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Acridone and its Analogues Emphasizing as Anticancer Agents

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ABSTRACT

The aim of this review is to provide the summaries of the research work and new developments in the research work associated with acridone and its derivatives. Cancer is the disease related with cells. Unlike normal cells, the cancerous cells divide and does not stop the growth which cause metastasis. There are many treatments for cancer like chemotherapy, radiotherapy and surgery but the drawback is they tend to cause lot of side effects. So, there is a need to synthesize new drug for the cure. Acridone and their derivatives are the alkaloid compounds, can be obtained by synthesizing with different substituents. They have various biological activities such as anti-viral, anti-microbial, anti-Alzheimer's disease, anti-bacterial and mainly as anti-cancer agents. It has been found that cancer is a big threat to be treated due to lack of specific site of action, its proliferating ability and efflux of xenobiotics. Multidrug resistance (MDR) is the drawback for cancer treatment and the major cause of MDR is Telomere and topoisomerase but they can be inhibited by designing the molecule with the alteration of acridone scaffold. So, Acridone plays an important role in the treatment of cancer due to its planar geometry. Various signalling pathways are involved to cause proliferation of the cells. The pathways help us to know the cause of cancer and ways for the treatment. Signalling pathway and the proteins involved in the pathway directs us to avoid the failure of molecule.

KEY WORDS: Anti-proliferative, Acridone, telomere, DNA-intercalation, Ullmann synthesis

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INTRODUCTION

Cancer is a disease characterised by the growth of abnormal cells which is uncontrollable and cause death of normal cells. Cancer is not only seen in humans but also can be seen in animals and other organisms¹. Cancer cells are metastatic, that is they have the ability to spread to different areas of the body. Even though many molecules are available in the market, they are not able to treat cancer due to metastatic ability of cancerous cells. From long time, acridone and its analogues has become the major interests in the drug which can be obtained by natural sources.

The physical characteristics of Acridones occurs in yellow solid form having the melting point of 354°C. It is insoluble in benzene, ethanol, ether, chloroform and water. Acridones are soluble in alcoholic potassium which gives yellow brown solution and on exposure aqueous environment gets completely decomposed.

Pharmacological uses of Acridone shows anticancer, antimalarial, anti-inflammatory, antiviral and antibacterial activities. It can also be used in the treatment of dementia and neurodegenerative disorder such as Alzheimer's disease.

Chemistry of Acridones: Acridone is an organic compound which is originated from the acridine skeleton with carbonyl group at the 9th position. Acridones constitutes the scaffold which shows various pharmacological activities. The molecule is planar with no atoms deviating by more than 0.2 Å from the molecular plane outlined by non-H ring atoms and therefore the gas atoms, all torsion angle lies within +1.5 to -1.5 of zero to one hundred eighty degrees. The molecules adopt a Herring bone Packing Arrangement terribly similar that found in anthraquinone and quinacridone atomic number one bonding is maximized in such structures².

Mechanism of action

- Acridone molecule with planar geometry is suitable for anticancer activity. Derivatives were developed to target the cellular factors like DNA, topoisomerase, telomere and cell cycle. DNA topoisomerase acts as an important cellular target of anticancer drugs such as Acridones by inhibiting the catalytic activity of Acridones. So, Good anticancer activity can be seen by intercalation of DNA.
- Telomere is also the target of anticancer because it protects the chromosomes from degradation and causes cell division and cell viability.
- Arrest of biological process of G₀/G₁, G₂, M phases is another strategic approach to tackle propagation of cancer. Hence, together with topoisomerase and telomere, cell cycle is a vital target of malignant tumour medicine.

- Enhance the neurotransmission of cholinergic synapses in the brain and thus increase the intellectual ability. By this mechanism acridone can be used as anti-Alzheimer's disease

Due to its mechanism of action and DNA intercalation property Acridones is a privileged synthon for the development of modern medicines³.

SYNTHESIS

LEHMSTED–TANASESCU Acridone Synthesis- Acridone was synthesised by condensation of *o*-nitro benzaldehyde and aryls using acid as a catalyst. A mixture of benzaldehyde (18.5g/mol, 0.1mol), chlorobenzene (78.7g, 0.7mol), concentrated H₂SO₄ was taken in a beaker and occasionally shaken for 9 hours. For total of 6 days it was allowed to stand for 15 hours. A mixture of H₂SO₄(10 ml) and NaNO₂(0.1g) was added at the end of each two days. After 6 days the mixture was poured into 500ml water and steam distilled. The residue was obtained after steam distillation which was filtered and digested with pH⁴.

Ullmann condensation- It is basically 2 pot synthesis procedure

Step 1- Synthesis of N-Phenylanthranilic acid

A mixture of 155g of aniline, 41 g of *o*-chlorobenzoic acid, 41 g of anhydrous potassium carbonate and 1g of copper oxide was refluxed for 2 hours in round bottom flask and was distilled to remove the excess aniline. Then 20g of decolourising carbon is added to residual solution. The mixture is boiled and filtered. Filtrate was added to the mixture of concentrated HCL and water. Then the precipitated acid is filtered with suction.

Step 2- Synthesis of acridone

A mixture of 42.7g of N-Phenylanthranilic acid and concentrated sulphuric acid in a flask and heated on a boiling water bath for four hours. Then 1 litre of boiling water was poured and boiled for 5 minutes, the yellow precipitate is obtained and filtered. To the precipitate, solution of 30g of sodium carbonate and water was added and boiled. Filtered and washed well with water⁵.

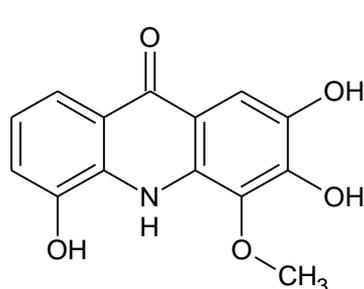
BIOLOGICAL ACTIVITY

Antimicrobial activity

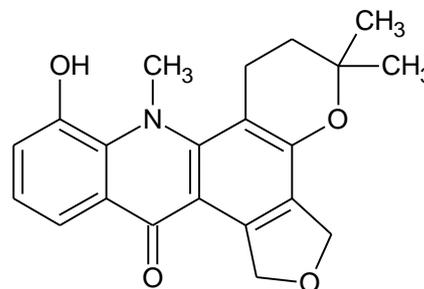
Acridone molecules such as Acrifoline, Atalaphyllidine, Chlorospermine A, Chlorospermine B were tested for the antimicrobial activity. The molecules were tested for DYRK1A, CLK1, CDK1, CDK5, GSK3, and CK1 activity whereas Acrifoline showed activity against DYRK1A, CLK1, GSK3, CDK1, and CDK5 with IC₅₀ values of 0.075, 0.17, 2, 5.3 and 9 μM. Compared to Acrifoline other molecules that

is Chlorospermine B and atalaphyllidine exhibited high inhibition of DYRK1A with IC_{50} of 5.7 and 2.2 μ M respectively. Chlorospermine A did not show any anti-microbial activity.

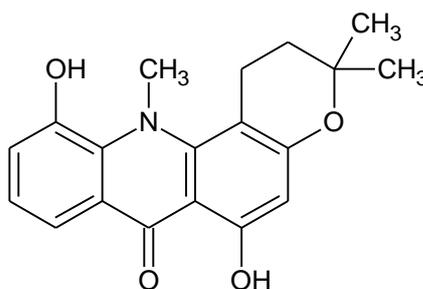
Citrusinine 1 acridone alkaloid and its derivatives obtained from *Swinglea glutinosa* showed the inhibition of photosynthesis.



Citrusinine-1



Chlorospermine B



Atalaphyllidine

Anti- Alzheimer's activity

Alzheimer's disease (AD) is the mental disorder caused due to degeneration of the brain can be treated with acridone alkaloids. Tacrine and its derivatives can be used as anti-AD. They work by the mechanism of cholinesterase inhibition which enhances the neurotransmission of cholinergic synapse in the brain⁶.

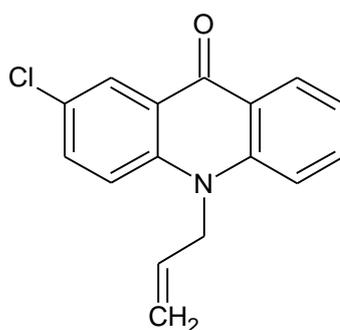
Anti-viral activity

N-Allyl acridone was used to exhibit antiviral activity. Dengue virus was used as a causative agent belonging to the family of Flaviviridae.

In the screening it was identified that N-allyl acridone derivatives were effective virus inhibitors. Different derivatives were synthesised and best fit score was found using docking studies. Crystal structure of proteins were taken and ligand structure was optimised for the docking studies.

10-allyl-7-chloro-9(10*H*)-acridone derivative was synthesised and tested for the antiviral activity by using Vero (African green monkey kidney) and HeLa (human cervical carcinoma) cells. Antiviral

activity was performed by virus yield inhibition assay, cell viability assay and cell protein synthesis. 10-allyl-7-chloro-9(10*H*)-acridone molecule strongly showed the inhibition of the infection caused by Vero virus with the effective concentration of 50% values in the range 12.5-27.1 μ M. Mode of action was shown by inhibiting Viral RNA synthesis and virus entry in to the host cell was not inhibited⁷.



10-allyl-7-chloro-9(10*H*)-acridone

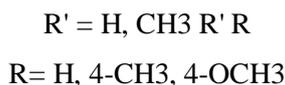
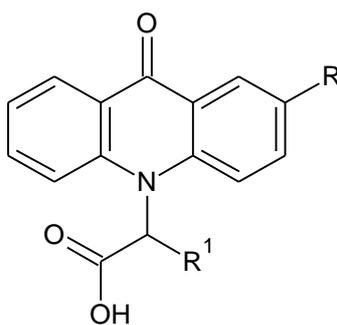
Anti-bacterial activity

Derivatives of acridone were synthesized such as 9-Acridone-N-acetic acid, 9-Acridone-N-2-propionic acid, 2-methyl-9-acridone-N-acetic acid, 2-methyl-9-acridone-N-2-propionic acid, 2-methoxy-9-acridone-N-acetic acid and 2-methoxy-9-acridone-N-2-propionic acid.

Synthesis was done by three steps

- 1 Synthesis of N-phenylanthranilic acid derivatives
- 2 Cyclisation of N-phenylanthranilic acid derivatives to acridone.
- 3 Synthesis of acetic acid derivatives of acridone

For the synthesised derivatives, antibacterial screening was performed *invitro* by serial dilution method. Antibacterial activity was performed against both gram positive and gram negative bacteria. Gram positive bacteria are *Staphylococcus aureus*, *Bacillus subtilis* and gram negative bacteria is *Escherichia coli*. In the result out of all the derivatives only three derivatives that is 9-Acridone-N-acetic acid, 9-Acridone-N-2-propionic acid, 2-methoxy-9-acridone-N-acetic acid showed effective inhibition against gram positive and gram negative bacteria⁸.



Biological study of acridone derivatives for anti-cancer activity

N-Phenyl ethylbenzamide derivative is isolated from *Swinglea glutinosa* was performed *invitro* cytotoxicity activity on cancer cell lines. *Swinglea glutinosa* belongs to rutaceae family provided 11 acridone alkaloids and 3 N-Phenyl ethyl benzamide derivatives *i.e.*, glycocitrine-IV, 1,3,5-trihydroxy-4-methoxy-10-methyl-2,8-bis(3-methylbut-2-enyl)acridin-9(10*H*)-one, 1,3,5-trihydroxy-2,8-bis(3-methylbut-2-enyl)-10-methyl-9-acridone, citbrasine, citrusinine-II, citrusinine-I, 5-dihydroxyacronycine, pyranofoline, 3,4-dihydro-3,5,8-trihydroxy-6-methoxy-2,2,7-trimethyl-2*H*-pyrano[2,3-*a*]acridin-12(7*H*)-one, 2,3-dihydro-4,9-dihydroxy-2(2-hydroxy-propan-2-yl)-11-methoxy-10-methylfuro[3,2-*b*]acridin-5(10*H*)-one, bis-5-hydroxyacronycine and N-(2-{4-[(3,7-dimethylocta-2,6-dien-1-yl)oxy] phenyl}ethyl)benzamide.

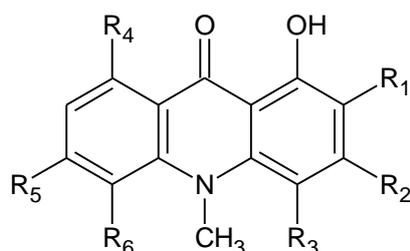
Identification of N-Phenyethyl benzamide derivatives was done by spectroscopic methods and the anti-cancer activity was performed by using cancer cell lines human lung carcinoma cell line, COR-L23, human breast adenocarcinoma cell line MCF7, the human melanoma cell line, C32 and normal human fetal lung cell line, MRC-5. *In vitro* biological assay was performed using cell lines.

Sulphurhodamine-B assay was performed to evaluate the growth inhibition of the cells where vinblastine sulfate was used as positive control. According to the results, amides showed high cytotoxic activity against COR-L23 and MCF7 compared to other molecules. In the previous studies it was proven that few molecules showed more activity than acronycine on human leukemic cell (HL-60). They couldn't be used as a drug for treatment of cancer due to their lack of selectivity.

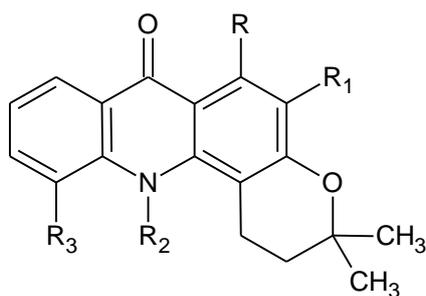
From the series of molecules and their effectiveness against cell lines, structure activity relationship can be known.

The result was found that glyofoline showed higher inhibition because of intramolecular hydrogen bonding seen between the 1-hydroxy and the peri-carbonyl function of the 1-hydroxy-9-acridone nucleus.

Results revealed that presence of secondary amine, hydroxyl group at 1st and 5th position and prenyl group 6th position enhances the anti-cancer activity⁹.



No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1	Prenyl	OH	OCH ₃	H	H	H
2	Prenyl	OH	OCH ₃	Prenyl	H	H
3	Prenyl	OH	H	Prenyl	H	H
4	OCH ₃	OCH ₃	OCH ₃	H	H	H
5	H	H	OCH ₃	H	H	H
6	H	OCH ₃	OCH ₃	H	H	H
7	OCH ₃	OCH ₃	OCH ₃	H	OH	OCH ₃

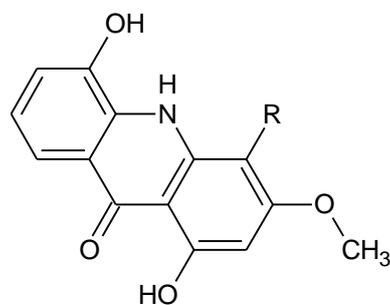


	R ₁	R ₂	R ₃	R ₄
8	H	H	CH ₃	OH
9	CH ₃	H	CH ₃	OH
10	H	H	H	H
11	H	Prenyl	H	OH
12	H	H	H	OH
13	H	Prenyl	CH ₃	H

According to the result, glyofoline showed higher inhibition because of intramolecular hydrogen bonding seen between the 1-hydroxy and the peri-carbonyl function of the 1-hydroxy-9-acridone nucleus. The presence of secondary amine, hydroxyl group at 1st and 5th position and prenyl group at 6th position enhances the anti-cancer activity⁹.

Acridone alkaloids were isolated from rutaceae family and then purified. This study was done to determine the efficiency of cell growth inhibition by using human promyelocytic leukemic cells (HL-60). Biological studies were done using the trypan blue exclusion method in which viable cells were determined and estimated in a haemocytometer.

Effect of the molecules on precursor incorporation into cellular DNA-The test was performed by incubating the cells in presence or absence of acridone molecule. Results showed that glycocitrine-2 as a potent inhibitor of cell DNA synthesis whereas Acronycine derivatives did not show good inhibitory activity.



Glycocitrine 2

Effect of molecules on the labelled precursor incorporation into RNA and protein.

The cell lines were incubated in the absence or presence of acridone derivatives. It was found that derivatives of acronycine and pyranofoline showed 90% of RNA and protein biosynthesis inhibition.

Effect of molecules on the growth of HL-60 cells.

Acronycine showed potent inhibition of cell growth and attempts were done to find out more potent compounds. It was found that acridin-9-one derivatives showed potent activity against human leukemic cells *in vitro*¹⁰.

The following structure activity relationship obtained from the results provides useful information regarding development of new antitumor agents.

- 1 Addition of 3 methyl-2-butenyl side chain at 5th position enhances the inhibition.
- 2 Substitution at 6th, 10th, 11th and 12th position increases the activity.
- 3 Penta substituent at C-4 shows good activity.
- 4 Disubstituted derivatives exhibits less activity.
- 5 N-methyl analogues showed significant activity
- 6 Addition of OH group at C-11 position showed good antitumor activity.

Synthesis of acridone derivatives and biological evaluation

Acridone derivatives were synthesised by Ullmann condensation method. By this method, different derivatives were obtained and tested for the potential cytotoxic activity. The activity was performed against melanotic and amelanotic cell lines. Cell cycle and cell death was analysed. Among the investigated analogues compound twelve exhibited the very best efficiency. FLICA check (flurochrome-labeled inhibitors of caspases) was performed. The test showed that this analogue considerably raised the content of cells among each malignant tumour cell line with activated caspases (C+). These changes in malignant neoplasm cells were less pronounced¹¹.

Effect of acridone and its derivatives against breast cancer cell lines.

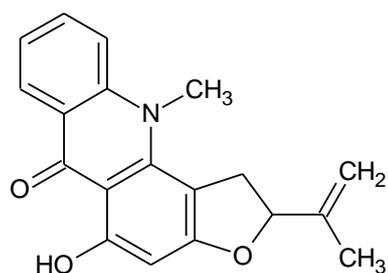
Breast cancer is one of the big threat which is caused by increase in oestrogen level and decrease in progesterone level. Breast cancer can be treated by increasing progesterone level and decreasing oestrogen level. Oestrogen and progesterone receptor acts as a marker in the detection of breast cancer¹²⁻¹⁴. To know the antitumor activity of acridone against breast cancer cell lines *i.e.*, MCF-7 *in vivo* experiment was performed. The experiment was carried by xenograft animal model using nude mice. In this experiment different concentration of acridone was administered and control was also used. With the help of different concentration, inhibition of growth rate was estimated and ABCG2 protein expression was estimated by western blot. Among different concentrations, high dose concentration showed more inhibition compared to medium dose and low dose concentration.

According to the results, it is proven that acridone helps in the treatment of breast cancer and also helps to study the mechanism involved in anti-proliferation of cancer cells. Anti-proliferation activity is seen due to cell apoptosis, inhibition of ABCG2 protein and decrease in the oestrogen level¹⁵.

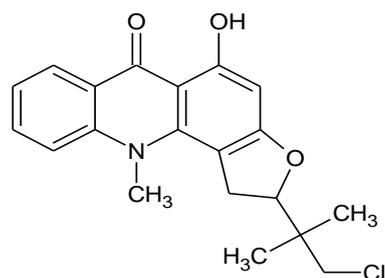
Antiproliferative Effects of Various Furanoacridones Isolated from *Ruta graveolens* on Human Breast Cancer Cell Lines

As breast cancer is the malignant disease, there is an urge to develop new anti-cancer agents for the treatment. The obtained furanoacridones from *Ruta graveolens* were elucidated by spectral analysis and then tested for the anti-cancer activity on breast cancer cell lines (MCF-7, MDA-MB-361, MDA-MB-231 and T47D). different cell lines were chosen because each have their specific profiles. MDA-MB-31 cell line is a triple negative cell line because it doesn't express both progesterone and oestrogen receptors, so it is difficult to treat such type of tumours. Therefore, it is necessary to design new chemotherapeutic agents which shows action on this type of tumours.

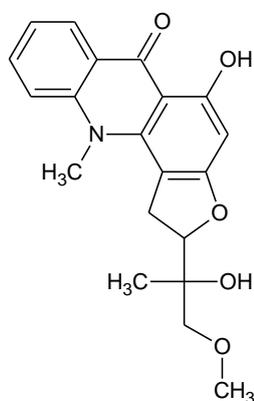
In this study, 6 different compounds (a-f) were isolated and checked for the activity.



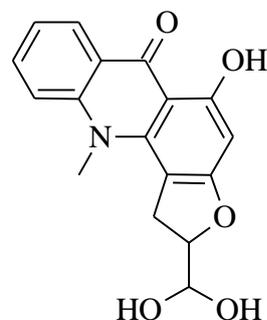
a) Rutacridone



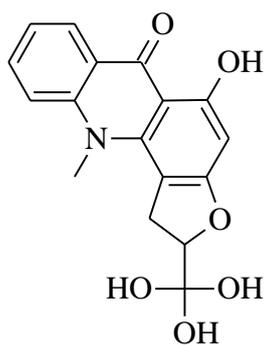
b) Isogravacridone chlorine



c) Gravacridonediol monomethyl ether



d) Gravacridonediol



e) Gravacridonetriol

All the six compounds were tested against the cell lines, in that triple negative cell line was found to be most sensitive cell line. According to the results obtained it was seen that compound (b) showed more potent anti-proliferative activity compared to positive control. Especially for the triple negative

cell line (MDA-MB-31) the compounds showed their efficiency in the sequence of $b > c > d > a$ but compound e and f did not show their anti-proliferative activity¹⁶.

Resistance of human cancer cells

Multidrug resistance is one of the major drawback which cause the failure in treatment of cancer. In case of Multidrug resistance tumour cells tend to survive even after exposure to chemotherapy¹⁷. The major cause of MDR is P-glycoprotein due to its efflux ability but still many compounds are able to overcome multiple drug resistance such as antibiotics, calcium channel blockers and immunosuppressant's¹⁸.

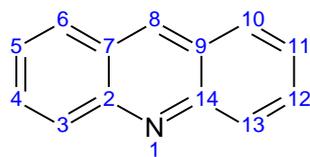
Different pathways are involved in the resistance by P-gp

- MAPK (Mitogen activated protein kinase) – Mostly identified as a stress kinase pathway where three consecutive kinase are involved in the pathway¹⁹.
- JNK (c-jun NH₂ terminal kinase) – It is basically a member of MAPK family. It shows its action by binding and phosphorylating the NH₂ terminal of the transcription factor²⁰. There is an evidence to prove that JNK pathway causes the specific changes in MDR phenotype development²¹⁻²³. It was found that JNK pathway may also be involved in the regulation of p-gp which cause resistance for the tumour cells²⁴.

These pathways have the ability to cause induction of P-gp and overexpression of ABCB1, leads to resistance of cancer cells.

ACRIDONE SCAFFOLD

Acridone scaffold is very important to know the physicochemical properties which will be helpful for the chemotherapy²⁵ as there is a relationship between acridone scaffold and DNA. Acridone is basically three fused aromatic rings which consist of nitrogen at 10th position. The size of the ring should be able to intercalate with the DNA base pairs for the biological activity²⁶. The length and flat shape of the three fused aromatic rings overlaps the DNA base pairs and aromatic rings have major role in π -stacking interactions²⁷. Interactions with DNA base pairs causes changes in the cell process and leads to the cell death²⁸⁻²⁹. The biological properties can be varied by changing the position and nature of the side chain attached to the heterocyclic core.



Acridone nucleus

DNA targets: Telomerase and topoisomerase

Telomerase

Telomere, a DNA-protein complex is the end part of chromosomes in eukaryotes and protects the genome from degradation^{30,31}. Acridone and its analogues plays a major role in the inhibition of telomerase activity for the inhibition of cancer cells.

Trisubstituted Acridones – Acridones with trisubstitution shows a potent activity against telomerase inhibition. It is proven by patent from intellectual property protection by cancer research technology that tri-substituted Acridones causes apoptosis and leads to inhibition of cell proliferation^{32,33}.

Pyridoacridones

Telomerase activity can be inhibited by pyridoacridones and it was proven by Stevens group that pentacyclic acridinium salts showed the potent action against telomerase overexpression which shows impact on cell proliferation³⁴⁻³⁷. The test was performed by cancer research ventures ltd where among 15 compounds, 3,6,8,11,13-pentamethyl-8 H -quino [4,3,2- kl] acridinium methosulfate (RHPS3) and 3,11-difluoro-6,8,13-trimethyl8 H -quino [4,3,2- kl] acridinium methosulfate (RHPS4) showed good activity³⁸.

Dibenzophenanthroline

Dibenzophenanthroline and its pentacyclic derivatives were developed and tested for its biological activity. It was proven that it showed G4 stabilising property³⁸⁻⁴⁰. The test was performed by TRAP assay, it showed IC₅₀ value of 28 nM. As a result, dibenzophenanthroline was proven as best telomere inhibitor⁴¹.

Topoisomerase

Topoisomerase are enzymes involved in the supercoiling of DNA. The enzymatic activity of topoisomerase enzymes helps in the conversion of negatively supercoiled DNA to a relaxed form^[42]. The action of topoisomerase involves three steps 1) Cleavage of DNA then forms enzyme-DNA intermediate 2) relaxation of DNA 3) Phosphodiester bond is re-ligated with DNA to repair DNA integrity. So compounds used to treat cancer mainly used to target enzyme-DNA intermediate cause DNA fragmentation in cancer cells^{43,44}. So the derivatives of acridone are designed and synthesised for the inhibition of telomerase and topoisomerase.

CONCLUSION

This article provides information about acridone, its occurrence, chemical constituents, synthesis procedure, mechanism and its biological activity. Acridone occurrence and its chemical constituents helps in the extraction and further biological studies. Analogues of acridone can be obtained by the synthesis procedure. Acridone mechanism of action helps to know the site of action.

It is concluded that acridone play an important role in the treatment of many diseases. Acridone acts as Anti-viral, Anti-microbial, Anti-herpes, Anti-bacterial, Anti-Alzheimer's disease and Anti-proliferative. More attention of acridone is seen on anti-cancer activity. Acridone due its Herringbonepacking arrangement and its substituents, it has the ability to inhibit the proliferation. The design of acridone derivatives can be done by changing the substituents in heterocyclic ring. The action of acridone on cancerous cells helps to know the root cause and mechanism of the cancer. The information obtained regarding the structure activity relationship of acridone provide important idea for the synthesis of new anti-cancer a

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