



## Tropical Journal of Pharmaceutical and Life Sciences

(An International Peer Reviewed Journal)

Journal homepage: <http://informativejournals.com/journal/index.php/tjpls>



# Synthesis, Characterization and Anticancer Study of Acridine Derivatives

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### ARTICLE INFO:

**Received:** 16<sup>th</sup> August 2023; **Received in revised form:** 2<sup>nd</sup> Sept. 2023; **Accepted:** 19<sup>th</sup> Sept. 2023; **Available online:** 24<sup>th</sup> Sept. 2023.

### Abstract

Cancer is one of the global problem and a major cause for mortality. many treatment strategies are available for cancer treatment, still there is a scope for novel treatment to avoid serious side effects of existing therapy. Novel DNA binding agents are needed for effective treatment of cancers. In the field of antitumor DNA-intercalating agents, 9-aminoacridines play an important role due to their antiproliferative properties. Several cancer chemotherapeutics such as amsacrine and nitracrine have been developed as anticancer agents. In present study, a series of new acridine-based derivatives numbered 3a–3j were synthesized and their anticancer activity against A549 (Human, small cell Lung Carcinoma) cell line was evaluated by MTT Assay. Out of the screened compounds, compound 3b exhibited potent anticancer activity with IC<sub>50</sub> 78.04 µg/ml for lung cancer cell (A-549) line. Further in vivo study of newly synthesized acridine derivative can explore a ray of light in the field of anticancer drugs.

**Keywords:** Acridine, MTT assay, Anticancer activity, Anticancer drugs.

### Introduction

Cancer is one of the most common malignant diseases obsessing mankind and new effective drugs are needed [1–6]. DNA topoisomerase, either in prokaryotes or eukaryotes, plays a very important role in cell proliferation, survival and apoptosis, which has been one of the most potential targets for the development of new anticancer agents [7–9]. Acridine analogs have been used for treatment of inflammation and cancer for many years. The unique planar ring structure makes its strong interaction with DNA base pairs [10,11]. A variety of acridine derivatives have been designed and synthesized, some of which have entered clinical studies, such as DACA [12–14], C-1305 [15] and m-AMSA, etc. (Fig. 1) [16]. Among them, m-AMSA was the first used in clinical treatment for several cancers as topoisomerase inhibitors and much attention had been paid to the modification of m-AMSA to improve its activity and bioavailability [17]. A variety of analogs of m-AMSA,

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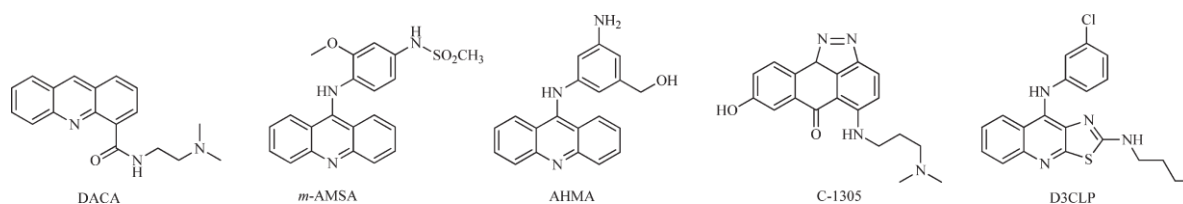
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such as AHMA and D3CLP (Fig. 1), have been developed [18,14]. By far, most of the modification of the m-AMSA was focused on the position and nature of substituents in the 9-aminobenzene moiety and acridine rings. A variety of bis-acridine derivatives have also been developed to increase the DNA binding affinity. However, little attention has been paid to the addition of benzene ring by naphthalene or heterocycles, such as pyridine.



**Figure1:** Acridine derivatives

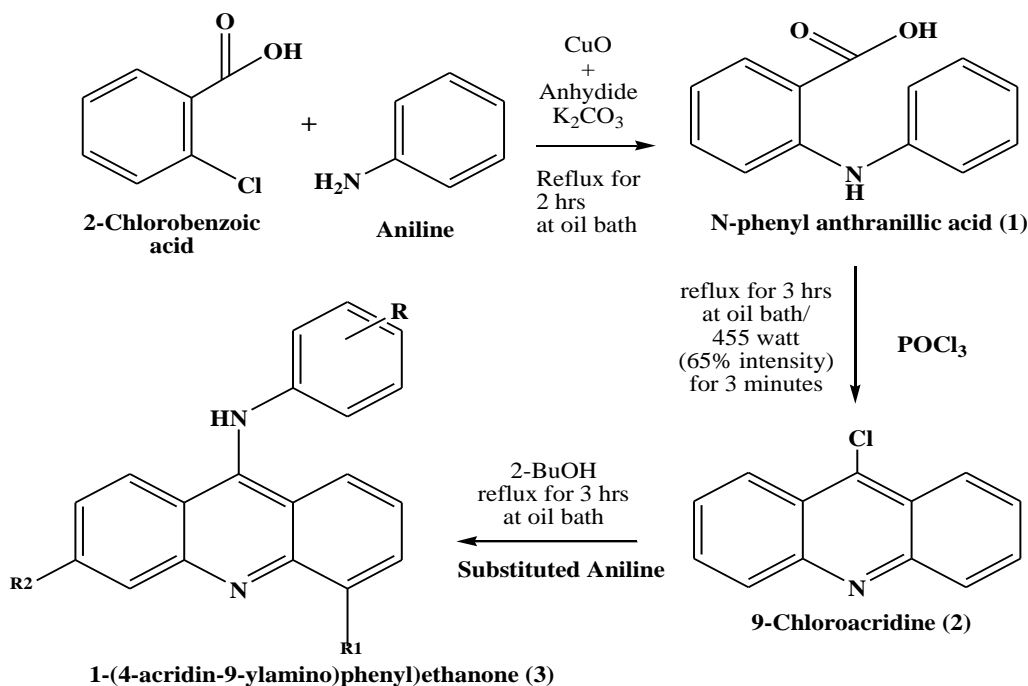
## 2.Experiment

All chemicals used were of reagent grade and purified as per need of the reaction. progress of the reaction was monitored by TLC using chloroform: methanol (10:1) system. 3-(4,5-Dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), Phosphate Buffered Saline (PBS), EDTA, Glucose and antibiotics from Hi-Media Laboratories Ltd., Mumbai. Dimethyl Sulfoxide (DMSO) from E. Merck Ltd., Mumbai, A549 cell (Human Lung Carcinoma Cell line) from National Centre for Cell Sciences (NCCS), Pune.

### 2.1 Characterization

Melting points were recorded in open capillaries. <sup>1</sup>H-NMR and spectra recorded in a Bruker 300 MHz spectrometer and Varian AS 400 (400MHz) in CDCl<sub>3</sub> with TMS as the internal standard. IR spectra were recorded in Perkin Elmer FT-IR 1600 spectrometer using KBr pallets. High resolution mass spectra were recorded on a Micromass QTOF ESI-MS instrument (model HAB273).

**2.2 General procedure:** The general procedure for synthesis of acridine derivatives shown in fig.no.02.



Where R = -NH-SO<sub>2</sub>-CH<sub>3</sub>, OMe  
 R<sub>1</sub> = -CO-NH<sub>2</sub>, -O-CH<sub>3</sub>-CH<sub>3</sub>-CH<sub>3</sub>, -NO<sub>2</sub>  
 R<sub>2</sub> = -Cl, -CH<sub>3</sub>, -NH-CH<sub>3</sub>

**Figure 2:** General procedure for acridine derivatives

### 2.1.1. Synthesis of N-phenyl anthranilic acid

In a 100 ml. flask equipped with air condenser, placed a mixture of substituted o-chlorobenzoic acid (1 mmol), substituted aniline (1 mmol), 4.1 g. of anhydrous potassium carbonate and 0.1 g of cupric oxide. Reflux the mixture in an oil bath for 1 hour. Allow to cool. Then added 2.0 g. of decolorizing carbon to the brown residual solution. Boil the mixture for 10 minutes, and filter at the vacuum pump. the filtrate was added with stirring to a mixture of 3.0 ml. of concentrated hydrochloric acid and 6 ml. of water, and allow to cool. Filter the product under suction, and dried to constant weight upon filter paper in the air.

### 2.1.2. Synthesis of 9-chloroacridine derivatives

A mixture of N-phenyl anthranilic acid (1 mmol) and 5 ml conc. Phosphorous oxychloride was heated in a 100 ml round bottom flask for 3 hours on a water bath. The reaction mixture was cooled and poured into cold water with vigorous shaking. The yellow precipitate of derivatives was filtered, warmed with 2% sodium carbonate solution to remove any unchanged N-phenylanthranilic acid and again filtered.

### 2.1.3. Synthesis of 9-substituted acridine derivatives

9-chloroacridine (1 mmol) and substituted aniline (1 mmol) was taken in 2-butanol solvent reflux in oil bath for 3 hrs. reaction progress was monitored by thin layer chromatography. After the completion of reaction, the mixture was cooled to room temperature. solvent was removed by suction pump and crude product was obtained which is further recrystallized from ethanol.

### 2.1.4. Spectral analysis of synthesized derivatives

Compound *3a*: mp: 229-231°C; IR (KBr),  $\text{cm}^{-1}$ : 3321(N-H),3040 (C-HAr),1612 (C=N),1568 (C=C),1267(C-N),1581(C-C),1170 (C-O),1660 (C=O),3350 (N-H),910 (S-N),1150 (S-O), 2945(C-H Ali).

$^1\text{H NMR}$  (500 MHz, Chloroform)  $\delta$  8.23 (dd,  $J = 7.4, 1.5$  Hz, 1H), 7.98 (dd,  $J = 7.5, 1.4$  Hz, 1H), 7.43 (t,  $J = 7.5$  Hz, 2H), 7.29 (dd,  $J = 7.5, 1.4$  Hz, 1H), 6.68 (dd,  $J = 5.9, 4.5$  Hz, 2H), 6.29 (d,  $J = 1.4$  Hz, 1H), 6.17 (dd,  $J = 7.5, 1.4$  Hz, 1H), 3.83 (d,  $J = 6.2$  Hz, 6H), 2.87 (s, 3H).

LCMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  for  $\text{C}_{24}\text{H}_{24}\text{N}_4\text{O}_5\text{S}$  found 481.54. Elemental Analysis: C, 59.99; H, 5.03; N, 11.66; O, 16.65; S, 6.67

Compound *3b*: mp: 229-231°C; IR (KBr),  $\text{cm}^{-1}$ :3342(N-H),3030 (C-HAr), 1645 (C=N), 1570 (C=C),1275(C-N), 1585(C-C), 1180 (C-O), 1256(C-O ether), 910 (S-N), 1150 (S-O), 2945(C-H Ali).

$^1\text{H NMR}$  (500 MHz, Chloroform)  $\delta$  8.02 (s, 2H), 7.75 (s, 2H), 7.55 (s, 2H), 7.35 (d,  $J = 4.5$  Hz, 4H), 7.16 (s, 2H), 6.99 (s, 2H), 6.74 (d,  $J = 9.8$  Hz, 4H), 6.20 (s, 2H), 6.05 (s, 2H), 4.18 (s, 2H), 4.01 – 3.97 (m, 4H), 3.86 – 3.82 (m, 6H), 3.06 – 3.02 (m, 6H), 1.89 – 1.85 (m, 3H), 1.02 – 0.98 (m, 6H).

LCMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  for  $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_4\text{S}$  found 452.24. Elemental Analysis: C, 63.84; H, 5.58; N, 9.31; O, 14.17; S, 7.10.

Compound *3c*: mp: 229-231°C; IR (KBr),  $\text{cm}^{-1}$ :3335(N-H),3025 (C-HAr), 1625 (C=N), 1570 (C=C),1275(C-N), 1585(C-C), 1175 (C-O), 553 (C-Cl), 910 (S-N), 1150 (S-O), 2945(C-H Ali).

$^1\text{H NMR}$  (500 MHz, Chloroform)  $\delta$  7.92 (s, 1H), 7.76 (s, 1H), 7.40 (s, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 6.74 (d,  $J = 6.3$  Hz, 2H), 6.18 (s, 1H), 6.05 (s, 1H), 4.46 (s, 1H), 3.93 – 3.89 (m, 3H), 3.86 – 3.82 (m, 3H), 3.04 – 3.00 (m, 3H).

LCMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  for  $\text{C}_{22}\text{H}_{20}\text{ClN}_3\text{O}_4\text{S}$  found 459.0. Elemental Analysis: C, 57.70; H, 4.40; Cl, 7.74; N, 9.18; O, 13.98; S, 7.00

Compound *3d*: mp: 229-231°C; IR (KBr),  $\text{cm}^{-1}$ :3325(N-H),3045 (C-HAr), 1615 (C=N), 1575 (C=C),1270(C-N), 1590(C-C), 1180 (C-O), 1665(C=O), 3355 (N-H), 920 (S-N), 1145 (S-O), 2960(C-H Ali).

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  8.24 (s, 1H), 7.98 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 7.33 (s, 1H), 6.68 (s, 1H), 6.29 (s, 1H), 6.18 (d, J = 4.6 Hz, 2H), 3.84 – 3.80 (m, 3H), 3.06 – 3.02 (m, 3H), 2.90 – 2.86 (m, 3H), 2.51 – 2.47 (m, 3H).

LCMS (ESI): m/z [M+H]<sup>+</sup> for C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>S found 464.54. Elemental Analysis: C, 62.05; H, 5.21; N, 12.06; O, 13.78; S, 6.90.

Compound 3e: mp: 229-231°C; IR (KBr), cm<sup>-1</sup>: 229-231°C; IR (KBr), cm<sup>-1</sup>: 3335(N-H), 3025 (C-HAr), 1625 (C=N), 1570 (C=C), 1275(C-N), 1585(C-C), 1175 (C-O), 553 (C-Cl), 910 (S-N), 1150 (S-O), 2945(C-H Ali

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  7.92 (s, 1H), 7.76 (s, 1H), 7.40 (s, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 6.74 (d, J = 6.3 Hz, 2H), 6.18 (s, 1H), 6.05 (s, 1H), 3.93 – 3.89 (m, 3H), 3.86 – 3.82 (m, 3H), 3.04 – 3.00 (m, 3H).

LCMS (ESI): m/z [M+H]<sup>+</sup> for C<sub>22</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>4</sub>S found 458.93. Elemental Analysis: C, 57.70; H, 4.40; Cl, 7.74; N, 9.18; O, 13.98; S, 7.00

Compound 3f: mp: 229-231°C; IR (KBr), cm<sup>-1</sup>: 3325 (N-H), 3045 (C-HAr), 1620 (C=N), 1570 (C=C), 1265 (C-N), 1585 (C-C), 1178 (C-O), 1665 (C=O), 3345 (N-H), 550 (C-Cl), 915(S-N), 1158 (S-O), 2940 (C-H Ali).

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  7.97 (dd, J = 23.9, 11.8 Hz, 4H), 7.70 (s, 1H), 7.41 (d, J = 2.6 Hz, 2H), 6.75 (s, 1H), 6.22 (s, 1H), 6.07 (s, 1H), 3.86 – 3.82 (m, 3H), 3.06 – 3.02 (m, 3H), 2.90 – 2.86 (m, 3H).

LCMS (ESI): m/z [M+H]<sup>+</sup> for C<sub>23</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S found 485.96. Elemental Analysis: C, 56.96; H, 4.36; Cl, 7.31; N, 11.55; O, 13.20; S, 6.61

Compound 3g: mp: 229-231°C; IR (KBr), cm<sup>-1</sup>: 3325 (N-H), 3045 (C-HAr), 1620 (C=N), 1570 (C=C), 1265 (C-N), 1585 (C-C), 1178 (C-O), 550 (C-Cl), 915(S-N), 1158 (S-O), 2940 (C-H Ali).

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  8.14 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.60 (d, J = 15.1 Hz, 2H), 7.42 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 6.36 (s, 1H), 6.20 (s, 1H), 3.66 – 3.62 (m, 3H), 3.01 – 2.97 (m, 3H).

LCMS (ESI): m/z [M+H]<sup>+</sup> for C<sub>21</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>3</sub>S found 428.40. Elemental Analysis: C, 58.95; H, 4.24; Cl, 8.28; N, 9.82; O, 11.22; S, 7.49

Compound 3h: mp: 229-231°C; IR (KBr), cm<sup>-1</sup>: 3320 (N-H), 3040 (C-HAr), 1625 (C=N), 1560 (C=C), 1270 (C-N), 1580 (C-C), 1175 (C-O), 910(S-N), 1158 (S-O), 2940 (C-H Ali).

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  8.08 – 7.93 (m, 2H), 7.80 – 7.65 (m, 2H), 7.57 – 7.51 (m, 2H), 7.36 – 7.32 (m, 2H), 6.84 (d, J = 4.8 Hz, 2H), 6.23 (s, 1H), 6.06 (s, 1H), 4.04 – 3.92 (m, 2H), 3.06 – 3.02 (m, 3H), 1.34 – 1.30 (m, 3H).

LCMS (ESI): m/z [M+H]<sup>+</sup> for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S found 408.49. Elemental Analysis: C, 64.85; H, 5.19; N, 10.31; O, 11.78; S, 7.87

Compound 3i: mp: 229-231°C; IR (KBr), cm<sup>-1</sup>: 3325 (N-H), 3050 (C-HAr), 1625 (C=N), 1568 (C=C), 1280 (C-N), 1580 (C-C), 1175 (C-O), 910 (S-N), 1150 (S-O), 2945 (C-H Ali).

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  7.65 (s, 1H), 7.30 (t, J = 9.2 Hz, 3H), 7.21 (s, 1H), 6.89 (s, 1H), 6.75 (s, 1H), 6.09 (d, J = 26.9 Hz, 2H), 4.41 (s, 1H), 3.86 – 3.82 (m, 3H), 3.06 – 3.02 (m, 3H), 2.96 – 2.92 (m, 3H), 2.62 – 2.58 (m, 3H)

LCMS (ESI): m/z [M+H]<sup>+</sup> for C<sub>23</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>S found 437.53. Elemental Analysis: C, 63.28; H, 5.54; N, 12.83; O, 11.00; S, 7.34

Compound 3j: mp: 229-231°C; IR (KBr), cm<sup>-1</sup>: 3328 (N-H), 3050 (C-HAr), 1630 (C=N), 1565 (C=C), 1270 (C-N), 1580 (C-C), 1175 (C-O), 1530(N-O), 910 (S-N), 1158 (S-O), 2940 (C-H Ali).

<sup>1</sup>H NMR (500 MHz, Chloroform)  $\delta$  8.21 – 8.04 (m, 3H), 7.89 (s, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 7.41 (s, 1H), 6.77 (s, 1H), 6.29 (s, 1H), 6.12 (s, 1H), 3.86 – 3.82 (m, 3H), 3.01 – 2.97 (m, 3H).

LCMS (ESI):  $m/z$   $[M+H]^+$  for C<sub>21</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>S found 439.46. Elemental Analysis: C, 57.53; H, 4.14; N, 12.78; O, 18.24; S, 7.31

### 3. Cytotoxicity

The majority of drugs used for the treatment of cancer today are cytotoxic drugs that work by interfering in some way with the operation of cell's DNA. 9-aminoacridine based drugs show good anticancer activity e.g. amascrine, nitracrine, DACA etc. Inspired from the anticancer activities of amascrine, we design new 9-aminoacridine derivatives for anticancer evaluation based upon molecular modification. All compounds were selected for an anticancer activity and it was done on cancer cell line A-459 (Human small cell lung carcinoma) by MTT assay. All the evaluated compounds showed activity against A-549 cell line. The highest cell inhibition was recorded was 59.79% for compound 3b at the highest concentration of 100  $\mu$ g/ml. The MTT assay results suggest that the compounds 3a, 3b, 3c and 3d have moderate cell inhibitory activity. Whereas, remaining compounds have comparatively less cell inhibitory activity.

**Table 1:** Percentage Inhibition and IC<sub>50</sub> values of compounds 3a to 3j

Compounds Code	5 $\mu$ g/ml	10 $\mu$ g/ml	25 $\mu$ g/ml	50 $\mu$ g/ml	100 $\mu$ g/ml	IC <sub>50</sub> ( $\mu$ g/ml)
Control	0	0	0	0	0	0
Std.	16.67	28.97	43.60	65.79	78.78	43.20
3a	7.17	13.86	21.51	36.34	57.95	81.70
3b	9.88	14.83	21.41	39.15	59.79	78.04
3c	9.40	16.28	22.58	40.12	56.40	81.48
3d	9.69	18.02	23.35	35.08	50.68	94.05
3e	6.88	17.73	20.06	34.59	45.25	105.66
3f	7.66	14.24	19.09	31.10	44.57	109.87
3g	9.79	13.66	17.25	20.54	37.60	148.61
3h	4.07	11.14	14.34	16.28	31.78	173.56
3i	6.98	11.63	17.15	17.15	26.26	233.23
3j	6.69	11.72	18.31	18.22	22.87	291.72

### 4. Conclusion

New acridine derivatives were prepared and evaluated for their anticancer activity. Various structural modifications were done on acridine ring as well as on aromatic ring attached to 9-position of acridine ring. A series of derivatives was prepared by substituting various electron withdrawing as well as electron releasing groups on acridine ring and the aromatic ring attached to 9-position of acridine ring. The new acridine derivatives are found to possess significant anticancer activity *in vitro*. Structural modifications may lead to synthesize more acridine derivatives and can be evaluated for their anticancer, antimalarial, anti-inflammatory activities *in vitro* as well as *in vivo*.

### Acknowledgment

I am very grateful to Dr. Ashutosh Das, for spectral analysis. I am very grateful to Dr. Amol More, Head & Leading at Biotox Laboratories, Nashik, India for anticancer evaluation. I am also grateful to Dr. Aman Uppanlawar for guidance in selection of cell line for anticancer activity.



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**How to cite this article:** Herole R A, and Rakesh Kumar Jat. "Synthesis, Characterisation and Anticancer Study of Acridine Derivatives". *Tropical Journal of Pharmaceutical and Life Sciences*, vol. 10, no. 5, Sept. 2023, pp. 50-56, <https://informativejournals.com/journal/index.php/tjpls/article/view/146>.

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