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Iodine-catalyzed three-component one-pot synthesis of novel 1,8-dioxo-decahydroacridines derivatives bearing benzene sulfonamide moiety

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Abstract An efficient synthetic method for 1,8-dioxo-decahydroacridines derivatives bearing the biologically active sulfonamide moiety is described. Aromatic aldehyde reacted with 5,5-dimethyl-1,3-cyclohexanedione and sulfanilamide, with molecular iodine as catalyst, to give 1,8-dioxo-decahydroacridines derivatives in high to excellent yield. The structures of these compounds were established on the basis of elemental (C, H and N) and spectral analysis (^{1}H NMR, ^{13}C NMR, MS and FTIR). All the compounds were tested for their cytotoxic activity in vitro against three human tumor cell lines: human mammary cancer cells (MCF-7), human cervical carcinoma cells (Hela), and human lung cancer cells (A549) by the 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Most of them showed moderate to potent cytotoxic activity against the tested cell lines. Among them, the most active compound **4e** exhibited more efficient activity (10.92 μM) against MCF-7 cells than cisplatin (11.06 μM).

Keywords 1,8-Dioxo-decahydroacridines · Sulfanilamide · Cytotoxicity · Molecular iodine

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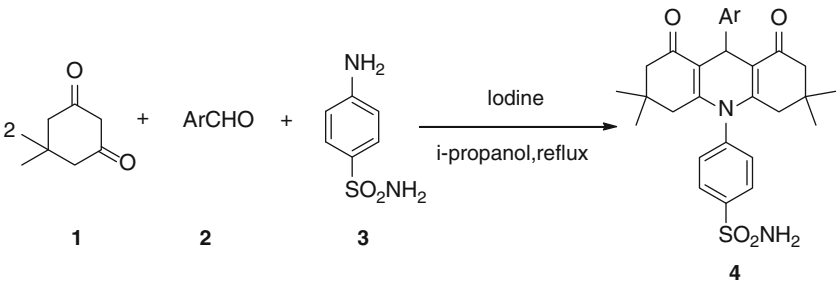
Introduction

1,8-Dioxo-9-aryl decahydroacridines and their derivatives are well-known polyfunctionalized 1,4-dihydropyridine derivatives, which have been widely explored as calcium channel blockers and used for the treatment of hypertension and defibrillation [1]. In addition, acridine derivatives have also been used to synthesize labeled conjugates with medicinals, peptides, proteins, and nucleic acids [2–4] that exhibit antitumor and DNA-binding properties. The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of continuing interest.

Consequently, there have been some reports in the literature on the synthesis of acridine derivatives containing 1,4-dihydropyridines. For example, preparation from dimedone, aldehyde and different nitrogen sources like urea [5], methyl amine [6], and different anilines or ammonium acetate [7] via traditional heating in organic solvents, promoted by triethylbenzylammonium chloride (TEBAC) [8], *p*-dodecylbenzenesulfonic acid (DBSA) [9], Proline [10], Amberlyst-15 [11], *tris*(pentafluorophenyl)borane [12], ammonium chloride or $Zn(OAc)_2{\cdot}2H_2O$ or L-proline [13], silica-bonded S-sulfonic acid (SBSSA) [14], sulfonic acid functionalized silica (SiO_2–Pr–SO_3H) [15] and MCM-41–SO_3H [16], under microwave irradiation [17–20], and using ionic liquids such as 1-methylimidazolium trifluoroacetate ([Hmim]TFA) [21] or bronsted acidic imidazolium salts containing perfluoroalkyl tails [22]. Each of these methods have their own advantages, but some of them often suffer from one or more disadvantages, such as poor yields, prolonged reaction time, harsh reaction conditions, tedious work-up processes, and expensive catalyst. Thus, the development of a simple, efficient and versatile method for the preparation of these compounds is an active area of research, and there is scope for further improvement towards milder reaction conditions and higher product yields.

Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available reagent for various organic transformations, affording the corresponding products with high selectivity in excellent yields [23–25]. The mild Lewis acidity associated with iodine has led to its use in organic synthesis using catalytic to stoichiometric amounts. Owing to numerous advantages correlative with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations [26, 27].



Scheme 1 Preparation of 1,8-dioxo-decahydroacridines derivatives **4a–4l**

Table 1 Optimizing the reaction conditions

Entry	Iodine (mol%)	Time (min)	Yield (%)
1	0	120	0
2	5	70	82
3	10	10	95
4	20	10	90

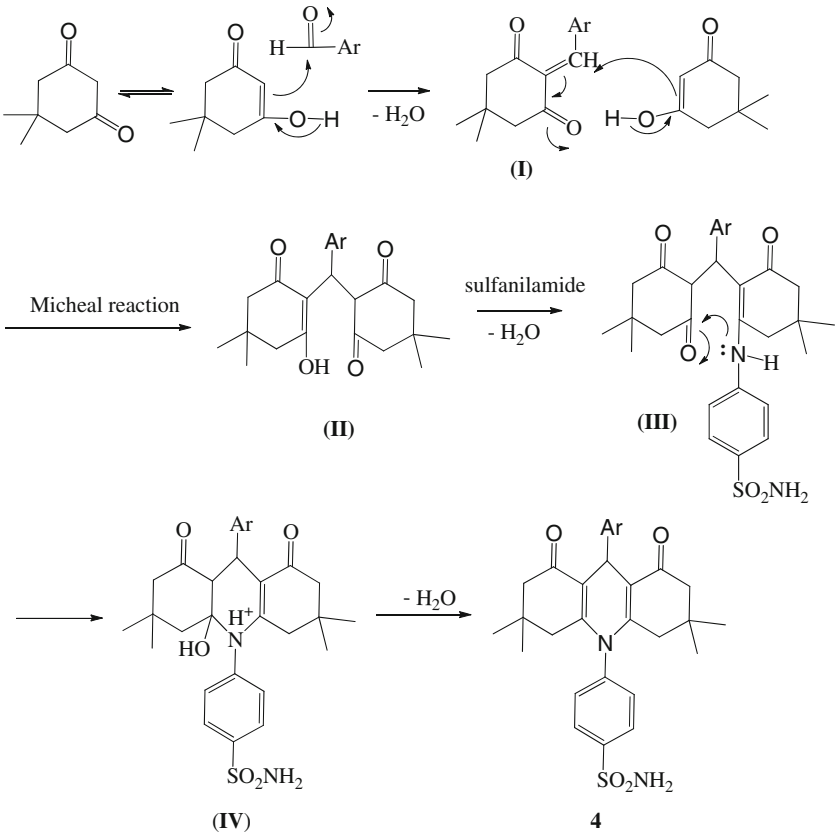
The sulfonamide is an important functional group. Compounds bearing sulfonamide group have been extensively used as pharmaceutical and agricultural agents because of their diverse biological properties. Representatives of this class of pharmacological agents are widely used in clinic as antibacterial, hypoglycemic, diuretic, anti-hypertensive, and antiviral drugs [28, 29]. Recently, enormous interest has also been directed toward a host of structurally novel sulfonamide derivatives which have shown promising bioactivities, such as antiviral, anti-inflammatory, and anti-cancer properties [30–32].

Keeping in mind the various biomedical applications of 1,8-dioxo-9-aryl decahydroacridines and sulfonamide derivatives, it was thought worthwhile to incorporate both these scaffolds in a single molecular framework to further assess the biological profile. To achieve this, novel 1,8-dioxo-decahydroacridines derivatives bearing benzene sulfonamide moiety were designed and synthesized by reaction of aromatic aldehyde with 5,5-dimethyl-1,3-cyclohexanedione and sulfanilamide in the presence of molecular iodine (Scheme 1). The cytotoxic activity of the obtained compounds **4a**–**4l** was evaluated in vitro against MCF-7, Hela, and A549 cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and found to possess moderate activity.

Table 2 Iodine catalyzed the synthesis of 1,8-dioxo-decahydroacridines derivatives

Entry	Ar-	Product (4)	Time (min)	Yields (%)[a]
1	4-ClC_6H_4	**4a**	10	95
2	2-ClC_6H_4	**4b**	12	92
3	2,4-$Cl_2C_6H_3$	**4c**	11	93
4	4-HOC_6H_4	**4d**	28	89
5	3-$NO_2C_6H_4$	**4e**	12	90
6	4-$NO_2C_6H_4$	**4f**	10	96
7	4-$CH_3OC_6H_4$	**4g**	15	92
8	3,4,5-$(CH_3O)_3C_6H_2$	**4h**	12	90
9	C_6H_5	**4i**	25	92
10	4-$CH_3C_6H_4$	**4j**	15	91
11	4-OH-3-$CH_3OC_6H_3$	**4k**	20	88
12	3,4-$OCH_2OC_6H_3$	**4l**	13	93

[a] Pure isolated yields



Scheme 2 The proposed mechanism

Results and discussion

In search of the best experimental conditions, 5,5-dimethyl-1,3-cyclohexanedione, *p*-chlorobenzaldehyde, and sulfanilamide were chosen as the three reactants, and iodine as well as various Lewis acids as the catalyst. In each case, two equivalents of 5,5-dimethyl-1,3-cyclohexanedione were added to the mixture of one equivalent of *p*-chlorobenzaldehyde and one equivalent of sulfanilamide and the catalyst. The progress of the reactions was monitored at an interval of 5 min by TLC.

In an initial endeavor, the condensation of 5,5-dimethyl-1,3-cyclohexanedione, *p*-chlorobenzaldehyde, and sulfanilamide was carried out in the absence of any catalyst, and after 2 h, the target product was not detected (Table 1, entry 1). Among various Lewis acids used, we initiated the study with molecular iodine. The reaction was monitored by TLC, and a clear spot of the product was obtained within 5 min, which indicated that the reaction is exceedingly fast. In order to improve the product yields and to optimize the reaction condition, the reaction was also performed using various amounts of iodine to determine the appropriate quantity of catalyst used, and it was found that the increase in the quantity of iodine from 5 to

10 mol% not only lessens the reaction time from 70 to 10 min, but also enhanced the product yield from 82 to 95 %. However, using 20 mol% of iodine as catalyst did not reduce the reaction time and increase the yield of the product **4a** (90 %). Thus, the use of 10 mol% iodine is ideal to achieve the desired product in good yields (Table 1).

To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions (*i*-PrOH, 20 mol% of I_2, air, reflux) and the results are summarized in Table 2. As shown in Table 2, this methodology is equally effective irrespective of the nature and positions (*o*-, *m*-, *p*-) of the substituents attached to the phenyl ring of the aromatic aldehyde. Strongly activating (**4**, **7**, **8**, **11**, and **12**), weakly activating (**10**), weakly deactivating (**1**–**3**), and strongly deactivating (**5** and **6**) systems all give products with nearly equal ease. The versatility of the method has also been demonstrated by the tolerance of a number of functional groups such as $–NO_2$ (**5** and **6**), –OMe (**7**, **8**, and **11**) and –OH (**4** and **11**).

On the basis of the reported literature, a possible reaction mechanism for the conversion of 5,5-dimethyl-1,3-cyclohexanedione, aromatic aldehyde, and sulfanilamide into corresponding 1,8-dioxo-decahydroacridines derivatives, with molecular iodine in isopropanol, is shown in Scheme 2. Initially, molecular iodine can serve as a Lewis acid catalyst for the reaction of 5,5-dimethyl-1,3-cyclohexanedione and aromatic aldehyde to give the intermediate (**I**) via Knoevenagel condensation. Then, the active methylene group of the second molecule of 5,5-dimethyl-1,3-cyclohexanedione reacts with (**I**) to give intermediate (**II**). Nucleophilic attack of amine group of sulfanilamide to carbonyl group creates intermediate (**III**). In the next step, cyclization will occur by the nucleophilic attack of amine group to carbonyl group to obtain intermediate (**IV**). Finally, by the removal of one molecule of water, the acridine derivatives **4** will be generated. It is worthy of mention that possible

Table 3 The cytotoxicity of the compounds (**4a**–**4l**) against MCF-7, Hela, and A549

Compounds	IC_{50} (μM)		
	MCF-7	Hela	A549
4a	16.90	22.55	24.41
4b	14.40	18.28	28.42
4c	13.78	19.36	26.56
4d	11.20	15.90	27.53
4e	10.92	14.88	23.26
4f	23.59	21.13	29.40
4g	21.15	19.50	28.46
4h	18.65	12.80	21.63
4i	15.13	20.81	23.47
4j	17.36	21.32	24.72
4k	17.35	19.82	22.68
4l	21.08	31.02	22.75
Cisplatin	11.06	8.61	8.25

interaction of molecular iodine with carbonyl oxygen has been previously indicated in the literature [33, 34].

Almost all the compounds showed moderate cytotoxic activity against MCF-7, Hela, and A549 cells. The cytotoxic activity data generated are tabulated in Table 3.

Conclusion

In conclusion, we have developed a convenient and efficient method for the synthesis of 1,8-dioxo-decahydroacridines derivatives bearing benzene sulfonamide moiety utilizing molecular iodine as a novel catalyst. The advantages of this method are short reaction times, operational simplicity, excellent product yields, and functional group tolerability. All the synthesized compounds were tested for their in vitro cytotoxic activity against MCF-7, Hela, and A549 cell lines, the obtained results revealing that most of the studied compounds exhibited moderate to potent cytotoxic activity. Among them, the most active compound, **4e**, exhibited more efficient activity (10.92 μM) against MCF-7 cells than cisplatin (11.06 μM).

Experimental

Materials and methods

RPMI-1640 medium, trypsin, and fetal bovine serum were purchased from Gibco. MTT, benzylpenicillin, and streptomycin were from Sigma. Three different human carcinoma cell lines: MCF-7 (human mammary cancer cells), Hela (human cervical carcinoma), and A549 (human lung cancer cells) were obtained from the American Type Culture Collection. Melting points were measured on an XT-4 microscopic melting-point spectrometer and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were obtained from solution in DMSO-d_6 with tetramethylsilane (TMS) as internal standard using a Bruker AVIII 600 NMR spectrometer. IR spectra were recorded using KBr pellets and a Perkin-Elmer Model-683 spectrophotometer. Mass spectra were measured by LC–MS apparatus Agilent 1200-6310. Elemental analysis was determined on an Elementar Vario EL III elemental analyzer.

General procedure for the synthesis of 1,8-dioxo-decahydroacridines derivatives

A mixture of 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), aromatic aldehyde (1 mmol), sulfanilamide (1 mmol), and iodine (10 mol%) was refluxed in isopropanol (3 mL) for the appropriate time (Table 2). After completion of the reaction as indicated by thin layer chromatography (TLC), the reaction mixture was cooled to room temperature and poured into 30 mL of sodium thiosulfate solution [34], and then the solid was precipitated, filtered, and recrystallized in EtOH to afford the title compound.

*4-(9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4a**)* Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,297 (NH_2), 3,292 (NH_2), 2,964 (CH_3), 1,640 (CO), 1371 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (d, J = 8.4 Hz, 2H, Ar–H), 7.67 (d, J = 8.4 Hz, 2H, Ar–H), 7.63 (s, 2H, –NH_2), 7.34–7.30 (m, 4H, Ar–H), 5 0.03 (s, 1H, –CH), 2.19 (d, J = 16.2 Hz, 4H, –CH_2), 2.02 (d, J = 15.6 Hz, 2H, –CH_2), 1.74 (d, J = 17.4 Hz,2H, –CH_2), 0.89 (s, 6H, –CH_3), 0.73 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.54, 150.40, 145.48, 145.24, 141.51, 130.80, 130.39, 129.96, 128.36, 128.30, 113.27, 49.93, 41.44, 32.53, 32.33, 29.63, 26.63; ESI–MS: m/z 562.5 $[M + Na]^+$; Anal. Calcd. for $C_{29}H_{31}N_2O_4SCl{\cdot}H_2O$: C 62.52, H 5.97, N 5.03. Found: C 62.81, H 5.35, N 5.07.

*4-(9-(2-Chlorophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4b**)* Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,355 (NH_2), 3,376 (NH_2), 2,957 (CH_3), 1,642 (CO), 1,371 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.04 (d, J = 7.8 Hz, 2H), 7.66 (d, J = 7.2 Hz, 2H, Ar–H), 7.61 (s, 2H, –NH_2), 7.51 (d, J = 7.8 Hz, 1H, Ar–H), 7.26 (t, J = 7.8 Hz, 2H, Ar–H), 7.11 (t, J = 7.8 Hz, 1H, Ar–H), 5.30 (s, 1H, –CH), 2.16 (d, J = 15.6 Hz, 2H, –CH_2), 2.15 (d, J = 17.4 Hz, 2H, –CH_2), 1.96 (d, J = 16.2 Hz, 2H, –CH_2), 1.73 (d, J = 17.4 Hz, 2H, –CH_2), 0.87 (s, 6H, –CH_3), 0.75 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.31, 150.65, 145.19, 143.37, 141.73, 133.07, 129.90, 127.87, 126.85, 112.50, 49.93, 41.70, 32.34, 29.70, 26.50; ESI–MS: m/z 561.8 $[M + Na]^+$; Anal. Calcd. for $C_{29}H_{31}N_2O_4SCl$: C 64.61, H 5.80, N 5.20. Found: C 64.40, H 5.72, N 5.05.

*4-(9-(2,4-Dichlorophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4c**)* Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,350 (NH_2), 3,199 (NH_2), 2,964 (CH_3), 1,657 (CO), 1,364 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (s, 2H, Ar–H), 7.67 (d, J = 9.0 Hz, 2H, Ar–H), 7.63 (s, 2H, –NH_2), 7.52 (d, J = 8.4 Hz, 1H, Ar–H), 7.41 (s, 1H, Ar–H), 7.32(dd, J_1 = 8.4, J_2 = 2.4 Hz, 1H, Ar–H), 5.23 (s, 1H, –CH), 2.16 (d, J = 16.2 Hz, 2H, –CH_2), 2.13 (d, J = 17.4 Hz,2H, –CH_2), 1.96 (d, J = 16.2 Hz, 2H, –CH_2), 1.73 (d, J = 17.4 Hz, 2H, –CH_2), 0.87 (s, 6H, –CH_3), 0.75 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.39, 150.95, 145.24, 141.60, 133.98, 131.41, 129.12, 127.00, 112.07, 49.85, 41.67, 32.35, 32.18, 29.65, 26.53; ESI–MS: m/z 596.8 $[M + Na]^+$; Anal. Calcd. for $C_{29}H_{30}N_2O_4SCl_2{\cdot}0.5H_2O$: C 59.79, H 5.36, N 4.81. Found: C 60.01, H 5.21, N 4.62.

*4-(9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4d**)* Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,292 (NH_2), 3,231 (NH_2), 2,962 (CH_3), 1,645 (CO), 1,376 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.11 (s, 1H, –OH), 8.02 (d, J = 8.4 Hz, 2H, Ar–H), 7.64–7.62 (m, 4H, –NH_2, Ar–H), 7.09 (d, J = 8.4 Hz, 2H, Ar–H), 6.62 (d, J = 9.0 Hz, 2H, Ar–H), 4.94 (s, 1H, –CH), 2.20 (d, J = 16.8 Hz, 2H, –CH_2), 2.17 (d, J = 15.6 Hz, 2H, –CH_2), 2.01 (d, J = 15.6 Hz, 2H, –CH_2), 1.71 (d,

J = 16.8 Hz, 2H, –CH_2), 0.88 (s, 6H, –CH_3), 0.74 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.57, 149.74, 145.12, 141.74, 137.24, 135.25, 129.37, 128.90, 115.26, 115.06, 114.11, 50.07, 41.43, 32.53, 31.26, 29.72, 26.60; ESI–MS: m/z 543.7 $[M + Na]^+$; Anal. Calcd. for $C_{29}H_{32}N_2O_5S{\cdot}H_2O$: C 62.66, H 6.36, N 5.20. Found: C 64.68, H 6.22, N 5.30.

*4-(3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4e**)* Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,311 (NH_2), 3,228 (NH_2), 2,959 (CH_3), 1,639 (CO), 1,347 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.15 (s, 1H, Ar–H), 8.07 (d, J = 8.4 Hz, 2H, Ar–H), 8.02 (d, J = 7.8 Hz, 1H, Ar–H), 7.79 (d, J = 7.8 Hz, 1H, Ar–H), 7.70–7.69 (m, 2H), 7.63 (s, 2H, –NH_2), 7.60 (t, J = 7.8 Hz, 1H, Ar–H), 5.15 (s, 1H, –CH), 2.40 (d, J = 16.2 Hz, 2H, –CH_2), 2.32 (d, J = 16.2 Hz, 2H, –CH_2), 2.03 (d, J = 16.2 Hz, 2H, –CH_2), 1.79 (d, J = 16.8 Hz, 2H, –CH_2), 0.90 (s, 6H, –CH_3), 0.73 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.63, 151.00, 148.52, 147.88, 145.34, 141.34, 134.74, 130.25, 122.67, 121.54, 112.84, 49.81, 41.42, 32.98, 32.60, 29.57, 26.57; ESI–MS: m/z 572.8 $[M + Na]^+$; Anal. Calcd. for $C_{29}H_{31}N_3O_6S{\cdot}H_2O$: C 61.36, H 5.86, N 7.40. Found: C 61.84, H 5.69, N 7.22.

*4-(3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4f**)* Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,304 (NH_2), 3,211 (NH_2), 2,964 (CH_3), 1,642 (CO), 1,347 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.15 (d, J = 8.4 Hz, 2H, Ar–H), 8.05 (d, J = 8.4 Hz, 2H, Ar–H), 7.74 (d, J = 8.4 Hz, 2H, Ar–H), 7.64 (s, 2H, –NH_2), 7.61 (d, J = 9.0 Hz, 2H, Ar–H), 5.14 (s, 1H, –CH), 2.23 (d, J = 16.8 Hz, 2H, –CH_2), 2.21 (d, J = 15.6 Hz, 2H, –CH_2), 2.02 (d, J = 15.6 Hz, 2H, –CH_2), 1.77 (d, J = 16.8 Hz, 2H, –CH_2), 0.89 (s, 6H, –CH_3), 0.72 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.52, 153.92, 150.93, 146.19, 145.33, 141.37, 129.47, 123.77, 112.64, 49.83, 41.45, 33.38, 32.55, 29.57, 26.64; ESI–MS: m/z 573.4 $[M + Na]^+$; Anal. Calcd. for $C_{29}H_{31}N_3O_6S{\cdot}H_2O$: C 61.36, H 5.86, N 7.40. Found: C 61.90, H 5.83, N 7.23.

*4-(9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide (**4g**)* Pale yellow solid; m.p. 235–236 °C; IR (cm^{-1}): 3,306 (NH_2), 3,223 (NH_2), 2,959 (CH_3), 1,642 (CO), 1,371 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (d, J = 8.4 Hz, 2H, Ar–H), 7.64 (d, J = 7.8 Hz, 2H, Ar–H), 7.63 (s, 2H, –NH_2), 7.22 (d, J = 8.4 Hz, 2H, Ar–H), 6.81 (d, J = 8.4 Hz, 2H, Ar–H), 4.99 (s, 1H, –CH), 3.69 (s, 3H, –OCH_3), 2.20 (d, J = 17.4 Hz, 2H, –CH_2), 2.18 (d, J = 15.6 Hz, 2H, –CH_2), 2.01 (d, J = 15.6 Hz, 2H, –CH_2), 1.73 (d, J = 17.4 Hz, 2H, –CH_2), 0.89 (s, 6H, –CH_3), 0.74 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.55, 157.79, 149.88, 145.16, 141.70, 138.87, 129.46, 129.01, 113.95, 113.74, 55.32, 50.03, 41.44, 32.52, 32.31, 29.70, 26.63; ESI–MS: m/z 557.5 $[M + Na]^+$; Anal. Calcd. for $C_{30}H_{34}N_2O_5S$: C 67.39, H 6.41, N 5.24. Found: C 67.09, H 6.59, N 5.25.

4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-(3,4,5-trimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide ***(4h)*** Pale yellow solid; m.p. 191–192 °C; IR (cm^{-1}): 3,389 (NH_2), 3,267 (NH_2), 2,962 (CH_3), 1,645 (CO), 1,364 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.04 (d, $J = 9.0$ Hz, 2H, Ar–H), 7.62 (s, 2H, –NH_2), 7.57 (d, $J = 9.0$ Hz, 2H, Ar–H), 6.55 (s, 2H, Ar–H), 5.05 (s, 1H, –CH), 3.74 (s, 6H, –OCH_3), 3.61 (s, 3H, –OCH_3), 2.23 (d, $J = 17.4$ Hz, 2H, –CH_2), 2.21 (d, $J = 16.2$ Hz, 2H, –CH_2), 2.07 (d, $J = 16.2$ Hz, 2H, –CH_2), 1.77 (d, $J = 17.4$ Hz, 2H, –CH_2), 0.90 (s, 6H, –CH_3), 0.79 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.73, 152.88, 150.30, 145.15, 142.04, 141.51, 136.08, 113.45, 104.91, 60.38, 56.11, 50.02, 41.49, 32.55, 32.06, 29.71, 26.56; ESI–MS: *m/z* 617.4 $[M + Na]^+$; Anal. Calcd. for $C_{32}H_{38}N_2O_7S{\cdot}1.5H_2O$: C 61.82, H 6.65, N 4.51. Found: C 61.84, H 6.14, N 4.58.

4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9)-yl)benzenesulfonamide ***(4i)*** Pale yellow solid; m.p. 197–198 °C; IR (cm^{-1}): 3,284 (NH_2), 3,062 (NH_2), 2,954 (CH_3), 1,640 (CO), 1,364 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.04 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.65 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.61 (s, 2H, –NH_2), 7.33 (d, $J = 7.2$ Hz, 2H, Ar–H), 7.25 (t, $J = 7.8$ Hz, 2H, Ar–H), 7.11 (t, $J = 7.2$ Hz, 1H, Ar–H), 5.06 (s, 1H, –CH), 2.22 (d, $J = 17.4$ Hz, 2H, –CH_2), 2.20 (d, $J = 16.2$ Hz, 2H, –CH_2), 2.02 (d, $J = 16.2$ Hz, 2H, –CH_2), 1.75 (d, $J = 17.4$ Hz, 2H, –CH_2), 0.89 (s, 6H, –CH_3), 0.73 (s, 6H, –CH_3); ESI–MS: *m/z* 527.5 $[M + Na]^+$; ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.55, 150.18, 146.53, 145.18, 141.63, 128.41, 128.06, 127.88, 126.31, 113.67, 50.00, 41.45, 32.53, 32.43, 29.69, 26.58. Anal. Calcd. for $C_{29}H_{32}N_2O_4S{\cdot}H_2O$: C 66.64, H 6.56, N 5.36. Found: C 66.06, H 6.21, N 5.34.

4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-p-tolyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl) benzenesulfonamide ***(4j)*** Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,299 (NH_2), 3,040 (NH_2), 2,952 (CH_3), 1,642 (CO), 1,366 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6) : δ 8.03 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.64 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.62 (s, 2H, –NH_2), 7.20 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.05 (d, $J = 7.8$ Hz, 2H, Ar–H), 5.01(s, 1H, –CH), 2.23 (s, 3H, –CH_3), 2.21 (d, $J = 17.4$ Hz, 2H, –CH_2), 2.18 (d, $J = 16.8$ Hz, 2H, –CH_2), 2.01 (d, $J = 16.8$ Hz, 2H, –CH_2), 1.73 (d, $J = 17.4$ Hz, 2H, –CH_2), 0.89 (s, 6H, –CH_3), 0.73 (s, 6H, –CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.53, 150.02, 145.16, 143.65, 141.68, 135.14, 128.99, 127.95, 113.81, 50.03, 41.44, 32.52, 31.93, 29.71, 26.61, 21.09; ESI–MS: *m/z* 541.6 $[M + Na]^+$; Anal. Calcd. for $C_{30}H_{34}N_2O_4S{\cdot}H_2O$: C 67.14, H 6.46, N 5.22. Found: C 67.09 H 6.56, N 5.20.

4-(9-(4-Hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzenesulfonamide ***(4k)*** Pale yellow solid; m.p. >250 °C; IR (cm^{-1}): 3,279 (NH_2), 3,084 (NH_2), 2,952 (CH_3), 1,642 (CO), 1,366 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.66 (s, 1H, –OH), 8.03 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.60 (s, 2H, –NH_2), 7.57 (d, $J = 8.4$ Hz, 2H, Ar–H), 6.81 (s, 1H, Ar–H), 6.70 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, 1H, Ar–H), 6.65 (d, $J = 8.4$ Hz, 1H, Ar–H),

4.98 (s, 1H, –CH), 3.73 (s, 3H, $–OCH_3$), 2.22 (d, $J = 17.4$ Hz, 2H, $–CH_2$), 2.19 (d, $J = 15.6$ Hz, 2H, $–CH_2$), 2.04 (d, $J = 15.6$ Hz, 2H, $–CH_2$), 1.74 (d, $J = 17.4$ Hz, 2H, $–CH_2$), 0.90 (s, 6H, $–CH_3$), 0.77 (s, 6H, $–CH_3$); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.66, 149.85, 147.41, 145.12, 145.03, 141.68, 137.74, 120.11, 115.57, 113.98, 112.09, 55.90, 50.07, 41.46, 32.53, 31.37, 29.75, 26.55; ESI–MS: m/z 573.3 $[M + Na]^+$; Anal. Calcd. for $C_{30}H_{34}N_2O_6S{\cdot}0.5H_2O$: C 64.38, H 6.30, N 5.01. Found: C 64.11 H 6.44, N 4.86.

4-(9-(Benzo[d][1,3]dioxol-5-yl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroanthracen-10-yl)benzenesulfonamide ***(4l)*** Pale yellow solid; m.p. 227–228 °C; IR (cm^{-1}): 3,365 (NH_2), 3,231 (NH_2), 2,962 (CH_3), 1,645 (CO), 1,366 (SO_2); ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.63 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.61 (s, 2H, $–CH_2$), 6.81–6.78 (m, 3H, Ar–H), 4.97 (s, 1H, –CH), 2.26 (d, $J = 16.2$ Hz, 1H, $–CH_2$), 2.20 (d, $J = 16.8$ Hz, 2H, $–CH_2$), 2.18 (d, $J = 16.2$ Hz, 2H, $–CH_2$), 2.11 (d, $J = 16.2$ Hz, 1H, $–CH_2$), 2.04 (d, $J = 16.2$ Hz, 2H, $–CH_2$), 1.75 (d, $J = 16.8$ Hz, 2H, $–CH_2$), 0.89 (s, 6H, $–CH_3$), 0.76 (s, 6H, $–CH_3$);, ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 195.61, 150.00, 147.18, 145.64, 145.17, 141.60, 140.80, 120.86, 113.74, 108.78, 108.28, 101.06, 50.00, 41.44, 32.54, 32.33, 29.63, 26.69; ESI–MS: m/z 571.5 $[M + Na]^+$; Anal. Calcd. for $C_{30}H_{34}N_2O_6S{\cdot}H_2O$: C 65.82, H 6.24, N 2.48. Found: C 65.31 H 5.94, N 2.27.

Cell culture

Three different human carcinoma cell lines: MCF-7, Hela, and A549 were cultured in RPMI-1640 medium supplemented with 10 % fetal bovine serum, 100 U/mL of penicillin, and 100 mg/mL of streptomycin. Cells were maintained at 37 °C in a humidified atmosphere of 5 % CO_2 in air.

Solutions

The obtained 1,8-dioxo-decahydroacridines derivatives, **4a**–**4l**, were dissolved in DMSO at a concentration of 5 mM as stock solution, and diluted in culture medium at concentrations of 1.0, 10, 100, and 500 mM as working solution. To avoid DMSO toxicity, the concentration of DMSO was less than 0.1 % (v/v) in all experiments.

Cytotoxicity analysis

The cells harvested from the exponential phase were seeded equivalently into a 96-well plate, and then the compounds were added to the wells to achieve final concentrations. Control wells were prepared by addition of culture medium. Wells containing culture medium without cells were used as blanks. All experiments were performed in quintuplicate. The MTT assay was performed as described by

Mosmann [35]. Upon completion of the incubation for 44 h, stock MTT dye solution (20 mL, 5 mg/mL) was added to each well. After 4 h incubation, 2-propanol (100 mL) was added to solubilize the MTT formazan. The optical density (OD) of each well was measured on a microplate spectrophotometer at a wavelength of 570 nm. The IC_{50} value was determined from plot of % viability against dose of compounds added.

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