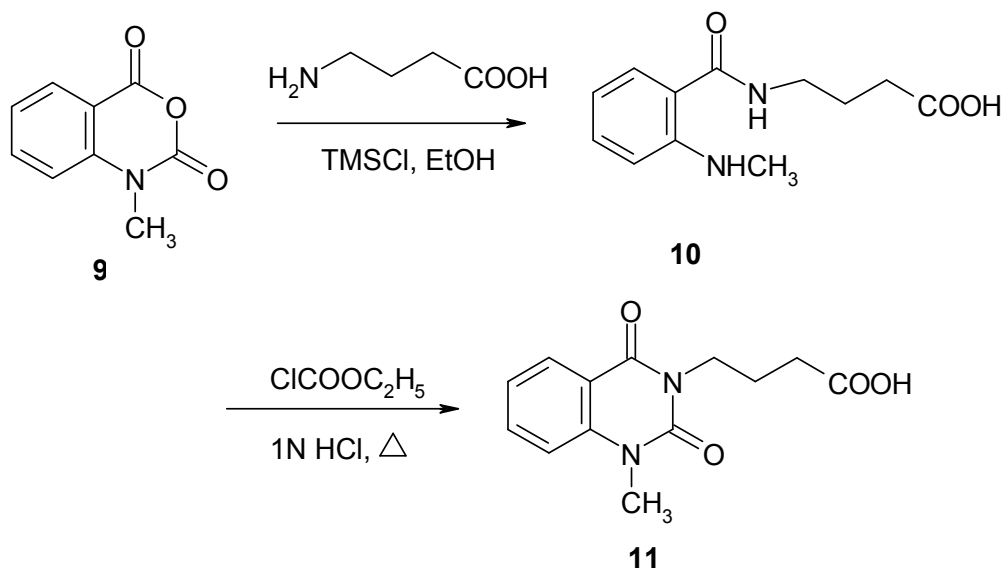
Substituents on position 1 and 2 of quinazolone molecule are known to have marked influence on anti-inflammatory activity with alkyl and aryl/substituted aryl groups respectively. Synthetic sequence^{6,7} of specific example starts from reaction of N-phenyl

anthranilic acid **1** with ethylchloroformate and 1-phenyl benzoxazin-2, 4-dione was obtained **2**, which is further hydrolysed to 1-(2- (phenylamino) phenyl) ethanone **3**. Product **3** is cyclised with benzaldehyde to give 2, 3-dihydro-quinazolin-4-one **4** followed by oxidation resulting in the formation of 1, 2-diphenyl quinazolin-4-one **5**. Sequence of these reactions is outlined below in **Scheme-1**.



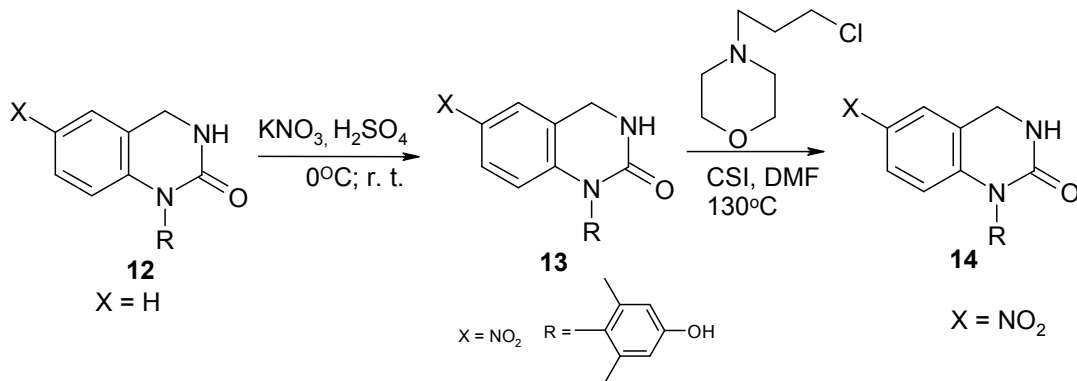
Similarly 1, 3-disubstituted quinazolin-2, 4-diones^{8,9} are also considered to show anti-inflammatory activity. Various substituents like alkyl, aryl and aralkyl groups have been introduced and the activity was observed in order to find an active quinazolone derivative. Synthetic efforts started from o-chlorobenzoic acid **6**. Amination **7**, esterification, followed by reaction with isocyanates resulted in 1, 3-disubstituted quinazol-2, 4-diones **8**. Alternately synthesis starts from 1-methyl-benzoxazin-2, 4-dione **9** in two steps. Primarily, reaction of 4-aminobutyric acid resulted in 4-(2-(methylamino) benzamido) butanoic acid **10** followed by cyclisation resulted in a product **11** (4-(1-methyl-2, 4-dioxo-1, 2-dihydroquinazolin-3(4H)-yl)butanoic acid). Reactions are given in **Scheme-2**.

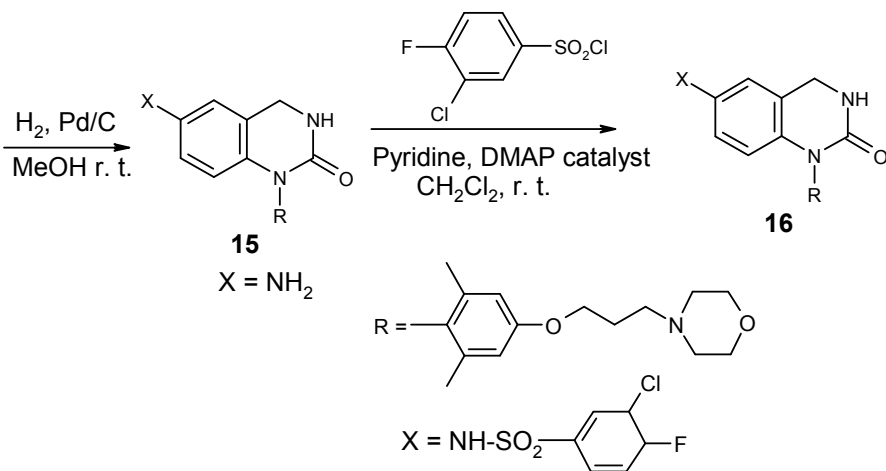




Scheme 2

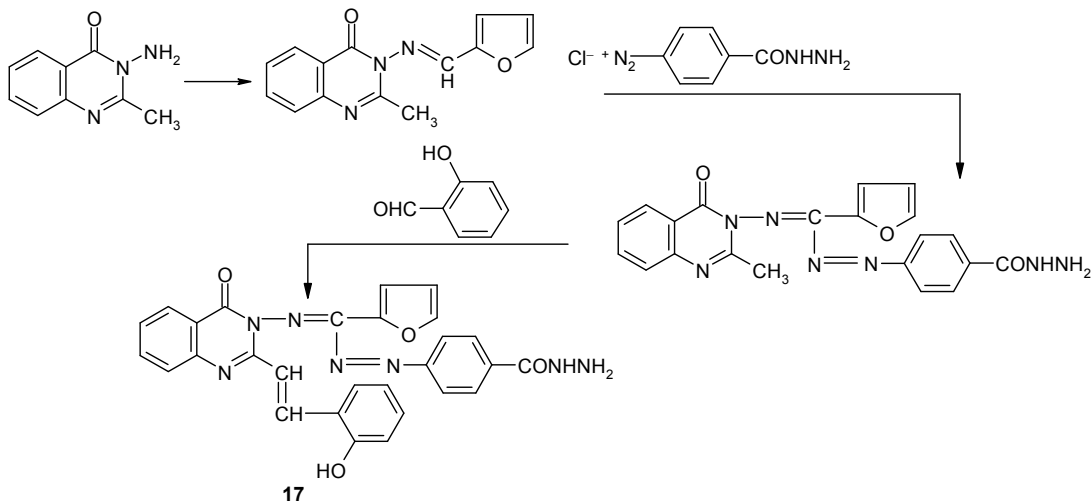
A number of 1, 6-disubstituted 3, 4-dihydroquinazolin-2(1H)-ones¹⁰ were synthesized and evaluated as anti-inflammatory agents. In order to show the activity, presence of substituent on position 1 of quinazolone molecule is crucial. In combination of position 1, 6th position is also introduced with aryl sulphonyl group. The synthetic sequence of these reactions is mainly nitration of 1-[4-(3-(3, 5-dimethyl phenoxy) propyl) morpholino] 3, 4-dihydroquinazolin-2(1H)-one **12** to nitro compound **13**, O-alkylation to compound **14** and reduction to compound **15** followed by sulfonylation, 6-[3-chloro-4-fluorocyclohexa-1, 5-diene-1-sulfonamido]1-[4-(3-(3, 5-dimethylphenoxy)propyl) morpholino] 3, 4-dihydroquinazolin-2(1H)-one **16** in as given was obtained **Scheme 3**.





Scheme 3

2, 3-Disubstituted quinazolinone derivatives¹¹⁻¹⁷ plays a prominent role in exhibiting anti-inflammatory activity. Among all the substituted quinazolones, a large number of 2, 3-disubstituted quinazolinone derivatives were reported.

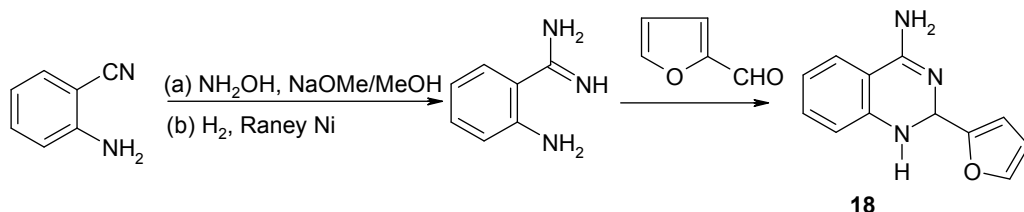


Scheme 4

In almost all, 2-position is substituted with alkyl group or substituted alkyl group, whereas position 3 is substituted with aryl, amine, substituted amine, pyrazole-fused, indole-fused and so on. Synthesis is mainly from anthranilic acid and a typical example is Schiff's base formation, diazotisation followed by reaction with aldehydes to yield 4-[[[2-

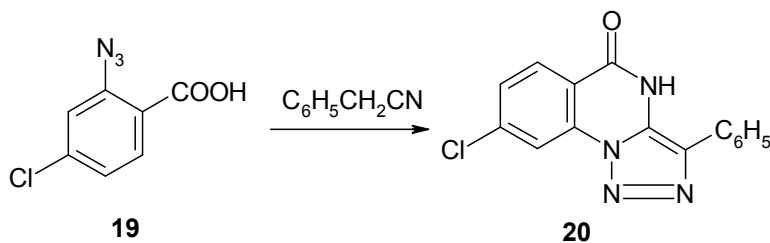
aryl ethynyl-4-oxo-3-(4H)quinazolino]-amino] furfuryl methyl]-azo] benzoic acid hydrazide **17**. The reaction scheme is outlined in **Scheme 4**.

A specific substituent on C-2 as well as on C-4 position of quinazoline ring show promising activity. Synthesis of 2, 4-disubstituted quinazolinone derivatives^{17, 18} have been reported in two different ways. One is starting from anthranilic acid and another is from o-aminobenzonitrile to yield 2-(furan-2-yl)-1, 2-dihydroquinazolin-4-amine **18**. Typical example has been outlined in **Scheme 5**.



Scheme 5

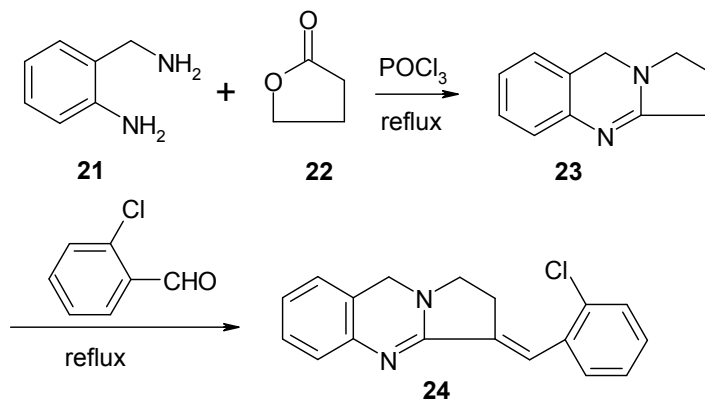
In addition to the number of various substituted quinazolines, some more quinazolines fused in 1, 2-position, 2, 3-position and 3, 4-position are also synthesized and found to show different activity than simple substituted quinazolines. More specifically 1, 2-fused quinazoline-4-ones¹⁹ are found as adenosine antagonists and are synthesised mainly from the reaction of 2-azido-4-chlorobenzoic acid **19** with benzyl nitrile resulted into 7-chloro-3-phenyl-[1, 2, 3] triazolo [1, 5-a] quinazolin-5(4H)-one **20** in a single step. The reaction is outlined in **Scheme 6**.



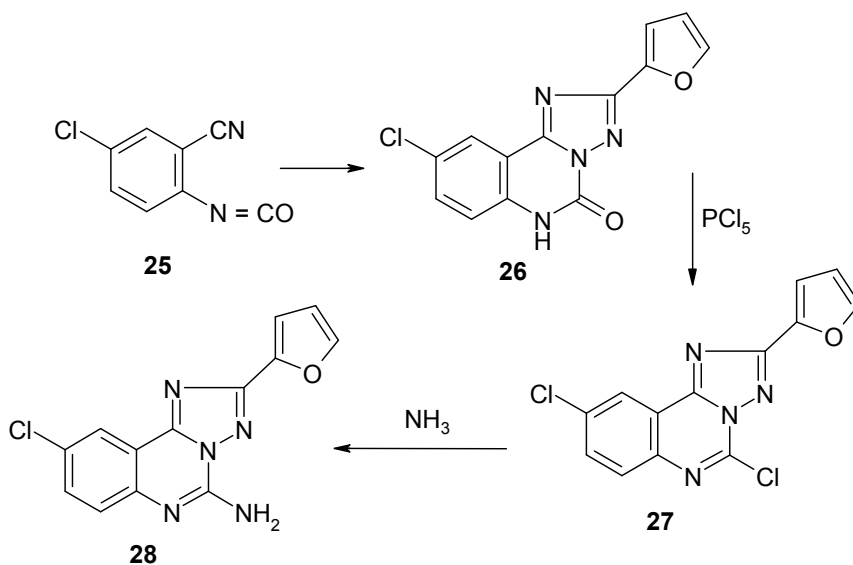
Scheme 6

Similarly, 2, 3-fused pyrrolidinoquinazolines²⁰ are also found to have great potential as drug in asthmatic diseases. Synthesis starting from condensation of 2-amino benzylamine **21** with γ -butyrolactone **22** gave the intermediate, 1, 2, 3, 9-tetrahydro pyrrolo[2, 1-b] quinazoline **23**, which was further condensed with benzaldehyde to yield the product (Z)-3-(2-chlorobenzylidene)-1, 2, 3, 9-tetrahydropyrrolo [2, 1-b] quinazoline

24 and details are given in **Scheme 7**.

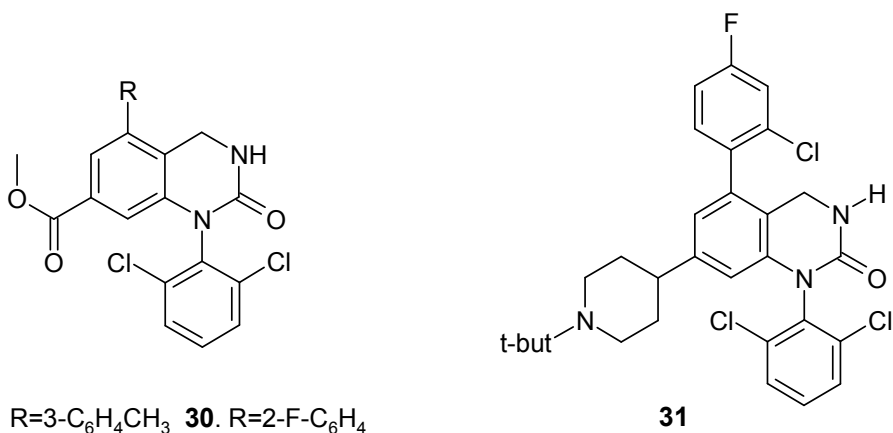


Further, 3, 4-fused triazolo quinazolines²¹ show activity as adenosine antagonists. Thus, *o*-isocyanato benzonitrile **25** on reaction with hydrazine produced 9-chloro-2-(furan-2-yl)-[1, 2, 4] triazolo[1, 5-*c*] quinazolin-5 (6H)-one **26** in step-1, which is further chlorinated to 5, 9-dichloro-2-(furan-2-yl)-[1, 2, 4] triazolo[1, 5-*c*] quinazoline **27** followed by amination the target compound 9-chloro-2-(furan-2-yl)-[1, 2, 4] triazolo[1, 5-*c*] quinazolin-5-amine **28** was obtained as shown in **Scheme 8**.

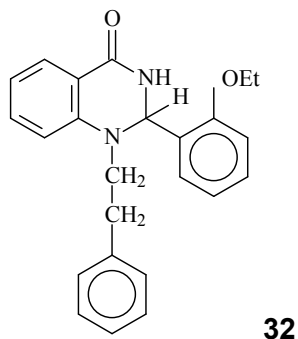


Pharmacological activity:

Gilberto et al.⁵ claimed that the methyl 1-(2, 6-dichloro phenyl)-2-oxo-m-tolyl-1, 2, 3, 4-tetrahydroquinazoline-7-carboxylate **29** and methyl 1-(2, 6-dichloro phenyl)-5-(2-fluorophenyl) -2-oxo- 1, 2, 3, 4-tetrahydroquinazoline-7-carboxylate **30** were found to have PIC_{50} (or) $\log (1/IC_{50})$ of 6.49 and 8.15, respectively as P_{38} MAPK inhibitors to treat chronic inflammatory states. Similarly Stelmach et. al²² reported 7-(1-tert-butyl piperidin-4-yl)-1-(2, 6-dichlorophenyl)-5-(4-fluorophenyl)-3, 4-dihydroquinazolin-2(1H)-one **31** as potent, orally bioavailable inhibitor of P_{38} MAP Kinase with IC_{50} 0.2 nM. The same compound also showed excellent suppression of TNF- α production in lipopolysaccharide (LPS) stimulated whole blood with IC_{50} 10 nM.



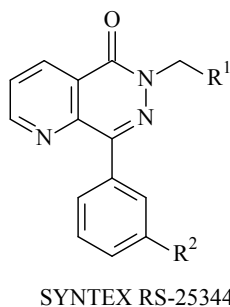
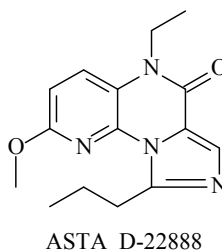
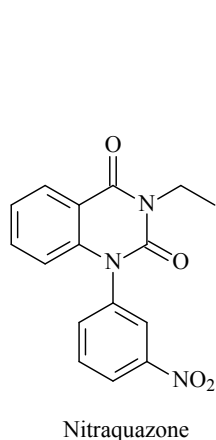
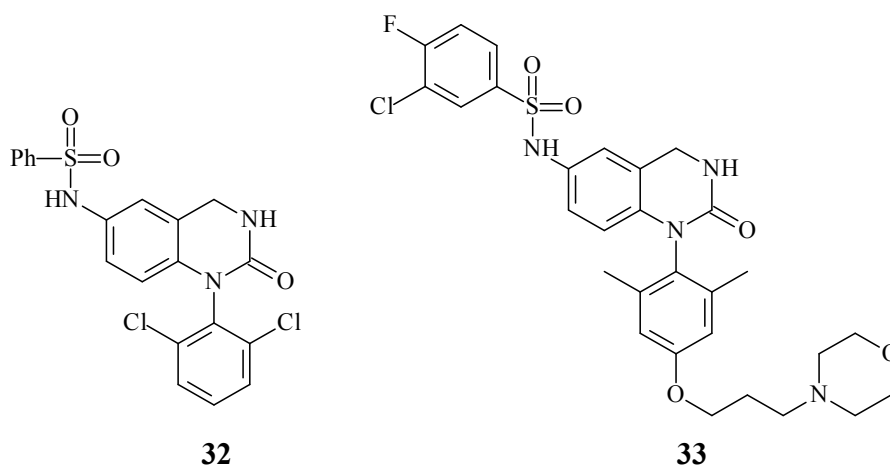
Ozaki et al.⁷ and Sadanandam et al.⁸ synthesized several 1, 2-disubstituted dihydroquinazolines.



A promising compound, such as 1-(β -phenethyl)-2-(2-ethoxyphenyl)- 2, 3-dihydro-4(1H) quinazolone **32** is considered as an anti-inflammatory agent with 55.13% inhibition

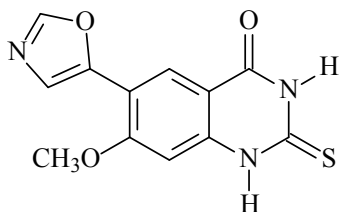
of the carrageenin-induced rat paw edema at 100 mg/kg (p. o.) higher than standard phenylbutazone, which exhibited 48.22% inhibition under similar conditions.

Schlapbach et al.¹⁰ presented dihydroquinazolinones **32,33** with P₃₈ kinase (MAPK) inhibitors as anti-inflammatory agents. Compound **32** was found to have potent activity as *in vitro* P₃₈ α IC₅₀ value of 0.053 μ M and *in vivo* (mouse) TNF- α release model, IC₅₀ value of 0.14 μ M. Compound **33** was better with greater potency and found to have *in vitro* P₃₈ α IC₅₀ value of 14 nM and 42% inhibition of TNF- α release after LPS stimulation in mice at a dose of 30 mg/kg (p. o.).

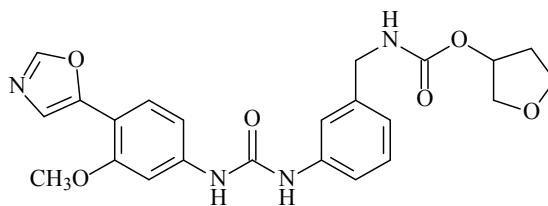


Piaz and Giovannoni²³, Lowe III et al.⁸ and Cottam et al.⁹ claimed some of the most interesting nitraquazone derived phosphodiesterase-4 (PDE 4) inhibitors as promising agents for the treatment of asthma. 3-Ethyl-1-(3-nitrophenyl) quinazoline-2, 4 (1H, 3H)-dione, nitraquazone was found to have an IC₅₀ value of 1.9 μM compared with its derivatives, Asta D-22888 and Syntex RS 25344 with IC₅₀ values of 3 μM and 0.28 μM, respectively.

A key enzyme involved in the de novo synthesis of guanosine nucleotides is inosine monophosphate dehydrogenase (IMPDH), which catalyses the oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP). Two isoforms of the enzyme have been identified and designated as type I and type II. Thus, inhibition of IMPDH II results in inhibition of cell proliferation in the immune system via inhibition of guanosine nucleotide production. This led to a number of researchers identifying IMPDH as a potential target for clinical intervention in diseases such as systemic lupus erythematosus, psoriasis and RA as well as organ transplant rejection. Efforts to find optimal replacements for the urea derivative VX-497¹⁸ led to the identification and development of cyclised quinazolinthione, a potent, selective inhibitor of IMPDH-II with improved pharmacological profile.



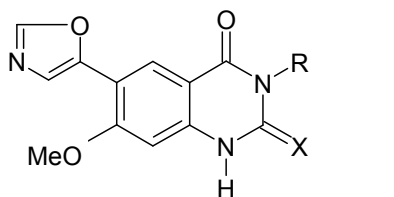
Quinazolinthione
IMPDH II (IC₅₀) = 30 nM



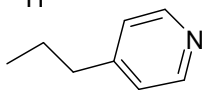
VX-497

Buckley et al.¹⁸ reported quinazoline thione **34** and quinazolin-dione **35** (with *in vitro* IMPDH II of 13 μM and 86 μM and *in vitro* peripheral blood mononuclear cells (PBMC) of 0.78 μM and 2.4 μM, respectively) as novel inhibitors of inosine

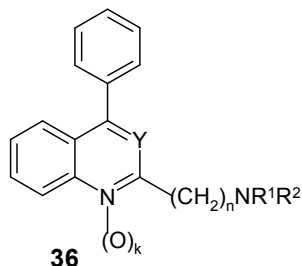
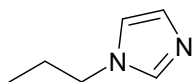
monophosphate dehydrogenase and as a potential target for medical intervention in diseases such as systemic lupus erythematosus, psoriasis and Sohda et al.²⁴ also reported compound **36**, with high (103%) edema inhibitory rate in rat adjuvant arthritis model as anti-inflammatory and anti-arthritis agent.



34 X=S; R=



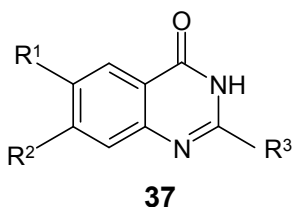
35 X=O; R=



36

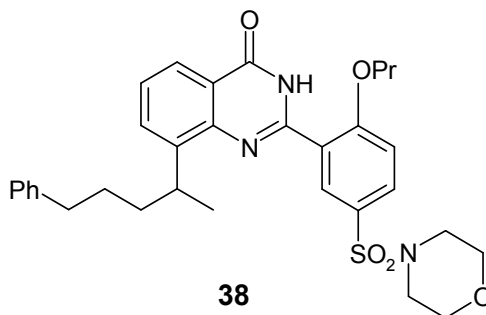
Y=N, CG, G=(un)esterified carboxyl group
 n=1-4; k=0, 1
 R¹, R²=H, (un)substituted hydrocarbon,
 (un)substituted heterocyclyl

Culshaw et al.²⁵ reported that the 2, 6, 7-trisubstituted-4-quinazolinones **37**, were effectively blocked calcium uptake in the range of about 1 nM – 10 μM as anti-hyperalgesic agent in fluorescence assay using Chinese Hoster Ovary (CHO) cells. Fred et al.²⁶ reported 2, 8-disubstituted quinazolinone **38**, with an IC₅₀ value of 0.5 nM for inhibition of PDE-II and an IC₅₀ value of 1 nM for inhibition of PDE-V as anti-inflammatory agent.



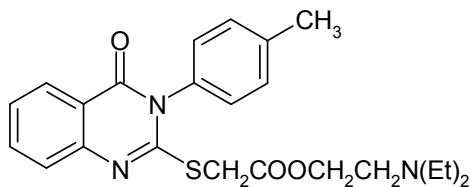
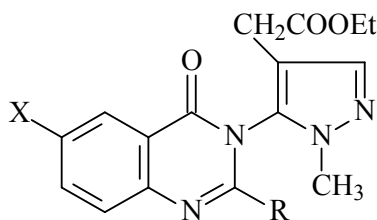
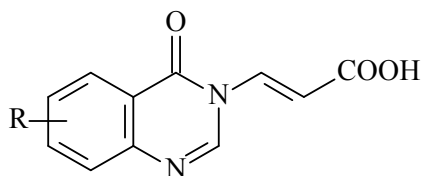
37

R¹ = Halo; R² = Halo, NO₂
 Alkyl Carbonyl, Alkyl, Cycloalkyl;
 R³ = Alkyl, alkoxy, NH₂



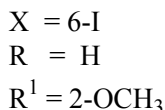
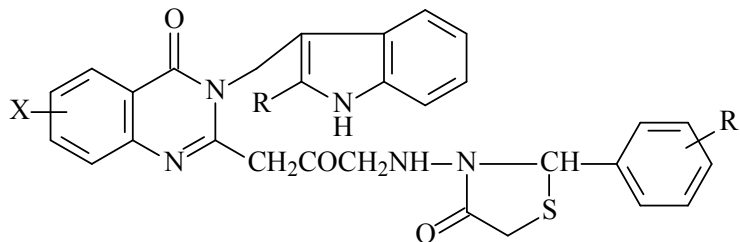
38

Our group, we^{11, 12} reported that the β-(N, N-diethylamino)ethyl-(3-(p-toluenyl)-3, 4-dihydro-4-oxo-quinazolin-2-yl) mercapto acetate **39** was found to show anti-histaminic activity with IC₅₀ 5 x 10⁻⁵ mol/litre. Similarly 2, 3-di-substituted quinazolones were reported by Kalsi et al.¹³, Algarsamy et al.^{14, 15} and Bansal et al.²⁷. However, these compounds showed moderate anti-inflammatory activity.

**39****40 X=H, R=CH₃, 41 X=Cl, R=H****42**

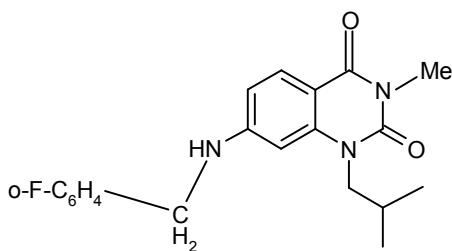
Daidone et al.¹⁶ and Maggio et al.²⁸ reported 2, 3-disubstituted quinazolones and 3, 6-disubstituted quinazolones, respectively. Specifically ethyl, 1-methyl-5-[2-substituted-4-oxo-3(4H)quinazolinyl]-1H-pyrazole-4-acetate **40** was found to show 33% and compound **41** showed 45% inhibition of carrageenan- induced rat paw edema at 100 mg/kg (p. o). LD₅₀(mg/kg, i. p) found to be greater than 750. Ronald et al.²⁹ reported 3, 6-di-substituted quinazolinone **42** analogues and considered them as anti-allergy agent in rat passive cutaneous anaphylaxis (PCA) test with 100% of inhibition at 16 mg/kg (i. p) and IC₅₀ 0.19 μM. Kumar et al.³⁰ reported 2, 3, 6-trisubstituted quinazolinones as potent anti-inflammatory, analgesic and cyclooxygenase-II (COX-II) inhibitors, of which 2-(O-methoxy phenylaminomethylacetyl-4'-oxo-1'-thiazolidinyl)-3-(indol-3'-yl)-6-iodo-4(3H)-quinazolinone **43** was found to have anti-inflammatory activity of 82.4% at 100 mg/kg (p. o) dose showing ulcerogenic activity of 10% of the animals with ulcers. The compound also showed 90% COX-II inhibitor activity with median effective dose, ED₅₀ of 35.4 mg/kg (p. o) along with approximate lethal dose, ALD₅₀ of >2000 mg/kg (p. o.). Similarly Saravana et al.³¹, Bhalla et al.³², Devsingh et al.³³ and Kumar et al.³⁴ reported 2, 3, 6-tri-

substituted quinazolinones as potent anti-inflammatory and analgesic agents.

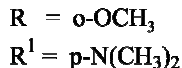
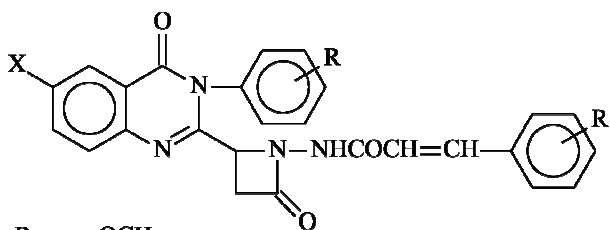


43

Michne et al.³⁵ reported several analogues of quinazolinones, of which 6-[[2-fluorophenyl) methyl] amino-3-methyl-1-(2-methylpropyl)quinazolin-2, 4-dione **44** was considered as potential immuno-suppressive and anti-inflammatory agent in nuclear factor of activated T-cells-1-regulated β -galactosidase expression (NFAT) with IC₅₀ 1.32 μ M. Rani et al.¹⁷ also reported 3-(o-methoxy phenyl)-2-(p-dimethylamino phenyl)-chalconylamino azetidinon-2'-yl)-quinazolin-4(3H)-one **45**, with less ulcerogenic potentiality as compared to phenylbutazone (UD₅₀ = 66.6mg/kg i. p.) showing anti-inflammatory activity of 66.64% reduction in paw edema at a dose of 100 mg/kg p. o with UD₅₀ value of 210 mg/kg i. p. along with ALD₅₀ value of >1000 mg/kg p. o.



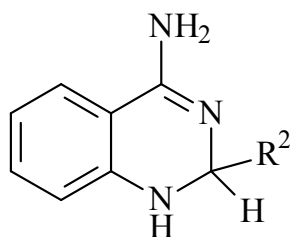
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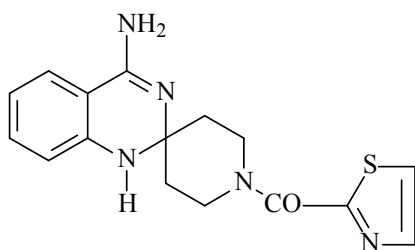
45

Nitric oxide synthases (NOS) are a family of closely related heme-based oxygenases, which synthesize nitric oxide from the natural amino acid L-arginine. Three isoforms of the enzyme have been characterized. Two of these, endothelial NOS (e-NOS) and neuronal NOS (n-NOS), are constitutive and calcium dependent. The third isoform, inducible NOS (i-NOS), is formed in response to pathological challenges. It is not

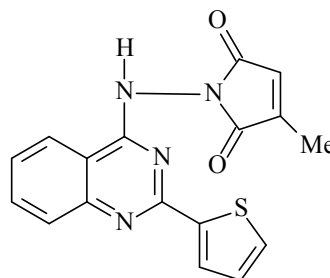
dependent on calcium and produces much higher concentrations of nitric oxide than the others. Overexpression of i-NOS has been implicated in a number of inflammatory diseases like, septic shock and RA. Tinker et al.³⁶ reported 2 – furanyl – 1, 2 – dihydro – 4 – quinazolinamine, **46** with i – NOS IC₅₀ value of 0.2 μM. Hamley et al.³⁷ reported compound **47**, a 2, 4-disubstituted quinazoline, with an IC₅₀ value of < 25 μM against nitric oxide synthase as anti-inflammatory agent. Palanki et al.³⁸ reported 2, 4-disubstituted quinazoline **48**, with an IC₅₀ value of 0.04 μM against NFκB for treating immunoinflammatory conditions such as osteoarthritis and autoimmune diseases like psoriasis, inflammatory bowel disease and glomerulonephritis.



46 R²= 2-furanyl



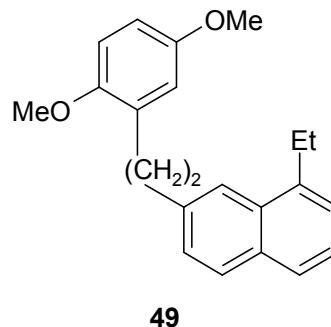
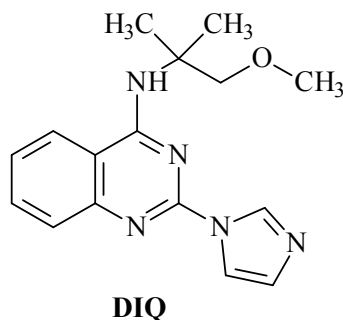
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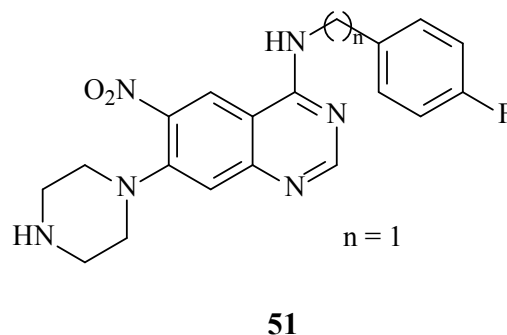
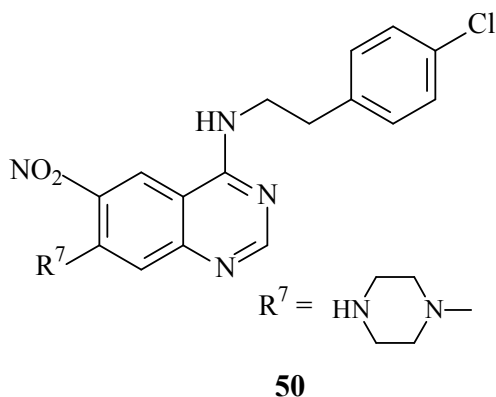
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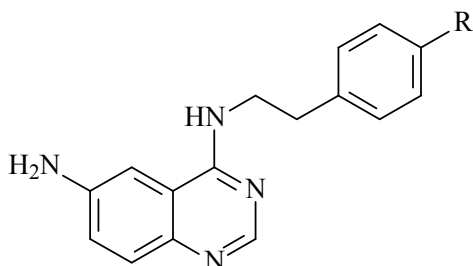
Macrophages and smooth muscle cells activated by cytokines and LPS release a large amount of NO, which plays a key role in the pathophysiology of a variety of diseases, including sepsis and inflammation. A series of compounds, which were developed as inhibitors of PDE types IV and V, by assessing their inhibitory effects on nitrite production by LPS-stimulated RAW 264.7 cells. 4-(1, 1-Dimethyl-1, 2-methoxy-ethylamino)-2-(imidazol-1-yl)quinazoline dihydrochloride, DIQ inhibited more than 95% of the nitrite production at 50 μM dose dependently³⁹. Nassbaumer⁴⁰ have reported compound **49**, a trisubstituted phenyl and quinazoline derivatives with an IC₅₀ value of 10 nM for the inhibition of proliferation in the human keratinocyte cell line HaCaT and IC₅₀ between 10

and 200 nM for the inhibition of tumor cell proliferation for the treatment of inflammatory and proliferative skin diseases and cancer.



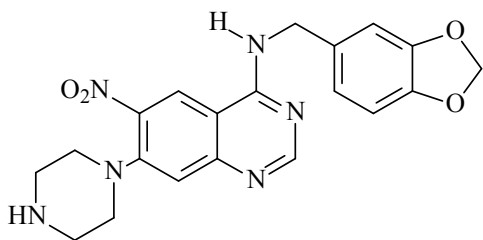
Tobe et al.^{41, 42} reported 4-chlorophenethyl aminoquinazoline derivative, **50** and 6-nitroquinazoline, **51** with IC_{50} values 0.8 μ M and 0.4 μ M, respectively for the inhibition of TNF- α production from human peripheral blood mononuclear cells (PBMCs) stimulated by LPS and IC_{50} values 1.1 and 3.0 of ConA-induced proliferation of mice spleen cells for inhibition of T-cell proliferation, respectively as novel and unique anti-inflammatory agents. The same group has reported^{43, 44} 4-phenethylaminoquinazoline **52** and 4-substituted-6-aminoquinazoline **53** with IC_{50} values 11 nM and 2 nM, respectively for the inhibition of NF κ B activation in human Jurkat cells transfected with path detect cis-reporter plasmid, stratagene, PNF κ B-Luc and IC_{50} values 7 nM and 3 nM for the inhibition of TNF- α production from murine splenocytes stimulated with LPS, respectively for anti-inflammatory activity.



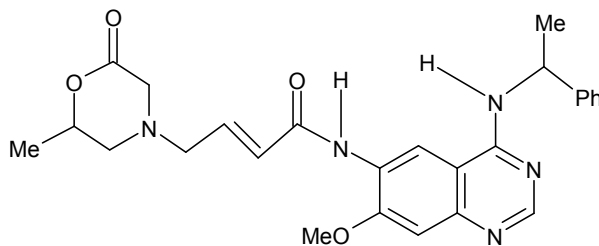


52 R = PhO; 53 R = n-pentyloxy

In continuation of their work, Tobe et al.⁴⁵ reported a 4-(substituted amino) - 6-nitro-7-(1-piperazino) quinazoline **54** with an IC_{50} value of 78 nM for inhibition of TNF- α production from human PBMCs stimulated by lipopolysaccharides (LPS), 2743 nM for inhibition of ConA-induced proliferation of mice spleen cells, 4240 nM for the growth inhibition of human PBMCs stimulated by LPS and ED_{50} of 26 mg/kg (p. o) as anti-inflammatory agent. Birgit et al.⁴⁶ reported compound **55**, a 4, 6, 7-trisubstituted quinazoline derivative, as tyrosine kinase inhibitor with ID_{50} of 0.3 mg/kg for the treatment of inflammatory illness.

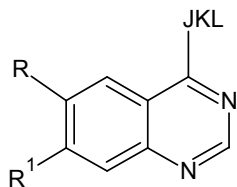


54



55

Timothy et al.⁴⁷ reported 4, 6, 7-trisubstituted quinazoline derivative **56** with an IC_{50} value $\leq 30 \mu M$ for inhibition of inflammation modulator, IKK β .

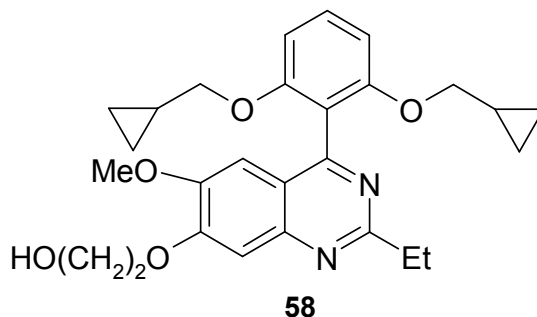
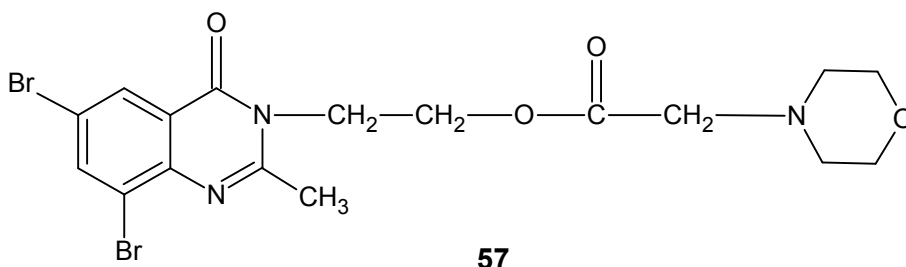


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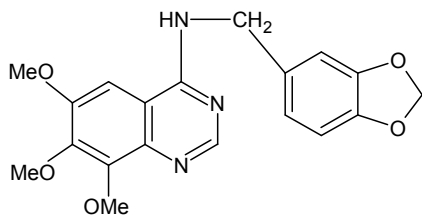
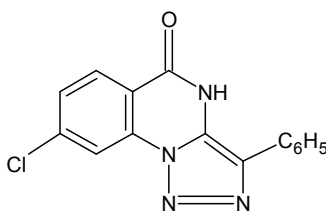
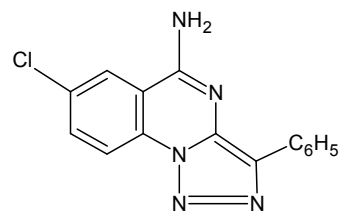
JK, JL, KL = Heterocyclic

R, R¹ = H, halogen, (un) substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, NH₂, cycloalkyl, heterocyclic, CN, NO₂, acyl, alkoxycarbonyl, CONH₂, SO₂, NH₂

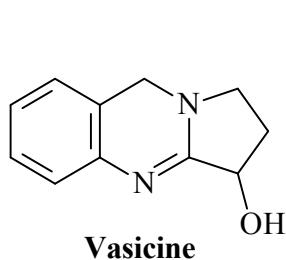
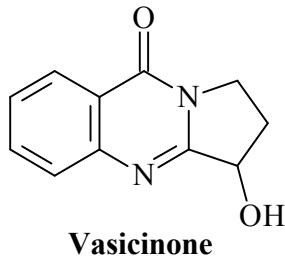
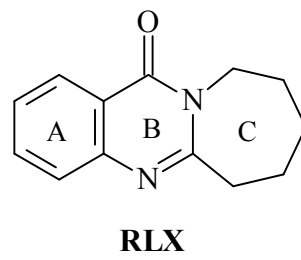
Reddy et al.^{48,49} and Ramasarma et al.⁵⁰ reported several 2, 3, 6, 8- tetra substituted quinazolone derivatives. Among them, a promising anti-inflammatory agent **57** showed 75% inhibition of rat paw edema at a dose of 100 mg/kg and LD₅₀ > 2000. Baba et al.⁵¹ and Charpiot et al.⁵² have been reported a number of analogues of 2, 4, 6, 7-tetrasubstituted quinazolones. A potential molecule **58** was found to be an inhibitor of the release of TNF- α induced by LPS and interferon- γ from human PBMCs with IC₅₀ 79 nM exhibiting anti-inflammatory properties.



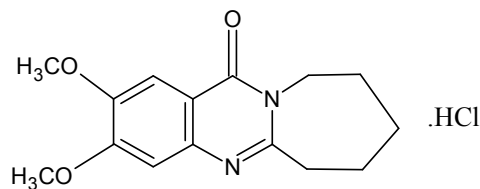
Takase et al.⁵³ reported a number of analogues of 4-((3, 4, -(methylene dioxy) benzyl)-mino)-6, 7, 8-trimethoxy quinazolines, **59** with cyclic guanosine monophosphate phosphodiesterase cGMP-PDE inhibitory activities on five PDE isozymes with PDE V (IC₅₀ 0.36 + 0.09 μ M and EC₅₀ 1.96 + 0.58 μ M) from the activation of guanylate cyclase *in vivo* experiments. Bertelli et al.¹⁹ reported 1, 2, 3-triazolo[1, 5-a]quinazolines **60**, **61** in high affinity receptor that inhibit adenylate cyclase, A₁ and low affinity receptor stimulatory to adenylate cyclase, A_{2A} adenosine receptor binding assays, whose K_i values in binding to A₁ adenosine receptor in bovine cortical membranes found to be 148 \pm 16 nM and 900 \pm 102 nM, respectively; whereas K_i values in binding to A_{2A} adenosine receptor in bovine striatal membranes found to be >10, 000 nM and 1667 \pm 118 nM, respectively.

**59****60****61**

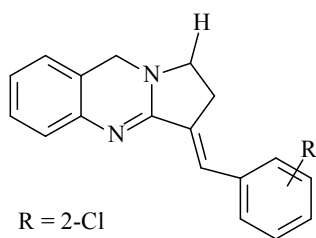
There are various factors such as exercise, allergen exposure, viral infections, irritants and environmental chemicals, etc., which are responsible for inducing symptoms of asthma and allergic asthma. It is a complex and chronic disease characterized by reversible airway obstruction, airways inflammation and bronchial hyper - responsiveness. The first and second reports of the national asthma education and prevention programme expert panel in US and similar reports from other countries have been beneficial in the management of asthma. Vasicine and its oxidized product vasicinone are the alkaloids obtained from the leaves of plant *Adhatoda vasica* Nees, family Acanthaceae and both possess *in vitro* and *in vivo* bronchodilatory activity.

**Vasicine****Vasicinone****RLX**

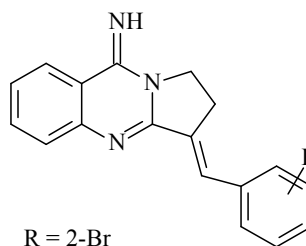
Vasicinone has been reported to possess antiasthmatic activity comparable to sodium chromoglycate. Several modifications on vasicine and vasicinone have been made to get better uterotonic or bronchodilatory effects. This resulted in the development of a compound 2, 3, 4, 5-tetrahydroazepino [2, 1-b] quinazolin-11(1H)-one, (RLX), which has been reported to be 6 to 10 times more potent than aminophylline⁵⁴. Jindal et al.⁵⁴ reported nitrogen bridge head compound **62** with *in vitro* bronchodilatory activity in guinea pig trachea precontracted with acetylcholine (1 μ g/mL) having % relaxation of 82.14 at 20 μ g/mL concentration.

**62**

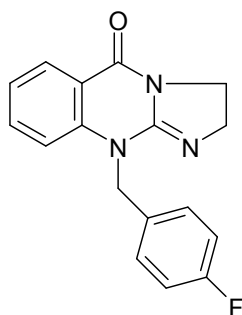
Anderskewitz et al.²⁰ reported pyrrolidinoquinazolinone **63** as human chemokine receptor (seven transmembrane G-protein coupled receptor), CCR₃ modulator proved to be an agonist with K_i value 28 nM. Starting with lead compound with K_i value of 110 nM, which turned out to be an antagonist of eotaxin at the CCR₃ receptor and have potential as drugs in asthmatic diseases. Hardtmann et al.⁵⁵ reported 2, 3-fused quinazolinone derivative **64** as bronchodilatory agent with 83% protection at 7.5 mg/kg (P. o).



R = 2-Cl

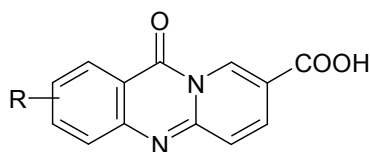


R = 2-Br

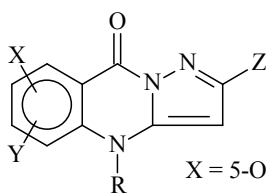
63**64**

Schwender et al.⁵⁶ reported 11-oxo-11H-pyrido[2, 1-b]quinazolin-8-carboxylic acid **65** with 100% inhibition at 0.5 mg/kg i. v., IC₅₀ value, 0.94 μM and ID₅₀ : 0.05 at 0.75 mg/kg p. o dose required to achieve 50% inhibition in passive cutaneous anaphylaxis (PCA) test showing antiallergy activity. Sircar et al.⁵⁷ reported 4, 9-dihydro-9-oxo-

pyrazo[5, 1-b]quinazoline-2-carboxylic acids **66** with 100 (0.1) % inhibition (i. v.) at 79 mg/kg p. o in the PCA test. They also reported 2-(1H-tetrazol-5-yl)pyrazolo [5, 1-b]quinazolin-9(4H)-one, **67** with 100 (0.1)% inhibition (i. v.) at 8 mg/kg p. o in the PCA test as antiallergy agents. Similarly, 2, 3-fused quinazoline derivatives were reported by Venuti et al.⁵⁸ and Kamal and Sattur⁵⁹.

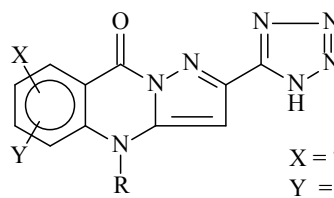


65 R = 2-CH₃



X = 5-OCH₃;
Y = H;
Z = COOH;
R = H

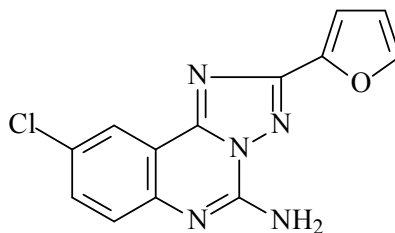
66



X = 7-F
Y = H;
R = CH₃

67

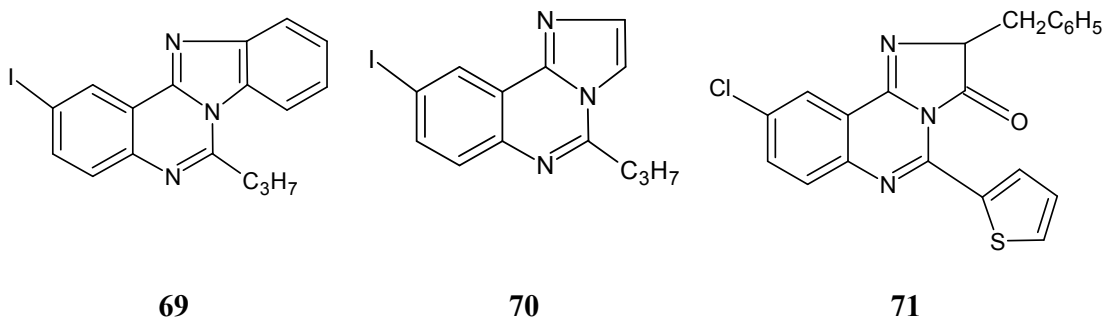
Francis et al.⁶⁰ reported a number of triazolo-quinazoline analogues and compound **68**, which was found with A₁ receptor binding IC₅₀ value 21 ± 3 nM and A₂ receptor binding IC₅₀ value of 3.3 ± 1.7 along with guinea pig cerebral cortex IC₅₀ 20 nM and guinea pig trachea IC₅₀ 3 nM as adenosine antagonists.



68

We have reported^{61,62}, 6-substituted benzimidazolo[1, 2-c]quinazoline **69** for its bronchodilatory activity with *in vivo* % protection of 75.7 and *in vitro* IC₅₀ 1.1 x 10³ ng/mL. Further 5-alkyl-2, 3-dihydroimidazo[1, 2-c]quinazoline **70** has been also for its bronchodilatory activity with *in vivo* % protection of 87.1 and *in vitro* IC₅₀ 1.1 x 10³

ng/mL. Similarly 3, 4-fused quinazolines **71** reported by El-Kerdawy et al.⁶³ found to show only 7.7% reduction of edema in carrageenan- induced rat paw edema model for anti-inflammatory activity. A dramatic decrease in activity was observed, when compared to 6-chloro-4-phenylalanine-2-thiophenoquinazoline, which showed 33.7%.



CONCLUSION

In general, quinazoline derivatives are known to possess wide range of activities. A specific activity depends on the substituent present at an appropriate position of quinazoline. Among the simple quinazoline derivatives, 1-substituted dihydroquinazolinones act as P₃₈ MAPK inhibitors for anti-inflammatory activity, whereas 1, 2-disubstituted quinazolinones exhibit both; analgesic and anti-inflammatory activities. On qcritical comparison between 1, 3-disubstituted quinazolin-2, 4-diones with no substitution in benzene ring it was found that they act as PDE 4 inhibitors for anti-asthmatic activity, whereas 1, 4-disubstituted quinazolin-2-one derivatives with substitution in benzene ring at position-6 act as bronchodilators. At the same time, both the analogues possess anti-inflammatory activity. It is interesting to note that 2-substituted quinazoline derivatives possess multiple therapeutic activities like anti-allergic, analgesic, PDE 2, PDE 5 inhibitors and anti-inflammatory, whereas 2, 3-disubstituted quinazolin-4-ones with substitution on benzene ring at positions-6, 8 show anti-histaminic, anti-writhmogenic and COX-II inhibitory activities. Similarly, 2, 4-disubstituted quinazoline derivatives with substitution on benzene ring at position-6 possess remarkable anti-inflammatory activity as NOS-II inhibitors, NFKB inhibitors, TNF- α inhibitors, IL-6 inhibitors and combined type 3 and 4 PDE inhibitors with both; bronchodilatory and anti-inflammatory properties. The piperazine ring on C (7) – position of quinazoline is considered as best framework to show activity. The introduction of a fluorine atom on the phenyl group resulted in reduced cell toxicity as well as improved inhibitory activities. Thus, 6-nitro-7-(1-piperazino) quinazolines exhibited inhibitory activities towards both

TNF- α production and T-cell proliferation *in vitro* on oral administration. Replacement of the NH group with several N-alkyl groups at C (4)- position of quinazoline and more specifically, N-methyl analogue improved lipophilicity as a result greater inhibitory activity on TNF- α production *in vivo* as well as oral bio-availability and it is used clinically as an anti-autoimmune disease agent. Further 3-pyrazole substituted 4-quinazolones were found to be associated with appreciable anti-exudative properties, reduced ulcerogenic effects and systemic toxicity. Another best basic framework identified was the 6-amino-4-phenethylamino quinazoline skeleton, which afforded highly potent inhibitory activities towards both NF κ B activation and TNF- α production along with an excellent *in vivo* efficacy by reducing the edema formation seen in carrageenin-induced inflammation of the rat hind paw. Alternately, among the fused substituted quinazolines, 1, 2-fused quinazolines are reported for A₁ and A_{2A} adenosine receptor binding assays whereas 2, 3-fused quinazolines have been reported as anti-allergies, bronchodilatory, adenosine antagonists and PDE inhibitors as promising agents in the treatment of asthma. Remarkable bronchodilatory and anti-inflammatory activities are reported for 3, 4-fused quinazolines.

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