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Review

Natural and synthetic acridines/acridones as antitumor agents: their biological activities and methods of synthesis

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Abstract:
Acridine derivatives constitute a class of compounds that are being intensively studied as potential anticancer drugs. Acridines are well-known for their high cytotoxic activity; however, their clinical application is limited or even excluded because of side effects. Numerous synthetic methods are focused on the preparation of target acridine skeletons or modifications of naturally occurring compounds, such as acridone alkaloids, that exhibit promising anticancer activities. They have been examined *in vitro* and *in vivo* to test their importance for cancer treatment and to establish the mechanism of action at both the molecular and cellular level, which is necessary for the optimization of their properties so that they are suitable in chemotherapy. In this article, we review natural and synthetic acridine/acridone analogs, their application as anticancer drugs and methods for their preparation.

Key words:
acridine/acridone analogs, synthesis, biological activity, anticancer activity

Abbreviations: ABC – ATP-binding cassette protein superfamily, ABCG2 – ATP-binding cassette, sub-family G (WHITE), member 2, CAN – ceric ammonium nitrate, CDI – 1,1'-carbonyldiimidazole, DIPEA – *N,N*-diisopropylethylamine, DMF – *N,N*-dimethylformamide, DMP – Dess-Martin reagent, EDCI – 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt – 1-hydroxybenzotriazole, IC_{50} – drug concentration at which 50% inhibition is observed, MDP – *N*-acetyl-muramyl-L-alanyl-D-isoglutamine (muramyl dipeptide), MS – molecular sieves, NAD^+ – nicotinamide adenine dinucleotide, NBS – *N*-bromosuccinimide, NMO – *N*-methylmorpholine *N*-oxide, nor-MDP – *N*-acetyl-nor-muramyl-L-alanyl-D-isoglutamine (nor-muramyl dipeptide), ODNs – oligodeoxynucleotides, PBO – benzoyl peroxide, P-gp – P-glycoprotein, PTSA – *p*-toluenesulfonic acid, TBS – *t*-butyldimethylsilyl, TEBAC – triethylbenzylammonium chloride, TMS – trimethylsilyl, Topo – topoisomerase, TPAP – tetrapropyl ammoniumperruthenate

Introduction

Numerous research groups have focused on the synthesis of new compounds that possess cytotoxic activity, among which acridine/acridone compounds play an important role. Acridine/acridone analogs are known anticancer drugs and cytotoxic agents, and they represent a very interesting class, displaying other forms of bioactivity [7, 20, 39–41, 56, 58, 62, 82]. They are used as biological fluorescent probes, anti-bacterial drugs, e.g., **1**–**6** [41], anti-protozoal drugs, e.g., **7**–**12** [20, 39–41, 82], anti-malarial agents, e.g., **13** [6], and anti-HIV drugs, e.g., **14** [40, 53] (Fig. 1).

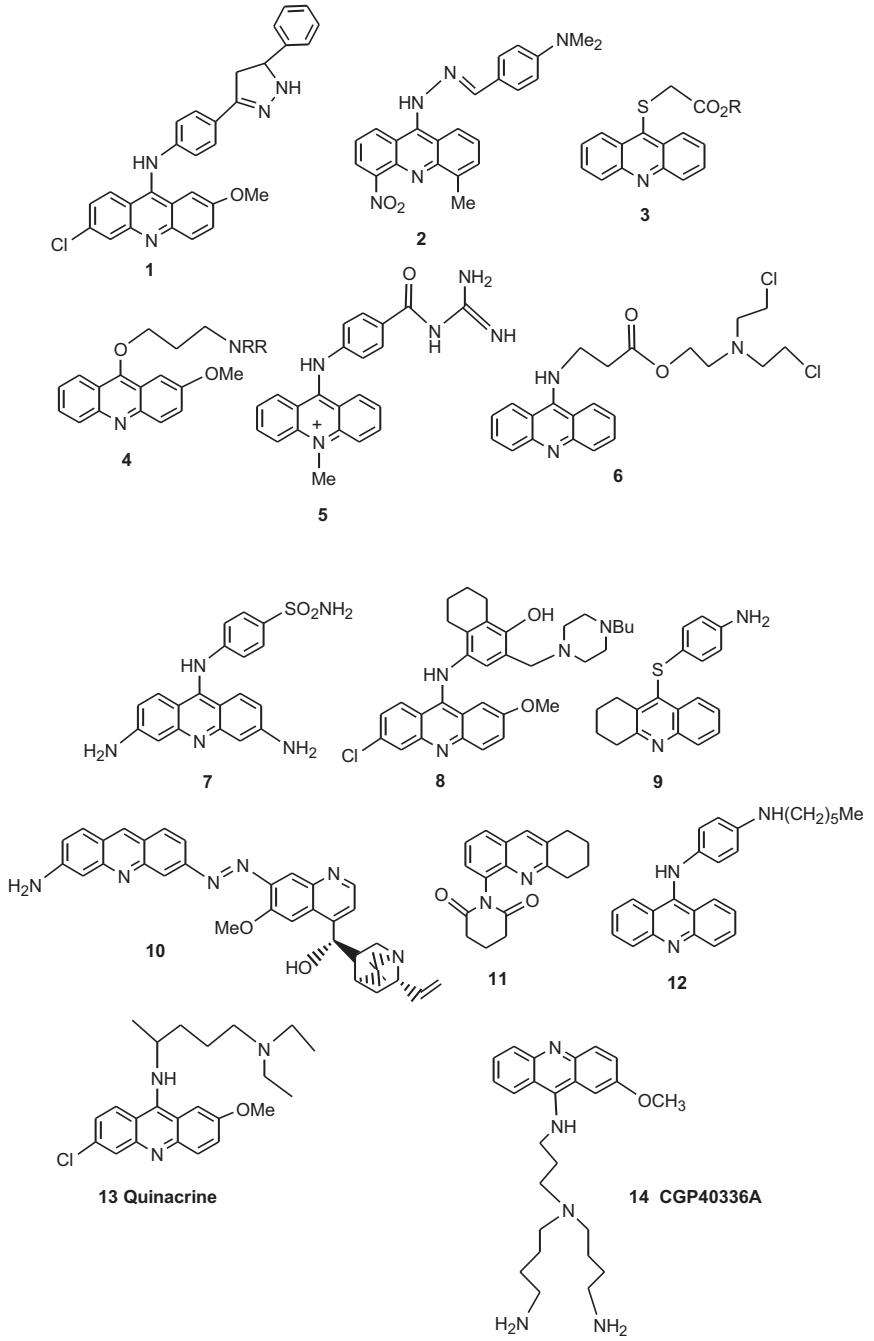


Fig. 1. Some acridine derivatives **1**–**14**

Many acridine/acridone compounds that have anticancer activity have been synthesized, including the following: asulacrine **15**; analogs with a 1'-carbamate **16**; acridine-carboxamides, e.g., *N*-(2-(dimethylamino) ethyl)acridine-4-carboxamide (DACA) **17**; nitroacridines, e.g., **18**; nitropyrazolo-acridine **19**; bis(acridines), e.g., **20**; and amsacrine **21** (Fig. 2) [41].

Examples of natural acridine/acridone analogs are acridone alkaloids isolated from plants and pyridoacridine alkaloids extracted from various marine organisms [40]. Synthetic or natural acridine/acridone drugs showed the ability to intercalate DNA and inhibit topoisomerase or telomerase enzymes [20, 40, 51]. Numerous reviews on the usefulness of acridine/acridone analogs in therapy have already been published [7, 20, 21, 32, 39–41, 56, 58, 62, 82]. In this survey, we describe interesting acridine/acridone analogs described since 2000, methods of their synthesis and their potential clinical applications.

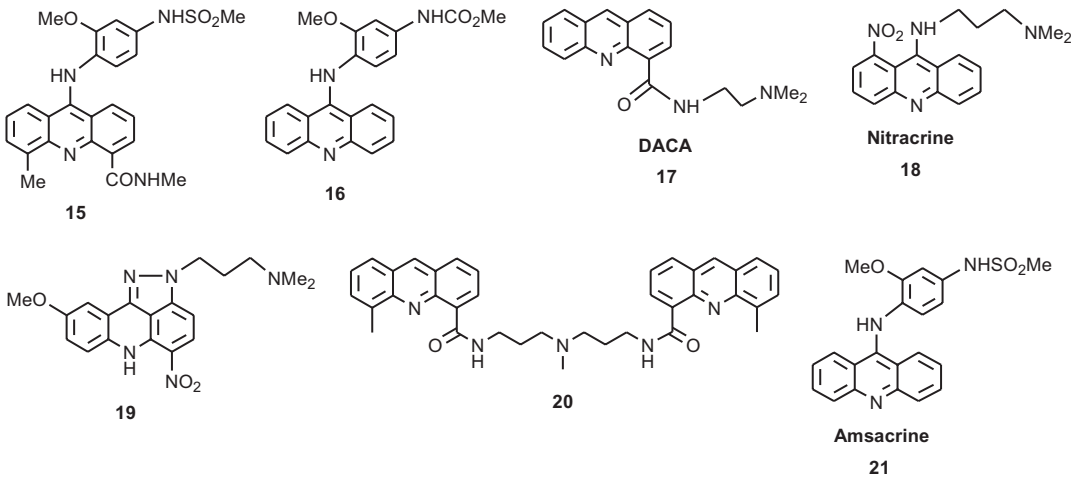


Fig. 2. Acridines **15**–**21** displaying anticancer activity

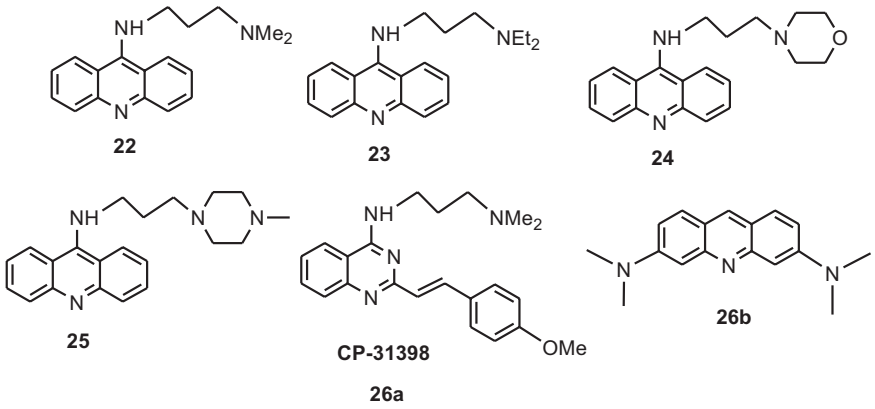


Fig. 3. DNA-targeting acridines **22**–**26b**

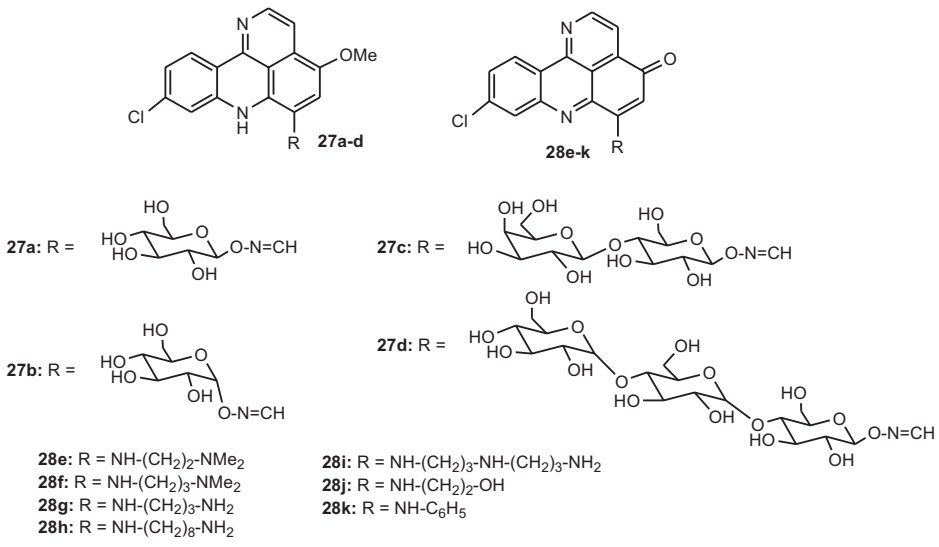


Fig. 4. Pyrido[4,3,2-*kl*]acridines **27a**–**d** and pyrido[4,3,2-*kl*]acridin-4-ones **28e**–**k** developed by Bouffier et al. [24]

Acridine/acridone as DNA-targeting agents

The utility of acridines as chemotherapeutics is due to their chemical and biological stability and their capability of effective binding to DNA or RNA [21], resulting in the disorder of the biological functions in living cells. The mechanism of their intercalation into DNA is based on π-stacking interaction with base pairs of double-stranded nucleic acids. The heterocyclic, polyaromatic flat structure of acridine fits effectively into the gap between two chains of polynucleotides, and the intercalation of the acridine moiety disturbs their crucial role in cell division. The ability of acridines to intercalate into DNA is necessary for their antitumor activity. The strength and kinetics of binding acridine to DNA have a crucial impact on the activity of this type of anticancer agent. Examination of a large number of such derivatives proved that there is a good correlation between their strength together with the time of binding to DNA and their biological activity. Acridine derivatives perturb the function of cancer cells by decreasing the activity of some enzymes that are crucial for proper DNA actions, such as topoisomerases, telomerases and cyclin-dependent kinases [20, 21, 39–41, 68].

In addition to a few natural acridine/acridone analogs, thousands of acridine/acridone compounds have been synthesized. Some of them have been used as anticancer chemotherapeutics (e.g., nitracrine **18** or amsacrine **21**) (Fig. 2). Nitracrine **18** (also known as ledakrin), developed by Ledóchowski's group, was clinically used for several years [99]. Amsacrine **21** (*m*-AMSA) [15, 41] was the first synthetic drug of the DNA-intercalating type to show clinical efficiency. Acridine derivatives having nitro, methoxy, methyl, amino acids, aminoalkylamino or hydroxyalkylamino substituents have been tested as potential anticancer agents [28, 100]. Among them, strong antitumor activity and lower toxicity was shown for 1-nitro-9-alkylamino-alkylamino-acridines [51, 64, 78] and 1-nitro-9-hydroxyalkylamino-acridines, which were patented by Wysocka-Skrzela et al. in 1981 [100]. Their properties were confirmed by many tests *in vitro* and *in vivo*.

Wang et al. [94] synthesized four acridine derivatives **22**–**26** with a similar structure to CP-31398 **26a** (Fig. 3).

CP-31398 is a small molecule that has been reported to stabilize the DNA-binding core domain of the human tumor suppressor protein p53 *in vitro*. The compound activates wild-type p53 by a still unknown mechanism, but it does not involve the phosphorylation of the amino-terminus of p53 and disassociation of MDM2. These four compounds **22**–**26** induced strong p53 transcription in cells with wild-type p53. Wang et al. [96] also found that several randomly chosen strong anticancer acridine derivatives, including 9-aminoacridine, quinacrine **13** (Fig. 1), amsacrine **21** (Fig. 2) and acridine orange **26b** (Fig. 3) induced p53 transcriptional activity. All of these acridine derivatives stabilized the p53 protein by blocking its ubiquitination without the phosphorylation of ser15 or ser20 on p53. In addition, *in vivo* delivery of quinacrine and amsacrine induced p53 transcriptional activity in tumor xenografts. These findings provide insights into p53 regulation in response to DNA-intercalating drugs and may assist new anticancer drug design [96].

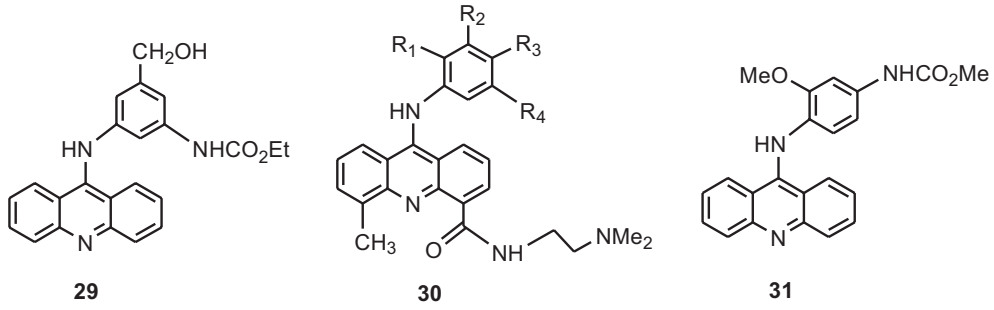
Bouffier et al. [24] presented the synthesis, antitumor activity, and DNA-binding kinetics of amino- and glycoconjugates of pyrido[4,3,2-*kl*]acridine **27a**–**d** and pyrido[4,3,2-*kl*]acridin-4-one **28e**–**k** (Fig. 4).

The amino conjugates **28e** and **28i** had the highest cytostatic activities against HT-29 cancer cells at micromolar concentrations. These molecules bind DNA by intercalation, and none of them inhibit topoisomerase activity.

Topoisomerase inhibition

DNA topoisomerases are a class of enzymes involved in the regulation of DNA supercoiling. Type I topoisomerases change the degree of supercoiling of DNA by causing single-strand breaks and religation, whereas type II topoisomerases cause double-strand breaks. The different roles of DNA topo I and II may indicate opposing roles in the regulation of DNA supercoiling. Both activities are necessary during DNA transcription, replication and chromatin condensation.

Two series of acridine derivatives, anilinoacridines and acridin-4-carboxamides, interfere to some extent with topoisomerase activities. Amsacrine (*m*-AMSA) **21** (Fig. 2), obtained by Denny's group [20, 39, 41], was the first synthetic drug that was shown to act as a topoisomerase inhibitor and that was approved for clinical usage. It has been used since 1976 in leukemia treatment. An interaction of amsacrine with topo II-DNA has been already shown. This interaction is due to its side chain, which influences inhibiting



AMT $R_1 = H; R_2 = CH_3; R_3 = H; R_4 = NH_2$
APT $R_1 = CH_3; R_2 = H; R_3 = H; R_4 = NH_2$
AOT $R_1 = H; R_2 = H; R_3 = CH_3; R_4 = NH_2$
AOA $R_1 = H; R_2 = H; R_3 = OCH_3; R_4 = NH_2$
AMA $R_1 = H; R_2 = OCH_3; R_3 = H; R_4 = NH_2$
APA $R_1 = OCH_3; R_2 = H; R_3 = H; R_4 = NH_2$

Fig. 5. Acridines **29**–**31** acting as topoisomerase inhibitors

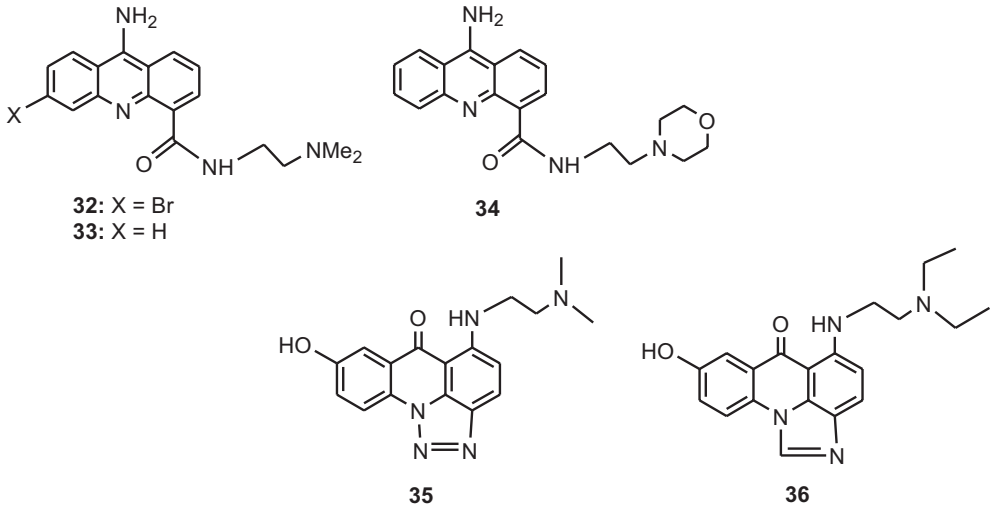
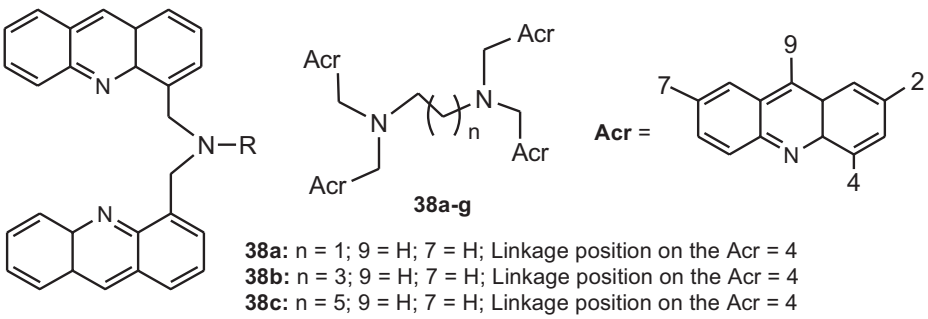


Fig. 6. Topoisomerase inhibitors **32**–**36**



37a: R = CN
37b: R = C_3H_7

38a: n = 1; 9 = H; 7 = H; Linkage position on the Acr = 4
38b: n = 3; 9 = H; 7 = H; Linkage position on the Acr = 4
38c: n = 5; 9 = H; 7 = H; Linkage position on the Acr = 4
38d: n = 7; 9 = H; 7 = H; Linkage position on the Acr = 4
38e: n = 1; 9 = NH_2; 7 = H; Linkage position on the Acr = 4
38f: n = 3; 9 = Cl; 7 = Br; Linkage position on the Acr = 4
38g: n = 7; 9 = H; 7 = H; Linkage position on the Acr = 2

Fig. 7. Bis- **37** and tetra-acridines **38** described by Vispè's group [93]

properties. Free radical production can be involved in amsacrine metabolism. Thus, DNA damage is possible in tumors and healthy cells. Reactive quininodiimine, produced as a result of the biooxidation of *m*-AMSA, reacts with nucleophiles present in cells. Some *m*-AMSA derivatives with stronger antitumor activity and weaker side effects were also obtained. Su and co-workers [86] developed compounds with substitutions in the *meta* position of the aniline residue, in relation to the 9-amino group. The leading compound in this series (5'-hydroxymethylaniline derivative (AHMA) **29** (Fig. 5)) exhibits higher efficiency in leukemia and solid tumor treatment in rodents, compared with *m*-AMSA.

The half-life of AHMA **29** in human blood plasma is also longer. The *meta* position occupied by the amino group prevents the transformation to the quininodiimine intermediate. AHMA is a topo II inhibitor. In 2003, Su's group [30] described the synthesis of some AHMA analogs **30** that have higher cytotoxicity than AHMA *in vitro*. Moreover, in *in vivo* studies on mice bearing human breast cancer cells MX-1, these analogs demonstrated activity and toxicity similar to AHMA. In these AHMA derivatives, AOA, AMA and APA, the methyl group in the *orto*, *meta* and *para* positions was substituted by a methoxy group, respectively. Among them, AOA exhibited the highest cytotoxicity. AMCA **31** is an amsacrine derivative that possesses a carbaminate group instead of a sulfamidate group. This compound displays high toxicity toward non-proliferative cells and has the ability to cross the membrane barrier in resistant cell lines [41].

4-Carboxyamido-acridines are another type of topoisomerase inhibitor based on acridine derivatives. DACA **17** (Fig. 2), prepared in 1987, is one of the exceptional compounds that inhibit two enzymes: topo I and II [20, 39–42]. This unusual property of DACA and its derivatives **32**–**34** (Fig. 6) was studied using x-ray evaluation of complexes formed with DNA sequences.

It was concluded that the acridine molecule intercalates within the base pair $d(CG)_2$, NMe_2H^+ group of 4-carboxyamide and participates in the hydrogen bond with the N7 atom of guanine in the major groove (similarly to the NH^+ morpholine group). Lack of activity in the case of morpholin-9-amino-DACA is probably due to the presence of the morpholine moiety. The shape of the morpholine molecule seems to disturb the formation of the stable resolving complex [1, 91].

Triazoleacridone (C-1305) **35** (Fig. 6), which was synthesized at Gdansk University of Technology, is a topo II inhibitor. Although its mechanism of action is still being investigated, it has been shown that C-1305 demonstrates strong inhibiting properties *in vitro* toward topo II, like amsacrine **21**. It was established that triazoleacridone causes structural changes in DNA sequences containing guanine triplets. These specific structural perturbations caused by C-1305 rationally explain its cytotoxicity and anticancer effect [59, 98]. Imidazoacridone (C-1311) **36** was synthesized in 1990 in the same laboratory. It is currently in the clinical phase of testing. Similarly to triazoleacridone, it inhibits the cell cycle in the G_2 phase in cancer cells. The molecular mechanism indicates its intercalation with DNA base pairs and the formula of a topo II-stabilizing complex. The presence of the 8-OH group in imidazoacridone explains the antitumor activity of compounds of this type. It is considerably more sensitive toward oxidative processes than compounds bearing the 8-OMe group, which also shows lower biological activity. Thus, it can be concluded that the activation of the heterocyclic ring is essential for the high anticancer activity of imidazoacridone [34, 65].

Vispè's group [93] proposed the mechanism of action of a novel series of bis-**37** and tetra-acridines **38** (Fig. 7). These derivatives of acridine can interact with DNA and, in most cases, inhibit topo II-mediated decatenation of DNA. They are cytotoxic to HL-60 human leukemia cells and maintain an equally potent cytotoxicity when the topo II activity of these cells is down-regulated. HL-60/MX2, which is resistant to the topo II poison mitoxantrone and cross-resistant to amsacrine, is not resistant to the acridine derivatives tested, suggesting that topo II is not the unique or primary target of these compounds. Searching for alternative targets, the authors identified the proteasome as a potential receptor for these compounds. In addition, these molecules are selective for the proteasome without any significant inhibition of four other proteases, calpain, trypsin, cathepsin B and chymotrypsin. The study provides the next opportunity to design molecules that are capable of interfering with two oncogenic targets at the same time, namely topo II and the proteasome. If the anticancer mechanism can be confirmed *in vivo* (e.g., compound **38b** which is currently tested in xenograft models), then the dual topo II/proteasome targeting could be a promising new anticancer strategy [93].

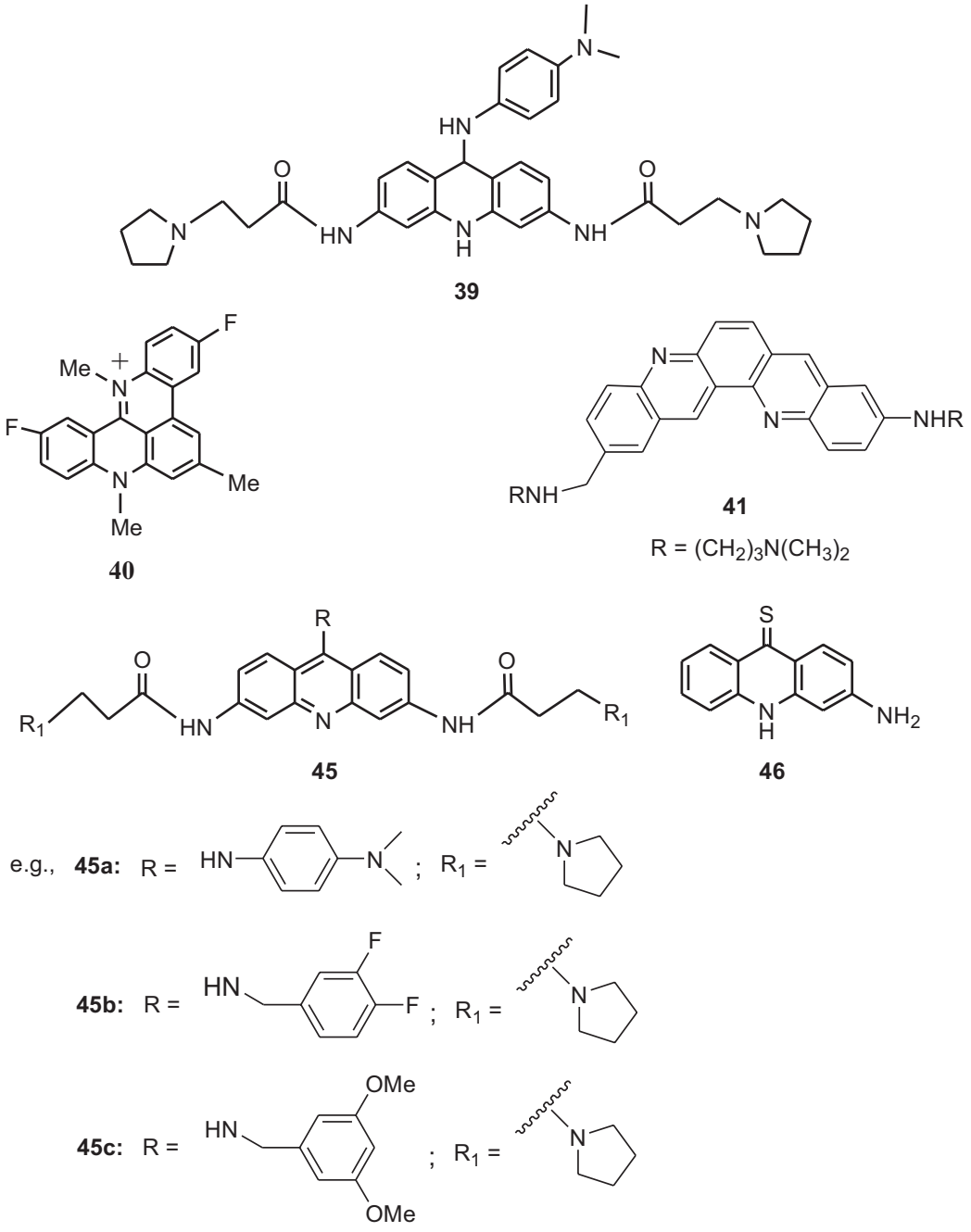
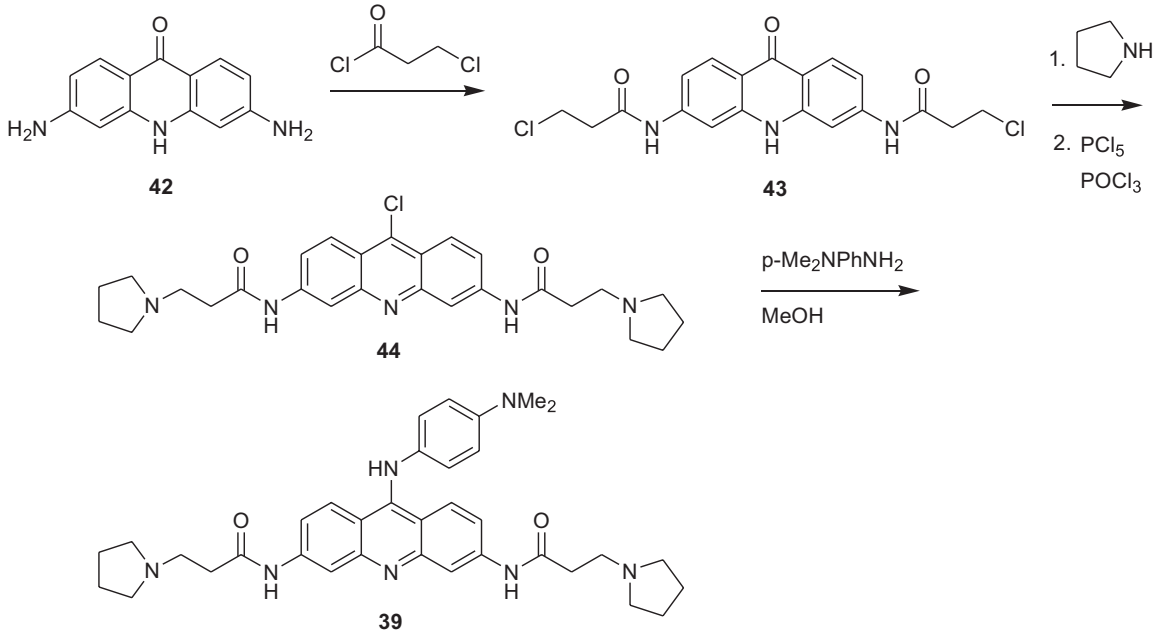


Fig. 8. Telomerase inhibitors

Telomerase inhibition and protein kinase inhibitors

Several small molecule structures have been described to inhibit telomere maintenance *via* the stabilization of the quadruplex G4 structure, thus inhibiting telomerase action. A number of studies have demonstrated that the inhibition of telomerase in cancer cells leads to senescence and apoptosis [20]. Among these studies, there are some acridine-based structures, which can be divided into three sub-familes: trisubstituted acridines, e.g., BRACO-19 **39**, pyridoacridines, e.g., **40**, and dibenzophenanthrolines, e.g., **41** (Fig. 8) [20].

Neidle's group synthesized a series of 3,6,9-trisubstituted acridines as potential telomerase inhibitors [28,



Scheme 1. Synthesis of BRACO-19 **39** [69]

52, 54, 63, 69, 79], one of which, BRACO-19 **39** (Scheme 1), has been studied in detail as a potent G-quadruplex binding molecule and telomerase inhibitor.

Results of the studies led to the conclusion that these molecules, acting as telomere-targeting agents, selectively uncapped telomerase at the telomere ends, resulting in the induction of rapid DNA damage and consequently cell death.

Diaminoacridone **42**, the starting material in the synthesis of BRACO-19, was acylated with 3-chloropropionyl chloride. Then, 3,6-bis(3-chloropropyl-amido) acridone **43**, after reaction with pyrrolidine, was treated with phosphorous pentachloride and phosphoryl chloride. Finally, 3,6-bis[3-(pyrrolidin-1-yl)propylamido]-9-chloroacridine **44**, heated in methanolic solution with *p-N,N*-dimethylaminoaniline, gave the expected product [69].

Gunaratnam et al. [52] suggested that the cellular activity of BRACO-19 can be ascribed to the uncapping of 3' telomere ends and telomere shortening, which may preferentially affect cells with short telomeres. In 2007, Neidle's group [63] presented the synthesis, biophysical and biochemical evaluation of a new series of benzylamino-substituted acridines as G-quadruplex-binding telomerase inhibitors **45** (Fig. 8). Replacement of an aniline substituent by a benzylamino group resulted in enhanced quadruplex interaction. The favorable ΔT_m and $^{tel}EC_{50}$ values for compound **45b** compared to BRACO-19, together with its lipophilicity and improved pharmacokinetic behavior, led to the selection of **45b** as a potential molecule for clinical treatment.

Another type of acridine derivatives, thioacridones, are effective kinase inhibitors. One compound of this type, 3-ATA **46** (Fig. 8), is a selective CDK4 inhibitor. It attenuates kainic acid-induced apoptosis in neurons and is able to prevent neuronal cell death induced by doxorubicine [20, 39].

The structures of MDR-overcoming acridine/acridone compounds

Antonini [7] synthesized two very interesting classes of acridine derivatives: tricyclic and polycyclic compounds. Structural modifications of pyrimido[5,6,1-de]acridines **47** included the preparation of pyrimido[4,5,6-kl]acridines **48**, bis(amine-functionalized) acridone-4-carboxamides **49**, bis(amine-functionalized)acridine-4-carboxamides **50** and pyrazolo[3,4,5-kl] acridine-5-carboxamides **51** (Fig. 9).

These compounds are composed of fused five- or six-membered heterocyclic rings, making them able to overcome multidrug resistance (MDR) [23]. Antonini et al. [10, 11] described a series of bis acridine

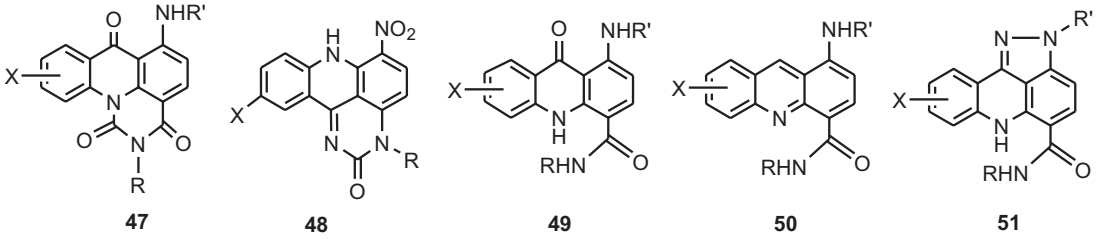
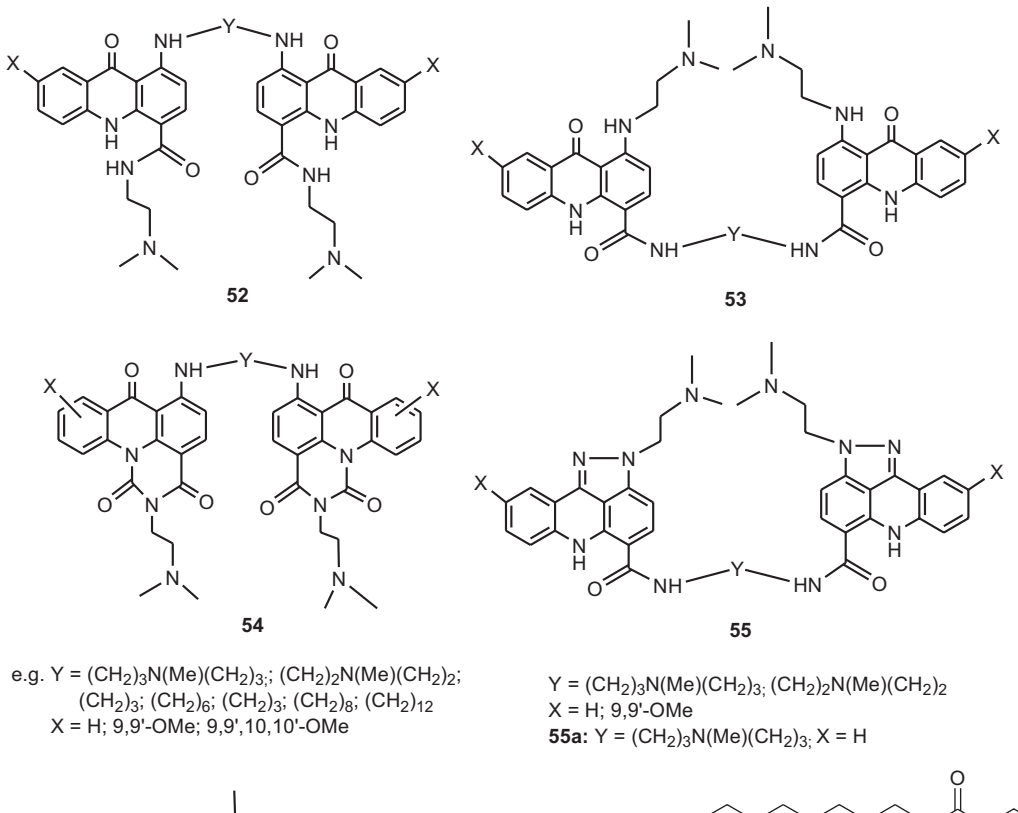


Fig. 9. Acridine/acridone derivatives developed by Antonini [7]



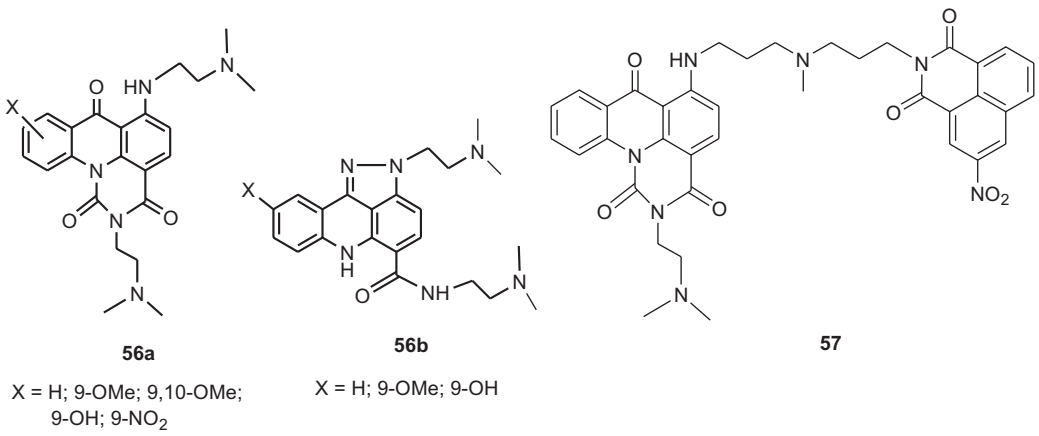


Fig. 10. Compounds described by Antonini et al. [7, 9, 10]

derivatives: bis(acridine-4-carboxamides) **52**, **53** [7] bis(pyrimido-acridines) **54** and bis(pyrazolo-acridine-carboxamides) **55** (Fig. 10).

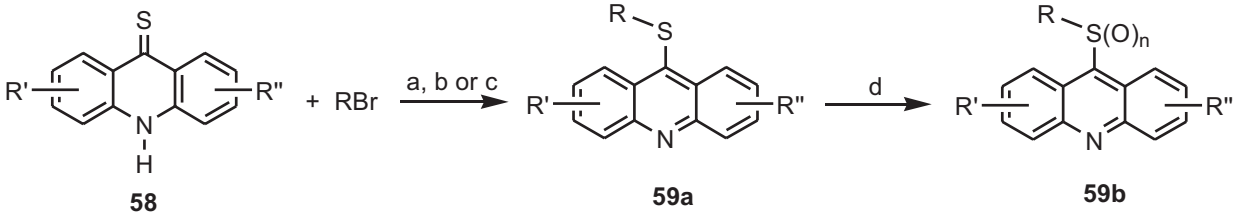
Results of a biological study indicate that the target compounds are excellent DNA ligands; the bis derivatives **54** and **55** are more DNA-affinic than corresponding monomers **56a** and **56b**, they are also less efficient in binding the related bis(acridine-4-carboxamides) **52** and **53**. Compound **55a** was selected for evaluation in a National Cancer Institute (NCI) *in vivo* hollow fiber assay [9]. In 2006, Antonini et al. [11] published a synthesis of asymmetrical bis derivatives endowed with noticeable DNA-binding properties and antiproliferative activity. In particular, compound **57** (Fig. 10), showing high DNA affinity, very potent cytostatic and cytocide action, and capacity of early apoptosis induction, may be a good candidate for *in vivo* preclinical studies.

Santelli-Rouvier et al. [81] described the syntheses of several acridine thioethers **58,** which after oxidation were converted into corresponding sulfoxides **59a** and sulfones **59b** (Scheme 2).

These compounds were tested *in vitro* against the human cancer cell line panel of NCI screening. The authors claimed that activity of these analogs was increased 5–10 fold when sulfides were converted into sulfoxides. Among derivatives substituted in the side chain, those possessing a sulfur mustard residue, epoxy sulfide and sulfoxide group displayed the highest activity.

A series of mono- and dinuclear isoquinolino[4,5-*bc*]acridine derivatives **60**–**65** (Fig. 11) was synthesized by Yang et al. [102, 103]. The DNA-binding affinity and cytotoxic activity of these compounds were evaluated. The authors showed that compound **65** exhibited the highest *in vitro* antitumoral activity against human lung cancer cells (A549), while **63** was the most active against murine leukemia cells (P388). DNA-binding studies and molecular modeling of the **64**/**65** DNA complexes indicated that **65**, having optimal linker length, exhibits higher DNA affinity than **64**.

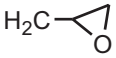
Stefańska et al. [84] synthesized a very promising group of 2,7-dihydro-3*H*-pyridazino[5,4,3-*kl*]acridin-3-one derivatives **66a-f** (Fig. 11). They were prepared in the reaction of 9-oxo-9,10-dihydroacridine-1-carboxylate with $POCl_3$, followed by the addition of the appropriate (alkylamino)alkylhydrazines. The cytotoxic activities of the examined compounds toward sensitive and resistant leukemia cell lines (L1210, K562, K562/DX, HL-60, HL-60/VINC, and HL-60/DX) with various types of MDR and MRP, was weaker than those of compounds that were previously described by the authors, due to a lower affinity for DNA [83, 85].



58 **59a** **59b**

e.g., R' = R" = H R = C_2H_4Cl n = 1
R' = R" = 2,7-$(OCH_3)_2$

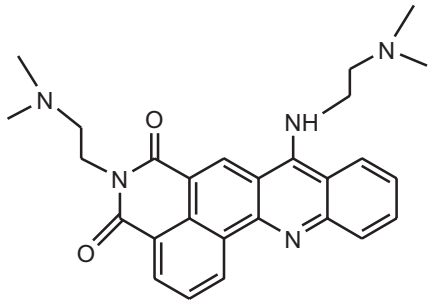
R' = R" = H R = C_4H_6Cl

R' = R" = H
R' = R" = 2,7-$(OCH_3)_2$ R = H_2C 

R' = R" = H
R' = R" = 2,7-$(OCH_3)_2$ R = $CH_2C_6H_4NO_2$ n = 1
n = 2

a. alkyl halide, TEBAC, toluene, 110°C; b. alkyl halide, DMF, K_2CO_3; c. alkyl halide, toluene, NaOH;
d. H_2O_2, $(NH_4)_6Mo_7O_{24}x\ 4H_2O$, THF, buffer pH = 6.8

Scheme 2. Synthesis of thioethers, sulfoxides and sulfones [81]



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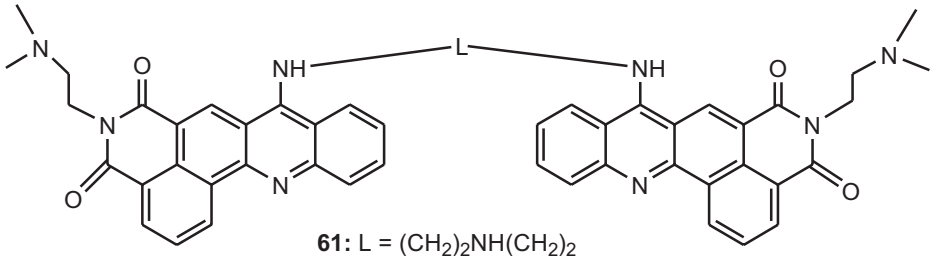
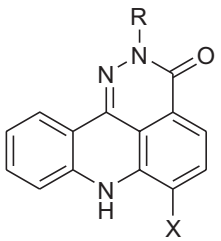
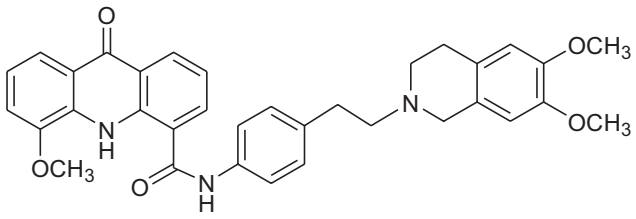


61: L = $(CH_2)_2NH(CH_2)_2$
62: L = $(CH_2)_3NH(CH_2)_3$
63: L = $(CH_2)_3NCH_3(CH_2)_3$
64: L = $(CH_2)_2NH(CH_2)_2NH(CH_2)_2$
65: L = $(CH_2)_2NH(CH_2)_3NH(CH_2)_2$



66



67 GF-1209189 (GG-918)

66a: R = $CH_2CH_2N(CH_3)_2$; X = H
66b: R = $CH_2CH_2CH_2N(CH_3)_2$; X = H
66c: R = $CH_2CH_2N(CH_2CH_2)_2$; X = H
66d: R = CH_2CH_2-c-$N(CH_2)_4O$; X = H
66e: R = CH_2CH_2-c-$N(CH_2)_5$; X = H
66f: R = $CH_2CH_2CH_2N(CH_3)_2$; X = H

Fig. 11. Derivatives synthesized by Stefańska et al. [84]

The syntheses of new 9-substituted acridine derivatives [2] and 5-(9-acridinyl-amino)anisidine derivatives [17] were also described. These compounds displayed the ability to inhibit various human tumor cells, showed inhibitory effects against topo II, and inhibited DNA interactions.

The 9-acridone derivative GF-120918 (elacridar) **67** (Fig. 11) is a potent inhibitor of multidrug resistance [80]. It has been shown that elacridar **67** acts on P-gp, and it is active in a cell sub-line expressing a newly identified mitoxantrone transporter (MXR). This compound is under clinical investigation (against malignant neoplastic disease and solid tumors) as an MDR-modulator [80].

Su's group [87] prepared a series of 9-anilinoacridine and derivatives bearing an alkylating *N*-mustard residue at C4 of the acridine chromophore **68**–**75** (Fig. 12).

These compounds were very potent *in vitro* cytotoxic agents against human leukemia and various

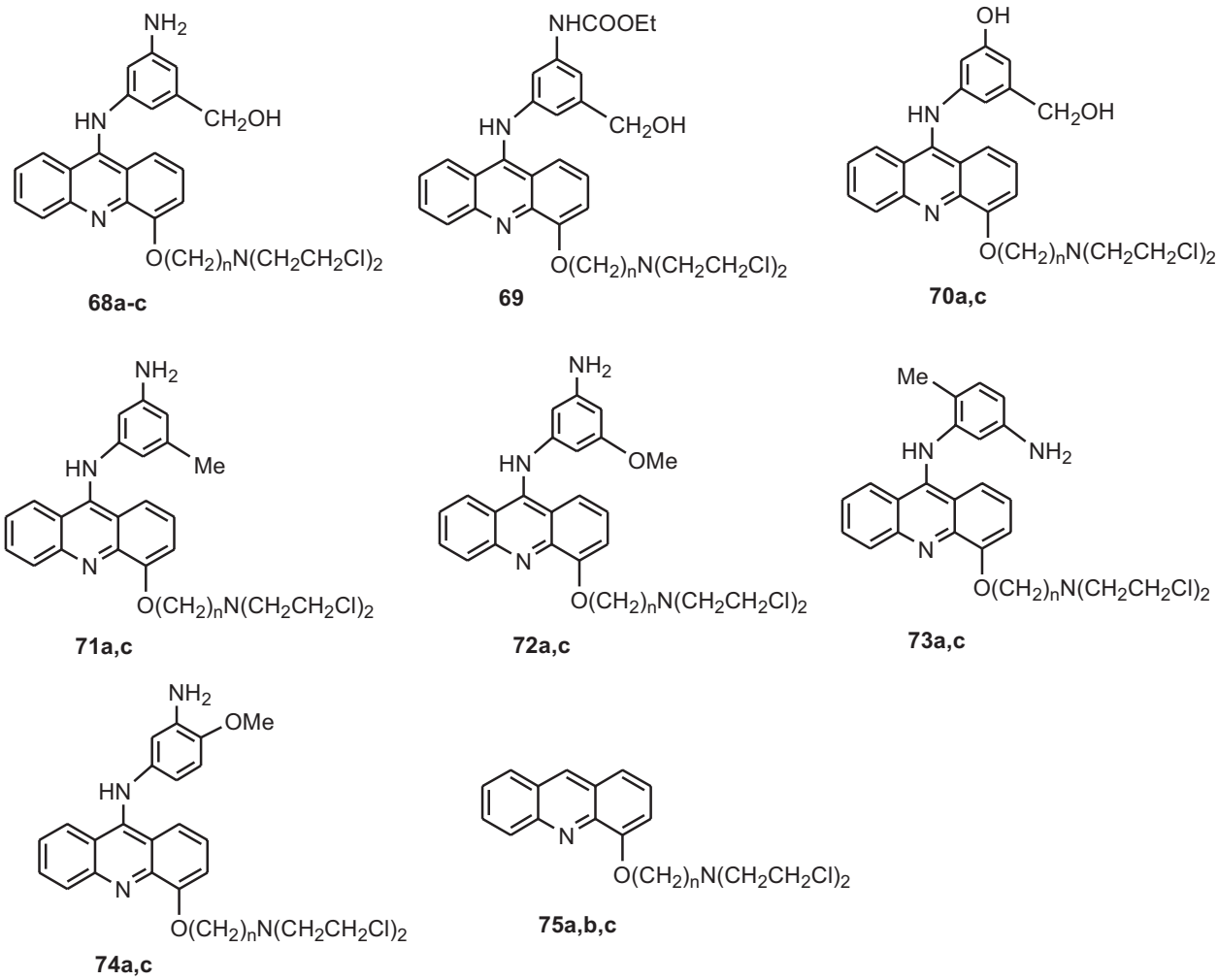


Fig. 12. Acridines prepared by Su's group [87]

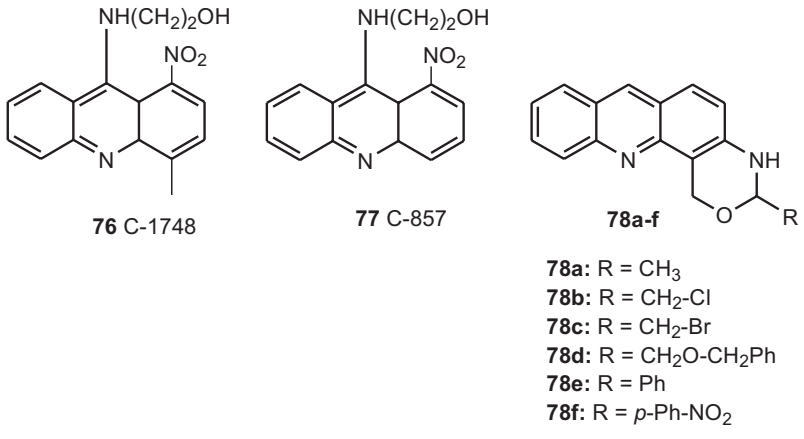


Fig. 13. Acridine derivatives described by Ashok et al. [13]

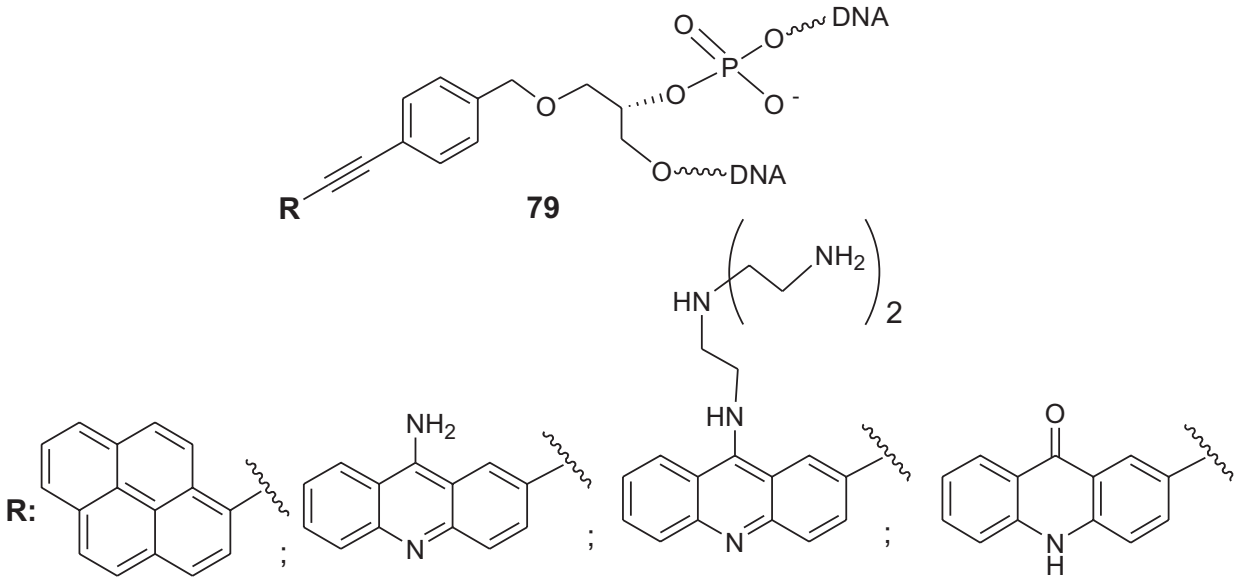


Fig. 14. Twisted intercalating nucleic acids (TINA) that have acridine moieties investigated by Geci et al. [50]

solid tumors. Compounds **72a** and **72c** were shown to have high antitumor activity in nude mice bearing the human breast carcinoma MX-1 xenograft. The therapeutic efficacy of these two agents is comparable to that of taxol.

Ashok et al. [13] presented the pre-clinical toxicology of 9-(2'-hydroxyethylamino)-4-methyl-1-nitroacridine (C-1748) **76** (Fig. 13), a novel anticancer agent in male beagle dogs. In separate studies, they observed that C-1748 **76** had lower mutagenic activity compared to 9-(2'-hydroxyethylamino)-1-nitroacridine (C-857) **77**. C-1748 **76** is a potential drug, as it shows low toxicity; only thrombocytopenia and leukopenia were observed at high doses. Based on the toxicity profile in dogs, it is feasible to test C-1748 in prostate cancer (CaP) patients, and it may be possible to predict that the drug will be well-tolerated [13].

Ouberai et al. [76] synthesized a series of 3,4-dihydro-1*H*-[1,3]oxazino[4,5-*c*]acridines **78a**–**f** (Fig. 13) whose cytotoxic activity has been evaluated against the HT29 colon carcinoma cell line. They found that the biological effect was dependent on the nature of the substituent present on position 2 of the oxazine ring. The authors showed that the presence of an electron-attracting substituent stabilizes the ring, and that effect is associated with a decrease in cytotoxicity. The activation of the nitro derivative **78f** by nitroreductase indicates its potency as a pro-drug for either gene-directed or antibody-directed enzyme therapies.

Geci et al. [50] described twisted intercalating nucleic acids (TINA) with acridine derivatives using postsynthetic modifications of oligonucleotides containing (*R*)-1-*O*-(4-iodobenzyl)glycerol or (*R*)-1-*O*-(4-ethynylbenzyl)glycerol at the 5' end or in the middle of the molecule as a bulge **79** (Fig. 14). Thermal denaturation studies and fluorescence properties of TINA-acridine oligonucleotide duplexes and triplexes were discussed.

The synthesis of 9-(alkylsulfanyl)- and 9-(arylsulfanyl)acridine derivatives and the study of their physicochemical properties were described by Nemcova et al. in 2006 [73]. The authors also presented the effect of the presence of (2-hydroxypropyl)cyclodextrins on the properties of such substituted acridines.

ABCG2 inhibitors

Recent developments led to the synthesis of 7-(*p*-bromophenyl)-10,10-dimethyl-8-alkylthio-7,9,10,11-tetrahydrobenz[*c*]acridines and 7-[(*o*-; and *p*-substituted) phenyl]-10,10-dimethyl-7,8,9,10,11,12-hexahydrobenz-[*c*]acridin-8-thiones [35], which are new acridine inhibitors, e.g., ABCG2. One of the acridone derivatives was even more potent than the reference inhibitor GF120918 **67** (Fig. 11), as shown by its strong ability to inhibit mitoxantrone efflux [26].

Amato et al. [5] described an easy and convenient method for the synthesis of ODNs containing a 3'-3'

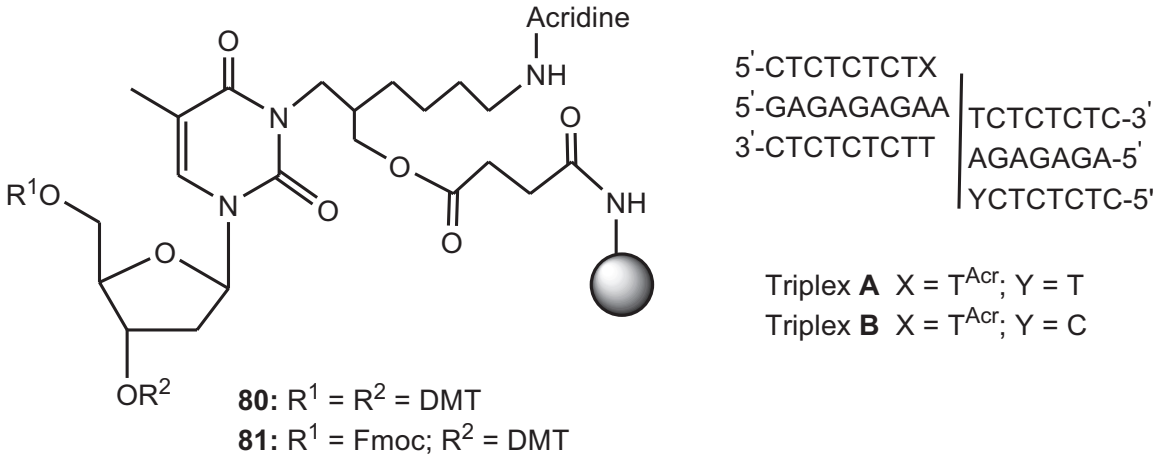


Fig. 15. Acridine derivatives synthesized by Amato et al. [5]

phosphodiester linkage and bearing an acridine residue on the thymidine base flanking 3'-3' junction. This synthesis was based on the preparation of a new kind of nucleoside-acridine solid support **80** or **81** (Fig. 15). They showed that the CD and UV melting data indicate that the acridine moiety, linked through a seven-atom spacer arm to the *N*-3 of a thymidine, does not hamper the formation of a triplex structure. Furthermore, the stabilization effect observed for triplexes **A** and **B** (Fig. 15) strongly suggests an intercalation of the acridine residue into the triplex structure.

Acridine/acridone alkaloids. Their synthesis and structural modifications

Promising anticancer drugs are based on acridine alkaloids and their derivatives. According to the cytotoxicity, some acridine alkaloids were tested with various cancer lines. They showed promising activity, and some efforts were taken to modify the natural molecules to meet requirements needed for clinical evaluation [66, 67].

Acronycine

Acronycine **82** (Fig. 16) is a natural alkaloid, isolated in 1948 from the bark of the Australian Rutaceous tree. The molecule, which shows interesting cytotoxic properties, includes a dimethyl-2*H*-pyran ring fused onto an acridone skeleton [20].

In 1966, Eli-Lilly Laboratories demonstrated its high activity against murine solid tumor models, such as S-180 and AKR sarcomas, X-5563 myeloma, S-115 carcinoma and S-91 melanoma. In contrast, its activity toward leukemias was slight [20]. In 1983, Scarff performed phase I-II clinical evaluations of acronycine for human patients with refractory multiple myeloma [20]. Orally administrated acronycine capsules resulted in disease remission for 72 weeks. The limited success of this experiment was probably due to the moderate potency of acronycine and its poor solubility in water (2–3 mg/l water) [20]. However, these results indicated significant antitumor properties of the agent and encouraged subsequent studies concerning the mechanism of and the design and synthesis of more efficient acronycine derivatives.

Results concerning the mechanism of action at the cellular and molecular levels are not unanimous. It was reported that the drug did not interact with DNA but acted primarily by the alteration of subcellular organelle membranes [20]. Alternatively, further experiments suggested an interaction of acronycine with DNA by non-covalent binding to the double helix. The investigations related to structure-activity relationships revealed that the 1,2-double bond in the pyran ring was essential for its antitumor activity. For example, 1,2-dihydroacronycine was not active in the experiments performed by Eli-Lilly Laboratories [20]. Isolation of the unstable acronycine epoxide **83** (Fig. 16) from several *New Caledonian Sarcomelicope* species suggests that oxirane **83** is an intermediate in the course of the bioactivation of acronycine *in vivo* [20]. The epoxide **83** in reaction with water gave a respec-

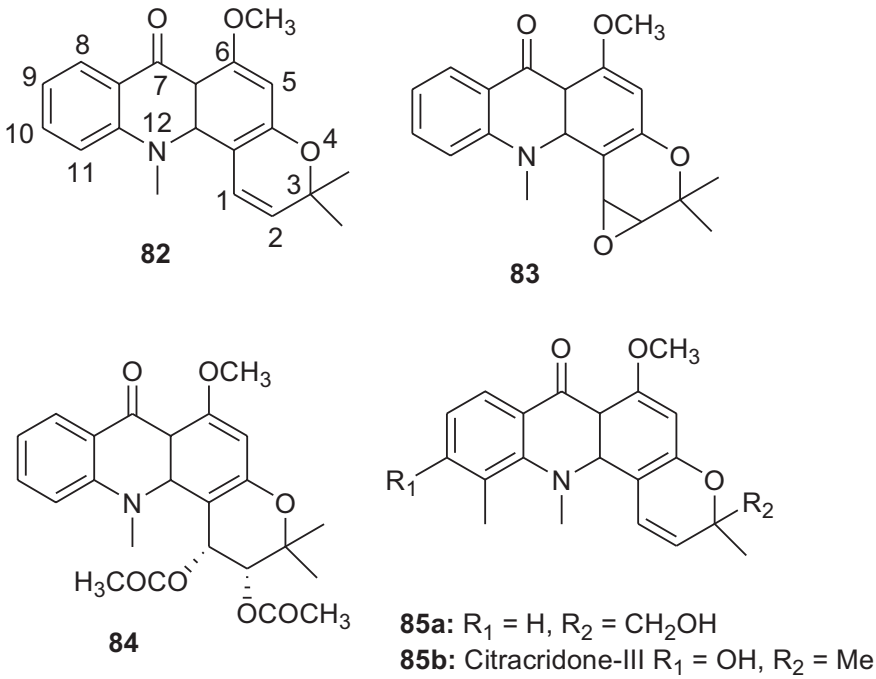


Fig. 16. Acronycine **82** and its derivatives

tive diol, which after activation, became an alkylating agent toward some nucleophilic targets in tumor cells [20]. Some *cis*- and *trans*-1,2-dihydroxy-1,2-dihydroacrynocine diesters exhibited significant antitumor properties. Finally, *cis*-1,2-diacetoxy-1,2-dihydroacronycine **84** was selected for further examination. However, its preclinical development failed because of high toxicity [20].

Other acronycine derivatives

Other alkaloids that are structurally related to acronycine were also found. For example, compound **85a** was isolated from the bark of *Citrus maxima*. It holds a hydroxymethyl group in the pyran ring (Fig. 16). More similar analogs turned out to be potent against HepG2 hepatoma and KB epidermoid cancer lines. Derivative **85a** was most active against KB cells (IC_{50} = 19.5 μM), while citracridone III **85b** was the strongest agent against the HepG2 cell line (IC_{50} = 17.0 μM) [66].

Benzo[*b*]acronycine

Interaction with DNA is known to occur mainly for coplanar aromatic chromophores, such as acridines, anthracenes, and pirydocarbazoles. Taking this into account, acronycines with an extended system of fused aromatic rings were developed. Benzo[*b*]acronycine **86** was synthesized in a reaction of 3-amino-2-naphthalene-carboxylic acid **87** and phloroglucinol **88**, followed by a reaction with 3-chloro-3-methylbut-1-yne *via* Claisen rearrangement of each respective ether **89** (Scheme 3).

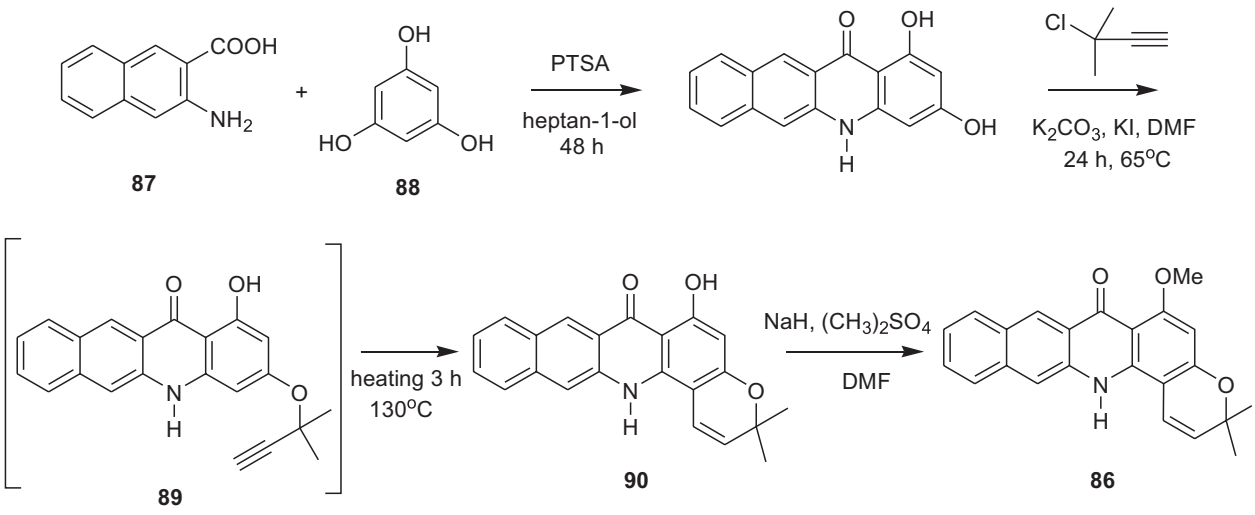
Finally, methylation of **90** with dimethyl sulfate gave benzo[*b*]acronycine **86** [36, 89], which was converted into corresponding diols **91** and **93** (Scheme 4).

The racemic *cis* diol **91** was obtained in OsO_4 oxidation. The racemic *trans* diol **93** was prepared in two stages. Benzo[*b*]acronycine **86** after oxidation with potassium permanganate to 2-hydroxy-1-oxo-1,2-dihydrobenzo[*b*]acronycine **92** was reduced with sodium borohydride [36, 89]. Acylation of both *cis* and *trans* diols **91**, **93** with an excess of acyl chloride or anhydride in the presence of pyridine yielded respective diesters **94**, **95** (Fig. 17).

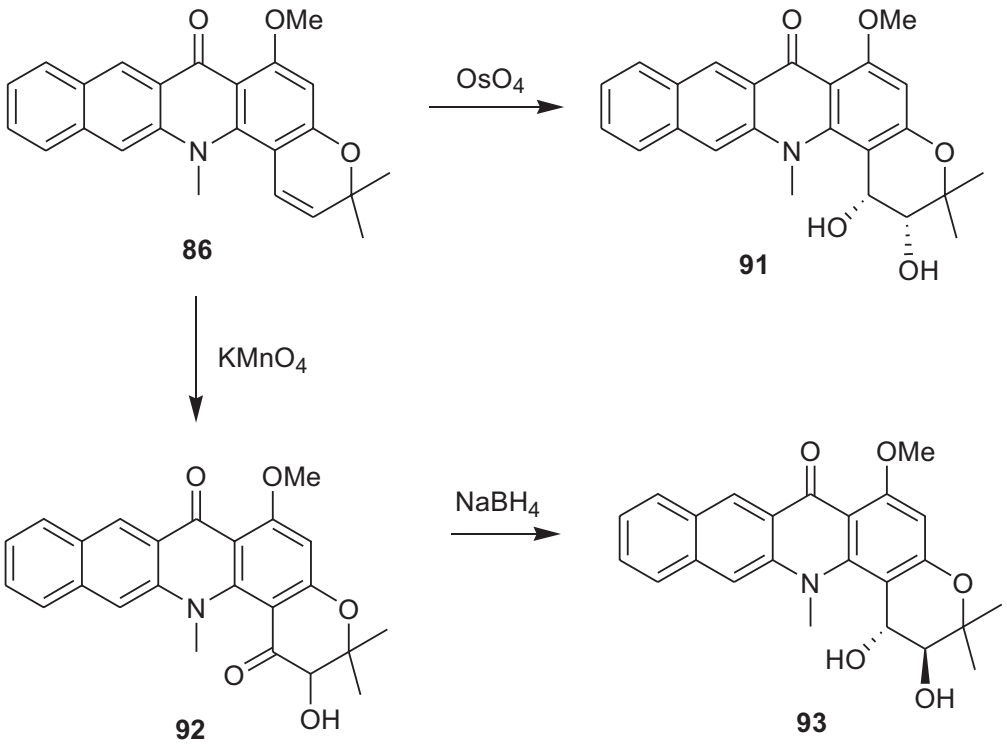
Reaction with one equivalent of acylating agent led to monoesters at the less hindered 2 position, received in good yield and with high regioselectivity. The racemic *cis* diol **91** was also converted to cyclic carbonate **96** with CDI [20, 36, 68, 89].

Some dialkyl esters **94**, **95** were studied *in vitro* on L1210 leukemia cells. In comparison with acronycine **82** (IC_{50} = 23 μM) or benzo[*b*]acronycine **86** (IC_{50} = 14.9 μM) [20], both diesters **94**, **95** were more cytotoxic (IC_{50} = 0.2–2.1 μM), whereas cyclic carbonate **96** was 1000-fold more potent (IC_{50} = 0.014 μM) than

the esters. Finally, *cis*-diacetate **94** R_1, R_2 = Ac (IC_{50} = 0.8 μM) was selected by Servier Laboratories for further evaluation as a drug candidate [20]. The high potencies of diesters **94**–**96** is correlated with their alkylating activity toward the exocyclic -NH_2 group in guanine [20, 89]. In other words, these compounds can bind covalently to DNA. In contrast, derivatives without a good leaving group at the benzylic position



Scheme 3. Synthesis of benzo[*b*]acronycine **86** by Tillequin [36, 89]



Scheme 4. Oxidation of benzo[*b*]acronycine **86** [36, 89]

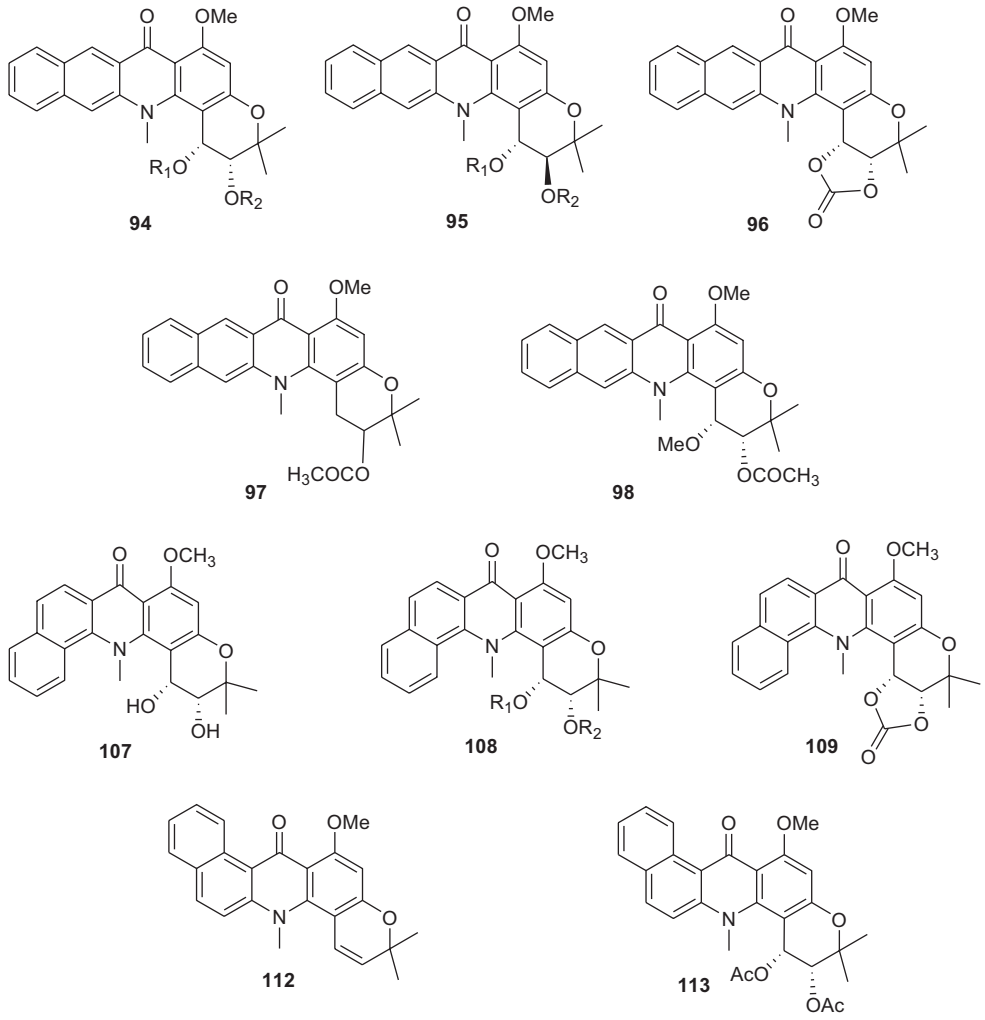
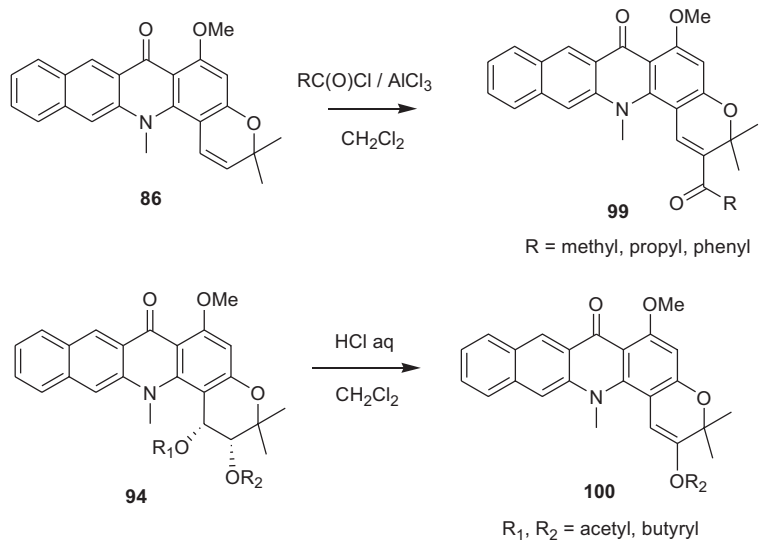


Fig. 17. Some derivatives of benzo[*b*]acronycine **94**–**98** and benzo[*c*]acronycine **107**–**109**, **112**, **113**



Scheme 5. Synthesis of benzo[*b*]acronycine derivatives [90]

1, like 2-acetoxy-1,2-dihydroacronycine **97** (IC_{50} = 17 μM) [20, 89] or *cis*-2-acetoxy-1-metoxy-1,2-dihydrobenzo[*b*]acronycine **98** (IC_{50} = 45 μM) [7, 41] are considerably less active (Fig. 17). The influence of electron density at the benzylic carbon at the 1 position was also investigated. Michael acceptors **99** in the benzo[*b*]acronycine were prepared in the Friedel-Crafts acylation of benzo[*b*]acronycine **86** with acyl chloride in dichloromethane (Scheme 5). Finally, some enolic esters **100** were synthesized upon acidic dehydration of diesters **94** [89].

Michael acceptors **99** have lower cytotoxity (IC_{50} = 20, 30, 50 μM, respectively) compared to benzo[*b*] acronycine **86** (IC_{50} = 15 μM) [90], despite the fact that position 1 should be highly reactive toward nucleophiles upon alkylation. This unexpected effect was explained by the high delocalization of the electrons in the structure of the benzo[*b*]acronycine chromophore. Thus, both enol esters **100** turned out to be highly potent agents with IC_{50} = 0.75 and 1.8 μM, respectively [90]. Moreover, no alkylation of purified DNA was observed in the case of enol esters **100**, which indicates an unknown mechanism of action of these derivatives, in contrast to alkylation [90].

Dimeric derivatives of benzo[*b*]acronycine

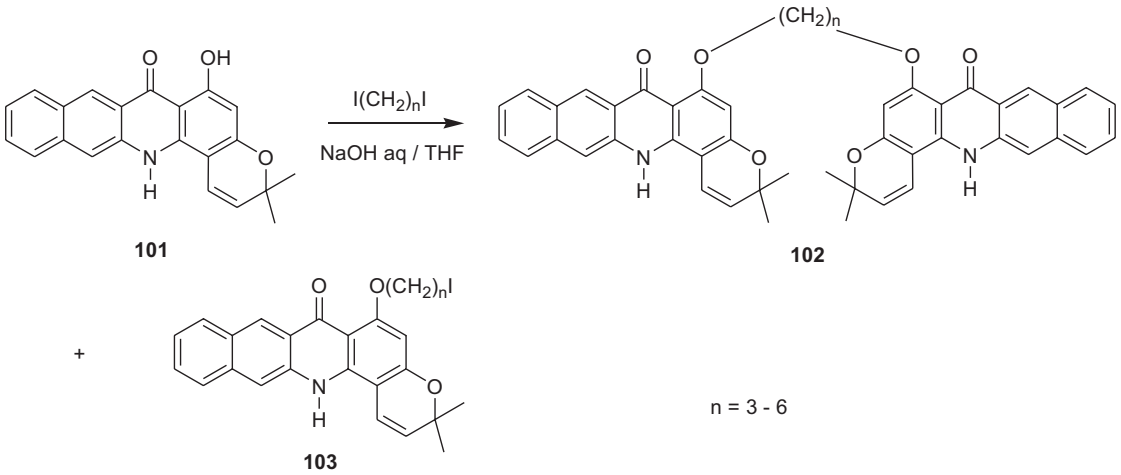
Tillequin et al. [49] published results concerning dimeric analogs of acronycine **102**. A synthesis of the desired products was based on the reaction of **101** with respective linkers – diiodoalkanes (Scheme 6) [49].

Compounds **102** (IC_{50} = 0.9–7.2 μM) and benzo[*b*]acronycines holding iodoalkylether side chain at position 6 **103** (IC_{50} = 2.0–4.1 μM) turned out to be more potent than acronycine **82** (IC_{50} = 23.2 μM) and benzo[*b*]acronycine **86** (IC_{50} = 14.9 μM). Among the dimers **102**, the length of the linker significantly influences the activity, and the highest cytotoxicity is provided by the alkyl chain with n = 5. It inhibited L1210 cell proliferation in the same range of IC_{50} values as *cis*-benzo[*b*]acronycine diacetate **94** (article analog containing R_1, R_2 = Ac is under clinical development) [49].

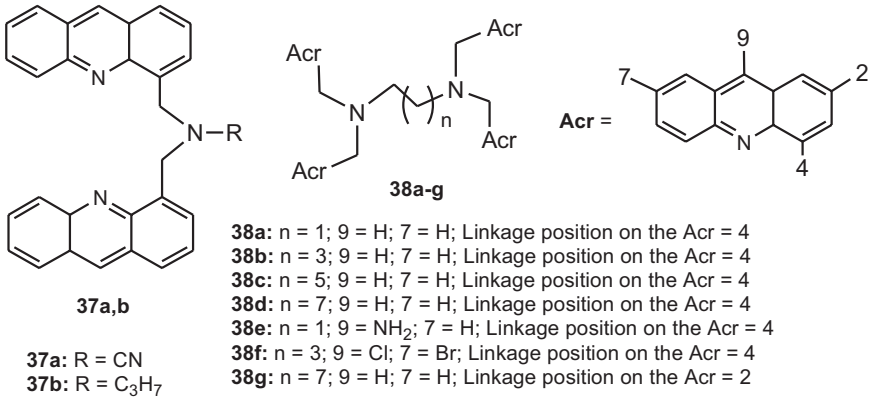
Benzo[*c*]acronycine

Seguin et al. [22] developed the synthesis of an acronycine derivative with an angularly fused benzene ring: benzo[*c*]pyrano[3,2-*h*]acridine-7-one **105**. They used 1-bromo-2-methylnaphthalene **104** as a starting material (Scheme 7).

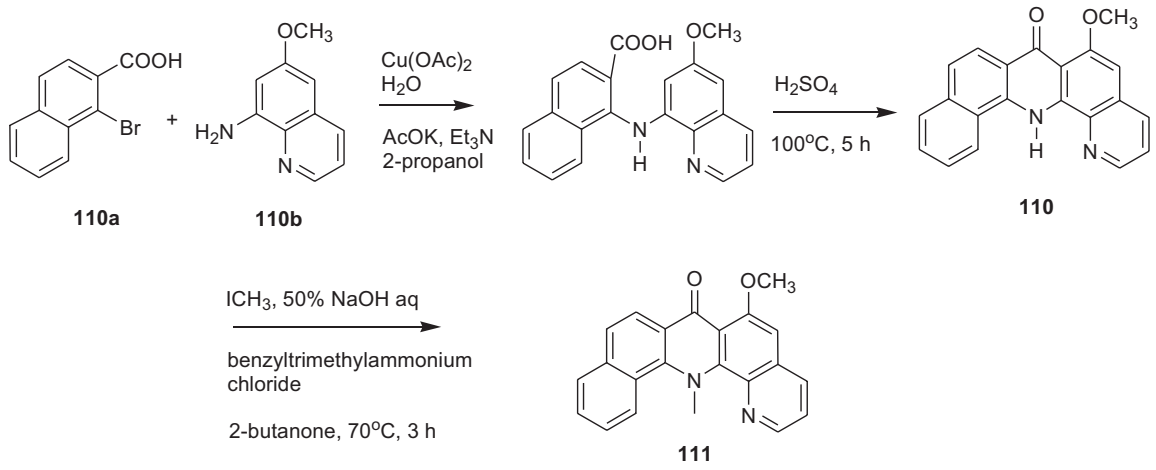
Finally, alkylation with iodomethane in the presence of potassium carbonate in acetone gave the desired *N*-methylated product **106a** (IC_{50} = 12.1 μM), which is considerably more active than its *O*-methylated counterpart **106b** (IC_{50} = 58 μM) [22]. Diol **107**, diesters **108** and cyclic carbonate **109** (Fig. 17) derived from benzo[*c*]pyrano[3,2-*h*]acridin-7-one were prepared from corresponding acridone **106a** by simple modifications of the synthesis presented above. The activities of these compounds were in the range of IC_{50} = 26.2 μM to 6.7 μM for the *cis*-diol **107**, meaning that they are less active than benzo[*b*]acronycine **86** (IC_{50} = 1.9 μM)



Scheme 6. Preparation of dimeric benzo[*b*]acronycines **102** [49]



Scheme 7. Synthetic route toward benzo[*c*]acronycines **105** [22]



Scheme 8. Synthetic pathway to naphtho[1,2-*b*][1,10]-phenanthrolin-7(14*H*)-ones **110**, **111** [22]

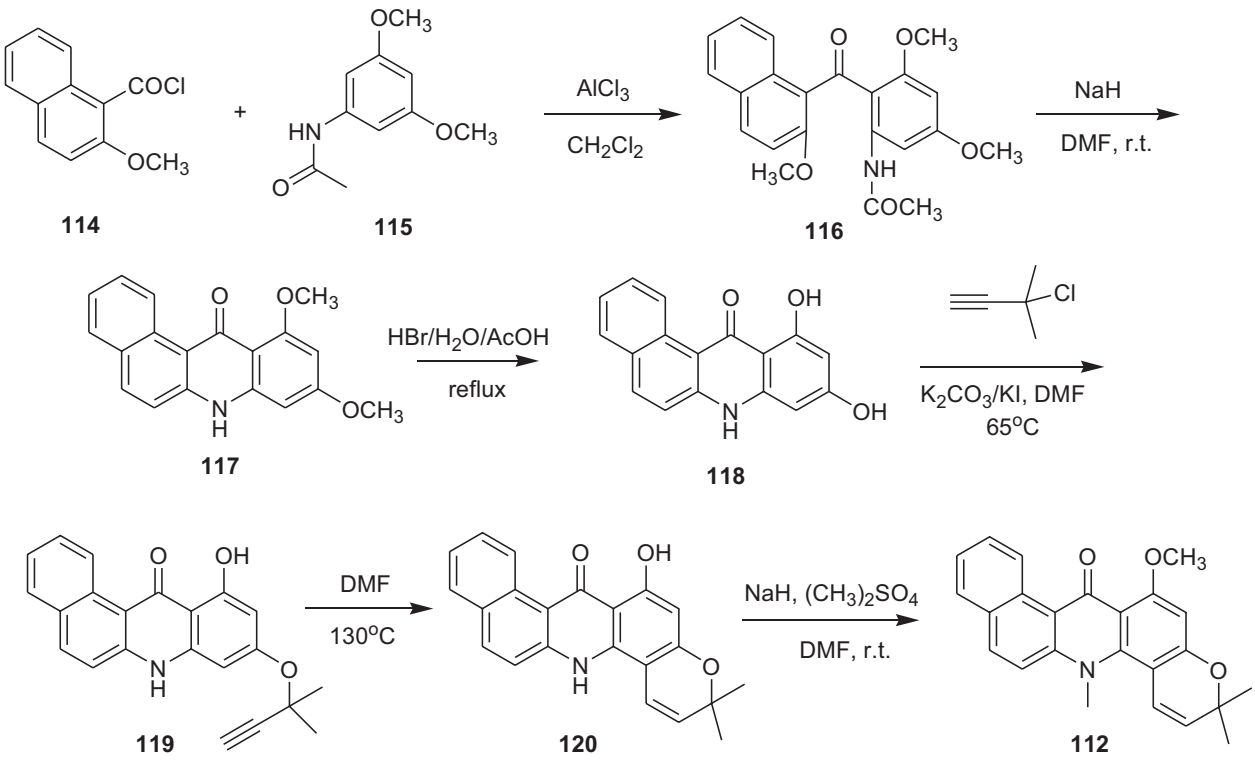
and more active than acronycine **82** (IC_{50} = 23 μM) [22]. Seguin et al. [22] reported the synthesis and pharmacological evaluation of the benzo[*c*]acronycine **110** and **111** series, in which the dimethylpyran ring is replaced by pyridine (Scheme 8).

In a similar pathway, 1-bromonaphthalene-2-carboxylic acid **110a** reacted with the corresponding quinoline derivative **110b** in the Ullmann condensation, followed by acidic cyclization and *N*-methylation [22]. It is noteworthy that the *N*-unmethylated derivative **110** (IC_{50} = 37 μM) is more cytotoxic than *N*-methylated **111** (IC_{50} 100 μM) [22], that is in contrast to benzo[*c*]pyrano[3,2-*h*]acridine-7-compounds **105** and **106a**. Moreover, compounds of the benzo[*c*] acronycine series with an angular ring system are less active in comparison with their benzo[*b*]acronycine analogs [22].

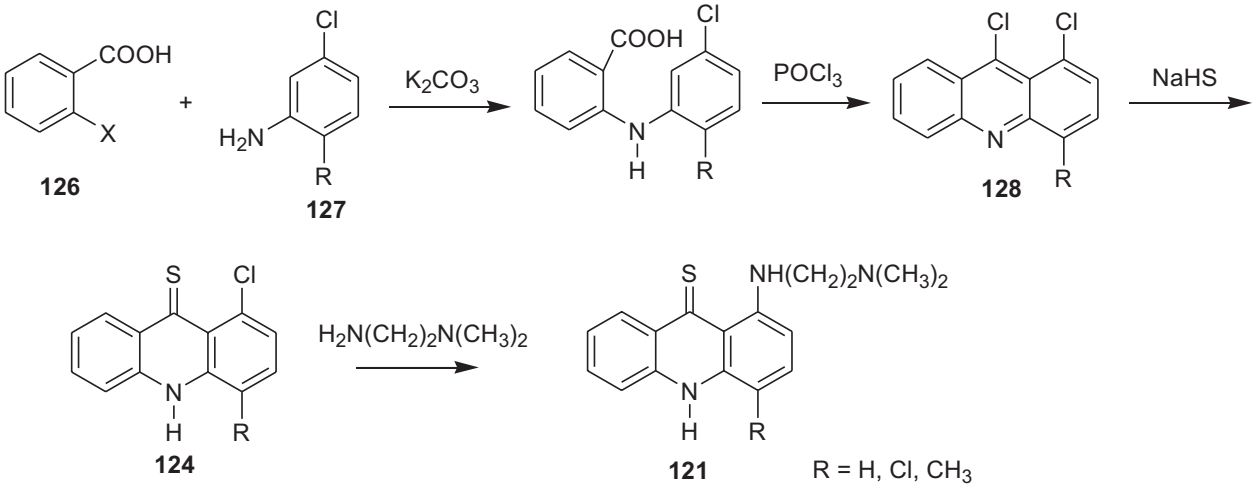
Benzo[*a*]acronycine

Benzo[*a*]acronycine **112** (Fig. 17), in contrast to benzo[*c*]acronycine, exhibited submicromolar toxicity on alkylation properties [74]. One of the most active compounds of this type was a *cis*-diacetoxy derivative **113** (IC_{50} = 0.7 μM against L1210 leukemia and 0.15 μM against human epidermoid carcinoma KB-3-1) [74]. Synthesis of benzo[*a*]acronycine **112** consisted of several steps (Scheme 9).

First, 3,5-dimethoxyacetanilide **115** took part in Friedel-Crafts acylation with 2-methoxy-1-naphthoyl chloride **114**. Subsequently, cyclization of 2-methoxy-1-naphthyl (6-acetamido-2,4-dimethoxy)phenyl ketone **116** in the presence of NaH in DMF gave 9,11-dimethoxybenzo[*a*]acridine-12(7*H*)-one **117**, followed by acidic treatment to produce 9,11-dihydroxy-ben-



Scheme 9. Synthesis of benzo[*a*]acronycine **112** [74]



Scheme 10. Synthesis of thioacridone derivative **121** [43]

zo[*a*]acridine-12(7*H*)-one **118**. Then, the reaction with 3-chloro-3-methylbut-1-yne led to 11-hydroxy-9-(1,1-dimethylpropyn-1-oxy)benzo[*a*]acridine-12(7*H*)-one **119**. The resulting ether **119**, heated in DMF, was converted into 6-hydroxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridine-7-one **120** *via* Claisen rearrangement. Finally, methylation in DMF with dimethyl sulfate in the presence of sodium hydride gave rise to **112** [74]. Benzo[*a*]acronycine **112** was more cytotoxic compared to acronycine **82** (Fig. 16) against the L1210 cell line (2.5 μM and 23 μM, respectively), but it was less cytotoxic against the KB-3-1 cell line (8.6 μM and 3.7 μM, respectively).

Thioacridone

The Van der Schyf [43] group worked out the synthesis and examination of thioacridone (Fig. 18), which is a derivative of acridone in which the C=O bond was replaced by C=S.

Thiocarbonyl compounds with different electronic configurations than carbonyl have other physicochemical and chemical properties, including molecular dipole and electrical charge distribution. Moreover, the larger atomic radius of sulfur and the longer C=S bond alters the geometry of the molecule in comparison with carbonyl analogues [43]. These molecular properties are interesting for the investigation of structure-activity relationships.

1-Aminothioacridones **121–123** and 1-chlorothioacridones **124**, **125** exhibited cytotoxicity *in vitro* (IC_{50} = 2.3–15 μM and IC_{50} = 6 to 26 μM, respectively) against HL-60 human promyelocytic leukemia cells. It is noteworthy that compounds **121** carrying the article $NH(CH_2)_2N(CH_3)_2$ group are more potent than derivatives **122** having article nitrogen mustard moiety, despite the fact that the latter seems to be a more reactive alkylating agent. The most active 1-(2-dimethyl-aminoethyl-amino)-9(10*H*)-thioacridone **121** R = H was obtained by an Ullmann reaction from 2-chlorobenzoic acid **126** (Scheme 10).

A condensation of **126** with an excess of aromatic amine **127**, followed by cyclization with phosphoryl chloride, gave dichloroacridine **128**. The reaction with sodium hydrogen sulfide provided 1-chlorothioacridones **124**, which, with an excess of dimethylaminoethylamine, gave rise to product **121** [43]. Studies concerning the DNA binding properties of these compounds indicated that the most active derivative **121** R = H, (IC_{50} 2.3 μg/mL) exhibited the lowest C_{50} (8.7 μM) value [43]. The latter factor correlates with the concentration of the drug necessary to reduce the fluorescence of initially DNA-bound ethidium by 50 % under standard assay conditions [43].

Additionally, thioacridones are promising antimalarial drugs; their antiplasmodial activity is in the range of IC_{50} from 0.4 to 27 μg/mL. The best result

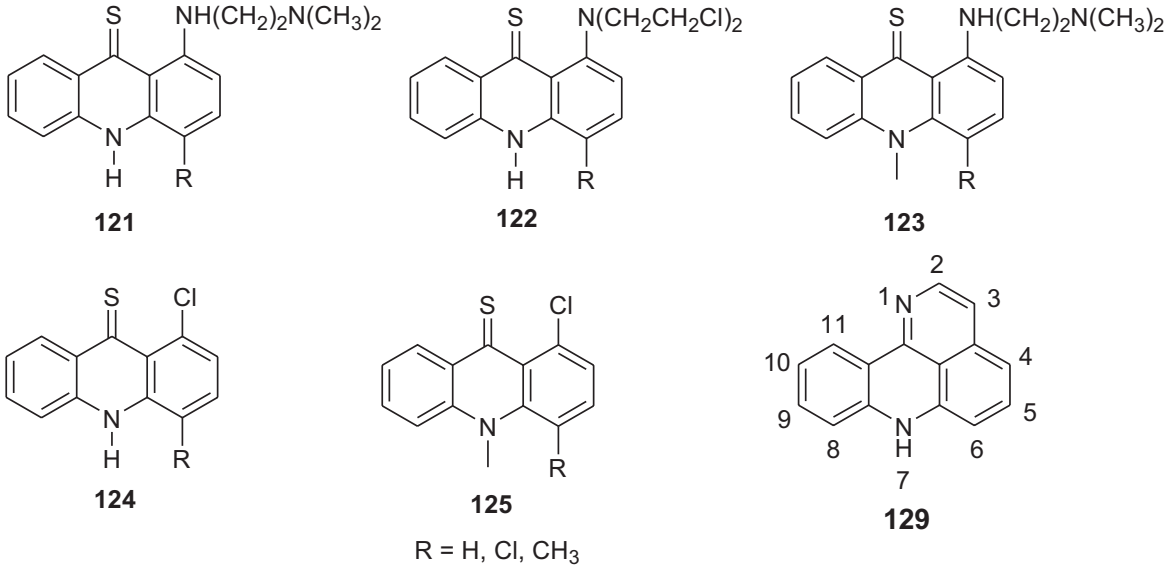
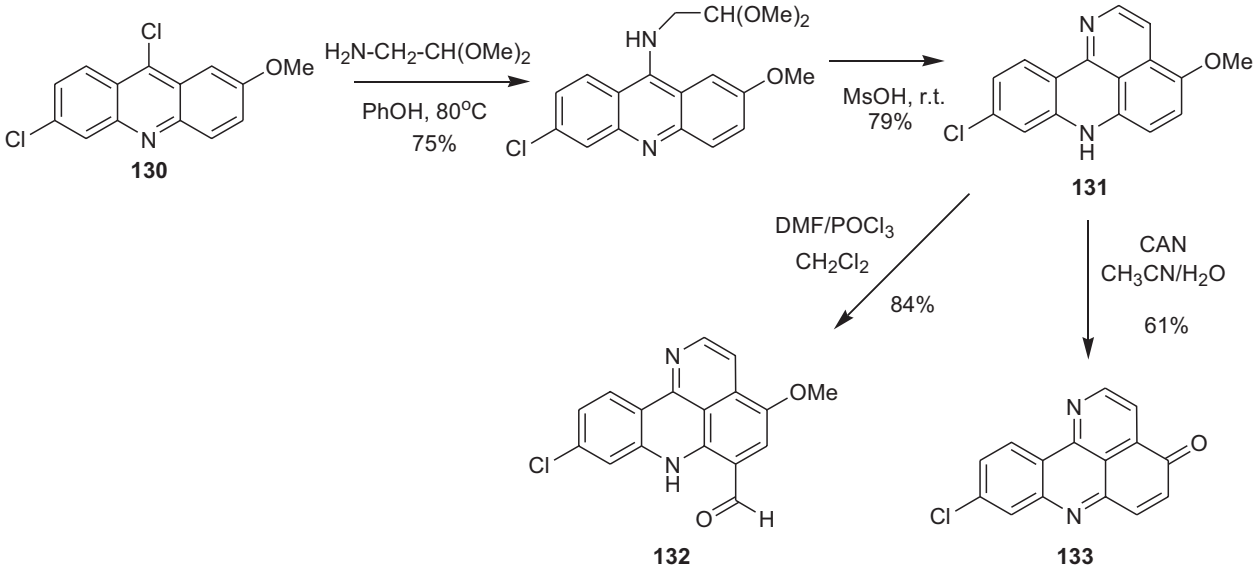


Fig. 18. Thioacridones **121**–**125** synthesized by Van der Schyf [43] and pyrido[4,3,2-*kl*]acridine **129** developed by Demeunynck [25]



Scheme 11. Preparation of 9-chloro-4-metoxypyrido[4,3,2-*kl*]acridine **131**, **132** and **133** [25]

was obtained for 1-(2-dimethyl-aminoethylamino)-9(10*H*)-thioacridone **121** R = H [67].

Pyrido[4,3,2-*kl*]acridine

Demeunynck and co-workers [25] investigated the synthesis and therapeutic properties of pyrido-[4,3,2-*kl*]acridine **129** (Fig. 18), which refers to skeletons of marine acridine alkaloids. The starting material, 6,9-dichloro-2-methoxyacridine **130** (Scheme 11), was converted in a two step sequence reaction into 9-chloro-4-methoxypyrido[4,3,2-*kl*]acridine **131** [25]. Further modification was performed in two pathways (Scheme 11). The Vilsmeier-Haack reaction ($DMF-POCl_3$) led to the formyl derivative at the 6 position **132**. Oxidation with CAN produced a type of Michael acceptor **133** [25]. The first key intermediate **132** was used to obtain glycoconjugates **134**, **135** in a reaction with adequate pyranosyl-oxyamine (Scheme 12).

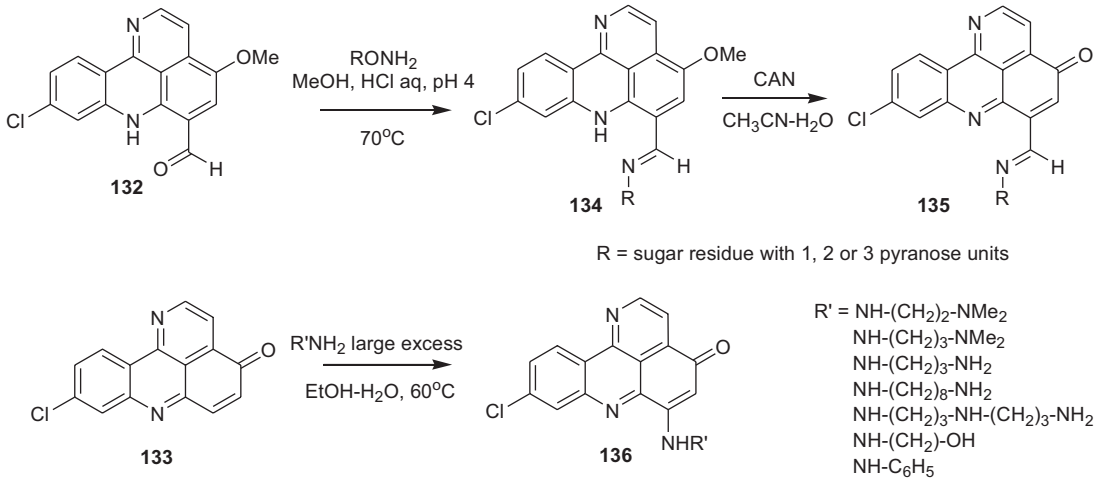
The second compound **133** under treatment with amines produced amino conjugates **136**. 1,4-Michael addition products undergo reoxidation to quinone and spontaneously forms **136** [25]. The glycoconjugates **134**, **135** showed low cytotoxity *in vitro* against HT29 cell lines (IC_{50} from 50 to 128 μM), but some of the amino conjugates **136** were much more cytotoxic (IC_{50} = 1.8 to 21 μM and 100 for $R' = C_6H_5$). The activity correlated with DNA-binding measurements was displayed in melting temperature experiments [25]. This binding seems to be reinforced by the interaction of protonated aliphatic amino groups with the phosphate backbone of DNA. In contrast to the generally observed results for acridine or pyridoacridine alkaloids, no inhibition of topoisomerase activity was observed [25].

3-Amino-4-hydroxymethylacridine

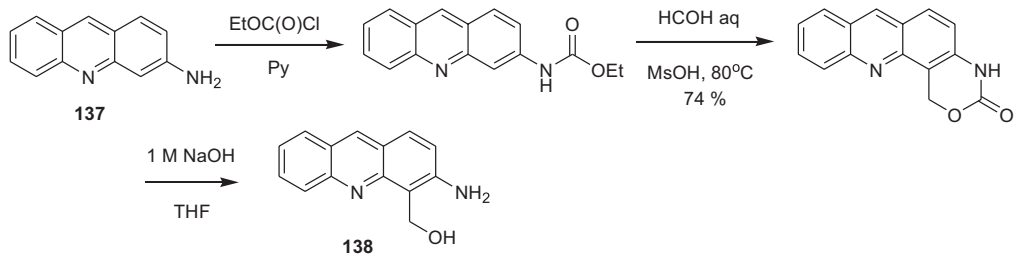
The next series of cytotoxic acridine analogues consists of derivatives of 3-amino-4-hydroxymethylacridine **138** (Scheme 13), which is very active against the HT29 cell line (IC_{50} = 0.025 μM) and can be obtained from 3-aminoacridine **137** in three steps [31].

The proposed mechanism of action of this compound (Scheme 14) assumes the formation of a non-covalent complex with DNA by intercalation, then slow alkylation of nucleophilic centers in the DNA. Strong electrophilic properties of 3-amino-4-hydroxymethylacridine **138** are explained by the formation of quinone-imine-methide intermediates **138a** upon intramolecular acid-base catalysis [31].

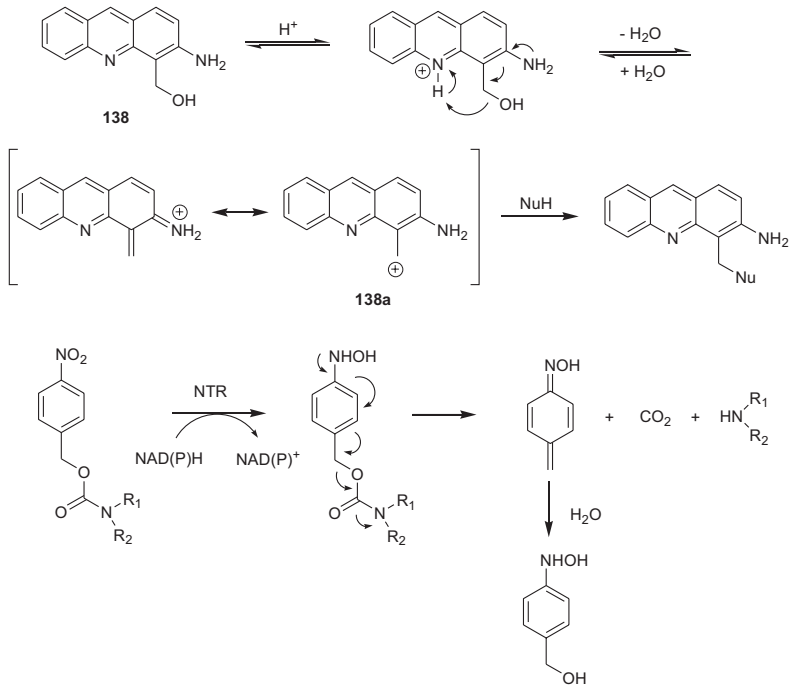
Such a high reactivity causes toxicity *in vivo* and requires modification to obtain analogs with better pharmacological properties [12]. Demeunynck et al. [12] developed *p*-nitrobenzyl-carbamate prodrugs of 3-amino-4-hydroxymethylacridine **139, 140** (Fig. 19),



Scheme 12. Preparation of glyco- and amino-conjugates **134**–**136** from pyrido[4,3,2-*kl*]acridines **132**, **133** [25]



Scheme 13. Synthesis of 3-amino-4-hydroxymethylacridine **138** [31]



Scheme 14. The proposed mechanism of action of 3-amino-4-hydroxymethylacridine **138** [31]

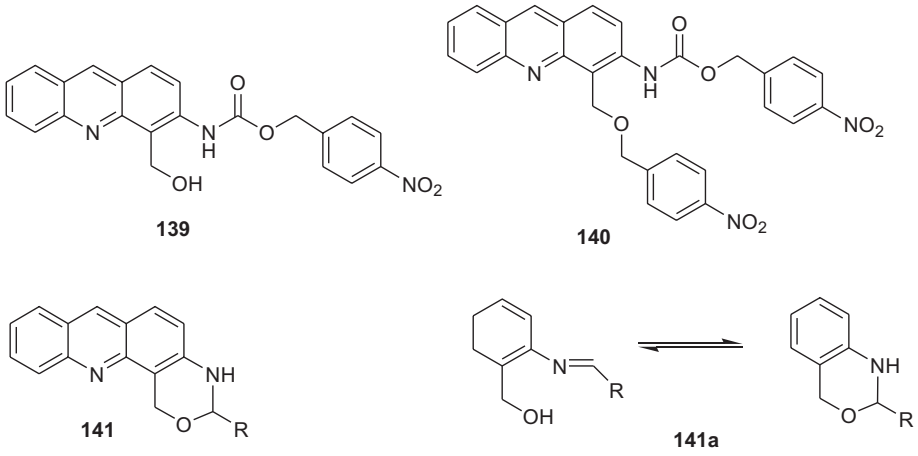


Fig. 19. Acridine derivatives investigated by Demeunynck et al. [12]

which could gradually release the cytotoxic substance **138**. These derivatives undergo bioactivation by the aerobic nitroreductase (NTR) from *Escherichia coli* in the presence of NADH as a cofactor (Scheme 14) [12]. The *in vitro* cytostatic activity against the HT29 cell line was IC_{50} = 2.5 μM and 9 μM for di(*p*-nitrobenzyl) derivative [12]. Another structural modification of 3-amino-4-hydroxymethylacridine **138** is based on [1,3]-oxazines **141** (Fig. 19), which are used in a reaction with an article-appropriate aldehyde under acidic conditions [75]. The 1,3-oxazines **141** are considered cyclic precursors of the potential drug because of ring-chain equilibrium (Fig. 19). Moreover, the stability of the ring form depends on the R substituent at position 2 [75].

Recent achievements in the synthesis of acridine/acridone analogs

In 2004, Chiron and Galy [32] studied the reactivity of the acridine ring, which is very important for the design of acridine analogs of high anticancer activity. Recently, Belmont et al. [20] described acridine and acridone derivatives, their anticancer properties and their synthetic methodologies. The previous routes leading to acridine/acridone ring formation and primarily the preparation of their analogs were based on the Ullman-Jourdan reaction [4]. This method is still widely used for this purpose. The reaction involves the condensation of respectively functionalized anilines with *o*-halogenobenzoic acid derivatives or halogenobenzene and *o*-aminobenzoic acid to give diphenylamino-2-carboxylic acids, which occurs when strong acids cyclize to corresponding acridones. Next, reductive conditions and harsh oxidative media are needed for the transformation of acridone to acridine [20]. This methodology makes possible the preparation of pyrimidoacridones **47**, **48** (Fig. 9) [8], pyridoacridines [38], DACA **17** and their derivatives [16], pyrazoloacridines **19** (Fig. 2) [61], C-857 **75**, C-1748 **76** [57] (Fig. 13) and 9-(ω-amino-alkyl)-amino-1-nitroacridine, e.g., **142**, 1-(ω-aminoalkyl)-amino-4-nitro-9(10*H*)acridone, e.g., **143**, *N*-(9-acridyl/1-acridone) amino acids, e.g., **144, 145** or 4-carboxamide-hydroxyalkyl-acridine/9-acridone analogs **146** (Fig. 20) [29, 44, 45, 101], which were used to synthesize their conjugates with muramyl dipeptide (MDP) or nor-muramyl dipeptide (nor-MDP) [44, 45].

Recently, Belmont et al. [19] described a new methodology for the synthesis of acridine derivatives **151a**–**d** (Scheme 15). Quinolines, which are commercially available starting materials, can be converted *via* five high-yielding steps to TBS-protected-alkyne **150**. The last step is a rhodium-catalyzed benzannulation of the quinoline intermediate yielding the desired poly-substituted acridine derivatives.

Patin and Belmont [77] presented another route toward acridines *via* the Pauson-Khand reaction on alkynes **153** or **155**, leading to tetrahydrocyclopenta-[*c*]acridine-2,5-diones **154a**–**e** and 1-aminoacridine **156** (Scheme 16). Zeghida and Demeunynck [104] recommended the article 2,2,2-trichloro-ethoxycarbonyl (Troc) group, which has been successfully used as a protective group for aminoacridines.

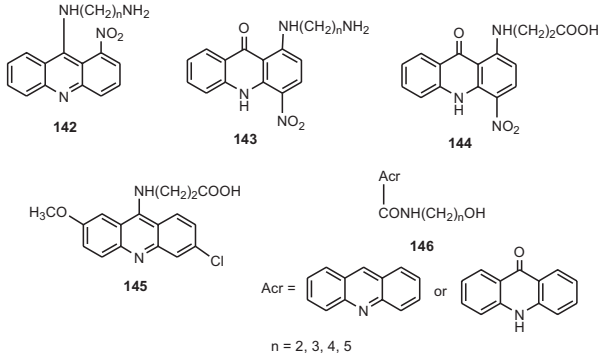
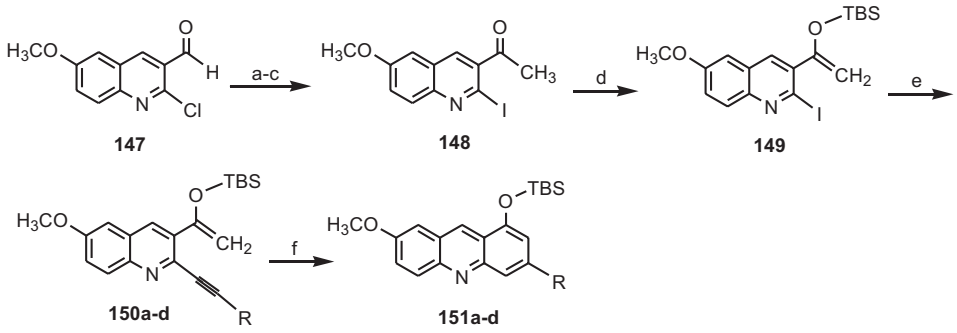


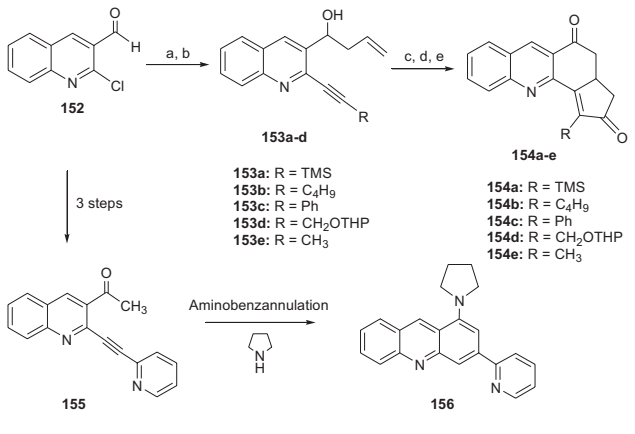
Fig. 20. Acridine/acridone derivatives prepared by Dzierzbicka et al. **142**–**146**



150a, **151a:** R = -C_4H_9
150b, **151b:** R = -Ph
150c, **151c:** R = -CH_2-O-THP
150d, **151d:** R = -$CH(OEt)_2$

a. MeMgBr, THF, 40°C; b. MnO_2, toluene, 80°C; c. NaI, CH_3CN, 4 M HCl, reflux; d. TBSOTf, Et_3N, CH_2Cl_2; e. 1-alkyne, $PdCl_2(PPh_3)_2$, CuI, Et_3N, toluene, r.t.; f. 10 mol % $[Rh(CO)_2Cl_2]$, toluene, 120°C.

Scheme 15. New methodology for acridine synthesis using a rhodium-catalyzed benzannulation [19]

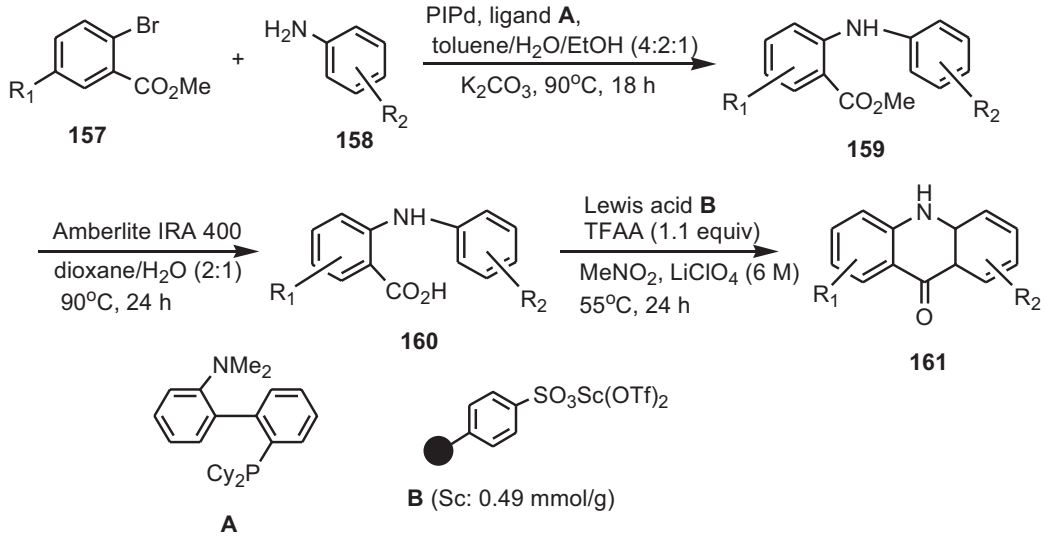


a. 1-alkyne, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, r.t.
b. AllylMgBr, THF, -78°C
c. Enynes **153a-d**, $Co_2(CO)_8$, CH_2Cl_2, r.t., 2 h; NMO, r.t., overnight
d. DMP, CH_2Cl_2, r.t.,
e. Enyne **153a**, $Co_2(CO)_8$, CH_2Cl_2, r.t., 2 h; NMO, r.t., overnight; TPAP and MS

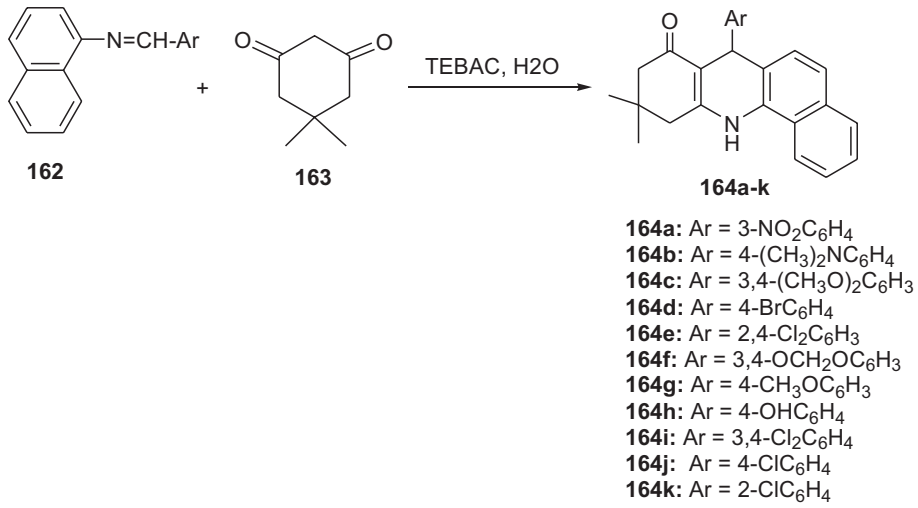
Scheme 16. A new route to acridine derivatives [20, 78]

Acridone analogues are promising antiviral agents [3, 48] and fluorescent labels in biodiagnostics [18, 46]. These compounds are important precursors for the creation of acridine derivatives with potential anticancer activities [20, 38, 40, 44, 45]. Acridones are usually prepared by Ullman condensation of anilines with 2-bromobenzoic acids to give *N*-phenylanthranilic acids, which undergo ring closure with sulfuric acid. Recently, Nishio et al. [75] presented a convenient method for the preparation of acridone derivatives (Scheme 17). The method is based on the combined use of polymer-supported palladium and scandium catalysts in arylic amination and intramolecular Friedel-Crafts acylation reactions, respectively. The approach uses several polymer-supported catalysts in multistep synthesis and would be useful for the construction of some compound libraries.

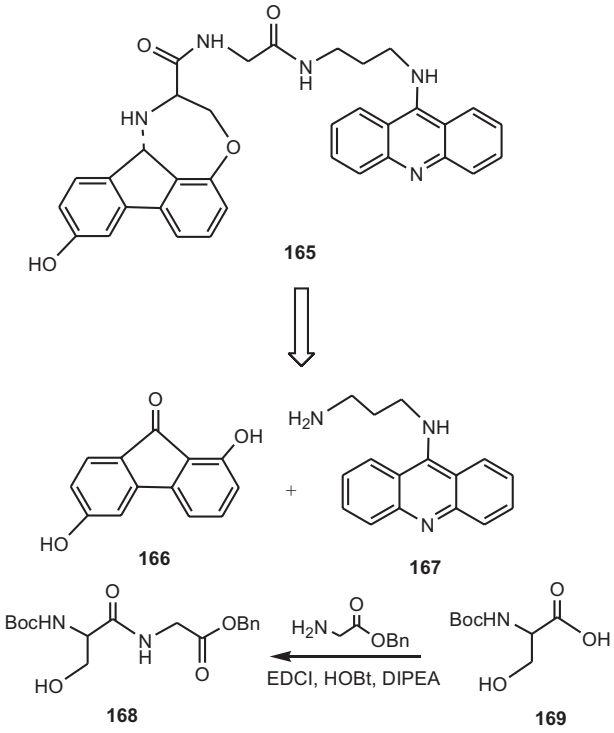
Wang et al. [97] reported the synthesis of 10,10-dimethyl-7-aryl-7,9,10,11-tetrahydro-9*H*-benzo[*c*]acridin-8-one derivatives **164a**–**k** *via* a reaction of *N*-arylidene-naphthalen-1-amine **162** with 5,5-dimethyl-



Scheme 17. Synthesis of acridine derivatives using polymer-supported palladium and scandium catalysts [75]



Scheme 18. Synthesis of benzo[c]acridine derivatives in aqueous medium catalyzed by TEBAC [97]



Scheme 19. Synthetic design of fluorenylaminoserine acridine conjugate [37]

1,3-cyclohexadione **163** in aqueous medium catalyzed by TEBAC (Scheme 18).

In comparison to other methods, this pathway has the advantage of high yields, mild reaction conditions, inexpensive reagents and an environmentally friendly procedure [97]. In 2007, Dai and Zhou [37] reported the synthesis of an *N*-(1-alkoxyl-9-fluorenyl)serine acridine conjugate **165** (Scheme 19), which was achieved by a tree-component (serine derivatives, fluorenone, aminoacridine) assembly approach *via* an intramolecular reductive amination process.

Some acridine derivatives have recently been synthesized from dimedone, 1,3-cyclohexanedione, cyclohexanone and phenols by reacting each of them with vinyl acetate in 2% sodium hydroxide, followed by treatment with ammonia [71]. In 2007, Tu et al. [92] reported a new reaction of Schiff's base with dimedone to produce acridine derivatives under microwave irradiation. Recently, Ma et al. [60] presented the reactivity of the 9-aminoacridine chromophore in guanidylation reactions. They developed new methodologies that allow the formation of two novel structural acridines of potential biological interest: incorporation of N9 atom into a five-membered cyclic guanidinium group and transformation of C9 atom into a spiro carbon as part of a triazine-type heterocycle [60].

Ishihara et al. [55] described article reaction of acridine with pyrazolone derivatives in the solid state (without solvent). Murugan's group [70] reported the synthesis of acridine derivatives fused with quinoline, pyran, pyridine, and benzene ring systems using a simple and convenient methodology. Condensation of cyclohexane-1,3-dione or dimedone with *o*-nitrobenzaldehyde and ammonium acetate/acetic anhydride furnished the corresponding acridinedione derivatives. Middle ring aromatization, followed by reductive cyclization, led to the respective condensed acridine systems **170**–**172** (Fig. 21).

Conclusions

Neoplastic diseases and bacterial and parasitic infections are still a serious challenge for many researchers

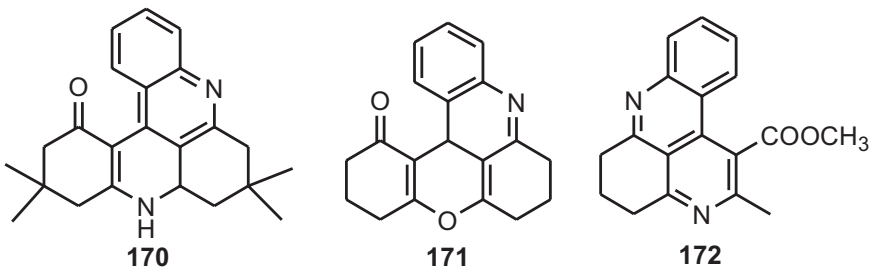
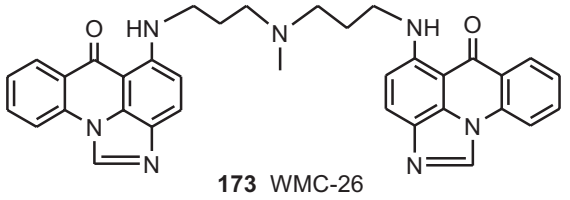
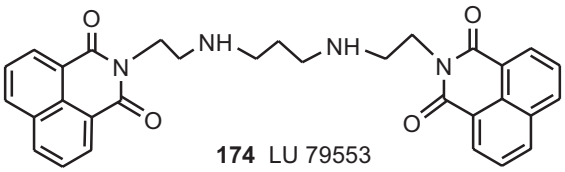


Fig. 21. Derivatives reported by Murugan's group [70]



173 WMC-26



174 LU 79553

Fig. 22. Example of symmetric bifunctional intercalators **173** and **174**

in various disciplines, including medicine, pharmacology, chemistry and biology. The clinical usefulness of acridine/acridone compounds is limited due to some of their drawbacks, such as high toxicity and tumor resistance. Borowski's group [23] described strategies for overcoming ABC-transporter-mediated MDR of tumor cells. Until now, numerous derivatives and analogs of acridines/acridones synthesized as potential anticancer agents showed a positive effect on overcoming multidrug resistance. Among them are imidazoacridones, triazoloacridones, pyrimido[5,6,1-*de*]acridines, pyrimido[4,5,6-*de*]acridines, pyrazoloacridones, pyrazolopyrimidoacridones, and pyridazinoacridones [23]. For several years, interest in symmetric bifunctional intercalators has been growing. A number of such derivatives employing different chromophores were synthesized [11], and their anticancer activities have been studied, e.g., WMC-26 **173** [33] similar to bis-naphthalimide LU 79553 **174** [27] (Fig. 22). These compounds show high effectiveness against tumors in xenograft tests *in vivo*.

Several acridine/acridone analogs are in use in clinics due to their anti-bacterial properties (acriflavine, aminacrine, ethacridine), their effectiveness against parasite infections (quinacrine, acranil) and as anticancer drugs (nitracrine, amsacrine). Others are under clinical trials, e.g., DACA **17** (phase II clinical trial), pyrazoloacridine **19** (phase I and II clinical trials), compound **20** (Fig. 2) and elacridal (GF 120918) **67** (Fig. 11) exhibited multidrug resistance (phase I clinical trials in combination with doxorubicin, in patients with solid tumors) [23]. Analogs of 9-alkyl-amino-1-nitroacridine – one of the most promising acridine derivatives showing anticancer activity – were patented by Konopa et al. in 2003 [57]. Among the 1-nitroacridine derivatives, 9-(2'-hydroxyethylamino)-4-methyl-1-nitroacridine (C-1748) **76** demonstrates high antitumor efficacy against human prostate cancer (Fig. 13) [13, 14, 72, 88].

The anticancer mechanism of acridine derivatives still remains largely unknown. It has been proposed that they may play a role in interrupting DNA synthesis by intercalating into the DNA and therefore inhibiting topo II or I [28, 47]. Wang's studies [96] provide novel insights into the anticancer effect of acridine derivatives and their effects on p53 signaling. The tumor suppressor protein p53 plays an important role in tumorigenesis and cancer therapy [95, 96].

Acknowledgment:
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