Design and Synthesis of a Novel Intercalating Isoxazolyl Bis-lexitropsin Conjugate

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9-Anthracene nitrile oxide directly generated from 9-anthracenealdoxime and *N*-chlorosuccinamide (NCS), reacts with dimethyl acetylenedicarboxylate (DMAD) and affords the corresponding 3-(9'-anthracenyl)-isoxazole-4,5-dicarboxylic acid ester (**3**) with good yield in a very short period. Double activation reaction between (**3**) and hydrogenated lexitropsin (**5**) in a 1:2 molar ratio, produced a bis-lexitropsin product (**6**) (major product) and mono-lexitropsin product (**7**).

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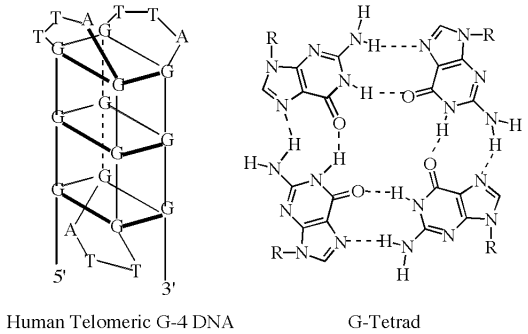
Telomeres are repeating DNA sequences at the end of chromosomes. The human telomeres consist of the sequence "5'-T-T-A-G-G-G" [1]. Progressive rounds of cell division result in a shortening of the telomeres by some 50-200 nucleotides per round, which appears to act like a biological clock [2], limiting the number of times a cell can replicate. However, in over 85-90% of human tumor cells, the enzyme telomerase is active, while it is low to undetectable in normal somatic cells [3]. The telomere length is maintained in cancer cells to a certain degree and ensures the cells' immortality [4], that is, their ability to reproduce without limit. Human telomerase has been proposed as a novel and potentially highly selective target for anti-tumor drug design [4][5][6].

Scheme 1

Human G-quadruplex DNA structure



Human Telomeric G-4 DNA G-Tetrad

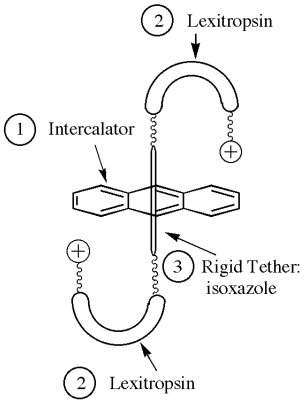
G-quadruplexes (or G-4) are folded conformations of DNA that form from the association of sets of four guanine residues into planar arrays. Although there are several types of G-quadruplexes, very few crystal structures of them have been reported [7][8]. G-quadruplex structures may be adopted by the single-strand DNA at the very end of telomeres (Scheme 1) [9]. The G-quadruplex--cancer connection is based on the notion that single-stranded telomeric DNA must be linear and unfolded for telomerase to be able to catalyze telomere extension and that G-quadruplex conformations prevent the enzyme from carrying out this function [10].

Although the *in vivo* existence of the G-quadruplex has not been proven unequivocally, the stabilization of the G-quadruplexes represents a target for rational design of telomerase inhibitors that may be anti-tumor drugs. Small organic molecules like Carbocyanin dyes [11], pyridinylporphyrins [12], PIPER [13] and anthraquinones [14], have already been found to bind to G-quadruplex telomeric DNA either by "intercalating" or by "external stacking" and shown to be telomerase inhibitors.

Our study is concerned with the design and syntheses of new molecules that could possibly bind to and stabilize G-quadruplex telomeric DNA structures, so as to inhibit telomerase and have increased potency as anti-tumor drugs. The design contains three essential functional components (Scheme 2).

Scheme 2

Designed structure of target molecule



A planar electron rich ring, such as anthracene or acridine, is believed to stack with the G-tetrad. Our previous report of an intercalating DNA binder [15], which contains this kind of intercalator, exhibited promising activity in the National Cancer Institute's 60 cell line screening protocol.

Lexitropsins [16][17] are one class of naturally occurring peptides, containing n-1 *N*-methyl pyrrole and n amide bonds. Design and synthesis of many Lexitropsin analogues has been recently reviewed by Bailly [18]. It was

found that Lexitropsins containing n amide bonds bind preferentially to DNA minor groove sites containing n+1 successive AT-rich base pairs, a behavior that Dervan has termed the "n+1" rule [17][19]. In the present application, the lexitropsin (n=2, dimer) moiety is expected to target the "TTA" loop of the G-quadruplex DNA structure. The tertiary amine ends of two lexitropsin chains can be protonated at physiological pH and help the molecule approach the negatively charged phosphonate backbone of G-quadruplex DNA.

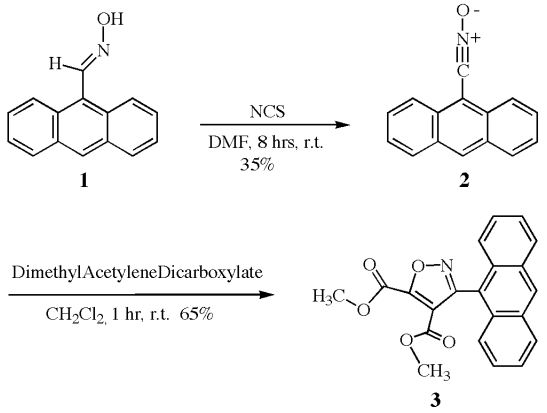
Using an isoxazole, as a rigid linker, should pre-organize the binding moieties in three dimentions and also serve as a prodrug for the delivery of an intercalating lexitropsin to the cellular DNA [20]. In addition, isoxazoles are usually easily metabolized, so that its metabolites will possibly reduce the cytotoxicity of the molecule.

It is proposed that the novel molecule could use its intercalating part to probe into the G-tetrad pocket and use two lexitropsin chains to preferentially bind to the "ATT" sequence and a potential second site in the G-quadruplex at the same time.

Synthetic routes are shown in Scheme 3 and Scheme 4. 9-Anthracene nitrile oxide was first prepared as a stable intermediate by dehydration of 9-anthracenylaldoxime by using sodium hypobromite [21] or sodium bromite/tri-*n*-butyltin chloride [22]. Indirect method includes chlorinating the 9-anthracenylaldoxime into corresponding hydroximinoyl chloride and then generating the nitrile oxide *in situ* by adding an appropriate base (*e.g.* triethylamine) [23]. In our study, chlorinating 9-anthracenylaldoxime in DMF with *N*-chlorosuccinamide (NCS) was performed, while HCl was not used as catalyst.

Scheme 3

Preparation of Dimethyl 3-(9'-Anthracenyl)-4,5-isoxazoledicarboxylate (**3**)



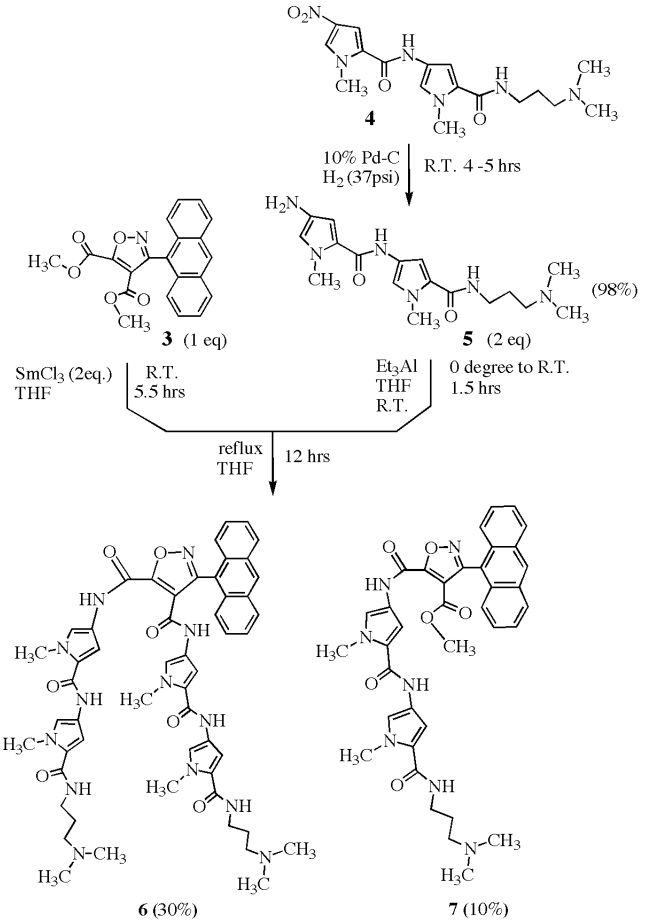
The nitrile oxide (**2**) was found to form directly, as evidenced by the IR absorption at 2250-2300 cm^{-1} (medium) characteristic for C≡N→O for the reaction mixture that was observed after isolation. Pure 9-anthracene nitrile oxide was separated and could be used directly for next step. The preparation of intercalating isoxazoledicarboxylic acid diester (**3**) was performed by applying 1,3-dipolar cyclo-addition reaction between 1,3-dipolarophile dimethyl acetylenedicarboxylate (DMAD) and 9-anthracene nitrile oxide.

Synthesis of isoxazole-intercalating bis-lexitropsin (**6**) (see Scheme 4) includes doubly activated amide formation between anthracenyl-isoxazolediester (**3**) and amino-lexitropsin (**5**), the amine activation methodology of which was reported by Weinreb [24] and was adopted recently by our laboratory [15]. The reaction gave smooth amide formation upon being refluxed, and gave the bis-lexitropsin conjugate as the major product with a reasonable yield.

Another product also isolated was found to have only one lexitropsin coupled with isoxazole. The product (**7**) was confirmed by NMR spectroscopy. The very symmetrical multiple signal resonating at 7.55-7.48 ppm in the proton NMR of (**3**), shows that the four hydrogens (2'H, 3'H; 7'H, 6'H) on the anthracene ring are symmetrical, so the average conformation for the anthracene ring is orthogonal to the isoxazole ring. That only 8 signals cor-

Scheme 4

Double Activation Syntheses of (**6**) and (**7**)



responding to anthracene in the ^{13}C nmr were observed also confirm this fact. The x-ray structure of a similar compound, ethyl 3-(9'-anthracenyl)-5-methyl-4-isoxazolecarboxylate, has already been reported by our laboratory [25], which in fact, adopts just such a conformation with isoxazole and anthracene orthogonal to each other. The two methyl groups (4-$COOCH_3$ and 5-$COOCH_3$) of (**3**) gave ^1H nmr resonances at δ = 3.42 ppm and 4.14 ppm respectively, since the 4-$COOCH_3$ adopts a conformation under the anthracene ring and is therefore shielded by the aromatic system. It was found that, the second product has a methyl group with δ = 3.28 ppm in its ^1H nmr, showing that the more shielded 4-$COOCH_3$ remains, while 5-$COOCH_3$ was reacted.

Regio-selectivity was observed as evidenced by the NMR chemical shift of carboxylic ester groups of isoxazole ring. It is believed that the first equivalent of (**5**) would prefer to react with the 5-$COOCH_3$ of (**3**), which is less hindered than the 4-$COOCH_3$ and it is reasonable to expect the 4-$COOCH_3$ to be attacked by the second equivalent of (**5**).

EXPERIMENTAL

Mass spectra were obtained on a JEOL JMS-AX505 HA. The NMR spectra (^1H and ^{13}C) were obtained on a Bruker AVANCE 500 Digital NMR (500 MHz) using SGI-IRIX 6.5. Elemental analyses were performed by Desert Analytics Laboratory, PO BOX 41838, Tucson, ARIZONA 85717. All reactions were performed under an inert atmosphere of nitrogen or argon. Tetrahydrofuran was distilled from sodium-benzophenone immediately before use. Flash chromatography was performed on silica gel (Merck 60Å, 230-400 mesh) with freshly distilled solvents. Lexitropsin dimmer (**4**): 3-[1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]dimethyl amino-propane was prepared according to a previously published method [16].

9-Anthracenyl-nitrile Oxide (**2**).

To a vigorously stirred solution of 9-anthracenylaldoxime (2.30 g, 10.40 mmol) in DMF (30.0 mL), was added *N*-chlorosuccinamide (2.08 g, 15.60 mmol) in DMF (20.0 mL) over 30 minutes at 0 °C. The reaction was allowed to warm up to room temperature with stirring for 8 hours under nitrogen. The reaction mixture was poured onto 100 mL ice water. The solid formed was collected by filtration and washed with DI water (20 mL × 5). The solid was purified by flash chromatography (silica gel, 5:1 hexane/ethyl acetate) to give an orange powder (Rf=0.43), which was crystallized from chloroform to yield 0.797 g (35%), mp 125-127 °C (ref. [21] 129 °C); ^1H nmr ($CDCl_3$): δ 8.56 (s, 1H, anthracene), 8.27 (dd, J = 1.10, 8.20 Hz, 2H, anthracene), 8.05 (dd, J = 1.10, 8.20 Hz, 2H, anthracene), 7.69-7.51 (m, 4H, anthracene); ir (Nujol): ν 2290cm^{-1} (C≡N→O).

Dimethyl 3-(9'-Anthracenyl)-4,5-isoxazole-dicarboxylate (**3**).

To a well-stirred solution of excess dimethyl acetylenedicarboxylate (DMAD) (0.956 g, 6.73 mmol) in CH_2Cl_2 (30 mL), was added drop-wise a solution of anthracene-9-nitrile oxide (0.737 g, 3.38 mmol) in CH_2Cl_2 (10 mL) over 10 minutes. The reaction was stirred under nitrogen for 1 hour at room temperature. Evaporation of solvent gave yellow oil. The oil was chromatographed on silica gel using hexane/ethyl acetate (8:1) to give a pale yellow solid (Rf=0.25). Recrystallization from cylcohexane afforded pure (**3**) 0.856 g (65%), mp 124-125 °C; ^1H nmr ($CDCl_3$): δ 8.651(s, 1H, anthracene), 8.10 (dd, J = 1.00, 8.50 Hz, 2H, anthracene), 7.65 (dd, J = 1.00, 8.50 Hz, 2H, anthracene), 7.55-7.48 (m, 4H, anthracene), 3.42 (s, 3H, 4-$COOCH_3$), 4.14 (s, 3H, 5-$COOCH_3$); ^{13}C nmr ($CDCl_3$): δ 161.2, 160.6, 157.3, 156.4, 137.6, 131.4, 131.3, 130.2, 129.1, 127.3, 125.9, 125.3, 120.3, 54.1, 53.0; ms-EI: m/z 361 (100%, M^+), 302 (29.19%, M-CH_3OCO), 242 (26.59%), 203 (27.54%, 9-cyanoanthracene), 177 (13.60%, anthracene-H).

Anal. Calcd. for $C_{21}H_{15}O_5N$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.54; H, 4.04; N, 3.95.

Double Activation Syntheses of 3-(9-Anthracenyl)-N,N'-bis[5-[[[5-[[[3-(dimethyl- amino) propyl]amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl]amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl]-4,5-isoxazoledicarboxamide (**6**) and 3-(9-Anthracenyl)-*N*-[5-[[[5-[[[3-(dimethyl-amino)propyl]amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl]amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl]-4-(methoxycarbonyl)-5-isoxazolecarboxamide (**7**).

Step 1: Activation of the Ester.

To a suspension of anhydrous $SmCl_3$ (0.565 g, 2.19 mmol) in THF (10 mL) was added (**3**) (0.395 g, 1.094 mmol) in dry THF (10 mL). The mixture was stirred under nitrogen at room temperature for 5.5 hours and was ready to be used in the following steps.

Step 2: Activation of the Amino-lexitropsin.

A suspension of 10 % Pd-C (300 mg) in a solution of (**4**) (1.04 g, 2.76 mmol) in methanol (30 mL), was stirred for 4.5 hours under an H_2 atmosphere (pressure 37 psi) at room temperature. The catalyst was removed by filtration, then the solvents removed *in vacuo*. A pale gray solid (**5**)(0.938 g) was collected rapidly under nitrogen and almost 100% transformation was found. The hydrogenation product was dissolved into dry THF (20 mL) and $(CH_3)_3Al$ (2*M* in hexane, 1.50 mL) was added at 0 °C during 30 minutes. The mixture turned brown. The reaction mixture was allowed warm to room temperature and the reaction was continued for another 1 hour., until it was ready to be transferred in next step.

Step 3: Amide Formation.

To the above-prepared mixture containing activated ester, was added the brown solution of the above prepared activated amino-lexitropsin (**5**) solution at room temperature during 10 minutes. The final mixture was refluxed for 12 hours, at which time $Na_2SO_4 \bullet 10H_2O$ (1.0 g) and cold methanol (30 mL) were added to the reaction mixture in order to quench the excess $(CH_3)_3Al$. The solid was removed by centrifuge and a red solution was collected. The red solution was concentrated, and then chromatography was performed on silica gel (200-400 mesh) using methanol/30% NH_4OH (95:5).

3-(9-Anthracenyl)-*N*,*N*'-bis[5-[[[5-[[[3-(dimethyl-amino)-propyl]amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl] amino] carbonyl]-1-methyl-1*H*-pyrrol-3-yl]-4,5-isoxazoledicarboxamide (**6**) (free base) and the Bis-oxalic Acid Salt.

The free base (**6**) was obtained as a yellow powder after chromatography (Rf = 0.27 in 95:5 methanol/30% NH_4OH) 0.325 g (30.0%), mp 240-241 °C(dec.). ^1H nmr (acetone-d_6): δ 11.95 (s. br, 1H, NH), 10.93 (s, br, 1H, NH), 9.44 (s, br, 1H, NH), 9.22 (s, br, 1H, NH), 8.82 (s, 1H, anthracene), 8.22 (dd, J = 0.90, 8.55 Hz, 2H,

anthracene), 7.84 (s, br, 1H, NH), 7.762(s, br, 1H, NH), 7.733 (dd, J = 0.90, 8.55 Hz, 2H, anthracene), 7.60 (d, J = 1.80 Hz, 1H, pyrrole), 7.59-7.55(m, 2H, anthracene), 7.51-7.47 (m, 2H, anthracene), 7.29 (d, J = 1.75 Hz, 1H, pyrrole), 7.24 (d, J = 1.80 Hz, 1H, pyrrole), 7.19 (d, J = 1.75 Hz, 1H, pyrrole), 6.94 (d, J = 1.85 Hz, 1H, pyrrole), 6.82 (d, J = 1.50 Hz, 1H, pyrrole), 6.71 (d, J = 1.80 Hz, 2H, pyrrole), 4.07 (s, 3H, N-CH_3), 3.93 (s, 3H, N-CH_3), 3.87 (s, 3H, N-CH_3), 3.84 (s, 3H, N-CH_3), 3.38 (m, 2H, N-CH_2-), 3.34 (m, 2H, N-CH_2-), 2.393 (t, J = 1.55 Hz, 2H, N-CH_2-), 2.37 (t, J = 1.55 Hz, 2H, N-CH_2), 2.24 (s, 6H, N-CH_3), 2.19 (s, 6H, N-CH_3), 1.72 (m, 2H, -CH_2-), 1.69 (m, 2H, -CH_2-); ^{13}C nmr (acetone-d_6): δ 163.9, 161.7, 161.7, 160.0, 158.8, 158.7, 155.1, 154.9, 131.7, 131.4, 129.7, 129.0, 128.0, 127.2, 126.8, 126.0, 125.8, 124.9, 124.2, 124.0, 123.8, 123.1, 122.9, 122.1, 120.7, 120.3, 118.6, 118.1, 117.9, 104.9, 103.6, 103.5, 103.3, 58.5, 58.4, 45.1, 45.1, 38.5, 38.5, 36.5, 36.1(3), 36.0(6), 35.9(7), 27.13, 27.0; ms-FAB: m/z 990 (20.95%, M+1), 251 (11.38%, $^{+}$O≡C-NH-C_5H_5N-CO-NH-$(CH_2)_3$-N$(CH_3)_2$), 244 (37.97%, 3-(9'-anthracenyl)-isoxazole, $C_{17}H_{10}NO^{+}$), 203 (20.97%, 9-Cyano-anthracene), 178 (27.70%, anthracene), 129 ($^{+}$O≡C-NH-$(CH_2)_3$-N$(CH_3)_2$), 107 (83.41%), 86 (88.72%, $(CH_2)_3N^{+}(CH_3)_2$), 84 (100%,CH_2=CH-CH=$N^{+}(CH_3)_2$).

To a solution of (**6**) 50 mg (0.05 mmol) in 5 mL absolute ethanol, was added a solution of oxalic acid dihydrate ($C_2O_4H_2$•$2H_2O$) (16 mg, 0.12 mmol). The mixture was stirred at room temperature until no more precipitate formed. The solid was collected by filtration and washed with absolute ethanol (5 mL × 5). The bis-oxalic acid salt of (**6**) was obtained after drying *in vacuo* to yield 54 mg (90%), mp 179.5-181.1 °C.

Anal. Calcd. for $C_{53}H_{59}N_{13}O_7$•$2C_2O_4H_2$•$2H_2O$: C, 56.76; H, 5.59; N, 15.09. Found: C, 56.85; H, 5.43; N, 14.81.

3-(9-Anthracenyl)-*N*- [5-[[[5-[[[3-(dimethyl-amino)propyl]-amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl] amino]carbonyl]-1-methyl-1*H*-pyrrol-3-yl]-4-(methoxycarbonyl)-5-isoxazolecarboxamide (**7)** (free base).

Compound (**7**) was also obtained after chromatography (Rf = 0.57 in 95:5 methanol/30% NH_4OH) to yield 73.9 mg (10%), mp 209.4-211.2 °C; ^{1}H nmr (methanol-d_4): δ 8.58 (s, 1H, anthracene), 8.04 (dd, J = 0.90, 8.30 Hz, 2H, anthracene), 7.72 (dd, J = 0.90, 8.30 Hz, 2H, anthracene), 7.69 (d, J = 1.80 Hz, 1H, pyrrole), 7.68-7.65 (m, 4H, anthracene), 7.32 (d, J = 1.85 Hz, 1H, pyrrole), 7.09 (d, J = 1.85 Hz, 1H, pyrrole), 7.02 (d, J = 1.85 Hz, 1H, pyrrole), 4.00 (s, 3H, pyrrole N-CH_3), 3.88 (s, 3H, pyrrole N-CH_3), 3.44 (t, J = 6.25 Hz, 2H, N-CH_2-), 3.28 (s, 3H, $COOCH_3$), 3.17 (t, J = 7.00Hz, 2H, CONH-CH_2-), 2.08 (m, 2H, -CH_2-); ^{13}C nmr (methanol-d_4): δ 166.9, 163.7, 162.2, 161.3, 160.0, 153.2, 133.9, 131.5, 131.1, 129.5, 128.8, 127.3, 127.0, 125.6, 125.0, 124.2, 123.0, 122.4, 120.3, 119.6, 113.7, 105.6, 104.8, 55.3, 52.0, 42.4, 36.1, 35.8, 35.7, 24.8; ms-FAB: m/z 676 (48.33%, M+1), 644 (13.98%, M-CH_3), 373 (17.35%, $^{+}$O≡C-NH-C_5H_5N-CO-NH-C_5H_5N-CO-NH-$(CH_2)_3$-N$(CH_3)_2$), 302 (20.97%, M-373), 251 (15.74%, $^{+}$O≡C-NH-C_5H_5N-CO-NH-$(CH_2)_3$-N$(CH_3)_2$), 244 (37.04%, 3-(9'-anthracenyl)-isoxazole, $C_{17}H_{10}NO^{+}$) 203 (24.25%, 9-cyanoanthracene), 178 (22.43%, anthracene), 129 (97.03%, $^{+}$O≡C-NH-$(CH_2)_3$-N$(CH_3)_2$), 107 (39.75%), 86 (57.02%, $(CH_2)_3N^{+}(CH_3)_2$), 84 (100%, CH_2=CH-CH=$N^{+}(CH_3)_2$); hrms(FAB): m/z Calcd. for $C_{37}H_{38}N_7O_6$(M+H), 676.2884. Found: 676.2816.

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