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METHODS OF SYNTHESIS OF QUINAZOLINES AND THEIR CONDENSED ANALOGUES – POTENTIAL ANTI-INFLAMMATORY AGENTS (REVIEW)

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Abstract

Present review is critical analysis of recently published data devoted to the search of the novel anti-inflammatory agents among substituted and condensed quinazolines. It has been shown that anti-inflammatory activity is typical for various quinazoline-containing compounds including substituted quinazolin-4-ones, quinazolin-4-amines, condensed and spiro-condensed quinazolines. The features of target compounds synthesis were systematized and discussed. It was shown that synthesis of quinazoline-containing anti-inflammatory agents in most of cases based on modification of anthranilic acid derivatives, substituted 2-aminobenzonitriles or isatoic anhydride. Particular attention was paid to the discussion of 2-azaheterylanilines as original initial compounds for synthesis of condensed quinazolines with promising anti-inflammatory activity. The mechanisms of quinazolines biological activity have been presented and discussed as well. It has been shown that described compounds can effect on COX-1, COX-2, LOX-15, NO, PGE2, IL-1b, IL-6, TNF-a and other typical for anti-inflammatory agents' biomolecular targets. For some series of compounds, the structure-biological activity relationships were discussed. The data presented in review substantiates the reasonability of the search of new highly effective and low-toxic drugs with anti-inflammatory activity among quinazoline containing compounds.

Keywords: quinazolones-4; quinazolin-4-amines; condensed and spiro-quinazolines; synthesis; anti-inflammatory activity.

МЕТОДИ СИНТЕЗУ ХІНАЗОЛІНІВ ТА ЇХ КОНДЕНСОВАНИХ ПОХІДНИХ – ПОТЕНЦІЙНИХ ПРОТИЗАПАЛЬНИХ АГЕНТІВ (ОГЛЯД)

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Анотація

Представлений огляд є критичним аналізом актуальних опублікованих даних, що присвячені пошуку нових протизапальних засобів серед заміщених та конденсованих похідних хіназоліну. Показано, що протизапальна активність характерна для різних хіназолін-вмісних сполук, зокрема заміщених хіназолін-4-онів, хіназолін-4-амінів, конденсованих та спіроконденсованих хіназолінів. Узагальнено та обговорено особливості синтезу цільових сполук. Показано, що синтез протизапальних агентів на основі похідних хіназоліну в більшості випадків базується на модифікації похідних антранілової кислоти, заміщених 2-амінобензонітрилів або ізатового ангідриду. Особливу увагу приділено обговоренню 2-азагетериланілінів як оригінальних вихідних сполук для синтезу конденсованих хіназолінів з перспективною протизапальною дією. Представлено та обговорено механізми біологічної активності хіназолінів. Показано, що описані сполуки можуть впливати на COX-1, COX-2, LOX-15, NO, PGE2, IL-1b, IL-6, TNF-a та інші типові для протизапальних засобів молекулярні мішені. Для деяких сполук обговорені взаємозв'язки «будова – біологічна активність». Наведені в огляді дані обґрунтовують доцільність пошуку нових високоефективних і малотоксичних препаратів з протизапальною дією серед хіназолін-вмісних сполук.

Ключові слова: хіназолони-4; хіназолін-4-аміни; конденсовані та спіро-конденсовані хіназоліни; синтез; протизапальна активність.

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Introduction.

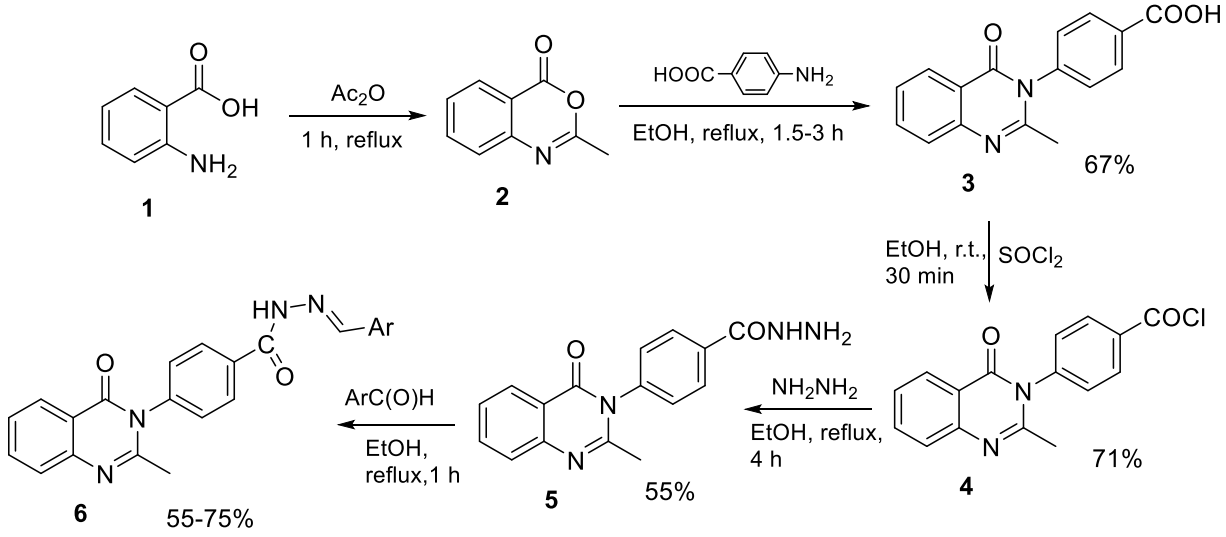
Quinazolines and their derivatives are quite studied objects of organic and medical chemistry, the investigation of which started in the 19-th century and has remained actual till nowadays. A large number of surveys [1–13] are dedicated to the fundamental aspects of chemistry of the considered class of compounds. The interest to quinazolines is firstly associated with high biological activity of their natural analogues [14–18], secondly, quinazolines and their derivatives are highly effective biologically active compounds with a wide spectrum of pharmacological action [5; 6; 8; 11; 12; 19–47]. Due to implementation and application of innovational technologies it has been established that the considered class of compounds has affinity for adenosine, benzodiazepine, NMDA, AMPA, KA, 5-HT3, tyrosine kinase, SYK-kinase, PARP-1-receptors, and they are inhibitors of phosphodiesterase 10A (PDE10A), dihydrofolate reductase, glucosidase, topoisomerase, thymi–dylate synthase etc. [6; 12; 19–47].

Thus, the considered class of compounds is characterized by hypoglycemic, diuretic, anti–convulsant, anti-tumor, anti-virus, anti-tuber–culosis, antimalarial, antibacterial and other types of activity. The above-mentioned led to implemen–tation into medical practice of a wide range of anti-tumor medical products («Gefinitib», «Erlotinib», «Vandetanib», «Lapatinib», «Dacomitinib», «Afatinib», «Trimetrexate» etc.) [27; 30; 31; 48]. It should be noted that quinazolines are also used in medical practice as hypotensive («Prazosin», «Doxazosin»), hypoglycaemic («Linagliptin»), diuretic («Metolazone», «Quinethazone»), anti-inflammatory («Proquazone»), antiviral, anti–bacterial medicaments [32–34]. Despite a great number of "classical" methods of synthesis of quinazolines [1; 2], numerous synthetic approaches to their formation with application of various technologies were generalized and revealed in recent years. Thus, the last review [49] is dedicated to the discussion of methods of obtaining the given heterocycle with application of heterogeneous catalysis, reactions of microwave synthesis, reactions based on ionic liquids and synthetic resins, catalytic reactions with the usage of transitional metals (ruthenium, zinc, rhodium, cobalt, nickel, copper, palladium etc.). However, significant academic achievements in chemistry and biology of quinazolines and their derivatives, steady saturation of pharmaceutical market with anti-tumor drugs keeps the mentioned class of substances promising in terms of search for anti-inflammatory medicaments [50]. Therefore, in this review we generalize the literary data of the last 10 years concerning the development of synthesis methods of quinazolines and their condensed analogues as potential anti-inflammatory agents.

1.1 Methods of synthesis of substituted quinazolin-4-ones

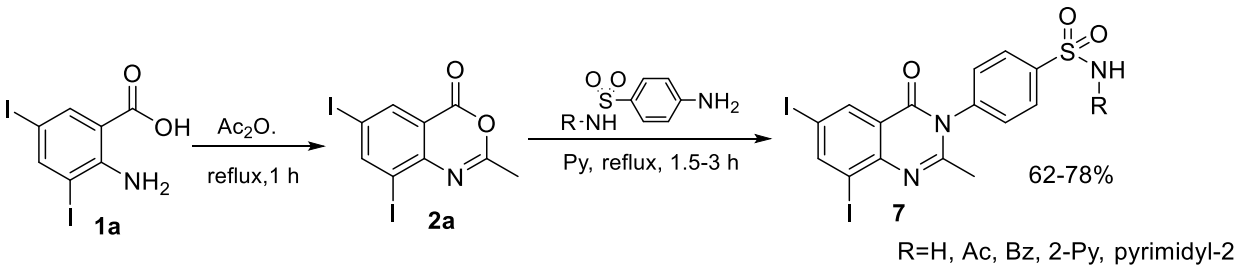
As it was noted, quinazolin-4-ones are quite studied objects in medical chemistry. Firstly, they have simple methods of synthesis, secondly, they are used as parent compounds for the synthesis of other functional derivatives of quinazolin, thirdly, they exert a wide spectrum of pharmacological action, including anti-inflammatory one. Thus, A. Narendra Babu's co-authored work is dedicated to the synthesis of perspective anti-inflammatory agents. The authors used a deliberately "pharmacophore" fragment – 2-aminobenzoic acid **1** (**Scheme 1**) [51]. The approach to synthesis of quinazolin-4-ones **3** is «traditional», namely the formation of 2-methylbenzooxazin-4-one **2** with 2-aminobenzoic acid and acetic anhydride, with subsequent interaction of the compound **2** with *p*-aminobenzoic acid. 4-(2-Methyl-4-oxoquinazolin-3(4*H*)-yl)benzohydrazide **5** was obtained by hydrazinolysis of the correspondent chloranhyd–ride **4**. The targeted *N'*-arylidene-4-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzohydrazide deri–vatives **6** were synthesized with the yield of 55-75% by interaction with hydrazide **5** with the range of benzaldehydes in an alcohol medium (**Scheme 1**). The compounds **6** showed a moderate anti-inflammatory activity (33-67 %) on the experimental carrageenan-induced rat paw edema model.

Zayed and co-authors described the synthesis and anti-inflammatory activity of the range of iodine-containing derivatives of quinazolin-4-one **7** with «pharmacophore» sulfonylamide fragments in the position 3 (**Scheme 2**) [52]. As the initial compound 3,5-diiodoanthranilic acid **1a** was used, which was transformed by the reaction with acetic anhydride into the correspondent 2-methyl–benzooxazin-4-one **2a.** The latter was involved into the reaction with correspondent sulfonamides. The research of anti-inflammatory activity of the synthesized compounds **7** allowed for the identi–fication of *N*-(4-(6,8-diiodo-2-methyl-4-oxo–quinazolin-3(4*H*)-yl)phenylsulfonyl)acetamide as a compound, which approximates to the medical product compared with «Ibuprofen» by the level of the stated pharmacological effect.



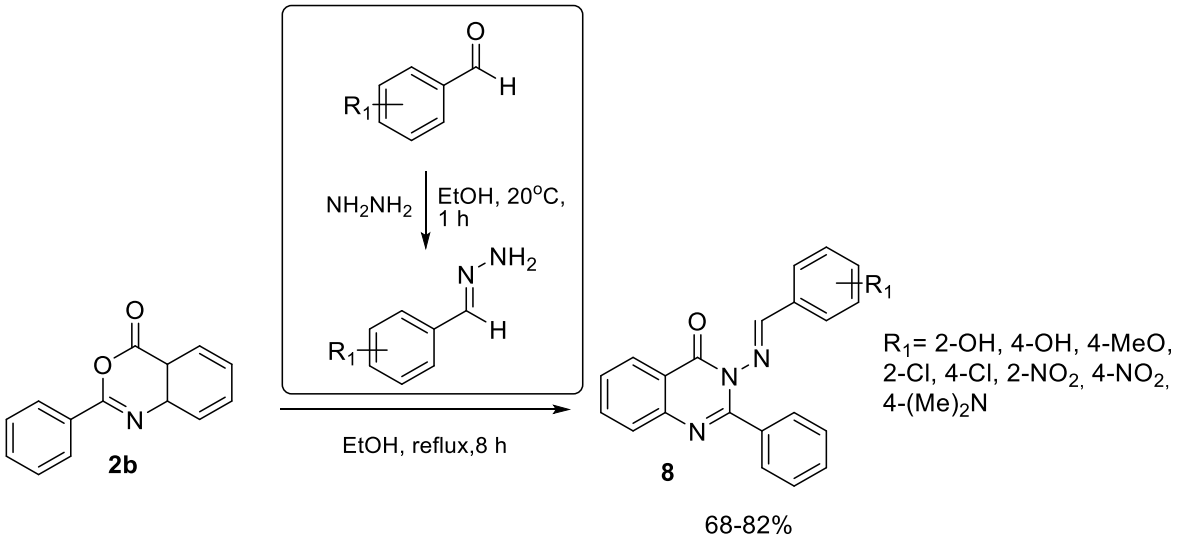
Ar=Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3-F-4-ClC_6H_3, 4-$(Me)_2NC_6H_4$

Scheme 1. Approaches to synthesis of 4-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzoic acid and its derivatives



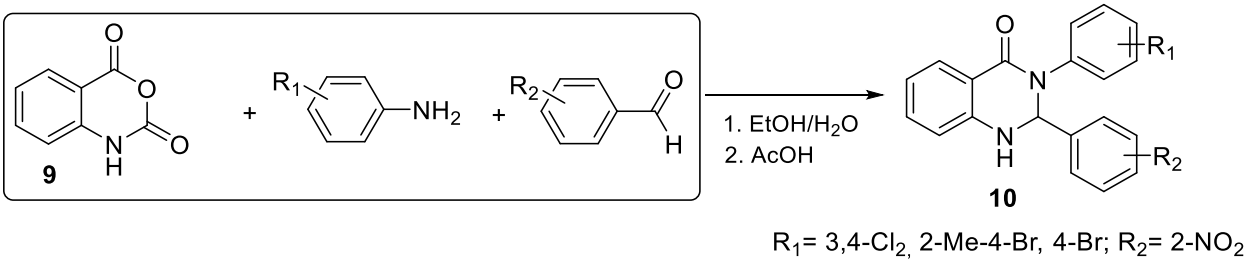
Scheme 2. Synthesis of iodine-containing quinazolin-4-ions with sulfonamide moiety

Kandapal's co-authored study [53] is dedicated to the determination of anti-inflammatory activity of the range of 3-arylidenamino-2-phenyl–quinazolin-4(3*H*)-one derivatives **8 (Scheme 3)**. The targeted compounds were obtained by the reaction of 2-phenyl-4a,8a-dihydro-4*H*-benzo[*d*]–[1,3]oxazin-4-one **2b** with arylidenehydrazine, which were obtained by the reaction of substituted aromatic aldehydes with hydrazine. The results of biological investigation showed that the synthesized compounds at a dose of 200 mg/kg appeared to be effective for the carrageen-induced rat paw edema since the 4th hour of experiment, competing with or approximating in efficiency to the reference product «Indomethacin».



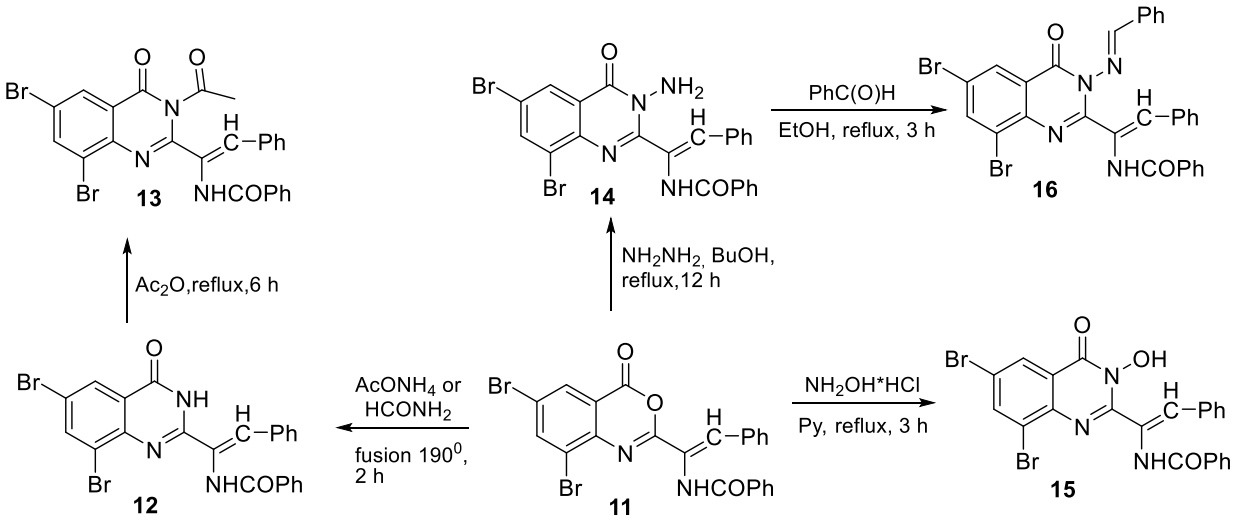
Scheme3. Synthesis of 3-arylideneamino-2-phenylquinazolin-4(3*H*)-ones

Ghodge and co-authors [54] conducted synthesis of a range of 2,3-disubstituted quinazolin-4(1H)-ones **10** and researched their anti-inflammatory activity. Thus, the authors used «one-pot/two-step» process for the synthesis of targeted compounds **10**, which involved the interaction of isatoic anhydride **9** and substituted anilines with subsequent condensation with aromatic aldehydes (**Scheme 4).** The synthesized compounds were investigated for the presence of anti-inflammatory activity. It should be noted that the authors didn't restrict themselves to one model of determination of anti-inflammatory activity, but they used such approaches as the carrageen-induced rat paw edema model, as well as the model of cotton pellet-induced granuloma. The results of conducted research allowed for the determination of the most active substance, namely 3-(4-bromophenyl)-2-(2-nitrophenyl)-2,3-dihydroqui-nazolin-4(1*H*)-one, which revealed pronounced anti-inflammatory activity on both models. However, the mentioned compound didn't exceed in efficiency the action of Diclofenac sodium.



Scheme 4. «One-pot/two-step» synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones

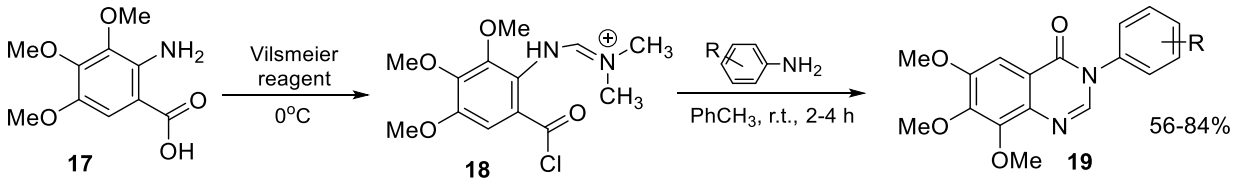
El-Hashash and co-authors [55] described the synthesis and anti-inflammatory activity of a range of substituted dibromo-derivatives of quinazolin **12–16** (**Scheme 5**). As a parent compound the authors used *N*-(1-(6,8-Dibromo-4-oxo-4*H*-benzo–[*d*][1,3]-oxazin-2-yl)-2-phenylvinyl)benzamilde **11**, which was synthesized by acylation 2-(2-benzamido-3-phenylacrylamido)-3,5-dibromo–benzoic acid of the acetic anhydride. The corresponding 4-oxo-4*H*-benzoxazin **11** in the reaction with various *N*-nucleophiles (hydrazinehydrate, formamide, ammonium acetate, hydroxylamine) are transformed into the targeted compounds **12–15** with the yield of 71–76 %. The compounds **12** and **14** were exposed to the further functionalization (reactions of acylation and condensation). The conducted screening research confirmed the perspectives of search for anti-inflammatory agents in this class of compounds. It has been noted, that the compound **13** has a higher efficiency than indomethacin.



Scheme 5. Synthesis of substituted dibromo-derivatives of quinazolin-4-ones

Krishnarth and co-authors [56] conducted synthesis of a range of 3-arylquinazolin-4(3*H*)-ones, which include methoxy-groups in the heterocycle. The indicated approach is rational because the specified functional groups are well-known pharmacophores. For synthesis of the compounds **19** there was used the approach, based on the reaction of 3,4,5-trimethoxyanthranilic acid **17** with Vilsmeier reagent with the subsequent interaction of the intermediate acylhalide **18** with anilines (**Scheme 6**). As a result of biological studies two

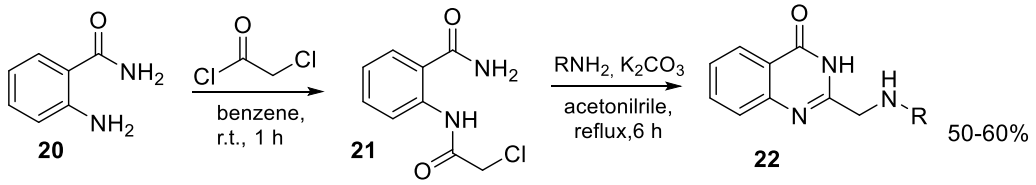
compounds were revealed, namely 3-(2,4-dinitrophenyl)-6,7,8-trimethoxyquinazolin-4(3*H*)-one and 3-(*o*-tolyl)-6,7,8-trimethoxy–quinazolin-4(3*H*)-one, which surpassed the product compared with «Diclofenac sodium» by the level of anti-inflammatory activity.



R= H, 4-NH_2, 2-CH_3, 3-OEt, 2-Cl, 2,4-$(NO_2)_2$, 4-NO_2

Scheme 6. Synthesis of 6,7,8-trimethoxy-3-arylquinazolin-4(3*H*)-ones

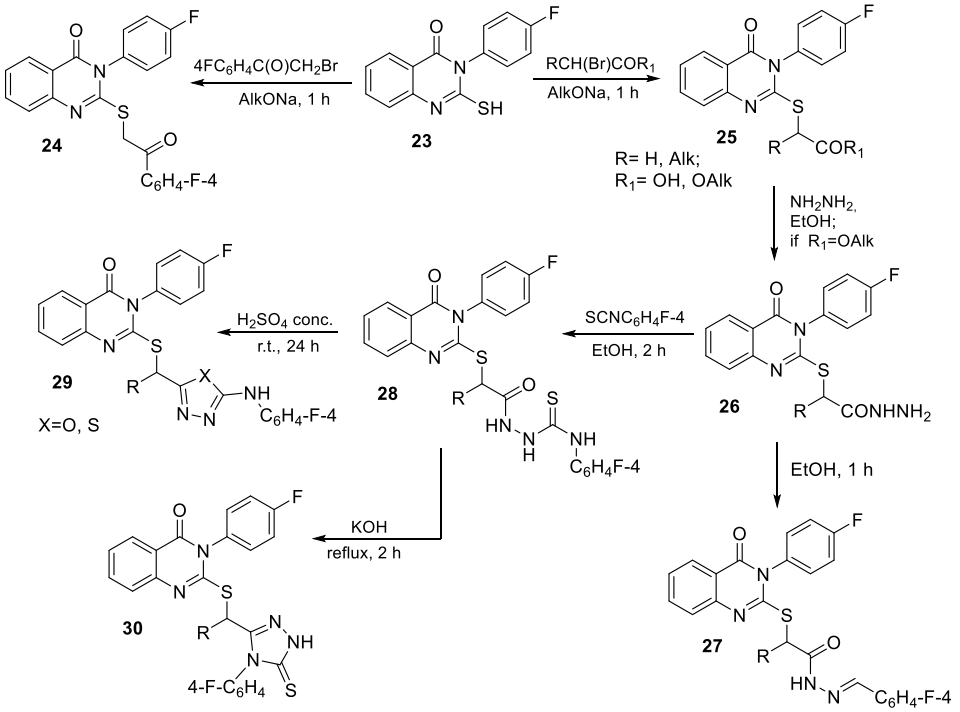
Serya and co-authors [57] published the results of the studies aimed at searching for anti-inflammatory agents among 2-((R-amino)–methyl)quinazolin-4(3*H*)-ones (**22**). The synthesis of the compounds **22** was carried out on the basis of interaction of 2-aminobenzamide **20** with 2-chloroacetyl chloride with the subsequent interaction of the intermediate product of the reaction **21** with amines in the presence of potassium carbonate. (**Scheme 7**). The studied compounds showed high anti-inflammatory activity in comparison with indomethacin with the significant decreasing of the level of TNF-α (the factor of tumor necrosis), not exhibiting gastrotoxicity at the same time.



R= 2-Me-4-$NO_2C_6H_3$, 2-$NH_2C(O)C_6H_4$, 2,4-$Cl_2C_6H_3$, CH_2COOH

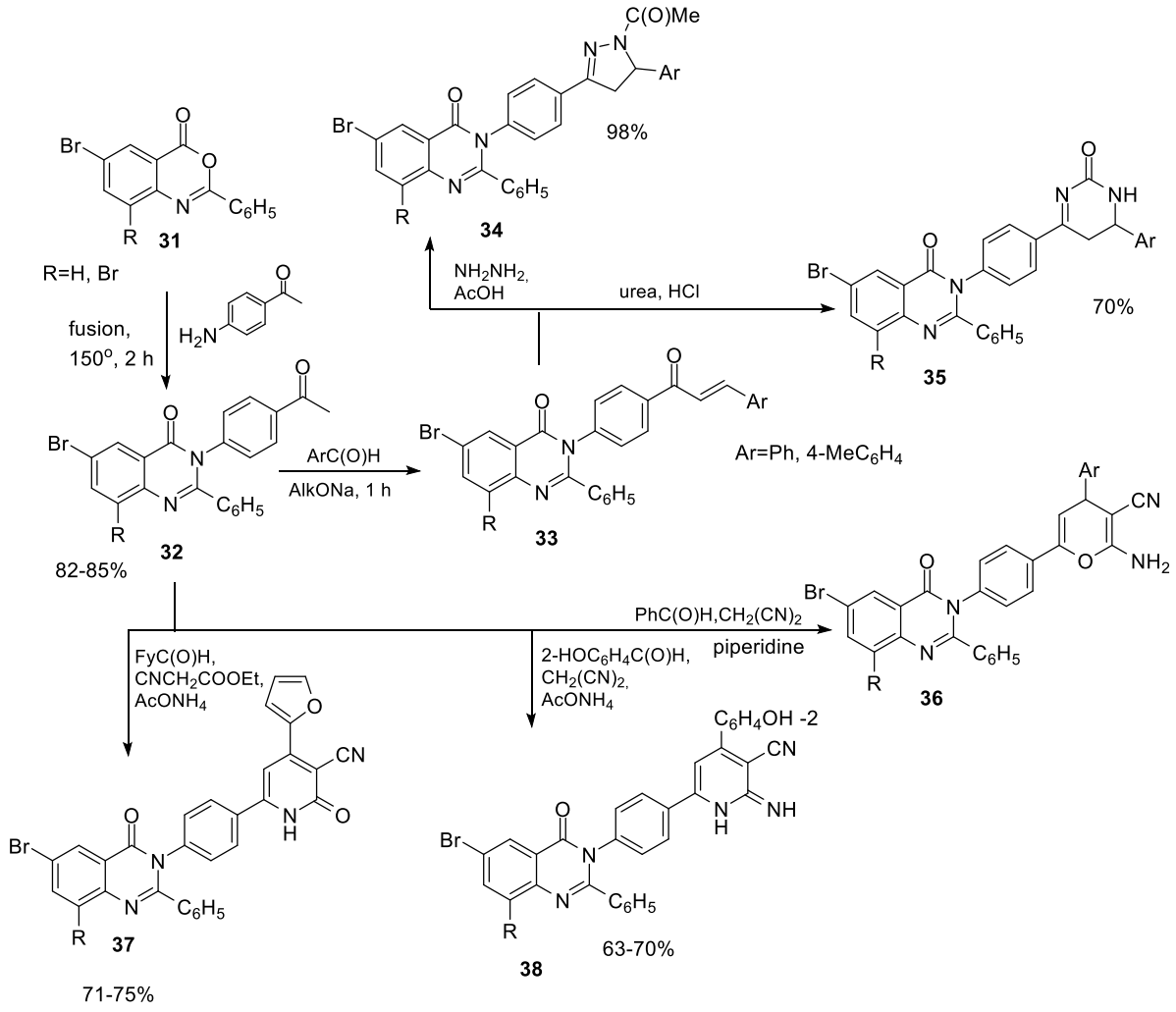
Scheme7. Synthesis of 2-((R-amino)methyl)quinazolin-4(3*H*)-ones

The series of new fluoridated S-substituted 2-mercaptoquinazolin-4(3*H*)-ones **24-30** was synthesized according to well-known approaches of usage of 3-(4-fluorophenyl)-2-mercapto–quinazolin-4(3*H*)-one **23** as a parent compound (**Scheme 8**) [58]. The authors previously carried out molecular docking all the compounds for the binding site COX-2. It has been determined that the compounds **29** and **30** with azole cycles have the highest affinity to the enzyme and have demonstrated the highest inhibiting action towards the sheep COX-2 *in vitro*.



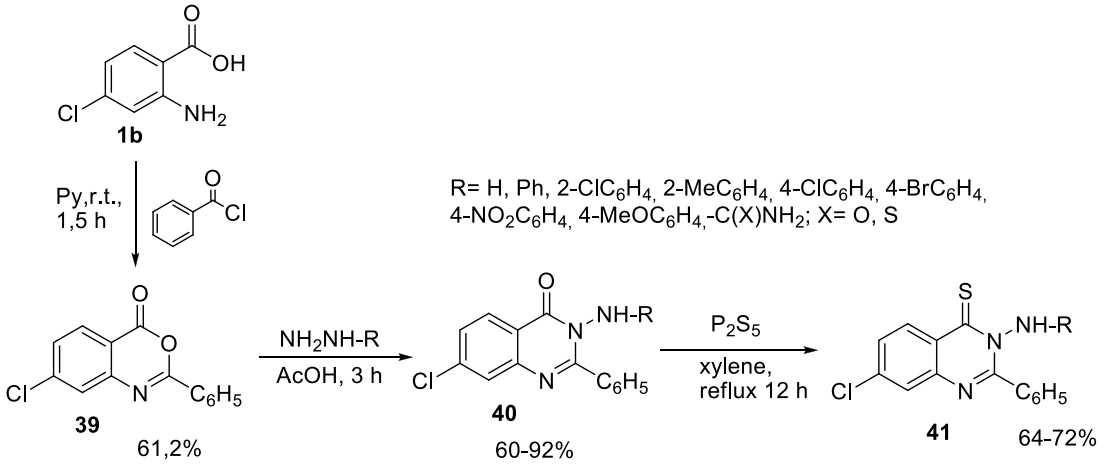
Scheme 8. Formation of S-substituted 3-(4-fluorophenyl)-2-mercaptoquinazolin-4(3*H*)-ones

Mohamed M.S. and co-authors developed the strategy of search for anti-inflammatory and analgesic agents with the usage of molecular docking and structural modification of mono- and dibromo 2-phenylquinazolin-4(3*H*)-one derivatives [59]. The specified modification is based on the ability of chalcones **33** to create functionalized derivatives **34**-**38** due to attachment of various nucleophiles (**Scheme 9**). The majority of the studied derivatives of quinazolin-4(3*H*)-one showed high anti-inflammatory and analgesic activity with a superior gastrointestinal safety profile in experimental rats. Thus, the compounds **36** demonstrated the anti-inflammatory effect, which was 25-40% higher than that of indomethacin. Besides, it has been established that monobromo derivatives have higher anti-inflammatory activity than dibromo derivatives.



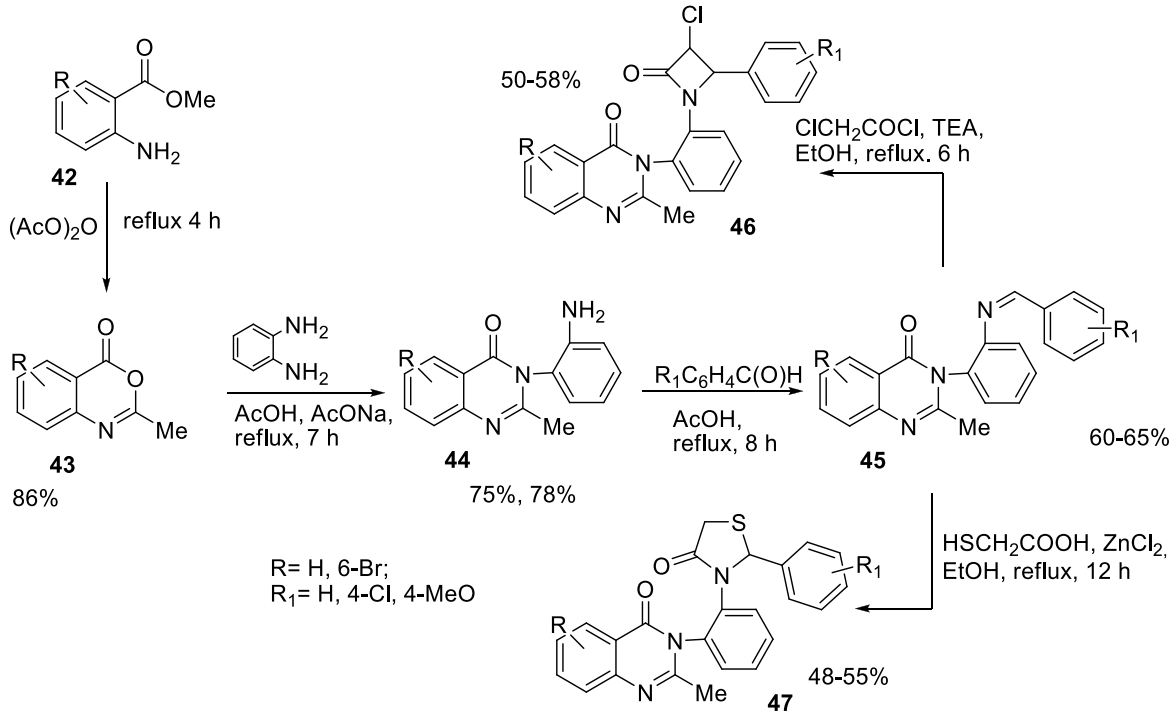
Scheme 9. Synthesis of mono- and dibromo substituted 3-(4-azolo-(azino-)phenyl]-2-phenylquinazolin-4(3*H*)-ones based on chalcones

Biswajit Dash's co-authored report [60] discusses synthesis and biological activity of 3-R-7-chloro-2-phenylquinazolin-4(3*H*)-ones (-thiones) **40**, **41.** The proposed derivatives were synthesized, as shown at **Scheme 10**, through the respective 7-chloro-2-phenyl-4H-benzo[*d*][1,3]oxazin-4-one **39**. The latter in the interaction with nucleophiles (hydrazine hydrate, aryl hydrazine, hydrazine carboxamide and hydrazine carbothioamide) forms 3-R-7-chloro-2-phenylquinazolin-4(3*H*)-ones **40**, the thionization of which leads to the corresponding thions **41**. It has been shown that synthesized compounds perform moderate analgesic and significant anti-inflammatory activities, approaching in the effect to the standard drug «Diclofenac sodium». It has been discussed that high anti-inflammatory activity is determined by the presence of amino-, carboxamide- and carbothioamide- groups in the 3-d position of 2-phenylquinazolin-4(3*H*)-one. The substitution of the oxo-group by the thioxo group in position 4 leads to a significant decrease of the abovementioned activity level. It is important that the mentioned compounds have low toxicity, their LD_{50} is in the range of 500-1000 mg/kg.



Scheme 10. Synthesis of 3-R-7-chloro-2-phenylquinazolin-4(3*H*)-ones (-thiones)

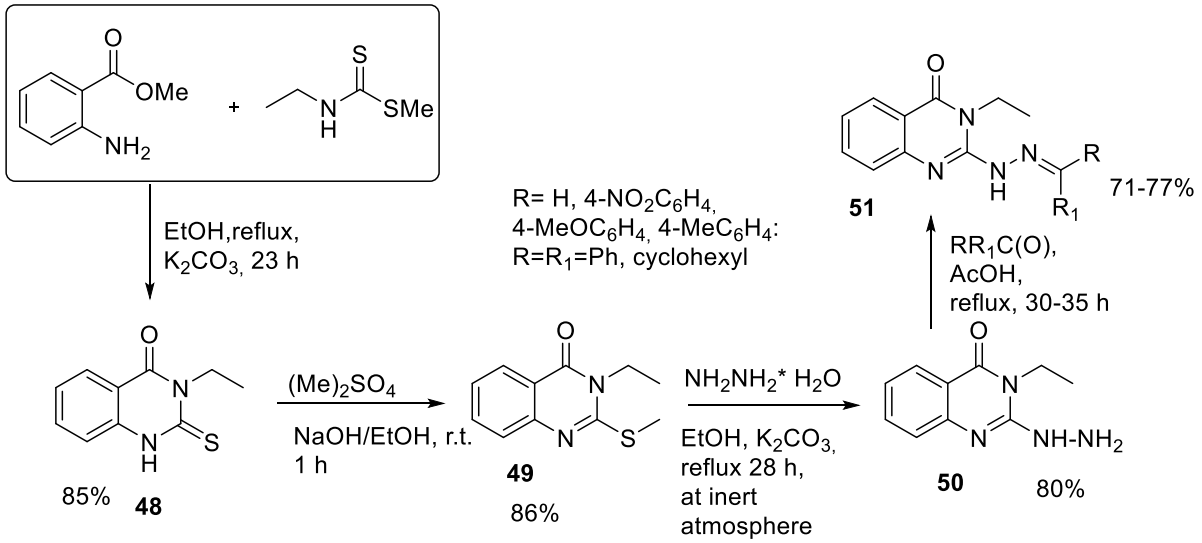
A similar approach for synthesis of substituted 3-(2-aminophenyl)-2-methylquinazo-lin-4(3*H*)-ones **44** with 2-methyl-4*H*-3,1-benzoxazin-4-ones **43** and benzene-1,2-diamine was applied by Rajput C.S. and Singhal S. (**Scheme 11**) [61]. From compounds **44** as starting materials, a range of 3-(2′-(R-benzylideneamino)phenyl)-2-methylquina–zolin-4(3*H*)-ones **45** was formed, from which, due to the presence of an azomethine bond, the structures with azetidinone **46** and 1,3-thiazolidinone **47** cycles were subsequently formed. However, all the synthesized compounds showed moderate anti-inflammatory and analgesic activities, being inferior to phenylbutazone at the same time. According to the authors, azetidinone **46** and thiazolidinone **47** derivatives were found to be more active than corresponding Schiff's base derivatives **45**.



Scheme 11. Synthesis quinazoline-azetidinone and and quinazoline-thiazolidinone hybrids as promising anti-inflammatory agents.

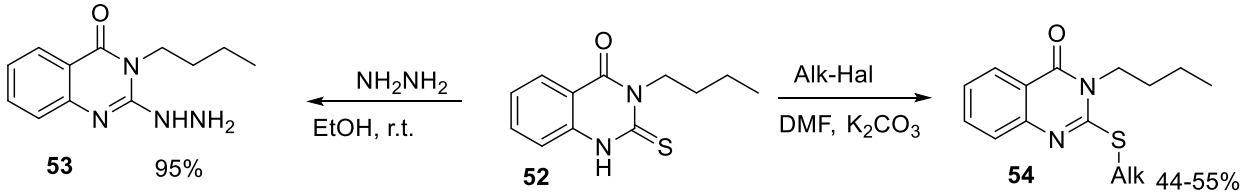
The study of Indian investigators [62] is dedicated to the targeted search for anti-inflammatory and analgesic agents among 3-ethyl-2-(2-R,R′-ylidenehydrazinyl)quinazolin-4(3*H*)-ones **51**. The authors developed an original synthesis of the corresponding thione **48** by condensation of methyl 2-aminobenzoate and methylethylcarbamodithioate (**Scheme 12**). The subsequent thione alkylation **48** leads to the corresponding S-methyl derivative **49**, which is converted by hydrazinolysis to 3-ethyl-2-hydrazinylquinazolin-4(3*H*)-one **50**. The latter in interaction with carbonyl compounds (aldehydes and ketones) forms hydrazones **51**, which have proved to be promising analgesic and anti-inflammatory agents. Thus, 3-ethyl-2-(cyclo–

hexylidenehydrazino)-3*H*-quinazolin-4-one performed high analgesic (63.89 %) and anti-inflammatory activities (60.00 %), compared to the reference standard – Diclofenac sodium (62.04 and 65.11 %, respectively).



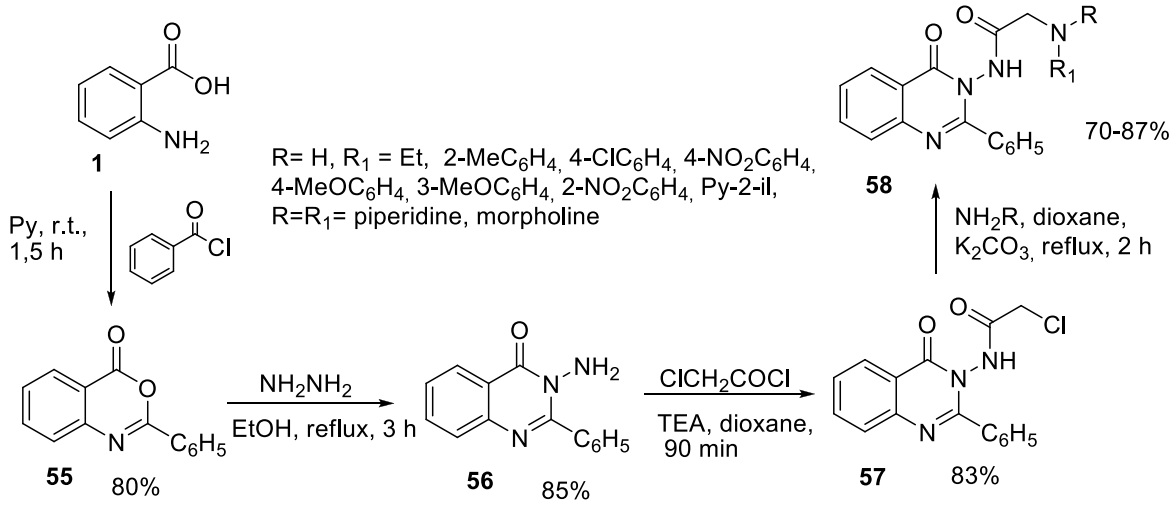
Scheme 12. Synthesis of 3-ethyl-2-(2-R,R'-ylidenehydrazinyl)quinazolin-4(3*H*)-ones

Abuelizz H. A. and co-authors researched 2-(R-thio)quinazolin-4(3*H*)-ones with a butyl substituent (increase in lipophilicity) in position 3 for anti-inflammatory activity [63]. Approaches to the synthesis of compounds **53** and **54** are shown at **Scheme 13**. The results of biological studies have shown that they are characterized by a significant anti-inflammatory activity. Additional testing was carried out on rats with arthritis for the compounds **54** with 2-methylbenzyl- and 3-methoxybenzyl- substitutes and the highest anti-inflammatory activity (≥80%). It has been established that the mentioned compounds significantly reduce the level of IL-1β, COX-2 and E2 in rats with complete Freund's adjuvant, as compared to the control. It has been researched and discussed that 3-butyl-2-(2-methyl–benzylthio)quinazolin-4(3*H*)-one is a non-selective inhibitor of COX-1 and COX2, and 3-butyl-2-(3-methoxybenzylthio)quinazolin-4(3*H*)-one is a selective inhibitor of COX-2. The authors recommend that the mentioned "small" molecules be used as templates for further search for potential anti-inflammatory agents.



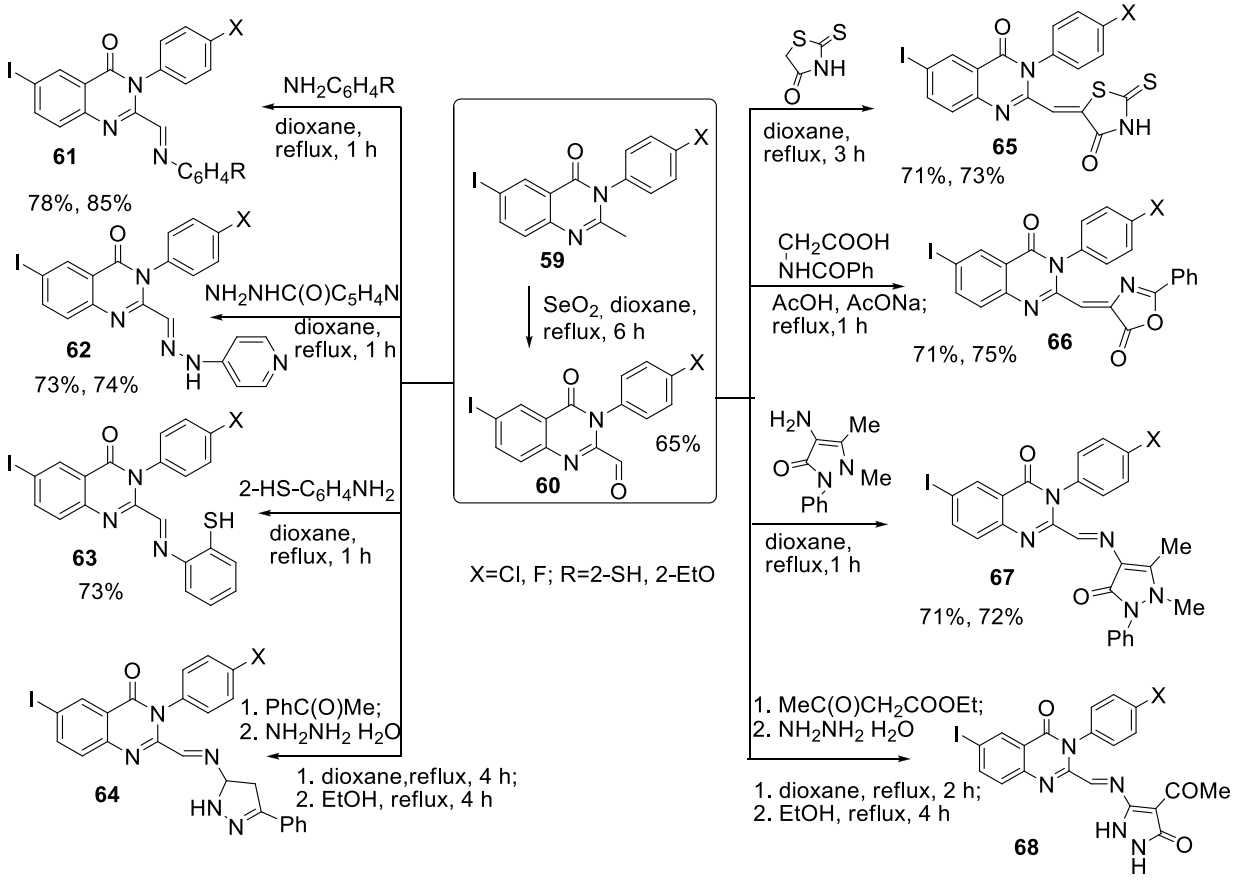
Scheme 13. Synthesis of 3-butyl-2-hydrazine- and 2-(R-thio)quinazolin-4(3*H*)-ones

V. Alagarsamy's co-authored study is devoted to the modifications of corresponding 3-amino-2-phenylquinazolin-4(3*H*)-one **56** by acetamide fragments, aiming at searching for effective anti-inflammatory agents [64]. 2-Substituted-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamides **58** were synthesized by the reaction of 2-chloro-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide **57** with various amines (**Scheme 14**). The considered compounds showed moderate anti-inflammatory activity. However, 2-(ethylamino)-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide performed anti-inflammatory activity, which is slightly stronger in comparison with the reference drug «Diclofenac». It is important that the studied compounds showed moderate ulcerogenic potential in comparison with aspirin.



Scheme 14. Synthesis of 2-substituted-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamides

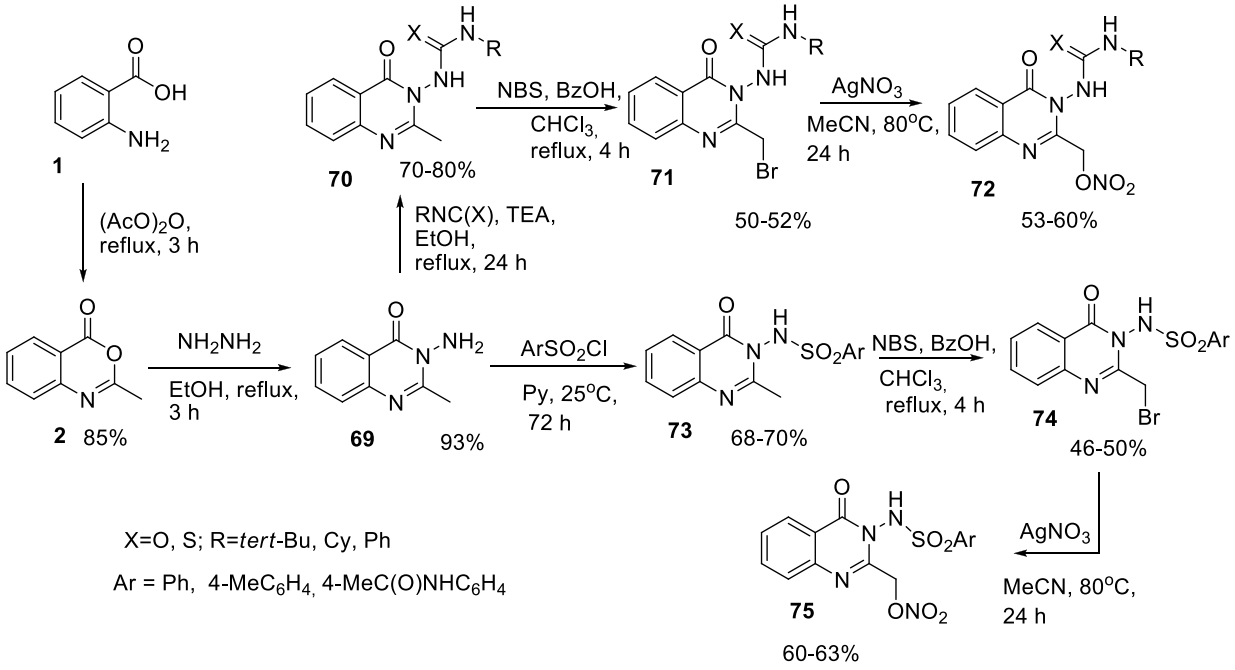
Farag and co-authors have synthesized and studied anti-inflammatory activity of a range of new derivatives 3-(4-chloro-(fluoro-)phenyl)-6-iodo-2-((substitutedimino)methyl)quinazolin-4(3*H*)-ones **61–68**, containing an azomethine, hydrazone fragment and a number of azoles (oxazolone, imidazolidine, thiazolidine and pyra–zolidine) in position 2 (**Scheme 15**) [65]. Research design is based on the interaction of 3-(4-chloro-(fluoro-)phenyl)-6-iodo-4-oxo-3,4-dihydroquina–zoline-2-carbaldehyde **60** with amino-derived or methylene-active compounds. It is shown that the obtained compounds exhibit anti-inflammatory activity in the acute and chronic test (38-73,5%), being slightly inferior to Indomethacin at the same time (78,3%). It has been established that they are also characterized by a moderate analgesic activity.



Scheme 15. Synthesis of quinazoline-containing Schiff's bases with additional heterocyclic fragment.

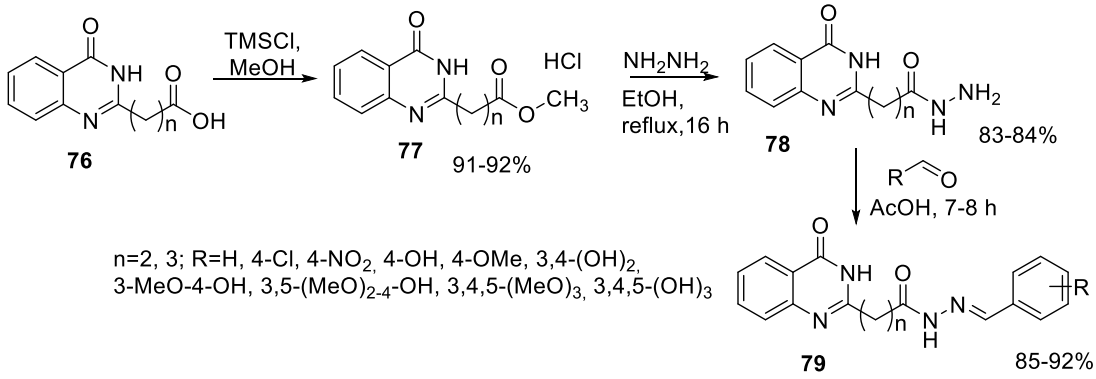
A team of Egyptian scientists synthesized a series of 1-substituted-3-(2-methyl-4-oxoquin-azolin-3(4*H*)-yl)urea(thiourea) **70** and *N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)arylsulfonamide

73, as well as their bromomethylderivatives **71**, **74** and nitroesters **72**, **75** (**Scheme 16**) and estimated their anti-inflammatory activity by *in vivo* and *in vitro* methodologies [66]. Apart from that, nitroesters **72**, **75** were examined for release of *NO* in serum using the diazotation Griess test, determination of the ulcer index and pathological investigation of the gastric mucosa. At the same time it was established that the compounds showed moderate anti-inflammatory activity as compared to the control drug «Meloxicam». The paper points out that nitroesters **72**, **75**, as compared to the compounds **70**, **73**, have higher activity and preferential selectivity for COX-2 and release of NO. The authors state that quinazolone derivatives with a nitroester group, which facilitate the release of NO, are attractive and selective inhibitors of COX-2 with fewer gastric side effects.



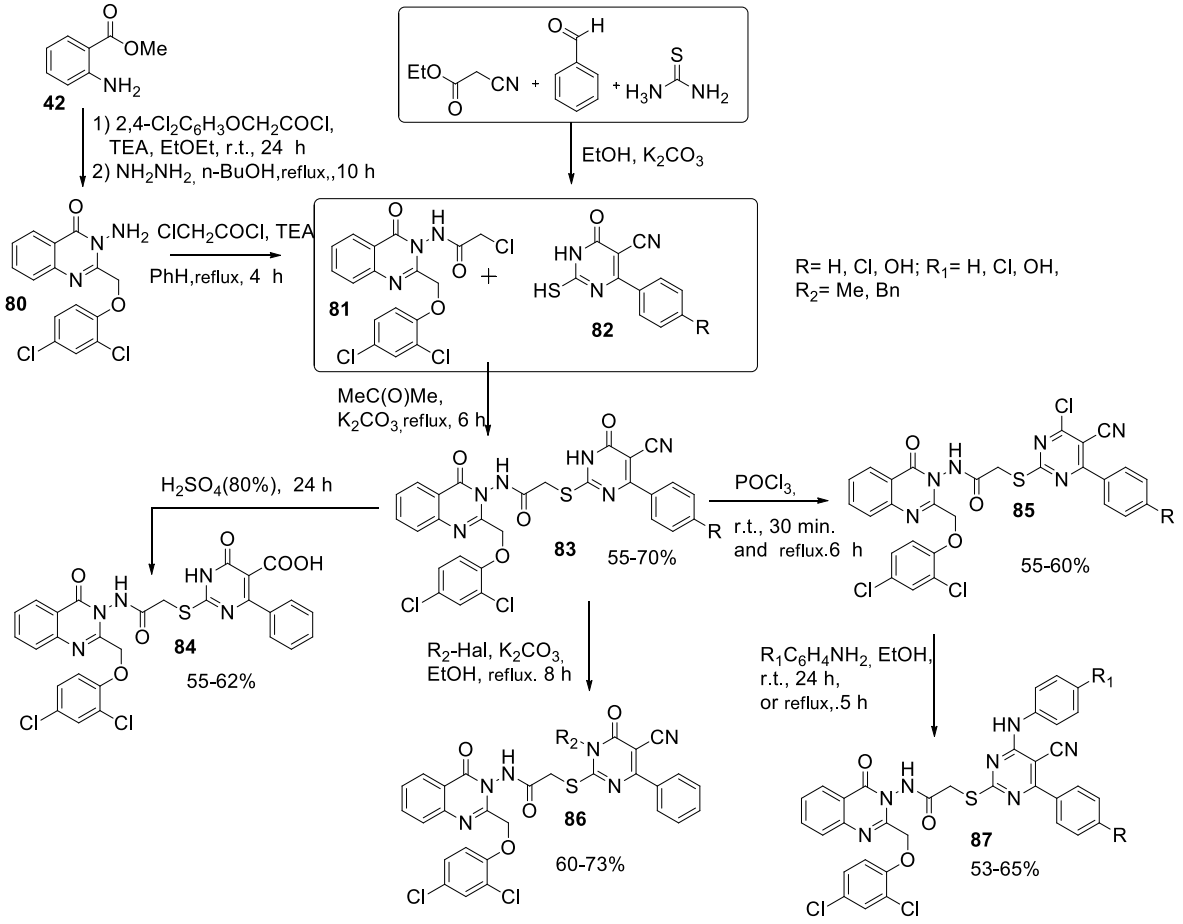
Scheme 16. Approaches to synthesis of 3-(3-R-ureido-(thioureido-,arylsulfonamide-)-4-oxo-3,4-dihydro–quinazolin-2-yl)methylnitrates

Rakesh's co-authored survey was dedicated to the search for anti-inflammatory agents and antioxidants among *N'*-arylidene-*N*-(4-oxo-3,4-dihydroquinazolin-2-yl)propane-(butane-)hydrazides**79** [67]. The synthesis of the letter was conducted using generally accepted methods and presented at **Scheme 17**. It was established that the antioxidant activities of some of obtained compounds exceeds the pharmacological standards (ascorbic and gallic acids, butylated hydroxytoluene and butylated hydroxyanisole). The conducted assessment of anti-inflammatory activity of the compounds (*in vitro* methodology) showed that the range of them (4-chloro-(nitro)derivatives) show activity higher than that of acetylsalicylic acid. The paper discusses the SAR-analysis and correlation between antioxidant and anti-inflammatory activity.



Scheme 17. Synthesis of *N'*-arylidene-*N*-(4-oxo-3,4-dihydroquinazolin-2-yl)propane-(butane-)hydrazides

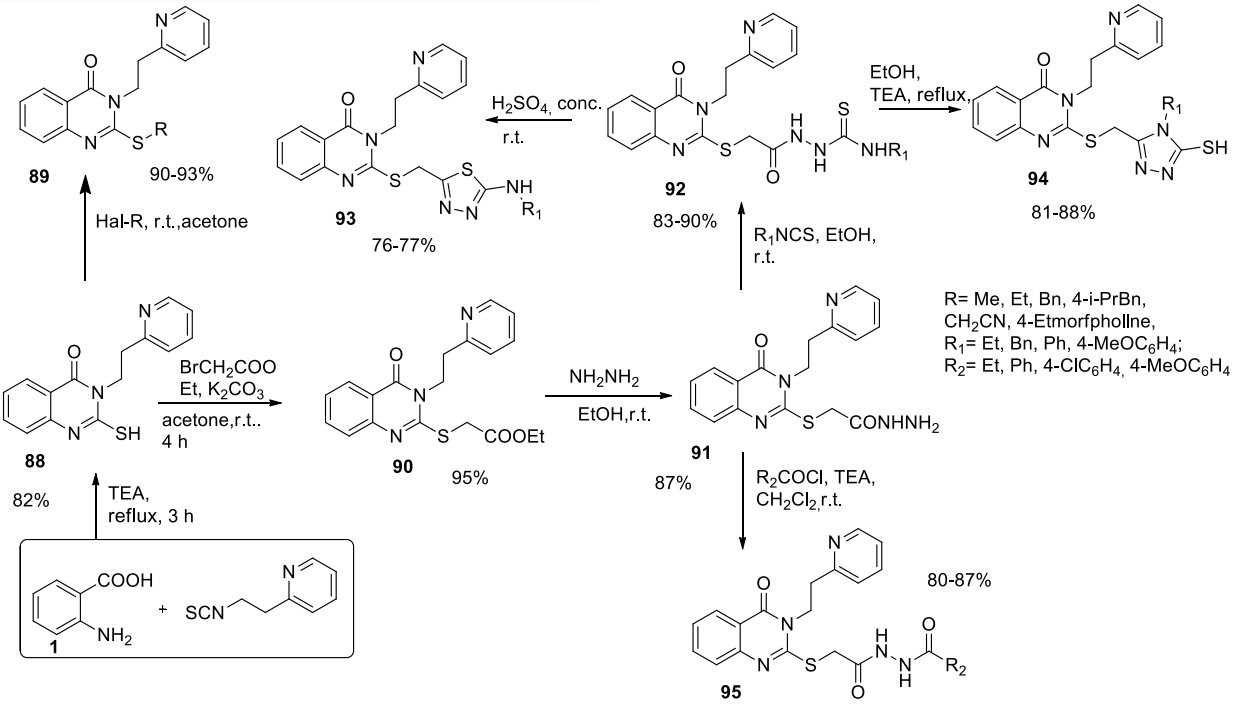
"Hybrid-pharmacophore" approach in search for anti-inflammatory agents was applied by the team guided by Abbas S. E. [68]. The authors combined in one molecule through the "linker" thioalkylamide group (2-((2,4-dichlorophenoxy)-methyl)-4-oxoquinazolin-3(4H)-yl)–acetamide **81** and 4-aryl-2-mercapto-6-oxo-1,6-dihydropyrimi–dine-5-carbonitrile **82** fragments. Approaches to their synthesis are shown on **Scheme 18**. The formed compounds **83** were subsequently subjected to hydrolysis reactions and *N*-alkylation with the formation of derivatives **84** and **86**, respectively. The chlorinated derivatives **85** were utilized in the reaction with anilines, at the same time, corresponding amino derivatives were formed **87**. Anti-inflammatory activity of the synthesized compounds was assessed on the carrageenan-induced rat paw edema model and the ulcer indexes were calculated for the most active compounds. Five compounds were more active and less ulcerogenic than Diclofenac, in particular, 2-((5-cyano-4-(4-hydroxyphenyl)-6-(phenylamino)pyrimidin-2-yl)thio)-*N*-(2-((2,4-dichlorophenoxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)acetamide (IC_{50} = 116,73 mmol/kg; ulcer index = 11,38). The specified compound turned out to be a selective inhibitor COX-2.



Scheme 18. "Hybrid-pharmacophore" approach in search for anti-inflammatory agents

A similar approach, namely, the combination of 2-mercaptoquinazolin-4(3H)-one with azole and azine cycles through "linker" fragments was developed by A. A.-M. Abdel-Aziz and co-authors **Scheme 19** [69]. 2-mercapto-3-(2-(pyridin-2-yl)–ethyl)quinazolin-4(3*H*)-one**88** was used as a parent compound, which was alkylated by different alkylhalides or ethyl-2-bromoacetate. Ethyl 2-((4-oxo-3-(2-(pyridin-2-yl)ethyl)-3,4-di–hydroquinazolin-2-yl)thio)acetate **90** was converted to hydrazide **91**, from which the substituted semicarbazones **95** and thiosemicarbazides **92** were formed using classical methods. The latter in the process of interaction with TEA or with concentrated sulfuric acid form the compounds **94** and **93** with 1,2,4-triazole and 1,3,4-thiadiazole cycles. All the compounds were investigated by the *in vivo* method for anti-inflammatory and analgesic activity, and by the *invitro* method – for the ability to inhibit COX-1/COX-2. At the same time, it was established that the compounds manifested high anti-inflammatory activity with the values ED_{50} 0.16–0.36 mmol/kg and strong analgesic activity

with the values ED_{50} 0.07–0.34 mmol/kg, approaching by the effect to Diclofenac (ED_{50} 0.35 та 0.31 mmol/kg), respectively). It is important that most of them showed significant inhibitory activity against COX-2 (IC_{50}0.70-2.0 μM), which was somewhat inferior comparing with Celecoxib (IC_{50} = 0.30 μM).



Scheme 19. Synthesis and structural modification of 2-mercapto-3-(2-(pyridin-2-yl)ethyl)–quinazolin-4(3*H*)-one

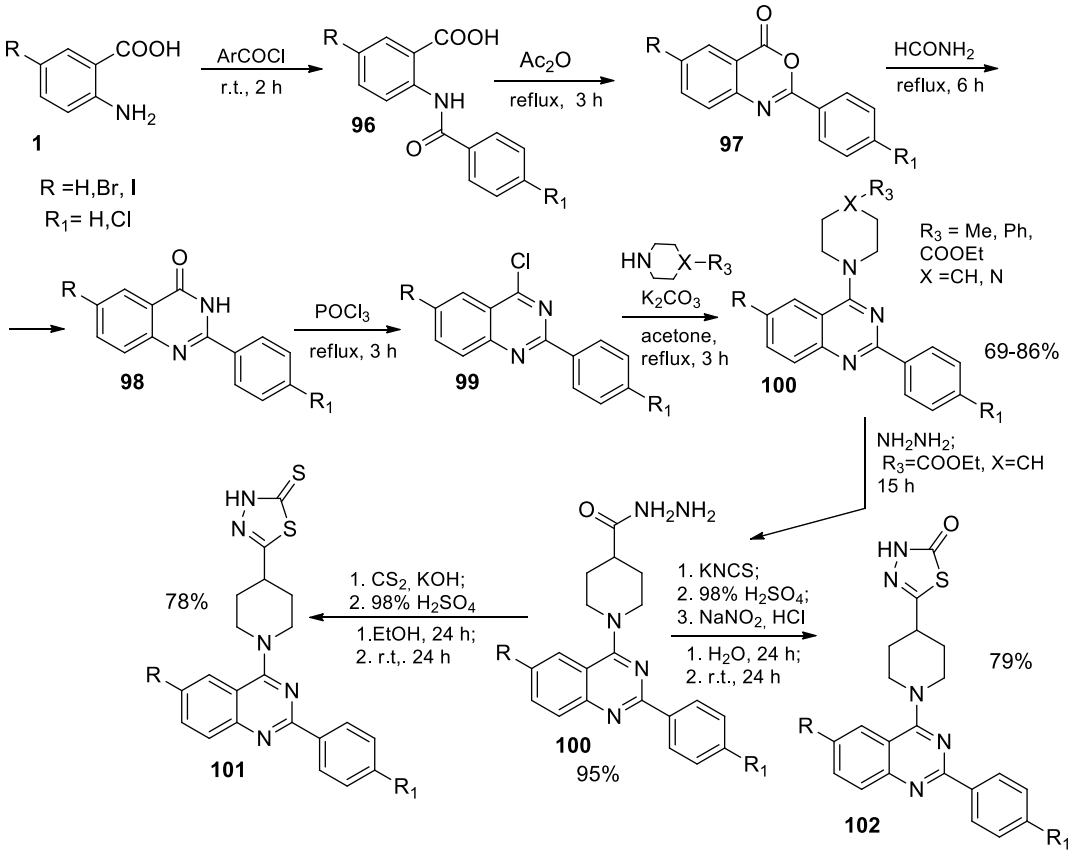
1.2 Substituted quinazolin-4-amines as potential anti-inflammatory agents.

Interesting anti-inflammatory agents are the derivatives of quinazolin-4-amines. The number of publications over the past 10 years, devoted to these compounds, is insignificant, which is due to certain aspects of their synthesis (chlorination reaction etc.). However, they reveal new and quite interesting areas of search for anti-inflammatory agents, which are based on the achievements of modern molecular pharmacology.

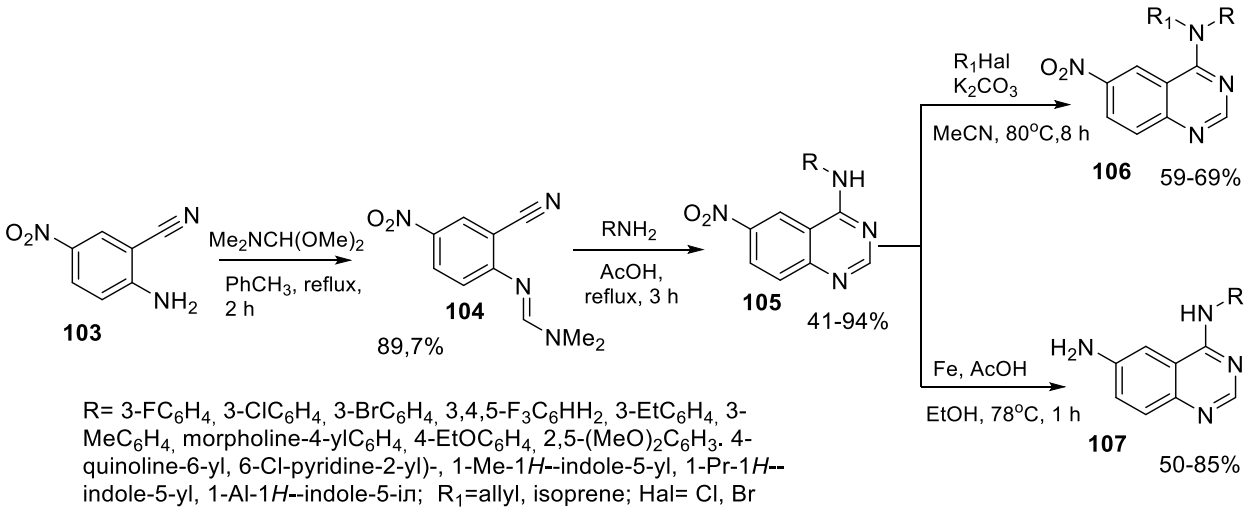
Ahmed M. Alafeefy's co-authored study is dedicated to the synthesis and research of anti-inflammatory, analgesics activities of the range of 2-aryl-4-(piperidine-1-yl-(piperazine-1-yl)quinazolines **100 Scheme 20.** [70]. Standard methods were used for their synthesis, namely the formation of benzoxazone cycle **97** from the substituted anthranilic acids **96**, the formation of 3*H*-quinazolin-4-one cycle **98** with its subsequent chlorination **99** and aminolysis **100**. An additional and rather interesting aspect of the work is the "hybrid-pharmacophore" approach, annamely, the formation of 1,3,4-thiadiazol-2(3H)-one (-thione) cycles (**101**, **102**) on the 2-aryl-4-(piperidine-1-yl)quinazolin framework. The research conducted upon the analgesic and anti-inflammatory activity allowed identifying 4 compounds with analgesics activity, which exceeds the one of Indomethacin, as well as of 13 compounds competing with the specified reference product for anti-infammatory activities. It is important that 7 compounds demonstrated both analgesic and anti-inflammatory activities. The compounds tested for acute toxicity showed no toxic symptoms or mortality during 24 hours after administration.

The study by Hu J. and co-authors is devoted to the synthesis of substituted 6-nitroquinazolin-4-amine derivatives as promising anti-inflammatory agents against acute lung injury in rats [71]. The overall search strategy consisted in the interaction of 2-amino-5-nitrobenzonitrile **103** with *N*,*N*-dimethylformamidedimethylacetal and obtaining formimidamide **104**, and the cyclisation of the latter with the corresponding amines in acetic acid led to the substituted 6-nitroquinazolin-4-amine **105** (**Scheme 21**). Reduction of the substituted 6-nitroquinazolin-4-amine **105** in the system Fe/EtOH/AcOH ensured obtaining of appropriate compounds **107**. In addition, for better understanding of the "structure-activity" relationship, the authors carried out alkylation on the substituted amino group of quinazolines by allyl bromide or 1-chloro-3-methylbut-2-ene for the synthesis of disubstituted derivatives **106.** The study of anti-inflammatory effects found out that most of the studied compounds showed significant activity on the model of the LPS induced expression of TNF-a and IL-6 *in vitro*. The

in vivo experiment has shown that N^4-(1-allyl-1H-indol-5-yl)–quinazoline-4,6-diamine attenuates the liposaccharide-induced model in rats by reducing cytokine synthesis, inflammatory protein concentration, pathological changes and macrophage infiltration. The authors state that quinazolines can serve as potential agents for the treatment of acute pneumonia.



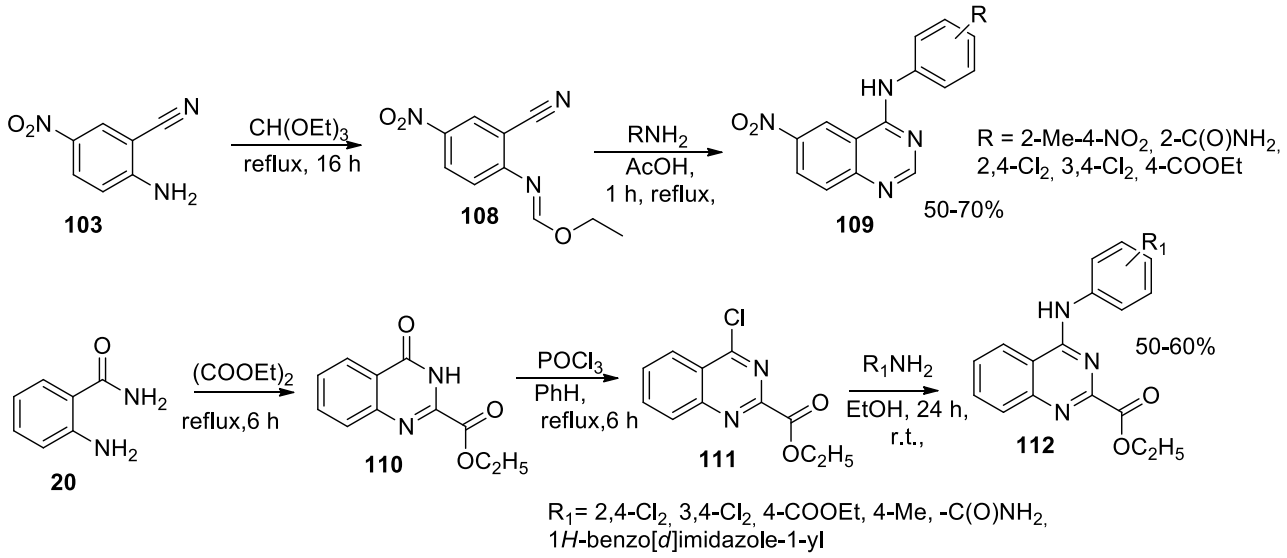
Scheme 20. Synthesis of 2-aryl-4-[(piperidine-1-yl-(piperazine-1-yl)]quinazolines and their derivatives



Scheme 21. Synthesis of substituted 6-nitro-(6-amino-)quinazolin-4-amines

The group of authors [57] performed synthesis of a number of *N*-substituted 6-nitroquinazolin-4-amines **109** based on interaction of 2-amino-5-nitrobenzonitrile **103** with triethoxymethane followed by condensation with amines (**Scheme 22**). Another area of synthetic studies was based on the condensation of 2-aminobenzamide **20** with diethyloxalate, which results in the formation of ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate **110**. In other words, the authors introduced "pharmacophore fragments" into the molecule for a more detailed comprehension of the structure-activity relationship. The compound **110** under the action

of phosphoryltrichloride was converted to ethyl 4-chloroquinazoline-2-carboxylate **111**, and the reaction of the latter with amines allowed obtaining a number of target compounds **112**. It has been established that most of the synthesized compounds exhibit anti-inflammatory activity, competing with Indomethacin for reducing the level of α-TNF and the absence of ulcerogenic effect. Thus, the compounds **109** and **112** with 2,4-dichloro and ethyl 4-carboxylate groups in the phenylamino fragment, performed the highest activity.

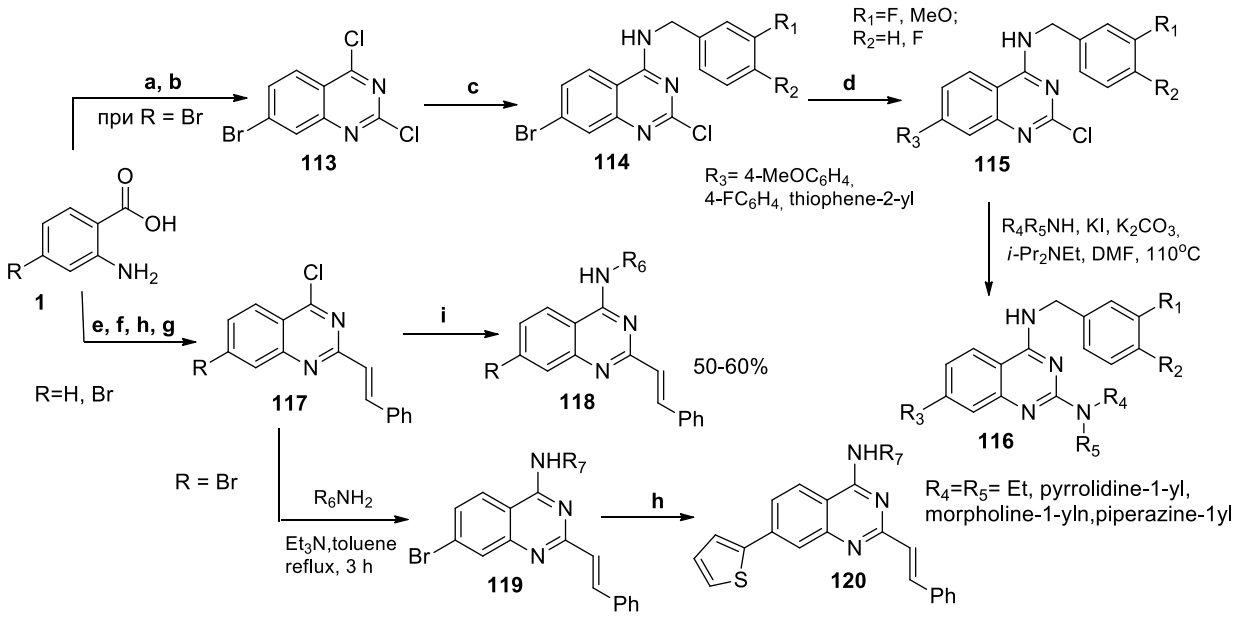


Scheme 22. Synthesis of 4-arylamino-6-nitroquinazolin-4-aminesandethyl 4-(arylamino)quinazoline-2-carboxylates

A group of Czech scientist [72] became interested in the search for selective inhibitors COX-1 among quinazolin-4-amines, when their attention was drawn to a study devoted to the discovery of upregulation of this enzyme in various types of cancer and its cardioprotective role in controlling platelet aggregation. Using "classical" approaches, the authors obtained 2-chloro- **(114)**, 2-styryl- **(118)** 7-bromo-*N*-aryl-(benzyl-)quina–zolin-4-amines and replaced bromine with aryl and thienyl fragments, using Suzuki reaction **(115**, **120**, **Scheme 23)**. The publication shows that quinazoline derivatives have a high ability to inhibit COX-1 (IC_{50} =0,064-3,14 μM) in the absence of inhibition of COX-2. At the same time, there were determined the compounds with the IC_{50} value which exceeds the activity of Ibuprofen (IC_{50} = 2,19 μM). It was discussed that the active compounds had quinazoline-substituted aniline or benzylamine in the position 4, and chloro or styryl fragment in the position 2. Presence of thiophene cycle in the position 7 also significantly increased the inhibitory activity and selectivity for COX-1. Docking studies have shown that the activity of 2,4-substituted quinazolines depends on the formation of a hydrogen bond between the secondary amine and the key residue of Tyr355 enzyme.

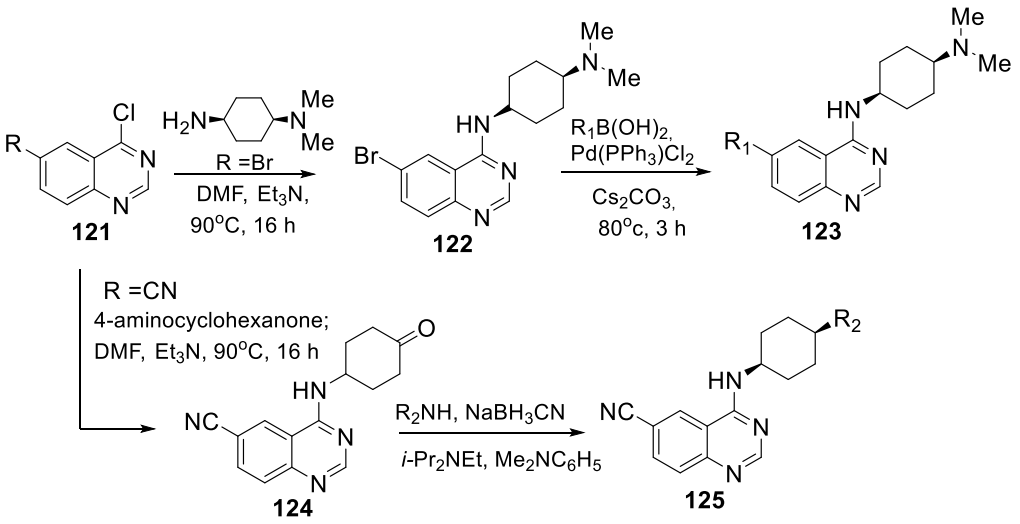
The search for anti-inflammatory agents among substituted quinazolin-4-amines based on selective inhibition of kinase activity of the TLR/IL-1R proteins is engaging and interesting [73]. By chemical optimization of the compounds of the companies «Merck» and «Schering-Plough», using molecular docking, the authors identified and synthesized new substances with excellent pharmacokinetic profile and selectivity for kinase. Rather simple approaches to synthesis were applied, namely the interaction of 6-R-4-chloroquinazolines with N^1,N^1-dimethylcyclo–hexane-1,4-diamine and 4-aminocyclohexanone (**122**, **124**, **Scheme 24**). Further, using Suzuki reactions, N^1-(6-bromoquinazolin-4-yl)-N^4,N^4-dimethylcyclohexane-1,4-diamine **122** was converted to various 6-substituted derivatives **123**, and 4-((4-oxocyclohexyl)amino)quinazoline-6-carbonitrile **124** was transformed into 4-((4-R-cyclohexyl)amino)quinazoline-6-carbonitrile **125** by reductive amination. The synthesized compounds with improved properties (lipo–philicity) allowed identifying kinase inhibitors (IRAK4) with high efficiency.

method **a**: $NH_2C(O)NH_2$, 200° C, 3 h; **b:** $POCl_3$, $Et_2NHC_6H_5$, 120°C, 4 h; **c:** NH_2CH_2Ar, AcONa, THF, 65°C, 3 h;
d: $R_3B(OH)_2$, K_2CO_3, $PdCl_2(PPh_3)_2$, toluene:1,4-dioxane: water(10:5:8), 90°C, 24 h; **e;** Ac_2O, 120°C, 3 h;
f: NH_4OH, reflux, 3 h; **h**: $C_6H_5C(O)H$, AcOH, reflux, 12 h; **g**: $POCl_3$, DMAP, toluene,reflux, 5 h;



R_6= 3,4-$Me_2C_6H_3$, 4-MeC_6H_4, 4-tret-BuC_6H_4, 2,4,6-$Me_3C_6H_2$, 4-$MeOC_6H_4$, 4-$PrOC_6H_4$, 4$EtOOCC_6H_4$, 2,4,6-$F_3C_6H_2$, 3,5-$(MeO)_2C_6H_3$, 4-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 4-$F_2C_6H_3$, 4-$NO_2C_6H_4$, piperazine-1-yl, quinoline-8-yl, pyridine-2-yl, 5-Me-pyrazole-3-yl; R_7= 4-MeC_6H_4;3,4-F_2Bn

Scheme 23. Approaches to synthesis of 2-substituted-7-R-*N*-aryl-(benzyl-)quinazolin-4-amines

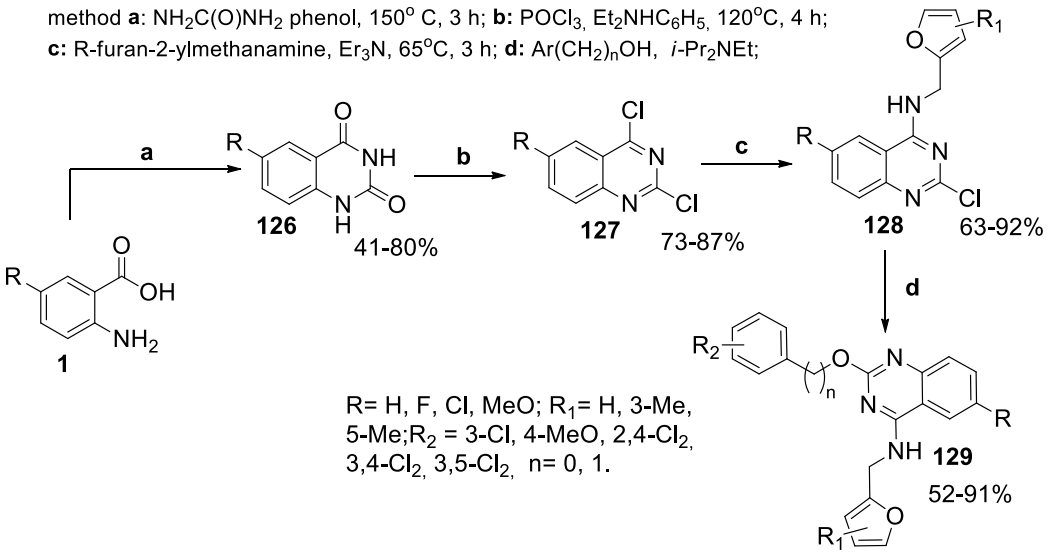


R= Br, CN; R_1= MeO, NO_2, CF_3, Pr, Cpr, F, Me; R_2= NMe_2, NH_2, Cpr, pyrrolidine-1-yl, 4-Me-piperazine, 4-F-piperidine, 4,-F_2-piperidine, morpholine, 4-methylsulfonyl)piperazine, 4-(cyclopropylsulfonyl)piperazine

Scheme 24. Synthesis of substituted 4-cyclohexylaminoquinazolines

Nam-ChulCho and co-authors [74] have shown that 2-aryl-(benzyl)-oxyquinazolin-4-amines are antagonistic to PAR_2 and can provide a rather interesting strategy for finding and treating inflammatory diseases. The synthesis of target compounds **129** was conducted by sequential nucleophilic substitution of chlorine atoms in 2,4-dichloroquinazolines **127** for R-furan-2-yl–methanamine **128** and substituted phenols or benzyl alcohol (**Scheme 25**). Among the studied compounds, the greatest antagonistic activity against PAR_2 was performed by 2-(3,5-di–chlorophenoxy)-6-fluoro-N-(R-furan-2-ylmethyl)–quinazolin-4-amine with the value IC_{50} 2,8 μM. The compound also showed significant inhibitory effects on LPS-activated pro-inflammatory mediators, namely NO, PGE2, IL-1b, IL-6 та TNF-a, by regulating various intracellular signaling pathways involving nuclear factor-jB (NF-jB), activator protein 1 (AP-1) and MAPK. In addition,

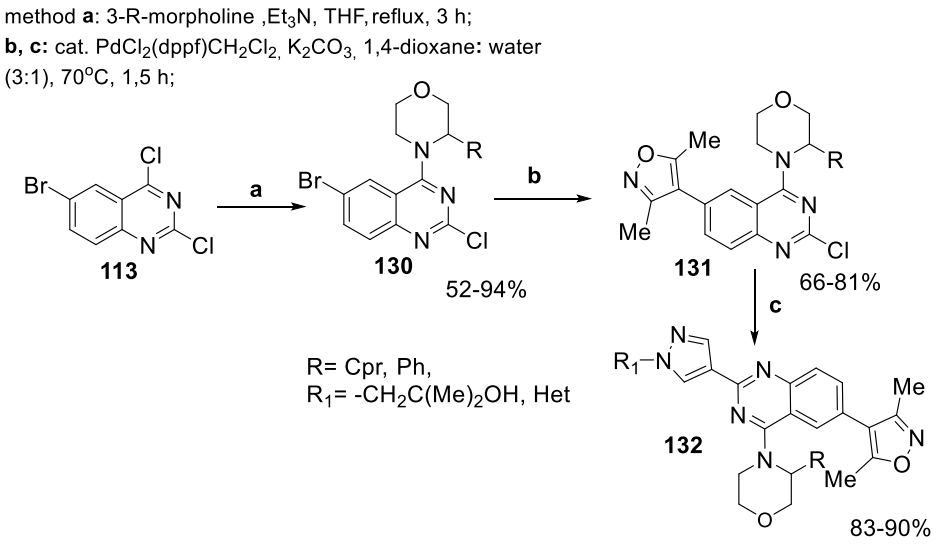
the administration of the considered compound reduced mortality from sepsis in mice. All these data point out the prospects of developing new antagonists to PAR_2 with anti-inflammatory activity among quinazolin-4-amines according to *in vitro* and *in vivo* methodology.



Scheme 25. Synthesis of 2-R_2-phenyl-(benzyl-)oxy)-*N*-(R_1-furan-2-ylmethyl)-6-R-quinazolin-4-amines

Yanga S.-M. and co-authors published a research paper [75], showing extensive structural modification based on 6-bromo-2,4-dichloro–quinazolines **113** for the search for anti-tumour and anti-inflammatory agents (**Scheme 26**). A series of successive reactions were applied for conversion of **113** to other structural analogues: nucleophilic substitution of chlorine for the morpholine fragment in the position 4 **130** and Suzuki reactions, namely, substitution of bromine in the position 6 for 3,5-dimethylisoxazoles **131** and chlorine in the position 2 for 1-R_1-pyrazoles **132**. The synthesized compounds were studied on the *in vivo* Kasumi-1 xenograft mouse model and collagen-induced arthritis (CIA) in mice. The conducted research and SAR-analysis have shown that more effective are the compounds with *S*-configuration of 3-phenylmorpholine and the simultaneous presence of (2-hydroxyl-2-methyl–propyl)pyrazole moiety in the position 2 of quinazoline.

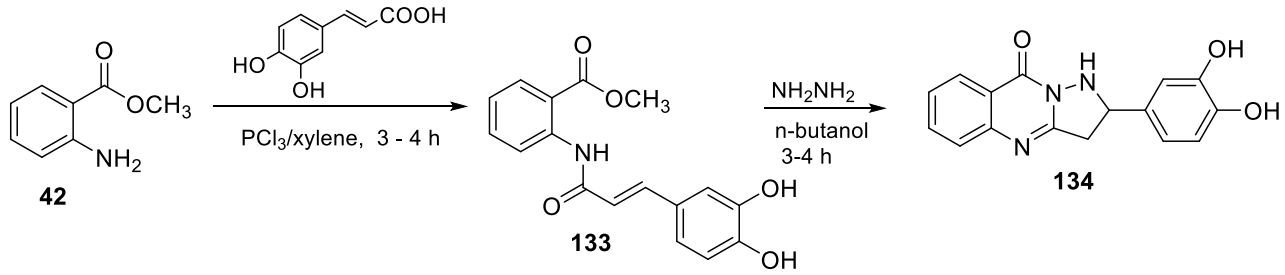
In addition to high efficiency of the *in vivo* Kasumi-1 xenograft mouse model, the determined (*S*)-1-(4-(6-(3,5-dimethylisoxazol-4-yl)-4-(3-phe–nylmorpholino)quinazolin-2-yl)-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol **132**, showed a significant improvement in the severity of collagen-induced arthritis (CIA) in the same animals. Therefore, these results point out the potential use of quinazoline-based compounds for the treatment of inflammatory diseases.



Scheme26. Synthesis and structural modification of 4-(6-bromo-2-chloroquinazolin-4-yl)-3-cyclopropyl-(phenyl-)morpholines

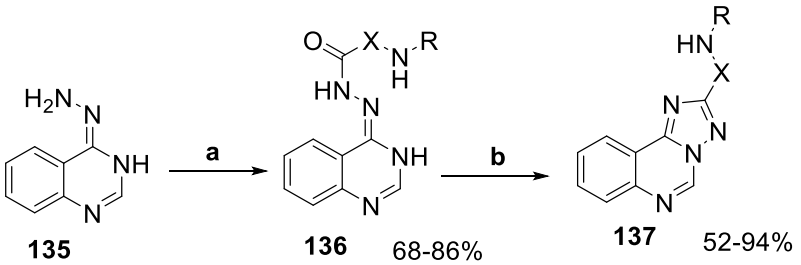
1.3 Condensed and spiro condensed quinazolines as potential anti-inflammatory agents

Recently, in the academic studies, more and more attention has been paid to the search for anti-inflammatory agents among condensed quina–zoline derivatives. Thus, Hussein's paper [76] describes the synthesis and anti-inflammatory activity of quinazoline annelated with pyrazole, namely 2-(3,4-dihydroxyphenyl)-2,3-dihydro–pyrazolo[5,1-*b*]quinazolin-9(1H)-one **134** (**Scheme 27**). The mentioned compound was synthesized in two stages on the basis of methylanthranilate **42**. At the first stage, the above-mentioned substance was introduced into the reaction with caffeic acid in the presence of PCl_3. The N-acylation product **133** was subjected to cyclization under the action of hydrazine, which allowed obtaining the target compound **134**. It has been established that the compounds **133** and **134** perform a pronounced anti-inflammatory and antipyretic activity. It should be noted that the activity of **134** exceeds the pharmacological activity of the intermediate product **133**, which demonstrates the decisive impact of the pyrazoloquinazoline system on the manifestation of the mentioned biological effects. In addition, the authors investigated the acute toxicity of the compound **134**, which constituted 495 mg/kg.



Scheme 27. Synthesis of methyl 2-(3,4-dihydroxyphenyl)-2,3-dihydropyrazolo[5,1-*b*]quinazolin-9(1*H*)-one as a promising anti-inflammatory agent

The work of Ukrainian investigators is devoted to the targeted search for anti-inflammatory agents among (quinazolin-4(3*H*)-ylidene)hydrazides of *N*-protected amino acids and their hetero–cyclization products [77]. For synthesis of the target compounds, the authors used 4-hydrazino–quinazoline **135** as a parent compound, which was acylated by *N*-protected amino acids, and the resulting *N*-acylated derivatives **136** were subjected to a heterocyclisation reaction (**Scheme 28**). At the same time, as a result of Dimrot's rearrangement, *N*-acyl-([1,2,4]triazolo–[1,5-*c*]quinazolin-2-yl)R-)amines **137** were formed with satisfactory yields. The results of screening of biological activity of the obtained compounds on the "formalin" test in rats allowed identifying the agents with a level of anti-inflammatory activity which significantly exceeds that of the comparison drug «Diclofenac sodium». The conducted SAR-analysis gave a possibility for the authors to identify critical "pharmacophore" fragments, and docking studies revealed the probable mechanism of action of the synthesized compounds.

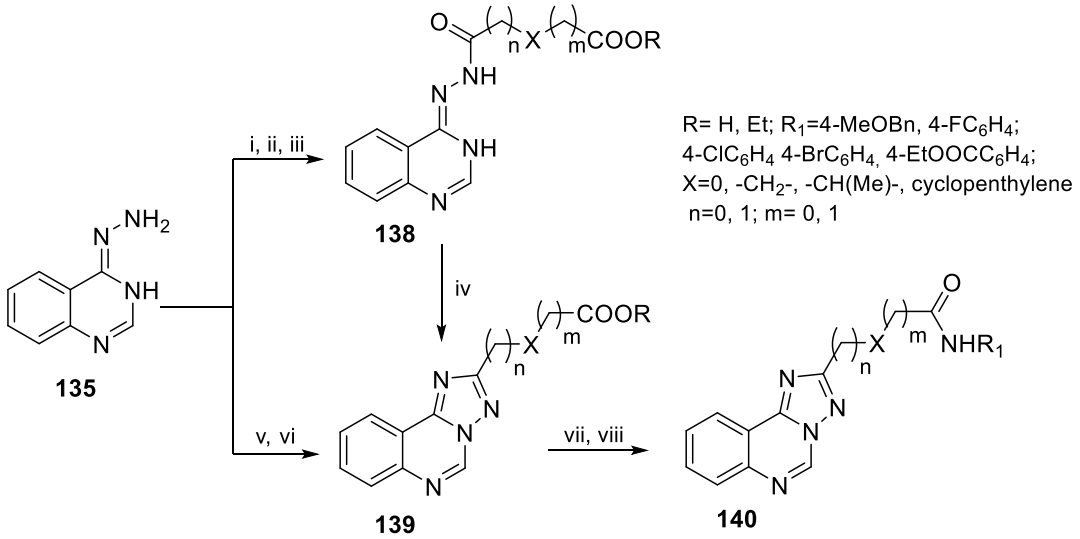


method **a**: RHNXCOOH, CDI, 1,4-dioxane, reflux, 60-90 min.; **b:** AcOH, reflux, 3-5 h;
X= -CH_2-, -$C_6H_4CH_2$-, C_6H_4-, -CH(Me)-, -$(CH_2)_2$-, -$(CH_2)_3$-, -CH(CH(Me)$_2$)-, -CH(CH_2CH(Me)$_2$)-, -CH(CH_2Ph)-, -CH(CH_2CHSMe)-, R = Ac, Bz, Boc

Scheme 28. Synthesis of (quinazolin-4(3*H*)-ylidene)hydrazides of *N*-protected aminoacids and [1,2,4]triazolo–[1,5-c]quinazolines on their basis

In continuation of the search for anti-inflammatory agents, the mentioned team synthesized the following compounds, using a similar approach – (quinazolin-4(3*H*)-ylidene)–hydrazides of dicarboxylic acids **138**, ([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)alkyl–

carboxylic acids **139** and their amides **140** [78]. The synthesis of hydrazides **138** was conducted by acylation of quinazolin-4(3*H*)-ylidene)hydrazine **135** by corresponding acyl halides, cyclic anhydrides and imidazolides of dicarboxylic acid monoesters (**Scheme 29**). Hydrazides **138** were converted to the compounds **139**, which were subsequently used as starting compounds for chemical modification aimed at introducing an amide fragment **140** into the molecule. The results of biological screening of the synthesized compounds on the model of carrageenan induced inflammation. showed that amides of ([1,2,4]triazolo[1,5-*c*]quinazolin-2-yl)alkylcarbo–xylic acids are more active anti-inflammatory agents, which compete in terms of activity with «Diclofenac sodium».



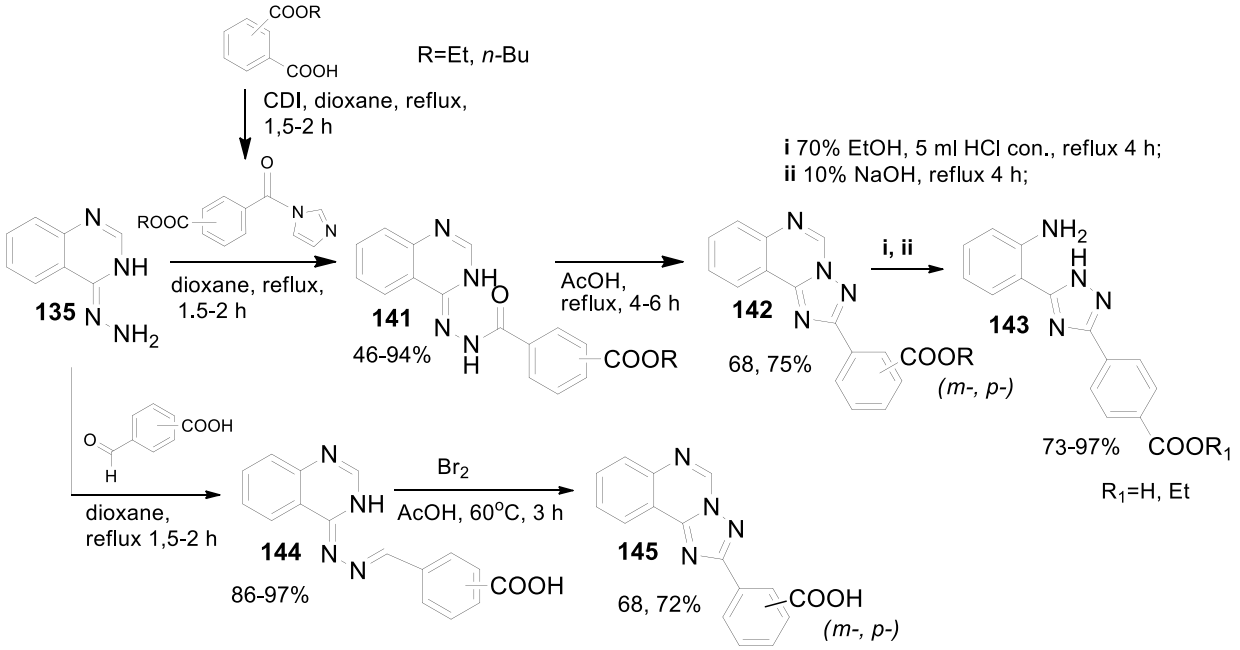
i: ClC(O)$(CH_2)_n$COOEt, dioxane, $N(Et)_3$, 0 - 5° C, 1.5 h; **ii**: 1) HCOO(CH_2)nCOOEt, CDI, dioxane, 80°C, 1.5-3 h; **iii**: anhydrides, dioxane, reflux, 80°C, 1-1.5 h or r.t., 24 h; **iv:** AcOH, reflux, 3-4 h; **v:** 1) ClC(O)(CH_2)nCOOEt, AcOH, AcONa, 0-5°C, 1.5 h; 2) reflux, 3 h: **vi:** anhydrides, AcOH, reflux, 3-4 h; **vii:** 4-MeOBnNH$_2$, 1-2 drop, 130-140°C, 3-4 h; **viii:** 1) dioxane, CDI. 80°C; 2) $ArNH_2$, reflux, 1.5 h.

Scheme 29. Synthesis and structural modification of (quinazolin-4(3*H*)-ylidene)hydrazides of dicarboxylic acids

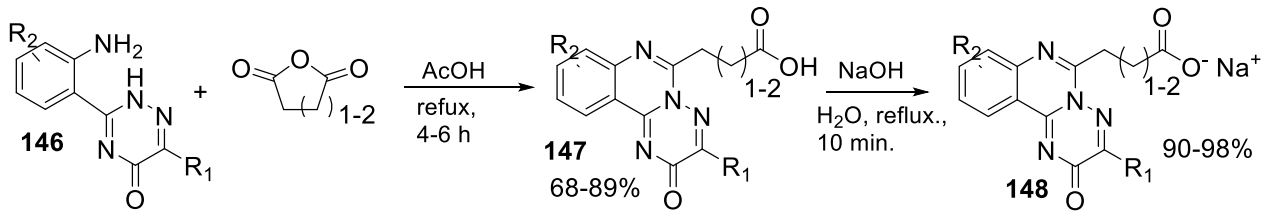
N. Krasovs'ka's paper is dedicated to the synthesis of ([1,2,4]triazolo[1,5-*c*]quinazolin-2-yl)benzoic acids **142** and their esters **145** as potential anti-inflammatory agents [79]. The authors describes that alkyl (2-(quinazolin-4(3*H*)-ylidene)hydrazine-1-carbonyl)benzoates **141** and (quinazolin-4(3*H*)-ylidene)hydrazineylidene)methyl)benzoic acids **144** under the conditions of heterocyclisation and oxidative cyclisation, form target compounds **142** and **145**, respectively (**Scheme 30**). The study discusses the factors limiting the course of the mentioned reactions. In addition, it is shown that it is impossible to conduct the synthesis of the corresponding acids **145** by hydrolysis of esters **141** due to additional hydrolytic cleavage of the pyrimidine cycle. At the same time the corresponding 4-(5-(2-amino–phenyl)-1*H*-1,2,4-triazol-3-yl)benzoic acid and its ethyl ester are formed **143**. The moderate anti-inflammatory activity of carboxy-containing quinazolines and [1,2,4]triazolo[1,5-*c*]quina–zolines has been revealed and the prospects for their further structural modification have been outlined.

A. Yu. Voskoboinik's co-authored work is dedicated to the targeted search for anti-inflammatory agents among the derivatives of a little-known [1,2,4]triazino[2,3-*c*]quinazolin-2-one system [80]. The authors show that the condensation of 3-(2-aminophenyl)-6-R_1-1,2,4-triazin-5-ones **146** with anhydrides of dicarboxylic acids in acetic acid leads to the formation of (3-R-2-oxo-2*H*-[1,2,4]triazino[2,3-c]quinazolin-6-yl)–carboxylic acid **147** with high yields (**Scheme 31**). The compounds **147** are converted to water-soluble salts **148** in order to improve their pharmaceutical and technological properties [81]. The obtained salts **140** were tested for anti-inflammatory activity [81], which allowed identifying an extremely promising anti-inflammatory agent, namely sodium 4-(3-methyl-2-oxo-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-6-yl)–butanoate with the level of activity exceeding that of the comparison drug Diclofenac sodium and having more favorable toxicity parameters. This compound was subsequently subjected to in-depth pharmacological studies, which established its effectiveness in the treatment of adjuvant

arthritis, however, unlike the comparison drug («Diclofenac»), the mentioned compound has a pronounced antisclerotic effect, as evidenced by a low degree of fibroblastic reaction [82]. Additionally, the study of biochemical parameters of blood in rats with adjuvant arthritis while introducing the compound was carried out and it has been determined that according to a number of indicators (levels of seromucoids, malon–dialdehyde, superoxide dismutase, γ-glutamyl transferase) they exceed the parameters of the reference drug «Diclofenac» [83].



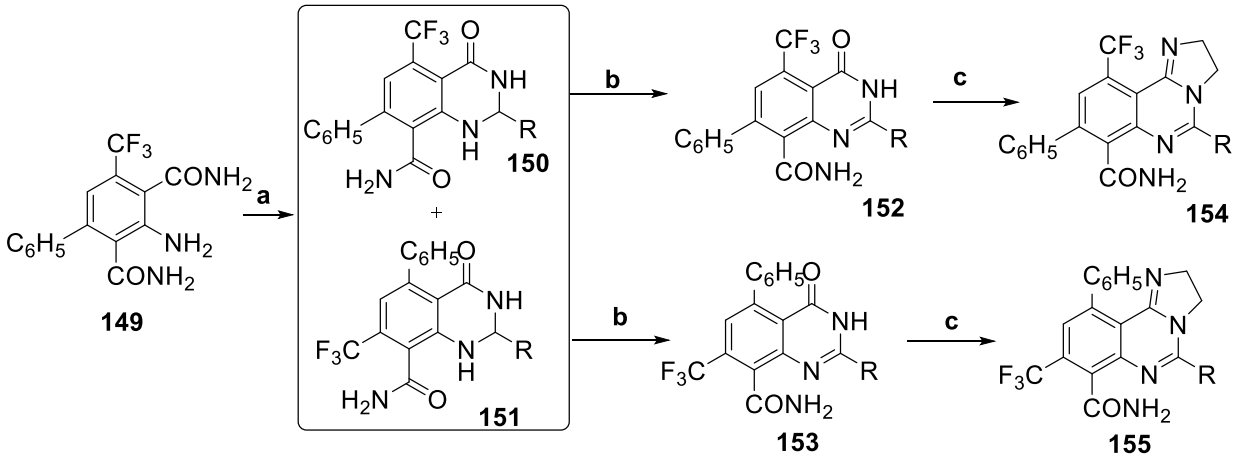
Scheme 30. Approaches to synthesis of ([1,2,4]triazolo[1,5-*c*]quinazolin-2-yl)benzoic acids and their ethyl esters



R_1 = Me, Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-i-PrC_6H_4, 4-BuC_6H_4; R_2 = H, Me, Hal, MeO

Scheme 31. Synthesis of (3-R-2-oxo-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-6-yl)carboxylic acid and their sodium salts

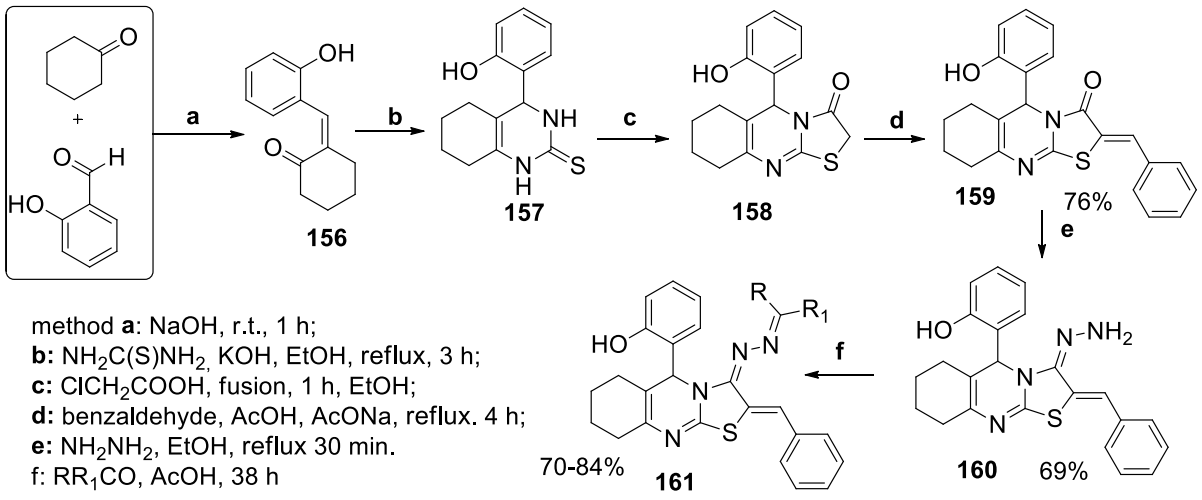
The research paper [84] is devoted to the search for anti-inflammatory drugs among new 5-R-10-phenyl-8(10)-(trifluoromethyl)-2,3-dihydroimida-zo[1,2-*c*]quinazoline-7-carboxamides. By cyclisa-tion of 3-amino-5-(trifluoromethyl)-[1,1'-bi–phenyl]-2,4-dicarboxamide **149** with aldehydes the authors obtained a mixture of regioisomers **150** and **151 (Scheme 32**), which was separated by column chromatography with n-hexane/ethyl acetate eluent. The isomers were further dehydrated, and the formed 4-oxo-3,4-dihydro–quinazoline **152** and **15**3 were subjected to cyclization with 2-chloroethylamine hydrochloride in the presence of $POCl_3$. As a results, the following target compounds are formed **154, 155** with the yields of 46-60%. The synthesized compounds were investigated *in vivo* (carrageenan-induced rat paw edema model) for their anti-inflammatory activity and *in silico* (docking) for binding with COX-1 and COX-2. It has been shown that the compounds **154** and **155** with the 4-hydroxyphenyl fragment in position 5 of the cycle inhibit the edema by 57 and 60 % (4 hours of experiment), competing at the same time with “Indometacin” (75 %). The paper presents the discussion of the docking results, showing an important role of the 4-hydroxyphenyl group in stacking interactions with enzymes, which, according to the authors, explains higher anti-inflammatory activity of compounds 154 and 155. in comparison with other analogues.



method **a**: RC(O)H, AcOH, r.t., 4 h; **b:** MnO_2, CH_2Cl_2, r.t., 2 h;
c: $POCl_3$. 2-Cl$(CH_2)_2NH_2$ HCl, reflux, 4 h;
R= fur-2-yl, thiophen-2-yl; 4-HOC_6H_4

Scheme 32. Synthesis of 5-R-10-phenyl-8(10)-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazoline-7-carboxamides

A series of new 6,7,8,9-tetrahydro-5H-5-hydroxyphenyl-2-benzylidinehydrazinothiazolo–[2,3-*b*]quinazolines **161** was synthesized for the targeted search of anti-inflammatory agents (**Scheme33**) [85]. The compounds **161** were formed by nucleophilic addition-cleavage reaction of the hydrazine derivative **160** with ketones or aldehydes in glacial acetic acid in the presence of anhydrous sodium acetate. The study of anti-inflammatory activity on the carrageenan-induced rat paw edema model allowed identifying a promising compound, namely 6,7,8,9-tetrahydro-5*H*-5-hydroxyphenyl-2-benzylidine-3-(*N*′-3-pen–tylidenehydrazino)thiazolo[2,3-b]quinazoline, which throughout the experiment (0.5; 1; 2 and 3 hours) exceeded the standard drug «Diclofenac sodium» by 0.3–0.6 times. Along with that, the mentioned compound has the lowest ulcer index (0.46 ± 1.26).



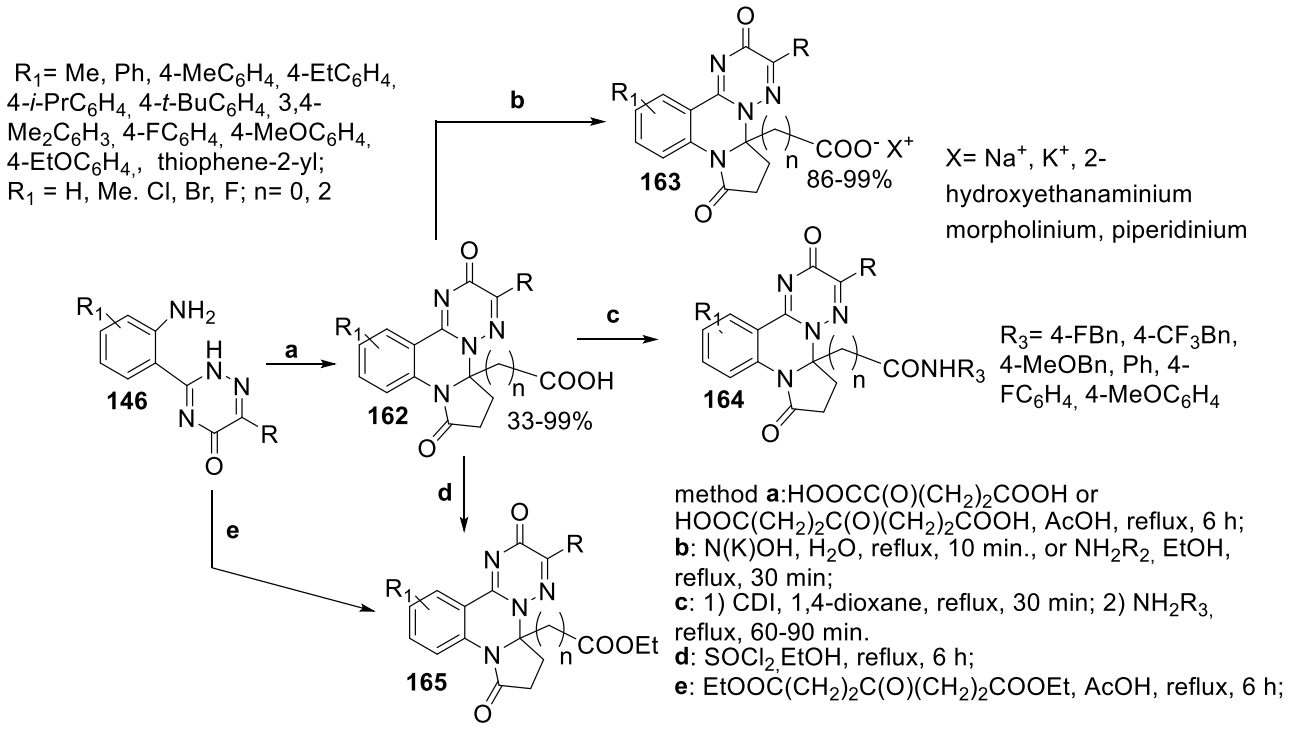
method **a**: NaOH, r.t., 1 h;
b: $NH_2C(S)NH_2$, KOH, EtOH, reflux, 3 h;
c: $ClCH_2COOH$, fusion, 1 h, EtOH;
d: benzaldehyde, AcOH, AcONa, reflux. 4 h;
e: NH_2NH_2, EtOH, reflux 30 min.
f: RR_1CO, AcOH, 38 h

R = H, Me, Et, Ph; R_1=Et, Pr, Ph, 2-ClC_6H_5 4-ClC_6H_5, 2-$NO_2C_6H_5$, 4-$NO_2C_6H_5$, 2-MeC_6H_5, 4-MeC_6H_5, 4-$MeOC_6H_5$

Scheme 33. Synthesis of 6,7,8,9-tetrahydro-5H-5-hydroxyphenyl-2-R,R1-lidinehydrazinothiazolo[2,3-*b*]quinazolines

By the tandem heterocyclisation reaction, Stavytskyi V. V. and co-authors annealed pyrrole and quinazoline with various aromatic and carboxyl fragments to the triazine cycle and tested their anti-inflammatory activity on formalin- and carrageenan-induced inflammation models [86–88]. The formation of 2*H*-pyrrolo[1,2-*a*][1,2,4]–triazino[2,3-*c*]quinazolines **162** was carried out through interaction of 2-(6-R-2,5-dihydro-5-oxo-1,2,4-triazino-3-yl)anilines **146** with keto–carboxylic acids (**Scheme 34**). In order to improve the pharmacokinetic, pharmacological and technological characteristics, the authors made a structural modification of the carboxylic group of

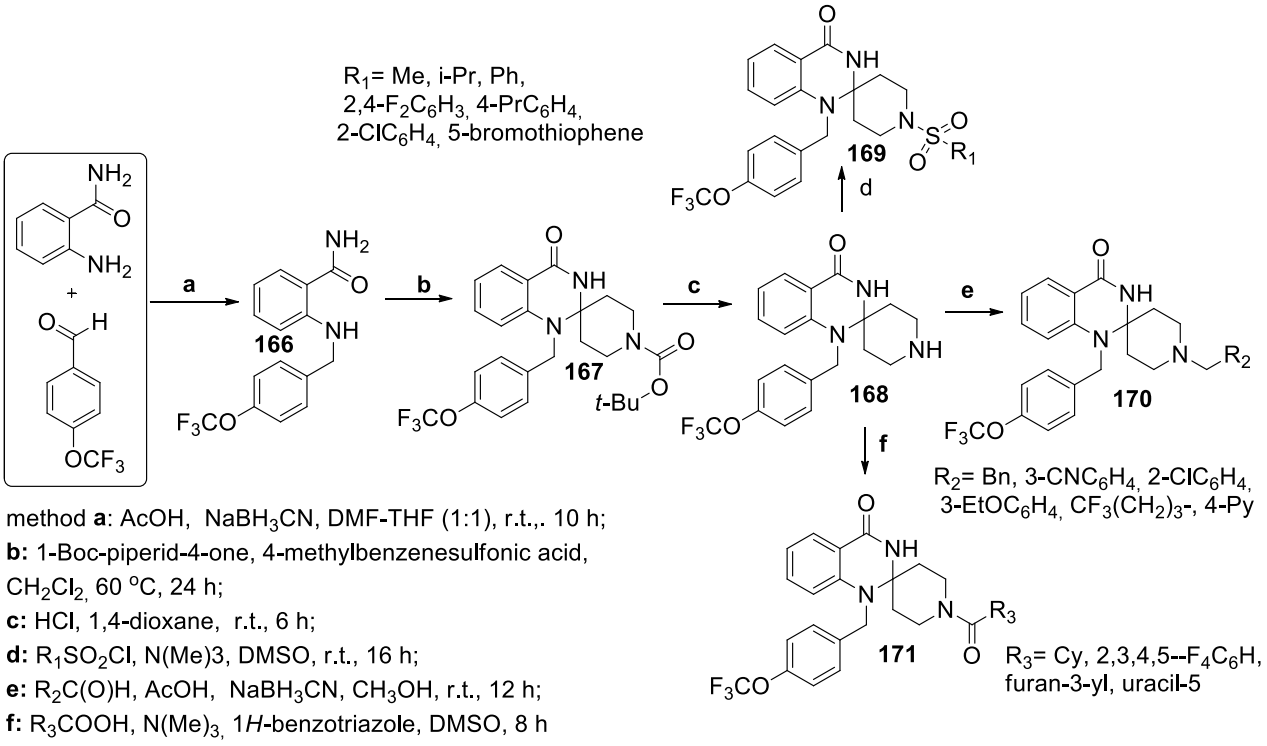
pyrrolo[1,2-*a*][1,2,4]triazolo-(triazino-)[*c*]quina–zolin-carboxylic (propanoic) acids, namely synthesized water-soluble salts with inorganic and organic bases **163**, esters **165** and amides **164** [86; 89]. The studied compounds have shown high anti-inflammatory activity in comparison with «Diclofenac sodium», and the compounds that contain propanoic acid in the angular position of the cycle exceed its activity by 1.2–26 %. The high anti-inflammatory activity, prognostic affinity values and visualization of the location of these compounds in the active sites of biotargets have become a theoretical platform for studying the probable mechanism of their action, namely inhibition of DPPH and LOX by *in vitro* methods [90]. It has been shown that the specified hetarylcarboxylic acids are characterized in most cases by high LOX inhibition activity (LOX inhibition up to 30%), which can be considered as one of the possible mechanisms of anti-infammatory activity.



Scheme 34. Synthesis and functionalization of 3-(3-R$_1$-2,8-dioxo-7,8-tetrahydro-2*H*-pyrrolo[1,2-*a*][1,2,4]triazino–[2,3-*c*]quinazolin-5a(6*H*)-yl)carboxylic acids

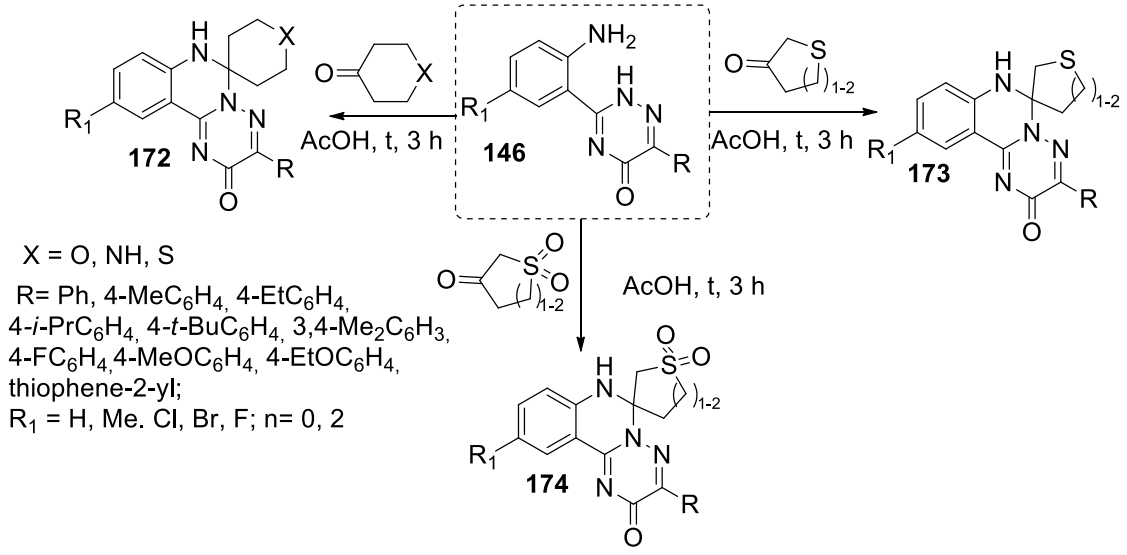
Subba Poojari and co-authors developed the synthesis of *N*-substituted1'-(4-(trifluoro-methoxy)benzyl)-1'*H*-spiro[piperidine-4,2'-quina-zolin]-4'(3'*H*)-ones **169–171** (**Scheme 35**) and investigated their anti-inflammatory and antimicrobial activity [91]. At the same time the synthesis of the parent compound **167** was conducted by condensation followed by cyclo–dehydration of 2-((4-(trifluoromethoxy)benzyl)–amino)benzamide **166** and *Boc*-protected piperidin-4-one in the presence of an acid catalyst. The protective group **160** was removed from intermediate compound (*tert*-butyl carbamate) with the aim of further functionalization of the formed product **167** 1'-(4-(trifluoromethoxy)–benzyl)-1'H-spiro[piperidine-4,2'-quinazolin]-4'(3'*H*)-one, which was subjected to functiona–lization using sulphochlorination reactions (compounds **169**), condensation with subsequent cyclodehydration **170** and acylation **171**. The estimation of anti-inflammatory activity of the synthesized compounds on the carrageenan-induced rat paw edema model allowed identifying a series of compounds, namely alkyl-(aryl-)sul-fonyls **169,** which inhibited edema by up to 56.19 %, while competing with «Ibuprofen» (66.6 %).

The study [92] is dedicated to the targeted search for anti-inflammatory agents among insufficiently known spiro[hetaryl-3(4)6′-[1,2,4]triazino[2,3-*c*]quinazoline-]-2'(7'*H*)-ones. The virtual combinatorial library created by the authors was identified by molecular docking for its ability to inhibit COX-2.



Scheme 35. Synthesis and functionalisation of 1'-(4-(Trifluoromethoxy)benzyl)-1'H-spiro[piperidine-4,2'-quinazolin]-4'(3'*H*)-ones

The potential anti-inflammatory agents **172–174** were synthesized by [5+1]-cyclocondensation of the substituted 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-one **146** with heterocyclic ketones (**Scheme 36**). The study of the obtained compounds on the formalin-induced rat paw edema model allowed identifying a range of promising anti-inflammatory agents, namely 1-methyl-3'-(4-tret-buthylphenyl)- and 1-methyl-3'-(4-methoxyphenyl)-spiro[pyperidine-4,6′-[1,2,4]triazino[2,3-*c*]–quinazoline]-2'(7'*H*)-one, which exceeded the comparison drug «Diclofenac sodium» by the level of pharmacological action (69.2 and 85.9 %). According to the authors, the combination of the triazino[2,3-*c*]quinazoline fragment with spiro-condensed fragments (pyridine) is a reasonable approach for the creation of new anti-inflammatory agents.



Scheme 36. Synthesis of spiro-condensed derivatives of triazino[2,3-*c*]quinazolines

In the last 2020-2021, there appeared a series of papers devoted to the chemistry of natural compounds and the study of new mechanisms of action of non-steroidal anti-inflammatory drugs. Thus, Wang, N.-N. and co-authors published a research paper on the study of anti-inflammatory

activity of the 12 new natural condensed quinazoline derivatives [93]. The specified compounds were isolated from the endophytic fungus *Aspergillussp*., their structures were confirmed by ^{1}H NMR and ^{13}C spectra. The anti-inflammatory test with mouse macrophages RAW 264.7 activated by lipopolysaccharide (LPS) has shown that a number of them are strong inhibitors of NO (IC_{50} 22.1–49.9 μM).

Duff M. R. and co-authors reported in the research paper on a new mechanism of action of NSAIDs (, containing carboxylic groups [94]. The authors investigated the interaction of studied compounds with the human DHFR on the basis of kinetic, NMR and X-ray crystallographic methods and characterized the region of the folate binding site. It has been established that NSAIDs, containing benzoate or salicylate groups, competitively inhibit DHFR and have the highest efficiency. According to the authors, the specified NSAIDs with different mechanisms of action (non-selective inhibitors of COX-1/COX-2, DHFR) reveal ways and opportunities for further structural optimization for the development of dual drugs.

Conclusions

The conducted literature review has shown that the targeted search for anti-inflammatory agents among substituted quinazolines and their condensed analogues is justified and the derivatives of the specified heterocyclic system have significant biological potential and are interesting for the search and development on their basis of new highly effective and low-toxic drugs with a multifaceted mechanism of action (inhibitors of COX-1, COX-2, LOX-15, NO, PGE2, IL-1b, IL-6, TNF-a).

References

[1] Armarego, W.L.F., Brown, D.J., (ed). (1967). *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines* (Part I; Vol. *24*(1)), Interscience Publishers: N.-Y. - London - Sydney.

[2] Brown, D.J., Suppl, I., Taylor, E.C., (ed). (1996). *The Chemistry of Heterocyclic Compounds*, (Vol. 55), J. Wiley & Sons Inc.: N.-Y. - Chichester - Brisbane - Toronto - Singapore - Weinheim.

[3] Witt, A., Bergman, J. (2003). Recent Developments in the Field of Quinazoline Chemistry. *Curr. Org. Chem,* 7: 659–677. http://dx.doi.org/10.2174/1385272033486738

[4] Connolly, D. J., Cusack, D., O'Sullivan, T. P., Guiry, P. J. (2005). Synthesis of quinazolinones and quinazolines. *Tetrahedron, 61*(43), 10153–10202. http://dx.doi.org/10.1016/j.tet.2005.07.010.

[5] Wang, D., Gao, F. (2013). Quinazoline derivatives: synthesis and bioactivities. *Chemistry Central Journal, 7*(1), 95. http://dx.doi.org/10.1186/1752-153x-7-95;

[6] Vinod G. Ugale, Sanjay B. Bari (2014). Quinazolines: New horizons in anticonvulsant therapy. *Eur. J. Med. Chem.,* 80. 447–501. http://dx.doi.org/10.1016/j.ejmech.2014.04.072.

[7] Mohammad, A. (2014). Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives. *International J. Med. Chem,* 27, 1–27. http://dx.doi.org/10.1155/2014/395637.

[8] Dumitrascu, F., Popa, M. M. (2014). Pyrrolo[1,2-*a*]–quinazolines. Synthesis and biological properties. *ARKIVOC*., (i). 428–452. http://dx.doi.org/10.3998/ark.5550190.p008.699.

[9] He, L., Li, H., Chen, J., Wu, X.-F. (2014). Recent advances in 4(3*H*)-quinazolinone syntheses. *RSC Adv.,* 4(24): 12065–12077. http://dx.doi.org/10.1039/c4ra00351a

[10] Al-Ebaisat, H. S. (2015). A Review on Synthesis and Spectral Properties of Quinazolines and Pyrimidines. *American Chemical Science Journal*. *6*(4), 213–223. http://dx.doi.org/10.9734/ACSj/2015/16128.

[11] Chaban, Z., Harkov, S., Chaban, T., Klenina, O., Ogurtsov, V., Chaban, I. (2017). Recent advances in synthesis and biological activity evaluation of condensed thiazoloquinazolines: a review. *Pharmacia. 64*(3). 52–66.

[12] Rakesh, K. P., Darshini, N., Shubhavathi, T., Mallesha, N. (2017). Biological Applications of Quinazolinone Analogues: A Review. *Organic & Medicinal Chem IJ*. *2*(2), 555585. http://dx.doi.org/10.19080/OMCIJ.2017.02.555585.

[13] Mohammadkhani, L., Heravi, M. M. (2020). Microwave-Assisted Synthesis of Quinazolines and Quinazolinones: An Overview. *Frontiers in Chemistry,* 8. http://dx.doi.org/10.3389/fchem.2020.580086

[14] D'yakonov, A. L., Telezhenetskaya, M. V. (1997). Quinazoline alkaloids in nature. *Chemistry of Natural Compounds*, 33: 221–267;

[15] Michael, J. P. (2001). Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep*. 18: 543–550.

[16] Mhaske, S. B. Argade, N. P. (2006). The Chemistry of Recently Isolated Naturally Occurring Quinazolinone Alkaloids. *Tetrahedron*, 62, 9787–9826. http://dx.doi.org/10.1016/j.tet.2006.07.098

[17] Joseph, M. P. (2007). Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.* 24. 223–246.

[18] Kshirsagar, U. A. (2015). Recent developments in the chemistry of quinazolinone alkaloids. *Organic & Biomolecular Chemistry*, *13*(36), 9336–9352. http://dx.doi.org/10.1039/c5ob01379h.

[19] Chandrika, P. M., Rao, R.R., Narsaiah, B., Raju, M.B. (2008). Quinazoline derivatives with potent anti-inflammatory and anti-allergic activities. *Int. J. Chem. Sci., 6*(3). 1119–1146.

[20] Selvam, T. P., Kumar, P. V. (2011). Quinazoline Marketed drugs – A Review. *Research in Pharmacy, 1*(1). 1–21.

[21] Parvez, A. N., Rana, A., Imran, M. (2011). An Updated Review: Newer Quinazoline Derivatives Under Clinical Trial. *International J. Pharmaceutical & Biological Archives, 2*(6), 1651–1657.

[22] Marzaro, G., Guiotto, A., Chilin, A. (2012). Quinazoline derivatives as potential anticancer agents: a patent review (2007 - 2010). *Expert Opin. Ther. Patents, 22*(3), 223–252. http://dx.doi.org/10.1517/13543776.2012.665876.

[23] Ravez, S., Castillo-Aguilera, O., Depreux, P., Goossens, L. (2015). Quinazoline derivatives as anticancer drugs: a patent review (2011 - present). *Expert Opin. Ther. Patents, 25*(7), 1–16. http://dx.doi.org/10.1517/13543776.2015.1039512

[24] Alam, J., Alam, O., Naim, M.J., Alam, P. (2015). A review: Recent investigations on Quinazoline Scaffold. *International J. Advanced Research. 3*(12), 1656–1664.
[25] Sukriti, S. (2015). Biological activity of Quinazoline: A Review. *International Journal of Pharma Sciences and Research (IJPSR). 6*(9), 1206–1213.
[26] Jafari, E., Khajouei, M. R., Hassanzadeh, F., Hakimelahi, G. H., Khodarahmi, G. A. (2016). Quinazolinone and quinazoline derivatives: recent structures with potent antimicrobial and cytotoxic activities. *Res Pharm Sci.*, *11*(1). 1–14.
[27] Ismail, R. S. M., Ismail, N. S. M., Abuserii, S., Abou El Ella, D. A. (2016). Recent advances in 4-aminoquinazoline based scaffold derivatives targeting EGFR kinases as anticancer agents. *Future Journal of Pharmaceutical Sciences*, *2*(1), 9–19. http://dx.doi.org/10.1016/j.fjps.2016.02.001
[28] Darwish, K.M., Dakhil, O.O. (2017). A Review on synthesis and biological profiles of some Quinazolines and (4*H*)-3,1-Quinazolin-4-ones of active substituents and their uses as starting materials in reaction schemes. *Libyan Journal of Science & Technology*, *6*(1). 8–13.
[29] Ajani, O.O., Audu, O. Y., Aderohunmu, D. V., Owolabi, F.E., Olomieja, A. O. (2017). Undeniable Pharmacological Potentials of Quinazoline Motifs in Therapeutic Medicine. *American Journal of Drug Discovery and Development*, 7: 1–24. http://dx.doi.org/10.3923/ajdd.2017.1.24.
[30] Reddy, A. G., Babu, V. Ha., Prakash Rao, Y. J. (2017). A Review on Quinazolines as Anticancer Agents. *Journal of Chemical and Pharmaceutical Sciences, 10*(3): 1492–1504.
[31] Shagufta, Ahmad, I. (2017). An insight into the therapeutic potential of quinazoline derivatives as anticancer agents. *Med. Chem. Commun*., 5, http://dx.doi.org/10.1039/c7md00097a.
[32] Hameed, A., al-Rashida, M., Uroos, M., Ali, S.A., Ishtiaq, A.M., Khan, K.M. (2018). Quinazoline and Quinazolinone as Important Medicinal Scaffoldes: A Comparative Patent Review (2011-2016*). Expert Opin. Ther. Patents*, *28*(4), 281–297 http://dx.doi.org/10.1080/13543776.2018. 1432596.
[33] Auti P. S., George G., Paul A. T. (2020). Recent advances in the pharmacological diversification of quinazoline /quinazolinone hybrids. *RSC Advances, 10*(68), 41353–41392. http://dx.doi.org/10.1039/d0ra06642g.
[34] Francis, J.E., Cash, W.D., Barbaz, W.D., Bernard, P.S., Lovell, R.A., Mazzenga G.C. (1991), Synthesis and benzodiazepine binding activity of a series of novel [1,2,4]triazolo[1,5-c]quinazolin-5(6H)-ones. *J. Med. Chem.* 34, 281–290. http://dx.doi.org/10.1021/jm00105a044.
[35] Jantova, S., Cipak, L., Slamenova, D., Horvatha, V., Rauko, P. (2003). Induction of cytotoxicity and sDNA breaks by 9-bromo-5-morpholino-tetrazolo[1,5-c]quinazoline in tumor cells cultured in vitro. *Toxicol. in Vitro*. 17, 457–463. http://dx.doi.org/10.1016/S0887-2333(03)00066-3.
[36] Okamura, T., Kurogi, Y., Hashimoto, K., Nishikawaa, H., Nagao, Y. (2004). Facile synthesis of fused 1,2,4-triazolo[1,5-*c*]pyrimidine derivatives as human adenosine A3 receptor ligands. *Bioorg. Med. Chem. Lett., 14*(10), 2443–2446. http://dx.doi.org/10.1016/j.bmcl.2004.03.010.
[37] Kim, Y.-C., Xiao-duo, Ji., Jacobson, K. A. (1996). Derivatives of the Triazoloquinazoline Adenosine Antagonist (CGS15943) Are Selective for the Human A3 Receptor Subtype. *J. Med. Chem, 39*(21), 4142–4148. http://dx.doi.org/10.1021/JM960482I.
[38] Kim Y.C., Zwart M.De., Chang L., Moro S., Kuenzel J., Melman N. (1998). Derivatives of the triazoloquinazoline adenosine antagonist (CGS15943) having high potency at the human A2B and A3 receptor subtypes. at al. *J. Med. Chem.,* 41, 2835–2845. http://dx.doi.org/10.1021/jm980094b.
[39] Gineinah, M.M., Nasr, M.N., Abdelal, A.M., El-Emam, A.A., Said, S.A. (2000). Synthesis and Antiinflammatory Evaluation of New 2- and 3-Substituted 1,2,4-Triazolo[4,3-*c*]- and [1,5-*c*]quinazoline Derivatives. *Med. Chem. Res. 10*(4), 243–252.
[40] Balo, C., Lopes, C., Brea, J.M., Fernandez, F., Caamano, O. (2007). Synthesis and Evaluation of Adenosine Antagonist Activity of a Series of [1,2,4]Triazolo[1,5-*c*]quinazolines. *Chem. Pharm. Bull., 55*(3), 372–375 http://dx.doi.org/10.1248/cpb.55.372.
[41] Avendano, C., Menendez, J. C. (2008). *Medical chemistry of anticancer drugs*. UK: Elsevier's Science & Technology Rights Department inOxford.
[42] Mani Chandrika, P., Raghu, A., Ram Rao, B., Narsaiah, M., Bhagawan Raju (2008). Quinazoline dersvatives with potent anti-inflammatory and antiallergic activities. *Int. J. Chem. Sci*., *6*(3), 1119–1146.
[43] Hussein, M. A. (2010). Structure anti-inflammatory activity relationship and biochemical evaluation of some novel triazoloquinazoline and triazino-quinazoline derivatives containing sulfacetamide moiety. *Int. J. Appl. Biol. Pharm. Tech., 1*(3), 1054–1066.
[44] Kehler, J., Ritzen, A., Langgard, M., Petersen, S.L., Farah, M.M., Bundgaard, C. Christoffersen C. T., Nielsen J., Kilburn J. P. (2011). Triazoloquinazolines as a novel class of phosphodiesterase 10A (PDE10A) inhibitors. *Bioorg. Med. Chem. Lett., 21*, 3738–3742. http://dx.doi.org/10.1016/j.bmcl.2011.04.067
[45] Levin, J. I., Laufer, S. (Eds) (2012). *Anti-Inflammatory Drug Discovery*. RSC Drug Discovery Series No. 26, Cambridge: Royal Society of Chemistry.
[46] Khan, I., Ibrar, A., Abbas, A., Abbas, N., Saeed, A. (2014). Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthesis approaches and multifarious applications. *Eur. J. Med. Chem*., 76, 193–244; htpp://dx.doi.org/10.1016/j.ejmech.2014.02.005.
[47] Khan, I., Ibrar, A., Ahmed, W., Saeed, A. (2015). Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: the advances continue. *Eur. J. Med. Chem.* 90, 124–169. http://dx.doi.org/10.1016/j.ejmech.2014.10.084.
[48] Faisal, M., Saeed, A. (2021). Chemical Insights Into the Synthetic Chemistry of Quinazolines: Recent Advances. *Front. Chem.,* https://doi.org/10.3389/fchem.2020.594717.
[49] Ali Gamal Al-kaf (Ed.) (2020). *Quinazolinone and Quinazoline Derivatives*. Acad. Sana'a University. https://doi.org/10.5772/intechopen.85315.
[50] Narendra, B. A., Rama, R. N. (2011). Synthesis of some new quinazolinone formazans as anti-Inflammatory and anthelmintic agents. *Journal of Pharmacy Research*, *4*(4), 983–985.
[51] Zayed, F. M., Hassan, H. M. (2014). Synthesis and biological evaluation studies of novel quinazolinone derivatives as antibacterial and anti-inflammatory agents. *Saudi Pharmaceutical Journal, 22*(2). 157–162.
[52] Kandpal, B., Meshram, J., Mohanram, I., Shaikh, A. (2014). Evaluation of newly synthesized quinazolinone derivatives of hydrazones as potent anti-inflammatory

and antbacterial agents. *Medicinal Chemistry Research*, 24(4), 1419–1426. http://dx.doi.org/10.1007/s00044-014-1226-3

[53] Ghodge, B., Kshirsagar, A., Navghare, V. (2020). Synthesis, characterization, and investigation of the anti-inflammatory effect of 2,3-disubstituted quinazoline-4(1*H*)-one. *Beni-Suef University Journal of Basic and Applied Sciences*. *9*(1), 30 (2020). https://doi.org/10.1186/s43088-020-00056-w

[54] El-Hashash, M. A. E.-A., Azab, M. E., Faty, R. A. E.-A., Amr, A. E.-G. E. (2016). Synthesis, Antimicrobial and Anti-inflammatory Activity of Some New Benzoxazinone and Quinazolinone Candidates. *Chemical & Pharmaceutical Bulletin*, *64*(3), 263–271. http://dx.doi.org/10.1248/cpb.c15-00904.

[55] Krishnarth, N., Verma, S. K., Chaudhary, A. (2020). Synthesis and Anti-Inflammatory Activity of Some Novel Quinazolinone Derivatives. *FABAD J. Pharm. Sci., 45*(3), 205–210.

[56] Serya, R. A. T., Abbas, A. H., Ismail, N. S. M., Esmat, A., Abou El Ella, D. A. (2015). Design, Synthesis and Biological Evaluation of Novel Quinazoline-Based Anti-inflammatory Agents Acting as PDE4B Inhibitors. *Chemical & Pharmaceutical Bulletin*, *63*(2). 102–116. https://doi.org/10.1248/cpb.c14-00737.

[57] El-Feky, A., Imran, S., Nayeem, N. (2017). Design, Synthesis, and Anti-inflammatory Activity of Novel Quinazolines*. Oriental Journal of Chemistry, 33*(2), 707–716. https://doi.org/10.13005/ojc/330217

[58] Mohamed, M.S., Kamel, M.M., Kassem, E.M., Abotaleb, N., Khedr, M., Ahmed, M.F. (2011). Synthesis, biological evaluation and molecular docking of quinazoline-4(1*H*)-one derivatives as anti-inflammatory and analgesic agents. *Acta Pol Pharm., 68*(5), 665–75.

[59] Dash, B., Dash, S., Laloo, D., Medhi, C. (2017). Design, Synthesis and Preliminary Pharmacological Screening (antimicrobial, analgesic and anti-inflammatory activity) of Some Novel Quinazoline Derivatives*. Journal of Applied Pharmaceutical Science, 7*(06), 83–96. https://doi.org/10.7324/JAPS.2017.70612

[60] Rajput, C.S., Singhal, S. (2013). Synthesis, Characterization, and Anti-Inflammatory Activity of Newer Quinazolinone Analogs. *Journal of Pharmaceutics, 2013*, 1–7. https://doi.org/10.1155/2013/907525

[61] Sheorey, R., Thangathiruppathy, A., Alagarsamy, V. (2013). Synthesis, Analgesic and Anti-inflammatory Activities of 3- Ethyl-2-substituted Amino-3*H*-quinazolin-4-ones. *Tropical Journal of Pharmaceutical Research*, *12*(4), 583–589. https://doi.org/10.4314/tjpr.v12i4.21

[62] Abuelizz, H. A., Hassane, A. E., Marzouk, M., Ezzeldin, E., Ali, A. A., Al-Salahi, R. (2017). Molecular modeling, enzyme activity, anti-inflammatory and antiarthritic activities of newly synthesized quinazoline derivatives. *Future Medicinal Chemistry*, *9*(17), 1995–2009. https://doi.org/10.4155/fmc-2017-0157

[63] Alagarsamy, V., Solomon, V. R., Sulthana, M. T., Vijay, M.S., Narendhar, B. (2015). Design and synthesis of quinazolinyl acetamides for their analgesic and anti-inflammatory activities. *Zeitschrift Für Naturforschung B, 70*(8), 597–604. https://doi.org/10.1515/znb-2015-0035.

[64] Farag, A. A., Khalifa, E. M., Sadik, N. A., Abbas, S. Y., Al-Sehemi, A. G., Ammar, Y. A. (2012). Synthesis, characterization, and evaluation of some novel 4(3*H*)-quinazolinone derivatives as anti-inflammatory and analgesic agents. *Medicinal Chemistry Research*, *22*(1), 440–452. https://doi.org/10.1007/s00044-012-0046-6

[65] Farag, D. B., Farag, N. A., Esmat, A., Abuelezz, S. A., Abdel-Salam, I. E., Abou El Ella, D. A. (2015). Synthesis, 3D pharmacophore, QSAR and docking studies of novel quinazoline derivatives with nitric oxide release moiety as preferential COX-2 inhibitors. *MedChemComm, 6*(2), 283–299. https://doi.org/10.1039/c4md00392f

[66] Rakesh, K. P., Manukumar, H. M., Gowda, D. C. (2015). Schiff's bases of quinazolinone derivatives: Synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants. *Bioorganic & Medicinal Chemistry Letters, 25*(5), 1072–1077. https://doi.org/10.1016/j.bmcl.2015.01.010

[67] Abbas, S. E., Awadallah, F. M., Ibrahin, N. A., Said, E. G., Kamel, G. M. (2012). New quinazolinone–pyrimidine hybrids: Synthesis, anti-inflammatory, and ulcerogenicity studies. *European Journal of Medicinal Chemistry*, 53, 141–149. https://doi.org/10.1016/j.ejmech.2012.03.050

[68] Abdel-Aziz, A. A.-M., Abou-Zeid, L. A., El Tahir, K. E. H., Ayyad, R. R., El-Sayed, M. A.-A., El-Azab, A. S. (2016). Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4(3*H*)-quinazolinones. *European Journal of Medicinal Chemistry, 121*, 410–421. https://doi.org/10.1016/j.ejmech.2016.05.066

[69] Alafeefy, A. M., Kadi, A. A., Al-Deeb, O. A., El-Tahir, K. E. H., Al-jaber Nabila, A. (2010). Synthesis, analgesic and anti-inflammatory evaluation of some novel quinazoline derivatives*. European Journal of Medicinal Chemistry, 45*(11), 4947–4952. https://doi.org/10.1016/j.ejmech.2010.07.067

[70] Hu, J., Zhang, Y., Dong, L., Wang, Z., Chen, L., Liang, D., Liang, G. (2014). Design, Synthesis, and Biological Evaluation of Novel Quinazoline Derivatives as Anti-inflammatory Agents against Lipopolysaccharide-induced Acute Lung Injury in Rats. *Chemical Biology & Drug Design*, *85*(6), 672–684. https://doi.org/10.1111/cbdd.12454

[71] Dvorakova, M., Langhansova, L., Temml, V., Pavicic, A., Vanek, T., Landa, P. (2021). Synthesis, Inhibitory Activity, and In Silico Modeling of Selective COX-1 Inhibitors with a Quinazoline Core. *ACS Medicinal Chemistry Letters, 12*(4), 610–616. https://doi.org/10.1021/acsmedchemlett.1c00004

[72] Smith, G. F., Altman, M. D., Andresen, B., Baker, J., Brubaker, J. D., Chen, H., Chen, Y., Childers, M., Donofrio, A., Northrup, A. (2017). Identification of quinazoline based inhibitors of IRAK4 for the treatment of inflammation. *Bioorganic & Medicinal Chemistry Letters*, *27*(12), 2721–2726. https://doi.org/10.1016/j.bmcl.2017.04.050

[73] Cho, N.-C., Cha, J. H., Kim, H., Kwak, J., Kim, D., Seo, S.-H., Shin, Ji-S., Kim, T., Duk, K., Lee, J., No, K. T., Kim, Y. K., Lee, K.-T., Pae, A. N. (2015). Discovery of 2-aryloxy-4-amino-quinazoline derivatives as novel protease-activated receptor 2 (PAR2) antagonists. *Bioorganic & Medicinal Chemistry*, *23*(24), 7717–7727. https://doi.org/10.1016/j.bmc.2015.11.016

[74] Yang, S.-M., Yoshioka, M., Strovel, J. W., Urban, D. J., Hu, X., Hall, M.D., Jadhav, A., Maloney D. J. (2019). Lead optimization and efficacy evaluation of quinazoline-based BET family inhibitors for potential treatment of cancer and inflammatory diseases. *Bioorg. Med Chem Lett*, *29*(10), 1220–1226. https://doi.org/10.1016/j.bmcl.2019.03.014

[75] Hussein, M. A. (2013). Synthesis, anti-inflammatory, and structure antioxidant activity relationship of novel 4-quinazoline. *Medicinal Chemistry Research, 22*(10), 4641–4653. https://doi.org/10.1007/s00044-013-0468-9

[76] Martynenko, Yu., Antypenko, O., Nosulenko, I., Berest, G., Kovalenko, S. (2019). Directed search of anti-inflammatory agents among (3*H*-quinazoline-4-ylidene)hydrazides of *N*-protected amino acids and their heterocyclization products. *Anti-Inflammatory & Anti-Allergy Agents in Med. Chem*., *19*(1), 60–71. https://doi.org/10.2174/1871523018666190115092215

[77] Krasovska, N., Stavytskyi, V., Nosulenko, I., Karpenko, O., Voskoboinik, O., Kovalenko, S. (2021). Quinazolin-containing hydrazydes of dicarboxylic acids and products of their structural modification – novel class of anti-inflammatory agents. *Acta Chimica Slovenica*, 68: 395–403. https://doi.org/10.17344/acsi.2020.6440.

[78] Krasovska, N.I. (2022). Approaches to synthesis of ([1,2,4]triazolo[1,5-*c*]quinazolin-2-yl)benzoic acids as potential anti-inflammators. *Farmatsevtychnyi zhurnal,* 3, 44–54. https://doi.org/10.32352/0367-3057.3.22.05.

[79] Voskoboynik, A. Yu., Scorina, D. Yu., Sergeieva, T. Yu., Kovalenko, S. I., Okovytyy, S. I., Omelchenko, I. V., Shishkin, O.V. (2016). Interaction of 3-(2-Aminophenyl)-6-R_1-1,2,4-triazin-5-ones with Acylating Reagents: An Efficient Method for Preparation of 6-Substituted 3-R1-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones. *J. Het. Chem. 5*(3), 776–783. https://doi.org/10.1002/jhet.2120

[80] Yakubovska, V. V., Seredinska, N. M., Voskoboynik, O. Yu., Stepanyuk, G. I., Kovalenko, S. I. (2016). [Purposeful search and characteristic of anti-inflammatory activity of sodium (3-R-2-oxo-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-6-yl)alkylcarboxylates and their halogen containing analogues]. *Aktualni pytannia farmatsevtychnoi i medychnoi nauky ta praktyky – Current issues in pharmacy and medicine: science and practice,* 1(20), 60-66 (in Ukrainian). https://doi.org/10.14739/2409-2932.2016.1.62036.

[81] Grib V.V., Vernigorodskiy S.V., Stepanyuk G.I. (2015). [Comparative analysis of the morphological changes of the joints when using the Sodium salt of 4- (3-methyl-2-oxo-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-6-yl)butyric acid (compound Dsk-38) and diclofenac on adjuvant arthritis model]. *Visnyk morfolohii – Reports of morphology*, 21(2), 340-343 (in Ukrainian).

[82] Grib, V. V., Doroshenko, E. N., Zaichko, N. V., Stepanyuk N. G. (2015). [Comparative characteristics of the sodium salt of of 4-(3-methyl-2-oxo-2*H*-[1,2,4] triazino[2,3-c]–quinazolin-6-yl)butyric acid (compound DSK-38) and diclofenac effects on hematological parameters and safety in ratswith adjuvant arthritis]. *Farmakolohiia ta likarska toksykolohiia - Pharmacology and Drug Toxicology,*. 6(46), 53-57 (in Ukrainian).

[83] Balakumar, C., Lamba, P., Pran Kishore, D., Lakshmi Narayana, B., Venkat Rao, K., Rajwinder, K., Narsaiah, B. (2010). Synthesis, anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines. *European Journal of Medicinal Chemistry, 45*(11), 4904–4913. https://doi.org/10.1016/j.ejmech.2010.07.063

[84] Selvam, T.P., Kumar, P.V. (2010). Synthesis of Novel 6,7,8,9-Tetrahydro-5*H*-5-hydroxyphenyl-2-benzylidine-3-substituted Hydrazino Thiazolo(2,3-*b*)Quinazoline as Potent Antinociceptive and Anti-inflammatory Agents. *Bull. Korean Chem. Soc. 31*(11), 3265–3271. https://doi.org/10.5012/bkcs.2010.31.11.3265

[85] Stavytskyi, V. V., Antypenko, O. M., Nosylenko, I. S., Berest, G. G., Voskoboinik, O. Yu., Kovalenko, S. I. (2020). Substituted 3-R-2,8-Dioxo-7,8-dihydro-2*H*-pyrrolo[1,2-*a*][1,2,4]triazino[2,3-*c*]quinazoline-5*a*(6*H*)carboxylic Acids and Their Salts – a Promising Class of Anti-inflammatory Agents. *Anti-Inflammatory & Anti-Allergy Agents in Med. Chem.*, 19, 1–17. https://doi.org/10.2174/1871523019666200505073232.

[86] Stavytskyi, V. V., Voskoboinik, O. Yu., Kazunin, M. S., Nosulenko, I. S., Shishkina, S., Kovalenko, S. I. (2020). Substituted pyrrolo[1,2-*a*][1,2,4]triazolo-([1,2,4]triazino-)[*c*]quinazoline-4*a*(5*a*)-propanoic acids: synthesis, spectral characteristics and anti-inflammatory activity. *Voprosy khimii i khimicheskoi tekhnologii*. *1*, 61–70. https://doi.org/10.32434/0321-4095-2020-128-1-61-70.

[87] Stavitskiy, V. V., Voskoboinik, O. Yu., Nosulenko, I. S., Klimova, O. O., Brazhko, O. A., Kovalenko S. I. (2019). [Substituted 3-R-7,8-dihydro-2*H*-pyrrolo[1,2-*a*][1,2,4]–triazino[2,3-*c*]quinazolin-5a-(6H)-alkylcarboxylic acids – promising class of low-toxic anti-inflammatory agentsv]. *Farmatsevtychnyi chasopys – . Pharmaceutical review.,* № 3. C. 5-12 (in Ukrainian). https://doi.org/10.11603/2312-0967.2019.3.10468

[88] Stavytskyi, V.V., Nosulenko, I.S., Kandybey, K.I., Voskoboinik, O.Yu., Kovalenko, S.I. (2020). Esters and amides of 3-R-2,8-dioxo-7,8-dihydro-2*H*-pyrrolo[1,2-*a*][1,2,4]triazino[2,3-*c*]quinazolin-5a(6*H*)-carboxylic (-propanoic) acids: synthesis and biological activity. *Journal of Organic and Pharmaceutical Chemistry*, 18(1), (69), 14–21. https://doi.org/10.24959/ophcj.20.192826.

[89] Stavytskyi, V. V., Nosulenko, I. S., Portna, O. O., Shvets, V. M., Voskoboynik, O. Yu., Kovalenko, S. I. (2020). Substituted pyrrolo[1,2-*a*][1,2,4]triazolo-(triazino-)-[*c*]quinazolines - a promising class of lipoxygenase inhibitors. *Current issues in pharmacy and medicine: science and practice*, 13, *1*(32), 4–10. https://doi.org/10.14739/2409-2932.2020.1.198109.

[90] Poojari, S., Parameshwar Naik, P., Krishnamurthy, G., Jithendra Kumara, K.S., Sunil Kumar, N., Sathish, N. (2017) Anti-inflammatory, antibacterial and molecular docking studies of novel spiro-piperidine quinazolinone derivatives, *Journal of Taibah University for Science*, 11(3), 497–511, https://doi.org/10.1016/j.jtusci.2016.10.003

[91] Kolomoets, O., Voskoboynik, O., Antypenko, O. Berest, G., Nosulenko, I., Palchikov, M., Karpenko, O., Kovalenko, S. (2017). Desing, synthesis and anti-inflammatory activity of dirivatives 10-R-3-aryl-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones of spiro-fused cyclic frameworks. *Acta Chim. Slov., 64*(4), 902–910. https://doi.org/10.17344/acsi.2017.3575

[92] Wang, N.-N., Liu, C.-Y., Wang, T., Li, Y.-L., Xu, K., Lou, H.-X. (2021). Two New Quinazoline Derivatives from the Moss Endophytic Fungus Aspergillus sp. and Their Anti-inflammatory Activity. *Natural Products and Bioprospecting,* 11, 105–110. https://doi.org/10.1007/s13659-020-00287-5

[93] Duff, M. R., Gabel, S. A., Pedersen, L. C., DeRose E. F., Krahn, J. M., Howell, E. E., London, R. E. (2020). The structural basis for NSAID inhibition of human dihydrofolate reductase. *J. Med. Chem.* 63, 8314–8324. https://doi.org/10.1021/acs.jmedchem.0c00546