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Original article

Synthesis of substituted acridinyl pyrazoline derivatives and their evaluation for anti-inflammatory activity

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ABSTRACT

A rapid preparation of compounds (**1**–**24**), with the objective of discovering novel and potent anti-inflammatory agent. All the compounds exhibited anti-inflammatory and analgesic activities at the dose 50 mg/kg p.o. The compound 1-(2′,4′-Chloroacridine-9′-yl)-3-(5′-pyridine-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazole-5-one **24** showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg p.o.

1. Introduction

The inflammation process involves a series of event that can be elicited by numerous stimuli (eg. infectious agents, ischemia, antigen–antibody interaction). Almost two decades ago, steroids namely prednisolone, dexamethasone, batamthansone etc were considered to be the choicest anti-inflammatory drugs. Owing to the several adverse effects caused by either short term or long term steroid therapy, these have been more or less replaced by much safer and better tolerated non steroidal anti-inflammatory drugs (NSAIDs). The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of NSAIDs since the past two decades [1,2]. NSAIDs have been highly useful for treating acute, self-limited inflammatory conditions. The development of NSAIDs has helped in understanding the tissue mechanism of inflammation. The pyrazolines have been gaining prominence due to the fact that its derivatives have been found to possess wide spectrum of activities like anti-inflammatory [3–7], analgesic [7] and anticonvulsant [8,9]. In addition various heterocyclic compounds containing acridinyl moieties [10] were also possess quite interesting anti-inflammatory activity. In the light of these facts the pyrazolines by incorporation of acridinyl at the first position and oxadiazolyl [11] moieties at third position have been synthesized.

2. Chemistry

The synthetic routes of compounds are outlined in Scheme 1. The chemical synthesis initiates with the reaction of 9-chloro, 2,4 disubstituted acridines and hydrazine hydrate to yield 2,4 disubstituted acridinyl-2-hydrazines i.e. compounds **1**–**6**.A mixture of compounds **1**–**6** and ethyl acetoacetate in the presence of methanol to give 1-(2′, 4′-disubstituted acridine-9′-yl-3-methyl) pyrazol-5-ones **7**–**12**. Compounds **7**–**12** further reacted with bromine and acetic acid to yield 1-(2′,4′-disubstituted acridine-9′-yl)-3-(bromomethyl)-pyrazol-5-ones (**13**–**18**). On the other hand compounds **13**–**18** were reacted with 5-(4-pyridinyl)-(1,3,4-oxadiazole-2-thiol to yield 1-(2′, 4′-disubstituted acridine-9′-yl)-3-(5′-pyridine-4-yl)-1,3,4-oxadizole-2-yl-thiomethyl)-pyrazole-5-ones **19**–**24**.

3. Pharmacological

The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70–95 days weighing 120–175 g. Acute toxicity was tested in albino mice (15–25 g). Food (chaw pallet) and water was given to the animals ad libitum. The compounds were dissolved in propylene glycol. Phenylbutazone and aspirin were used as reference drugs.

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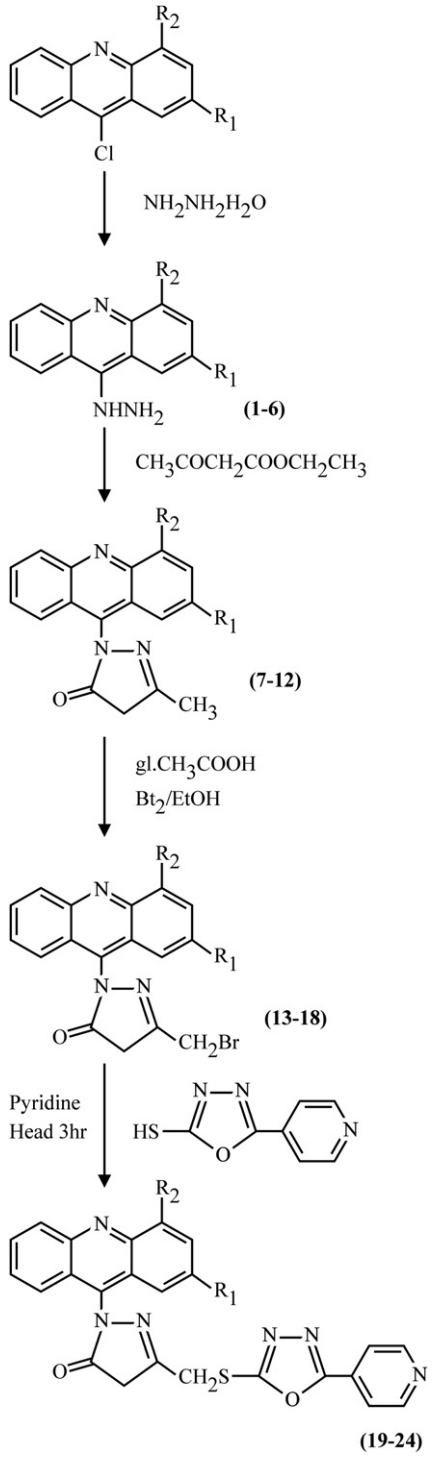

Scheme 1.

3.1. Anti-inflammatory activity

This study was done by following the procedure of Winter et al. [12]. The rats were divided into three groups (control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline), 0.05 mL was injected under the planter aponeurosis of the right hind paw of each rat. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1h before the carrageenan injection. The paw volume of each rat was measured before 1 h and after 3 h of carrageenan treatment with the help of a Plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below.

Percentage of inhibition of oedema $= (1 - V_t/V_c) \times 100$

Where V_t and V_c are the volume of oedema in drug, treated and control group, respectively.

3.2. Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Berkowitz et al. [13]. Test compounds were given to the animals at the dose of 50 mg/kg, 30 min later the animals were injected inter peritoneally with 0.25 mL/mouse of 0.5% acetic acid. The mean number of writhes for each experimental groups and percentage decrease compared with the control group was calculated after 60 min.

3.3. Acute toxicity

Acute Lethal dose (ALD_{50}) of all the compounds were investigated by the method of Smith, Q.E [14].

4. Results and discussion

All the newly synthesized compounds are screened for their anti-inflammatory and analgesic activities. All the compounds have shown anti-inflammatory activity ranging from 10.8 to 40.8% at the dose of 50 mg/kg, p.o. In addition of anti-inflammatory activity these compounds have also exhibited analgesic activity in the ranging from 8.6 to 33.5% at the dose of 50 mg/kg, i.p. given in Table 1. When the compounds were substituted with chloro group at the

Table 1
Pharmacology evaluations of the synthesized compounds **7**–**12**, **13**–**18** and **19**–**24**.

Comp. No.	Dose (mg/kg p.o.)	Anti-inflammatory activity % oedema inhibition relative to control	Analgesic activity % decrease of writhes in 60 min after treatment relative to control	ALD_{50}
7	50	10.8*	8.6*	>1000
8	50	13.5*	12.6**	>1000
9	50	11.5**	10.8**	>1000
10	50	12.6*	12.9*	>1000
11	50	14.4**	13.4**	>1000
12	50	17.6**	14.7**	>1000
13	50	12.8***	13.2***	>1000
14	50	15.9**	16.4**	>1000
15	50	13.5**	15.9**	>1000
16	50	17.1**	13.6**	>1000
17	50	18.6**	16.3**	>1000
18	50	20.7**	18.6**	>1000
19	50	24.1***	25.9***	>1000
20	50	27.2***	30.6***	>1000
22	50	31.2***	29.7***	>1000
22	50	31.5***	28.8***	>1000
23	50	25.6***	26.4***	>1000
24	25	32.1***	30.6***	>1400
	50	40.8***	33.5**	
	100	66.5***	42.4***	
Phenyl	25	31.4***	31.0***	
Butazone	50	40.6***	32.5***	
	100	63.4***	42.6***	
Aspirin	25	30.25***	30.2***	
	50	38.4***	45.5***	
	100	60.8***	59.3***	

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

2,4-position of acridine nucleus showed better anti-inflammatory and analgesic activities than other groups. The anti-inflammatory and analgesic activities of compounds **7**–**12** are 10.8–17.6% and 8.6–14.7% while **13**–**18** have shown ranging from 12.8 to 20.7% and 13.2–18.6% respectively. Among the compounds **7**–**18**, compound **18** which was substituted with 2,4-dichloro at acridinyl pyrazoline ring exhibited 20.7% protection against carrageenan induced oedema. In addition of anti-inflammatory, this compound has shown 18.6% protection against phenyl quinone induced analgesia. On the other hand compounds **19**–**24** showed activities i.e. anti-inflammatory ranging from 24.1 to 40.8% and analgesic 18.6–33.5%. Out of the sixteen 1-(2′,4′-disubstitutedacridine-9′-yl)-3-(5′-pyridine-4-yl)-(1,3,4-oxadizole-2-yl-thiomethyl)-pyrazole-5- ones, the compound **24** tested three graded doses at of 25, 50 and 100 mg/kg, p.o. showed most potent anti-inflammatory 26.4, 40.8, 60.5% activity and this compound also associated with analgesic activity 25.6, 33.5 and 60.4% respectively. The compound **24** was compared with reference drugs phenylbutazone and aspirin and at all the three graded doses this compound elicited better both activities than reference drugs.

5. Conclusion

While considering all the newly synthesized compounds of this series together, we may conclude that:

- Chloro group at 2nd and 4th position at acridine ring showed more potent activities than other substituted acridine.
- Presence of electronegative atom (chlorine) plays a pivotal role to increase the anti-inflammatory and analgesic activities.

6. Experimental protocols

6.1. Chemistry

The melting points of compounds were determined in open capillaries and are uncorrected. Homogeneity of the synthesized compounds was routinely checked by thin layer chromatography on Silica Gel-G plates. The eluent was a mixture of different polar and nonpolar solvent in different proportion and spots were located by iodine. The IR spectra were recorded on Bruker IFS-66V FT-IR (ν_{max} in cm^{-1}). The ^1H NMR spectra were recorded by Brucker DRX-400 FT-NMR instrument using $CDCl_3$ as solvent and tetramethyl silane (TMS) as internal reference standard. All exchangeable protons were confirmed by the addition of D_2O. ^{13}C NMR spectra were recorded on Bruker AC 200/DPX 400 MHz. All Chemical shift values were recorded in ppm. Elemental analysis (C, H, N) of these newly synthesized compounds were performed on a Carlo Erba-1108 elemental analyzer.

6.1.1. General procedure for the synthesis of 2,4 di substituted 9-hydrazinyl acridines (*1*–*6*)

A mixture of 2,4-di substituted acridines (0.01 mol) and hydrazine hydrate (0.02 mol) in methanol (50 mL) by warming. These solutions were cooled at room temperature and then mixed together. The reaction contents were allowed to stand at room temperature for nine days solvents were removed under reduced pressure and the solid residue left behind was suspended in 10%, Na_2CO_3 solution (25 mL) and stirred for 30 min. It was then filtered and washed thoroughly with distilled water and air dried to give crude products (**1**–**6**). Compounds **1**–**6** were recrystallized from appropriate solvents to give pure condensed product.

6.1.2. 9-Hydrazinyl acridine (*1*)

Yield (86%), (Methanol), m.p: 195 °C; IR (KBr) ν_{max} in cm^{-1}: 3325/3240 (NH/NH_2), 3028 (C–H aromatic), 1615 (C═C); ^1H NMR ($CDCl_3$) δ in ppm: 7.70 (m, 8H, Ar–H), 7.54 (s, 1H, NH), 4.14 (brs, 2H, NH_2); Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08; Found: C, 74.40; H, 5.66; N, 20.25%. MS: $[M]^+$ at *m*/*z* 209.25.

6.1.3. 2-Chloro-9-hydrazinyl acridine (*2*)

Yield (80%), (Chloroform), m.p: 174 °C; IR (KBr) ν_{max} in cm^{-1}: 3335/3247 (NH/NH_2), 3030 (C–H aromatic), 1518 (C═C); ^1H NMR ($CDCl_3$) δ in ppm : 7.75 (m, 7H, Ar–H), 7.57 (s, 1H, NH), 4.18 (brs, 2H, NH_2); Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24; Found: C, 64.27; H, 4.06; N, 17.40%; MS: $[M]^+$ at *m*/*z* 243.69.

6.1.4. 2-Methoxy-9-hydrazinyl acridine (*3*)

Yield (75%), (Ethyl acetate), m.p: 226 °C; IR (KBr) ν_{max} in cm^{-1}: 3328/3237 (NH/NH_2), 3026 (C–H aromatic), 2925 (C–H aliphatic), 1517 (C═C); ^1H NMR ($CDCl_3$) δ in ppm : 7.71 (m, 7H, Ar–H), 7.55 (s, 1H, NH), 4.12 (brs, 2H, NH_2), 3.70 (s, 3H, OCH_3); Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56; Found: C, 70.15; H, 5.48; N, 17.56%; MS: $[M]^+$ at *m*/*z* 239.69.

6.1.5. 2-Bromo-9-hydrazinyl acridine (*4*)

Yield (72%), (Ethanol), m.p: 252 °C; IR (KBr) ν_{max} in cm^{-1}: 3323/3225 (NH/NH_2), 3024 (C–H aromatic), 1518 (C═C); ^1H NMR ($CDCl_3$) δ in ppm : 7.72 (m, 7H, Ar–H), 7.52 (s, 1H, NH), 4.14 (brs, 2H, NH_2); Anal. Calcd for $C_{13}H_{10}N_3$ Br: C, 54.19; H, 3.50; N, 14.58; Found: C, 54.32; H, 3.35; N, 14.40%; MS: $[M]^+$ at *m*/*z* 288.14.

6.1.6. 4-Chloro-9-hydraziny-2-methoxy acridine (*5*)

Yield (70%) (Methanol) : m.p 235 °C; IR (KBr) ν_{max} in cm^{-1}: 3328/3244 (NH/NH_2), 3037 (C–H aromatic), 940 (C–H aliphatic), 1522 (C═C); ^1H NMR ($CDCl_3$) δ in ppm : 7.75 (m, 6H, Ar–H), 7.60 (s, 1H, NH), 4.15 (s, 2H, NH_2), 3.72 (s, 3H, OCH_3); Anal. Calcd for $C_{14}H_{12}ClN_3O$: C, 61.43; H, 4.42; N, 15.35; Found: C, 61.72; H, 4.54; N, 15.16%; MS: $[M]^+$ at *m*/*z* 273.72.

6.1.7. 2,4-Dichloro-9-hydrazinyl acridine (*6*)

Yield (78%), (Acetone), m.p: 240 °C; IR (KBr) ν_{max} in cm^{-1}: 3345/3254 (NH/NH_2), 3040 (C–H aromatic), 1530 (C═C); ^1H NMR ($CDCl_3$) δ in ppm : 7.80 (m, 6H, Ar–H), 7.62 (s, 1H, NH), 4.20 (s, 2H, NH_2); Anal. Calcd for $C_{13}H_9Cl_2N_3$: C, 56.14; H, 3.26; N, 15.11; Found: C, 56.07; H, 3.40; N, 15.24%; MS: $[M]^+$ at *m*/*z* 278.14.

6.1.8. General procedure for the synthesis of 1-(2′,4′-di substituted acridin-9′-yl)-3-methyl pyrazol-5-one (*7*–*12*)

A mixture of compounds **1**–**6** (0.01 mol) and ethyl acetoacetate (0.01 mol) was refluxed in methanol (25 mL), containing concentrated hydrochloric acid (1 mL) for 10–15 h on a water bath. The resulting solution was then concentrated and cooled at room temperature. The solid thus separated was washed with methanol, dried and recrystallized from suitable solvent.

6.1.9. 1-(Acridin-9′-yl)-3-methyl pyrazol-5-one (*7*)

Yield (70%), m.p: 202 °C; IR (KBr) ν_{max} in cm^{-1}: 3051 (C–H of aromatic), 2946 (C–H of aliphatic), 1715 (C═O), 1608 (C═N), 1540 (C═C of aromatic ring), 1280 (N–N); ^1H NMR ($CDCl_3$) δ in ppm : 7.75 (m, 8H, Ar–H), 3.39 (s, 2H, CH_2CO), 2.58 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 167, 155.1, 148.5, 148.4, 129.5, 129.1, 125.9, 123.4, 111.4, 35.5, 20.4.; Anal. Calcd for $C_{17}H_{13}N_3OCl$: C, 74.17; H, 4.76; N, 15.26; Found: C, 74.38; H, 4.55; N, 15.35%; MS: $[M]^+$ at *m*/*z* 275.30.

6.1.10. 1-(2-′Chloroacridin-9′-y)l-3-methyl pyrazol-5-one (*8*)

Yield (64%), (Ethanol), m.p:185 °C; IR (KBr) ν_{max} in cm^{-1}: 3053 (C–H of aromatic), 2948 (C–H of aliphatic), 1716 (C═O), 1610 (C═N), 1542 (C═C of aromatic ring), 1282 (N–N); ^1H NMR ($CDCl_3$) δ in ppm : 7.76 (m, 7H, Ar–H), 3.42 (s, 2H, CH_2CO), 2.56 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 168.2, 155.4, 150.2, 148.9, 148.7,132.4, 130.6,

130.1, 129.6, 128.9, 125.1, 120.2, 117.4, 104.2, 35.2, 20.2.; Anal. Calcd for $C_{17}H_{12}N_3OCl$: C, 65.92; H, 3.90; N, 13.57; Found: C, 65.80; H, 3.76; N, 13.72%; MS: $[M]^+$ at *m*/*z* 309.07.

*6.1.11. 1-(2′-Methoxyacridin-9′-y)l-3-methyl pyrazol-5-one (**9**)*

Yield (57%), (Methanol), m.p: 231–232 °C; IR (KBr) ν_{max} in cm^{-1}: 3050 (C–H of aromatic), 2945 (C–H of aliphatic), 1715 (C═O), 1612 (C═N), 1544 (C═C of aromatic ring), 1285 (N–N); ^1H NMR ($CDCl_3$) δ in ppm : 7.78 (m, 7H, Ar–H), 3.71(s, 3H, OCH_3), 3.41 (s, 2H, CH_2CO), 2.54 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 168.5, 158.1,155.2, 150.4, 149.5, 148.2, 130.5, 129.5, 128.6, 125.2, 122.2, 120.4, 117.7, 105.3, 56.2, 35.5, 20.; Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.94; N, 13.76; Found: C, 70.92; H, 4.84; N, 13.62%; MS: $[M]^+$ at *m*/*z* 305.33.

*6.1.12. 1-(2′-Bromoacridin-9′-y)l-3-methyl pyrazol-5-one (**10**)*

Yield (60%), (Ethyl acetate), m.p:241 °C; IR (KBr) ν_{max} in cm^{-1}: 3052 (C–H of aromatic), 2948 (C–H of aliphatic), 1718 (C═O), 1614 (C═N), 1543 (C═C of aromatic ring), 1282 (N–N); ^1H NMR ($CDCl_3$) δ in ppm: 7.79 (m, 7H, Ar–H), 3.43 (s, 2H, CH_2CO), 2.52 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 168.1, 155.4, 150.3, 149.6, 148.8, 132.4, 130.7, 129.4, 128.8, 125.0, 120.2, 120.0, 117.5, 35.4, 20.1.; Anal. Calcd for $C_{17}H_{12}N_3OBr$: C, 57.65; H, 3.41; N, 11.86; Found: C,57.82; H, 3.34; N, 11.72%; MS: $[M]^+$ at *m*/*z* 354.20.

*6.1.13. 1-(4′-Chloro-2′-methoxyacridin-9′-y)l-3-methyl pyrazol-5-one (**11**)*

Yield (53%), (DMF/Water), m.p:247 °C; IR (KBr) ν_{max} in cm^{-1}: 3055 (C–H of aromatic), 2952 (C–H of aliphatic), 1720 (C═O), 1615 (C═N), 1545 (C═C of aromatic ring), 1285 (N–N); ^1H NMR ($CDCl_3$) δ in ppm : 7.83 (m, 6H, Ar–H), 3.74 (s, 3H, OCH_3),3.45 (s, 2H, CH_2CO), 2.55 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 168.3, 157.6, 155.5, 150.4, 149.3, 148.6, 134.4, 129.7, 128.9, 125.3, 122.2, 120.4, 117.7, 56.1, 35.2, 20.; Anal. Calcd for $C_{18}H_{14}N_3O_2Cl$: C, 63.63; H, 4.15; N, 12.37; Found: C, 63.46; H, 4.06; N, 12.47%. MS: $[M]^+$ at *m*/*z* 339.78.

*6.1.14. 1-(2′, 4′-Dichloroacridin-9′-yl)-3-methyl pyrazol-5-one (**12**)*

Yield (50%), (Acetone), m.p: 255 °C; IR (KBr) ν_{max} in cm^{-1}: 3056 (C–H of aromatic), 2953 (C–H of aliphatic), 1722 (C═O), 1616 (C═N), 1548 (C═C of aromatic ring), 1288 (N–N); ^1H NMR ($CDCl_3$) δ in ppm: 7.85 (m, 6H, Ar–H), 3.46 (s, 2H, CH_2CO), 2.56 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 168.1, 155.6, 150.4, 149.6, 148.5, 134.7, 131.5, 130.5, 129.7, 128.8, 125.3, 120.2, 120.0, 117.6, 35.6, 20.2.; Anal. Calcd for $C_{17}H_{11}N_3OCl_2$: C, 59.32; H, 3.22; N, 12.21; Found: C, 59.46; H, 3.26; N, 12.06%. MS: $[M]^+$ at *m*/*z* 344.19.

*6.1.15. General procedure for the synthesis of 1-(2′,4′-di substituted acridin-9′-yl)-3-(bromomethyl)-pyrazol-5-ones (**13**–**18**)*

The compounds **13**–**18** were synthesized by adding solution of bromine (0.02 mol) in acetic acid drop wise with constant stirring in the cold solution of compounds **7**–**12** (0.01 mol). The reaction mixture was distilled off and the residue thus obtained was washed with water, filtered, dried and recrystallized with appropriate solvent to give compounds **13**–**18**.

*6.1.16. 1-(Acridin-9′-yl)-3-(bromomethyl)-pyrazol-5-one (**13**)*

Yield (72%), m.p:201 °C. IR (KBr) ν_{max} in cm^{-1}: 3052 (C–H of aromatic), 2945 (C–H of aliphatic), 1712 (C═O), 1610 (C═N), 1542 (C═C of aromatic ring), 1281 (N–N), 610 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm : 7.74 (m, 8H, Ar–H), 3.40 (s, 2H, CH_2CO), 2.55 (s, 2H, CH_2Br); ^{13}C NMR ($CDCl_3$) δ ppm: 168.0, 155.5, 149.7, 149.4, 129.4, 129.0, 125.5, 123.7, 37.6, 31.5.; Anal. Calcd for $C_{17}H_{12}N_3OBr$: C, 57.65; H, 3.41; N, 11.86; Found: C, 57.55; H, 3.55; N, 11.75%; MS: $[M]^+$ at *m*/*z* 354.20.

*6.1.17. 1-(2-′Chloroacridin-9′-yl)-3-(bromomethyl)-pyrazol-5-one (**14**)*

Yield (74%), (Acetone), m.p:185 °C; IR (KBr) ν_{max} in cm^{-1}: 3055 (C–H of aromatic), 2946 (C–H of aliphatic), 1714 (C═O), 1612 (C═N), 1545 (C═C of aromatic ring), 1283 (N–N), 612 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm : 7.75 (m, 7H, Ar–H), 3.42 (s, 2H, CH_2CO), 2.52 (s, 2H, CH_2Br); ^{13}C NMR ($CDCl_3$) δ ppm: 168.0, 155.7, 149.6, 148.4, 132.3, 130.4, 130.0, 129.5, 128.8, 125.2, 120.2, 117.5, 37.4, 31.2.; Anal. Calcd for $C_{17}H_{11}N_3OBrCl$: C, 52.54; H, 2.85; N, 10.81; Found: C, 52.44; H, 2.65; N, 10.65%; MS: $[M]^+$ at *m*/*z* 388.65.

*6.1.18. 1-(2′-Methoxyacridin-9′-yl)-3-(bromomethyl)-pyrazol-5-one (**15**)*

Yield 71% (Methanol): m.p 192 °C. IR (KBr) ν_{max} in cm^{-1}: 3052 (C–H of aromatic), 2944 (C–H of aliphatic), 1716 (C═O), 1615 (C═N), 1544 (C═C of aromatic ring), 1280 (N–N), 615 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm : 7.72 (m, 7H, Ar–H), 3.73 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2CO), 2.54 (s, 2H, CH_2Br); ^{13}C NMR ($CDCl_3$) δ ppm: 168.1, 158.2, 155.5, 150.2, 149.7, 148.6, 130.6, 129.5, 128.7, 125.0, 122.4, 117.8, 105.3, 56.2, 37.6, 31.4.; Anal. Calcd for $C_{18}H_{14}N_3O_2Br$: C, 56.27; H, 3.67; N, 10.94; Found: C, 56.38; H, 3.56; N, 10.84%. MS: $[M]^+$ at *m*/*z* 383.03.

*6.1.19. 1-(2′-Bromoacridin-9′-yl)-3-(bromomethyl)-pyrazol-5-one (**16**)*

Yield (65%), (Methanol), m.p: 176 °C; IR (KBr) ν_{max} in cm^{-1}: 3054 (C–H of aromatic), 2946 (C–H of aliphatic), 1714 (C═O), 1612 (C═N), 1546 (C═C of aromatic ring), 1282 (N–N), 616 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm : 7.70 (m, 7H, Ar–H), 3.42 (s, 2H, CH_2CO), 2.52 (s, 2H, CH_2Br); ^{13}C NMR ($CDCl_3$) δ ppm: 168.0, 155.6, 150.5, 149.4, 148.7, 130.7, 129.6, 128.9, 125.3, 120.2, 117.7, 104.2, 37.5, 31.8.; Anal. Calcd for $C_{17}H_{11}N_3OBr_2$: C, 47.14; H, 2.56; N, 9.70; Found: C, 47.28; H, 2.46; N, 9.84%; MS: $[M]^+$ at *m*/*z* 430.93.

*6.1.20. 1-(4′-Chloro-2′-methoxyacridin-9′-yl)-3-(bromomethyl)-pyrazol-5-one (**17**)*

Yield (62%), (Ethanol), m.p: 210 °C; IR (KBr) ν_{max} in cm^{-1}: 3056 (C–H of aromatic), 2944 (C–H of aliphatic), 1716 (C═O), 1615 (C═N), 1548 (C═C of aromatic ring), 1285 (N–N), 614 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm : 7.72 (m, 6H, Ar–H), 3.75 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2CO), 2.54 (s, 2H, CH_2Br); ^{13}C NMR ($CDCl_3$) δ ppm: 168.4, 155.7, 150.3, 149.7, 148.6, 134.5, 129.5, 128.7, 125.0, 120.4, 117.8, 104.2, 37.5, 31.6.; Anal. Calcd for $C_{18}H_{13}N_3O_2BrCl$: C, 51.64; H, 3.13; N, 10.04; Found: C, 51.48; H, 3.26; N, 10.14%. MS: $[M]^+$ at *m*/*z* 418.67.

*6.1.21. 1-(2′, 4′-Dichloroacridin-9′-yl)-3-(bromomethyl)-pyrazol-5-one (**18**)*

Yield (68%), (DMF/Water), m.p: 207 °C; IR (KBr) ν_{max} in cm^{-1}: 3054 (C–H of aromatic), 2946 (C–H of aliphatic), 1720 (C═O), 1616 (C═N), 1550 (C═C of aromatic ring), 1286 (N–N), 615 (C–Br); ^1H NMR ($CDCl_3$) δ in ppm : 7.70 (m, 6H, Ar–H), 3.42 (s, 2H, CH_2CO), 2.56 (s, 2H, CH_2Br);^{13}C NMR ($CDCl_3$) δ ppm: 168.0, 155.9, 150.5, 149.1, 148.4, 134.6, 129.6, 128.9, 125.2, 120.3, 117.7, 104.4, 37.6, 31.5.; Anal. Calcd for $C_{17}H_{10}N_3OBrCl_2$: C, 48.26; H, 2.38; N, 9.93; Found: C, 48.38; H, 2.16; N, 9.80%; MS: $[M]^+$ at *m*/*z* 423.09.

*6.1.22. General procedure for the synthesis of 1-(2′,4′-di substituted acridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4 oxadizol-2-yl-thiomethyl)-pyrazol-5-one (**19**–**24**)*

The solution of **13**–**18** (0.01 mol) in pyridine (80 mL) and 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol (0.01 mol) were refluxed for 5 h. The reaction mixture was concentrated and poured it crushed ice. The separated solid was filtered, dried and recrystallized with appropriate solvent to give compounds **19**–**24**.

*6.1.23. 1-(Acridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazol-5-one (**19**)*

Yield(65%), m.p: 220 °C. IR (KBr) ν_{max} in cm^{-1}: 3050 (C–H of aromatic), 2935 (C–H of aliphatic), 1695 (C=O), 1598 (C=N), 1540 (C=C of aromatic ring), 1635,1610,1580,1420,1070 (str of oxadiazole),1286 (N–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.21(dd, $J = 8$ Hz, 2H, Pyr H2), 7.30–8.10 (m, 10H, 8Ar–H,2H, Pyr H3), 3.42 (s, 2H, CH_2CO), 3.05 (s, 2H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ ppm: 168.1, 155.5, 150.3, 149.5, 143.4, 129.4, 129.0, 125.7, 123.6, 122.4, 111.4, 39.6, 32.4.; Anal. Calcd for $C_{24}H_{16}N_6O_2S$: C, 63.70; H, 3.56; N, 18.57; Found: C, 63.28; H, 3.16; N, 18.80%; MS: $[M]^+$ at *m*/*z* 452.49.

*6.1.24. 1-(2′-Chloroacridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazol-5-one (**20**)*

Yield (62%), (Ethanol), m.p:217 °C; IR (KBr) ν_{max} in cm^{-1}: 3050 (C–H of aromatic), 2935 (C–H of aliphatic), 1705 (C=O), 1610(C=N), 1547 (C=C of aromatic ring), 1640,1612, 1582, 1420,1071 (str of oxadiazole),1290 (N–N); ^{1}H NMR ($CDCl_3$) δ in ppm:8.25 (dd, $J = 8$ Hz, 2H, Pyr H2), 7.37–8.15 (m, 9H, 7Ar–H, 2H, Pyr H3), 3.48 (s, 2H, CH_2CO), 3.15 (s, 2H, CH_2–S);^{13}C NMR ($CDCl_3$) δ ppm: 168.2, 155.6, 150.4, 149.4, 148.4, 143.5, 130.5, 130.0, 129.5, 129.1, 126.2, 125.4, 122.1, 120.4, 117.5, 104.4, 39.7, 32.2.; Anal. Calcd for $C_{24}H_{15}N_6O_2SCl$: C, 59.20; H, 3.10; N, 17.26; Found: C, 60.35; H, 3.65; N, 17.86%; MS: $[M]^+$ at *m*/*z* 486.06.

*6.1.25. 1-(2′-Methoxyacridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazol-5-one (**21**)*

Yield (60%), (Ethyl acetate), m.p:196 °C; IR (KBr) ν_{max} in cm^{-1}: 3048 (C–H of aromatic), 2940 (C–H of aliphatic), 1703 (C=O), 1615 (C=N), 1545 (C=C of aromatic ring), 1641,1607,1578,1424,1071 (str of oxadiazole),1290 (N–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.23(dd, $J = 8$ Hz, 2H, Pyr H2), 7.33–8.11 (m, 9H, 7Ar–H, 2H, Pyr H3), 3.70 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2CO), 3.11 (s, 2H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ ppm: 168.0, 155.1, 150.3, 149.6, 148.5, 143.5, 130.7, 129.5, 128.1, 125.2, 122.1, 120.2, 117.7, 104.3, 39.5, 32.0.; Anal. Calcd for $C_{25}H_{18}N_6O_3S$: C, 62.23; H, 3.76; N, 17.42; Found: C, 62.75; H, 3.45; N, 17.89%; MS: $[M]^+$ at *m*/*z* 482.51.

*6.1.26. 1-(2′-Bromoacridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazol-5-one (**22**)*

Yield (55%), (Methanol), m.p:190 °C; IR (KBr) ν_{max} in cm^{-1}: 3050 (C–H of aromatic), 2942(C–H of aliphatic), 1702 (C=O), 1610(C=N), 1545 (C=C of aromatic ring), 1638,1610,1580,1416,1071 (str of oxadiazole),1290 (N–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.22(dd, $J = 8$ Hz, 2H, Pyr H2), 7.35–8.10 (m, 9H, 7Ar–H, 2H, Pyr H3), 3.45 (s, 2H, CH_2CO), 3.16 (s, 2H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ ppm: 168.4, 155.4, 150.5, 149.7, 148.8, 143.8, 130.3, 129.6, 128.8, 125.1, 122.4, 120.3, 117.8, 104.2, 39.4, 32.1.; Anal. Calcd for $C_{24}H_{15}N_6O_2SBr$: C, 54.25; H, 2.85; N, 15.82; Found: C, 54.65; H, 2.45; N, 15.40%; MS: $[M]^+$ at *m*/*z* 482.51.

*6.1.27. 1-(4′-Chloro-2′-Methoxyacridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazol-5-one (**23**)*

Yield (46%), (Ethyl acetate), m.p: 250 °C; IR (KBr) ν_{max} in cm^{-1}: 3049 (C–H of aromatic), 2944(C–H of aliphatic), 1706 (C=O), 1617(C=N), 1548 (C=C of aromatic ring), 1640,1603,1572,1424,1071 (str of oxadiazole), 1290 (N–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.21(dd, $J = 8$ Hz, 2H, Pyr H2), 7.31–8.10 (m, 8H, 6Ar–H, 2H, Pyr H3), 3.72 (s, 3H, OCH_3), 3.43 (s, 2H, CH_2CO), 3.10 (s, 2H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ ppm: 168.2, 155.4, 150.5, 149.7, 148.8, 143.8, 130.3, 129.6, 128.8, 125.1, 122.4, 120.3, 117.8, 104.2, 39.4, 32.1.; Anal. Calcd for $C_{25}H_{17}N_6O_3SCl$: C, 58.08; H, 3.31; N, 16.26; Found: C, 58.55; H, 3.75; N, 16.86%; MS: $[M]^+$ at *m*/*z* 516.96.

*6.1.28. 1-(2′,4′-Chloroacridin-9′-yl)-3-(5′-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazol-5-one (**24**)*

Yield (40%), (Ethanol), m.p: 245 °C; IR (KBr) ν_{max} in cm^{-1}: 3055 (C–H of aromatic), 2940(C–H of aliphatic), 1715 (C=O), 1616(C=N), 1552 (C=C of aromatic ring), 1645,1616,1584,1427,1070 (str of oxadiazole),1295 (N–N); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.30 (dd, $J = 8$ Hz, 2H, Pyr H2), 7.40–8.21 (m, 8H, 6Ar–H, 2H, Pyr H3), 3.40 (s, 2H, CH_2CO), 3.16 (s, 2H, CH_2–S); ^{13}C NMR ($CDCl_3$) δ ppm: 168.5, 155.0, 150.4, 149.5, 148.7, 134.5, 131.5, 130.2, 129.5, 128.7, 125.2, 125.0, 122.1, 120.4, 117.5, 104.0, 39.5, 32.0.; Anal. Calcd for $C_{24}H_{14}N_6O_2SCl_2$: C, 55.29; H, 2.71; N, 16.12; Found: C, 55.65; H, 2.64; N, 16.56%; MS: $[M]^+$ at *m*/*z* 521.38.

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