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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis, chemical characterization of novel 1,3-dimethyl acridones as cytotoxic agents, and their DNA-binding studies

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**Abstract** A series of new 1,3-dimethyl acridone derivatives were synthesized with different alkyl side chain (propyl and butyl) substitution at $N^{10}$-position and highly basic amine groups at terminal end of alkyl side chain. All the synthesized molecules were screened for their cytotoxic activity against human breast adenocarcinoma (MCF-7) and human promyelocytic leukemia (HL-60) cell lines. DNA binding constants ($K_i$) of selected compounds were determined with calf-thymus DNA. Results showed that the molecules **7, 8, 10, 11, 12, 13, 14,** and **15** exhibited good cytotoxic activity with $IC_{50}$ value $<10$ μM. Compound **14** having ($\beta$-hydroxyethyl) piperazine butyl side chain exhibited potent cytotoxic activity against MCF-7 cell line and DNA-intercalating properties. Examination of the relationship between lipophilicity and acridone derivatives showed poor correlation.

**Keywords** 1,3-Dimethyl acridone derivatives · DNA-intercalating · Cytotoxic · MCF-7 · HL-60

## Introduction

Chemical modification of bioactive components is one of the most common approaches in drug discovery with improved therapeutic effect (Tan *et al.*, 2006). The acridone alkaloid, acronycine, was isolated from *Acronychia baueri* in 1948 (Hughs *et al.*, 1948) and found to have potent anticancer activity. A series of naturally occurring acridone alkaloids were found to be potent molecules for

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inhibition of human Promyelocytic leukemia cells (Moon Woo Chun *et al.*, 1997). Glyfoline, another natural acridone alkaloid isolated from *Glycosmis citrifolia*, was found to be the most potent molecule for inhibition of human leukemic HL-60 cells (Tzeng *et al.*, 1989). Several 9-acridone derivatives with or without an alkyl side chain attached to the N-position were found to exhibit anticancer and antibacterial activities.

Kamata *et al.* (2004) reported in vitro and in vivo anticancer activities of novel pyrimidoacridones, pyridophenoxadines, and pyrimidocarbazones and suggested that anticancer topoisomerase II inhibitors, such as amonafide, amsacrine, doxorubicin, and ellipticine contain a planar chromophore, which can intercalate into the DNA helix.

Pyrrolobenzodiazepine hybrid linked to acridone ring system designed to exhibit significant DNA-binding and shows promising in vitro anticancer activity (Kamal *et al.*, 2004). The triazoloacridones ($C_{1305}$ and $C_{1533}$) showed potent antitumor activity towards a wide range of different experimental tumors in vitro and in vivo, including both murine and human colon carcinomas (Fig. 1). These studies showed that the anticancer activity is due to DNA-intercalation (Lemke *et al.*, 2005). Later imidazoacridone derivatives showed very good cytotoxicity against number of human cancer cell lines. The most prominent analog, $C_{1311}$, is currently in clinical trials (Fig. 1). It has been found that $C_{1311}$ binds non-covalently to DNA to induce its cytotoxic effect (Cholody *et al.*, 1990).

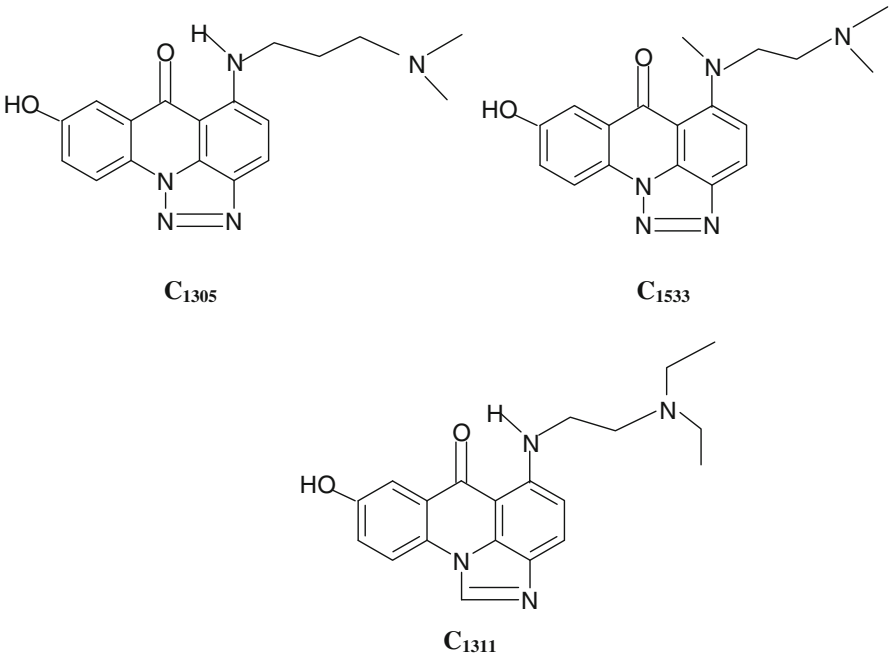



**Fig. 1**

A series of 1-amino thioacridones were designed as DNA-intercalating agents or DNA-intercalating agents with covalent bond formation potential. Studies showed that one of the compounds exhibited the most promising anticancer activity and may be useful as a lead compound in the search for more potent anticancer agents (Dheyongera *et al.*, 2005).

There are two common characteristics for many DNA-intercalators: a planar polycyclic chromophore able to intercalate between DNA base pairs, and the presence of a basic side chain (Miri *et al.*, 2004). The side chain can increase DNA-binding affinity and, depending on its hydrophilicity, may increase the solubility of a compound.

Based on literature review, the 1,3-dimethyl acridone ring nucleus substituted at $N^{10}$-position with tertiary amino groups at a distance of 3 to 4 carbons from the hydrophobic acridone ring have not been reported. With the intension of discovering good cytotoxic and DNA-binding agents, the authors have synthesized a series of 1,3-dimethyl acridones (Table 1, **1**–**15**). Their activity has been tested against MCF-7 and HL-60 cell lines and tried to correlate the lipophilicity and DNA-binding properties with cytotoxic activity.

## Results and discussion

### Chemistry

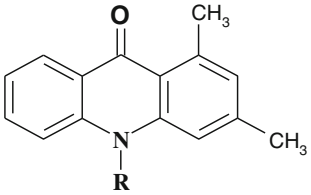
1,3-Dimethyl acridone **1** and its derivatives **2–15** were synthesized by the Scheme 1. Parent 1,3-dimethyl acridone was synthesized by cyclization of anthranilic acid **(I)** and 3,5-dimethyl phenol **(II)** by using p-toluene sulfonic acid to get 1,3-dimethyl acridone with better yield was obtained.

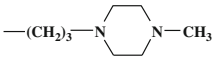
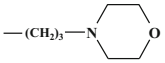
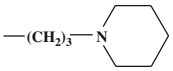
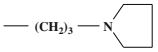
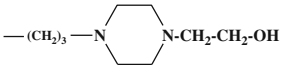
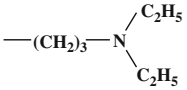
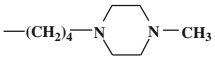
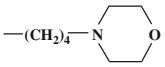
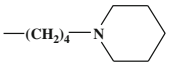
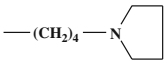
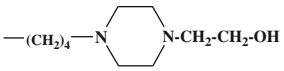
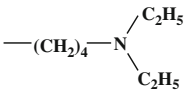
Usually N-alkylation with alkyl halides is difficult due to the weak basic nature of nitrogen of the acridone nucleus. However, it can be achieved in the presence of a strong base, such as sodium amide or sodium hydroxide under anhydrous condition. The reaction of parent acridone with chlorobromoalkanes in the presence of sodium amide in anhydrous conditions gave respective $N^{10}$-(chloroalkyl) acridones. Besides requiring drastic experimental conditions, the $N^{10}$-alkylation using sodium amide resulted in a very low yield. To overcome this drawback, $N^{10}$-alkylation was performed in the presence of phase transfer catalyst (PTC), which was easier to work with and gives better yield than the previously described methods.

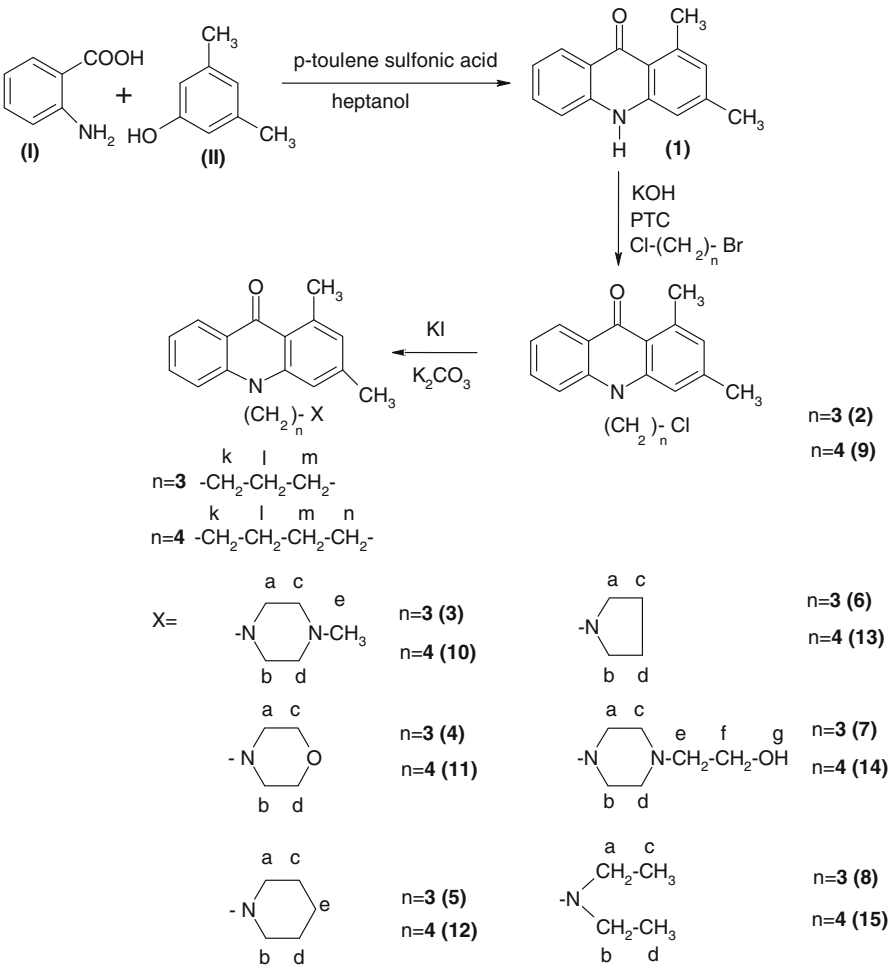
Stirring of 1,3-dimethyl acridone **1** at room temperature with alkylating agent 1-bromo-3-chloro propane or 1-bromo-4-chloro butane in a two-phase system consisting of an organic solvent (THF) and aqueous potassium hydroxide solution in the presence of tetra butyl ammonium bromide (PTC) to synthesize compounds **2** and **9** respectively in good yields.

Iodide catalyzed nucleophilic substitution reaction of the $N^{10}$-chloropropyl or $N^{10}$-chlorobutyl 1,3-dimethyl acridones was performed with various secondary

**Table 1** Lipophilicity of the different N-substituted acridones derivatives



| Comp. No. | R | $\log_{10}P^{a}$ |
|---|---|---|
| **1** | –H | 3.48 |
| **2** | $-CH_2-CH_2-CH_2-Cl$ | 4.33 |
| **3** |  | 3.37 |
| **4** |  | 3.33 |
| **5** |  | 4.05 |
| **6** |  | 3.66 |
| **7** |  | 2.99 |
| **8** |  | 3.82 |
| **9** | $-CH_2-CH_2-CH_2-CH_2-Cl$ | 4.74 |
| **10** |  | 3.75 |
| **11** |  | 3.46 |
| **12** |  | 4.41 |
| **13** |  | 4.06 |
| **14** |  | 3.31 |
| **15** |  | 4.10 |




**Scheme 1** Cyclization of anthranilic acid (1) and 3,5-dimethyl phenol using p-toulene sulfonic acid to yield 1,3-dimethyl acridone. N-alkylation using phase transfer catalyst (PTC). Iodide catalysed nucleophilic substitution reaction with different secondary amines

amines N-methylpiperazine, piperidine, morpholine, ($\beta$-hydroxyethyl) piperazine, N, N-diethylamine, and pyrrolidine, by refluxing for 15 hours in the presence of anhydrous potassium carbonate in acetonitrile gave the free bases **3–8** and **10–15**.

All the products were separated and purified by column chromatography or recrystallization method and dried under high vacuum for more than 12 hours. The purified compounds were characterized by $^{1}$H-NMR and $^{13}$C-NMR and mass spectroscopic methods and elemental analysis. The assignment of protons was fully supported by the integration curves, and all the derivatives showed the characteristic chemical shifts for the acridone nucleus. The assignment of the $^{13}$C-resonance of acridone derivatives is in close agreement with an analogous compound N$^{10}$-substituted acridone.

## Biological activity

### Lipophilicity

Lipophilicity of the compounds was determined using the software ALOGPS. The efficiency of an anticancer drug depends in part on its ability to accumulate in cells. Lipophilicity of compounds plays a vital role in cytotoxicity effect of the compounds. The acridone derivatives are weak bases and able to exist in both charged (protonated) and uncharged (unprotonated) forms. The lipophilicity data of **1–15** varying from 2.99–4.74, expressed in $\log_{10}P$ are shown in Table 1. Substitution of hydrogens by $CH_3$ in positions C-1 and C-3 resulted in a slight enhancement in the $\log_{10}P$ values. Additionally, the acridone nucleus with methyl groups at positions C-1 and C-3 may exhibit higher affinity for membranes or more readily taken up into the cells than that with hydrogen atoms. Analysis of the relationship between $\log_{10}P$ values and the cytotoxic activity in cancer cells showed poor correlation. The major outlier in this analysis was parent nucleus (**1, 2,** and **9**) are comparatively having higher $\log_{10}P$ values than any of this substituted derivatives, yet these were not very effective at increasing cytotoxic activity. In contrast, compound **12** with $\log_{10}P$ values (4.41) did not show the maximum activity. 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.

### Cytotoxic activity against MCF-7 and HL-60 cell lines

The cytotoxicity of 15 compounds was examined on MCF-7 and HL-60 cell lines by Trypan blue exclusion method with several concentrations of acridones. The $IC_{50}$ values of $N^{10}$-chloropropyl substituted and chlorobutyl substituted 1,3-dimethyl acridone derivatives against MCF-7 and HL-60 cells revealed that cytotoxic activity relatively increased as the chain length increased from three to four, suggesting that hydrophobicity plays an important role in biological activity. The increase of distance between the ring nucleus and amino group increased the cytotoxic activity of these compounds. It is clear from the data that the comparison of the cytotoxicity against MCF-7 cell lines (Table 2) of the butyl derivatives has shown that the cell killing potency follows the order **14 > 13 > 12 > 15 > 11 > 10 > 9** and propyl derivatives **7 > 8 > 6 > 3 > 5 > 4 > 2**. The cytotoxicity against HL-60 cell lines (Table 3) of the butyl derivatives has shown that the cell killing potency follows the order **15 > 14 > 13 > 11 > 12 > 10 > 9** and propyl derivatives **8 > 7 > 6 > 4 > 5 > 3 > 2**. However, **c**omparison of $IC_{50}$ values within the series revealed that the butyl derivatives have higher potency than propyl derivatives. Cytotoxicity results showed that the derivatives **13** and **14** exhibited good cytotoxic activity against MCF-7 cell lines compared with cyclophosphamide. Compounds **8, 10, 11, 12,** and **15** exhibited good cytotoxic activity against HL-60 cell lines compared with doxorubicin.

**Table 2** Cytotoxicity of compounds **1–15** against MCF-7 cell lines

| Compounds | $IC_{50}$ (μM) |
|---|---|
| **1** | 78.9 |
| **2** | 54.36 |
| **3** | 28.54 |
| **4** | 43.86 |
| **5** | 34.56 |
| **6** | 19.67 |
| **7** | 7.87 |
| **8** | 11.23 |
| **9** | 34.36 |
| **10** | 8.96 |
| **11** | 8.45 |
| **12** | 6.67 |
| **13** | 4.56 |
| **14** | 4.0 |
| **15** | 7.98 |
| Cyclophosphamide | 0.16 |

**Table 3** Cytotoxicity of compounds **1–15** against HL-60 cell lines

| Compounds | $IC_{50}$ (μM) |
|---|---|
| **1** | 19.98 |
| **2** | 16.45 |
| **3** | 15.39 |
| **4** | 13.71 |
| **5** | 14.06 |
| **6** | 14.59 |
| **7** | 10.90 |
| **8** | 1.65 |
| **9** | 14.25 |
| **10** | 1.74 |
| **11** | 0.51 |
| **12** | 1.41 |
| **13** | 14.11 |
| **14** | 11.01 |
| **15** | 0.45 |
| Doxorubicin | 0.020 |

It can be concluded that the structural features required with in the series of acridone derivatives to cause a maximum cytotoxic activity against MCF-7 and HL-60 cell lines is hydrophobic substituted acridone ring with an butyl side chain and positively charged tertiary amino groups preferably pyrrolidine, ($\beta$-hydroxy-ethyl) piperazine, and diethyl amino groups.

## DNA-binding properties

The DNA-binding properties of the compounds **3, 4, 7, 8,** and **10–15** (**1, 2, 5, 6,** and **9** not done because of poor solubility) were evaluated based on their affinity or intercalation with CT-DNA measured with absorption titration (Zhong *et al.*, 2001). Figure 2 shows the representative absorption spectrum of the compound **7** (15 μm) in the presence of increasing concentration of CT-DNA (0–100 μm). Figure 3 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 isobestic point depending on the alkyl amino side chains. These results were consistent with previous reports on the absorption titration of acridine derivatives, and the hypochromicity of acridine in the presence of DNA is believed to be a result of their intercalation with the DNA (Bhattacharya and Thomas, 1988).

The selection of ionic strength (150 mM NaCl) in the absorption titration experiment was mainly based on the avoidance of DNA deposition in all drug solution (15 μm). The DNA-binding constants summarized in Table 4 are related to the properties of acridones after intercalation with CT-DNA. The relative binding affinities as indicated by the binding constant $K_i$ are in the order of **14 > 10 > 3 > 11 > 4 > 15 > 12 > 7 > 13 > 8**. Among the derivatives those with strong DNA-binding affinities **3, 4, 10, 11, 14,** and **15** exhibited hypochromicity and isobestic points. Compound **14** showed higher DNA-binding constant ($K_i$) 10.32 × 10 × $M^{-1}$; this compound also showed relatively better cytotoxic activity against tumor cell lines, which may be attributed, at least in part, to its intercalative association and high binding affinity with the DNA. As for the structure-activity relationship, compound **14** bearing the planar tricyclic ring with butyl (*β*-hydroxyethyl)

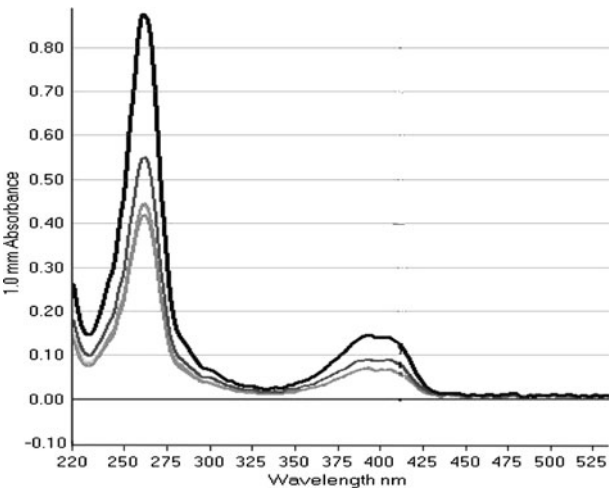



**Fig. 2** Absorption titration of **7** at 15 μM in 20 mM of sodium phosphate buffer (pH 6.5) with 150 mM of NaCl at increasing CT DNA concentration

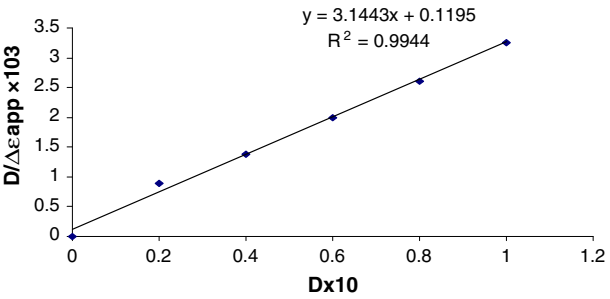



**Fig. 3** Half-reciprocal plot for binding of **7** with CT DNA

**Table 4** Binding constant ($K_i$) and photometric properties of acridones in contact with CT-DNA

| Compound | $K_i$ ($\times 10 \times M^{-1}$) ± SE | $\lambda_{max}$ (nm) | Isobestic point | Hypochromicity (%) |
|---|---|---|---|---|
| **3** | 4.82 ± 0.035 | 262 | Unclear | 48 |
| **4** | 4.04 ± 0.018 | 262 | 275 | 13 |
| **7** | 2.63 ± 0.023 | 262 | 338 | 52 |
| **8** | 0.66 ± 0.037 | 262 | 310 | 40 |
| **10** | 6.21 ± 0.006 | 263 | Unclear | 51 |
| **11** | 4.17 ± 0.015 | 263 | 325 | 35 |
| **12** | 2.68 ± 0.088 | 263 | Unclear | 50 |
| **13** | 1.03 ± 0.009 | 263 | 295 | 29 |
| **14** | 10.32 ± 0.012 | 263 | Unclear | 53 |
| **15** | 3.50 ± 0.090 | 263 | Unclear | 52 |

piperazine side chain showed stronger binding properties than the compounds studied.

## Conclusions

The new acridone analogues derived from acridone with different amine groups at the terminal end of the alkyl side chains have shown strong inhibiting activity against MCF-7 and HL-60 cell lines, which may be associated with their DNA-binding capacity. In particular, the effect is more pronounced when acridones have propyl and butyl side chain. Comparison of the derivatives for their ability to bind with DNA revealed that they largely follow the order $N^{10}$-butyl side chain more than $N^{10}$-propyl side chain. The substitution of hydrogen by $CH_3$ increased the ability to bind to DNA. Careful examination of the results obtained revealed that the butyl derivatives have higher activity than propyl derivatives.

With respect to these observations, we conclude that this series could be developed as promising cytotoxic agents and DNA-Intercalators.

## Experimental

### Chemistry

Reactions were monitored by TLC. Column chromatography utilized silica gel Merck Grade 60 (230–400 mesh, 60 Å). Melting points were recorded on a Tempirol hot-stage with microscope and are uncorrected. Elemental analyses were performed by Flash/-EA 1112 series CHNSO Analyzer, and found values are within 0.4% of theoretical values unless otherwise noted. $^{1}$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ and DMSO $d_6$ solutions in a 5-mm tube on a Bruker DRX 300 Fourier transform spectrometer with tetramethylsilane as internal standard. Chemical shifts are expressed as $\delta$ (ppm) values. Mass spectra were recorded on Micromass Q-TOF and Shimadzu LCMS 2010A Mass Spectrometer. DNA-binding studies of synthesized compounds were performed by Nano Drop ND-1000 UV Spectrophotometer.

### Synthesis of 1,3-dimethyl-10H-acridinone (**1**)

A solution that contained anthranilic acid (5 g, 0.0036 mol), 3,5-dimethyl phenol (4.48 g, 0.0036 mol) and p-toluene sulfonic acid (5.91 g, 0.036 mol) in heptanal (30 ml) was refluxed for 48 hours using Dean-Stark trap to remove water. The solvent was evaporated under reduced pressure and the dark brown residue, purified by column chromatography to give 1,3-dimethyl-10H-acridinone. Yield 60%, M.p. 301–306°C.

$^{1}$H-NMR (DMSO $d_6$) $\delta = 6.8$ (s, 1H, Ar–$H_2$), 7.1 (s, 1H, Ar–$H_4$), 7.2–7.45 (m, 3H, Ar–H, J = 8), 8.1 (d, 1H, Ar–$H_8$, J = 8), 2.39, 2.85 (2s, 6H, 2$CH_3$), 11.42 (s, 1H, NH). $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.64$ ($C_9$), 142.78 ($C_{9'}$, $C_{8'}$), 140.57 ($C_{10'}$, $C_{4'}$), 133.05 ($C_2$, $C_7$), 126.34 ($C_4$), 125.51 ($C_5$), 120.76 ($C_8$), 123.0 ($C_6$), 116.82 ($C_1$), 114.47 ($C_3$), 23.75 ($C_1$–$CH_3$), 21.47 ($C_3$–$CH_3$). MS *m/z:* 224 $(M + H)^+$; Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.71; H, 5.82; N, 6.27. Found: C, 80.63; H, 5.71; N, 6.00.

### General method for the synthesis of 10-(Chlorobromoalkyl)-1,3-dimethyl-10H-acridinone (**2**) and (**9**)

One gram (0.0044 mol) of 1,3-dimethyl-10H-acridinone was dissolved in 25 ml tetrahydrofuran and then 20 ml (0.04 mol) of potassium hydroxide and 0.5 g (0.015 mol) of tetrabutylammonium bromide was added to it. The reaction mixture was stirred at room temperature for 30 minutes and added chlorobromoalkanes (0.015 mol) slowly into the reaction mixture and stirred for 24 hours at room temperature. Tetrahydrofuran was evaporated and the aqueous layer was extracted with chloroform. The chloroform layer was washed with water and organic layer was dried over anhydrous sodium sulfate and rotavaporated. The crude product was purified by column chromatography by using the solvent system chloroform/methanol (9:1) to give a yellow solid of **(2)** and **(9)**.

10-(3-chloropropyl)-1,3-dimethyl-10H-acridinone (**2**)

Yield: 55%, M.p. 180–190°C.$^{1}$H-NMR (DMSO $d_6$) $\delta = 6.70$ (s, 1H, Ar–$H_2$), 7.13 (s, 1H, Ar–$H_4$), 7.39–7.55 (m, 3H, Ar–H, J = 8), 8.45 (d, 1H, Ar–$H_8$, J = 8), 2.05 (m, 2H, $H_l$), 3.99 (t, 2H, $H_k$), 3.55 (t, 2H, $H_m$), 2.36, 2.88 (2s, $2CH_3$), $^{13}$C-NMR (DMSO $d_6$): 178.56 ($C_9$), 143.81 ($C_{9'}$, $C_{8'}$), 141.04 ($C_{10'}$, $C_{4'}$), 133.98 ($C_7$), 126.38 ($C_4$), 132.65 ($C_5$), 127.08 ($C_6$), 125.48 ($C_2$), 121.34 ($C_8$), 116.98 ($C_1$), 115.61 ($C_3$), 53.12 ($C_k$), 56.34 ($C_m$), 43.56 ($C_l$), 23.65 ($C_1$–$CH_3$), 21.58 ($C_3$–$CH_3$); MS *m/z*: 299 $[M]^+$.

General procedure for the synthesis of 10-(N-substituted alkyl)-1,3-dimethyl-10H-acridinones (**3–8** and **10–15**)

10-(chloroalkyl)-1,3-dimethyl acridone (0.0044 mol) was dissolved in 30 ml of anhydrous acetonitrile and 1.68 g potassium iodide and 3.3 g of potassium carbonate were added and refluxed for 30 minutes. Different secondary amines (0.0044 mol) were added into it slowly and refluxed for 15 hours 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 an oily product. The semisolid residue was purified by column chromatography using the solvent system chloroform/methanol (9:1) to give the product of 10-(3′-[N-substituted] alkyl)-1,3-dimethyl acridone. An acetone solution of the free base was treated with ethereal hydrochloride to give the hydrochloride salt, which was dried over high vacuum to obtain pure solid.

10-(3′-N-(Methylpiperazino) propyl-1,3-dimethyl-10H-acridinone (**3**)

Yield: 91%, M.p. 165–170° C. $^{1}$H-NMR (DMSO $d_6$) $\delta = 6.56$ (s, 1H, Ar–$H_2$), 6.6–7.2 (m, 4H, Ar–H, J = 8), 8.15 (d, 1H, Ar–$H_8$, J = 8), 3.4–4.3 (m, 12H, $H_k$, $H_m$, $H_a$, $H_b$, $H_c$, and $H_d$), 2.1–2.4 (m, 2H, $H_l$), 2.5, 2.6 (2s, 6H, 2 $CH_3$), 3.1 (s, 3H, $H_e$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.63$ ($C_9$), 143.70 ($C_{9'}$, $C_{8'}$), 141.12 ($C_{10'}$, $C_{4'}$), 134.05 ($C_2$), 133.12 ($C_7$), 126.38 ($C_4$), 125.60 ($C_5$), 123.20 ($C_6$), 121.35 ($C_8$), 116.83 ($C_1$), 116.82 ($C_3$), 57.98 ($C_k$), 52.52 ($C_m$), 49.40 ($C_a$), 48.00 ($C_b$), 43.33 ($C_c$, $C_d$), 26.54 ($C_e$), 24.29 ($C_l$), 23.75 ($C_1$–$CH_3$), 21.47 ($C_3$–$CH_3$); MS *m/z*: 364 $(M + H)^+$, Anal. Calcd. for $C_{23}H_{29}N_3O$: C, 72.72; H, 7.98; N, 11.57. Found: C, 72.52; H, 7.43; N, 11.13.

10-[3′-N-Morpholinopropyl]-1,3-dimethyl-10H-acridinone (**4**)

Yield: 83%, M.p. 165–170°C. $^{1}$H-NMR (DMSO $d_6$) $\delta = 6.6$ (s, 1H, Ar–$H_2$), 6.84 (s, 1H, Ar–$H_4$), 7.26–7.57 (m, 3H, Ar–H, J = 4), 8.24 (d, 1H, Ar–$H_8$, J = 4), 3.2–4.3 (m, 12H, $H_k$, $H_m$, $H_a$, $H_b$ $H_c$ and $H_d$), 2.2–2.3 (m, 2H, $H_l$), 2.7, 3.3 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$): 178.46 ($C_9$), 143.91 ($C_{9'}$, $C_{8'}$), 141.00 ($C_{10'}$, $C_{4'}$), 133.90 ($C_7$), 126.29 ($C_4$), 132.60 ($C_5$), 127.04 ($C_6$), 125.47 ($C_2$), 121.24 ($C_8$), 116.94 ($C_1$), 115.66 ($C_3$), 53.01 ($C_k$), 51.27 ($C_m$), 58.13 ($C_a$, $C_b$), 63.39 ($C_c$, $C_d$), 26.31 ($C_l$),

21.95 ($C_1$–$CH_3$), 23.80 ($C_3$–$CH_3$); MS *m/z*: 351 $(M + H)^+$. Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.42; H, 7.42; N, 8.00. Found: C, 75.18; H, 7.21; N, 8.12.

10-[3′-N-Piperidinopropyl]-1,3-dimethyl-10H-acridinone (**5**)

8.33. Yield: 76%, M.p. 112–116°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.8 (s, 1H, Ar–$H_4$), 7.1–7.6 (m, 3H, Ar–H, J = 8), 8.44 (d, 1H, Ar–$H_8$, J = 8), 3.2–4.4 (m, 8H, $H_k$, $H_m$, $H_a$ and $H_b$), 1.1–2.0 (m, 8H, $H_l$, $H_c$ and $H_d$ and $H_e$), 2.35, 2.92 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.94$ ($C_9$), 143.97 ($C_{9'}$, $C_{8'}$), 140.46 ($C_{10'}$, $C_{4'}$), 133.93 ($C_7$), 126.35 ($C_4$), 125.67 ($C_5$), 133.19 ($C_6$), 123.26 ($C_2$), 121.37 ($C_8$), 118.53 ($C_1$), 116.95 ($C_3$), 58.30 ($C_k$), 54.48 ($C_m$), 67.36 ($C_a$, $C_b$), 67.79 ($C_c$, $C_d$), 26.35 ($C_l$), 24.51 ($C_e$), 22.73 ($C_1$–$CH_3$), 21.52 ($C_3$–$CH_3$); MS *m/z*: 349 $(M + H^+)$; Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.31; H, 8.04; N, 8.04. Found: C, 78.98; H, 7.80; N, 7.91.

10-(3′-N-Pyrrolidinopropyl)-1,3-dimethyl-10H-acridinone (**6**)

Yield: 60%, M.p.110–112°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.9–7.5 (m, 4H, Ar–H, J = 8), 8.45 (d, 1H, Ar–$H_8$, J = 8), 3.5–4.4 (m, 8H, $H_k$, $H_m$, $H_a$ and $H_b$), 1.0–2.4 (m, 6H, $H_l$, $H_c$ and $H_d$), 2.35, 2.92 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$)) $\delta = 178.25$ ($C_9$), 143.48 ($C_{9'}$, $C_{8'}$), 133.72 ($C_{10'}$, $C_{4'}$), 141.11 ($C_7$), 126.88 ($C_4$), 126.11 ($C_5$), 123.10 ($C_6$), 121.08 ($C_2$), 120.65 ($C_8$), 114.0 ($C_3$), 116.08 ($C_1$), 54.79 ($C_k$, $C_m$), 45.56 ($C_a$, $C_b$), 23.90 ($C_c$, $C_d$), 24.64 ($C_l$), 21.92 ($C_1$–$CH_3$), 21.42 ($C_3$–$CH_3$); MS *m/z*: 335 $(M + H)^+$. Anal. Calcd. for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.78; H, 8.22; N, 4.12.

10-(3′-N-[(*β*-Hydroxyethyl)piperazine] propyl)-1,3-dimethyl-10H-acridinone (**7**)

Yield: 88%, M.p. 114–118°C.$^1$H-NMR (DMSO $d_6$) $\delta = 6.6$ (s, 1H, Ar–$H_2$), 6.9 (s, 1H, Ar–$H_4$), 7.2–7.8 (m, 3H, Ar–H, J = 4), 8.2 (d, 1H, Ar–$H_8$, J = 4), 3.0–3.5 (m, 14H, $H_k$, $H_m$, $H_a$, $H_b$, $H_c$, $H_d$ and $H_e$), 2.2 (t, 2H, $H_l$), 2.5, 3.0 (2s, 6H, 2 $CH_3$), 4.15 (s, 1H, OH); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.63$ ($C_9$), 144.03 ($C_{9'}$, $C_{8'}$), 141.41 ($C_{10'}$, $C_{4'}$), 134.06 ($C_2$, $C_7$), 127.11 ($C_4$), 126.42 ($C_5$), 123.30 ($C_6$), 121.40 ($C_8$), 118.57 ($C_1$), 113.76 ($C_3$), 58.14 ($C_f$), 55.73 ($C_k$, $C_m$), 48.42 ($C_a$, $C_b$), 43.68 ($C_c$, $C_d$), 28.54 ($C_e$), 26.82 ($C_l$), 24.53 ($C_1$–$CH_3$), 22.47 ($C_3$–$CH_3$); MS *m/z*: 394 $(M + H)^+$. Anal. Calcd. for $C_{24}H_{31}N_3O_2$: C, 73.28; H, 7.88; N, 10.68. Found: C, 73.00; H, 7.62; N, 10.49.

10-[3′-(N-Diethyl amino) propyl)-1,3-dimethyl-10H-acridinone (**8**)

Yield: 75, M.p. 108–112°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.8 (s, 1H, Ar–$H_4$), 7.1–7.5 (m, 3H, Ar–H, J = 8), 8.3 (d, 1H, Ar–$H_8$, J = 8), 3.1–4.3 (m, 8H, $H_k$, $H_m$, $H_a$ and $H_b$), 2.19 (m, 2H, $H_l$), 2.8 (2s, 6H, 2 $CH_3$), 1.1–1.4 (m, 6H, $H_c$ and $H_d$); $^{13}$C-NMR (DMSO $d_6$) 178.14 ($C_9$), 143.60 ($C_{9'}$, $C_{8'}$), 142.78 ($C_{10'}$, $C_{4'}$), 133.51 ($C_2$), 132.7 ($C_7$), 125.28 ($C_4$), 126.92 ($C_5$), 125.92 ($C_6$), 120.98 ($C_8$), 120.53 ($C_1$), 118.34 ($C_3$), 58.08 ($C_k$), 57.92 ($C_m$), 67.52 ($C_a$, $C_b$), 8.47 ($C_c$, $C_d$), 30.01 ($C_l$),

24.18 ($C_1$–$CH_3$), 21.58 ($C_3$–$CH_3$); MS *m/z*: 334 $(M + H)^+$. Anal. Calcd. for $C_{22}H_{28}N_2O$: C, 78.57; H, 8.33; N, 8.33. Found: C, 78.28; H, 8.12; N, 7.98.

10-(4′-Chlorobutyl)-1,3-dimethyl-10H-acridinone (**9**)

Yield: 62%, Mp:130°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.8–7.6 (m, 4H, Ar–H, J = 8), 8.2 (d, 1H, Ar–$H_8$, J = 8), 2.05 (m, 2H, $H_l$), 3.75 (t, 2H, $H_k$), 4.2 (t, 2H, $H_n$), 1.6–2.26 (m, 4H, $H_l$ and $H_m$), 2.4, 2.9 (2s, 2$CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.68$ ($C_9$), 143.46 ($C_{9'}$, $C_{8'}$), 142.00 ($C_{10'}$, $C_{4'}$), 133.58 ($C_2$), 132.24 ($C_7$), 128.06 ($C_4$), 126.09 ($C_5$), 123.43 ($C_6$), 121.84 ($C_8$), 115.10 ($C_1$), 113.21 ($C_3$), 53.82 ($C_k$), 52.49 ($C_n$), 24.29 ($C_l$), 23.28 ($C_m$) 22.52 ($C_1$–$CH_3$), 22.11 ($C_3$–$CH_3$);MS *m/z*: 313 $(M)^+$.

10-[4′-N-(Methylpiperazino) butyl]-1,3-dimethyl-10H-acridinone (**10**)

Yield: 80%, M.p. 121–123°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.8–7.6 (m, 4H, Ar–H, J = 8), 8.2 (d, 1H, Ar–$H_8$, J = 8), 4.3 (m, 8H, $H_a$, $H_b$ $H_c$ and $H_d$), 3.0 (m, 6H, $H_k$, $H_n$ and $H_e$), 1.9–2.5 (m, 4H, $H_l$ and $H_m$) 2.8, 3.1 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.57$ ($C_9$), 143.36 ($C_{9'}$, $C_{8'}$), 141.0 ($C_{10'}$, $C_{4'}$), 133.45 ($C_2$), 132.12 ($C_7$), 127.05 ($C_4$), 126.08 ($C_5$), 123.32 ($C_6$), 120.84 ($C_8$), 115.07 ($C_1$), 113.13 ($C_3$), 53.98 ($C_k$), 52.52 ($C_n$), 45.67 ($C_a$, $C_b$, $C_c$, $C_d$), 24.32 ($C_e$), 24.11 ($C_l$), 23.02 ($C_m$) 22.62 ($C_1$–$CH_3$), 22.05 ($C_3$–$CH_3$); MS *m/z*: 378 $(M + H)^+$. Anal. Calcd. for $C_{24}H_{31}N_3O$: C, 76.39; H, 8.22; N, 11.14. Found: C, 75.89; H, 8.09; N, 10.92.

10-(4′-N-Morpholinobutyl)-1,3-dimethyl-10H-acridinone (**11**)

Yield: 81%, M.p. 134–138°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.8–7.73 (m, 4H, Ar–H, J = 4), 8.25 (d, 1H, Ar–$H_8$, J = 4), 3.5–4.2 (m, 4H, $H_c$ and $H_d$), 3.0–3.2 (m, 8H, $H_k$, $H_n$, $H_a$ and $H_b$), 1.8–2.5 (m, 4H, $H_m$ and $H_l$), 2.8 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.56$ ($C_9$), 143.79 ($C_{9'}$, $C_{8'}$), 141.34 ($C_{10'}$, $C_{4'}$), 133.94 ($C_2$), 132.99 ($C_7$), 127.07 ($C_4$), 126.26 ($C_5$), 123.28 ($C_6$), 121.21 ($C_8$), 115.65 ($C_1$), 113.64 ($C_3$), 55.82 ($C_k$), 51.28 ($C_n$), 45.72 ($C_a$, $C_b$,) 63.38 ($C_c$, $C_d$), 24.49 ($C_l$, $C_m$) 22.06 ($C_1$–$CH_3$), 20.28 ($C_3$–$CH_3$); MS *m/z*: 365 $(M + H^+)$. Anal. Calcd. for $C_{23}H_{28}N_2O_2$: C, 75.82; H, 7.69 N, 7.69. Found: C, 75.62; H, 7.41; N, 7.51.

10-(4′-N-Piperidinobutyl)-1,3-dimethyl-10H-acridinone (**12**)

Yield: 75%. M.p. 120–122°C. $^1$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 7.0–7.63 (m, 4H, Ar–H, J = 8), 8.4 (d, 1H, Ar–$H_8$, J = 8), 3.4–4.3 (m, 8H, $H_k$, $H_n$, $H_a$ and $H_b$), 1.6–2.3 (m, 8H, $H_l$, $H_m$, $H_c$ and $H_d$), 1.18 (m, 2H, $H_e$), 2.35, 2.92 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.16$ ($C_9$), 143.39 ($C_{9'}$, $C_{8'}$), 141.06 ($C_{10'}$, $C_{4'}$), 133.56 ($C_7$), 126.80 ($C_4$), 125.94 ($C_5$), 123.03 ($C_6$), 121.74 ($C_2$), 120.90 ($C_8$), 115.33 ($C_1$), 113.69 ($C_3$), 52.30 ($C_k$, $C_n$), 45.40 ($C_l$, $C_m$), 60.27 ($C_a$, $C_b$), 55.37 ($C_c$, $C_d$), 29.05 ($C_e$), 22.17 ($C_1$–$CH_3$), 20.32 ($C_3$–$CH_3$); MS *m/z*: 363 $(M + H)^+$. Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.55; H, 8.28; N, 7.73. Found: C, 79.42; H, 8.12; N, 7.58.

10-(4′-N-Pyrrolidinobutyl)-1,3-dimethyl-10H-acridinone (**13**)

Yield: 65 M.p. 148–150°C.$^{1}$H-NMR (DMSO $d_6$) $\delta = 6.7$ (s, 1H, Ar–$H_2$), 6.9–7.5 (m, 4H, Ar–H, J = 8), 8.3 (d, 1H, Ar–$H_8$, J = 8), 4.2 (m, 2H, $H_k$), 3.8 (m, 6H, $H_n$, $H_a$ and $H_b$), 2.0–2.3 (m, 8H, $H_l$, $H_m$, $H_c$ and $H_d$) 2.7, 3.2 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.28$ ($C_9$), 143.58 ($C_{9'}$, $C_{8'}$), 133.78 ($C_{10'}$, $C_{4'}$), 141.10 ($C_7$), 126.86 ($C_4$), 126.10 ($C_5$), 123.04 ($C_6$), 121.07 ($C_2$), 120.64 ($C_8$), 114.0 ($C_1$), 116.08 ($C_3$), 54.80 ($C_k$, $C_n$), 45.58 ($C_a$, $C_b$), 23.90 ($C_c$, $C_d$), 24.33 ($C_l$, $C_m$) 21.91 ($C_1$–$CH_3$), 21.41 ($C_3$–$CH_3$); MS *m/z*: 349 $(M + H)^+$.

10-(4′-N-[(*β*-Hydroxyethyl)piperazine] butyl)-1,3-dimethyl-10H-acridinone (**14**)

Yield: 85, M.p. 138–142°C. $^{1}$H-NMR (DMSO $d_6$) $\delta = 6.5$ (s, 1H, Ar–$H_2$), 6.8–7.4 (m, 4H, Ar–H, J = 8), 8.14 (d, 1H, Ar–$H_8$ J = 8), 3.7–4.1 (m, 9H, $H_k$, $H_c$, $H_d$, $H_e$ and OH), 3.0 (m, 2H, $H_n$), 1.7–1.9 (m, 4H, $H_l$ and $H_m$), 2.13 (t, 2H, $H_f$), 2.6, (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.53$ ($C_9$), 143.66 ($C_{9'}$, $C_{8'}$), 141.11 ($C_{10'}$, $C_{4'}$), 133.96 ($C_2$), 133.07 ($C_7$), 127.09 ($C_4$), 126.50 ($C_5$), 121.25 ($C_6$), 118.51 ($C_8$), 115.68 ($C_1$), 113.66 ($C_3$), 55.53 ($C_f$), 48.44 ($C_e$), 45.75 ($C_k$, $C_n$), 24.45 ($C_c$, $C_d$), 24.45 ($C_a$, $C_b$), 24.05 ($C_l$, $C_m$), 21.15 ($C_1$–$CH_3$), 20.65 ($C_3$–$CH_3$); MS *m/z*: 408 $(M + H)^+$. Anal. Calcd. for $C_{26}H_{33}N_3O_2$: C, 76.65; H, 8.10; N,10.31. Found: C, 76.28; H, 7.91; N, 10.11.

10-[4′-(N-Diethylamine) butyl)-1,3-dimethyl-10H-acridinone (**15**)

Yield: 75, M.p. 118–122°C. $^{1}$H-NMR (DMSO $d_6$) $\delta = 6.6$ (s, 1H, Ar–$H_2$), 6.9–7.5 (m, 4H, Ar–H, J = 4), 8.2 (d, 1H, Ar–$H_8$, J = 4), 4.2 (t, 2H, $H_k$), 2.9 (m, 6H, $H_n$, $H_a$ and $H_b$), 1.9 (m, 4H, $H_l$ and $H_m$) 2.2, 2.7 (2s, 6H, 2 $CH_3$); $^{13}$C-NMR (DMSO $d_6$) $\delta = 178.60$ ($C_9$), 143.86 ($C_{9'}$, $C_{8'}$), 141.38 ($C_{10'}$, $C_{4'}$), 134.01 ($C_7$), 126.32 ($C_4$), 133.11 ($C_5$), 127.10 ($C_6$), 123.30 ($C_2$), 121.29 ($C_8$), 115.78 ($C_1$), 113.75 ($C_3$), 46.60 ($C_k$), 45.82 ($C_n$), 50.74 ($C_a$,s $C_b$), 8.82 ($C_c$, $C_d$), 24.57 ($C_l$, $C_m$), 22.12 ($C_1$–$CH_3$), 21.58 ($C_3$–$CH_3$); MS *m/z*: 351 $(M + H)^+$. Anal. Calcd. for $C_{23}H_{30}N_2O$: C, 78.85; H, 8.57; N, 8.00. Found: C, 78.52; H, 8.34; N, 7.89.

## Cytotoxicity assay against MCF-7and HL-60 cell lines

The trypan blue dye exclusion test was used to determine drug-mediated cytotoxicity as described previously (Sezgün *et al.*, 2002). Briefly, $1 \times 10^4$ target tumor cells resuspended in 1 ml. Two milliliters of cell suspension were distributed into each well of a 6-well plate, and medium at the desired concentration was added into each well. Each plate was incubated for 48 hours at 37°C and 5% $CO_2$ atmosphere. After the incubations, 100 µl of the trypan was added into 100 µl of cell suspension. After this process, viable and dead cells were counted and percentage cytotoxicity was calculated. The $IC_{50}$ was determined from concentration percentage cytotoxicity curve.

## DNA binding assay by absorption titration

The spectrometric titration was conducted by Nano Drop ND-1000 UV. Spectrophotometer at room temperature (~30°C). The CT DNA (Sigma, St. Louis, MO) was dissolved in double-distilled deionized water with 50 mM NaCl, and dialyzed against a buffer solution for 2 days. Its concentration was determined by absorption spectrometry at 260 nm using a molar extinction coefficient 6600 $M^{-1}$ $cm^{-1}$. The ratio A260/A280 >1.80 was used as an indication of a protein-free DNA. Absorption titration was performed at a fixed concentration of drugs (15 μM) in a sodium phosphate buffer (20 mM sodium phosphate, 150 mM NaCl, pH 6.5). Small aliquots of concentrated CT DNA were added into the solution at final concentrations from 0 to 100 μM, and stirred for 5 minutes before measurement. The parameters, $\lambda_{max}$, hypochromicity, isobestic point, and binding constant were found from the absorption spectra. The intrinsic binding constant ($K_i$) (Chandramouli *et al.*, 2004) for a given complex with DNA was obtained from a plot of $D/\Delta\varepsilon_{app}$ versus D according to equation, $D/\Delta\varepsilon_{app} = D/\Delta\varepsilon + 1/\Delta\varepsilon \times K$, in which D = concentration of DNA in base molarities, $\Delta\varepsilon_{app} = |\varepsilon_a - \varepsilon_f|$ and $\Delta\varepsilon = |\varepsilon_b - \varepsilon_f|$, in which $\varepsilon_a$ and $\varepsilon_f$ are respective extinction coefficient of the complex in the presence and absence of DNA. The apparent extinction coefficient $\varepsilon_a$ is obtained by calculating $A_{obs}$/[acridone]. The data were fitted to the equation with a slope equal to $1/\Delta\varepsilon$ and Y-intercept equal to $1/(\Delta\varepsilon \times K)$. The intrinsic binding constant ($K_i$) is determined from the slope of Y-intercept. The percentage hypochromism was calculated as % hypochromism = $[(\varepsilon_{free} - \varepsilon_{bound)} \times 100]/\varepsilon_{free}$.

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