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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 antitumor (thymidylate synthase inhibition [3], inhibitors of tubuline polymerization [4]), antibacterial and antifungal [5], anti-HIV[6], antihypertensives [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_{ATP} 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 quinazolinone 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 Niementowski 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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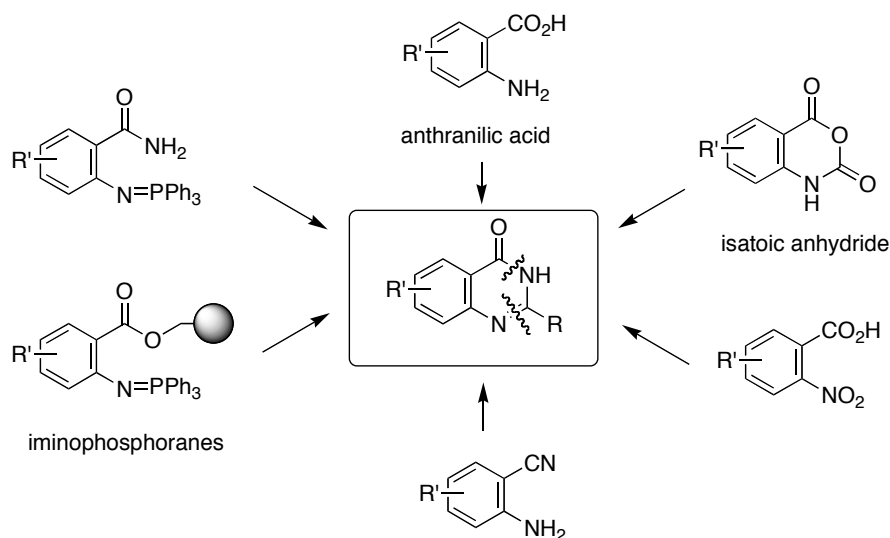


Fig. (1). General synthetic routes to quinazolinones.

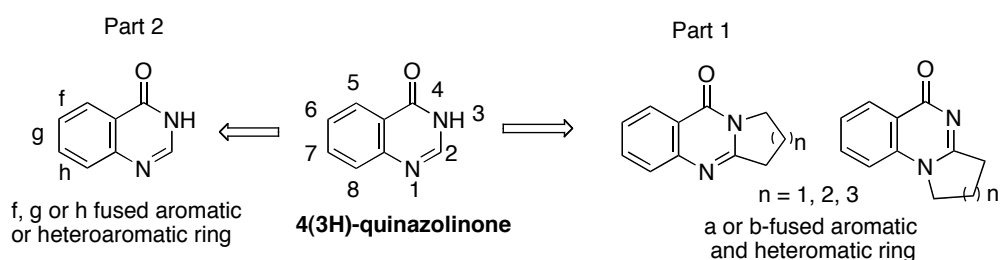


Fig. (2). General structures of quinazolin-4-ones containing fused heterocycles.

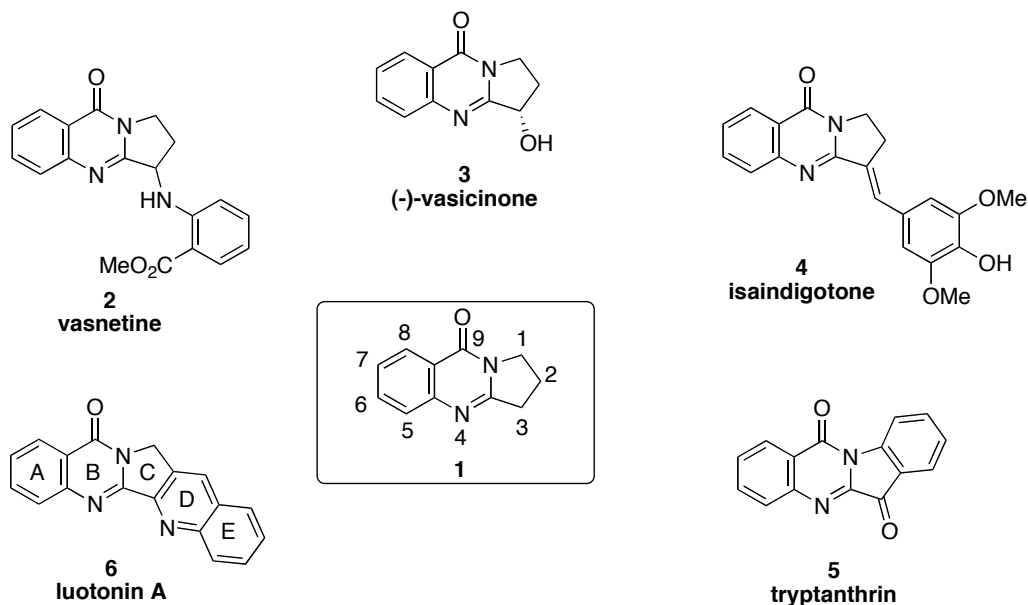


Fig. (3). Quinazolinone alkaloids containing fused pyrrole.

irradiation assisted domino reaction (Fig. 5) [37]. One compound (12), 6-membered ring analogue of isaindigotone 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 antimetabolic 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

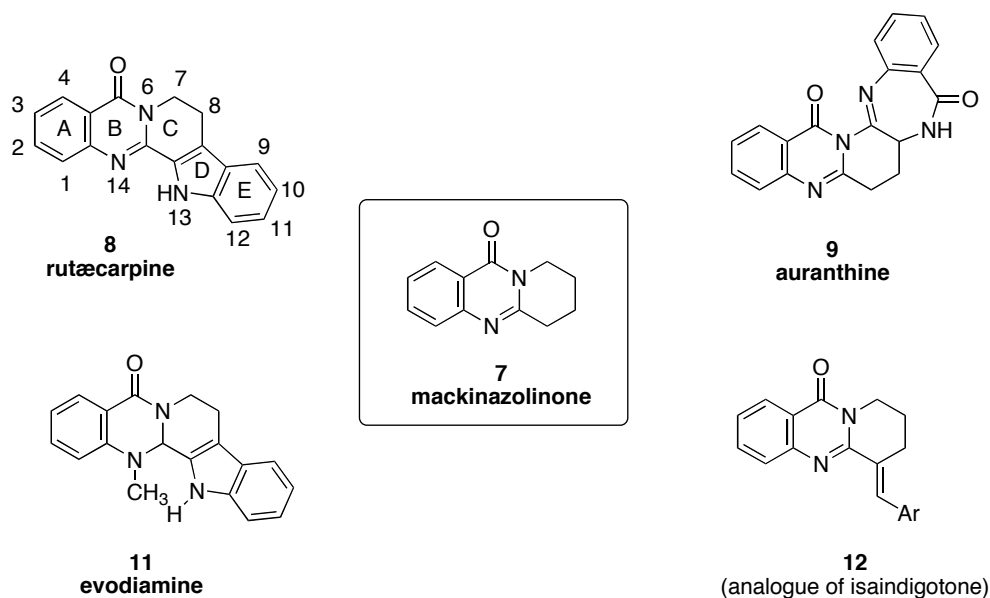


Fig. (4). Quinazolinone alkaloids containing fused piperidine.

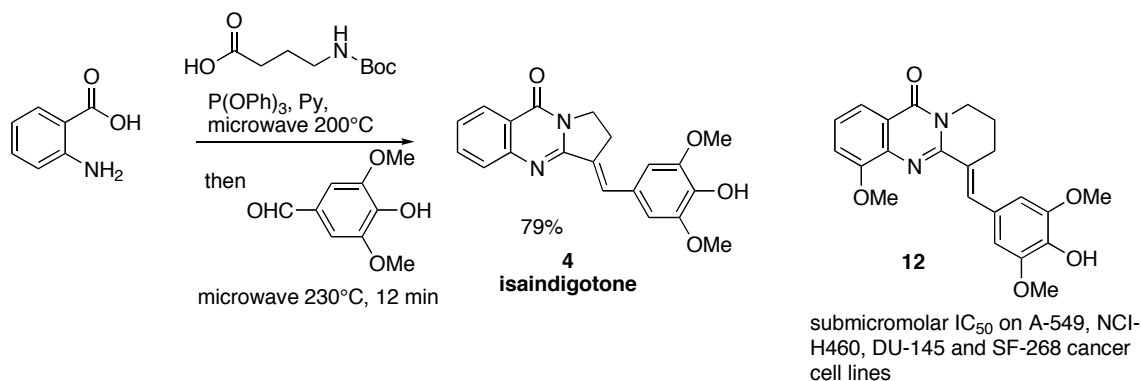


Fig. (5).

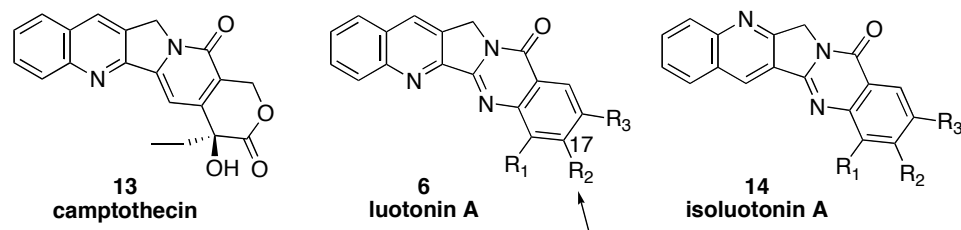


Fig. (6).

the most cytotoxic derivative having an IC₅₀ close to that of luotonin A itself (IC₅₀ 15.7 and 5.58 μM 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-aminoisindolo [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.

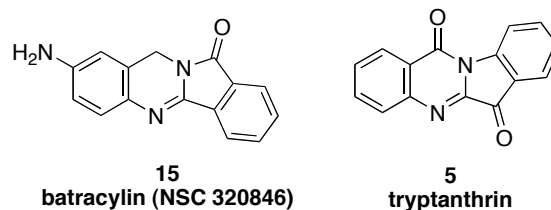


Fig. (7).

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

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

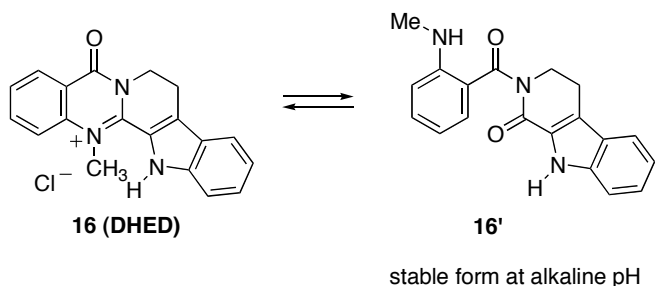


Fig. (8).

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].

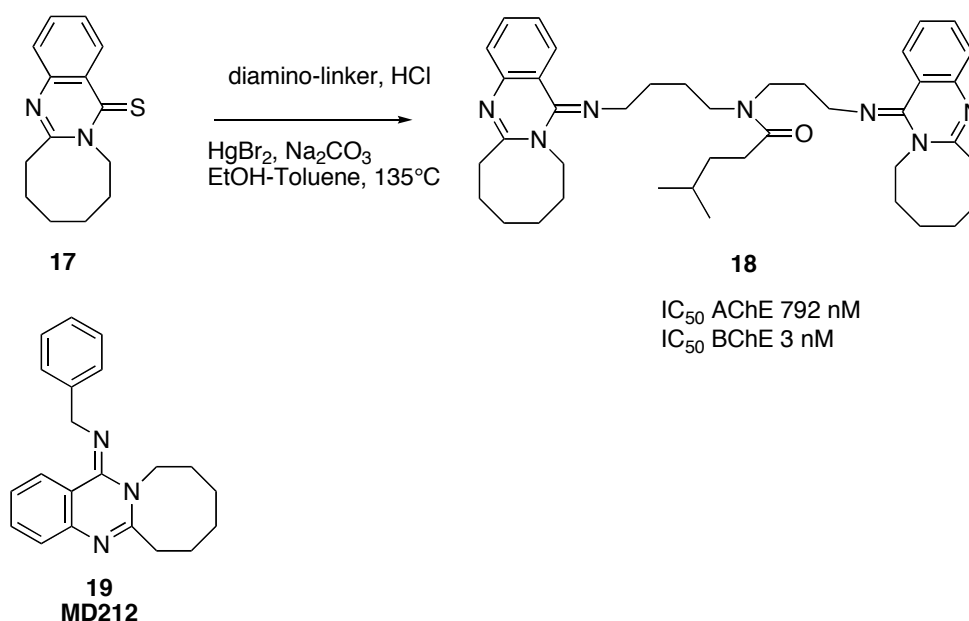


Fig. (9).

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 3×10^{-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 β -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**

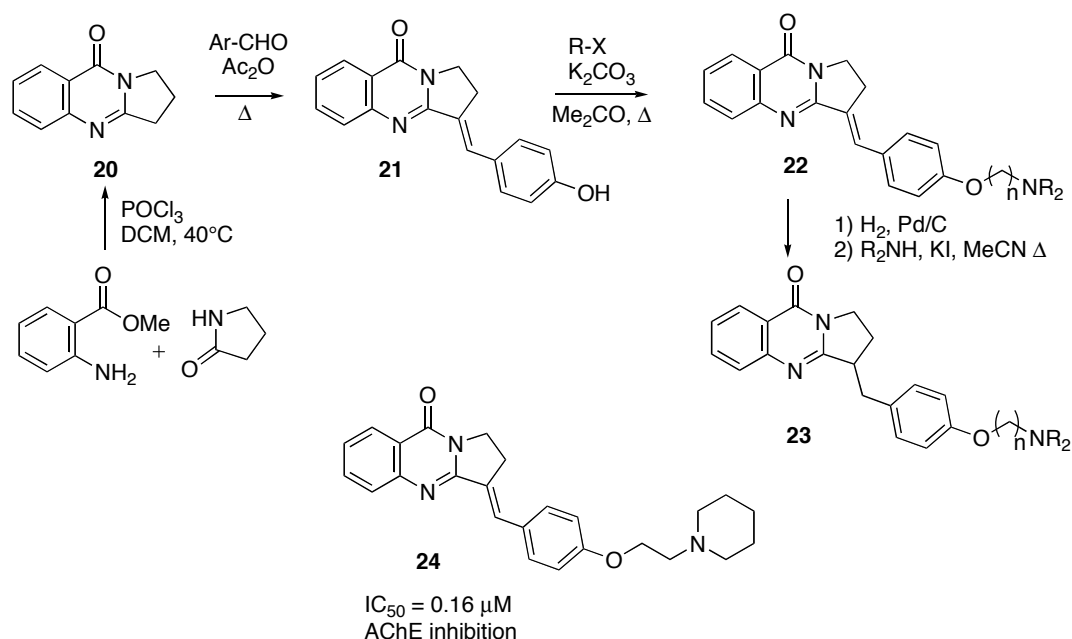


Fig. (10).

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.

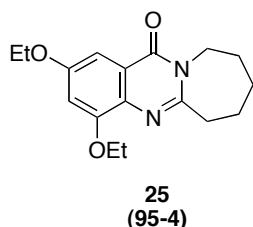


Fig. (11).

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 anatine, 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 (-)-

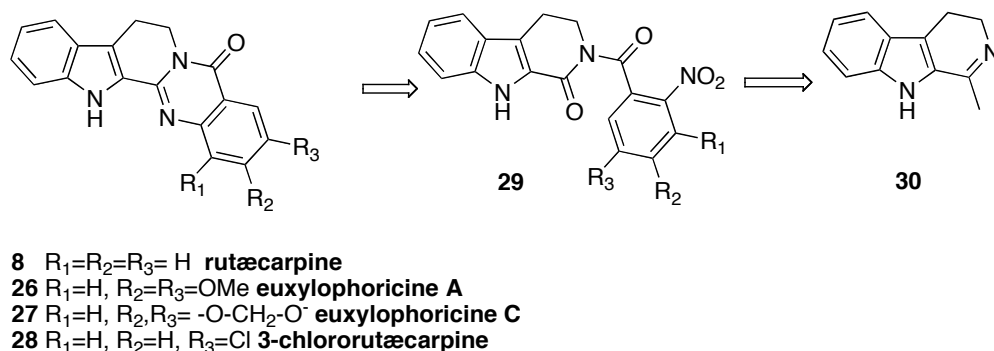


Fig. (12).

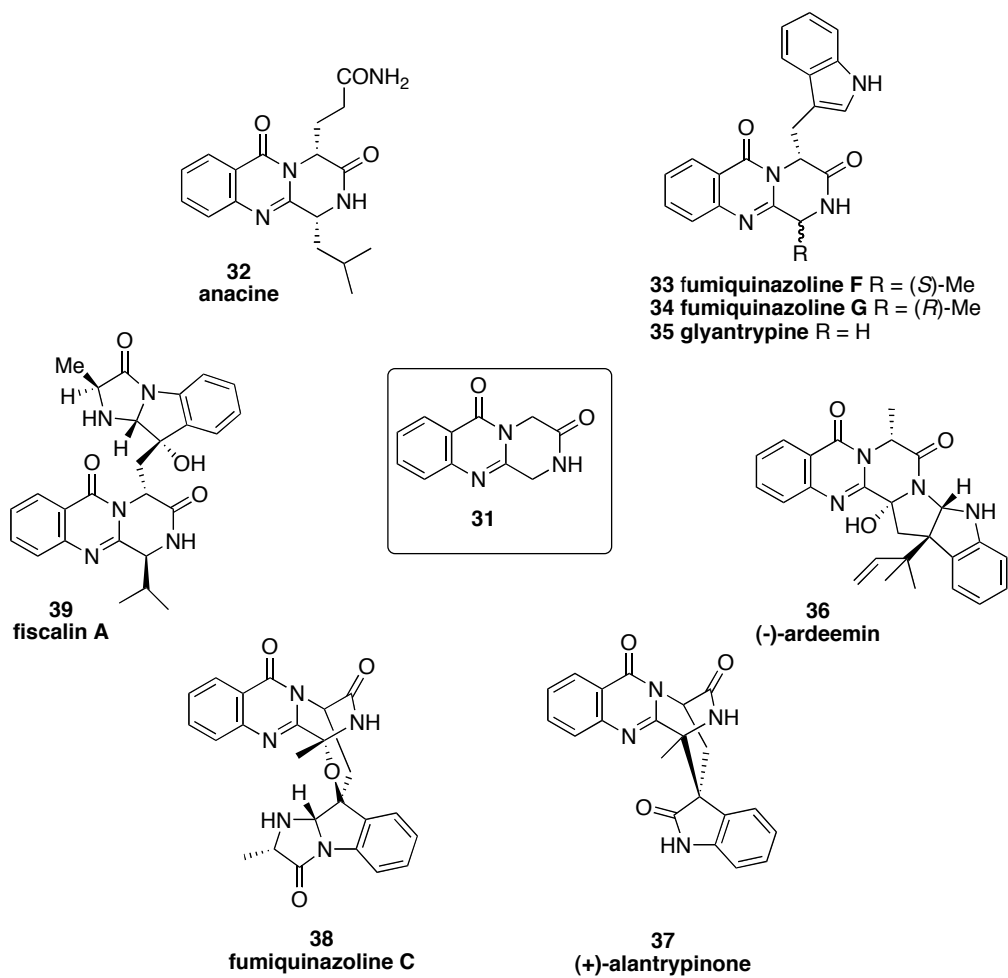


Fig. (13). Quinazolinone alkaloids with a fused piperazine.

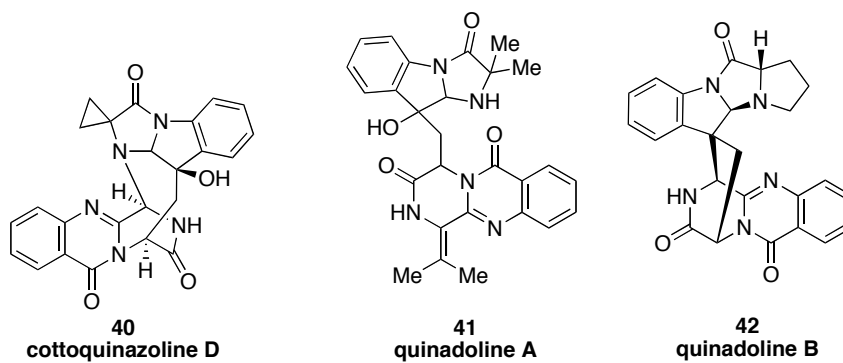


Fig. (14).

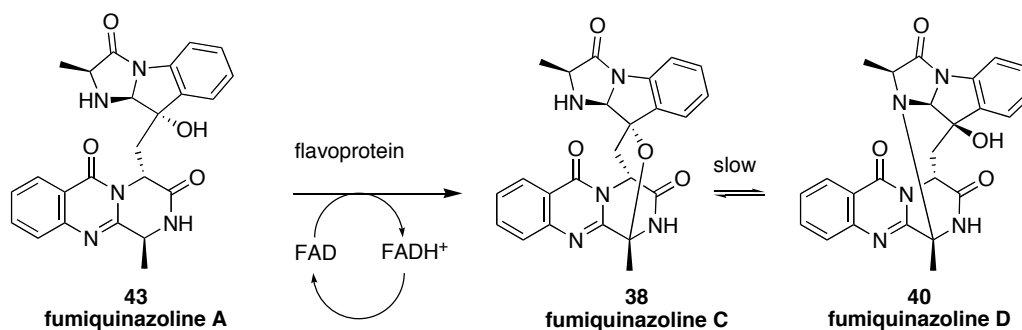


Fig. (15). Biosynthetic pathway to fumiquinazolines C/D.

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*]quinazolinones 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 α -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 (IC₅₀ 70-100 μ 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.

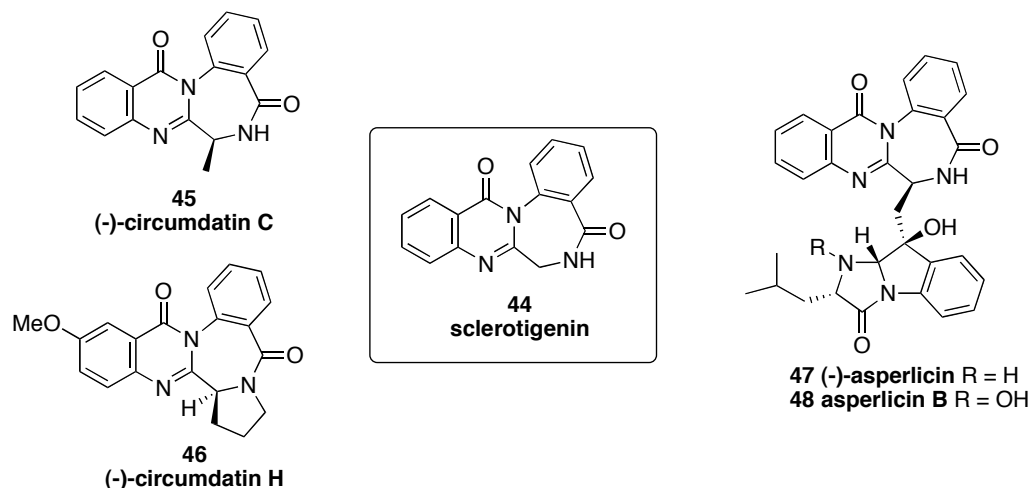


Fig. (16). Quinazolinone alkaloids with a fused benzodiazepine.

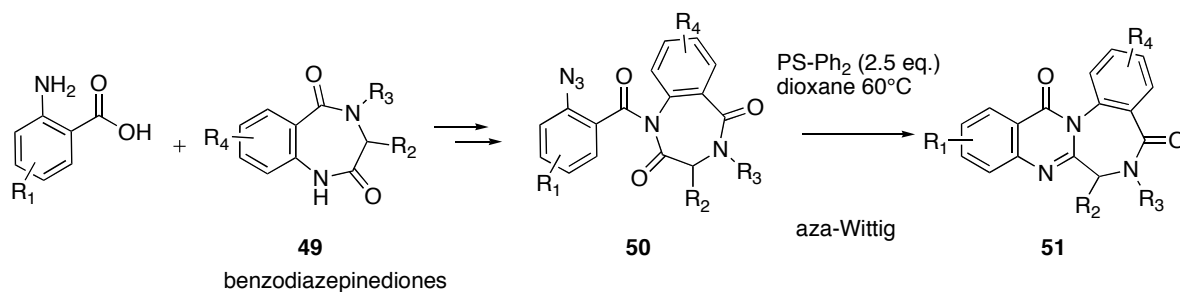


Fig. (17).

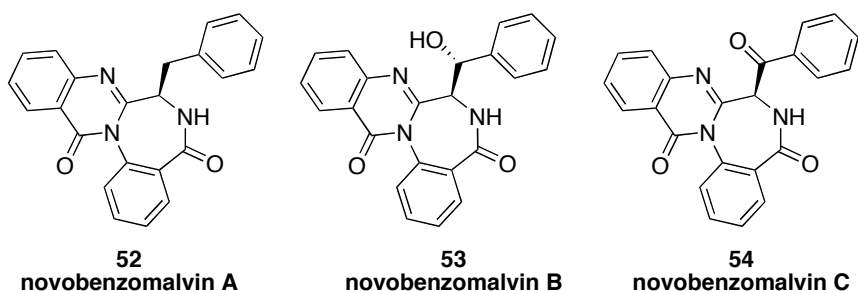


Fig. (18).

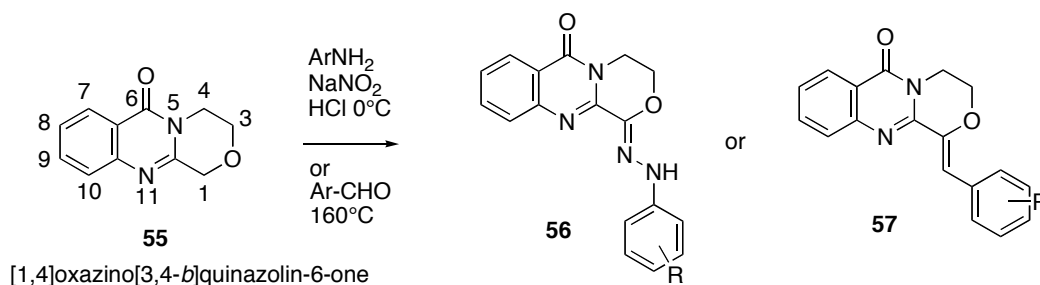


Fig. (19).

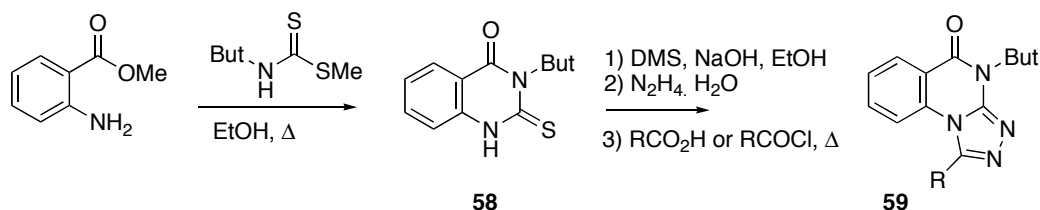


Fig. (20).

Antimicrobial and Antifungal Activities

Fused 1,2,4-triazolo-, 1,2,4-triazino- and 1,2,3,4-tetraazinoquinazolinones (**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, R=OMe/R'=2-Cl and R=4-Cl/R'=2-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 quinazolinone analogues confirm the interest of the tricyclic [1,2,4]triazolo[4,3-*a*]quinazolinone 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 μM IC₅₀.

2.5. Synthetic Methodologies

The synthesis of 2,3-polymethylene-quinazolinones may easily be achieved by reacting anthranilic acid with the corresponding lactam and SOCl₂ [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 benzylthioxazolinone 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

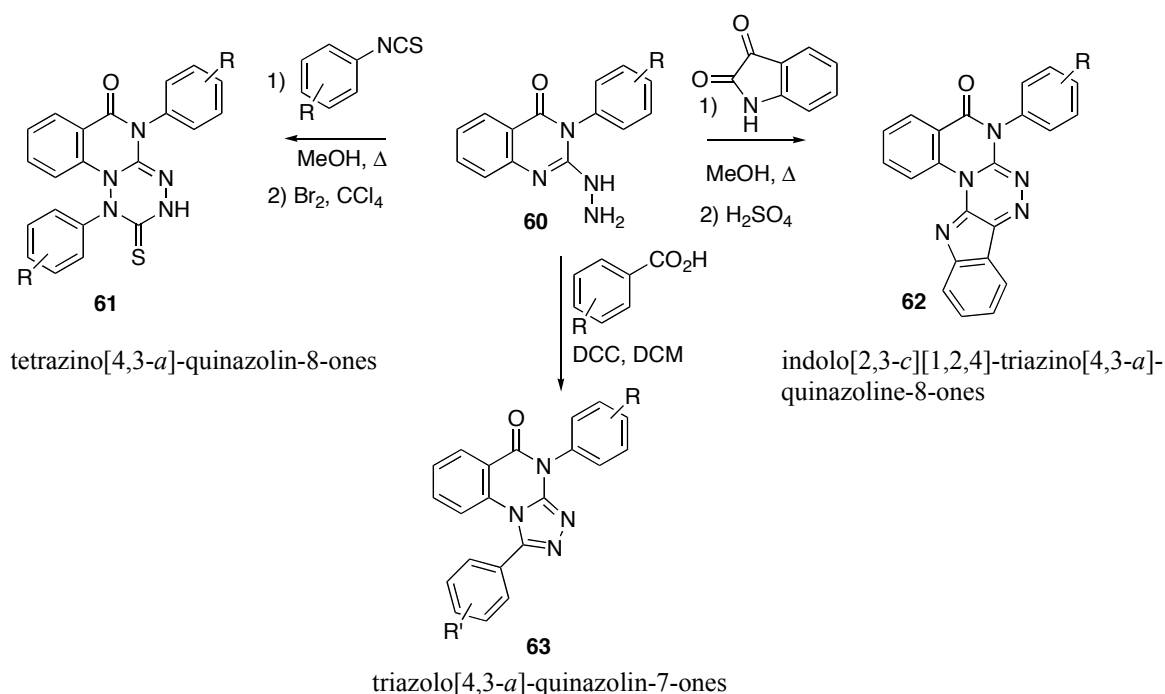


Fig. (21).

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.

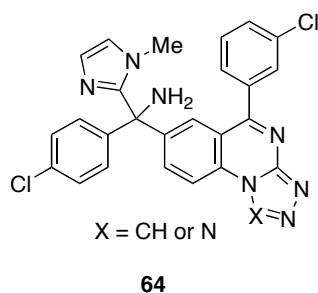


Fig. (22).

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 (dTMP). 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 foylpolylglutamate 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 α -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 α -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

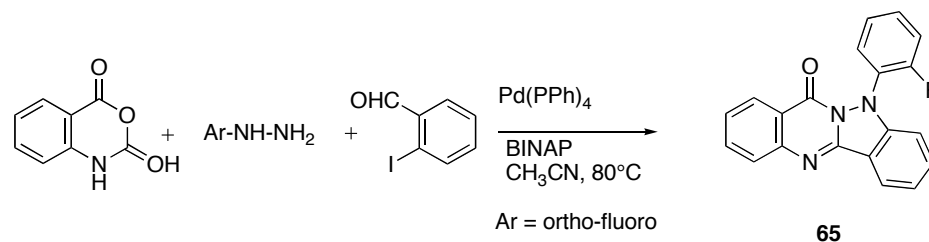


Fig. (23).

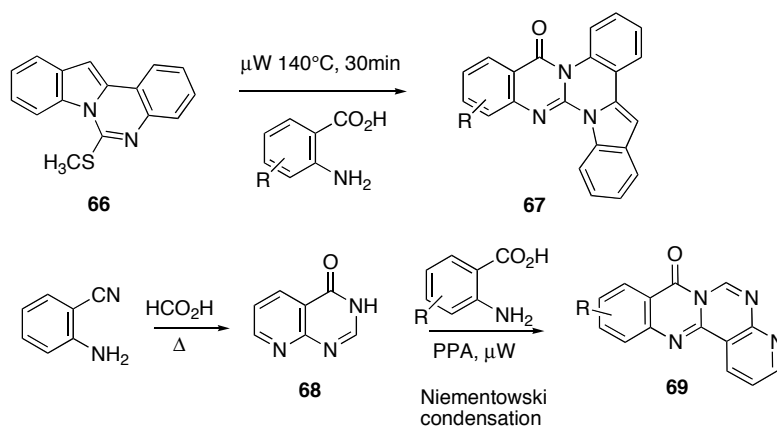


Fig. (24).

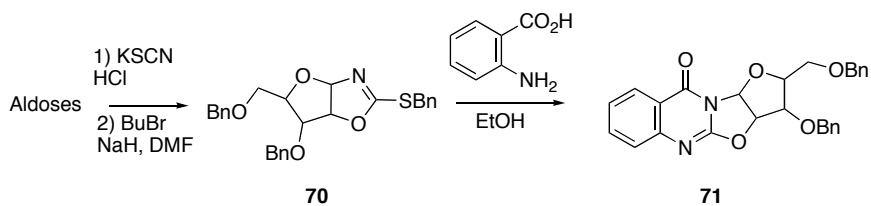


Fig. (25).

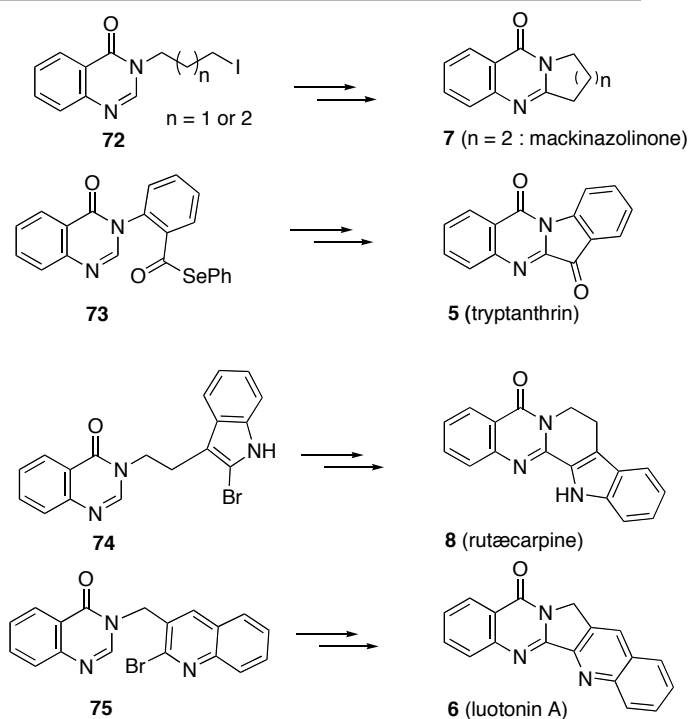
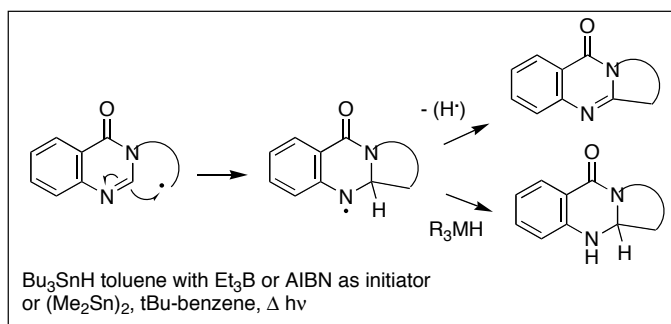


Fig. (26).

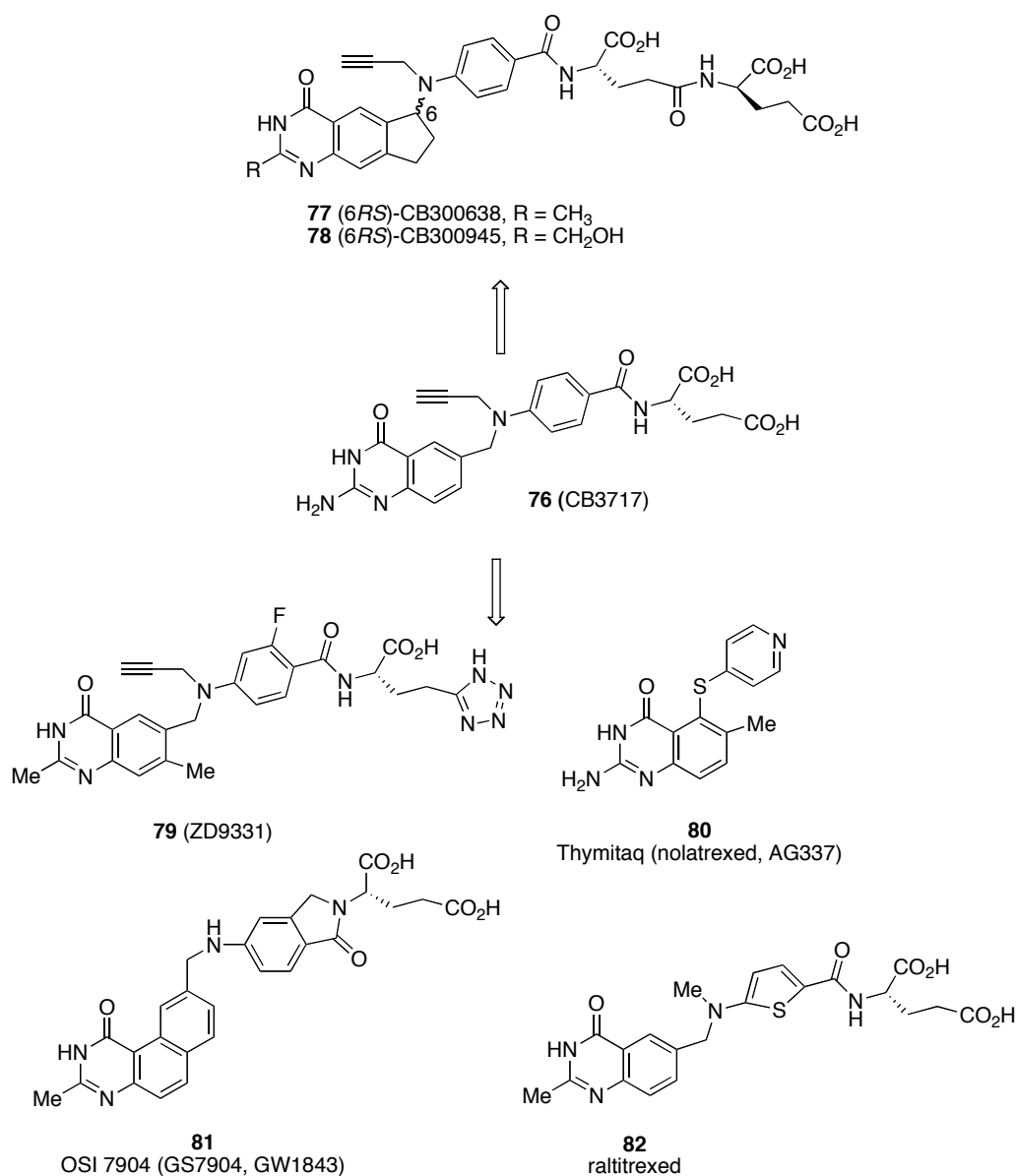


Fig. (27).

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)Co₂(CO)₆⁺ 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 = NH₂) 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]dioxanoquinazolines (**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

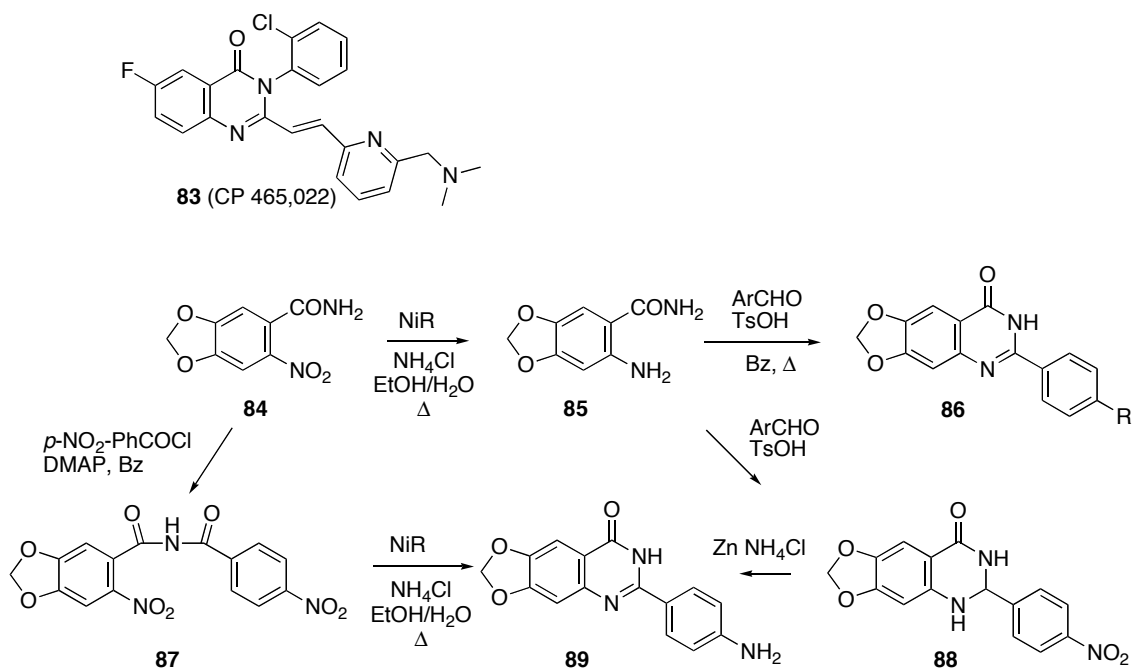


Fig. (28).

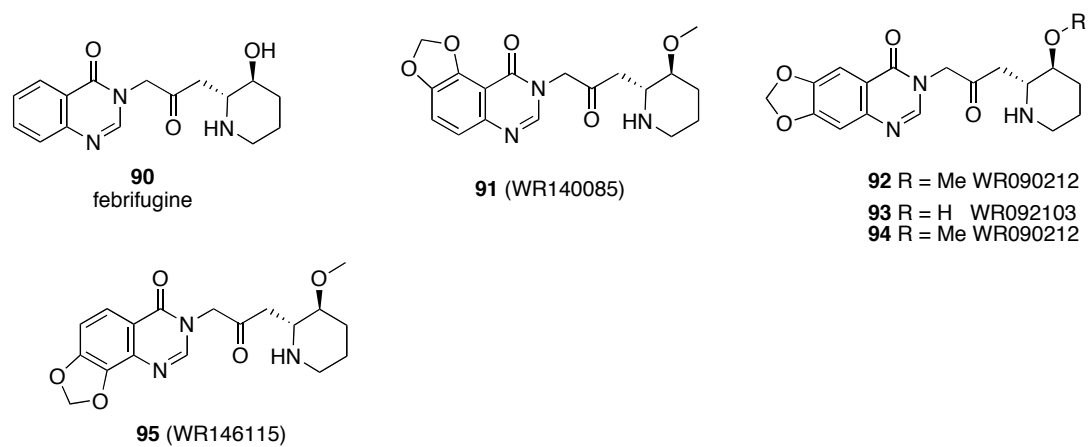


Fig. (29).

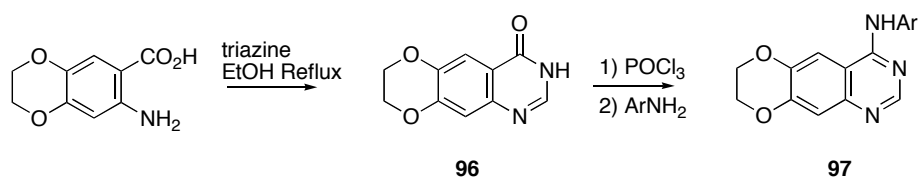


Fig. (30).

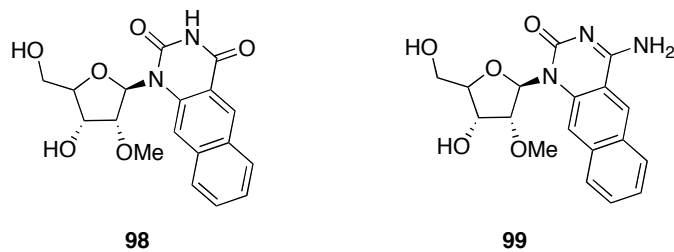


Fig. (31).

[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].

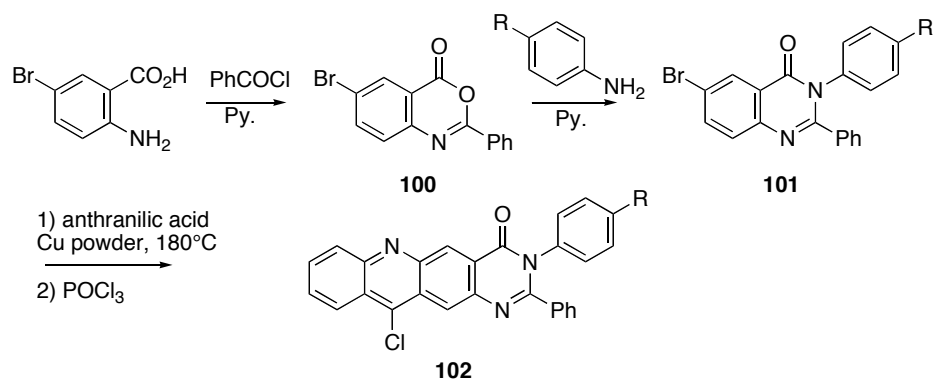


Fig. (32).

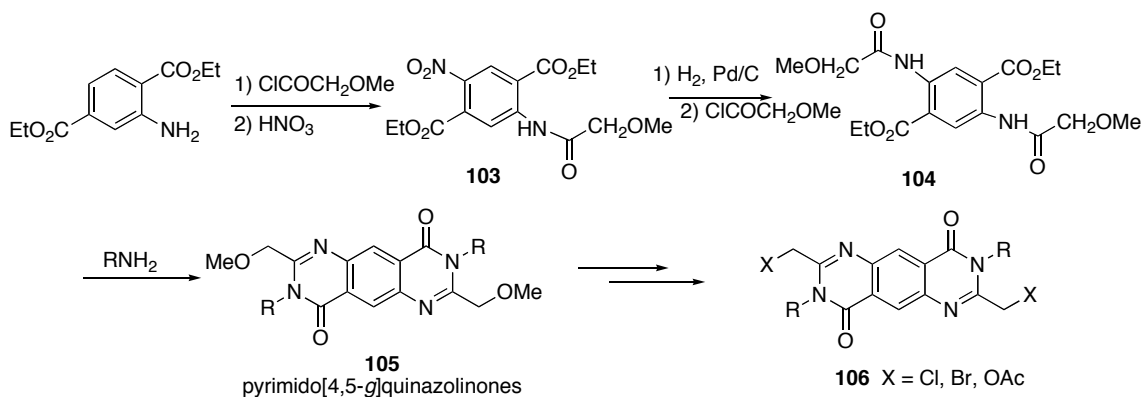


Fig. (33).

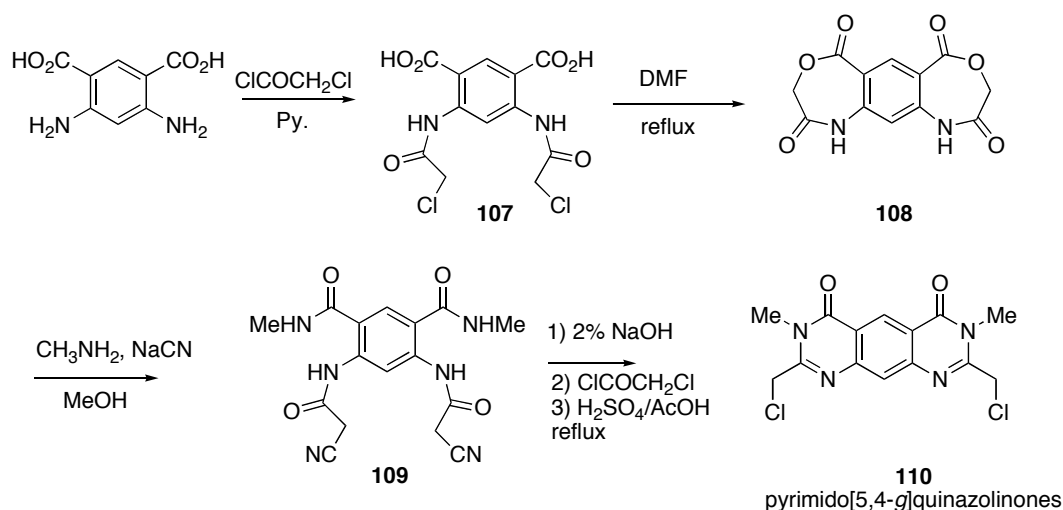


Fig. (34).

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 μ 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.

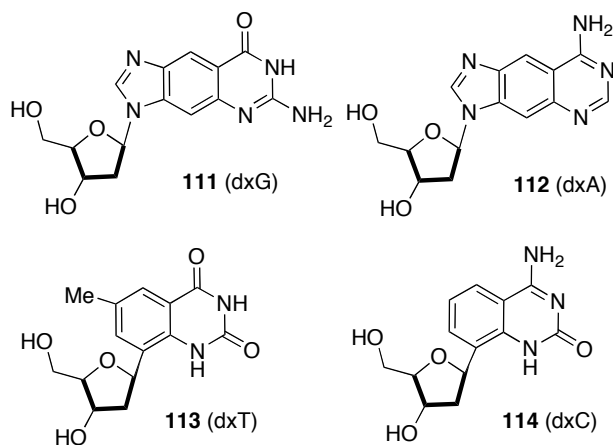


Fig. (35).

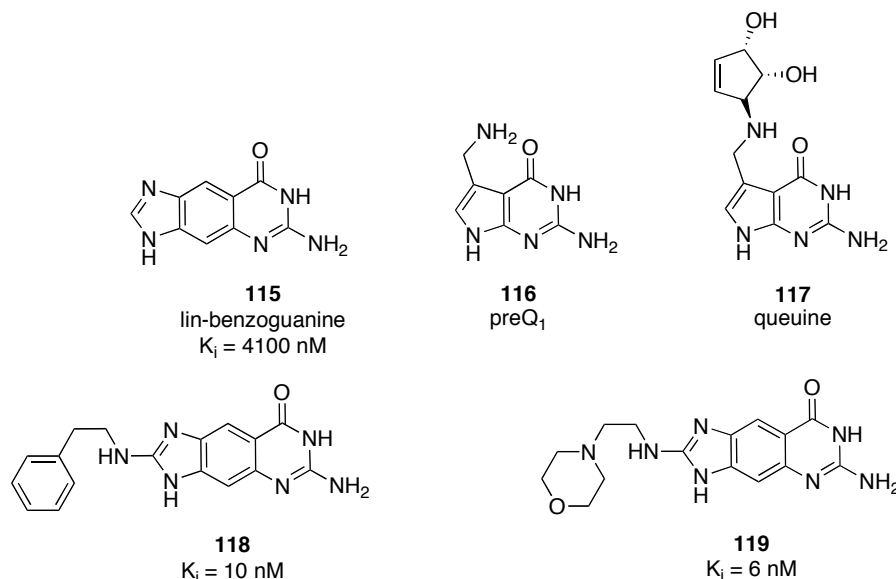


Fig. (36).

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 preQ₁ **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 preQ₁.

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 μ 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 quinazolinone 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

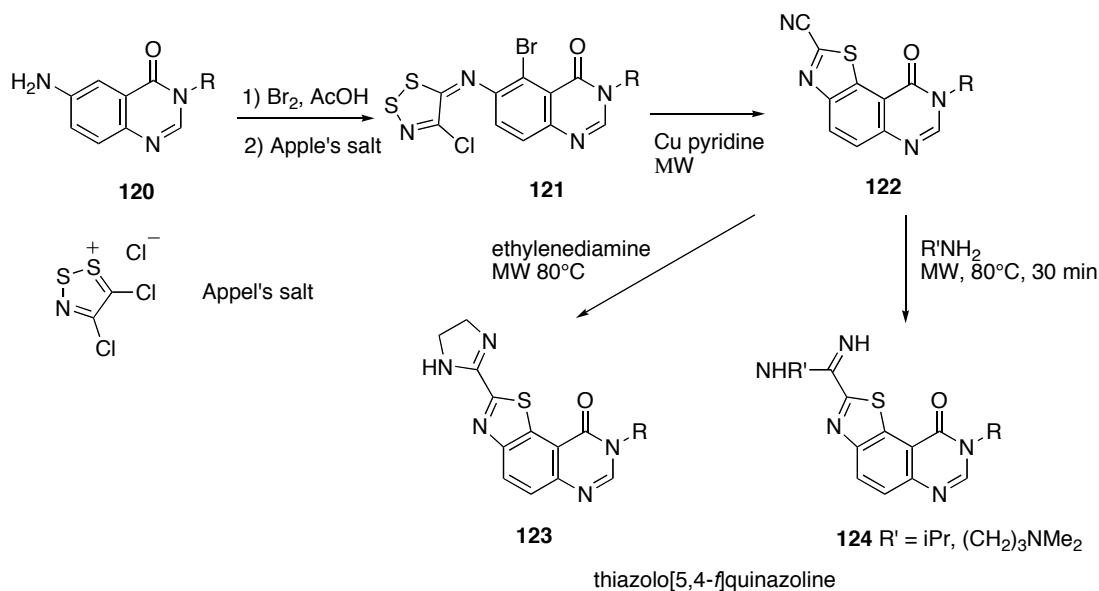


Fig. (37).

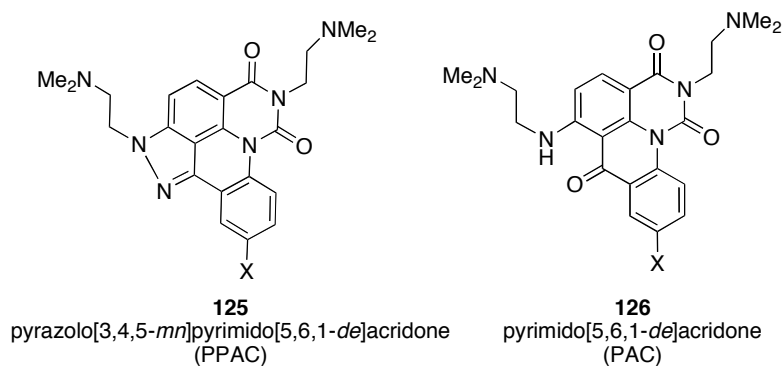


Fig. (38).

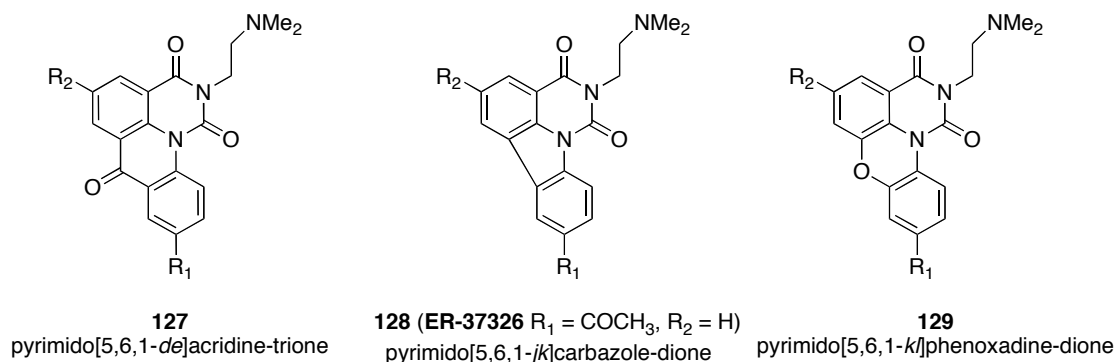


Fig. (39).

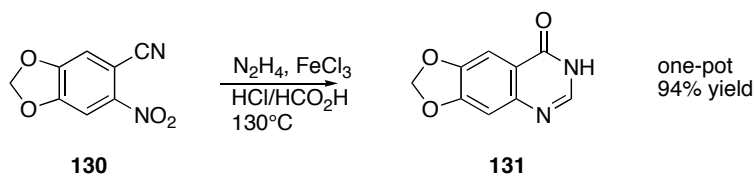


Fig. (40).

presence of hydrophobic substituent ($X = \text{OCH}_3$) markedly increased the cellular uptake compared to hydrophilic ($X = \text{OH}$) 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

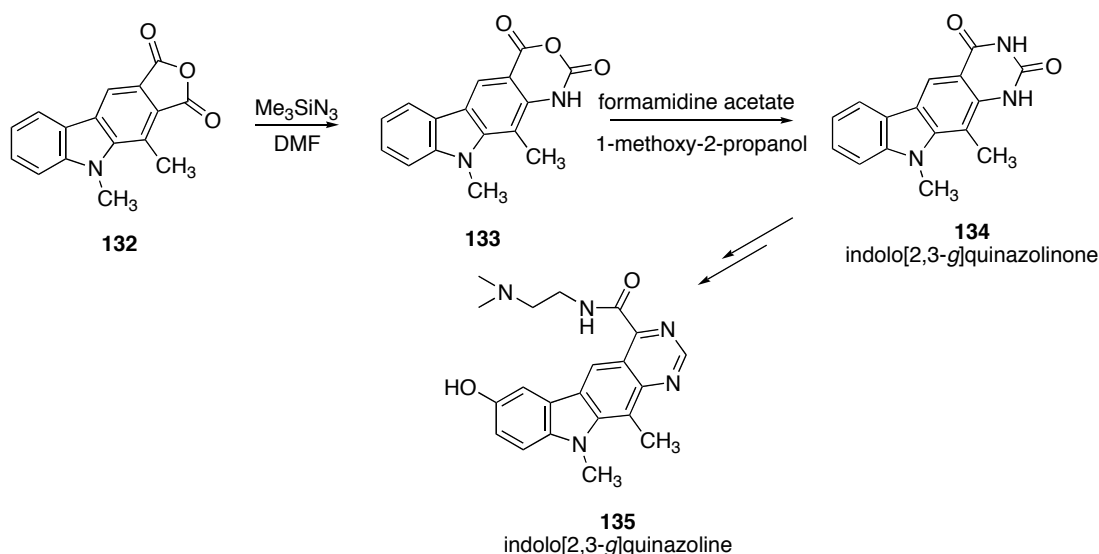


Fig. (41).

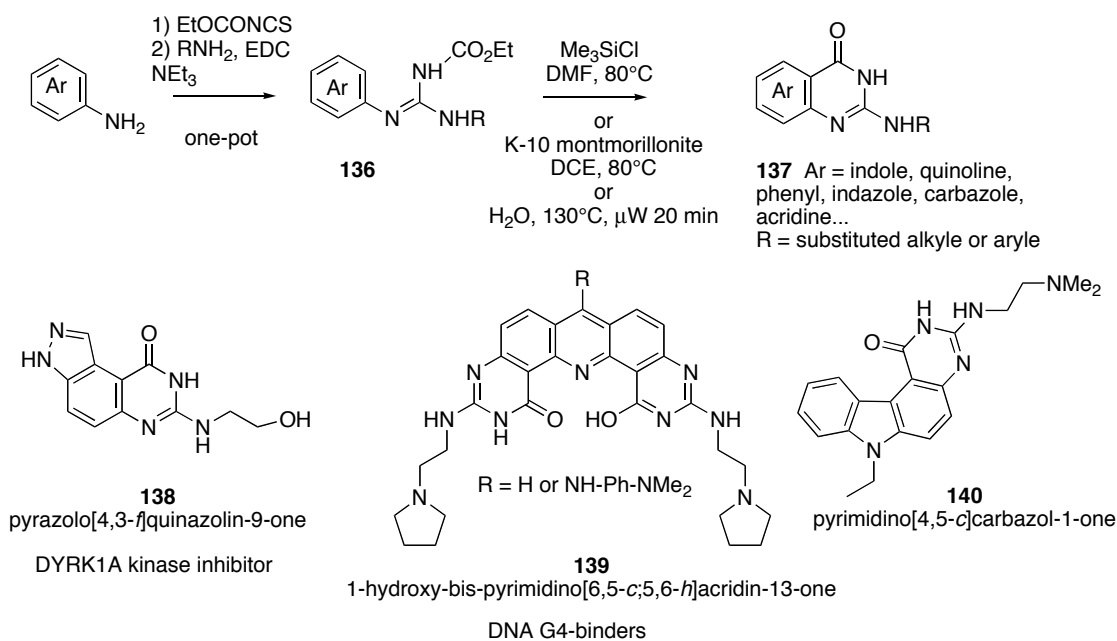


Fig. (42).

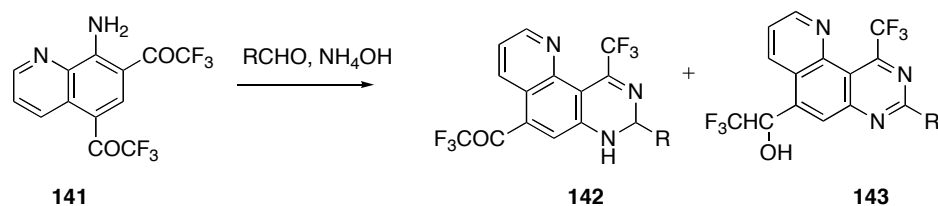


Fig. (43).

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 (CH₂)₃-N(CH₃)-(CH₂)₃ conferring higher affinity constant for DNA and generally better activity as shown by submicromolar IC₅₀. Compared to other chromophores (acridine, pyrazoloacridine) the pyrimidoacridone conferred higher cytotoxicity (IC₅₀ < 0.1 nM against HT29 colon adenocarcinoma cell line).

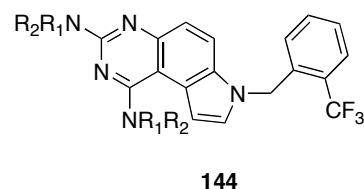


Fig. (44).

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 IC₅₀ 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 LC₅₀ (lethal concentration) ranging from 2.9 to 20 μM 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 quinazolines **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 N₂H₄.H₂O/FeCl₃).

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 quinazolines 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 (IC₅₀ 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

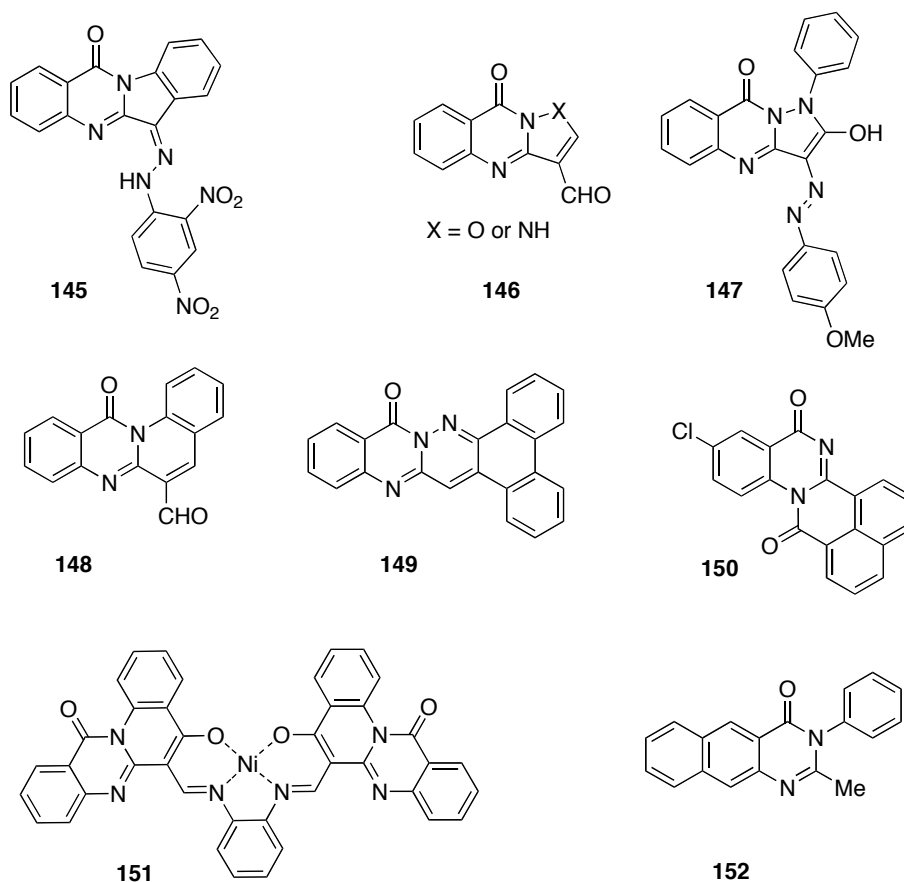


Fig. (45).

molecules show some selectivity for DYRK1A and CLK1, with submicromolar IC₅₀. 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 (IC₅₀ < 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 quinazolinone 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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REFERENCES

- Arora, R.; Kapoor, A.; Gill, N.S.; Rana, A.C., Quinazolinone: an overview. *Int. Res. J. Pharm.*, **2011**, *2*, 21-28.
- Sharma, P.C.; Kaur, G.; Pahwa, R.; Sharma, A.; Rajak, H., Quinazolinone analogs as potential therapeutic agents. *Curr. Med. Chem.*, **2011**, *18*, 4786-4812.
- Pendergast, W.; Johnson, J.V.; Dickerson, S.H.; Dev, I.K.; Duch, D.S.; Ferone, R.; Hall, W.R.; Humphrey, J.; Kelly, J.M.; Wilson, D.C., Benzoquinazolinone inhibitors of thymidylate synthase: enzyme inhibitory activity and cytotoxicity of some 3-amino- and 3-methylbenzo[*f*]quinazolin-1(2*H*)-ones. *J. Med. Chem.*, **1993**, *36*, 2279-2291.
- Hour, M.J.; Huang, L.J.; Kuo, S.C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K.H., 6-Alkylamino- and 2,3-dihydro-3'-methoxy-2-phenyl-4-quinazolinones and related compounds: their synthesis, cytotoxicity, and inhibition of tubulin polymerization. *J. Med. Chem.*, **2000**, *43*, 4479-4487.
- Pendergast, W.; Dickerson, S.H.; Dev, I.K.; Ferone, R.; Duch, D.S.; Smith, G.K., Benzo[*f*]quinazolinone inhibitors of thymidylate synthase: methyleneamino-linked aroylglutamate derivatives. *J. Med. Chem.*, **1994**, *37*, 838-844.
- De Clercq, E., New developments in anti-HIV chemotherapy. *Curr. Med. Chem.*, **2001**, *8*, 1543-1572.
- Chern, J.-W.; Tao, P.-L.; Wang, K.-C.; Gutcait, A.; Liu, S.-W.; Yen, M.-H.; Chien, S.-L.; Rong, J.-K., Studies on quinazolines and 1,2,4-benzothiadiazine 1,1-dioxides. 8. Synthesis and pharmacological evaluation of tricyclic fused quinazolines and 1,2,4-benzothiadiazine 1,1-dioxides as potential α 1-adrenoceptor antagonists. *J. Med. Chem.*, **1998**, *41*, 3128-3141.
- Grosso, J.A.; E., N.D.; Kohli, J.D.; Glock, D., Synthesis of 2-(alkylamino)-5,6- and -6,7-dihydroxy-3,4-dihydroquinazolines and evaluation as potential dopamine agonists. *J. Med. Chem.*, **1982**, *25*, 703-708.
- Somers, F.; Ouedraogo, R.; Antoine, M.-H.; de Tullio, P.; Becker, B.; Fontaine, J.; Damas, J.; Dupont, L.; Rigo, B.; Delarge, J.; Lebrun, P.; Piroette, B., Original 2-alkylamino-6-halogenoquinazolin-4(3*H*)-ones and K_{ATP} channel activity. *J. Med. Chem.*, **2001**, *44*, 2575-2585.
- Alagarsamy, V.; Solomon, V.R.; Murugan, M., Synthesis and pharmacological investigation of novel 4-benzyl-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones as new class of H1-antihistaminic agents. *Biorg. Med. Chem.*, **2007**, *15*, 4009-4015.
- Kumar, A.; Rajput, C.S., Synthesis and anti-inflammatory activity of newer quinazolin-4-one derivatives. *Eur. J. Med. Chem.*, **2009**, *44*, 83-90.
- Alafeefy, A.M.; Kadi, A.A.; El-Azab, A.; Abdel-Hamide, S.G.; Daba, M.-H.Y., Synthesis, Analgesic and Anti-Inflammatory Evaluation of Some New 3*H*-Quinazolin-4-one Derivatives. *Arch. Pharm. Chem. Life Sci.*, **2008**, *341*, 377-385.
- Marzaro, G.; Guiotto, A.; Chilin, A., Quinazolinone derivatives as potential anticancer agents: a patent review (2007-2010). *Expert Opin. Ther. Patents*, **2012**, *22*, 223-252.
- Genady, A.R., Promising carboranylquinazolines for boron neutron capture therapy: Synthesis, characterization, and *in vitro* toxicity evaluation. *Eur. J. Med. Chem.*, **2008**, *asap*.
- Patil, D.A.; Patil, P.O.; Patil, G.B.; Surana, S.J., Synthesis of 2, 3-disubstituted-Quinazolin-4(3*H*)-ones. *Mini Rev Med Chem*, **2011**, *11*, 633-641.
- Okuzumi, T.; Nakanishi, E.; Tsuji, T.; Makino, S., Efficient solid-phase synthesis of quinazolinone-2,4-diones with various substituents on aromatic rings. *Tetrahedron*, **2003**, *59*, 5603-5608.
- Connolly, D.J.; Cusak, D.; O'Sullivan, T.P.; Guiry, P.J., Synthesis of quinazolinones and quinazolines. *Tetrahedron*, **2005**, *61*, 10153-10202.
- Mhaske, S.B.; Argade, N.P., The chemistry of recently isolated naturally occurring quinazolinone alkaloids. *Tetrahedron*, **2006**, *62*, 9787-9826.
- Eguchi, S., Quinazolinone alkaloids and related chemistry. *Top. Heterocycl. Chem.*, **2006**, *6*, 113-156.
- Vögtle, M.M.; Marzinzik, A.L., Synthetic approaches towards quinazolines, quinazolinones and quinazolinodions on solid phase. *QSAR Comb. Sci.*, **2004**, *23*, 440-459.
- Michael, J.P., Quinoline, quinazolinone and acridone alkaloids. *Nat. Prod. Rep.*, **2008**, *25*, 166-187.
- Kundu, B.; Partani, P.; Duggineni, S.; Sawant, D., Solid-phase synthesis of 2-aminoquinazolinone derivatives with two- or three-point diversity. *J. Comb. Chem.*, **2005**, *7*, 909-915.
- Weber, C.; Bielik, A.; Szendrei, G.; Greiner, I., Novel solid-phase synthesis of 2,6-disubstituted 4(3*H*)-quinazolinones for combinatorial library generation. *Tetrahedron Lett.*, **2002**, *43*, 2971-2974.
- Weber, C.; Demeter, A.; Szendrei, G.I.; Greiner, I., Solid-phase synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinones via palladium-catalysed amination. *Tetrahedron Lett.*, **2003**, *44*, 7533-7536.
- Yang, R.-Y.; Kaplan, A., A concise and efficient solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones. *Tetrahedron Lett.*, **2000**, *41*, 7005-7008.
- Gopalsamy, A.; Yang, H., Combinatorial synthesis of heterocycles: solid-phase synthesis of 2-amino-4(1*H*)-quinazolinone derivatives. *J. Comb. Chem.*, **2000**, *2*, 378-381.
- Cledera, P.; Sanchez, J.D.; Caballero, E.; Yates, T.; Ramirez, E.G.; Avendano, C.; Ramos, M.T.; Menendez, J.C., Microwave-assisted, solvent-free synthesis of several quinazolinone alkaloid frameworks. *Synthesis*, **2007**, 3390-3398.
- Alexandre, F.-R.; Berecibar, A.; Besson, T., Microwave-assisted Niementowski reaction. Back to the roots. *Tetrahedron Lett.*, **2002**, *43*, 3911-3913.
- Órfi, L.; Waczek, F.; Pato, J.; Varga, I.; Hegymegi-Barakonyi, B.; Houghten, R.A.; Kéri, G., Improved, High Yield Synthesis of 3*H*-Quinazolin-4-ones, the Key Intermediates of Recently Developed Drugs. *Curr. Med. Chem.*, **2004**, *11*, 2549-2553.
- Siddiqui, I.R.; Singh, P.K.; Srivastava, V.; Yadav, S.; Singh, J., A novel versatile strategy for synthesis of new series of 4(3*H*)-quinazolinone N-nucleosides. *Indian J. Chem., Section B: Organic Chemistry*, **2010**, *49*, 1535-1541.
- Molina, P.; Alajarin, M.; Vidal, A., New methodology for the preparation of quinazolinone derivatives via tandem Aza-Wittig/heterocumulene-mediated annulation. Synthesis of 4(3*H*)-quinazolinones, benzimidazo[1,2-*c*]quinazolines, quinazolino[3,2-*a*]quinazolines and benzothiazolo[3,2-*c*]quinazolines. *Tetrahedron*, **1989**, *45*, 4263-4286.
- Zhang, W.; Mayer, J.P.; Hall, S.E.; Weigel, J.A., A polymer-bound iminophosphorane approach for the synthesis of quinazolines. *J. Comb. Chem.*, **2001**, *3*, 255-256.
- Yu, Y.; Ostresh, J.M.; Houghten, R.A., A traceless approach for the parallel

- solid-phase synthesis of 2-(arylamino)quinazolines. *J. Org. Chem.*, **2002**, *67*, 5831-5834.
- [34] Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M.P., A catalyst- and solvent-free selective approach to biologically important quinazolines and benzol[*g*]quinazoline. *Tetrahedron*, **2005**, *61*, 3533-3538.
- [35] El-Hiti, G.A.; Abel-Megeed, M.F., Synthesis of glycosides containing quinazolin-4(3H)-one ring system. *Heterocycles*, **2005**, *65*, 3007-3041.
- [36] Liu, J.-F., Rapid syntheses of biologically active quinazolinone natural products using microwave technology. *Curr. Org. Synthesis*, **2007**, *4*, 223-237.
- [37] Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C.M.; Wilson, C.J.; Ng, A.M., Novel one-pot total syntheses of deoxyvasicinone, mackinazolinone, isaindigotone, and their derivatives promoted by microwave irradiation. *Org. Lett.*, **2005**, *7*, 3363-3366.
- [38] Liu, J.F.; Wilson, C.J.; Ye, P.; Sprague, K.; Sargent, K.; Si, Y.; Beletsky, G.; Yohannes, D.; Ng, S.C., Privileged structure-based quinazolinone natural product-templated libraries: identification of novel tubulin polymerization inhibitors. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 686-690.
- [39] Cagir, A.; Eisenhauer, B.M.; Gao, R.; Thomas, S.J.; Hecht, S.M., Synthesis and topoisomerase I inhibitory properties of luotonin A analogues. *Bioorg. Med. Chem.*, **2004**, *12*, 6287-6299.
- [40] Rao, V.A.; Agama, K.; Holbeck, S.; Pommier, Y., Batracylin (NSC 320846), a dual inhibitor of DNA topoisomerases I and II induces histone gamma-H2AX as a biomarker of DNA damage. *Cancer Res.*, **2007**, *67*, 9971-9979.
- [41] Park, E.-J.; Suh, Y.-H.; Kim, J.-Y.; Choi, S.; Lee, C.-J., Long-lasting facilitation by dehydroevodiamine. HCl of synaptic responses evoked in the CA1 region of rat hippocampal slices. *NeuroRep.*, **2003**, *14*, 399-403.
- [42] Peng, J.-H.; Zhang, C.E.; Wei, W.; Hong, X.-P.; Pan, X.-P.; Wang, J.-Z., Dehydroevodiamine attenuates tau hyperphosphorylation and spatial memory deficit induced by activation of glycogen synthase kinase-3 in rats. *Neuropharm.*, **2007**, *52*, 1521-1527.
- [43] Wang, H.-H.; Chou, C.-J.; Liao, J.-F.; Chen, C.F., Dehydroevodiamine attenuates β -amyloid peptide-induced amnesia in mice. *Eur. J. Pharm.*, **2001**, *413*, 221-225.
- [44] Decker, M., Novel inhibitors of acetyl- and butyrylcholinesterase derived from the alkaloids dehydroevodiamine and rutaecarpine. *Eur. J. Med. Chem.*, **2005**, *40*, 305-313.
- [45] Decker, M., Homobivalent quinazolinimines as novel nanomolar inhibitors of cholinesterases with dirigible selectivity toward butyrylcholinesterase. *J. Med. Chem.*, **2006**, *49*, 5411-5413.
- [46] Chen, X.; Tikhonova, I.G.; Decker, M., Probing the mid-gorge of cholinesterases with spacer-modified bivalent quinazolinimines leads to highly potent and selective butyrylcholinesterase inhibitors. *Bioorg. Med. Chem.*, **2011**, *19*, 1222-1235.
- [47] Appenroth, D.; Decker, M.; Tränkle, C.; Mohr, K.; Lehmann, J.; Fleck, C., *In vivo* investigations on the cholinesterase-inhibiting effects of tricyclic quinazolinimines: Scopolamine-induced cognitive impairments in rats are attenuated at low dosage and reinforced at higher dosage. *PLoS Arch. Eur. J. Physiol.*, **2008**, *455*, 895-901.
- [48] Pan, L.; Tan, J.-H.; Hou, J.-Q.; Huang, S.-L.; Gu, L.-Q.; Huang, Z.-S., Design, synthesis and evaluation of isaindigotone derivatives as acetylcholinesterase and butyrylcholinesterase inhibitors. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 3790-3793.
- [49] Zabeer, A.; Bhagat, A.; Gupta, O.P.; Singh, G.D.; Youssouf, M.S.; Dhar, K.L.; Suri, O.P.; Suri, K.A.; Satti, N.K.; Gupta, B.D.; Qazi, G.N., Synthesis and bronchodilator activity of new quinazolin derivative. *Eur. J. Med. Chem.*, **2006**, *41*, 429-434.
- [50] Chen, Z.; Hu, G.; Li, D.; Chen, J.; Li, H.; Zhou, H.; Xie, Y., Synthesis and vasodilator effects of rutaecarpine analogues which might be involved transient receptor potential vanilloid subfamily, member 1 (TRPV1). *Bioorg. Med. Chem.*, **2009**, *17*, 2351-2359.
- [51] Astulla, A.; Zaima, K.; Matsuno, Y.; Hirasawa, Y.; Ekasari, W.; Widyawaruyanti, A.; Zaini, N.C.; Morita, H., Alkaloids from the seeds of *Peganum harmala* showing antiplasmodial and vasorelaxant activities. *J. Nat. Prod.*, **2008**, *62*, 470-472.
- [52] Pandey, S.K.; Singh, A.; Nizamuddin, Antimicrobial studies of some novel quinazolines fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings. *Eur. J. Med. Chem.*, **2009**, *44*, 1188-1197.
- [53] Buttachon, S.; Chandrapatya, A.; Manoch, L.; Silva, A.; Gales, L.; Bruyere, C.; Kiss, R.; Kijjoa, A., Sartorymensin, a new indole alkaloid, and new analogues of tryptovaline and fiscalins produced by *Neosartorya siamensis* (KUFC 6349). *Tetrahedron*, **2012**, *68*, 3253-3262.
- [54] Zhuang, Y.; Teng, X.; Wang, Y.; Liu, P.; Li, G.; Zhu, W., New quinazolinone alkaloids within rare amino acid residue from coral-associated fungus, *Aspergillus versicolor* LCJ-5-4. *Org. Lett.*, **2011**, *13*, 1130-1133.
- [55] Fremlin, L.J.; Piggott, A.M.; Lacey, E.; Capon, R.J., Cottoquinazoline A and cotteslosins A and B, metabolites from an Australian marine-derived strain of *Aspergillus versicolor*. *J. Nat. Prod.*, **2009**, *72*, 666-670.
- [56] Koyama, N.; Inoue, Y.; Sekine, M.; Hayakawa, Y.; Homma, H.; Oinmura, S.; Tomoda, H., Relative and absolute stereochemistry of quinadoline B, an inhibitor of lipid droplet synthesis in macrophages. *Org. Lett.*, **2008**, *10*, 5273-5276.
- [57] Xin, Z.H.; Fang, Y.; Du, L.; Zhu, T.; Duan, L.; Chen, J.; Gu, Q.-Q.; Zhu, W.-M., Aurantiomides A-C, quinazolinone alkaloids from the sponge-derived fungus *Penicillium aurantiogriseum* SP0-19. *J. Nat. Prod.*, **2007**, *70*, 853-855.
- [58] Ames, B.D.; Haynes, S.W.; Gao, X.; Evans, B.S.; Kelleher, N.L.; Tang, Y.; Walsh, C.T., Complexity Generation in Fungal Peptidyl Alkaloid Biosynthesis: Oxidation of Fumiquinazoline A to the Heptacyclic Hemiaminal Fumiquinazoline C by the Flavoenzyme Af12070 from *Aspergillus fumigatus*. *Biochemistry*, **2011**, *50*, 8756-8769.
- [59] Ames, B.D.; Liu, X.; Walsh, C.T., Enzymatic processing of fumiquinazoline F: A tandem oxidative-acylation strategy for the generation of multicyclic scaffolds in fungal indole alkaloid biosynthesis. *Biochemistry*, **2010**, *49*, 8564-8576.
- [60] Ames, B.D.; Walsh, C.T., Anthranilate-activating modules from fungal nonribosomal peptide assembly lines. *Biochemistry*, **2010**, *49*, 3351-3365.
- [61] Gao, X.; Chooi, Y.-H.; Ames, B.D.; Wang, P.; Walsh, C.T.; Tang, Y., Fungal indole alkaloid biosynthesis: genetic and biochemical investigation of the tryptoguanine pathway in *Penicillium aethiopicum*. *J. Am. Chem. Soc.*, **2011**, *133*, 2729-2741.
- [62] Haynes, S.W.; Ames, B.D.; Gao, X.; Tang, Y.; Walsh, C.T., Unraveling Terminal C-Domain-Mediated Condensation in Fungal Biosynthesis of Imidazoindolone Metabolites. *Biochemistry*, **2011**, *50*, 5668-5679.
- [63] Wang, Y.; Kong, C.; Du, Y.; Song, H.; Zhang, D.; Qin, Y., Silver-promoted Friedel-Crafts reaction: concise total synthesis of (-)-ardeemin, (-)-acetylardeemin and (-)-formylardeemin. *Org. Biomol. Chem.*, **2012**, *10*, 2793-2797.
- [64] He, B.; Song, H.; Du, Y.; Qin, Y., Total Synthesis of (-)-Ardeemin. *J. Org. Chem.*, **2009**, *74*, 298-304.
- [65] Takiguchi, S.; Iizuka, T.; Kumakura, Y.-s.; Murasaki, K.; Ban, N.; Higuchi, K.; Kawasaki, T., Total Syntheses of (-)-Fructigenine A and (-)-5-N-Acetylardeemin. *J. Org. Chem.*, **2010**, *75*, 1126-1131.
- [66] Leca, D.; Gaggini, F.; Cassayre, J.; Loiseau, O.; Pieniazek, S.N.; Luft, J.A.R.; Houk, K.N., Acid-Catalyzed Aza-Diels-Alder Reactions for the Total Synthesis of (+)-Lapatin B. *J. Org. Chem.*, **2007**, *72*, 4284-4287.
- [67] Chen, Z.; Fan, J.; Kende, A.S., Total Synthesis of (-)-Alantrypinone by Hetero Diels-Alder Reaction. *J. Org. Chem.*, **2004**, *69*, 79-85.
- [68] Hart, D.J.; Oba, G., Synthesis and absolute configuration of (-)-serantrypinone. *Tetrahedron Lett.*, **2007**, *48*, 7069-7071.
- [69] Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C.M., Three-Component One-Pot Total Syntheses of Gyantrypinone, Fumiquinazoline F, and Fiscalin B Promoted by Microwave Irradiation. *J. Org. Chem.*, **2005**, *70*, 6339-6345.
- [70] Tseng, M.-C.; Chu, Y.-H., Zinc triflate-catalyzed synthesis of pyrazino[2,1-b]quinazoline-3,6-diones. *Tetrahedron*, **2008**, *64*, 9515-9520.
- [71] Watanabe, T.; Arisawa, M.; Narusuye, K.; Alam, M.S.; Yamamoto, K.; Mitomi, M.; Ozoe, Y.; Nishida, A., Alantrypinone and its derivatives and Synthesis and antagonist activity toward insect GABA receptors. *Bioorg. Med. Chem.*, **2009**, *17*, 94-110.
- [72] Kuriyama, T.; Kakemoto, E.; Takahashi, N.; Imamura, K.-i.; Oyama, K.; Suzuki, E.; Harimaya, K.; Yaguchi, T.; Ozoe, Y., Receptor assay-guided isolation of anti-gabaergic insecticidal alkaloids from a fungal culture. *J. Agric. Food Chem.*, **2004**, *52*, 3884-3887.
- [73] Pereira, M.D.F.; Chevrot, R.; Rosenfeld, E.; Thiery, V.; Besson, T., Synthesis and evaluation of the antimicrobial activity of novel quinazolines. *J. Enzyme Inhib. Med. Chem.*, **2007**, *22*, 577-583.
- [74] Sorra, K.; Pusuluri, S.; Mukkanti, K., Palladium catalyzed synthesis of quinazolino [1,4] benzodiazepine alkaloids and analogous. *Tetrahedron*, **2012**, *68*, 2001-2006.
- [75] Fang, J.; Zhou, J., Efficient syntheses of 2,3-disubstituted natural quinazolines via iridium catalysis. *Org. Biomol. Chem.*, **2012**, *10*, 2389-2391.
- [76] Tseng, M.-C.; Lai, C.-Y.; Chu, Y.-W.; Chu, Y.-H., Tin triflate-mediated total synthesis of circumdatin F, sclerotigenin, asperlicin C, and other quinazolinol[3,2-a][1,4]benzodiazepines. *Chem. Commun.*, **2009**, 445-447.
- [77] Kshirsagar, U.A.; Argade, N.P., Copper-catalyzed intramolecular N-arylation of quinazolines: facile convergent approach to (-)-circumdatins H and J. *Org. Lett.*, **2010**, *12*, 3716-3719.
- [78] Tseng, M.-C.; Yang, H.-Y.; Chu, Y.-H., Total synthesis of asperlicin C, circumdatin F, demethylbenzomalvin A, demethoxycircumdatin H, sclerotigenin, and other fused quinazolines. *Org. Biomol. Chem.*, **2010**, *8*, 419-427.
- [79] Liu, J.-F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C.M., Microwave-Assisted Concise Total Syntheses of Quinazolinobenzodiazepine Alkaloids. *J. Org. Chem.*, **2005**, *70*, 10488-10493.
- [80] Grieder, A.; Thomas, A.W., A Concise Building Block Approach to a Diverse Multi-Arrayed Library of the Circumdatin Family of Natural Products. *Synthesis*, **2003**, 1707-1711.
- [81] Zhichkin, P.E.; Jin, X.; Zhang, H.; Peterson, L.H.; Ramirez, C.; Snyder, T.M.; Burton, H.S., A concise synthesis of enantiopure circumdatins E, H and J. *Org. Biomol. Chem.*, **2010**, *8*, 1287-1289.
- [82] Ishikawa, K.; Hosoe, T.; Itabashi, T.; Sato, F.; Wachi, H.; Nagase, H.; Yaguchi, T.; Kawai, K.-i., Quinazolinobenzodiazepine derivatives, novobenzomalvins A-C: fibronectin expression regulators from *Aspergillus novofumigatus*. *Sci. Pharm.*, **2011**, *79*, 937-950.
- [83] Örfi, L.; Kökösi, J.; György, S.; Kövesdi, I.; Mak, M.; Teplan, I.; Kéri, G., Heterocondensed quinazolines: synthesis and protein-tyrosine kinase

- inhibitory activity of 3,4-dihydro-1H,6H-[1,4]oxazino[3,4-b]quinazolin-6-one derivatives. *Bioorg. Med. Chem.*, **1996**, *4*, 547-551.
- [84] Alagarsamy, V.; Shankar, D.; Murugesan, S., Synthesis of 4-butyl-1-substituted-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones as new class of H1-antihistaminic agents. *Biomed. Pharmacother.*, **2008**, *62*, 173-178.
- [85] Alagarsamy, V.; Meena, S.; Ramaseshu, K.V.; Solomon, V.R.; Kumar, T.D.A., 4-Cyclohexyl-1-substituted-4H-[1,2,4]triazolo[4,3-a] quinazolin-5-ones: Novel Class of H1-antihistaminic Agents. *Chem. Biol. Drug Des.*, **2007**, *70*, 158-163.
- [86] Angibaud, P.; Bourdrez, X.; End, D.W.; Freyne, E.; Janicot, M.; Lezouret, P.; Ligny, Y.; Mannens, G.; Damsch, S.; Mevellec, L.; Meyer, C.; Muller, P.; Pilatte, I.; Poncet, V.; Roux, B.; Smets, G.; Van Dun, J.; Van Remoortere, P.; Venet, M.; Wouters, W., Substituted Azoloquinolines and -quinazolines as New Potent Farnesyl Protein Transferase Inhibitors. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4365-4369.
- [87] Kumar, K.S.; Kumar, P.M.; Rao, V.S.; Jafar, A.A.; Meda, C.L.; Kapavarapu, R.; Parsa, K.V.; Pal, M., A new cascade reaction: concurrent construction of six and five membered rings leading to novel fused quinazolinones. *Org. Biomol. Chem.*, **2012**, *10*, 3098-3103.
- [88] Jahng, K.C.; Kim, S.; Kim, D.H.; Seo, C.S.; Son, J.-K.; Lee, S.H.; Lee, E.S.; Jahng, Y., One-Pot Synthesis of Simple Alkaloids: 2,3-Polymethylene-4(3H)-quinazolinones, Luotonin A, Tryptanthrin, and Rutacarpine. *Chem. Pharm. Bull. (Tokyo)*, **2008**, *56*, 607-609.
- [89] Lee, C.-S.; Liu, C.-K.; Chiang, Y.-L.; Cheng, Y.-Y., One-pot reductive-cyclization as key step for the synthesis of rutacarpine alkaloids. *Tetrahedron Lett.*, **2008**, *49*, 481-484.
- [90] Domon, L.; Le Coeur, C.; Grelard, A.; Thiéry, V.; Besson, T., Efficient modified von Niementowski synthesis of novel derivatives of 5a,14b,15-triazabenz[a]indeno[1,2-c]anthracen-5-one from indolo[1,2-c]quinazoline. *Tetrahedron Lett.*, **2001**, *42*, 6671-6674.
- [91] Laddha, S.S.; Bhatnagar, S.P., Efficient Niementowski synthesis of novel 1,3,10,12-tetra-substituted-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-ones. *Arkivoc*, **2007**, (xvi), 1-11.
- [92] Girmiene, J.; Apremont, G.; Tatibouët, A.; Sackus, A.; Rollin, P., Small libraries of fused quinazolinone-sugars. Access to quinazolinone nucleosides. *Tetrahedron*, **2004**, *60*, 2609-2619.
- [93] Bowman, W.R.; Elsegood, M.R.J.; Stein, T.; Weaver, G.W., Radical reactions with 3H-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutacarpine and tryptanthrin. *Org. Biomol. Chem.*, **2007**, *5*, 103-113.
- [94] Desjardins, J.; Emerson, D.L.; Colagiovanni, D.B.; Abbot, E.; Brown, E.N.; Drolet, D.W., Pharmacokinetics, Safety, and Efficacy of a Liposome Encapsulated Thymidylate Synthase Inhibitor, OSI-7904L [(S)-2-[5-[(1,2-Dihydro-3-methyl-1-oxobenzof[quinazolin-9-yl)methyl]amino-1-oxo-2-isoindolyl]-glutaric Acid] in Mice. *J. Pharm. Exp. Ther.*, **2004**, *309*, 894-902.
- [95] Bavetsias, V.; Marriott, J.H.; Melin, C.; Kimbell, R.; Matusiak, Z.S.; Boyle, F.T.; Jackman, A.L., Design and Synthesis of Cyclopenta[g]quinazoline-Based Antifolates as Inhibitors of Thymidylate Synthase and Potential Antitumor Agents. *J. Med. Chem.*, **2000**, *43*, 1910-1926.
- [96] Jackman, A.L.; Theti, D.S.; Gibbs, D.D., Antifolates targeted specifically to the folate receptor. *Adv. Drug Deliv. Rev.*, **2004**, *56*, 1111-1125.
- [97] Pillai, R.G.; Forster, M.; Perumal, M.; Mitchell, F.; Leyton, J.; Aibgirhio, F.I.; Golovko, O.; Jackman, A.L.; Oboagye, E.O., Imaging Pharmacodynamics of the α -Folate Receptor-Targeted Thymidylate Synthase Inhibitor BGC 945. *cancer Res.*, **2008**, *68*, 3827-3834.
- [98] Theti, D.S.; Bavetsias, V.; Skelton, L.A.; Titley, J.; Gibbs, D.; Jansen, G.; Jackman, A.L., Selective Delivery of CB300638, a Cyclopenta[g]quinazoline-based Thymidylate Synthase Inhibitor into Human Tumor Cell Lines Overexpressing the α -Isoform of the Folate Receptor. *Cancer Res.*, **2003**, *63*, 3612-3618.
- [99] Henderson, E.A.; Bavetsias, V.; Theti, D.S.; Wilson, S.C.; Clauss, R.; Jackman, A.L., Targeting the α -folate receptor with cyclopenta[g]quinazoline-based inhibitors of thymidylate synthase. *Bioorg. Med. Chem.*, **2006**, *14*, 5020-5042.
- [100] Gibbs, D.D.; Theti, D.S.; Wood, N.; Green, M.; Raynaud, F.; Valenti, M.; Forster, M.D.; Mitchell, F.; Bavetsias, V.; Henderson, E.; Jackman, A.L., BGC 945, a Novel Tumor-Selective Thymidylate Synthase Inhibitor Targeted to α -Folate Receptor-Overexpressing Tumors. *Cancer Res.*, **2005**, *65*, 11721-11728.
- [101] Bavetsias, V.; Clauss, R.; Henderson, E.A., Antifolate chemistry: synthesis of 4-[N-[(6RS)-2-methyl-4-oxo-3,4,7,8-tetrahydro-6H-cyclopenta[g]quinazolin-6-yl]-N-(prop-2-ynyl)amino]benzoic acid via a (propargyl)Co₂(CO)₈ complex. *Org. Biomol. Chem.*, **2003**, *1*, 1943-1946.
- [102] Lazzaro, J.T.; Paternain, A.V.; Lerma, J.; Chenard, B.L.; Ewing, F.E.; Huang, J.; Welch, W.M.; Ganong, A.H.; Menniti, F.S., Functional characterization of CP-465,022, a selective, noncompetitive AMPA receptor antagonist. *Neuropharm.*, **2002**, *42*, 145-153.
- [103] Zappalà, M.; Grasso, S.; Micale, N.; Zuccalà, G.; Menniti, F.S.; De Sarro, G.; De Micheli, C., 1-Aryl-6,7-methylenedioxy-3H-quinazolin-4-ones as Anticonvulsant Agents. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4427-4430.
- [104] Micale, N.; Postorino, G.; Grasso, S.; Zappalà, M.; Zuccalà, G.; Ferreri, G.; De Sarro, G., Synthesis of Novel 3-(Alkylcarbamoyl)-2-aryl-1,2-dihydro-6,7-(methylenedioxy)-3H-quinazolin-4-ones as Anticonvulsant Agents. *Chem. Biodiversity*, **2006**, *3*, 304-311.
- [105] Jiang, S.; Zeng, Q.; Gettayacamin, M.; Tungtaeng, A.; Wannaying, S.; Lim, A.; Hansurkariya, P.; Okunji, C.O.; Zhu, S.; Fang, D., Antimalarial Activities and Therapeutic Properties of Febrifugine Analogs. *Antimicrob. Agents Chemother.*, **2005**, *49*, 1169-1176.
- [106] Lee, J.Y.; Park, Y.K.; Seo, S.H.; So, I.-K.; Chung, H.-K.; Yang, B.-S.; Lee, S.J.; Park, H.; Lee, Y.S., 1,4-Dioxane-fused 4-anilinoquinazoline as inhibitors of epidermal growth factor receptor kinase. *Arch. Pharm. Chem. Life Sci.*, **2001**, *334*, 357-360.
- [107] Lee, J.Y.; Park, Y.K.; Seo, S.H.; Yang, B.-S.; Park, H.; Lee, Y.S., 7-Substituted-[1,4]dioxano[2,3-g]quinazolines as Inhibitors of Epidermal Growth Factor Receptor Kinase. *Arch. Pharm. Chem. Life Sci.*, **2002**, *10*, 487-494.
- [108] Lee, Y.S.; Seo, S.H.; Yang, B.-S.; Lee, J.Y., Synthesis and Biological Evaluation of Bis(methoxymethyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolines as EGFR Tyrosine Kinase Inhibitors. *Arch. Pharm. Chem. Life Sci.*, **2005**, *338*, 502-505.
- [109] Ha, J.D.; Kang, S.K.; Kim, K.-D.; Choi, J.-K.; Kong, J.Y.; Ahn, C.H., Design and Synthesis of Novel Epidermal Growth Factor Receptor Kinase Inhibitors. *Bull. Korean Chem. Soc.*, **2005**, *26*, 959-965.
- [110] Chilin, A.; Conconi, M.T.; Marzaro, G.; Guiotto, A.; Urbani, L.; Tonus, F.; Parnigotto, P., Exploring epidermal growth factor receptor (EGFR) inhibitor features: the role of fused dioxogenated rings on the quinazoline scaffold. *J. Med. Chem.*, **2010**, *53*, 1862-1866.
- [111] Godde, F.; Toulme, J.J.; Moreau, S., 4-Amino-1H-benzo[g]quinazolin-2-one: a fluorescent analog of cytosine to probe protonation sites in triplex forming oligonucleotides. *Nucleic Acids Res.*, **2000**, *28*, 2977-2985.
- [112] Arzumanov, A.; Godde, F.; Moreau, S.; Toulme, J.J.; Weeds, A.; Gait, M.J., Use of the fluorescent nucleoside analogue benzo[g]quinazoline 2'-O-methyl- β -D-ribofuranoside to monitor the binding of the HIV-1 Tat protein or of antisense oligonucleotides to the TAR-RNA stem-loop. *Helv. Chim. Acta*, **2000**, *83*, 1424-1436.
- [113] Patel, B.B.; Patel, R.G.; Patel, J.M., Synthesis and studies of the biological activity of novel pyrimido fused acridine derivatives. *J. Serb. Chem. Soc.*, **2006**, *71*, 1015-1023.
- [114] Skibo, E.B.; Huang, X.; Martinez, R.; Lemus, R.H.; Craigo, W.A.; Dorr, R.T., Pyrimidoquinazoline-Based Antitumor Agents. Design of Topoisomerase II to DNA Cross-linkers with Activity against Protein Kinases. *J. Med. Chem.*, **2002**, *45*, 5543-5555.
- [115] Krueger, A.T.; Lu, H.; Lee, A.H.F.; Kool, E.C., Synthesis and Properties of Size-Expanded DNAs: Toward Designed, Functional Genetic Systems. *Acc. Chem. Res.*, **2007**, *40*, 141-150.
- [116] Liu, H.; Gao, J.; Kool, E.T., Size-expanded analogues of dG and dC: synthesis and pairing properties in DNA. *J. Org. Chem.*, **2005**, *70*, 639-647.
- [117] Lee, A.H.F.; Kool, E.C., Exploring the Limits of DNA Size: Naphtho-Homologated DNA Bases and Pairs. *J. Am. Chem. Soc.*, **2006**, *128*, 9219-9230.
- [118] Hörtnner, S.; Ritschel, T.; Stengl, B.; Kramer, C.; Schweizer, W.B.; Wagner, B.; Kansy, M.; Klebe, G.; Diederich, F., Potent Inhibitors of tRNA-Guanine Transglycosylase, an Enzyme Linked to the Pathogenicity of the *Shigella* Bacterium: Charge-Assisted Hydrogen Bonding. *Angew. Chem. Int. Ed.*, **2007**, *46*, 8266-8269.
- [119] Meyer, E.A.; Donati, N.; Guillot, M.; Schweizer, W.B.; Diederich, F., Synthesis, Biological Evaluation, and Crystallographic Studies of Extended Guanine-Based (lin-Benzoguanine) Inhibitors for tRNA-Guanine Transglycosylase (TGT). *Helv. Chim. Acta*, **2006**, *89*, 573-597.
- [120] Stengl, B.; Meyer, E.A.; Heine, A.; Brenk, R.; Diederich, F.; Klebe, G., Crystal Structures of tRNA-guanine Transglycosylase (TGT) in Complex with Novel and Potent Inhibitors Unravel Pronounced Induced-fit Adaptations and Suggest Dimer Formation Upon Substrate Binding. *J. Mol. Biol.*, **2007**, *370*, 492-511.
- [121] Stengl, B.; Reuter, K.; Klebe, G., Mechanism and Substrate Specificity of tRNA-Guanine Transglycosylases (TGTs): tRNA Modifying Enzymes from the Three Different Kingdoms of Life Share a Common Catalytic Mechanism. *ChemBioChem*, **2005**, *6*, 1926-1939.
- [122] Testard, A.; Logé, C.; Léger, B.; Robert, J.-M.; Lozach, O.; Blairvacq, M.; Meijer, L.; Thiéry, V.; Besson, T., Thiazolo[5,4-f]quinazolin-9-ones, inhibitors of glycogen synthase kinase-3. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 3419-3423.
- [123] Testard, A.; Picot, L.; Lozach, O.; Blairvacq, M.; Meijer, L.; Murillo, L.; Piot, J.-M.; Thiéry, V.; Besson, T., Synthesis and evaluation of the antiproliferative activity of novel thiazoloquinazolinone kinases inhibitors. *J. Enz. Inhib. Med. Chem.*, **2005**, *20*, 557-568.
- [124] Tarasiuk, J.; Majewska, E.; Seksek, O.; Rogacka, D.; Antonini, I.; Garnier-Suillerot, A.; Borowski, E., The role of structural factors in the kinetics of cellular uptake of pyrazoloacridines and pyrazolopyrimidoacridines Implications for overcoming multidrug resistance towards leukaemia K562/DOX cells. *Biochem. Pharmacol.*, **2004**, *68*, 1815-1823.
- [125] Antonini, I.; Polucci, P.; Magnano, A.; Sparapani, S.; Martelli, A., Rational design, synthesis, and biological evaluation of bis(pyrimido[5,6,1-de]acridines) and bis(pyrazolo[3,4,5-k]acridine-5-carboxamides) as new anticancer agents. *J. Med. Chem.*, **2004**, *47*, 5244-5250.
- [126] Antonini, I.; Santoni, G.; Lucciarini, R.; Amantini, C.; Sparapani, S.; Magnano, A., Synthesis and biological evaluation of new asymmetrical

- bisintercalators as potential antitumor drugs. *J. Med. Chem.*, **2006**, *49*, 7198-7207.
- [127] Kamata, J.; Okada, T.; Kotake, Y.; K., N.; Uenaka, T.; Yamaguchi, A.; Tsukahara, K.; Nagasu, T.; Koyanagi, N.; Kitoh, K.; Yoshimatsu, K.; Yoshino, H.; Sugumi, H., Synthesis and evaluation of novel pyrimido-acridone, -phenoxazine, and -carbazole as topoisomerase II inhibitors. *Chem. Pharm. Bull., (Tokyo)*, **2004**, *52*, 1071-1081.
- [128] Nakamura, K.; Uenaka, T.; Nagasu, T.; Sugumi, H.; Yamaguchi, A.; Kotake, Y.; Okada, T.; Kamata, J.; Nijima, J.; Taniguchi, T.; Koyanagi, N.; Yoshino, H.; Kitoh, K.; Yoshimatsu, K., A novel carbazole topoisomerase II poison, ER-37328: potent tumoricidal activity against human solid tumors *in vitro* and *in vivo*. *Cancer Sci.*, **2003**, *94*, 119-124.
- [129] Nakamura, K.; Taniguchi, T.; Funahashi, Y.; Yoshimatsu, K., Effects of ER-37328 on primary tumor, liver metastasis, and life span in a murine colon 38 orthotopic transplantation model. *Mol. Cancer Ther.*, **2003**, *2*, 59-64.
- [130] Chandregowda, V.; Rao, G.V.; Reddy, G.C., One-pot conversion of 2 nitrobenzonitriles to quinazolin-4(3H)-ones and synthesis of gefitinib and erlotinib hydrochloride. *Heterocycles*, **2007**, *71*, 39-48.
- [131] Guillonneau, C.; Nault, A.; Raimbaud, E.; Léonce, S.; Kraus-Berthier, L.; Pierré, A.; Goldstein, S., Cytotoxic and antitumoral properties in a series of new, ring D modified, olivacine analogues. *Bioorg. Med. Chem.*, **2005**, *13*, 175-184.
- [132] Zeghida, W.; Debray, J.; Chierici, S.; Dumy, P.; Demeunynck, M., Concise synthesis of 2-amino-4(3H)quinazolinones from simple (hetero)aromatic amine. *J. Org. Chem.*, **2008**, *73*, 2473-2475.
- [133] Debray, J.; Zeghida, W.; Baldeyrou, B.; Mahieu, C.; Lansiaux, A.; Demeunynck, M., Montmorillonite K-10 catalyzed cyclization of N-ethoxycarbonyl-N0-arylguanidines: Access to pyrimido[4,5-c]carbazole and pyrimido[5,4-b]indole derivatives. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 4244-4247.
- [134] Debray, J.; Bonte, S.; Lozach, O.; Meijer, L.; Demeunynck, M., Catalyst-free synthesis of quinazolin-4-ones from (hetero)aryl-guanidines: application to the synthesis of pyrazolo[4,3-f]quinazolin-9-ones, a new family of DYRK1A inhibitors. *Mol. Diversity*, **2012**, *16*, 659-667.
- [135] Debray, J.; Zeghida, W.; Jourdan, M.; Monchaud, D.; Dheu-Andries, M.-L.; Teulade-Fichou, M.P.; Demeunynck, M., Synthesis and evaluation of fused bispyrimidoacridines as novel pentacyclic analogues of quadruplex-binder BRACO-19. *Org. Biomol. Chem.*, **2009**, *7*, 5219-5228.
- [136] Okada, E.; Tsukushi, N., A facile and convenient synthetic method for fluorine-containing 1,2-dihydropyrido[3,2-h]quinazolines and pyrido[3,2-h]quinazolines. *Heterocycles*, **1999**, *51*, 2471-2478.
- [137] Guan, J.; Zhang, Q.; O'Neil, M.; Obaldia III, N.; Ager, A.; Gerena, L.; Lin, A.J., Antimalarial Activities of New Pyrrolo[3,2-f]Quinazoline-1,3-Diamine Derivatives. *Antimicrob. Agents Chemother.*, **2005**, *49*, 4928-4933.
- [138] Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T., Efficient synthesis of thiazoloquinazolinone derivatives. *Tetrahedron Lett.*, **2003**, *44*, 4455-4458.
- [139] Bhatti, H.S.; Seshadri, S., Chromophoric potential of the 4(3H)-quinazolinones: a review. *Color. Technol.*, **2004**, *120*, 101-107.

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