Molbank **2010**, M704; doi:10.3390/M704

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

1,1',1'',1'''-[Porphyrin-5,10,15,20-tetrayltetrakis(3,1-phenylenemethylene)]tetraquinolinium Tetrabromide

Yoshinobu Ishikawa [1,2,*], Takeshi Yamashita [2], Satoshi Fujii [1] and Tadayuki Uno [3]

[1] School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

[2] Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

[3] Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

* Author to whom correspondence should be addressed; E-Mail: ishi206@u-shizuoka-ken.ac.jp.

Received: 8 October 2010 / Accepted: 28 October 2010 / Published: 1 November 2010

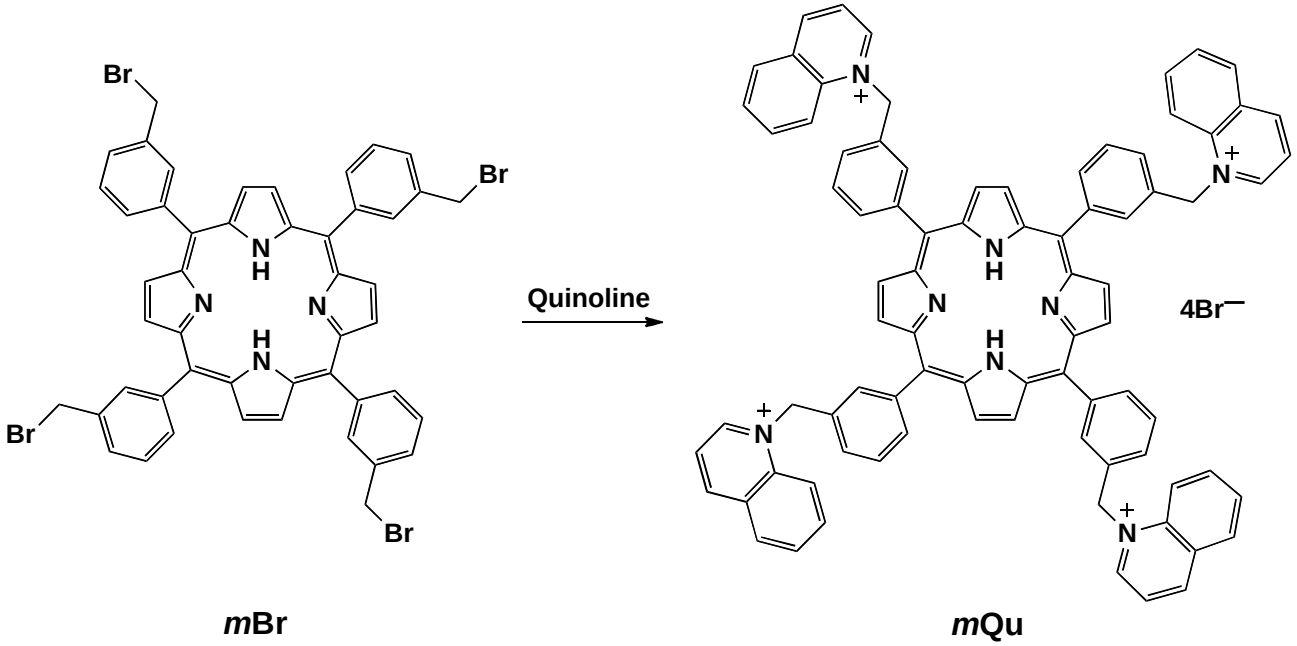
Abstract: Cationic porphyrins interact strongly with guanine quadruplex DNA (G-quadruplex). We herein report the preparation of a cationic porphyrin bearing quinolinium side arms, 1,1',1'',1'''-[porphyrin-5,10,15,20-tetrayltetrakis(3,1-phenylenemethylene)]-tetraquinolinium tetrabromide (***m*Qu**), as a potential G-quadruplex ligand.

Keywords: porphyrin; quinoline; quadruplex

Guanine quadruplex DNA (G-quadruplex) of a single-stranded overhang at the end of chromosomes is an attractive drug target for cancer treatment, because macrocyclic compounds like cationic tetra-(*N*-methyl-4-pyridyl)porphyrin (**TMPyP4**) stabilize G-quadruplex structures, and thus show anti-telomerase and anti-cancer activity [1–4]. We previously synthesized G-quadruplex-interacting porphyrins with cationic side arms at *para*- or *meta*-position of all phenyl groups of tetratolyl porphyrin [5]. These porphyrins were found to stabilize an anti-parallel G-quadruplex more greatly than **TMPyP4**. Among those cationic porphyrins, 1,1',1'',1'''-[porphyrin-5,10,15,20-tetrayltetrakis(3,1-phenylenemethylene)]tetrapyridinium tetrabromide (***m*Py**) exhibited the highest ability to stabilize the G-quadruplex. Cationic porphyrins with more hydrophobic side arms could stabilize the G-quadruplex more greatly, because hydrophobic interaction is entropically favorable in water, which determines the Gibbs energy of binding (*i.e.*, binding affinity). Thus, we herein report the

preparation of a cationic porphyrin bearing quinolinium side arms, 1,1',1'',1'''-[porphyrin-5,10,15,20-tetrayltetrakis(3,1-phenylenemethylene)]tetraquinolinium tetrabromide (***m*Qu**), as a potential G-quadruplex ligand.

Scheme 1. Preparation of ***m*Qu**.



The title compound was prepared successfully by the reaction of ***m*Br** with an excess of quinoline. The ^{1}H-NMR, ESI-MS and elemental analyses gave satisfactory results.

Experimental

^{1}H-NMR spectra were recorded on a JEOL GX-400 spectrometer. Electrospray-ionization time-of-flight (ESI-TOF) mass spectrum was recorded on a Micromass LCT Premier™. Elemental analysis was performed at the Analytical Center, Kumamoto University. The starting material ***m*Br** was synthesized according to a previously published method [6].

1,1',1'',1'''-[Porphyrin-5,10,15,20-tetrayltetrakis(3,1-phenylenemethylene)]tetraquinolinium tetrabromide (***m*Qu**)

A solution of ***m*Br** (42 mg, 0.043 mmol) in quinoline (5 mL) was refluxed for 1 h with stirring. After cooling to room temperature, the purple solids were collected and dried *in vacuo* (yield: 87%). ^{1}H-NMR (DMSO-d_6): 6.78 (s, 8H, -CH_2-), 7.87–8.03 (m, 8H, phenyl H-5 and H-6), 8.18 (t, J = 6.2 Hz, 4H, quinoline H-6), 8.21 (d, J = 6.4 Hz, 4H, phenyl H-4), 8.29 (m, 8H, pyridyl H-3 and H-5), 8.33 (s, 4H, phenyl H-2), 8.33 (m, 4H, quinoline H-3), 8.44 (t, J = 6.2 Hz, 4H, quinoline H-7), 8.65 (d, J = 7.0 Hz, 4H, quinoline H-5), 8.70 (s, 4H, β-pyrrolic H), 8.76 (s, 4H, β-pyrrolic H), 8.87 (d, J = 6.2 Hz, 4H, quinoline H-8), 9.52 (m, 4H, quinoline H-4) , 10.05 (m, 4H, quinoline H-2). ESI-TOF MS (*m/z*): Calcd for $C_{84}H_{62}N_8$, 295.63 $[M]^{+4}$. Found: 295.61. Elemental analysis: Calcd. for $C_{84}H_{62}N_8Br_4$ 4 H_2O

C_7H_7N: C, 65.54; H, 4.55; N, 7.40. Found: C, 65.58; H, 4.44; N, 7.23. UV-vis [λ, nm (ε, $cm^{-1}M^{-1}$); DMSO]: 422 (1.72×10^5), 515 (2.36×10^4), 550 (1.17×10^4), 590 (1.72×10^3), 646 (6.46×10^3).

Acknowledgements

This work was supported by grants (Nos. 12771437 and 14771311 to Y.I.) for Science Research from Japan Society for Promotion of Science.

References and Notes

1. Han, F.X.G.; Wheelhouse, R.T.; Hurley, L.H. Interactions of TMPyP4 and TMPyP2 with quadruplex DNA. Structural basis for the differential effects on telomerase inhibition. *J. Am. Chem. Soc*. **1999**, *121*, 3561–3570.
2. Izbicka, E.; Wheelhouse, R.T.; Raymond, E.; Davidson, K.K.; Lawrence, R.A.; Sun, D.Y.; Windle, B.E.; Hurley, L.H.; Von Hoff, D.D. Effects of cationic porphyrins as G-quadruplex interactive agents in human tumor cells. *Cancer Res*. **1999**, *59*, 639–644.
3. De Cian, A.; Cristofari, G.; Reichenbach, P.; De Lemos, E.; Monchaud, D.; Teulade-Fichou, M.P.; Shin-Ya, K.; Lacroix, L.; Lingner, J.; Mergny, J.L. Reevaluation of telomerase inhibition by quadruplex ligands and their mechanisms of action. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17347–17352.
4. Mikami-Terao, Y.; Akiyama, M.; Yuza, Y.; Yanagisawa, T.; Yamada, O.; Kawano, T.; Agawa, M.; Ida, H. Yamada, H. Antitumor activity of TMPyP4 interacting G-quadruplex in retinoblastoma cell lines. *Exp. Eye. Res*. **2009**, *89*, 200–208.
5. Yamashita, T.; Uno, T.; Ishikawa, Y. Stabilization of guanine quadruplex DNA by the binding of porphyrins with cationic side arms. *Bioorg. Med. Chem*. **2005**, *13*, 2423–2430.
6. Bookser, B.C.; Bruice, T.C. Syntheses of quadruply two- and three-atom, aza-bridged, cofacial bis(5,10,15,20-tetraphenylporphyrins). *J. Am. Chem. Soc*. **1991**, *113*, 4208–4218.