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ACRIDONE ALKALOIDS – A BRIEF REVIEW


Amit Giridhar

Amit Giridhar [a], Amit Chawla [a], Sandeep Jain[b], Neelam Jain[c], Shikha Giridhar[a]

[a] Seth G.L. Bihani S.D. College of Technical Education, Sriganganagar-335001, Rajasthan, India
[b] Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India
[c] Jan Nayak Ch. Devi Lal Memorial College of Pharmacy, Sirsa-125055, Haryana, India
Email: amit_girdhar15@yahoo.co.in

ABSTRACT:

Acridones having unique molecular structure of two benzene rings fused together having nitrogen atom at 10th position and a keto group at 9th position, which carries a wide range of biological activities. The present study includes brief review about chemistry, synthesis, applications and various pharmacological actions of acridone alkaloids reported in literature i.e. Anticancer, Antiherpes, Antimalarial, Antileishmanial, Nuclease activity etc. It has also antibacterial and antipsoriatic activity but need to be explored in future.

Keywords: Acridone, Antimalarial, Anticancer.

INTRODUCTION AND MATERIALS & METHODS

INTRODUCTION

The journey of acridones as pharmaceuticals was started by Paul Ehrlich in late nineteenth century. Acridone is a tricyclic ring having nitrogen at 10th position and keto group at 9th position. The planar structure of these acridones facilitates to act on nucleotides by intercalating DNA and RNA strands, there by emerging as potent anticancer agents. They posses sufficient Hydrophilic Lipophilic Balance to traverse biological membranes to reach nucleus for exerting their action. Since they act on the nucleotides; they are also tried for antiviral, anti-AIDS and anti-fungal properties. Promising results are also obtained during their primary screening. This exceptionally unique chromophore which was first introduced as a trypnomocide; however they also exert lethal action against many pathogenic microorganisms. The screening of acridone derivatives as anti-microbial is under pipeline and getting promising observations. Their potential as anti-microbial is faded under limelight of sulfonamides and penicillin in the 19th era due to their highly beneficial effects and ease of synthesis and cheaper cost. However due to emergence of microbial resistance it seems that acridones regaining their place in anti-microbial chemotherapy now a days.

Acridone derivatives are also found in natural plant sources, which are proving worthwhile in various disorders. Many plants, particularly plants pertaining to Rutaceae species possess maximum number of acridone derivatives. Acridone derivatives are also found in natural plant sources, which are proving worthwhile in various disorders [1].

In the review of acridine alkaloids by *J.R. Prince*, Which appeared around 30 years ago, the author recognized a relatively small group of acridone alkaloids present in the bark & leaves of certain Rutaceae species found in northern Australia's tropical rain forests. These acridone alkaloids reported in the period from 1948 to 1952 by prince [2, 3]. Lahey and their associates at the university of Sydney and Melbourne, include alkylated derivatives of 1,3- dihydroxy-N-methylacridone(Acronycine);1,2,3-trihydroxy-N-methylacridone (Evoxanthine) and 1,2,3,4-tetrahydroxy-N-methyl acridone (melicopine, melicopidine & melicopicine) all of which have an 1-*o*-mehyl substituent in common while differing in the respective pattern of alkylation at O-2, O-3. Two further members of this group reported by Australian coworkers are evoxanthidine and xanthevodine shown to be de-N-methyl congeners of evoxanthine & melicopine respectively.

In 1966, three further simple acridone alkaloids, close relative to acronycine, were obtained from a Rutaceae species in India [4]. In the same year, the Lilly research laboratories reported the isolation of the de-1-*o*-methyl congeners of Melicopine, Melicopidine and Melicopicine from the bark of Australian *acronychia baueri* schott[5, 6]. The possibility of inadvertent, facile conversion of natural 1-*o*-methyl alkaloid to the de-*o*-methyl analog under the influence of acidic conditions used in the isolation procedure had already been recognized [7, 8].

CHEMISTRY

The molecule is planer with no atoms deviating by more than 0.02 Å from the molecular plane defined by non-H ring atoms and the oxygen atoms, all torsion angle lies with in +1.5 to -1.5 of 0 to 180 degree. The molecules adopt a Harringbone Packing Arrangement very similar that found in anthraquinone & quinacridone. Hydrogen bonding is maximized in such structures.

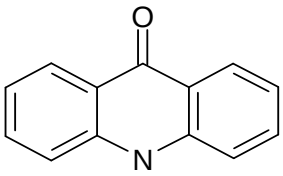


Fig. 1: 9(10H)-acridone

Synonyms of 9(10H)-acridone are: 9(10H)-Acridinone; Acridine-9-one; NIST 578-95-0; 9-Acridanone; Acridine-9, 10-dihydro-9-oxo; 9, 10-dihydro-9-oxoacridine; 9-azanthracene-10-ones.

The molecular packing arrangement in acridones ($C_{13}H_9NO$) is characterized by two major interaction types.

(a) N-H…O hydrogen bonds between glide-related molecules, with an N…O distance 2.782 Å, such that each molecule is hydrogen bonded to two adjacent molecules.

(b) □□ interaction between molecules stacked along short crystal axis [9].

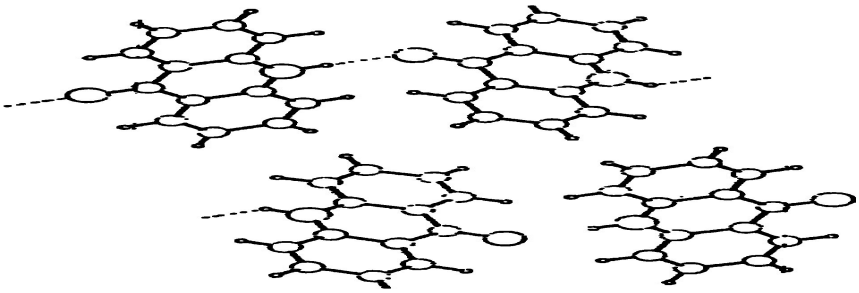
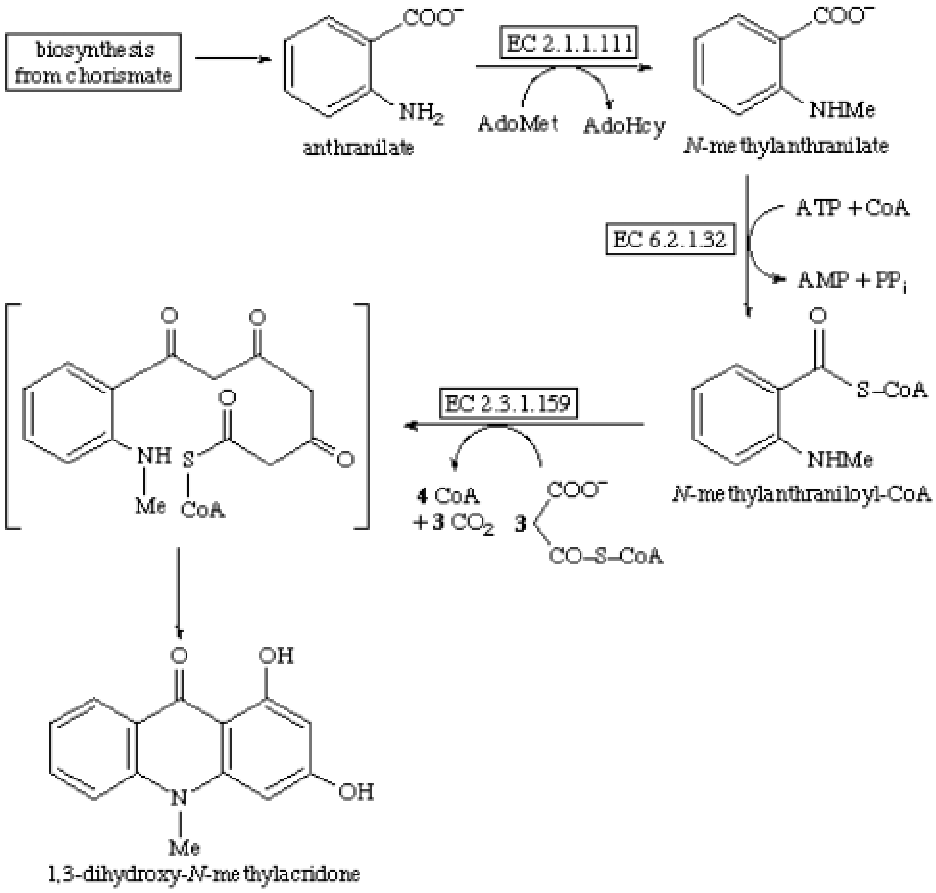


Fig.2: Crystal structure of acridone with the hydrogen bonds

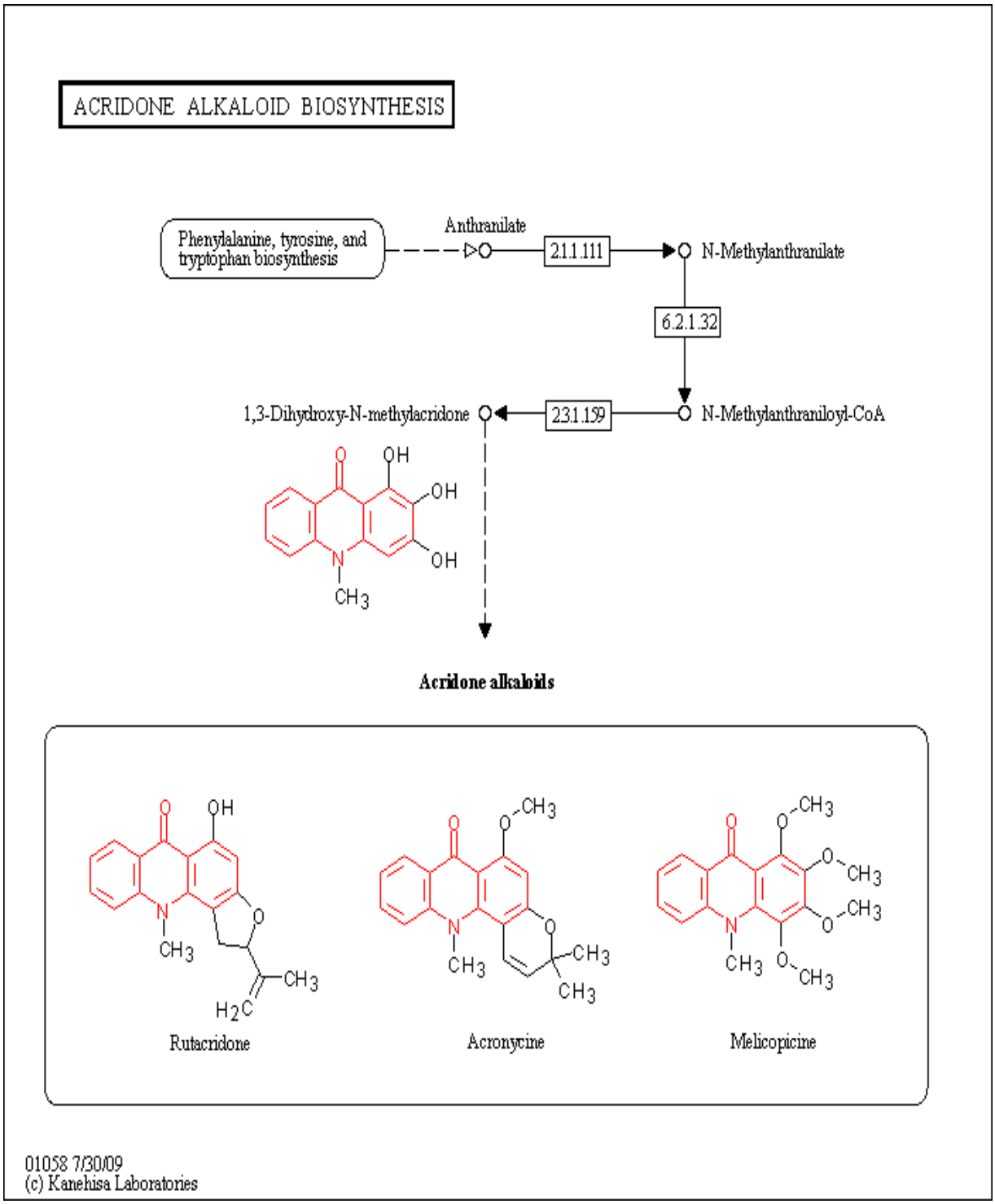
BIOSYNTHESIS

Biosynthesis [10, 11] of acridone alkaloids is given in scheme-1 and scheme-2 as following:



EC 2.1.1.111 - anthranilate *N*-methyltransferase; EC 2.3.1.159 - acridone synthase; EC 6.2.1.32- anthranilate—CoA ligase

SCHEME-1


ACRIDONE ALKALOID BIOSYNTHESIS
Phenylalanine, tyrosine, and tryptophan biosynthesis
Anthranilate
2.1.1.111
N-Methylanthranilate
6.2.1.32
1,3-Dihydroxy-N-methylacridone
2.3.1.159
N-Methylanthraniloyl-CoA
Acridone alkaloids
Rutacridone
Acronycine
Melicopicine
01058 7/30/09
(c) Kanehisa Laboratories

SCHEME-2

The following acridone alkaloids can be isolated from plants [12-14]**:**

1. ***Citrus funadoko*** [15]***:***

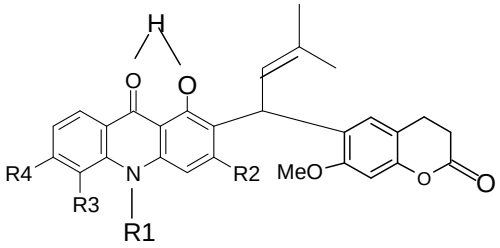


Fig.3

Acrimarine A: R_1= Me, R_2 = OH, R_3 = R_4 = OMe
Acrimarine B: R_1= H, R_2 =R_3 = R_4 = OMe
Acrimarine E: R_1= H, R_2 = R_3= OMe, R_4 = OH

2. ***Citrus grandis*** [16]*:*

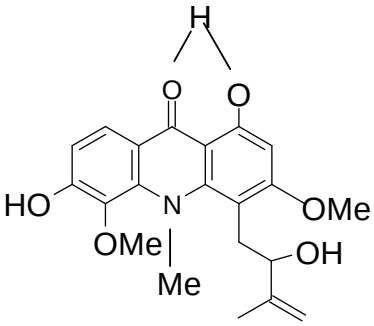


Fig.4: Buntamine A

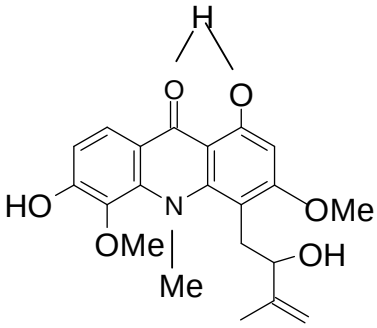


Fig.5: Atalafoline

3. ***Citrus hybrids*** [17, 18]*:*

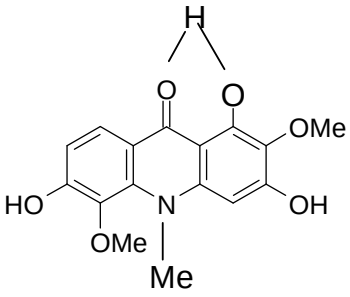


Fig.6: Citramine

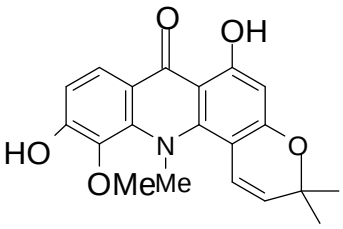


Fig.7: 11-methoxynoracronycine (baiyemine-A)

4. ***Citrus junos*** [19]***:***

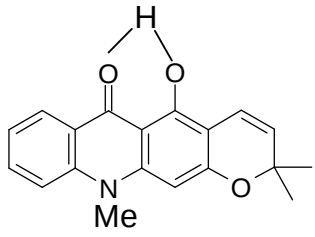


Fig.8: Junosidine

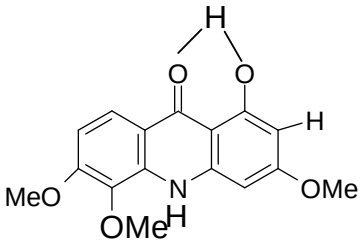


Fig.9: Natsucitrine – II

5. Citrus limonia [20]***:***

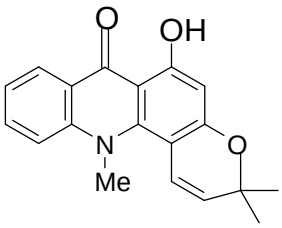


Fig.11: Citrusinine

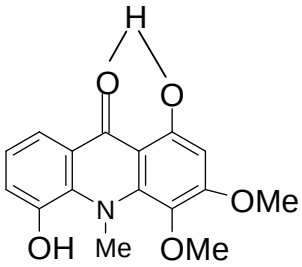


Fig.12: 5- hydroxylnoracronycine

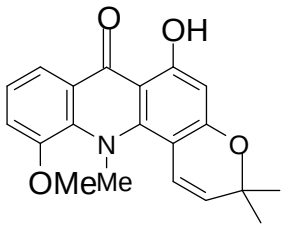


Fig.10: Citracridone – I

6. Citrus paradise [17]***:***

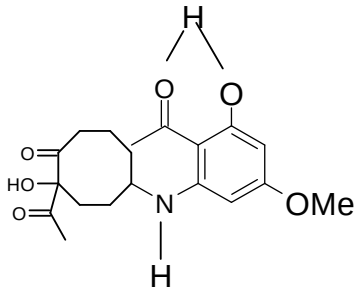


Fig.13: (+)-Citropone C

7. Glycosmis mauritiana [21]***:***

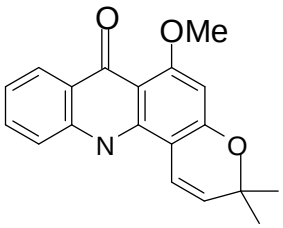


Fig.14: Des-N-methylacronycine

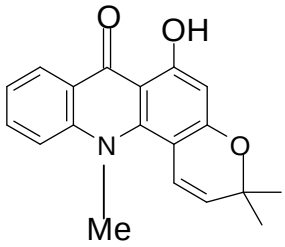


Fig.15: Noracronycine

8. Pleospermium alatum [22]***:***

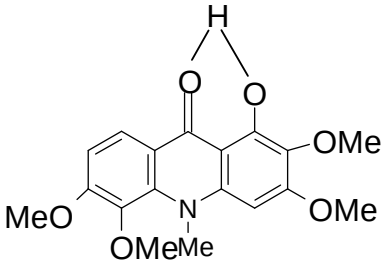


Fig.16: 1-hydroxy-2, 3, 5, 6- tetramethoxy-N-methylacridone

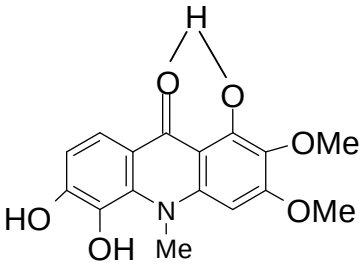


Fig.17: 1, 5, 6-Trihydroxy-2, 3-dimethoxy–N-methylacridone

9. *Ruta chalepensis* [23]***:***

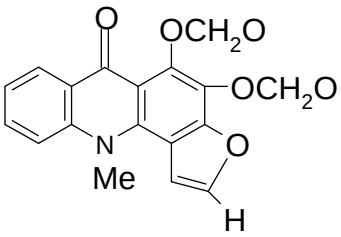


Fig.18: Chaloridone

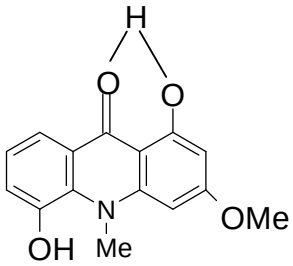


Fig.19: Citrusamine

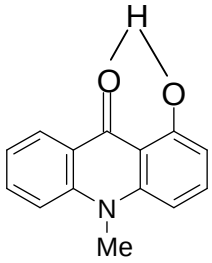


Fig.20: 1-hydroxy-N-methylacridone

10. Ruta graveolans [24]***:***

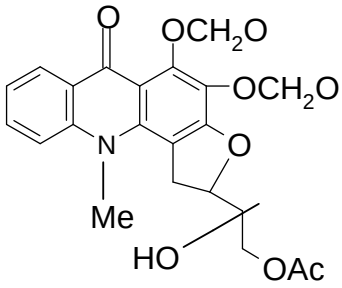


Fig.21: (+)-Gravacridondiolactate

11. *Sarcomelicopine dogniensis* [25]**:**

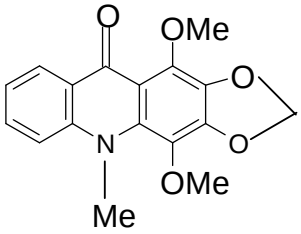


Fig.22: Melicopidine

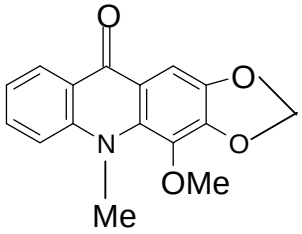


Fig.23: Normelicopidine

12. Verpis bitoravina and Verpis macrophylla [26]***:***

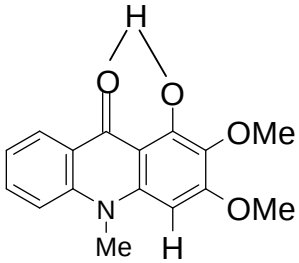


Fig.24: Arborinine

13. Zantoixylum leprierii [27]***:***

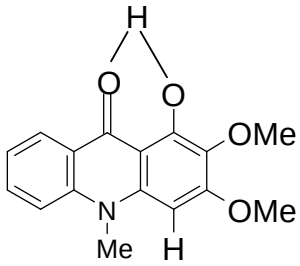


Fig.25: 1, 3-dimethoxy-10-methyacridin-9-one

14. Citrus hybrids kiyomo [18]*:*

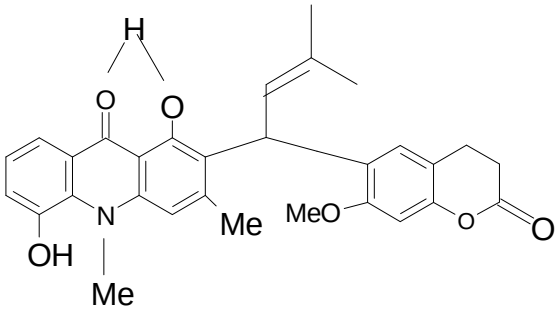
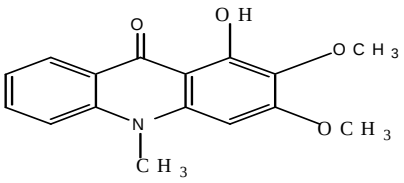


Fig.26: Acrimarine-H

15. Teclea boiviniana [28]*:*



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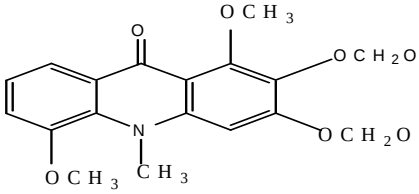

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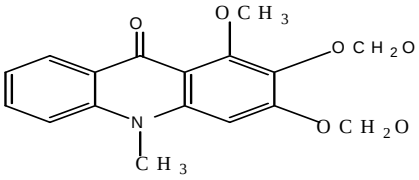
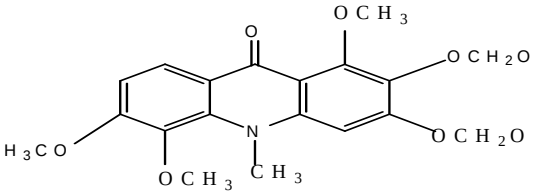
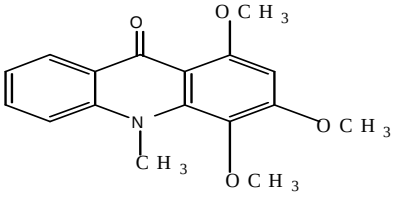


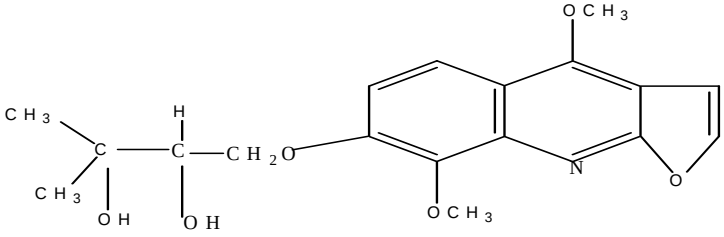
E v o x a n t h i n e



6 - m e t h o x y t e c l e a n t h i n e



1 , 3 , 4 - t r i m e t h o x y -
N - m e t h y l - a c r i d o n e



E v o x i n e

Fig.27: Different *Teclea boiviniana* alkaloids

16. Glycosmis citrifolia [29]***:***

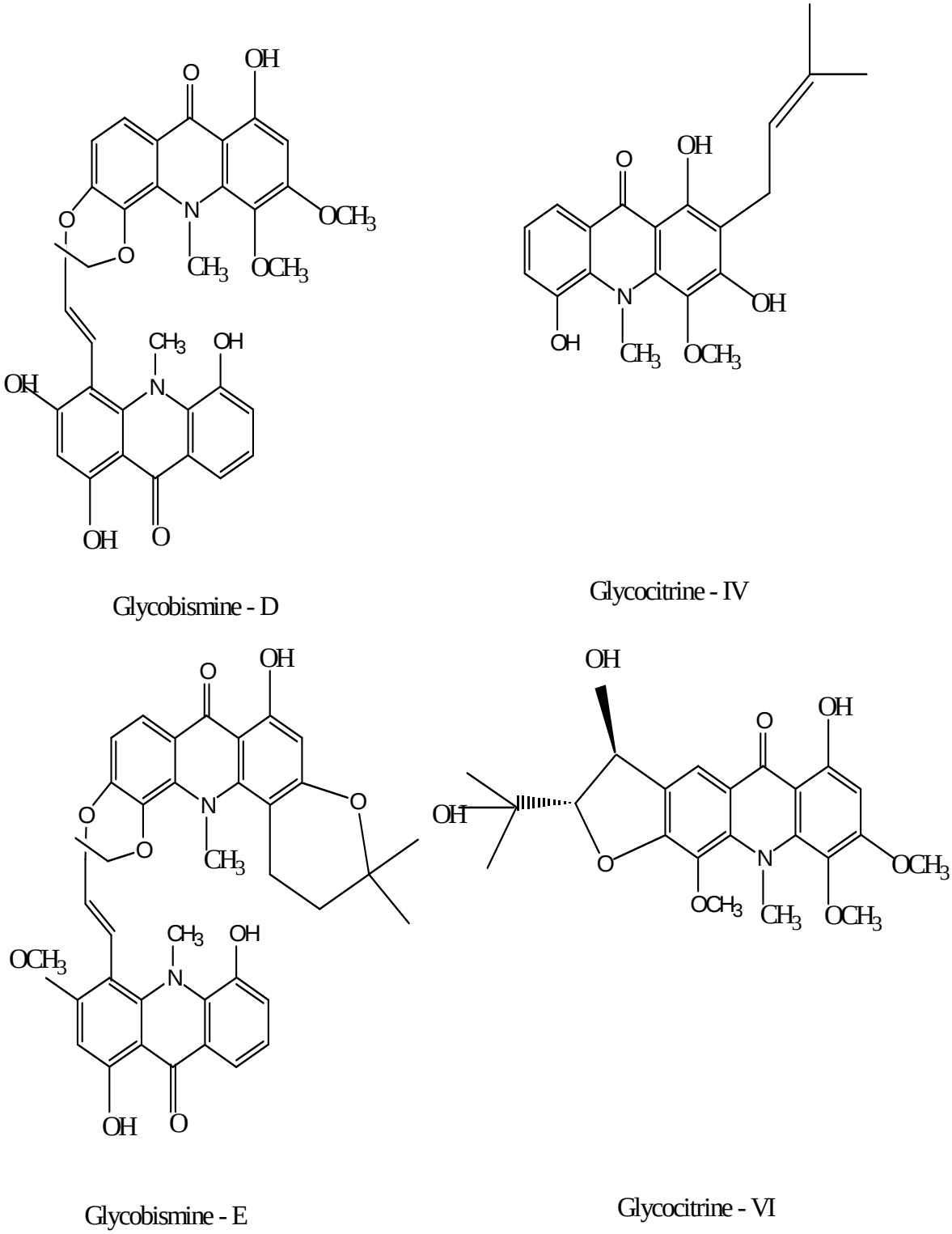


Fig.28: Different *Glycosmis citrifolia* alkaloids

MATERIAL & METHODS

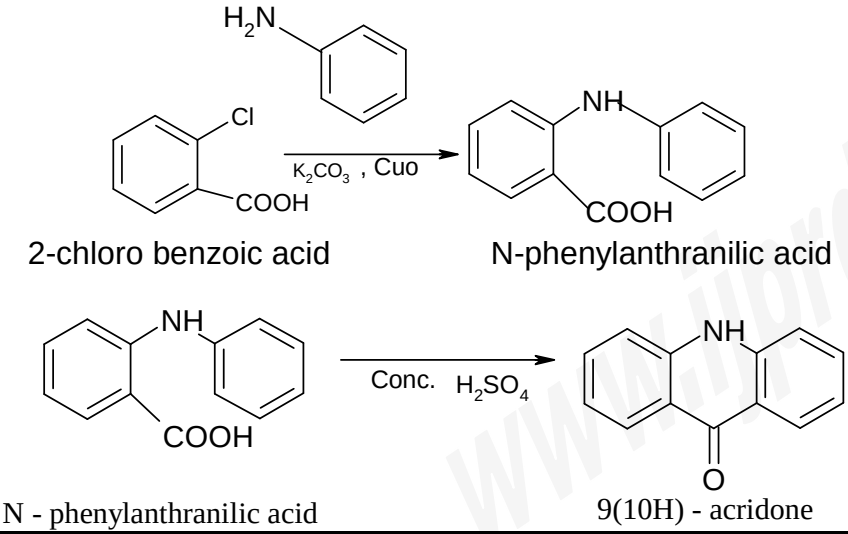
Method1:

General procedure for synthesis of N-phenylanthranilic acid derivatives:

A mixture of 5.5 mL (0.06 M) of aniline, 9.4 g (0.06 M) of *o*-chlorobenzoic acid, 8.3 g (0.06 M) of anhydrous potassium carbonate and 3.0 g of copper oxide was boiled under reflux for 4-5 hrs. After which arrangement for steam-distillation was made. The crude product was steam-distilled until all the excess of aniline had been removed. The residual solution now contained the potassium N-phenylanthranilate. To this 2.0 g of animal charcoal was added and boiled for about 5 minutes, and filtered hot. Dilute hydrochloric acid (1:1 by volume) was added to the filtrate until no further precipitation occurred, and then cooled in ice water with stirring. The *N*-phenylanthranilic acid was filtered off at the pump, washed, drained and dried. The acid was recrystallised from aqueous ethanol with addition of charcoal [30, 31].

General procedure for cyclization of N-phenylanthranilic acid derivatives to acridones:

A mixture of 4.26 g (0.02 M) of *N*-phenylanthranilic acid and 10 mL of concentrated sulphuric acid were heated for 4 hrs on a steam bath. The hot dark green solution was poured slowly and cautiously into 200 mL of boiling water in a 500 mL beaker. The mixture was boiled for 5 minutes, and it was filtered whilst hot through a Buchner funnel. The acridone thus collected was washed on the filter paper with hot water. For purification, the acridone was transferred to a solution of 4 gm of hydrated sodium carbonate in 50 mL of water, boiled the mixture for 5 minutes, and then filtered it hot. The acridone was washed with boiling water and dried thoroughly. The acridone thus prepared had a rather dull yellow color. Recrystallisation from acetic acid using charcoal or better sublimation, gives the bright yellow product [30, 31].

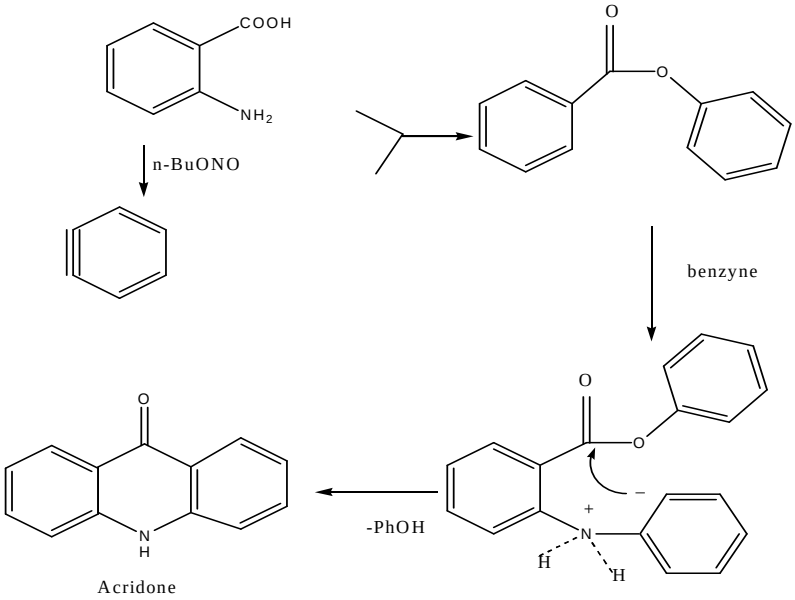


SCHEME-3

Method II:

Diazotization of anthranilic acid:

A mixture of anthranilic acid (5.0 g) and n-butyl nitrite (4.0g) in THF (20ml) was refluxed for 16 hrs. The reaction mixture was cooled, evaporated, and the residue was washed with 10% NaOH and then triturated with dichloromethane. The residue was essentially pure acridone (1.12 g, m.pt. 359-361^{o}C) [32].

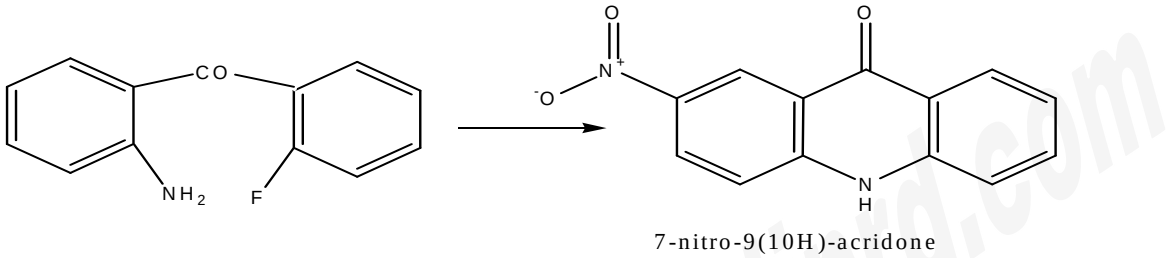


SCHEME-4

Method III:

From 2-amino-2'-fluorobenzophenones

A solution of 2-amino-2'-fluoro-5-nitrobenzophenone and Potassium carbonate in DMF was refluxed for 17 hrs which give 7-nitro-9-acridone (87%) [33].

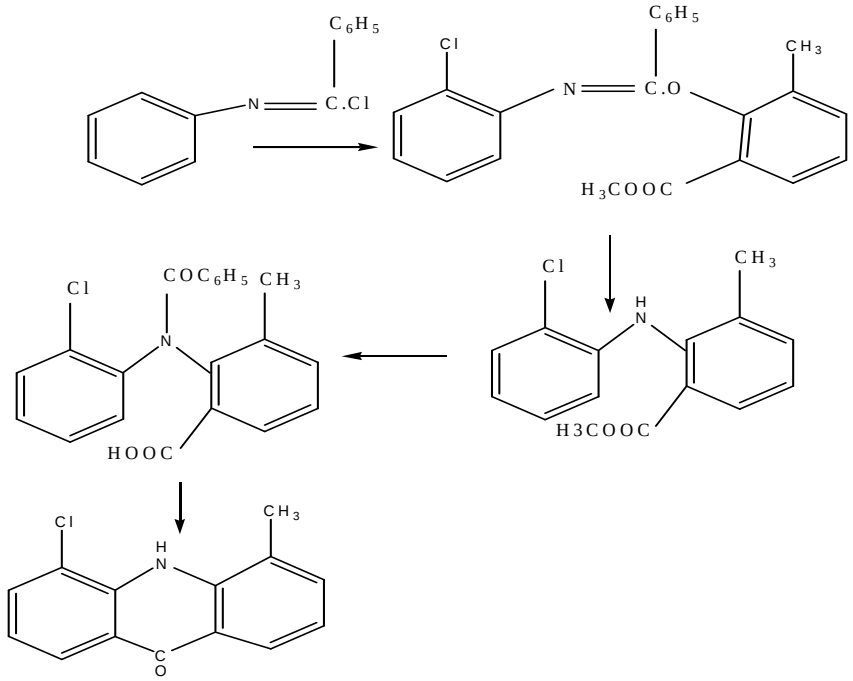


SCHEME-5

Method IV:

Chapman rearrangement:

Methyl-*o*-cresotate was added to a solution of sodium in alcohol at 25°C, benz-*o*-chloroanilide iminochloride in dry ether added, allowed to stand for 2 hrs, most of the alcohol distilled off, and poured into water & converted into *o*-chlorophenylbenzimino-6'-carbomethoxy-2'-methylphenyl ether (72%), this when heated yields methyl-2-chloro-N-benzoyl-2'-methyldiphenylamine-6'-carboxylate, which when refluxed for 1.5 hrs with aq. alc. NaOH at 100°C & converted into 2-chloro-N-benzoyl-2'-methyldiphenylamine-6'-carboxylic acid (92%) heated for 10 min. at 240-275°C to obtained 1-chloro-9-methylacridone (86%). Contrary to the previous observation it was found that the yield of the iminoester increases when less cresotate (about 1 mole) is used [34].



SCHEME-6

PHARMACOLOGICAL ACTIONS

Anti-herpes activity:

Yamamoto *et. al* (1989) synthesized citrusinine-I, a new acridone alkaloid, and related compounds isolated from the root bark of *citrus sinensis* osbeck var., *brasiliensis tanaka* (Rutaceae), exhibited potent activity against *herpes simplex* virus (HSV) type I and Type II and cytomegalo virus (CMV) at low concentration relative to their toxicity [35].

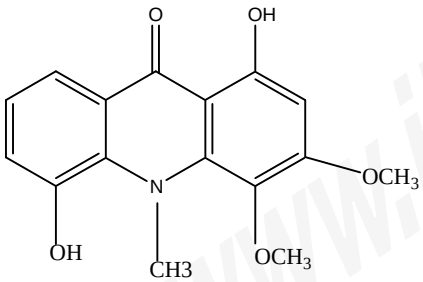


Fig.29: Citrusinine-I

Anticancer activity:

Tsann-long Su *et al.* (1992) synthesized glyfolene & its congeners & evaluated their cytotoxicity. These compounds were evaluated for their ability to inhibit human leukemia HL-60 cell growth in culture. These results show that 1-hydroxy-9-acridone are more active than their corresponding 1-*o*-methylated derivatives, indicating the presence of intermolecular hydrogen bond in 1-hydroxy-9-acridone played an important role for their cytotoxicity [36-38].

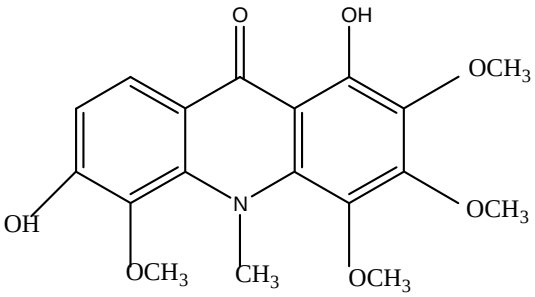


Fig.29: Glyfoline

Oriana Tabrinii *et al.* (1999) studied the design and synthesis of modified quinolones as antitumor acridones. Out of several derivatives these two were found to have potent carcinogenic property. These two compounds were found to have important anti-proliferative activity [39].

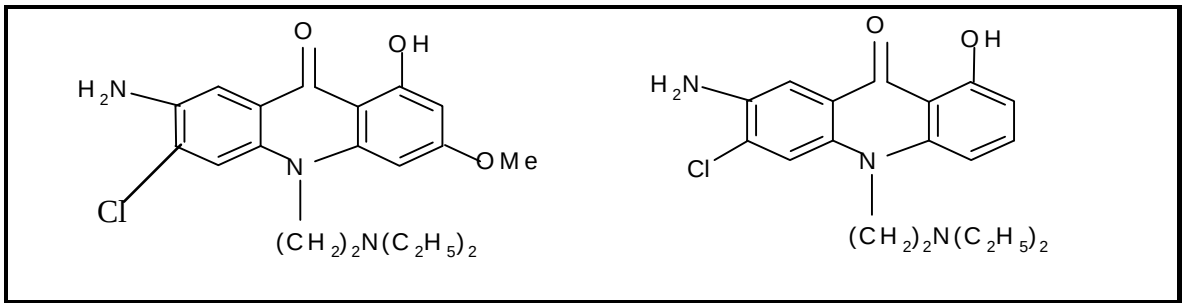


Fig.30: Anti-proliferative agents

Anti malarial activity:

Basco *et al*. (1994) studied *in vitro* activity of fluoroquinoline several natural synthetic acridone derivatives possess potent antimalarial property against chloroquine-susceptible HB3 and the chloroquine resistant W2 clones of *Plasmodium falciparam*. Furoquinoline and acridone alkaloids were isolated from three new Caledonian plants, *Geijera balansae, Sarcomelicopine glauca and Sarcomelicopine dogniensis*. Acronycine was moderately active against *P. falciparum*. 2-Nitroacronycine; 2-(-)-1,2-dihydroacronycine-2-yl-3-amino-2,3,6 trideoxy-alpha-L-arabino hexopyranose; 2-(R)(-)-1,2 dihydro acronycine-2-yl-(4-O-acetyl-3-bronmo)-2,3,6 trideoxy-alpha-L-arabino hexopyranose; 2-(S)(-)-1,2-dihydro acronycine-2-yl-(4-O-acetyl-3-bromo)-2,3,6 trideoxy-alpha-L-arabino hexopyranose have shown similar or greater antimalarial activity than that of parent compound (chloroquine). Several synthetic furoquinolines have been shown to be active against rodent malaria [40].

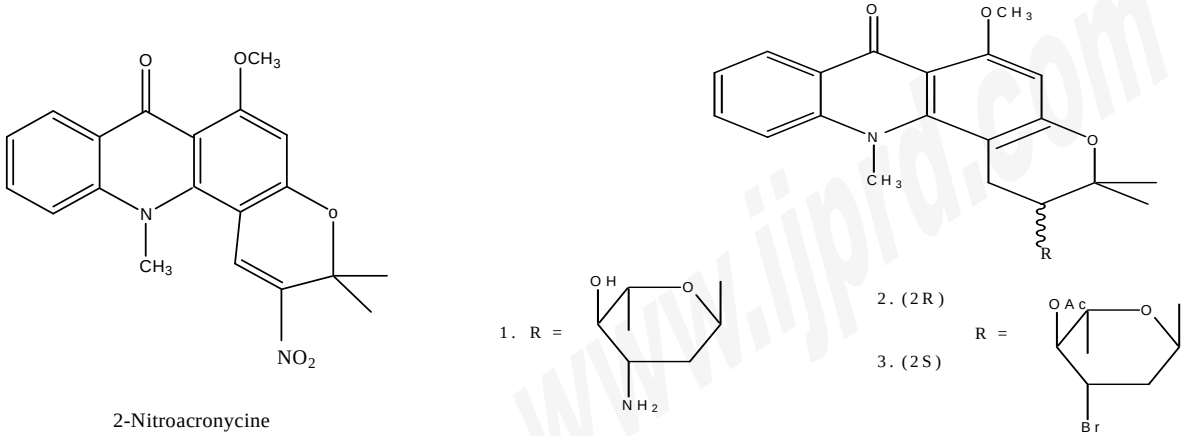


Fig.31: Acridones having antimalarial activity

Anti-leishmanial activity:

Delmas *et al.* (2004) synthesized via a procedure based on the Ullman reaction and were assayed for their antileishmanial and Anti-HIV activity. Two derivatives 4-(6-nitro-benzothiazole-2-ylamino)-10H-acridin-9-one and 1-(6-amino-benzothiazole-2-ylamino)-10H-acridin-9-one were found to have selective antileishmanial activity, mainly due to amastigote specific toxicity [41,42].

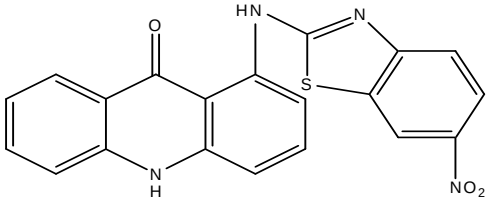


Fig.32: 4-(6-nitro-benzothiazole-2-ylamino)-10H-acridin-9-one[43]

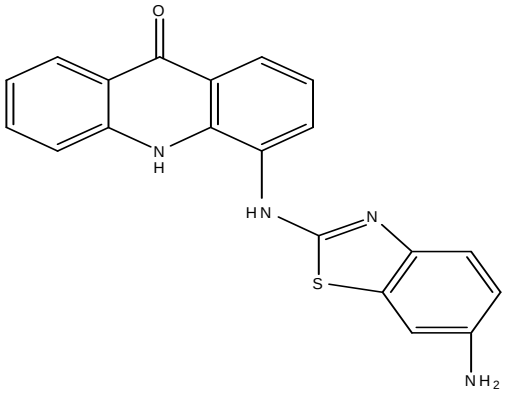


Fig.33: 1-(6-amino-benzothiazole-2-ylamino)-10H-acridin-9-one[44]

Fujiwara *et al.* (1999) studied that acridone derivatives are selective inhibitors of HIV-replication in chronically infected cells [45].

Nuclease activity:

Mehta *et al.* (2004) synthesized some 'porphyrine acridone' hybrid molecules and reported their photoinitiated nuclease activity [46].

ACRIDONES AS PROTONOPHORES:

Although the interaction of proton conducting ionophores (protonophores) with photosynthetic electrone transport has been extensively studied during the past decade, the mode of action of protonophores remained uncertain. For a better understanding of the molecular mechanism of the action of protonophores, the introduction of chemically new types of molecules will be required. In this work, the author demonstrated that acridones (9-azanthracene-10-ones) completely fulfill this requirement. At the low concentrations of acridones, the thermoluminescence bands at + 20^{o}C and + 10^{o}C were strongly inhibited, while normal electron transport activity was retained.This indicates that the concentrations of S_2 and S_3 states involved in the generation of these bands are reduced. At higher concentrations, an increased activity of electron transport was observed, which is attributed to the typical uncoupler effect of protonophores. Indeed, acridones accelerate the decay of the electrochromic absorbance change at 515 nm and also inhibit the generation of the transmembrane proton gradient, measured as an absorbance transient of neutral red. Variable fluorescence absorbance was quenched even at low concentrations of acridones but was restored by either a long-term illumination or high light intensity. Acridones, Similarly to the other protonophores, promoted the autooxidation of the high potential form of cytochrome b_{559} and partially converted it to the lower potential forms. These results suggest that acridones, acting as typical protonophores, uncouple electrone transport, accelerate the deactivation of S_2 and S_3 stages on the donor side, and facilitate the oxidation of cytochrome b_{559} on the acceptor side of photo system II [47].

STRUCTURE & EXCITED-STATE DYNAMICS OF ACRIDONE CLUSTERS:

Clusters containing acridone molecules are model system for elucidating intermolecular interaction that control macroscopic properties of the molecules in condensed phases, such as liquids & crystals. There was a correlation of dynamical behavior of photo-excited aromatic chromophore to geometry & bonding topology of the clusters. Especially, it is critically important to definitely characterize the cluster structure; the study implemented various laser-based methods, such as IR-UV double resonance and rotational coherence spectroscopy (RCS), in conjunction with molecular-orbital calculations [48].

REFERENCES

1. Wainwright M, Acridine-a neglected antibacterial chromophore, Journal of Antimicrobial Chemotherapy, 47, 2001, 1-13.
2. Hughes G.K., Lahey F.N., Prince J.R., Webb L.J., Nature (London) 162, 1948,223.
3. Hughes G.K., Neill K.G.,Aust.J.Sci.Res.Ser. A2, 1949, 429.
4. Govindachari T.R., Pai B.R., Subramaniam P.S., Tetrahedron 22, 1966, 3245.
5. Svoboda G.H., Poore G.A., Simpson P.J., Boder G.A., J.Pharm. Sci. 55,1966,758.
6. Svoboda G.H., Lloydia 29(3), 1966, 217.

7. Manske R.H.F., Holmes H.L., Price J.R., The Alkaloids, Academic Press, New York 1952, p 353.
8. Crow W.D., Prince J.R., Aust.J.Sci.Res.Ser. A2, 1949, 255.
9. Pohs GD, Jones W., 9(10H)-Acridone, Acta Cryst., C51, 1995, 267-268.
10. http://www.chem.qmul.ac.uk/iubmb/enzyme/reaction/alkaloid/acridone.html
11. http://www.genome.jp/kegg/pathway/map/map01058.html
12. Michael JP., Quninoline, Quinazoline and Acridone Alkaloids, Natural Product Reports 10, 1990, 136-138.
13. Michael JP., Quninoline, Quinazoline and Acridone Alkaloids, Natural Product Reports 10, 1992, 30-35.
14. Michael JP., Quninoline, Quinazoline and Acridone Alkaloids, Natural Product Reports 10, 1993, 105-108.
15. Furukawa H, Ito C., Spectrometric elucidation of acrimarines, the first naturally occurring acridone-coumarin dimers, J. Chem. Soc., Perkin Trans I, 1,1990, 1593.
16. Huang SC, Chen MT. Phytochemistry; 1928: 3574.
17. Ito C, Tanahashi S et al., Chem. Pharm. Bull, 38, 1990, 181.
18. Ito C, Tanahashi S et al., Isolation of New Constituents from Citrus Plants, Chem. Pharm. Bull, 38, 1990, 2586.
19. Ju-ichi M, Inoue M et al., Heterocycles, 26, 1987, 2077.
20. Chang SH., Phytochemistry, 29, 1990, 351.
21. Kumar V, Reisch J., Glycomaurin and Glycomaurrol, New Carbazole Alkaloids From *Glycosmis mauritiana* (Rutaceae) Bark, Aust. J.of. Chem, 42, 1989, 1375.
22. Bandara BMR, Gunatilaka EMK., Acridone alkaloids and coumarins from Pleiospermium alatum, Phytochemistry, 29, 1990, 297.
23. Ulubelen A, Tan N., A moskachan from the roots of Ruta chalepensis, Phytochemistry 29, 1990, 3991
24. Paulini H, Popp R., Water-Soluble Glycosides from Ruta graveolens, Planta Medica 57, 1991, 82.
25. Mitaku S, Skaltsounis F. et al., In vitro and in vivo activities of atalaphillinine and related acridone alkaloids against rodent malaria, Ann. Pharm. Fr., 471989, 149-156.
26. Koffi Y, Gleye J et al., Pyranoquinolones and acridones from Vepris bilocularis, Planta Med., 53, 1987, 570.
27. Adesina SK., Further new constituents of Zanthoxylum leprieurii, Fitoterapia, 58, 1987, 123.
28. Vaquette J et al., Alkaloids from leave of Teclea boiviniaana, Planta Medica, 60, 1978, 78-84.
29. Ito C, Kondo Y.Chemical Constituents of Glycosmis Citrifolia (WILLD.) LINDL. Structures of Four New Acridones and Three New Quinolone Alkaloids, Chem. Pharm. Bull., 48, 2000, 65.
30. Mann FG, Saunders BC. Practical Organic Chemistry**;** 1978.p.303-304.
31. McKee GHW, Allen CHF., Acridone, Organic Syntheses 2, 2005, 15-16.
32. Ho TL, Jou DG, Generation of 9(10H)-Acridone from Anthranilic Acid, Journal of Chinese Chemical society, 48, 2001, 81-82.
33. Fryer RI, Earley J, Sternbach LH, Soc. 1963, 4979.
34. Hall DM, Turner EE, Soc.1945, 694.
35. Yamamoto N, Furukawa H et al., Anti-herpesvirus activity of citrusinine-I, a new acridone alkaloid, and related compounds, Antiviral Research, 12, 1989, 21-35.
36. Long Su T, Kohler B et al., Glyfolene & its congeners, Journal of Medicinal Chemistry, 35, 1992, 2703-2710.
37. Itoigawa M, Cancer chemo preventive activity of acridone alkaloids on Epstein–Barr virus activation and two-stage mouse skin carcinogenesis, Cancer Letters, 193 Suppl 2 .p. 133
38. Bernard W, Byung HU. et al, Bioactive Acridone Alkaloids from Swinglea glutinosa, J. Nat. Prod, 64 Suppl 9, 2001, 1221–1223.
39. Tabarrini O, Cecchetti Vet al.,Design and Synthesis of Modified Quinolones an Antitumor Acridones, Journal of Medicinal Chemistry, 42 Suppl 2, 1999, 2136-2144.
40. Basko LK, Mitaku S et al., Invitro Activities of Furoquinoline and Acridone Alkaloids against plasmodium Falciparum, Antimicrobial agents and Chemotherapy, 1994, 1169-1171.
41. Delmas F, Avellaneda A. et al., Synthesis and Antileishmanial Activity of (1, 3-

Benzothiazol-2-yl) Amino-9-(10H)-acridinone Derivatives, European Journal of Medicinal Chemistry, 39, 2004, 685-690.
42. Ogunkolade BW, Colomb-Valet I et al, Acta Trop, 47, 1990, 171–176.
43. Bsiri N, Johnson C. et al, Ann. Pharm, 54, 1996, 27–33.
44. Hanoun JP, Galy A et al, Synth. Commun., 25, 1995, 2443-2448.
45. Fujiwara M, Okamoto M et al, Antiviral Research, 43, 1999, 183-199.
46. Mehta G, Sambaiah T et al., Synthesis and Nuclease Activity of Some 'Porphyrin-Acridone' Hybrid Molecules, Journal of Chemical Society Perkins Trans, 1, 1993, 2667-2669.
47. Horvath G, Droppa M et al., Acridones: A chemically new group of protonophores, Proc. Natl.Acad. Sci., 93, 1996, 3876-3880.
48. Mitsui M et al., Structure and Excited-State Dynamics of Aromatic Clusters, Research Activities III, 2001, 78-80.