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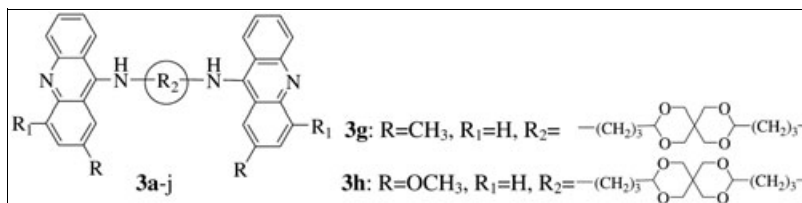
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Received January 21, 2011

DOI 10.1002/jhet.985

Published online 7 March 2013 in Wiley Online Library (wileyonlinelibrary.com).



A series of bis-acridine derivatives **3a–j** and **5a–j** have been synthesized by condensation of 9-chloro-2,4-(un)substituted acridines (**1a–e**) and 9-isothiocyanato-2,4-(un)substituted acridines (**4a–e**) with diamine **2a** and **2b**, respectively. These bis-acridines were evaluated *in vitro* for activity against a panel of human cancer cell lines of lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15), and liver (HepG2). Several bis-acridines were found to possess good anticancer activity against various cancer cell lines. Of these, compound **3h** exhibited good anticancer activity against all cancer cell lines tested except liver (HepG2) cell line. In addition to this, these compounds were screened for anti-inflammatory activity at a dose of 50 mg/kg *p.o.* Compound **3g** exhibited 41% anti-inflammatory activity, which is better than most commonly used standard drug ibuprofen, which showed 39% anti-inflammatory (at 50 mg/kg *p.o.*) activity.

J. Heterocyclic Chem., **50**, 252 (2013).

INTRODUCTION

Cancer and inflammatory diseases are of serious concern throughout the world in terms of direct mortality and morbidity. For the treatment of inflammation, various drugs available in the market have serious side effects such as dyspepsia, gastroduodenal ulcers, gastritis bleeding, so on [1] and, hence, cannot be used continuously for long time. Prolonged inflammation can cause various types of cancer, such as colon, cervix, and breast cancer [2,3]. Limited number of anticancer drugs are available in the market indicate that, there is an urgent need to develop novel, safe, and cost-effective new anticancer agents [4] and anti-inflammatory drugs [5–7].

Known since 19th century, acridines have been extensively used in medical sciences for their therapeutic properties. These pharmacophores were first developed for their fungicidal [8,9], antiparasitic [10], and antimicrobial [11,12] activities. In addition to this, acridines have also been identified as highly potent antitumor agents [13–15]. Acridines were reported to possess anti-inflammatory and analgesic [16–19] activities. A number of substituted acridine derivatives, that is, amsacrine (*N*-(4-(acridin-9-ylamino)-3-methoxyphenyl)methanesulfonamide) (Fig. 1, **A**), NC-NO (Nitracrine *N*-oxide) (Fig. 1, **B**),

and BRACO-19 (9-(4-(*N,N*-dimethylamino)phenylamino)-3,6-bis(3-pyrrolidinopropion amido) acridine) (Fig. 1C) are used clinically for the treatment of cancer [20,21]. Anticancer activity of acridines is based on their capacity to interact with nucleic acids, either (i) *via* intercalation between double-stranded DNA base pairs and inhibition of a DNA topoisomerase II enzyme (Fig. 1A) or (ii) *via* stabilization of alternative four stranded DNA structures called G-quadruplexes (Fig. 1C) [22,23]. Interestingly, it is clearly established that large number of acridine derivatives having an amino substituent at position C-9 in 9-aminoacridines (Fig. 1) showed *in vitro* anticancer properties. Bis-acridine heterocycles are dimeric acridine analogs, whereby two bioactive acridine heterocycles are tethered *via* a flexible linker. They were first developed as anticancer agents based on their enhanced DNA-binding properties compared with those of the respective monoacridines heterocycles [24–26]. Along with the anticancer activity bis-acridine derivatives also possess potent antialzheimer and antiprion activity [27].

Motivated by this hypothesis and wide range of biological activities possessed by monoacridine derivatives and in continuation of our efforts in search of potential anti-inflammatory and anticancer agents [28–31], we have synthesized two series of bis-acridine derivatives in which two bioactive acridine heterocycles are tethered *via* a flexible linker. These bis-acridines have been

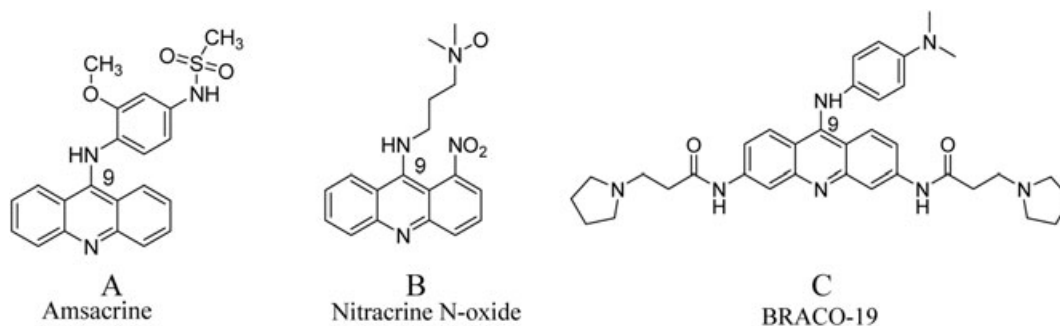


Figure 1. Clinically used acridine derived anticancer agents.

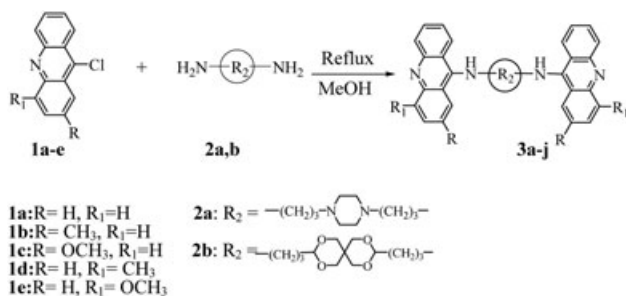
screened for anticancer and anti-inflammatory activities, which we wish to report in this article.

CHEMISTRY

9-Chloro-2,4-(un)substituted acridines (**1a–e**; Scheme 1) [32,33] and 9-isothiocyanato-2,4-(un)substituted acridines (**4a–e**; Scheme 2) [34] were synthesized by following reaction procedure reported in literature and used for the synthesis of bis acridine heterocycles. These starting materials (**1a–e** and **4a–e**) were fully characterized by IR,

NMR, and GC-MS data. 9-Chloroacridine (**1a**; Scheme 1) and 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine (**2a**; Scheme 1) were dissolved in methanol and refluxed for 17 h, and then solvent was removed under reduced pressure. The solid residue left behind was treated with 10% cold aqueous sodium bicarbonate solution and then washed with cold water. Solid so obtained was air dried to give crude condensed product, which was further purified by column chromatography over silica gel to give pure product **3a**, that is, *N*-(3-(4-(3-(acridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (Scheme 1) in

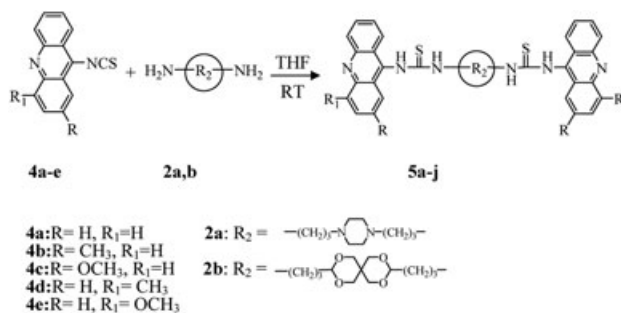
Scheme 1. Synthesis of bis-acridine derivatives **3a–j**.



For Compounds **3a–j**

	R	R ₁	R ₂
3a	H	H	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
3b	CH ₃	H	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
3c	OCH ₃	H	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
3d	H	CH ₃	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
3e	H	OCH ₃	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
3f	H	H	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
3g	CH ₃	H	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
3h	OCH ₃	H	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
3i	H	CH ₃	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
3j	H	OCH ₃	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$

Scheme 2. Synthesis of acridine derivatives **5a–j**.



For Compounds **5a–j**

	R	R ₁	R ₂
5a	H	H	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
5b	CH ₃	H	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
5c	OCH ₃	H	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
5d	H	CH ₃	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
5e	H	OCH ₃	$-(\text{CH}_2)_3\text{-N(CH}_2)_2\text{-N(CH}_2)_2-$
5f	H	H	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
5g	CH ₃	H	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
5h	OCH ₃	H	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
5i	H	CH ₃	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$
5j	H	OCH ₃	$-(\text{CH}_2)_3\text{-O(CH}_2)_2\text{-O(CH}_2)_2-$

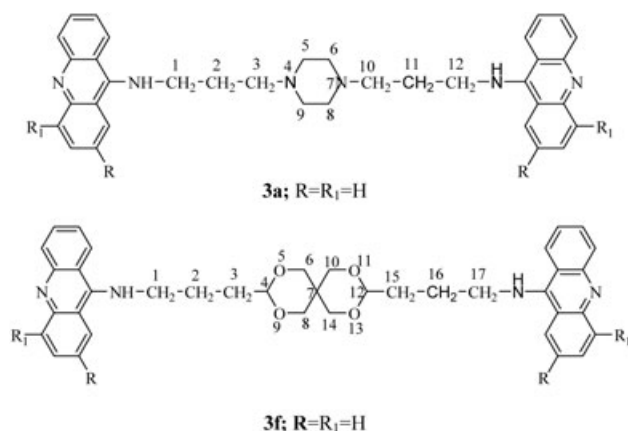


Figure 2. Numbering of **3a** and **3f** for interpretation of $^1\text{H-NMR}$ data.

43% yield. IR spectrum of **3a** depicted absorption signal at 3434 cm^{-1} , which is attributed to NH functional group and strong absorption signals at 1632 , 1589 , 1530 cm^{-1} correspond to aromatic region of acridinyl moiety. ($^1\text{H-NMR}$ data are interpreted by following numbering of **3a** and **3f** as mentioned in Fig. 2) $^1\text{H-NMR}$ of compound **3a** exhibited signals at δ 8.077–8.095 (d, 4H, $J = 9\text{ Hz}$, Ar), 7.775–7.806 (m, 4H, Ar), 7.474–7.491 (d, 4H, $J = 9\text{ Hz}$, Ar), 7.381–7.411 (t, 4H, $J = 7.5$ and 15 Hz , Ar), 3.964–3.992 (t, 4H, $J = 7$ and 14 Hz $2\times\text{CH}_2$, C^1 , C^{12}), 2.622–2.651 (m, 12H, $6\times\text{CH}_2$, C^3 , C^5 , C^6 , C^8 , C^9 , C^{10}), 2.028–2.057 (t, 4H, $J = 7$ and 14 Hz $2\times\text{CH}_2$, C^2 , C^{11}), $^{13}\text{C-NMR}$ data of **3a** exhibited signals at δ : 150.609 (2C), 149.279 (4C), 130.360 (4C), 129.143 (4C), 123.767 (4C), 122.041 (4C), 113.418 (4C), 56.373 (4C), 53.089 (2C), 40.562 (2C) and 30.855 (2C). Compound **3a** exhibited MH^+ ion peak at m/z 555.40 (100%). Spectral and analytical data of **3a** fully support the structure assigned to it.

Similarly 9-chloroacridine **1a** and diamine **2b**, that is, 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropane amine on refluxing in methanol for 18 h gave condensed product **3f**, which was purified by column chromatography over silica gel to give pure product **3f**, that is, acridin-9-yl-[3-(9-[(3-[(acridin-9-ylamino)]-propyl])-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine (Scheme 1) in 42% yield. IR spectrum of **3f** exhibited absorption signal at 3374 cm^{-1} (NH) functional group and strong absorption signals at 1629 , 1560 , and 1515 cm^{-1} correspond to aromatic region. Although interpreting $^1\text{H-NMR}$ data of **3f**, peak positions were assigned with the help of $^1\text{H-NMR}$ of starting material, that is (**2b**) and similar compounds reported in literature [35]. It is considered that dioxane ring starting with C_4 is in the plane and dioxane ring starting with C_{12} is out of plane. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) data of **3f** depicted signals at δ 9.877 (s, 1H, NH exch), 9.829 (s, 1H, NH exch), 8.575–8.708 (bs, 4H, Ar), 7.904–8.024 (m, 8H, Ar), 7.53–7.549 (d, 4H, $J = 9.5\text{ Hz}$ Ar), 4.482–4.542 (m, 2H, C^{10b} ,

C^{14b}), 4.164–4.186 (d, 1H, $J = 11\text{ Hz}$ CH, C^{12}), 4.096 (s, 4H, C^6 , C^8), 3.716–3.739 (d, 1H, $J = 11.5\text{ Hz}$, CH, C^4), 3.522–3.546 (t, 4H, $J = 6$ and 12 Hz $2\times\text{CH}_2$, C^1 , C^{17}), 3.145–3.165 (t, 2H, $J = 5$ and 10 Hz C^{10a} , C^{14a}), 1.960–1.989 (m, 4H, $2\times\text{CH}_2$, C^3 , C^{15}), 1.656–1.679 (m, 4H, $2\times\text{CH}_2$, C^2 , C^{16}), $^{13}\text{C-NMR}$ data of **3f** exhibited signals at δ : 151.102 (2C), 149.426 (4C), 131.070 (4C), 129.574 (4C), 124.013 (4C), 122.671 (4C), 113.705 (4C), 102.158 (2C), 69.946 (2C), 69.423 (2C), 41.476 (2C), 32.326 (1C), 32.151 (2C), and 27.183 (2C), which satisfy the carbon skeleton of compound **3f**. MH^+ ion peak of **3f** was observed at m/z 629.53 (100%). Spectral and analytical data of **3f** fully support the structure assigned to it. By following similar procedure acridine derivatives, **3b–e** and **3g–i** were synthesized. Spectral and analytical data of **3a–j** fully support the structures assigned to them.

9-Isothiocyanatoacridine (**4a**; Scheme 2) and 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine (**2a**; Scheme 2) were dissolved in THF (10 mL) separately and mixed together with constant stirring and allowed to stand at room temperature. After standing for 2 h solid started separating out, which was further allowed to stand for 6 h, and the reaction contents were filtered. Solid residue so obtained was purified by column chromatography over silica gel to give pure product **5a**, that is, 1-(3-(4-(3-(9-acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(acridin-9-yl) thiourea (**5a**; Scheme 2) in 37% yield. IR spectrum of **5a** give absorption signal at 3425 and 1621 cm^{-1} , which are due to NH and $\text{C}=\text{S}$ functional groups respectively and strong absorption signals at 1586 cm^{-1} and 1523 cm^{-1} arise due to aromatic region of acridinyl moiety. $^1\text{H-NMR}$ data of **5a** exhibited signals at δ : 8.104–8.136 (m, 4H, Ar), 7.524–7.623 (m, 4H, Ar), 7.343–7.415 (m, 4H, Ar), 7.074–7.168 (m, 4H, Ar), 3.508–3.519 (d, 2H, $J = 5.5\text{ Hz}$, C^{1b} , C^{12b}), 3.052 (bs, 2H, C^{1a} , C^{12a}), 2.018–2.192 (m, 12H, $6\times\text{CH}_2$, C^3 , C^5 , C^6 , C^8 , C^9 , C^{10}), 1.642–1.675 (m, 2H, C^{2b} , C^{11b}), 1.454 (bs, 2H, C^{2a} , C^{11a}), $^{13}\text{C-NMR}$ data of **5a** exhibited signals at δ : 176.967 (2C), 151.109 (2C), 149.009 (4C), 131.161 (4C), 130.143 (4C), 124.747 (4C), 123.551 (4C), 112.418 (4C), 56.308 (4C), 52.749 (2C), 40.442 (2C), and 30.745 (2C). Spectral and analytical data of **5a** is in full agreement with the structure assigned to compound **5a**. Similarly compounds **5b–j** (Scheme 2) were synthesized and purified by column chromatography over silica gel. Spectral and analytical data of **5a–j** fully support the structures assigned to them.

PHARMACOLOGICAL RESULTS AND DISCUSSION

In vitro anticancer activity [36,37] evaluation of compounds **3a–j** and **5a–j** was carried out against five human cancer cell lines consisting of lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15), and liver (HepG2).

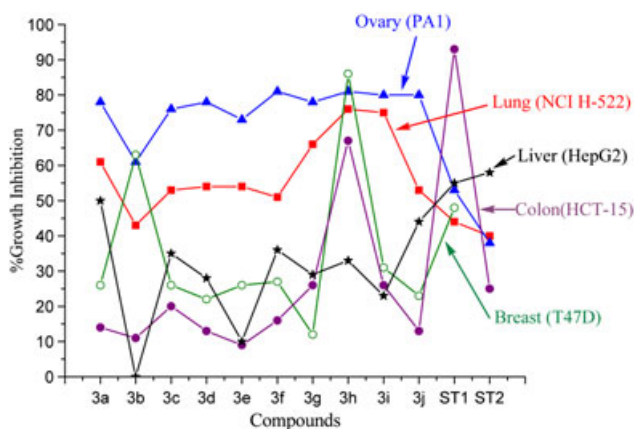


Figure 3. Graphical representation of anticancer activity of compounds **3a–j** and ST1 (adriamycin) and ST2 (mitomycin C) against five human cancer cell lines. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Percentage (%) growth inhibition of compounds **3a–j** and **5a–j** against various cancer cell lines was determined at a concentration of 10 μ M and graphical representations of these results are summarized in Figures 3 and 4, respectively.

From Figure 3, it is evident that bis-acridine derivatives **3a–j** are more effective than standard drugs (ST1 = Adriamycin, ST2 = Mitomycin C) for ovary (PA1) and lung (NCI H-522) cancer cell lines which are shown in blue and red colors in Figure 3. For breast cancer cell line only, two compounds **3b** and **3h** exhibited good anticancer activity, that is, 63 and 86% respectively, whereas others showed moderate anticancer activity. In case of colon cancer cell line compound **3h** and for liver cancer cell line compound **3a** showed good anticancer activity while others did not show significant activity. Of compounds **3a–j**, compound **3h** exhibited good anticancer activity against four human cancer cell lines, that is, lung (NCI H-522), ovary (PA1), breast (T47D), and colon (HCT-15). In this series, bis-acridines **3a–j**, compounds having flexible linker, that is, 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropyl (**3f–j**) exhibited better anticancer activity than those having 1,4-dipropylpiperazine as flexible linkage that is (**3a–e**).

In second series (compounds **5a–j**), compound **5g** exhibited good anticancer activity against breast cancer cell line while all other compounds exhibited moderate activity. For liver cancer cell line only two compounds **5c** and **5e** showed moderate activity while other compounds are inactive. From Figure 4, it can be concluded that compounds **5f–j** exhibited better anticancer activity than **5a–e**. In compounds **5f–j**, two acridine moieties are tethered *via* a flexible linker 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropyl and in compounds **5a–e** two acridine moieties are tethered *via* a flexible linker 1,4-dipropylpiperazine. All the data of anticancer activity against five human cancer cell lines, that is, lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15), and liver (HepG2) is summarized in Table 1. From the activity data of two series of

compounds, it can be concluded that 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropyl is a better flexible linker than 1,4-dipropylpiperazine.

Anti-inflammatory activity [38] evaluation of **3a–j** and **5a–j** was carried out using carrageenan induced paw oedema assay and results are summarized in the Table 1. A look at the Table 1 indicates that out of these compounds, that is, **3a–j** and **5a–j** compound **3g** exhibited interesting, that is, 41% anti-inflammatory activity, whereas most commonly used standard drug ibuprofen exhibited 39% anti-inflammatory activity at 50 mg/kg *p.o.* It is concluded that acridine derivatives **3a–j** exhibited better anticancer and anti-inflammatory activity when compared with **5a–j**. This may be due to the fact that in case of **3a–j** both acridine moieties may be able to interact with DNA more effectively as compared to in case of **5a–j** where acridine moieties are far apart of each other and this may hinder their effective interaction with DNA.

CONCLUSION

A number of acridine derivatives **3a–j** and **5a–j** have been synthesized and screened for anti-inflammatory and anticancer activities. Compound **3g** exhibited anti-inflammatory activity better than standard drug ibuprofen and compound **3h** exhibited good anticancer activity against four human cancer cell lines, that is, lung (NCI H-522), ovary (PA1), breast (T47D), and colon (HCT-15). Collectively, these results indicate that bis-acridines represent a novel class of anticancer agents, which deserve further evaluation for their potential usefulness in anticancer research.

EXPERIMENTAL

General. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. ^1H and ^{13}C -NMR spectra

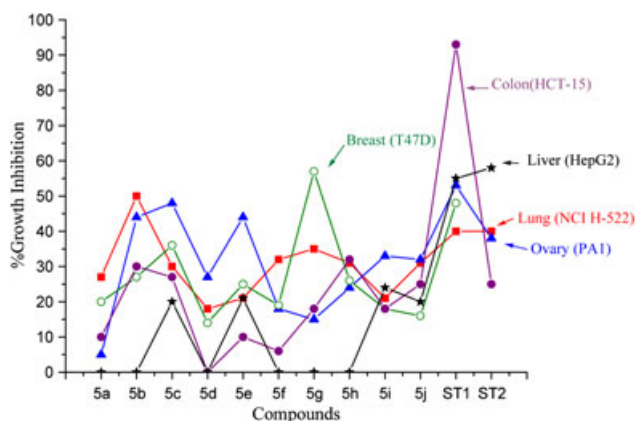


Figure 4. Graphical representation of anticancer activity of compounds **5a–j** and ST1 (adriamycin) and ST2 (mitomycin C) against five human cancer cell lines. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1
Anti-inflammatory and *in vitro* anticancer activity evaluation of compounds **3a–j** and **5a–j**.

Compd. No.	Anti-inflammatory activity (%) at 50 mg/kg p.o.	Anticancer activity at a concentration of 1×10^{-5} M				
		Lung NCI H-522	Ovary PA1	Breast T47D	Colon HCT-15	Liver HepG2
3a	16	61	78	26	14	50
3b	17	43	61	63	11	00
3c	00	53	76	26	20	35
3d	07	54	78	22	13	28
3e	13	54	73	26	09	10
3f	19	51	81	27	16	36
3g	41	66	78	12	26	29
3h	24	76	81	86	67	33
3i	00	75	80	31	26	23
3j	24	53	80	23	13	44
5a	08	27	05	20	10	00
5b	34	50	44	27	30	00
5c	34	30	48	36	27	20
5d	09	18	27	14	00	00
5e	09	21	44	25	10	21
5f	00	32	18	19	16	00
5g	28	35	15	57	09	00
5h	10	31	24	26	06	00
5i	15	21	33	18	18	24
5j	21	31	32	16	32	02
Ibuprofen	39	–	–	–	–	–
Adriamycin	–	44	–	–	93	55
Mito-C	–	40	48	–	25	58
Paclitaxel	–	51	–	65	–	75
5-FU	–	0	39	0	29	29

were recorded on a Bruker WH-500 spectrometer at a about 5–15% (*w/v*) solution in DMSO-*d*₆, CH₃OD, and D₂O. APCI mass was recorded using Finnigan Mat LCQ Mass Spectrometer. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck), and spots were visualized by iodine vapor or by irradiation with ultraviolet light (short wave length, 254nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh).

General procedure for condensation of 9-chloro-2,4-(un)substituted acridines (1a–e) with various amines (2a,b), N-(3-(4-(3-(Acridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (3a). 9-Chloroacridine (200 mg, 0.92 mmol) was taken in methanol (20 mL) and to it was added 3-(4-(3-aminopropyl)piperazin-1-yl) propan-1-amine (90 mg, 0.45 mmol). Reaction contents were heated under reflux for 17 h. Solvent was removed under reduced pressure and the residue left behind was treated with 10% cold aqueous sodium bicarbonate solution (5 mL), then washed with cold water to give crude product, which was purified by column chromatography over silica gel to give pure product **3a**. Solvent of elution: CHCl₃: MeOH (7:3, *R*_f = 0.6); Yield: 238 mg (43%); mp: >300°C; IR(KBr) ν_{\max} : 3434 (NH), 1632, 1589, 1530, and 1472 (Ar) cm⁻¹. ¹H-NMR (500 MHz, D₂O) δ : 8.077–8.095 (d, 4H, *J* = 9 Hz, Ar), 7.775–7.806 (m, 4H, Ar), 7.474–7.491 (d, 4H, *J* = 9 Hz, Ar), 7.381–7.411 (t, 4H, *J* = 7.5 and 15 Hz, Ar), 3.964–3.992 (t, 4H, *J* = 7 and 14 Hz 2xCH₂, C¹, C¹²), 2.622–2.651 (m, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 2.028–2.057 (t, 4H, *J* = 7 and 14 Hz 2xCH₂, C², C¹¹),

¹³C-NMR (125 MHz, DMSO-*d*₆) δ : 150.609 (2C), 149.279 (4C), 130.360 (4C), 129.143 (4C), 123.767 (4C), 122.041 (4C), 113.418 (4C), 56.373 (4C), 53.089 (2C), 40.562 (2C), and 30.855 (2C). APCI-MS: *m/z* 555.40, (MH⁺, 100%). Anal. Calcd for C₃₆H₃₈N₆: C, 77.98; H, 6.86; N, 15.16 Found C, 77.63; H, 6.70; N, 15.30.

2-Methyl-N-(3-(4-(3-(2-methylacridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (3b). Solvent of elution: CHCl₃: MeOH (8:2), yield: 48%, mp: >300°C; IR (KBr) ν_{\max} 3412(NH), 1626, 1590, 1531 (Ar) cm⁻¹. ¹H-NMR (500 MHz, CD₃OD) δ : 8.463–8.480 (d, 2H, *J* = 8.5 Hz, Ar), 8.252 (s, 2H, Ar), 7.890–7.920 (t, 2H, *J* = 7.5 and 15 Hz, Ar), 7.730–7.803 (t, 4H, *J* = 7.5 and 15 Hz, Ar), 7.714–7.731 (d, 2H, *J* = 8.5 Hz, Ar), 7.496–7.526 (t, 2H, *J* = 7.5 and 15 Hz, Ar), 4.238–4.264 (t, 4H, *J* = 6.5 and 13 Hz, 2xCH₂, C¹, C¹²), 2.488–2.632 (s + bs, 18H, 2xCH₃, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 2.077–2.102 (t, 4H, 2xCH₂, *J* = 6.5 and 13 Hz, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 150.609 (2C), 149.079 (2C), 148.780 (2C), 134.042 (2C), 130.360 (2C), 129.143 (2C), 127.129 (2C), 126.163 (2C), 124.447 (2C), 123.767 (2C), 122.041 (2C), 114.279 (2C), 113.418 (2C), 56.363 (4C), 53.086 (2C), 40.572 (2C), 30.775 (2C), and 18.795 (2C), APCI-MS: *m/z* 583.40, (MH⁺, 100%). Anal. Calcd for C₃₈H₄₂N₆: C, 78.35; H, 7.22; N, 14.43 Found C, 78.70; H, 7.34; N, 14.20.

2-Methoxy-N-(3-(4-(3-(2-methoxyacridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (3c). Solvent of elution: CHCl₃: MeOH (8:2), yield: 43%, mp: >300°C; IR (KBr) ν_{\max} 3414(NH), 1587, 1571, 1529, (Ar) cm⁻¹. ¹H-NMR (500 MHz,

D₂O) δ : 7.802–7.787 (d, 2H, J = 7.5 Hz, Ar), 7.592–7.652 (m, 3H, Ar), 7.273–7.290 (d, 2H, J = 8.5 Hz, Ar), 7.182–7.221 (m, 5H, Ar), 6.874 (s, 2H, Ar), 3.77 (s, 10H, 2xOCH₃, 2xCH₂, C¹, C¹²), 2.462 (bs, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.894 (bs, 4H, 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 154.719 (2C), 150.509 (2C), 149.078 (2C), 147.770 (2C), 131.060 (2C), 128.841 (2C), 127.009 (2C), 126.063 (2C), 125.101 (2C), 123.817 (2C), 121.941 (2C), 114.281 (2C), 113.018 (2C), 57.795 (2C), 56.261 (4C), 53.186 (2C), 40.572 (2C), and 30.771 (2C), APCI-MS: m/z 615.47, (MH⁺, 100%). Anal. Calcd for C₃₈H₄₂N₆O₂: C, 74.26; H, 6.84; N, 13.68 Found C, 73.92; H, 6.64; N, 13.41.

4-Methyl-N-(3-(4-(3-(4-methylacridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (3d). Solvent of elution: CHCl₃: MeOH (8 : 2), yield: 41%, mp: >300°C: IR (KBr) ν_{\max} 3412(NH), 1590, 1531 (Ar) cm⁻¹. ¹H-NMR (500 MHz, D₂O) δ : 7.879–7.895 (d, 2H, J = 8 Hz, Ar), 7.708–7.738 (t, 2H, J = 7.5 and 15 Hz, Ar), 7.660–7.676 (d, 2H, J = 8 Hz, Ar), 7.528–7.545 (d, 2H, J = 8.5 Hz Ar), 7.478–7.492 (d, 2H, J = 7 Hz, Ar), 7.303–7.333 (t, 2H, J = 7.5 and 15 Hz, Ar), 7.146–7.177 (t, 2H, J = 7.5 and 15 Hz, Ar), 3.779–3.804 (t, 4H, J = 6.5 and 13 Hz, 2xCH₂, C¹, C¹²), 2.549–2.574 (m, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 2.275 (s, 6H, 2xCH₃), 1.938–1.964 (t, 4H, J = 6.5 and 13 Hz 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 150.609 (2C), 149.089 (2C), 148.775 (2C), 134.041 (2C), 130.373 (2C), 128.941 (2C), 127.129 (2C), 126.767 (2C), 124.542 (2C), 123.767 (2C), 122.143 (2C), 114.259 (2C), 113.419 (2C), 57.160 (4C), 54.186 (2C), 41.572 (2C), 31.444 (2C), and 19.075 (2C) APCI-MS: m/z 583.40, (MH⁺, 100%). Anal. Calcd for C₃₈H₄₂N₆: C, 78.35; H, 7.22; N, 14.43 Found C, 78.55; H, 7.12; N, 14.18.

4-Methoxy-N-(3-(4-(3-(acridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (3e). Solvent of elution: CHCl₃: MeOH (8.5:1.5), yield: 47%, mp: >300°C: IR (KBr) ν_{\max} 3384 (NH), 1580, 1535, 1478 (Ar) cm⁻¹. ¹H-NMR (500 MHz, D₂O) δ : 7.771 (s, 2H, Ar), 7.66–7.69 (t, 2H, J = 7.5 and 15 Hz, Ar), 7.370–7.390 (d, 2H, J = 10 Hz Ar), 7.268 (s, 4H, Ar), 7.102 (s, 2H, Ar), 6.977 (s, 2H, Ar), 3.805 (s, 6H, 2xOCH₃), 3.695 (bs, 4H, 2xCH₂, C¹, C¹²), 2.768 (bs, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.967 (bs, 4H, 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 154.509 (2C), 150.710 (2C), 149.078 (2C), 147.770 (2C), 131.060 (2C), 128.841 (2C), 127.009 (2C), 126.063 (2C), 125.101 (2C), 123.915 (2C), 122.233 (2C), 114.001 (2C), 112.616 (2C), 57.775 (2C), 56.371 (4C), 53.173 (2C), 40.577 (2C) and 30.456 (2C), APCI-MS: m/z 615.40, (MH⁺, 100%). Anal. Calcd for C₃₈H₄₂N₆O₂: C, 74.26; H, 6.84; N, 13.68 Found C, 74.47; H, 6.79; N, 13.82.

(Acridin-9-yl)-[3-(9-[3-(acridin-9-ylamino)]-propyl]-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine (3f). Solvent of elution: CHCl₃: MeOH (8:2), yield: 42%, mp: >300°C: IR (KBr) ν_{\max} 3374(NH), 1560, 1515 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 9.877 (s, 1H, NH exch), 9.829 (s, 1H, NH exch), 8.575–8.708 (bs, 4H, Ar), 7.904–8.024 (m, 8H, Ar), 7.53–7.549 (d, 4H, J = 9.5 Hz Ar), 4.482–4.542 (m, 2H, C^{10b}, C^{14b}), 4.164–4.186 (d, 1H, J = 11 Hz CH, C¹²), 4.096 (s, 4H, C⁶, C⁸), 3.716–3.739 (d, 1H, J = 11.5 Hz, CH, C⁴), 3.522–3.546 (t, 4H, J = 6 and 12 Hz 2xCH₂, C¹, C¹⁷), 3.145–3.165 (t, 2H, J = 5 and 10 Hz C^{10a}, C^{14a}), 1.960–1.989 (m, 4H, 2xCH₂, C³, C¹⁵), 1.656–1.679 (m, 4H, 2xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 151.102 (2C), 149.426 (4C), 131.070 (4C), 129.574 (4C), 124.013 (4C), 122.671 (4C), 113.705 (4C), 102.158 (2C), 69.946 (2C), 69.423 (2C), 41.476 (2C), 32.326 (1C), 32.151 (2C) and 27.183 (2C), APCI-MS: m/z 629.53, (MH⁺, 100%). Anal. Calcd

for C₃₉H₄₀N₄O₄: C, 74.52; H, 6.37; N, 8.92 Found C, 74.13; H, 6.20; N, 8.81.

(2-Methyl-acridin-9-yl)-[3-(9-[3-(2-methyl-acridin-9-ylamino)]-propyl]-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine (3g). Solvent of elution: CHCl₃: MeOH (8:2), yield: 43%, mp: >300°C: IR (KBr) ν_{\max} 3414 (NH), 1587, 1529, 1463 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.517 (bs, 2H, Ar), 8.386 (bs, 2H, Ar), 7.896–7.969 (m, 4H, Ar), 7.877–7.812 (m, 4H, Ar), 7.508–7.538 (t, 2H, J = 7.5 and 15 Hz, Ar), 4.501–4.520 (t, 2H, J = 5 and 10 Hz C^{10b}, C^{14b}), 4.106–4.128 (t, 2H, J = 5.5 and 11 Hz C⁴, C¹²), 4.046–4.075 (m, 4H, 2xCH₂, C⁶, C⁸), 3.457–3.502 (m, 4H, 2xCH₂, C¹, C¹⁷), 3.301–3.324 (d, 2H, J = 11.5 Hz C^{10a}, C^{14a}), 2.524 (s, 6H, 2xCH₃), 1.983–1.919 (m, 4H, 2xCH₂, C³, C¹⁵), 1.644–1.684 (m, 4H, 2xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 151.207 (2C), 149.701 (2C), 148.917 (2C), 134.201 (2C), 130.767 (2C), 129.537 (2C), 127.781 (2C), 126.763 (2C), 124.987 (2C), 123.981 (2C), 122.501 (2C), 114.901 (2C), 114.001 (2C), 102.207 (2C), 69.901 (2C), 69.517 (2C), 41.560 (2C), 32.725 (1C), 32.371 (2C), 27.185 (2C) and 18.910 (2C), APCI-MS: m/z 657.60, (MH⁺, 100%). Anal. Calcd for C₄₁H₄₄N₄O₄: C, 75.00; H, 6.70; N, 8.54 Found C, 75.39; H, 6.41; N, 8.26.

(2-Methoxy-acridin-9-yl)-[3-(9-[3-(2-methoxy-acridin-9-ylamino)]-propyl]-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine (3h). Solvent of elution: CHCl₃: MeOH (8:2), yield: 39%, mp: >300°C: IR (KBr) ν_{\max} 3387(NH), 1593, 1539, 1463 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.409–8.426 (d, 2H, J = 8.5 Hz, Ar), 7.886–7.917 (t, 2H, J = 7.5 and 15 Hz, Ar), 7.792–7.851 (m, 6H, Ar), 7.645–7.669 (dd, 2H, J = 2.5 and 9.5 Hz Ar), 7.486–7.517 (t, 2H, J = 7.5 and 15 Hz, Ar), 4.508–4.528 (t, 2H, J = 5 and 10 Hz, C^{10b}, C^{14b}), 4.093–4.118 (t, 2H, J = 6.5 and 13 Hz, C⁴, C¹²), 4.042–4.070 (m, 4H, 2xCH₂, C⁶, C⁸), 3.925 (s, 6H, 2xOCH₃), 3.447–3.494 (m, 4H, 2xCH₂, C¹, C¹⁷), 3.293–3.316 (d, 2H, J = 11.5 Hz, C^{10a}, C^{14a}), 1.896–1.939 (m, 4H, 2xCH₂, C³, C¹⁵), 1.600–1.639 (m, 4H, 2xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 155.529 (2C), 151.307 (2C), 149.778 (2C), 147.999 (2C), 131.817 (2C), 129.321 (2C), 127.710 (2C), 126.631 (2C), 125.821 (2C), 124.234 (2C), 122.309 (2C), 121.941 (2C), 114.569 (2C), 113.441 (2C), 103.111 (2C), 70.254 (2C), 69.687 (2C), 57.199 (2C), 41.752 (2C), 32.710 (1C) and 32.451 (2C), APCI-MS: m/z 689.40, (MH⁺, 100%). Anal. Calcd for C₄₁H₄₄N₄O₆: C, 71.51; H, 6.40; N, 8.14 Found C, 71.89; H, 6.81; N, 8.60.

(4-Methyl-acridin-9-yl)-[3-(9-[3-(4-methyl-acridin-9-ylamino)]-propyl]-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine (3i). Solvent of elution: CHCl₃: MeOH (8:2), yield: 36%, mp: >300°C: IR (KBr) ν_{\max} 3419(NH), 1589, 1533 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.558 (s, 2H, Ar), 8.471 (s, 2H, Ar), 8.303–320 (d, J = 8.5 Hz, 2H, Ar), 7.963–7.992 (t, 2H, J = 7.5 and 15 Hz, Ar), 7.831–7.844 (d, 2H, J = 6.5 Hz, Ar), 7.558–7.571 (t, 2H, J = 7.5 and 15 Hz, Ar), 7.450–7.481 (t, 2H, J = 7.5 and 15 Hz, Ar), 4.523–4.542 (t, 2H, J = 5 and 10 Hz C^{10b}, C^{14b}), 4.183–4.204 (t, 2H, J = 5 and 10 Hz, C⁴, C¹²), 4.072 (bs, 4H, 2xCH₂, C⁶, C⁸), 3.515–3.550 (m, 4H, 2xCH₂, C¹, C¹⁷), 3.175–3.184 (d, 2H, J = 4.5 Hz, C^{10a}, C^{14a}), 2.731 (s, 6H, 2xCH₃), 1.954–1.982 (m, 4H, 2xCH₂, C³, C¹⁵), 1.642–1.666 (m, 4H, 2xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 151.391 (2C), 149.807 (2C), 149.114 (2C), 134.721 (2C), 130.901 (2C), 129.437 (2C), 127.777 (2C), 126.998 (2C), 124.879 (2C), 124.102 (2C), 122.624 (2C), 114.591 (2C), 113.813 (C), 102.511 (2C), 69.899 (2C), 69.599 (2C), 41.761 (2C), 32.795 (1C), 32.409

(2C), 27.185 (2C) and 19.107 (2C), APCI-MS: m/z 657.53, (MH⁺, 100%). Anal. Calcd for C₄₁H₄₄N₄O₄: C, 75.00; H, 6.70; N, 8.54 Found C, 75.46; H, 6.96; N, 8.79.

(4-Methoxy-acridin-9-yl)-[3-(9-[3-(4-methoxy-acridin-9-ylamino)]propyl)-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl]propyl-amine (3j). Solvent of elution: CHCl₃: MeOH (8:2), yield: 38.2%, mp: >300°C: IR (KBr) ν_{\max} 3419(NH), 1576, 1536, 1474 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.441–8.457 (d, 2H, *J* = 8 Hz, Ar), 8.150–8.187 (d, 2H, *J* = 8.5 Hz, Ar), 8.000–8.015(d, 2H, *J* = 7.5 Hz, Ar), 7.910–7.941 (t, 2H, *J* = 7.5 and 15 Hz, Ar), 7.443–7.546 (m, 6H, Ar), 4.527–4.546 (t, 2H, *J* = 5 and 10 Hz, C^{10b}, C^{14b}), 4.130–4.152 (t, 2H, *J* = 5.5 and 11 Hz, C⁴, C¹²), 4.071 (s, 6H, 2xOCH₃), 4.023–4.051 (m, 4H, 2xCH₂, C⁶, C⁸), 3.447–3.494 (m, 4H, 2xCH₂, C¹, C¹⁷), 3.313–3.336 (d, 2H, *J* = 11.5 Hz, C^{10a}, C^{14a}), 1.901–1.959 (m, 4H, 2xCH₂, C³, C¹⁵), 1.609–1.647(m, 4H, 2xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 155.137 (2C), 151.149 (2C), 149.579 (2C), 147.991 (2C), 131.201 (2C), 129.347 (2C), 127.729 (2C), 126.539 (2C), 125.783 (2C), 124.391 (2C), 122.701 (2C), 114.326 (2C), 113.601 (2C), 102.579 (2C), 69.817 (2C), 69.432 (2C), 57.283 (2C), 41.819 (2C), 32.675 (1C), 32.271 (2C) and 27.288 (2C), APCI-MS: m/z 689.53 (MH⁺, 100%). Anal. Calcd for C₄₁H₄₄N₄O₆: C, 71.51; H, 6.40; N, 8.14 Found C, 71.94; H, 6.14; N, 8.49.

General procedure for condensation of 9-isothiocyanato-2-4-(un)substituted acridines (4a-e) with diamines (2a, b). **1-(3-(4-(3-(9-Acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(acridin-9-yl)thiourea (5a).** 9-Isothiocyanatoacridine (300 mg, 1.27 mmol) and 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine (127 mg, 0.63 mmol) were dissolved separately in THF (10 mL) and mixed together with constant stirring and allowed to stand at room temperature for 6 h. Solid product separated out was filtered and purified by column chromatography over silica gel to give pure product **5a**. Solvent of elution: CHCl₃: MeOH (8:2, *R_f* = 0.6); Yield: 248 mg (37%); mp: >300°C: IR (KBr) ν_{\max} 3425 (NH), 1586, 1523, 1462 (Ar) cm⁻¹. ¹H-NMR (500MHz, DMSO-*d*₆ + D₂O) δ : 8.104–8.136 (m, 4H, Ar), 7.524–7.623 (m, 4H, Ar), 7.343–7.415 (m, 4H, Ar), 7.074–7.168 (m, 4H, Ar), 3.508–3.519 (d, 2H, *J* = 5.5 Hz, C^{1b}, C^{12b}), 3.052 (bs, 2H, C^{1a}, C^{12a}), 2.018–2.192 (m, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.642–1.675 (m, 2H, C^{2b}, C^{11b}), 1.454 (bs, 2H, C^{2a}, C^{11a}), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 176.967 (2C), 151.109 (2C), 149.009 (4C), 131.161 (4C), 130.143 (4C), 124.747 (4C), 123.551 (4C), 112.418 (4C), 56.308 (4C), 52.749 (2C), 40.442 (2C) and 30.745 (2C), APCI-MS: m/z 673.39, (MH⁺, 53%). Anal. Calcd for C₃₈H₄₀N₈S₂: C, 67.86; H, 5.95; N, 16.67; S, 9.52 Found C, 67.47; H, 6.19; N, 16.89; S, 9.50.

Similarly, compounds **5b–h** were synthesized.

1-(3-(4-(3-(2-Methyl-9-acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(2-methylacridin-9-yl)thiourea (5b). Solvent of elution: CHCl₃: MeOH (8:2), yield: 39%, mp: >300°C: IR (KBr) ν_{\max} 3439 (NH), 1572, 1523, 1460 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.055–8.072 (d, 2H, *J* = 8.5 Hz, Ar), 7.938–7.955 (d, 2H, *J* = 8.5 Hz, Ar), 7.890–7.901 (d, 2H, *J* = 5.5 Hz, Ar), 7.609–7.636 (t, 2H, *J* = 7 and 14 Hz, Ar), 7.474–7.486 (d, 2H, *J* = 6 Hz, Ar), 7.243 (bs, 2H, Ar), 7.134 (bs, 2H, Ar), 3.313 (bs, 4H, 2xCH₂, C¹, C¹²), 2.620 (s, 6H, 2xCH₃), 2.074–2.175 (m, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.622–1.646 (m, 4H, 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 177.187 (2C), 151.103 (2C), 149.373 (2C), 148.580 (2C), 135.145 (2C), 131.160 (2C), 130.040 (2C), 127.167 (2C), 126.118 (2C), 124.767 (2C), 123.760 (2C), 122.049 (2C),

114.573 (2C), 113.416 (2C), 56.095 (4C), 52.383 (2C), 41.012 (2C), 30.555 (2C) and 17.955 (2C) APCI-MS: m/z 701.22, (MH⁺, 47%). Anal. Calcd for C₄₀H₄₄N₈S₂: C, 68.57; H, 6.29; N, 16; S, 9.14 Found C, 68.84; H, 6.53; N, 15.87; S, 9.49.

1-(3-(4-(3-(2-Methoxy-9-acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(2-methoxyacridin-9-yl)thiourea (5c). Solvent of elution: CHCl₃: MeOH (8:2), yield: 40%, mp: >300°C: IR (KBr) ν_{\max} 3414 (NH), 1584, 1520, 1465 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.091–8.108 (d, 2H, *J* = 8.5 Hz, Ar), 7.828 (bs, 2H, Ar), 7.685–7.702 (d, 2H, *J* = 8.5 Hz, Ar), 7.570–7.599 (t, 2H, *J* = 7.5 and 15 Hz, Ar), 7.101–7.181 (m, 6H, Ar), 3.901 (s, 6H, 2xOCH₃), 3.355–3.517 (m, 2H, C^{1b}, C^{12b}), 3.158–3.196 (m, 2H, C^{1a}, C^{12a}), 2.039–2.155 (m, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.606–1.617 (m, 4H, 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 178.043 (2C), 154.760 (2C), 150.289 (2C), 149.558 (2C), 147.333 (2C), 131.010 (2C), 128.841 (2C), 126.819 (2C), 125.963 (2C), 125.111 (2C), 122.810 (2C), 120.741 (2C), 114.251 (2C), 113.198 (2C), 57.115 (2C), 56.261 (4C), 52.180 (2C), 40.572 (2C) and 31.101 (2C), APCI-MS: m/z : 733.23, (MH⁺, 100%). Anal. Calcd for C₄₀H₄₄N₈O₂S₂: C, 65.57; H, 6.01; N, 15.3; S, 8.74 Found C, 65.89; H, 6.47; N, 15.68; S, 8.49.

1-(3-(4-(3-(4-Methyl-9-acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(4-methylacridin-9-yl)thiourea (5d). Solvent of elution: CHCl₃: MeOH (8:2), yield: 41%, mp: >300°C: IR (KBr) ν_{\max} 3426 (NH), 1586, 1522, 1463 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.059–8.042 (d, 2H, *J* = 8.5 Hz, Ar), 7.925–7.942 (d, 2H, *J* = 8.5 Hz, Ar), 7.877–7.888 (d, 2H, *J* = 5.5 Hz, Ar), 7.461–7.473 (d, 2H, *J* = 6 Hz, Ar), 7.596–7.623 (t, 2H, *J* = 7 and 14 Hz, Ar), 7.229 (bs, 2H, Ar), 7.121 (bs, 2H, Ar), 3.281–3.352 (bs, 4H, 2xCH₂, C¹, C¹²), 2.607 (s, 6H, 2xCH₃), 2.162 (bs, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.609–1.633 (m, 4H, 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 178.257 (2C), 151.791 (2C), 149.991 (2C), 149.215 (2C), 135.779 (2C), 131.432 (2C), 130.483 (2C), 127.679 (2C), 126.619 (2C), 126.573 (2C), 125.237 (2C), 124.143 (2C), 122.473 (2C), 114.957 (2C), 113.758 (2C), 56.521 (2C), 52.543 (2C), 40.749 (2C), 30.619 (2C), 17.955 (2C), and APCI-MS: m/z : 701.26, (MH⁺, 84%). Anal. Calcd for C₄₀H₄₄N₈S₂: C, 68.57; H, 6.29; N, 16.00; S, 9.14 Found C, 68.11; H, 6.74; N, 16.00; S, 9.31.

1-(3-(4-(3-(4-Methoxy-9-acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(4-methoxyacridin-9-yl)thiourea (5e). Solvent of elution: CHCl₃: MeOH (8:2), yield: 33%, mp: >300°C: IR (KBr) ν_{\max} 3432 (NH), 1540, 1505, 1477 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.035–8.051 (d, 2H, *J* = 8 Hz, Ar), 7.702–7.803 (m, 6H, Ar), 7.251–7.397 (m, 6H, Ar), 3.808 (s, 6H, 2xOCH₃), 3.369 (bs, 4H, 2xCH₂, C¹, C¹²), 2.074–2.121 (m, 12H, 6xCH₂, C³, C⁵, C⁶, C⁸, C⁹, C¹⁰), 1.599–1.644 (m, 4H, 2xCH₂, C², C¹¹), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 179.278 (2C), 155.505 (2C), 152.010 (2C), 149.678 (2C), 148.220 (2C), 131.565 (2C), 129.121 (2C), 127.527 (2C), 126.770 (2C), 125.651 (2C), 123.918 (2C), 122.373 (2C), 114.271 (2C), 112.776 (2C), 56.945 (2C), 56.101 (4C), 53.323 (2C), 40.907 (2C) and 31.236 (2C), APCI-MS: m/z 733.22, (MH⁺, 32%). Anal. Calcd for C₄₀H₄₄N₈O₂S₂: C, 65.57; H, 6.01; N, 15.30; S, 8.74 Found C, 65.39; H, 6.00; N, 14.98; S, 8.64.

1-(3-(9-(3-(9-Acridinylamine)methanethioamidopropyl)2,4,8,10-tetraoxa-spiro[5,5]undecane-3-yl)propyl)-3-(acridin-9-yl)thiourea (5f). Solvent of elution: CHCl₃: MeOH (8:2), yield: 37%, mp: >300°C: IR (KBr) ν_{\max} 3421 (NH), 1590, 1525, 1471 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.052–8.069 (d, 4H, *J* = 8.5 Hz, Ar), 7.699–7.762 (m, 4H, Ar), 7.582–7.612 (t, 4H, *J* = 7.5 and 15 Hz, Ar), 7.187–7.217 (t, 4H, *J* = 7.5 and 15 Hz,

Ar), 4.526–4.543 (t, 2H, $J = 4.5$ and 9 Hz, C^{10b}, C^{14b}), 4.263–4.284 (t, 2H, $J = 5$ and 10 Hz, C⁴, C¹²), 3.514–3.563 (m, 4H, 2xCH₂, C⁶, C⁸), 3.328–3.351 (m, 6H, C¹, C¹⁷, C^{10a}, C^{14a}), 1.646–1.673 (m, 4H, 4xCH₂, C³, C¹⁵), 1.615–1.628 (m, 4H, 4xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 177.391 (2C), 151.614 (2C), 149.401 (4C), 131.771 (4C), 130.617 (4C), 125.208 (4C), 123.731 (4C), 112.839 (4C), 103.218 (2C), 70.157 (2C), 69.847 (2C), 41.877 (2C), 32.470 (1C), 32.281 (2C) and 27.455 (2C), APCI-MS: m/z 747.32, (MH⁺, 23%). Anal. Calcd for C₄₁H₄₂N₆O₄S₂: C, 65.95; H, 5.63; N, 11.26; S, 8.57 Found C, 65.87; H, 5.43; N, 11.19; S, 8.43.

1-(3-(9-(3-(2-Methyl-9-acridinylamine)methanethioamidopropyl)-2,4,8,10-tetraoxa-spiro[5.5]undecane-3-yl)propyl)-3-(2-methylacridin-9-yl)thiourea (5g). Solvent of elution: CHCl₃: MeOH (8:2), yield: 39%, mp: >300°C: IR (KBr) ν_{\max} 3425 (NH), 1578, 1525, 1464 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.052–8.069 (d, 4H, $J = 8.5$ Hz, Ar), 7.29–7.762 (m, 4H, Ar), 7.582–7.612 (t, 4H, $J = 7.5$ and 15 Hz, Ar), 7.187–7.217 (t, 4H, $J = 7.5$ and 15 Hz, Ar), 4.531–4.548 (t, 2H, $J = 4.5$ and 9 Hz C^{10b}, C^{14b}), 4.261–4.287 (t, 2H, $J = 6.5$ and 13 Hz C⁴, C¹²), 3.514–3.579 (m, 4H, 2xCH₂, C⁶, C⁸), 3.152–3.357 (m, 6H, 2xCH₂, C¹, C¹⁷, C^{10a}, C^{14a}), 2.611 (s, 6H, 2xCH₃), 1.644–1.675 (m, 4H, 4xCH₂, C³, C¹⁵), 1.619–1.629 (m, 4H, 4xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 178.148 (2C), 151.571 (2C), 149.730 (2C), 149.006 (2C), 135.547 (2C), 130.193 (2C), 127.474 (2C), 126.370 (2C), 125.401 (2C), 124.877 (2C), 123.769 (2C), 122.199 (2C), 114.703 (2C), 113.457 (2C), 102.531 (2C), 69.911 (2C), 69.731 (2C), 41.632 (2C), 32.337 (1C), 32.170 (2C), 27.366 (2C) and 18.915 (2C) APCI-MS: m/z 775.43, (MH⁺, 8%). Anal. Calcd for C₄₃H₄₆N₆O₄S₂: C, 66.67; H, 5.94; N, 10.85; S, 8.27 Found C, 66.94; H, 5.62; N, 11.20; S, 8.61.

1-(3-(9-(3-(2-Methoxy-9-acridinylamine)methanethioamidopropyl)-2,4,8,10-tetraoxa-spiro[5.5]undecane-3-yl)propyl)-3-(2-methoxyacridin-9-yl)thiourea (5h). Solvent of elution: CHCl₃: MeOH (8:2), yield: 38%, mp: >300°C: IR (KBr) ν_{\max} 3425 (NH), 1573, 1529, 1479 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.321–8.575 (m, 2H, Ar), 7.901–7.995 (m, 8H, Ar), 7.525–7.551 (m, 4H, Ar), 4.530–4.555 (t, 2H, $J = 6.5$ and 13 Hz, C^{10b}, C^{14b}), 4.181–4.202 (t, 2H, $J = 5.5$ and 11 Hz, C⁴, C¹²), 4.051–4.081 (m, 4H, 2xCH₂, C⁶, C⁸), 3.908 (s, 6H, 2xOCH₃), 3.499–3.554 (m, 6H, C¹, C¹⁷, C^{10a}, C^{14a}), 1.908–1.984 (m, 4H, 2xCH₂, C³, C¹⁵), 1.575–1.679 (m, 4H, 2xCH₂, C², C¹⁶), APCI-MS: m/z 808.35, (MH⁺ + 1, 21%). Anal. Calcd for C₄₃H₄₆N₆O₆S₂: C, 64.00; H, 5.75; N, 10.41; S, 7.95 Found C, 64.29; H, 5.42; N, 10.97; S, 8.14.

1-(3-(9-(3-(4-Methyl-9-acridinylamine)methanethioamidopropyl)-2,4,8,10-tetraoxa-spiro[5.5]undecane-3-yl)propyl)-3-(4-methylacridin-9-yl)thiourea (5i). Solvent of elution: CHCl₃: MeOH (8:2), yield: 37%, mp: >300°C: IR (KBr) ν_{\max} 3425 (NH), 1586, 1523, 1462 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.041–8.057 (d, 2H, $J = 8$ Hz, Ar), 7.830–7.942 (d, 2H, $J = 6$ Hz, Ar), 7.628 (bs, 2H, Ar), 7.489 (bs, 2H, Ar), 7.231 (bs, 2H, Ar), 7.139 (bs, 2H, Ar), 4.487 (bs, 2H, C^{10b}, C^{14b}), 4.246–4.267 (t, 2H, $J = 5.5$ and 11 Hz, C⁴, C¹²), 3.273–3.497 (m, 10H, C⁶, C⁸, C¹, C¹⁷, C^{10a}, C^{14a}), 2.593 (s, 6H, 2xCH₃), 1.628–1.655 (m, 4H, 2xCH₂, C³, C¹⁵), 1.559–1.616 (m, 4H, 2xCH₂, C², C¹⁶), ¹³C-NMR (125MHz, DMSO-*d*₆) δ : 178.449 (2C), 151.972 (2C), 150.319 (2C), 149.677 (2C), 136.303 (2C), 131.533 (2C), 130.342 (2C), 127.514 (2C), 126.701 (2C), 125.311 (2C), 124.079 (2C), 122.789 (2C), 114.761 (2C), 114.107 (2C), 102.279 (2C), 69.895 (2C), 69.671 (2C), 41.571 (2C), 32.139 (1C), 32.089 (2C), 27.179 (2C) and 18.858 (2C), APCI-MS: m/z 775.42, (MH⁺, 12%). Anal. Calcd for C₄₃H₄₆N₆O₄S₂: C, 66.67; H, 5.94; N, 10.85; S, 8.27 Found C, 66.98; H, 5.42; N, 10.97; S, 8.20.

1-(3-(9-(3-(4-Methoxy-9-acridinylamine)methanethioamidopropyl)-2,4,8,10-tetraoxa-spiro[5.5]undecane-3-yl)propyl)-3-(4-methoxyacridin-9-yl)thiourea (5j). Solvent of elution: CHCl₃: MeOH (8:2), yield: 39%, mp: >300°C: IR (KBr) ν_{\max} 3425 (NH), 1565, 1538, 1483 (Ar) cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆ + D₂O) δ : 8.322–8.576 (m, 2H, Ar), 7.900–7.994 (m, 8H, Ar), 7.524–7.558 (m, 4H, Ar), 4.525–4.545 (t, 2H, $J = 5$ and 10 Hz, C^{10b}, C^{14b}), 4.168–4.189 (t, 2H, $J = 5$ and 10 Hz, C⁴, C¹²), 4.091–4.102 (m, 4H, 2xCH₂, C⁶, C⁸), 3.912 (s, 6H, 2xOCH₃), 3.522–3.546 (m, 6H, C¹, C¹⁷, C^{10a}, C^{14a}), 1.962–1.991 (m, 4H, 2xCH₂, C³, C¹⁵), 1.632–1.681 (m, 4H, 2xCH₂, C², C¹⁶), APCI-MS: m/z 808.48, (MH⁺ + 1, 43%). Anal. Calcd for C₄₃H₄₆N₆O₆S₂: C, 64.00; H, 5.75; N, 10.41; S, 7.95 Found C, 64.10; H, 5.81; N, 10.69; S, 8.07.

In vitro cytotoxicity against human cancer cell lines [36,37]. The human cancer cell lines procured from National Cancer Institute, Frederick, USA were used in this study. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4 supplemented with 10% fetal bovine serum, 100 μ g/mL streptomycin and 100 units/mL penicillin) in a carbon dioxide incubator (37°C, 5% CO₂, 90% RH). The cells at subconfluent stage were harvested from the flask by treatment with trypsin (0.05% in PBS (pH 7.4) containing 0.02% EDTA). Cells with viability of more than 98%, as determined by trypan blue exclusion, were used for determination of cytotoxicity. The cell suspension of 1 \times 10⁵ cells/mL was prepared in complete growth medium.

Stock 4 \times 10⁻² M compound solutions were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50 μ g/mL of gentamycin to obtained working test solution of required concentrations.

In vitro cytotoxicity against various human cancer cell lines was determined (Monks *et al.*) [36] using 96-well tissue culture plates. The 100 μ L of cell suspension was added to each well of the 96-well tissue culture plates. The cells were allowed to grow in CO₂ incubator (37°C, 5% CO₂, 90% RH) for 24 h. The test materials in complete growth medium (100 μ L) were added after 24 h incubation to the wells containing cell suspension. The plates were further incubated for 48 h (37°C in an atmosphere of 5% CO₂ and 90% relative humidity) in a carbon dioxide incubator after addition of test material and then the cell growth was stopped by gently layering trichloroacetic acid (50% TCA, 50 μ L) on top of the medium in all the wells. The plates were incubated at 4°C for 1 h to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove TCA, growth medium low molecular weight metabolites, serum proteins, so on, and air dried. Cell growth was measured by staining with sulforhodamine B dye (Skehan *et al.*) [37]. The adsorbed dye was dissolved in Tris-HCl Buffer (100 μ L, 0.01M, pH 10.4), and plates were gently stirred for 10 min on a mechanical stirrer. The optical density was recorded on ELISA reader at 540nm.

Anti-inflammatory activity [38]. Paw oedema inhibition test was used on albino rats of Charles Foster by adopting the method of Winter *et al.* [38]. Groups of five animals of both sexes (body weight 120–160g), excluding pregnant females, were given a dose of test compound. Thirty minutes later, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the hind paw, and the volume was measured by a water plethysmometer apparatus and then measured again 1–3 h later. The mean increase of paw volume at each interval was compared with that of control group (five rats treated with

carrageenan but not with test compound) at the same intervals and percent inhibition value calculated by the formula given below.

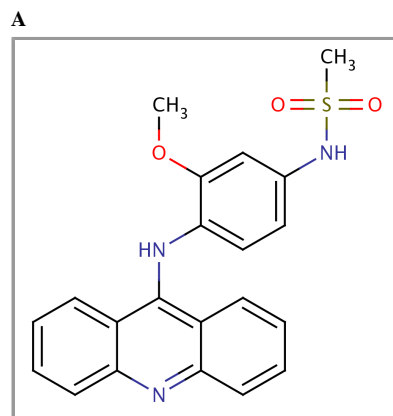
$$\% \text{Anti-inflammatory activity} = [1 - D_t/D_c] \times 100$$

D_t and D_c are paw volumes of oedema in tested and control groups, respectively. Compounds **3a-j** and **5a-j** were screened for anti-inflammatory activity and results are summarized in Table 1.

Acknowledgments. The authors are thankful to technical staff of the Chemistry Department, I. I. T. Roorkee, for spectroscopic studies and elemental analysis. Mr. Sandeep Kumar is thankful to MHRD New Delhi and Ms. Reshma Rani is thankful to CSIR New Delhi for financial assistance.

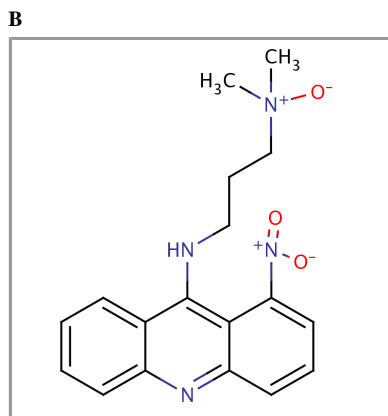
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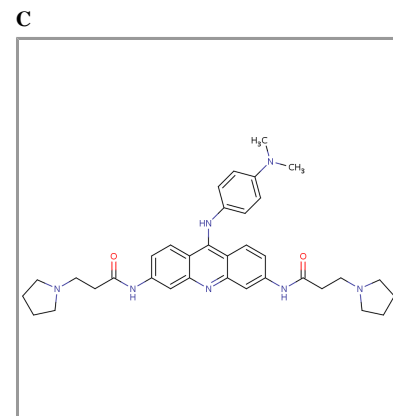
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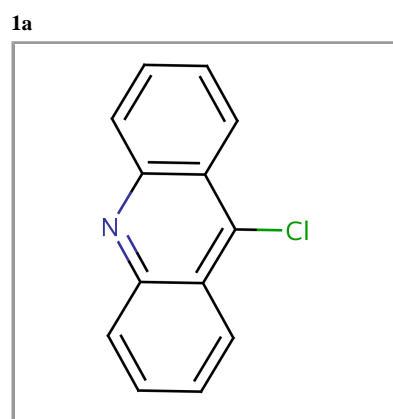
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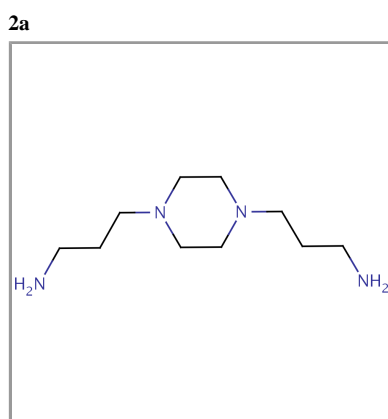
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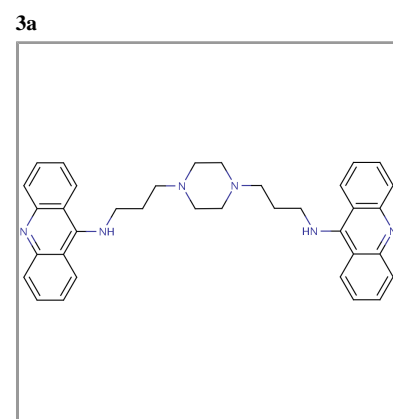
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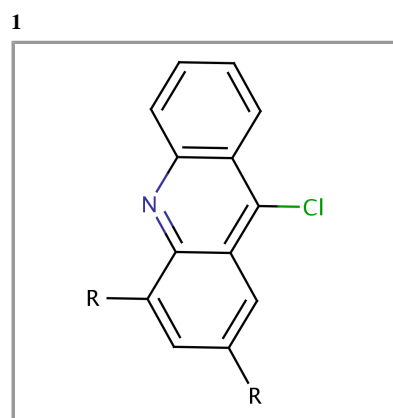
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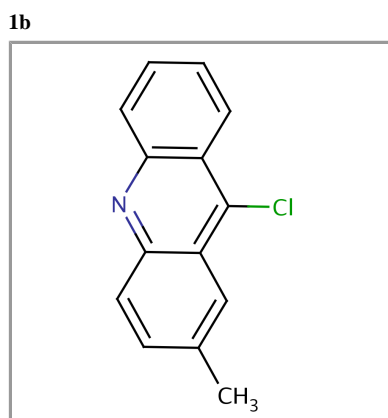
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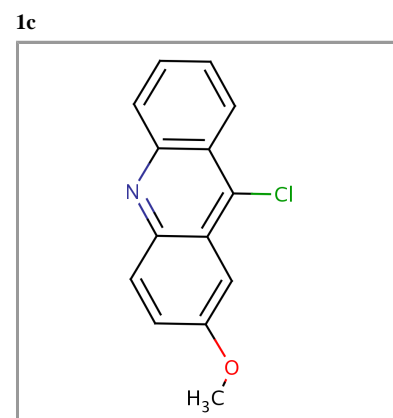
[Compound Details](#)

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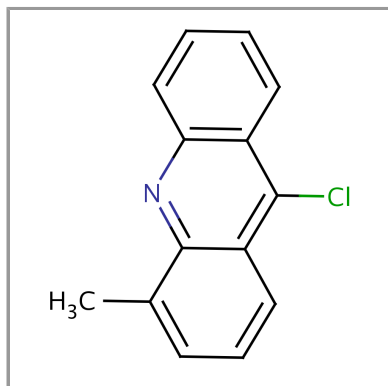
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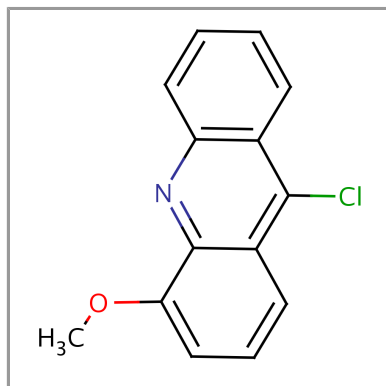
1d



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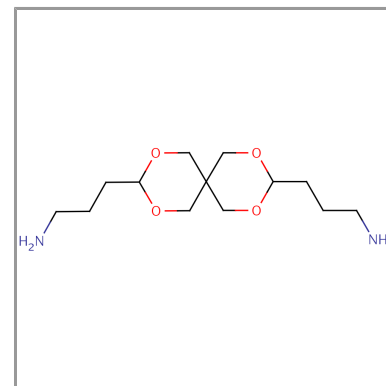
1e



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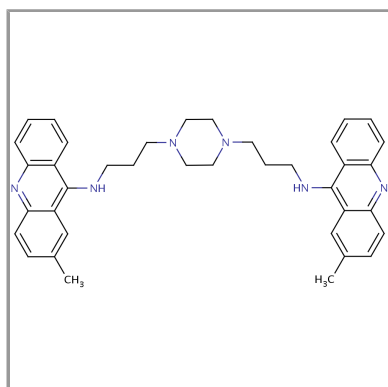
2b



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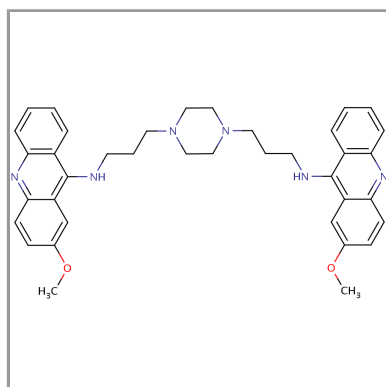
3b



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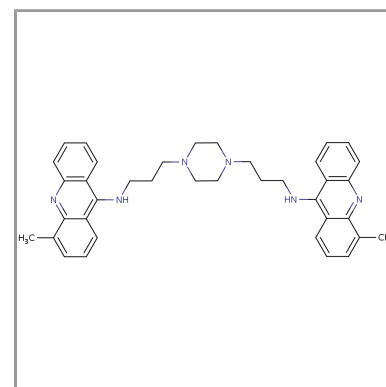
3c



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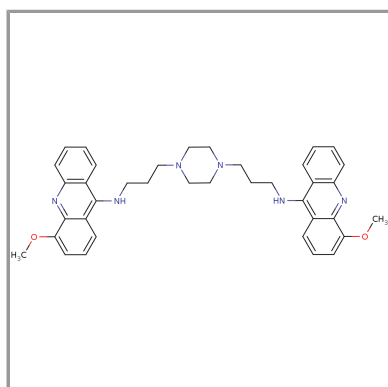
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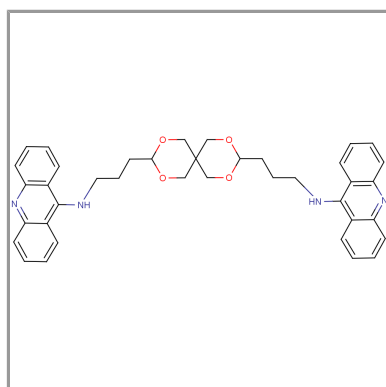
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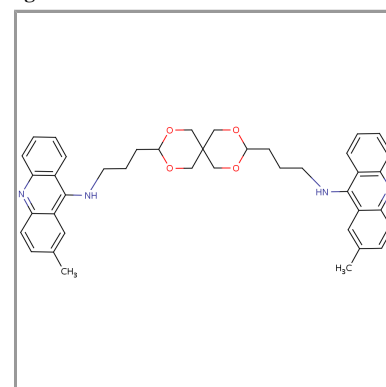
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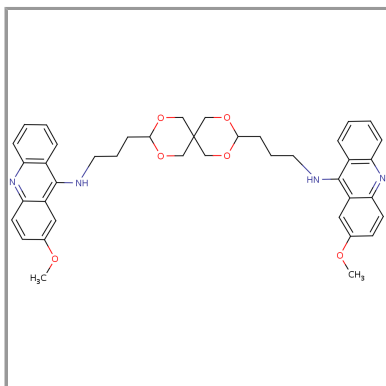
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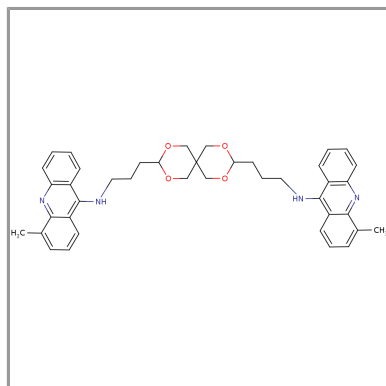
3h



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[Structure Search](#)

3i



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[Structure Search](#)

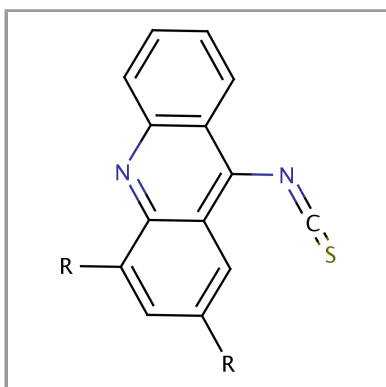
3j



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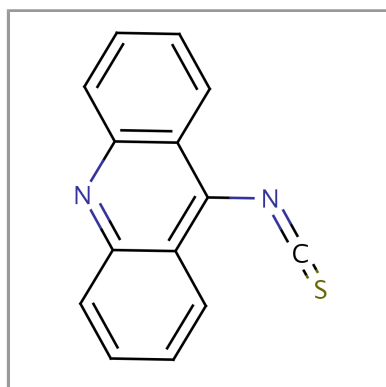
4



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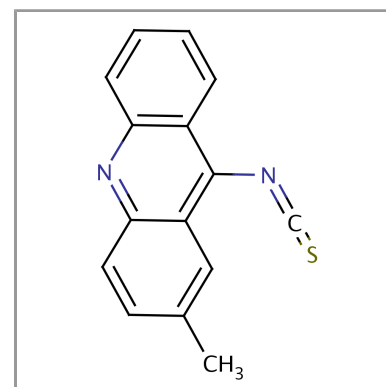
4a



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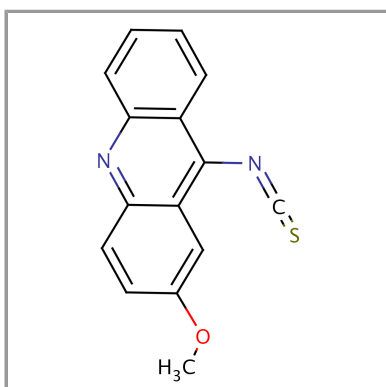
4b



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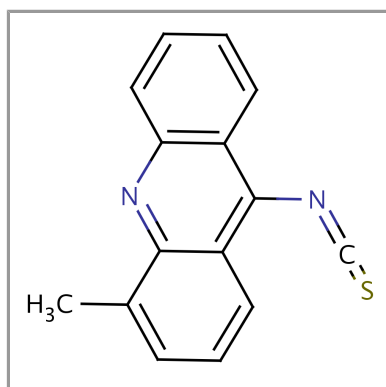
4c



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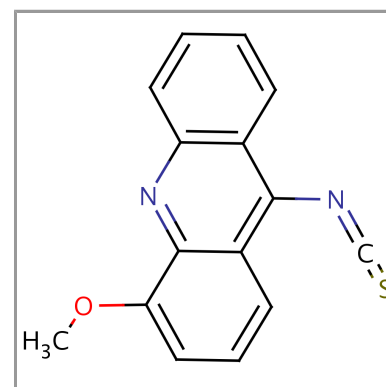
4d



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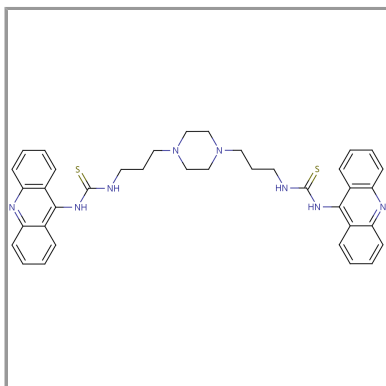
4e



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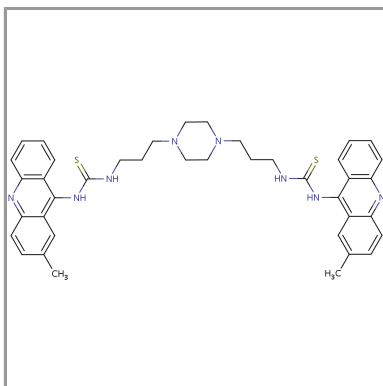
5a



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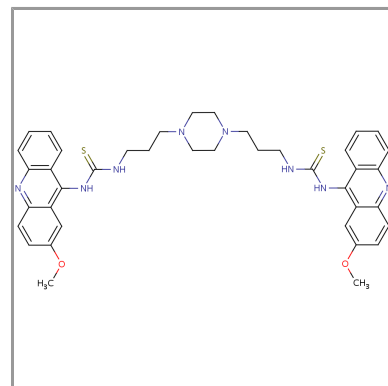
5b



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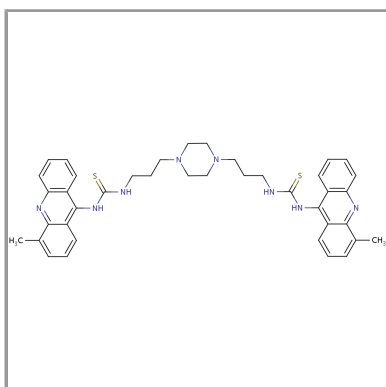
5c



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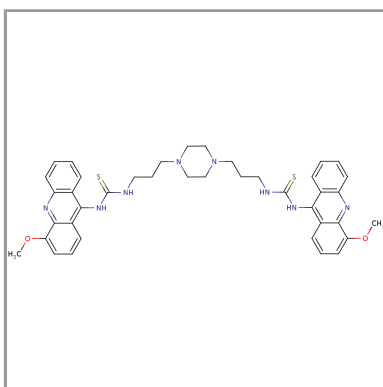
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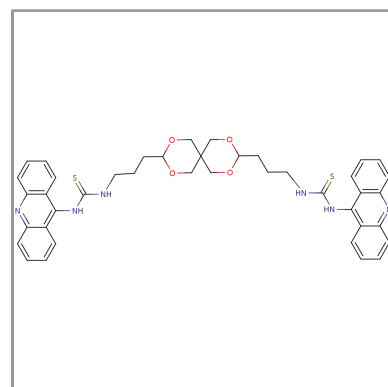
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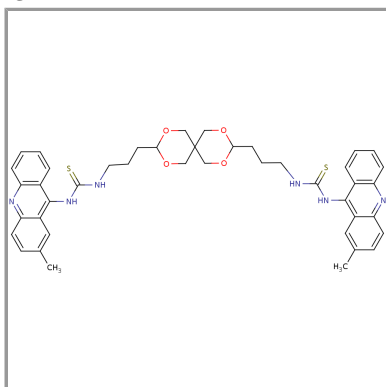
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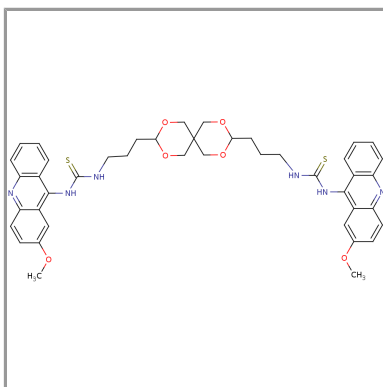
5g



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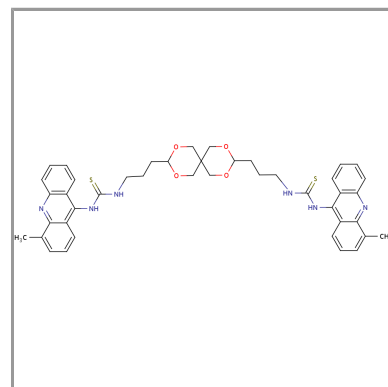
5h



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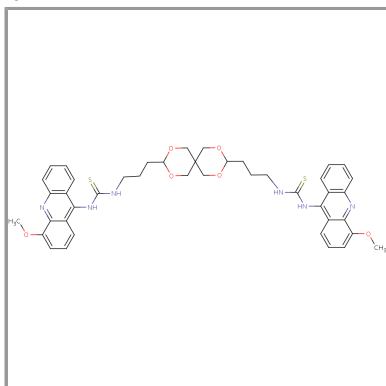
5i



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[Structure Search](#)

5j



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