Synthesis of 4-[3-(1*H*)-Indolyl]-2-[*N*-guanidinomethyl]thiazole Dihydrochloride

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The title compound **3b** was synthesized in three steps from acetaminothioacetamide (**4b**) in 15% overall yield. This represents the first synthesis of a 2-guanidinomethylthiazole, which is a homolog of an important pharmacophore, 2-guanidinothiazole.

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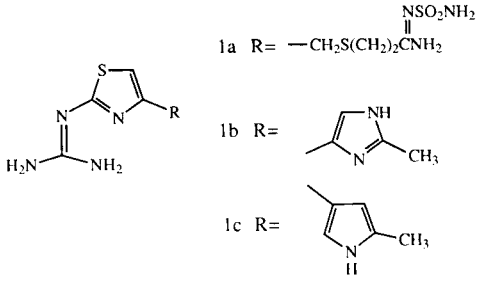
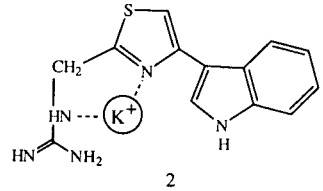
Guanidinothiazoles are important pharmacophores in antiulcer therapy. For example, famotidine (**1a**) [1] and zaltidine (**1b**) [2] exhibit activity as H_2-antagonists. Furthermore, 4-[2-methyl-(1*H*)-pyrrol-4-yl]-2-guanidinothiazole (**1c**) [3] and 4-[(1*H*)-indol-3-yl]-2-guanidinothiazole (**3a**) [4] are guanidinothiazoles that demonstrate both potent inhibition of the gastric H^+/K^+-ATPase and cytoprotective activity. Despite the interest in these compounds, there are no published reports of the synthesis of analogs wherein a methylene is inserted between the guanidine and thiazole. We describe here a novel method for synthesizing guanidinomethylthiazoles.

Figure 1



We were intrigued by our hypothesis that the guanidinothiazoles **1c** and **3a** might possess H^+/K^+-ATPase inhibiting activity by virtue of their ability to form a suitably sized pocket for chelating with a potassium ion **2** and thereby inhibit potassium transport.

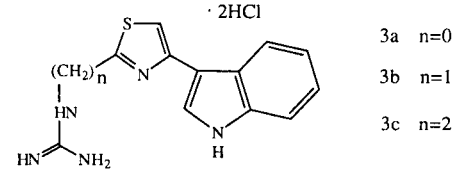
Figure 2



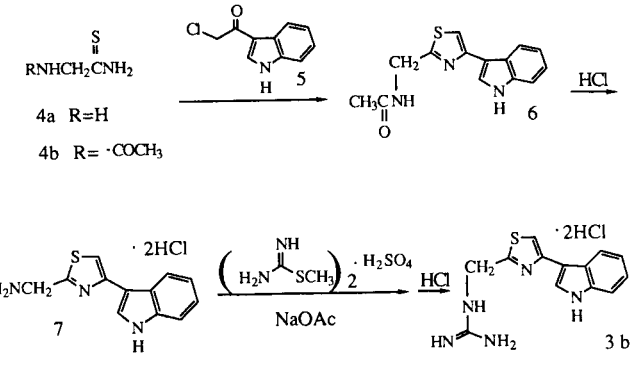
2

Studies of crown ethers indicate that the optimum hole size for potassium is 2.7-3.2 Å [5]. While computer modeling of minimized energy structures predicted **3a** would have a pocket size of 2.57 Å, it appeared that a compound with one methylene group between the guanidine and thiazole **3b** would have a pocket of 3.12 Å, suggesting that the latter might be a better chelator for potassium and thus a better gastric acid antisecretory agent. Modeling also predicted that a compound with two methylene groups **3c** would not be as good a chelator since the pocket would be too large. It should be noted [6,7] that compounds which act as chelators have had some success as gastrointestinal agents. These compounds acted as antisecretory agents, but their mechanism of action was not known. Based on this information, we decided to synthesize **3b**.

Figure 3



We originally atempted to prepare the target compound **3b** *via* **7** from aminothioacetamide hydrochloride (**4a**) [8] and the 3-chloroacetylindole (**5**). However, attempted condensations were unsuccessful and instead afforded either unreacted starting materials or decomposition products. We believe the decomposition pathway involved formation of the thiazole followed by facile elimination of ammonia. In order to prevent this we protected the amine by acetylation. Scheme I illustrates the synthetic route that was successfully used.



Acetaminothioacetamide (**4b**) was prepared from aminoacetonitrile in two steps in an overall yield of 47% according to the procedure of Johnson and Gatewood [9]. 3-Chloroacetylindole (**5**) was prepared in 44% yield by reaction of chloroacetyl chloride with indole [10]. Compounds **4b** and **5** were condensed in refluxing ethanol to give **6** in 36% yield. Treatment of **6** with refluxing concentrated hydrochloric acid cleaved the acetyl group, providing **7** in 75% overall yield as the dihydrochloride salt. Reaction of **7**, 2-methyl-2-thiopseudourea sulfate and sodium acetate in refluxing isopropanol afforded guanidinomethylthiazole **3b**, which was converted to the dihydrochloride salt using standard methods in 54% overall yield.

The biological activity of **3b** did not meet our expectations and thus did not support our hypothesis. However, the insertion of the methylene group not only changes the size of the hypothesized potassium pocket, but it also greatly affects the p*K*a of this system. This change in basicity may have more of an effect on activity than any enhanced chelating ability of the molecule.

In conclusion, a novel method for synthesizing guanidinomethylthiazoles has been presented. This should find utility as a general method for the synthesis of this system.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H nmr and ^{13}C nmr spectra were recorded on either a Varian XL-300 or a Bruker WM-250 instrument. Chemical shifts are expressed in ppm relative to internal deuteriodimethyl sulfoxide. Infrared spectra were taken in potassium bromide pellets with a Perkin-Elmer 283B infrared spectrometer. Low resolution mass spectra were recorded on a Finnigan 4510 GC mass spectrometer. Exact masses were determined on an A.E.I.-MS30 mass spectrometer. Elemental analyses were determined by Pfizer's Central Research Analytical Department.

The solvents and reagents used were commercially available and used directly without further purification. All reactions were monitored by thin-layer chromatography on 0.25 mm x 5 cm x 10 cm silica gel 60 GF-254 (Merck) plates using uv light for visualization. Flash chromatography was performed using 32-63 μm silica gel (Woelm) according to the method of Still *et al.* [11].

2-Acetaminomethyl-4-[3-(1*H*)-indolyl]thiazole (**6**).

A solution of 3-chloroacetylindole (**5**) (12.59 g, 65 mmoles) and acetaminothioacetamide (**4b**) (8.59 g, 65 mmoles) in ethanol (750 ml) was refluxed for 17 hours, then cooled to room temperature. The reaction mixture was evaporated *in vacuo* to give 20.96 g of brown solid, which was triturated with 1:9 methanol:chloroform (75 ml). The resulting mixture was filtered and the filtrate was evaporated *in vacuo* to give a brown residue which was purified by flash chromatograph, eluting with 1:9 methanol:chloroform to give 6.77 g of solid. This solid was recrystallized from ethanol (30 ml) to give 4.66 g (26% yield) of tan solid, mp 143-144°. An additional 1.63 g of product was obtained from the mother liquors to give a total yield of 36%; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 11.34 (br s, 1H, indole NH), 8.77 (t, J = 6 Hz, 1H, amide NH), 8.06 (d, J = 8 Hz, 1H, indole H_4), 7.81 (d, J = 2 Hz, 1H, indole H_2), 7.62 (s, 1H, thiazole H_5), 7.41 (d, J = 7 Hz, 1H, indole H_7), 7.12 (dd, J = 6 Hz, J = 7 Hz, 1H, indole H_5), 7.08 (dd, J = 6 Hz, J = 8 Hz, 1H, indole H_6), 4.57 (d, J = 6 Hz, 2H, CH_2), 1.92 (s, 3H, CH_3); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 169.6 (CO), 168.6 (thiazole C_2), 150.5 (thiazole C_4), 136.6 (indole C_{7a}), 124.6 (indole C_2), 124.5 (indole C_{3a}), 121.6 (indole C_5), 120.1 (indole C_4), 119.7 (indole C_6), 111.9 (indole C_7), 111.0 (indole C_3), 109.4 (thiazole C_5), 40.6 (CH_2), 22.5 (CH_3); ir (potassium bromide): 3370, 3310 (NH stretch), 1645 (CO stretch), 1535 (NH bend) cm^{-1}; ms: m/e (relative intensity) 271 (M^+, 52), 228 (100), 201 (7), 141 (11); high resolution ms: Calcd. for $C_{14}H_{13}N_3OS$: m/e 271.0779. Found: m/e 271.0781.

Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.66; H, 4.86; N, 15.36.

2-Aminomethyl-4-[3-(1*H*)-indolyl]thiazole Dihydrochloride (**7**).

A solution of **6** (1.20 g, 4.4 mmoles) in concentrated hydrochloric acid (40 ml) was refluxed for 30 minutes, then allowed to cool to room temperature. The solid that separated was collected, washed with ether (20 ml) and air-dried to give 1.28 g of yellow solid. This was dissolved in ethanol (150 ml) and ether (1000 ml) was added with stirring. The solid that separated was collected, washed with ether (40 ml) and dried *in vacuo* to give 0.95 g (75% yield) of tan solid, mp 262-263°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 11.62 (br s, 1H, indole NH), 8.92 (br s, 1H, thiazole NH^+), 8.15 (d, J = 8 Hz, 1H, indole H_4), 7.91 (d, J = 2 Hz, 1H, indole H_2), 7.81 (s, 1H, thiazole H_5), 7.45 (d, J = 8 Hz, 1H, indole H_7), 7.13 (dd, J = 7 Hz, J = 8 Hz, 1H, indole H_5), 7.10 (dd, J = 7 Hz, J = 8 Hz, 1H, indole H_6), 5.81 (br s, 3H, NH_3^+), 4.46 (q, J = 6 Hz, 2H, CH_2); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 160.9 (thiazole C_2), 150.6 (thiazole C_4), 136.6 (indole C_{7a}), 125.0 (indole C_2), 124.5 (indole C_{3a}), 121.7 (indole C_5), 120.4 (indole C_4), 119.7 (indole C_6), 111.9 (indole C_7), 111.2 (thiazole C_5), 110.4 (indole C_3), 39.4 (CH_2); ir (potassium bromide): 3330, 3290, 2940, 2710-2170 (NH stretch), 1605, 1585, 1570 (NH bend), 1235 (CN stretch) cm^{-1}; ms: m/e (relative intensity) 229 (M^+, 100), 201 (83), 173 (55), 141 (27), 129 (24), 102 (10); high resolution ms: Calcd. for $C_{12}H_{11}N_3S$: m/e 229.0674. Found: m/e 229.0664.

Anal. Calcd. for $C_{12}H_{11}N_3S \cdot 1.8HCl$: C, 48.87; H, 4.37; N, 14.25. Found: C, 48.85; H, 4.46; N, 14.09.

4-[3-(1*H*)-Indolyl]-2-[*N*-guanidinomethyl]thiazole Dihydrochloride (**3b**).

A suspension of **7** (0.880 g, 2.7 mmoles), 2-methyl-2-thiopseudourea sulfate (3.674 g, 13.2 mmoles) and sodium acetate (2.223 g, 27.1 mmoles) in 2-propanol (120 ml) was refluxed for 17 hours, then cooled to room temperature. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give 2.677 g of tan residue. This was purified by flash chromatography, eluting with methanol to give 0.744 g of white solid. This solid (0.732 g) was suspended in acetone (40 ml). Concentrated hydrochloric acid (1.2 ml) was added and a yellow precipitate formed immediately. After stirring for 10 minutes, the solid was collected, washed with acetone (10 ml) and dried *in vacuo* at 110° for 19 hours to give 0.500 g (54% yield) of yellow solid, mp 237-239°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 11.59 (d, J = 3 Hz, 1H, indole NH), 8.59 (t, J = 6 Hz, 1H, guanidine NH), 8.07 (d, J = 7 Hz, 1H, indole H_4), 8.00 (br s, 1H, thiazole NH^+), 7.86 (d, J = 3 Hz, 1H, indole H_2), 7.73 (s, 1H, thiazole H_5), 7.43 (d, J = 7 Hz, 1H, indole H_7), 7.13 (dd, J = 7 Hz, J = 6 Hz, 1H, indole H_5), 7.09 (dd, J = 7

Hz, J = 6 Hz, 1H, indole H_6), 5.97 (br s, 4H, guanidine NH) 4.86 (d, J = 6 Hz, 2H, CH_2); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 166.2 (thiazole C_2), 157.6 (guanidine), 151.0 (thiazole C_4), 136.6 (indole C_{7a}), 124.8 (indole C_{3a}), 124.5 (indole C_2), 121.7 (indole C_5), 120.1 (indole C_4), 119.8 (indole C_6), 111.9 (indole C_7), 110.7 (indole C_3), 109.6 (thiazole C_5), 42.3 (CH_2); ir (potassium bromide): 3310, 2760-2340 (NH stretch), 1675 (CN stretch), 1610 (NH bend) cm^{-1}; ms: m/e (relative intensity) 271 (M^+, 25), 254 (11), 238 (10), 229 (22), 201 (16), 173 (39), 141 (100), 129 (41), 126 (41), 114 (16), 102 (20), 85 (20), 72 (58), 59 (12); high resolution ms: Calcd. for $C_{13}H_{13}N_5S$ m/e 271.0892. Found: m/e 271.0873.

Anal. Calcd. for $C_{13}H_{13}N_5S \cdot 1.6HCl$: H, 4.46; N, 21.24. Found: H, 4.08; N, 21.56.

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