The Synthesis of Substituted Imidazo[4,5-*d*]isothiazoles via the Ring Annulation of Isothiazole Diamines: An Investigation of the Chemical, Physical, and Biological Properties of Several Novel 5:5 Fused Analogs of the Purine Ring System

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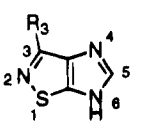
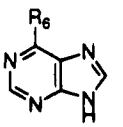
A series of imidazo[4,5-*d*]isothiazoles have been prepared from isothiazole precursors via a strategy employing ring annulation of the appropriate isothiazole diamine. In this manner, several 4,5-diaminoisothiazoles were converted into the corresponding 5-(alkylthio)imidazo[4,5-*d*]isothiazoles via a two-step, one-pot procedure in good yield. This methodology proved quite general and allows for the introduction of various substituents onto the 3-, 5-, and 6-positions of this ring system. Reaction with Raney nickel destroyed the ring system, presumably through removal of the sulfur at the 1-position, and the 5-mercapto substituent could not be removed selectively. Ring annulation with diethoxymethyl acetate provided the 5-unsubstituted imidazo[4,5-*d*]isothiazoles but was less general, and only the 3-methyl derivatives could be prepared. Imidazo[4,5-*d*]isothiazoles bearing no substituents on nitrogen readily underwent alkylation to afford mixtures of the N-4- and N-6-substituted compounds. The chemical and physical properties of these novel heterocycles were studied in detail, and the structure of 3-methyl-5-methanesulfonyl-6-(phenylmethyl)imidazo[4,5-*d*]isothiazole was verified by single crystal X-ray diffraction studies.

Introduction

The purine ring system has been one of the most thoroughly investigated heterocyclic systems, and a plethora of purine derivatives have been reported.[1] Many of these analogs, such as 6-mercaptopurine[2,3] and 6-methylpurine,[4] possess significant biological activity, and some have found use as medicinal agents. While modifications of purine have been extensive, they have for the most part conserved the 6:5 fused heterocyclic system of the purine ring. As part of our program to prepare a series of novel purine analogs, we have investigated the substitution of the C2–N3 linkage of the purine ring with a single sulfur atom, leading to the novel 5:5 fused imidazo[4,5-*d*]isothiazole ring system. The sulfur atom is significantly larger than the second row elements, and this size difference, coupled with the ability of sulfur's d-orbitals to participate in aromatic resonance, has led to the comparison of a bivalent sulfur atom in heteroaromatic systems to a CH=CH group in aromatic systems.[5] In order to gauge whether this effect would hold for our newly designed ring system, we embarked upon a molecular-modeling study of a hypothetical imidazo[4,5-*d*]-isothiazole.[6,7] This study also demonstrated the ring-enlarging effect of the sulfur atom in heteroaromatic systems, causing the five-membered isothiazole ring to occupy a space similar to that of the six-membered pyrimidine ring of the purine system. In fact, our model suggests a separation of only 0.4 Å between the 6-substituent of a purine and the 3-substituent of an imidazo-[4,5-*d*]isothiazole, when the imidazole portions of the two molecules are superimposed. These considerations imply that the proposed imidazo[4,5-*d*]isothiazoles should retain similar spatial characteristics relative to the corresponding purines. However, due to the increased electron density expected in a 5:5 fused ring system versus a 6:5 fused system, the electronic character of these imidazo-[4,5-*d*]isothiazoles would be very different when compared to the parent purines.



Imidazo[4,5-*d*]isothiazole ring system



Purine ring system

Monocyclic isothiazoles[8,9] and their fused derivatives,[10] particularly benzisothiazoles, have been extensively studied, and many derivatives of this ring system have been reported in the literature. Much less is known about fully unsaturated 5:5 fused isothiazole-containing systems,

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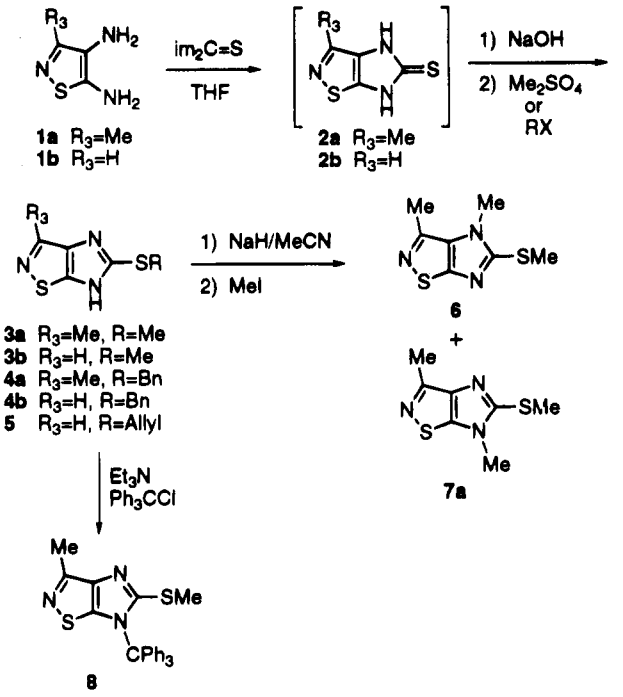
especially those having no heteroatoms at the ring juncture, and only a few examples have been reported. Most of these are thieno[*c*]isothiazoles[11] or thieno[*d*]-isothiazoles[12] with a very small number of azole-containing isothiazoles known in the literature. Several thiazolo-[4,5-*c*]isothiazoles[13] have been prepared, as has an interesting C-2 symmetrical isothiazoloisothiazole.[14] Reports of isothiazoles fused to five-membered rings containing no sulfur heteroatoms are even more rare. The isothiazoloisoxazole ring system is known,[15] and several pyrazolo[3,4-*c*]isothiazoles have been prepared as antifungal agents.[16] Among the 1,2-fused azoloisothiazoles, there is a single report of the isothiazolo[4,5-*d*]-*v*-triazole ring system,[17] one report on the synthesis of the pyrrolo-[3,2-*d*]- and pyrazolo[3,4-*d*]isothiazole ring systems,[18] and no examples of the imidazo[4,5-*d*]isothiazole system previous to our preliminary report of this work.[19] In fact, imidazoisothiazoles having no bridgehead heteroatoms were unknown, although the synthesis of the imidazo-[4,5-*d*]isothiazole ring system was apparently attempted by Holland and co-workers in 1965.[20] This paucity of azoloisothiazoles reported in the literature invites a detailed investigation of the chemistry of these interesting compounds and indicates that their synthesis is nontrivial. Since our goal was to study the chemical and biological properties of these novel purine analogs, we investigated some strategies to prepare the imidazo[4,5-*d*]isothiazole ring system.

Results and Discussion

In our initial report on the synthesis of the imidazo-[4,5-*d*]isothiazole ring system,[19] we detailed the synthesis of the isothiazole diamines **1a** and **1b** (Scheme 1), as well as the ring annulation reactions of these derivatives. The initial disclosure of **1a** in the literature[20] reported that a reaction of **1a** with diethoxymethyl acetate gave only (acetoxymethylene)aminoisothiazoles. Our initial attempts at ring annulation of **1a** utilizing this reagent, as well as triethyl orthoformate, ethyl formate, formic acid, and formamidine acetate, all gave no cyclized material in a variety of solvents, even at high temperatures or upon acid catalysis. We next attempted to annulate **1a** with cyanogen bromide, carbonyldiimidazole, potassium ethyl xanthate, and thiophosgene under a variety of different conditions; however, none of these attempts was successful. Reaction of 4,5-diaminoisothiazoles with (thiocarbonyl)diimidazole, however, provided the unstable 5-mercaptoimidazo[4,5-*d*]isothiazoles, which decomposed upon all attempts at isolation, but were readily alkylated *in situ*. In this manner, good yields of

Scheme 1



the 5-(methylthio)imidazo[4,5-*d*]isothiazoles **3a** and **3b** have been prepared via treatment of the sodium salts of **2a** and **2b** with Me_2SO_4. These sodium salts were also subject to alkylation with other electrophiles, as reaction with either benzyl or allyl bromide gave the corresponding imidazo[4,5-*d*]isothiazoles **4a**, **4b**, and **5** in similar yields.

The ability of the imidazo[4,5-*d*]isothiazole ring system to undergo substitution on a ring nitrogen atom was demonstrated via the sodium salt alkylation[21] of **3a** with MeI to provide a 1:1 mixture of the *N*-4- and *N*-6-methyl derivatives **6** and **7a**. Treatment of **3a** with triphenylmethyl chloride under mildly basic conditions led to the exclusive formation of the *N*-6-trityl derivative **8** in good yield. The regiochemistry of alkylation was determined on the basis of a comparison of the ultraviolet spectrum of **8** with the spectra of the methylated derivatives **6** and **7a**. The structure of **6** was unambiguously assigned by observing the NOE enhancement of both the 3-methyl (5%) and the 5-methylthio (2%) signals in the ^1H NMR spectrum upon irradiation of the signal corresponding to the *N*-methyl group. The structure of the other regioisomer was assigned via the direct synthesis of **7a**, which was conveniently prepared from **9a** (Scheme 2). Compounds **9a** and **9b**[19] were converted to their sodium salts with NaH and then alkylated in good yield with either BnBr or MeI to afford the corresponding 5-(*N*-alkylamino)-4-nitroisothiazoles. That alkylation had occurred on the exocyclic amine was evident from the ^1H NMR spectrum of compounds **10a**, **10b**, and **11**, as the benzylic or methyl signal appeared as a doublet which collapsed to a singlet upon D_2O exchange. Reduction of the nitro group to **12a**, **12b**, and **13** followed by ring closure and alkylation afforded the desired 6-alkyl-3-methyl-5-(methylthio)imidazo[4,5-*d*]isothiazoles **7a**, **7b**, and **14**. Both the N-4 isomer (**6**) and the N-6 isomer (**7a**) exhibited characteristic ultraviolet (UV) spectra, and a comparison of the UV spectra provided a convenient means for the assignment of other N-alkylated imidazo[4,5-*d*]isothi-

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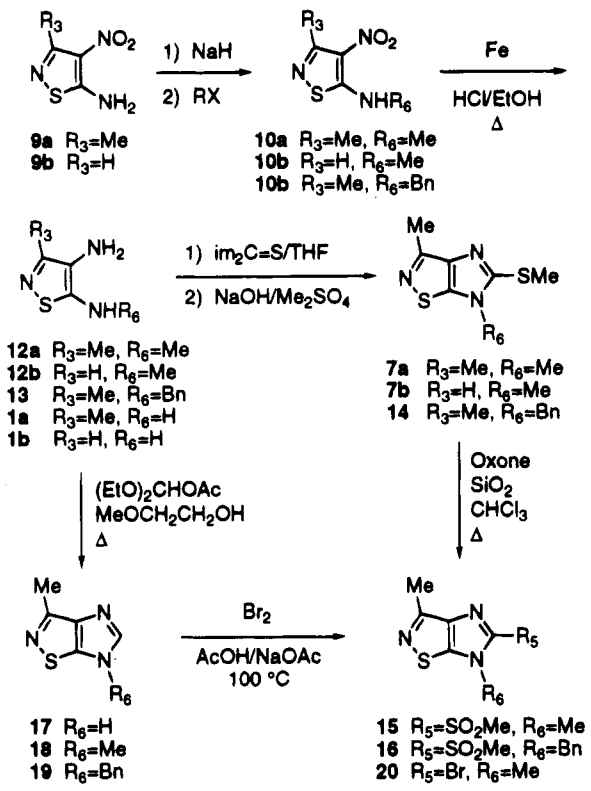
Scheme 2



azoles. In general, the N-6 isomers showed a medium absorption with a λ_{max} in the 270 nm region, and the N-4 isomers showed a stronger absorption with a λ_{max} in the 275 nm region and a distinctive shoulder at about 255 nm. Analysis of the UV spectra suggests that the unsubstituted 5-(alkylthio)imidazo[4,5-*d*]isothiazoles exist primarily as the 4*H* tautomers, since their UV spectra exhibit a pattern similar to that shown by **6**.

2-Mercaptoimidazoles as well as the corresponding 2-(alkylthio)imidazoles are readily desulfurized by Raney nickel.[22] However, an attempted desulfurization reaction of compounds **3a**, **3b**, **7a**, **7b**, and **14** with several different grades[23] of freshly prepared Raney nickel or nickel boride generated *in situ*[24] failed to provide the corresponding 5-unsubstituted imidazo[4,5-*d*]isothiazoles, affording monocyclic imidazoles as the only isolable products. We then attempted to block the approach of the catalyst to the isothiazole ring sulfur atom by utilizing the 6-triphenylmethyl derivative **8** as a substrate for the dethiation reaction. The presence of the bulky triphenylmethyl moiety completely suppressed the reduction of the imidazo[4,5-*d*]isothiazole ring by Raney nickel; however, the 5-methylthio group still proved inert, even to alkaline nickel–aluminum alloy,[25] which has been described as one of the strongest dethiation conditions known.[26] Additionally, we attempted the reduction of imidazo[4,5-*d*]isothiazoles **3a**, **3b**, **7a**, **7b**, **8**, and **14** with several hydride-reducing agents, including $LiAlH_4$, $LiAlH_4/TiCl_4$,[27] Red Al (Aldrich),[28] DIBALH, and Bu_3SnH, and also with a $NiCl_2/Ph_3P$-catalyzed procedure.[29] Although these reagents are known to effect certain dethiation reactions, we were unable to isolate any dethiated imidazo[4,5-*d*]isothiazole products and obtained only unreacted starting material or decomposition products upon the use of these reagents under a variety of temperature and solvent conditions. Simple catalytic hydrogenation employing several different palladium catalysts under both acidic and basic conditions also failed to yield any 5-unsubstituted imidazo[4,5-*d*]isothiazoles. Since thiols and thiolate anions are known to be more reactive than thioethers toward Raney nickel, the intermediates in the synthesis of compounds **3a**, **3b**, **7a**, and **7b** were subjected to dethiation conditions. The desired 5-mercapto derivatives were obtained by reacting the starting diaminoisothiazole with (thiocarbonyl)diimidazole and partitioning the reaction mixture between water and an organic solvent, and the corresponding thiolate anions were obtained by extracting the 5-mercaptoimidazo[4,5-*d*]isothiazoles from the organic layer with aqueous NaOH. Attempts to desulfurize these unstable intermediates using the methods similar to those described above failed, as did a reaction with diimide, which has been found to desulfurize a heteroaromatic system containing a thiocarbonyl moiety.[30] In all cases, either no reaction or preferential reduction of the imidazo[4,5-*d*]isothiazole ring system over the 5-substituent was observed and would seem to preclude the use of a desulfurization reaction to obtain 5-unsubstituted derivatives.

Methyl sulfones have been shown to be excellent leaving groups in the nucleophilic aromatic substitution reaction[31] and prompted us to prepare some 5-methanesulfonylimidazo[4,5-*d*]isothiazoles. The methyl sulfones **15** and **16** were readily prepared by an oxidation of the corresponding methylthio derivatives **7a** and **14** with oxone/wet alumina in $CHCl_3$ at reflux.[32] That oxidation had occurred on the 5-methylthio group and not on the 1-sulfur atom of the ring was inferred from a large downfield shift of the peak assigned to the 5-methylthio group in the ^1H NMR spectra of **15** and **16**. Surprisingly, all attempts to effect a substitution of the 5-methanesulfonyl moiety on the imidazo[4,5-*d*]isothiazole ring system were unsuccessful. Treatment of **15** or **16** with liquid ammonia in a sealed reaction vessel at 130 °C afforded only starting material, as did a reaction with NaN_3 at temperatures up to 150 °C, at which point slow decomposition occurred. The 5-position of **15** and **16** was also unreactive toward nucleophiles under acidic conditions, such as treatment with HCl/CH_2Cl_2, HBr/CH_2Cl_2, or PCl_5 in $POCl_3$ which gave no reaction and/or decomposition upon prolonged reaction. An attempted direct reduction of the 5-methanesulfonyl moiety with hydride reagents led to the decomposition of the imidazo[4,5-*d*]-isothiazole ring system, in a manner similar to that seen for the 5-methylthio derivatives. This inability to effect a nucleophilic displacement at the 5-position of the imidazo[4,5-*d*]isothiazole system is presumably due to the uncharacteristically high electron density resulting from the fusion of two five-membered rings.

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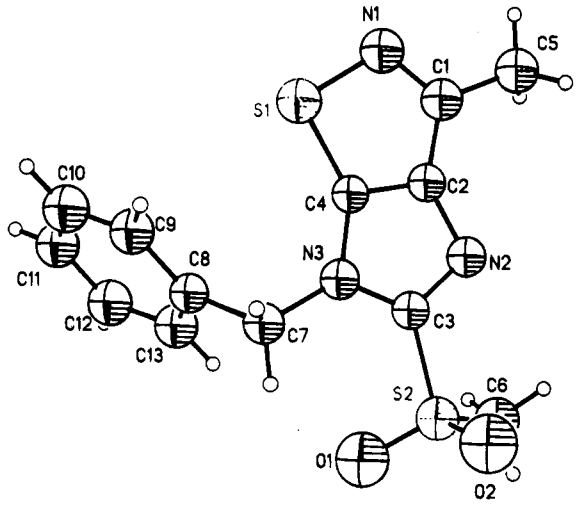
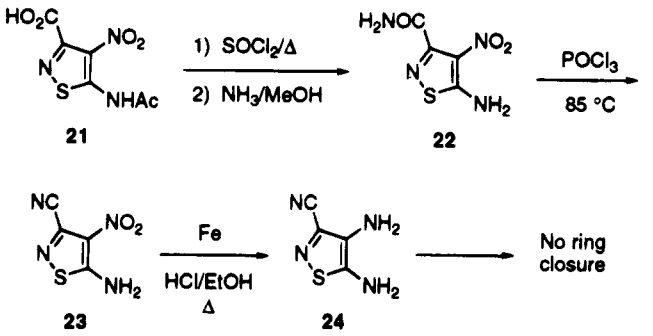


Figure 1. Computer-generated X-ray crystal structure of 3-methyl-5-methanesulfonyl-6-(phenylmethyl)imidazo[4,5-*d*]-isothiazole (**16**).

The structure of **16**, as well as that of the new imidazo-[4,5-*d*]isothiazole ring system, was unequivocally determined by X-ray crystallographic studies (Figure 1). As expected, the ring system is planar, and the fusion of two five-membered rings creates considerable strain about the ring junction carbon atoms. This is evident from the large C3–C3a–N4 (138°) and S1–C6a–N6 (142°) bond angles. The effect that the isothiazole sulfur atom has on substituent orientation is also demonstrated, since both the S1–N2 (1.69 Å) and S1–C6a (1.71 Å) bonds are long compared to the N2–C3 (1.31 Å), C3–C3a (1.43 Å), and C3a–C6a (1.37 Å) bonds. Furthermore, the C6a–S1–N2 bond angle is only 92°, compared to the other bond angles within the isothiazole ring, which fall between 110 and 114°. This combination of long bond lengths and a short bond angle effectively forces the 3-substituent of the imidazo[4,5-*d*]isothiazole to occupy a position very similar to that found for a 6-substituted purine. The structure of the ring system is remarkably similar to that which was predicted by our modeling studies, except that the ring enlargement effects due to the isothiazole sulfur atom are more pronounced than predicted. Experimental details, crystallographic parameters, and structural data are available from the Cambridge Crystallographic Data Centre.[33]

The inability to desulfurize 5-mercaptoimidazo[4,5-*d*]-isothiazoles and obtain the 5-unsubstituted derivatives prompted us to reinvestigate the ring closure of **1a** with formate derivatives. After many unsuccessful attempts, it was found that a reaction of **1a** and diethoxymethyl acetate in 2-methoxyethanol at 150 °C in a steel reaction vessel led to a mixture of products, from which a 27% yield of 3-methylimidazo[4,5-*d*]isothiazole (**17**) could be isolated after column chromatography (Scheme 1).[19] In a similar manner, the N-alkylated derivatives **12a** and **13** reacted readily with diethoxymethyl acetate in 2-methoxyethanol at reflux to give the desired 3-methylimidazo-[4,5-*d*]isothiazoles **18** and **19** in over 60% yield (Scheme 2). Unfortunately, a reaction of **1b** and **12b** under similar conditions furnished a complex reaction mixture, from which no 3-unsubstituted imidazo[4,5-*d*]isothiazoles could

Scheme 3



be isolated. We expected that the 5-position of the imidazo[4,5-*d*]isothiazole ring system would undergo electrophilic aromatic substitution reactions, since the fusion of two five-membered rings should result in an electron rich ring system. An attempted nitration of **18** employing either nitric acid in sulfuric acid or nitronium tetrafluoroborate afforded only unreacted starting material; however, treatment of **18** with bromine in buffered acetic acid gave a good yield of 5-bromo-3,6-dimethylimidazo[4,5-*d*]isothiazole (**20**).

We next investigated the synthesis of imidazo[4,5-*d*]-isothiazoles possessing various functional groups at the 3-position (Scheme 3). Treatment of the carboxylic acid **21**[19] with $SOCl_2$ gave the corresponding acid chloride, which was converted in high yield to the 3-carboxamide with a concomitant deprotection by methanolic ammonia to afford 5-amino-4-nitroisothiazole-3-carboxamide (**22**). Dehydration of **22** with $POCl_3$ gave 5-amino-4-nitroisothiazole-3-carbonitrile (**23**), which was reduced to 4,5-diaminoisothiazole-3-carbonitrile (**24**) via a chemical reduction in 62% yield. A reaction of **24** with diethoxymethyl acetate gave no reaction, even at 120 °C, with slow decomposition upon extended reaction times. The low reactivity of **24** was also evident upon its reaction with (thiocarbonyl)diimidazole, as at room temperature, the reaction was very sluggish, and the attempted alkylation of this reaction mixture yielded an intractable mixture of products. At higher temperatures, the reaction of **24** with (thiocarbonyl)diimidazole resulted in rapid decomposition. The low reactivity of **24** to ring annulation conditions is presumably due to the deactivation of the amino groups by the electron-withdrawing moiety. This apparently precludes the synthesis of imidazo[4,5-*d*]isothiazoles bearing an electron-withdrawing group at the 3-position from an isothiazole via these methods.

Utilizing 3-amino-5-(*N*-methylamino)isothiazole-4-carboxylate (**25**, Scheme 4), which has recently been prepared from ethyl cyanoacetate, methyl isothiocyanate, and aqueous chloramine,[34] we attempted the synthesis of 3-aminoimidazo[4,5-*d*]isothiazoles via our ring annulation methods. Hydrolysis of the ester with aqueous KOH, followed by neutralization with a calculated amount of HCl, gave a nearly quantitative yield of the 3-amino-5-(*N*-methylamino)isothiazole-4-carboxylic acid (**26**). Decarboxylation followed by acetylation of the crude 3,5-diaminoisothiazole afforded 3-acetamido-5-(*N*-methylacetamido)isothiazole (**27**) in high yield. Nitration of **27** under standard conditions failed; however, reaction of **27** with nitronium triflate[35] gave 3-acetamido-5-(*N*-methylacetamido)-4-nitroisothiazole (**28**). Selective removal of

(33) X-ray data, analyses, and experimental details have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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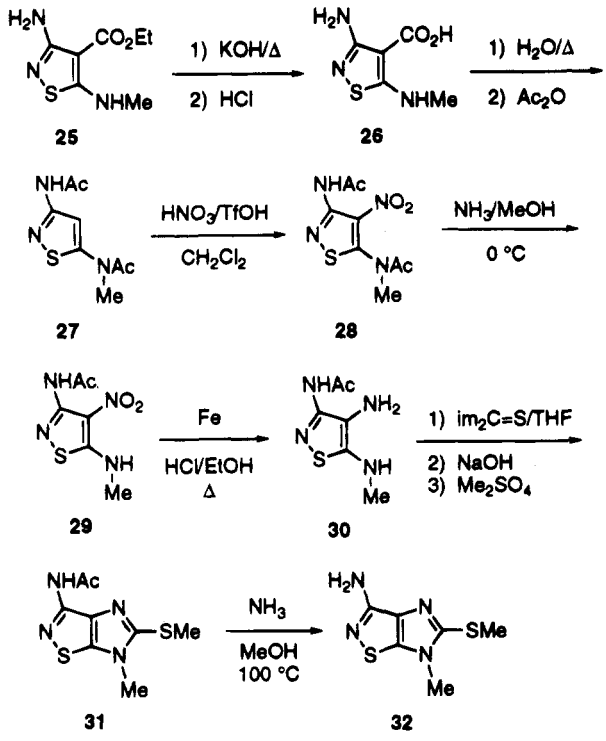
Scheme 4



the 5-acetyl group with cold methanolic ammonia afforded 3-acetamido-5-(*N*-methylamino)-4-nitroisothiazole (**29**), and chemical reduction of this derivative provided 3-acetamido-4-amino-5-(*N*-methylamino)isothiazole (**30**). Reaction of this diamine with diethoxymethyl acetate in 2-methoxyethanol gave only (acetoxymethylene)amino isothiazoles and decomposition products at high reaction temperatures. However, treatment of **30** with (thiocarbonyl)diimidazole in anhydrous 1,4-dioxane followed by alkylation with Me_2SO_4 afforded a good yield of 3-acetamido-6-methyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (**31**). Removal of the acetyl-protecting group with methanolic ammonia at high temperature provided 3-amino-6-methyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (**32**). Several attempts at diazo transformations of the 3-amino substituent, including the classical Sandmeyer reaction, $NaNO_2$/AcOH,[36] $NaNO_2/H_3PO_4$, and nonaqueous diazotization conditions,[37,38] all failed to yield any product, affording only decomposition products. The failure of the 3-aminoimidazo[4,5-*d*]isothiazole derivative **32** to undergo the usually accommodating Sandmeyer reaction further indicates the resistance of this ring system to common reactions and functional group transformations.

Since the imidazo[4,5-*d*]isothiazole ring system contains four carbon atoms, only two of which can bear proton substituents, ^{13}C NMR[39] was utilized to rigorously characterize derivatives of this new ring system. Presumably due to rapid interchange between the N-4 and N-6 tautomers, imidazo[4,5-*d*]isothiazoles unsubstituted on nitrogen showed no resolved ^{13}C signals in the aromatic region. However, the corresponding N-substituted derivatives gave sharply resolved spectra, and four distinct imidazo[4,5-*d*]isothiazole carbon resonances could

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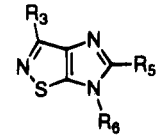
Table 1. ^{13}C Resonances of Several Imidazo[4,5-*d*]isothiazoles



compd no.	substituent R_3	R_5	R_6	chemical shift (ppm)[a] C3	C3a	C6a	C5
6	Me	SMe	*N*-4 Me	147.2[b]	137.4	161.7[b]	154.7
7a	Me	SMe	Me	152.1	146.7	151.0	152.6
7b	H	SMe	Me	143.5[b]	148.1	151.7	153.1
14	Me	SMe	Bn	151.9[b]	146.9[b]	149.8[b]	152.1[b]
18	Me	H	Me	153.4	148.7	149.6	146.8[b]
19	Me	H	Bn	153.3[b]	148.7[b]	148.1[b]	146.0[b]
32	NH_2	SMe	Me	151.5	136.6	148.9[b]	149.7[b]

[a] Assignments by analogy and chemical shifts unless otherwise specified. [b] Unequivocally assigned from fully or partially coupled spectra.

be observed. The assignments for these signals (Table 1) were made on the basis of the fully coupled and partially decoupled spectral data, as well as on chemical shift trends. The 3- and 5-unsubstituted derivatives (**7b**, **18**, and **19**) have nonquaternary ring carbons, which could readily be assigned due to the presence of a large one-bond coupling (J_{CH}). The bridgehead and other quaternary ^{13}C resonances were readily assigned by observing the partially decoupled spectra. For example, irradiation at the frequency of the resonance due to the 3-methyl peak of the 6-benzylimidazo[4,5-*d*]isothiazole derivative **14** in the ^1H NMR spectrum decouples the C3 and C3a resonances, which appear as sharp singlets at 151.9 and 146.9 ppm, respectively. The C3 is assigned as the most downfield resonance on the basis of its chemical shift in relation to the 3-unsubstituted derivative **7b**. The introduction of a methyl group at the 3-position causes the expected large downfield shift (~8–9 ppm) of the C3 carbon, while the downfield shift of the C3a carbon is only ~1 ppm. In contrast, the quaternary resonances of the 3-unsubstituted derivative **7b** displayed chemical shifts similar to those of the 3-methyl derivatives **7a** and **14**, as expected. Furthermore, the absolute intensity of the C3 signal in the partially decoupled spectrum of **14** is much larger than that of the C3a resonance, due to the NOE enhancement provided by decoupling the adjacent methyl protons. C6a of **14** shows a three-bond coupling to the benzylic protons ($^3J_{CH}$ = 3.5 Hz) and appears as a triplet at 149.8 ppm. C5 appears as a multiplet at 152.1 ppm, due to the presence of two three-bond couplings. The imidazo[4,5-*d*]isothiazole resonances of the 6-benzyl derivative **19** were assigned via the same method. Irradiation at the frequency of the resonance due to the 3-methyl peak in the ^1H NMR spectrum decouples the C3 and C3a resonances. The C3 appears as a singlet at 153.3 ppm, while the C3a is a doublet at 148.7 ppm, due to a three-bond coupling from the H5 proton ($^3J_{CH}$ = 11 Hz). The C6a resonance is a multiplet at 148.1 ppm, while the C5 appears as a doublet of triplets at 145.0 ppm (J_{CH} = 211 Hz, $^3J_{CH}$ = 3 Hz).

Assignment of the 6-methyl derivative **7a** was accomplished by correlation of the chemical shifts to the 6-benzyl analog. A small downfield shift was evident for C5 (0.5 ppm) and C6a (1.2 ppm) upon replacement of the 6-benzyl group of **14** with a 6-methyl group. In contrast, this substitution affected the chemical shifts of the C3 and C3a resonances only slightly. A similar downfield

shift was also evident for the C5 (0.8 ppm) and C6a (1.5 ppm) signals upon substitution of the 6-benzyl group of **19** with the methyl group of **18**. Due to the closer proximity of these resonances in the 5-unsubstituted analogs **18** and **19**, this shift causes the C6a signal to appear upfield of the C3a signal in the spectrum of the 6-benzyl derivative **19**, while it appears downfield of the C3a signal in the spectrum of the 6-methyl analog **18**. The fully coupled spectrum of the 3-aminoimidazo[4,5-*d*]isothiazole **32** allows for the unequivocal assignment of the C5 and C6a resonances, as C6a appears as a quartet ($^3J_{CH}$ = 3 Hz), and C5 appears as a multiplet, due to the presence of two three-bond couplings. These two signals are shifted upfield slightly (2–3 ppm) relative to the 3-unsubstituted derivative **7b**, while the resonance attributed to the C3a carbon atom shows a large upfield shift (~11 ppm) and appears at 136.9 ppm as a triplet ($^3J_{CH}$ = 4 Hz). In contrast, the C3 signal is shifted downfield 8 ppm and appears as a singlet, presumably due to a very small two-bond coupling to the amino group. These patterns are consistent with those seen between the ^{13}C spectra of 9-methylpurine and 9-methyladenine.[40]

The 4-methyl derivative **6** exhibited a ^{13}C spectrum vastly different from that of the 6-substituted analogs. A large upfield shift of 10 ppm is seen for C3a, whereas a large downfield shift of 10 ppm is evident for C6a, with respect to the 6-methyl derivative **7a**. A similar but smaller shift pattern is evident for the C5 and C3 signals, with C5 shifted downfield 2 ppm and C3 shifted upfield 5 ppm. The fully coupled spectrum of **7a** allows for the unambiguous assignment of the C6a and C3 signals, since they appear as a singlet and a quartet ($^2J_{CH}$ = 6.5 Hz), respectively. The C5 and C3a signals both appear as multiplets but can be readily assigned on the basis of their chemical shifts, since the upfield shift of C3a and downfield shift of C5 with respect to the 6-methyl derivative are analogous to those seen in the purine system. For example, 7-methylpurine, which is analogous to a 4-methylimidazo[4,5-*d*]isothiazole, shows an upfield shift of 8 ppm for C5 (C3a of **7a**) relative to 9-methylpurine, which is analogous to a 6-methylimidazo[4,5-*d*]isothiazole. Similarly, the C4 (C6a of **7a**) and C8 (C5 of **7a**) resonances for 7-methylpurine are shifted downfield 9 and 2 ppm relative to 9-methylpurine, respectively. These effects combine to create a "spreading out" of the ^{13}C signals of the 4-substituted derivative, while the ^{13}C signals of the 6-substituted analogs are bunched closer together. This distinctive pattern shown by N-4- and N-6-substituted imidazo[4,5-*d*]isothiazoles provides a simple means for the assignment of the regiochemistry of N-substituted imidazo[4,5-*d*]isothiazole derivatives.

Conclusions and Biological Activity

In summary, the chemical and physical properties of the imidazo[4,5-*d*]isothiazole ring system have been investigated, and several differentially substituted members of this new ring system have been prepared from isothiazole diamines. This approach appears to be fairly general for the preparation of 5-alkylthio derivatives but is successful only for the preparation of 5-unsubstituted compounds only when a methyl group is present at the 3-position, presumably due to electronic effects. Imidazo[4,5-*d*]isothiazole derivatives unsubstituted at nitrogen alkylate readily to give a mixture of the N-4 and N-6 isomers, and a 5-unsubstituted imidazo[4,5-*d*]isothiazole derivative (**18**) underwent an electrophilic bromination reaction to afford 5-bromo-3,6-dimethylimidazo[4,5-*d*]-isothiazole (**20**). The ^{13}C resonances of several N-substituted imidazo[4,5-*d*]isothiazoles have been unequivocally assigned, and fundamental patterns in the chemical shifts have been determined. The structure of the sulfone **16**, a representative imidazo[4,5-*d*]isothiazole, was verified by X-ray crystallographic studies, which supported our hypothesis that the size and substituent orientation of the imidazo[4,5-*d*]isothiazole ring system closely resembles that of purine.

These imidazo[4,5-*d*]isothiazoles may be viewed as analogs of the biologically significant purine ring system and were therefore evaluated for their antiviral and antitumor activity in preliminary screens.[41] None of the imidazo[4,5-*d*]isothiazoles showed selective activity against HSV-1 or HCMV, as there was no separation between antiviral activity and the toxicity shown toward uninfected HFF and KB cells. Several of the new imidazo-[4,5-*d*]isothiazoles were found to modestly inhibit the growth of L1210 cells.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used as provided. THF (Na/benzophenone), toluene (Na/benzophenone), MeCN (CaH_2), CH_2Cl_2 (P_2O_5), DMF (CaO), and methoxyethanol (CaO) were distilled from the indicated drying agent and stored over activated 4 Å molecular sieves under a positive pressure of argon if not used immediately. Triethylamine and pyridine were stored over KOH. Methanolic ammonia was prepared by saturating MeOH with anhydrous ammonia at 0 °C and was stored at −15 °C. Other general experimental procedures were carried out as described previously.[19]

General Procedure A (Ring Annulation with (Thiocarbonyl)diimidazole). The appropriate 4,5-diaminoisothiazole (1 equiv) was dissolved in dry THF (0.2 M) under an argon atmosphere. To this solution at rt was added (thiocarbonyl)-diimidazole (1.05 equiv) in one portion, and the solution was stirred at rt for 0.5 h. An equal volume of water was added and the solution stirred for 1 min, after which 1 N NaOH (2.1 equiv) was added in one portion. After the mixture was stirred for 1 min, the appropriate alkylating agent (1.1 equiv) was added dropwise and the solution stirred for 1 h at rt. The solution was then poured into EtOAc (60 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide the crude product.

3-Methyl-5-[(phenylmethyl)thio]imidazo[4,5-*d*]isothiazole (4a). Material obtained from **1a** (0.65 g, 5 mmol) and BnBr (0.66 mL, 5.5 mmol) following general procedure A was chromatographed ($CHCl_3$ to 1% MeOH/$CHCl_3$) and then precipitated from ether/petroleum ether to yield 0.80 g (61%) of **4a**: mp 110–112 °C; R_f 0.70 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 13.23 (br s, 1H, D_2O exchangeable), 7.41–7.24 (m, 5H), 4.49 (s, 2H), 2.46 (s, 3H); UV λ_{max} (ε) (EtOH) 254 (11 070), 278 (14 680); (pH 1) 212 (16 950), 276 (10 380); (pH 11) 221 (16 320), 254 (8880), 285 (12 570) nm. Anal. Calcd for $C_{12}H_{11}N_3S_2$: C, 55.15; H, 4.24; N, 16.08. Found: C, 55.31; H, 4.46; N, 15.96.

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(41) Antitumor assay data were obtained by the laboratories of Linda L. Wotring (Department of Pharmaceutical Chemistry, College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109). Antiviral assay data were obtained by the laboratories of John C. Drach (Department of Biologic and Material Sciences, School of Dentistry, The University of Michigan, Ann Arbor, MI 48109). The methods for these assays have been described previously: Swayze, E. E.; Shannon, W. M.; Buckheit, R. W.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *Nucleosides Nucleotides* **1992**, *11*, 1507–1527.

5-[(Phenylmethyl)thio]imidazo[4,5-*d*]isothiazole (4b). Material obtained from **1b** (1.38 g, 12 mmol) and BnBr (1.57 mL, 13.2 mmol) following general procedure A was chromatographed (40% EtOAc/hexane) and then recrystallized from EtOAc/hexane to yield 1.06 g (36%, mp 165–166 °C) of **4b**. A second crop gave an additional 0.38 g (13%, mp 164–165 °C) of product for a combined yield of 49%: R_f 0.60 (50% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 13.27 (br s, 1H, D_2O exchangeable), 8.51 (s, 1H), 7.42–7.24 (m, 5H), 4.51 (s, 2H); UV λ_{max} (ϵ) (MeOH) 251 (9920), 280 (14 300) nm. Anal. Calcd for $C_{11}H_9N_3S_2$: C, 53.42; H, 3.67; N, 16.99. Found: C, 53.64; H, 3.80; N, 16.74.

5-(Allylthio)-3-methylimidazo[4,5-*d*]isothiazole (5). Material obtained from **1a** (0.65 g, 5 mmol) and allyl bromide (0.48 mL, 5.5 mmol) following general procedure A was chromatographed ($CHCl_3$ to 1% MeOH/$CHCl_3$) and then crystallized from EtOH/water to yield 0.58 g (54%) of **5**: mp 118.8–119.3 °C; R_f 0.69 (10% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 13.22 (br s, 1H, D_2O exchangeable), 6.03–5.88 (m, 1H), 5.29–5.06 (m, 2H), 3.89–3.85 (m, 2H), 2.46 (s, 3H); UV λ_{max} (ϵ) (EtOH) 256 (7610), 276 (14 410); (pH 1) 217 (11 990), 245 (9530), 274 (12 010); (pH 11) 221 (13 620), 252 (9370), 283 (13 250) nm. Anal. Calcd for $C_8H_9N_3S_2$: C, 45.47; H, 4.29; N, 19.89. Found: C, 45.50; H, 4.53; N, 19.73.

General Procedure B (Sodium Salt Alkylations). The starting heterocycle (1 equiv) was dissolved in dry MeCN (0.1 M). NaH (80% w/w dispersion in mineral oil, 1.2 equiv) was added in one portion and the resulting suspension stirred at rt for 1 h. Alkylating agent (1.2 equiv) was added dropwise over a period of 5 min, and the mixture was stirred at rt until the reaction was judged to be complete (3–24 h) by TLC. Saturated aqueous NH_4Cl (1 mL/mmol) was added, and the suspension was concentrated to a small volume and then partitioned between water and EtOAc. The organic layer was removed and the aqueous layer extracted with EtOAc, and the combined organic layers were washed with brine, then dried over a small amount of $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude product.

3,4-Dimethyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (6). TLC analysis of material obtained from **3a** (810 mg, 4.37 mmol) and MeI (0.326 mL, 5.24 mmol) via general procedure B indicated two products, which were separated after repeated (4×) column chromatography ($CHCl_3$). Fractions containing only the slower moving product (R_f 0.49, 2% MeOH/$CHCl_3$) were pooled and concentrated to yield **7a** (0.22 g, 25%). A portion of this material was recrystallized from ether/petroleum ether to provide needles (mp 83–84 °C) identical with **7a** prepared via ring closure of **10a**. Fractions containing only the faster moving product (R_f 0.54, 2% MeOH/$CHCl_3$) were pooled and concentrated, and the resulting solid was crystallized from water/EtOH to yield **6** (0.39 g, 45%): mp 88–89 °C; ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 3H), 2.68 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 161.70 (C6a), 154.67 (C5), 147.19 (C3), 137.42 (C3a), 31.45, 17.15, 14.88; UV λ_{max} (ϵ) (EtOH) 215 (9240), 258 (13 410, shoulder), 276 (16 470); (pH 1) 220 (9750), 242 (9420), 273 (13 480); (pH 11) 220 (9820), 258 (12 210, shoulder), 277 (15 640) nm. Anal. Calcd for $C_7H_9N_3S_2$: C, 42.19; H, 4.55; N, 21.09. Found: C, 42.15; H, 4.73; N, 21.15.

3-Methyl-5-(methylthio)-6-(triphenylmethyl)imidazo[4,5-*d*]isothiazole (8). To a solution of **3a** (185 mg, 1 mmol) and triethylamine (0.15 mL, 1.05 mmol) in DMF (5 mL) was added Ph_3CCl (Fluka, 293 mg, 1.05 mmol) in one portion. The solution was stirred for 18 h at rt and poured into cold water (20 mL). The suspension was allowed to stand at 5 °C overnight and the solid collected and dried to yield a crude product, which was chromatographed (25% EtOAc/hexane). The resulting oil crystallized upon addition of pentane to yield 375 mg of **8** (88%, mp 168–170 °C). Recrystallization from MeOH gave 312 mg (73%) of **8** as colorless prisms: mp 175–177 °C; R_f 0.30 (20% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 7.47–7.18 (m, 15H), 2.43 (s, 3H), 2.28 (s, 3H); UV λ_{max} (ϵ) (MeOH) 273 (8960) nm. Anal. Calcd for $C_{25}H_{21}N_3S_2$: C, 70.23; H, 4.95; N, 9.83. Found: C, 70.42; H, 4.98; N, 9.90.

3-Methyl-5-(*N*-methylamino)-4-nitroisothiazole (10a). Material obtained from **9a** (7.96 g, 50 mmol) and MeI (3.42 mL, 55 mmol) via general procedure B was crystallized from EtOAc/hexane to yield 6.9 g (80%) of **10a** in two crops: mp 153–154.5 °C; R_f 0.42 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 9.16 (br s, 1H, D_2O exchangeable), 2.98 (d, J = 5.0 Hz, 3H, collapses to singlet with D_2O exchange), 2.52 (s, 3H). Anal. Calcd for $C_5H_7N_3O_2S$: C, 34.68; H, 4.07; N, 24.26. Found: C, 34.73; H, 4.03; N, 24.50.

5-(*N*-Methylamino)-4-nitroisothiazole (10b). 5-Amino-4-nitroisothiazole (**9b**, 2.20 g, 15.2 mmol) was dissolved in dry DMF (60 mL) under an inert atmosphere and then the solution cooled to 0 °C. NaH (80% w/w dispersion in mineral oil, 0.50 g, 16.7 mmol) was added in one portion and the resulting suspension stirred at 0 °C for 1 h. MeI (2.37 g, 16.7 mmol) was added dropwise over 7 min, and the mixture was allowed to warm to rt over 18 h. Saturated aqueous NH_4Cl (16 mL) was added, and the suspension was slowly diluted with water (150 mL) and then cooled to 0 °C. The solid was collected, washed with cold water, dried *in vacuo*, then triturated with hexane (2 × 15 mL), and dried to yield 1.62 g of crude product (mp 173–180 °C). The crude material was recrystallized from EtOH (75 mL) to yield 1.48 g of **10b** (61%, mp 189–191 °C), which was homogeneous by TLC and ^{1}H NMR, and suitable for use in further reactions. Recrystallization of a portion of this material from toluene (80% recovery) gave light yellow needles: mp 189.5–191.5 °C; R_f 0.32 (20% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 9.17 (br s, 1H, D_2O exchangeable), 8.69 (s, 1H), 3.16 (d, J = 5.3 Hz, 3H, collapses to singlet with D_2O exchange). Anal. Calcd for $C_4H_5N_3O_2S$: C, 30.19; H, 3.17; N, 26.40. Found: C, 30.28; H, 2.97; N, 26.00.

3-Methyl-4-nitro-5-[*N*-(phenylmethyl)amino]isothiazole (11). Material obtained from **9a** (3.21 g, 20.2 mmol) and BnBr (2.64 mL, 22.2 mmol) via general procedure B was crystallized from EtOAc/hexane to yield 4.19 g (83%) of **11**: mp 135–136 °C; R_f 0.49 (20% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 9.75 (br s, 1H, D_2O exchangeable), 7.38–7.29 (m, 5H), 4.54 (s, 2H), 2.49 (s, 3H). Anal. Calcd for $C_{11}H_{11}N_3O_2S$: C, 52.99; H, 4.45; N, 16.86. Found: C, 52.96; H, 4.49; N, 16.73.

General Procedure C (Reduction of Nitroisothiazoles). The appropriate 4-nitroisothiazole (1 equiv) was dissolved in warm 50% aqueous EtOH (0.1 M), and iron powder (6 equiv) was added. To the rapidly stirred suspension was added 1 N HCl (0.25 equiv), and the suspension was heated at reflux for 1 h in the dark under an inert atmosphere. The reaction mixture was allowed to cool briefly, and Dowex-2 (−OH, 1 mL/equiv, washed with EtOH) was added. The mixture was stirred for 0.5 h and filtered through Celite, and the filter cake was washed with warm EtOH. The combined filtrates were concentrated in the dark to a small volume (not to dryness), and the resulting slurry was lyophilized in the dark. These 4,5-diaminoisothiazoles slowly decompose to brightly colored products upon exposure to light but can be stored indefinitely in the freezer.

4-Amino-3-methyl-5-(*N*-methylamino)isothiazole (12a). From **10a** (7.20 g, 41.6 mmol) according to general procedure C was obtained 5.59 g (94%) of **12a**: mp 128–129 °C; R_f 0.33 (5% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 5.83 (br s, 1H, D_2O exchangeable), 3.62 (s, 2H, D_2O exchangeable), 2.74 (d, J = 5.1 Hz, 2H, collapses to singlet with D_2O exchange), 2.10 (s, 3H). Anal. Calcd for $C_5H_9N_3S$: C, 41.94; H, 6.33; N, 29.34. Found: C, 41.87; H, 6.27; N, 28.99.

4-Amino-5-(*N*-methylamino)isothiazole (12b). From **10b** (1.16 g, 7.3 mmol) according to general procedure C was obtained 0.91 g (97%) of **12b** (mp 107–108 °C), which was suitable for use in subsequent reactions. Chromatography of the crude material in the dark afforded 0.66 g (70%) of **12b**: mp 114.5–115 °C; R_f 0.52 (10% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.72 (s, 1H), 5.90 (br s, 1H, D_2O exchangeable), 3.85 (br s, 2H), 2.75 (d, J = 5.1 Hz, 3H, collapses to singlet with D_2O exchange). Anal. Calcd for $C_4H_7N_3S$: C, 37.19; H, 5.46; N, 32.53. Found: C, 37.50; H, 5.39; N, 31.92.

4-Amino-3-methyl-5-[*N*-(phenylmethyl)amino]isothiazole (13). From **11** (4.0 g, 16 mmol) according to general procedure C was obtained 3.36 g (95%) of **13**: mp 105–107 °C; R_f 0.51 (5% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.40–7.22 (m, 5H), 6.37 (t, J = 5.5 Hz, 1H, D_2O exchangeable), 4.20 (d, J = 5.5 Hz, 2H, collapses to singlet with D_2O exchange), 3.77 (s, 2H, D_2O exchangeable), 2.09 (s, 3H). Anal. Calcd for

$C_{11}H_{13}N_3S$: C, 60.25; H, 5.97; N, 19.16. Found: C, 60.62; H, 5.91; N, 18.98.

3,6-Dimethyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (7a). Material obtained from **12a** (1.58 g, 11 mmol) and Me_2SO_4 (1.1 mL, 11.6 mmol) following general procedure A was chromatographed ($CHCl_3$), and the resulting oil was crystallized from ether/petroleum ether to yield 1.53 g (70%) of **7a** after three crops: mp 82–83 °C; R_f 0.49 (2% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H), 2.65 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 152.56 (C5), 152.13 (C3), 151.05 (C6a), 146.75 (C3a), 32.99, 16.39, 15.26; UV λ_{max} (ϵ) (EtOH) 219 (19 930), 270 (9800); (pH 1) 237 (11 740), 272 (14 050); (pH 11) 223 (17 240), 272 (9960) nm. Anal. Calcd for $C_7H_9N_3S_2$: C, 42.19; H, 4.55; N, 21.09. Found: C, 42.16; H, 4.74; N, 21.23.

6-Methyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (7b). Material obtained from **12b** (129 mg, 1 mmol) and Me_2SO_4 (0.10 mL, 1.05 mmol) following general procedure A was chromatographed (1% MeOH/$CHCl_3$) to yield 127 mg of **7b** (67%, mp 61–62 °C). A sample was recrystallized from EtOH/water for analysis: mp 61–62 °C; R_f 0.83 (10% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.51 (s, 1H), 3.77 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 153.07 (C5), 151.68 (C6a), 148.13 (C3a), 143.46 (C3), 33.00, 15.04; UV λ_{max} (ϵ) (MeOH) 220 (15 340), 273 (7610) nm. Anal. Calcd for $C_6H_7N_3S_2$: C, 38.89; H, 3.81; N, 22.69. Found: C, 38.98; H, 3.76; N, 22.31.

3-Methyl-5-(methylthio)-6-(phenylmethyl)imidazo[4,5-*d*]isothiazole (14). Material obtained from **13** (3.36 g, 15.3 mmol) and Me_2SO_4 (1.52 mL, 16.1 mmol) following general procedure A was chromatographed ($CHCl_3$) and the resulting oil crystallized from 1:1 ether/petroleum ether to yield **14** (2.18 g, mp 88–89 °C). The filtrate was combined with chromatography fractions containing product contaminated with a faster moving impurity, rechromatographed (20% EtOAc/hexane), and then crystallized from 1:1 ether/petroleum ether to give an additional 1.12 g of **14** (mp 87–88 °C). The combined yield was 3.3 g (78%): R_f 0.61 (5% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.43–7.33 (m, 5H), 5.28 (s, 2H), 2.69 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 152.09 (C5), 151.91 (C3), 149.75 (C6a), 146.90 (C3a), 134.31, 128.92, 128.73, 128.60, 49.43, 16.24, 15.41; UV λ_{max} (ϵ) (EtOH) 212 (20 630), 270 (8240); (pH 1) 239 (11 210), 271 (12 630); (pH 11) 222 (16 580), 272 (9050) nm. Anal. Calcd for $C_{13}H_{13}N_3S_2$: C, 56.69; H, 4.76; N, 15.26. Found: C, 56.80; H, 4.90; N, 15.22.

3,6-Dimethyl-5-methanesulfonylimidazo[4,5-*d*]isothiazole (15). 3,6-Dimethyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (**7a**, 0.45 g, 2.25 mmol) in $CHCl_3$ (15 mL) was refluxed with oxone (Aldrich, 4.15 g, 6.75 mmol) and 2.25 g of wet alumina (20 mL water per 100 g of neutral activated alumina) for 20 h. The reaction mixture was concentrated and the resulting residue chromatographed ($CHCl_3$ to 1% MeOH/$CHCl_3$) to yield 0.30 g (58%) of **15**: mp 148–150 °C; R_f 0.73 (5% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 4.13 (s, 3H), 3.53 (s, 3H), 2.54 (s, 3H); UV λ_{max} (ϵ) (MeOH) 220 (17 430), 258 (10 320) nm. Anal. Calcd for $C_7H_9N_3S_2O_2$: C, 36.35; H, 3.92; N, 18.17. Found: C, 36.41; H, 4.12; N, 17.92.

3-Methyl-5-methanesulfonyl-6-(phenylmethyl)imidazo[4,5-*d*]isothiazole (16). 3-Methyl-5-(methylthio)-6-(phenylmethyl)imidazo[4,5-*d*]isothiazole (**14**, 475 mg, 1.72 mmol), oxone (3.17 g, 5.16 mmol), and 1.72 g of wet alumina were reacted in the same manner as for **15**. The resulting residue was chromatographed (30% EtOAc/hexane) and the crude material crystallized from ether/pentane to yield 324 mg (61%) of **16**: mp 104.8–105.5 °C; R_f 0.55 (2% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.48 (br s, 5H), 5.71 (s, 2H), 3.61 (s, 3H), 2.49 (s, 3H); UV λ_{max} (ϵ) (MeOH) 217 (18 630), 258 (9810), nm. Anal. Calcd for $C_{13}H_{13}N_3S_2O_2$: C, 50.80; H, 4.26; N, 13.67. Found: C, 50.90; H, 4.32; N, 13.77.

3,6-Dimethylimidazo[4,5-*d*]isothiazole (18). 4-Amino-3-methyl-5-(*N*-methylamino)isothiazole (**12a**, 1.43 g, 10 mmol) was dissolved in 25 mL of dry 2-methoxyethanol in the dark under an inert atmosphere. The solution was heated to 120 °C, and diethoxymethyl acetate (1.70 g, 10.5 mmol) was added dropwise over a period of 10 min. The solution was refluxed for 1.5 h, cooled, and poured into cold water (50 mL) containing $NaHCO_3$ (1.0 g, 12 mmol). Silica (15 g) was added, and the mixture was cautiously concentrated *in vacuo* and azeotroped with toluene (2 × 50 mL). The adsorbed material was applied to a column and chromatographed (4% MeOH/$CHCl_3$) and then crystallized from water to yield 0.89 g (58%) of **18**: mp 100.5–101.5 °C; R_f 0.63 (10% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.99 (s, 1H), 3.85 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 153.41 (C3), 149.55 (C6a), 148.66 (C3a), 146.84 (C5), 33.49, 16.38; UV λ_{max} (ϵ) (EtOH) 246 (5320); (pH 1) 248 (7120); (pH 11) 249 (5290) nm; MS (EI) *m/e* 153 (M^+); HRMS calcd for $C_6H_7N_3S$ 153.0361, found 153.0357. Anal. Calcd for $C_6H_7N_3S$: C, 47.04; H, 4.61; N, 27.43. Found: C, 47.38; H, 4.68; N, 27.21.

5-Bromo-3,6-dimethylimidazo[4,5-*d*]isothiazole (20). Br_2 (0.13 mL, 5 mmol) was added dropwise to a solution of **18** (153 mg, 1 mmol) and NaOAc (0.82 g, 10 mmol) in AcOH (10 mL) at room temperature. The flask was stoppered tightly, and then the mixture was stirred at 100 °C for 3.5 h, at which time a white precipitate had formed. The mixture was allowed to cool to room temperature, the solvent removed under reduced pressure, and the residue azeotroped with toluene (2 × 10 mL). The resulting solid was partitioned between water (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The crude material was chromatographed (30% EtOAc/hexane) to provide 158 mg (68%) of **20**: mp 142–143 °C dec; R_f 0.36 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 152.21 (C3), 149.91 (C6a), 145.59 (C3a), 127.63 (C5), 34.56, 16.09; UV λ_{max} (ϵ) (MeOH) 212 (15 020), 255 (5950) nm. Anal. Calcd for $C_6H_6N_3SBr$: C, 31.05; H, 2.61; N, 18.10. Found: C, 31.22; H, 2.52; N, 17.75.

3-Methyl-6-(phenylmethyl)imidazo[4,5-*d*]isothiazole (19). 4-Amino-3-methyl-5-[*N*-(phenylmethyl)amino]isothiazole (**13**, 1.64 g, 7.5 mmol) was dissolved in 20 mL of dry 2-methoxyethanol in the dark under an inert atmosphere. The solution was heated to 120 °C, and diethoxymethyl acetate (1.70 g, 10.5 mmol) was added dropwise over 10 min. The solution was heated at reflux for 3 h, cooled, and poured into cold water (20 mL) containing 0.68 g (8 mmol) of $NaHCO_3$. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a dark red oil. The crude product was chromatographed twice (EtOAc, then 1% MeOH/$CHCl_3$) and then crystallized from MeOH/water to provide 0.88 g (48%) of **19**: mp 88–89 °C; R_f 0.34 (EtOAc); ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 7.44–7.31 (m, 5H), 5.41 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 153.27 (C3), 148.65 (C3a), 148.10 (C6a), 146.03 (C5), 135.09, 128.95, 128.52, 128.50, 49.99, 16.27; UV λ_{max} (ϵ) (EtOH) 250 (7190); (pH 1) 249 (8810); (pH 11) 250 (7490) nm. Anal. Calcd for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.84; H, 4.96; N, 18.24.

5-Amino-4-nitroisothiazole-3-carboxamide (22). 5-Acetamido-4-nitroisothiazole-3-carboxylic acid (**21**, 2.31 g, 10 mmol) was suspended in thionyl chloride (50 mL) and heated at reflux for 35 min. The solvent was removed and the residue azeotroped with CH_2Cl_2 (10 mL) and then toluene (3 × 10 mL). The resulting solid was cooled on ice under an inert atmosphere, and cold (−15 °C) methanolic ammonia (100 mL) was added in one portion. The mixture was stirred at 0 °C until all solid had dissolved, transferred to a pressure bottle, and stirred at rt for 24 h. The solvent was evaporated and the residue recrystallized from water (50 mL) to give 1.78 g (90%) of **22** hemihydrate as light yellow plates: mp 213–214 °C; R_f 0.28 (10% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.83 (br s, 2H, D_2O exchangeable), 7.96 (br s, 1H, D_2O exchangeable), 7.67 (br s, 1H, D_2O exchangeable); IR (KBr) 3420–3150, 1660, 1613, 1585, 1556, 1475, 1446, 1375, 1272, 1022, 769, 650 cm^{-1}. Anal. Calcd for $C_4H_4N_4O_3S \cdot {}^1/_2H_2O$: C, 24.37; H, 2.56; N, 28.42. Found: C, 24.50; H, 2.52; N, 28.13.

5-Amino-4-nitroisothiazole-3-carbonitrile (23). 5-Amino-4-nitroisothiazole-3-carboxamide (**22**, 1.50 g, 8.0 mmol) was suspended in phosphorus oxychloride (16 mL). The suspension was heated to 85 °C for 1.25 h, at which point all solid had dissolved. The solvent was removed and the residue partitioned between EtOAc (25 mL) and water (25 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine and then dried over $MgSO_4$. The solvent

was removed and the crude product recrystallized from 50% aqueous EtOH to afford 0.98 g (72%) of **23**: mp 185–186 °C; R_f 0.56 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 9.12 (br s, 2H, D_2O exchangeable); IR (KBr) 3400–3150, 2260, 1615, 1560, 1540, 1450, 1370, 1273, 1061, 868, 814, 767 cm^{-1}. Anal. Calcd for $C_4H_2N_4O_2S$: C, 28.24; H, 1.18; N, 32.93. Found: C, 28.41; H, 1.02; N, 32.92.

4,5-Diaminoisothiazole-3-carbonitrile (24). Compound **23** (0.34 g, 2 mmol) was reacted according to general procedure C, except the solution was refluxed for only 20 min. The lyophilized residue was purified by chromatography (4% MeOH/$CHCl_3$) to afford 0.17 g (62%) of **24**, which was homogeneous by TLC and ^1H NMR, but did not give a satisfactory elemental analysis: mp 151–152 °C; R_f 0.41 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 6.36 (s, 2H, D_2O exchangeable), 4.41 (s, 2H, D_2O exchangeable); IR (KBr) 3450–3150, 2243, 1618, 1560, 1441, 1382, 1295, 835 cm^{-1}; MS (EI) *m/e* 140 (M^+); HRMS calcd for $C_4H_4N_4S$ 140.0157, found 140.0157. Anal. Calcd for $C_4H_4N_4S$: C, 34.28; H, 2.88; N, 39.97. Found: C, 36.25; H, 3.20; N, 39.50.

3-Amino-5-(*N*-methylamino)isothiazole-4-carboxylic Acid (26). A suspension of ethyl 3-amino-5-(*N*-methylamino)-isothiazole-4-carboxylate (**25**, 3.30 g, 16.4 mmol) in 1 N potassium hydroxide (30 mL) was heated at reflux for 0.5 h. The resulting solution was cooled on ice and then neutralized with the dropwise addition of ice cold 1 N hydrochloric acid (30 mL). The resulting solid was collected and then dried to constant mass *in vacuo* (0.1 mmHg) over potassium pentoxide to yield 2.7 g (93%) of **26** which retained 0.25 mol of water: mp 120.7–121 °C dec; ^1H NMR (DMSO-d_6) δ 12.67 (br s, 1H, D_2O exchangeable), 7.67 (br s, 1H, D_2O exchangeable), 6.27 (br s, 2H, D_2O exchangeable), 2.82 (d, 3H). Anal. Calcd for $C_5H_7N_3O_2S \cdot 1/4H_2O$: C, 33.80; H, 4.25; N, 23.65. Found: C, 33.80; H, 4.18; N, 23.63.

3-Acetamido-5-(*N*-methylacetamido)isothiazole (27). A suspension of **26** (2.00 g, 11.25 mmol) in water (55 mL) was heated at reflux for 0.25 h, at which point all the solid had dissolved. The solution was allowed to cool and then concentrated and azeotroped with toluene (2 × 20 mL). Acetic anhydride (20 mL) was added, and the resulting suspension was stirred for 48 h at rt. The mixture was poured onto 100 mL of ice–water, and the walls of the reaction flask were washed with additional ice–water (100 mL). The mixture was allowed to warm to rt while it was stirred and then allowed to stand at 0 °C. The solid was collected, washed with cold water, and dried to yield 2.31 g (96%) of **27**: mp 255–257 °C dec; R_f 0.68 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 10.74 (s, 1H, D_2O exchangeable), 7.38 (s, 1H), 3.52 (s, 3H), 2.37 (s, 3H), 2.04 (s, 3H). Anal. Calcd for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.70. Found: C, 45.09; H, 5.06; N, 19.47.

3-Acetamido-5-(*N*-methylacetamido)-4-nitroisothiazole (28). To a solution of trifluoromethanesulfonic acid (7.1 mL, 80 mmol) in dry CH_2Cl_2 (200 mL) at rt was added fuming nitric acid (90%, 1.9 mL, 40 mmol) with vigorous stirring. The resulting suspension was cooled to −78 °C, and **27** (2.13 g, 10 mmol) was added in one portion. The reaction mixture was allowed to warm to 0 °C over 1.5 h and then poured onto 200 g of ice. The organic layer was removed, and the aqueous layer was washed with $CHCl_3$ (2 × 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ (50 mL), dried with a small amount of $MgSO_4$, filtered, and then concentrated *in vacuo*. The resulting residue was recrystallized from boiling EtOH (70 mL) to yield **28** (2.01 g, 78%) as light yellow needles: mp 163–165 °C; R_f 0.51 (5% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.24 (s, 1H, D_2O exchangeable), 3.44 (s, 3H), 2.44 (s, 3H), 2.39 (s, 3H); MS (EI) *m/e* 258, 216, 174; HRMS calcd for $C_8H_{10}N_4O_4S$ 258.0423, found 258.0418. Anal. Calcd for $C_8H_{10}N_4O_4S$: C, 37.21; H, 3.90; N, 21.69. Found: C, 37.32; H, 3.72; N, 21.55.

3-Acetamido-5-(*N*-methylamino)-4-nitroisothiazole (29). To **28** (1.94 g, 7.5 mmol) at 0 °C under an inert atmosphere was added a cold solution of methanolic ammonia (75 mL). The resulting solution was stirred for 1.25 h at 0 °C and the solvent removed *in vacuo* at 0 °C. The residue was recrystallized from EtOH to yield 1.50 g (93%) of **29** as yellow crystals: mp 175–176 °C; R_f 0.55 (EtOAc); ^1H NMR ($CDCl_3$) δ 10.08 (br s, 1H, D_2O exchangeable), 8.35 (br s, 1H, D_2O exchangeable), 7.26 (s, 1H), 3.16 (d, J = 5.3 Hz, 3H, collapses to singlet with D_2O exchange), 2.36 (s, 3H). Anal. Calcd for $C_6H_8N_4O_3S$: C, 33.33; H, 3.73; N, 25.91. Found: C, 33.53; H, 3.61; N, 25.74.

3-Acetamido-4-amino-5-(*N*-methylamino)isothiazole (30). Compound **29** (1.45 g, 6.7 mmol) was reacted according to general procedure C for 45 min at reflux. After workup with Dowex-2, filtration, and concentration to a small volume (~40 mL), a precipitate began to form. The mixture was allowed to stand overnight at 5 °C and the resulting solid collected and dried *in vacuo* to yield 0.76 g of pure **30** (61%). Lyophilization of the filtrate provided additional material (~0.5 g, mp <175 °C), which contained a base line impurity by TLC, but was of sufficient purity for use in further reactions: mp 183–185 °C dec; R_f 0.28 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 10.14 (br s, 1H, D_2O exchangeable), 6.13 (q, J = 5.0 Hz, 1H, D_2O exchangeable), 3.67 (br s, 2H, D_2O exchangeable), 2.74 (d, J = 5.0 Hz, 3H, collapses to singlet with D_2O exchange), 2.02 (s, 3H). Anal. Calcd for $C_6H_{10}N_4OS$: C, 38.70; H, 5.41; N, 30.08. Found: C, 38.62; H, 5.37; N, 29.90.

3-Acetamido-6-methyl-5-(methylthio)imidazo[4,5-*d*]-isothiazole (31). Compound **30** (0.19 g, 1 mmol) was dissolved in 30 mL of warm, anhydrous 1,4-dioxane and then cooled to rt with a cool water bath. Before the starting material precipitated, (thiocarbonyl)diimidazole (0.19 g, 1 mmol) was added in one portion, and the resulting solution was stirred for 1 h at rt. Water (10 mL), 1 N NaOH (1.1 mL), and Me_2SO_4 (132 mg, 1.05 mmol) were added sequentially. The resulting solution was stirred for 1 h at rt and then concentrated *in vacuo*. The gum was chromatographed (1% MeOH/$CHCl_3$ to 2% MeOH/$CHCl_3$) to provide 128 mg (53%) of **31**: mp 183–185 °C; R_f 0.61 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 10.54 (s, 1H, D_2O exchangeable), 3.73 (s, 3H), 2.63 (s, 3H), 2.09 (s, 3H); UV λ_{max} (ϵ) (MeOH) 224 (12 940), 247 (10 960), 277 (10 900) nm; MS (EI) *m/e* 242, 200, 185, 167; HRMS calcd for $C_8H_{10}N_4OS_2$ 242.0296, found 242.0304. Anal. Calcd for $C_8H_{10}N_4OS_2 \cdot 3/4H_2O$: C, 37.56; H, 4.53; N, 21.90. Found: C, 37.65; H, 4.60; N, 21.50.

3-Amino-6-methyl-5-(methylthio)imidazo[4,5-*d*]isothiazole (32). To **31** (0.86 g, 3.55 mmol) in a stainless steel bomb was added methanolic ammonia (35 mL). The reaction vessel was sealed and heated to 100 °C for 18 h. The resulting solution was cooled to rt and then allowed to stand at −15 °C overnight. The solid was collected, washed with cold MeOH, and dried to provide 0.55 g (78%) of **32**: mp 206.5–207 °C dec; R_f 0.48 (990:9:1 EtOAc/MeOH/water); ^1H NMR (DMSO-d_6) δ 6.33 (s, 2H, D_2O exchangeable), 3.66 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 151.51 (C3), 149.71 (C5), 148.85 (C6a), 136.63 (C3a), 32.52, 15.71; UV λ_{max} (ϵ) (MeOH) 228 (14 890), 246 (shoulder), 263 (shoulder); (pH 1) 227 (14 040), 242 (shoulder), 276 (9730); (pH 11) 223 (39 560), 342 (6550) nm. Anal. Calcd for $C_6H_8N_4S_2$: C, 35.98; H, 4.03; N, 27.97. Found: C, 36.21; H, 3.90; N, 27.78.

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