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A REVIEW OF PUBLISHED DATA ON ACRIDINE DERIVATIVES WITH DIFFERENT BIOLOGICAL ACTIVITIES

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ABSTRACT. Acridine ring can be found in molecules used in many different spheres, including industry and medicine. Nowadays, even acridines with antibacterial activity are of research interest due to increasing bacterial resistance. Some acridine derivatives showed antimalarial or antiviral activity. Acridine derivatives were also investigated for antitumor activity due to the interaction with topoisomerase II and DNA base pairs. Considering these possible uses of acridine derivatives, this work was made as overview of all significant structure characteristics for specific action of these compounds.

Keywords: acridine, antiparasitic, antibacterial, antiviral, antitumor activity, DNA.

INTRODUCTION

Acridines are compounds known ever since 19th century. When these substances were isolated from crude anthracene, one of them was named acridine (acridine means sharp, painful) since it had itching and inflammatory properties (REINHARDT and TRAVIS, 2000). Correct structure of acridine was established by Carl Riedel, who also established acridine, quinoline and pyridine structure relationships. Almost at the same time, acridine was successfully synthesized (REINHARDT and TRAVIS, 2000). Structure of acridine and its numeration are shown in Fig. 1 (GRAEBE and LAGODZINSKI, 1893). Acridine can also be named as 10-azaanthracene and dibenzo[b,e]pyridine.

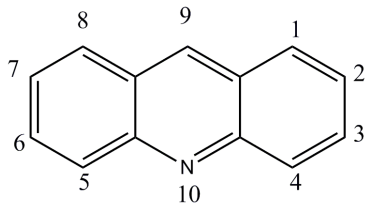


Figure 1. Acridine structure and numeration.

Acridine ring can be found in molecules used in many different spheres, including industry and medicine (ALBERT, 1966; BROWNING, 1937; BROWNING, 1964).

Acridine derivatives, such as acriflavine and proflavine, were used during the World War I as topical antibacterial agents. Later, quinacrine was discovered and used during World War II as antimalarial agent (NASIM and BRYCHCY, 1979). Chemical structures of these acridine derivatives are presented in Fig. 2.

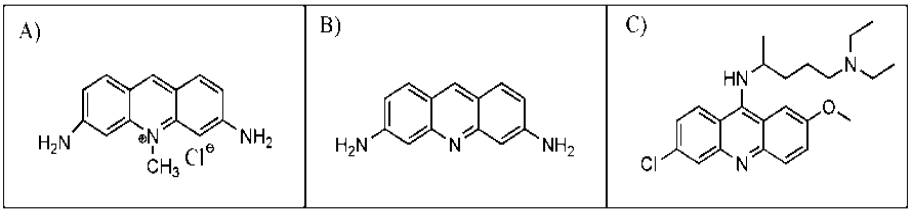


Figure 2. Chemical structure of several acridine derivatives:
A) acriflavine; B) proflavin; C) quinacrine.

Soon after World War II, penicillines and other antibiotics replaced acridine based drugs with antibacterial properties. However, other acridine derivatives which had different targets were still in use. Nowadays, even acridines with antibacterial activity are of research interest due to increasing bacterial resistance (KUMAR *et al*., 2012).

During 1980s, many antitumor drugs which were in clinical trials or in clinical use actually interacted with DNA. One of those derivatives was 4'-(9-acridinylamino)methanesulphon-m-anisidide (m-AMSA) (Fig. 3). m-AMSA was developed as a result of SAR study conducted on sulfonanilide ring substituted compounds (CAIN *et al*., 1975). These authors used murine L1210 leukemia cells as a test system, while BAGULEY and NASH (1981) showed later good correlation between in vitro and in vivo antitumor activity using the same cells.

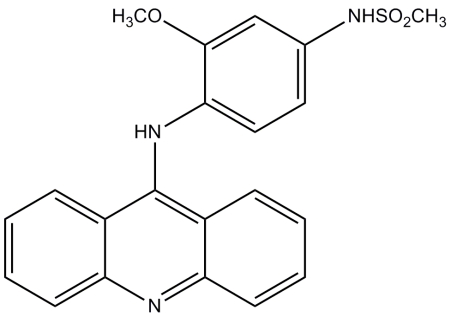


Figure 3. Chemical structure of *m*-AMSA.

ROWE *et al*. (1986) proved theory that activity of DNA topoisomerase II may be affected by antitumor acridines, including m-AMSA. Several other groups of acridine derivatives also have antibacterial (BROWNING *et al*., 1922; ALBERT *et al*., 1949) and antitumor activity (JIANG *et al*., 2016; CUI *et al*., 2016).

Some acridine derivatives showed antimalarial activity (CHAVALITSHEWINKOON *et al*., 1993; COGGESHALL, 1952). According to CHAVALITSHEWINKOON *et al*. (1993), 9-anilinoacridines with specific substituents inhibited the decatenation activity of *Plasmodium falciparum* DNA topoisomerase II.

SUVEYZDIS *et al*. (2000) published a research which confirmed that some aminoacridine derivatives possess antiviral activity.

ACRIDINE-DNA INTERACTIONS

Acridine derivatives can interact with DNA by intercalating between DNA base pairs (PEACOCKE and SKERRETT, 1956; RAMSTEIN *et al*., 1972; GEORGHIOU, 1975). The interaction of acridine with DNA was also evaluated by CHOUDHURY and BASU (1995), using absorption and fluorescence spectroscopy. DNA based electrochemical biosensors were successfully used for investigation of interactions between DNA and other molecules (DICULESCU *et al*., 2016; ALEKSIĆ and KAPETANOVIĆ, 2013; ALEKSIĆ and KAPETANOVIĆ, 2014), such as proteins (ŽIVANOVIĆ *et al*., 2010) and different drugs (RADULOVIĆ *et al*., 2012a; RADULOVIĆ *et al*., 2012b; PANTIĆ *et al*., 2016; LIJESKIĆ *et al*., 2014).

Different electrodes may be used in voltammetric methods with aim to prove electroactivity of compounds containing acridine ring (GIROUSI *et al*., 2008; PONTINHA *et al*., 2013). PANTIĆ *et al*. (2016) proved interaction of 9-chloroacridine with double-stranded calf thymus DNA using square wave voltammetry and DNA-modified glassy carbon electrode.

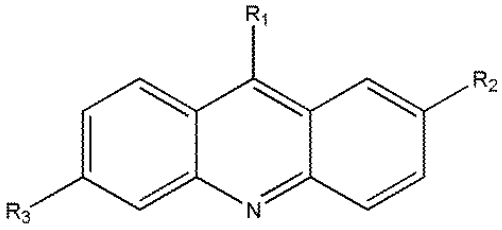
ANTIPARASITIC ACTIVITY OF ACRIDINE DERIVATIVES

Antimalarial activity of acridine derivatives is based on several mechanisms of action: hemozoin targeting (KUMAR *et al*., 2007), DNA topoisomerase inhibition (FERGUSON and DENNY, 2007; CHAVALITSHEWINKOON *et al*., 1993), folate metabolism inhibition (SANTELLI-ROUVIER *et al*., 2004) and plasmepsin II inhibition (AZIM *et al*., 2008).

SANTELLI-ROUVIER *et al*. (2004) synthesized arylacridinylsulfones which showed activity against *Plasmodium falciparum*. These compounds (Fig. 4) showed activity due to structural similarity with dapsone and its derivatives (POPOFF *et al*., 1971) or acridine derivatives (FIGGITT *et al*., 1992). According to SANTELLI-ROUVIER *et al*., activities were not dependent on the presence of *para*-aminobenzoic acid (PABA) and acridine ring was part of the compounds responsible for the particular antimalarial activity. The sulfone group is also important for their activity. These authors suggested that there might be relationship between the activity and the ability of cleavage of the S-9C bond in acridine compound structure.

AZIM *et al*. (2008) used virtual screening for identification of acridine derivatives which may have significant activity against *P. falciparum*. They showed that potency was improved, and selective aspartic protease activity was achieved with different substituents (Fig. 5).

YU *et al*. (2012) synthesized new *N*-alkylaminoacridine derivatives (Fig. 6) with heterocyclic ring in the position C9 which significantly increased the activity against *P. falciparum*. Compounds with chloro and methoxy substituents in the acridine structure had higher inhibitory activity on the β-hematin formation, but inhibition was not in correlation with antimalarial activity. Morpholinyl compounds showed modest activity and also were highlighted for antimalarial activity by other authors (OPSENICA *et al*., 2011).



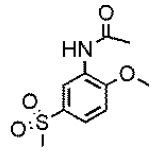
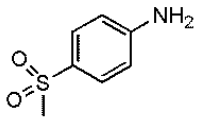
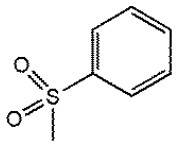
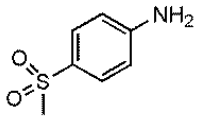
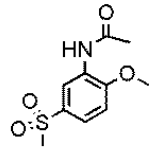
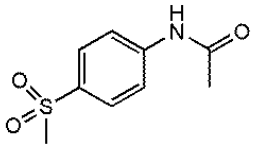
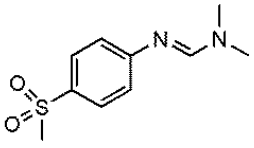
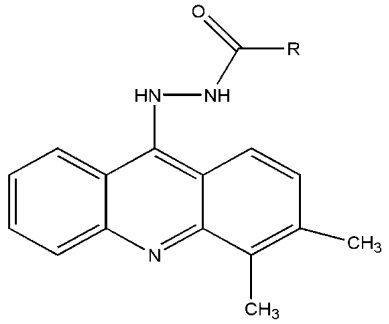
Compound	R_1	R_2	R_3
1		$-OCH_3$	-H
2		-H	-Cl
3		$-OCH_3$	-Cl
4		$-OCH_3$	-Cl
5		$-OCH_3$	-Cl
6		$-OCH_3$	-Cl
7		$-OCH_3$	-Cl

Figure 4. Arylacridinyl sulfones.



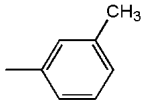
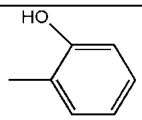
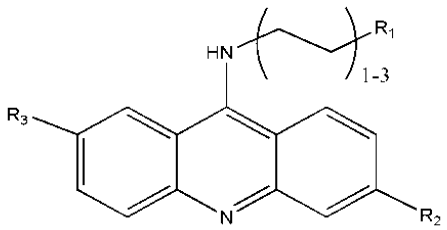
Compound	R
1	
2	

Figure 5. Acridinyl derivatives with selective aspartic protease activity.



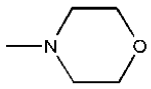
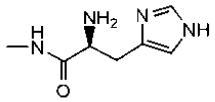
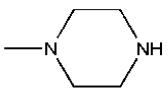
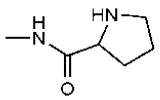
R_1	R_2	R_3
	$-OCH_3$	-Cl
$-NH_2$	$-OCH_3$	-Cl
	-H	-H
	$-OCH_3$	-Cl
	-H	-H
	$-OCH_3$	-Cl
	-H	-H
	$-OCH_3$	-Cl
	-H	-H

Figure 6. Acridine derivatives proposed to have antimalarial activity or activity against β-hematin formation.

ANTIVIRAL ACTIVITY OF ACRIDINE DERIVATIVES

Series of acridinylaminoalcohols and acridinylaminoacid esters were syntesized and their activity against herpes simplex virus (HSV) was investigated (SUVEYZDIS *et al.*, 2000). Maximum activity was established with compounds Ia and Ic. Compounds IIa - IId, as well as reference drugs (camedone and amyxin) were inactive. Also, the authors annotated the inversion of relative activity of enantiomers (compounds Ic and Id) on passage from the *in vivo* to the *in vitro* model.

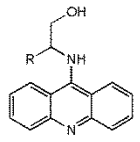
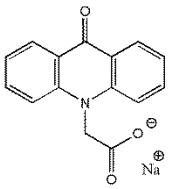
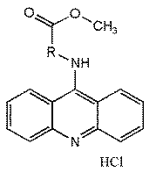
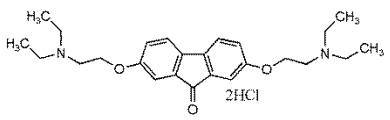
Compound I		R	CAMEDONE
	Ia	L-CH_3	
	Ib	L-$(CH_3)_2CHCH_2$	
	Ic	L-$CH_2C_6H_5$	
	Id	D-$CH_2C_6H_5$	
Compound II		R	AMYXIN
	IIa	L-$CH_3CH(CH_3)_2$	
	IIb	D-$CH_3CH(CH_3)_2$	
	IIc	-$(CH_2)_2$-	
	IId	-$(CH_2)_5$-	

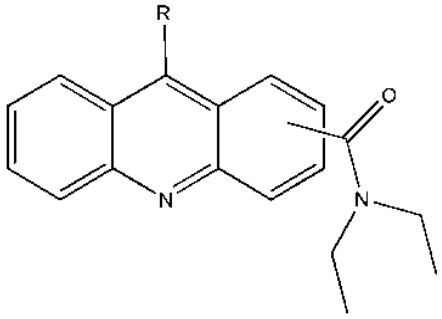
Figure 7. Structures of synthesized acridinylaminoalcohols (I), acridinylaminoacid esters (II), camedone and amyxin.

Compounds presented in Fig. 7 were of interest for new antiviral acridine derivatives research.

GOODELL *et al.* (2006) also examined anti-herpes activity of a group of acridine derivatives. They suggested that some derivatives (Fig. 8) interrupt enzyme/DNA interaction due to their capacity to intercalate DNA. Their anti-herpes activity is in correlation with catalytic inhibition of topoisomerase II, but some acridines which haven't showed activity in the topoisomerase II relaxation assay still had anti-herpes activity. This may be explained with non-specific binding of the acridines by intercalation. Acridine substituents affect electronic or steric properties of these compounds and thus cause different binding tendency. The carboxamides which contain diethylamine in C2 and C3 positions had the highest activity. Acridine derivatives with carboxamide in C2 and C3 positions and bulky 9-amino groups inhibited herpes infections.

ARTUSI *et al.* (2015) conducted research on HSV-1 genome and evidenced extended G-quadruplex sites. They suggested that replication of HSV DNA may be stopped by G-quadruplex ligands, such as BRACO-19 (Fig. 9). BRACO-19 is a 3,6,9-trisubstituted acridine derivative which stabilizes G-quadruplex (READ *et al.*, 2001), inhibits telomerase activity (HARRISON *et al.*, 2003) and has antitumor activity (BURGER *et al.*, 2005).

PEPIN *et al.* (2017) used sub-toxic concentrations of acriflavine and proflavine mixture to encourage a cyclic-GMP-AMP (cGAMP) synthase (cGAS)-dependent type-I IFN antiviral response. This mixture reduced rhinovirus infection. These compounds showed antiviral effects in mammalian cells as indirect antagonists of cGAS.



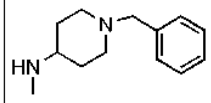
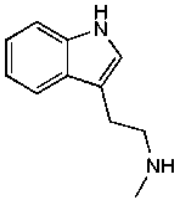
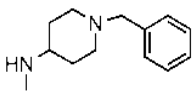
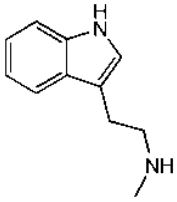
Compound	1	2	3	4
Ring sub	3	3	2	2
R				

Figure 8. Acridine derivatives with anti-herpes activity.

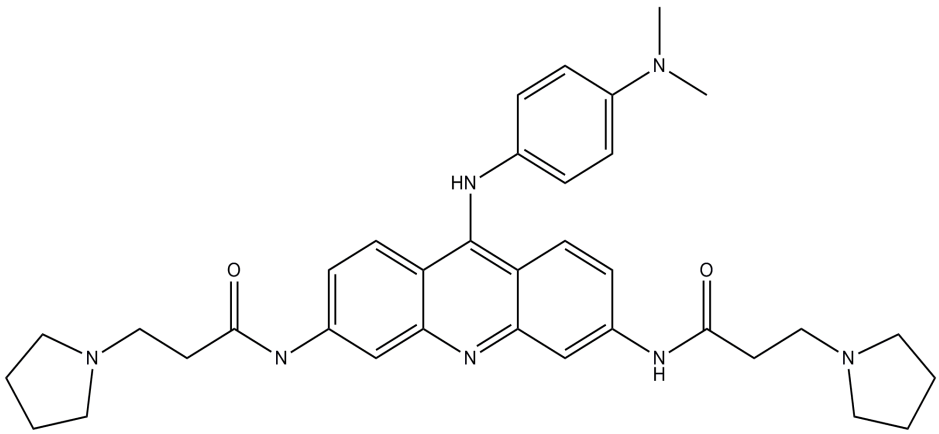
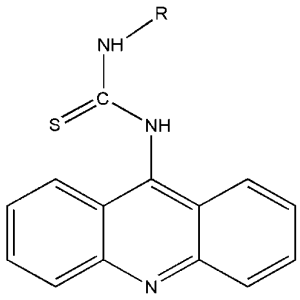


Figure 9. Chemical structure of BRACO-19.

ANTIBACTERIAL ACTIVITY OF ACRIDINE DERIVATIVES

STEWART (1973) synthesized derivatives of acridine with carbamic and thiocarbamic acid esters, urea and thiourea substituents at C9 (Fig. 10). Compounds containing thiourea group (I and II) showed antibacterial activity against *Staphylococcus aureus*, *Proteus vulgaris*, *Salmonella pullorum*, *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Diplococcus pneumoniae*. Compound II inhibited also *Proteus mirabilis*, *Streptococcus pyogenes* and *Pasteurella multocida*.

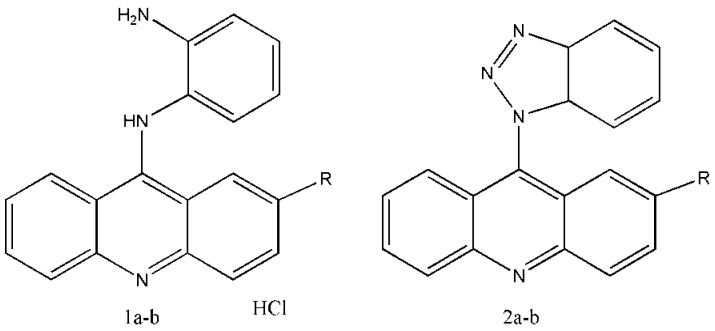


Compound	R
I	$-C_6H_5$
II	$-CH_2C_6H_5$

Figure 10. Chemical structures of acridine derivatives with thiourea substituents at C9 evaluated for antibacterial activity.

ALBERT (1966) conducted research on antibacterial activity of acridines and found parameters obligatory for this activity. These parameters include cation formation, high levels of ionization at neutral pH and planar molecule surface area. Electronic conjugation between nitrogen atom in acridine ring and amino group and resulting ionization were responsible for their high activity. Positions C3, C6 and C9 were also important for antibacterial activity (ALBERT *et al.*, 1945). DNA intercalation of some aminoacridines was responsible for antibacterial activity and this led to anticancer compounds development (LERMAN, 1963).

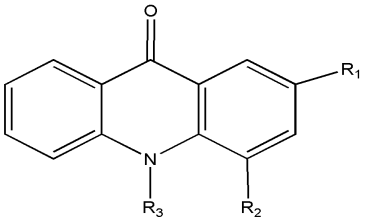
SINGH *et al.* (2011) synthesized benzotriazole substituted acridines with aim to determine their antibacterial activity. Compounds 1a and 1b (Fig. 11) showed moderate antibacterial activity, probably due to unsubstituted aromatic amino group, whereas compounds 2a and 2b showed good antibacterial activity. These authors suggested that presence of $-OCH_3$ or $-CH_3$ at C2 position of acridine ring increased antibacterial activity.

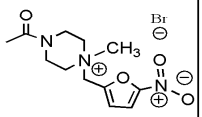
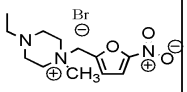
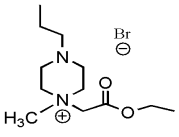
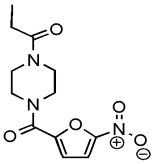


Compound	R
1a	$-OCH_3$
1b	$-CH_3$
2a	$-OCH_3$
2b	$-CH_3$

Figure 11. Compounds with moderate (1a-b) and good (2a-b) antibacterial activity.

According to KUDRYAVTSEVA *et al.* (2017), 9-oxoacridines have antibacterial properties which are result of DNA intercalation. They synthesized derivatives of 9-oxoacridines and acridine-9-carboxylic acid which had 5-nitrofurantoin as a substituent. Antimicrobial activity of compounds 1 and 3 (Fig. 12) was comparable to standard (ethacridine lactate), compound 1 had more potent inhibition effect compared to standard, while 4 and 5 showed moderate activity. Compound without 5-nitrofurantoin as a substituent (3) had the lowest activity against tested strains.



Compound	1	2	3	4
R_1	-H	-H		-H
R_2		-H	-H	-H
R_3	-H		-H	

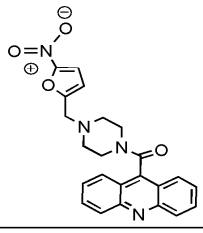
Compound 5	

Figure 12. Derivatives of 9-oxoacridines and acridine-9-carboxylic acid.

ANTITUMOR ACTIVITY OF ACRIDINE DERIVATIVES

GAO *et al.* (1998) conducted quantitative structure-activity relationship analysis (QSAR) of 9-anilinoacridines with antitumor activity (including inhibitory activity on tumor cells and binding to DNA). They suggested that electronic effects of substituents affected drug's binding site. Hydrophobicity affected the entrance of the drug to the active site and

substituent's steric effects influenced binding to the active site. On the basis of the previous work (GAO *et al.*, 1998), Bacherikov *et al.* (2005) synthesized a series of 5-(9-acridinylamino)anisidines, such as 5-(9-acridinylamino)-*m*-anisidines (AMAs), 5-(9-acridinylamino)-*o*-anisidines (AOAs) and 5-(9-acridinylamino)-*p*-anisidines (APAs) (Fig. 13), in order to investigate inhibition of tumor cell growth in different cell cultures, topoisomerase II inhibition and interaction with DNA.

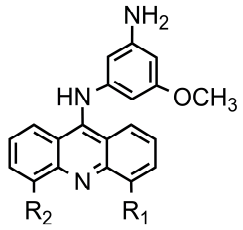
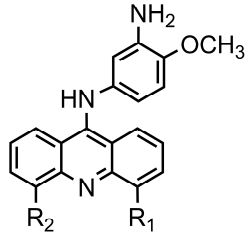
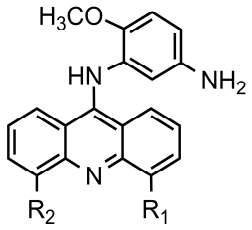
Compound	1 	2 	3 
a	R_1–H	R_1=H	R_1–H
	R_2=H	R_2= H	R_2=H
b	R_1=CH_3	R_1=CH_3	R_1=CH_3
	R_2=H	R_2= H	R_2= H
c	R_1=$CONHCH_2CH_2N(CH_3)_2$	R_1=$CONHCH_2CH_2N(CH_3)_2$	R_1=$CONHCH_2CH_2N(CH_3)_2$
	R_2=H	R_2=H	R_2=H
d	R_1=$CONHCH_3$	R_1=$CONHCH_3$	R_1= $CONHCH_3$
	R_2=CH_3	R_2–CH_3	R_2= CH_3
e	R_1=$CONHCH_2CH_2N(CH_3)_2$	R_1=$CONHCH_2CH_2N(CH_3)_2$	R_1=$CONHCH_2CH_2N(CH_3)_2$
	R_2=CH_3	R_2=CH_3	R_2=CH_3

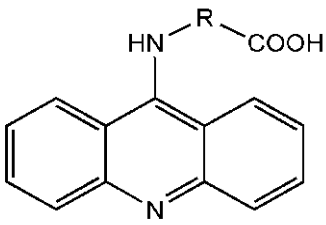
Figure 13. Structures of 5-(9-acridinylamino)-*m*-anisidines (AMAs) 1a-e; 5-(9-acridinylamino)-*o*-anisidines (AOAs) 2a-e; 5-(9-acridinylamino)-*p*-anisidines (APAs) 3a-e.

Previous reports (CAIN *et al.*, 1975) showed that -OCH_3 group, with electron-donating effect on the aniline ring of 9-anilinoacridine derivatives, increased antitumor potency and it was suggested that replacing -CH_3 group with -OCH_3 may increase cytotoxicity of 5-(9-acridinylamino)toluidines.

CHANG *et al.* (2003) showed that 5-(9-acridinyl- amino)toluidine derivatives with -$CONHCH_2CH_2N(CH_3)_2$ and -CH_3 substituents at C4 and C5 of the acridine ring were more toxic than the parent AHMA (3-(9-acridinylamino)-5-hydroxymethyl- aniline), in contrast to the simple 5-(9-acridinylamino)toluidines. According to these results, it was easy to define factors that influence the cytotoxicity of 9-anilinoacridines.

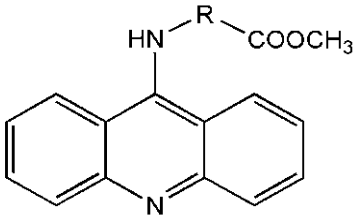
BACHERIKOV *et al.* (2005) showed that AOA (2e) (Fig. 13) was the most potent agent among tested compounds. These authors also suggested that the drug/DNA binding affinity was dominant factor that affects their cytotoxicity.

LYAKHOV *et al.* (1997) synthesized acridinyl- amino acids and their methyl esters and investigated their cytostatic activity using root test. The polymethylene chain's length influence on the character of the action of synthesized compounds was examined (Fig. 14).



Compound	R	Compound	R
4	$-CH_2-$	16	(D)-CH(i-Bu)-
5	$-(CH_2)_2-$	17	(L)-CH(sec-Bu)-
6	$-(CH_2)_3-$	18	(D)-CH(sec-Bu)-
7	$-(CH_2)_4-$	19	(L)-CH(CH_2Ph)-
8	$-(CH_2)_5-$	20	(D)-CH(CH_2Ph)-
9	(L)-CH(CH_3)-	21	(L)-CH(CH_2Ind*)-
10	(D)-CH(CH_3)-	22	(D)-CH(CH_2Ind*)-
11	(L)-CH(i-Pr)-	23	(L)-CH($CH_2CH_2SCH_3$)-
12	(D)-CH(i-Pr)-	24	(D)-CH($CH_2CH_2SCH_3$)-
13	(L)-CH(n-Pr)-	25	(L)-CH(CH_2OH)-
14	(D)-CH(n-Pr)-	26	(D)-CH(CH_2OH)-
15	(L)-CH(i-Bu)-	27	(L)-CH(CH_2Im**)-

Ind* - Indolyl-3; Im** - Imidazolyl-4



Compound	R	Compound	R
28	(L)-CH(CH_3)-	32	$-(CH_2)_3-$
29	(D)-CH(CH_3)-	33	$-(CH_2)_4-$
30	$-CH_2-$	34	$-(CH_2)_5-$
31	$-(CH_2)_2-$		

Figure 14. Structures of acridinylamino acids and their methyl esters.

Compounds 30 and 31 had stimulatory effect on the cell-division process, but when used in higher concentrations they showed depressing effect. Stimulatory effect of compound 32 was less pronounced, while compounds 33 and 34 had inhibitory effect even in low concentrations (LYAKHOV *et al.*, 1997). They also concluded that there were no significant differences in cytotoxicity of acridinylamino acids and corresponding methyl esters.

SONDHI *et al.* (2010) synthesized and evaluated a series of acridine derivatives (1a-o and 2a-g) for anti-inflammatory and anticancer activities. The most active compounds with

anticancer activity were 1g and 1m. Compounds 2d, 2f and 2g also showed good anticancer activity due to electronic and stereochemical effects of substituents (Fig. 15).

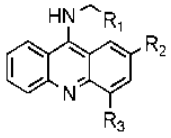
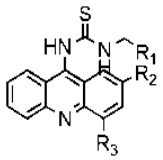
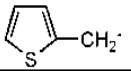
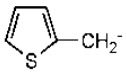
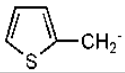
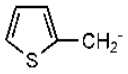
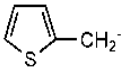
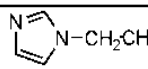
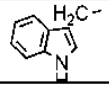
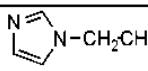
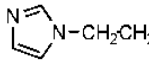
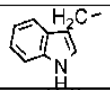
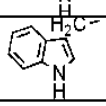
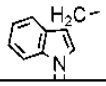
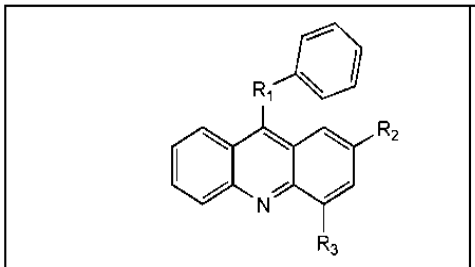
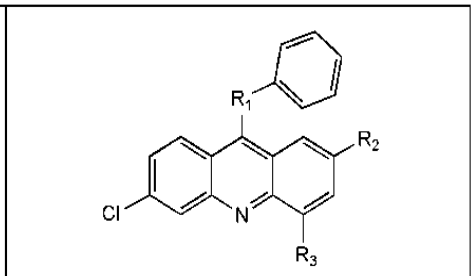
Compound	1 			2 		
	R_1	R_2	R_3	R_1	R_2	R_3
a		-H	$-OCH_3$		$-OCH_3$	-H
b		$-OCH_3$	-H		$-OCH_3$	-H
c		-H	$-CH_3$		$-OCH_3$	-H
d		-H	$-OCH_3$		-H	$-CH_3$
e		$-OCH_3$	-H		-H	$-CH_3$
f		-H	$-CH_3$		-H	$-CH_3$
g		-H	$-OCH_3$		-H	$-CH_3$
h		$-OCH_3$	-H			
i		-H	$-CH_3$			
j		-H	$-OCH_3$			
k		$-OCH_3$	-H			
l		-H	$-CH_3$			
m		-H	$-OCH_3$			
n		$-OCH_3$	-H			
o		-H	$-CH_3$			

Figure 15. Acridine derivatives with anti-inflammatory and anticancer activities.

LANG *et al.* (2013) synthesized a series of acridine derivatives (Fig. 16). They were focused on the linker between acridine ring and phenyl group and its effect on the antiproliferative activity and DNA-binding ability. Examined cytotoxicity of acridine compounds depends on the structure of the linker between acridine ring and phenyl group.

The length of the alkyl chain has modest influence on the cytotoxic activity. Compound 1 with the shortest linker showed better cytotoxicity than compounds 2 and 3, so it was suggested that the increase in chain length leads to modest reduction of cytotoxic activity. Introduction of alkoxy or acylamino linker decreased antiproliferative activity. Methyl group at C4 position and chloro group at C6 position of acridine ring had no obvious effect on the activity. Finally, compound 7 with -OCH_3 group at C2 position showed greatest cytotoxic activity, affecting DNA topoisomerase I inhibition and caspase-dependent intrinsic mitochondrial pathway.





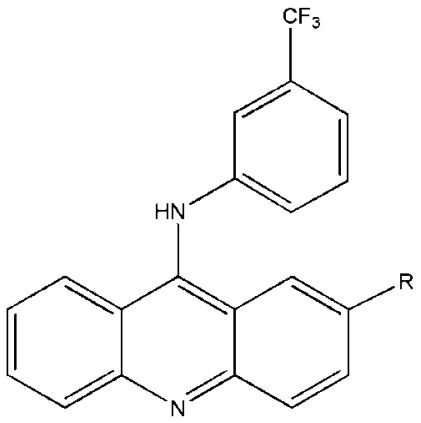
Compound	R_1	R_2	R_3	Compound	R_1	R_2	R_3
4	-CH_2O-	-H	-H	1	-CH_2NH-	-OCH_3	-H
5	-CONH-	-H	-H	2	-$(CH_2)_2NH$-		-H
6	-CH_2NH-	-H	-H	3	-$(CH_2)_3NH$-	-OCH_3	-H
7	-CH_2NH-	-OCH_3	-H	8	-CH_2NH-	-H	-H
10	-CH_2NH-	-H	-CH_3	9	-CH_2NH-	-OCH_3	-CH_3

Figure 16. Acridine derivatives with different linker between acridine and benzene ring and different substituents on acridine ring.

Effects on DNA synthesis and biochemical pathways, including protein and lipid metabolism, suggest that acridine derivatives may be considered as multi-target compounds.

KUMAR *et al.* (2013) synthesized a series of 9-aminoacridine derivatives and tested their anticancer activity (Fig. 17). Compounds 1 and 2 exhibited good activity against lung cancer (A-549) and cervical cancer (HeLa) cell lines. SAR analysis showed that substitution by -OCH_3 group at position C2 of acridine ring and -CF_3 group at position C3 of benzene ring attached to the acridine ring resulted in compounds with potent activity against tested cancer cell lines. Also, presence of an electron donating group on acridine ring at position C2 increased anticancer activity.

DOBRIČIĆ *et al.* (2016a) designed new acridine derivatives with potential multi-target action [DNA intercalation and inhibition of kinases - Src, MEK and VEGFR-2 (CUI *et al.*, 2016)]. These compounds contain aminoacids (L-glycine, L- and D-phenylalanine, L-histidine and L-asparagine) or corresponding dipeptides in C9 side chain (Fig. 18). Their potential to interact with selected targets was tested using molecular docking studies. Obtained results showed that binding of designed compounds to DNA, with exception of compounds 3, 4, 5 and 6, was similar to amsacrine, which was used as standard. Derivatives with lowest binding energies that form key binding interactions with MEK were 4, 6, 9, 10, 11, 12, 13, 15, 16, 18 and 19, with VEGFR-2 were 8, 11 and 16, whereas with Src were 4 and 6.



Compound	R
1	-H
2	$-OCH_3$

Figure 17. Structure of 9-aminoacridine derivatives tested for anticancer activity.

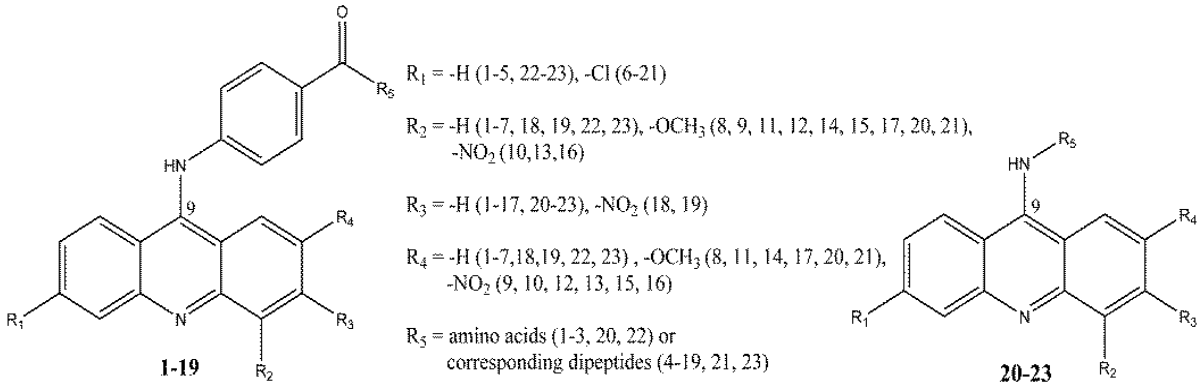


Figure 18. Chemical structures of designed acridines with potential multi-target action.

The same authors designed additional group of 9-aminoacridine derivatives (Fig. 19) and examined their interaction with same targets (DNA, Src, MEK and VEGFR-2) using molecular docking (DOBRIČIĆ *et al.*, 2016b).

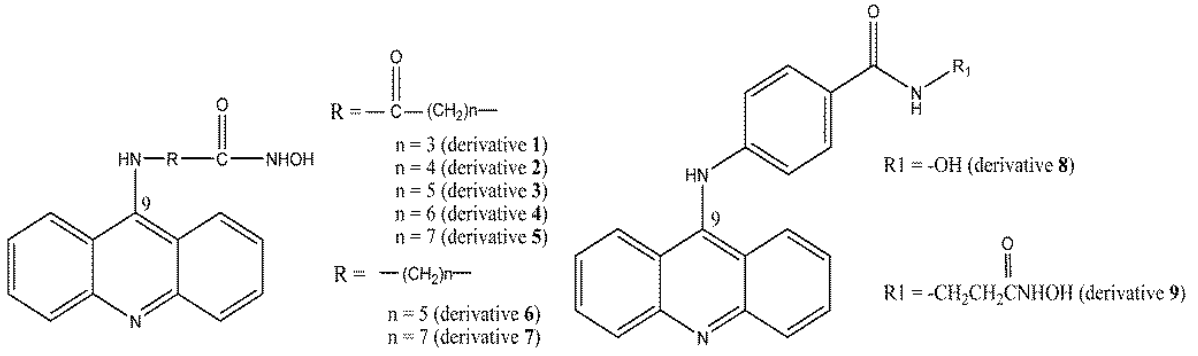


Figure 19. Additional group of 9-aminoacridine derivatives with potential multi-target action.

All compounds showed DNA binding affinity similar to amsacrine. Compounds 3, 4, 5, 6, 7 and 9 formed significant interactions with MEK, whereas compounds 1, 3, 7 and 8 showed significant binding to Src. Derivatives 3, 4, 5, 8 and 9 formed some of the important interactions with VEGFR-2, but according to their binding energies, moderate activity towards VEGFR-2 can be expected.

CONCLUSION

Although introduced in 19th century, acridine derivatives are still of scientific interest. In this review, acridine derivatives with various biological activity (antiparasitic, antiviral, antibacterial and antiproliferative), as well as their structure-activity relationship analyses are presented. Although several mechanisms of their action are known, only important are discussed here. It can be concluded that dominant mechanisms are DNA intercalation and interactions with enzymes.

Acknowledgments

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