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Acridones as versatile biological scaffolds: A review

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ABSTRACT

The planar structure and the fluorescence nature of the acridone nucleus has been extensively exploited in numerous biological systems. From the monitoring of the biological processes to the designing of the biologically active compounds the acridone nucleus has played a pivotal role. Especially in the development of anticancer therapy, the commend ability of the acridone nucleus is numerous. The acridone nucleus is known to halt DNA duplication as well as arrests the cell cycle. Besides, the acridone nucleus also finds implications in the development of the oxidative stress therapy to cure cancer. Being a highly conjugated system, there is delocalization of the free electrons in the acridone nucleus which helps in the creation of oxidative stress as well as scavenging the free radicals in the cells. The current review comprehensively deals with the various biological applications of the acridone nucleus.

KEY WORDS: Acridone, Acridine.

1. INTRODUCTION

Monitoring the working of biochemical reactions, understanding the mode of action of the enzymes during their catalytic phase and improving the effectiveness of drugs along with minimizing their side effects are some interrelated challenges to the contemporary bioorganic and medicinal research. The development of efficient probes for the monitoring of biochemical reactions may prove as better diagnostic tools whereas the understanding of the mechanism of enzyme catalysis has a direct impact on the drug designing process. Sensing of the biological entities like adenosine monophosphate (AMP), adenosine diphosphate (ADP) and adenosine triphophate (ATP) is one of the most popular tools to visualize the complicated biological processes due to the fact that almost all the biochemical reactions are coupled with ADP – ATP inter-conversions for the sake of either getting energy or storage of energy. Likewise, the enzyme models provide a simplified alternative route to the complex enzymatic reactions and give fruitful information about the mechanism of enzyme catalyzed reactions. In fact, the working success of the biological sensors, enzyme mimicking and drug development processes is primarily based on the intelligent and intuitive tailor-made design of the molecule/s. However, the rational design of ligands for a specific host and mimicking/targeting a particular enzyme is a complex process and get setback due to the structural changes that the host/enzymes may undergo in the physiological conditions.

Despite the wide range of studies for the design and synthesis of new molecules for their use as biological probes as well as the enzyme models and even the drugs, a number of bottleneck including selectivity, solubility, robustness, efficiency, economical synthesis, side effects etc. are still there. Since Nature runs a large number of chemical reactions in a very efficient and un-interrupted manner, the fascinating natural products provide guidance for the development of desired synthetic molecules. Hence, the modification of natural molecules may advantageously be done for constructing new molecules of choice. Hypothesizing this model, herein, we used small natural molecules viz. acridine, amino alcohol and amino acids for constructing desirable molecules. Acridine was used as the template and derivatized with amino alcohol and amino acids.

DISCUSSION

Acridine based molecular probes: A number of acridine based cation selective, anion selective, pH sensitive, ATP selective and DNA binding probes are developed for the detection of ions, biological materials and monitoring of the biochemical pathways.

Acridone based cation selective probes: As a simplest case, probe 1(Chart.1) undergoes quenching of fluorescence in presence of Cr^{3+}. Probe 2 (Chart 1) also shows enhancement of fluorescence in the presence of Cr^{3+} and the complex 2-Cr^{3+} undergoes quenching on addition of phosphate**.** Further, probe 3 (Chart 1) exhibits quenching of fluorescence with Cu^{2+} in SDS micelle at pH 2 and pH 8. In the presence of TX micelle, 3 shows enhancement with Cu^{2+} at pH8. Acridine based probe 4 (Chart 1) exhibits enhancement in fluorescence in the presence of Zn^{2+} at neutral pH whereas compound 5 (Chart.1) shows similar effect in the presence of Cd^{2+}. Probe 6 (Chart.1) is selective to Hg^{2+} and fluorescence enhancement is reported at pH 6.0.

Acridine based anion selective probes: Chemosensor 7 (Chart 2) exhibits quenching of fluorescence with the incremental addition of CN^- (DMSO-water, 95:5 v/v as the medium) whereas probe 8 (Chart.2) shows enhancement in the fluorescence intensity in the presence of HCO_3^-. Some of the acridine based fluorescent indicator dyes 9-16 (Chart.2) undergo fluorescence quenching on addition of Cl^- in the aqueous medium. Acridine based receptors 17 (Chart.2) was showing selective interaction with $H_2PO_4^-$ resulting in Fluorescence enhancement.

Acridine based pH sensitive probes: Protonation – deprotonation of compound 18 (Chart.3) at different pH of the solution make it to undergo change in fluorescence intensity and λ_{em}. Acridine based fluorescent probe 19 (Chart.3) shows quenching of fluorescence with the change in pH from 4.2 to 10.0 in the phosphate buffer. Probe 19 also shows change in fluorescence in the presence of DNA in phosphate buffer. The acridine based fluorescent sensor 20 (Chart.3) undergoes quenching of fluorescence when pH of the solution was changed from 3 to 12. The fluorescent probe 21 also exhibits fluorescence quenching with the change in pH from 0.77 to 14.0.

Acridine based ATP selective probes: The fluorescent probes 22-24 (Chart.4) are selectively showing the quenching in fluorescence with addition of ATP in HEPES buffer. Probe 22 was also employed for the Monitoring of the biochemical reactions**.**

Acridine based DNA binding probes: The planar geometry of the acridine molecule makes it suitable to intercalate with DNA. Interactions of compounds 25-30 (Chart.5) with DNA are studied by monitoring the change in fluorescence and UV-vis absorption of the compound – DNA solutions.

Other acridine based fluorescent probes: In addition to the above reports, acridine based fluorescent probe 31 (Chart.6) shows interaction with acetylcholinesterase. Probe 32 (Chart.6) is used as fluorophore for tracking the protein-protein interactions and stability of the protein whereas probe 33 (Chart.6) shows interaction with bovine albumin serum protein. It is also used as photosensitizer in photodynamic therapy. The biosensor **3**4 (Chart.6) is used as electrochemical indicator to detect the nuclear factor kappa B in serum.

Acridine based Anti-cancer agents: Acridine derivatives, targeting the cellular factors like DNA, topoisomerase, telomere and cell cycle etc are developed for cancer therapy.

Acridine based DNA intercalators as anticancer agents: Compounds 56-59 (Chart.9) show good antiproliferative activity on L1210 and KB-3-1 cell lines whereas compound 58 causes alkylation of DNA guanine units. Compound 60 (Chart.7) with significant DNA binding property was active for the antitumor activity. Compounds 61-64 (Chart.7) are reported to have DNA binding features and show anticancer activity against 60 human tumor cell lines. The anticancer activity of compounds 65-70 (Chart.8) is mainly due to their intercalation with DNA.

Acridine based topoisomerase inhibitors as anticancer agents: Their significant role during the process of DNA replication makes DNA topoisomerase as the potential cellular target of anticancer drugs. Acridine derivative 71 (Chart.11) shows cytotoxicity against human cancerous cells and it is found to inhibit the catalytic activity of topoisomerases. Compound 72 and 73 (Chart.9) also exhibit similar mode of action for their anticancer activity.

Acridine based telomere inhibitors as anticancer agents: Telomere protects the chromosomes from degradation and plays important role in the cell division and cell viability. These features of telomere make it the target of many reported anticancer drugs. Compound 74-75 (Chart.10) exhibit antiproliferative activity Due to the telomere inhibition.

Cell cycle arrest by acridine based anticancer agents: Arrest of cell division at the G0/G1, G2 and M phases is another strategic approach to tackle propagation of cancer. Hence, along with topoisomerase and telomeres, cell cycle is the important target of anticancer drugs. Compound 76-77 (Chart.11) were active for the antiproliferative activity against human cancer cell lines by cell cycle arrest. Similarly, compound 78-79 (Chart.13) also exhibit antitumor activity with cell cycle inhibition.

Therefore it is apparent from the brief review of literature that the acridine template is a versatile synthon. Besides acting as the fluorescent moiety, its biological acceptance and planar geometry also provide unique features to the molecule. The acridine based molecules are found to interact with DNA, ATP, ADP and some specific enzymes.

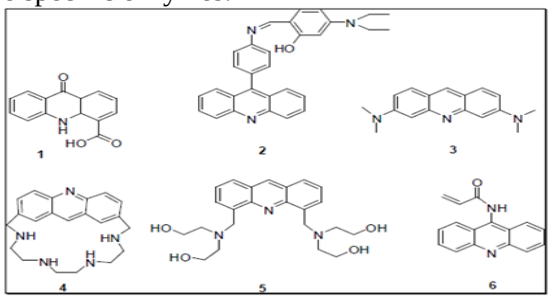


Chart.1

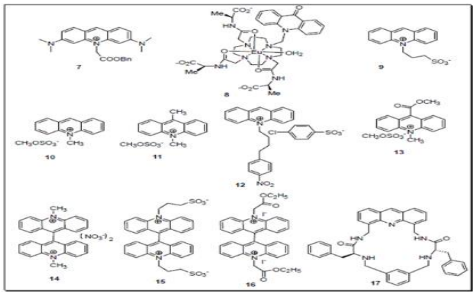
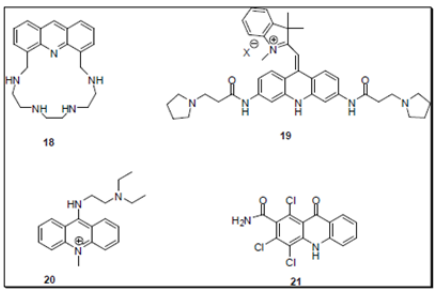


Chart.2



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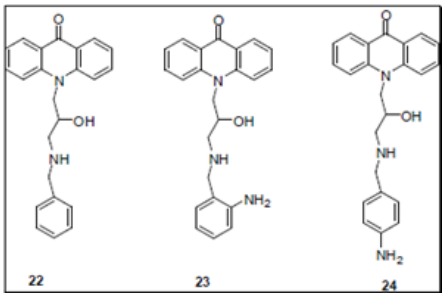
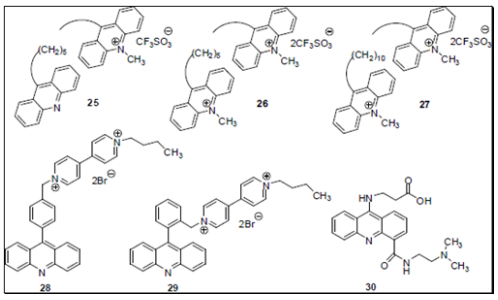


Chart.4



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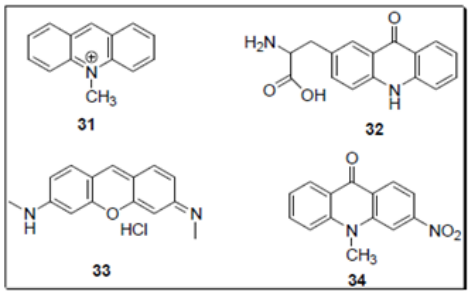

Chart.6

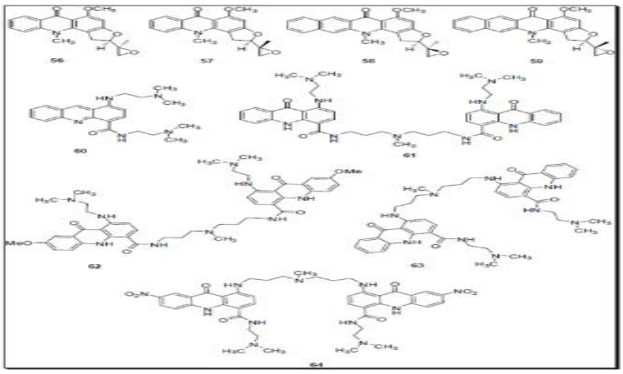

Chart.7

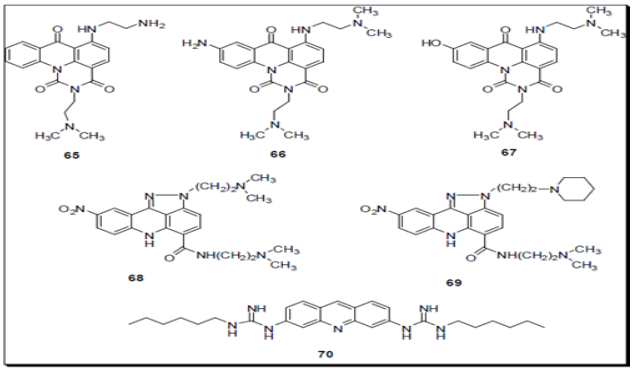

Chart.8

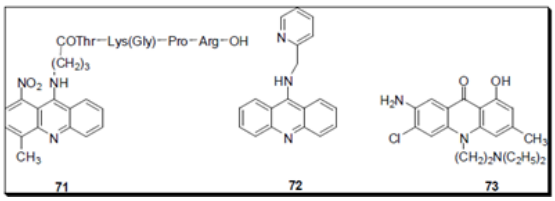

Chart.9

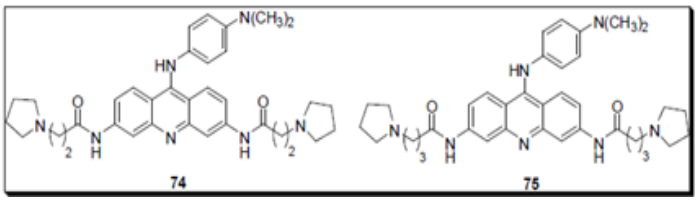

Chart.10

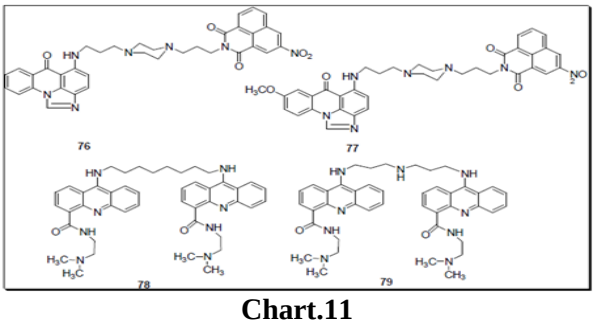

Chart.11

2. CONCLUSION

The implications of acridone nucleus are therefore commendable not only as a basic scaffold but also as an active pharmacophore. A planar structure, fluorescent behavior and DNA intercalation property makes acridones a privileged synthon for the development of modern medicines. Besides, the acridone nucleus is also a useful moiety in the development of target based drug delivery therapy for preparing the hit to lead molecules.

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