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Acridine Derivatives and Their Pharmacology

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ABSTRACT

Acridine is a heterocyclic nucleus. It plays an important role in various medicines. A number of therapeutic agents are based on acridine nucleus such as quinacrine (antimalarial), acriflavine and proflavine (antiseptics), ethacridine (abortifacient), amsacrine and nitracine (anticancer), and tacrine. Acridine undergoes a number of reactions such as nucleophilic addition, electrophilic substitution, oxidation, reduction, reductive alkylation, and photoalkylation. Acridine derivatives constitute a class of compounds that are being intensively studied as potential anticancer drugs. The most well-known acridine derivatives, their pharmacological properties, action mechanisms and outlooks for practical application are described in this article. The unique qualities of acridines are primarily attractive due to the possibility of using them for the purpose-oriented designing of drugs. Thus, acridines were used as a basis to create the specific regulatory HIV-1 elements, proliferation inhibitors of leukemia cells and new anti-tumor drugs. The elaboration of complexes of acridines derivatives combined with peptides intercalating specifically into the DNA big or small grooves is the most outstanding trend of acridines' research. Acridines are well-known for their high cytotoxic activity; however, their clinical application is limited or even excluded because of side effects. DNA is considered as one of the main targets for anticancer drug design. The planar structure of acridines confers to the molecules the ability to bind DNA by intercalation and to interfere with metabolic processes. A large number of natural alkaloids and synthetic acridine derivatives have been tested as anticancer agents. Acridine derivatives display other pharmacological properties such as antibacterial and antimalarial activities. They are also tested for Alzheimer's disease.

1. INTRODUCTION TO ACRIDINE:

Acridine is an organic compound and a nitrogen heterocycle, with the formula $C_{13}H_9N$. Acridine is a heterocyclic nucleus. It plays an important role in various medicines. A number of therapeutic agents are based on acridine nucleus such as quinacrine (antimalarial), acriflavine and proflavine (antiseptics), ethacridine (abortifacient), amsacrine and nitracine (anticancer), and tacrine. Acridine is obtained from the high boiling fraction of coal tar. It is also obtained in nature from a plant and marine sources. Acridine undergoes a number of reactions such as nucleophilic addition, electrophilic substitution, oxidation, reduction, reductive alkylation, and photoalkylation.

STRUCTURE AND NUMBERING:

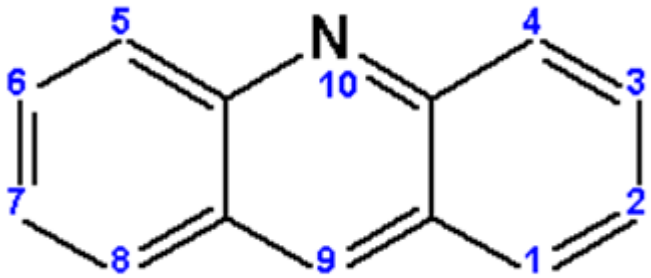


Figure 1: Structure and numbering of Acridine

IUPAC name-Acridine

Systematic IUPAC name-Dibenzo[b,e]pyridine

Isolation and syntheses

Acridine is separated from coal tar by extracting with dilute sulfuric acid.Acridine and its derivatives can be prepared by many synthetic processes. In the Bernthsenacridine synthesis. Diphenylamine is condensed with carboxylic acids in the presence of zinc chloride. When formic acid is the carboxylic acid, the reaction yields the parent acridine. With the higher larger carboxylic acids, the derivatives substituted at the meso carbon atom are generated.

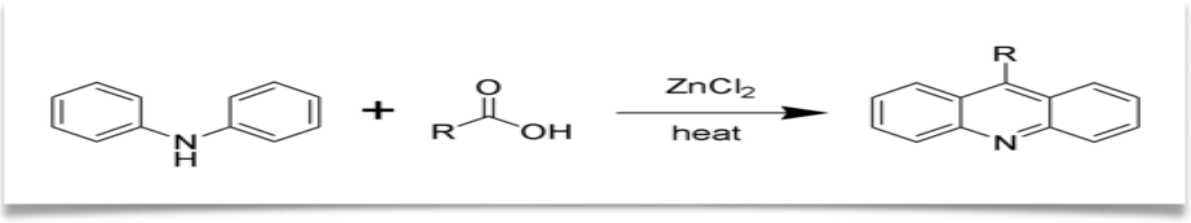


Figure 2: Isolation and synthesis of Acridine

Reactions of acridine:

Electrophilic substitutions of acridine

The electrophilic substitution takes place in the benzenoid ring. Halogenation gives a mixture of addition and substitution products. Bromination of acridine gives 2-and a,7-di2-anda,7-dibromobromo products

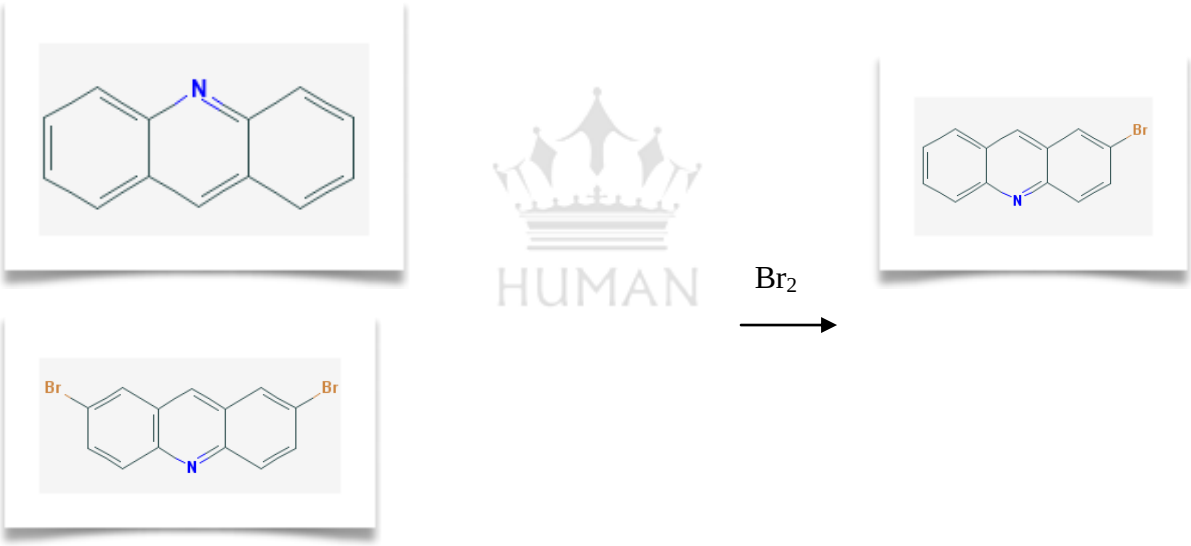


Figure 3: Electrophilic substitution reaction of acridine

Nitration yields mixed isomers. Acridine N-oxide, however, undergoes nitration (HNO_3, H_2SO_4,0^0C) to produce 9-nitro acridine-N-oxide.

Nucleophilic substitution of acridine:

Nucleophilic attack of acridine takes place at the 9-position. This is due to electron density decrease at this position in comparison to 1-,2-,3-and 4-positions. Thus reaction of acridine with sodium amide in liquid ammonia gives 9-aminoacridine. This compound is a strong base

and its hydrochloride is used as an anti-bacterial agent. The quaternary salts of acridine are also more reactive towards nucleophilic reagents.

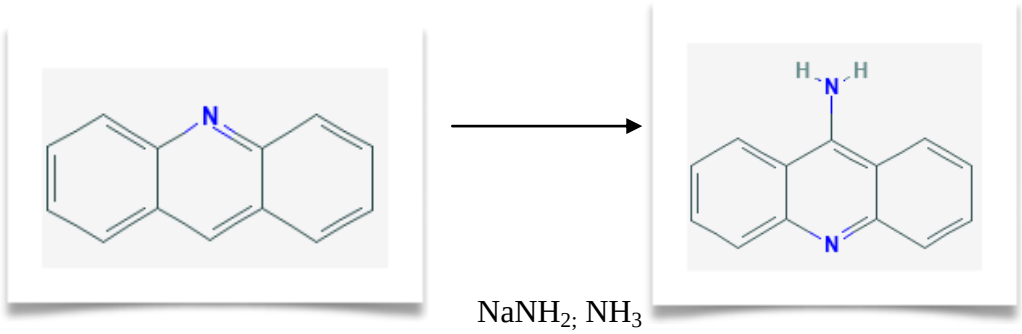
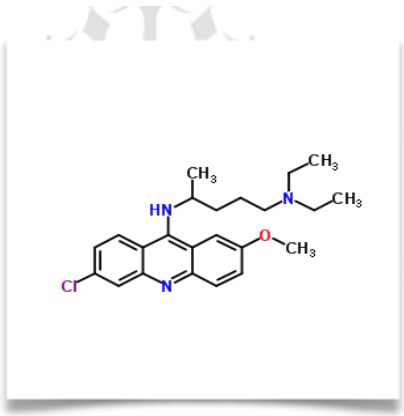


Figure 4: Nucleophilic substitution of acridine

2. TYPES OF ACRIDINES:

a.9-Arylaminoacridines:

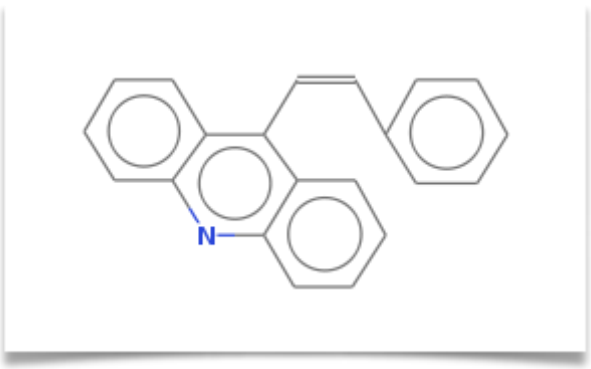
Drug: Mepacrinechromophore (3-chloro-7-methoxy acridine)



Uses:	Side effects:
➢ Anti-leishmanial	➢ Dizziness.
➢ Anti-streptococcal	➢ Headache.
➢ Anti-malarial\protozoal	➢ Disturbances of the gut such as
➢ Anti-cancer	diarrhea, constipation, nausea, vomiting
➢ Anti-bacterial	or abdominal pain.
➢ Anti-dysentric	➢ Inflammation of the liver (hepatitis).
	➢ Visual disturbances and discoloration of cornea.
	➢ Partial or total failure of blood cell development (aplastic anemia).
	➢ Skin disorders.
	➢ Inflammation and flaking of the skin (exfoliative dermatitis).
	➢ Yellow discoloration of the skin and urine on long-term treatment.
	➢ Loss of contact with reality (psychosis).
	➢ Blue/black discoloration of palate and nails.

b.Styrylacridines

Drug: 9-styrylacridine



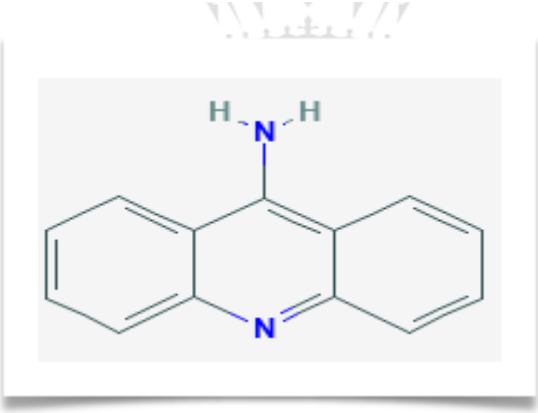
Uses:
➢ Trypanocidal agent
➢ Anti-bacterial

C. Aminoacridines:

Drug:

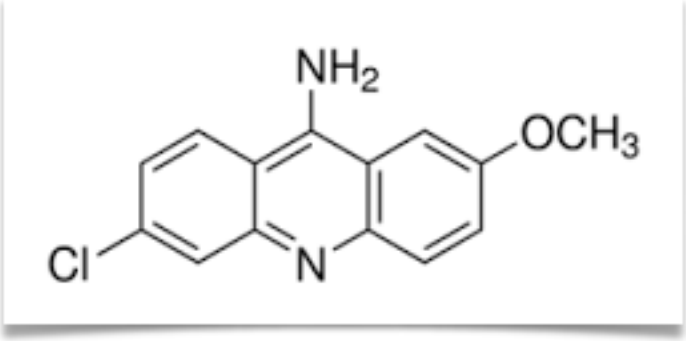
➢ 3- or 9-aminoacridine derivatives (Diflavine)

Uses:	Side effects:
➢ Anti-bacterial	➢ Nausea
	➢ Vomiting
	➢ Headache
	➢ Stomach upset
	➢ Loss of appetite



d. Halogenoacridines

Drugs: Chloroaminoacridines



Uses:
➢ Anti-bacterial
➢ Anti-microbial
➢ Anti-cancer
➢ Treatment of clinical typhus
➢ Topical antiseptic
➢ Intracellular pH indicator
➢ Fluorescent dye

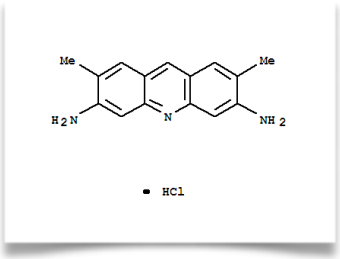
e. Nitroacridines

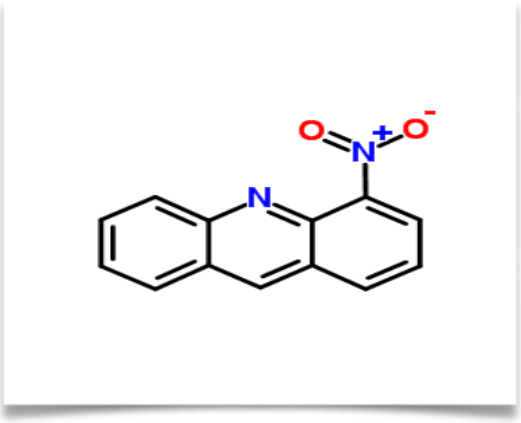
Uses:
➢ Anti-bacterial

Drug:3-nitro-9-aminoacridine (Nitroakridin ,Ledakrin)

f. Quaternaryacridines

Drug: Sinflavin, Flaccid



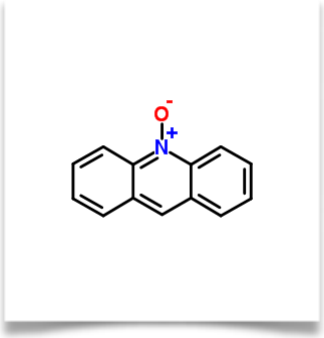


Uses:

- ➢ Anti-bacterial
- ➢ Amoebocide

g.Acridine N-oxides

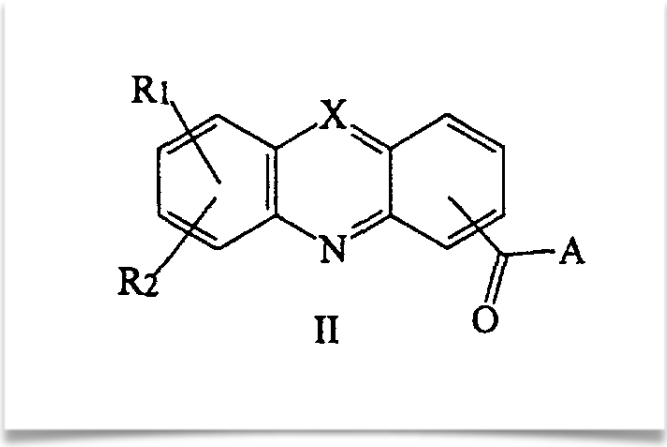
Drug: Acridine N-oxide



Uses:	Side effects:
➢ Amoebocide	➢ mild bladder irritation,
➢ Anti-bacterial	➢ dizziness,
	➢ headache,
	➢ increased sweating,
	➢ nausea,
	➢ vomiting,
	➢ abdominal pain,
	➢ diarrhea,
	➢ upset stomach,
	➢ frequent urination, or stomach cramps.
	➢ Side effects of doses include chest pain and confusion.

h. Aza analogues

Drug: 9-(2-(2′,3′-dihydroxypropylamino) ethylamino) acridine

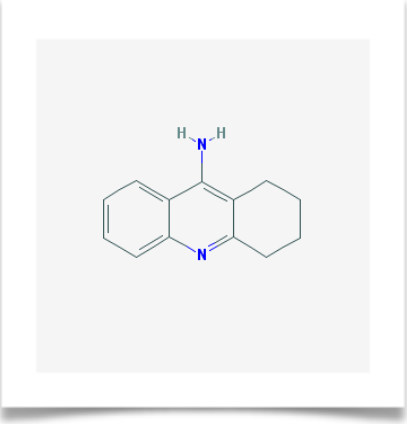


II

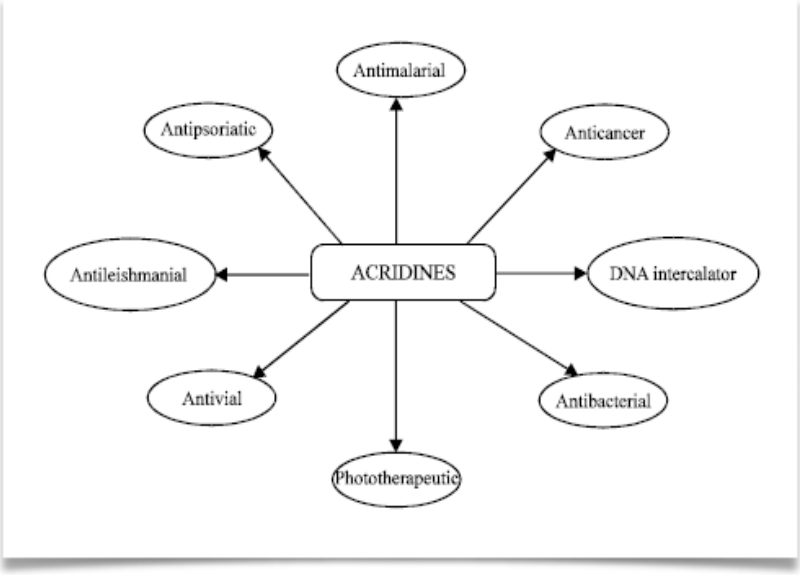
Uses:
➢ Anti-malarial
➢ Active against human schistosomiasis
➢ Active against hemolytic streptococcal strain

i. Reducedacridine system:

Drug: 9-amino-1,2,3,4-tetrahydoacridine (tacrine)



Uses:	Side effects:
➢ prototypical cholinesterase inhibitor for the treatment of Alzheimer's disease	➢ Clumsiness or unsteadiness
➢ a beneficial effect on cognition	➢ diarrhea
➢ The analeptic agent used to promote mental alertness.	➢ loss of appetite
	➢ nausea
	➢ vomiting
	➢ Liver problems



3. ROLE OF ACRIDINE

1.An interest of acridine derivatives in the anticancer chemotherapy:

DNA is considered as one of the main targets for anticancer drug design.The planar structure of acridines confers to the molecules the ability to bind DNA by intercalation and therefore to interfere with the metabolic process. A large number of natural alkaloids and synthetic acridine derivatives have been tested as anticancer agents.

Mechanism of action:

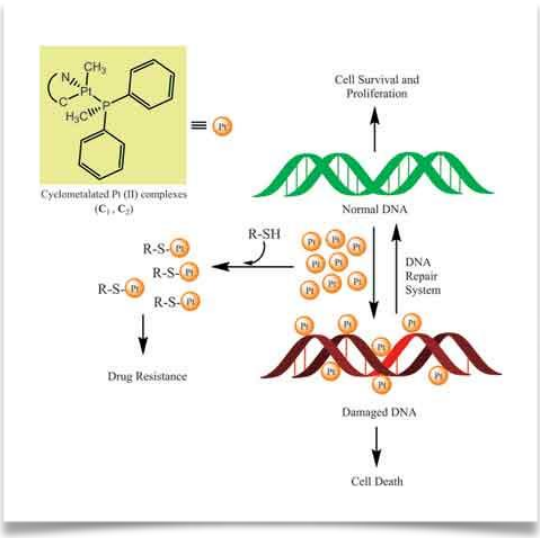
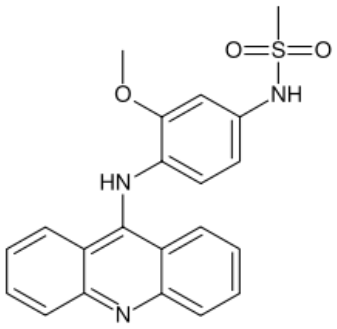


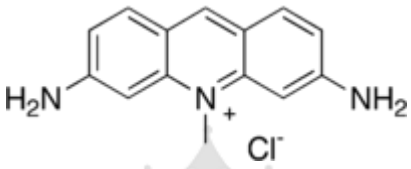
Figure 5: Mechanism of action of acridine as anticancer

2. Anticancer properties and synthetic methods: DNA intercalation:



Amsacrine (m-AMSA) is an anticancer agent that displays activity against refractory acute leukemia as well as Hodgkin and non-Hodgkin's lymphomas.

3. Acridine—a neglected antibacterial chromophore:



Acriflavine

Acriflavine is an antiseptic agent causing both apoptosis and necrosis in yeast. Its effect on the structure and function of catalase, a vital enzyme actively involved in protection against oxidative stress. Acriflavine inhibits the enzymatic activity in a competitive manner.

4. Acridine in protozoal infections:

The malaria protozoan, Plasmodium berghei, exhibits features typical of metazoan apoptotic cells including condensation of chromatin, fragmentation of the nuclear DNA and movement of phosphatidylserine from the inner to the outer lamellae of the cell membrane.

In addition, proteins with caspase-like activity were identified in the cytoplasm of the ookinete suggesting that the cellular mechanism of cell death may be similar to that of multicellular eukaryotes.

5. Acridine in prion diseases:

Quinacrine and chlorpromazine have been used in humans for many years as antimalarial and antipsychotic drugs, respectively, and are known to pass the blood-brain barrier, we suggest

that they are immediate candidates for the treatment of Creutzfeldt-Jakob disease and other prion diseases.

6. Acridine in viral diseases:

The anti-schizophrenic activity of phenothiazine drugs and their tendency to elicit extrapyramidal symptoms are thought to involve blockade of synaptic dopamine receptors in the brain.

7. Acridine in malarial diseases:

Since the emergence of chloroquine-resistant Plasmodium falciparum and reports of parasite resistance to alternative drugs, there has been renewed interest in the antimalarial activity of acridines and their congeners, the acridinones.

Natural acridinone alkaloids and synthetic 9-substituted acridines, acridinediones, haloalcoxyacridinones and 10-N-substituted acridinones are used for the antimalarial activity.Acronycine was first isolated from the Australian scrub ash Acronychiabaueri, it showed antineoplastic and anti-parasitic activity.

8. Acridine in Psoriasis:

Dithranol is highly effective in the treatment of psoriasis.

The drug inhibits keratinocyte hyperproliferation, granulocyte function and, in addition, may exert an immunosuppressive effect.

Free radicals, histamine, eicosanoids, and platelet-activating factor have been shown to be involved in dithranol-induced dermatitis, and the oxidation products of the drug are responsible for the staining.

9. Acridine in leishmaniasis:

Chlorpromazine and quinacrine are concentrated in tissues that are susceptible to infection by Leishmania.

NEW MODELS AND CURRENT STATUS OF ACRIDINE:

Pyrazoloacantiprotozoalridine appears to Intercalate into DNA and inhibit RNA synthesis, DNA synthesis, and the activities of topoisomerase I and II, thereby causing cytotoxicity.

Acridine derivatives are interesting chemotherapeutic agents that were first used as antibacterial and antiparasitic agents.

Recent progress of acridine derivatives with anti-tumor activity:

Some recent progress in the research of the anti-tumor activity of acridine derivatives, including as the inhibition of telomerase, topoisomerase I and II, tubulin, ABCG2/P-gP, protein kinases, etc.

CONCLUSION:

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 focused primarily in these areas, but recent work shows they are active also as anticholinesterase agents.

The molecular docking studies showed a good correlation between their short-term anticancer activity and exhibited the highest potential binding affinity research many useful medicinal compounds.

REFERENCES:

1. A TEXTBOOK OF ORGANIC CHEMISTRY, Fifth Edition Author: Bansal, R.K., Formerly Professor, Department of Chemistry, IIT, New Delhi.
2. Swarna A. Gamage, Julie A. Spicer, Graham J. Attwell, Graeme J. Finlay, Bruce C. jm980687m, and William A. Denny *Auckland Cancer Society Research Centre, Faculty of Medicine and Health Science, The University of Auckland, Private Bag 92019, Auckland 1000, New Zealand
3. J. Med. Chem., 1999, 42 (13), pp 2383–2393
DOI: 10.1021/jm980687m
Publication Date (Web): June 15, 1999
Copyright © 1999 American Chemical Society
4. Current Medicinal Chemistry
Author(s): Bruce C. Baguley, Laurence P.G. Wakelin, Jason D. Jacintho and Peter Kovacic
Affiliation: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand.
5. Anti-Cancer Agents in Medicinal Chemistry

Author(s): Philippe Belmont, Johann Bosson, Thomas Godet and Martin Tiano
Affiliation: University Claude Bernard -Lyon I, UMR CNRS 5181, Methodologie de Synthese et Molecules Bioactives. Laboratoire de Synthese et MethodologieOrganiques, Batiment CPE,43 boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France.
6. Current Organic Chemistry Volume 4, Number 9, 1 September 2000,
Authors: Graves, D.E.; Velea, L.M.
Publisher: Bentham Science Publishers
7. Abstract 2529: Structure-activity relationship studies of the type II topoisomerase poison amsacrine
Adam Ketron, David E. Graves, and Neil Osheroff
DOI: 10.1158/1538-7445.AM2011-2529 Published 15 April 2011
8. Citation Format: {Authors}. {Abstract title} [abstract]. In: Proceedings of the 102nd Annual Meeting of the American Association for Cancer Research; 2011 Apr 2-6; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2011;71(8 Suppl): Abstract nr 2529. doi:10.1158/1538-7445.AM2011-2529
©2011 American Association for Cancer Research.
9. Attar F1, Khavari-Nejad S, Keyhani J, Keyhani E.
Author information
Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran.
10. MicrobiolImmunol. 2009 Sep;
Kawai M1, Yamagishi J.
Faculty of Pharmaceutical Sciences, Himeji Dokkyo University, 7-2-1 Kamiohno,
Himeji, Hyogo.
11. Antibiotics - MedlinePlus Health Information
Pierce KK1, Kirkpatrick BD.
Department of Medicine, Unit of Infectious Diseases, University of Vermont College of Medicine, Burlington, Vermont 05405, USA.
12. Chemical Induction of Cancer: Structural Bases and Biological Mechanisms
Thomas Gessner and Udo Mayer "Triarylmethane and Diarylmethane Dyes" in Ullmann's Encyclopedia of Industrial Chemistry 2002, Wiley-VCH.
13. http://ki.se/sites/default/files/goran_kronvall_ao_staining_mini-review.pdf
14. Chloroquine inhibits cell growth and induces cell death in A549 lung cancer cells. Bioorganic & Medicinal Chemistry. 2006 May 1; 14(9):3218-3222.
15. Author: Denny, William A. Source: Medicinal Chemistry Reviews - Online, Volume 1, Number 3, July 2004, pp. 257-266(10)
Publisher: Bentham Science Publishers
16. Gardette M1, Papon J, Bonnet M, Desbois N, Labarre P, Wu TD, Miot-Noirault E, Madelmont JC, Guerquin-Kern JL, Chezal JM, Moins N.
Author information: Inserm UMR 990, BP 184, Clermont-Ferrand, Cedex 63005, France.