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Review

Amino acid or peptide conjugates of acridine/acridone and quinoline/quinolone-containing drugs. A critical examination of their clinical effectiveness within a twenty-year timeframe in antitumor chemotherapy and treatment of infectious diseases

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ABSTRACT

Acridines/acridones, quinolines/quinolones (chromophores) and their derivatives constitute extremely important family of compounds in current medicine. Great significance of the compounds is connected with antimicrobial and antitumor activities. Combining these features together in one drug seems to be long-term benefit, especially in oncology therapy. The attractiveness of the chromophore drugs is still enhanced by elimination their toxicity and improvement not only selectivity, specificity but also bioavailability. The best results are reached by conjugation to natural peptides. This paper highlights significant advance in the study of amino acid or peptide chromophore conjugates that provide highly encouraging data for novel drug development. The structures and clinical significance of amino acid or peptide chromophore conjugates are widely discussed.

1. Introduction

Acridines/acridones and quinolines/quinolones are heterocyclic compounds which constitute important part of organic chemistry not only by the structure reactivity but also by a wide range of biological activities. They are a major area of research due to antimicrobial (Kavitha, 2004; Kharb and Kaur, 2013; Wainwright, 2001), antiviral (Briguglio et al., 2011; Fujiwara et al., 1999; Luedtke et al., 2003; Taraporewala, 1999), antimalarial (Fernandez-Calienes Valdes, 2011; Golden et al., 2015), antiprion (Korth et al., 2001; May et al., 2003) and especially antitumor properties (Belmont et al., 2007; Belmont and Dorange, 2008; Charmantray et al., 2003; Dopierała et al., 2011; El-Gohary, 2013; Heald and Stevens, 2003; Hegde et al., 2004; Heiniger et al., 2010; Kimura et al., 1992; Kumar et al., 2009), which cause them classified as attractive chemotherapeutic agents used in treatment of oncology patients. The mechanism, by which the chromophores may act, includes the interaction with topoisomerases, telomerase, protein kinase enzymes that are necessary to physiological cycle cell progression. Furthermore, the compounds of this group affect the proper action of membrane proteins and interfere with the functioning of DNA, upon intercalation and alkylation between the base pairs of the double-stranded helix (Demeunynck, 2004; Sebestík et al., 2007). Chromophores are also known as photodynamic or radiodynamic therapy agents because of their photosensitizing effect that is used in visualizing tumors during the surgery or irradiation process (Kusuzaki et al., 2000; Maruo et al., 2012; Marno et al., 2012). Interestingly, a history of clinical significance of chromophores goes back over two hundred years. The first fully-fledged Polish anticancer drug from the group of acridine/acridone was Ledakrin (**1**, C-283, Nitracrine) (Fig.1), discovered by the team of Ledóchowski (at Gdansk University of Technology, Poland) and registered in 1974 as a product administered by subcutaneous injection (25 mg/mL of nitracrine) (Ledóchowski, 1976). The compound exhibits high activity against many solid tumors, such as lung, skin, breast, ovarian. Ledakrin (**1**) undergoes metabolic activation inside cells, its generated metabolites bind with nucleic acid and are also able to cross linking of the target DNA and other cellular molecules (topoisomerase I (TopoI)) (Gorlewska et al., 2001; Pawlak et al., 1984). Besides positive effect, the most common Ledakrin side effects reported are toxic activity, strong abdominal discomfort, emesis and biliousness. That is the reason to limit their clinical usage and recommended this drug in treatment only for the necessary cases in some kind of skin cancers (Tadi et al., 2007). The drugs known as class of topoisomerase II (TopoII) inhibitors with clinical efficiency apart from etoposide, doxorubicin, idarubicin, epirubicin and mitoxantrone constitutes also acridine derivative of methyl *N*-(4′-(9-acridinylamino)-3-methoxyphenyl)methane sulfonamide (**2a**) (m-AMSA, amsacrine, AMSIDYL),

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discovered in 1976 (at University of Auckland, New Zeland) by Bruca Caine (Cain et al., 1975). Actually, m-AMSA is applied in treatment of acute leukemia (Marsoni and Wittes, 1984; Winton et al., 1983) and multidrug resistance phenomena leukemia (Legha et al., 1982) as a product subcutaneously administered (50 mg/mL).

It has been proved its affinity to specific interaction with TopoII independently of the stable cleavable complex with DNA. One of the side effects of m-AMSA is the possibility of generating free radicals during metabolism, resulting in the failure of DNA normal cells as well. In the subsequent years, the significance played also two acridine/acridone derivatives such as 3-(9-acridinylamino)-5-(hydroxymethyl) aniline (**3**) (AHMA), methyl *N*-(4′-(9-acridinylamino)-phenyl) carbamate hydrochloride (**2b**) AMCA with more efficiency, selectivity and longer half-life (Demeunynck, 2004; Su et al., 1995; Zhang et al., 2014).

The first drug from the group of quinolones, indicated for treatment of acute myeloid leukemia, was Voreloxin (Vosaroxin) (**5**), developed by Sunesis Pharmaceuticals. Voreloxin as a TopoII poison is currently under clinical trials (phase II) in treatment of platinum-resistant ovarian cancer. In 2011, Sunesis Pharmaceuticals announced that a phase II/III study on Voreloxin being achieved by the Cardiff University. Both the safety and efficacy feature of Voreloxin with low dose cytarabine in elderly patients suffering from acute myeloid leukemia and high-risk myelodysplastic syndrome is currently tested (Dennis et al., 2015; Hawtin et al., 2010; Krug et al., 2011). Besides, the family of chromophores gained clinical importance in antimicrobial therapy. The most popular and the oldest (1920) acridine based drug is ethacridine (**6a**, Rivanol) introduced by Julius Morgenroth, representing high activity especially against Gram-positive bacteria e.g. *Staphylococci* and protozoan (Morgenroth et al., 1921). The Rivanol used as 0.01% solution of lactate salt was approved for the oral treatment of enteric disease, traveller's diarrhea and shigellosis because of its poor absorption. The acridine was also applied to infected wounds such as ulcers and burns. The mechanism of its antibacterial action seems to be connected with the intercalation to DNA and also enzymes damage (Wainwright, 2001; Lipsky and Hoey, 2009). The great advantage of clinical usage of Rivanol is the lack of multidrug resistance. In the second group of compounds, fluoroquinolones exhibit clinical efficacy. One of a second generation broad-spectrum antibiotic of the fluoroquinolone drug class is well known ciprofloxacin (Cipro) (**7**), discovered in 1981 and used as alternative to treatment a wide variety of infections e.g. bones, joints, endocarditis. It may be administered as tablets, suspension or intravenous solutions, exhibiting high activity against both Gram-negative (*Salmonella*, *Shigella*, *Pseudomonas*, *E. coli* spp.) and Gram-positive (*S. aureus* spp.) microorganisms (Ball, 2000; Collin et al., 2011; Oliphant and Green, 2002; Stahlmann and Lode, 1999). The mechanism of its bactericidal action results from the inhibition of TopoII.

Interestingly, other chromophores, showing positive results, are under clinical trials such as DACA (**8a**) (phase II) and pyrazoloacridine (**9**) (phase I/II) (Galanis et al., 2005). However, two chromophores such as elacridar (**10**) (based on an acridone pattern) and compound **11** (based on bis(acridines) pattern) displayed in a phase I clinical trials highly effective therapies of multidrug-resistant solid tumors in co-administration with doxorubicin (Borowski et al., 2005; Cholewiński and Dzierzbicka, 2011; Denny, 2002).

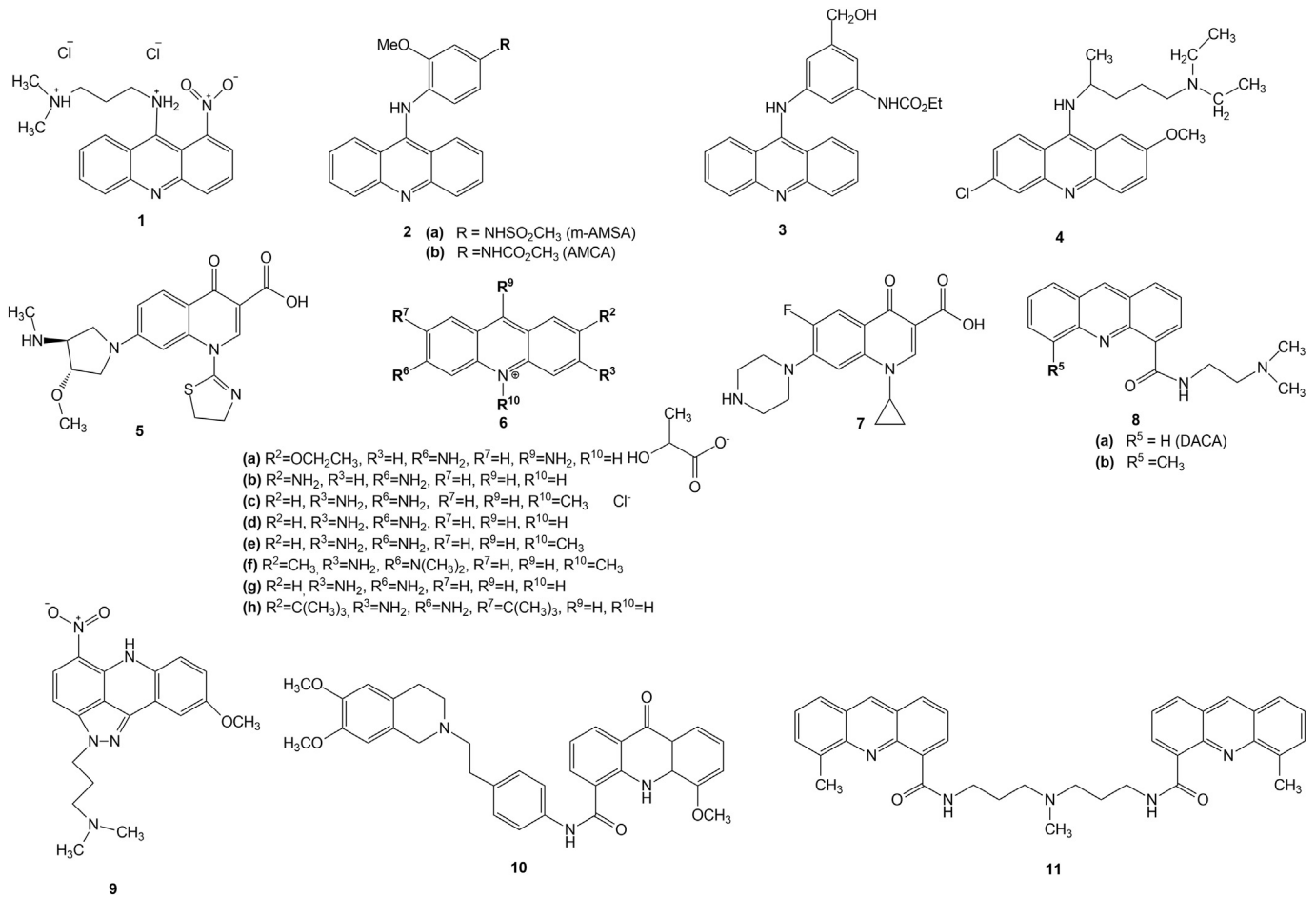

Fig. 1. Chemical structures of selected acridines/acridones and quinolines/quinolones with clinical efficacy (Ball, 2000; Borowski et al., 2005; Cain et al., 1975; Cholewiński and Dzierzbicka, 2011; Collin et al., 2011; Dennis et al., 2015; Denny, 2002; Galanis et al., 2005; Gorlewska et al., 2001; Hawtin et al., 2010; Krug et al., 2011; Li and Crothers, 1969; Morgenroth et al., 1921; Muller et al., 1973; Oliphant and Green, 2002; Pawlak et al., 1984; Stahlmann and Lode, 1999; Su et al., 1995; Wainwright, 2001; Young and Chin, 1995; Zhang et al., 2014).