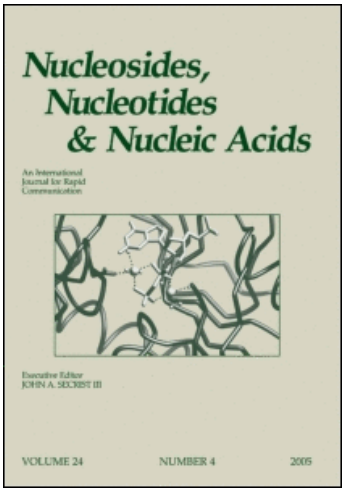

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Synthesis and Biological Activity of 5-Fluorotubercidin[†]

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ABSTRACT

The electrophilic fluorination of 4-chloropyrrolo[2,3-*d*]pyrimidine (**1**) was studied culminating a 59% conversion of compound **1** to 4-chloro-5-fluoropyrrolo[2,3-*d*]-pyrimidine (**2**) using Selectfluor. This transformation proceeded via the 4-chloro-5,6-dihydro-5-fluoro-6-hydroxypyrrolo[2,3-*d*]pyrimidine (**3**) in a 9:1 trans:cis ratio. The trans isomer of compound **3** was studied by ^{1}H NMR and ^{19}F NMR, and the 5-H tautomer (**4**) was observed as another intermediate. A modified Vorbruggen procedure of compound **2** and tetra-O-acetylribose gave 4-chloro-5-fluoro-7-(2,3,5,-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**6**) in a 65% yield. Treatment of compound **6** with ammonia (*l*) in dioxane gave 5-fluorotubercidin (**7**). No antibacterial activity was observed. An MTT assay (Promega) against Huh-7 liver cells, normal mouse spleen cells stimulated with Con A (a T-cell mitogen), and normal mouse spleen stimulated with LPS (a B-cell mitogen) showed no significant toxicity. Increased activity of **7** over tubercidin was observed against L-1210 cells and toxicity in fibroblast cells was reduced.

Key Words: 5-fluorotubercidin; MTT assay; LPS.

[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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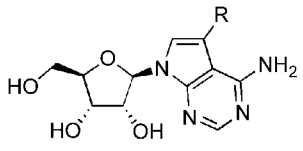
INTRODUCTION

Pyrrolo[2,3-*d*]pyrimidine nucleosides have received considerable interest as biologically active molecules.[1,2] In particular, extensive synthetic and biological studies[3] have been carried out on the naturally occurring tubercidin and its 5-substituted derivatives, toyocamycin and sangivamycin (Figure 1). Tubercidin is closely related in structure to adenosine and is rapidly converted to its 5′-monophosphate by adenosine kinase and subsequently to the higher phosphates.[4] Not surprisingly then, a vast array of biological activities have been reported for tubercidin and its derivatives which include; in vitro cytotoxicity in mammalian cell strains,[5] significant in vivo antitumor activity,[6,7] inhibition of RNA and DNA virus replication[8–11] and the inhibition of the growth of a variety of microorganisms.[12] Despite the reported antitumor activity of tubercidin, its toxicity has precluded its use in the clinic.[13] Subsequently, considerable effort has been expended in the search for derivatives with a greater selectivity in their biological response. For example, the related halogenated analogs such as 5-iodotubercidin, 5-bromotubercidin and 5-chlorotubercidin have been prepared (Figure 1), and were found to have cytotoxic effects and antiviral activities.[13–17] However, the 5-fluoro analog of tubercidin, or any pyrrolo[2,3-*d*]-pyrimidine, has never been reported in the literature, perhaps due to the synthetic difficulties associated with direct electrophilic fluorinations. The present study describes the one-pot electrophilic fluorination of a pyrrolo[2,3-*d*]pyrimidine culminating in the synthesis of 5-fluorotubercidin and its subsequent evaluation in a variety of cell lines for antiproliferative activity.

RESULTS AND DISCUSSION

In general 5-halogenated pyrrolo[2,3-*d*]pyrimidines nucleosides can be prepared by a direct halogenation of an appropriately protected tubercidin. For example, direct bromination of tubercidin with NBS in DMF gives the 5-bromotubercidin, while the use of NBS in a KOAc-buffered medium gives 6-bromotubercidin.[18] In a similar fashion, the 5-iodo and 5-chloro analogs can also be prepared. However, we found that the direct fluorination of pyrrolo[2,3-*d*]pyrimidine nucleosides resulted in no reaction or cleavage of the glycosidic bond, as determined with a variety of electrophilic fluorinating conditions (vida infra).



Tubercidin; R = H
Toyocamycin; R = CN
Sangivamycin; R = $CONH_2$
5-Iodotubercidin; R = I
5-Chlorotubercidin; R= Cl
5-Bromotubercidin; R = Br

Figure 1. Several 5-substituted pyrrolo[2,3-*d*]pyrimidines.

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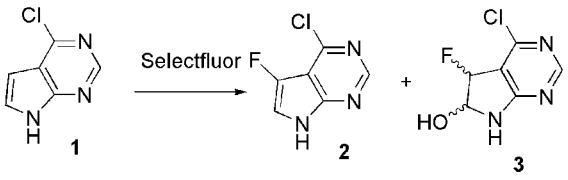
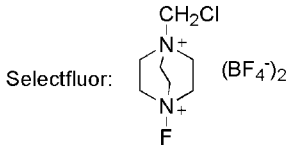
Due to this difficulty, we determined to first prepare the 5-fluoropyrrolo[2,3-*d*]pyrimidine heterocycle followed by coupling to an appropriately substituted ribose. We chose 4-chloropyrrolo[2,3-*d*]pyrimidine (**1**) as our starting material, as we believed that a 4-amino group would interfere with the electrophilic fluorination process. Generally electrophilic fluorination of heterocycles is carried out using the highly reactive fluorine gas or acetyl hypofluorites.[19] We, however, had hoped that a more mild fluorination could be carried out directly on the electron-rich 5-position of pyrrolo[2,3-*d*]pyrimidine **1** using commercially available reagents, although such a reaction was unprecedented. A variety of conditions and electrophilic fluorinating reagents[20,21] were tested (NFSI, Selectfluor[22] in acetonitrile, DMF and dichloromethane at various temperatures), Selectfluor/acetonitrile proved to be the most promising.

Treatment of compound **1** with Selectfluor in wet acetonitrile for 4 h at room temperature, gave compound **3** as a (9:1) mixture of diastereoisomers as the main products (Scheme 1). Alternatively, a similar reaction in scrupulously dried acetonitrile in the presence of activated molecular sieves gave product **2**; however, the reaction was very sluggish and we never achieved greater than 33% conversion. Additionally, we found it laborious to achieve the anhydrous conditions required to consistently prevent the formation of compound **3**. We then attempted to affect a one-pot hydrofluorination–elimination by adding TFA or AcOH, as both of these acids had been successfully used in pyrrolo[2,3-*d*]pyrimidine 5,6-dehydrations.[23] However, there was no reaction with either acid at room temperature. Increasing the reaction temperature to 70–80°C for 30 min in the presence of TFA resulted in a mixture of starting material



Solvent	Additions	Condition	Result
DCM	none	23°C / 14 h	no reaction
DMF	none	23°C / 14 h	no reaction
CH_3CN	H_2O	23°C / 4 h	**1** + **3** (major)
CH_3CN	3Å MS	23°C / 14 h	**1** + **2**
CH_3CN	AcOH	70°C / 14 h	**2**

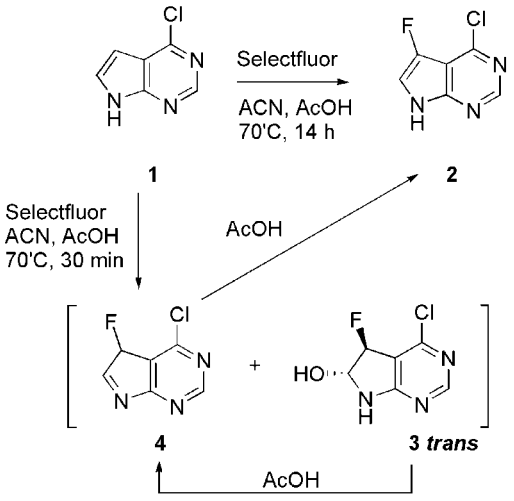


Scheme 1. Electrophilic fluorination of 5-chloropyrrolo[2,3-*d*]pyrimidine.

and both products **2** and **3**. Prolonged heating resulted in decomposition. In contrast, the dehydration was successful using AcOH at elevated temperature, as treatment of **1** with Selectfluor in the presence of AcOH at 70–80°C affected smooth conversion to the desired compound **2**. Furthermore, this process was amenable to scale-up, as compound **2** was obtained in a 59% yield on a 5 gram reaction.

It is of interest to note that after about 30 min at 70°C, most of starting material **1** was consumed and one LC/MS peak (retention time 2.6 min) corresponding to the mass of compound **2** was observed. After 2 h, an additional peak (retention time 2.7 min) was formed having a mass spectrum identical to that of the peak at 2.6 min. After running the reaction overnight, only the peak at 2.7 min remained. We had speculated that the 5-H tautomer **4** (Scheme 2) might be the peak observed at 2.6 min, and is formed as an intermediate between compounds **2** and **3**. This tautomer is unprecedented in the pyrrolo[2,3-*d*]pyrimidine ring system; however, an analogous tautomer has been reported for indoles.[24]

In order to more fully explore our hypothesis, the major diastereomer (9:1 ratio) of compound **3** was isolated by silica gel chromatography. The structure was determined to have the hydroxy and fluoro groups in a *trans* orientation (**3 *trans***) since the coupling constant (close to 0 Hz) of the 5,6-hydrogens for the major isomer is less than the one for minor isomer (5.8 Hz). The dehydration of compound **3 *trans*** was investigated by ^{1}H NMR in presence of AcOD–d_3 in Acetonitrile–d_3 at 70°C (Figure 2) and by ^{19}F NMR (not shown). It can be clearly observed that after heating for 2.5 h at 70°C, tautomer **4** is present as a significant product (together with small amount of tautomer **2** and compound **3 *trans***). After further heating, compound **2** was observed as the major product. This confirms our hypothesis that **4** is an intermediate between compound **3 *trans*** and **2**; however, we cannot conclusively rule out that some portion of **3 *trans*** is converted directly to **2**. Also we do not know the fate of **3 *cis***; however, it seems that a direct **3 *cis*** to **2** conversion is more likely, as the H-5 proton and hydroxy group are anti-periplanar.



Scheme 2. Mechanism of electrophilic fluorination.

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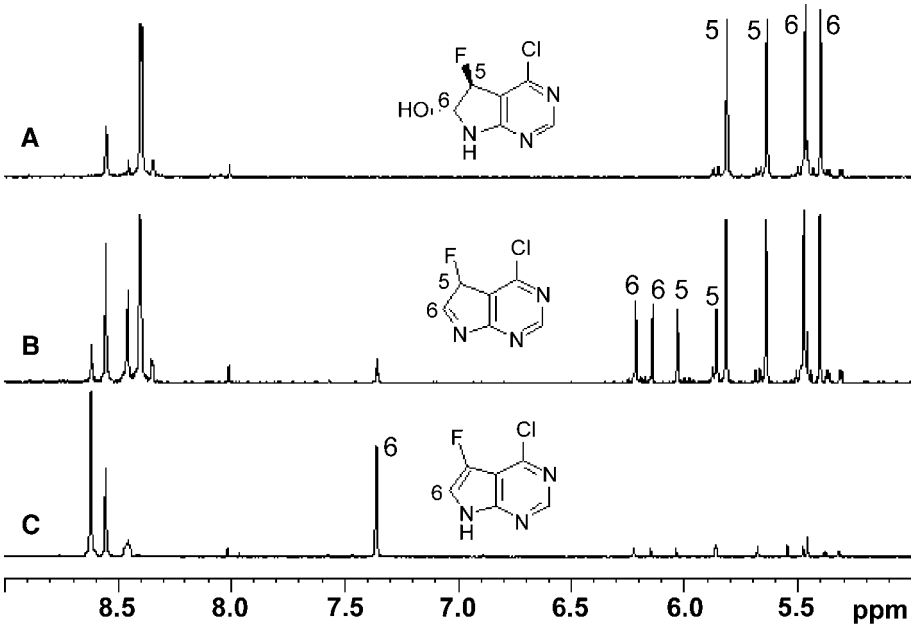
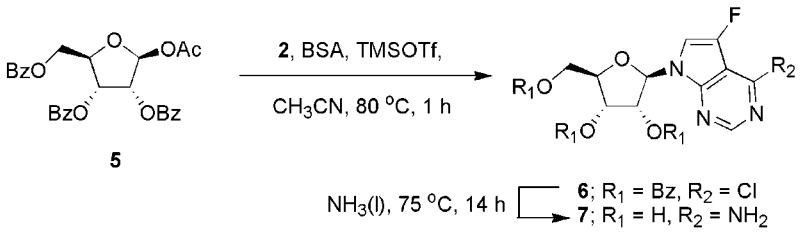


Figure 2. ^{1}H NMR spectra of dehydration. A) 25°C, 5 min; B) 70°C, 2.5 h; C) 70°C, 14 h.

With 4-chloro-5-fluoropyrrolo[2,3-*d*]pyrimidine (**2**) in hand we set out to prepare 5-fluorotubercidin (**7**). Our first attempts using sodium salt glycosylation[25,26] were unsuccessful. This is potentially due to the electron withdrawing effects of the 5-fluorine substitution, which are likely to stabilize the pyrrolo[2,3-*d*]pyrimidine anion, and thereby reduce its nucleophilicity. Subsequently we used a modified Vorbruggen procedure[27,28] and achieved a successful conversion to the 4-chloro-5-fluoro pyrrolo[2,3-*d*]pyrimidine nucleoside **6** in a 65% yield. Treatment of compound **6** with ammonia (l) in dioxane gave the target compound **7** (Scheme 3).

5-Fluorotubercidin, along with 5-iodotubercidin and tubercidin, were tested for their ability to inhibit bacterial trancription/translation as well as antibacterial activity versus *E. coli* and *S. aureus*. No antibacterial activity was observed at concentrations of up to 100 uM. Additionally, evaluations of cellular cytotoxicity were carried out in an MTT assay (Promega) against Huh-7 liver cells, normal mouse spleen cells



Scheme 3. Synthesis of 5-fluorotubercidin.

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stimulated with Con A (a T-cell mitogen), normal mouse spleen stimulated with LPS (a B-cell mitogen), L-1210 lymphoblastoid cells and fibroblast cells. We found that all compounds were non toxic (IC50 > 200 uM) for Huh-7 liver epithelial cells, normal mouse spleen cells stimulated with Con A (a T-cell mitogen), and normal mouse spleen stimulated with LPS (a B-cell mitogen). However, activity was observed against L-1210 cells (> 10 μM for 5-iodotubercidin, 2–3 μM for tubercidin and 1 μM for 5-fluorotubercidin). Interestingly, toxicity in fibroblast cells was observed at concentrations above 12 μM for tubercidin, while no toxicity was observed for 5-fluorotubercidin in concentration of up to 200 μM. This indicates that 5-fluorotubercidin may be less cytotoxic than its parent tubercidin, which could translate to a greater therapeutic index for antitumor indications if the antitumor activity of tubercidin is maintained. Further studies to more rigorously assess the antitumor potential of 5-fluortubercidin are ongoing.

EXPERIMENTAL

General. NMR spectra were recorded on a 300 M Hz Bruker. Silica gel 60 from EM Science was used for purification. Compound **1** was purchased from Toronto Research Chemicals. Selectfluor was purchased from Aldrich.

Coupled bacterial transcription/translation assay. The DNA template, pBest Luc™ (Promega), is a plasmid containing a reporter gene for firefly luciferase fused to a strong *tac* promoter and ribosome binding site. Messenger RNA from 1 μg pBestLuc was transcribed and translated in *E. coli* S30 bacterial extract in the presence or absence of test compound. Compounds were tested in a black 96 well microtiter plate with an assay volume of 35 μL. Each test well contained: 5 μL test compound, 13 μL S30 premix (Promega), 4 μL 10 × complete amino acid mix (1 mM each), 5 μL *E. coli* S30 extract and 8 μL of 0.125 μg/μL pBest Luc™. The transcription/translation reaction was incubated for 35 minutes at 37°C followed by detection of functional luciferase with the additon of 30 μL LucLite™ (Packard). Light output was quantitated on a Packard TopCount.

Minimum inhibitory concentrations (MICs). The assays are carried out in 150 μL volume in duplicate in 96-well clear flat-bottom plates. The bacterial suspension from an overnight culture growth in appropriate medium is added to a solution of test compound in 2.5% DMSO in water. Final bacterial inoculum is approximately 10^2–10^3 CFU/well. The percentage growth of the bacteria in test wells relative to that observed for a control wells containing no compound is determined by measuring absorbance at 595 nm (A_{595}) after 20–24 h at 37°C. The MIC is determined as a range of concentration where complete inhibition of growth is observed at the higher concentration and bacterial cells are viable at the lower concentration. Both ampicillin and tetracycline are used as antibiotic positive controls in each screening assay for *E. coli* (ATCC 25922) and *S. aureus* (ATCC13709).

MTT assays. MTT proliferation assays were purchased as kits from Promega and were run according to the manufacturers protocol.

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4-Chloro-5-fluoro-7H-pyrrolo[2,3-*d*]pyrimidine (2). 4-Chloro-7*H*-pyrrolopyrimidine **1** (5 g, 32.7 mmol) and Selectfluor (17.35 g, 49 mmol) were placed in a r.b. flask, followed by the addition of dry acetonitrile (250 mL) and AcOH (50 mL). The solution was then heated at 70°C for 14 h under N_2. After cooling to rt, the solvent was removed in vacuo and co-evaporated with toluene (50 mL × 2). The solid was dissolved in a mixture of DCM:EtOAc (1:1) and filtered through a pad of silica gel which was thoroughly washed. The combined washings were evaporated. And the crude product was then subjected to column chromatography with DCM:EtOAc (4:1) to give 3.3 g (59% yield) of **2** as a white solid. ^{1}H NMR (DMSO−d_6) δ 7.73 (s, 1H), 8.64 (s, 1H), 12.5 (br s, 1H); ^{13}C NMR (DMSO−d_6) δ 105.3 (d, J = 14.3 Hz), 111.0 (d, J = 25.5 Hz), 139.6 (d, J = 244.5 Hz), 146.7 (d, J = 1.5 Hz), 148.5 (d, J = 3.8 Hz), 151.0; ^{19}F NMR (DMSO−d_6) δ − 170.7 (d, J = 1.6 Hz): MS calcd for $C_6H_3ClFN_3$ (M + H): 172.0, observed: 172.0.

***Trans*-4-Chloro-5-fluoro-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-6-ol (3 *Trans*).** 4-Chloro-7*H*-pyrrolopyrimidine **1** (10 mg, 0.065 mmol) and Selectfluor (115 mg, 0.33 mmol) were placed in a r.b. flask, followed by the addition of acetonitrile (1 mL) and two drops of water. The mixture was then stirred at rt for 4 h. After evaporation, the crude product was purified by column chromatography using DCM:MeOH (98:2) to give 5 mg of a brownish solid. ^{1}H NMR (CD_3CN) δ 8.19 (d, 1H, J = 1.9 Hz), 5.51 (d, 1H, J = 53.9 Hz), 5.19 (d, 1H, J = 21.9 Hz); ^{19}F NMR (CD_3CN) δ − 177.5 (ddd, J = 1.9, 21.6, 53.6 Hz): MS calcd for $C_6H_5ClFN_3O$ (M + H): 190.0, observed: 190.1.

4-Chloro-5-fluoro-7-(2,3,5,-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (6). *N*,*O*-Bis(trimethylsilyl)acetamide (BSA, 0.16 mL, 0.64 mmol) was added to a stirred suspension of 4-chloro-5-fluoro-7H-pyrrolo[2,3-*d*]pyrimidine (0.1 g, 0.58 mmol) in dry acetonitrile (4 mL). After stirring at rt for 10 min, 1-*O*-acetyl-2,3,5,-tri-*O*-benzoyl-β-D-ribofuranose (0.322 g, 0.64 mmol) was added, followed by the addition of trimethylsily trifluoromethanesulfonate (0.115 mL, 0.64 mmol). The reaction was stirred at rt for 15 min after which it was transferred to a preheated oil bath at 80°C. After stirring for 1 h at 80°C, the reaction was cooled to rt and diluted with EtOAc (25 mL). The organic phase was then sequentially washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated to provide the crude nucleoside. Purification by column chromatography (SiO_2, 10−25% EtOAc in hexanes) provided protected nucleoside (**6**) as a white foam (232 mg, 65%). ^{1}H NMR ($CDCl_3$) δ: 8.63 (s, 1H), 8.11 (d, 2H, J = 7.1 Hz), 8.01 (d, 2H, J = 7.1 Hz), 7.91 (d, 2H, J = 7.1 Hz), 7.65−7.33 (m, 9H), 7.17 (d, 1H, J = 2.6 Hz), 6.69 (dd, 1H J = 6.2, 1.1 Hz), 6.09 (m, 2H), 4.87 (dd, 1H, J = 12.1, 3.0 Hz), 4.78 (dd, 1H, J = 7.2, 3.7 Hz), 4.67 (dd, 1H, J = 12.1, 3.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.1, 165.4, 165.1, 151.9, 151.1, 147.1, 143.7−140.3 (C−F-coupling), 133.8, 133.7, 133.6, 129.8, 129.8, 129.7, 129.3, 128.7, 128.7, 128.6, 128.5, 128.4, 109.5−109.1 (C−C−F-coupling), 108.3−108.1 (C−C−F-coupling), 86.3, 80.6, 73.9, 71.4, 63.6. MS (M + H): 616.1, observed: 616.1.

5-Fluorotuberidicin (7). 4-Chloro-5-fluoro-7-(2,3,5,-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine **6** (230 mg, 0.42 mmol) was dissolved in dioxane (3 mL) and liquid ammonia (8−10 mL). The reaction was sealed in a steel bomb and

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heated in an oil bath at 75°C for 14 h. The reaction was then cooled and the solvent evaporated to provide the crude nucleoside. Purification by column chromatography (SiO_2, 5–15% MeOH in $CHCl_3$) provided 5-fluorotubericidin (**7**) as a white solid (77 mg, 73%). Mp 221–222°C; ^{1}H NMR (DMSO–d_6) δ: 8.06 (s, 1H), 7.34 (d, 1H, J = 2 Hz), 6.99 (s, br, 2H), 6.06 (dd, 1H, J = 6.1, 1.7 Hz), 5.28 (d, 1H, J = 6.4 Hz), 5.10 (m, 2H), 4.31 (m, 1H), 4.05 (m, 1H), 3.85 (m, 1H), 3.7–3.14 (m, 2H). ^{13}C NMR (DMSO–d_6) δ: 156.3, 152.6, 146.7, 144.7–141.4 (C–F coupling), 105.0–104.6 (C–C–F coupling), 93.1–92.9 (C–C–F coupling), 86.4, 84.9, 73.7, 70.4, 61.5. ^{19}F NMR (DMSO–d_6) δ: − 167.73. MS $(M + H)^+$: 285.1, observed: 284.9.

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