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Synthesis and evaluation of the antitumor activity of polyhalo acridone derivatives†

Chao Huang,[ab] Sheng-Jiao Yan,*[a] Xiang-Hui Zeng,[a] Bo Sun,[c] Min-Bo Lan*[c] and Jun Lin*[a]

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A series of polyhalo acridone heterocyclic compounds were synthesized and evaluated for their *in vitro* antitumor activity. It was noteworthy that halogen atoms were present at the 1, 3 and 4 sites of the compounds, and an amide group or a cyano group was at the 2 site. The antitumor bioactivity screening revealed that all the compounds exhibited potent antitumor activity. In particular, compounds **4d**, **4o**, **5j** and **5k** showed good antineoplastic selectivity, with a survival rate above 50% in NIH3T3 mouse embryonic cells. The IC_{50} values were 8.69–13.06 μM in A431 cells. A preliminary assessment of the structure–selectivity relationship of the compounds was also performed.

Introduction

Acridone compounds exist extensively in natural products. As a macro-cyclic conjugated system with a rigid planar structure on the acridine ring, acridone can be embedded in biological macromolecules (Fig. 1), such as DNA,[1] and possess potent antitumor,[2] antiviral,[3] antimalarial[4] and antimicrobial[5] bioactivity. Owing to its strong fluorescence emission, it has also been applied to cell labeling and medical testing as a fluorescent pH indicator.[6]

Recently, reports on halogen compounds, especially fluorinated compounds, have gradually increased in medicinal chemistry research[7] because of their recognized environmentally-friendly features and the improved bioactivity of target compounds due to the introduction of fluoride.[8] Previous studies have revealed that organic halides show good antitumor and antibacterial activity.[9] Meanwhile, as imitative halogens, cyano groups also play an important role in the activity of drugs on account of their inherently strong electronegativity and coordination property with amino acids and metal ions, cyanide-containing drugs are constantly emerging.[10] Our team has committed to the research on halogen and cyano compounds, and we discovered polyhalo heterocyclic ketene aminals[11] with antitumor activity and polyhalo isophthalonitriles[12] with antimicrobial activity. The synthesis of acridone and the study of its application as a fluorescent pH indicator have also seen some progress.[13] In this paper, we present our work on the rational design and synthesis of novel polyhalo acridone derivatives. We also evaluate their *in vitro* antitumor activity with a view to obtaining acridone antineoplastic compounds.

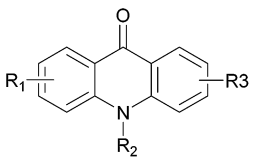

Fig. 1 The structure of acridone compounds.

The oxidation of acridines[14] and intramolecular cyclization of substituted diaryl amines[15] are common methods of acridone synthesis. Intramolecular cyclization is more generic. PPA[16] and phosphorus oxychloride[17] are usually used as the reagents of ring closure. Here, we used polyhalo isophthalonitriles as raw materials, affording intermediates by a substitution reaction of their halogen atoms and anilines, to prepare different substituted polyhalo acridones with side chains containing amide or cyano groups catalyzed by concentrated sulfuric acid (Scheme 1).

Results and discussion

In DMF solution, polyhalo isophthalonitriles **1** and substituted anilines **2** can produce intermediates **3** with potassium carbonate as the catalyst. The intramolecular cyclization of **3** runs easily in sulfuric acid heated for 45 min at 90 °C, affording polyhalo acridones **4** with side chains containing amide groups

[a]*Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China. E-mail: yanshengjiao@126.com; linjun@ynu.edu.cn; Fax: +86 871 65033215*

[b]*Key Laboratory of Ethnic Medicine Resource Chemistry, State Ethnic Affairs Commission & Ministry of Education, School of Chemistry and Biotechnology, Yunnan Minzu University, Kunming 650050, P. R. China*

[c]*Shanghai Key Laboratory of Functional Materials Chemistry and Research Centre of Analysis and Test, East China University of Science and Technology, Shanghai 200237, P. R. China. E-mail: minbolan@ecust.edu.cn*

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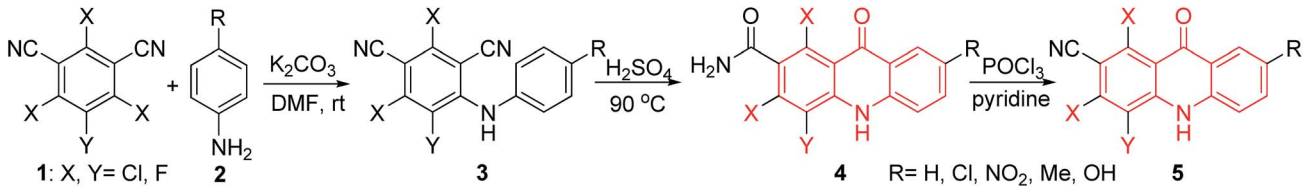


Scheme 1

Table 1 Cytotoxic activity of polyhalo acridones *in vitro*[a] (IC_{50}, μM[b])

				Anti-cancer activity IC_{50} (μM)						
Entry	Compound	Gibbs energy[c] [kJ mol^{-1}]	*C* log *P*	HL60	K562	A431	HepG-2	Skov-3	HT-29	A549
1	**4a**	181.46	0.98	5.7	7.7	1.2	1.9	28.0	—	—
2	**4b**	−184.3	0.80	0.2	0.2	0.08	0.2	4.0	—	—
3	**4c**	−367.18	0.16	2.0	4.5	0.05	6.5	4.5	—	—
4	**4e**	−205.86	1.53	16.6	3.0	0.3	3.4	5.3	—	—
5	**4f**	−388.74	0.89	1.3	2.7	0.3	4.3	3.9	—	—
6	**5a**	377.11	3.23	2.02	5.70	3.41	—	—	6.45	10.57
7	**5b**	11.35	2.48	0.00711	2.50	6.97	—	—	0.0334	0.0348
8	**5c**	−171.53	1.83	12.31	19.25	21.07	—	—	33.26	64.51
9	**5e**	−10.21	3.19	0.58	2.55	2.99	—	—	16.31	4.61
10	**5f**	−193.09	2.55	20.46	1.52	23.99	—	—	30.26	6.29
11	**5h**		2.24	20.77	0.37	2.44	—	—	10.30	2.3
12	**5i**		1.60	5.47	1.59	2.83	—	—	29.84	4.98
	DDP			3.1	8.5	2.3	8.2	10.7		
	ADM			2.02	0.11	0.12			0.053	0.44

[a] Cytotoxicity as IC_{50} for each cell line, refers to the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay. [b] Data represent the mean values of three independent determinations. [c] Gibbs energy and *C* log *P* values of the compounds were calculated by ChemDraw Ultra 11.0.

in high yields. Then, polyhalo acridones **5** with side chains containing cyano groups can be generated by the phosphorus oxychloride catalyzed reduction of the amide group of **4**. All the target compounds have been well characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS (Table 1).

Firstly, the *in vitro* antitumor activity of representative polyhalo acridones **4a–f** with side chains containing amide group and polyhalo acridones **5a–i** with side chains containing cyano groups were evaluated by MTT assay against the human myeloid leukemia cell lines HL-60 and K562,[18] epidermoid carcinoma cell line A431, ovarian cancer cell line Skov-3, laryngeal carcinoma cell line Hep-2, adenomatous tumor cell line HT-29 and lung cancer cell line A549, using ADM and DDP as the positive controls. As the results show in Table 1 (**4a–f**, **5a–i**), all the tested compounds displayed good antitumor activity with IC_{50} values in the range of 0.00711–64.51 μM. Therefore, it is reasonable to believe that polyhalo acridones in this paper indicated favorable *in vitro* cytotoxicity. It is worth noting that all the compounds **4** were sensitive against A431 with IC_{50} values in the range of 0.05–1.2 μM, and exhibited better inhabitation than DDP. Among them, **4b**, with IC_{50} values in the range of 0.08–4.0 μM and **5b**, with IC_{50} values in the range of 0.00711–6.97 μM, show outstanding activity. Based on the cytotoxic inhibition screening, the introduction of fluorine atoms improved the antitumor activity against cancer cell lines (**4b**, **4c** *vs.* **4a**, **5b** *vs.* **5a**), while amide or cyano groups on the side chain of polyhalo acridones exhibited weak cytotoxic effects (**4a** *vs.* **5a**, **4b** *vs.* **5b**, **4c** *vs.* **5c**).

Next, the antitumor selectivity against the mouse embryonic cell NIH3T3 of polyhalo acridones **4** and **5** was analyzed by the MTT assay to perform a safety evaluation of the prepared compounds using normal cells. Survival rates were obtained after 72 h of treatment at the concentration of 10 μM, as shown in Table 2. The survival rates for compounds **4a**, **4d**, **4m**, **5j** and **5k** were found to be higher than 50%, while those of compounds **4c**, **4i**, **4j**, **4l**, **4n** and **4o** were found to be in the range of 11.47% to 41.63%; the rest was in the range of 0.66–8.52% under similar conditions. The results illustrate that although the compounds in this paper showed cytotoxicity against normal cells, some of them were weakly toxic and relatively safe.

Among those compounds with a survival rate above 50%, compounds **4a**, **4d**, **4m** and **5j** contain fluorine atoms, indicating that fluorine atoms may have a positive influence on antitumor activity against cancer cell lines, as well as cytotoxicity in normal cells. It is important to point out that amide groups in the halogen-containing benzene ring of **4a**, **4d** and **4m** were relatively safe for normal cells, while the reduction of cyano groups of **5a** and **5d** from amide groups increased cytotoxicity against normal cells. Moreover, **5j** and **5k**, compounds containing methyl and cyano groups at the *ortho*-position in the benzene ring, and the corresponding amide acridones **4j** and **4k** also exhibited strong cytotoxic activity. Then, antitumor activity

Table 2 Cytotoxic activity of polyhalo acridones *in vitro* (IC_{50}, μM[a])

Entry	Compound	Gibbs energy[b] [kJ mol^{-1}]	*C* log *P*	X	Y	R	Yield[c] (%)	Survival rate (%)
1	**4a**	181.46	3.26	Cl	Cl	H	84	>50
2	**4b**	−184.3	2.46	F	Cl	H	76	2.60
3	**4c**	−367.18	2.06	F	F	H	86	17.16
4	**4d**	159.9	3.81	Cl	Cl	Cl	80	>50
5	**4e**	−205.86	3.01	F	Cl	Cl	85	7.90
6	**4f**	−388.74	2.61	F	F	Cl	81	8.52
7	**4g**		2.87	Cl	Cl	NO_2	78	5.70
8	**4h**		1.91	F	Cl	NO_2	83	1.46
9	**4i**		1.42	F	F	NO_2	82	15.54
10	**4j**	180.25	3.74	Cl	Cl	Me	82	11.47
11	**4k**	−185.51	2.94	F	Cl	Me	85	1.52
12	**4l**	−368.39	2.54	F	F	Me	83	21.13
13	**4m**	26.84	2.87	Cl	Cl	OH	83	>50
14	**4n**	−338.92	2.07	F	Cl	OH	86	20.69
15	**4o**	−521.8	1.67	F	F	OH	87	41.63
16	**5a**	377.11	4.38	Cl	Cl	H	73	0.96
17	**5b**	11.35	3.58	F	Cl	H	72	1.87
18	**5c**	−171.53	3.18	F	F	H	77	1.36
19	**5d**	355.55	4.94	Cl	Cl	Cl	76	1.31
20	**5e**	−10.21	4.14	F	Cl	Cl	75	3.29
21	**5f**	−193.09	3.74	F	F	Cl	78	0.66
22	**5g**		3.66	Cl	Cl	NO_2	75	2.44
23	**5h**		2.70	F	Cl	NO_2	72	1.54
24	**5i**		2.21	F	F	NO_2	70	2.31
25	**5j**	375.9	4.87	Cl	Cl	Me	80	>50
26	**5k**	10.14	4.07	F	Cl	Me	83	>50
27	**5l**	−172.74	3.67	F	F	Me	83	1.31

[a] Cytotoxicity as IC_{50} for each cell line, refers to the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay. [b] Gibbs energy and *C* log *P* values of the compounds were calculated by ChemDraw Ultra 11.0. [c] Isolated yield by silica gel column chromatography.

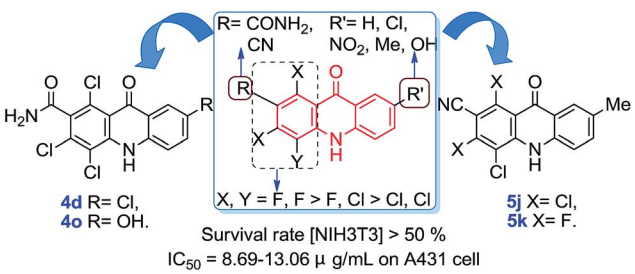
of relatively safer compounds with survival rates above 50% against cell line NIH3T3, was evaluated to find novel antitumor leads with high selectivities. The apoptosis ratios in the epidermoid carcinoma cell line A431 treated with **4a**, **4d**, **4m**, **4o**, **5j** and **5k** for 72 h, respectively, are shown in Table 3. As suggested by the results, all the tested compounds showed potent *in vitro* antitumor activity. Especially, **4d**, **4o**, **5j** and **5k** exhibited excellent antitumor selectivity as inhibition in A431 was more significant, but weaker in normal cells. These compounds also showed good inhibition both in normal cell lines (NIH3T3) and cancer cell lines (A431), such as the randomly selected compounds **4k** and **5a** (shown in Table 3), characterized by poor antitumor selectivity. The IC_{50} values showed the same trend by the SRB method *in vitro* against human lung cancer (A549) and human liver cancer (HepG2).

Table 3 Cytotoxic activity of polyhalo acridones *in vitro*[a]

Compounds	IC_{50} (μM)		
	A431	A549	HepG2
4a	25.3 ± 0.41	1.32	1.75
4d	8.69 ± 3.52	1.75	1.45
4k	1.78 ± 0.08	0.23	0.25
4m	26.45 ± 0.13	7.16	7.16
4o	10.71 ± 0.19	—	—
5a	5.97 ± 0.1	0.90	4.74
5j	12.1 ± 0.34	1.05	3.80
5k	13.06 ± 0.47	0.97	3.23

[a] The IC_{50} value of A431 was determined using the MTT assay. IC_{50} value of A549 and HepG2 were determined using the SRB assay.

Based on the above observations, the preliminary structure–selectivity relationship of polyhalo acridones was determined and shown in Scheme 2. The fluorine atoms of the compounds described in this study, which reduced the Gibbs energy and *C* log *P* values of molecules, may result in an enhancement in cytotoxic activity. As the antitumor activity results of these compounds were in a relatively narrow range, the basic structure of the polyhalo acridones appeared to have the greatest influence, while the cyano and amide groups on the side chain



Scheme 2 The preliminary structure–selectivity relationship of polyhalo acridones.

had little effect on activity, as well as the substitution position in the aromatic ring. The *in vitro* evaluation of antitumor activity and cytotoxicity against normal cell lines and cancer cell lines found that compounds **4d**, **4o**, **5j** and **5k** possessed antitumor selectivity. The above results have laid the foundation for further research on the antitumor activity of polyhalo acridones.

Conclusions

In summary, the evaluation of the *in vitro* antitumor activity of 27 polyhalo acridone compounds revealed that representative compounds had potent cytotoxicity. By conducting the *in vitro* safety evaluation against the normal mouse embryo cell line NIH3T3 and further screening of the inhibitory effect of the compounds on the A431 tumor cell line, where the results showed a survival rate of more than 50%, it is suggested that compounds **4d**, **4o**, **5j** and **5k** showed good anticancer selectivity. The above screening results provide not only a reference to developing antitumor drugs with high selectivity, but also a basis for further research into polyhalo acridones in medicinal chemistry.

Experimental section

General information

All compounds were fully characterized by spectroscopic techniques. The NMR spectra were recorded on a Bruker-Avance 500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz) with tetramethylsilane (TMS) as the internal standard (δ 0.0 ppm). Chemical shifts (δ) are expressed in ppm and J values are given in Hz. Deuterated DMSO and DMF were used as the solvents. IR spectra were recorded on an FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using neutral alumina. The melting points were determined on an XT-4A melting point apparatus and are uncorrected. HRMS was performed on an Agilent LC-MSD TOF instrument.

1a, **1c** and **2** were purchased from Aldrich Corporation Limited. All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

General procedure for the synthesis of polyhalo isophthalonitrile 3

A 50 mL round-bottom flask was charged with polyhaloisophthalonitrile **1** (5 mmol), DMF (30 mL), aniline derivatives **2** (6.0 mmol) and potassium carbonate 1.4 g (10 mmol), and the solution was stirred for 0.5–18 h at room temperature until the polyhaloisophthalonitrile **1** was completely consumed. The mixture was dumped into a beaker (100 mL) and quenched by the addition of water (30 mL). The mixture was filtered off and the residue was washed with water to give a crude product that was purified by flash column chromatography. The desired compounds **3** were formed in excellent yields: 84–96%.

General procedure for the synthesis of polyhalo acridone with side chains containing amide group 4

Polyhalo isophthalonitrile **3** (2 mmol) was dissolved in 6 mL 95–98% sulfuric acid, and the solution was stirred for 1 h at 90 °C. The mixture was cooled to room temperature, and then was poured into a 100 mL beaker, then 50 mL of water was added under stirring. The pH of the mixture was adjusted to 9–10 using solid potassium carbonate. The mixture was filtered off and the residue was washed with water to give a crude product that was purified by flash column chromatography. The desired compounds **4** were formed in good yields: 76–86%.

1,3,4-Trichloro-9-oxo-9,10-dihydroacridine-2-carboxamide (4a). Yellow solid; mp: 251–252 °C; IR (KBr) (ν_{max}, cm^{-1}) 3478, 3416, 1665, 1568, 1398, 1326, 1164, 755, 612; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.48–8.18 (m, 3H, PhH), 7.95–7.80 (m, 3H, NH_2, PhH), 7.48 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.7, 152.5, 148.5, 145.5, 132.2, 131.9, 130.7, 130.0, 129.2, 125.4, 124.4, 123.4, 115.1, 108.4; HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_8Cl_3N_2O_2^+$ [(M + H)$^+$], 340.9646; found, 340.9644.

4-Chloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4b). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3486, 3371, 3246, 1679, 1559, 1382, 1260, 834, 759, 601 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.52–7.77 (m, 6H, PhH, NH_2), 7.46–7.43 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.3, 156.2 (d, J = 267.5 Hz), 154.8 (d, J = 258.8 Hz), 151.8, 149.5, 145.2, 132.5, 129.1, 123.8, 123.4, 114.1, 111.6, 109.1 (t, J = 27.5 Hz), 101.2 (d, J = 32.5 Hz); ^{19}F NMR (470 MHz, DMSO-d_6): δ −111.3 (d, J = 4.7 Hz, 1F), −111.7 (d, J = 4.7 Hz, 1F); HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_8ClF_2N_2O_2^+$ [(M + H)$^+$], 309.0237; found, 309.0233.

1,3,4-Trifluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4c). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3526, 3421, 3151, 1685, 1557, 1388, 1265, 967, 758, 602 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.53–7.78 (m, 6H, PhH, NH_2), 7.44 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.0, 152.6 (d, J = 261.3 Hz), 151.2, 149.4, 145.3 (d, J = 252.5 Hz), 140.5 (d, J = 248.8 Hz), 140.4, 132.4, 129.1, 123.7, 123.5, 114.1, 108.4 (t, J = 25.0 Hz), 101.2; HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_8F_3N_2O_2^+$ [(M + H)$^+$], 293.0532; found, 293.0529.

1,3,4,7-Tetrachloro-9-oxo-9,10-dihydroacridine-2-carboxamide (4d). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3297, 1637, 1553, 1437, 1234, 1094, 824, 637, 508 cm^{-1}; HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_4Cl_4N_2O_2^{2-}$ [(M − 2H)$^{2-}$], 371.9038; found, 371.9045.

4,7-Dichloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4e). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3433, 3353, 3245, 1650, 1554, 1376, 1251, 1102, 834, 630 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.67 (br, 1H, NH), 8.28–7.74 (m, 5H, PhH, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.0, 156.0 (d, J = 255.0 Hz), 155.0 (d, J = 247.5 Hz), 151.2, 147.9, 145.4, 132.9, 131.3, 128.2, 122.4, 114.6, 111.8, 109.9 (t, J = 26.3 Hz), 101.2; HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_7Cl_2F_2N_2O_2$ [(M + H)$^+$], 342.9847; found, 342.9845.

7-Chloro-1,3,4-trifluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4f). Yellow solid; mp: 181–185 °C; IR (KBr) (ν_{max}, cm^{-1}) 3494, 3347, 3181, 1661, 1558, 1376, 1117, 976, 829, 654 cm^{-1}; ^{1}H

NMR (500 MHz, DMSO-d_6): δ 8.64 (br, 1H, NH), 8.29–7.73 (m, 5H, PhH, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.8, 152.5 (d, J = 257.5 Hz), 150.7, 147.6, 145.6 (d, J = 247.5 Hz), 140.4 (d, J = 247.5 Hz), 140.3, 132.9, 131.0, 128.2, 122.4, 114.5, 109.1 (t, J = 25.0 Hz), 101.4; ^{19}F NMR (467 MHz, DMSO-d_6): δ −115.4 (d, J = 14.1 Hz, 1F), −139.3 (s, 1F), −155.9 (d, J = 14.1 Hz, 1F); HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_7ClF_3N_2O_2^+$ [(M + H)$^+$], 327.0143; found, 327.0140.

1,3,4-Trichloro-7-nitro-9-oxo-9,10-dihydroacridine-2-carboxamide (4g). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3369, 1567, 1498, 1329, 1182, 849, 748 cm^{-1}; ^{1}H NMR (500 MHz, DMF-d_6): δ 9.21 (br, 1H, NH), 8.48–7.84 (m, 5H, PhH, NH_2); HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_4Cl_3N_3O_4^{2-}$ [(M − 2H)$^{2-}$], 382.9278; found, 382.9278.

4-Chloro-1,3-difluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carboxamide (4h). Yellow solid; mp: 219–221 °C; IR (KBr) (ν_{max}, cm^{-1}) 3375, 1676, 1541, 1500, 1331, 1244, 1128, 914, 837, 745 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.60 (br, 1H, NH), 8.36–7.86 (m, 5H, PhH, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.8, 157.0, 155.1, 154.5, 151.5, 147.0, 142.4, 130.5, 125.3, 122.5, 112.4, 112.1, 110.3 (t, J = 27.5 Hz), 101.7; HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_4ClF_2N_3O_4^{2-}$ [(M − 2H)$^{2-}$], 350.9869; found, 350.9878.

1,3,4-Trifluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carboxamide (4i). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3409, 3233, 1656, 1501, 1332, 1252, 1127, 978, 616 cm^{-1}; ^{1}H NMR (500 MHz, DMF-d_6): δ 10.15 (br, 1H, NH), 9.74–8.17 (m, 5H, PhH, NH_2); ^{13}C NMR (125 MHz, DMF-d_6): δ 159.8, 159.0, 154.3 (d, J = 252.5 Hz), 150.1 (d, J = 251.3 Hz), 144.1, 143.1, 136.8 (d, J = 250.0 Hz), 132.6, 130.3, 122.8, 121.3, 112.7, 111.8 (d, J = 20.0 Hz), 101.5; ^{19}F NMR (467 MHz, DMF-d_6): δ −116.8 (s, 1F), −131.5 (d, J = 14.0 Hz, 1F), −159.4 (s, 1F); HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_4F_3N_3O_4^{2-}$ [(M − 2H)$^{2-}$], 335.0165; found, 335.0176.

1,3,4-Trichloro-7-methyl-9-oxo-9,10-dihydroacridine-2-carboxamide (4j). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3389, 1682, 1631, 1456, 1329, 1258, 826, 648 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.48 (br, 1H, NH), 8.30–7.65 (m, 5H, PhH, NH_2), 2.51–2.48 (m, 3H, CH_3); HRMS (TOF ES$^-$) m/z calcd for $C_{15}H_7Cl_3N_2O_2^{2-}$ [(M − 2H)$^{2-}$], 351.9584; found, 351.9596.

4-Chloro-1,3-difluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carboxamide (4k). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3358, 1634, 1556, 1372, 1258, 1047, 828, 630 cm^{-1}; ^{1}H NMR (500 MHz, DMF-d_6): 7.65–6.88 (m, 6H, PhH, NH, NH_2), 2.33–2.12 (m, 3H, CH_3). ^{13}C NMR (125 MHz, DMF-d_6): δ 160.8, 155.9 (d, J = 267.5 Hz), 154.3 (d, J = 260.0 Hz), 150.5, 147.6, 144.3, 133.9, 133.0, 128.3, 120.8, 113.5, 111.3, 108.7 (t, J = 26.3 Hz), 100.6, 20.5; ^{19}F NMR (467 MHz, DMF-d_6): δ −112.9 (s, 1F), −113.4 (s, 1F); HRMS (TOF ES$^-$) m/z calcd for $C_{15}H_7ClF_2N_2O_2^{2-}$ [(M − 2H)$^{2-}$], 320.0175; found, 320.0183.

1,3,4-Trifluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carboxamide (4l). Yellow solid; mp: 177–178 °C; IR (KBr) (ν_{max}, cm^{-1}) 3394, 1658, 1562, 1467, 1375, 1268, 1134, 972, 628 cm^{-1}; ^{1}H NMR (500 MHz, DMF-d_6): δ 8.39–7.65 (m, 6H, PhH, NH, NH_2), 2.95–2.74 (m, 3H, CH_3); ^{13}C NMR (125 MHz, DMF-d_6): δ 161.7, 153.4 (d, J = 252.5 Hz), 150.9, 148.9, 145.8 (d, J = 247.5 Hz), 141.4 (d, J = 248.8 Hz), 140.7, 134.9, 134.0, 129.5, 121.9, 114.6, 109.2 (t, J = 26.3 Hz), 101.9 (d, J = 10.0 Hz), 21.5; ^{19}F NMR (467 MHz, DMF-d_6): δ −117.5 (d, J = 18.7 Hz, 1F), −142.5 (d, J = 18.7 Hz, 1F), −157.7 (t, J = 14.0 Hz, 1F); HRMS (TOF ES$^-$) m/z calcd for $C_{15}H_7F_3N_2O_2^{2-}$ [(M − 2H)$^{2-}$], 304.0471; found, 304.0480.

1,3,4-Trichloro-7-hydroxy-9-oxo-9,10-dihydroacridine-2-carboxamide (4m). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3399, 1634, 1502, 1455, 1407, 1332, 1244, 837, 602; ^{1}H NMR (500 MHz, DMF-d_6): δ 10.29 (br, 1H, NH), 8.43–7.55 (m, 5H, PhH, NH_2), 3.08–2.74 (m, 1H, OH); ^{13}C NMR (125 MHz, DMF-d_6): δ 166.1, 155.2, 150.3, 144.3, 143.8, 132.2, 131.1, 128.7, 125.5, 125.2, 116.6, 108.2, 103.2, 88.9; HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_5Cl_3N_2O_3^{2-}$ [(M − 2H)$^{2-}$], 353.9377; found, 353.9385.

4-Chloro-1,3-difluoro-7-hydroxy-9-oxo-9,10-dihydroacridine-2-carboxamide (4n). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3398, 1641, 1463, 1366, 1243, 1067, 835, 630; ^{1}H NMR (500 MHz, DMF-d_6): 10.34 (br, 1H, NH), 8.36–6.82 (m, 5H, PhH, NH_2), 2.99–2.73 (m, 1H, OH); ^{13}C NMR (125 MHz, DMF-d_6): δ 161.3, 156.3 (d, J = 250.0 Hz), 154.8, 152.3 (d, J = 317.5 Hz), 150.0, 147.0, 144.6, 143.1, 125.8, 115.4, 114.7, 109.7, 103.4, 101.0; ^{19}F NMR (467 MHz, DMF-d_6): δ −112.5 (s, 1F), −113.2 (s, 1F); HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_5ClF_2N_2O_3^{2-}$ [(M − 2H)$^{2-}$], 321.9968; found, 321.9975.

1,3,4-Trifluoro-7-hydroxy-9-oxo-9,10-dihydroacridine-2-carboxamide (4o). Yellow solid; mp: 197–198 °C; IR (KBr) (ν_{max}, cm^{-1}) 3379, 1657, 1465, 1369, 1259, 1129, 977; ^{1}H NMR (500 MHz, DMF-d_6): δ 10.19 (br, 1H, NH), 8.36–7.54 (m, 5H, PhH, NH_2), 3.09–2.57 (m, 1H, OH); ^{13}C NMR (125 MHz, DMF-d_6): δ 161.7, 155.1, 154.0, 152.0, 149.5, 145.6, 144.1, 139.2, 131.3, 126.1, 115.9, 109.2, 103.7, 101.6; ^{19}F NMR (467 MHz, DMF-d_6): δ −117.9 (d, J = 14.1 Hz, 1F), −143.7 (d, J = 14.0 Hz, 1F), −157.7 (t, J = 14.0 Hz, 1F); HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_5F_3N_2O_3^{2-}$ [(M − 2H)$^{2-}$], 306.0263; found, 320.0272.

General procedure for the synthesis of polyhalo acridone with side chains containing cyano group 5

Polyhalo acridone with side chains containing an amide group **4** (2 mmol) was dissolved in 8 mL of dry pyridine, the phosphorus oxychloride (0.5 mL) was added in an ice bath, and the solution was stirred for 1 h until the polyhalo acridone with side chains containing an amide group **4** was completely consumed. The reaction mixture was added to a beaker filled with crushed ice, and neutralized by Na_2CO_3 under stirring. The mixture was filtered off and the residue was washed with water to give a crude product that was purified by flash column chromatography. The desired compounds **5** were formed in good yields: 70–83%.

1,3,4-Trichloro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5a). Yellow solid; mp: 242–243 °C; IR (KBr) (ν_{max}, cm^{-1}) 3394, 2229, 1633, 1563, 1335, 1167, 756, 599 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60–7.49 (m, 5H, PhH, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 154.3, 149.2, 146.6, 137.4, 133.9, 131.4, 131.2, 129.6, 125.5, 124.2, 115.8, 115.6, 108.8, 106.6; HRMS (TOF ES$^-$) m/z calcd for $C_{14}H_3Cl_3N_2O^{2-}$ [(M − 2H)$^{2-}$], 319.9322; found, 321.9456.

4-Chloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5b). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1})

3394, 2237, 1634, 1559, 1382, 1262, 1078, 760 cm^{-1}; ^1H NMR (500 MHz, DMF-d_6): δ 8.60–7.50 (m, 5H, PhH, NH); ^{13}C NMR (125 MHz, DMF-d_6): δ 161.6, 154.8 (d, $J = 260.0$ Hz), 153.0, 150.1, 146.6, 133.5, 129.3, 124.7, 123.3, 114.6, 112.4, 110.1, 100.5, 83.4 (t, $J = 21.3$ Hz); ^{19}F NMR (467 MHz, DMF-d_6): δ −100.5 (s, 1F), −110.3 (s, 1F); HRMS (TOF ES^-) m/z calcd for $C_{14}H_4ClF_2N_2O^-$ $[(M - H)^-]$, 288.9986; found, 288.9998.

1,3,4-Trifluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5c). Yellow solid; mp: 196–197 °C; IR (KBr) (ν_{max}, cm^{-1}) 3369, 3232, 2237, 1660, 1563, 1499, 1273, 1144, 981, 763, 598 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.57–7.51 (m, 5H, PhH, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.0, 159.9, 152.2, 149.8, 146.3, 142.1, 133.7, 129.1, 124.7, 123.8, 114.5, 110.5, 100.9, 82.4 (d, $J = 32.5$ Hz); ^{19}F NMR (467 MHz, DMSO-d_6): δ −102.6 (d, $J = 14.0$ Hz, 1F), −138.1 (s, 1F), −154.5 (t, $J = 18.7$ Hz, 1F); HRMS (TOF ES^-) m/z calcd for $C_{14}H_3F_3N_2O^{2-}$ $[(M - 2H)^{2-}]$, 272.0208; found, 272.0216.

1,3,4,7-Tetrachloro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5d). Yellow solid; mp: 240–241 °C; IR (KBr) (ν_{max}, cm^{-1}) 3403, 2235, 1636, 1555, 1312, 1253, 1085, 870, 610 cm^{-1}; ^1H NMR (500 MHz, DMF-d_6): δ 8.77–7.97 (m, 4H, PhH, NH); ^{13}C NMR (125 MHz, DMF-d_6): δ 162.8, 159.5, 142.6, 138.4, 137.7, 135.0, 128.9, 125.2, 124.4, 122.2, 121.4, 116.6, 114.1, 109.5; HRMS (TOF ES^-) m/z calcd for $C_{14}H_5Cl_3N_2O^-$ $[(M - Cl)^-]$, 321.9473; found, 321.9483.

4,7-Dichloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5e). Yellow solid; mp: >300 °C; IR (KBr) (ν_{max}, cm^{-1}) 3446, 2239, 1622, 1543, 1333, 1245, 1140, 841, 596 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.61–7.75 (m, 4H, PhH, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.7 (dd, $J1 = 270.0$ Hz, $J2 = 8.8$ Hz), 154.7 (d, $J = 243.8$ Hz), 152.0, 148.2, 146.5, 133.9, 131.2, 129.2, 122.7, 114.9, 112.2 (d, $J = 13.8$ Hz), 110.3, 100.6 (d, $J = 6.3$ Hz), 83.9 (t, $J = 22.5$ Hz); ^{19}F NMR (467 MHz, DMSO-d_6): δ −98.7 (s, 1F), −108.7 (s, 1F); HRMS (TOF ES^-) m/z calcd for $C_{14}H_2Cl_2F_2N_2O^{2-}$ $[(M - 2H)^{2-}]$, 321.9523; found, 321.9532.

7-Chloro-1,3,4-trifluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5f). Yellow solid; mp: 240–241 °C; IR (KBr) (ν_{max}, cm^{-1}) 3452, 3216, 2923, 2234, 1663, 1559, 1500, 1248, 985, 833, 594 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.60–7.77 (m, 4H, PhH, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.6 (d, $J = 267.5$ Hz), 151.4, 148.1, 145.2 (dt, $J1 = 253.8$ Hz, $J2 = 8.8$ Hz), 142.1, 140.1 (d, $J = 241.3$ Hz), 133.9, 131.2, 129.1, 122.7, 114.9, 110.3, 100.9 (d, $J = 6.3$ Hz), 83.0 (t, $J = 21.3$ Hz); ^{19}F NMR (467 MHz, DMSO-d_6): δ −102.6 (d, $J = 14.0$ Hz, 1F), −137.4 (d, $J = 18.7$ Hz, 1F), −154.0 (t, $J = 18.7$ Hz, 1F); HRMS (TOF ES^-) m/z calcd for $C_{14}H_2ClF_3N_2O^{2-}$ $[(M - 2H)^{2-}]$, 305.9819; found, 305.9830.

1,3,4-Trichloro-7-nitro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5g). Yellow solid; mp: 201–203 °C; IR (KBr) (ν_{max}, cm^{-1}) 3426, 3175, 2238, 1681, 1608, 1555, 1335, 1251, 743, 614 cm^{-1}; HRMS (TOF ES^-) m/z calcd for $C_{14}H_2Cl_3N_3O_3{}^{2-}$ $[(M - 2H)^{2-}]$, 364.9173; found, 364.9173.

4-Chloro-1,3-difluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5h). Yellow solid; mp: 251–252 °C; IR (KBr) (ν_{max}, cm^{-1}) 3445, 2925, 2243, 1625, 1334, 1245, 742, 610 cm^{-1}; HRMS (TOF ES^-) m/z calcd for $C_{14}H_2ClF_2N_3O_3{}^{2-}$ $[(M - 2H)^{2-}]$, 332.9764; found, 332.9775.

1,3,4-Trifluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5i). Yellow solid; mp: 255–256 °C; IR (KBr) (ν_{max}, cm^{-1}) 3443, 3369, 3268, 2241, 1655, 1500, 1335, 1254, 1142, 982, 609 cm^{-1}; ^1H NMR (500 MHz, DMF-d_6): δ 9.78 (br, 1H, NH), 8.75–7.98 (m, 3H, PhH); ^{13}C NMR (125 MHz, DMF-d_6): δ 159.2, 144.5 (d, $J = 166.3$ Hz), 144.4, 143.6, 136.3, 131.2, 129.2, 123.3, 122.8, 122.1, 120.7, 113.9, 108.7, 102.3; ^{19}F NMR (467 MHz, DMF-d_6): δ −103.6 (s, 1F), −130.3 (s, 1F), −164.7 (s, 1F); HRMS (TOF ES^-) m/z calcd for $C_{14}H_2F_3N_3O_3{}^{2-}$ $[(M - 2H)^{2-}]$, 317.0059; found, 317.0068.

1,3,4-Trichloro-7-methyl-9-oxo-9,10-dihydroacridine-2-carbonitrile (5j). Yellow solid; mp: 197–198 °C; IR (KBr) (ν_{max}, cm^{-1}) 3391, 2925, 2230, 1640, 1563, 1496, 1085, 831, 723, 553 cm^{-1}; ^1H NMR (500 MHz, DMF-d_6): δ 10.83–10.09 (m, 1H, NH), 8.35–7.43 (m, 3H, PhH), 2.48–2.32 (m, 3H, CH_3); ^{13}C NMR (125 MHz, DMF-d_6): δ 159.1, 140.3, 139.4, 138.4, 137.7, 137.1, 134.5, 123.7, 122.1, 119.7, 114.6, 113.5, 110.5, 109.1, 20.8; HRMS (TOF ES^-) m/z calcd for $C_{15}H_5Cl_3N_2O^{2-}$ $[(M - 2H)^{2-}]$, 333.9478; found, 333.9486.

4-Chloro-1,3-difluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carbonitrile (5k). Yellow solid; mp: 237–238 °C; IR (KBr) (ν_{max}, cm^{-1}) 3344, 2924, 2235, 1639, 1548, 1391, 1296, 1083, 866, 619 cm^{-1}; ^1H NMR (500 MHz, DMF-d_6): δ 8.29–7.65 (m, 4H, PhH, NH), 2.54–2.46 (m, 3H, CH_3); ^{13}C NMR (125 MHz, DMF-d_6): δ 155.7, 149.9, 142.7, 136.4, 136.2, 129.2, 125.7, 124.5, 122.6, 122.6, 119.3, 110.6, 108.6, 88.7, 21.6; ^{19}F NMR (467 MHz, DMF-d_6): δ −102.9 (s, 1F), −104.0 (s, 1F); HRMS (TOF ES^-) m/z calcd for $C_{15}H_6ClF_2N_2O^-$ $[(M - H)^-]$, 303.0142; found, 303.0153.

1,3,4-Trifluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carbonitrile (5l). Yellow solid; mp: 213–214 °C; IR (KBr) (ν_{max}, cm^{-1}) 3387, 2925, 2235, 1658, 1562, 1388, 1266, 1047, 609 cm^{-1}; ^1H NMR (500 MHz, DMF-d_6): δ 9.02–7.72 (m, 4H, PhH, NH), 2.53 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMF-d_6): δ 160.6, 152.0, 149.2, 142.2, 142.1, 140.1, 136.1, 135.1, 129.6, 122.4, 114.9, 110.6, 101.5, 82.9, 21.5; ^{19}F NMR (467 MHz, DMF-d_6): δ −104.6 (d, $J = 14.0$ Hz, 1F), −140.3 (d, $J = 18.7$ Hz, 1F), −155.5 (t, $J = 14.0$ Hz, 1F); HRMS (TOF ES^-) m/z calcd for $C_{15}H_5F_3N_2O^{2-}$ $[(M - 2H)^{2-}]$, 286.0365; found, 286.0378.

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