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Original article

Synthesis of new chalcone derivatives containing acridinyl moiety with potential antimalarial activity

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ABSTRACT

A series of novel chalcones bearing acridine moiety attached to the amino group in their ring A have been synthesized through noncatalyzed nucleophilic aromatic substitution reaction between various 3′-aminochalcone or 4′-aminochalcones and 9-chloroacridine. The synthesized chalcone derivatives have been characterized and screened for *in vitro* antimalarial activity against *Plasmodium falciparum* NF-54. All the chalcones showed complete inhibition at concentration of 10 μg/mL and above while three compounds showed significant inhibition at concentration of 2 μg/mL. The three most active chalcone derivatives were screened for *in vivo* activity as well, but no significant inhibition in parasitaemia was observed when given intraperitoneally to *Plasmodium yoelii* infected mice model.

1. Introduction

In developing countries diseases particularly of protozoan origin such as malaria, amoebiosis, sleeping sickness, leishmaniasis and others are prevalent and is of great concern. The world is still under the devastating effects of malaria caused by various species of *Plasmodium,* especially *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium falciparum*, and *Plasmodium vivax.* Among all these agents, *P. falciparum* resistance to common antimalarials is a major obstacle for malaria control [1,2]

Attempts to develop chloroquine-resistant strains of *Plasmodium*, particularly of *P. falciparum* have been continuing [3,4] for several decades.

The identification of new targets, that are critical to the disease process or essential for the survival of the parasite are of major concern. The design of noble chemical entities specifically affecting these targets could lead to availability of better drugs for the treatment of malaria [5].

In the same context, chalcones have gained strong ground for various biological and antioxidant activities [6–10]. Some new chalcones having potent antimicrobial activities have been evaluated by our group [11]. The antimalarial activity of chalcones was apparent after the first report on licochalcone A with potent *in vivo* and *in vitro* antimalarial activity [12]. Another synthetic analogue, 2,4-dimethoxy-4′-butoxychalcone, a novel compound [13] also possessed outstanding antimalarial activities both against human (*in vitro*) and rodent (*in vivo*) parasites with no observable signs of toxicity. Studies by Li et al. [14], Liu et al. [15] and Go et al. [16] have revealed *in vitro* antimalarial activity of chalcones against a chloroquine-resistant human malarial parasite, *P. falciparum* (K1). Natural chalcones, 5-Prenylbutein, licoagrochalcone A and homobutein [17] showed *in vitro* antiplasmodial activity against the chloroquine-sensitive (D6) and the chloroquine-resistant (W2) strains of *P. falciparum* with IC_{50} values in the range 10.3–16.1 μM. Another prenylated chalcone, Crotaorixin [18] exhibited 100% inhibition of maturation of *P. falciparum* NF-54.

Reports on various quinolinyl chalcone analogues [19], prenylated chalcones [20], sulfonamide chalcones [21], phenylsulphonyl urenyl chalcones [22], ferrocenyl chalcones [23,24] are available in the literature. The *in vivo* antimalarial activity of Retinoid-like chalcones [25] and bischalcones against chloroquine-sensitive and resistant strains of *Plasmodium berghei* in mice has also been reported [26,27].

Acridines are being extensively explored in several therapeutic areas and reported to possess potent antimalarial activities [28–31].

The reported diverse biological activities of the chalcone derivatives and acridines are really inspiring and provided impetus to synthesize substituted analogue at 4-position of the styryl phenyl ring (ring B), as this site is especially prone to metabolic oxidation [32]. In this paper synthesis, characterization and antimalarial activity of eleven new 9-acridinylamino chalcone derivatives are presented and discussed.

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2. Chemistry

Chemically chalcone is a generic term given to compounds bearing the 1,3-diphenylprop-2-en-1-one framework. Chalcones have shown potent pharmacological profile and are associated with a plethora of biological activities.

Heteroaryl-substituted chalcones are of special interest because of their potent biological activites. Acridine derivatives are known for antibacterial, metabolic, parasitologic and antiprotozoal activities [33,34]. With this view in mind we decided to synthesize various 9-substituted acridine derivatives. α,β-Unsaturated carbonyl system is a special structural feature of chalcones with the phenyl ' ring A' attached to C-1 and phenyl 'ring B' attached to C-3 of the α, β-unsaturated carbonyl system [35]. Hence various 3′ and 4′ amino (attached to ring A) chalcones were reacted with 9-chloroacridine to obtain the desired acridinyl chalcone derivatives

Synthesis and evaluation of the activity of new acridinyl chalcone detrivatives against a chloroquine-sensitive strain, *P. falciparum* are described in this paper. Syntheses of 4′-aminochalcone or 3′-aminochalcone derivatives **1a–k** were carried out through Claisen–Schmidt condensation [36] of 3- or 4-amino acetophenones with the corresponding substituted benzaldehyde (where R_2 = H, 3-NO_2, 3-CH_3, 4-CH_3, 4-OCH_3, 4-Cl, 3,4,5-tri-OCH_3) and also with cinnamaldehyde derivatives using sodium hydroxide as catalyst in methanol at room temperature (Scheme 1).

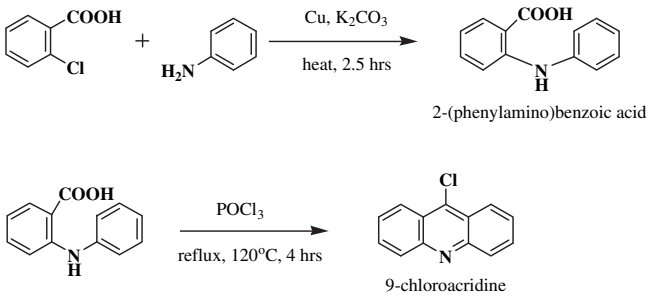
The chalcones were obtained in high yields (>80%). 9-Chloroacridine was synthesized by the condensation of N-arylanthranilic acid with phosphorus oxychloride [37] (Scheme 2).

Subsequent treatment of chalcone derivatives **1a–k** with 9-chloroacridine in 2-butanol yielded compounds, **1–11** (Scheme 3) which were purified by column chromatography to get pure solid compounds. The final yield of the derivatives was in the range of 59–67%. The compounds obtained were stable in the solid as well as in the solution state. The compounds have been characterized by IR, UV–Visible, ^{1}H and ^{13}C NMR and mass spectral data.

3. Pharmacology

Chalcone derivatives possess a diverse range of pharmacological activities, like antiplasmodial [17], inhibitory effect on COX-2 and 5-lipoxygenase [22], antimalarial [2,3,25,28–31], antileishmanial [38,39], antiviral [40], anti-inflammatory [41], antiprotozoal [42], antiplatelet [43], anti-AIDS [44] and so on.

Hence all the acridinyl chalcone derivatives, **1–11**, were screened for *in vitro* antimalarial activity against chloroquine-sensitive NF-54 strain of *P. falciparum* which was cultured *in vitro* according to the method described by Trager and Jensen [45] with minor modifications. Of the eleven new acridinyl chalcone derivatives, five showed enhanced activity.



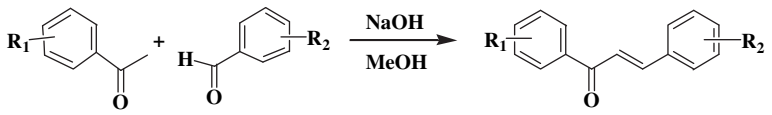
Scheme 2. Synthesis of 9-chloroacridine.

3.1. In vitro antimalarial assay

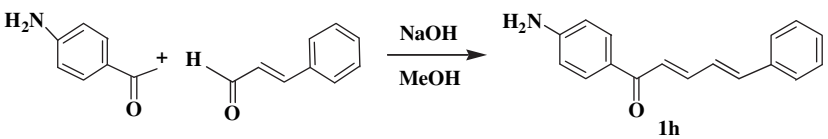
The *in vitro* antimalarial assay was carried out in 96 well microtitre plates according to the microassay protocol of Rieckmann et al. [46] with minor modifications. The cultures of *P. falciparum* NF-54 strain were routinely maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 0.5% ALBUMAX-II. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 1.0–1.5% at 3% haematocrit in a total volume of 200 μL of medium RPNI with 10% fetal bovine serum [47] was uniformly maintained. A stock 5 mg/mL concentrate of the given test sample was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted test samples in 20 μL volume were added to the test wells so as to obtain final concentrations (at five fold dilutions) ranging between 0.4 μg/mL and 100 μg/mL in duplicate wells containing parasitized cell preparation. The culture plates were incubated at 37 °C in a CO_2 incubator. After 36–40 h incubation, the blood smears from each well were prepared and stained with Giemsa stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts with different concentrations of the compounds.

4. Results and discussion

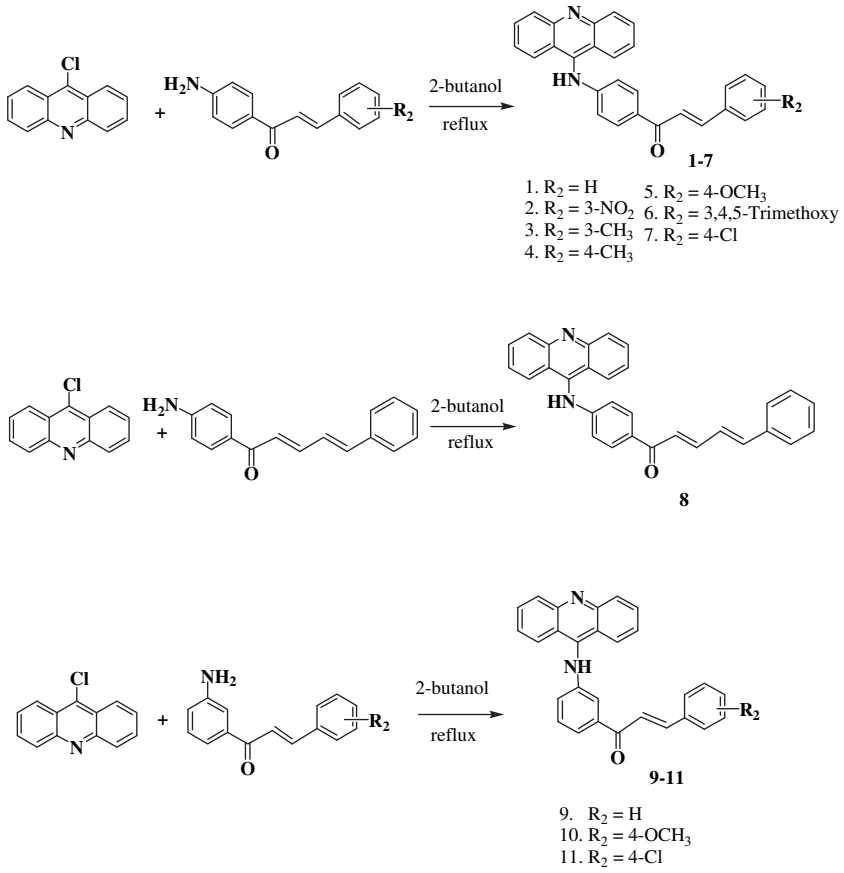
For *in vitro* antimalarial assay, the test concentration, which inhibited the complete maturation into schizonts, was recorded as



(1a) R_1 = 4-NH_2 R_2 = H **(1f)** R_1 = 4-NH_2 R_2 = 3,4,5-triOCH_3
(1b) R_1 = 4-NH_2 R_2 = 3-NO_2 **(1g)** R_1 = 4-NH_2 R_2 = 4-Cl
(1c) R_1 = 4-NH_2 R_2 = 3-CH_3 **(1i)** R_1 = 3-NH_2 R_2 = H,
(1d) R_1 = 4-NH_2 R_2 = 4-CH_3 **(1j)** R_1 = 3-NH_2 4-OCH_3
(1e) R_1 = 4-NH_2 R_2 = 4-OCH_3 **(1k)** R_1 = 3-NH_2 R_2 = 4-Cl



Scheme 1. Synthesis of 1-(4(or 3-)-aminophenyl)-3-(substituted)phenyl- prop-2-en-1-one.



Scheme 3. Synthesis of 1-(4-(9-acridinylamino)phenyl)-3(substituted) phenylprop-2-en-1-one.

the minimum inhibitory concentration (MIC). Chloroquine was used as the standard reference drug. The mean number of rings, trophozoites and schizonts recorded per 100 parasites from duplicate wells after incubation for 38 h and percent maturation inhibition with respect to untreated control group are shown in Table 1.

All the anilinoacridine chalcone derivatives inhibited the maturation of parasite fully at 10 μg/mL level. Seven compounds showed activity upto 2 μg/mL concentration. Chalcones **1**, **4**, **6** and **8** showed 42.8, 42.8, 57.1 and 64.3% maturation inhibition respectively at 2 μg/mL. Out of eleven, three samples **5**, **9** and **10** exhibited >70% inhibition at 2 μg/mL concentration. Particularly compound **5** inhibited 85.7%, 71.4% and 14.3% maturation of parasite into schizonts at 2 μg/mL, 0.4 μg/mL and 0.08 μg/mL concentrations respectively, while **9** and **10** showed 97.1% and 71.4% inhibition of parasite at 2 μg/mL level followed by low inhibition of 4.3% and 7.1% at 0.4 μg/mL levels. In a broad sense compounds with 3′-amino group were more reactive compared to 4′-amino chalcones. Alkoxylated chalcones **5** and **10** showed good antimalarial activity but trialkyloxy-substituted chalcones showed reduced activity. Investigation on the activity of chalcones resulted in the identification of three inhibitors with low micromolar efficacy against *P. falciparum* strain (NF-54) *in vitro*.

These new chalcone derivatives showed much enhanced activity relative to other chalcone derivatives [8,14,18,23,24]. Three compounds (**5**, **9** and **10)** were further screened for *in vivo* efficacy against a chloroquine-resistant rodent malaria parasite *Plasmodium yoelii* (strain N-67) in Swiss mice model. The out-bred Swiss mice (weights = 23 ± 2 g) of either sex were inoculated intraperitoneally with 1×10^6 *P. yoelii* parasitized RBC and the day of inoculation was designated as 'Day 0'.The aqueous suspensions of the compounds were prepared after making a paste with a few drops of Tween-80. The volume was adjusted so as to obtain the required 50 mg/kg doses in 0.5 mL volume. The treatment to each of the three groups of *P. yoelii* infected mice was administered via intraperitoneal route, once daily for four consecutive days from day 0 to day 3. One group of 6 mice was administered the aqueous vehicle used for preparing suspension and served as untreated control. The thin blood smears were prepared from each animal on day 4 i.e. 24 h after the last treatment dose and again on day 6. The degree of infection was microscopically recorded in terms of number of *P. yoelii* infected cells per 100 RBC (i.e. percent parasitaemia). The mean value determined for a group of 6 mice was used to calculate the percent suppression of parasitaemia with respect to the untreated control group. The degree of parasitaemia on day 4 and day 6 for the treated groups and the relative suppression of parasitaemia with respect to control group are indicated in Table 2.

These inhibitors were found to be inactive when given intraperitoneally in a *P. yoelii* infected mice model. Metabolic instability may be responsible for the lack of activity *in vivo* due to possible significant degradation of compounds upon their exposure to a liver microsome preparation. The degree of parasitaemia suppression on day 4 and day 6 for the treated groups and the relative suppression of parasitaemia with respect to control group is indicated in Table 2 that indicates no significant inhibition in parasitaemia with any of the three samples.

From the results of *in vitro* study on the antimalarial activity it is evident that 1-(3-(Acridin-9-ylamino)phenyl)-3-phenylprop-2-en-1-one derivatives are more potent than 1-(4-(Acridin-9-ylamino)phenyl)-3-phenylprop-2-en-1-one derivatives. In the latter case, substituents at 4′ position of ring B were more potent than

Table 1
In vitro antimalarial activity of acridinyl chalcone derivatives.

Compound	Concentrations evaluated (μg/mL)	Number of parasites/100 infected RBCs			Percent schizont maturation inhibition
		Rings	Trophozoites	Schizonts	
Control	–	0	30	70	–
1	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	0	60	40	42.8
2	100	100	0	0	100
	50	100	0	0	100
	10	30	70	0	100
	2.0	0	30	70	0
3	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	0	30	70	0
4	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	0	60	40	42.8
5	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	50	40	10	85.7
	0.4	5	75	20	71.4
	0.08	0	40	60	14.3
6	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	0	70	30	57.1
	0.4	0	34	66	5.7
7	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	0	30	70	0
8	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	15	60	25	64.3
	0.4	0	30	70	0
9	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	25	73	02	97.1
	0.4	3	30	67	4.3
10	100	100	0	0	100
	50	100	0	0	100
	10	60	40	0	100
	2.0	20	60	20	71.4
	0.4	0	35	65	7.1
11	100	100	0	0	100
	50	100	0	0	100
	10	100	0	0	100
	2.0	0	30	70	0
Chloroquine	0.50	100	0	0	100
	0.25	100	0	0	100
	0.125	95	3	2	97.1
	0.0625	70	32	18	74.3
	0.50	100	0	0	100

3′-substituents. It is evident that substituents play a vital role in interaction with the enzyme that perturb the concerned chalcone from binding on the active site of the enzyme. It seems that chalcones exert their antimalarial efficacy through multiple mechanisms and different substituted chalcones exert their antimalarial activity through different pathways.

5. Conclusion

A series of novel chalcones bearing acridine moiety in one of the rings has been synthesized through noncatalysed nucleophilic aromatic substitution with 3′-aminochalcone and also with 4′-aminochalcone.

Table 2
In vivo antimalarial activity of acridinyl chalcone derivatives.

Code of test sample	Dose (mg/kg)	No. of mice	Mean percent parasitaemia on		Suppression of parasitaemia on		Mean survival time ± SE (days)
			Day 4	Day 6	Day 4	Day 6	
5	50	6	6.48 ± 0.94	14.58 ± 1.20	Nil	Nil	10.67 ± 2.17
9	50	6	6.45 ± 0.54	15.0 ± 0.93	Nil	Nil	15.50 ± 2.23
10	50	6	6.03 ± 0.43	15.0 ± 0.41	6.22	Nil	15.20 ± 1.45
Control	–	6	6.43 ± 0.73	15.08 ± 0.88	–	–	15.83 ± 1.25

All the synthesized chalcones have been evaluated for *in vitro* antimalarial activity against *P. falciparum* NF-54. All of them inhibited the maturation of parasite at concentration of 10 μg/mL and above.

Chalcone derivatives **5**, **9** and **10** exhibited >71% inhibition at 2 μg/mL concentration. Compound **5** showed 71.4% inhibition of parasite even at a low concentration of 0.4 μg/mL.

It is also evident that location and nature of the substituent(s) in ring B of the chalcone derivative are crucial. Derivatives **5**, **9** and **10** have potent antimalarial activity and are likely to be useful as drugs after further refinement. These derivatives will encourage to help design future antimalarials with therapeutic potentials.

6. Experimental protocol

All the organic solvents used were of high purity unless otherwise stated. The reactions were monitored by TLC on precoated TLC aluminium plate (Merck Germany) silica gel $60F_{254}$ thin layer plates. Elemental analysis (C, H, N; Elementar Vario EL III Instrument), Melting points (open capillary method on a Perfit Melting Point apparatus), Electronic spectra (Shimadzu-1601 PC UV–VIS spectrophotometer), IR spectra (Nexus FT-IR spectrophotometer), ^{1}HNMR and ^{13}C NMR (Bruker Spectrospin 500 MHz Spectrometer) spectra have been recorded. The EI Mass spectra of the compounds were recorded on a Perkin–Elmer Clarus 500 GC-Mass Spectrometer. Fab Mass spectra of the final compounds were recorded on a JEOL JMS600 Mass Spectrometer. Analytical HPLC was performed on an Agilent 1100 preparative HPLC system employing a VWL detector. The compounds were analyzed in solution (1 μM in MeOH) by HPLC with a ZORBAX EclipseXDB-C8 column (4.6 × 150 mm, 5 μm) using elution system (system: 50% MeOH in H_2O; gradient elution 10/90–90/10 at a flow rate of 0.5 mL/min). System was used with UV (254 nm) detection and t_R values were reported in min with the analytical data.

6.1. Synthesis and characterisation of the compounds

6.1.1. Synthesis of chalcones *1a–k*

The amino chalcones were synthesized by using general Claisen–Schimdt condensation (Scheme 1).

6.1.2. Synthesis of 9-chloroacridine

9-chloroacridine was synthesized by the cyclisation of N-arylantranilinic acid with phosporus oxychloride as reported [37] (Scheme 2)

6.2. Synthesis of acridinyl chalcone derivatives

Synthesis of acridinyl chalcones was carried out on a millimolar scale. The method used is as follows:

6.2.1. 1-(4-(Acridin-9-ylamino)phenyl)-3-phenylprop-2-en-1-one (*1*)

Chalcone **1a** 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (1.12 g, 5 mM) and 9-chloroacridine (1.07 g, 5 mM) were dissolved in minimum amount of 2-butanol (15 mL). One drop of HCl was added to the reaction mixture to catalyse the reaction. The contents were refluxed at 110 °C over a silicone oil bath for 6–8 h. The completion of the reaction was checked by TLC. The reaction mixture was allowed to cool to room temperature and then poured into ice water (25 mL). The precipitate formed, was filtered off with suction, washed with water, and chromatographed on a silica gel column (6 × 25 cm) using PE/EA (8:2 v/v) as the eluant. The fractions containing the product were combined and evaporated in vacuo to dryness. The solid residue was recrystallized from methanol to get **1:** Orange crystals (methanol); Yield = 1.18 g (59%); m.p. 205–206 °C; t_R (min): 5.215; Anal calc. for ($C_{28}H_{20}N_2O$) C, 83.98, H,5.03; N, 7.00; %; found; C,83.53; H, 5.23; N, 7.14%; UV/VIS; λ_{max} (nm): 208, 250, 319, 398; IR: ν_{max} (cm^{-1}), 3428 (NH), 2925 (C–H), 1638 (C═O), 1621 (C═C), 1589 (C═N), 1470, 1409, 1336, 1172, 1016 (C–N), 931(trans ethylenic H), 841, 779 (CH arom bend); FAB–MS *m/z*: 401.14 $[M+H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.21 (1H, s, exchangeable NH), 8.39 (2H, d, J = 8.0 Hz, ArH), 8.21 (1H, d, J = 15.5 Hz, H_β), 7.97 (2H, d, J = 8.5 Hz), 7.78 (2H, t, J = 7.5 Hz, Acri), 7.59–7.52 (3H, m, J_1 = 8.0 Hz, J_2 = 15.5 Hz, H_α), 7.47 (2H, d, J = 8.5 Hz), 7.34 (2H, t, J = 7.5 Hz, Acri), 6.92–6.86 (3H, m) 6.65 (2H, d, J = 8.0 Hz, ArH); ^{13}C NMR (DMSO-d_6) (δ, ppm): 182.9, 153.8, 149.8, 142.3, 140.3, 137.1, 135.2, 131.4, 130.9, 130.2, 129.4, 129.3, 128.9, 127.6, 126.7, 126.4, 121.9, 119.4, 115.9,

6.2.2. 1-(4-(Acridin-9-ylamino)phenyl)-3-(3-nitrophenyl)prop-2-en-1-one (*2*)

Compound **2** was prepared as per procedure followed for **1**, using 1-(4-aminophenyl)-3-(3-nitrophenyl)prop-2-en-1-one (**1b**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Bright yellow crystals (methanol); Yield: 1.51 g (68%); m.p.: 248 °C (d); t_R (min): 5.714; Anal calc. for ($C_{28}H_{19}N_3O_3$) C, 75.49; H, 4.30; N, 9.43; found; C, 75.80, H, 4.04, N, 9.57%; UV/VIS; λ_{max} (nm): 213, 250, 398; IR: ν_{max} (cm^{-1}), 3455 (NH), 2834 (C–H), 1664 (C═O), 1630 (C═C), 1582 (C═N), 1530 and 1350 (-NO_2), 1272, 1219, 1170, 1033 (C–N), 969 (trans ethylenic H), 804, 752 (CH arom bend); FAB–MS *m/z*: 445.23 $[M]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.37 (1H, s, exchangeable NH), 8.41 (1H, s), 8.24 (2H, d, J = 8.0 Hz, ArH), 8.10 (1H, d, J = 15.5 Hz, H_β), 7.99 (2H, d, J = 8.5 Hz, ArH), 7.84 (1H, d, J = 15.5 Hz, H_α), 7.73 (2H, t, J = 7.5 Hz, Acri), 7.57 (2H, d, J = 8.5 Hz, ArH), 7.49 (1H, t, J = 8.5 Hz, ArH), 7.38 (2H, d, J = 8.5 Hz, ArH), 7.26 (2H, t, J = 8.0 Hz, Acri), 6.94 (2H, d, J = 8.5 Hz, ArH); ^{13}C NMR (DMSO-d_6) (δ, ppm):183.8, 149.8, 147.5, 142.1, 132.9, 132.8, 132.7, 131.9, 131.1, 130.42, 129.8, 128.5, 127.9, 127.2, 126.4, 122.3, 120.1, 115.5, 113.1.

6.2.3. 1-(4-(Acridin-9-ylamino)phenyl)-3-m-(tolyl)prop-2-en-1-one (*3*)

Compound **3** was prepared using 1-(4-aminophenyl)-3-(3-methylphenyl)prop-2-en-1-one (**1c**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Orange crystals (methanol); Yield: 1.39 g (67%); m.p.: 185–186 °C; t_R (min): 5.281; Anal calc. for ($C_{29}H_{22}N_2O$) C, 84.03; H, 5.35; N, 6.76%; found; C, 84.36; H, 5.66; N, 6.47%; UV/VIS; λ_{max} (nm): 213, 250, 320, 397; IR: ν_{max} (cm^{-1}), 3414 (NH), 3235, 2852 (C–H), 1637 (C═O), 1619 (C═C), 1589 (C═N), 1470, 1385, 1336, 1172, 1095 (C–N), 939 (trans ethylenic H), 752 (CH arom bend); FAB–MS *m/z*: 415.24 $[M+H]^+$; ^{1}H NMR (DMSO-d_6) (δ,

ppm): 11.64 (1H, s, exchangeable NH), 8.41 (1H, s), 8.32 (2H, d, $J = 8.0$ Hz, ArH), 8.18 (1H, d, $J = 15.5$ Hz, H_β), 8.07–7.84 (4H, m), 7.71 (1H, d, $J = 15.5$ Hz, H_α), 7.59 (2H, d, $J = 8.5$ Hz, ArH), 7.38 (2H, t, $J = 7.5$ Hz, Acri), 7.29 (2H, d, $J = 8.5$ Hz, ArH), 7.16 (1H, t, $J = 8.5$ Hz, ArH), 6.72 (2H, d, $J = 8.5$ Hz, ArH), 2.83 (3H, s-CH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 189.6, 153.8, 146.3, 142.2, 141.7, 136.4, 130.9, 130.6, 129.7, 129.2, 126.6, 126.5, 123.3, 121.9, 120.8, 119.5, 115.9, 27.7.

6.2.4. 1-(4-(Acridin-9-ylamino)phenyl)-3-p-(tolyl) prop-2-en-1-one (**4**)

Compound **4** was prepared as per method used for synthesis of **1**, using 1-(4-aminophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**1d**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Orange-red crystals (methanol); Yield: 1.53 g (74%); m.p.: 144–146 °C; t_R (min): 5.233; Anal calc. for ($C_{29}H_{22}N_2O$) C, 84.03; H, 5.35; N, 6.76%; found; C, 84.34; H, 5.63; N, 6.51%; UV/VIS; λ_{max} (nm): 249, 327, 400; IR: ν_{max} (cm^{-1}), 3454 (NH), 2929, 2855 (C–H), 1602 (C═O), 1587 (C═C), 1551(C═N), 1511, 1482, 1340, 1227, 1175, 1023 (C–N), 987 (trans ethylenic H), 808, 761 (CH arom bend); FAB–MS m/z: 415.04 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 10.81 (1H, s, exchangeable NH), 8.42 (2H, d, $J = 7.5$ Hz), 8.32 (2H, d, $J = 7.5$ Hz), 8.08 (1H, d, $J = 15.5$ Hz, H_β), 7.92 (2H, d, $J = 7.5$ Hz), 7.86 (1H, d, $J = 15.5$ Hz, H_α), 7.72 (2H, t, $J = 8.5$ Hz, Acri), 7.42 (2H, d, $J = 8.0$ Hz), 7.24 (2H, t, $J = 8.5$ Hz, Acri), 7.06 (2H, d, $J = 8.5$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 2.21 (3H, s, -CH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 186.5, 148.2, 144.5, 137.6, 132.8, 132.1, 130.9, 129.7, 129.4, 128.5, 127.9, 126.3, 121.7, 120.8, 120.0, 115.4, 108.5, 108.1, 26.4.

6.2.5. 1-(4-(Acridin-9-ylamino)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**5**)

Compound **5** was prepared using 1-(4-aminophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1e**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Yellow-orange crystals (methanol); Yield: 1.68 g (78%); m.p.: 159–161 °C; t_R (min): 5.650; Anal calc. for ($C_{29}H_{22}N_2O_2$) C, 80.91; H, 5.15; N, 6.51%; found; C,80.63; H, 5.61; N, 6.4; UV/VIS; λ_{max} (nm): 208, 248, 341, 399; IR: ν_{max} (cm^{-1}) 3462 (NH), 2952, 2832 (C–H), 1626 (C═O), 1595 (C═C), 1511 (C═N), 1443, 1378, 1252, 1178, 1026 (C–N), 920 (trans ethylenic H), 834, 747 (CH arom bend); FAB–MS m/z: 431.02 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.12 (1H, s, exchangeable NH), 8.43 (2H, d, $J = 8.0$ Hz, ArH), 8.07 (2H, d, $J = 8.0$ Hz, ArH), 7.99 (1H, d, $J = 16.5$ Hz, H_β), 7.95–7.82 (4H, m), 7.78 (1H, d, $J = 16.5$ Hz, H_α), 7.73 (2H, d, $J = 8.0$ Hz, ArH), 7.44 (2H, t, $J = 8.5$ Hz, Acri), 7.10 (2H, d, $J = 8.0$ Hz, ArH), 6.86(2H, d, $J = 8.5$ Hz, ArH), 3.85 (3H, s, –OCH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 181.6, 152.4, 140.1, 135.5, 134.9, 132.4, 130.1, 126.2, 124.8, 121.7, 121.6, 120.4, 120.1, 119.7, 117.3, 113.5, 112.4, 111.9, 110.2, 108.4, 108.2 57.6.

6.2.6. 1-(4-(Acridin-9-ylamino)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**6**)

Compound **6** was prepared as per procedure for the synthesis of **1**, using 1-(4-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**1f**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Orange crystals (methanol); Yield: 1.08 g (44%); mp 175–176 °C; t_R (min): 6.017; Anal calc. for ($C_{31}H_{26}N_2O_4$) C, 75.90; H, 5.34; N, 5.71%; found; C,75.63; H, 5.63; N, 5.48%; UV/VIS; λ_{max} (nm): 212, 249, 327, 360; IR: ν_{max} (cm^{-1}), 3434 (NH), 2920, 2737 (C–H), 1635 (C═O), 1580 (C═C), 1513 (C═N), 1416, 1327, 1272, 1216, 1168, 1091, 1014 (C–N), 970 (trans ethylenic H), 815, 753 (CH arom bend); EI-MS m/z: 491 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.17 (1H, s, exchangeable NH), 8.24 (2H, d, $J = 8.0$ Hz, ArH), 7.97 (1H, d, $J = 16.0$ Hz, H_β), 7.81 (2H, d, $J = 8.5$ Hz, ArH), 7.74 (2H, t, $J = 8.0$ Hz, Acri), 7.56 (2H, d, $J = 8.0$ Hz, ArH), 7.48 (1H, d, $J = 16.5$ Hz, H_α), 7.39 (2H, s, ArH), 7.27 (2H, t, $J = 8.0$ Hz, Acri), 7.19 (2H, d, $J = 8.5$ Hz, ArH), 3.88 (6H, s, –OCH_3), 3.72 (3H, s, –OCH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 186.3, 149.3, 147.5, 132.9, 132.8, 132.5, 131.9, 131.1, 130.4, 128.8, 127.2, 122.4, 122.3, 120.1, 115.5, 106.3, 62.1, 56.6.

6.2.7. 1-(4-(9-Acridinylamino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (7)

Compound **7** was prepared using 1-(4-aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**1g**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Orange-red crystals (methanol); Yield: 1.37 g (63%); m.p. 227–228 °C; t_R (min): 6.383; Anal calcd. for ($C_{28}H_{19}ClN_2O$) C, 77.33; H, 4.40; N, 6.44%; found; C, 77.63; H, 4.63; N, 6.48%; UV/VIS; λ_{max} (nm): 205, 246, 317, 420; IR: ν_{max} (cm^{-1}), 3434 (NH), 2921, 2737, 1637 (C═O), 1614 (C═C), 1579 (C═N), 1513, 1416, 1327, 1272, 1213, 1169, 1092, 1014 (C–N), 970 (trans ethylenic H), 815, 753 (CH arom bend); EI-MS m/z: 435 $[M + H]^+$; ^{1}H NMR (CD_3OD) (δ, ppm): 11.63 (1H, s, exchangeable NH), 8.32 (2H, d, $J = 8.5$ Hz, ArH), 8.26 (2H, d, $J = 8.5$ Hz, ArH), 8.17 (1H, d, $J = 17.5$ Hz, H_β), 8.09 (2H, t, $J = 7.5$ Hz, Acri), 8.05 (2H, d, $J = 8.5$ Hz, ArH), 7.99 (1H, d, $J = 17.5$ Hz, H_α), 7.86 (2H, d, $J = 8.0$ Hz, ArH), 7.81 (2H, d, $J = 8.0$ Hz ArH), 7.57 (2H, t, $J = 7.5$ Hz, ArH), 7.49 (2H, d, $J = 7.5$ Hz, ArH); ^{13}C NMR (DMSO-d_6) (δ, ppm): 187.5, 148.1, 143.2, 141.4, 140.8, 133.9, 132.6, 131.9, 131.3, 130.7, 129.9, 129.2126.5, 121.5, 120.9, 117.8, 115.8, 113.5, 112.7.

6.2.8. 1-(4-(Acridin-9-ylamino)phenyl)-5-(phenyl)penta-2,4-dien-1-one (**8**)

Compound **8** was prepared following procedure for the synthesis of **1**, using 1-(4-aminophenyl)-5-phenylpenta-2,4-dien-1-one (**1h**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Yellow powder (methanol); Yield: 1.09 g (51%); m.p. 196–197 °C; t_R (min): 5.856; Anal calc. for ($C_{30}H_{22}N_2O$) C, 84.48; H, 5.20; N, 6.57%; found; C, 84.26; H, 5.21; N, 6.85%; UV/VIS; λ_{max} (nm): 213, 248, 360; IR: ν_{max} (cm^{-1}), 3472 (NH), 2913, 2833 (C–H), 1635 (C═O), 1592 (C═C), 1571 (C═N), 1469, 1384, 1265, 1165, 1030 (C–N), 934 (trans ethylenic H), 812, 752(CH arom bend); ESI–MS m/z: 427 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.77 (1H, s, exchangeable NH), 8.34 (2H, d, $J = 8.0$ Hz, ArH), 8.23–8.12 (3H, m, ArH), 7.83 (2H, t, $J = 7.5$ Hz, Acri), 7.77 (1H, d, $J = 15.5$ Hz, H_α), 7.69–7.53 (4H, m), 7.48 (2H, t, $J = 7.5$ Hz, Acri), 7.34 (1H, d, $J = 8.5$ Hz, ArH), 7.21–7.08 (3H, m), 6.91 (1H, d, $J = 14.5$ Hz, ArH), 6.79 (2H, d, $J = 8.5$ Hz, ArH); ^{13}C NMR (DMSO-d_6) (δ, ppm): 184.7, 153.5, 148.7, 144.1, 140.3, 137.4, 136.2, 135.9, 131.8, 131.3, 129.5, 128.9, 128.2, 126.8, 121.8, 120.1, 119.6, 115.8.

6.2.9. 1-(3-(Acridin-9-ylamino)phenyl)-3-(phenyl)prop-2-en-1-one (**9**)

Compound **9** was prepared as per method used for synthesis of **1**, using 1-(3-aminophenyl)-3-phenylprop-2-en-1-one (**1i**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Bright yellow crystals (methanol); Yield: 1.38 g (69%); m.p. 201–202 °C; t_R (min): 5.133; Anal calc. for ($C_{28}H_{20}N_2O$) C, 83.98; H, 5.03; N, 7.00%; found; C,83.53; H, 5.13; N, 7.11%; UV/VIS; λ_{max} (nm): 250, 319, 398; IR: ν_{max} (cm^{-1}), 3452 (NH), 2925, 2822 (C–H), 1638 (C═O), 1625 (C═C), 1529 (C═N), 1475, 1338, 1186, 1035 (C–N), 847, 743 (CH arom bend); FAB–MS m/z: 401.24 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.74 (1H, s, exchangeable NH), 8.39 (2H, d, $J = 8.0$ Hz), 8.21 (1H, d, $J = 15.5$ Hz, H_β), 7.97 (2H, d, $J = 8.5$ Hz), 7.91 (1H, s), 7.85–7.76 (1H, m), 7.69 (2H, t, $J = 7.5$ Hz Acri), 7.63 (1H, d, $J = 15.5$ Hz, H_α), 7.51 (2H, d, $J = 8.0$ Hz), 7.39 (2H, t, $J = 7.5$ Hz, Acri), 7.27–7.18 (3H, m), 7.13 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (DMSO-d_6) (δ, ppm): 183.1, 153.7, 148.0, 145.1, 143.5, 141.9, 140.2, 135.3, 134.9, 128.8, 128.2, 127.1, 125.7, 123.9, 123.8, 119.3, 115.4, 114.2.

6.2.10. 1-(3-(Acridin-9-ylamino) phenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (**10**)

Compound **10** was prepared according to the synthesis of **1**, using 1-(3-aminophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one

(**1j**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Yellow-orange powder (methanol); Yield: 1.53 g (71%); mp 225–226 °C; t_R (min): 4.466; Anal calc. for ($C_{29}H_{22}N_2O_2$) C, 80.91; H, 5.15; N, 6.51%; found; C,80.21; H, 5.55; N, 6.67%; UV/VIS; λ_{max} (nm): 212, 249, 341, 397; IR: ν_{max} (cm^{-1}), 3462 (NH), 2931, 2846 (C–H), 1626 (C═O), 1595 (C═C), 1579 (C═N), 1473, 1252, 1178, 1026 (C–N), 920 (trans ethylenic H), 747(CH arom bend); FAB–MS *m*/*z*: 431.06 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.11 (1H, s, exchangeable NH), 8.17 (2H, d, $J = 8.0$ Hz, ArH), 7.79 (1H, d, $J = 17.5$ Hz, H_β), 7.66 (2H, t, $J = 8.5$ Hz, acri), 7.59–7.46 (2H, m, $J_1 = 8.5$ Hz, $J_2 = 17.5$ Hz, H_α), 7.41 (2H, d, $J = 8.5$ Hz), 7.37 (1H,s), 7.32 (1H, d, $J = 8.5$ Hz), 7.25 (2H, t, $J = 7.5$ Hz, acri), 7.13 (1H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.0$ Hz), 3.81 (3H, s, –OCH_3); ^{13}C NMR (DMSO-d_6) (δ, ppm): 182.3, 148.3, 144.6, 142.3, 140.5, 135.4, 134.6, 133.8, 130.1, 129.9, 128.7, 128.1, 125.4, 124.8, 122.0, 119.6, 115.1, 60.1.

*6.2.11. 1-(3-(Acridin-9-ylamino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**11**)*

Compound **11** was prepared according to the synthesis of **1**, using 1-(3-aminophenyl)-3-(4-chlrophenyl)prop-2-en-1-one (**1k**) instead of 1-(4-aminophenyl)-3-phenylprop-2-en-1-one (**1a**). Bright-orange crystals (methanol); Yield: 1.22 g (56%); m.p. 215–216 °C; t_R (min): 5.091; Anal calc. for ($C_{28}H_{19}ClN_2O$) C, 77.33; H, 4.40; N, 6.44%; found; C,77.63; H, 4.63; N, 6.48%; UV/VIS; λ_{max} (nm): 214, 248, 313, 399; IR: ν_{max} (cm^{-1}), 3459 (NH), 2923, 2851(C–H), 1628 (C═O), 1596 (C═C), 1561 (C═N), 1474, 1341, 1262, 1193, 1028 (C–N), 939 (trans ethylenic H), 819, 752(CH arom bend); EI-MS *m*/*z*: 435 $[M + H]^+$; ^{1}H NMR (DMSO-d_6) (δ, ppm): 11.86 (1H, br s, exchangeable NH), 8.22 (1H, d, $J = 8.0$ Hz, ArH), 8.15 (2H, d, $J = 8.0$ Hz, ArH), 7.91 (1H, d, $J = 15.5$ Hz, H_β), 7.86 (2H, d, $J = 8.0$ Hz, ArH), 7.82 (3H, m, $J_1 = 8.5$ Hz, $J_2 = 15.5$ Hz, H_α), 7.70 (2H, t, $J = 8.5$ Hz, Acri), 7.62 (2H, d, $J = 9.0$ Hz, ArH), 7.47 (2H, d, $J = 8.5$ Hz, Acri), 7.22 (2H, d, $J = 7.5$ Hz, ArH); ^{13}C NMR (DMSO-d_6) (δ, ppm):175.5, 161.1, 148.4, 143.4, 141.1, 134.4, 133.1, 131.6, 129.4, 129.1, 128.7, 128.3, 128.2, 127.6, 126.4, 123.3.

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