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Short communication

Synthesis and in vitro cytotoxicity of 9-anilinoacridines bearing *N*-mustard residue on both anilino and acridine rings

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ABSTRACT

A series of 9-anilinoacridines having an alkylating *N*-mustard pharmacophore on both anilino (C-3′ or C-4′) and acridine (C-4) rings with *O*-ethyl (*O*-C_2) or *O*-butyl (*O*-C_4) spacer were synthesized to evaluate their cytotoxicity against human lymphoblastic leukemia (CCRF-CEM) cell growth in vitro. It was revealed that these conjugates exhibited significant in vitro cytotoxicity. Among these agents, compound **13** was the most cytotoxic with IC_{50} value of 1.3 nM and is as potent as taxol ($IC_{50} = 1.1$ nM). The structure–activity relationship study showed that the length of the spacer and the position of the substituent do affect their cytotoxicity.

1. Introduction

Nitrogen mustards (chlorambucil, melphalan) are bifunctional DNA-alkylating agents and are widely used in the treatment of a variety of malignant diseases [1–3]. These agents are able to cross-link cellular DNA and thereby interfere with the DNA replication. However, because of their high reactivity, they are chemically unstable and produce many unwanted side effects including bone marrow toxicity and genotoxicity [4,5]. To improve the drawbacks of nitrogen mustards, one effective strategy is to design and synthesize DNA-directed alkylating agents by linking the *N*-mustard residue to DNA-affinic molecules such as DNA-intercalators [e.g., anthraquinone [6], cyclopentanthraquinone [7] quinoline [8,9], 9-aminoacridine [10,11], 9-anilinoacridine [11–14] (**1**–**5**, Chart 1)] and DNA minor groove binders (e.g., distamycin A and its analogues [15–21] such as tallimustine [21]). In general, these conjugates are more potent than their corresponding unmasked nitrogen mustards and yet have higher sequence specificity for DNA interaction.

Recently, we have synthesized a series of 9-anilinoacridines bearing a *N*-mustard pharmacophore on the C-3 or C-4 of anilino ring via a linker with various lengths such as methyl, *O*-ethyl (*O*-C_2) or *O*-butyl (*O*-C_4) spacer [13]. We demonstrated that these agents were about 100-fold more cytotoxic than the parent 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA, **6**) [22]. Of these compounds, BO-0742 (**3**) exhibited potent cytotoxicity against various human leukemia and solid tumor cell growth in vitro [13]. Furthermore, BO-0742 exhibited a broad spectrum of antitumor activity against various human solid tumor xenografts in vivo [13]. Total tumor remission was achieved in nude mice bearing human breast carcinoma MX-1 xenograft. We have also synthesized a series of 9-anilinoacridines having *N*-mustard residue on the C-4 of the acridine chromophore [14]. Among these derivatives, compounds **4** and **5** were shown to have potent antitumor activity in nude mice bearing MX-1 xenograft. The therapeutic efficacies of BO-0742, **4** and **5** are comparable to those of taxol. The topoisomerase II-mediated DNA cleavage by these agents has been studied and suggested that they are DNA cross-linking agents rather than topoisomerase II poisons [13,14]. Our unpublished results showed that BO-0742 was about 10-fold less toxic to human normal hemopoietic stem cells (CFU-E, BFU-E and CFU-GM) than leukemic CCRF-CEM suggesting that this agent has low toxicity to human bone marrow.

As a part of our ongoing research on searching new potent DNA-directed alkylating agents, we have synthesized 9-anilinoacridine analogues bearing the *N*-mustard residue on both anilino and acridine rings for antitumor evaluation. The results revealed that the newly synthesized derivatives exhibited significant in vitro cytotoxicity. Herein, we describe the synthesis and biological evaluation of the new *N*-mustard conjugates.

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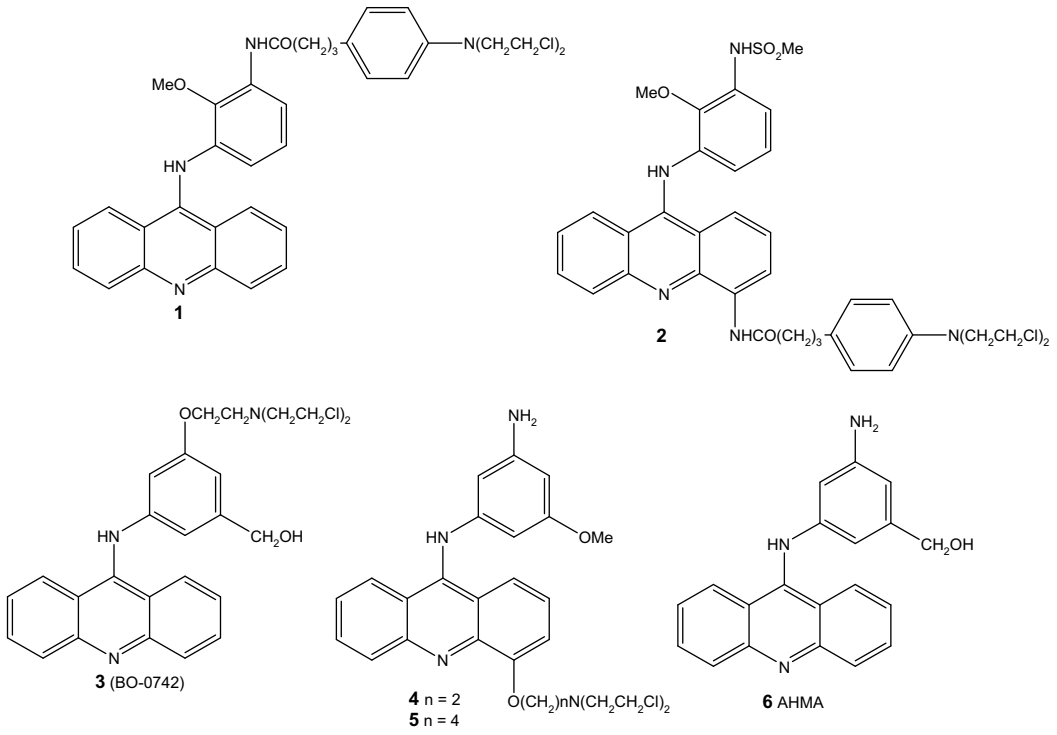


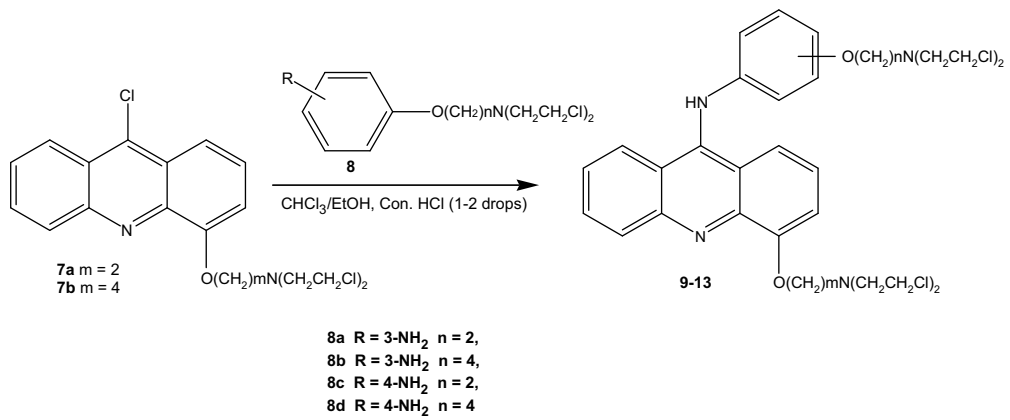
Chart 1.

2. Results and discussion

The synthetic route for the 9-anilinoacridines bearing an alkylating *N*-mustard residue on both anilino and acridine rings with *O*-ethyl (*O*-C_2) and *O*-butyl (*O*-C_4) linkers is shown in Scheme 1. Intermediates, 9-chloroacridines (**7**) and aniline-*N*-mustard conjugates (**8**), were prepared by following the procedure previously developed in our laboratory [13,14]. Synthesis of conjugates **9**–**13** having *N*-mustard residues on both anilino and acridine rings was achieved by the reaction of freshly prepared 9-chloroacridines (**7a**,**b**) with anilines (**8a**, **8b**, **8c** and **8d**) in ethanol at −5 °C. After completion of the reaction, the desired products were purified by column chromatography.

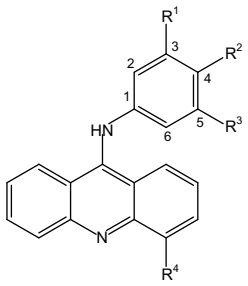
The cytotoxic effects of the newly synthesized derivatives against human T-cell acute lymphocytic leukemia CCRF-CEM cell growth were determined by XTT-tetrazolium assay [23] and compared with *N*-mustards linked to either anilino ring or acridine chromophore of the 9-anilinoacridines [13,14], AHMA (**6**) and taxol. As shown in Table 1, it is clearly demonstrated that all of the new compounds were about 30- to 580-fold more potent than AHMA (**6**). Of these agents, compound **13** was the most cytotoxic with IC_{50} value of 1.3 nM and was as potent as taxol ($IC_{50} = 1.1$ μM). The cytotoxicity of compounds bearing *N*-mustard pharmacophore at C-4 on the acridine ring having –*O*–$(CH_2)_2$– linker revealed that derivatives bearing *N*-mustard residue at C-3′ were as potent as or more potent than the corresponding derivatives having this residue on C-4′ (**9** vs **11** and **10** vs **12**). Compounds having –*O*–$(CH_2)_n$– linker at C-3′ yielded higher in vitro activity when $n = 4$ than $n = 2$ (**9** was 3-fold more potent than **10**). In contrast, the conjugates bearing linker at C-4′ position afforded higher cytotoxicity when $n = 2$ than $n = 4$.

Previously, we have demonstrated that *N*-mustards linked to 9-anilinoacridines on the anilino ring with –*O*–$(CH_2)_n$– spacer between mustard residue and the anilino ring (i.e., **14**–**17**, Table 1) yielded higher in vitro activity when $n = 2$ than $n = 4$ [13]. While in contrast, 9-anilinoacridine derivatives bearing *N*-mustard residue



Scheme 1. Synthesis of 9-anilinoacridine analogues (**9**–**13**) bearing the *N*-mustard residue on both anilino and acridine rings.

Table 1
Analytical data and cytotoxicity of *N*-mustard derivatives against human lymphoblastic leukemic cell (CCRF-CEM) growth in vitro



Compound	R^1	R^2	R^3	R^4	Mp (°C)	Yield (%)	Anal. Calcd	IC_{50} (nM)
9	A	H	H	A	108–109	39.5	C, H, N	17.0
10	B	H	H	A	98–99	40	C, H, N	6.0
11	H	A	H	A	105–106	62	C, H, N	14.2
12	H	B	H	A	95–96	24	C, H, N	21.0
13	H	A	H	B	101–102	63	C, H, N	1.3
14 [13]	A	H	H	H				86.0
15 [13]	B	H	H	H				392.0
16 [13]	H	A	H	H				20.0
17 [13]	H	B	H	H				56.0
4 [14]	NH_2	H	OMe	A				6.7
5 [14]	NH_2	H	OMe	B				4.2
AHMA [22]	NH_2	H	CH_2OH	H				753.0
Taxol								1.1

$A = O(CH_2)_2N(CH_2CH_2Cl)_2$. $B = O(CH_2)_4N(CH_2CH_2Cl)_2$.
Cell growth inhibition was measured by the XTT assay for leukemic cells after 72 h incubation using a micro-plate spectrophotometer as described previously [23]. IC_{50} values were determined from dose–effect relationship at six or seven concentrations of each drug by using the CompuSyn software based on the median–effect principle and plot [24,25].

on the C-4 of acridine chromophore having $-O-(CH_2)_n-$ linker yielded higher in vitro activity when $n = 4$ than $n = 2$ (**4** vs **5**) [14]. Based on the present structure–activity relationship study and the previous results, it suggested that introducing a $-O-(CH_2)_4-$ spacer on the acridine ring can enhance the cytotoxicity of this series of compounds. The new *N*-mustard conjugates were subjected to in vivo antitumor evaluation, however, we found that these agents have poor solubility in intravenous injection vehicle (DMSO/Tween 80/normal saline) and are very toxic to mice; mice died at the dose of 2 mg/kg, QD × 3, via intravenous injection demonstrating that these agents were more toxic than BO-0742.

3. Conclusion

We have synthesized a series of 9-anilinoacridines bearing an alkylating *N*-mustard residue on both anilino and acridine rings. It was revealed that these agents exhibited significant cytotoxicity against human lymphoblastic leukemia CCRF-CEM cell growth in vitro. The length of the spacer used to connect the *N*-mustard residue and DNA-affinic carrier significantly affected the cytotoxicity of these agents. Among these agents, compound **13** was found to be the most potent being equivalent to taxol. Although these derivatives possessed significant in vitro cytotoxicity, they have poor solubility and are more toxic than BO-0742 when the antitumor experiments were carried out in animal model. So far, all *N*-mustard derivatives linked to 9-anilinoacridines synthesized from our laboratory can be considered as alkyl *N*-mustard analogues. The inductive effect of the alkyl function may enhance the formation of the active aziridium cation intermediate, which is able to react rapidly with nucleophile, such as the deoxyguanosine (dG) residue of DNA, resulting in high in vitro cytotoxicity, but possess low stability. While the phenyl *N*-mustards, they are less reactive probably due to the electron-withdrawing property of the phenyl ring. To find stable *N*-mustard analogues with potent antitumor activity, we have recently designed and synthesized a series of new phenyl *N*-mustards linked to DNA-affinic molecules (9-anilinoacridines and 4-aminoquinolines) via a urea spacer [26]. These derivatives were quiet stable and yet exhibited potent therapeutic efficacy in inhibiting various human tumor xenografts in nude mice. The results will be reported separately.

4. Experimental

Melting points were determined on Fargo melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel G60 (70–230 mesh). Thin-layer chromatography was performed on silica gel G60 F_{254} (Merck) with short-wavelength UV light for visualization. Elemental analyses were done on a Heraeus CHN-O Rapid instrument. ^{1}H NMR spectra were recorded in DMSO-d_6 solution on a 400 MHz Bruker AVANCE 400 DRX spectrometer. Chemical shifts (δ) are reported in parts per million, relatively to TMS.

4.1. General procedure for the synthesis of compounds *9–13*

A solution of freshly prepared 9-chloroacridines (**7**) [14] in $CHCl_3$ was added into a suspension of freshly prepared anilines (**8**) [13] in ethanol at −5 °C for 1 h and then stirred at room temperature for 5–7 h. The reaction mixture was evaporated to dryness under vacuum and the desired products were obtained after chromatography (silica gel column, solvent: $CHCl_3$/MeOH, 10:1 v/v). The detailed synthetic procedure for representative compound **9** is described below.

4.1.1. (4-{2-[Bis(2-chloroethyl)amino]ethoxy}acridin-9-yl)-(3-{2-[bis(2-chloroethyl)amino]ethoxy}phenyl)amine (*9*)

A solution of freshly prepared 9-chloroacridine (**7a**, 193 mg, 0.5 mmol) in $CHCl_3$ (25 mL) was added into a solution of freshly prepared aniline (**8a**) in EtOH (10 mL) containing two drops of concd HCl at −5 °C. After being stirred for 1 h, the solution was allowed to stir at room temperature for additional 6 h. The solution was concentrated *in vacuo* and the residue was chromatographed on a silica gel column using $CHCl_3$/MeOH (10:1 v/v) as an eluent. The fractions containing the main product were combined and concentrated *in vacuo* and the residue was dissolved in 4.2 N HCl in ethyl acetate solution and concentrated again *in vacuo*. The residue was triturated well with EtOAc (20 mL) and the precipitates were collected by filtration and dried to give **9** as hydrochloride salt, 252 mg (39.5%); mp 108–109 °C; ^{1}H NMR (DMSO-d_6) δ 3.60 (4H, br s, 2 × CH_2), 3.78 (6H, m, 3 × CH_2), 3.96 (2H, m, CH_2), 4.07 (4H, m, 2 × CH_2), 4.20 (4H, m, 2 × CH_2), 4.46 (2H, br s, OCH_2), 4.72 (2H, br s, OCH_2), 7.13 (2H, d, $J = 8.3$ Hz, 2 × ArH), 7.40–7.45 (4H, m, 4 × ArH), 7.57 (1H, m, ArH), 7.89 (1H, m, ArH), 7.98 (1H, m, ArH), 8.26 (1H, m, ArH), 8.89 (1H, m, ArH), 11.90 (1H, br s, exchangeable, NH). Anal. Calcd for $C_{31}H_{36}N_4O_2Cl_4 \cdot 3HCl \cdot 4.01H_2O$: C, 45.33; H, 5.77; N, 6.82. Found: C, 45.32; H, 5.72; N, 6.50.

By following the same procedure as that for **9**, the following compounds (**10**–**13**) were synthesized.

4.1.2. (4-{2-[Bis(2-chloroethyl)amino]ethoxy}acridin-9-yl)-(3-{2-[bis(2-chloroethyl)amino]butoxy}phenyl)amine (*10*)

Compound **10** was prepared from 4-{2-[bis(2-chloroethyl)-amino]ethoxy}-9-chloro acridine (**7a**, 193 mg, 0.5 mmol) and bis(2-chloroethyl)-[2-(3-nitro-phenoxy)butyl]amine (**8b**, 335 mg, 1 mmol). Yield: 242 mg (40%); mp 98–99 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (2H, m, CH_2), 1.85 (2H, m, CH_2), 3.56 (4H, m, 2 × NCH_2), 3.81 (4H, m, 2 × NCH_2), 3.99 (4H, m, 3 × CH_2), 4.09 (6H, m, 3 × CH_2), 4.22

(4H, m, 2 × CH_2), 4.74 (2H, br s, OCH_2), 6.99 (2H, m, 2 × ArH), 7.12 (1H, m, ArH), 7.37–7.48 (3H, m, 3 × ArH), 7.58 (1H, m, ArH), 7.99 (2H, m, 2 × ArH), 8.37 (1H, m, ArH), 8.97 (1H, m, ArH), 12.0 (1H, br s, exchangeable, NH). Anal. Calcd for $C_{33}H_{40}N_4O_2Cl_4 \cdot 5HCl \cdot 0.3H_2O$: C, 50.43; H, 5.71; N, 6.81. Found: C, 50.43; H, 5.30; N, 6.35.

4.1.3. (4-{2-[Bis(2-chloroethyl)amino]ethoxy}acridin-9-yl)-(4-{2-[bis(2-chloroethyl)amino]ethoxy}phenyl)amine (**11**)

Compound **11** was prepared from 4-{2-[bis(2-chloroethyl)-amino]ethoxy}-9-chloro acridine (**7a**, 569 mg, 1.5 mmol) and bis(2-chloroethyl)-[2-(4-nitro-phenoxy)ethyl]amine (**8c**, 617 mg, 1.8 mmol). Yield: 595 mg (62%); mp 105–106 °C; ^{1}H NMR (DMSO-d_6) δ 3.38 (4H, br s, 3 × CH_2), 3.73 (6H, br s, 3 × CH_2), 3.90 (2H, br s, CH_2), 4.01 (4H, m, 2 × CH_2), 4.15 (4H, m, 2 × CH_2), 4.43 (2H, br s, OCH_2), 4.69 (2H, br s, OCH_2), 7.14 (2H, d, $J = 8.5$ Hz, 2 × ArH), 7.38–7.45 (4H, m, 4 × ArH), 7.57–7.59 (1H, m, ArH), 7.85–7.87 (1H, m, ArH), 7.97–8.01 (1H, m, ArH), 8.21–8.23 (1H, m, ArH), 8.84–8.86 (1H, m, ArH), 11.80 (1H, exchangeable, NH). Anal. Calcd for $C_{31}H_{36}Cl_4N_4O_2 \cdot 6HCl \cdot 3H_2O$: C, 40.85; H, 5.31; N, 6.14. Found: C, 40.87; H, 5.09; N, 6.03.

4.1.4. (4-{2-[Bis(2-chloroethyl)amino]ethoxy}acridin-9-yl)-(4-{2-[bis(2-chloroethyl)amino]butoxy}phenyl)amine (**12**)

Compound **12** was prepared from 4-{2-[bis(2-chloroethyl)-amino]ethoxy}-9-chloro acridine (**7a**, 455 mg, 1.2 mmol) and bis(2-chloroethyl)-[2-(4-nitro-phenoxy)butyl]amine (**8d**, 588 mg, 1.5 mmol). Yield: 115 mg (24%); mp 95–96 °C; ^{1}H NMR (DMSO-d_6) δ 1.88 (2H, br s, CH_2), 1.97 (2H, br s, CH_2), 3.36 (2H, br s, CH_2), 3.63 (4H, br s, 2 × CH_2), 3.84 (4H, br s, 2 × CH_2), 4.01 (4H, br s, 2 × CH_2), 4.16 (4H, br s, 2 × CH_2C), 4.25 (4H, br s, 2 × CH_2Cl), 4.77 (2H, br s, OCH_2), 7.12 (2H, m, 2 × ArH), 7.45–7.47 (5H, m, 5 × ArH), 7.61 (1H, m, ArH), 8.02 (1H, m, ArH), 8.40 (1H, m, ArH), 8.99 (1H, br s, NH), 11.90 (1H, exchangeable, NH). Anal. Calcd for $C_{33}H_{40}Cl_4N_4O_2 \cdot 7HCl \cdot 4H_2O$: C, 42.9; H, 6.00; N, 6.07. Found: C, 43.63; H, 6.10; N, 6.02.

4.1.5. (4-{2-[Bis(2-chloroethyl)amino]butoxy}acridin-9-yl)-(4-{2-[bis(2-chloroethyl)amino]ethoxy}phenyl)amine (**13**)

Compound **13** was prepared from 4-{2-[bis(2-chloroethyl)-amino]butoxy}-9-chloro acridine (**7b**, 407 mg, 1.0 mmol) and bis(2-chloroethyl)-[2-(4-nitro-phenoxy)ethyl]amine (**8c**, 412 mg, 1.2 mmol). Yield: 375 mg (63%); mp 101–102 °C; ^{1}H NMR (DMSO-d_6) δ 1.64–1.72 (2H, m, CH_2), 1.94–2.01 (2H, m, CH_2), 2.65–2.69 (2H, t, $J = 7.0$ Hz, CH_2), 2.90 (4H, t, $J = 8.9$ Hz, 2 × CH_2), 3.02–3.05 (6H, m, 3 × CH_2), 3.51–3.78 (8H, m, 8 × CH_2), 4.03 (2H, t, $J = 5.6$ Hz, OCH_2), 4.16 (2H, t, $J = 6.4$ Hz, OCH_2), 7.17 (2H, m, 2 × ArH), 7.32–7.37 (2H, m, 2 × ArH), 7.40–7.42 (3H, m, 3 × ArH), 7.52 (1H, m, ArH), 7.87 (1H, m, ArH), 7.95 (1H, m, ArH), 8.31 (1H, m, ArH), 8.78 (1H, m, ArH), 11.71 (1H, br s, exchangeable, NH). Anal. Calcd for $C_{33}H_{40}Cl_4N_4O_2 \cdot 8HCl \cdot 6H_2O$: C, 39.81; H, 6.75; N, 5.63. Found: C, 39.63; H, 6.14; N, 5.66.

4.2. Cytotoxicity assays

The effects of the compounds on cell growth were determined in T-cell acute lymphocytic leukemia CCRF-CEM, in a 72 h incubation, by XTT-tetrazolium assay, as described by Scudiero et al. [23]. After the addition of phenazine methosulfate–XTT solution at 37 °C for 6 h, absorbance at 450 and 630 nm was detected on a microplate reader (EL 340; Bio-Tek Instruments Inc., Winooski, VT). Six to seven concentrations of each compound were used. The IC_{50} and dose–effect relationships of the compounds for antitumor activity were calculated by a median–effect plot [24] using a computer program on an IBM-PC workstation [25].

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