Review Article Open Access

ARTICLE LINK

ISSN: 2349-9818
NOVEMBER - DECEMBER 2022, VOL. 9 (6), 01-12

TROPICAL JOURNAL OF PHARMACEUTICAL AND LIFE SCIENCES
(An International Peer Reviewed Journal)
Journal homepage: http://informativejournals.com/journal/index.php/tjpls

A REVIEW ON ACRIDINE, XANTHENE AND ITS DERIVATIVES: SYNTHESIS, PHYSICAL AND PHARMACOLOGICAL PROPERTIES

Herole RA*, Rakesh Kumar Jat and Rajendra D Dighe

Department of Pharmaceutical Chemistry,
Institute of Pharmacy, Shri Jagdish Prasad Jhabarmal Tibrewala University,
Vidyanagri, Jhunjhunu, Rajasthan-333001

ARTICLE INFO:
Received: 4th Nov. 2022; **Received** in revised form: 26th Nov. 2022; **Accepted:** 15th Dec. 2022; **Available online:** 27th Dec. 2022.

ABSTRACT

Acridine derivatives are one of the oldest category of bioactive, globally used as anticancer, antiprotozoal agents and antibacterial. The class of acridine derivatives constitutes an interesting group of nitrogen-containing tricyclic compounds that caught the scientific group's attention, mainly due to its wide range of pharmaceutical properties. The synthesis of new polycyclic acridine skeletons fused with a five or six-membered rings, have been extensively studied because they play important roles in some DNA-intercalating anticancer drugs. Benzoacridine derivatives have been recently synthesized by a number of methods via one-pot multi-component condensation reactions of dimedone, naphthylamines, and aldehydes in different conditions, for example, using triethylbenzylammonium chloride/H_2O, ionic liquid, under microwave irradiation, or ultrasound irradiation. A xanthene is found to most multifaceted heterocyclic ring having as it is having variety of activity and utilization. Xanthine derivatives are medications used to treat bronchospasm caused by lung conditions such as asthma. Xanthenes dyes shows antiviral activity, anti-tubercular, anticancer, anti-microbial, malonate derivatives was having anti-spasmodic activity. Benzoxanthenes are tetracyclic dibenzopyrans with diverse biological and therapeutic properties such as antibacterial, antitumor, anti-inflammatory, antiviral, pesticidal activities, and antimalarial.

Keywords: Acridines, Xanthenes, Benzoacridine, Benzoxanthene, Docking, Alkaloids, Anticancer, Antibacterial.

INTRODUCTION

Acridine derivatives are one of the oldest classes of bio-actives, broadly used as anticancer, antibacterial and antiprotozoal agents. Some work in these areas continues, but recent research has focused mainly on

***Corresponding Author:**
Herole RA,
Institute of Pharmacy,
SJPJT, University,
Jhunjunu, Rajasthan, India

© 2022 The Authors. Tropical Journal of Pharmaceutical and Life Sciences (**TJPLS Journal**) Published by **Informative Journals** (Jadoun Science Publishing Group India)
This article is an open access article distributed under the terms and conditions of the CC BY-NC-ND 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/)

their use as anticancer drugs, because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase enzymes. And the xanthene derivatives methantheline (Banthine) and propantheline (Pro-Banthine) are effective compounds for the treatment of ulcers and gastrointestinal disorders, reducing the volume and acidity of gastric secretions.

ACRIDINES:

The class of acridine derivatives (figure 1) constitutes an interesting group of nitrogen-containing tricyclic compounds that caught the scientific community's attention, mainly due to its wide range of pharmaceutical properties.[1,2] This type of compound's unique physical and chemical properties allows several derivatives to have been associated with numerous bioactivities, such as anti-inflammatory, antimicrobial, anti-cancer, anti-tubercular, anti-parasitic, antimalarial, antiviral, and fungicidal activities (figure 2). Furthermore, several methodologies have been developed to obtain a more extensive range of acridine-based compounds throughout the years. These methodologies include the Bernthsen synthesis, the first synthetic method for the obtention of an acridine, the Ullmann reaction, and the Friedlander synthesis.[3,4] Acridine derivatives can also be obtained by the manipulation of acylated diphenylamines, reduction of acridones, or the functionalization of 9-chloroacridines.[3]

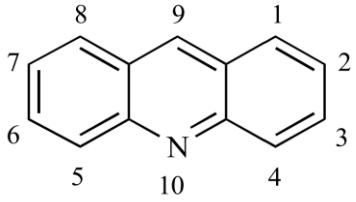


Figure 1: Structure of Acridine

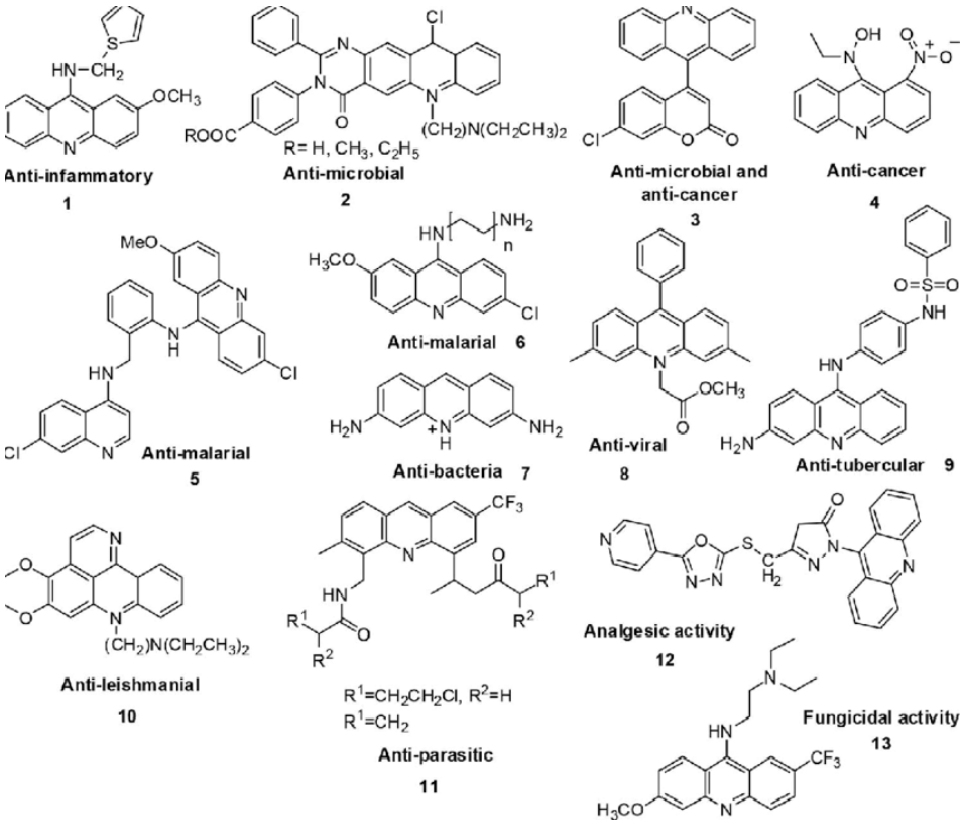


Figure 2: Structure of potent bioactive acridine derivatives

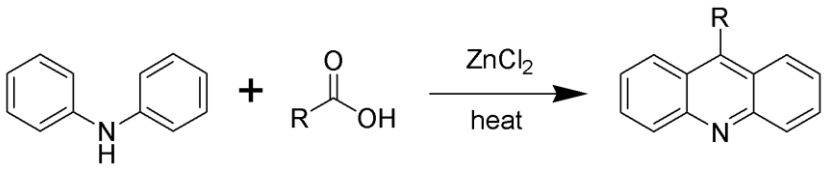
Due to the special functional structural units and important applications in many fields, the study of acridine derivatives has become a hot topic worldwide. The large conjugated ring enables these dyes to be markers for fluorescence and imaging. The ability of embedding into DNA chain, they have a wide range of applications in medicine and other fields. These dyes have the very similar color index value to that of the natural compounds.[5] As an alternative to metal semiconductor material, acridines have presented potential value in the field of organic semiconductor materials.

In recent years, emerging of the new and simple preparation technique, such as microwave assisted synthesis, metal free catalysis, one pot synthesis, and so on, has brought more attention to the synthesis and application of acridines. In this paper, various synthetic methods of acridine derivatives since 2010 and their applications in medicine, fluorescent materials, industrial dyeing materials and electroluminescence are introduced. The work about acridines accomplished in our group is also introduced. In the end, the future prospective of synthesis and application of acridine derivatives is proposed.[6]

Isolation and Synthesis of acridine:

Carl Grabe and Heinrich Caro first isolated acridine in 1870 from coal tar.[7] Acridine is separated from coal tar by extracting with dilute sulfuric acid. Addition of potassium dichromate to this solution precipitates acridine bichromate. The bichromate is decomposed using ammonia.

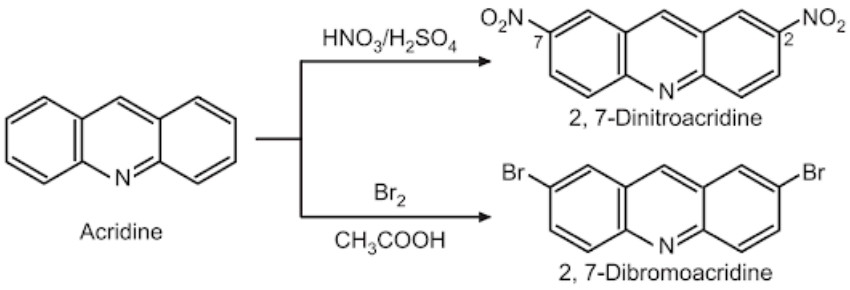
Acridine and its derivatives can be prepared by many synthetic processes. In the Bernthsen acridine synthesis, diphenylamine is condensed with carboxylic acids in the presence of zinc chloride. When formic acid is the carboxylic acid, the reaction yields the parent acridine. With the higher larger carboxylic acids, the derivatives substituted at the meso carbon atom are generated.



Other older methods for the organic synthesis of acridines include condensing diphenylamine with chloroform in the presence of aluminium chloride, by passing the vapours of ortho amino diphenyl methane over heated litharge, by heating salicylaldehyde with aniline and zinc chloride or by distilling acridone (9-position a carbonyl group) over zinc dust.[8] Another classic method for the synthesis of acridones is the Lehmstedt-Tanasescu reaction. Acridine displays the reactions expected of an unsaturated N-heterocycle. It undergoes N-alkylation with alkyl iodides to form alkyl acridinium iodides, which are readily transformed by the action of alkaline potassium ferricyanide to N-alkyl acridones.[9-11]

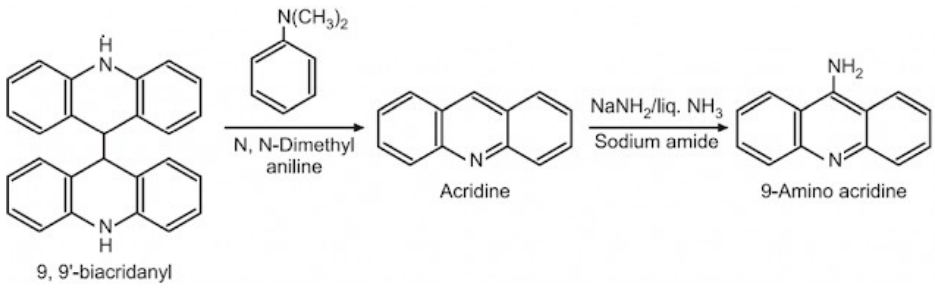
Electrophilic substitutions of acridine:

The electrophilic substitution takes place in the benzenoid ring. Halogenation gives a mixture of addition and substitution products. A benzenoid ring is attacked by the electrophile preferably in the 2- or 7-position, resulting in di-substitution. For example



Nucleophilic substitutions of acridine:

Nucleophilic reagent interact more strongly with quaternary salts of acridine. Compared with position 1-, 2-, 3-, and 4- position-9 of acridine has a low electron density. Therefore nucleophiles prefer to attack at 9-position.



Benzoacridine derivatives:

Benzoacridine derivatives have been currently synthesized by a number of methods via one-pot multi-component condensation reactions of dimedone naphthylamines, and aldehydes in different conditions, for example, using [8]triethylbenzylammonium chloride/H_2O, ionic liquid , under microwave irradiation (MWI) or ultrasound irradiation (USI).[6,12]

In recent years, the one-pot multi-component reactions have received significant attention because two or more steps in the synthetic sequence can be carried out without the isolation of intermediates which leads to reduction of time and energy for developing new pharmaceutically important compounds.[13] Recently, our research group has developed various multi-component reactions which can provide easy access to useful functionalized multiple ring structures of chemical and pharmaceutical interest.[12, 13]

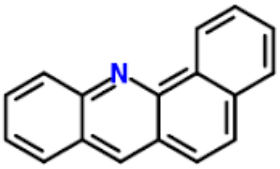


Figure 3: Benz(c) Acridine

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 anticancer antibacterial and antiparasitic agents.[14]

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.[15]

Docking of Benzo-acridine:

The crystal structure of an Benzo-acridine in complex with a DNA dodecamer was downloaded from Protein Data Bank and edited using PyMOL v.1.4.1 software, after edition the structure was minimizing with WHAT IF: A molecular modeling and drug design program and ready for docking studies. All docking studies were performed with Auto Dock 4.2. Software employing the Lamarckian Genetic Algorithm, generating 20 independent docking poses for each compound. In all the cases the population size was set to 150 and the maximal number of evaluations was set to 5,000,000. The position of the docking grid was centered at the position of the original co-crystallized ligand which was removed. The dimension of the grid was 100 Å × 100 Å × 100 Å points with spacing of 0.375 between the grid points.

The DNA was considered as rigid molecule, while the ligands were considered as flexible molecules. The best binding mode was selected based on the lowest binding free energy and the largest cluster size. Ligands equilibrium geometries.[16]

All calculations were performed with SPARTAN'08® software Molecules were built by assembling standard fragments and the resulting geometries were optimized by molecular mechanics. Conformational analysis of the compounds by Systematic Search protocol around rotable bonds was performed using the MMFF94 force field. The most frequent conformer for each compound was selected and geometry optimization was carried out with semi empirical AM1 method. Due to the basic properties of the tertiary amino side chain at 2- position, the protonated form of the compounds with this substituent was used in the docking studies and neutral form was also used.[17,18]

XANTHENES:

The class of xanthene derivatives 51 constitutes an important class of oxygen-containing tricyclic compounds, characterized by a dibenzo(*b,e*)pyran core, widely associated with a broad range of pharmaceutical and biological properties, such as antimicrobial, antiproliferative, antiviral, antioxidant, and anti-inflammatory activities, amongst others (figure 4).[19,20]

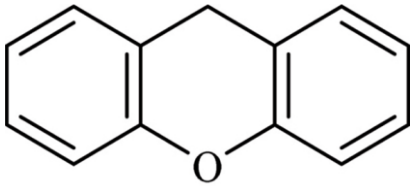


Figure 4: Structure of Xanthene

Even though numerous reports have described these compounds as constituents of natural extracts throughout the past decades, the majority of the known xanthenes are synthesized. The synthesis of this type of compound might be performed through the cyclization of specific building blocks or by modifying a most commonly found class of xanthene derivatives, namely xanthones. This versatile structural fragment allows the introduction of virtually any substituent group in its core. Depending on the substituent group desired, different synthetic approaches might be performed to obtain the intended xanthene derivative. Described one of the first syntheses of the xanthene nucleus in 1925, in which 3-hydroxyxanthene was obtained through the condensation of saligenin and resorcinol.[21]

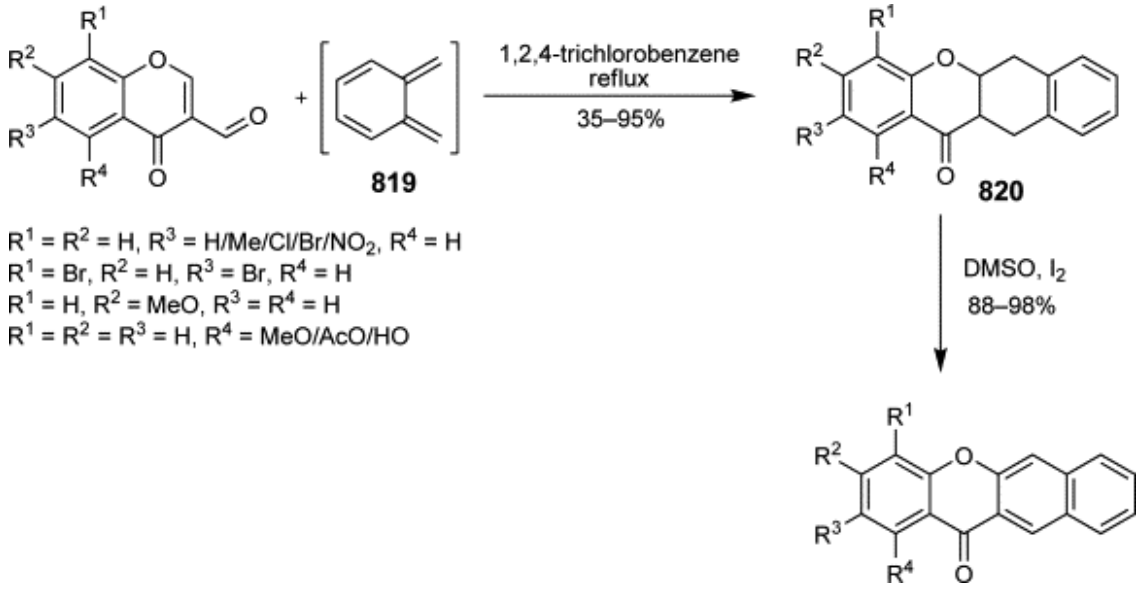


Figure 5: Xanthene derivatives

After that, numerous synthetic methods for the obtention of xanthenes with distinct substitution patterns have been described in literature, including the functionalization of particular core positions to synthesize broad spectra of xanthenes and the application of greener procedures.[22,23,24] Thus, this has allowed the use of xanthene in a huge range of biological activities, leading to the increasing importance of xanthenes in medicinal chemistry.[25] Besides its biological properties, this type of compound has been widely used for a broad range of applications, such as sensitizers in PDT, dyes in the food industry, industrial materials, and chemical probes for the visualization of biomolecules.[26,27]

How do xanthene derivatives work?

Xanthine derivatives are medications used to treat bronchospasm caused by lung conditions such as asthma. Xanthine is a naturally occurring compound in the human body and is also found in plant products such as tea, coffee, and cocoa beans.[28]

Xanthine derivatives are a group of alkaloids that work as mild stimulants and bronchodilators. Xanthine derivatives ease symptoms of bronchospasm and make breathing easier by relaxing the smooth muscles of the respiratory tract and reducing the airway's hypersensitive response to stimuli.[29,30] Xanthine derivatives increase the cellular levels of signaling molecules known as cyclic adenosine monophosphate (cAMP) by inhibiting the activity of phosphodiesterase, an enzyme that regulates cAMP levels. An increase in tissue concentration of cAMP results in bronchial smooth muscle relaxation and bronchodilation.[31]

Synthesis of Xanthene:

Xanthene is the organic compound with the formula $CH_2[C_6H_4]_2O$. It is a yellow solid that is soluble in common organic solvents. Xanthene itself is an obscure compound, but many of its derivatives are useful dyes.[32] The metal oxides such as ZnO, CdO and TiO2, for the synthesis of 1,8-dioxo-octahydroxanthenes and other related heterocycles. Most actual synthetic protocols include the use of solvent and co-solvents(s) which are either volatile, thus diffusing volatile organic compounds in the atmosphere, corrosive or harmful to the environment.[33] Therefore, employing water (as green solvent) or no other solvent for the reaction can be considered an eco-friendly approach.

Synthesis of 9-aryl-1, 8-dioxooctahydroxanthenes from aromatic aldehyde and dimedone (figure 6) over nanotitania was reported, where catalyst could be reused 12 times without significant loss in its activity.[34, 35] X-ray diffraction analysis of crystalline TiO2 nanoparticles confirmed the formation of rutile phase. The average crystallite size of titania sample was found to be 63 nm. In the initial studies, reaction of 4-nitrobenzaldehyde and dimedone over 10 mol% Titania nanoparticles as a catalyst was carried out in the presence of different solvents under reflux condition. In the presence of solvents, like ethanol, acetonitrile, acetone, chlorinated solvents, the yield was observed to be less than 50%. The maximum yield (43%) was achieved in case of ACN in 2.5 h. Under solvent-free conditions, the model reaction was carried out at various temperatures and with different catalyst loading. 10 mol% loading and 100 °C found optimum with 96% isolated yield in 15 min. The developed protocol showed wide substrate compatibility with comparable yields of corresponding products in short period of time. Anatase and rutile phases of titania are known for its photocatalytic activity.[36,37,38] When the reaction was carried out at 25 °C in the presence of UV light, negligible product formation was observed; this ruled out any photocatalytic effect of titania. When the model reaction was carried out in the dark at 100 °C, 96% isolated yield was achieved. This demonstrates the reaction follows catalytic pathway and not photocatalytic.[34,35]

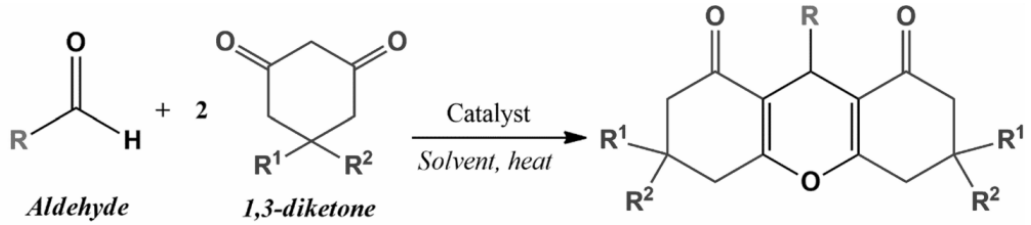


Figure 6: Synthesis of 1,8-dioxooctahydroxanthene from aldehyde and dimedone

One-pot synthesis of benzoxanthene derivatives:

n this report, the three-component, one-pot condensation of lawsone (2-hydroxy-1,4naphthoquinone), dimedone (5,5-dimethyl-1,3-cyclohexanedione), and aromatic aldehyde was studied in the presence of the Bi(OTf)3 catalyst for the preparation of 3,3-dimethyl-12-aryl-3, 4-dihydro-1H-benzoxanthene-1,6,11-(2H,12H) triones (figure 8). Bi (OTf)3 catalyst is first tried in this study in such compound synthesis. In this study, 10 substances were synthesized.[37]

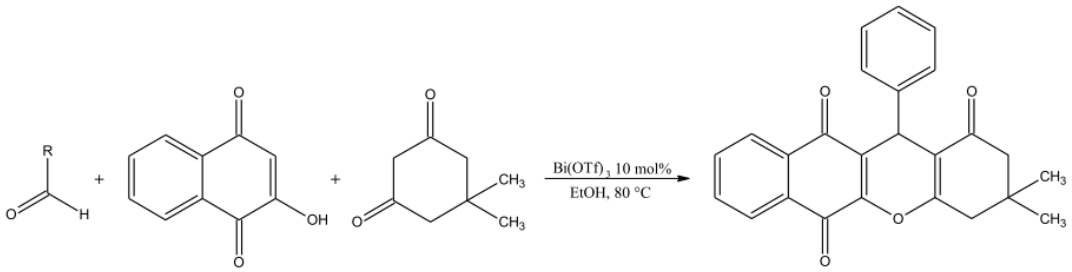


Figure 8: The one-pot synthesis of benzoxanthene derivatives. Bi(OTf)3, bismuth(III) triflate; EtOH, ethyl alcohol

Current status of Xanthenes:

The development of small molecule fluorescent dyes and sensors is a fast-growing field. Xanthene based dyes are a group of attractive molecules in this field due to their excellent photophysical properties. A large number of xanthene dyes have been reported so far. Nevertheless, further development/optimization processes challenges due to the massive amount of discrete data and unavoidable human errors in analyzing the data. Inspired by recent progresses in data-driven chemical discoveries we explored the possibility of applying deep learning technology in new xanthene dye discovery in this study.[38] We systematically analyzed published data on xanthene-based dyes and established a database which covered their 'ring-opened' form's smiles strings and some key parameters including quantum yields, excitation, and emission wavelengths. Based on the database, a machine learning model was developed and used to predict essential properties, such as excitation and emission wavelength, of new xanthene dyes.[36,38]

Benzoxanthene Derivatives:

Benzoxanthenes are tetracyclic dibenzopyrans with diverse biological and therapeutic properties such as antibacterial, antiviral, anti-inflammatory, antitumor, antimalarial, and pesticidal activities.[39,40] These heterocyclic compounds, also known as leuco dyes that are pH-sensitive fluorescent materials, can be used in photodynamic therapy, polymer photo imaging systems, and laser technologies due to the fluorescence activities of the naphthoquinone nucleus.[41] Despite continued research efforts toward the development of anticancer drugs, cancer remains a primary cause of death. It is well established that small heterocyclic molecules are the predominant building blocks for biologically active compounds. Xanthene, one of these building blocks, is an important structural unit commonly found in natural products. Molecular scaffolds of xanthene are important as PIM1 kinase inhibitors. Epicalyx is the most potent member of this class as an anticancer agent against human HT-1080 fibrosarcoma and murine 26-L5 carcinoma.[42]

In recent decades, the development of a faster and more efficient synthesis of heterocyclic compounds containing xanthene and benzoxanthene scaffolds in their structures has attracted considerable attention. A number of methodologies for the synthesis of these compounds have been reported, which include various catalysts, such as aqueous systems[43,44,] P_2O_5, DABCO-based ionic liquid, $[NMP]H_2PO_4$, LiCl, Fe_3O_4 nanoparticles, nano- Fe_3O_4/PEG/succinic anhydride, poly(4-vinyl-pyridinium) hydrogen sulfate, nanocatalytic Zn/MCM-41-SO_3H, $CuSO_4 \cdot 5H_2O$, $GaCl_3$, AlHMS, LPCAS, tetrapropyl ammonium bromide, H- zeolite, STA, and various ionic liquids.[39,41-47] However, most of the catalysts in question have led

researchers to search for different catalysts, as they have one or more drawbacks, such as being uneconomical and useless methods, and carrying out the reaction with lower yields.

Sulfonamides forms the basis for a large multiplicity of drugs and are known for antibacterial[48], antiviral [49], diuretic[50], antimalarial[51], anticonvulsant[52], hypoglycemic[53], anti-carbonic anhydrase[54,55] and ant thyroid[56] activities. A marketable sulfonamide derivative, KCN1 was shown to display both in vitro and in vivo antitumor activity.[54] Recently evaluated benzoxazine-6-sulfonamides (e) as activators of the tumor cell specific M2 isoform of pyruvate kinase.[55] Newly, certain benzoxazine and sulfonamides (Figure 7), have been reported to exhibit interesting antibacterial and anticancer activity.[56] The piperazine-based heterocyclic nuclei are a varied class of chemical compounds, some of which demonstrate significant pharmacological properties. A small adjustment in the additional design in the piperazine core causes obvious distinction in their biological events. A few related arylsulfamides with a spacer to phenyl-piperazine were testified as active structure for 5-HT7 antagonist.[54] Considering the importance of benzoxazine-6- sulfonamide, and in continuation of our research program to discover and develop novel biologically active compounds[57], we have planned to synthesize a new series of compounds having benzoxazine-6-sulfonamide moiety and screened them for their antimicrobial activities. The antibacterial and antifungal activities of all the newly synthesized compounds were evaluated in vitro against one Gram-positive bacterium, three Gram-negative bacteria and one fungus.[56-58]

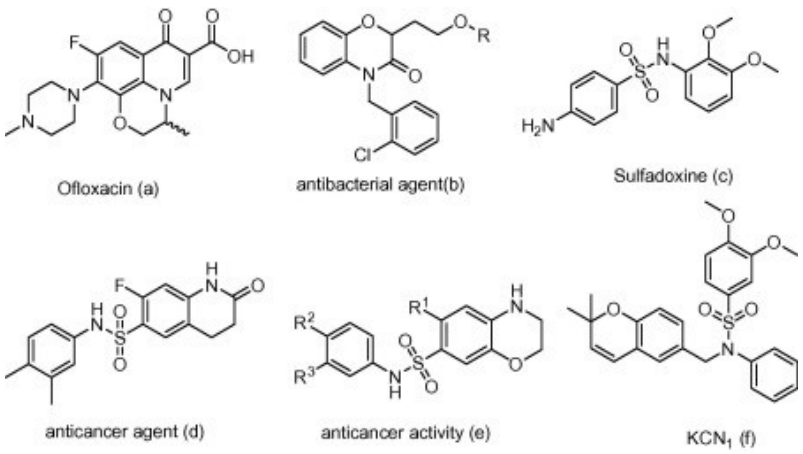


Figure 7: Benzoxanthene Derivatives

Molecular docking of Benzoxanthenes:

Molecular field mapping and alignment studies were performed using FORZE V10 software. Docking calculations were carried out using Docking Server.[59] Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on 1M17 protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools.[60] Affinity (grid) maps of xx A˚ grid points and 0.375 A˚ spacing were generated using the Autogrid program.[61] AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 A˚, and quaternion and torsion steps of 5 were applied.[62]

CONCLUSION:

Acridines have the ability to form both binary drug/DNA complexes and ternary drug/DNA/topo complexes. The latter is the mechanism of their anticancer activity, and quite possibly also of their antiprotozoal activity and anticancer activity and xanthane derivatives are bioactive compounds with diverse activities such as anti-bacterial, anti-fungal, anti-cancer, and anti-inflammatory as well as therapeutic effects on diabetes and Alzheimer. The anti-cancer activity of such compounds has been one of the main research fields in pharmaceutical chemistry.

REFERENCES:

1. Gensicka-Kowalewska, M.; Cholewiński, G.; Dzierzbicka, K. Recent Developments in the Synthesis and Biological Activity of Acridine/Acridone Analogues. RSC Adv. 2017, 7, 15776–15804.
2. Sabolova, D.; Kristian, P.; Kozurkova, M. Proflavine/Acriflavine Derivatives with Versatile Biological Activities. J. Appl. Toxicol. 2020, 40, 64–71.
3. Ji Ram, V.; Sethi, A.; Nath, M.; Pratap, R. Six-Membered Heterocycles. In The Chemistry of Heterocycles; Elsevier: Amsterdam, The Netherlands, 2019; pp. 3–391. ISBN 9780128192108.
4. Borowski, A. Preparation of Acridine Derivatives Bearing Saturated Rings. Curr. Org. Chem. 2016, 21, 86–93.
5. Guo QL, Su HF, Wang N, Liao SR, Lu YT, Ou TM, et al. Synthesis and evaluation of 7-substituted-5, 6-dihydrobenzo [c] acridine derivatives as new c-KIT promoter G-quadruplex binding ligands. Eur J Med Chem 2017; 130:458-71.
6. Songbuer, Li Minghui, Imerhasan Mukhtar. Synthesis and Application of Acridine Derivatives[J]. Chin. J. Org. Chem., 2018, 38(3): 594-611.
7. Gräbe, C.; Caro, H. "Ueber Acridin". Berichte der Deutschen Chemischen Gesellschaft (in German). 1970; 3 (2): 746–747.
8. Maier W, Baumert A, Schumann B, Furukawa H, Groger D. "Synthesis of 1,3-dihydroxy-N-methylacridone and its conversion to rutacridone by cell-free extracts of Ruta-graveolens cell cultures". Phytochemistry. 1993; 32 (3): 691–698.
9. Joseph R. Lakowicz. Principles of Fluorescence Spectroscopy 3rd edition. Springer (2006). ISBN 978-0387-31278-1. Chapter 7. page 260.
10. Scott, L.T. Polycyclic aromatic hydrocarbon bowls, baskets, balls, and tubes: Challenging targets for chemical synthesis. Polycyclic. Aromat. Comp. 2010, 30, 247–259.
11. Liu, B.; Liu, J.; Li, H.; Bhola, R.; Jackson, E.A.; Scott, L.T.; Page, A.; Irle, S.; Morokuma, K.; Zhou, C. Nearly Exclusive Growth of Small Diameter Semiconducting Single-Wall Carbon Nanotubes from Organic Chemistry Synthetic End-Cap Molecules. Nano Lett. 2015, 15, 586–595.
12. Nuñez YO, Salabarria IS, Collado IG, Hernández-Galán R. Screening Study of Potential Lead Compounds for Natural Product Based Fungicides from Juniperus lucayana. Nat Product Commun. 2008;3(4):1934578X0800300401.
13. Salih AM, Al-Qurainy F, Khan S, Tarroum M, Nadeem M, Shaikhaldein HO, Alabdallah NM, Alansi S, Alshameri A.BMC Plant Biol. 2021 Apr 21;21(1):192.
14. Cain B.F., Atwell G.J., Denny W.A. Potential antitumor agents 17. 9-Anilino-10-Methylacridinium Salts. J. Med. Chem. 1976;19:772–777.
15. Lang X., Luan X., Gao C., Jiang Y. Recent Progress of Acridine Derivatives with Antitumor Activity. Prog. Chem. 2012; 24:1497–1505.
16. A. Vieira, I. R. Brandao, W. O. Valenca, C. A. de Simone, B. C. Cavalcanti, C. Pessoa, T. R. Carneiro, A. L. Braga, E. N. da Silva, Eur. J. Med. Chem. 2015, 101, 254.

17. Murugesan, R.M. Gengan, A. Krishnan, Sulfonic acid functionalized boron nitride nano materials as a microwave-assisted efficient and highly biological active one-pot synthesis of piperazinyl-quinolinyl fused Benzo[c]acridine derivatives, Materials Chemistry and Physics (2017).
18. C. Li et al. Synthesis and electroluminescent properties of Ir complexes with benzo[c]acridine or 5,6-dihydro-benzo[c]acridine ligands: Thin solid films (2008).
19. Khandelwal S., Tailor Y.K., Rushell E., Kumar M. Green Approaches in Medicinal Chemistry for Sustainable Drug Design. Elsevier; Amsterdam, The Netherlands: Use of sustainable organic transformations in the construction of heterocyclic scaffolds; 2020 pp. 245–352.
20. Maia M., Resende D.I.S.P., Durães F., Pinto M.M.M., Sousa E. Xanthenes in Medicinal Chemistry—Synthetic Strategies and Biological Activities. Eur. J. Med. Chem. 2021;210:113085.
21. Sen R.N., Sarkar N.N. The Condensation of Primary Alcohols with Resorcinol and o-hydroxy aromatic compounds. *J. Am. Chem. Soc.* 1925; 47:1079–1091.
22. Sadeghpour M., Olyaei A., Adl A. Recent Progress on the Synthesis of Henna-Based Dibenzoxanthenes. *New J. Chem.* 2021; 45:13669–13691.
23. Burange A.S., Gadam K.G., Tugaonkar P.S., Thakur S.D., Soni R.K., Khan R.R., Tai M.S., Gopinath C.S. Green Synthesis of Xanthene and Acridine-Based Heterocycles of Pharmaceutical Importance: A Review. *Environ. Chem. Lett.* 2021; 19:3283–3314.
24. Colas K., Doloczki S., Posada Urrutia M., Dyrager C. Prevalent Bioimaging Scaffolds: Synthesis, Photophysical Properties and Applications. *Eur. J. Org. Chem.* 2021; 2021:2133–2144.
25. Sato S., Nojiri T., Okuyama N., Maeda K., Kirigane A. Synthesis and evaluation of a new water-soluble fluorescent red dye, xanthene bis-C-glycoside. *J. Heterocycl. Chem.* 2020; 57:3342–3349.
26. Rajapaksha I., Chang H., Xiong Y., Marder S., Gwaltney S.R., Scott C.N. New Design Strategy Toward NIR I Xanthene-Based Dyes. *J. Org. Chem.* 2020; 85:12108–12116.
27. Mohamed M.B.I., Aysha T.S., Elmorsi T.M., El-Sedik M., Omara S.T., Shaban E., Kandil O.M., Bedair A.H. Colorimetric Chemosensor and Turn on Fluorescence Probe for PH Monitoring Based on Xanthene Dye Derivatives and Its Bioimaging of Living Escherichia Coli Bacteria. *J. Fluoresc.* 2020; 30:601–612.
28. Coelho A., Fraichard S., Le Goff G., Faure P., Artur Y., Ferveur J.-F. Cytochrome P450-dependent metabolism of caffeine in Drosophila melanogaster. PLoS One. 2015;10
29. Ogawa K., Takagi K., Satake T. Mechanism of xanthine-induced relaxation of Guinea-pig isolated trachealis muscle. Br. J. Pharmacol. 1989;97:542–546
30. Meskini N., Némoz G., Okyayuz-Baklouti I., Lagarde M., Prigent A.-F. Phosphodiesterase inhibitory profile of some related xanthine derivatives pharmacologically active on the peripheral microcirculation. Biochem. Pharmacol. 1994; 47:781–788.
31. Van der Walt M.M., Terre'Blanche G. 1,3,7-Triethyl-substituted xanthines—possess nanomolar affinity for the adenosine A1 receptor. Bioorg. Med. Chem. 2015; 23:6641–6649.
32. Gessner, Thomas; Mayer, Udo. "Triarylmethane and Diarylmethane Dyes". Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH 2000.
33. Yuan B, Shao M, Lu S, Wang B Source profles of volatile organic compounds associated with solvent use in Beijing, China. Atmo Environ 2010; 44:1919–1926.
34. Khazaei A, Moosavi-Zare A, Mohammadi Z, Zare A, Khakyzadeha V, Darvishid G Efcient preparation of 9-aryl-1,8-dioxooctahydroxanthenes catalyzed by nano-TiO2 with high recyclability. RSC Adv 2013; 3:1323–1326.
35. Kulkarni DG, Kulkarni MAV, Viswanath AK, Gopinath CS Template Free Synthesis of Mesoporous TiO2 with High Wall Thickness in Nanocrystalline Framework. J Nanosci Nanotech 2009; 9:371–377.

36. Tudu B, Nalajala N, Reddy KP, Saikia P, Gopinath CS. Electronic integration and thin flm aspects of Au–Pd/rGO/TiO2 for improved solar hydrogen generation. ACS Appl Mater Interfaces 2019; 11:32869–32878.
37. Tudu B, Nalajala N, Saikia P, Gopinath CS. Cu–Ni bimetal integrated TiO2 thin flm for enhanced solar hydrogen generation. Solar RRL 2020; 4:1900557.
38. Sathish M, Viswanathan B, Viswanathan RP, Gopinath CS. Synthesis, characterization, electronic structure, and photocatalytic activity of nitrogen-doped TiO2 nanocatalyst. Chem Mater 2005; 17:6349–6353.
39. Chenlu Dai, Naili Luo, Shan Wang, Cunde Wang. Cesium-Carbonate-Mediated Benzalation of Substituted 2-Aryl-3-nitro-2H-chromenes with Substituted 4-Benzylidene-2-phenyloxazol-5(4H)-ones. Organic Letters 2019, *21* (8), 2828-2832.
40. Amol Milind Garkhedkar, Gopal Chandru Senadi, and Jeh-Jeng Wang. ZnBr2-Mediated Cascade Reaction of o-Alkoxy Alkynols: Synthesis of Indeno[1,2-c]chromenes. Organic Letters 2017, *19* (3) , 488-491.
41. Wei Chen, Xin-wen Peng, Lin-xin Zhong, Yuan Li, and Run-cang Sun. Lignosulfonic Acid: A Renewable and Effective Biomass-Based Catalyst for Multicomponent Reactions. ACS Sustainable Chemistry & Engineering 2015, *3* (7), 1366-1373.
42. Sandile B. Simelane, Henok H. Kinfe, Alfred Muller, and D. Bradley G. Williams. Aluminum Triflate Catalyzed Tandem Reactions of d-Galactal: Toward Chiral Benzopyrans, Chromenes, and Chromans. Organic Letters 2014, *16* (17), 4543-4545.
43. Hong-Juan Wang, Li-Ping Mo, and Zhan-Hui Zhang. Cerium Ammonium Nitrate-Catalyzed Multicomponent Reaction for Efficient Synthesis of Functionalized Tetrahydropyridines. ACS Combinatorial Science 2011, *13* (2), 181-185.
44. Atul Kumar, Suman Srivastava, Garima Gupta, Vinita Chaturvedi, Sudhir Sinha, and R. Srivastava. Natural Product Inspired Diversity Oriented Synthesis of Tetrahydroquinoline Scaffolds as Antitubercular Agent. ACS Combinatorial Science 2011, *13* (1) , 65-71.
45. Atul Kumar, Garima Gupta and Suman Srivastava. Diversity Oriented Synthesis of Pyrrolidines via Natural Carbohydrate Solid Acid Catalyst. Journal of Combinatorial Chemistry 2010, *12* (4), 458-462.
46. Vellaisamy Sridharan and J. Carlos Menéndez. Cerium (IV) Ammonium Nitrate as a Catalyst in Organic Synthesis. Chemical Reviews 2010, *110* (6), 3805-3849.
47. C. Liu, J. Pan,S. Li, Y. Zhao,L. Y. Wu, C. E. Berkman, A. R. Whorton,M.Xian,Angew.Chem.Int. Ed.2011,50, 10327–10329; Angew.Chem.2011,123,10511–10513.
48. Chohan, Z. H.; Youssoufi, M. H.; Ben, H. T.; Jarrahpour, A. Eur. J. Med. Chem. 2010, 45, 1189.
49. Belinda, L.; Luciano, V.; Mok, B. J.; Lee, C. C.; Fitzmaurice, R. J.; Caddick, S.; Fassati, A. Chem. Biol. Drug. Des. 2010, 75, 461.
50. Maren, T. H. Annu. Rev. Pharmacol. Toxicol. 1976, 16, 309.
51. Boechat, N.; Pinheiro, L. C. S.; Santos-Filho, O. A.; Silva, I. C.; Molecules. 2011, 16, 8083.
52. Koller, M.; Kurt, L.; Markus, S.; Ivan-Toma, V.; Joerg, K.; Yves, P. A.; David, A. C.; Henri, M.; Silvio, O.; David, O.; Stephan, U. Bioorg. Med. Chem. Lett. 2011, 21, 3358.
53. E. Boyd 3rd; Diabetes. 1988. 37. 847.
54. Supuran, C. T.; Scozzafava, A. Exp. Opin. Ther. Patents. 2000, 10, 575.Scozzafava, C. T.; A. Curr.
55. Med. Chem. Immunol. Endocr. Metabol. Agents. 2001, 37, 61.
56. Thornber, C. W. Chem. Soc. Rev.1979, 8, 563. 17.
57. Jiyoung, M.; Adnan, A. J.; Narra, S. D.; Yuan, L.; Erwin, G. V. M.; Mark, M. G. Bioorg. Med. Chem. 2012, 20, 4590.

58. Wang, W.; Ao, L.; Rayburn, E. R.; Xu, H.; Zhang, X.; Zhang, X.; Nag, S. A.; Wu, X.; Wang, M. H.; Wang, H.; Van Meir, E. G.; Zhang, R. PLoS One. 2012, 7, 44883.
59. Bikadi Z, Hazai E. Application of the PM-6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock. J Cheminf 2009: 1:1–16.
60. Halgren TA. Merck molecular force field I Basis, form, scope, parametrization, and performance of MMFF94. J Comp Chem 1998; 17:490–519.
61. Morris GM, Goodsell DS, Olson AJ. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comp Chem 1998; 19:1639–1662.
62. Solis FJ, Wets RJB. Minimization by random search techniques. Math Method Oper Res 1981: 6:19–30.

How to cite this article: Herole RA, Rakesh Kumar Jat, and Rajendra D Dighe. "A REVIEW ON ACRIDINE, XANTHENE AND ITS DERIVATIVES: SYNTHESIS, PHYSICAL AND PHARMACOLOGICAL PROPERTIES". *Tropical Journal of Pharmaceutical and Life Sciences*, vol. 9, no. 6, Dec. 2022, pp. 01-12, https://informativejournals.com/journal/index.php/tjpls/article/view/108.

PUBLISHED BY:
INFORMATIVE JOURNALS
JADOUN SCIENCE PUBLISHING GROUP INDIA