Preparation and Bioactivity of Cationic Porphyrins Bearing Mixed 3-quinolyl and 3-pyridyl Meso Groups

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【ABSTRACT】 AIM: To search for the potent telomerase inhibitors with structures of cationic porphyrins to improve the interactions between G-quadruplex and porphyrins by systematically varying the meso substituents. METHOD: Porphyrins bearing mixed 3-quinolyl/3-pyridyl meso groups were synthesized using the Adler-Longo method by condensation of aldehydes with pyrrole, followed by methylation and ion-exchange. The compounds were tested for the telomerase inhibitory activity and *c-Myc* inhibitory activity. RESULT: All compounds were found to be potent and approximately equivalent in terms of their ability to inhibit the action of telomerase in a cell-free assay. Compound 4 had the best inhibitory activity on *c-Myc*.

【KEY WORDS】 Telomerase; Telomerase inhibitors; G-quadruplex; Porphyrin; *c-Myc* inhibitory activity
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1 Introduction

In addition to the familiar duplex DNA, certain DNA sequences can fold into secondary structures that are four-stranded, because they are made up of guanine (G) bases, and such structures are called G-quadruplexes (Fig 1a). Considerable circumstantial evidence suggests that these structures can exist *in vivo* in G-rich DNA regions of the genome including the telomeric ends of chromosomes and oncogene regulatory regions and may be influential in a variety of biological processes[1, 2]. Telomerase, the enzyme responsible for extending telomeric length, is active in over 90% of human tumor cell lines and is low or undetectable in normal somatic cells[3, 4]. These observations have led to the proposal that telomerase and its action could be important targets for anti-cancer drug design[5].

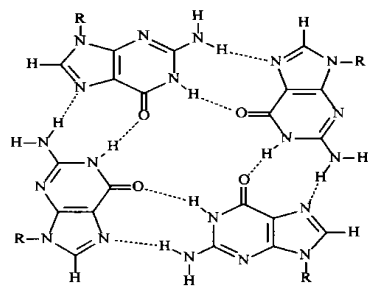

Fig 1a. Four guanine residues form a planar structure termed a G-tetrad

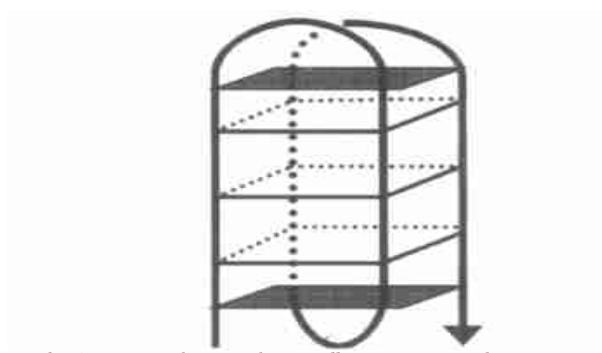

Fig 1b. Cationic porphyrin stack externally to guanine tetrads

c-Myc and *mad* also play critical roles in proliferation and differentiation, respectively. *c-Myc* controls levels of hTERT, the catalytic subunit of telomerase. The relative amounts of *c-Myc* and *mad* determine the proliferation or differentiation capability of cells. In many types of cancers, *c-Myc* expression is deregulated due to chromosomal translocation or gene amplification. The deregulated expression of *c-Myc* occurs in many human cancers such as lymphomas,

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leukaemias, and lung, cervical, ovarian, breast, and gastric cancers. The *c-Myc* gene has been found to contain G-rich sequences that have a propensity to form G-quadruplex structures. Simonsson and co-workers postulated that a G-quadruplex structure might act as a element for transcription initiation of *c-Myc*[6].

It has been widely shown that cationic porphyrins based on 5, 10, 15, 20-tetra (*N*-methyl-4-pyridyl) porphyrin (TMPyP4, **1**, Figure 2), can interact with quadruplex DNA structures by stacking externally to guanine tetrads[7] (Figure 1b). As a result of this close association, cationic porphyrins have the ability to inhibit the action of telomerase in cell-free assays, by the stabilization of quadruplex DNA structures[8].

It is theorized that these cationic porphyrins do not inhibit telomerase directly, but instead do so through a mechanism involving the inhibition of *c-Myc*. The *c-Myc* family of oncogenes encodes proteins that are responsible for activating telomerase.

The formation of DNA G-quadruplexes is necessary to activate the *c-Myc* gene. It is thought that cationic porphyrins bind to the human G-quadruplex structure and inhibit the expression of *c-Myc*. This in turn results in the down regulation of telomerase.

A wide range of TMPyP4 analogues have previously been synthesized and assayed against telomerase. Structure-activity relationships (SARs) have been explored and summarized below based on the telomerase inhibition.

(a) *Stacking interactions*. The face of the porphyrin must be available for stacking with the G-tetrad. In addition, when a porphyrin bears meso aryl substituents there is usually some rotation possible about the bond between the porphyrin and aryl rings, as in the case of TMPyP4 and TMPyP3 (**2**, Figure 1). Moreover, in TMPyP2, the 2-substituent lies partly over the face of the porphyrin thus posing a block to stacking, and this compound is a poor inhibitor of telomerase.

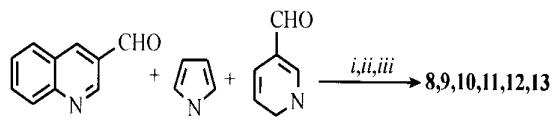
(b) *Substituent bulk*. The grooves of the intramolecular quadruplex are not all the same size, i.e., a very narrow grove lies opposite a wide groove with two intermediate-width grooves between. Compounds were designed to explore the importance of fitting the bulk of the meso substituents to the width of the grooves. Thus, replacing one of the 3-quinolyl groups of QP3 (**3**, Figure 2) with the smaller pyridyl group may fit better into the minor groove of the quadruplex.

(c) *Charge effects*. The significance of the number and positioning of the charged groups was explored. In the 4-pyridyl series the general trend was that the telomerase inhibition was charge-dependent such that the tetracationic compounds were the better inhibitors and the uncharged analogue inactive.

Based on the structure data and modelling studies, structural modifications to the cationic *meso* groups can effect the binding properties of the porphyrin to both quadruplex and duplex DNA[7]. As part of a continuing investigation into the structure activity relationships for these types of porphyrins we have sought to further modify the nature of the *meso* groups. Substituting 3-quinolyl in place of the 3-pyridyl groups of TMPyP3 would allow us to examine the effects of increased steric bulk and charge delocalisation over a greater surface area. So we designed novel cationic porphyrins with quinolyl substituents on the porphyine core. A series of cationic porphyrins with various combinations of 3-pyridyl and 3-quinolyl substituents were synthesized. Thus it was proposed to create a non-symmetrical distribution of shape and charge around the porphyrin core. This latter proposal recognizes that some quadruplex structures, for example intramolecular fold-over structures, are not symmetrical and may require non-symmetrical porphyrins to maximise molecular interaction[9].

2 Results and Discussion

2.1 *Porphyrin synthesis*



Scheme 1 Reagents and conditions: *i*, propionic acid, reflux; *ii*, MeI/$CHCl_3$; *iii*, ion-exchange

The mixed 3-quinolyl/3-pyridyl porphyrin precursors required for the synthesis of **4**, **5**, **6**, and **7** were

synthesized in one pot using the Adler-Longo[10] method by condensing 3-quinolinecarboxaldehyde and 3-pyridinecarboxaldehyde with pyrrole in propionic acid. Compounds **9**, **10**, **11** and **12** (Figure 3) were separated and purified by chromatography over silica eluting as fractions II, III, IV and V, respectively. Methylation of the quinolyl nitrogen atoms and anion exchange afforded the desired compound as its chloride salt. Scheme 1.

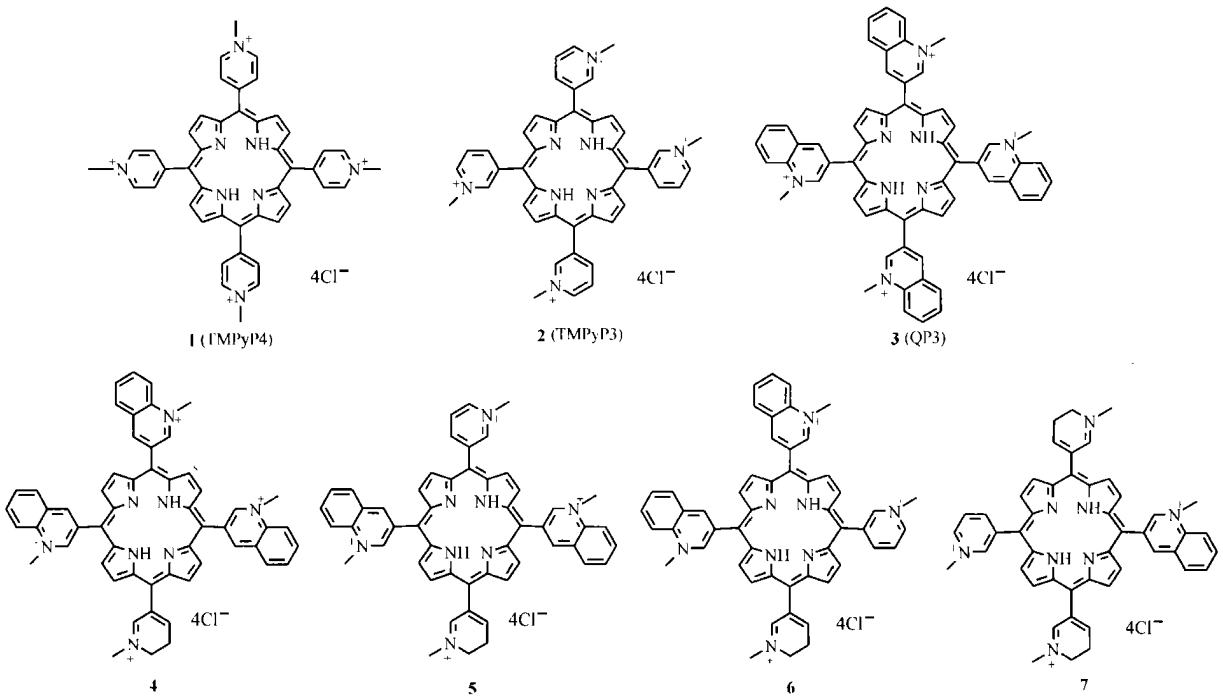


Fig 2 Cationic porphyrins

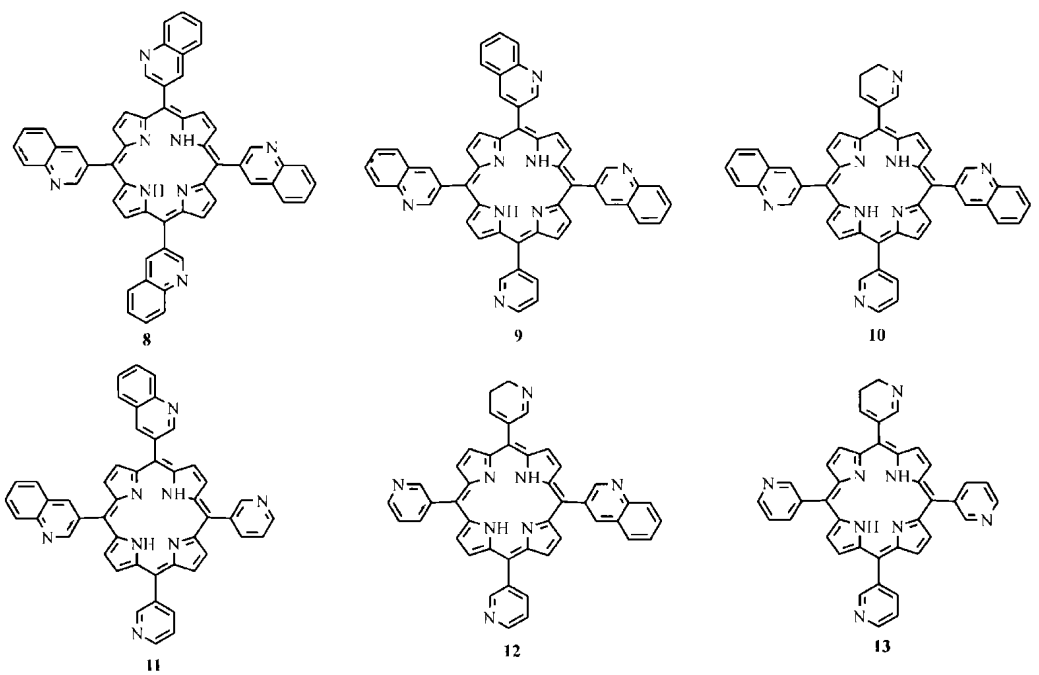


Fig 3 Symmetrical or unsymmetrical quinolyl/pyridyl precursor porphyrins

2.2 *Telomerase inhibition*

An assay using HeLa cell lysate as a source of telomerase activity was used to determine the inhibitory effects of porphyrins **2**~**7** against telomerase. At 12.5 μm drug concentration the inhibitory values were as follows:

Compd.	QP3	**4**	**5**	**6**	**7**	TMPyP3
Inhibition(%)	58	94	94	92	94	66

It is apparent from these results that all of the quinolyl-based porphyrins are more potent inhibitors of telomerase in comparison to TMPyP3 (**2**) and QP3 (**3**). Therefore it is likely that the increased steric size and positive charge delocalisation associated with the quinolyl *meso* group replacement effect the binding of the porphyrin to the quadruplex structure(s), associated with the telomeric repeats present in the assay.

2.3 *c-Myc inhibition*

A specific reverse transcriptase polymerase chain reaction (RT-PCR) assay was used to determine the inhibitory effects of expression levels of *c-Myc* by porphyrins compounds (**4** ~ **7**). The inhibitory activities were as follows:

Compd	**4**	**5**	**6**	**7**
Inhibition	Inhibit	No effect	Inhibit	No effect
Comment	+++		++	

It is also apparent from these results that **5** and **7** didn't have the inhibitory effect of *c-Myc*, while **4** and **6** showed good inhibitory activities, especially **4** was the best. So it is likely that *c-Myc* inhibition is associated with the steric size and positive charge delocalisation around the porphyrin core.

In summary, a series of cationic porphyrins bearing mixed 3-quinolyl and 3-pyridyl meso groups were synthesized by the application of Adler-Longo methodology using corresponding aromatic aldehydes with pyrrole. All target compounds were found to be potent inhibitors of telomerase activity in a cell-free assay and some had *c-Myc* inhibitory effects.

The ability of these new compounds to interfere with other biological processes associated with the formation of G-quadruplex structures, is currently under investigation. Additionally, the methodology developed here will be used to continue the diversification of cationic porphyrin meso group structure.

3 Experimental

3.1 *Synthesis*

Materials and Instrumentation

All chemicals unless otherwise stated were purchased from Sigma-Aldrich Company Ltd (USA). Silica gel chromatography was performed using 230-400 mesh silica purchased from EM science. NMR spectra were recorded on a Bruker AC250 NMR spectrometer. J values are given in Hz throughout. Mass spectra (low and high resolution) were performed by the Mass Spectrometry Center at The University of Texas at Austin. Low-resolution mass spectra were obtained with ether a Finnigan-MAT 4023 or Bell and Howell 21-491 instrument; fast atom bombardment mass spectra (FAB MS) were determined with a finnigan-MAT TSQ-70 instrument; high-resolution mass spectra were recorded on a Bell and Howell 21-110B instrument.

General method 1: N-*methylation and anion exchange*

Porphyrin free base (0.05 mmol) was dissolved in chloroform (5 ml) and diluted with nitromethane (5 ml). Iodomethane (3 ml) was added and the mixture was heated at reflux under argon for 6h and then stirred overnight at room temperature. After removal of solvent in vaccuo, water (5 ml) was added to the residue and treated with Dowex 1x 2-200 anion exchange resin (2 g, chloride form), shaking slowly for 2 h. The resin was filtered off, washed with water, and the filtrate lyophilized to give the chloride salt. The salt could be further purified by chromatography on lipophilic Sephadex using methanol as eluent.

Preparation of the intermediate compounds——Condensation step

A mixture of 3-pyridinecarboxaldehyde (0.68 g, 6.36 mmol), 3-quinolinecarboxaldehyde (1.0 g, 6.36 mmol) and pyrrole (0.85 g, 12.7 mmol) was dissolved in propionic acid (200 ml). The mixture was warmed at 80 ℃ and then heated to reflux for 1 h. After cooling to room temperature, the solvent was evaporated to dryness under high vacuum. The compounds were separated and

purified by chromatography on silica gel using chloroform-methanol (95∶5) as eluent. The order of elution and the chemical yields were as follows:

5, 10, 15-*tri* (3-*quinolyl*)-20-(3-*pyridyl*) *porphyrin* (**9**) (3.12%)

δ_H (250 MHz; $CDCl_3$) 9.80 (3H, s, 2-quinolyl), 9.40 (1H, s, 2-pyridyl), 8.98 (4H, br s, 4-quinolyl, 6-pyridyl), 8.89-8.84 (8H, m, β-pyrrole), 8.53 (1H, d, 4-pyridyl), 8.47 (3H, d, 8-quinolyl), 8.09 (3H, d, 5-quinolyl), 7.96 (3H, t, 7-quinolyl), 7.81-7.71 (4H, m, 6-quinolyl, 5-pyridyl), -2.65 (2H, s, 1-pyrrole); *m/z* (CI) 769 (MH^+, 100%).

5, 15-*bis* (3-*quinolyl*)-10, 20-*bis* (3-*pyridyl*) *porphyrin* (**10**) (2.81%)

δ_H (250 MHz; $CDCl_3$) 9.78 (2H, s, 2-quinolyl), 9.34 (2H, s, 2-pyridyl), 8.96 (2H, br s, 6-pyridyl), 8.93 (2H, s, 4-quinolyl), 8.89 (4H, d, β-pyrrole), 8.82 (4H, br s, β-pyrrole), 8.51 (2H, d, 4-pyridyl), 8.48 (2H, d, 8-quinolyl), 8.11 (2H, d, 5-quinolyl), 7.99 (2H, t, 7-quinolyl), 7.81 (2H, t, 6-quinolyl), 7.72 (2H, t, 5-pyridyl), -2.71 (2H, s, 1-pyrrole); δ_C (250 MHz; $CDCl_3$) 154.2, 153.5, 149.3, 147.6, 140.9, 140.3, 137.6, 134.9, 130.5, 129.8, 128.4, 127.9, 126.8, 122.1, 116.8; *m/z* (CI) 719 (MH^+, 100%).

5, 10-*bis* (3-*quinolyl*)-15, 20-*bis* (3-*pyridyl*) *porphyrin* (**11**) (2.88%)

δ_H (250 MHz; $CDCl_3$) 9.82 (2H, s, 2-quinolyl), 9.49 (2H, s, 2-pyridyl), 9.05 (2H, d, 6-pyridyl), 8.99 (2H, s, 4-quinolyl), 8.93-8.88 (8H, m, β-pyrrole), 8.55 (2H, d, 4-pyridyl), 8.48 (2H, d, 8-quinolyl), 8.10 (2H, d, 5-quinolyl), 7.97 (2H, t, 7-quinolyl), 7.80-7.75 (4H, m, 6-quinolyl, 5-pyridyl), -2.66 (2H, s, 1-pyrrole); δ_C (250 MHz; $CDCl_3$) 154.1, 153.5, 149.2, 147.5, 140.8, 140.2, 137.5, 134.8, 130.3, 129.7, 128.3, 127.8, 126.7, 122.0, 116.8, 116.7; *m/z* (CI) 719 (MH^+, 100%).

5-(3-*quinolyl*)-10, 15, 20-*tri* (3-*pyridyl*) *porphyrin* (**12**) (6.10%)

δ_H (250 MHz; $CDCl_3$) 9.81 (1H, s, 2-quinolyl), 9.47 (3H, s, 2-pyridyl), 9.03 (3H, d, 6-pyridyl), 8.97 (1H, s, 4-quinolyl), 8.92-8.87 (8H, m, β-pyrrole), 8.53 (3H, d, 4-pyridyl), 8.47 (1H, d, 8-quinolyl), 8.06 (1H, d, 5-quinolyl), 7.96 (1H, t, 7-quinolyl), 7.79-7.72 (4H, m, 6-quinolyl, 5pyridyl), -2.74 (2H, s, 1-pyrrole); *m/z* (CI) 669 (MH^+, 100%).

5, 10, 15-*tri* (*N*-*methyl*-3-*quinolyl*)-20-(*N*-*methyl*-3-*pyridyl*) *porphyrin chloride* (**4**)

Prepared from compound **9** with iodomethane according to general method, yield 68.2%.

δ_H (250 MHz; DMSO-d_6) 10.74 (3H, s, 2-quinolyl), 10.10 (4H, br s, 2-pyridyl, 4-quinolyl), 9.61 (1H, d, 6-pyridyl), 9.38-9.28 (9H, br m, β-pyrrole, 4-pyridyl), 8.92 (3H, d, 8-quinolyl), 8.79 (3H, m, 5-quinolyl), 8.64-8.54 (4H, m, 7-quinolyl, 3-pyridyl), 8.32 (3H, t, 6-quinolyl), 4.97 (9H, s, *N*-CH_3-quinolyl), 4.72 (3H, s, *N*-CH_3-pyridyl), -2.96 (2H, s, 1-pyrrole); *m/z* (FAB) 827 (M^+-1, 79%). (Found: M^+-1, *m/z* 827.3569. $C_{56}H_{43}N_8$ requires 827.3611).

5, 15-*bis* (*N*-*methyl*-3-*quinolyl*)-10, 20-*bis* (*N*-*methyl*-3-*pyridyl*) *porphyrin chloride* (**5**)

Prepared from compound **10** with iodomethane according to general method, yield 69.9%

δ_H (250 MHz; DMSO-d_6) 10.72 (2H, s, 2-quinolyl), 10.10 (4H, br s, 2-pyridyl, 4-quinolyl), 9.61 (2H, d, 6-pyridyl), 9.37-9.27 (10H, br m, β-pyrrole, 4-pyridyl), 8.92 (2H, d, 8-quinolyl), 8.79 (2H, m, 5-quinolyl), 8.65-8.55 (4H, m, 7-quinolyl, 3-pyridyl), 8.33 (2H, t, 6-quinolyl), 4.97 (6H, s, *N*-CH_3-quinolyl), 4.71 (6H, s, *N*-CH_3-pyridyl), -3.02 (2H, s, 1-pyrrole); *m/z* (FAB) 777 (M^+-1, 87%). (Found: M^+-1, *m/z* 777.3430. $C_{52}H_{41}N_8$ requires 777.3454.

5, 10-*bis* (*N*-*methyl*-3-*quinolyl*)-15, 20-*bis* (*N*-*methyl*-3-*pyridyl*) *porphyrin chloride* (**6**)

Prepared from compound **11** with iodomethane according to general method, yield 61.7%. δ_H (250 MHz; DMSO-d_6) 10.73 (2H, s, 2-quinolyl), 10.09 (4H, br s, 2-pyridyl, 4-quinolyl), 9.61 (2H, d, 6-pyridyl), 9.37-9.28 (10H, br m, β-pyrrole, 4-pyridyl), 8.91 (2H, d, 8-quinolyl), 8.78 (2H, m, 5-quinolyl), 8.66-8.54 (4H, m, 7-quinolyl, 3-pyridyl), 8.32 (2H, t, 6-quinolyl), 4.96 (6H, s, *N*-CH_3-quinolyl), 4.71 (6H, s, *N*-CH_3-pyridyl), -3.02 (2H, s, 1-pyrrole); *m/z* (FAB) 777

(M^+-1, 98%). (Found: M^+-1, *m/z* 777.3418. $C_{52}H_{41}N_8$ requires 777.3454).

5-(N-*methyl*-3-*quinolyl*)-10, 15, 20-*tri* (N-*methyl*-3-*pyridyl*)*porphyrin chloride* (**7**)

Prepared from compound **12** with iodomethane according to general method, yield 56.1%. δ_H (250 MHz; DMSO-d_6) 10.69 (1H, s, 2-quinolyl), 10.11 (4H, br s, 2-pyridyl, 4-quinolyl), 9.63 (3H, d, 6-pyridyl), 9.37-9.28 (11H, br m, β-pyrrole, 4-pyridyl), 8.92 (1H, d, 8-quinolyl), 8.79 (1H, m, 5-quinolyl), 8.66-8.54 (4H, m, 7-quinolyl, 3-pyridyl), 8.32 (1H, t, 6-pyridyl), 4.98 (3H, s, *N*-CH_3-quinolyl), 4.72 (9H, s, *N*-CH_3-pyridyl), -3.08 (s, 1-pyrrole, 2H); *m/z* (FAB) 727 (M^+-1, 63%). (Found: M^+-1, *m/z* 727.3266. $C_{48}H_{39}N_8$ requires 727.3298).

3.2 Telomerase Assay

Materials

Streptavidin-coated Dynabeads suspension (Dynabeads M-280 Streptavidin) was purchased from Dynal Co. and 5′-biotinylated (TTAGGG)$_3$ primer from Genosys. [α-^{32}P]-dGTP was from NEN Dupont, X-ray film, intensifying screens, and developing chemicals were from Kodak.

Methods

HeLa cell lysate (S-100) was used as a source of telomerase activity. Briefly, cultured HeLa cells (National Cell Culture Institute, MN) were washed once in PBS, resuspended in ice-cold buffer containing 10 mmol HEPES-KOH (pH 7.5), 1.5 mmol $MgCl_2$, 10 mmol KCl, and 1 mmol DTT, and pelleted at 10 000 g for 1 min at 4 ℃. Pelleted cells were resuspended in ice-cold lysis buffer containing 10 mmol Tris-HCl (pH 7.5), 1 mmol $MgCl_2$, 1 mmol EDTA, 0.1 mmol PMSF, 5 mmol BME, 1 mmol DTT, 0.5% CHAPS and 10% glycerol (10^6 cells/20 μl of buffer), incubated for 60 min on ice, and then centrifuged for 1 h in an ultracentrifuge at 100 000 g at 4 ℃. The assay was performed by using 5′ end-biotinylated (TTAGGG)3 as a telomere primer. Reaction mixtures (20 μl) containing 4 μl of cell lysate, 50 mmol Tris-OAc (pH 8.5), 50 mmol KCl, 1 mmol $MgCl_2$, 5 mmol BME, 1 mmol spermidine, 1 μm telomere primer, 2.4 μm [α-^{32}P]-dGTP (800 Ci/mmol), 1 mmol dATP, and 1 mmol dTTP were incubated at 37 ℃ for 1h, otherwise described. Reactions were terminated by adding 20 μl of prewashed Dynabeads suspension containing 10 mmol Tris-HCl (pH 7.5) and 2 mol KCl. The reaction product was immobilized to Dynabeads by incubation for at least 15 min at room temperature keeping the Dynabeads suspended by agitating tubes in vortex. The immobilized reaction product was separated from the suspension using a magnet (Dynal MPC) and washed several times with washing buffer [1 M NaCl and 10 mmol Tris-HCl (pH 7.5)] to eliminate [α-^{32}P]-dGTP background. The washed immobilized products were resuspended in 200 μl of 5.0 mol guanidine-HCl solution and incubated at 90 ℃ for 30 min. The reaction products were dissociated from Dynabeads by placing the tubes in magnetic rack (Dynal MPC) and transfering the supernatant containing reaction products to a new tube. Following ethanol precipitation, telomerase reaction products were analyzed on 8% polyacrylamide gel electrophoresis. Gels were dried on filter paper and developed by autoradiography on a sensitive film (Kodak, Biomax-MS).

3.3 c-Myc Assay

Materials

OmniScript RT Kit was purchased from QIAgen. Primers for PCR:

c-Myc 1: 5′AGAGAAGCTGGCCTCCTACC 3′

c-Myc 2: 5′AGCTTTTGCTCCTCTGCTTG 3′

Actin Primer Pair and Actin Competimers were purchased from Ambion.

Methods

To determine the expression levels of *c-Myc* in response to treatment, we performed specific reverse transcriptase polymerase chain reaction (RT-PCR) assays for each gene. Total RNA was isolated from untreated and compounds **4**, **5**, **6** or **7** treated cells over a time course of 12, 24, 36, and 48 h using the RNeasy RNA isolation kit from Qiagen. 2 μg of total RNA was then reverse transcribed using the OmniScript RT Kit from Qiagen. 2 μl of this first strand synthesis product was then used in a PCR amplification reaction containing the primer sets for each gene product. The sequences for the 3′ and 5′ primers for *c-Myc* were 5′ AGAGAAGCTGGCCTCC-

TACC 3′ and 5′ AGCTTTTGCTCCTCTGCTTG 3′ and for hTERT the primer sequences were 5′ AACGTTCCGCAGAGAAAAGA 3′ and 5′ AAGCGTAGGAAGACGTCGAA 3′. The Actin Primer Pair and Actin Competimers were purchased from Ambion and run in the same reaction as an internal control. The PCR was run for 25 cycles of 94 ℃ for 1 min., 60 ℃ for 1 min. and 72 ℃ for 1 min. After PCR amplification 5 μl gel-loading buffer was added to each completed reaction, and 15 μl was loaded on a 1% agarose/ 1x TBE gel with ethidium bromide. The gel was run in an electric field of 50 Volts (constant voltage) until the dye front migrated approximately 5 cm. A visual image of the gel was captured using an Eagle Eye II image capture apparatus, from Stratagene.

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3-喹啉/3-吡啶混合取代阳离子型卟啉化合物的制备和生物活性研究

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【摘要】 目的: 寻找具有阳离子型卟啉结构的强效端粒酶抑制剂。方法: 采用 Adler-Longo 卟啉合成法通过芳香醛和吡咯的缩合反应制得各种组合的 3-喹啉/3-吡啶基卟啉碱基, 再经甲基化、离子交换得阳离子型卟啉化合物。测试所合成化合物的端粒酶抑制活性和 *c-Myc* 抑制活性。结果: 非细胞试验显示所合成的化合物具有强的端粒酶抑制活性; 而化合物 4 显示最强的 *c-Myc* 抑制活性。

【关键词】 端粒酶; 端粒酶抑制剂; G-四链体; 卟啉; *c-Myc* 抑制活性; 制备