Synthesis of 2-Guanyl-4-(3-substituted-phenyl)thiazoles with Potent Histamine H_2-Antagonism Activity

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The syntheses of novel 2-guanyl-4-(3-substituted-phenyl)thiazoles showing potent histamine H_2-antagonism activity is reported. The most potent compound is **17** where the substitution at the 3-position of the phenyl ring is an *N*-methylamidino function.

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Since the introduction of cimetidine and ranitidine [1] (Figure 1) as useful healing agents for gastric and duodenal ulcers, there has been an intensification of effort on the part of medicinal chemists to synthesize more efficacious drugs with fewer side effects. These derivatives block the action of histamine by binding to the H_2-histamine receptor and thus prevent the secretion of gastric acid. The inhibition of gastric acid released by H_2-receptor antagonists makes these drugs useful in the treatment of conditions caused or exacerbated by gastric acidity such as peptic ulcers. A third clinically useful drug, famotidine [2] was subsequently added to the list of efficacious ulcer healing H_2-receptor antagonists. Other experimental drugs resembling famotidine which are potent anti secretory H_2-receptor antagonists are tiotidine [3] and zaltidine [4]. The latter three drugs contain the 2-guanylthiazole moiety as a common structural feature.

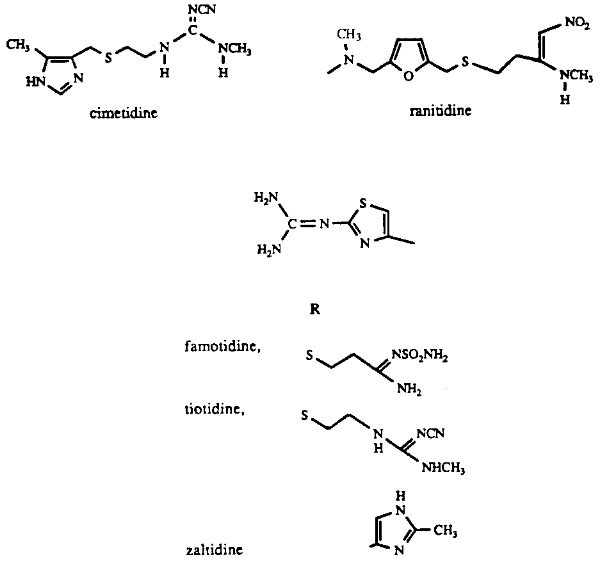


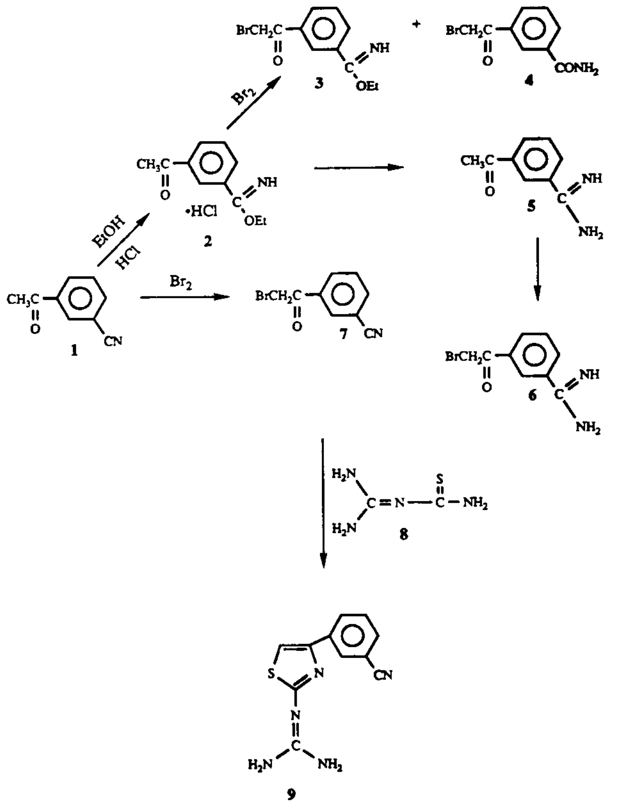
Figure 1

We now report the syntheses of novel 2-guanylthiazoles showing potent histamine H_2-antagonism activity. These are the title compounds, 2-guanyl-4-(3-substituted-phenyl)-thiazoles.

Chemistry.

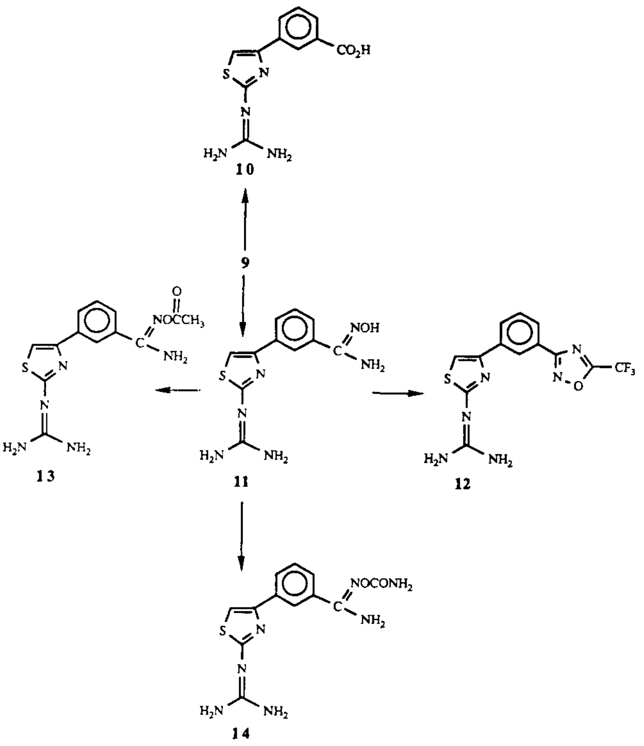
A key 2-guanylthiazole intermediate in this series, compound **9**, was prepared in a "one pot" reaction starting with *m*-cyanoacetophenone, **1**. Bromination of **1** afforded the α-bromo-*m*-cyanoacetophenone, **7**. Treatment of **7** with amidinothiourea, **8**, *in situ* gave the 2-guanylthiazole **9** (Scheme 1).

Scheme 1

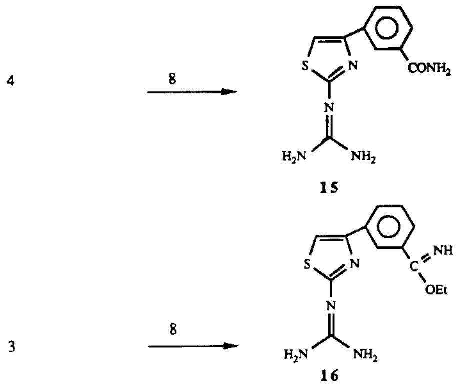


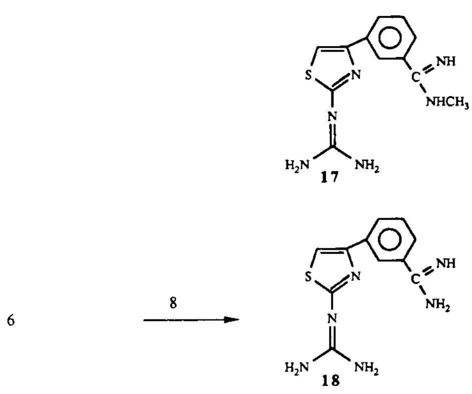
The reaction of **9** with hydroxylamine afforded the amide oxime **11** (Scheme 2). Cyclization of **11** to the corresponding 1,2,4-oxadiazole **12** was effected by reaction with trifluoroacetic anhydride. Treatment of **11** with acetic anhydride at room temperature afforded *O*-acetylamide oxime **13**, while reaction of **11** with potassium cyanate afforded the *O*-carbamylamide oxime **14**. Hydrolysis of nitrile **9** under acidic conditions gave the corresponding carboxylic acid derivative **10**. Thiazoles **15**, **16** and **18** (Scheme 3) were prepared *via* the reactions of **8** with the corresponding α-bromoacetophenones **5**, **3** and **6** respectively, whose syntheses are given in Scheme 1. The *N*-methamidino derivative **17** was obtained from the reaction of the iminoether **16** with methylamine.

Scheme 2



Scheme 3





Biological Results.

Compounds **9-11**, **13-15** and **17-18** were tested for their histamine H_2-antagonism activity by a standard previously described method [5]. Compounds **11**, **13**, **14**, **15**, **17** and **18** all proved to be more potent histamine H_2-antagonists than cimetidine with compound **17** being the most potent in the series. The apparent dissociation constant (pA_2) of the H_2-antagonist cimetidine as determined by the assay is 6.5 while that of compound **17** is 8.2. Compounds **9** and **10** had pA_2 values comparable to cimetidine [6].

EXPERIMENTAL

Melting points were measured in a Thomas-Hoover oil bath melting point apparatus and are reported uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 289 infrared spectrophotometer and the ^1H nmr spectra were measured on a Varian XL-100, FT-80A or JEOL-60 spectrometer. All spectra were consistent with the assigned structures. The reported values for ir are cm^{-1} and ^1H nmr are δ (ppm). Combustion analyses were performed on a Perkin Elmer Model 240 elemental analyzer and were within ±0.4% of the theoretical values.

[4-(3-Cyanophenyl)-2-thiazolyl]guanidine Hydrobromide (**9**).

To a solution of 4.35 g (0.03 mole) of *m*-cyanoacetophenone in 75 ml of chloroform was added 4.77 g (0.03 mole) of bromine. The solution was stirred at room temperature for 20 minutes. The solution was then evaporated in a rotary evaporator and the residue was dissolved in 20 ml of acetonitrile. To this solution was added a hot solution of 3.54 g (0.03 mole) of amidinothiourea in 75 ml of ethanol. The mixture was heated under reflux for 1 hour. The mixture was filtered and the filter cake was recrystallized from water. The product was dried *in vacuo* at 100° for 3 hours providing 2.4 g (23%) of product, mp 292-294° dec; ir (potassium bromide): 2240, 1686, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.78 (m, 2H), 8.10 (s, 1H), 8.30 (bs, 4H), 8.41 (m, 2H), 11.0 (vbs, 1H).

Anal. Calcd. for $C_{11}H_{10}BrN_5S \cdot H_2O$: C, 38.60; H, 3.54; N, 20.47. Found: C, 38.65; H, 3.35; N, 20.49.

3-[2-[(Aminoiminomethyl)amino]-4-thiazolyl]benzoic Acid Hydrochloride (**10**).

A mixture of 1 g (0.003 mole) of **9** in 30 ml of concentrated hydrochloric acid was heated under reflux for 12 hours. The mixture was filtered and the precipitate was triturated with 50 ml of 20% sodium hydroxide solution. The insoluble material was removed by filtration and the filtrate was acidified with concentrated hydrochloric acid. The resulting precipitate was removed by filtration and was recrystallized from ethanol (water was added to provide a solution). There was obtained 0.3 g (35%) of product, mp 305-307° dec; ir (potassium bromide): 1669, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.6 (t, 1H), 7.96 (s, 2H), 8.17-9.0 (bm, 8H).

Anal. Calcd. for $C_{11}H_{10}N_3O_2S{\cdot}HCl$: C, 44.22; H, 3.71; N, 18.75. Found: C, 44.05; H, 3.82; N, 18.84.

3-[2-[(Aminoiminomethyl)amino]-4-thiazolyl]-*N*-hydroxybenzenecarboximidamide Dihydrochloride (**11**).

A stirred mixture of 3.4 g (0.01 mole) of **9**, 1.38 g (0.02 mole) of hydroxylamine hydrochloride and 4.24 g (0.04 mole) of sodium carbonate in 60 ml of dry *N,N*-dimethylformamide was heated under reflux for 6 hours. The mixture was filtered and the filtrate was diluted with a few ml of water. The precipitate which resulted was collected and recrystallized from *N,N*-dimethylformamide. The product was added to 150 ml of saturated ethanolic hydrogen chloride solution and the solution was filtered to remove solid particles. The filtrate on cooling in ice gave 0.4 g (11%) of product, mp 246° dec; ir (potassium bromide): 1680, 1616 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.72 (m, 2H), 8.01 (s, 1H), 8.25-8.65 (bm, 7H), 9.21 (bs, 2H), 11.43 (bs, 1H), 13.10 (bs, 1H).

Anal. Calcd. for $C_{11}H_{12}N_6OS{\cdot}2HCl$: C, 37.83; H, 4.04; N, 24.07. Found: C, 37.68; H, 4.02; N, 23.80.

[4-[3-[5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]-2-thiazoyl]-guanidine Hydrochloride (**12**).

A mixture of 1 g (0.003 mole) of **11** in 60 ml of trifluoroacetic anhydride was stirred at room temperature for 30 minutes. The insoluble material was collected on a filter and was then triturated with 50 ml of 20% sodium carbonate solution. The crude product was recrystallized from ethanol and then dissolved in hot ethanol. The solution was acidified with ethereal hydrochloric acid solution. On cooling in ice there was obtained 0.4 g (36%) of product, mp 240-243°; ir (potassium bromide): 1708, 1598 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.68 (t, 1H), 8.0 (s, 1H), 8.05-8.55 (bm, 6H), 12.7 (bs, 2H).

Anal. Calcd. for $C_{13}H_9N_6F_3OS{\cdot}HCl$: C, 39.95; H, 2.58; N, 21.51. Found: C, 39.85; H, 2.63; N, 21.39.

N-(Acetyloxy)-3-[[2-[(aminoiminomethyl)amino]-4-thiazolyl]benzenecarboximidamide Dihydrochloride (**13**).

A mixture of 1 g (0.003 mole) of powdered **11** in 150 ml of acetic anhydride was stirred at room temperature for 1 hour. The mixture was filtered and the precipitate was triturated with 100 ml of 20% sodium carbonate solution. The insoluble material was recrystallized from 2-ethoxyethanol with the addition of petroleum ether to induce precipitation. The purified free base thus obtained was added to 50 ml of hot saturated ethanolic hydrogen chloride solution. The solution was cooled in ice and was diluted to the cloudy point with petroleum ether. There was obtained 0.15 g (13%) of product, mp 260° dec; ir (potassium bromide): 1800, 1748, 1672, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.19 (s, 3H), 4.70 (vbs, 3H), 7.50 (t, 1H), 7.72 (d, 1H), 7.87 (s, 1H), 8.10 (d, 1H), 8.15 (bs, 1H), 8.43 (bs, 4H), 12.83 (vbs, 1H).

Anal. Calcd. for $C_{13}H_{14}N_6O_2S{\cdot}2HCl$: C, 39.90; H, 4.12; N, 21.48. Found: C, 40.25; H, 4.08; N, 21.61.

N-[(Aminocarbonyl)oxy]-3-[2-[(aminoiminomethyl)amino]-4-thiazolyl]benzenecarboximidamide Hydrochloride Hemihydrate (**14**).

To a solution of 0.698 g (0.002 mole) of **11** in 40 ml of water was added 0.162 g (0.002 mole) of potassium cyanate. The mixture was stirred at room temperature for 2 hours. The precipitate was collected and dissolved in boiling water. The solution was cooled to room temperature. An equal volume of ethanol was added. On cooling the solution in ice there was obtained 0.3 g (41%) of product, mp 222-224° dec; ir (potassium bromide): 1710, 1613, 1590 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.91 (bs, 2H), 6.97 (bs, 2H), 7.51 (t, 1H), 7.89 (d, 1H), 7.92 (s, 1H), 8.13 (d, 1H), 8.4 (bs, 6H).

Anal. Calcd. for $C_{12}H_{13}N_7O_2S{\cdot}HCl{\cdot}1/2H_2O$: C, 39.51; H, 4.14; N, 26.89. Found: C, 39.26; H, 4.03; N, 29.61.

3-Acetylbenzenecarboximidic Acid Ethyl Ester Hydrochloride (**2**).

Into an ice-cooled solution of 29 g (0.2 mole) of *m*-cyanoacetophenone in 375 ml of dry toluene, containing 13 ml (0.2 mole) of absolute ethanol was bubbled a stream of hydrogen chloride gas for 2 hours. The solution was allowed to stand overnight in the refrigerator. There was obtained 34 g (75%) of product which was used directly without purification. An analytical sample (mp 130-132°) was obtained by recrystallization of a sample from ethanol-petroleum ether; ir (potassium bromide): 2810, 1675, 1630 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO_2{\cdot}HCl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 59.16; H, 5.93; N, 6.61.

3-(Bromoacetyl)benzenecarboximidic Acid Ethyl Ester Hydrobromide (**3**).

To 350 ml of glacial acetic acid warmed to 60° was added 4.54 g (0.02 mole) of **2**. To this solution was added 3.18 g (0.02 mole) of bromine. After removal of the heat source the solution was allowed to stir until a colorless solution was obtained (approximately 1 hour). Anhydrous ethyl ether was added to the point where a cloudy solution was obtained. The precipitate which resulted was collected to give 4.5 g (83%) (mp 125° dec) of a mixture of predominantly 3-(bromoacetyl)benzenecarboximidic acid ethyl ester, hydrobromide (**3**) and a small amount of 3-(bromoacetyl)benzenecarboxamide (**4**). Recrystallization of the mixture from a large volume of ethyl acetate gave 3.5 g (64%) of **3** with mp 130-132°; ir (potassium bromide): 3410, 2930, 1695, 1625 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.55 (t, 3H), 4.68 (q, 2H), 5.04 (s, 2H), 7.88 (t, 2H), 8.38 (d, 1H), 8.42 (d, 1H), 8.68 (bs, 1H).

Anal. Calcd. for $C_{11}H_{12}BrNO_2{\cdot}HBr$: C, 37.63; H, 3.73; N, 3.99. Found: C, 37.21; H, 3.55; N, 3.87.

3-(Bromoacetyl)benzenecarboxamide (**4**).

The filtrate from the recrystallization of **3** was evaporated to dryness. The residue was recrystallized from acetonitrile to give a first crop of solid. Further cooling of the filtrate afforded a second crop of purer product. The product was further purified by recrystallization from ethyl acetate to give 0.5 g (10%) of product of approximated 85% purity (mp 133-136°) which was used in the next step to prepare **15**.

3-Acetylbenzenecarboximidamide Hydrochloride (**5**).

A mixture of 14 g (0.06 mole) of **2** and 14 g (0.15 mole) of finely ground ammonium carbonate in 100 ml of ethanol was heated for

3 hours at boiling temperature. The solution was allowed to cool and the first small amount of precipitate that was found was discarded. On further cooling the filtrate, there was obtained 6.7 g (54%) of the product, mp 193° dec; ir (potassium bromide): 2985, 1665 cm^{-1}.

Anal. Calcd. for $C_9H_{10}N_2O{\cdot}HCl{\cdot}1/5H_2O$: C, 53.44; H, 5.68; N, 13.85. Found: C, 53.87; H, 5.55; N, 13.68.

3-Bromoacetylbenzenecarboximidamide Hydrochloride (**6**).

To a solution of 0.594 g (0.003 mole) of **5** in 10 ml of glacial acetic acid was added 0.477 g (0.003 mole) of bromine. After standing overnight the precipitate that was formed was collected and recrystallized from ethanol-petroleum ether to give 0.3 g (35%) of an analytical sample of **6**, mp 157-159°; ir (potassium bromide): 3410, 3281, 3180, 3079, 2928, 1664 cm^{-1}.

Anal. Calcd. for $C_9H_9BrN_2O{\cdot}HCl{\cdot}1/2H_2O$: C, 37.72; H, 3.87; N, 9.78. Found: C, 37.74; H, 3.60; N, 9.50.

3-[2-[(Aminoiminomethyl)amino]-4-thiazolyl]benzenecarboxamide Hydrobromide (**15**).

A stirred mixture of 0.48 g (0.002 mole) of **4** and 0.24 g (0.002 mole) of **8** in 20 ml of a 50:50 mixture of acetonitrile-ethanol was heated under reflux for 5 minutes. The crude product was removed by filtration and was dissolved in a minimum volume of boiling water. An equal volume of ethanol was added after the solution had cooled. On cooling the solution in ice, there was obtained 0.25 g (36%) of product mp 304-306° dec; ir (potassium bromide): 1688, 1659, 1612 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 7.46 (bs, 1H), 7.51 (t, 1H), 7.88 (s, 1H), 7.90 (s, 1H), 8.03-8.48 (bm, 7H), 12.05 (vbs, 1H).

Anal. Calcd. for $C_{11}H_{11}N_5OS{\cdot}HBr$: C, 38.60; H, 3.54; N, 20.46. Found: C, 38.54; H, 3.56; N, 20.33.

3-[2-[(Aminoiminomethyl)amino]-4-thiazolyl]benzenecarboximidic Acid Ethyl Ester (**16**).

A mixture of 3.5 g (0.01 mole) of **3** and 1.18 g (0.01 mole) of **8** in 50 ml of ethanol was heated under reflux for 10 minutes. The mixture was filtered and the filter cake was then dissolved in 75 ml of water. The solution was basified with 20% sodium carbonate solution. The resulting precipitate was collected and dissolved in 50 ml of ethanol. The ethanol solution was diluted with 50 ml of water and was cooled in ice. The precipitate was recrystallized from ethanol to give 0.3 g (10%) of product, mp 205-207° dec; ir (potassium bromide): 1628, 1610, 1580 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.38 (t, 3H), 4.25 (q, 2H), 6.97 (bs, 4H), 7.30 (s, 1H), 7.51 (t, 1H), 7.78 (d, 1H), 7.98 (d, 1H), 8.31 (s, 1H), 8.92 (bs, 1H).

Anal. Calcd. for $C_{13}H_{15}N_5OS$: C, 53.96; H, 5.23; N, 24.20. Found: C, 53.75; H, 5.26; N, 24.07.

3-[2-[(Aminoiminomethyl)amino]-4-thiazolyl]-*N*-methylbenzenecarboximidamide Quarter Hydrate (**17**).

A mixture of 0.89 g (0.003 mole) of **16** in 20 ml of a saturated ethanolic methylamine solution was heated under reflux for 3 hours. The solution was cooled and was diluted with water to the cloudy point. The solution was cooled in ice and the resulting precipitate was recrystallized twice from acetonitrile to give 0.2 g (24%) of product, mp 197-199° dec; ir (potassium bromide): 1640, 1598 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.83 (t, 3H), 6.98 (bs, 6H), 7.21 (s, 1H), 7.31 (t, 1H), 7.67 (d, 1H), 7.89 (d, 1H), 8.18 (bs, 1H).

Anal. Calcd. for $C_{12}H_{14}N_6S{\cdot}1/4H_2O$: C, 51.68; H, 5.24; N, 30.14. Found: C, 51.96; H, 5.34; N, 30.13.

3-[2-(Aminoiminomethyl)amino]-4-thiazolyl]benzenecarboximidamide Dihydrobromide Hemiethanolate (**18**).

A mixture of 3.96 g (0.02 mole) of **5** in 25 ml of glacial acetic acid was warmed to obtain a solution. The solution was cooled to room temperature and 3.18 g (0.02 mole) of bromine was added. After stirring at room temperature for 15 minutes the orange mixture was warmed to afford a solution and was stirred an additional 20 minutes without heat. The resulting yellow solution was evaporated to dryness in a rotary evaporator. The residual oil was dissolved in 50 ml of a 50:50 mixture of acetonitrile ethanol. To this solution was added 2.36 g (0.02 mole) of **8**. The mixture was heated under reflux for 10 minutes and was filtered. The filter cake was recrystallized from boiling ethanol using a minimum of water to produce a solution. On cooling in ice, there was obtained 3.0 g (34%) of product, mp 315° dec; ir (potassium bromide): 1660, 1609 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 7.73 (t, 1H), 7.97 (d, 1H), 8.16 (s, 1H), 8.23 (bm, 7H), 9.69 (bs, 2H).

Anal. Calcd. for $C_{11}H_{12}N_6S{\cdot}2HBr{\cdot}1/2C_2H_5OH$: C, 32.37; H, 3.85; N, 18.89. Found: C, 32.26; H, 3.74; N, 19.18.

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