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Natural and synthetic acridines/acridones as antitumour agents.

Their biological activity and methods of synthesis

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Abbreviations list

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; IC₅₀, 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 ammonium perruthenate;

Abstract

Acridine derivatives constitute a class of compounds 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 focusing on preparation of target acridine skeletons or modification of naturally occurring compounds like acridone alkaloids exhibiting promising anticancer activity. They are examined *in vitro* and *in vivo* to test their importance for cancer treatment and also to establish the mechanism of their action at both the molecular and cellular level, which is necessary for optimization of their properties suitable in chemotherapy. In this article we review natural and synthetic acridine/acridone analogues and their application of anticancer drugs and methods for their preparation.

Key words:

acridine/acridone analogues, synthesis, biological activity, anti-cancer activity

1. Introduction

Numerous research groups have paid much attention to synthesis of new compounds possessing cytotoxic activity, among which acridine/acridone compounds play an important role. Acridine/acridone analogues are known not only as anticancer drugs and cytotoxic agents but also as a very interesting class displaying other forms of bioactivity [7, 20, 39, 40, 41, 56, 58, 64, 84]. They are used as biological fluorescent probes, anti-bacterial drugs e.g. **1-6** [41], anti-protozoal drugs e.g. **7-12** [39, 40, 41, 20, 84] anti-malarial agents e.g. **13** [6] and anti-HIV, e.g. **14** [40, 53] (Fig. 1).

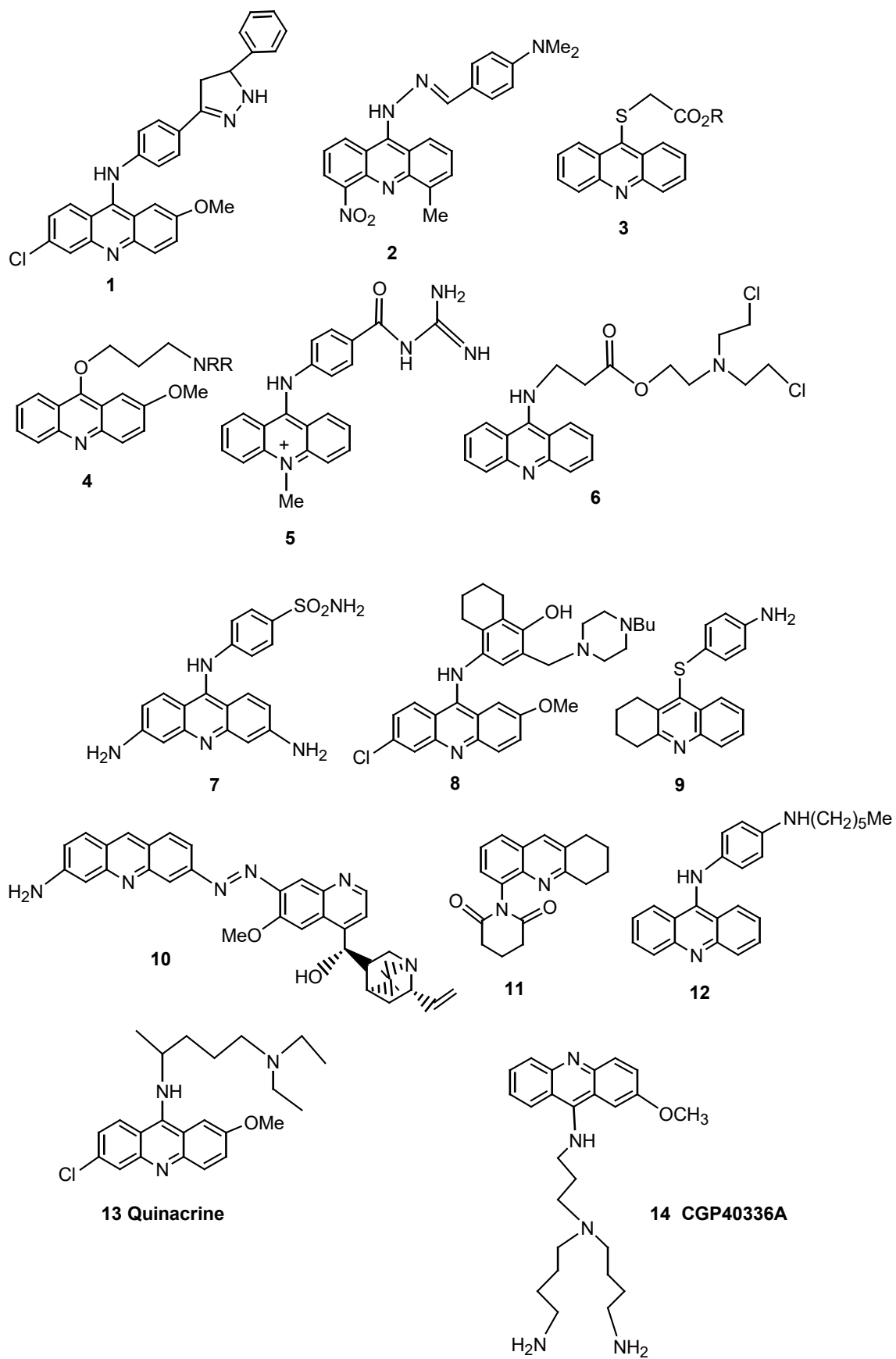


Figure 1. Some acridine derivatives 1-14.

Many acridine/acridone compounds displaying anti-cancer activity have been synthesized, among which are: asulacrine **15**; analogs with a 1'-carbamate **16**; acridine-carboxamides, e.g. DACA **17**; nitroacridines, e.g. **18**; nitropyrazolo-acridine **19**; bis(acridines), e.g. **20**; amsacrine **21** (Fig. 2) [41].

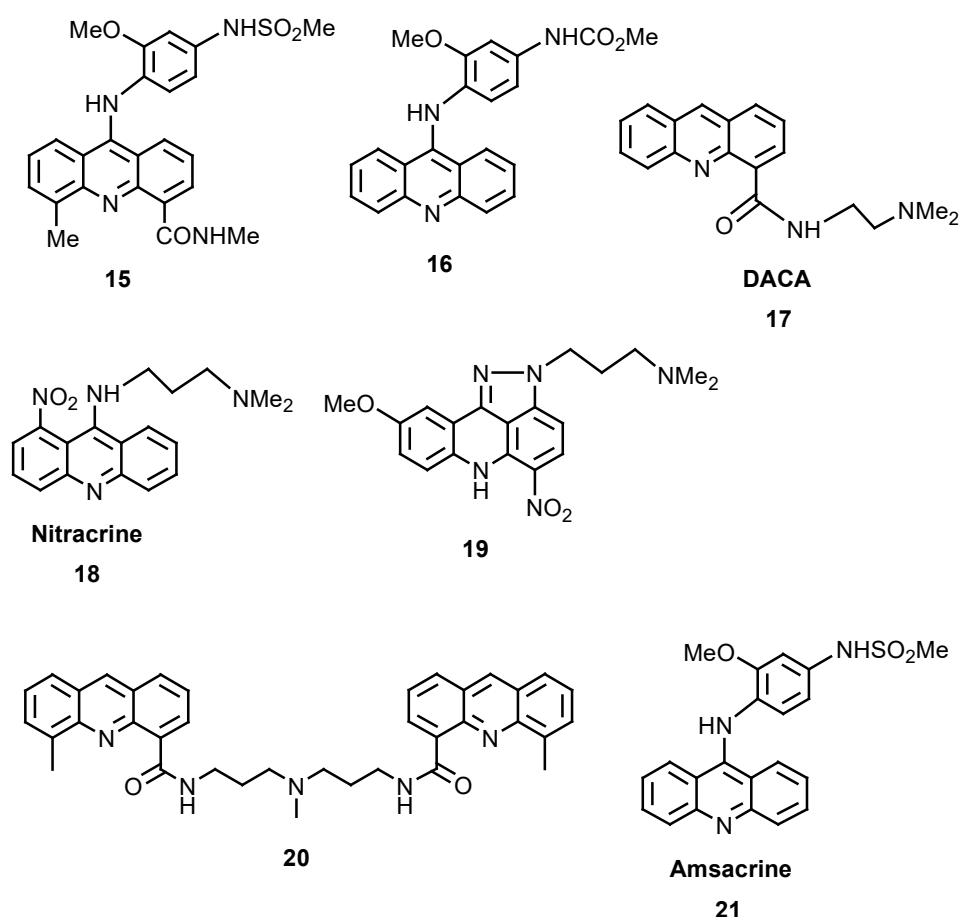


Figure 2. Acridines **15-21** displaying anti-cancer activity.

Examples of natural acridine/acridone analogues are acridone alkaloids isolated from plants and pyridoacridine alkaloids extracted from various marine organisms [40]. Synthetic or natural acridine/acridone drugs showed ability to intercalate DNA and inhibit topoisomerase or telomerase enzymes [20, 40, 51]. Numerous reviews on usefulness of acridine/acridone analogues in therapy have been already published [7, 20, 21, 32, 39, 40, 41, 56, 58, 64, 84]. In

this survey we describe interesting acridine/acridone analogues described since 2000, methods of their synthesis and their potential clinical application.

2. Acridine/acridone as DNA targeting agents

Utility of acridines as chemotherapeutics is due to their chemical and biological stability, capability of effective binding to DNA or RNA [21] resulting in the disordering of the biological functions in living cells. Mechanism of their intercalation to DNA is based on π -stacking interaction with base pairs of double-stranded nucleic acids. The heterocyclic, polyaromatic flat structure of acridine fits effectively in to the gap between two chains of polynucleotides and intercalation of acridine moiety disturbs their crucial role in cell division. The ability of acridines to intercalate to 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 anti-cancer agents. Examinations of a large number of such derivatives proved that there is good correlation between their strength together with the time of binding to DNA and their biological activity. Acridine derivatives also perturb functioning of cancer cells by decreasing activity of some enzymes which are crucial for proper DNA actions, like topoisomerases, telomerases, cycline-dependent kinases [20, 21, 39, 40, 41, 70].

Besides few natural acridine/acridone analogues, thousands of acridine/acridone compounds have been synthesized. Some of them found application as anticancer chemotherapeutics (e.g. nitracrine **18** or amsacrine **21**) (Fig. 2). Nitracrine **18** (also known as ledakrin) developed by Ledochowski's group was clinically used for several years some time ago [99]. Amsacrine **21** (*m*-AMSA) [15, 41] was the first synthetic drug of 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 than in the other known derivatives of acridines was shown by 1-nitro-9-alkylamino-alkylamino-acridines [51, 66, 79] and 1-nitro-9-hydroxyalkylamino-acridines, 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 4 acridine derivatives **22-26** with a similar structure to CP-31398 **26a** (Fig. 3).

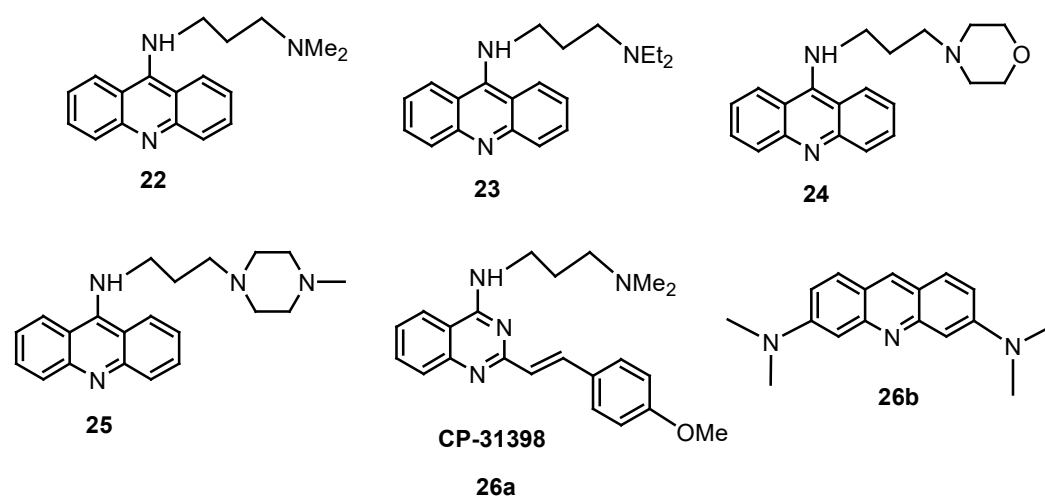


Figure 3. DNA targeting Acridines **22-26b**.

CP-31398 is a small molecule that has been reported to stabilize *in vitro* the DNA-binding core domain of the human tumor suppressor protein p53. The compound activates wild-type p53 by a still unknown mechanism which does not involve 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 anti-cancer acridine derivatives, including 9-aminoacridine, quinacrine **13** (Fig. 1), amsacrine **21** (Fig. 2) and acridine orange **26b** (Fig. 3) induced p53 transcriptional activity. All these acridine derivatives stabilized p53 protein by blocking its ubiquitination, without 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 anti-cancer 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).

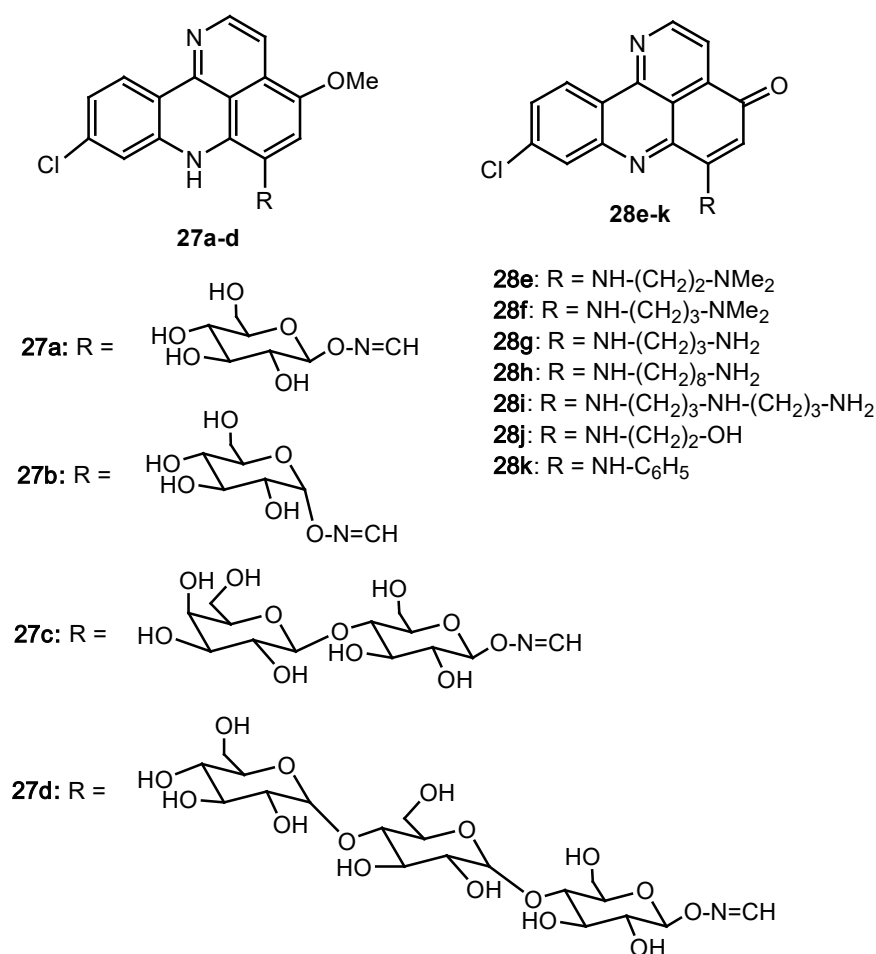


Figure 4. Pyrido[4,3,2-*kl*]acridines **27a-d** and pyrido[4,3,2-*kl*]acridin-4-ones **28e-k** developed by Bouffier et al.[24].

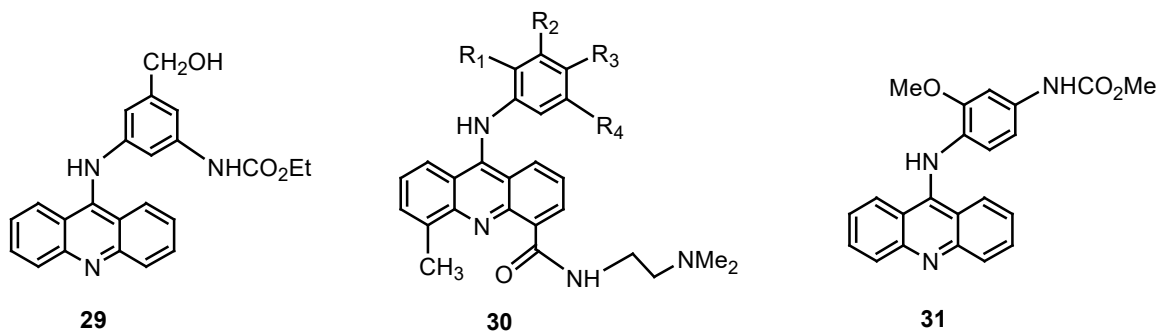
The amino conjugates **28e** and **28i** indicated the highest cytostatic activity against HT-29 cancer cells at micromolar concentration. These molecules bind DNA by intercalation, none of them inhibits topoisomerase activity.

2.1. 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 acting as topoisomerase inhibitor which obtained approval for clinical usage. It is used since 1976 in leukemia treatment. An interaction of amsacrine with topo II-DNA has been already proved. This interaction is due to its side chain, which influences inhibiting properties. Free radical production can be involved in amsacrine metabolism. Thus, damage of DNA is possible both in tumor and healthy cells. Reactive quinonodimine, produced as a result of biooxidation of *m*-AMSA reacts with nucleophiles present in cells. Some *m*-AMSA derivatives having stronger antitumor activity with weaker side effects were also obtained. Su and co-workers [88] developed compounds substituted in the *meta* position of the aniline residue, in relation to 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 in comparison with *m*-AMSA.





AMT R₁ = H; R₂ = CH₃; R₃ = H; R₄ = NH₂
APT R₁ = CH₃; R₂ = H; R₃ = H; R₄ = NH₂
AOT R₁ = H; R₂ = H; R₃ = CH₃; R₄ = NH₂
AOA R₁ = H; R₂ = H; R₃ = OCH₃; R₄ = NH₂
AMA R₁ = H; R₂ = OCH₃; R₃ = H; R₄ = NH₂
APA R₁ = OCH₃; R₂ = H; R₃ = H; R₄ = NH₂

Figure 5. Acridines **29-31** acting as topoisomerase inhibitors.

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

4-Carboxyamido-acridines are an other type of topoisomerase inhibitors based on acridine derivatives. DACA **17** (Fig. 2), prepared in 1987, is one of the exceptional compounds which inhibit two enzymes: topo I and II [20, 39, 40, 41, 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.



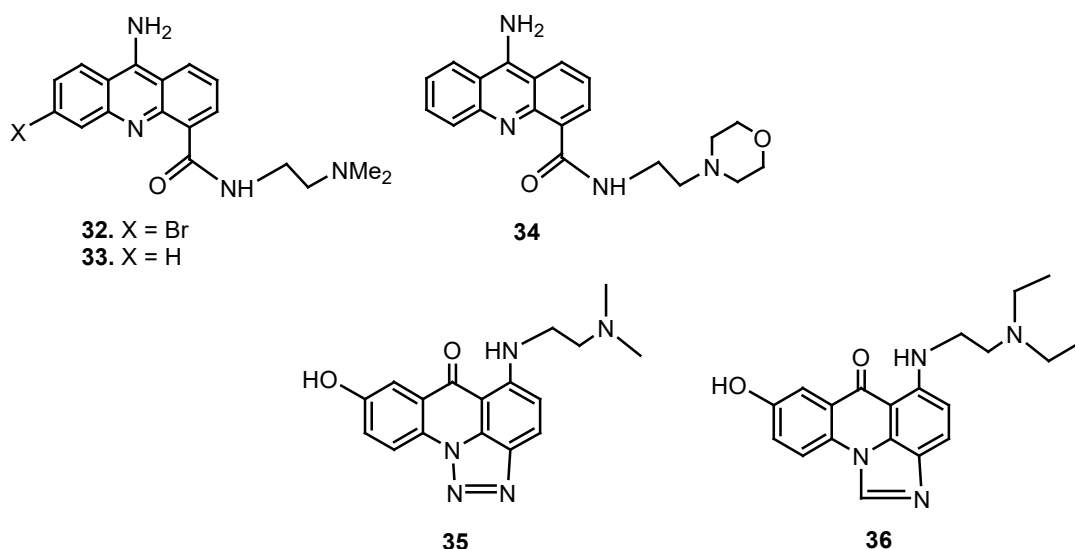


Figure 6. Topoisomerase inhibitors **32-36**.

It was concluded that acridine molecule intercalates within 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 morpholine moiety. The shape of the morpholine molecule seems to disturb the forming 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 proved that C-1305 demonstrates a strong inhibiting properties *in vitro* towards 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 the cytotoxicity and anticancer effect of this compound [59, 98]. Imidazoacridone (C-1311) **36** is the next compound 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 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 hydroxyl group in imidazoacridone explain the antitumor activity of compounds of this type. It is considerably more sensitive towards oxidative processes than compounds bearing the 8-OMe group, which also shows lower biological activity. Thus it can be concluded that activation of heterocyclic ring is essential for the high anticancer activity of imidazoacridone [34, 67].

Vispè's group [93] proposed the mechanism of action of a novel series of bis- **37** and tetra-acridines **38** (Fig. 7).

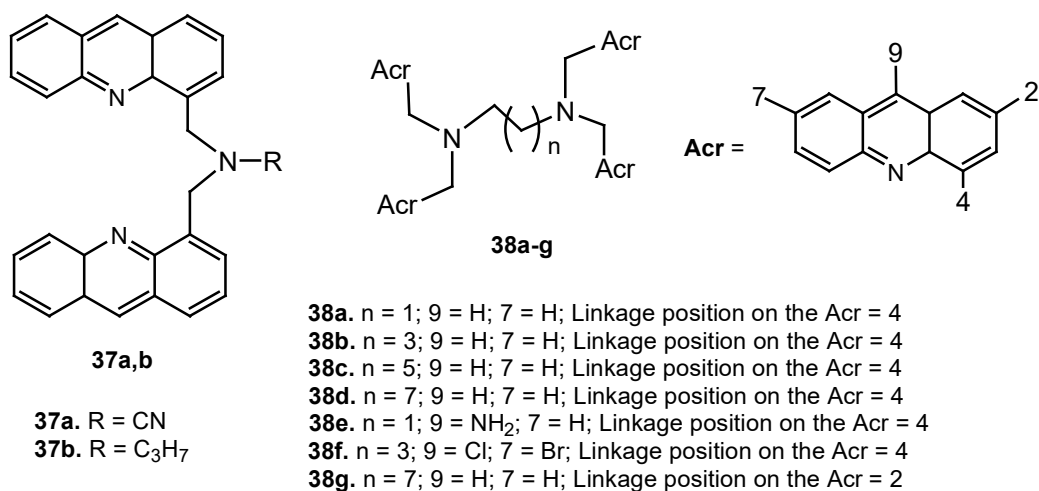


Figure 7. Bis- **37** and tetra-acridines **38** described by Vispè's group [93].

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, 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 turned out to be selective for the proteasome without any significant inhibition of four other proteases, i.e. calpain, trypsin, cathepsin B and chymotrypsin. The study provides

next opportunity to design molecules capable of interfering with two oncogenic targets at the same time, namely topo II and the proteasome. If the anti-cancer mechanism was to be confirmed *in vivo* (e.g. compound **38b** which is currently tested in xenograft models), the dual topo II/proteasome targeting could turn out to be a promising new anti-cancer strategy [93].

2.2. Telomerase inhibition and protein kinases inhibitors

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

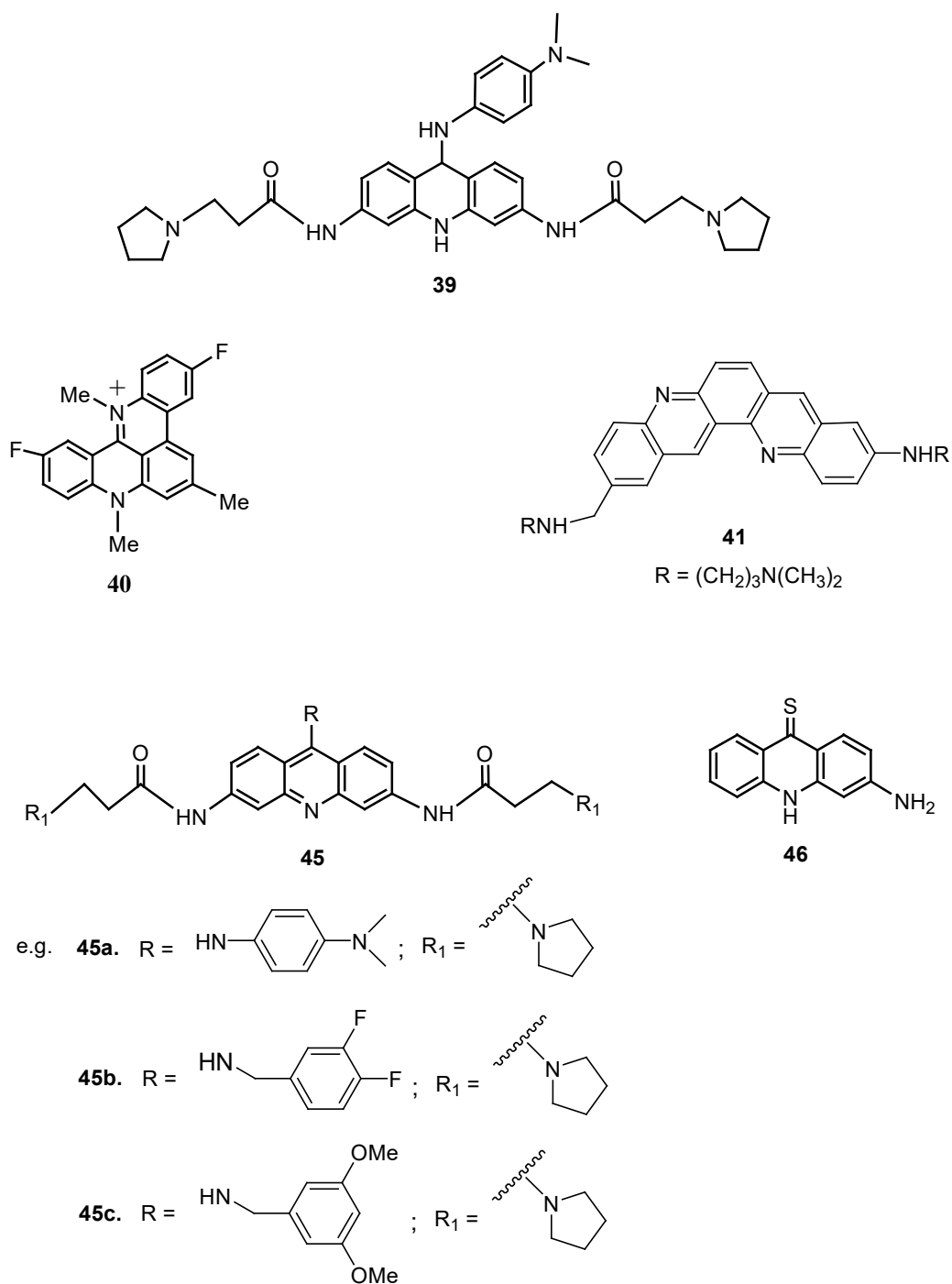


Figure 8. Telomerase inhibitors.

Neidle's group synthesized a series of 3,6,9-trisubstituted acridines as potential telomerase inhibitors [28, 52, 54, 65, 71, 81] one of which, BRACO-19 **39** (Scheme 1), has been studied in detail as a potent G-quadruplex binding molecule and telomerase inhibitor.

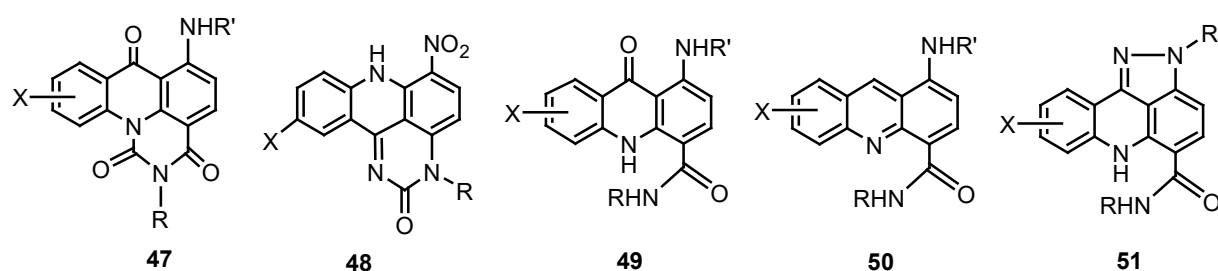


a benzylamino group resulted in enhanced quadruplex interaction. The favourable ΔT_m and $^{tel}EC_{50}$ values for compound **45b** compared to BRACO-19, together with its lipophilicity and improved pharmacokinetic behaviour, led to the selection of **45b** as a potential molecule for clinical treatment.

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

2.3. The structures of MDR-overcoming acridine/acridone compounds

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

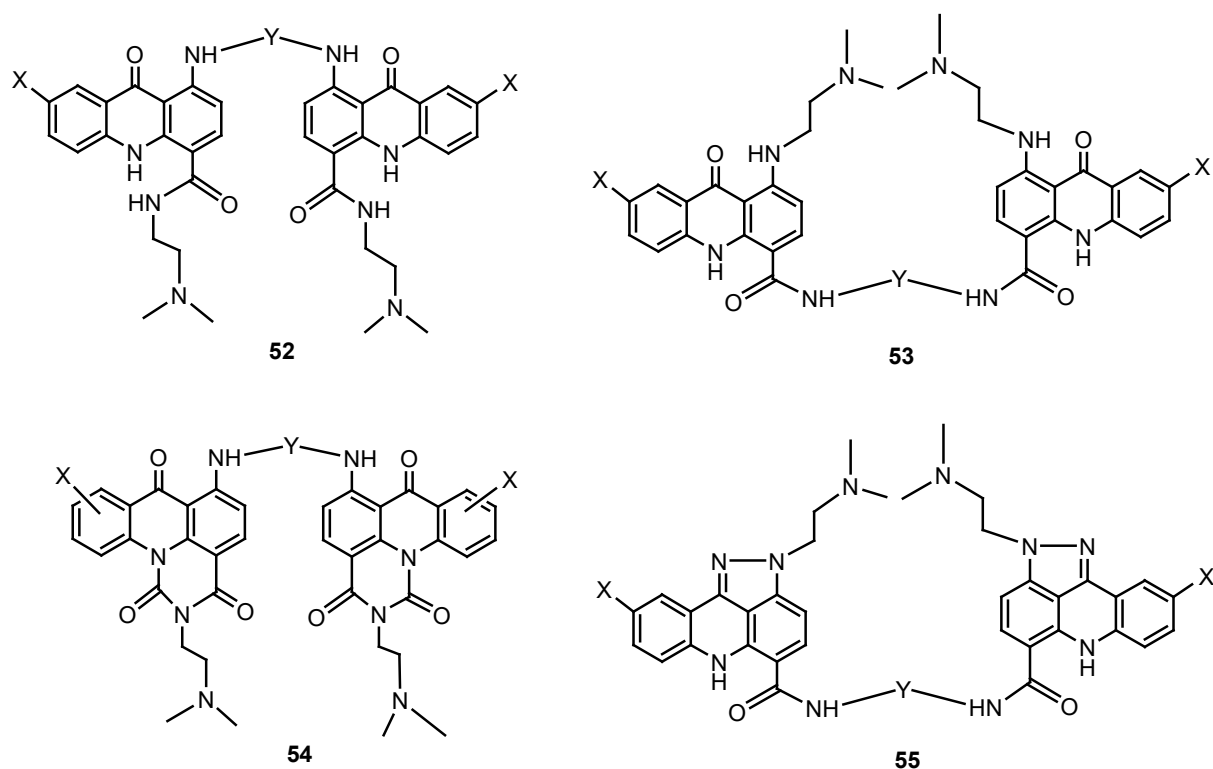


X = H, NO₂; R - *N*-aminoalkyl derivatives e.g. CH₂N(Me)₂, (CH₂)₃N(Et)₂, N(Me)₂

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



These compounds fused five- or six-membered heterocyclic ring make these molecules able to overcome multidrug resistance (MDR) [23]. Antonini et al. [9, 10] also described a series of bis acridine derivatives: bis(acridine-4-carboxamides) **52**, **53** [7] bis(pyrimido-acridines) **54** and bis(pyrazolo-acridinecarboxamides) **55** (Fig. 10).



e.g. Y = (CH₂)₃N(Me)(CH₂)₃; (CH₂)₂N(Me)(CH₂)₂;
(CH₂)₃; (CH₂)₆; (CH₂)₃; (CH₂)₈; (CH₂)₁₂
X = H; 9,9'-OMe; 9,9',10,10'-OMe

Y = (CH₂)₃N(Me)(CH₂)₃; (CH₂)₂N(Me)(CH₂)₂
X = H; 9,9'-OMe
55a. Y = (CH₂)₃N(Me)(CH₂)₃; X = H

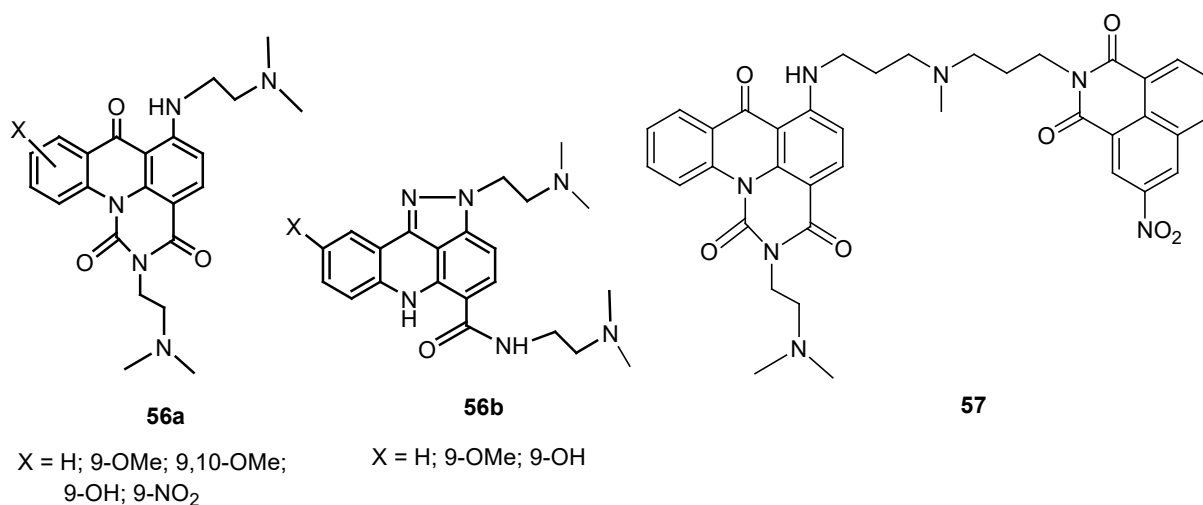
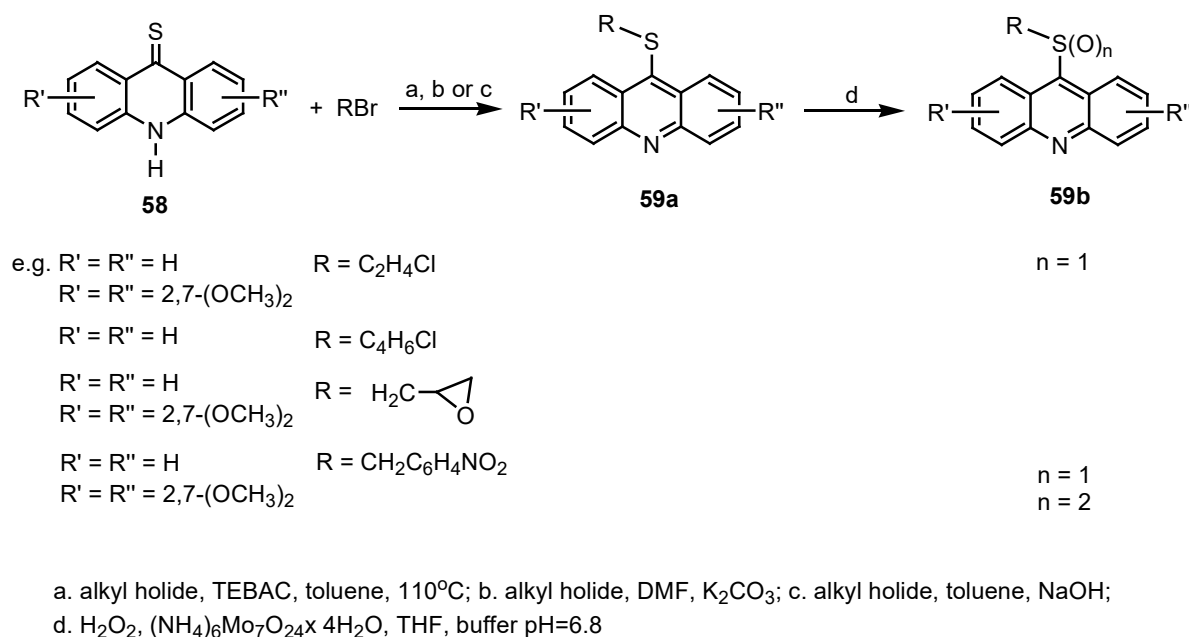


Figure 10. Compounds described by Antonini et al. [7, 9, 10].

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 than related bis(acridine-4-carboxamides) **52** and **53**. The compounds **55a** was selected for evaluation in a National Cancer Institute (NCI) *in vivo* hollow fiber assay [11]. In 2006 Antonini et al. [9] 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. [83] described a synthesis of several acridine thioethers **58** which after oxidation were converted into corresponding sulfoxides **59a** and sulfones **59b** (Scheme 2).



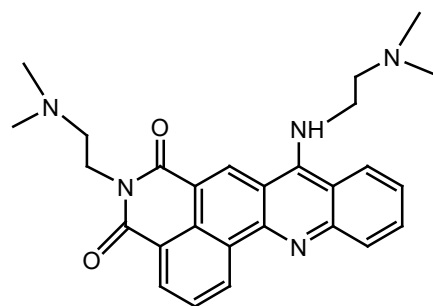
Scheme 2. Synthesis of thioethers, sulfoxides and sulfones [83].

These compounds were tested *in vitro* against the human cancer cell lines panel of NCI screening. The authors claimed that activity of these analogues was increased 5-10 times

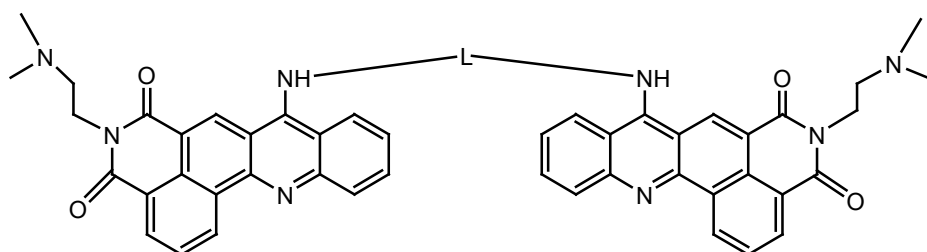
while sulfides were converted into sulfoxides. Among derivatives substituted in the side chain, those possessing a sulfur mustard residue, epoxy sulfide and sulfoxide group displayed the highest activity.

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 was 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 study and molecular modeling of the **64/65** DNA complexes indicated that **65**, having optimal length of the linker exhibits higher DNA affinity than **64**.

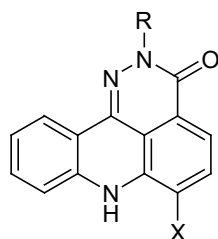
Stefańska et al. [86] synthesized a very promising group of 2,7-dihydro-3*H*-pyridazino[5,4,3-*kl*]acridin-3-one derivatives **66a-f** (Fig. 11).



60

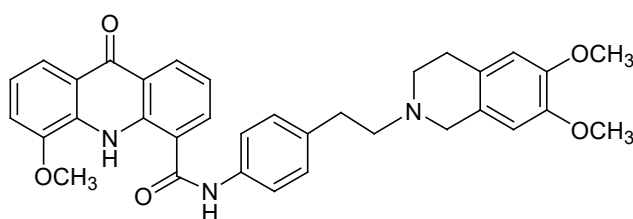


61. L = (CH₂)₂NH(CH₂)₂
 62. L = (CH₂)₃NH(CH₂)₃
 63. L = (CH₂)₃NCH₃(CH₂)₃
 64. L = (CH₂)₂NH(CH₂)₂NH(CH₂)₂
 65. L = (CH₂)₂NH(CH₂)₃NH(CH₂)₂



66

- 66a. R = CH₂CH₂N(CH₃)₂; X = H
 66b. R = CH₂CH₂CH₂N(CH₃)₂; X = H
 66c. R = CH₂CH₂N(CH₂CH₂)₂; X = H
 66d. R = CH₂CH₂-c-N(CH₂)₄O; X = H
 66e. R = CH₂CH₂-c-N(CH₂)₅; X = H
 66f. R = CH₂CH₂CH₂N(CH₃)₂; X = H



67 GF-1209189 (GG-918)

Figure 11. Derivatives synthesized by Stefańska et al. [86].

They were prepared in the reaction of 9-oxo-9,10-dihydroacridine-1-carboxylate with POCl₃, followed by addition of the appropriate (alkylamino)alkylhydrazines. The cytotoxic activity 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 type of multi-drug resistance



(MDR and MRP), was however weaker than that of compounds described previously by the authors, due lower affinity to DNA [85, 87].

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 inhibition of various human tumor cells, showed inhibitory effects against topo II, and DNA interaction.

The 9-acridone derivative GF-120918 (elacridar) **67** (Fig. 11) is a potent inhibitor of multidrug resistance [82]. It has been shown that elacridar **67** acts on P-gp, but it is also active in a cell subline expressing a newly identified mitoxantrone transporter (MXR). This compound is under clinical investigation (against malignant neoplastic disease and solid tumors) as MDR-modulator [82].

Su's group [89] prepared a series of 9-anilinoacridine and derivatives bearing an alkylating *N*-mustard residue at C4 of the acridine chromophore **68-75** (Fig. 12).

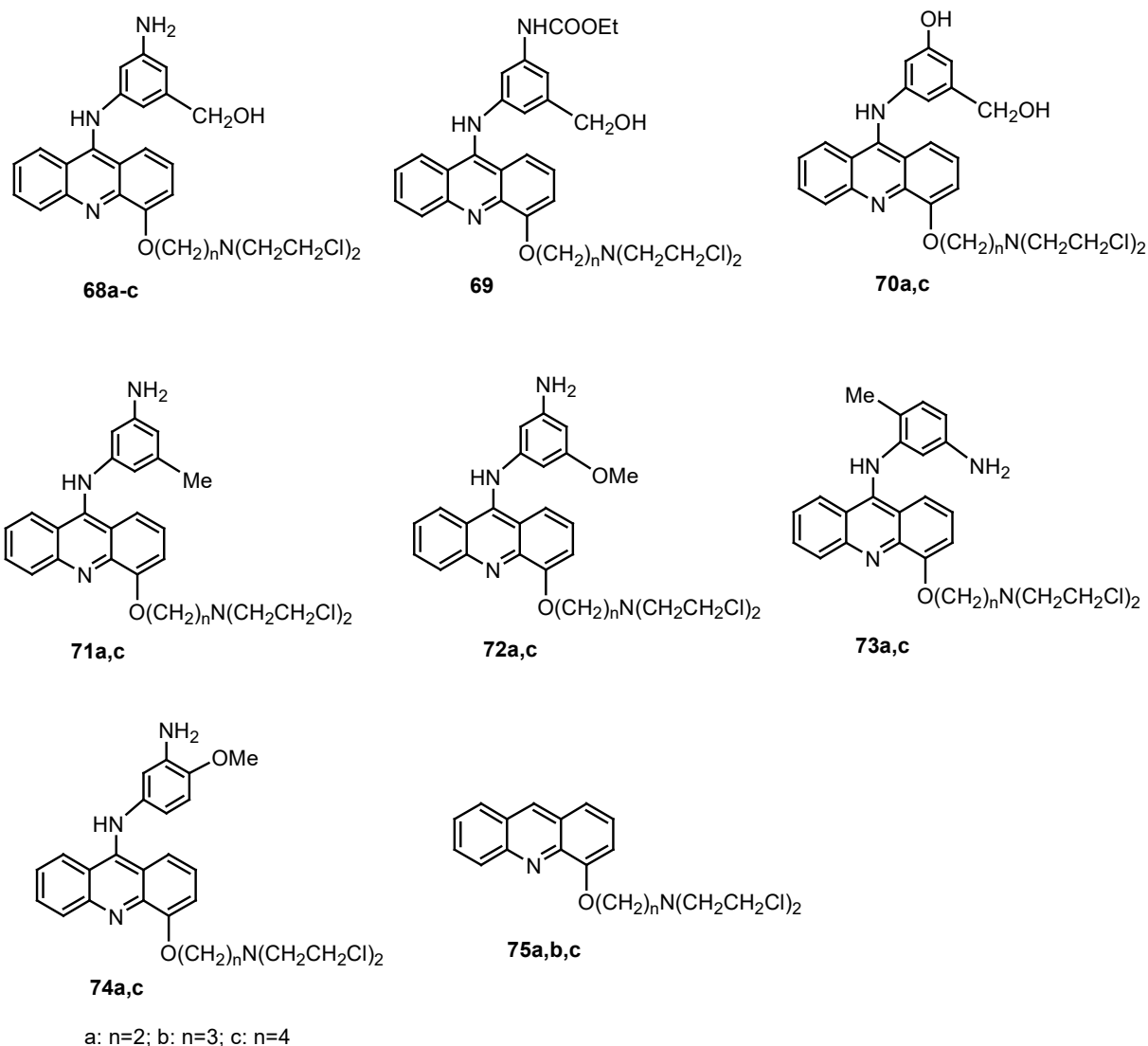


Figure 12. Acridines prepared by Su's group [89].

These compounds were very potent *in vitro* cytotoxic agents against human leukemia and various 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'-hydroxy-ethylamino)-4-methyl-1-nitroacridine (C-1748) **76** (Fig. 13), a novel anti-cancer agent in male beagle dogs.

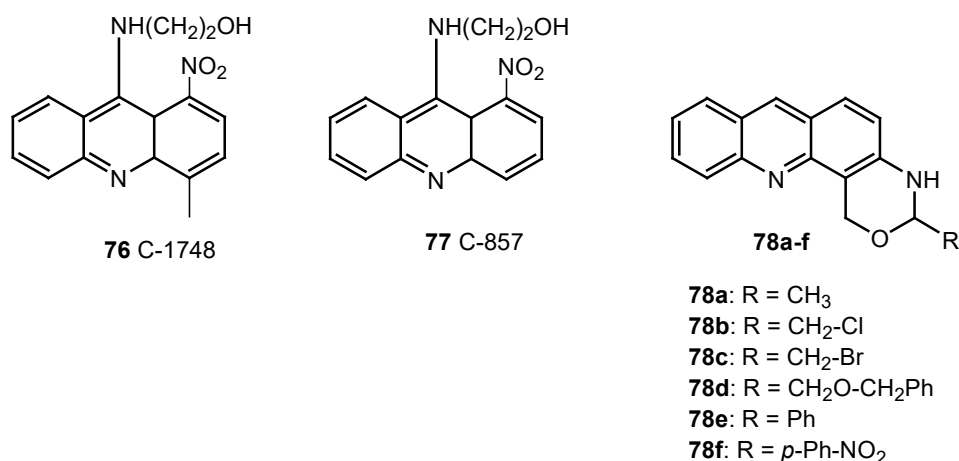


Figure 13. Acridine derivatives described by Ashok et al. [13].

In separate studies, they observed that C-1748 **76** has 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 leucopenia was observed with 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 drug may be well tolerated [13].

Ouberai et al. [78] 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 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 form and that effect is associated with a lowering of cytotoxicity. The activation of nitro derivative **78f** by nitroreductase indicating its potency as prodrug for either gene-directed or antibody-directed enzyme therapies.

Geci et al.[50] described twisted intercalating nucleic acids (TINA) having acridine derivatives using the 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.

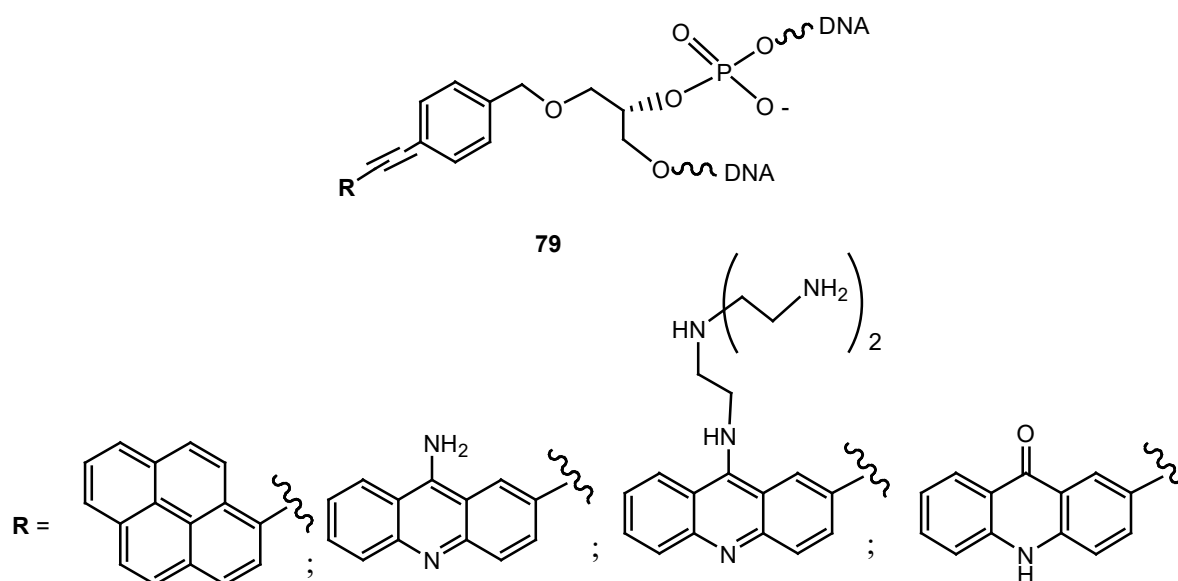


Figure 14. Twisted intercalating nucleic acids (TINA) having acridine moieties investigating by Geci et al.[50].

The synthesis of 9-(alkylsulfanyl)- and 9-(arylsulfanyl)acridine derivatives and study of their physicochemical properties was described by Nemcova et al. in 2006 [75]. The authors also presented the effect of the presence of (2-hydroxypropyl)cyclodextrins on properties of such substituted acridines.

2.4. ABCG2 inhibitors

Recent developments led to the synthesis of 7-(*p*-bromophenyl)-10,10-dimethyl-8-alkylthio-7,9,10,11-tetrahydro-benz[*c*]acridines and 7-[(*o*-; and *p*-substituted)phenyl]-10,10-dimethyl-7,8,9,10,11,12-hexahydrobenz[*c*]acridin-8-thione [35], 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' 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).

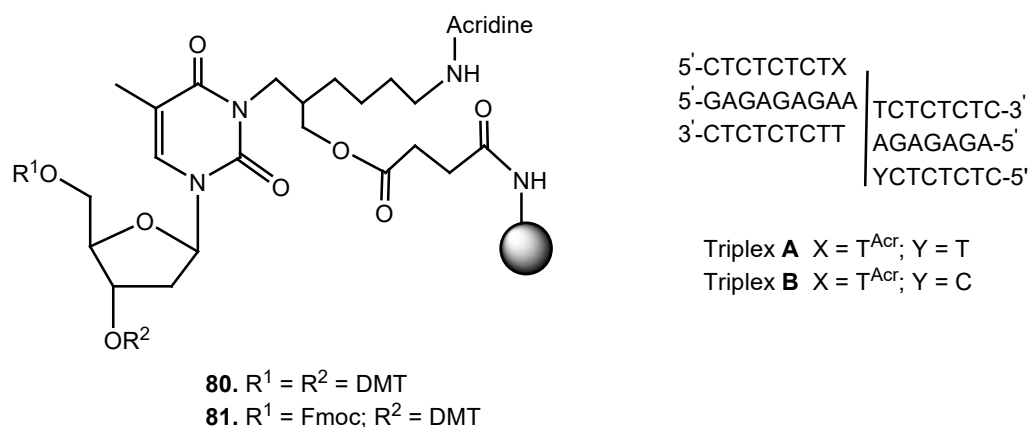


Figure 15. Acridine derivative synthesized by Amato et al. [5].

They showed that the both 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.

3. Acridine/acridone alkaloids. Their synthesis and structural modifications

Promising anticancer drugs are based on acridine alkaloids and their derivatives. According to the cytotoxicity of 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 [68, 69].

3.1. Acronycine

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

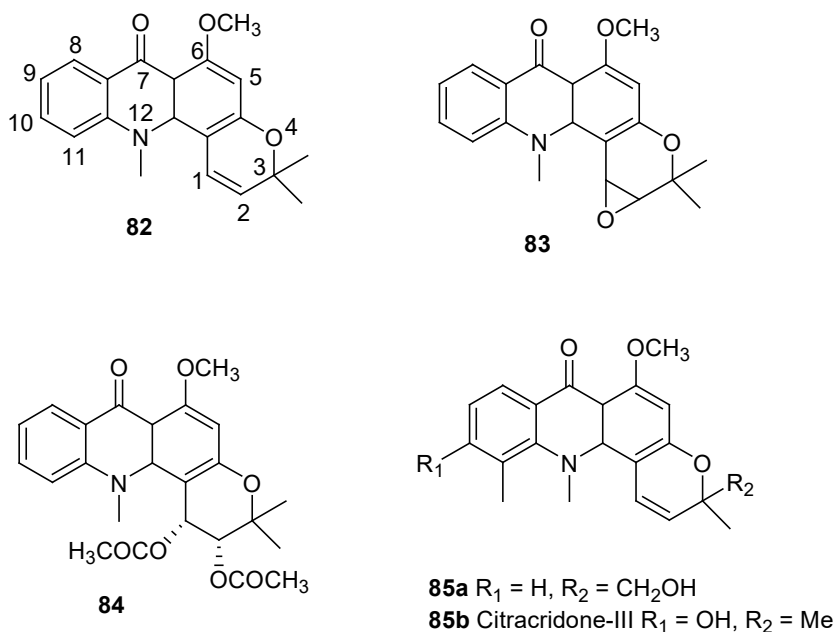


Figure 16. Acronycine **82** and its derivatives.

In 1966 Eli-Lilly Laboratories demonstrated its high activity against murine solid tumor models like S-180 and AKR sarcomas, X-5563 myeloma, S-115 carcinoma and S-91 melanoma. In contrast, activity towards leukemias was slight [20]. In 1983 Scarff performed phase I-II clinical evaluation of acronycine for human patients with refractory multiple myeloma [20]. Orally administrated acronycine capsules gave a disease remission for 72 weeks. The limited success of this experiment was probably due to moderate potency of acronycine and its poor solubility in water (2-3 mg/1L water) [20]. However, these results indicated significant antitumor properties of the agent and encouraged subsequent studies

concerning mechanism of action as well as design and synthesis of more efficient acronycine derivatives.

Results concerning the mechanism of action at the cellular and molecular level are not unanimous. It was reported that the drug did not interact with DNA but acted primarily by alteration of subcellular organelle membranes [20]. On the other hand, further experiments suggested interaction of acronycine with DNA by non-covalent binding to the double helix. The investigations related to structure – activity relationships revealed that 1,2-double bond in the pyran ring was essential for its antitumor activity. For example, 1,2-dihydro-acronycine 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 leads hypothesis that oxirane **83** is an intermediate in the course of bioactivation of acronycine *in vivo* [20]. The epoxide **83** in reaction with water gave respective diol, which after activation became an alkylating agent towards 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].

3.2. Other acronycine derivatives

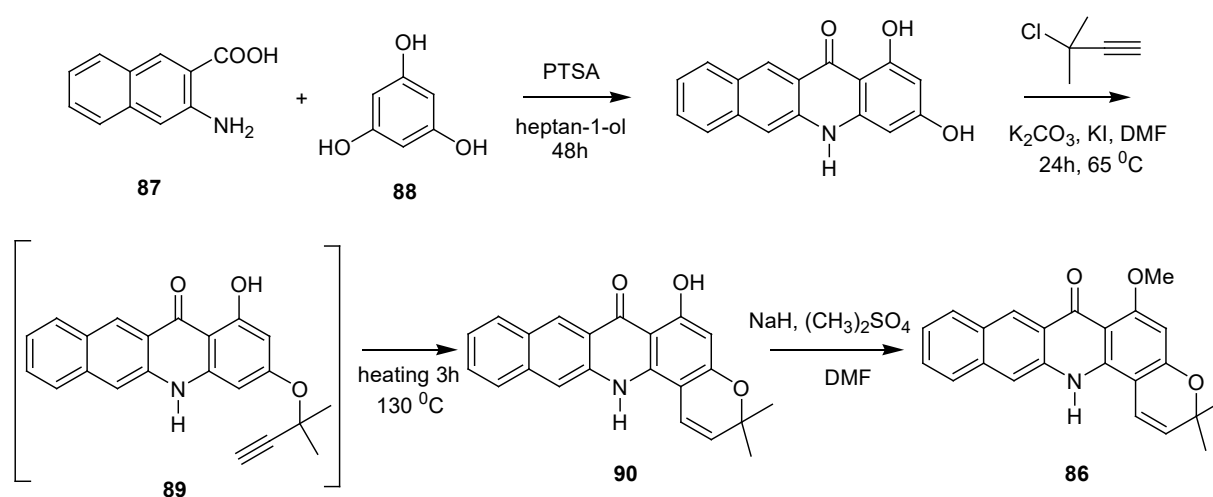
Other alkaloids structurally related to acronycine were also found. As an example, from the bark of *Citrus maxima* compound **85a** was isolated. It holds hydroxymethyl group in the pyran ring (Fig. 16). Most similar analogues turned out to be potent against HepG2 hepatoma and KB epidermoid cancer lines. Derivative **85a** was most active towards the 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) [68].

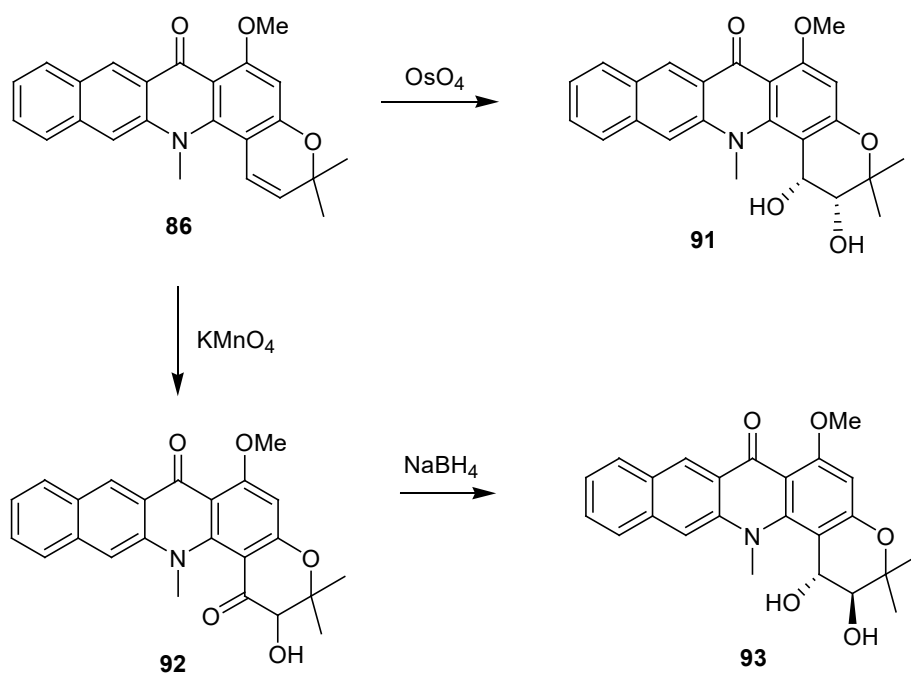
3.3. Benzo[*b*]acronycine

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



Scheme 3. Synthesis of benzo[*b*]acronycine **86** by Tillequin [36, 62].

Finally, methylation of **90** with dimethyl sulfate gave benzo[*b*]acronycine **86** [36, 62], which was converted into corresponding diols **91** and **93** (Scheme 4).



Scheme 4. Oxidation of benzo[*b*]acronycine **86** [36, 62].

The racemic *cis* diol **91** was obtained in the 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, 62]. Acylation of both *cis* and *trans* diols **91**, **93** with excess of acyl chloride or anhydride in the presence of pyridine yielded respective diesters **94**, **95** (Fig. 17).

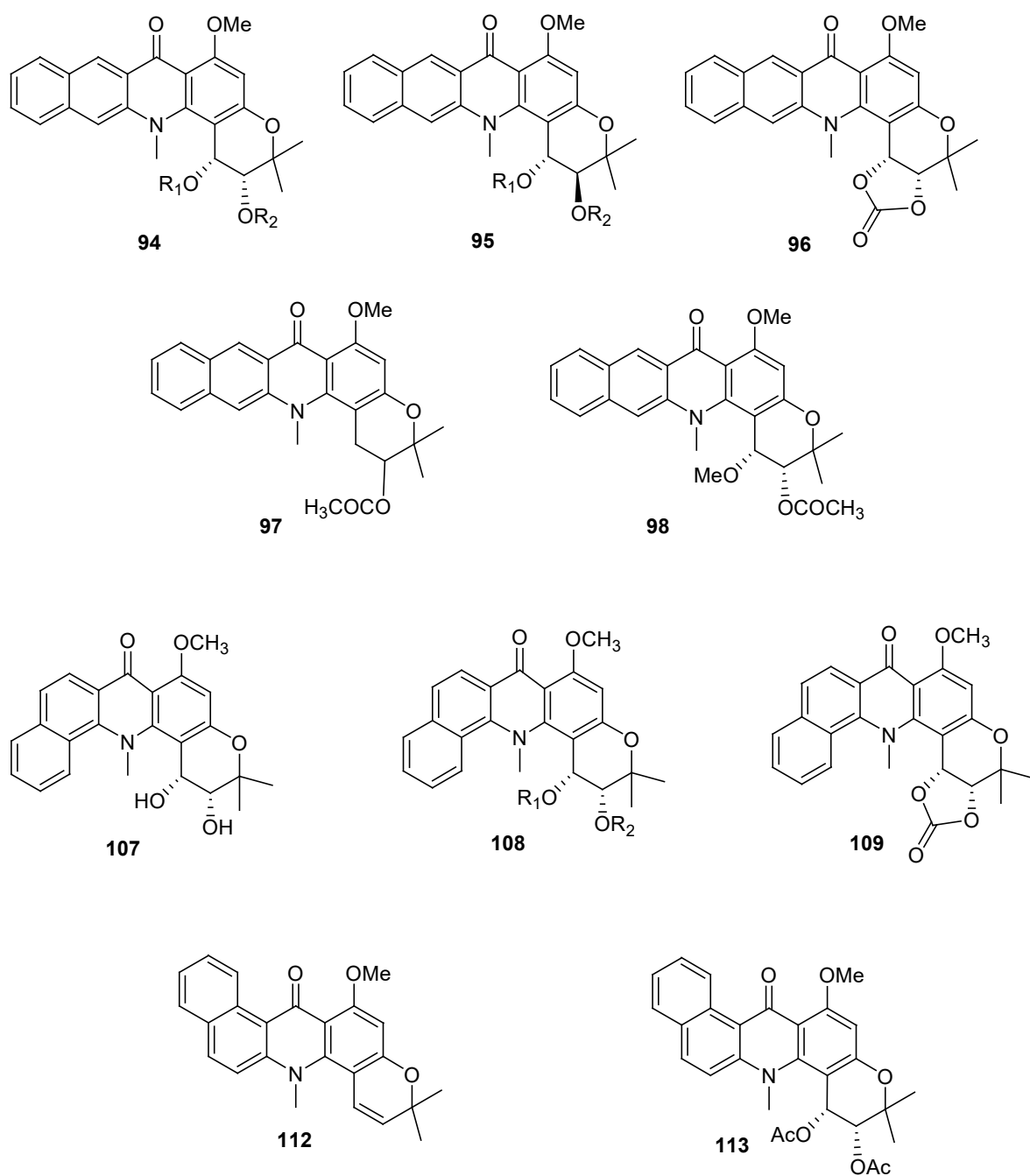
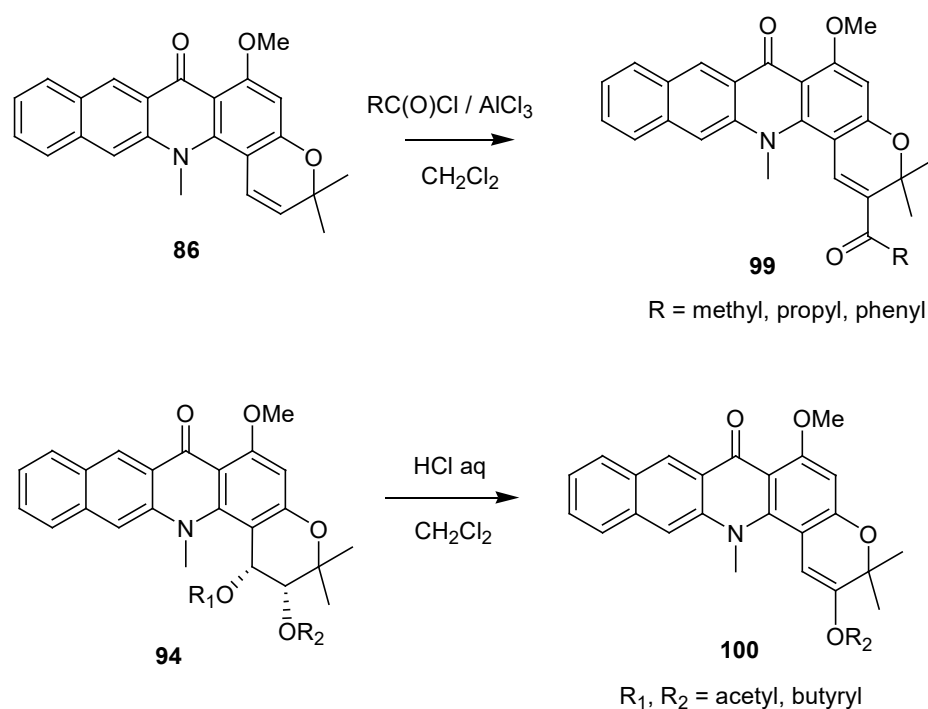


Figure 17. Some derivatives of benzo[*b*]acronycine **94-98** and benzo[*c*]acronycine **107-109**, **112**, **113**.

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, 62, 70].

Some dialkyl esters **94**, **95** were studied *in vitro* on L1210 leukemic cells. In comparison with acronycine **82** ($IC_{50} = 23 \mu\text{M}$) or benzo[*b*]acronycine **86** ($IC_{50} = 14.9 \mu\text{M}$) [20], both diesters **94**, **95** were more cytotoxic ($IC_{50} = 0.2 - 2.1 \mu\text{M}$), whereas cyclic carbonate **96** was even 1000-fold more potent ($IC_{50} = 0.014 \mu\text{M}$) than the esters. Finally, *cis*-diacetate **94** $R_1, R_2 = \text{Ac}$ ($IC_{50} = 0.8 \mu\text{M}$) was selected by Servier Laboratories for further evaluation of drug candidate [20]. The high potency of diesters **94-96** is correlated with their alkylating activity toward the exocyclic $-\text{NH}_2$ group in guanine [20, 62]. In other words, these compounds can bind to DNA covalently. In contrast to that, derivatives without a good leaving group at the benzylic position 1, like 2-acetoxy-1,2-dihydroacronycine **97** ($IC_{50} = 17 \mu\text{M}$) [20, 62] or *cis*-2-acetoxy-1-methoxy-1,2-dihydrobenzo[*b*]acronycine **98** ($IC_{50} = 45 \mu\text{M}$) [7, 41] are considerably less active (Fig. 17). The influence of electron density at 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). Next some enolic esters **100** were synthesized upon acidic dehydration of diesters **94** [62].

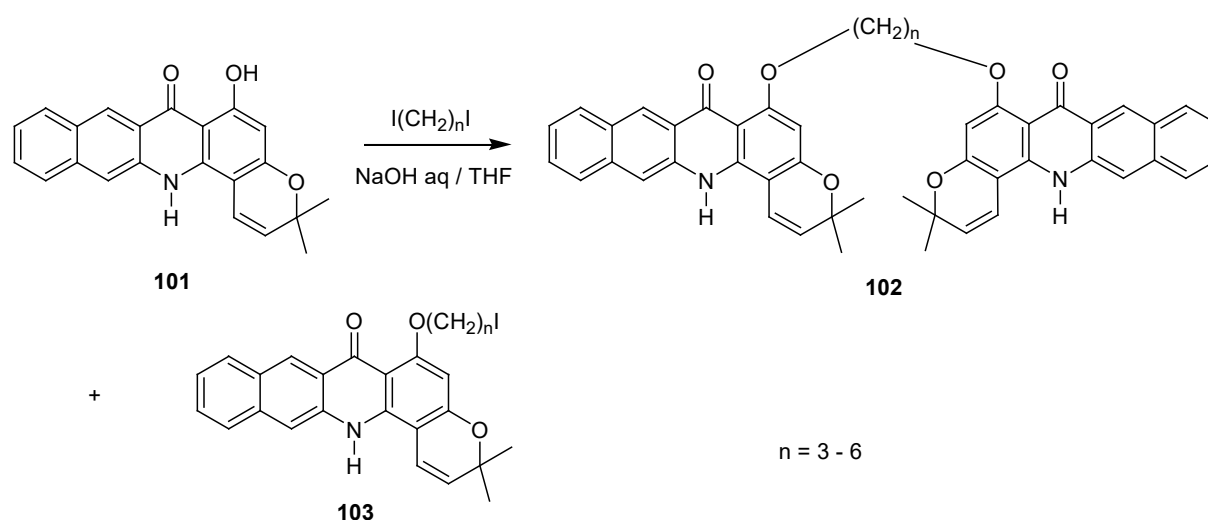


Scheme 5. Synthesis of benzo[*b*]acronycine derivatives [63].

Michael acceptors **99** have lower cytotoxicity ($IC_{50} = 20, 30, >50 \mu\text{M}$ respectively) compared to benzo[*b*]acronycine **86** ($IC_{50} = 15 \mu\text{M}$) [63], despite the fact that position 1 should be highly reactive towards 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 $1.8 \mu\text{M}$ respectively [63]. 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, different from alkylation [63].

3.4. 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].

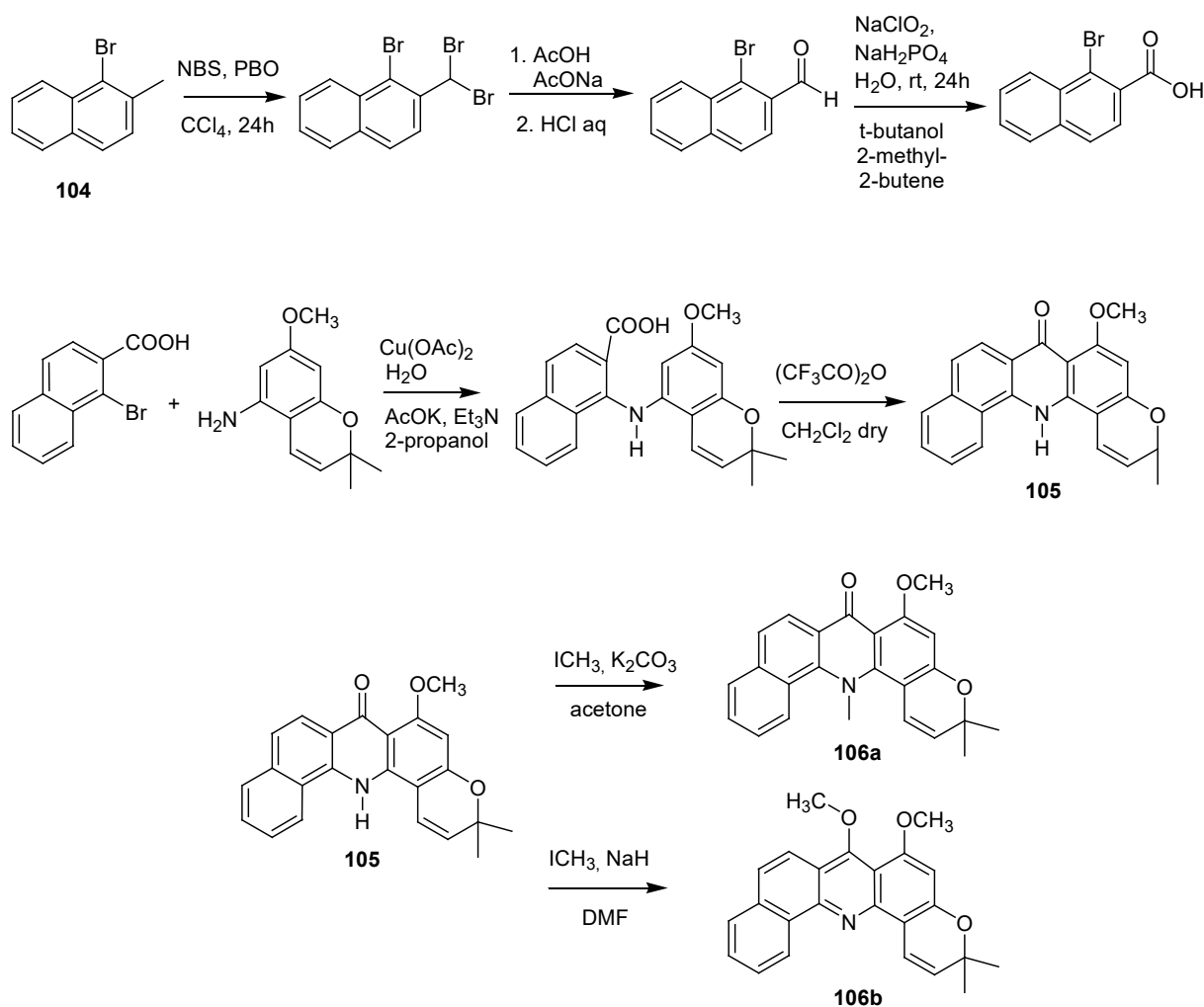


Scheme 6. Preparation of dimeric benzo[*b*]acronycines **102** [49].

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

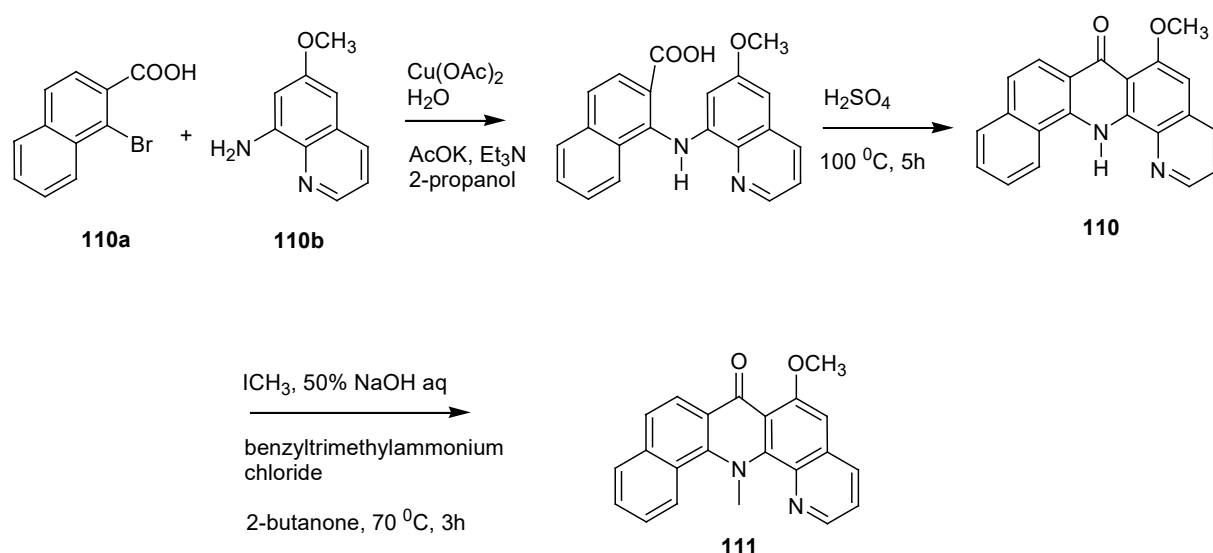
3.5. Benzo[*c*]acronycine

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



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

Finally, alkylation with iodomethane in presence of potassium carbonate in acetone gave the desired *N*-methylated product **106a** with (IC₅₀ = 12.1 μM), which is considerably more active than its *O*-methylated counterpart **106b** (IC₅₀ = 58 μM) [22]. Diol **107**, diesters **108** and cyclic carbonate **109** (Fig. 17) derived from benzo[*c*]pyrano[3,2-*h*]acridine-7-one were prepared from corresponding acridone **106a** by simple modifications of the synthesis presented above. The activity of these compounds was in the range of IC₅₀ = 26.2 μM to 6.7 μM for the *cis*-diol **107**, and it means that they are less active than benzo[*b*]acronycine **86** (IC₅₀ = 1.9 μM), and more than acronycine **82** (IC₅₀ = 23 μM) [22]. Seguin et al.[22] reported also synthesis and pharmacological evaluation of the benzo[*c*]acronycine **110** and **111** series, in which dimethylpyran ring is replaced by pyridine (Scheme 8).



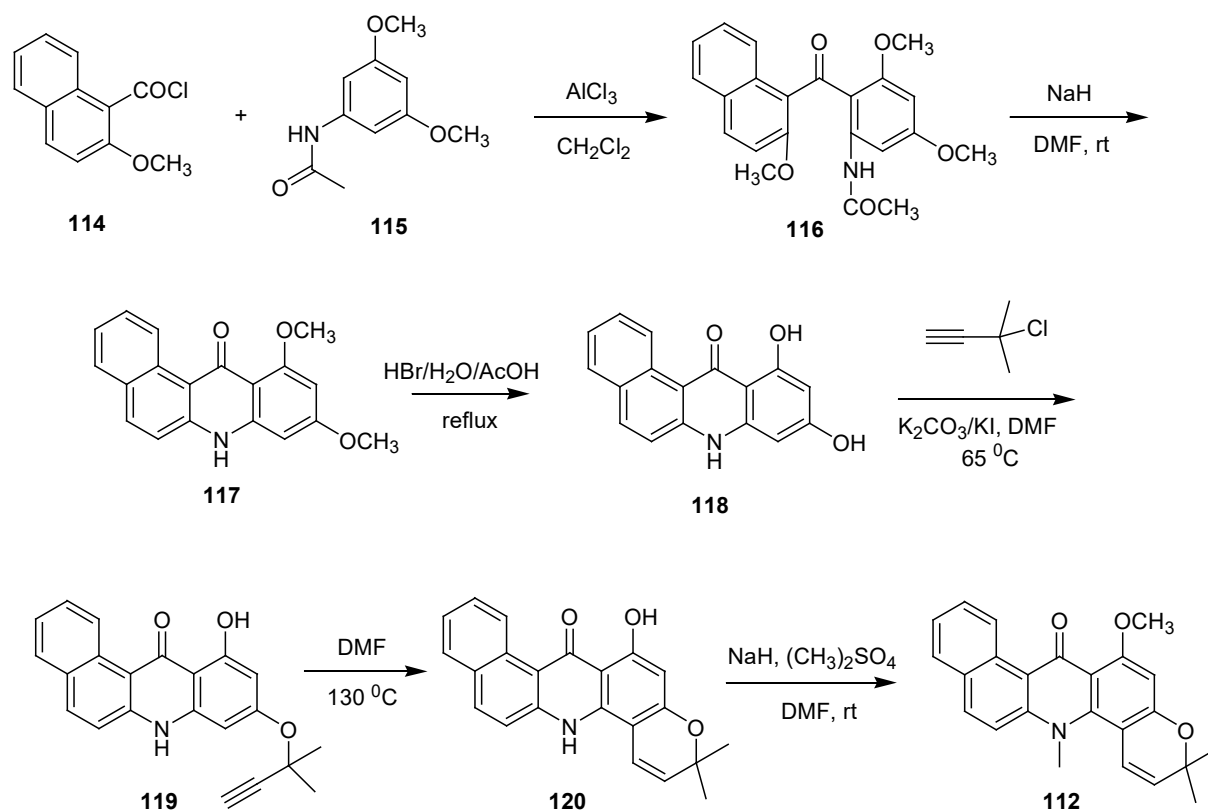
Scheme 8. Synthetic pathway to naphtho[1,2-*b*][1,10]-phenanthroline-7(14*H*)-ones **110**, **111** [22].

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 *N*-unmethylated derivative **110** ($\text{IC}_{50} = 37\ \mu\text{M}$) is more cytotoxic than *N*-methylated **111** ($\text{IC}_{50} > 100\ \mu\text{M}$) [22], which is in contrast to benzo[*c*]pyrano[3,2-*h*]acridine-7-ones **105** and **106a**. Moreover, compounds of benzo[*c*]acronycine series holding an angular ring system are less active in comparison with their benzo[*b*]acronycine analogues [22].

3.6. Benzo[*a*]acronycine

Benzo[*a*]acronycine **112** (Fig. 17), in contrast to benzo[*c*]acronycine, exhibited submicromolar toxicity on alkylation properties [76]. One of the most active compounds of this type, turned out to be a *cis*-diacetoxy derivative **113** ($\text{IC}_{50} = 0.7\ \mu\text{M}$ against L1210

leukemia and 0.15 μM against human epidermoid carcinoma KB-3-1) [76]. Synthesis of benzo[*a*]acronycine **112** consisted of several steps (Scheme 9).



Scheme 9. Synthesis of benzo[*a*]acronycine **112** [76].

Firstly, 3,5-dimetoxyacetanilide **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-dihydroxybenzo[*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 **112** [76]. Benzo[*a*]acronycine **112** occurred to be more cytotoxic in comparison with acronycine **82**

(Fig. 16) against L1210 cell line (2.5 μM and 23 μM respectively), but less cytotoxic against KB-3-1 cell line (8.6 μM and 3.7 μM respectively).

3.7. Thioacridone

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

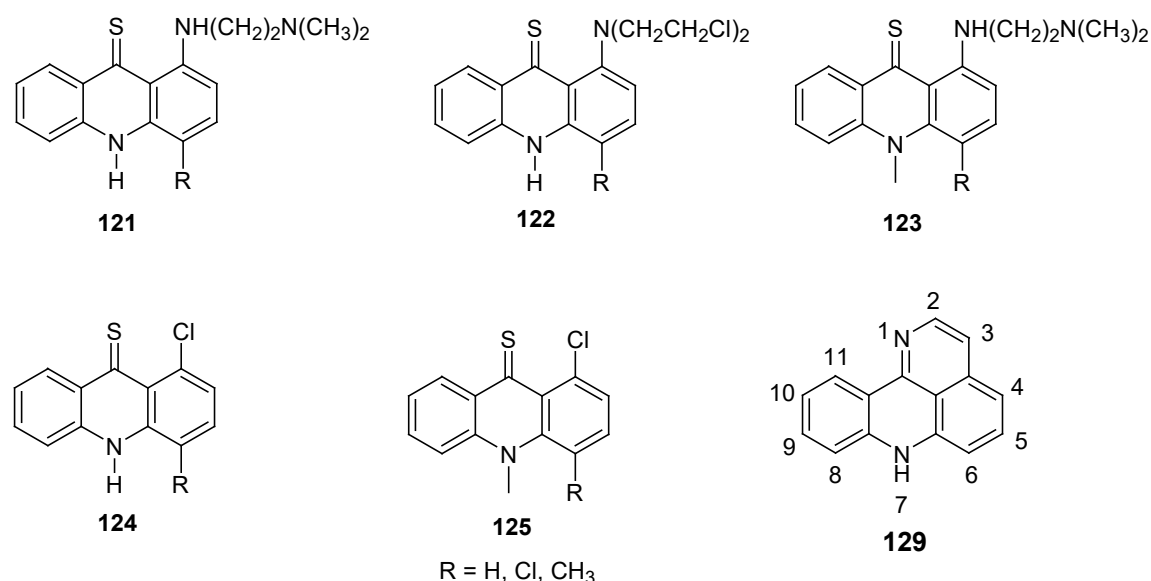
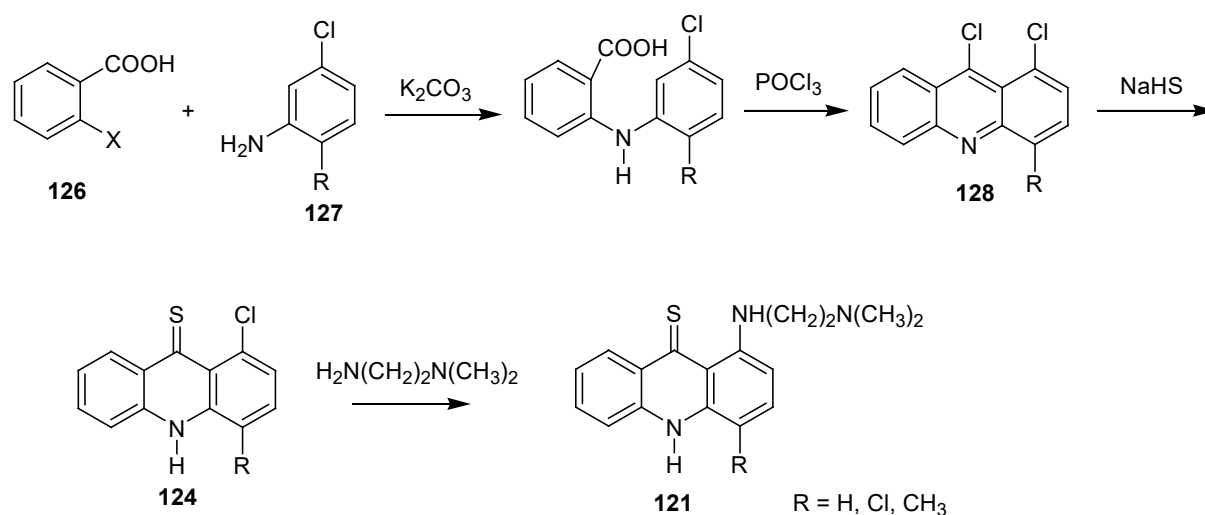


Figure 18. Thioacridones **121-125** synthesized by Van der Schyf [43] and pyrido[4,3,2-*k*]acridine **129** developed by Demeunynck [25].

Thiocarbonyl compounds with different electronic configuration 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 geometry of the molecule in comparison with carbonyl analogues [43]. These molecular properties turn out to be interesting for investigation of structure-activity relationship.

1-Aminothioacrydones **121-123** and 1-chlorothioacrydones **124, 125** exhibited cytotoxicity *in vitro* ($\text{IC}_{50} = 2.3\text{--}15 \mu\text{M}$ and $\text{IC}_{50} = 6$ to $>26 \mu\text{M}$ respectively), against HL-60 human

promyelocytic leukemia cells. It is noteworthy that compounds **121** carrying article $\text{NH}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ group are more potent than derivatives **122** having article nitrogen mustard moiety, despite the fact that the latter seem 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 Ullmann reaction from 2-chlorobenzoic acid **126** (Scheme 10).



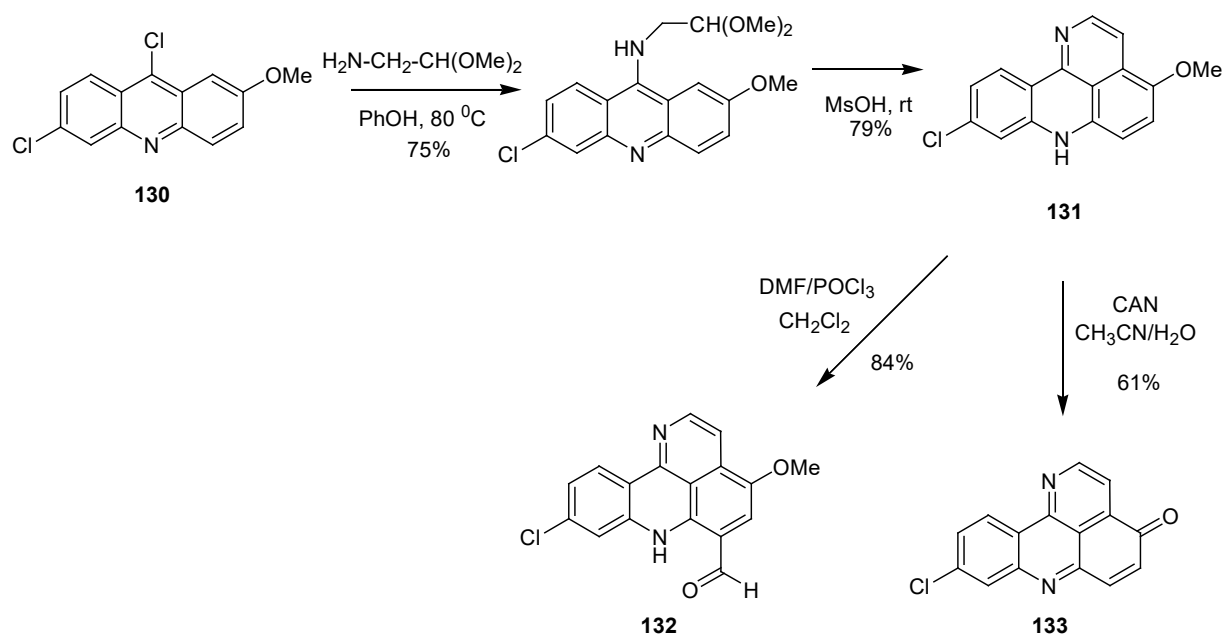
Scheme 10. Synthesis of thioacridone derivative **121** [43].

A condensation of **126** with an excess of aromatic amine **127**, followed by cyclization with phosphoryl chloride, gave dichloroacridine **128**. Then the reaction with sodium hydrogen sulfide provided 1-chloro-thioacridones **124**, which with an excess of dimethylaminoethylamine gave rise to the product **121** [43]. Studies concerning of the properties DNA binding of these compounds indicated that the most active derivative **121** R = H, (IC_{50} (2.3 $\mu\text{g}/\text{mL}$) exhibited also 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, thioacrydones are promising antimalarial drugs, their antiplasmodial activity is in the range of IC₅₀ from 0.4 to 27 µg/mL. The best result was obtained for 1-(2-dimethyl-aminoethylamino)-9(10*H*)-thioacridone **121** R = H [69].

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

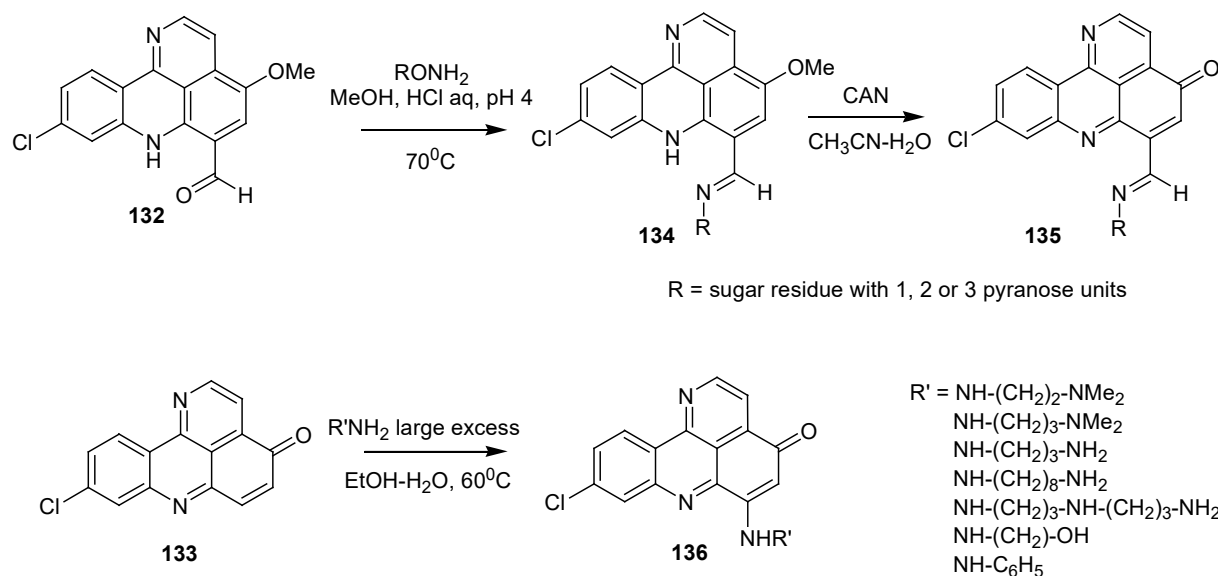
Demeunynck and co-workers [25] investigated the synthesis and therapeutic properties of pyrido[4,3,2-*kl*]acridine **129** (Fig. 18), which refers to skeletons of marine acridine alkaloids. The starting material, 6,9-dichloro-2-methoxyacridine **130** (Scheme 11), was converted in a two step sequence reaction into 9-chloro-4-metoxypyrido[4,3,2-*kl*]acridine **131** [25]. Further modification was performed in two pathways (Scheme 11).



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

The Vilsmeier-Haack reaction ($\text{DMF}-\text{POCl}_3$) led to formyl derivative at the 6 position **132**. Secondly, 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).

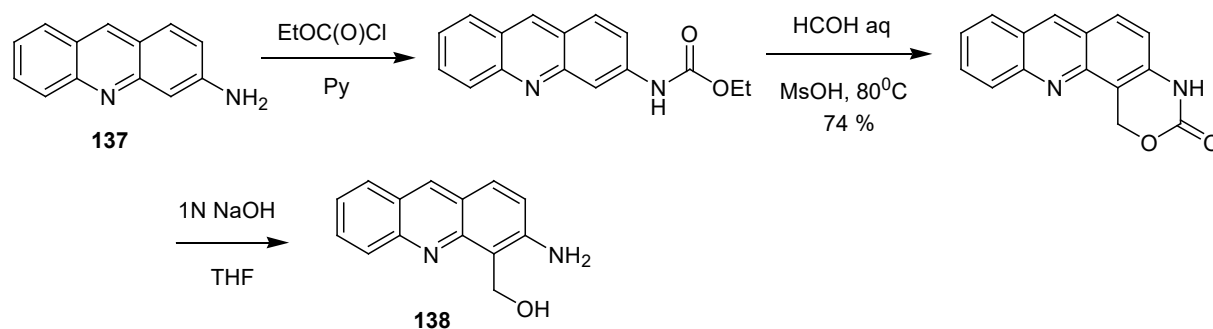


Scheme 12. Preparation of glyco- and amino conjugates **134-136** from pyrido[4,3,2-*kl*]acridines **132**, **133** [25].

The second one **133** under treatment with amines produced amino conjugates **136**. 1,4-Michael addition products undergo reoxidation to quinone forms **136** spontaneously [25]. The glycoconjugates **134**, **135** showed low cytotoxicity *in vitro* against HT29 cell lines (IC₅₀ from >50 to 128 μM), but some of the amino conjugates **136** turned out to be much more cytotoxic (IC₅₀ = 1.8 to 21 μM and >100 for R' = C₆H₅). 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 found [25].

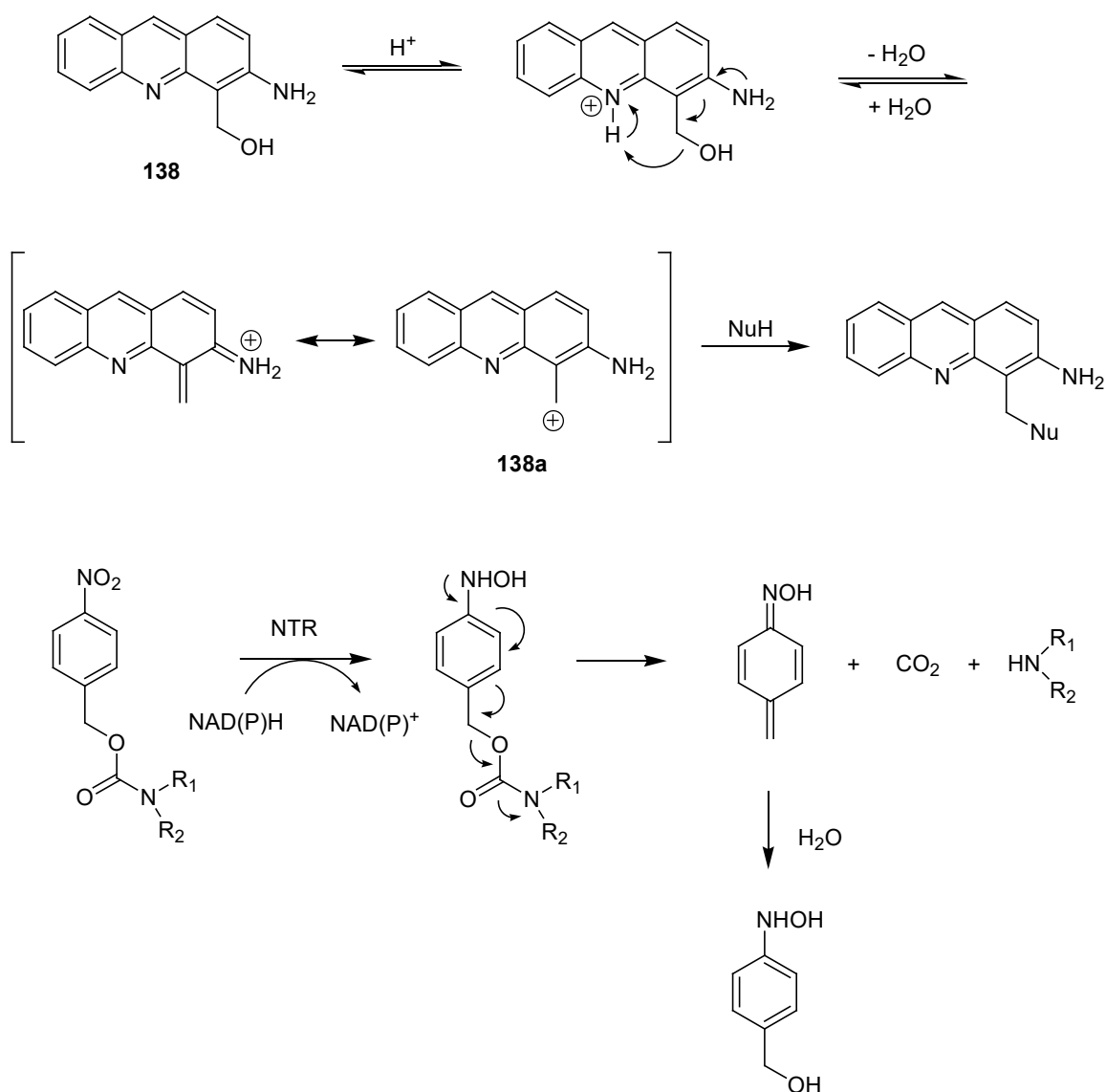
3.9. 3-Amino-4-hydroxymethylacridine

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



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

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



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

Such a high reactivity causes toxicity *in vivo* and required modification to get analogues with better pharmacological properties [12]. Demeunynck et al. [12] developed *p*-nitrobenzyl-carbamate prodrugs of 3-amino-4-hydroxymethylacridine **139**, **140** (Fig. 19) 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 cofactor (Scheme 14) [12]. The *in vitro* cytostatic activity against HT29 cell line was $IC_{50} = 2.5 \mu\text{M}$ and $9 \mu\text{M}$ for di(*p*-nitrobenzyl) derivative respectively [12]. An other structural modification



of 3-amino-4-hydroxymethylacridine **138** is based on [1,3]-oxazines **141** (Fig. 19), which are using in a reaction with article appropriate aldehyde under acidic conditions [77]. The [1,3]-oxazines **141** are considered cyclic precursors of the potential drug because of ring-chain equilibrium (Fig. 19). Moreover, stability of the ring form depends on R substituent at the position 2 [77].

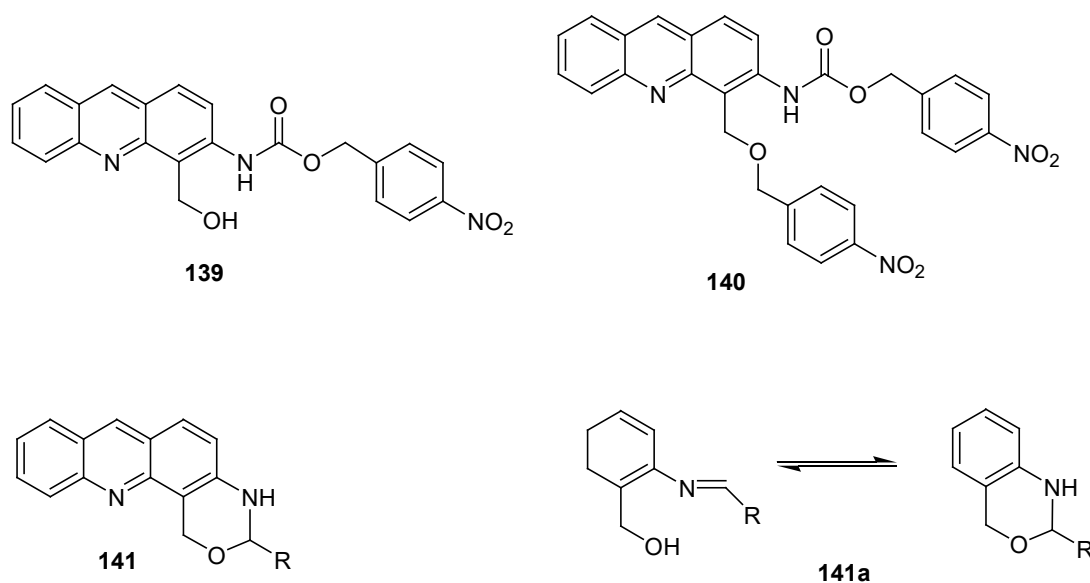


Figure 19. Acridine derivatives investigated by Demeunynck et al. [12].

4. Recent achievements in synthesis of acridine/acridone analogues

In 2004 Chiron and Galy [31] studied reactivity of the acridine ring, which is very important for the design of acridine analogues of high anti-cancer activity. Recently, Belmont et al. [20] described acridine and acridone derivatives, their anti-cancer properties and synthetic methodologies. The previous routes leading to acridine/acridone ring formation and primarily the preparation of their analogues were based on the Ullman-Jourdan reaction [4]. This method is still widely used for this purpose. The reaction involves condensation of respectively functionalized anilines with *o*-halogenobenzoic acid derivatives or

halogenobenzene and *o*-aminobenzoic acid to give diphenylamino-2-carboxylic acids, which in the presence of strong acids cyclise to corresponding acridones. Next, reductive conditions and then harsh oxidative media are needed for the transformation of acridone to acridine [20]. This methodology makes possible the preparation of e.g. 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 analogues **146** (Fig. 20) which were used to synthesis of their conjugates with muramyl dipeptide (MDP) or nor-muramyl dipeptide (nor-MDP) [44, 45].

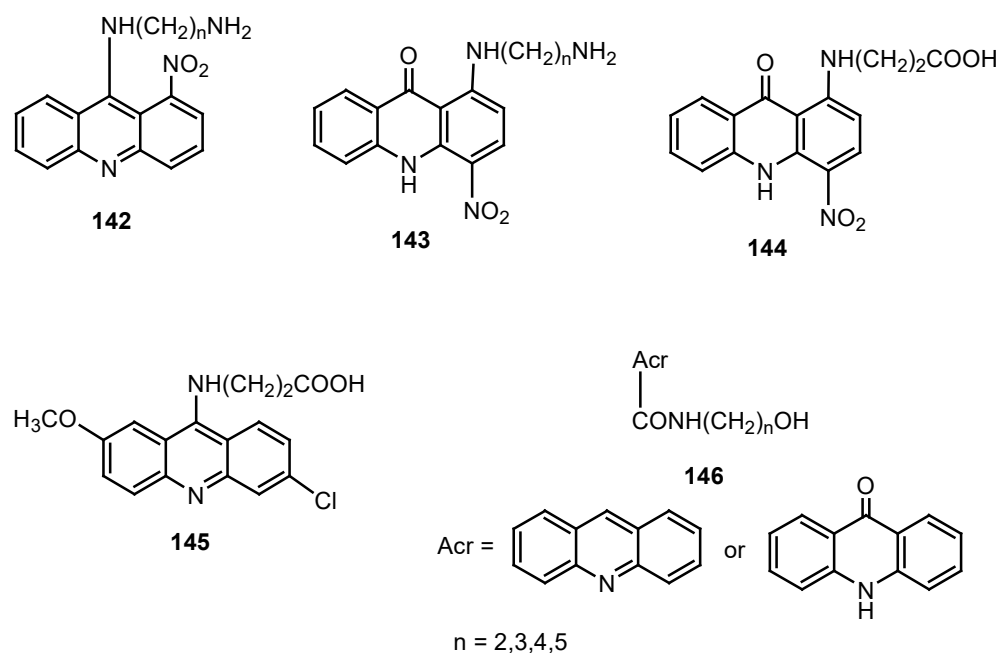
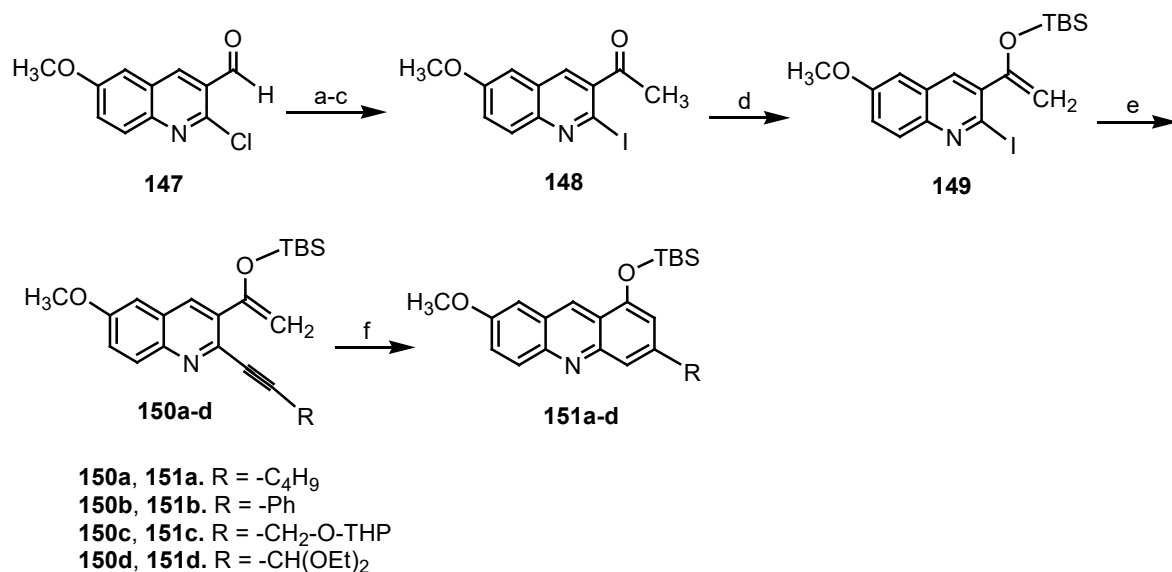


Figure 20. New acridine/acridone derivatives **142-146**.

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

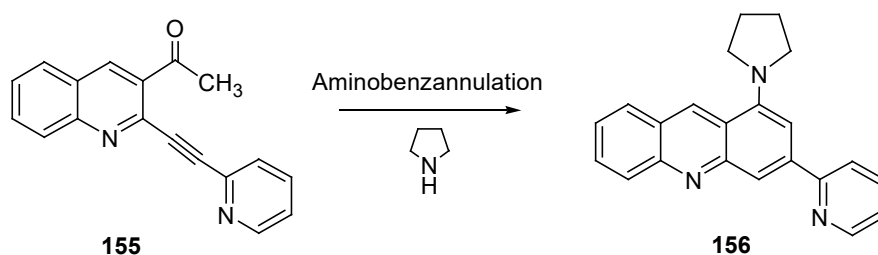
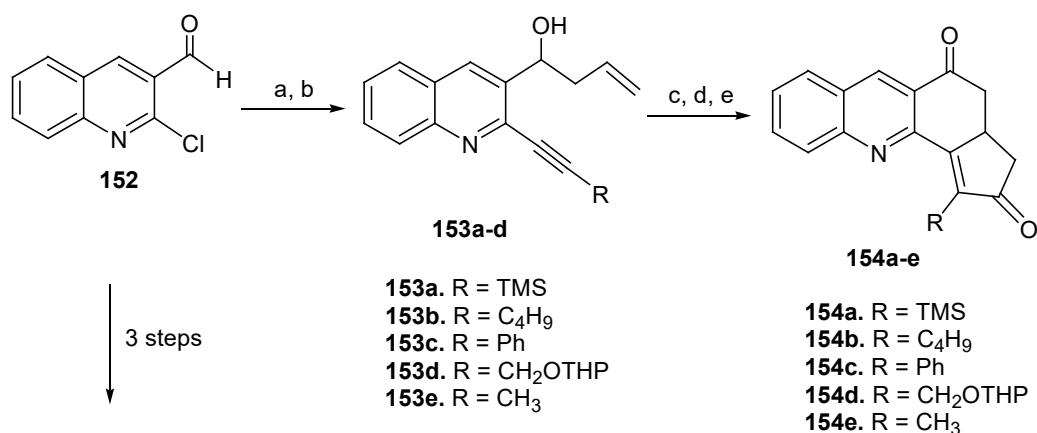
rhodium-catalyzed benzannulation of the quinoline intermediate yielding the desired poly-substituted acridine derivatives.



a. MeMgBr, THF, 40°C; b. MnO₂, toluene, 80°C; c. NaI, CH₃CN, HCl 4N, reflux; d. TBSOTf, Et₃N, CH₂Cl₂; e. 1-alkyne, PdCl₂(PPh₃)₂, CuI, Et₃N, toluene, rt; f. 10 mol % [Rh(CO)₂Cl₂], toluene, 120°C.

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

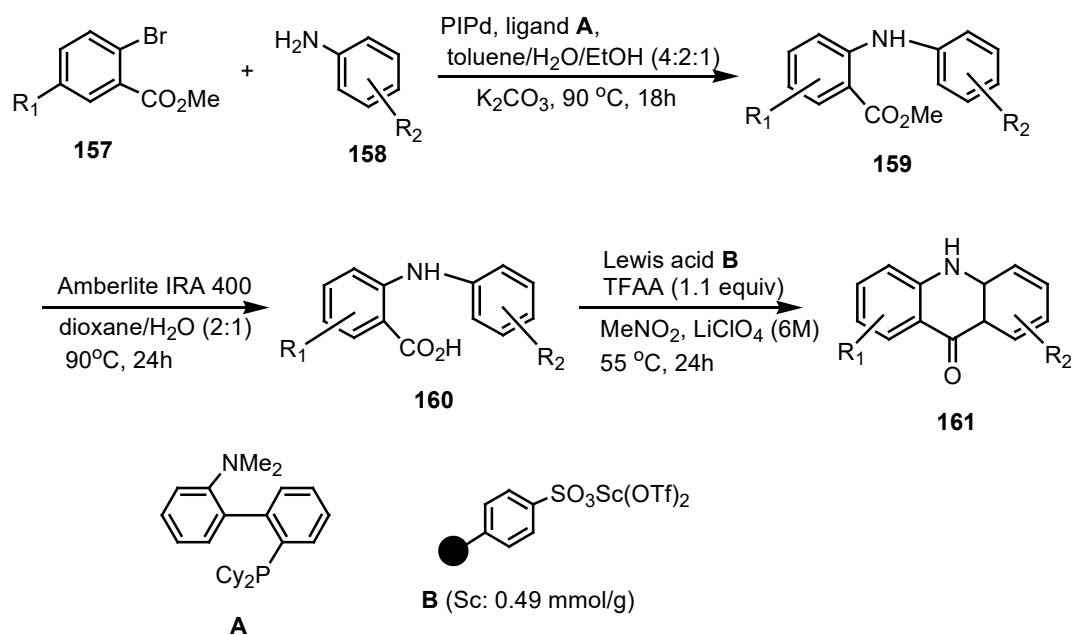
Patin and Belmont [80] presented another route towards acridines via the Pauson-Khand reaction on alkynes **153** or **155**, leading to tetrahydrocyclopenta[*c*]acridine-2,5-diones **154a-e** and 1-amino-acridine **156** (Scheme 16). Demeunynck et al. [104] recommended article 2,2,2-trichloro-ethoxycarbonyl (Troc) group which has been successfully used as a protecting group for aminoacridines.



- a. 1-alkyne, PdCl₂(PPh₃)₂, CuI, Et₃N, DMF, r.t.
 b. AllylMgBr, THF, -78 °C
 c. Enynes **153a-d**, Co₂(CO)₈, CH₂Cl₂, r.t., 2 h; NMO, r.t., overnight
 d. DMP, CH₂Cl₂, r.t.,
 e. Enyne **153a**, Co₂(CO)₈, CH₂Cl₂, r.t., 2 h; NMO, r.t., overnight; TPAP and MS

Scheme 16. A new route to acridine derivatives [20, 80].

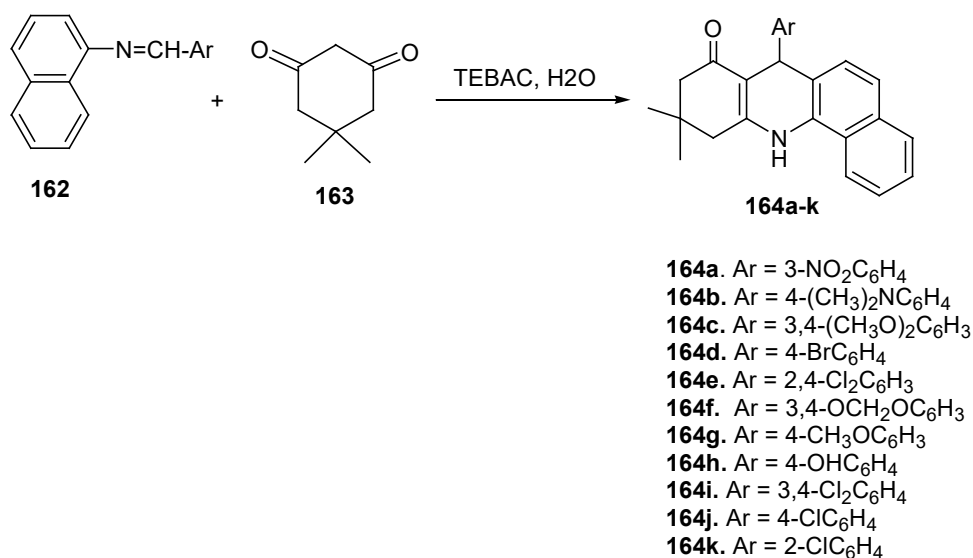
Acridone analogues are promising antiviral agents [3, 48] as well as fluorescent labels in biodiagnostics [18, 46]. These compounds are also important precursors for the creation of acridine derivatives with potential anti-cancer activity [20, 38, 40, 44, 45]. Acridones are usually prepared by Ullman condensation of anilines with 2-bromobenzoic acids to give *N*-phenyl anthranilic acids, which undergo ring closure with sulfuric acid. Recently, Nishio et al. in 2006 [77] presented a convenient method for the preparation of acridone derivatives (Scheme 17).



Scheme 17. Synthesis of acridine derivatives using polymer-supported palladium and scandium catalysts [77].

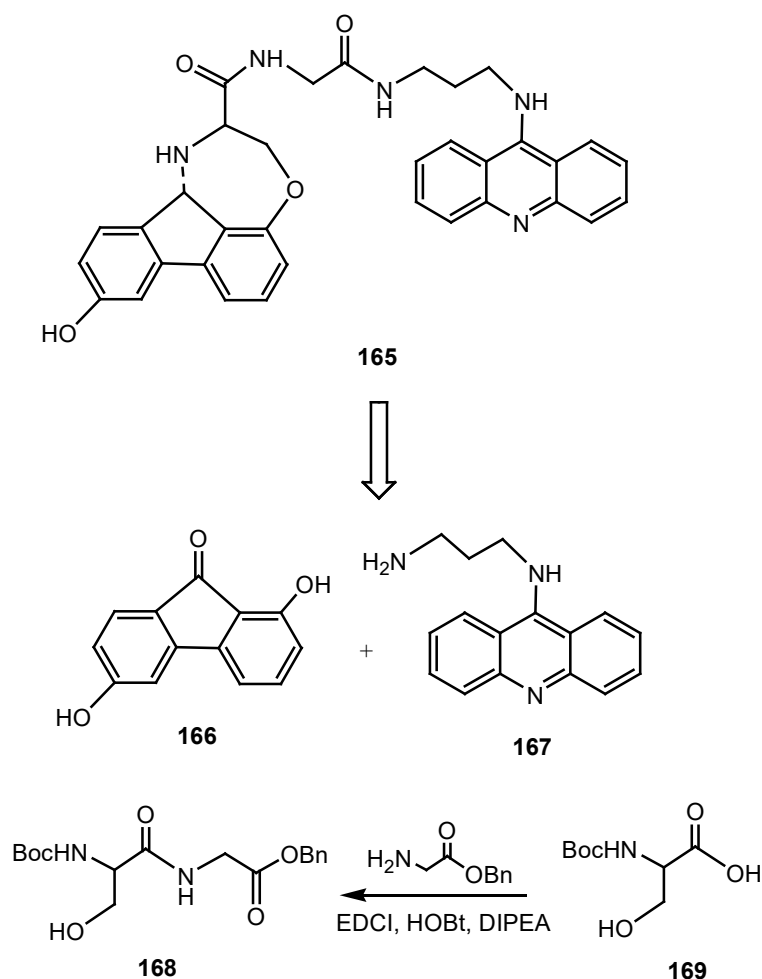
The method is based on combined use of polymer-supported palladium and scandium catalysts in aryl amination and intramolecular Friedel-Crafts acylation reactions, respectively. The approach using several polymer-supported catalysts in multistep synthesis would be useful for construction of some compound 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-1,3-cyclohexadione **163** in aqueous medium catalyzed by TEBAC (Scheme 18).



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

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



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

Some acridine derivatives have been recently 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 [73]. Tu et al. in 2007 [92] reported a new reaction of Schiff's base with dimedone to produce acridine derivatives under microwave irradiation. Recently, Ma et al. in 2007 [60] presented the reactivity of the 9-amino-acridine chromophore in guanidylation reactions. They developed new methodologies that allow the formation of two novel structural acridines of potential biological interest: incorporation of N9 into a five-membered cyclic guanidinium group and transformation of C9 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 [72] 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).

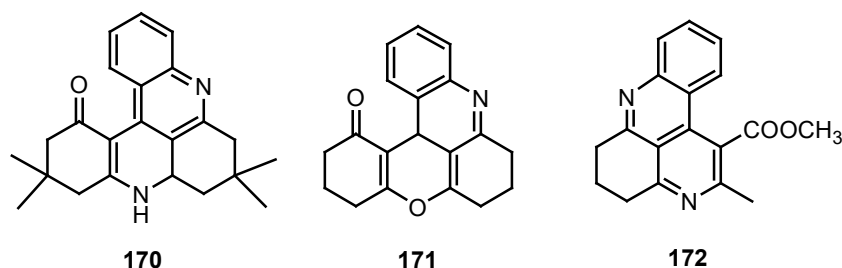


Figure 21. Derivatives reported by Murugan's group [72].

5. Conclusions

Neoplastic diseases, bacterial and parasitic infections are still a serious challenge for many researchers 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 multidrug resistance (MDR) of tumor cells. Up to now numerous derivatives and analogues of acridines/acridones synthesized as potential anti-cancer 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, pyrazolo-acridones, pyrazolopyrimidoacridones, 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 anti-cancer activity has 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*.

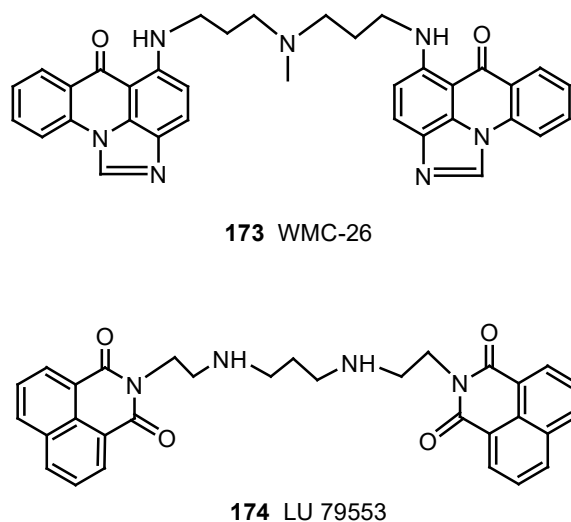


Figure 22. Example of symmetric bifunctional intercalators **173** and **174**.

Several acridine/acridone analogues are in use in clinics due to their anti-bacterial properties (acriflavine, aminacrine, ethacridine), against parasite infections (quinacrine, acranil) and as anti-cancer 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 tumours) [23]. Analogues 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 of 1-nitro-acridine derivatives, 9-(2'-hydroxy-ethylamino)-4-methyl-1-nitro-acridine (C-1748) **76** demonstrates notably high antitumor efficacy against human prostate cancer (Fig. 13) [13, 14, 74, 90].

The anti-cancer mechanism of acridine derivatives still remains largely unknown. It has been thought that they may play a role in interrupting DNA synthesis by intercalating in to DNA and therefore inhibiting topo II or I [28, 47]. Wang's studies [96] provide novel insights into

the anti-cancer 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].

Acknowledgments

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