SYNTHESIS OF *MESO*-TETRAKIS (CHROMENE-3-YL) PORPHYRINS

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Abstract: Porphyrins and chromene-4-ones are known active anticancer agents. This has generated a thought that a combination of these two compounds may result in a more potent anticancer agent. To this end, an attempt was made to synthesize porphyrins using chromene-3-carbaldehydes bearing electron donating and electron withdrawing groups adopting Macdonald's method of synthesis. This paper describes the design and synthesis of chromene porphyrins.

Introduction

A survey of existing literature has elicited the information that porphyrins and chromene-4-ones exhibit anticarcinogenic and other biological activity[1-5]. Tetra phenyl porphyrin was first synthesized many years ago by Rothemund[6] but yields were low due to tar formation. Lindsey[7,8,9] and co-workers improved upon his method of synthesis and achieved increased yields. Milgrom synthesized[10] *meso*-tetrakis (imidazol-2-porphyrin) compound, which exhibited solid state conductivity. A similar synthesis was reported[11] recently from our laboratories.

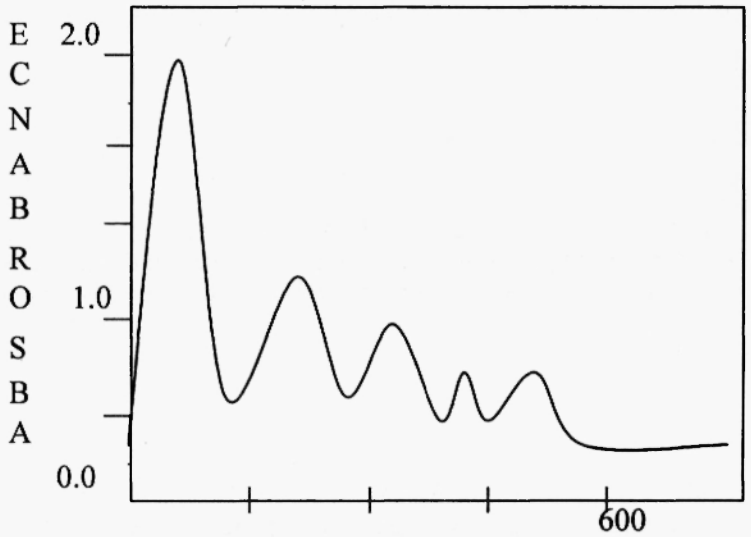
However, chromene porphyrins were not studied with relation to the anticarcinogenic activity previously. Synthesis of *meso*-tetrakis (chromene-3-yl) porphyrins was undertaken with a view to conduct a study of this and other biological activities. The anticancer activity of these compounds is under progress. The starting materials, simple and substituted 4-oxo-4H-chromene-3-carbaldehydes with electron donor and withdrawing groups (**1a-f**) were synthesized[12] by using Vilsmeier-Haack reagent.

Results and discussion

Then, an equimolar mixture of simple and substituted 4-oxo-4H-chromene-3-carbaldehydes (**1a-f**) were condensed with pyrrole in TFA at room temperature as shown in **scheme 1**. The reaction was monitored over TLC and refluxed by adding DDQ, which oxidizes the intermediate; porphyrinogen to give *meso*-tetrakis (chromene-3-yl) porphyrins (**2a-g**) 25-30% yields. Purple colored porphyrins of high purity resulted by flash chromatography using dichloromethane. All chromatography materials and solvents were supplied by Aldrich and were used as they were unless otherwise stated. The structures of the porphyrins were confirmed by a variety of spectroscopic techniques. The Uv-Vis spectra of the free base porphyrins were recorded at $2x10^{-5}$ mol concentrations in

chloroform. The more intense B band, around 425nm and four much less intense Q bands are observed around 450-600nm. Briefly for **2a** the Soret band is prominent as a single absorption at 422 nm. The splitting of the B band is clearly observed when one drop of HCl is added to the solution at the same concentration.

Figure 1 Uv-Vis spectra of **2a** in chloroform



The IR spectra of all compounds showed the broad peak at 3448 cm^{-1}, chromene carbonyl str is at 1625, ω-aliphatic str at 2950, 2830, ω- porphyrin microcyclic bend at 940. The FAB mass spectrum confirmed the composition and the solution structures were assigned by detailed ^1H NMR experiments. For **2a** Pyrrole β-CH protons appear as doublet at 9.12 ppm. The C-2H protons of chromene appeared as singlet at 8.0 ppm. The two inner NH protons resonates at –2.5 ppm. The chemical shift difference (Δδ) between most shielded and the most deshielded protons in the ^1H NMR spectrum confirm all the compounds are aromatic[13].

Experimental

Melting points were determined in open capillaries and are uncorrected. The UV spectra were recorded on a Shimadzu UV-160A UV-Vis-NIR spectrophotometer. IR spectra on a Shimadzu FTIR model 8010 spectrophotometer, ^1H NMR spectra in DMSO-d_6 on a Varian C_{17}-20-ZM-390-20 MHz spectrophotometer using TMS as an internal standard and mass spectra on EIMS at 70ev. The C, H, N and O analysis of compounds were done on a Carlo Erba model EA1108 CHNS-O elemental analyzer.

Synthesis of *meso*- tetrakis (chromene-3-yl) porphyrins (2a)

4 mmol of 4-oxo-4H-chromene-3-carbaldehyde and 4 mmol pyrrole were magnetically stirred together in an inert atmosphere. The nitrogen flow rate is maintained at about 2 mL per minute and anhydrous TFA (4 mmol) was added via syringe. After

2 h, 200 mg DDQ was added to the reaction mixture. The flask was then immersed in a water bath pre heated to 45 ^{0}C and the solution was refluxed for 1 h. The resultant product was poured into the flash column packed with dry florisil. The column was washed with CH_2Cl_2 containing 10-20% ethyl acetate to elute porphyrin. On concentration, **2a** was obtained in dark purple solid form. Yield, 30%, M.P: >300°C, M.F: $C_{56}H_{30}N_4O_8$ (886), FABS M^+, 887, Anal. Calcd (%): C, 75.84; H, 3.41; N, 6.32, Found (%): C, 75.82; H, 3.43; N, 6.33. ^{1}H NMR (δ *ppm*), 9.12 (d, 8H, pyrrole C-H), 8.0 (s, 4H, chromene C-2H), 7.2 (m, 16H, C-5, C- 6, C-7, C-8 chromene), –2.5 (s, 2H, porphyrin N-H).

Similarly **2b-f** were prepared.

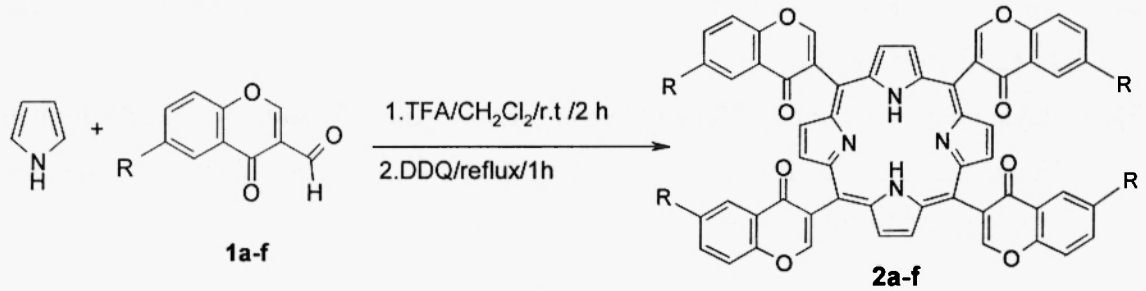
2b. Yield, 28%, M.P: >300°C, M.F: $C_{60}H_{38}N_4O_8$ (942), FABS M^+, 943, Anal. Calcd (%): C, 76.42; H, 4.06; N, 5.94, Found (%): C, 76.44; H, 4.08; N, 5.96. ^{1}H NMR (δ *ppm*), 9.1 (d, 8H, pyrrole C-H), 8.0 (s, 4H, chromene C-2H), 7.2 (m, 12H, C-5, C-7, C-8 chromene), 2.2 (s, 12H, CH_3), –2.3 (s, 2H, porphyrin N-H).

2c. Yield, 28%, M.P: >300°C, M.F: $C_{56}H_{26}Cl_4N_4O_8$ (1022), FABS M^+, 1023, Anal. Calcd (%): C, 65.64; H, 2.56; N, 5.47; Cl. 13.84, Found (%): C, 65.62; H, 2.58; N, 5.44; Cl, 13.85. ^{1}H NMR (δ *ppm*), 9.2 (d, 8H, pyrrole C-H), 8.0 (s, 4H, chromene C-2H), 7.2 (m, 12H, C-5, C-7, C-8 chromene), -2.3 (s, 2H, porphyrin N-H).

2d. Yield, 26%, M.P: >300°C, M.F: $C_{56}H_{30}N_4O_8$ (1202), FABS M^+, 1203, Anal. Calcd (%): C, 55.94; H, 2.18; N, 4.66; Br, 26.58, Found (%): C, 55.95; H, 2.16; N, 4.65; Br, 26.57. ^{1}H NMR (δ *ppm*), 9.12 (d, 8H, pyrrole C-H), 8.0 (s, 4H, chromene C-2H), 7.2 (m, 12H, C-5, C-7, C-8 chromene), –2.3 (s, 2H, porphyrin N-H).

2e. Yield, 25%, M.P: >300°C, M.F: $C_{60}H_{38}N_4O_{12}$ (1006), FABS M^+, 1007, Anal. Calcd (%): C, 71.57; H, 3.80; N, 5.56, Found (%): C, 71.55; H, 3.82; N, 5.57. ^{1}H NMR (δ *ppm*), 9.22 (d, 8H, pyrrole C-H), 8.0 (s, 4H, chromene C-2H), 7.6 (m, 16H, C-5, C-7, C-8 chromene), –2.1 (s, 2H, porphyrin N-H), 3.8 (s, 12H, OCH_3).

2f. Yield, 27%, M.P: >300°C, M.F: $C_{56}H_{26}N_8O_{16}$ (1066), FABS M^+, 1067, Anal. Calcd (%): C, 63.05%; H, 2.46%; N, 10.50% Found (%): C, 63.10%; H, 2.44%; N, 10.51%. ^{1}H NMR (δ *ppm*), 9.0 (d, 8H, pyrrole C-H), 8.0 (s, 4H, chromene C-2H), 7.8 (m, 12H, C-5, C-7, C-8 chromene), –2.4(s, 2H, porphyrin N-H).



Compound	2a	2b	2c	2d	2e	2f
R	H	CH_3	Cl	Br	OCH_3	NO_2

Scheme 1

Acknowledgement

The authors greatly acknowledge the UGC for financial assistance and Director National Institute of Technology Warangal for providing facilities.

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Received on December 18, 2003.