



# Survey of Recent Literature Related to the Biologically Active 4(3H)-Quinazolinones Containing Fused Heterocycles

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# Survey of Recent Literature Related to the Biologically Active 4(3*H*)-Quinazolinones Containing Fused Heterocycles

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**Abstract:** the present review focuses on the synthesis and biological evaluation of polycyclic 4(3*H*)-quinazolinones containing fused aromatic or heteroaromatic rings. The first part of the review is related to compounds with ring fused to the pyrimidine part of the quinazolinone core. Most of the quinazolinone alkaloids belong to this class of molecules. The second part presents molecules bearing extra ring(s) fused to the benzo moiety of the quinazolinone skeleton. Their structural diversity opens new fields in the search of active molecules.

**Keywords:** Quinazoline, quinazolinone, nitrogen heterocycles, antitumor agents, antiviral.

## 1. INTRODUCTION

Quinazolines and quinazolinones constitute a major class of biologically active molecules both from natural and synthetic sources. We will limit this review to compounds possessing the 4(3*H*)-quinazolinone skeleton, which is found in compounds displaying significant biological and pharmacological properties.

The importance of the 4(3*H*)-quinazolinone scaffold as therapeutic agents with a large range of activities (antibacterial, antifungal, antiviral, anticonvulsant, antitumor, sedative, antihypertensive...) has been highlighted in two recent reviews [1, 2]. Quinazolinone derivatives have been developed as antitumour (thymidylate synthase inhibition [3], inhibitors of tubuline polymerization [4]), antibacterial and antifungal [5], anti-HIV[6], antihypertensors [7] or dopamine agonists [8]. This class of compounds was also shown to interfere with insulin secretion and smooth muscle contractile activity by targeting K<sub>ATP</sub> channel activity[9] and such molecules were tested as analgesic and anti-inflammatory agents [10-12]. In a patent review, Marzaro and collaborators present the interest of quinazoline derivatives as anticancer agents [13].

Boron-containing quinazolines have been prepared and are currently evaluated as boronated agents for boron neutron capture therapy[14].

Several key-reviews report on the preparation of quinazolines and quinazolinones [15-20] and on the isolation and structure characterization [21] of quinazolinone alkaloids.

Considering the richness of the chemical, physicochemical and pharmacological properties of quinazolinone derivatives, their preparation still remains an important field of research. A recent review by Connolly *et al.* covers the literature data up to 2004 [17]. We present in (Fig. 1) the general strategies using ortho-substituted anilines such as 2-aminobenzoic acid (anthranilic acid) and its analogues, or isatoic anhydride as starting materials, which are condensed with acid chlorides [9], imidates or aldehydes. Several polymer-supported adaptations have been described, improving the yields and increasing the structural diversity through combinatorial strategies [16, 20, 22-26]. Microwave irradiation was also proven very useful to improve the yields [27] and in particular it has been successfully applied to the Niemietowski procedure involving the fusion of anthranilic acid with formamide [28, 29]. Solvent-free conditions using clays such as K-10 montmorillonite, constitute an interesting alternative to ease product isolation and purification [30]. In 2004 Örfi and coll have reviewed the industrially applicable processes [29]. Recent innovative or original methodologies will be discussed in the present review.

The use of iminophosphoranes has been developed by several groups following a tandem aza-Wittig approach [31, 32]. Yu *et al.* [33] have prepared 2-arylaminoquinazolinones by formation and cyclization of a guanidine intermediate. The solvent-free adaptation of this methodology has been reported recently [34].

The literature data concerning the synthesis of *N*-glycosyl amines, *N*- and *S*-glycosides containing quinazolin-4(3*H*)-one ring system has been reviewed in 2005 [35]. These conjugates are obtained by condensation of amino or thio substituted quinazolinones with monosaccharides.

We will focus the present review on the synthesis and biological evaluation of polycyclic 4(3*H*)-quinazolinones containing fused aromatic or heteroaromatic rings.

The review will be articulated in two main sections as depicted in (Fig. 2). The first section will be related to compounds with ring fused to the pyrimidine part of the quinazolinone core. A number of quinazolinone alkaloids belong to this class of molecules. The second part will present molecules bearing extra ring(s) fused to the benzo moiety of the quinazolinone skeleton. Their structural diversity has been explored by a number of academic and industrial groups in the search of active molecules. To our best knowledge, these compounds have not been reviewed so far.

## 2. PART 1. QUINAZOLINONES CONTAINING A RING FUSED WITH THE PYRIMIDINE MOIETY

The first section of the review concerns compounds in which a ring is fused with the pyrimidine part of the quinazolinone core. Most of the quinazolinone alkaloids belong to this class of compounds. They differ by the nature of the ring (pyrrole, indole, pyrroloquinoline, piperidine, pyrazine or diazepine), which may be fused with the 1,2-, 2,3- or 3,4-bond of the pyrimidine moiety.

This important family of alkaloids has been the subject of several recent reviews emphasizing the isolation [21 and precedent papers], and the synthesis [18, 19, 36] of new compounds. In the present review we will update the literature data and put the accent on non-natural analogues of biological interest.

### 2.1. Quinazolinone with Fused Pyrrole or Piperidine

As exemplified in (Fig. 3 and 4), quinazolinones containing a five or six member ring (pyrrole or piperidine) fused to the pyrimidine part form a large family of heterocycles displaying ring size and geometry diversities.

Most of recent works are related to the synthesis of derivatives of the known alkaloids and evaluation of their therapeutic usefulness.

#### Antitumor Agents

Deoxyvasicinone, mackinazolinone 7, isaindigotone 4 and their derivatives have been prepared in a one-pot process via microwave

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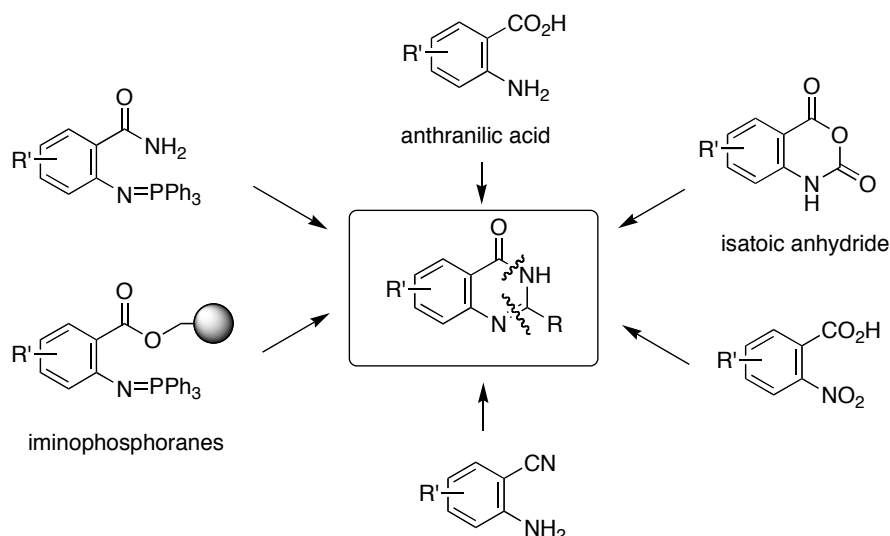


Fig. (1). General synthetic routes to quinazolinones.

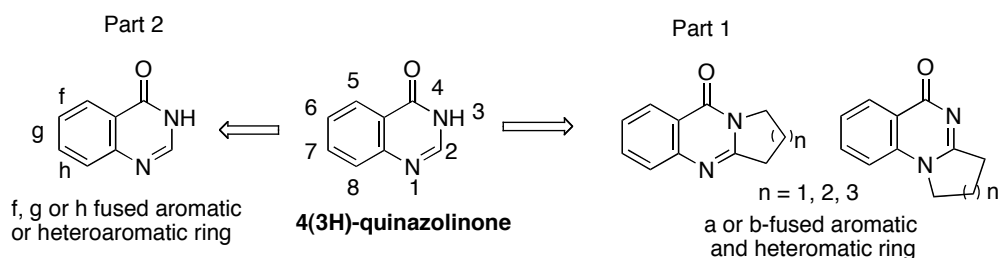


Fig. (2). General structures of quinazolin-4-ones containing fused heterocycles.

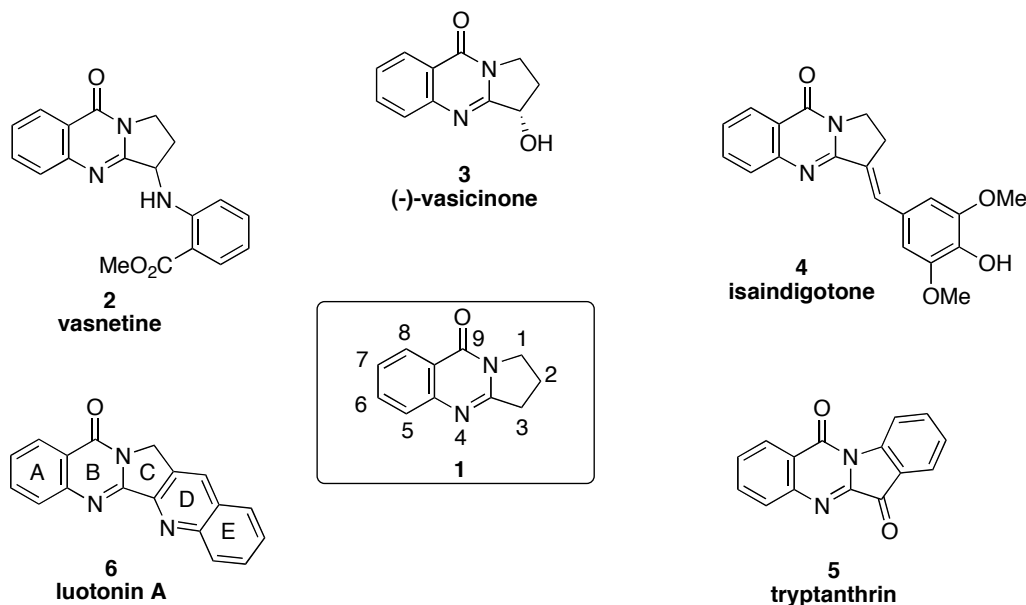


Fig. (3). Quinazolinone alkaloids containing fused pyrrole.

irradiation assisted domino reaction (Fig. 5) [37]. One compound (**12**), 6-membered ring analogue of isa-indigotone showed submicromolar activity against several cancer cell lines. The process was applied to the preparation of a small library of similar hybrid molecules. The molecules were identified as antimitotic agents acting through destabilization of tubulin polymerization [38].

The structure of luotonin **6**, a pyrrolo-quinazolinoquinazoline alkaloid isolated from *Peganum nigellastrum*, is similar to that of

camptothecin (**13**, CPT), a well-known inhibitor of topoisomerase I (Fig. 6). Hecht and coll. have explored modifications of the E-ring of luotonin [39]. The new analogues were evaluated for their ability to modulate stabilization of the covalent complex formed between topoisomerase I and DNA and for their activity towards a yeast strain expressing the human topoisomerase I. Luotonin **6** and isoluotonin **14** derivatives carrying a substituent (Cl, F or amino) in position 17 act as topoisomerase I poisons. 17-Aminoluotonin was

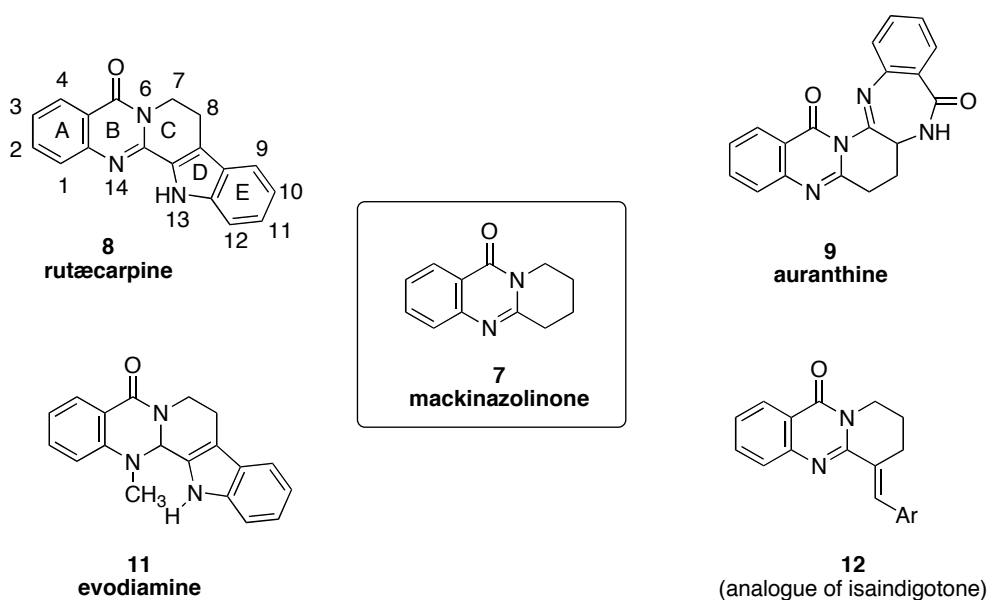


Fig. (4). Quinazolinone alkaloids containing fused piperidine.

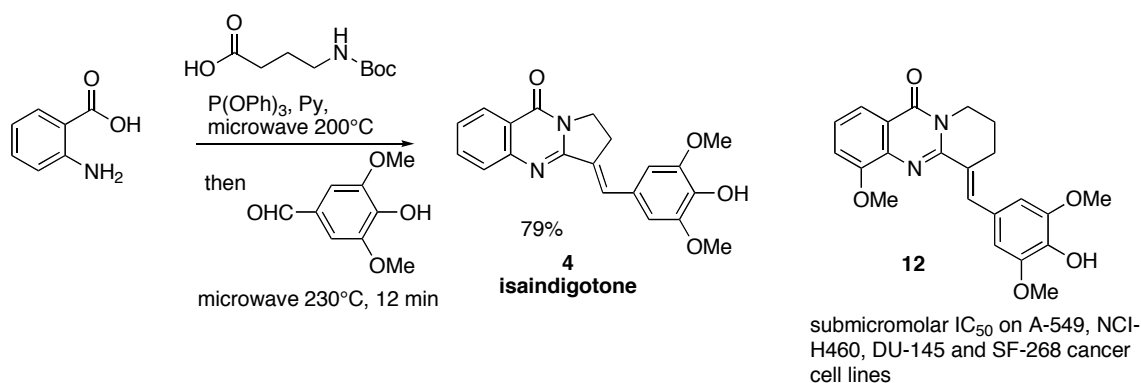


Fig. (5).

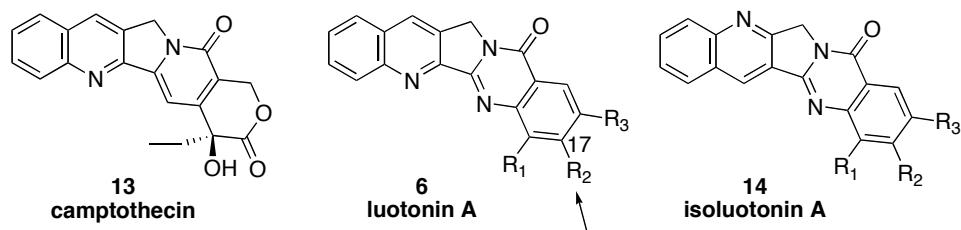


Fig. (6).

the most cytotoxic derivative having an  $IC_{50}$  close to that of luotonin A itself ( $IC_{50}$  15.7 and 5.58  $\mu M$  respectively). The comparison of the impact of substituents on the biological properties (cytotoxicity and topoisomerase inhibition) of camptothecin **13** and luotonin A **6** derivatives indicates that in spite of their structural similarities the binding of the two molecules to the topoisomerase I/DNA complex probably differs.

Interestingly batracyclin **15**, the 8-aminoisoidolo [1,2-b]quinazolin-10(12H)-one (NSC 320846), a close structural analogue of tryptanthrin **5** (Fig. 7), is a dual inhibitor of topoisomerases I and II under clinical evaluation as antitumor agent both against solid tumors and adriamycin-resistant leukemia [40].

#### Treatment of Alzheimer's Disease

Considering the involvement of cholinesterases in neurological disorders such as the Alzheimer's disease, several groups have de-

veloped quinazolinone analogues in the search of efficient inhibitors of this class of enzymes.

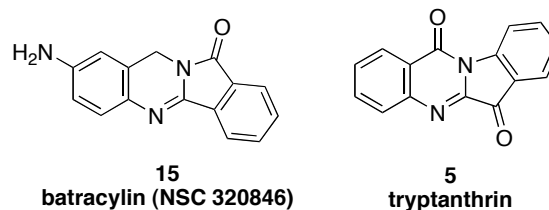


Fig. (7).

It has been shown that dehydroevodiamine (**16**, DHED, Fig. 8) isolated from the Chinese herb *Evodia rutaecarpa*, displayed potent

antiamnesic activity *in vivo* associated with acetylcholinesterase inhibition [41]. DHED also reduces tau hyperphosphorylation induced by glycogen synthase kinase-3 (GSK-3) [42] and  $\beta$ -amyloid peptide induced amnesia in mice [43].

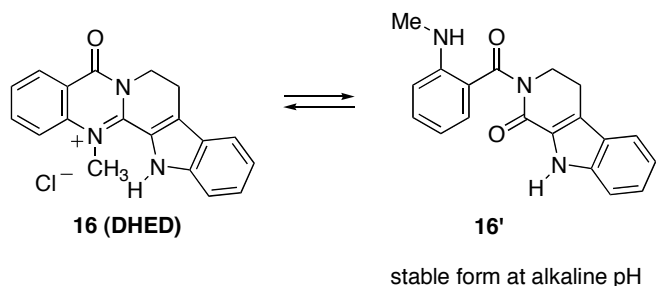


Fig. (8).

In the search of cholinesterase inhibitors, Decker and collaborators have developed a series of molecules derived from rutæcarpine **8** and DHED alkaloids **16**, and tacrine [44, 45]. More recently, the same group reported a series of homodimeric compounds prepared from quinazolin-4-thiones **17** to probe cholinesterase mid-gorge [46]. The homo-dimeric compounds **18** showed > 100-fold increase of activity compared to the monomers with nanomolar  $IC_{50}$  (Fig. 9). The nature and length of the spacer is determinant both for the activity and selectivity (butyryl versus acetyl cholinesterases). A high degree of selectivity for BChE was achieved ( $IC_{50}$  BChE/AChE = 264).

Investigation on the effect of MD212 (**19**, tricyclic quinazolinimine) on the cholinesterase activity in rats in which cognitive impairment was reversibly induced by scopolamine (0.05 mg/100 g body weight). A dose dependence effect is observed. MD212 showed attenuation of cognitive deficits at a low dosage (0.01 mg/100 g body weight), whereas at a high dosage (>0.1 mg/100 g body weight) the effect of scopolamine is markedly reinforced. Receptor-binding studies show that MD212 stabilizes N-methylscopolamine binding to muscarinic receptors allosterically [47].

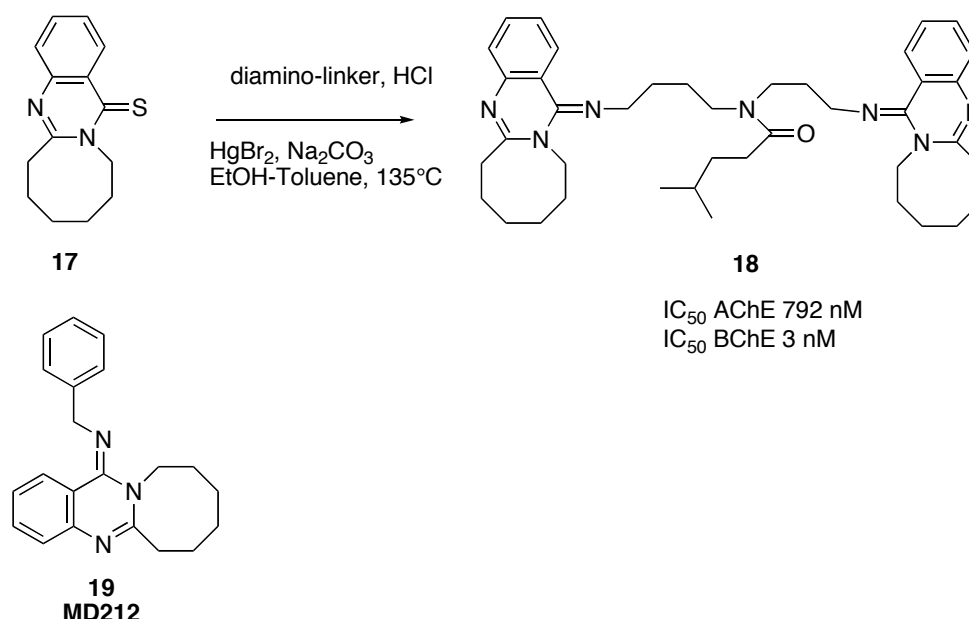


Fig. (9).

Several analogues of isaindigotone (**4**), in which the pendant substituent has been modified, have been prepared and tested as inhibitors of AChE and BChE (Fig. 10). The activity appeared strongly dependent on the nature of the substituent, however all the tested compounds were more active on AChE than on BChE. The most potent molecule (**24**) inhibits the BChE at submicromolar concentration [48].

### Bronchodilators

Analogues of vasicinone **3** in which the pyrrole five-member ring was replaced by the larger azepino seven-member ring have been prepared (Fig. 11). The resulting compound **25** (95-4) showed marked bronchodilatory activity with concomitant relaxant effect on intestinal smooth muscle [49].

### Hypertension and Vasodilatation Treatment

Evodiamine **11** and rutæcarpine **8** (see structures in Fig. 4) are isolated from *Evodiae fructus* which has been prescribed for the treatment of hypertension in traditional Chinese medicine. A series of analogues were prepared and their vasodilator effects were evaluated [50]. The efficiency of rutæcarpine was not improved, but the data support a mechanism of action involving the stimulation of CGRP (calcitonin gene related peptide) release via activation of TRPV1 (vanilloid receptor subtype 1).

Unlike its close derivative deoxyvasicinone, vasicinone (**3** Fig. 3) isolated from *Pegnum harmala* also displayed a vasorelaxant activity at  $3 \times 10^{-5}$  M against phenylephrine-induced contraction of isolated rat aorta [51]. The effect is inhibited by  $N^G$ -monomethyl-L-arginine indicating that the activity may be mediated through the increased release of NO from endothelial cells.

### Platelet Aggregation Inhibitors

A methodology of synthesis of rutæcarpine derivatives (**8**, **26-28**) starting from  $\beta$ -carboline **30** allowed the formation of a series of compounds that showed promising inhibitory effect on platelet aggregation (Fig. 12) [52].

### 2.2. Quinazolinone with a Fused Piperazine

This family covers a large structural diversity as exemplified in (Fig. 13). It includes compounds containing a substituted piperazine ring such as anacine **32**, fumiquinazolines F or G (**33** and **34**

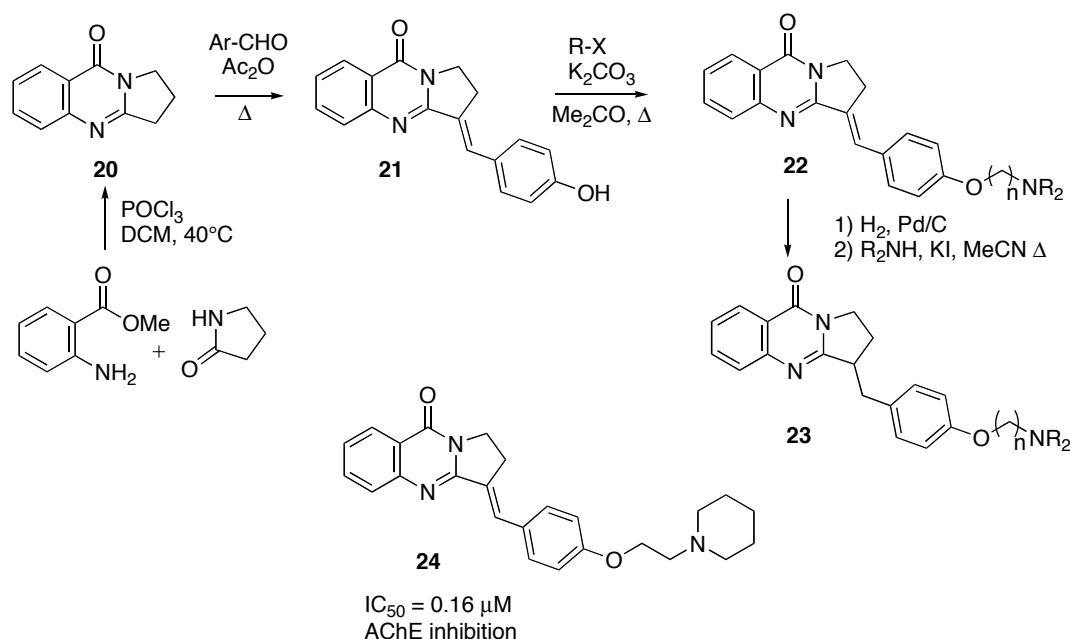


Fig. (10).

respectively) or fiscalin A **39**, or more complex structures with several fused cycles such as ardeemin **36** that contains a prenylated indole. Spiro compounds, such as fumiquinazoline C **36** or alantrypinone **37** are also structurally related.

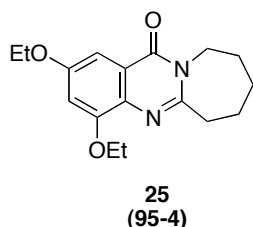


Fig. (11).

New structures are frequently isolated from natural sources. The structure elucidation remains challenging. Among the new compounds that were recently described and evaluated as bioactive molecules we may cite new fiscalin analogues from *Neosartorya siamensis* that were evaluated as cytotoxic agents against a panel of cancer cell lines [53], the cottoquinazoline D **40** containing a rare cyclopropyl aminoacid residue isolated from coral-associated fungus *Aspergillus versicolor* (Fig. **14**) [54, 55] or quinadolines A and B (**41,42**), isolated from culture broth of *Aspergillus* sp. Quinal-

doline B **42** displayed moderate activity as inhibitor of lipid droplet synthesis in mouse macrophages [56].

Three new molecules, the aurantiomides A-C structurally related to anacine, were identified from sponge-derived fungus *Penicillium aurantiogriseum* and their cytotoxicity tested against a panel of four cancer cell lines [57]. Aurantiomides B and C only showed moderate activities ( $IC_{50}$  values of 52-54  $\mu g/mL$  against HL-60 and P-388 for aurantiomide B and  $IC_{50}$  values of 48-62-54  $\mu g/mL$  against P-388 and BEL-7402 for aurantiomide C).

In a series of papers, the group of Walsh reported their studies concerning fungal alkaloid biosynthesis [58-62]. Recently, they described the biosynthetic pathways by the way fungi assemble fumiquinazoline A **43** from anthranilic acid and the oxidative transformation of fumiquinazoline A to the heptacyclic hemiaminal fumiquinazoline C (Fig. **15**) [58].

The total synthesis of the complex molecules depicted in (Fig. **13**) constitutes an important and active field of research among chemists. Recently, (-)-ardeemin **36**, and its acetyl and formyl derivatives have been obtained from bromopyrroloindoline [63, 64]. Total syntheses of (-)-fructigenin A and (-)-5-N-acetylardeemin were realized through a common imine intermediate [65]. Acid-catalyzed aza-Diels-Alder reactions allowed the total synthesis of ( $\pm$ )-lapatin B [66]. Hetero Diels-Alder reaction was also applied to the synthesis of ( $\pm$ )-alantrypinone **37** [67]. The synthesis of (-)-

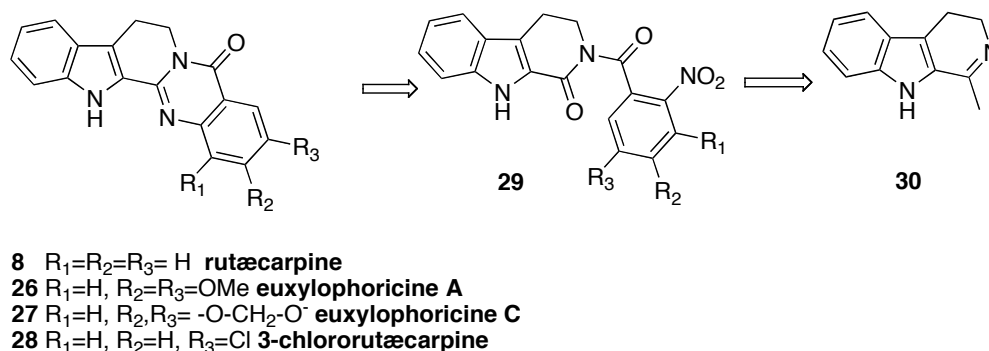
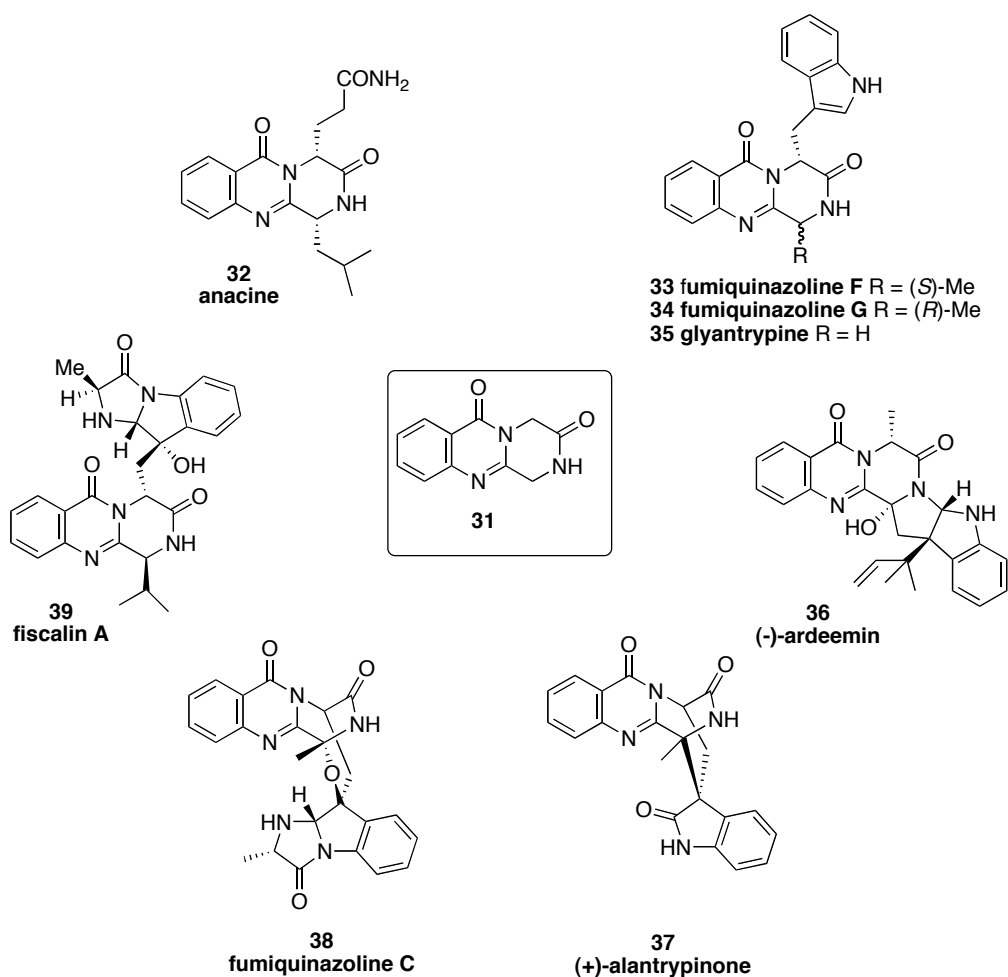
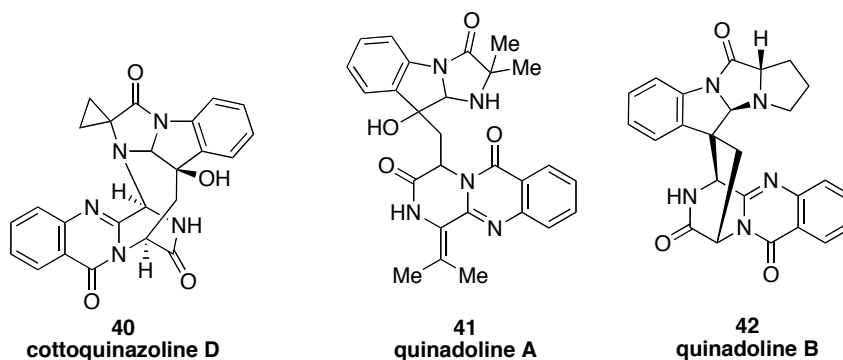


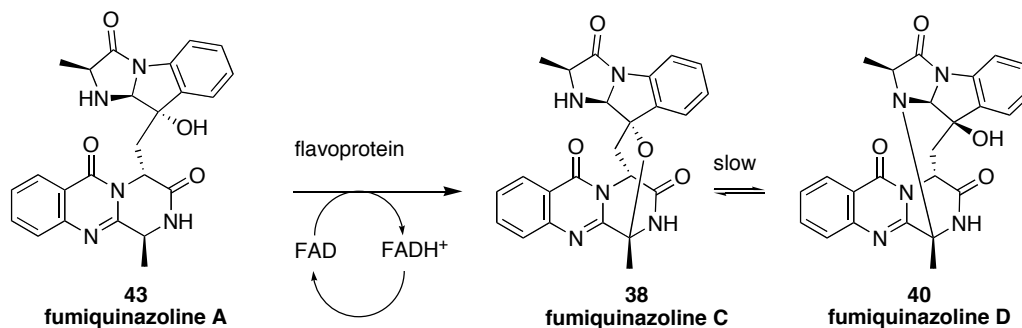
Fig. (12).



**Fig. (13).** Quinazolinone alkaloids with a fused piperazine.



**Fig. (14).**



**Fig. (15).** Biosynthetic pathway to fumiquinazolines C/D.

serantrypinone and the determination of absolute configuration were realized [68]. A three-component one-pot reaction promoted by microwave irradiation was applied to the synthesis of gyantrypine **35**, fumiquinazoline **F 33** and fiscaline **B 39** [69].

New methodologies were also reported to prepare various pyrazino[2,1-*b*]quinazolines as exemplified by the use of zinc triflate to catalyse a one-pot double cyclodehydration of linear tripeptides on solid support [70], or the use of microwave irradiation for solvent-free synthesis [27].

Alantrypinone derivatives were synthesized for their antagonist activity toward insect GABA receptors [71]. Indeed, molecules selectively targeting insect GABA receptors are of major importance for the development of safer insecticides and alantrypinone constitutes a lead compound with insecticidal activity against *Myzus persicae* in the range of 100-500 ppm [72]. Simple 1-aminopyrazino[2,1-*b*]quinazolinones were also prepared and evaluated as antimicrobial agents [73]. One molecule showed some activities against Gram negative bacteria (*Escherichia coli* and *Shigella sonnei*).

### 2.3. Quinazolinone with a Fused Benzodiazepine

Sclerotigenin **44** represents the basic skeleton of this class of alkaloids, that include circumdatins **45,46** (Fig. 16). In the asperlicin alkaloids isolate from *aspergillus alliaceus*, the pendent indolo substituent is similar to that found in fumiquinazoline **C 38** that was isolated from *aspergillus fumigatus*.

Search for similar structures from natural sources and improvement of the chemical synthesis of known molecules are ongoing tasks worldwide. In most cases, the key step of the chemical synthesis is an intramolecular cyclization. Recent papers report on the use of metal catalysts (palladium [74], iridium [75], tin [76] or

copper [77]), Lewis acids (scandium triflate [78]), or alternative technologies such as microwave irradiation [78, 79]. The synthesis of a library of circumdatins (**51**) was achieved from concise building blocks (benzodiazepinediones **49** and anthranilic acids) and using a polymer-supported phosphine mediated intramolecular aza-Wittig reaction (Fig. 17) [80]. It is worth noting that the benzodiazepinedione synthons are prepared from anthranilic acid and  $\alpha$ -substituted amino-acids.

Other improvements concern the synthesis of enantiopure molecules [77, 81].

Among the new structures that have been isolated we can cite the novobenzomalvins A-C **52-54** shown in (Fig. 18) (from *Aspergillus novofumigatus*) that act as fibronectin expression regulators [82]. The molecules increased the fibronectin expression in normal human neonatal dermal fibroblast cells.

### 2.4. Other tri- or Polycyclic Quinazolinone Analogues

#### Antitumor Agents

Taking advantage of the strongly reactive methylene at position 1 of the [1,4]oxazino[3,4-*b*]quinazolinone **55**, Örfi *et al.* have prepared variously substituted derivatives that were tested as protein kinase inhibitors (Fig. 19). Four of the benzylidene substituted analogues (**57**) showed significant ability to inhibit tyrosine kinase on SW620 colon tumor cells (IC<sub>50</sub> 70-100  $\mu$ M) [83].

#### H1-Antihistaminic Agents

Tricyclic [1,2,4]triazolo[4,3-*a*]quinazolinones **59** were designed as non-sedative antihistaminic drugs [84, 85]. Several series of molecules varying by the nature of the N-3 substituent (Fig. 20, R = alkyl, benzyl, aryl) were successively reported and showed promising properties against histamine induced bronchospasms.

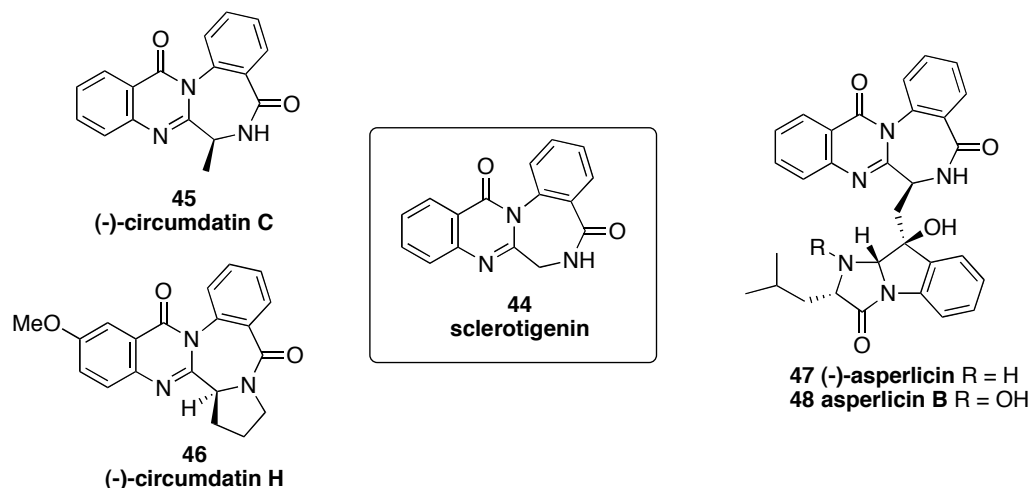


Fig. (16). Quinazolinone alkaloids with a fused benzodiazepine.

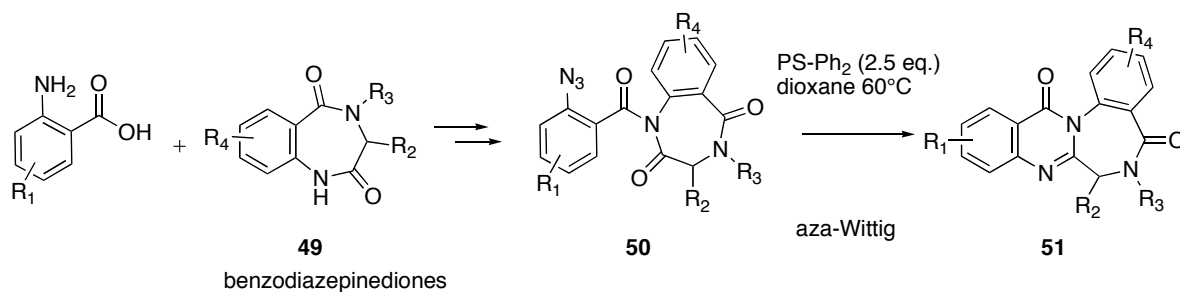


Fig. (17).



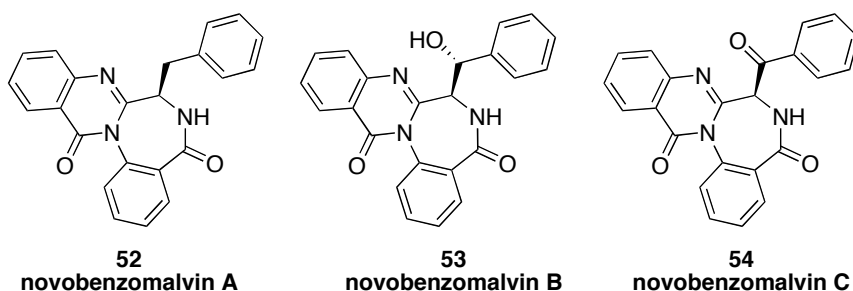


Fig. (18).

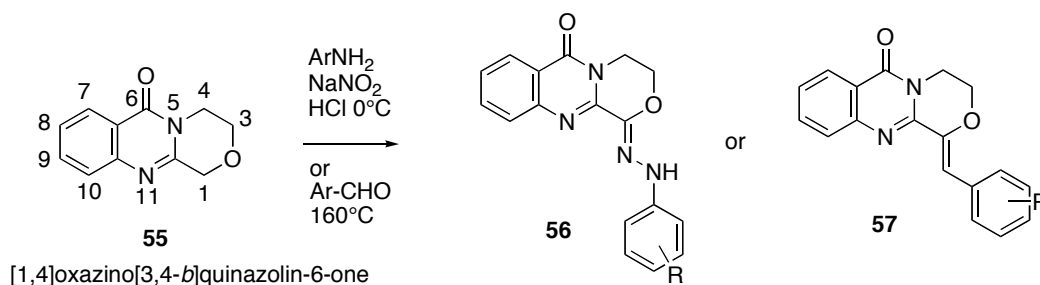


Fig. (19).

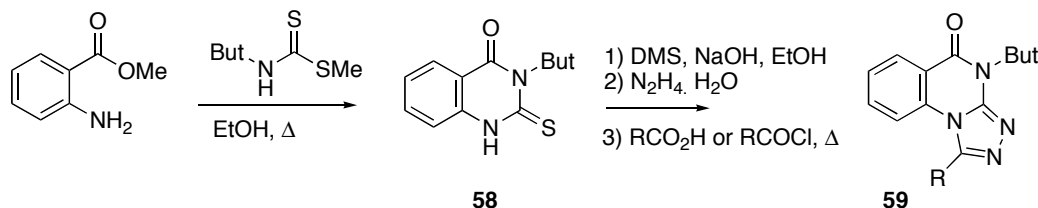


Fig. (20).

### Antimicrobial and Antifungal Activities

Fused 1,2,4-triazolo-, 1,2,4-triazino- and 1,2,3,4-tetrazinoquinazolinones (**61**, **62** and **60** respectively, Fig. 21) were prepared and their antimicrobial and antifungal activities were evaluated [52]. The molecules were tested against Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa* and Gram-positive bacteria, *Streptococcus pneumoniae*, *Bacillus subtilis*. The most active compounds showed interesting activities with MIC 1.56  $\mu\text{g/mL}$  and 3.12  $\mu\text{g/mL}$  against both Gram positive *B. subtilis* and Gram-negative *E. coli* or *P. aeruginosa*. Some compounds also demonstrated significant antifungal activities against *Aspergillus fumigatus*, *Aspergillus flavus* (MIC 3.12 and 6.25  $\mu\text{g/mL}$  respectively), and *Aspergillus niger* (MIC 1.56  $\mu\text{g/mL}$ ). It turned out that triazolo[4,3-*a*]quinazolin-7-ones **63** seem to be more potent than tetrazino[4,3-*a*]quinazolin-8-ones **60** and indolo[2,3-*c*][1,2,4]-triazino[4,3-*a*]quinazolin-8-ones **62**. Indeed several derivatives belonging to the triazolo[4,3-*a*]quinazolinone (**63**, Fig. 21,  $\text{R}=\text{OMe}/\text{R}'=2\text{-Cl}$  and  $\text{R}=4\text{-Cl}/\text{R}'=2\text{-Cl}$ ) series showed the best activities both as antibacterial and antifungal agents.

A series of 4-phenylazoloquinazolines (**64**, Fig. 22) was synthesized as farnesyl protein transferase inhibitors [86]. These quinazoline analogues confirm the interest of the tricyclic [1,2,4]triazolo[4,3-*a*]quinazoline skeleton as basic structure for drug design.

### Other Activities

A new cascade reaction was designed to prepare a series of indazolo[3,2-*b*]quinazolinones (**65**, Fig. 23) [87] similar to evodia-mine. The molecules were evaluated as phosphodiesterase (PDE) inhibitors. One molecule showed good inhibitory activity with 1  $\mu\text{M}$   $\text{IC}_{50}$ .

### 2.5. Synthetic Methodologies

The synthesis of 2,3-polymethylene-quinazolinones may easily be achieved by reacting anthranilic acid with the corresponding lactam and  $\text{SOCl}_2$  [88]. The reaction was applied to the preparation of luotonin A **6**, tryptanthrin **5** and rutæcarpine **8** (see structures in Fig. 2 and 3) [89].

Iridium catalyst was used to prepare 2,3-disubstituted natural quinazolinones from aminobenzamides. The methodology was applied to the synthesis of sclerotigenin, pegamine, deoxyvasicinone, mackinazolinone **7** and rutæcarpine **8** (see structures in Fig. 2 and 3) [75].

The preparation of polyheterocyclic derivatives containing the quinazolinone core still attracts attention. Alternative technologies such as microwave irradiation have been used to prepare new polyheterocycles or to improve known synthetic pathways. As an example, microwave-assisted methodologies were used for the synthesis of triazabenz[*a*]indeno[1,2-*c*]anthracen-5-ones **67** [90], and pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones **69** (Fig. 24) [91].

An original series of fused quinazolinone-sugars (**71**, Fig. 25) has been prepared from benzylthioxazoline intermediates formed in two steps from various aldoses [92].

Alternatively, radical reactions were performed on 3H-quinazolin-4-ones to prepare mackinazolinone **7**, luotonin A **6**, rutæcarpine **8** and tryptanthrin **5** (Fig. 26) [93]. In this strategy, the alkylation at the N3 yields the key intermediates, which are ultimately cyclized using radical reactions.

### 3. PART 2. QUINAZOLINONES CONTAINING A RING FUSED WITH THE BENZENE MOIETY

The introduction of an extra ring fused to the benzene part of the quinazolinone largely contributes to the structural diversity of

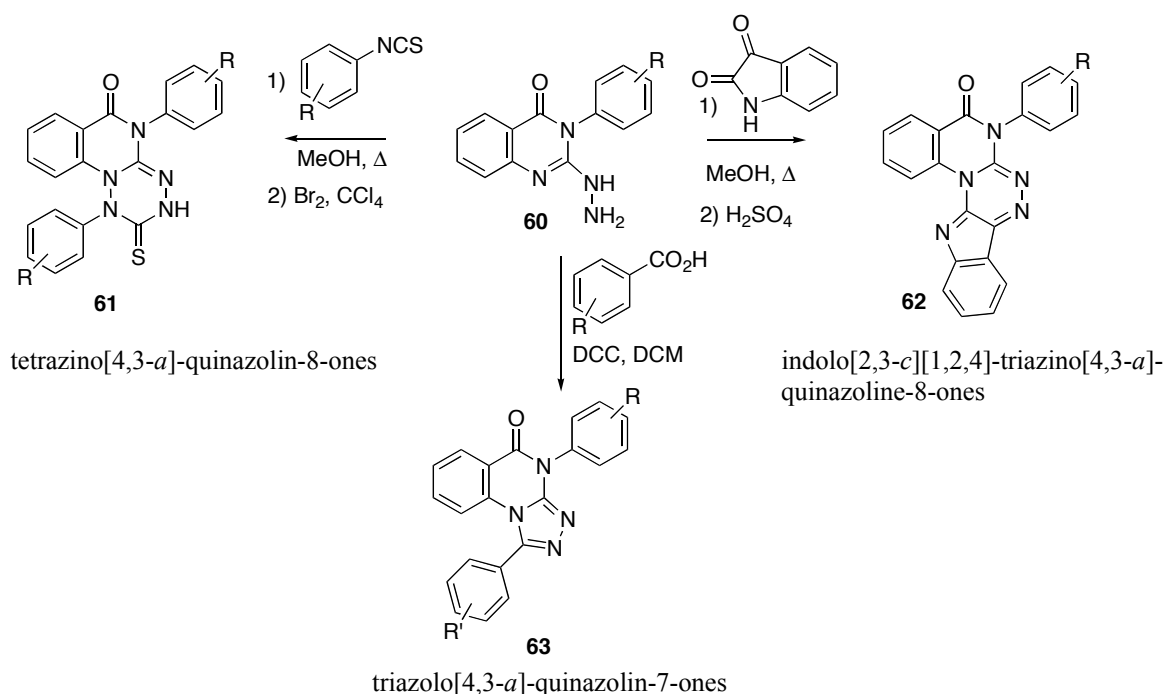


Fig. (21).

this important class of molecules. The nature and position of the extra ring may have determinant effects on the biological properties, however this approach has not been fully explored. We will survey the novel bioactive structures and their associated biological properties.

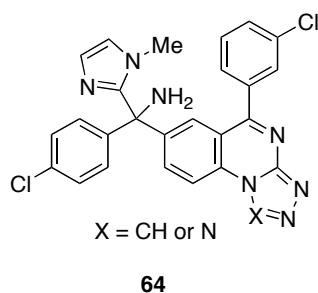


Fig. (22).

### 3.1. Quinazolinone with a Fused Aliphatic Ring

#### Cyclopenta[g]quinazolines

The cyclopenta[g]quinazolines were designed as a new generation of antifolate antitumor agents. Their structures (**77**, **78**, Fig. 27) were based on the results obtained with CB3717 **76** in the early 1980's. This molecule that acted as inhibitor of thymidylate syn-

thase, went to phase I but was withdrawn due to nephrotoxicity. Thymidylate synthase is a folate-dependent enzyme that catalyzes the reductive methylation of 2'-deoxyuridine-5'-monophosphate (dUMP) to 2'-deoxythymidine-5'-monophosphate (dTTP). This pathway is the unique intracellular source of dTTP and therefore this enzyme represents a critical target in cancer chemotherapy. Among the antifolate analogs currently being evaluated in the clinic, raltitrexed **82**, nolatrexed **80** (Thymitaq, AG337), ZD9331 **79**, and GS7904L **81** (GS7904 or GW1843) [94] derive from **76**.

In the search for molecules that would circumvent the mechanisms of resistance associated with the folypolyglutamate synthetase expression and/or the reduced-folate carrier expression novel series of cyclopenta[g]quinazolines are under investigation. The structures of the most active compounds **77** (CB300638) and **78** (CB300945 also known as BGC 638 or 945) are depicted in (Fig. 27) [95].

It has been later shown that cyclopenta[g]quinazolinones displayed high affinities for the  $\alpha$ -folate receptor that is overexpressed in some tumors compared to normal tissues. This transport mechanism is therefore an interesting target for antifolate drugs [96]. Both **78** and its analogue **77** selectively inhibited thymidylate synthase in  $\alpha$ -folate receptor-overexpressing tumors [97-100]. The data published so far suggest that these compounds have potential as anti-tumor agents with a high therapeutic index.

An original route to the benzoic acid intermediate was reported by Bavetsias [101]. In this pathway the C6-N10 bound was

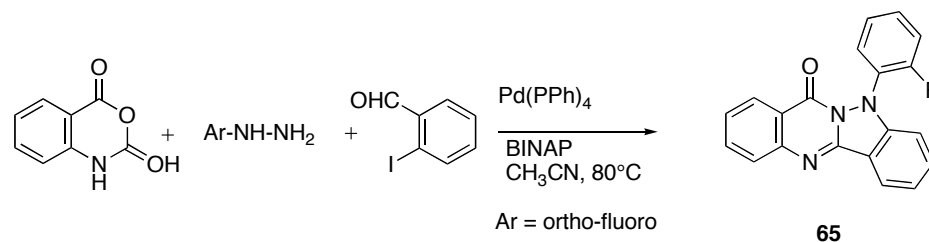


Fig. (23).

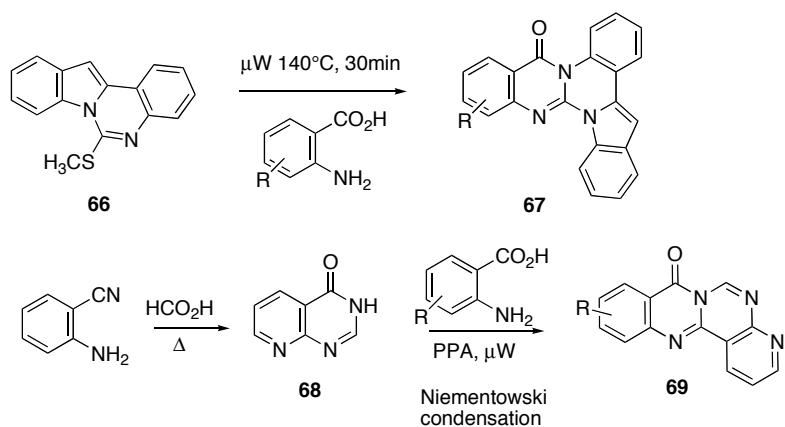


Fig. (24).

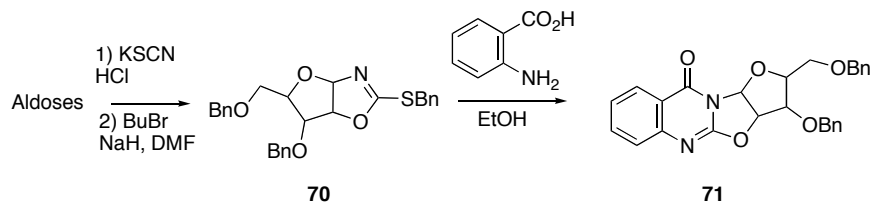


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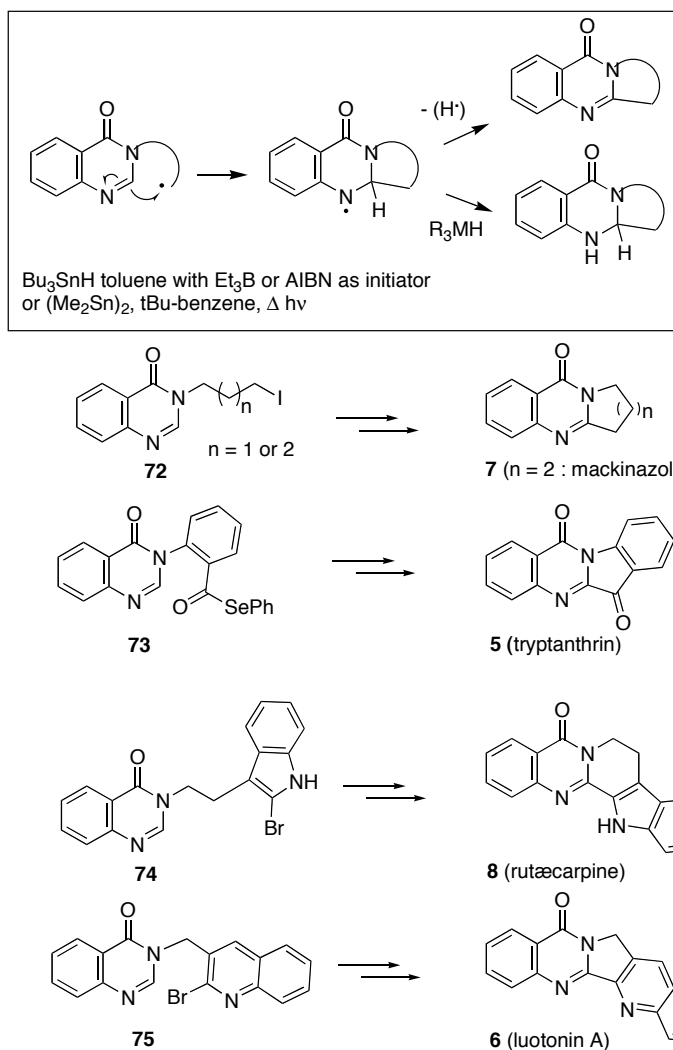


Fig. (26).

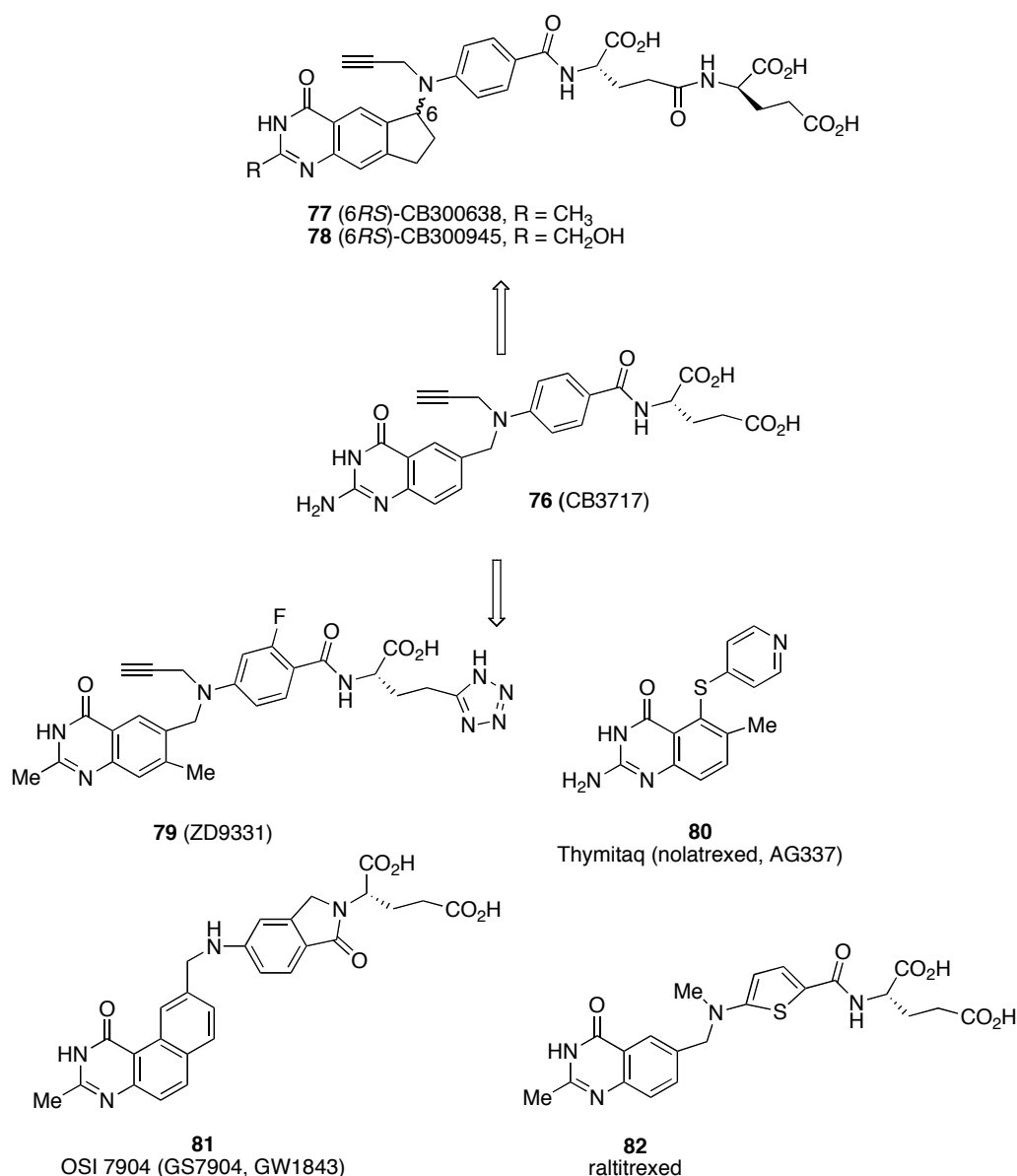


Fig. (27).

constructed by reductive amination of indane-1-one reagent prior to the formation of the cyclopenta[g]quinazolinone. The propargyl group was introduced using the electrophilic (propargyl)Co<sub>2</sub>(CO)<sub>6</sub><sup>+</sup> complex.

### 6,7-Methylenedioxy-quinazolinones

Methylenedioxy-quinazolinones (Fig. 28) are currently developed in the field of anticonvulsant drugs following data obtained with the quinazolinone-based **83** (CP465,022) [102]. This molecule was shown to be a potent and highly specific antagonist of AMPA receptors. AMPA receptors are implicated in the glutamate synaptic transmission and are strongly involved in the central nervous system functions. AMPA and the other glutamate receptors such as the NMDA receptors have been identified as cellular targets in the search of novel treatments against neurodegeneration and epilepsy. Methylenedioxy analogues were prepared following the route depicted in (Fig. 28) [103, 104]. The molecules were tested as anticonvulsant agents in animal models. The most active compounds (**86** R = Cl and R = NH<sub>2</sub>) presented promising activities but recent results [103] questioned their binding to AMPA receptors. Their mode of action remains unclear.

Derivatives of 6,7-methylenedioxy-quinazolinone (**90-95**, Fig. 29) have been prepared as analogues of febrifugine **90**, which is the active component of a Chinese traditional herbal antimalarial treatment. Febrifugine was shown to be 50 to 100 times as active as quinine in animal models, but gastrointestinal side effects precluded further developments in therapeutic. Synthetic analogues containing various substituents were prepared and four of them were evaluated [105]. They show antimalarial properties, however the data point to a potential toxicity due to the sensibility of the macrophage cells to these compounds.

### [1,4]Dioxinoquinazolinones

Quinazolinones fused with a 1,4-dioxane ring (**96**) are intermediates in the synthesis of the 4-anilino-[1,4]dioxanoquinazolinones (**97**, Fig. 30) that have been designed as inhibitors of epidermal growth factor tyrosine kinase [106-110].

### 3.2. Quinazolinone with a Fused Aromatic Ring

#### Benzo[g]quinazolinones

The intrinsic high fluorescence of the benzo[g]quinazolinone has been used to design fluorescent nucleoside analogues

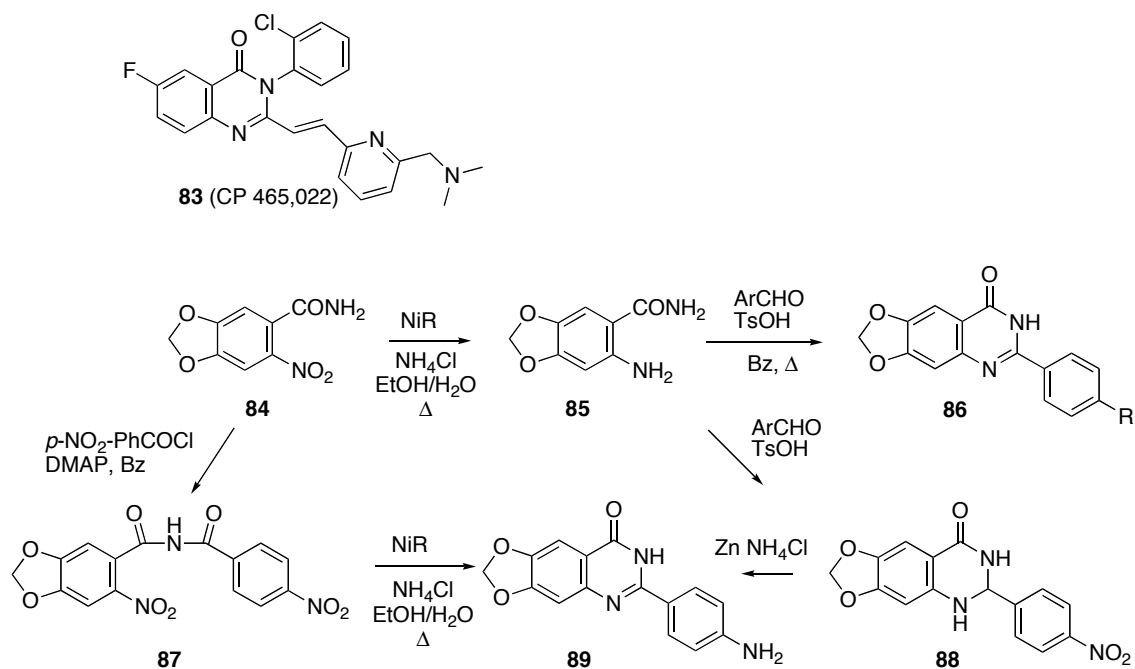


Fig. (28).

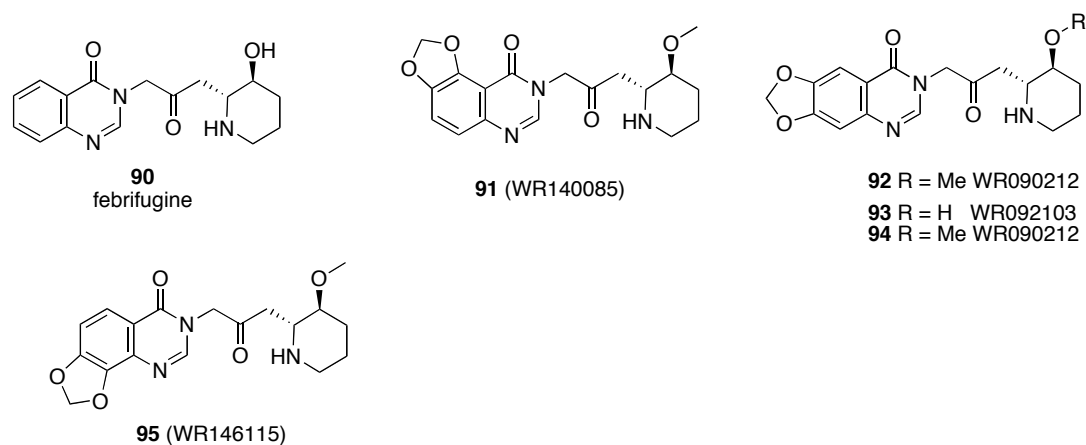


Fig. (29).

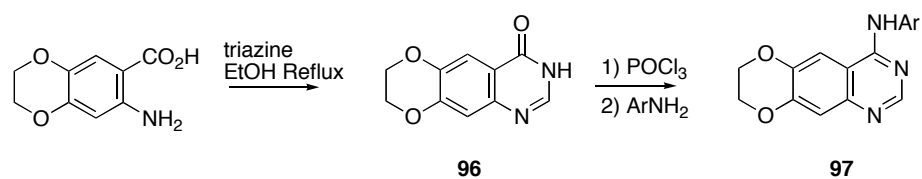


Fig. (30).

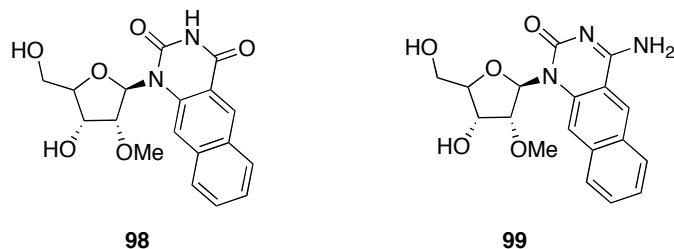


Fig. (31).

[111, 112]. Tricyclic analogues of thymine and cytosine (**98** and **99** respectively, Fig. **31**) have been incorporated into oligonucleotide

sequences to probe triplex formation [111] or protein-oligonucleotide interaction with the example of TAR-Tat [112].

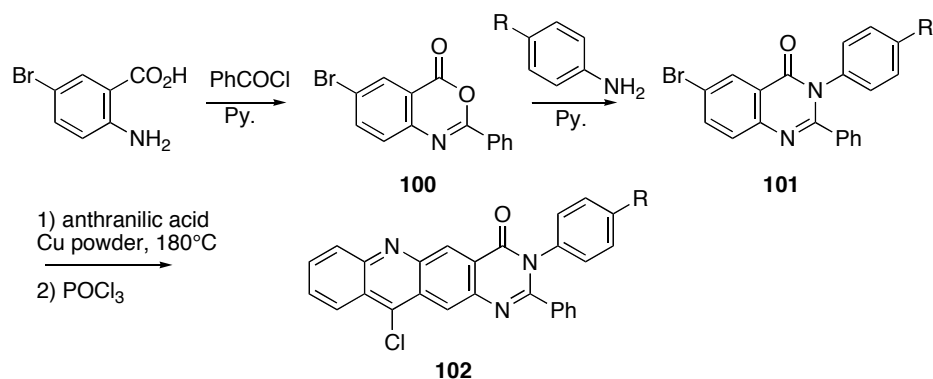


Fig. (32).

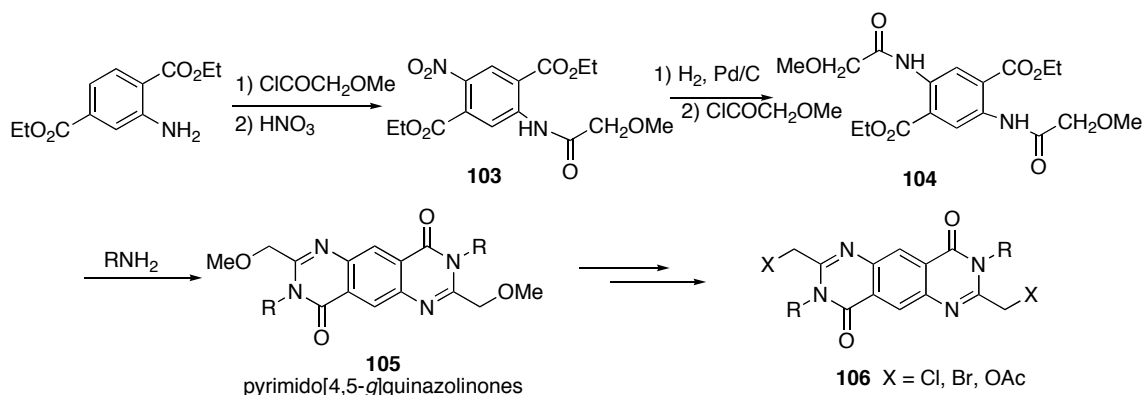


Fig. (33).

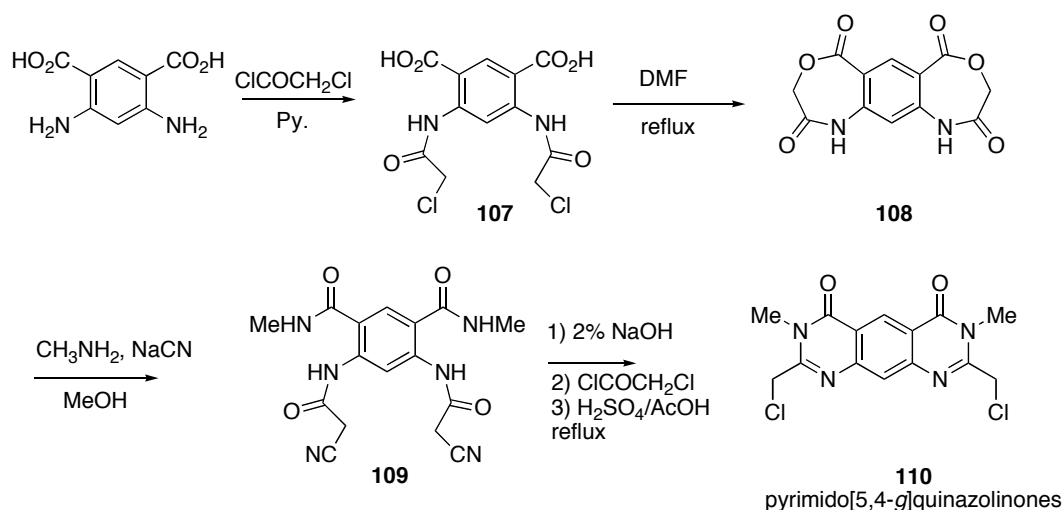


Fig. (34).

Formation of the complexes induces strong and characteristic emission fluorescence shifts allowing the direct monitoring and quantification of the interaction.

#### Quinazolinones Fused with a Quinoline

In 2006, Patel described the synthesis of 11-chloropyrimido[4,5-b]acridin-4(3H)ones **102** (Fig. 32) in an effort to combine the biological properties of acridine and pyrimidine [113]. The molecules were tested against various gram positive and gram negative bacteria and showed poor to moderate activities. It should be noted that the quinazolinone ring was built first and appeared stable in the harsh conditions required in the Ullmann-type formation of the acridine ring.

#### Pyrimidoquinazolinones

Skibo and coll. prepared a series of pyrimidoquinazoline analogues **106** and **110** [114]. The molecules were designed as electron deficient anthraquinones possessing alkylating substituents to either cross-link DNA with proteins such as topoisomerase II or cleave DNA. Two isomeric series, **106** [4,5-g] and **110** [5,4-g], were prepared in order to orientate the alkylating groups in different directions.

The synthetic pathways are shown in (Fig. 33 and 34).

If the methodology was straightforward for the preparation of pyrimido[4,5-g] isomer **106**, the access to the [5,4-g] isomer **110**

involved the formation of a benzodiazepine intermediate **108**. The aminolysis step required the presence of NaCN, thus leading to the formation of cyanoacetamides **109**. The desired pyrimidoquinazolinone **110** was then obtained in three steps.

The molecules were tested against various human cancer cell lines. The ring fusion, [4,5-g] or [5,4-g], does not influence cytotoxicity. The most active derivatives displayed submicromolar  $IC_{50}$  (0.1  $\mu$ M against HT-29 colon cell line). The presence of the two alkylating groups was critical for the DNA-protein cross-linking as evidenced by alkaline elution assay. DNA single and double strand breaks took place. COMPARE studies revealed high correlation with topoisomerase II and protein kinase inhibitors.

#### Quinazolinones Fused with Imidazole: Size-Expanded Analogues of Nucleosides

Kool has developed a series of analogues of nucleosides (called "xDNA") in which the base is expanded by benzo homologation [115-117]. Representative structures (**111-114**) are shown in (Fig. 35). The presence of the extra benzene ring does not modified hydrogen-bonding properties. xDNA base pairs can be assembled into helices that are more stable than the natural DNA. However, introduction of a single expanded nucleoside destabilizes the natural duplex. These size-expanded analogues are fluorescent and show potential interest as reporter groups for molecular biology.

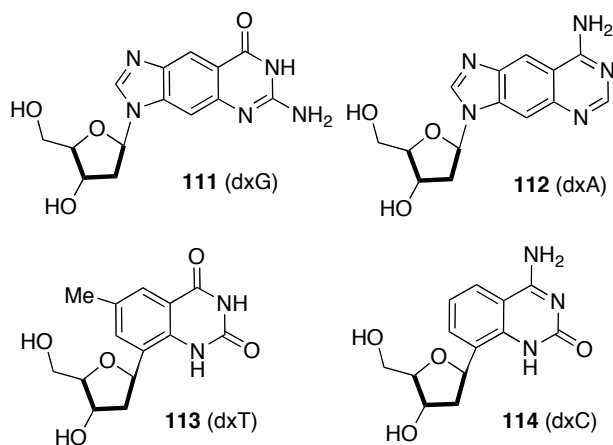


Fig. (35).

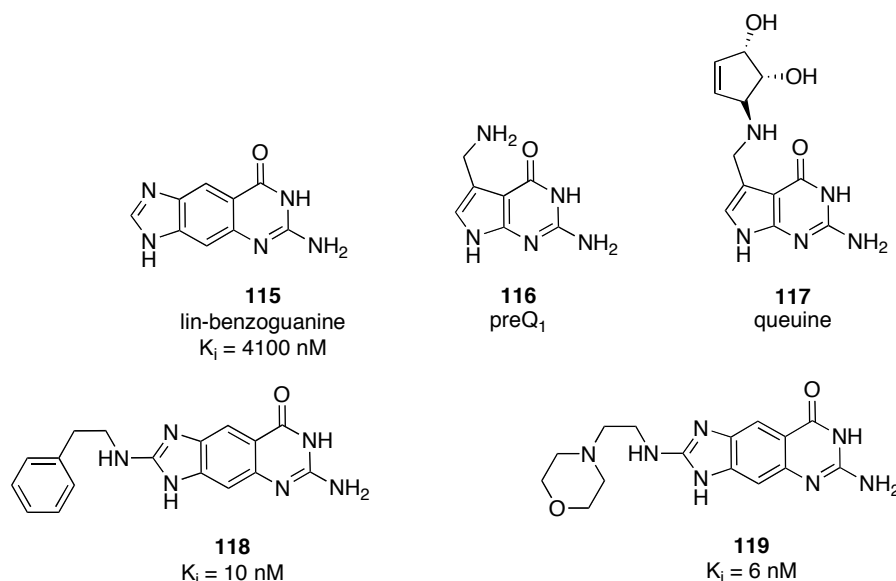


Fig. (36).

Imidazo quinazolinones (lin-benzoguanine **115**, Fig. 36) also have applications as inhibitors of tRNA-guanine transglycosylase [118-120]. This enzyme is found in all organisms from bacteria to humans, however its substrate specificity offers an opportunity for the selective inhibition of bacterial enzyme. The enzyme catalyzes the exchange of a guanine residue by preQ<sub>1</sub> **116** in bacteria and by queuine **117** in eukariotes [121]. The tRNA-guanine transglycosylase has been linked to the pathogenicity of *shigella* bacterium. This enzyme is a key target for structure-based drug design of selective treatment against bacillary dysentery as its structure is well-documented following crystallographic analysis. Lin-benzoguanine is a nucleobase analogue of the natural substrate that was shown to fill the pocket occupied by preQ<sub>1</sub>.

Derivatives of lin-benzoguanine have been prepared, and show good to excellent enzyme inhibition. In particular, various amines were introduced on the imidazole ring. All new compounds display a fully competitive behavior, the best compounds **118** and **119** shown in (Fig. 36) displaying nanomolar inhibitory constants.

#### Quinazolinones Fused with Thiazole

Besson and coll. reported the preparation and evaluation of thiazolo[5,4-f]quinazolinones as inhibitors of glycogen synthase kinase-3 (GSK-3) [122, 123]. GSK-3 is implicated in critical cellular processes such as apoptosis in cell cycle control and developmental regulation, and is therefore considered as important target in drug design. Several thiazoloquinazolinones were evaluated as cyclin-dependent kinase (CDK1/cyclin B, CDK5/p25) or GSK-3 inhibitors. The most promising series **123** and **124** depicted in (Fig. 37), inhibited GSK-3 at micromolar concentration ( $IC_{50}$  0.5-4  $\mu$ M) with good to high selectivity compared to CDK inhibition. In silico docking showed that the most selective GSK-3 inhibitors made a critical hydrogen bond between the quinazoline N-6 and Val-135 of the ATP-binding site and interacted with specific hydrophobic pocket of the enzyme.

#### Antitumor Pyrazolopyrimidoacridines and Pyrimidoacridines

In the search for non-cross resistant drugs able to overcome MDR by diffusion to tumor cells with velocity surpassing drug efflux by MDR transporters, the importance of structural factors for the kinetics of cellular uptake was studied on pyrazoloacridines **126** (PAC) and pyrazolopyrimidoacridines **125** (PPAC) shown in (Fig. 38) [124]. It was found that pentacyclic structure **125** favored more rapid cellular diffusion than tetracyclic structure **126** and that the

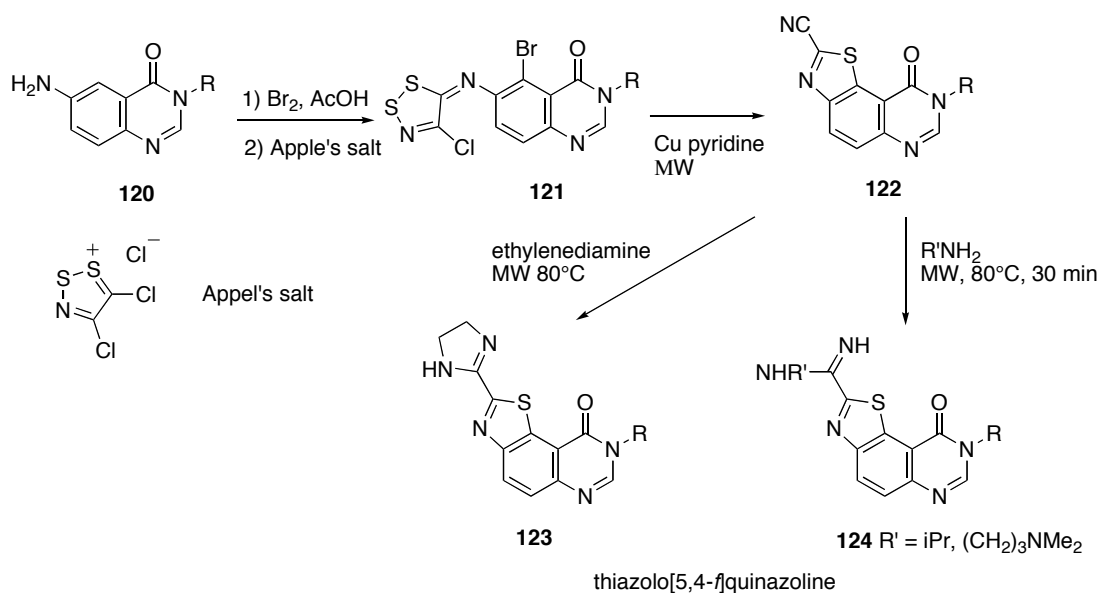


Fig. (37).

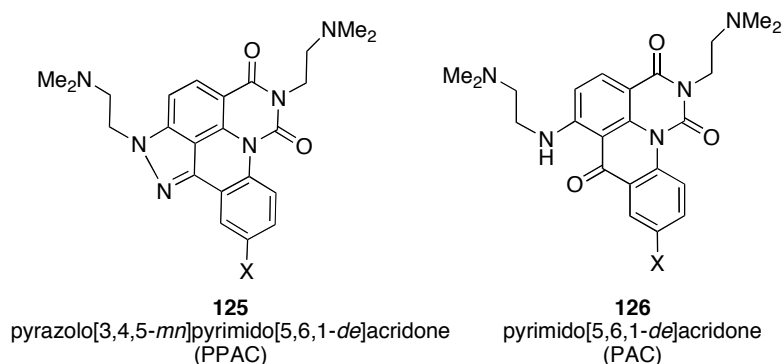


Fig. (38).

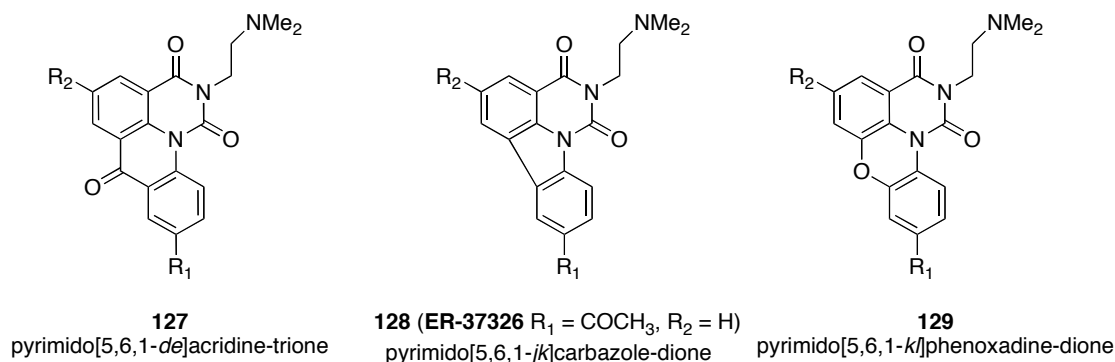


Fig. (39).

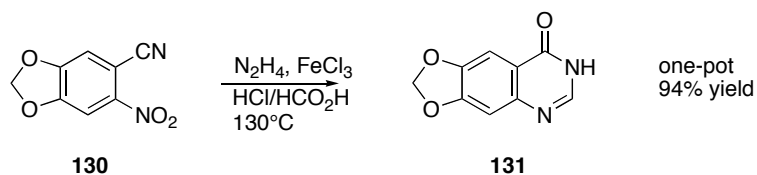


Fig. (40).

presence of hydrophobic substituent (X = OCH<sub>3</sub>) markedly increased the cellular uptake compared to hydrophilic (X = OH) substituent that exhibited very low kinetics of cellular uptake.

Antonini's group has modified the pyrimido[5,6,1-*de*]acridone chromophore present in PAC to form symmetrical [125] and asymmetrical [126] bisintercalators in the search of anticancer



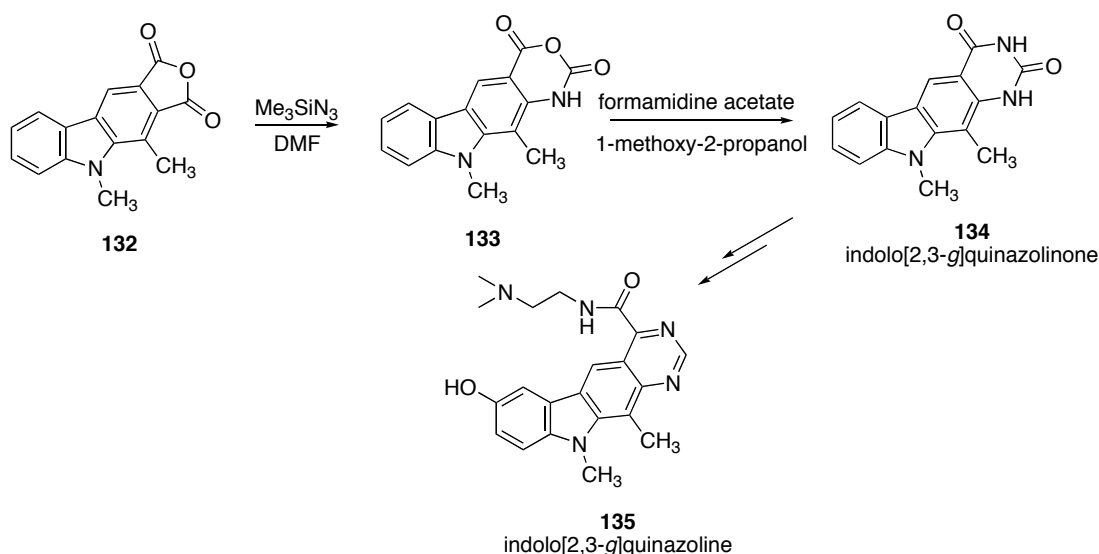


Fig. (41).

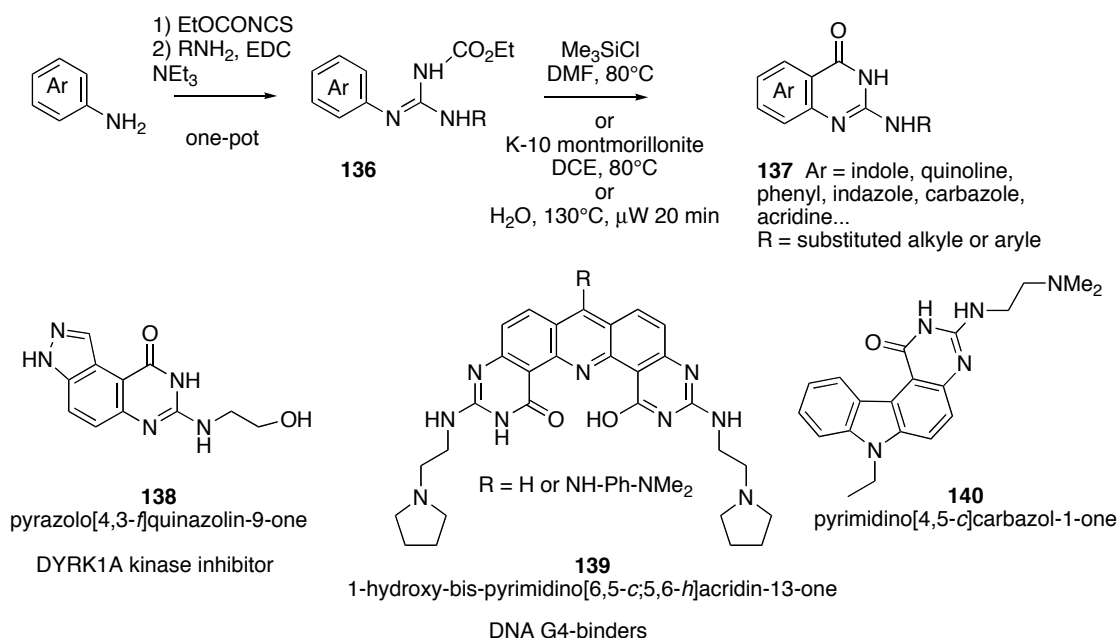


Fig. (42).

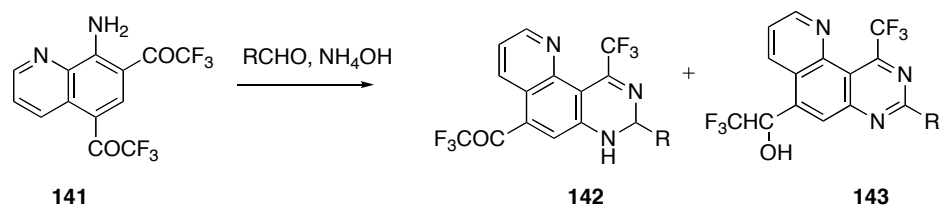


Fig. (43).

agents. As it is known with bisintercalators, the studies confirmed the importance of the length and nature of the linking chain, linkers containing amine(s) such as (CH<sub>2</sub>)<sub>3</sub>-N(CH<sub>3</sub>)-(CH<sub>2</sub>)<sub>3</sub> conferring higher affinity constant for DNA and generally better activity as shown by submicromolar IC<sub>50</sub>. Compared to other chromophores (acridine, pyrazoloacridine) the pyrimidoacridone conferred higher cytotoxicity (IC<sub>50</sub> < 0.1 nM against HT29 colon adenocarcinoma cell line).

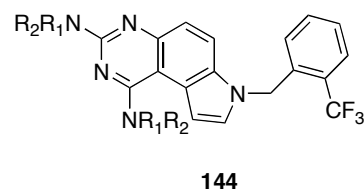


Fig. (44).

Kamata *et al.* have prepared series of pyrimidoacridones (**127**), pyrimidocarbazoles (**128**) and pyrimidophenoxadines (**129**) (Fig. 39), and compared their potency as topoisomerase II inhibitors [127]. The molecules were tested *in vitro* (P388 and KB cancer cell lines) and *in vivo* (P388 leukemia and M5076 sarcoma in mice). Pyrimidophenoxadines and pyrimidocarbazoles were more potent than their pyrimidoacridines with submicromolar IC<sub>50</sub> against P388 and KB cell lines. Pyrimidophenoxadines were highly potent *in vitro* but showed severe toxicity *in vivo*. In the subset of pyrimidocarbazoles, 8-substitution appeared a positive modification for *in vivo* activity. ER-37326 **128** inhibited the tumor growth of mouse sarcoma M5076 implanted into mice with T/C values of 42% at 3.13 mg/kg/d. It was found that this molecule also increased the level of DNA-topoisomerase II cross-linking in P388 cells. A close analogue, ER-37328 ((12,13-dihydro-5-[2-(dimethylamino)ethyl]-4-H-benzo[*c*]pyrimido[5,6,1-*jk*]carbazole-4,6,10(5H,11H)-trione), displayed potent tumoricidal activity against human solid tumors both *in vitro* and *in vivo* [128]. The molecule showed more potent cell-killing activities than etoposide with LC<sub>50</sub> (lethal concentration) ranging from 2.9 to 20  $\mu$ M against a panel of human cancer cell lines. When **128** (10 mg/kg) was administered i.v. at 11 or 20 days after transplantation of a murine colon 38, strong regression of the primary tumor was observed. In addition, administration on a schedule of every 7 days four times caused a significant increase of life span (79%) [129].

### 3.3. Recent Advances in Synthetic Methodologies

Reddy and coll. recently improved the conversion of 2-nitrobenzonitriles **130** to quinazolinones **131** by performing three reactions (reduction, formylation and hydrolysis) in one pot (Fig. 40) [130]. The reaction occurs in high yields in acidic conditions in

the presence of reducing agent (Sn/HCl, Fe/HCl or N<sub>2</sub>H<sub>4</sub>.H<sub>2</sub>O/FeCl<sub>3</sub>).

In the course of a project devoted to the synthesis of analogues of the antitumor olivacine, Guillonnet and coll. have prepared the indolo[2,3-*g*]quinazolinone **134** as key-intermediate in the synthesis of indoloquinazoline (**135**, Fig. 41) [131].

We have designed a simple and efficient methodology allowing the preparation of 2-amino substituted quinazolinones containing a fused ring from the corresponding aromatic amines (**137**, Fig. 42) [132]. The key-step involved a Lewis acid catalyzed Friedel-Craft type cyclization starting from the carbamoylated guanidine intermediates **136**. The reaction was compatible with both electron-rich and electron-deficient heterocycles. The cyclization step was regioselective. As a first approach of greener methodology the reaction was performed in the presence of the acidic montmorillonite K-10 clay [133]. More recently a green, very efficient and general cyclization process was optimized by thermolysis in water (130°C, 20 min under microwave irradiation) [134]. Small libraries were easily obtained. Depending of the ring size and geometry, the new molecules were evaluated as DNA targeting agents or kinase inhibitors. Unlike the structurally related ellipticine, the pyrimidino[4,5-*c*]carbazol-1-one **140** showed poor topoisomerase II activity and moderate cytotoxicity (IC<sub>50</sub> 17 mM against HL60 cancer cell line) [133]. The bispyrimidino [6,5-*c*;5,6-*h*]acridines **139**, prepared as pentacyclic analogues of BRACO-19 developed by Neidle's group, were tested as DNA quadruplex binders (G4-binders) [135]. The two molecules displayed a good affinity for the G4-structures and a significant G4 versus duplex selectivity.

A selected library of compounds was tested against five kinases [134]. A new heterocyclic structure emerges from this study, the 2-alkylamino-pyrazolo[4,3-*f*]quinazolin-9-one **138**. The most active

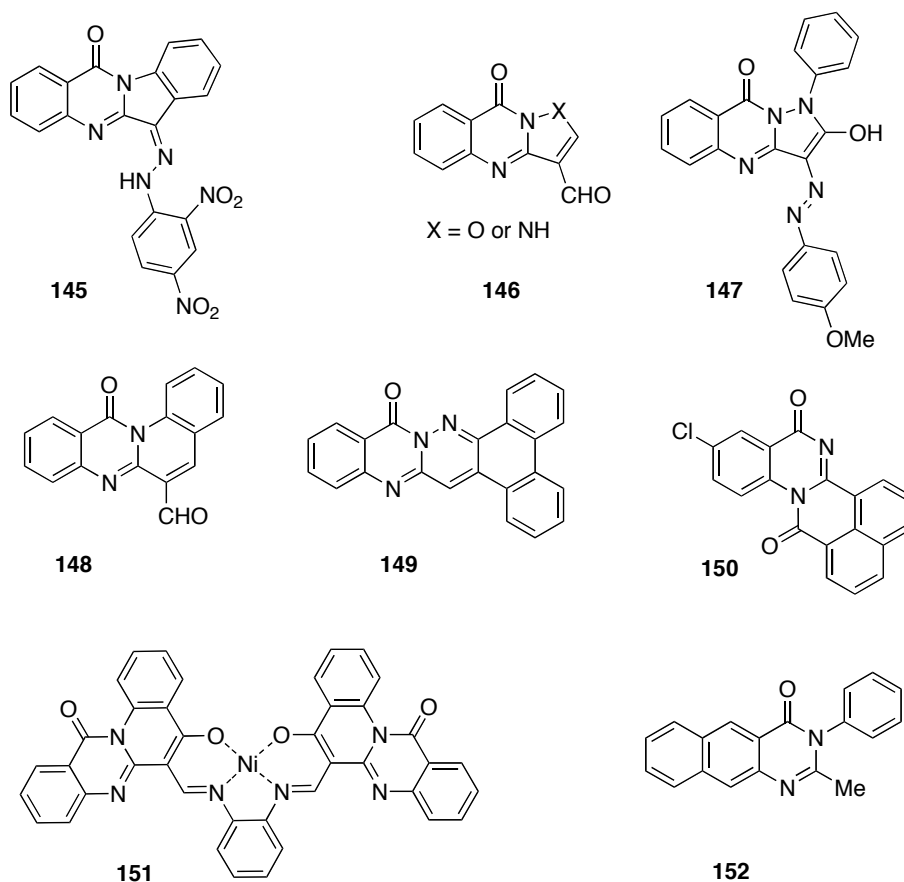


Fig. (45).

molecules show some selectivity for DYRK1A and CLK1, with submicromolar IC<sub>50</sub>. These data highlight the potential interest of this tricyclic heterocycle, pyrazolo[4,3-*f*]quinazolin-9-one, as a new pharmacophore in the field of drug design.

Quinazolinones with a fused pyridine ring (**143**) have been reported earlier by Okada (Fig. **43**) [136].

It is worth noting that diamino substituted pyrrolo[3,2-*f*]quinazolines (**144**, Fig. **44**) displayed promising antimalarial activity [137]. The most interesting molecules inhibited plasmodium falciparum growth at low concentration (IC<sub>50</sub> < 0.1 ng/ml). The molecules retained their activity *in vivo* and showed low toxicity.

The efficient preparation of 8*H*-thiazolo[5,4-*f*]quinazolin-9-one (**123**, **124**, Fig. **37**) and 7*H*-thiazolo[4,5-*h*]quinazolin-6-one was realized by fusion under microwave irradiation of a thiazole and a quinazoline ring via Appel's salt chemistry [138].

## CONCLUSION

The synthesis and study of new natural and synthetic analogues of 4(3*H*)-quinazolinones bearing a fused ring constitute a fruitful strategy in the search of new treatments for major diseases such as the viral and bacterial infections, cancer or neurologic pathologies including Alzheimer or Parkinson's diseases. The presence of the ring fused with the quinazolinone core greatly increases the structural diversity, as it is possible to adjust the size of the fused cycle, its nature (aliphatic, aromatic or heteroaromatic rings), its substituents and its location. Recent improvements in the synthetic methodologies, with the use of solid-phase and microwave technologies, opened the way to combinatorial approaches. 4(3*H*)-Quinazolinones are also useful intermediates for the preparation of more complex molecules, but little has been done to explore the chemical reactivity of the analogues containing a fused heterocycles. A few examples have been presented in this review. To our opinion, this aspect deserves to be developed.

It is also worth noting that fused 4(3*H*)-quinazolinones also display interesting physicochemical properties, and in particular as chromophores in dyestuffs and pigments [139]. A few structures (**145-151**) are represented in (Fig. **45**). Their variety is another example of the structural diversity of this class of heterocycles.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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Declared none.

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