COMMUNICATION

SYNTHESIS OF GLUCOSE ATTACHED PSORALEN DERIVATIVES AS POTENTIAL PHOTOCHEMICAL BLOOD STERILIZER

Kwang-Jin Hwang[*1], Hokyoung Kang[1], Sung Ki Kim[2] and Sang Chul Shim[*2]

[1]Department of Industrial Chemistry, Hongik University, Jochiwon 339-800, Korea
[2]Department of Chemistry, The Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

Psoralen derivatives have been well known as photo-therapeutic agents for the treatment of skin diseases such as psoriasis and vitiligo.[1] These biological activities of psoralens are attributed to the photocycloaddition to the thymidine bases of interacting DNA.[2] PUVA (Psoralen plus UVA) therapy, in particular, is currently attracting a lot of interest in blood sterilization since there is no DNA in blood and only infected virus or bacteria can be destroyed without undesirable side effects.[3] The poor solubility of psoralens in a physiological medium, however, has been one of the most serious constraints in PUVA therapy (J. Hearst, in personal communication). Most of the psoralen derivatives showed microgram/ml solubility in water.[4] Introduction of amine salts enhanced solubilities up to 15 mg/ml.[5] However, the addition of salts may alter the physiological properties of the medium such as protein aggregation and DNA binding.

With this problem in mind, we have been interested in the development of psoralen derivatives with high water solubility in neutral conditions. Carbohydrates show high hydrophilicity due to the polyhydroxyl groups in each pyranose unit and show almost non-toxicity to the human body.[6] We, therefore, designed glucose-linked psoralens **A** and **B** (Fig. 1) and report the synthesis and water solubility of these compounds.

The synthesis of psoralen **A** and **B** was carried out by the substitution of pyranosylbromide **2** with the corresponding psoralens **1** and **4** respectively as a key step as shown in Scheme 1.[7] A typical procedure is as follows. To a solution of 8-hydroxypsoralen **1** (100 mg, 0.49 mmol) in acetonitrile (15 ml) was added K_2CO_3 (220 mg, 1.59 mmol) and refluxed for 2 hours. The mixture was annealed to 0°C in ice-water bath and added dropwise a solution of α-D-glucopyranosyl bromide **2** in acetonitrile (5 ml) for 10 min. The mixture was stirred at room temperature for 24 hours. After usual work up, column chromatography over silica gel (40% ethyl acetate/*n*-hexane) gave psoralen **3**.[8] Deacylation of the psoralen **3** was conducted using sodium methoxide by the following procedure: The psoralen
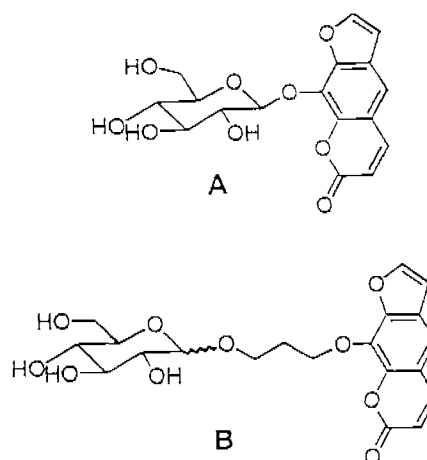

Figure 1. Structure of glucose attached psoralen derivatives.

tetraacetate **3** (53 mg, 0.3 mmol) in methanol (2 ml) was reacted with sodium methoxide (Na/MeOH; 7 mg/ 0.5 ml) for 4 hours at room temperature. After the reaction mixture was concentrated, the residue was dissolved in the solution of HCl (3M, 1 ml) and methanol (2 ml), then the precipitated white solids were collected by filtration. Further purification by column chromatography (20% MeOH/CH_2Cl_2) afforded psoralen **A** (29 mg, 78%).[9]

The propyloxyglucose substituted psoralen **B** was prepared by the similar procedure: The catalyst K_2CO_3 was not suitable for the substitution of pyranose **2** with psoralen **4** probably due to the weak nucleophilicity of primary OH group. Instead, silver catalyst was utilized. To a solution of pyranosylbromide **2** (711 mg, 1.73 mmol) and psoralen **4** (300 mg, 1.15 mmol) in THF (10 ml) were added AgOTf (148 mg, 0.58 mmol) and Ag_2CO_3 (159 mg, 0.58 mmol) then stirred for 3h in the dark under nitrogen. After usual workup, column chromatography (40% ethyl acetate/*n*-hexane) gave psoralen **5** (105 mg, 10%).[10] Subsequent treatment of tetraacetate **5** (90 mg, 0.15 mmol) in MeOH (1 ml) with sodium methoxide (0.61 mmol) gave the psoralen **B** (10 mg, 12%).[11]

---

* To whom correspondence should be addressed.
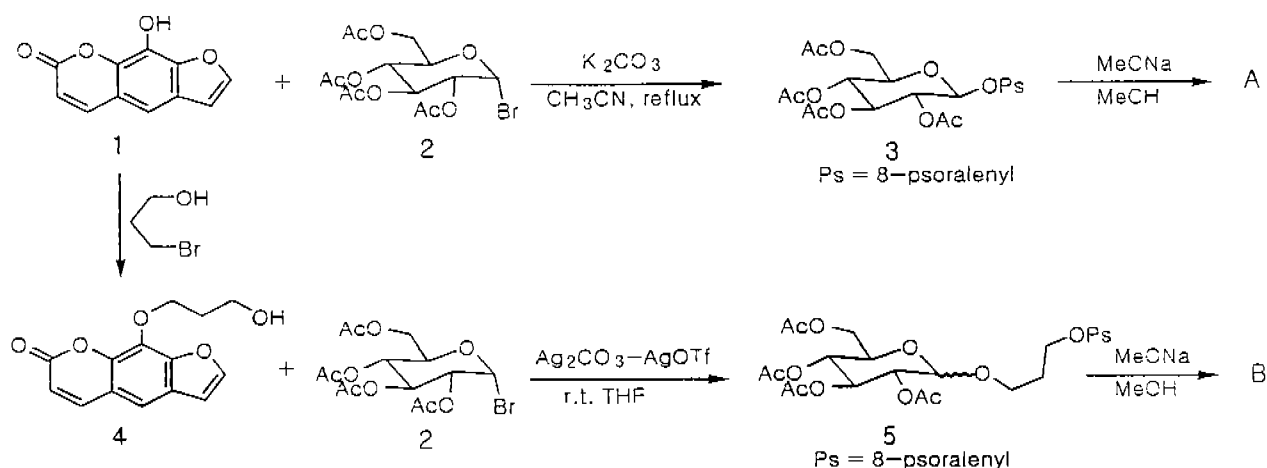
Scheme 1.

Regioselectivity of the glucosylation was dependent on the nucleophile. With 8-hydroxypsoralen, only β-isomer was obtained due to the steric bulkiness of psoralen at the axial position of pyranose. Reaction of psoralen **4** with pyranosyl bromide **2** gave a mixture of α- and β-isomers (50:50, NMR data).

The solubility of glucose-psoralen **A** was determined by the known procedure and all the measurements were triplicated.[4] The water solubility of psoralen **A** was 2254 μg/ml, 46 times greater than that of 8-methoxypsoralen; the highest water solubility of psoralen derivatives in neutral form known up to date.

Preliminary results indicated the similar DNA binding affinity of the psoralen **A** and inhibition of polymerase chain reaction with those of 8-methoxypsoralen suggesting the compound to be an efficient photochemical blood sterilizer by PUVA therapy.

REFERENCES

1. a) Schmitt, I. M., S. Chimenti and F. Gasparro (1995) Psoralen-protein photochemistry - a forgotten field. *J. Photochem. Photobiol. B: Biol.* **27**, 101-107. b) Shim, S. C., Y. H. Jeon, D. W. Kim, G. S. Han and D. J. Yoo (1995) Photochemistry and photobiology of psoralens. *J. Photosci.* **2**, 37-45. c) Potapenko, A. Y. (1991) Mechanisms of photodynamic effects of furocoumarins. *J. Photochem. Photobiol. B: Biol.* **9**, 1-33. d) Song, P.-S. and K. J. Tapley Jr. (1979) Photochemistry and photobiology of psoralens. *J. Photochem. Photobiol.* **29**, 1177-1197.

2. a) Han, G. S., D. J. Yoo, S. K. Kim, S. C. Shim and H. K.

Kang (1996) Photophysical properties of pyrazinopsoralen, a new monofunctional psoralen. *Photochem. Photobiol.* **64**, 525-530. b) Decout, J-L, A. Guendouz and J. Lhomme (1996) Thymidine-psoralen photoaddition: Stereoselective formation of a *trans-syn* pyrone adduct. *Photochem. Photobiol.* **64**, 75-79. c) Averbeck D., S. Averbeck and E. Cundari (1987) Mutagenic and recombinogenic action of DNA monoadducts photo-induced by the bifunctional furocoumarin 8-methoxyp-soralen in yeast. *J. Photochem. Photobiol.* **45**, 371-379. d) Shim S. C. and Y. Z. Kim (1983) Photoreaction of 8-methoxypsoralen with thymidine. *Photochem. Photobiol.* **38**, 265-271.

3. a) Ben-Hur, E. and B. Horowitz (1997) Improved blood safety with light introduction. *Photochem. Photobiol.* **65**, 427. b) Ben-Hur, E. and B. Horowitz (1995) Advances in photochemical approches for blood sterilization. *Photochem. Photobiol.* **62**, 383-388. c) Rai S., C. Kasturi, J. Grayzar, M. S. Platz, R. P. Goodrich, N. R. Yerram, V. Wong and B. H. Tay-Goodrich (1993) Dramatic improvements in viral inactivation with brominated psoralens, naphthalenes and anthracenes. *Photchem. Photobiol.* **58**, 59-65.

4. Yokobata, K.E., J. M. Jordan, O. Chapman and C. Kreil (1986) Psoralenamines. 3. Synthesis, pharmacological behavior, and DNA binding of 5-(aminomethyl)-8-methoxy-, 5-[[(3-aminopropyl)oxy]methyl]-, and 8-[(3-aminopropyl)oxy]psoralen derivatives. *Photochem. Photobiol.* **43**, 391-401.

5. β-(8-psoralenoxy)ethylamine hydrogen bromide

6. Jeffrey G. A. and W. Saenger (1991) *Hydrogen Bonding in Biological Structures*, pp. 169-219, Springer-Verlag Press, Berlin.

7. a) Nishizawa, M., W. Shimomoto, F. Momii and H. Yanada (1992) Stereoselective thermal glucosylation of 2-deoxy-2-acetoamino-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride. *Tetrahedron Letters* **33**, 1907-1908. b) Nishizawa M., Y. Kan, W. Shimomoto and H. Yamada (1990) α-Selective thermal glucosylation of rhamnosyl and mannosyl chloride. *Tetrahedron Letters* **31**, 2431-2434.

8. Analytical data for the psoralen **3**: ¹H-NMR (300MHz;

CDCl$_3$) δ 7.76 (1H, d, J = 9.7 Hz, 4-H'), 7.71 (1H, d, J = 1.8 Hz, 5'-H'), 7.43 (1H, s, 5-H'), 6.79 (1H, d, J = 1.8 Hz, 4'-H'), 6.34 (1H, d, J = 9.7 Hz, 3-H'), 5.42 (1H, d, J = 1.8 Hz, 1-H'), 5.39-5.14 (3H, m, 2-H, 3-H, 4-H), 4.25 (1H, ddd, J = 12.2 Hz, 4.9, 1.6, 6-Ha), 4.07 (1H, dd, J = 12.3 Hz, 2.1, 6-Hb), 3.74 (1H, m, 5-H), 2.15 (3H, s), 2.03 (3H, s), 1.99 (3H, s), 1.92 (3H, s); ^{13}C-NMR δ 170.6, 170.0, 169.8, 169.5, 150.7, 147.9, 146.9, 144.4, 142.9, 128.5, 125.9, 116.4, 115.3, 114.8, 106.6, 101.5, 72.7, 72.1, 71.4, 68.4, 61.7, 20.7.

9. Analytical data for the psoralen A: mp = 195-196 °C; IR (KBr, cm^{-1}) 3312, 1718 ; UV (H$_2$O) 246 (ϵ = 20,000), 299nm (ϵ =10,700); ^{1}H-NMR (300 MHz; CDCl$_3$) δ 7.87 (1H, d, J = 9.7 Hz, 4-H'), 7.79 (1H, d, J = 1.8 Hz, 5'-H'), 7.47 (1H, s, 5-H'), 6.85 (1H, d, J = 1.8 Hz, 4'-H'), 6.29 (1H, d, J = 9.7 Hz, 3-H'), 5.60 (1H, d, J = 7.5 Hz, 1-H), 3.54 (2H, d, J = 3.6 Hz, 6-H), 3.51 (1H, d, J = 7.9 Hz, 2-H), 3.48-3.36 (3H, m, 3-H, 4-H, 5-H); ^{13}C-NMR δ 159.6, 146.6, 146.0, 144.6, 141.9, 128.7, 125.7, 115.9, 113.9,

113.3, 106.3, 101.7, 76.7, 76.6, 73.5, 69.4, 60.0; FAB Mass m/e, 365.0873 (M+1); calcd (C$_{17}$H$_{16}$O$_9$) 365.0794.

10. Analytical data for the psoralen 5: ^{1}H-NMR (200MHz; CDCl$_3$) δ 7.69 (1H, d, J = 9.7 Hz, 4-H'), 7.65 and 7.61 (1H, d, J = 1.8 Hz, 5'-H'), 7.29 (1H, s, 5-H'), 6.72 (1H, br, 4'-H'), 6.26 (1H, d, J = 9.7 Hz, 3-H'), 4.86-5.20 (3.5H, m, 2-H, 3-H, 4-H and 1 β-H), 4.46 (2.5H, br, CH$_2$CH$_2$OPs and 1α -H), 4.10-4.20 (2H, m, 6-H), 3.93-4.06 (2H, m, glu-O-CH$_2$CH$_2$), 3.61-3.68 (1H, m, 5-H), 2.03-2.13 (2H, OCH$_2$CH$_2$CH$_2$O), 1.90-2.03 (12H, m, OCOCH3).

11. Analytical data for the psoralen B: ^{1}H-NMR (300 MHz; DMSO-d$_6$) δ 7.91 (1H, br, 4-H'), 7.83 (1H, br, 5'-H'), 7.47 (1H, s, 5-H'), 6.85 (1H, s, 4'-H'), 6.28 (1H, d, J = 9.7 Hz, 3-H'), 4.72 (0.5H, d, J = 3.3 Hz, 1β-H), 4.50 (2H, t, J = 6.1 Hz, CH$_2$CH$_2$OPs), 4.19 (0.5H, d, J = 7.7 Hz, 1α -H), 4.13 (1H, m, glu-O-CH$_2$CH$_2$), 3.92 (1H, m, glu-O-CH$_2$CH$_2$), 3.19-3.67 (m, other glu-H), 2.02 (2H, m, OCH$_2$CH$_2$CH$_2$O).