Chemotherapeutic Effects of Acridine Derivatives

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Abstract: Acridine derivatives show a broad range of biological activities. They have primarily been explored as chemotherapeutic agents (anticancer, antibacterial, antiprotozoal), because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase and telomerase enzymes. Research continues to be focussed primarily in these areas, but recent work shows they are active also as anticholinesterase agents.

Keywords: Acridine, Antibacterial, Anticancer, Antiprotozoal, Anticholinesterase, Telomerase.

INTRODUCTION

Acridine derivatives are one of the oldest and most successful classes of bioactive agents. Proflavine (**1**) and acriflavine (a mixture of proflavine and euflavine: **2**) were used as topical antibacterials in the early 20th century [1], superseded in the 1940s by another acridine, aminacrine (9-aminoacridine: **3**) [2]. Acridines have also found wide use as antimalarial agents from the 1940s to the present day, primarily in the form of mepacrine (**4**) and pyronaridine (**5**) [3]. Euflavine, acriflavine, and the related acridine yellow (**6**) were shown to have weak antitumour activity in animal models, and mepacrine was used quite widely as an adjunct cancer treatment [2]. However, the first acridine-based agents designed specifically for cancer treatment were developed in the 1970s; the 1-nitroacridine derivative nitracrine (**7**) in Poland [4] and the 9-anilinoacridine amsacrine (**8**) in New Zealand [5]. Despite this long history, acridines are still being explored for all of the above therapeutic areas, and this review will focus primarily on recent work.

INTERACTION OF ACRIDINES WITH DNA

The reasons for the wide usefulness of the acridines as broadly active chemotherapeutic agents are varied, but include their ready synthesis [6], biological stability, and an ability to bind efficiently to DNA and disrupt cellular DNA function. It has long been known that acridines bind preferentially to DNA in cells [2]. The concept of intercalation (insertion of a flat polyaromatic chromophore between the basepairs of double-helical DNA, driven by stacking and charge-transfer interactions between the aromatic systems of the ligand and the DNA bases, causing unwinding of the helix) was first demonstrated with proflavine (**1**) [7], and later with other acridines [8]. A number of aspects of the binding of acridines to DNA have been considered relevant to their chemotherapeutic effects, and particularly to their anticancer activity [9]. These are:

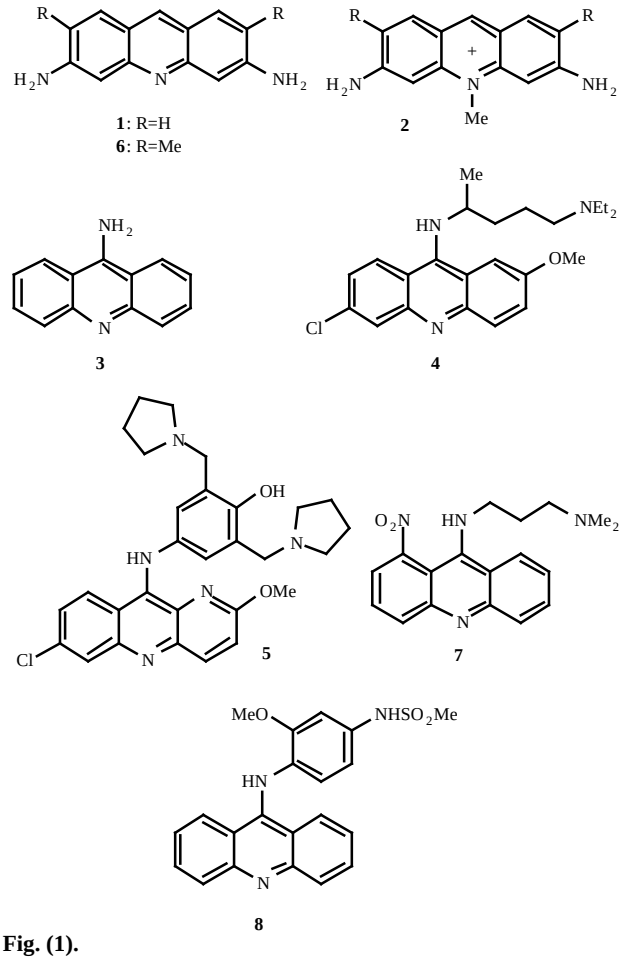

Fig. (1).

Mode of Binding

Binding by intercalation is a requirement for effective anticancer activity by acridines, as shown by several structure-activity studies on diverse classes of compounds (reviewed in ref. 9); this is presumably due to a requirement for intercalative binding to effectively inhibit topoisomerase enzymes (see later).

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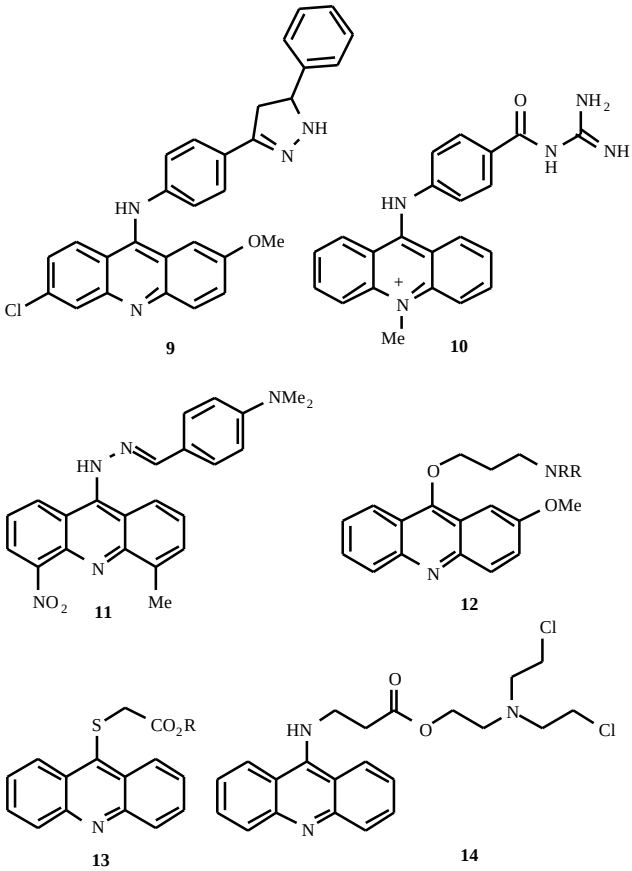


Fig. (2).

Strength of Binding

One important factor influencing the chemotherapeutic potency of acridines (again, primarily as anticancer drugs) is the strength of DNA binding, with many demonstrations of this reported (reviewed in ref. 9).

Kinetics of Binding

Several reports [e.g., 10, 11] have suggested that, for intercalating agents, the average residence time of the drug *at a particular DNA site* is relevant to biological activity, with longer average residence times being more favourable. This has led to the development of dimeric acridines as bis-intercalating agents (see later) and compounds with two large attached side chains as "DNA-threading" agents (see later).

ACRIDINES AS ANTIBACTERIAL DRUGS

While acridines have not been in major use as antibacterial drugs for many years, due to the development of more potent agents, the recent rise in multi-drug-resistant bacterial infections has led to a resurgence in interest. New acridines screened for antibacterial activity include 9-amino derivatives (**9** and analogues [12] and **10** and analogs [13]), 9-hydrazino derivatives (**11** and analogues [14]), 9-methoxy derivatives (**12** and analogues [15]) and 9-thioalkyl derivatives (**13** and related compounds [16, 17]). However, none of these had striking potencies or breadth of activity. Of interest was the observation [18] that low-power light potentiates the antibacterial effects of topically applied existing aminoacridines.

Because of their tight binding to DNA, acridines have also been used to target reactive agents to DNA (see ref. 19). A recent novel application is the compound S-303 (**14**), designed to bind to and inactivate the genomes of viral and bacterial pathogens in plasma and red blood cell preparations destined for clinical testing or transfusion. The ester link in **14** is designed to hydrolyse quickly, ensuring only a short half-life for the compound [20]. This and related compounds have also been suggested for use in inhibiting the proliferation of smooth muscle cells at a site of vascular injury [21], and inactivating leukocytes to prevent graft-versus-host disease [22].

ACRIDINES AS ANTIPROTOZOAL DRUGS

Antimalarials

Derivatives of the 9-oxilinoacridine class to which pyronaridine belongs are still being studied. Tetrahydro-naphthalene analogues (e.g., **15**) were reported to be as active as chloroquine against *P. berghei* in culture [23]. 9-Anilinoacridines related to the topo II inhibitor and antitumour agent amsacrine were studied, to see whether they could distinguish between human and parasite topoisomerase [24]. As example, the 3,6-disubstituted compound (**16**) had a high *in vitro* therapeutic index (1000) and was a potent inhibitor of both chloroquine-resistant *P. falciparum in vitro* (IC_{50} 20 nM) and *P. falciparum*-derived topo II. However, **16** was inactive against *P. berghei* in mice [25, 26]. Tetrahydroacridines have also been reported as active antimalarial agents; compound **17** effected 100% cures of *P.berghei* in a CD1 mouse model with a single s.c. dose of 0.05 mmol/kg (quinine sulfate in the same assay cured 6/10 mice at 1 mmol/kg) [27]. A recent study used a proflavine carrier to enhance the cellular uptake of 7-aminoquinine; the conjugate (**18**) had modestly higher actitvity and potency against the blood stage of a cloned parasite strain of human *P. falciparum* D6 *in vitro* [28].

Other Protozoal Diseases

A series of 9-thioacridines (e.g., **19**) were evaluated against the bloodstream forms of *Trypanosoma rhodesiense* and *T. brucei* [29]. Many had high therapeutic indices (ratios of parasite MIC versus mammalian cell cytotoxcity), but were not as potent as existing agents, and were not active in *in vivo* mouse models. Anilinoacridines with lipophilic electron-donating 1'-anilino substituents (e.g., **20**) are active agents against both the promastigote and amastigote forms of *Leishmania major, L donovani, T. cruzi* and *T. brucei*, but no consistent structure-activity relationships could be discerned in these different test systems [30]. At cytotoxic concentrations they give cleavable complex in intact *L. chagasi* promastigotes in whole cell assays, suggesting they affect a nuclear topo II in the parasite. They linearise kinetoplast DNA minicircles, implicating a kinetoplast topo II in the cleavage process [31].

Acridone derivatives (e.g., **21**, 22) are reported to be active against *Leishmania donovani* infections [32].

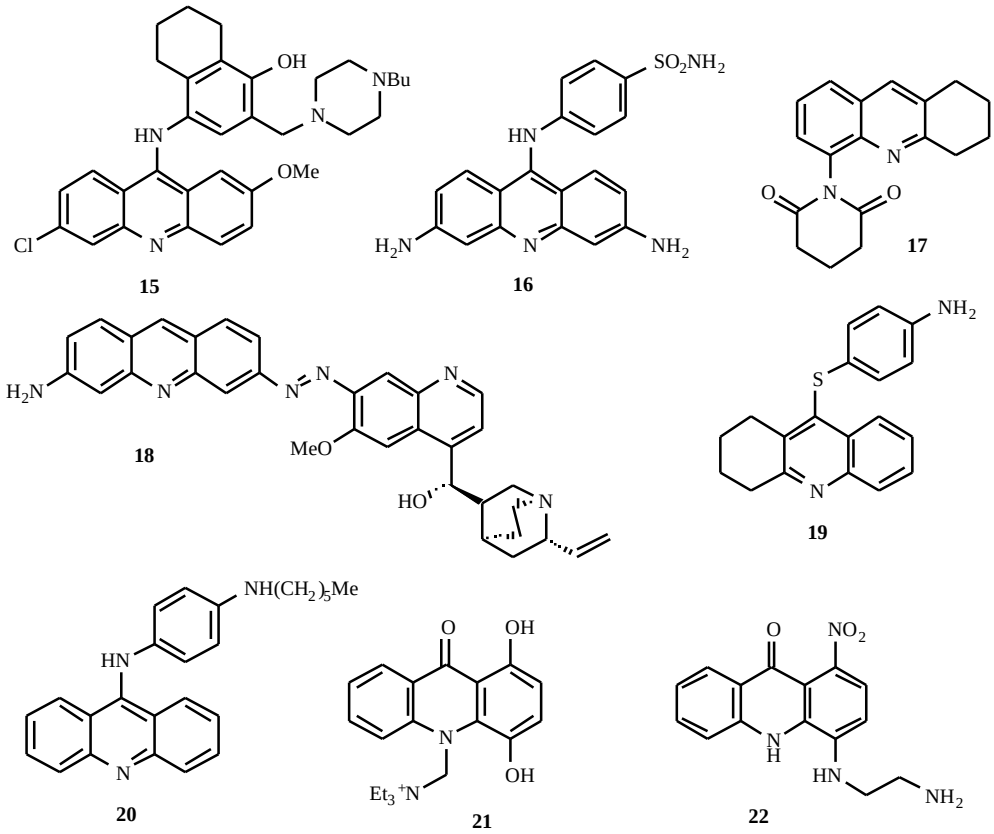


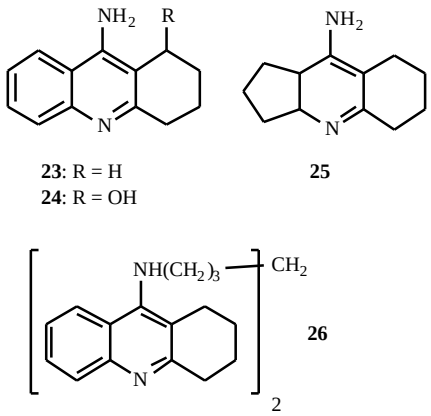
Fig. (3).

TETRAHYDROACRIDINES AS ACETYLCHOLINESTERASE INHIBITORS

The 9-aminotetrahydroacridine derivative tacrine (Cognex; **23**) is an anticholinesterase agent with weak potassium channel antagonist properties, and is used for the treatment of Alzheimer's disease. Studies in neuroblastoma cells show that tacrine affects the processing of β-amyloid precursor protein by alterations in trafficking and/or increased intracellular proteolysis, suggesting this as well as its cholinergic effects may be responsible for its therapeutic activity in Alzheimer's disease [33]. Tacrine is reported to provide statistically significant reductions in cognitive dysfunction, but not all studies on this seem to agree [34,35]. In particular, it significantly improves cognitive performance in patients lacking the apoE4 allele, compared with patients possessing two E4 alleles [36]. Long-term use of tacrine appeared to result in lesser decline in basic living activity [37]. Tacrine is mutagenic in Salmonella, but did not produce chromosome damage in CHO cells, in mouse bone marrow cells, or in the micronucleus assay [38]. The 1-hydroxy analogue velnacrine (**24**) was also clinically evaluated for Alzheimer's disease. It showed modest but significant benefits, but accompanied with significant adverse clinical effects, including reversible abnormal liver function [39,40]. Its use was discontinued because of a risk/benefit ratio that was not superior to that of similar drugs.

The related drug ipidacrine (**25**, amiridin) is a moderately potent inhibitor of acetylcholinesterase, and has shown improvement of cognitive function in animal models [41]. It is very lipophilic, and enters the brain rapidly [42]. A single clinical study reported in 1991 [43], suggest the drug was effective in about a third of patients, but no further development has been reported.

The bis(tacrine) derivative (**26**) is a more potent *in vitro* acetylcholinesterase inhibitors than tacrine (Ki = 3.7 nM and 89 nM, respectively). It is also a competitive GABA A receptor antagonist (IC_{50} 6 μM), 18-fold more potent for these receptors than tacrine [44-46]. It showed efficacy in rats with lesion-induced amnesia, dose-dependently reversed the observed increase in escape latency and decrease in choline acetyltransferase activity in the cerebral cortex [47].



23: R = H
24: R = OH

25

26

Fig. (4).

9-ANILINOACRIDINES AS ANTICANCER DRUGS

Amsacrine

Mechanism of Cytotoxicity

Amsacrine (**8**) was introduced into clinical use in 1976 [48]. It was one of the first drugs recognised to work by forming a ternary complex with DNA and the enzyme topo II, trapping a reaction intermediate termed the "cleavable complex" [49]. However, details of this mechanism are still not clear, and much work in the last few years has been focussed on the mechanistic details of the interaction of amsacrine with DNA and topoisomerases. Resonance Raman studies of amsacrine with calf thymus DNA supported an intercalative binding mode [50], and similar spectroscopy of ternary complexes of amsacrine with plasmid DNA and topo II showed [51] acridine intercalates via π-π interactions with the DNA base pairs, with anilino rings in the DNA minor groove. Computer modelling studies of complexes of amsacrine with B-DNA were also consistent with intercalative binding [52]. Mutation studies with human topo IIα have identified several amino acid changes in the coding region of the gene that confer resistance to amsacrine; these include Ala642 to threonine or glycine [53], changes in amino acid 824 [54], Gly437 to serine (in the absence of ATP, due to instability of the mutant enzyme) [55], and Arg450 to Gln and Pro803 to Ser (impaired ATP utilisation) [56].

In a panel of human breast cancer cell lines, sensitivity to amsacrine was shown to correlate better with the level of expression of the topo IIα protein rather than the level of topo IIα mRNA [57]. A panel of stable cell lines developed for resistance to etoposide or amsacrine had a median of 38% less topo IIα mRNA and elevated median levels of topo IIβ (165%), also suggesting that the former is the most important mechanism of resistance to these topo II inhibitors [58]. Amsacrine appears unique among topo II poisons in that its ability to trap both topo IIα and topo IIβ induced lesions is only modestly reduced in ATP-depleted cells. It is suggested that amsacrine produces mainly prestrand passage DNA lesions, upstream of the DNA cleavage step by enhancing the stabilisation of cleavable complexes at a single major site, whereas other topo II poisons only stabilise poststrand passage DNA lesions in intact cells [59,60]. Amsacrine and other topo II poisons can induce cell death by apoptosis [61,62], but the details of this are still not clear. Although treatment with amsacrine did not alter the expression of several genes (c-myc, bcl2, c-jun, p53) involved in the apoptotic pathway [63], it did elevate the level of cyclin E and decrease the level of c-myc mRNA in a dose-dependent manner [64,65].

Genotoxicity

Amsacrine is an efficient mutagen [66], with the most common event being genomic deletions/rearrangements [67]. The larger deletions may be mediated by subunit exchanges between overlapping topo II dimers at the bases of replicons [68]. Exposure of human peripheral blood lymphocytes, using a fluorescence in situ hybridization assay, showed that the highest frequencies of translocations were in chromosomes 2, 4 and 8 [69]. Carcinogenesis studies of amsacrine in Wistar rats resulted in a high incidence of normally rare small intestinal adenocarcinomas, probably due to the known biliary excretion route resulting in high direct exposure [70]. In female Wistar rats, significantly increased incidences of mammary tumours were seen [71]. However, follow-up studies of 174 patients with acute myeloid leukaemia treated with combinations of cytosine arabinoside, anthracyclines and amsacrine did not show any significant excess of secondary malignancies [72].

Clinical Studies.

The clinical use of amsacrine focuses mainly on acute myeloid leukaemia (AML) [73,74]. A randomised study of amsacrine/etoposide therapy in relapsed childhood AML concluded that the two-drug regimen was effective (34% complete responses), and that the addition of azacytidine did not improve response rates [75]. Amsacrine has also been used successfully in the treatment of acute promyelocytic leukaemia [76], adult acute lymphoblastic leukaemia [77,78] and adult acute myeloid leukaemia [79]. In contrast, it has generally not been succesful in the treatment of solid tumours, although a re-evaluation in untreated advanced (grade III/IV) carcinomas of the hypopharynx showed high-dose (255 mg/m^2 per dose cycle) amsacrine to be a toxic but very effective drug for first-line treatment, achieving a response rate of 65% [80].

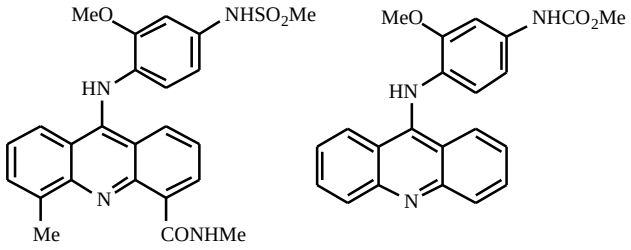
Asulacrine

This compound (**27**; CI-921, NSC 343499) was selected for development following extensive structure-activity relationship [81] and animal model [82,83] studies, primarily because of its broader spectrum of action than amsacrine in the latter. The mechanism of action of asulacrine was shown to be very similar to that of amsacrine, via inhibition of topo II, resulting in DNA protein cross-links and DNA breaks [84,85]. Animal studies in mice with both intraperitoneally and intravenously implanted P388 leukaemia, and with advanced stage sub-cutaneously implanted LC-12 squamous cell carcinoma, showed that combinations of **27** and cisplatin or carboplatin were significantly superior to therapy with the best single agent alone, suggesting that such combinations may have clinical potential [86]. In the clinic, some drug-induced remissions were seen with **27** in non-small cell lung cancer and breast cancer, but not in colorectal and gastric cancer [87,88]. A pilot study of a trial of oral administration has been reported [89], but there are no reports of asulacrine being used clinically in combination therapy.

9-Anilinoacridine Carbamates

Analogues with a 1′-carbamate (e.g., **28**) are of interest due to their relatively higher (2-3 fold) activity than amsacrine against non-cycling plateau-phase cells [90]. Compound **28** generated quite different topoisomerase-induced cleavage sites than amsacrine in pBR322, c-myc and SV40 DNA, and this was attributed to the presence of the carbamate group [91]. Studies in yeast strains transfected with human topoisomerases showed that **28** was active against both topo IIα and topo IIβ, whereas other acridine derivatives had preferential activity against topo IIα. In agreement with this, loss of topo IIα activity in human cells with defined topo lesions had little effect on the cytotoxicity of **28**, suggesting this carbamate analogue can recognise both isoforms [92].

The sensitivity of **28** to resistant DC-3F/9-OH-E cells was not restored by transfection with wild-type human topo IIα [93]. These studies support the higher activity of 28 against plateau-phase cells being due to its ability to target topo IIβ, which has increased expression (relative to topo IIα) in non-cycling cells.



27 **28**

Fig. (5).

ACRIDINECARBOXAMIDES AS ANTICANCER DRUGS

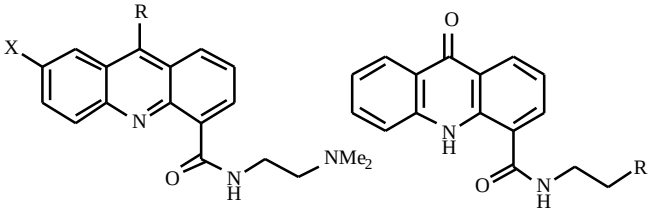
Structure-Activity Relationships

The 9-aminoacridine-4-carboxamides (e.g., **29**) were first reported in 1984, as a new class of DNA-intercalating agents with potent cytotoxicity and *in vivo* antileukaemic activity [94]. Structure-activity studies showed that these activities were closely related to the kinetics of dissociation of the drugs from DNA, with slower off-rates correlating with good activity [95]. Tight structure-activity relationships were seen for both acridine substituents and the nature of the 4-carboxamide side chain, and were interpreted in terms of a binding model where the acridine chromophore intercalated parallel to the base pair long axis, with the side chain located in the minor groove [95]. Later crystal structure studies [96,97] of complexes of 9-aminoacridine-4-carboxamides with hexanucleotides clarified this model, but showed the side chain to lie in the major groove [98].

The related lower pKa acridine-4-carboxamide analogue **30** (DACA; NSC 601316, XR-5000) showed broader *in vivo* activity than the 9-aminoacridine-4-carboxamides, with remarkable effects against the refractory Lewis lung carcinoma [99] and against multidrug resistant cells [100], and was developed for clinical trial. The need to avoid the use of toxic mercury salts and the lachrymatory acridine-4-carboxylic acid for commercial manufacture, led to the later development of an improved and more versatile synthesis of DACA that avoids these [101]. This was used to prepare a series of new analogues, and structure-activity studies with these suggested that activity correlated with the steric bulk of the substituents, but was independent of their electronic properties [102]. Many 5-substituted derivatives were more cytotoxic than DACA, but were less effective in mutant leukaemia cell lines with lower levels of topo II, suggesting a mode of cytotoxicity largely mediated by effects on topo II [102]. However, 5,7-disubstituted derivatives retained both the higher cytotoxic potency of the 5-monosubstituted analogues and the broad-spectrum effectiveness of the 7-monosubstituted analogues [103].

Mechanism of Cytotoxicity

DACA binds to DNA by intercalation, with a binding constant to calf thymus DNA of 7.4×10^4 M^{-1} (20 °C, 10 mM ionic strength), 6-fold lower than that of the 9-amino analogue **29** [104]. It stimulates the formation of cleavable complexes between topo II and DNA, inducing both DNA breakage and the formation of DNA protein cross-links [85]. DACA induced breakage of supercoiled plasmid DNA with purified topo II enzyme but not with topo I, whereas the 7-chloro analogue (**31**) showed converse activity, showing that acridine substituents on DACA can substantially influence its interaction with topoisomerases [105]. DACA is relatively unaffected by transport-mediated multidrug resistance (MDR), being much more effective than idarubicin (an anthracycline analog known for its relative ability to circumvent MDR) in P-glycoprotein-expressing CEM/VLB100 cells [106]. Studies with ^{3}H-labelled DACA showed that the kinetics of both uptake and efflux are very rapid, probably because of its high affinity for membranes, and it is suggested that this rapid uptake allows it to overcome transport-mediated MDR [107]. The primary route of metabolism of DACA is oxidation at C-9 by aldehyde oxidase to give the acridone **32**, although oxidative demethylation of the side chain dimethylamino group has also been observed [108]. DACA binds avidly to plasma proteins (mainly α1-acid glycoprotein, followed by albumin), with a free fraction of only 3.4% in human plasma [109]. PET scanning using ^{11}C-DACA showed rapid clearance of drug in both humans and rat plasma, with the generation of several metabolites, one identified as the acridone N-oxide **33** [110]. PET scanning in the rat showed little retention of radioactivity in major organs, with rapid excretion via the gut and kidney. Overall there was no unexpected interspecies difference in metabolism [111].



29: R=NH_2, X=H
30: R=H, X=H
31: R=H, X=Cl

32: R=NMe_2
33: R=$N(O)Me_2$

Fig. (6).

Clinical Studies

A Phase I trial of DACA, using a 3-h infusion regimen repeated 3-weekly, indicated a maximum tolerated dose of 750 mg/m^2, with the dose-limiting toxicity being infusional arm pain of unknown cause. No activity was seen, but calculations based on rodent models suggested this dose is sub-therapeutic in humans [112,113].

NITROACRIDINES AS ANTICANCER DRUGS

Nitracrine

The 1-nitroacridine derivative nitracrine (**34**, Ledakrin;) was developed in Poland [4] and was used there briefly

clinically as an anticancer drug [114]. Structure-activity relationships in this series are very narrow, with a 1-nitro group being essential for activity. Nitracrine is an extremely potent cytotoxin, and binds to DNA by intercalation [115], but topoisomerase inhibition is probably not the mechanism of action. Nitracrine is known to alkylate DNA following reduction by thiols or enzymes, but the nature of the metabolites is still debated. Recent studies [116,117] have failed to trap the putative 1-hydroxylamine, but showed a range of metabolites, including **35** and **36**. Because of the bioreductive nature of its activation, nitracrine has modest (ca. 10-fold in AA8 cells) selective toxicity for hypoxic cells [115], but did not show significant activity against hypoxic cells in mouse solid tumour models [118], probably because of a combination of rapid metabolism [119] and poor extravascular diffusion rates [120].

Nitracrine N-oxide (**37**) is a bis-bioreductive agent (both the nitro and N-oxide must be reduced by oxygen-inhibitable processes for full activation), and is 1000-1500 fold selective for hypoxic over aerobic AA8 cells in culture [121]. It also showed little activity *in vivo* against the hypoxic sub-fraction of cells in KHT tumorus [122], considered due to too-rapid metabolism. Modulation of this by lowering the reduction potential of the nitro group through chromophore substitution [122], or by changing the steric environment of the aliphatic N-oxide [123] to give an analogues such as **38**, did not show significantly improved *in vivo* activity.

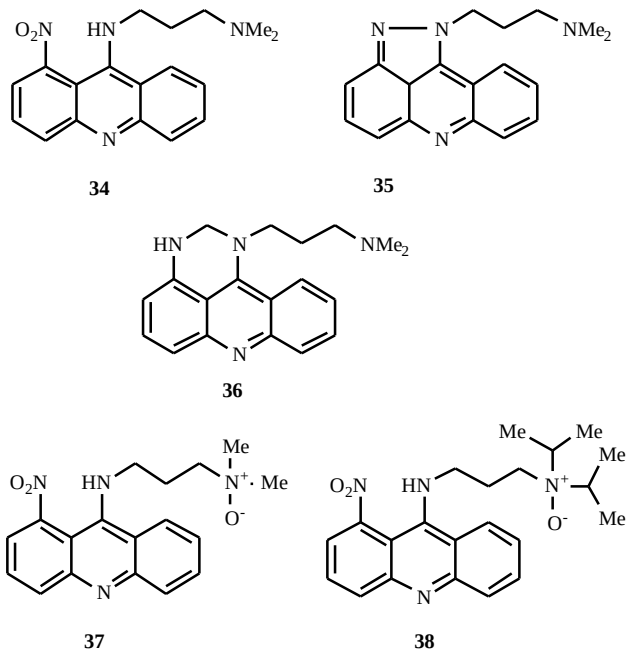


Fig. (7).

Nitropyrazoloacridine

This series was initially developed at Parke-Davis, and the lead compound **39** (pyrazoloacridine, NSC 366140) was selected for its high activity against a range of solid tumours *in vivo* [124]. Pyrazoloacridine abolishes the catalytic activity of both topo I and topo II at clinically achievable concentrations, but without stabilising covalent topo-DNA complexes, suggesting a novel mechanism of action [125]. Combination studies with other anticancer agents in a number of human and animal tumour cell lines showed it was not synergistic with antimetabolites or antimicrotubule agents, due to its arrest of cells in both G1 and G2 phases of the cell cycle. However, good synergy was seen with cisplatin, due to inhibition of the removal of platinum-DNA adducts. [126]. Pyrazoloacridine is hypoxia-selective [125], and the 5-amino derivative **40** is a major metabolite in mice [127].

Phase I clinical studies using a variety of protocols showed that the primary dose-limiting toxicity in patients was myelosuppression rather than neurologic effects [128-130], although the latter were seen at the highest dose (720 mg/m^2 in a 1-hour infusion protocol) [131]. Responses were seen in one study [129] in platinum- and taxane-refractory ovarian carcinoma, and in cervical and colorectal carcinomas. The drug was well tolerated in Phase II studies, but proved inactive in advanced renal cell carcinoma [132], transitional cell carcinoma [133], advanced colorectal cancer [134], cisplatin-resistant germ cell tumours [135] and hormone-resistant prostate cancer [136] (a single response was seen in the latter 17-patient trial). However, a review [137] of the clinical trials concluded that results from ongoing trials are needed before utility can be defined, and urged combination studies with other antineoplastic agents because of the unique properties (solid tumour selectivity, activity against hypoxic cells, and cytotoxicity in non-cycling cells.

Other Pyrazoloacridines

From a series of pyrazoloacridines developed from the DACA lead [138,139], the bis-cationic derivative (**41**) showed potent broad-spectrum cytotoxicity, with the extraordinary IC_{50} value of 0.04 nM against the human colon adenocarcinoma HT29 cell line [140]. The compound was a much tighter DNA binder than DACA (Kapp 150 x 10^{-7} compared to 0.11 x 10^{-7} M^{-1} to calf thymus DNA [138], and is a DNA intercalating agent.

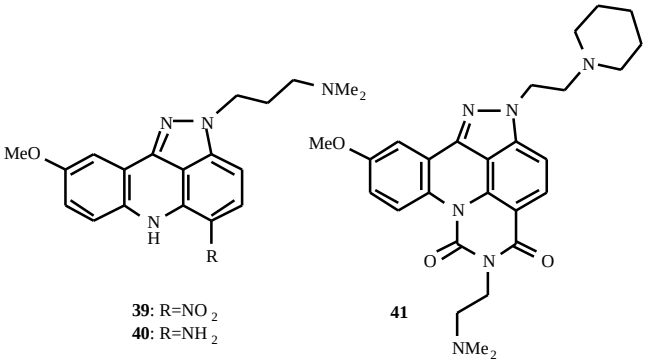


Fig. (8).

POLYSUBSTITUTED ACRIDINES AS TELOMERASE INHIBITORS

Telomeres are DNA sequences that occur as multiple repeats of guanine-rich segments at the 3' ends of chromosomes. Some of these G-rich repeats are lost each time a cell divides, since DNA polymerase is unable to fully

replicate the 3' ends of the telomeres, and this limits the number of times normal cells can divide before cellular senescence occurs. The reverse transcriptase enzyme telomerase has the function of rebuilding telomeric repeats that are lost during replication [141]. It is active in normal cells, but is expressed in almost all tumour cells [142], contributing to their immortality. Telomerase has thus become a target for anticancer drugs. Most of these prevent the efficient functioning of telomerase function by stabilising the G4 quadruplexes [143] formed by free telomeric DNA, [144].

Typical inhibitors possess tricyclic chromophores that are able to form π-π interactions with the quadruplex, and with cationic side chains positioned to bind in the quadruplex grooves. Molecular modelling studies showed that 3,6-disubstituted acridines such as **42** should bind well to the folded human telomere DNA quadruplex, and this was verified by association constants derived from isothermal titration calorimetry [145]. These compounds showed IC_{50} values of 2-8 μM against telomerase, as measured by the telomerase repeat amplification protocol (TRAP) assay [146]. A later comparison of 2,6,9-, 2,7,9- and 3,6,9-trisubstituted analogues (e.g., **43**-**45**) showed that the 3,6,9-isomers were the most potent in the TRAP assay (e.g., 270, 570 and 18 nM respectively for **43**-**45** [147]. A marked reduction in the growth of 21NT cells (possessing relatively short telomeres) was seen after twice-weekly dosing with T4 at 2 μM, but no effects were seen on SKOV3 cells (with longer telomeres). However, no decrease in telomere length in the 21NT cells was detected. The drug was not active as monotherapy in A431 human squamous cell carcinoma xenografts, but in combination with paclitaxel it showed significant additional antitumour effect (as growth delay) compared with paclitaxel alone, with no additional toxicity [148].

The pentacyclic acridinium salt **46** was shown recently to have telomerase activity, with an IC_{50} of 330 nM in the TRAP assay, good water-solubility, and efficient uptake into cells [149].

Dimeric acridines such as **47** also form stable complexes with quadruplex-like polymorphs of $d(CGTACG)_2$, demonstrating hitherto unsuspected modes of interaction between drugs and quadruplex DNA [150], but have not been reported as telomerase inhibitors.

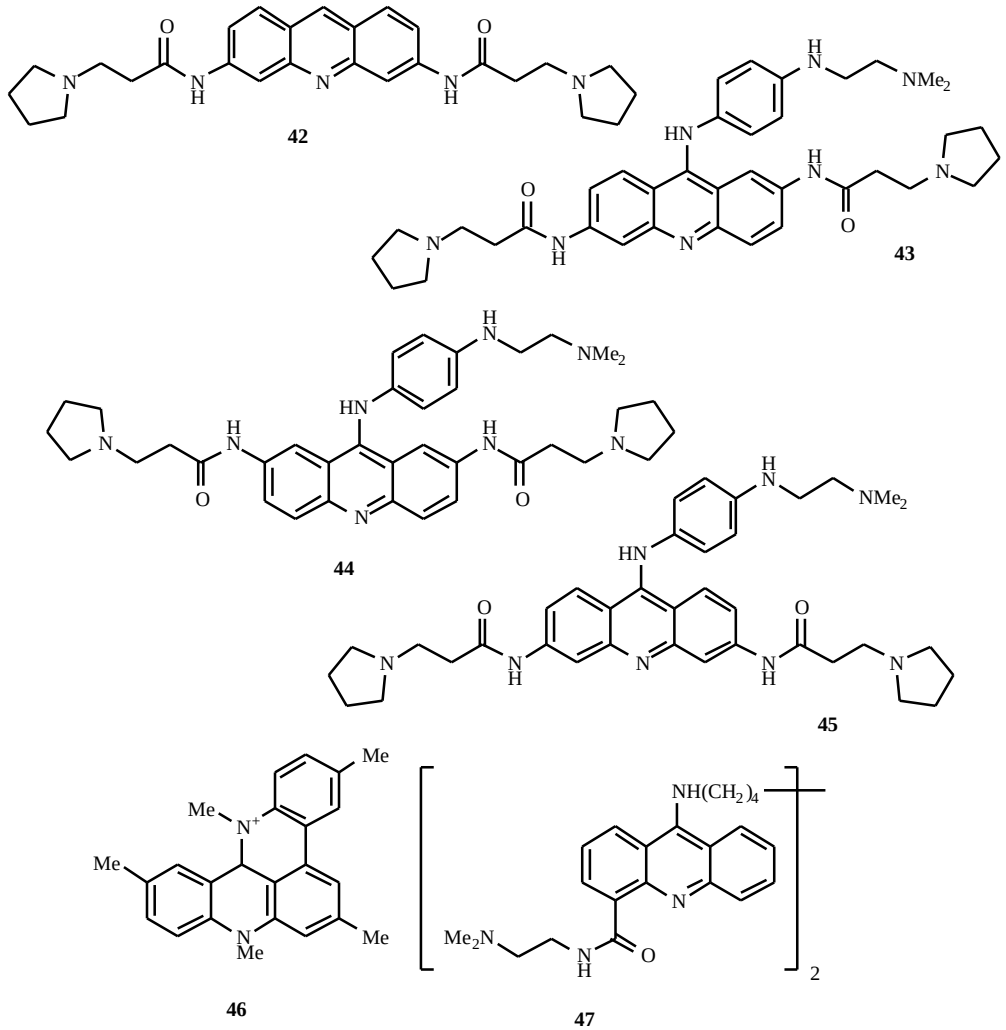


Fig. (9).

Bis(ACRIDINES)

Early work on bis(acridines) focussed on this as a means of generating very tight DNA binding agents of potentially high cytotoxicity, and centred around bis(9-alkylamino) analogues of high chromophore pK_a. However, a combined NMR/stopped flow spectrophotometry study [11] suggested that slow off-rates from DNA of bis(acridines) linked by polymethylene chains masked relatively fast exchange kinetics of the individual chromophores from individual binding sites. These could be as fast as the off-rates of acridine monomers if the linker chain was flexible enough to allow hand-over-hand "creeping" of the drug along the helix. These individual chromophore exchange kinetics could be greatly slowed by the use of cationic or rigid linker chains.

The hexane-1,6-diamine derivative **48** (NSC 219733) was considered for clinical trial but did not proceed [151], and interest was lost until the recent discovery that dimeric analogues of weakly basic or non-basic chromophores, such as **49** (DMP-840), had excellent activity in human tumour xenografts [152]. The selection of **49** for clinical trial [153] led to an interest in the use of other weakly basic chromophores. A comparison of the relative potencies of various possible chromophores concluded that one of the most interesting was the DACA chromophore (acridine-4-carboxamide) [154]. Structure-activity studies of substituted bis(acridine-4-carboxamides) linked by a mono-cationic chain showed that small substituents at the acridine 5-position gave the most cytotoxic compounds, (e.g., **50**) with IC_{50}s as low as 2 nM against Lewis lung carcinoma cells. Cell line and biochemical studies [155] suggest that the bis(acridine-4-carboxamides), and related bis(phenazine-1-carboxamides) [156] act primarily through topo I rather than topo II inhibition. Several bis(acridine-4-carboxamide) analogues such as **50** produced significant growth delays in the relatively refractory sc colon 38 tumour model *in vivo* at substantially lower doses than DACA [155].

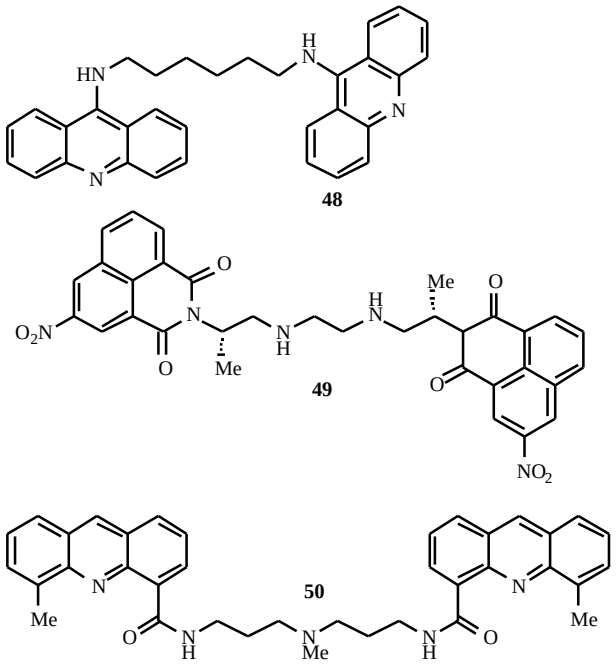


Fig. (10).

CONCLUSIONS

Acridines have the ability to form both binary drug/DNA complexes (thus being excellent drug targeting and carrying moieties) and ternary drug/DNA/topo complexes (hence their topo poisoning ability). The latter is the mechanism of their anticancer activity, and quite possibly also of their antiprotozoal activity. While recent work has been reported on acridine derivatives with antibacterial, antoprotozoal and (tetrahydroacridines) anti-acetylcholinesterase activity, the main focus is still on anticancer agents, both as topoisomerase and telomerase inhibitors.

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