V. RESULTS AND DISCUSSION

5.1. Docking studies of synthesized compounds

Some novel 9-anilinoacridine derivatives are designed by molecular docking studies against topo isomerase II (1ZXM) by using Schrödinger software maestro 9.2 version.

Molecular docking studies was employed for the analysis of proposed compounds whose inhibitory activities are unknown, in order to find out the molecular facilities responsible for biological activities. Standard and all derivatives of 9-anilinoacridine were taken for docking study. Docked poses of compounds in the target binding site were visualized using XP visualizer Tools.

Almost all the compounds used for docking showed best fit (Root Mean Square Difference [rmsd] value of 0.30 with topo isomerase II (1ZXM).

Ligand docking was performed using OPLS force field. The receptor grid defined in the receptor grid generation folder was selected for the docking of ligands prepared using Ligprep module. Flexible docking was performed using the Extra Precision (XP) feature of Glide module.

The XP-Glide score of active compounds in the proposed Scheme I and II were summarized and the fitness scores for each ligand in topo II are presented in Table 9a-g. When compared with the Glide score of standard compound containing acridine derivative, ie. Ledacrine (anti cancer agent) and ICRF 193(topo II inhibitor), most of the proposed compounds have good Glide scores.

When compared to the standard acridine derivative ledacrine (Glide score -5.24), which is used as anticancer agent and ICRF 193(Glide score -6.58) which is a potent topo II inhibitor, most of the proposed compounds in the scheme I and II (4-9 series)
showed good inhibition with more binding affinity. The Glide score of the proposed 144 compounds are more than that of standard except the compounds 6q-PATH (-4.87), 6v-PAPr(-4.89), 6w-PABu(-4.73), 9a-OAB(-5.13), 9i-OApn (-4.77), 9l-OAopdm(-4.91).

The compounds 6f-PAoh (Gscore-8.26), 9s-OA3Py (Gscore-8.06), 9r-OA2Py (Gscore-7.67), 8t-TA4Py (Gscore-7.54) showed highest Glide scores. The compound 6f-PAoh (Gscore-8.26) showed highest Glide score due to the more electrostatic force (-5.33). All the compounds showed good Glide score due to the more lipophilic evidence than the std ledacrine (-2.94) as well as ICRF 193(-1.25).

Fig-2 Cluster of compounds 5a-x with Topoisomerase II(1ZXM)

Fig-3 Cluster of compounds 6a-x with Topoisomerase II(1ZXM)
Fig-4 Cluster of compounds 7a-x with Topoisomerase II(1ZXM)

Fig-5 Cluster of compounds 8a-x with Topoisomerase II(1ZXM)
Fig-6 Cluster of compounds 9a-x with Topoisomerase II(1ZXM)

Fig-7 Lipophilic evidence for 9l-OAmpdm
Many of the compounds have good hydrogen bonding with various amino acids of topoisomerase II. For examples, The compounds 7n-PhPAVn(-1.81), 4n-CAVn(-1.66), 5n-IAVn(-1.08), 5t-IA4Py(-1.04), 6n-PAVn(-1.78), 6l-PAmpdm (-1.62), 8t-TA4Py(-1.93), 8n-TAVn(-1.81), 9s-OA3Py(-1.88), 9r-OA2Py(-1.31) showed good Glide scores due to hydrogen bonding.

**Fig-8 Hydrogen bonding interaction for 5n-IAVn**

The electrostatic force is also implicated to increase the Glide score of many compounds. For example the electrostatic force for the compound 6f-PAoh(-5.33) plays the major role for the binding affinity. But the Glide scores for some compounds in 6, 8, 9 series have been decreased by rotational penalty.

The details of the docking studies for the proposed compounds with topoisomerase II (1ZXM) are shown in the tables 9a-g.

All the molecules were screened *in silico* for catalytic inhibition of human topoisomerase IIα (htopoIIα) at the ATP site. The docking scores and the structural descriptors data in extra precision (XP) docking studies revealed remarkable H-bond interactions with crucial amino acids of the protein including Asn91, Asn95, Ser148, Ser149, Arg98, Asn120, Gly124, Ile217, Thr215, Ile125, His130, Phe142 and Lys123.
Table-9a Docking studies for compounds 4a-x with topoisomerase II (1ZXM)

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Table-9b Docking studies for compounds 5a-x with topoisomerase II (1ZXM)

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Table-9c Docking studies for compounds 6a-x with topoisomerase II (1ZXM)

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### Table-9d Docking studies for compounds 7a-x with topoisomerase II (1ZXM)

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Table-9e Docking studies for compounds 8a-x with topoisomerase II (1ZXM)

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<th>RotPenal</th>
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### Table-9f Docking studies for compounds 9a-x with topoisomerase II (1ZXM)

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Table-9g Docking studies for std compounds with topoisomerase II (1ZXM)

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5.1.1 In silico ADME Properties of compounds

The ADME properties for the proposed compounds (4-9 series) can be determined in-silico by using qikprop module of Schrödinger suite 2009.

The computed dipole moment of the molecule are in the range of 1.2 -8.7. Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution of the compounds are in the range of 1-4. Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution of the compounds are in the range of 2.5-6. Predicted octanol/water partition coefficient value of the compounds are in the range of 4.4 -9.6. The compound 7o-PhPACa has highest QPlogP value. Number of likely metabolic reactions of the compounds are in the range of 1-6. Prediction of binding to human serum albumin for the compounds are in the range of 0.85-2.46. Number of violations of Lipinski’s rule of five is 0-2. Many of the compounds have % Human Oral Absorption in the range of 90-100%. So almost all the properties of the compounds are within the recommended values.

The details of the properties for the compounds 4-9 series are shown in the tables 10a-f.
### Table-10a- Result of *in silico* ADME screening for Compounds 4a-x

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**Dipole**- Computed dipole moment of the molecule,

**Donor HB** - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.

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**%Human oral absorption**- Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model.
Table-10b Result of *in silico* ADME screening for Compounds 5a-x

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<th>#metab</th>
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**Recommended values**

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<th>&gt;80% is high</th>
<th>&lt;25% is poor</th>
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<table>
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<th>Compound</th>
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</table>

**Dipole** - Computed dipole moment of the molecule,

**donorHB** - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.

**acceptHB** - Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution.

**QPlogPo/w** - Predicted octanol/water partition coefficient.

**#metab** - Number of likely metabolic reactions.

**QPlogKhsa** - Prediction of binding to human serum albumin.

**RuleOfFive** Number of violations of Lipinski’s rule of five.

**%Human** - Oral**Absorption** - Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model.
Table-10d Result of *in silico* ADME screening for compounds 7a-x

<table>
<thead>
<tr>
<th>Compound</th>
<th>dipole</th>
<th>Donor HB</th>
<th>Acceptor HB</th>
<th>logP o/w</th>
<th>#metab</th>
<th>QPlogKhsa</th>
<th>Rule of Five</th>
<th>% Human Oral Absorption</th>
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**Recommended values**

- Dipole: Computed dipole moment of the molecule,
- donorHB: Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.
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- #metab: Number of likely metabolic reactions.
- QPlogKhsa: Prediction of binding to human serum albumin.
- RuleOfFive: Number of violations of Lipinski’s rule of five.
- %Human- Oral absorption: Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model.
Table-10e Result of *in silico* ADME screening for compounds 8a-x

<table>
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<tr>
<th>Compound</th>
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<th>Acceptor HB</th>
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<th># metab</th>
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**Recommended values**

- 1- 12.5
- 0– 6
- 2-20
- 2-6.5
- 1 – 8
- –1.5 –
- 1.5
- max
- 4
- >80% is high
- <25% is poor

**Dipole**- Computed dipole moment of the molecule,

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Table-10f Result of *in silico* ADME screening for compounds 9a-x

<table>
<thead>
<tr>
<th>Compound</th>
<th>dipole</th>
<th>Donor HB</th>
<th>Accep HB</th>
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<td>94.85</td>
</tr>
<tr>
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<td>3</td>
<td>4.5</td>
<td>3.962</td>
<td>3</td>
<td>0.75</td>
<td>0</td>
<td>93.75</td>
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<tr>
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<td>2.346</td>
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<td>4.367</td>
<td>3</td>
<td>0.856</td>
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<td>100</td>
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<tr>
<td>9w-OABu</td>
<td>1.775</td>
<td>3</td>
<td>4.5</td>
<td>4.743</td>
<td>3</td>
<td>0.978</td>
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<td>100</td>
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<tr>
<td>9x-OACr</td>
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<td>4.5</td>
<td>4.676</td>
<td>3</td>
<td>0.971</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

**Recommended values**

- Dipole- Computed dipole moment of the molecule,
- donorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.
- accepHB- Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution.
- QPlogPo/w - Predicted octanol/water partition coefficient.
- #metab- Number of likely metabolic reactions.
- QPlogKhsa- Prediction of binding to human serum albumin.
- RuleOfFive Number of violations of Lipinski’s rule of five.
- %Human- Oral absorption- Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model.
Figure-8: Best affinity mode of docked compounds (4series) with topo II(1ZXM)

<table>
<thead>
<tr>
<th>4n-CAVn</th>
<th>4m-CApdma</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="4n-CAVn" /></td>
<td><img src="image" alt="4m-CApdma" /></td>
</tr>
<tr>
<td>4s-CA3Py</td>
<td>4o-CACa</td>
</tr>
<tr>
<td><img src="image" alt="4s-CA3Py" /></td>
<td><img src="image" alt="4o-CACa" /></td>
</tr>
<tr>
<td>4t-CA4Py</td>
<td>4l-CApdm</td>
</tr>
<tr>
<td><img src="image" alt="4t-CA4Py" /></td>
<td><img src="image" alt="4l-CApdm" /></td>
</tr>
</tbody>
</table>
Figure-9: Best affinity mode of docked compounds (5 series) with Topo II (1ZXM)
Figure-10: Best affinity mode of docked compounds(6series) with Topo II(1ZXM)
Figure-11: Best affinity mode of docked compounds(7series) with Topo II(1ZXM)
Figure-12: Best affinity mode of docked compounds (8series) with Topo II (1ZXM)
Figure-13: Best affinity mode of docked compounds(9series) with topoII(1ZXM)
Results and discussion
5.2. Analytical data of synthesized compounds

All the synthesized compounds were first analyzed by performing thin layer chromatography until to get single spot and determining the melting points which are uncorrected. The synthesized compounds were completely characterized by IR, $^1$H NMR, $^{13}$C NMR, mass spectral data. The IR spectra of compounds showed intense bands in the region 1200-1300 cm$^{-1}$ due to carbonyl stretching and broad bands in the region 3200-3400 cm$^{-1}$ due to NH stretching. The $^1$H NMR, $^{13}$C NMR spectra also support the structure of the synthesized compounds. All the compounds showed the peaks for aromatic hydrogens in $^1$H NMR spectroscopy between 6-6 δ ppm. All the compounds showed the peaks for aromatic carbons in $^{13}$C NMR spectroscopy between 110-180 δ ppm. The mass spectra of all compounds showed molecular ion peaks confirming their molecular weight. All the analytical data showed satisfactory results.

5.3. Anti-bacterial screening

The synthesized compounds were screened for their anti-bacterial activity against Gram-positive bacterium such as Staphylococcus aureus and Bacillus megaterium as well as Gram-negative bacterium such as Escherichia coli and Klebsiella pneumoniae by cup and plate method. All the compounds were tested for antibacterial activity against the bacteria at the concentration 100, 50 and 25µg/ml; solutions were prepared in DMSO (solvent). The activity towards the bacterium was calculated from the zone of inhibition. Both the standard drug Gentamycin and solvent control were maintained for the study.

The following compounds showed significant activity against various bacteria compared to standard drug.
Gram positive bacteria

All the synthesized final compounds (4-9 series) showed activity against *S. aureus* and *B. megaterium* at concentration about 100 and 50 µg/ml. But among those compounds 4g, 4h, 4j, 4l, 4m, 4n, 4p, 4r, 4s, 4t, 5e, 5h, 5l, 6c, 6g, 6i, 6n, 8h, 8j, 8l, 8p, 9l, 9p and 9v were showed significant activity even at the concentration of 25µg/ml against *S. aureus* and the compounds 4i, 4l, 4n, 4o, 4p, 4r, 4s, 4t, 4u, 4v, 4x, 5n, 6c, 6g, 6h, 8c, 8j, 8p, 9g, 9l, 9r, 9s, 9t, 9v and 9x were showed significant activity even at the concentration of 25µg/ml against *B. megaterium*.

Gram negative bacteria

All the synthesized final compounds (4-9 series) showed activity against *K. pneumoniae* and *E. coli* at concentration about 50 and 100µg/ml and compounds 4g, 4j, 4p, 4r, 4s, 4t, 4x, 6i, 6n, 8c, 8e, 8h, 8j, 8p, 8s, 9r, 9s, 9t, 9u and 9x showed significant activity even at the concentration of 25µg/ml against *K. pneumoniae* and the compounds 4e, 4j, 4m, 4u, 4v, 4x, 6e, 6g, 6h, 6i, 6n, 8c, 8e, 8l, 8s, 9j, 9p, 9s, 9t and 9v showed significant activity even at the concentration of 25µg/ml against *E. coli*.

The results of antibacterial activity against various bacteria are shown in tables 11a - c.
Table- 11a Antibacterial activity of chalcone substituted 9-anilino acridines (4 series) by cup & plate method

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.aureus (G+ve) (µg/ml)</td>
</tr>
<tr>
<td></td>
<td>Ct 25 50 100 25 50 100 25 50 100 25 50 100 25 50 100</td>
</tr>
<tr>
<td>4b-CAoc</td>
<td>-- - 14 16 9 16 18 - 9 18 - 9 15</td>
</tr>
<tr>
<td>4c-CAmc</td>
<td>-- - 10 15 - 13 16 - 10 17 - 10 16</td>
</tr>
<tr>
<td>4e-CAopdc</td>
<td>-- - 12 18 - 12 17 - 16 19 10 15 20</td>
</tr>
<tr>
<td>4f-CAoh</td>
<td>-- - 14 15 - 13 15 - 12 15 - 13 16</td>
</tr>
<tr>
<td>4g-CAph</td>
<td>-- 8 11 19 - 10 15 9 11 14 - 15 16</td>
</tr>
<tr>
<td>4h-CAmn</td>
<td>-- 7 16 19 - 11 16 - 13 16 - 11 16</td>
</tr>
<tr>
<td>4i-CApn</td>
<td>-- - 14 17 11 17 19 - 15 19 - 11 16</td>
</tr>
<tr>
<td>4j-CApm</td>
<td>-- 8 17 20 - 12 20 11 12 18 9 11 18</td>
</tr>
<tr>
<td>4l-CAmpdm</td>
<td>-- 8 16 21 11 18 20 - 13 18 - 14 18</td>
</tr>
<tr>
<td>4m-CApdma</td>
<td>-- 12 19 21 - 12 17 - 15 18 9 12 19</td>
</tr>
<tr>
<td>4n-CAVn</td>
<td>-- 11 16 20 10 14 19 - 10 15 - 11 16</td>
</tr>
<tr>
<td>4o-CACa</td>
<td>-- 7 12 16 10 19 22 - 11 16 - 11 17</td>
</tr>
<tr>
<td>4p-CAFu</td>
<td>-- 11 19 22 10 14 20 8 14 19 - 16 19</td>
</tr>
<tr>
<td>4r-CA2Py</td>
<td>-- 10 17 20 8 12 18 8 13 19 - 13 18</td>
</tr>
<tr>
<td>4s-CA3Py</td>
<td>-- 11 16 21 9 13 18 10 14 20 - 12 16</td>
</tr>
<tr>
<td>4t-CA4Py</td>
<td>-- 10 13 19 10 14 19 10 13 19 - 12 16</td>
</tr>
<tr>
<td>4u-CAA Ac</td>
<td>-- - 14 17 12 18 19 - 16 20 9 12 15</td>
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<tr>
<td>4v-CApr</td>
<td>-- - 14 17 12 18 19 - 16 20 9 12 15</td>
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<tr>
<td>4x-CACr</td>
<td>-- - 12 16 10 16 20 9 14 19 9 13 16</td>
</tr>
<tr>
<td>Standard Gentamycin (25 µg/ml)</td>
<td>14 16 21 20</td>
</tr>
</tbody>
</table>
Table 11b Antibacterial activity of isoxazole and pyrazole substituted 9-anilino acridines (5 & 6 series) by cup & plate method

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S. aureus (G+ve) (µg/ml)</td>
</tr>
<tr>
<td></td>
<td>Ct 25 50 100</td>
</tr>
<tr>
<td>5c-IAmc</td>
<td>- 13 15 - 12 16 - 12 16 - 9 12</td>
</tr>
<tr>
<td>5e-IAopdc</td>
<td>- 10 17 18 - 10 16 - 10 15 - 11 16</td>
</tr>
<tr>
<td>5h-IAmn</td>
<td>- 10 14 18 - 10 14 - 11 11 - 9 14</td>
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<tr>
<td>5l-IAmpdm</td>
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<td>5m-IApdma</td>
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<tr>
<td>5n-IAVn</td>
<td>- 9 17 21 8 11 16 - 9 12 - 10 13</td>
</tr>
<tr>
<td>5o-IACa</td>
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<tr>
<td>5p-IAFu</td>
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<tr>
<td>6c-PAmc</td>
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</tr>
<tr>
<td>6e-PAopdc</td>
<td>- 13 15 19 12 14 17 - 11 15 12 13 17</td>
</tr>
<tr>
<td>6g-PAoh</td>
<td>- 13 15 19 12 14 17 - 11 15 12 13 17</td>
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<td>- 10 13 11 13 15 - 12 15 15 17 19</td>
</tr>
<tr>
<td>6i-PApn</td>
<td>- 10 15 17 - 10 14 20 25 29 15 18 21</td>
</tr>
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<td>6m-PApdma</td>
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</tr>
<tr>
<td>6n-PAVn</td>
<td>- 11 13 15 - 12 14 11 13 15 14 17 20</td>
</tr>
<tr>
<td>Standard Gentamycin (25 µg/ml)</td>
<td>14 16 21 20</td>
</tr>
</tbody>
</table>
### Table- 11c Antibacterial activity of thiazine and oxazine substituted 9-anilino acridines (8 & 9 series) by cup & plate method

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.aureus (G+ve) (µg/ml)</td>
</tr>
<tr>
<td></td>
<td>Ct</td>
</tr>
<tr>
<td>8b-TAoc</td>
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</tr>
<tr>
<td>8c-TAmc</td>
<td>-</td>
</tr>
<tr>
<td>8e-TAopdc</td>
<td>-</td>
</tr>
<tr>
<td>8h-TAmn</td>
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<tr>
<td>8j-TApm</td>
<td>12</td>
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<td>8l-TAmpdm</td>
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<td>8p-TAFu</td>
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<tr>
<td>8s-TA3Py</td>
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</tr>
<tr>
<td>9e-OAopdc</td>
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</tr>
<tr>
<td>9g-OAph</td>
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</tr>
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<td>9j-OApm</td>
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<td>9v-OAPr</td>
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<tr>
<td>9x-OACr</td>
<td>--</td>
</tr>
<tr>
<td>Standard Gentamycin (25 µg/ml)</td>
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</tbody>
</table>
5.4. Anti fungal screening

The synthesized compounds were screened for their antifungal activity against the fungi *Candida albicans* and *Aspergillus niger* by cup and plate method. The activity towards the fungi was calculated from the zone of inhibition. All the compounds were tested for antifungal activity against the fungus at the concentration 100, 50 and 25 µg/ml; solutions were prepared in DMSO (Solvent). Both the standard drug amphotericin-B and solvent control were maintained for the study.

All the synthesized compounds showed activity against *Candida albicans* and *Aspergillus niger* at concentration about 100µg/ml. But among those compounds 4o, 4r, 4s, 5c, 5o, 6e, 6g, 6m, 9e, 9l, 9n and 9t were showed significant activity even at the concentration of 50µg/ml against *Candida albicans* and the compounds 6g, 6m, 8e, 9n and 9s showed significant activity even at the concentration of 50µg/ml against *Aspergillus niger*. The results of antifungal activity are shown in table 12a-c.
### Table 12a Antifungal activity of chalcone substituted 9-anilino acridines (4 series) by cup & plate method

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. albicans(µg/ml)</td>
</tr>
<tr>
<td></td>
<td>Ct 25 50 100</td>
</tr>
<tr>
<td>4b-CAoc</td>
<td>- - -</td>
</tr>
<tr>
<td>4c-CAmc</td>
<td>- - -</td>
</tr>
<tr>
<td>4e-CAopdc</td>
<td>- - -</td>
</tr>
<tr>
<td>4f-CAoh</td>
<td>- - -</td>
</tr>
<tr>
<td>4g-CAph</td>
<td>- - -</td>
</tr>
<tr>
<td>4h-CAmn</td>
<td>- - -</td>
</tr>
<tr>
<td>4i-CApn</td>
<td>- - -</td>
</tr>
<tr>
<td>4j-CApm</td>
<td>- - -</td>
</tr>
<tr>
<td>4l-CAmpdm</td>
<td>- - -</td>
</tr>
<tr>
<td>4m-CApdma</td>
<td>- - -</td>
</tr>
<tr>
<td>4n-CAVn</td>
<td>- - -</td>
</tr>
<tr>
<td>4o-CACa</td>
<td>- - 9</td>
</tr>
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<td>4p-CAFu</td>
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<tr>
<td>4r-CA2Py</td>
<td>- - 10</td>
</tr>
<tr>
<td>4s-CA3Py</td>
<td>- - 9</td>
</tr>
<tr>
<td>4t-CA4Py</td>
<td>- - -</td>
</tr>
<tr>
<td>4u-CAAac</td>
<td>- - -</td>
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<tr>
<td>4v-CApr</td>
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<tr>
<td>4x-CACr</td>
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</tr>
<tr>
<td>Standard Gentamycin (25 µg/ml)</td>
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</tr>
<tr>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>
Table- 12b Antifungal activity of isoxazole and pyrazole substituted 9-anilino acridines (5 & 6 series) by cup & plate method

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Zone of inhibition in mm</th>
<th>C. albicans(µg/ml)</th>
<th>A. niger(µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ct</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>5c-IAmc</td>
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<td>-</td>
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</tr>
<tr>
<td>5e-IAopdc</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>5h-IAmn</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5l-IAmpdm</td>
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<tr>
<td>5m-IApdma</td>
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<td>5n-IAVn</td>
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<td>5o-IACa</td>
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<td>9</td>
</tr>
<tr>
<td>5p-IAFu</td>
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</tr>
<tr>
<td>6b-PAoc</td>
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<td>6c-PAmc</td>
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<tr>
<td>6e-PAopdc</td>
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<td>10</td>
</tr>
<tr>
<td>6g-PAoh</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>6h-PAmn</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6i-PApn</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6m-PApdma</td>
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<tr>
<td>6n-PAVn</td>
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<td>-</td>
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</tr>
<tr>
<td>Std Amphoterici n-B (50 µg/ml)</td>
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<td>22</td>
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</tr>
</tbody>
</table>
Table 12c Antifungal activity of thiazine and oxazine substituted 9-anilino acridines (8 & 9 series) by cup & plate method

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. albicans(µg/ml)</td>
</tr>
<tr>
<td></td>
<td>Ct 25 50 100</td>
</tr>
<tr>
<td>8c-TAmc</td>
<td>- - - 14</td>
</tr>
<tr>
<td>8e-TAopdc</td>
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</tr>
<tr>
<td>8h-TAmn</td>
<td>- - - 10</td>
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<tr>
<td>8j-TApm</td>
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<td>8l-TAmpdm</td>
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<td>9g-OAph</td>
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<td>9j-OApm</td>
<td>- - - 11</td>
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<td>9p-OAFu</td>
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<td>9u-OAAC</td>
<td>- - - 11</td>
</tr>
<tr>
<td>9v-OAPr</td>
<td>- - - 10</td>
</tr>
<tr>
<td>9x-OACr</td>
<td>- - - 10</td>
</tr>
<tr>
<td>Std Amphoterici n-B (50 µg/ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 22 -</td>
</tr>
</tbody>
</table>
5.5. Short term study for *in vitro* anti tumor activity

All the synthesized compounds were screened for their short term *in vitro* anti tumor activity against Daltons Lymphoma Ascites (DLA) cells.

All the compounds have significant cytotoxic activity against DLA cells.

Among those compounds, the isoxazole substituted 9-anilino acridines 5e, 5h, 5m and 5n have more significant CTC$_{50}$ value in the range of 245-271 $\mu$g/ml. All the pyrazole substituted 9-anilino acridines have more significant CTC$_{50}$ value in the range of 102-161$\mu$g/ml. All the thiazine substituted 9-anilino acridines have more significant CTC$_{50}$ value in the range of 90-210 $\mu$g/ml. All the oxazine substituted 9-anilino acridines have more significant CTC$_{50}$ (concentration required to reduce viability by 50%) value in the range of 96-385 $\mu$g/ml. The results of cytotoxicity study are shown in table 13a-d.
Table 13a- Short term \textit{in vitro} anti tumour activity of synthesized compounds (5series) against Daltons Lymphoma Ascites (DLA) cells

<table>
<thead>
<tr>
<th>S.No</th>
<th>compound</th>
<th>Conc.(µg/ml)</th>
<th>% viability</th>
<th>% cytotoxicity</th>
<th>CTC$_{50}$ (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>500</td>
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Table 13c- Short term *in vitro* anti tumour activity of synthesized compounds (8series) against Daltons Lymphoma Ascites (DLA) cells

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Table 13d- Short term *in vitro* anti tumor activity of synthesized compounds(9series) against Daltons Lymphoma Ascites (DLA) cells

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5.6. *Invivo* anti tumor activity

Among the synthesized compounds which show potent *invitro* anti tumor activity against DLA cells, a subset was selected and screened for their *invivo* anti tumor activity against DLA cells.

The compounds 5h-IAmn, 5c-IAmc, 6h-PAmn, 6c-PAmc, 9j-OApm, 9t-OA4Py, 8b-TAoc, 8l-TAmpdm, 8j-TApm were screened for their *in vivo* anti tumor activity against DLA cells.

The body weight analysis, mean survival time and % increase in life span at the dose of 10 and 20 mg/kg body weight in Swiss albino mice inoculated with DLA cells (1 X 10^6) were calculated and the results are shown in the table 14a-e.

The *in vivo* study was carried out for 24 days. The body weight was gradually increased for many groups. The mean survival time (MST) for treated groups was in the range of 17.3 – 23.66 days which was more than the MST of control (13days). The % increase in life span was 33.3 – 82% when compared to control.
Results and discussion

In vivo anti tumour activity of some synthesized compounds against (DLA) cells

Table 14a- Effect on body weight of some synthesized compounds

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<th>Group 3</th>
<th>Group 4</th>
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<td>Control CMC(0.05%) 10 ml/kg p.o.</td>
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<td>Comp. 6h-PAmn 20 mg/ kg p.o.</td>
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Values are mean ± SD, n=6
### Results and discussion

Table 14b Effect on body weight of some synthesized compounds

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<tr>
<th>Group</th>
<th>Treatment</th>
<th>Day 0</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 8</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 14</th>
<th>Day 16</th>
<th>Day 18</th>
<th>Day 20</th>
<th>Day 22</th>
<th>Day 24</th>
</tr>
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<td>Gr-10</td>
<td>Comp. 6c-PAmc 10mg/ kg p.o.</td>
<td>30.83±6.4</td>
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<td>33± 1.5</td>
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<td>36.16± 3.9</td>
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<td>Comp. 6c-PAmc 20 mg/ kg p.o.</td>
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<td>36.5± 4.3</td>
<td>36.66± 3.6</td>
<td>30.17± 3.2</td>
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<td>Gr-12</td>
<td>Comp. 9j-OApm 10 mg/ kg p.o.</td>
<td>32± 7.2</td>
<td>33.33±3.4</td>
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<td>37.5± 4.6</td>
<td>37.5± 3.51</td>
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<td>Gr-13</td>
<td>Comp. 9j-OApm 20 mg/ kg p.o.</td>
<td>32.33±6.8</td>
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<td>Gr-14</td>
<td>Comp. 9t-OA4Py 10 mg/ kg p.o.</td>
<td>32.5± 5.7</td>
<td>34.33±3.6</td>
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<td>32.83±2.9</td>
<td>30.5± 2.2</td>
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<td>Gr-16</td>
<td>Comp. 8b-TAoc 10 mg/ kg p.o.</td>
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<td>Comp. 8b-TAoc 20 mg/ kg p.o.</td>
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<td>39.66±3.1</td>
<td>41± 3.5</td>
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<td>Gr-18</td>
<td>Comp. 8l-TAmpdm 10mg /kg p.o.</td>
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<td>Gr-19</td>
<td>Comp. 8l-TAmpdm 20mg /kg p.o.</td>
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<td>41.38±2.2</td>
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Legend:
- **---** indicates no data available.

Note: The values are given in grams with standard deviation.
**Results and discussion**

Table-14c - body weight change for some synthesized compounds

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<tr>
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<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>Group 9</th>
</tr>
</thead>
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<tr>
<td>Treatment</td>
<td>Normal CMC(0.05%) 10 ml/kg p.o.</td>
<td>Control CMC(0.05%) 10 ml/kg p.o.</td>
<td>Standard 5-F. uracil 10 mg/kg i.p.</td>
<td>Comp. 5h-IAmn 10 mg/kg p.o.</td>
<td>Comp. 5h-IAmn 20 mg/kg p.o.</td>
<td>Comp. 5c-IAmc 10 mg/kg p.o.</td>
<td>Comp. 5c-IAmc 20 mg/kg p.o.</td>
<td>Comp. 6h-PAmn 10 mg/kg p.o.</td>
<td>Comp. 6h-PAmn 20 mg/kg p.o.</td>
</tr>
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Values are mean ± SD, n= 6, p<0.05 when compared to Normal.
### Results and discussion

Table 14d- body weight change for some synthesized compounds

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<tr>
<th>Group</th>
<th>Gr-10</th>
<th>Gr-11</th>
<th>Gr-12</th>
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<th>Gr-20</th>
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<tr>
<td>Treatment</td>
<td>Comp. 6c-PAmc 10mg/kg p.o.</td>
<td>Comp. 6c-PAmc 20mg/kg p.o.</td>
<td>Comp. 9j-OApm 10mg/kg p.o.</td>
<td>Comp. 9j-OApm 20mg/kg p.o.</td>
<td>Comp. 9t-OA4Py 10mg/kg p.o.</td>
<td>Comp. 9t-OA4Py 20mg/kg p.o.</td>
<td>Comp. 8b-TAoc 10mg/kg p.o.</td>
<td>Comp. 8b-TAoc 20mg/kg p.o.</td>
<td>Comp. 8l-TAmpdm 10mg/kg p.o.</td>
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<td>3.6±1.5</td>
<td>3.8±1.6</td>
<td>4.1±1.4</td>
<td>6.1±1.7</td>
<td>5.3±1.5</td>
<td>3.6±1.5</td>
<td>5.8±1.5</td>
<td>4.3±2.1</td>
<td>9.0±3.1</td>
<td>5.5±2.1</td>
<td>4.4±1.8</td>
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<td>Day 14</td>
<td>4.5±2.1</td>
<td>4.8±2.7</td>
<td>4.8±2.1</td>
<td>7.0±2.3</td>
<td>6.0±2.3</td>
<td>4.6±1.8</td>
<td>6.7±2.3</td>
<td>5.1±2.5</td>
<td>9.8±2.7</td>
<td>6.0±1.8</td>
<td>5.5±2.2</td>
</tr>
<tr>
<td>Day 16</td>
<td>5.3±2.2</td>
<td>5.7±2.3</td>
<td>5.3±3.1</td>
<td>7.6±1.8</td>
<td>7.2±3.3</td>
<td>5.8±2.7</td>
<td>8.1±3.2</td>
<td>6.4±1.9</td>
<td>11.3±4.1</td>
<td>6.8±2.4</td>
<td>6.5±3.7</td>
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<tr>
<td>Day 18</td>
<td>6.5±3.2</td>
<td>6.6±3.0</td>
<td>6.6±3.5</td>
<td>8.7±4.1</td>
<td>8.5±1.9</td>
<td>7.4±3.7</td>
<td>9.5±4.1</td>
<td>7.7±2.8</td>
<td>12.7±5.1</td>
<td>8.0±4.2</td>
<td>7.4±4.7</td>
</tr>
<tr>
<td>Day 20</td>
<td>---</td>
<td>7.8±4.2</td>
<td>---</td>
<td>9.6±4.5</td>
<td>9.7±5.1</td>
<td>8.6±4.3</td>
<td>11.6±3.8</td>
<td>9.3±3.7</td>
<td>13.7±3.8</td>
<td>9.1±3.7</td>
<td>8.8±3.1</td>
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<tr>
<td>Day 22</td>
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<td>8.5±3.8</td>
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<td>11.0±5.2</td>
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<td>9.4±4.7</td>
<td>13.8±2.5</td>
<td>11.6±3.5</td>
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<td>10.8±5.1</td>
<td>10.3±4.5</td>
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<td>9.7±4.3</td>
<td>---</td>
<td>12.52±6.0</td>
<td>---</td>
<td>10.5±4.8</td>
<td>---</td>
<td>13.6±4.1</td>
<td>---</td>
<td>11.9±3.8</td>
<td>---</td>
</tr>
</tbody>
</table>
Table 14c- MST and % ILS for some synthesized compounds

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose</th>
<th>Compound</th>
<th>MST (In Days)</th>
<th>% ILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(control)</td>
<td>10 ml/kg</td>
<td>CMC (0.05%)</td>
<td>13±2.7</td>
<td>--</td>
</tr>
<tr>
<td>3(Standard)</td>
<td>10 mg/ kg</td>
<td>5-Fluoro uracil</td>
<td>23.66±0.8</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>10 mg/kg</td>
<td>5h-IAmn</td>
<td>17.66±1.5</td>
<td>35.85</td>
</tr>
<tr>
<td>5</td>
<td>20 mg/kg</td>
<td>5h-IAmn</td>
<td>23.33±1.0</td>
<td>79.46</td>
</tr>
<tr>
<td>6</td>
<td>10 mg/kg</td>
<td>5c-IAmc</td>
<td>19±1.6</td>
<td>46.15</td>
</tr>
<tr>
<td>7</td>
<td>20 mg/kg</td>
<td>5c-IAmc</td>
<td>23±1.6</td>
<td>76.92</td>
</tr>
<tr>
<td>8</td>
<td>10 mg/kg</td>
<td>6h-PAmn</td>
<td>18±1.7</td>
<td>38.4</td>
</tr>
<tr>
<td>9</td>
<td>20 mg/kg</td>
<td>6h-PAmn</td>
<td>23.66±0.8</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>10 mg/kg</td>
<td>6c-PAmc</td>
<td>17.66±1.5</td>
<td>35.85</td>
</tr>
<tr>
<td>11</td>
<td>20 mg/kg</td>
<td>6c-PAmc</td>
<td>22.33±2.6</td>
<td>71.77</td>
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<tr>
<td>12</td>
<td>10 mg/kg</td>
<td>9j-OApm</td>
<td>17.33±1.6</td>
<td>33.30</td>
</tr>
<tr>
<td>13</td>
<td>20 mg/kg</td>
<td>9j-OApm</td>
<td>23.33±1.0</td>
<td>79.46</td>
</tr>
<tr>
<td>14</td>
<td>10 mg/kg</td>
<td>9t-OA4Py</td>
<td>19.33±1.0</td>
<td>48.69</td>
</tr>
<tr>
<td>15</td>
<td>20 mg/kg</td>
<td>9t-OA4Py</td>
<td>23.33±1.1</td>
<td>79.46</td>
</tr>
<tr>
<td>16</td>
<td>10 mg/kg</td>
<td>8b-TAoc</td>
<td>22.66±1.5</td>
<td>73.84</td>
</tr>
<tr>
<td>17</td>
<td>20 mg/kg</td>
<td>8b-TAoc</td>
<td>23.66±1.5</td>
<td>82</td>
</tr>
<tr>
<td>18</td>
<td>10 mg/kg</td>
<td>8l-TAmpdm</td>
<td>19.33±1.1</td>
<td>48.68</td>
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<tr>
<td>19</td>
<td>20 mg/kg</td>
<td>8l-TAmpdm</td>
<td>23.33±1.1</td>
<td>79.46</td>
</tr>
<tr>
<td>20</td>
<td>20 mg/kg</td>
<td>8j-TApm</td>
<td>21.66±1.5</td>
<td>66.62</td>
</tr>
</tbody>
</table>

MST Values are mean ± SD, n= 6,
5.7. Structure Activity Relationship (SAR) studies for synthesized compounds

The SAR of the synthesized compounds are discussed on the basis of the cytotoxic activities.

All the synthesized final compounds (5-9 series) show significant cytotoxicity. Among these compounds, many of the pyrazole and thiazine substituted 9-anilino acridines are more potent than the isoxazole and oxazine substituted 9-anilino acridines.

Among the isoxazole substituted 9-anilino acridines, the 5\textsuperscript{th} position of isoxazole ring substituted with o,p-dichloro, m-nitro, 4-hydroxy,3-methoxy and p-dimethylamino -phenyl groups increases the cytotoxic activity.

Among the pyrazole substituted 9-anilino acridines, the 5\textsuperscript{th} position of pyrazole ring substituted with o- or m -chloro, o,p dichloro, m-nitro and p-dimethylamino - phenyl groups increases the cytotoxic activity.

Among the thiazine substituted 9-anilino acridines, the 4\textsuperscript{th} position of thiazine ring substituted with o-chloro, m-choro, o,p-dichloro, m-nitro, m,p- dimethoxy and p-methoxy - phenyl groups increases the cytotoxic activity.

Among the oxazine substituted 9-anilino acridines, the 4\textsuperscript{th} position of oxazine ring substituted with p-methoxy phenyl, pyridine, furan and propyl - groups increases the cytotoxic activity.

5.8. 3D- QSAR studies for synthesized compounds

The model generated by Phase module of Schrodinger is summarized in Table 15. They were analyzed for their predictive ability for training set as well as test set molecules. Final models were selected primarily based on the values of better cross-validated $r^2$, predictive $r^2$ and SD values of test set molecules.
Good and consistent external predictivity was observed a good $R^2$ value for the training set (0.9937). A good Pearson-R value of 0.2959 was also observed. Actual and predicted values of the training set and test set molecules are given in table 16a and 16b.

The relation between experimental and predicted activity values of training set and Test set models are given in the figure 14a and 14b.

### Table 15- Parameters of Hypotheses

<table>
<thead>
<tr>
<th># Factors</th>
<th>SD</th>
<th>$R^2$</th>
<th>Stability</th>
<th>F</th>
<th>P</th>
<th>RMSE</th>
<th>$Q^2$</th>
<th>Pearson-r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1382</td>
<td>0.6866</td>
<td>0.689</td>
<td>35.1</td>
<td>2.15E^{-15}</td>
<td>0.21</td>
<td>0.0431</td>
<td>0.3404</td>
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<tr>
<td>2</td>
<td>0.0631</td>
<td>0.9388</td>
<td>0.516</td>
<td>115.1</td>
<td>7.93E^{-10}</td>
<td>0.21</td>
<td>0.0509</td>
<td>0.2693</td>
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<tr>
<td>3</td>
<td>0.047</td>
<td>0.9682</td>
<td>0.568</td>
<td>142.3</td>
<td>1.01E^{-10}</td>
<td>0.22</td>
<td>0.0106</td>
<td>0.2387</td>
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<tr>
<td>4</td>
<td>0.0285</td>
<td>0.9892</td>
<td>0.56</td>
<td>297.9</td>
<td>1.22E^{-12}</td>
<td>0.21</td>
<td>0.0364</td>
<td>0.2675</td>
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<tr>
<td>5</td>
<td>0.0226</td>
<td>0.9937</td>
<td>0.529</td>
<td>380.7</td>
<td>8.79E^{-13}</td>
<td>0.21</td>
<td>0.0586</td>
<td>0.2959</td>
</tr>
</tbody>
</table>
Table 16a: Experimental –log (CTC$_{50}$) and corresponding model predicted values of molecules used in training sets

<table>
<thead>
<tr>
<th>Ligand Name</th>
<th>QSAR Set</th>
<th>Activity(CTC$_{50}$)</th>
<th>Predicted Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8b-TAoc</td>
<td>training</td>
<td>4.046</td>
<td>4.10365</td>
</tr>
<tr>
<td>8l-TAmpdm</td>
<td>training</td>
<td>4.009</td>
<td>4.04908</td>
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<tr>
<td>6b-PAoc</td>
<td>training</td>
<td>3.991</td>
<td>3.72988</td>
</tr>
<tr>
<td>8j-TApm</td>
<td>training</td>
<td>3.991</td>
<td>4.01864</td>
</tr>
<tr>
<td>9s-OA3Py</td>
<td>training</td>
<td>3.979</td>
<td>3.97464</td>
</tr>
<tr>
<td>6h-PAmn</td>
<td>training</td>
<td>3.971</td>
<td>4.07587</td>
</tr>
<tr>
<td>8h-TAmn</td>
<td>training</td>
<td>3.947</td>
<td>4.03455</td>
</tr>
<tr>
<td>6c-PAmc</td>
<td>training</td>
<td>3.939</td>
<td>3.82363</td>
</tr>
<tr>
<td>8e-TAopdc</td>
<td>training</td>
<td>3.939</td>
<td>4.03065</td>
</tr>
<tr>
<td>9v-OAPr</td>
<td>training</td>
<td>3.939</td>
<td>3.90438</td>
</tr>
<tr>
<td>9r-OA2Py</td>
<td>training</td>
<td>3.936</td>
<td>3.95152</td>
</tr>
<tr>
<td>9p-OAFu</td>
<td>training</td>
<td>3.928</td>
<td>3.94232</td>
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<tr>
<td>6e-PAopdc</td>
<td>training</td>
<td>3.921</td>
<td>3.98459</td>
</tr>
<tr>
<td>9u-OAAC</td>
<td>training</td>
<td>3.854</td>
<td>3.93932</td>
</tr>
<tr>
<td>6n-PAVn</td>
<td>training</td>
<td>3.81</td>
<td>3.89129</td>
</tr>
<tr>
<td>8p-TAFu</td>
<td>training</td>
<td>3.745</td>
<td>3.86218</td>
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<tr>
<td>9l-OAmpdm</td>
<td>training</td>
<td>3.721</td>
<td>3.71642</td>
</tr>
<tr>
<td>5m-IApdma</td>
<td>training</td>
<td>3.611</td>
<td>3.61008</td>
</tr>
<tr>
<td>5e-IAopdc</td>
<td>training</td>
<td>3.602</td>
<td>3.66394</td>
</tr>
<tr>
<td>5h-IAmn</td>
<td>training</td>
<td>3.569</td>
<td>3.61153</td>
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<td>training</td>
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<td>3.68466</td>
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<td>training</td>
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<td>5c-IAMc</td>
<td>training</td>
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</table>
Table 16b: Experimental –log (CTC$_{50}$) and corresponding model predicted values of molecules used in test sets

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ligand Name</th>
<th>QSAR Set</th>
<th>Activity(CTC$_{50}$)</th>
<th>Predicted Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9t-OA4Py</td>
<td>test</td>
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<td>3.73223</td>
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<tr>
<td>2</td>
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<td>test</td>
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<td>3.9022</td>
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<tr>
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<td>9j-OApm</td>
<td>test</td>
<td>3.971</td>
<td>3.95378</td>
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<td>4</td>
<td>6i-PApn</td>
<td>test</td>
<td>3.921</td>
<td>3.74916</td>
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<tr>
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<td>6m-PAdma</td>
<td>test</td>
<td>3.921</td>
<td>3.71781</td>
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<td>6</td>
<td>6f-PAoh</td>
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<td>10</td>
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<td>11</td>
<td>5l-IAmpdm</td>
<td>test</td>
<td>3.357</td>
<td>3.65625</td>
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</table>

Figure 14a: Relation between experimental and predicted activity values of training set model
Figure 14b: Relation between experimental and predicted activity values of test set model

The features represented by the model with hydrogen bond donor, electron withdrawing group and hydrophobic/ non polar group are given in the figure 15 - 18. The blue colour region represents the favorable position for substitution and the red colour region represents the non favorable position for substitution of groups.
Figure 15a: 3-D QSAR model based on compounds (5series) illustrating hydrogen bond donor feature
Figure 15b: 3-D QSAR model based on compounds (5series) illustrating Electron withdrawing group feature
Figure 15c: 3-D QSAR model based on compounds (5series) illustrating hydrophobic/non polar group feature
Figure 16a: 3-D QSAR model based on compounds (6series) illustrating hydrogen bond donor feature
Figure 16b: 3-D QSAR model based on compounds (6series) illustrating electron withdrawing group feature

<table>
<thead>
<tr>
<th>6bPAoc</th>
<th>6c-PAmc</th>
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<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
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<tr>
<td>6e-PAopdc</td>
<td>6f-PAoh</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>6h-PAmn</td>
<td>6i-PApn</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>6m-PApdma</td>
<td>6n-PAVn</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
</tbody>
</table>
Figure 16c: 3-D QSAR model based on compounds (6series) illustrating hydrophobic/non polar group feature

- 6bPAoc
- 6c-PAmc
- 6e-PAopdc
- 6f-PAoh
- 6h-PAmn
- 6i-PApn
- 6m-PApdma
- 6n-PAVn
Figure 17a: 3-D QSAR model based on compounds (8series) illustrating hydrogen bond donor feature
Figure 17b: 3-D QSAR model based on compounds (8series) illustrating electron withdrawing group feature

<table>
<thead>
<tr>
<th>8b-TAoc</th>
<th>8c-TAmc</th>
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<tr>
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</tr>
<tr>
<td>8e-TAopdc</td>
<td>8h-TAmn</td>
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<tr>
<td><img src="image" alt="8e-TAopdc" /></td>
<td><img src="image" alt="8h-TAmn" /></td>
</tr>
<tr>
<td>8j-TApm</td>
<td>8l-TAmpdm</td>
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<tr>
<td><img src="image" alt="8j-TApm" /></td>
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<td>8s-TA3Py</td>
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<tr>
<td><img src="image" alt="8p-TAFu" /></td>
<td><img src="image" alt="8s-TA3Py" /></td>
</tr>
</tbody>
</table>
Results and discussion

Figure 17c: 3-D QSAR model based on compounds (8series) illustrating hydrophobic/non polar group feature
Figure 18a: 3-D QSAR model based on compounds (9series) illustrating hydrogen bond donor feature
Figure 18b: 3-D QSAR model based on compounds (9series) illustrating electron withdrawing group feature

<table>
<thead>
<tr>
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<th>9g-OAph</th>
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<tbody>
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<td><img src="image2.png" alt="Image" /></td>
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<td>9l-OAmpdm</td>
</tr>
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<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>9n-OAVn</td>
<td>9p-OAFu</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td>9r-OA2Py</td>
<td>9r-OA3Py</td>
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<td><img src="image7.png" alt="Image" /></td>
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<tr>
<td>9s-OA4Py</td>
<td>9u-OAAc</td>
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<tr>
<td><img src="image9.png" alt="Image" /></td>
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</tr>
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<td>9v-OAPr</td>
<td>9x-TACr</td>
</tr>
<tr>
<td><img src="image11.png" alt="Image" /></td>
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Figure 18c: 3-D QSAR model based on compounds (9series) illustrating hydrophobic/non polar group feature

<table>
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<th>9c-OA0opdc</th>
<th>9g-OAph</th>
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<td><img src="image" alt="9g-OAph" /></td>
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Therefore the following can be concluded from the 3D QSAR study, as the features represented.

- The hydrogen bond donor, electron withdrawing group and hydrophobic/ non polar group are substituted in the blue colour region are implicated to increase the cytotoxic activities.

- But the hydrogen bond donor, electron withdrawing group and hydrophobic/ non polar group are substituted in the red colour region are implicated to decrease the cytotoxic activities.