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THIAZOLO[5,4-*b*]ACRIDINES AND THIAZOLO[4,5-*b*]ACRIDINES: PROBABLE PHARMACOPHORES OF ANTIVIRAL AND ANTI-TUMOR MARINE ALKALOIDS

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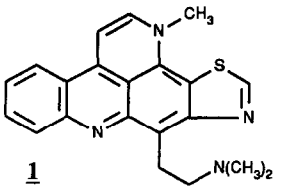
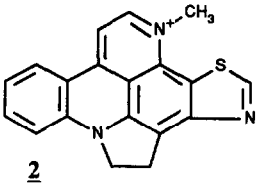
SUMMARY: Structural simplification of pentacyclic and hexacyclic antiviral and anti-tumor acridine alkaloids such as dercitin, cyclodercitin and kuanoniamine led to the identification of the thiazolo[5,4-*b*]acridine or the isomeric thiazolo[4,5-*b*]acridine nucleus as the putative pharmacophore. Synthetic approaches towards these tetracyclic ring systems and regiochemistry of the thiazole ring in cyclodehydration reactions are discussed.

Polycyclic fused ring alkaloids have been isolated from a variety of marine sources including tunicates, sponges and molluscs. Many among this class of compounds have been reported to have cytotoxic, anti-tumor and antiviral activities (1). Of these, the pentacyclic alkaloid dercitin **1** isolated from the sponge *Dercitus* has a range of activity against tumor cell lines and RNA/DNA viruses (2). Its hexacyclic analog, cyclodercitin **2** is active against P388 leukemia cell lines (3). These compounds have a common pyrido[4,3,2-*mn*]thiazolo[5,4-*b*]acridine nucleus. Kuanoniamine A, **3** is a structurally similar pentacyclic alkaloid isolated from a marine mollusc *Chelynotus semperi* (4); this compound has cytotoxicity against a KB (human nasopharyngeal cancer) cell line and incorporates a thiazolo[4,5-*b*]acridine structure in which the orientation of the thiazole ring is isomeric to that in **1** and **2**.



1



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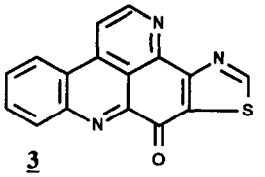

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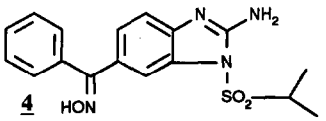
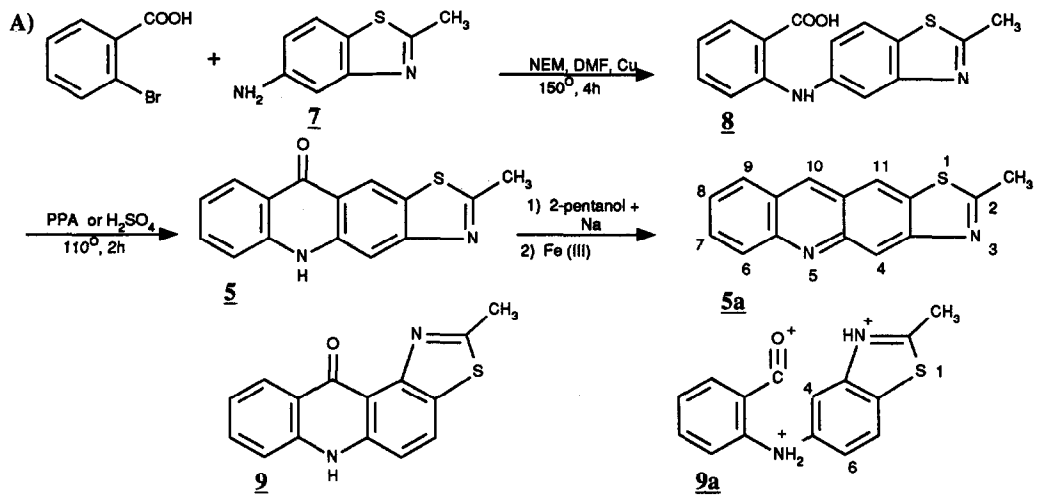


4

The synthetic antiviral drug enviroxime **4**, which has a broad spectrum of activity against picornaviruses (5) also shows some structural features in common with the natural products **1** - **3**, being a non-bridged analog in which an imidazole ring replaces the thiazole.

Due to the striking biological activities of the marine alkaloids and with a view towards identifying the pharmacophore within their structures, it was of interest to prepare truncated analogs of **1**, **2** and **3** in which the non-linearly fused pyrido[4,3,2-*mn*] ring was deleted. Accordingly, the tetracyclic thiazolo[5,4-*b*]acridines and isomeric thiazolo[4,5-*b*]acridines **5** and **6** were prepared (Schemes A and B) using extensions of synthetic methodology used to prepare tricyclic acridines (6).



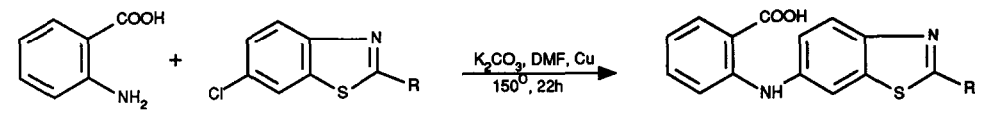
Representative examples are provided by the synthesis of analogs **5**, **5a**, **6a** and **6b**. When 2-bromobenzoic acid was condensed with 5-amino-2-methylbenzothiazole in a Type I Ullmann-Jourdan reaction a 67% isolated yield of *N*-(2-methyl-benzothiazol-5-yl)anthranilic acid **8** was obtained. Polyphosphoric acid cyclodehydration of **8** provided in near quantitative yield a single product, identified as **5**. Theoretically, cyclodehydration of **8** could occur in two ways by an intramolecular Friedel-Crafts acylation at either the C-4 or the C-6 position of the benzothiazole to give both **5** and the thiazolo[4,5-*a*]acridine isomer **9**. The sole product isolated from the reaction was assigned the structure **5** rather than **9** because (i) the UV and NMR spectral characteristics were similar to the published spectra of **1** and **2** (2,3) and related thiazole derivatives (7). (ii) The ^{1}H-NMR spectrum showed aromatic proton peaks for hydrogens on the benzene ring fused to the thiazole ring consistent with the para-oriented protons in **5** (two singlets, 8.06 and 8.5 ppm) rather than the coupling pattern expected from the vicinal protons in **9**. (iii) No significant alteration in the 9-oxoacridine carbonyl absorption (ca. 1645 cm^{-1}) was observed in the IR spectrum upon protonation of the thiazole nitrogen when the hydrochloride derived from the reaction product was analyzed. The lack of formation of **9** may be explained on the basis of the structure of the putative transition state acyl cation **9a** in which the positively charged protonated thiazole nitrogen in the highly acid medium repels the attack at C-4 by the proximal acylium ion.

The thiazolo[4,5-*b*]acridine derivatives **6a** and **6b** were obtained by the condensation of anthranilic acid with either of the 6-chlorobenzothiazoles **10a** and **10b** in a Type II Ullmann-Jourdan reaction. Yields were lower (38% and 47% respectively) than in the corresponding Type I reaction above involving reaction of a 2-halobenzoic acid with a 5-aminobenzothiazole. Polyphosphoric acid cyclization of the products **11a** and **11b** provided the required thiazolo[4,5-*b*]acridine **6a** and **6b** respectively. That the regiochemical orientation of the thiazole ring is as shown was indicated by the chemical shift of the proton on C-2 in the benzothiazole ring (s, 1 H, 9.06 ppm in DMSO-d_6, 9.29 in TFA) in **6a**. This value is close to the range of 9.07-9.28 reported for the C-2 thiazole proton in the kuanoniamine series (4). The isomeric thiazolo[5,4-*b*]acridines related to **1** and **2** on the other hand show chemical shifts for this proton at

9.58-9.88 ppm in TFA (3).

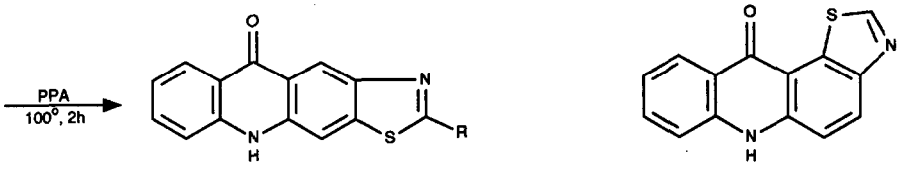
A small amount of the thiazolo[5,4-*a*]acridine **12** was also formed (~10% by NMR), as a by-product from the cyclodehydration of **11a**. Similarly, **11b** gave 18% of the isomer of **6b**. Isomeric mixtures were separable by flash chromatography (SiO_2; $CHCl_3$/MeOH/AcOH - 8:2:.1).

B)



R = H, 10a
R = NHCOCH$_3$, 10b

R = H, 11a
R = NHCOCH$_3$, 11b



R = H, 6a
R = NHCOCH$_3$, 6b

12

The 9-oxo acridine **5** could conveniently be converted to the acridine **5a** by means of a reduction with sodium in 2-pentanol (6).

Thiazolo[5,4-*b*]acridines such as **5** and thiazolo[4,5-*b*]acridines **6** are being employed as synthons in the development of total syntheses of dercitin, cyclodercitin and kuanoniamines. They are also being evaluated as antiviral and anti-tumor agents in conjunction with a series of structurally analogous imidazo[4,5-*b*]acridines. Full details of syntheses and biological activity will be reported elsewhere.

Preliminary studies using fluorescence-based nucleic acid binding techniques (8) suggest that **5**, **5a**, and **6a** intercalate with DNA; such binding may account for the anti-tumor and antiviral activity of the marine alkaloids **1**-**3** and their congeners. Linearly fused tetracyclic compounds such as the anticancer anthracycline antibiotic daunomycin are known intercalating agents. However, **4**, an antiviral drug that does not intercalate with nucleic acid acts by inhibiting viral RNA synthesis; this indicates that other modes of action may also be involved.

In conclusion, the linear fused tetracyclic systems of **5** and **6** derived by a strategy of elision from lead compounds **1**-**3** may represent the active pharmacophore within the more complex pentacyclic and hexacyclic alkaloids. Their facile syntheses should provide access to potential new non-nucleoside antiviral and anti-tumor agents incorporating thiazolo[5,4-*b*]acridine and thiazolo[4,5-*b*]acridine structures (9,10).

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9. Synthesis of thiazolo[5,4,-*b*]acridines is not previously reported. The preparation of phenyl thiazolo[4,5-*b*]acridines has been reported earlier in a Romanian language publication in which the isomeric nature of reaction products is not clearly defined; V. Farcasan, I. Balazs, Stud. Univ. Babes-Bolyai, Ser. Chem., **14**, 43 (1969); Chem. Abstr., **72**, 43555p (1970).
10. New compounds were characterized by TLC, infra-red and NMR spectra and gave combustion analyses and mass spectra consistent with assigned structures. Representative synthetic procedures illustrating the synthetic sequences are described.

    Compound **8**: A mixture of 2-bromobenzoic acid (2.01 g, 10 mmol), 5-amino-2-methylbenzothiazole dihydrochloride (2.37 g, 10 mmol), *N*-ethyl morpholine (3.68 g, 32 mmol), copper powder (26 mg), copper (I) bromide (37 mg), and DMF (45 ml) was heated (150°, 4 h); the cooled mixture diluted (200 ml H_2O), decolorized (0.5 g Norit A) and filtered. The filtrate was acidified (3 *N* HCl), the resulting precipitate filtered and washed (H_2O). Recryst. (acetone) gave buff flakes, 1.905 g, mp. 183-186° (dec.); $C_{15}H_{12}N_2O_2S$ (C,H,N,S); MS: *m/e* 284 (M^+).

    Compound **5**: To well stirred polyphosphoric acid (15 ml), preheated to 90°C was added **8** (1.42 g, 5 mmol, powdered). The mixture was stirred (110°C, 2 h), decomposed on ice, neutralized (6 *N* aq. ammonia), filtered and washed (sat. $NaHCO_3$, H_2O). The solid was dried, chromatographed on a neutral alumina-packed Ace-Kauffman extraction column eluting with methanol. The eluate was evaporated, giving 1.27 g of lemon-yellow solid, recryst. (methanol), mp. 278-281° (dec.); $C_{15}H_{10}N_2OS$ (C,H,N,S); MS: *m/e* 266 (M^+); ν_{max} (KBr): 3420, 1642 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.82 (s, 3 H, C-2-CH_3), 7.30(dd, 1 H, J = 8 Hz, 7 Hz, C8-H), 7.62(dd, 1 H, J = 8 Hz, 7 Hz, C7-H), 7.81(d, 1 H, J = 8 Hz, C6-H), 8.12(d, 1 H, J = 8 Hz, C9-H), 8.06, 8.5(two s, 1 H, 1 H, C4-H and C11-H), 12.2(bs, ex, 1 H, NH).

    Compound **5a**: Compound **5** (665 mg, 2.5 mmol) was added to 2-pentanol (12 ml). Sodium metal (345 mg, 12.5 mmol) was added in portions; the mixture was heated (80°C, 30 min. N_2 atm). The cooled mixture was carefully neutralized (3 *N*, HCl); $FeCl_3 \cdot 6H_2O$ (1.35 g) and H_2O (5 ml) were added, stirred under exposure to air (1 h). Solvent was removed *in vacuo*, the residue dissolved (MeOH), decolorized (Norit A), evaporated; recryst. (MeOH) gave orange plates, mp. 130-132°; $C_{15}H_{10}N_2S \cdot CH_3OH$ (C,H,N,S); MS: *m/e* 250 (M^+); ^{1}H-NMR ($CDCl_3$ + CD_3OD): δ 2.77(s, 3 H, C2-CH_3), 6.80(dd, 1 H, J = 8 Hz, 7 Hz, C8 H), 6.91(dd, 1 H, J = 8 Hz, 7 Hz, C7-H), 7.32-7.45(m, 2 H, C9-H and C6-H), 7.38(s, 1 H, C10-H), 7.62(s, 1H, C11-H), 7.84(s, 1 H, C4-H).

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