Synthesis and Anti-Staphylococcal Activity of New Halogenated Pyrroles Related to Pyrrolomycins F

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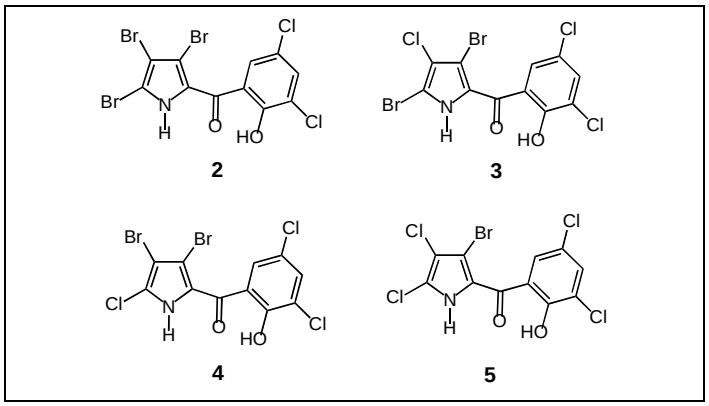

The chemical synthesis of new halogenated pyrroles related to pyrrolomycins F is described and the anti-staphylococcal activity compared. The replacement of 4'-bromo atom of parent compounds with two chloro atoms at 3' and 5' position increase the antibacterial activity against a reference strain of *S. aureus*.

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INTRODUCTION

Antibiotic resistance of important Gram-positive pathogens as *Staphylococcus aureus*, is currently a significant global health problem. The overuse of antibiotics, both in human and animal population, played an important role in the beginning of drug-resistant strains. Furthermore, bacteria can survive and thrive in hostile environments, forming, on living and nonliving surfaces, as indwelling medical devices, organized communities of bacterial cells (biofilms), that are difficult or impossible to treat with conventional antibiotics [1]. There is an urgent need to develop new agents against these pathogens and an interesting resource of new antibiotics is represented by some natural halogenated pyrroles, known as pyrrolomycins (Figure 1). Such molecules, isolated from culture broth of *Actinosporangium vitaminophilum* SF-2080 [2-5], have a good activity especially against Gram-positive bacteria, in particular *Staphylococcus aureus*.

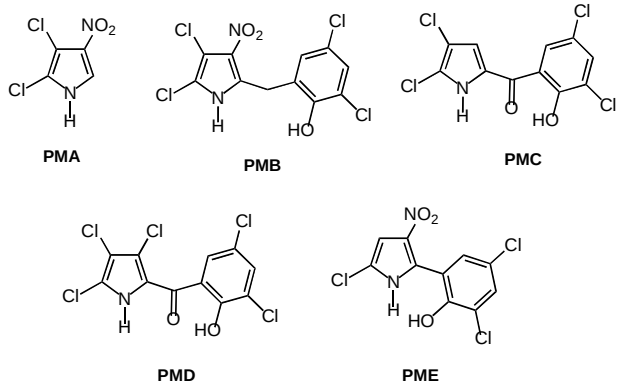

Figure 1

A different group of pyrrolomycins, generically named PM-F, has been produced from *A. vitaminophilum* SF-2080 when bromide ion was added to the fermentation medium [6] (Figure 2).

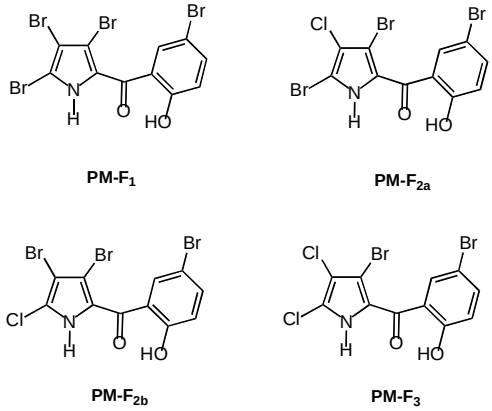

Figure 2

Some PM-F components possessed equal or more potent activity, against some Gram-positive bacteria, than

PM-D, the most active component among PM-A to E [6].

We have previously described the synthesis of some brominated pyrrolomycin analogs [7] and their activity against antibiotic sensitive and resistant *S. aureus* clinical strains [8]. The most active member of this series, the 3,4,5,3',5'-pentabromo-2-(2'-hydroxybenzoyl)pyrrole **1** (Figure 3), bromo analog of pyrrolomycin D and strictly related to pyrrolomycin F_1, exhibited an interesting activity against *S.aureus* ATCC 25923 and promising effects against preformed *Staphylococcus epidermidis* and *S. aureus* biofilms [9].

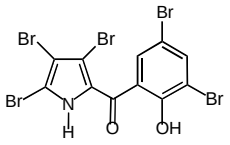

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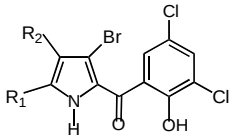
Figure 3

On the basis of the known importance of electron attractive effect of substituents on the phenolic ring on the antibacterial activity of monodeoxypyoluteorin [10], we investigated if the introduction of chloro atoms in 3,5-positions of phenolic ring of F pyrrolomycins could improve the antibacterial activity of this class of compounds. For this purpose we synthesized the compounds **2-5** (Fig. 4), whose phenolic moiety was identical to that of pyrrolomycins B-E, and we evaluated their anti-staphylococcal activity against *S.aureus* ATCC 25923.



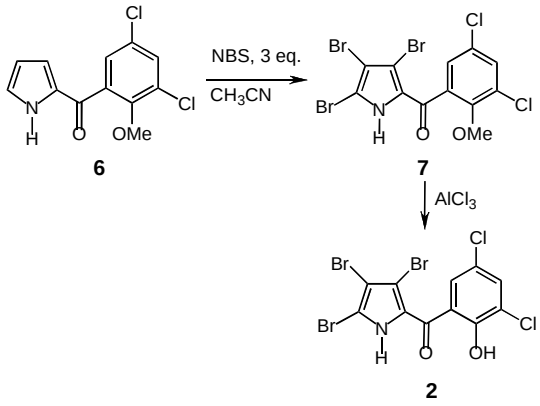
2: $R_1 = R_2 = Br$
3: $R_1 = Br$, $R_2 = Cl$
4: $R_1 = Cl$, $R_2 = Br$
5: $R_1 = R_2 = Cl$

Figure 4

RESULTS AND DISCUSSION

The molecular skeleton of **2** was assembled by allowing pyrrylmagnesium bromide to react with 3,5-dichloro-2-methoxybenzoyl chloride according to procedures previously reported by Davies and Hodge for the synthesis of 2-(2',6'-dimethoxybenzoyl)pyrrole [11]. The 3',5'-dichloro-2-(2'-methoxybenzoyl)pyrrole **6**, so obtained, was purified by column chromatography. The subsequent halogenation of compound **6**, was carried out using *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) in acetonitrile as previously described [12-13]; so the bromination of **6** using three molar equivalents of NBS afforded the 3,4,5-tribromoderivative **7**. Demethylation of **7** with aluminium chloride in anhydrous dichloromethane at room temperature, afforded to the 2'-hydroxy derivative **2** in excellent yield (Scheme 1).

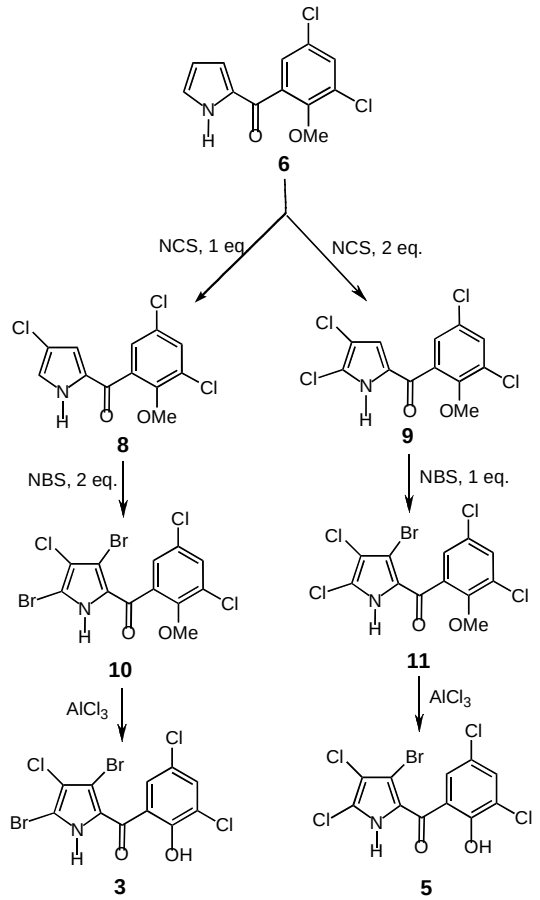
Scheme 1



6 **7** **2**

The reaction of **6** with one molar equivalent of *N*-chlorosuccinimide (NCS) gave a trichloroderivative to whom the structure **8** was assigned on the basis of ^1H nmr spectrum. In fact this compound exhibit two doublets at 6.64 and 7.42 δ (j=1.5 Hz) unequivocally attributable to

Scheme 2

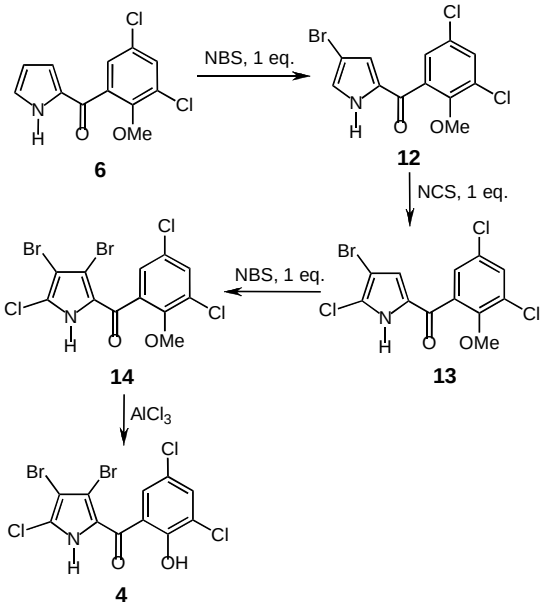


6 **8** **9** **10** **11** **3** **5**

H-3 and H-5 protons respectively of pyrrolic ring. The unusual chemical shift of 3-proton, more shielded than that expected from 2-carbonyl pyrroles, was due to the anisotropic effect of phenyl ring, twisted with respect to the plane of pyrrolic ring. According to what previously observed by P. Hodge and R. W. Rickards [14], the introduction of chlorine (or bromine) substituents into pyrrole rings cause only minor shifts in the resonance frequencies of the remaining hydrogens. On the contrary, the reaction of **8** with two molar equivalent of NCS gave the 4,5-dichloroderivative **9** (chemical shift for H-3 = 6.84 δ) which was brominated with NBS to give **11** whose demethylation with aluminium chloride afforded to **5** in excellent yield (Scheme 2).

Compound **4** was synthesized from **6**, which was brominated at 4-position (H-3 and H-5 at 6.69 and 7.43 δ respectively) using one molar equivalent of NBS (Scheme 3).

Scheme 3



The 4-bromo-3',5'-dichloro-2-(2'-methoxybenzoyl) pyrrole **12**, was chlorinated at 5-position (H-3 at 6.81 δ) with one molar equivalent of NCS, to give **13** which was in turn brominated at 3-position with NBS. The subsequent demethylation of compound **14**, so obtained, gave **4**.

The structures of all the newly prepared compounds were confirmed by analytical and spectroscopic data.

According to the procedures just described, the already known pyrrolomycins F_1, F_{2a}, F_{2b}, F_3 and D were prepared and their antibacterial activity toward *S. aureus* ATCC 25923 was compared with that of new synthesized derivatives. Vancomicin, penta-bromo derivative **1**, PM-C and PM-D were also used as standards.

The results of antibacterial screening, expressed as minimum inhibitory concentration (*mic*), are reported in Table 1.

Table 1

Antibacterial Activity (*mic*/μg per ml)

Compound	*S. aureus* ATCC 25923
Pyrrolomycin F_1	0.02
Pyrrolomycin F_{2a}	0.005
Pyrrolomycin F_{2b}	0.01
Pyrrolomycin F_3	0.02
Pyrrolomycin C	0.18
Pyrrolomycin D	≤ 0.001
Vancomycin	1.0
1	0.005
2	≤ 0.001
3	≤ 0.001
4	≤ 0.001
5	≤ 0.001

CONCLUSIONS

The results of antibacterial screening showed that the introduction of two chloro atoms at 3' and 5' positions of phenolic ring carried to an increase of activity. All new pyrrolomycins analogs synthesized were in fact more active than pyrrolomycin $F_{2a,}$ the most active member of PM-F, to inhibit the staphylococcal growth. The *in vitro* activity against *S. aureus* ATCC 25923 of new compounds is comparable to that of PM-D that, against this strain, showed more potent activity than PM-F components. Moreover, we are going to test the activity of new compounds against a wide panel of Gram-positive strains and against preformed biofilms of staphylococci.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli micro melting point apparatus and are uncorrected. The ir spectra were recorded at room temperature in Nujol mulls with a Perkin Elmer Infrared 137 E spectrometer. The ^{1}H-nmr spectra were recorded at room temperature on a Bruker SF 250 spectrometer in DMSO-d_6, unless otherwise specified, using tetramethylsilane as the internal standard. Microanalyses (C, H, N) were carried out with Elemental Vario EL III apparatus and were in agreement with theoretical values ± 0.4%.

Chromatographic separations were carried out on columns packed with Macherey Nagel Kieselgel 60 (70-230 mesh ASTM). All reactions were monitored by tlc on precoated aluminium sheets 20 x 20 (0.2 mm Kieselgel 60 G F254, Merck) and C-18 reverse phase (RP-18 F254, Merk) using UV light at 254 nm for visualization. All reagents and solvents were from Aldrich, Fluka, Merk or J.T.Baker.

All the compounds were tested for their *in vitro* growth inhibitory activity against *Staphylococcus aureus* ATCC 25923. PM-D and vancomycin were used for comparative purposes and quality control of the methods. MICs against bacterial strains were determined using the broth dilution micro-method as described [6].

3',5'-Dichloro-2-(2'-methoxybenzoyl)pyrrole (6). 4.42 g (20 mmoles) of 3,5-dichloro-2-methoxybenzoic acid, commercially available, and 15 ml (24.50 g, 200 mmoles) of thionyl chloride were refluxed until the generation of hydrochloric acid ceased (approximately 8 hours). The excess thionyl chloride was removed under vacuum and the crude 3,5-dichloro-2-methoxybenzoyl chloride, dissolved in 100 ml of anhydrous diethyl ether, was added, dropwise under nitrogen atmosphere, to a stirred solution of pyrrylmagnesium bromide (20 mmoles in 150 ml of anhydrous diethyl ether). The reaction mixture was refluxed for 0.5 hours, cooled to room temperature, then quenched with 10% sulphuric acid (100 ml). After stirring for 1 hour, the ethereal layer was separated and the aqueous phase extracted with diethyl ether (2 x 100 ml). The combined extracts were washed with water (2 x 50 ml), dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography using 85/15 *(v/v)* cyclohexane/ethyl acetate mixture as eluent to give 3',5'-dichloro-2-(2'-methoxy-benzoyl)pyrrole (**6**) (2.75 g, 51% yield), mp 114-115°C (from ethanol) [2]; ^{1}H nmr: δ 3.72 (s, 3H, CH_3), 6.23 (br q, 1H, H-4), 6.56 (br q, 1H, H-3), 7.27 (br q, 1H, H-5), 7.46 (d, 1H, J = 2.3 Hz, H-6'), 7.80 (d, 1H, J = 2.3 Hz, H-4'), 12.23 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3287 (NH), 1636 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_9Cl_2NO_2$: C, 53.36% (53.60%); H, 3.36% (3.24%); N, 5.19% (4.98%).

3,4,5-Tribromo-3',5'-dichloro-2-(2'-methoxybenzoyl)pyrrole (7). To a solution of 2.70 g (10.0 mmoles) of **6** in acetonitrile (50 ml), 5.34 g (30.0 mmoles) of solid NBS were added, portion-wise under stirring. After 24 hours the reaction mixture was evaporated under reduced pressure and the residue was partitioned between water (100 ml) and diethylether (100 ml) and, subsequently, extracted twice with diethyl ether (100 ml). The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated. The crude product was crystallized from acetonitrile to give **7** (3.45 g, 68% yield) as white needles, m.p. 209-210°C; ^{1}H nmr: δ 3.70 (s, 3H, CH_3), 7.53 (d, 1H, J = 2.5 Hz, H-6'), 7.64 (d, 1H, J = 2.5 Hz, H-4'), 13.70 (br s, 1H, exchangeable with D2O, NH); ir: ν 3204 (NH), 1625 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_6Br_3Cl_2NO_2$: C, 28.44% (28.65%); H, 1.19% 1.27%); N, 2.76% (2.64%).

4,3',5'-Trichloro-2-(2'-methoxybenzoyl)pyrrole (8). To a solution of 2.70 g (10.0 mmoles) of **6** in 50 ml of acetonitrile, 1.50 g (11.0 mmoles) of solid NCS were added under stirring. After 24 hours the mixture was evaporated. The residue was suspended in 100 ml of water then extracted with diethyl ether (3 x 50 ml). The combined extracts, dried over anhydrous sodium sulfate, were evaporated and the residue was purified by column chromatography, using 85/15 (*v/v*) cyclohexane/ethyl acetate as eluent. 1.85g of **8** were obtained (yield 61%) as white crystals from ethanol, m.p.115-116°C; ^{1}H nmr: δ 3.74 (s, 3H, CH_3), 6.64 (d, 1H, J = 1.5 Hz, H-3), 7.42 (d, 1H, J = 1.5 Hz, H-5), 7.50 (d, 1H, J = 2.5 Hz, H-6'), 7.82 (d, 1H, J = 2.5 Hz, H-4'), 12.54 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3253 (NH), 1629 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_8Cl_3NO_2$: C, 47.32% (47.49%); H, 2.65% (2.73%); N, 4.60% (4.70%).

3,5-Dibromo-4,3',5'-trichloro-2-(2'-methoxybenzoyl)pyrrole (10). To a solution of **8** (1.52 g, 5.0 mmoles) in 50 ml of acetonitrile, a solution of NBS (1.78 g, 10.0 mmoles) in 50 ml of acetonitrile was added drop by drop under stirring. After 12 hours, the reaction mixture was evaporated and the residue was purified as previously described for the preparation of **8**. The crude product was crystallized from ethanol to give **10** (1.88 g, 81% yield) as white crystals, m.p.175-176°C. ^{1}H nmr: δ 3.70 (s, 3H, CH_3), 7.53 (d, 1H, J = 2.5 Hz, H-6'), 7.84 (d, 1H, J = 2.5 Hz, H-4'), 13.68 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3213 (NH), 1618 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_6Br_2Cl_3NO_2$: C, 31.17% (31.29%); H, 1.31% (1.36%); N, 3.03% (2.98%).

4,5,3',5'-Tetrachloro-2-(2'-methoxybenzoyl)pyrrole (9). To a stirred solution of 2.70 g (10.0 mmoles) of compound **6** in acetonitrile (100 ml), 2.70 g (20.0 mmoles) of solid NCS were added. After 24 hours the mixture was evaporated. The residue was partitioned between water (100 ml) and diethyl ether (100 ml). The aqueous layer was separated and extracted with diethyl ether (2 x 50 ml). The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated. The crude product was crystallized from acetonitrile to give **9** (2.30 g, 68% yield) as white crystals, m.p. 139-140°C; ^{1}H nmr: δ 3.70 (s, 3H, CH_3), 6.84 (s, 1H, H-3),7.57 (d, 1H, J = 2.5 Hz, H-6'), 7.88 (d, 1H, J = 2.5 Hz, H-4'), 13.57 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3219 (NH), 1635 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_7Cl_4NO_2$: C, 42.52% (42.74%); H, 2.08% (2.21%); N, 4.13% (4.33%).

3-Bromo-4,5,3',5'-tetrachloro-2-(2'-methoxybenzoyl)pyrrole (11). A solution of **9** (1.70 g, 5.0 mmoles) and NBS (1.78 g, 5.0 mmoles) in 50 ml of acetonitrile was allowed to stand at room temperature. After 24 hours, the reaction mixture was evaporated and the residue was purified as described previously for the preparation of **7**. The crude product was crystallized from acetonitrile to give **11** (1.55 g, 74% yield), m.p.193-194°C; ^{1}H nmr: δ 3.77 (s, 3H, CH_3), 7.58 (d, 1H, J = 2.6 Hz, H-6'), 7.87 (d, 1H, J = 2.6 Hz, H-4'), 13.86 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3202 (NH), 1626 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_6BrCl_4NO_2$: C, 34.49% (34.76%); H, 1.45% (1.58%); N, 3.35% (3.21%).

4-Bromo-3',5'-dichloro-2-(2'-methoxybenzoyl)pyrrole (12). To a stirred solution of **6** (2.70 g, 10.0 mmoles) in acetonitrile (100 ml), a solution of NBS (1.96 g, 11.0 mmoles, in 30 ml of acetonitrile) was added drop by drop.

After 6 hours the solvent was evaporated and the residue, obtained as previously described for the preparation of **8**, was purified by column chromatography, using cyclohexane/ethyl acetate 85/15 (*v/v*) as eluent. **12** was obtained as white crystals from ethanol, m.p. 120-121°C (2.48 g, 71% yield); ^{1}H nmr: δ 3.72 (s, 3H, CH_3), 6.69 (s, 1H, H-3), 7.43 (s, 1H, H-5), 7.49 (d, 1H, J = 2.5 Hz, H-6'), 7.81 (d, 1H, J = 2.5 Hz, H-4'), 12.58 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3250 (NH), 1630 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_8BrCl_2NO_2$: C, 41.30% (41.61%); H, 2.31% (2.48%); N, 4.01% (4.34%).

4-Bromo-5,3',5'-trichloro-2-(2'-methoxybenzoyl)pyrrole (13). This compound was synthesized from **12** (1.75 g, 5.0 mmoles) and NCS (0.68 g, 50.0 mmoles) in 2.5 ml of acetonitrile with the same procedure just described for the preparation of **8**. The crude product was chromatographed using cyclohexane/ethyl acetate 90/10 (*v/v*) as eluent. 1.55 g of white crystals, m.p.162-163°C from ethanol (81% yield) were obtained; ^{1}H nmr: δ 3.72 (s, 3H, CH_3), 6.81 (s, 1H, H-3), 7.51 (d, 1H, J = 2.5 Hz, H-6'), 7.82 (d, 1H, J = 2.5 Hz, H-4'), 13.57 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3188 (NH), 1616 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_7BrCl_3NO_2$: C, 37.59% (37.68%); H, 1.84% (1.87%); N, 3.65% (3.57%).

3,4-Dibromo-5,3',5'-trichloro-2-(2'-methoxybenzoyl)pyrrole (14). A solution of **13** (1.15 g, 30.0 mmoles) and NBS (0.54 g, 30 mmoles) was allowed to stand at room temperature. After 12 hours, the reaction mixture was evaporated and the residue was

purified as described previously for the preparation of **7**. Compound **14** was obtained as white crystals from acetonitrile, m.p.200-201°C (1.0 g, 73% yield). ^{1}H nmr: δ 3.70 (s, 3H, CH_3), 7.52 (d, 1H, J = 2.6 Hz, H-6'), 7.62 (d, 1H, J = 2.6 Hz, H-4'), 13.62 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3192 (NH), 1626 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{12}H_6Br_2Cl_3NO_2$: C, 31.17% (31.32%); H, 1.31% (1.40%); N, 3.03% (2.97%).

General procedure for the demethylation of O-methyl derivatives. In a typical experiment, to a stirred suspension of 30 mmoles of aluminum chloride in 20 ml of dichloromethane in ice bath, were added 3.0 mmoles of O-methyl derivative in 20 ml of the same solvent. The reaction mixture was stirred for 12 hours at room temperature, decomposed with a solution of ice / 5% sulfuric acid, then extracted with diethyl ether (2 x 100 ml). The combined extracts were dried over anhydrous sodium sulfate and evaporated. The crude compounds, obtained in almost quantitative yields, were crystallized from ethanol.

3,4,5-Tribromo-3',5'-dichloro-2-(2'-hydroxybenzoyl)pyrrole (2). This compound was obtained as yellow needles, mp 204-205°C; ^{1}H nmr: δ 7.35 (d, 1H, J = 2.4 Hz, H-6'), 7.68 (d, 1H, J = 2.4 Hz, H-4'), 10.25 (br s, 1H, exchangeable with D_2O, OH), 13.60 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3263 (NH), 1571 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{11}H_4Br_3Cl_2NO_2$: C, 26.81% (26.87%); H, 0.82% (0.84%); N, 2.84% (2.68%).

3,5-Dibromo-4,3',5'-trichloro-2-(2'-hydroxybenzoyl)pyrrole (3). This compound was obtained as yellow needles, mp 200-201°C; ^{1}H nmr: δ 7.35 (d, 1H, J = 2.4 Hz, H-6'), 7.68 (d, 1H, J = 2.4 Hz, H-4'), 10.27 (br s, 1H, exchangeable with D_2O, OH), 13.60 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3266 (NH), 1570 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{11}H_4Br_2Cl_3NO_2$: C, 29.47% (29.59%); H, 0.90% (0.96%); N, 3.12% (3.04%).

3,4-Dibromo-5,3',5'-trichloro-2-(2'-hydroxybenzoyl)pyrrole (4). This compound was obtained as yellow needles, mp 209-211°C; ^{1}H nmr: δ 7.36 (d, 1H, J = 2.5 Hz, H-6'), 7.69 (d, 1H, J = 2.5 Hz, H-4'), 10.25 (br s, 1H, exchangeable with D_2O, OH), 13.72 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3270 (NH), 1611 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{11}H_4Br_2Cl_3NO_2$: C, 29.47% (29.64%); H, 0.90% (0.95%); N, 3.12% (2.99%).

3-Bromo-4,5,3',5'-tetrachloro-2-(2'-hydroxybenzoyl)pyrrole (5). This compound was obtained as yellow needles, mp 168-169°C; ^{1}H nmr: δ 7.37 (d, 1H, J = 2.5 Hz, H-6'), 7.69 (d, 1H, J = 2.5 Hz, H-4'), 10.32 (br s, 1H, exchangeable with D_2O, OH), 13.73 (br s, 1H, exchangeable with D_2O, NH); ir: ν 3272 (NH), 1578 (CO) cm^{-1}. *Anal.* Calc. (Found) for $C_{11}H_4BrCl_4NO_2$: C, 32.71% (32.60%); H, 1.00% (0.95%); N, 3.47% (3.32%).

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