

## SYNTHESIS AND DNA-BINDING STUDIES OF NOVEL 2-NITRO ACRIDONES AS ANTI-CANCER AGENTS

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### ABSTRACT

A series of novel N<sup>10</sup>-substituted 2-nitro acridones were synthesized as potent anti-tumor agents. DNA-binding studies of these compounds were carried out by UV spectroscopy using Calf thymus DNA (CT DNA) based on their affinity or intercalation with CT-DNA measured with absorption titration. The binding constants were determined at the range of  $K=0.49-1.92 \times 10^4 \text{ M}^{-1}$  and the percentage of hypochromicity was calculated using absorption values ranges from 30-71.26%. The compound **7** bearing nitro group with planar tricyclic ring linked to butyl morpholine side chain showed highest binding affinity with binding constant  $1.92 \times 10^4 \text{ M}^{-1}$  and with lipophilicity value of 3.30-3.74. The compound **6** showed high lipophilicity value. The examination of the relationship between lipophilicity and binding ability of the acridones showed poor correlation.

**Keywords:** 2-Nitroacridone, DNA-binding, Calf-Thymus DNA, UV spectroscopy and Lipophilicity.

### INTRODUCTION

The attractive target for the design of new anti-tumor agents was DNA. There is a considerable interest taken in the development of new drugs with low molecular weight to bind with DNA towards their application in cancer treatment<sup>1</sup>. Understanding of the structural and thermodynamic aspects of the interactions between the drug and the DNA helps in designing the potential anti-cancer agents. It has been found that many cytostatic drugs interacts with DNA by different ways a) Intercalation or through minor groove binding b) Cross linking or combination of these modalities.<sup>2</sup>

A drug molecule is acting against cancer means it has the ability to reach target site and specific to cancer cell, capable of binding to multiple targets might be beneficial and may also prevent in acquiring drug resistance.<sup>7,10</sup>

Several structural classes of compounds were discovered against tumour involves alkylating agents, anti-metabolites, microtubule damaging agents, topoisomerase-2 inhibitors, topoisomerase-1 inhibitors, antibiotics, anthracenediones, hormones and miscellaneous drugs. Planar molecules with tricyclic structures were reported to possess

significant cytotoxic and cytostatic potencies, mainly by DNA interaction. In the year 1960s, Lerman by conducting a number of physical studies concluded that large number planar aromatic polycyclic molecules binds to the DNA by the process of intercalation<sup>1</sup>. It may include Anthraquinones, acridines and Xanthenes.

The first broad spectrum natural anti-cancer agent which was discovered by random screening was doxorubicin despite of its several cardiotoxicity. The first DNA-intercalating agent widely used as an anti-cancer agent was Actinomycin-D, which entered clinical use in 1960's.

There are numerous biologically active fused heterocyclic rings. Among these acridones are the interesting heterocyclic compounds to medicinal chemist as they exhibits a wide range biological activity. The acridone alkaloid Acronine also known as Acronine was first isolated from the bark of Australian tree *Acronychia baurri* in 1948 and found that it showed potent activity against cancer.

Acridone is a versatile heterocyclic structure having a unique chemical properties like planar structure which exists in both protonated and unprotonated forms. It has the

ability to intercalate with DNA and also as a substrate to p-glycoprotein which was one of the essential target for multidrug resistance in cancer. The ideal and unique properties of acridones has drawn the attention of medicinal chemists and few of acridone derivatives are under clinical trials.<sup>13</sup>

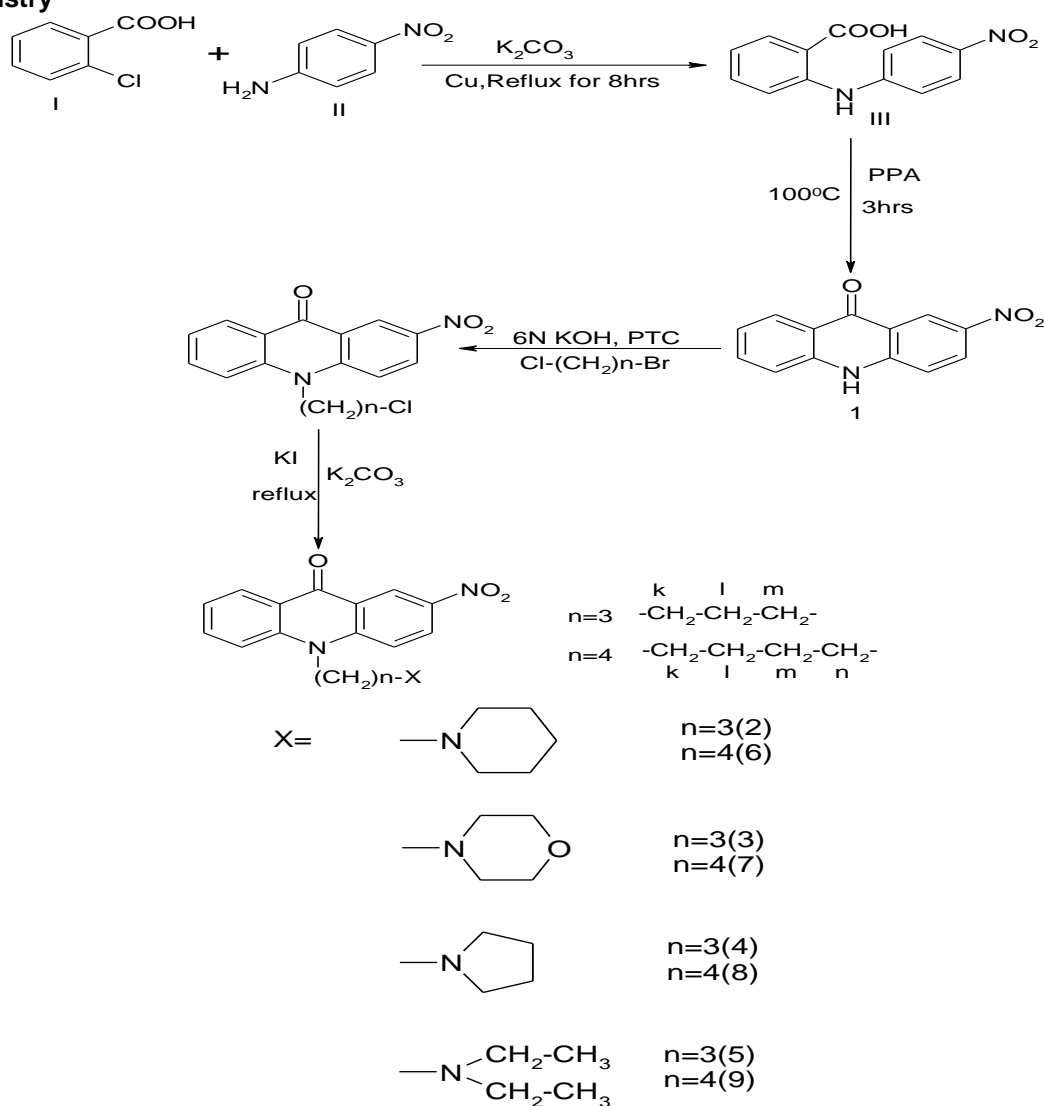
Literature survey revealed that sathish NK et al. synthesized 1,3-dimethyl acridones<sup>14</sup> and 1,3-diacetoxy acridones<sup>16</sup>, and their DNA-binding studies were carried out by absorption titration using CT-DNA. The compounds with acetoxy groups showed good binding properties compared to methyl groups. In 2008 Jinghua Chen et al. carried out the synthesis and DNA binding studies of 2-nitro acridone (NAD) using salmon sperm DNA by electrochemical method. The compound NAD showed good binding property with DNA. This showed that electron withdrawing groups

attached to acridone nucleus helps in improving binding ability of acridones towards DNA.

Keeping these importance of acridones scaffolds, an effective anticancer which is specific to cancer cell, capable of binding multiple targets and devoid of acquiring drug resistance needs to be synthesized. However, the literature survey revealed that various acridones are reported to possess anticancer and anti-MDR activities, it was believed that the anticancer activity is due to their DNA intercalation property.<sup>16</sup> DNA binding studies helps to determine the binding ability of different derivatives towards DNA. Higher the binding ability more will be the cytotoxicity of drug. In the present study an attempt was made to design and synthesize newer series of N<sup>10</sup>-substituted acridones for their DNA-binding properties and Lipophilicity.

## MATERIALS AND METHODS

### Chemistry



Scheme. 1:

**Scheme 1**

2-Nitroacridone(1) and its derivatives **2-9** were synthesized by the **scheme-1**, parent 2-nitroacridone (1) was synthesized by the Ullmann condensation reaction of o-chloro benzoic acid and 4-nitro aniline to 4'-nitrodiphenylamine-2-carboxylic acid (III). The 4'-nitrodiphenylamine-2-carboxylic acid (III) was cyclized with polyphosphoric acid instead of sulfuric acid on water bath at 100° C to get only single product of 2-nitroacridone (1) with better yield (95%) was obtained.

*N*-alkylation of the 2-nitroacridone was achieved by using Phase transfer catalyst (PTC) because nitrogen atom of the acridone nucleus is generally resistant to undergo *N*-alkylation with alkyl halides due to their weakly basic in nature. Stirring of 2-nitroacridone (1) at room temperature with alkylating agents 1-bromo-3-chloro propane or 1-bromo-4-chloro butane in a two phase system consisting of an organic solvent (tetrahydrofuran) and 6N aqueous potassium hydroxide solution in the presence of tetra butyl ammonium bromide (PTC) to synthesize the compounds 10-(3'-chloropropyl)-2-nitroacridone and 10-(4'-chlorobutyl)-2-nitroacridone respectively in good yields. Here, catalyst (PTC) transports the OH<sup>-</sup> ion from the aqueous phase to organic phase where actual reaction takes place. The ion formed may be regarded as phenolate stabilized anion, which subsequently undergoes alkylation to form the aromatized system.

Iodide catalyzed nucleophilic substitution reaction of the *N*<sup>10</sup>-chloropropyl or *N*<sup>10</sup>-chlorobutyl 2-nitroacridone is carried out with various secondary amines (piperidine, morpholine, pyrrolidine, diethyl amine) by refluxing for different time intervals in the presence of anhydrous potassium carbonate in acetonitrile gave the free bases **2-5** and **6-9**.

All the molecules were separated and purified by recrystallization method and dried under high vacuum for more than 12 h. The purified compounds were characterized by <sup>1</sup>H-NMR and mass spectral methods. The assignment of protons is fully supported by the integration curves and all the derivatives showed the characteristic chemical shifts for the acridone nucleus.

**Experimental Section**

Reactions were monitored by TLC. Melting points were recorded using thiele's tube apparatus. <sup>1</sup>H-NMR were recorded in DMSO and D<sub>2</sub>O in a 5-mm tube on a Bruker drx 500 Fourier transform spectrometer with tetramethylsilane as internal standard.

Chemical shifts are expressed as  $\delta$  (ppm) values. The spectrometer were internally locked to deuterium frequency of the solvent. To obtain the molecular weight information, acridone derivatives were analysed by LC-MS spectrometry. DNA-binding studies of the synthesized compounds were performed by UV Spectrophotometer.

**Synthesis of 4'-nitro diphenylamine-2-carboxylic Acid****Ullmann Condensation**

To a mixture of o-chlorobenzoic acid (5 g, 0.032 mol), 4-nitroaniline (4.416g, 0.032 mol) and copper powder (0.2 g) in 30 ml isoamylalcohol, anhydrous potassium carbonate (5 g) was slowly added and the contents were allowed to reflux for 8 h on an oil bath. The isoamylalcohol was removed by steam distillation and the mixture poured into 1lit of hot water and acidified with concentrated hydrochloric acid. Precipitate formed was filtered, washed with hot water and collected. The crude acid was dissolved in aqueous sodium hydroxide solution, boiled in the presence of activated charcoal and filtered. On acidification of the filtrate with concentrated hydrochloric acid, precipitate was obtained which was washed with hot water and recrystallized from methanol to give a yellow solid (yield 85%), m.p. 180-185° C.

**Synthesis of 2-nitroacridone (1)**

Five grams of 4'-nitrodiphenylamine-2-carboxylic acid was taken in a flask to which was added 50 g of polyphosphoric acid. Shaken well and heated on a water bath at 100 °C for 4 h. Appearance of yellow color indicated the completion of the reaction. Then, it was poured into 1lit of hot water and made alkaline by liquor ammonia and the yellow precipitate formed was filtered, washed with hot water and collected. The sample of 2-nitro 9(10-H) acridone (1) was recrystallized from acetic acid (yield 95%). M.p. above 300° C

**2-nitroacridone (1)**

Yield:60%, M.p. Above 300°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.37-8.9 (m, 7H, Ar-H), 12.4 (s, 1H, cyclic NH); MS m/z: 241.029(M<sup>+</sup>).

**Synthesis of N<sup>10</sup>-alkylated Acridones via Phase Transfer Catalysis****General method for the Synthesis of 10-(Chloroalkyl)-2-nitroacridone**

One gram (0.0042 mol) of 2-nitroacridone(1) was dissolved in 25 mL tetrahydrofuran and 17.5ml of 6N potassium hydroxide and 0.43 g (0.0013 mol) of tetrabutylammonium bromide

was added to it. The reaction mixture was stirred at room temperature for 30 min and added 1-bromo-3-chloropropane (0.013 mol)/1-bromo-4-chlorobutane (0.013 mol) slowly into the reaction mixture and stirred for 24 h at room temperature. Tetrahydrofuran was evaporated and the aqueous layer was extracted with chloroform. The chloroform layer was washed with water and organic layer dried over anhydrous sodium sulfate and rotavaporated. The crude product was purified by column chromatography by using the solvent system chloroform/ acetone (8:1) to give a yellow solid of 10-(chloroalkyl)-2-nitroacridone (yield 50%).

#### 10-(3'-chloropropyl)-2-nitroacridone

Yield: 52%, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=7.4-8.6 (m, 7H, Ar-H), 2.1(m, 2H, H<sub>i</sub>), 3.8(t, 2H, H<sub>k</sub>), 3.4(t, 2H, H<sub>m</sub>); MS m/z: 317.7(M<sup>+</sup>).

#### 10-(4'-chlorobutyl)-2-nitroacridone

Yield: 50%, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=7.2-8.7(m, 7H, Ar-H), 2.1(m, 2H, H<sub>i</sub>), 3.52(t, 2H, H<sub>k</sub>), 4.11(t, 2H, H<sub>n</sub>), 1.5-2.26 (m, 4H, H<sub>l</sub> and H<sub>m</sub>)

#### General method for the synthesis of derivatives.(2-9)

10-(chloroalkyl)-2-nitroacridone 0.005 mol was dissolved in 60 ml of anhydrous acetonitrile and 1.68g potassium iodide and 3.3 g of potassium carbonate were added and refluxed for 30 min. Added 0.009mol of different secondary amines into it slowly and refluxed for 15 h until a substantial amount of the product was formed as evidenced by TLC. The contents were cooled, diluted with water and extracted with chloroform. The chloroform layer was washed with water thrice, dried over anhydrous sodium sulfate and evaporated to give product. An acetone solution of the free base was treated with ethereal hydrochloride to give the hydrochloride salt, which was dried over high vacuum to get pure solid.

#### 10-[3<sup>1</sup>-N-piperidino propyl]-2-nitroacridone (2)

Yield: 50%, M.p. 260<sup>0</sup>C. <sup>1</sup>H NMR (DMSO) δ=7-8.2(m, 7H, Ar-H), 3.2-4.2(m, 8H, H<sub>a</sub>, H<sub>b</sub>, H<sub>k</sub>, H<sub>m</sub>), 1.4-2.8(m, 8H, H<sub>l</sub>, H<sub>c</sub>, H<sub>d</sub>, H<sub>e</sub>); MS m/z: 366.05 (M<sup>+</sup>)

#### 10-[3<sup>1</sup>-N-morpholino propyl]-2-nitroacridone (3)

Yield: 45%, 200<sup>0</sup>C. <sup>1</sup>H NMR(DMSO) δ=7.4-9(m, 7H, Ar-H), 3.3-4.5(m, 8H, H<sub>a</sub>, H<sub>b</sub>, H<sub>k</sub>, H<sub>m</sub>), 3.6(d, 4H, H<sub>c</sub>, H<sub>d</sub>), 2.5(m, 2H, H<sub>l</sub>); MS m/z: 368.1 (M<sup>+</sup>)

#### 10-[3<sup>1</sup>-N-pyrrolidino amino propyl]-2-nitroacridone (4)

Yield: 40%, <sup>1</sup>H NMR(DMSO) δ=7.2-8.5(m, 7H, Ar-H), 3.3-4.7(m, 8H, H<sub>k</sub>, H<sub>m</sub>, H<sub>a</sub>, H<sub>b</sub>), 3.2(d, 4H, H<sub>c</sub>, H<sub>d</sub>), 1.7(M, H<sub>l</sub>); MS m/z: 352.3 (M<sup>+</sup>)

#### 10-[3<sup>1</sup>-N-diethyl amino propyl]-2-nitroacridone (5)

Yield: 40%, <sup>1</sup>H NMR(DMSO) δ=6.8-8(m, 7H, Ar-H), 3-4.5(m, 8H, H<sub>k</sub>, H<sub>m</sub>, H<sub>a</sub>, H<sub>b</sub>), 2.2(t, 2H, H<sub>c</sub>, H<sub>d</sub>), 1.8(M, H<sub>l</sub>); MS m/z: 354.12 (M<sup>+</sup>)

#### 10-(4<sup>1</sup>-N-Piperidinobutyl)-2-nitroacridone (6)

Yield: 50%, M.p. 250<sup>0</sup>C. <sup>1</sup>H NMR (DMSO) δ=7.2-8.5(m, 7H, Ar-H), 3.2-4(m, 10H, H<sub>a</sub>, H<sub>b</sub>, H<sub>c</sub>, H<sub>d</sub>, H<sub>k</sub>, H<sub>n</sub>), 1.8-2.8(m, 4H, H<sub>l</sub>, H<sub>m</sub>), 3.4(m, H<sub>e</sub>); MS m/z: 380.17 (M<sup>+</sup>)

#### 10-[4<sup>1</sup>-N-morpholino butyl]-2-nitroacridone (7)

Yield: 40%, 195<sup>0</sup>C. <sup>1</sup>H NMR(DMSO) δ=6.4-8.6(m, 7H, Ar-H), 3.3-4.5(m, 8H, H<sub>a</sub>, H<sub>b</sub>, H<sub>k</sub>, H<sub>n</sub>), 3.6(t, 4H, H<sub>c</sub>, H<sub>d</sub>), 1.5-2.8(m, 4H, H<sub>l</sub>, H<sub>m</sub>); MS m/z: 382.15 (M<sup>+</sup>)

#### 10-(4<sup>1</sup>-N-Pyrrolidinobutyl)-2-nitroacridone (8)

Yield: 40%, M.p. 160<sup>0</sup>C, <sup>1</sup>H NMR(DMSO) δ=7.2-8.5(m, 7H, Ar-H), 3-4.6(dm, 8H, H<sub>a</sub>, H<sub>b</sub>, H<sub>k</sub>, H<sub>n</sub>), 1.5-2.8(m, 8H, H<sub>c</sub>, H<sub>d</sub>, H<sub>l</sub>, H<sub>m</sub>); MS m/z: 366.16 (M<sup>+</sup>)

#### 10-[3-(N-Diethylaminobutyl)]-2-methylacridone (9)

Yield: 40%, <sup>1</sup>H NMR(DMSO) δ=7-8.2(m, 7H, Ar-H), 4.5(t, 2H, H<sub>k</sub>), 3.2(m, 6H, H<sub>a</sub>, H<sub>b</sub>, H<sub>n</sub>), 1.9(m, 4H, H<sub>l</sub>, H<sub>m</sub>); MS m/z: 368.14 (M<sup>+</sup>)

## RESULTS AND DISCUSSIONS

### BIOLOGICAL ACTIVITY

#### Lipophilicity

The compounds lipophilicity was determined using the software ALOGPS. The efficacy of a cytotoxic drug will depend in part on its ability to accumulate in cells. The efficiency of cytotoxicity mainly concentrates on accumulation of drugs within the cells. This helps in predicting the potency of drug. The acridone derivatives are weak bases and able to exist in both charged (protonated) and uncharged (unprotonated) forms. The lipophilicity data varying from 2.92-4.62, expressed in log<sub>10</sub> P, are given in Table 1. In order to elucidate the role played by the -NO<sub>2</sub> group at position C-2 of the acridone ring, the lipophilicity data of 1-9. Substitution of hydrogen by nitro group in position C-2 of the acridone ring and alkyl side chain with different secondary amino group resulted in a slight enhancement in the log<sub>10</sub> P values.

Additionally, it is speculated that the acridone nucleus with nitro group at position C-2 may exhibit higher affinity for membranes or are more readily taken up into the cells than that with hydrogen atoms. Compound **6** with  $\log_{10}P$  (4.06-4.62) showed maximum binding of DNA. Therefore the degree of lipophilicity of each drug would seem to be important, but it is not the sole determinant for cytotoxicity of acridone derivatives.

#### DNA-binding properties

The DNA-binding properties of the compounds 2-9 were studied by monitoring the changes in the UV-Visible absorption spectra of the acridone derivatives upon addition of CT-DNA. In the range from 200-300 all acridone derivatives exhibited strong absorption peaks. Progressive addition of DNA led to strong hypochromism in the absorption intensities in all the compounds studied. The percentage hypochromism were found to be 58.46, 52.66, 30, 36.5, 43.84, 34.33 and 71.26. The **Fig.1** shows the representative absorption spectrum of the compound **7** (15 $\mu$ M) in presence of increasing concentration of CT-DNA (0-100 $\mu$ M). The **Fig.2** shows Half-reciprocal plot for binding of **7** with CT DNA. The compound exhibited the similar absorption spectra pertaining to the chromophore but with the hypochromicity and isobastic point depending on the alkyl amino side chains. These results were consistent with the previous reports on the absorption titration of acridone derivatives and the hypochromicity of acridones in the presence of DNA is believed to be a result of their intercalation with the DNA.

The selection of ionic strength (150mM NaCl) in the absorption titration experiment was mainly based on the avoidance of DNA deposition in all drug solution (15 $\mu$ M). The **Table.2** summarizes the DNA-binding constants and related properties of acridones after intercalation with CT-DNA. The relative binding affinities as indicated by the binding

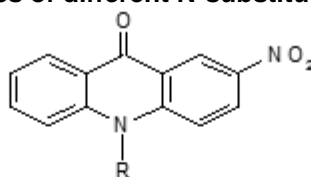
constant  $K_i$  were in the order of **7>8>6>5>3>9>2>4**. Among the derivatives synthesized compound **7** and **8** showed strong DNA-binding affinity. However, a highest binding affinity and cytotoxic activity were observed for compound **7** bearing planar tricyclic ring with electron withdrawing nitro groups, linked with butyl morpholine side chain. There is a considerable shift in the absorption wavelength was observed when drug binds with DNA




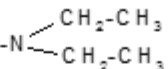



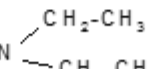
#### CONCLUSION

The new acridone analogues derived from acridone containing secondary amino group at the terminal end of alkyl chain have been showed their strong DNA binding ability through intercalation using CT DNA. In particular the effect is more pronounced with butyl side chain compare to propane chain. Comparison of the derivatives for their ability to bind with DNA revealed that they largely follow the order N<sup>10</sup>-butyl side chain more than N<sup>10</sup>-propyl side chain. The substitution of hydrogen by NO<sub>2</sub> increased their ability to bind to DNA. Careful examination of the results revealed that the nitro butyl derivatives have higher activity than nitro propyl derivatives. With respect to these observations, we concluded that this series could be developed as a promising cytotoxic agents as DNA intercalators

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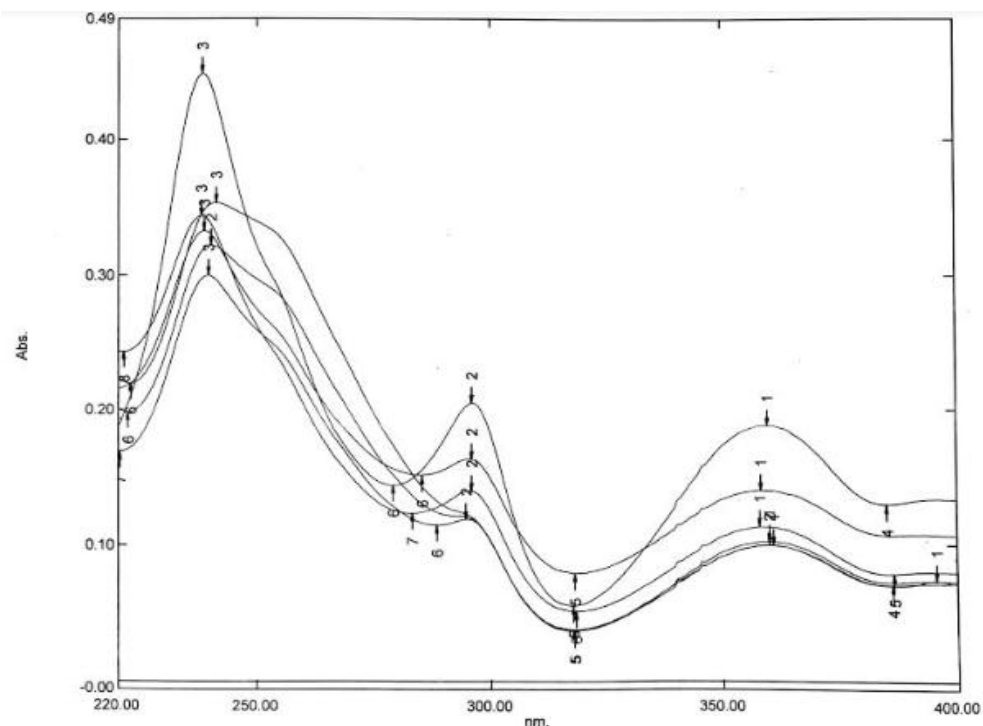
**Table 1: Lipophilicity values of different N-substituted Acridone Derivatives**

Compound NO.	R	Log <sub>10</sub> P
1	-H	3.31-3.67
2	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	4.20-4.24
3	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	2.92-3.51
4	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	3.80-3.85
5	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	3.91-4.01
6	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	4.06-4.62
7	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	3.30-3.74
8	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	4.20-4.24
9	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -N 	4.28-4.36

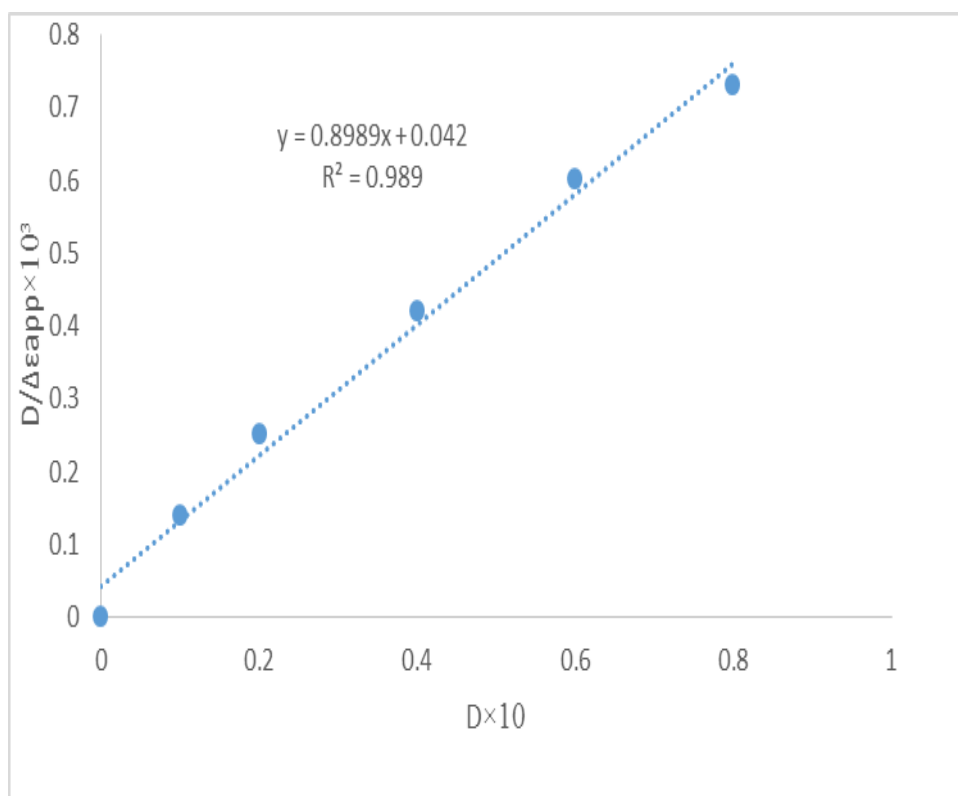
Lipophilicity was determined using the ALOGPs Software

**Table 2: Binding constant (K<sub>i</sub>) and photometric properties of acridones in contact with CT-DNA**

Compound	K <sub>i</sub> (×10×M <sup>-1</sup> )	λ <sub>max</sub> (nm)	shift in λ <sub>max</sub>	Hypochromicity (%)
2	0.592	238	239	58.46
3	1.17	238	240	52.66
4	0.49	201	-	30
5	1.178	234	237	64.28
6	1.35	238	240.20	43.84
7	1.92	238	241.20	34.33
8	1.5	238	239.20	64.4
9	0.646	274	-	71.26



**Fig. 1: Absorption titration of 7 at 15  $\mu$ m in 20mM sodium phosphate buffer (PH 6.5) with 150mM NaCl at Increasing CT DNA concentration**



**Fig. 2: Half-reciprocal plot for binding of 7 with CT DNA**

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