Synthesis and Biological Activities of Substituted Dihydrobenzo[*h*]-pyrimido[4,5-*b*]quinolines as Tetracyclic 5-Deaza Nonclassical Folates [1]

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Novel tetracyclic compounds **1-4** have been synthesized *via* a regiospecific cyclocondensation reaction between substituted 6-aminopyrimidines **5-7** and chlorovinyl aldehydes **13 and 14**. The linear structures of these compounds were established by ^{1}H nmr and ^{13}C nmr spectral data and also by synthesis of the compounds *via* an unambiguous route. The growth of Manca human lymphoma cells was inhibited 50% by **1** and **4** at 4.5 x 10^{-6} *M* and 1.2 x 10^{-6} *M* respectively. These compounds also inhibited human dihydrofolate reductase (DHFR) by 50% at 4.4 x 10^{-6} *M* and 1.4 x 10^{-6} *M* respectively and *L. casei* DHFR at 1.9 x 10^{-5} *M* and 1.1 x 10^{-5} *M* respectively. Compound **16**, a positional isomer of **1**, was the most potent of the compounds studied, it inhibited the growth of Manca human lymphoma cells by 50% at 9 x 10^{-8} *M*. The IC_{50} values of **16** for the inhibition of human DHFR and *L. casei* DHFR were 8 x 10^{-8} *M* and 1.9 x 10^{-5} *M* respectively.

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The pyrimidine ring and the pyrido[2,3-*d*]pyrimidine ring systems form part of the heterocycles of compounds that have shown significant antitumor activity [2-6]. Our interest in the development of novel nonclassical antifolates directed us toward the synthesis of four new tetracyclic 5-deaza nonclssical folates **1-4** possessing the pyrido[2,3-*d*]pyrimidine ring as part of their ring systems.

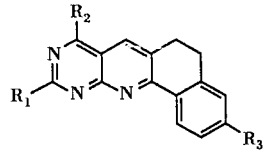
A single step synthesis of the dihydrobenzo[*h*]pyrimido-[4,5-*b*]quinoline ring system was anticipated *via* the cyclocondensation of an appropriately substituted 6-aminopyrimidine and a biselectrophile derived from 1-tetralone (**11**). This cyclocondensation reaction can however give substituted dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline (**9**) or its angular regioisomer a substituted dihydrobenzo[*f*]-pyrimido[4,5-*c*]isoquinoline (**10**) or a mixture of both isomers. Gangjee *et al.* [7,8] and Taylor and Warner [9] have reported the cyclocondensation of cyclic chlorovinyl aldehydes and vinyl aldehydes with substituted 6-aminopyrimidines. These workers have noted that the direction of ring closure in such cyclocondensation reactions is difficult to predict since the regiochemistry of such reactions is sensitive to changes in the substitution pattern of the pyrimidine, the biselectrophile, and in some cases the solvent employed in the cyclocondensation reaction.

Chlorovinyl aldehydes **13** and **14** were synthesized from **11** and 6-methoxy-1-tetralone (**12**) respectively by Vilsmeier chloroformylation with dimethylformamide and phosphorus oxychloride as previously reported for the formylation of 2-tetralone [10].

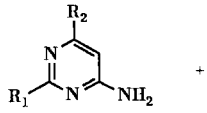
Cyclocondensation of chlorovinyl aldehyde **13** with either pyrimidine **5, 6** or **7** in glacial acetic acid afforded a single product in each case (compounds **1, 2,** and **3** respectively) as determined by tlc analysis in three different systems: a) silica gel: methylene chloride-methanol, 3:1 (v/v); b) silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:2:1 (v/v); and c) cellulose: butanol-water-acetic acid, 3:3:1 (v/v). Similarly condensation of chlorovinyl aldehyde **14** with pyrimidine **5** afforded compound **4** as the only product.

Assignment of linear structures to these compounds was based on ^{1}H nmr and ^{13}C nmr spectral data. We [10-12] and others [13-16] have established that the protons of the pyridine ring in heteroaromatic systems (*eg.* H_7 in **9**) resonate around 9.00 ppm in acidic solvents if these protons are gamma to the nitrogen atom of the pyridine ring (*ie* linear compounds, *eg.* **9**) and about 0.50 ppm upfield from this position if the protons are alpha (*eg.* H_6 in **10**) to the nitrogen atom of the pyridine ring (*ie* angular compounds, *eg.* **10**). Compounds **1, 2, 3** and **4** had the aromatic proton attached to the pyridine moiety of the heterocycle (*ie.* H_7) resonating at 9.17, 8.98, 9.04, and 8.98 ppm respectively in deuteriotrifluoroacetic acid. These resonance positions are close to 9.00 ppm and hence establish the linear structures of these compounds as designated.

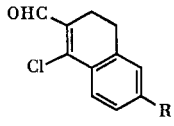
Further evidence for the linear structure of compounds **1-4** was obtained from the ^{13}C nmr spectra and the magnitude of the one bond coupling constants $^1J_{C_7-H}$. The C_7 carbon of **1, 2, 3,** and **4** resonated at 137.9 ppm, 140.4



1 $R_1 = R_2 = NH_2, R_3 = H$
2 $R_1 = NH_2, R_2 = OH, R_3 = H$
3 $R_1 = R_2 = OH, R_3 = H$
4 $R_1 = R_2 = NH_2, R_3 = OMe$



5 $R_1 = R_2 = NH_2$
6 $R_1 = NH_2, R_2 = OH$
7 $R_1 = R_2 = OH,$



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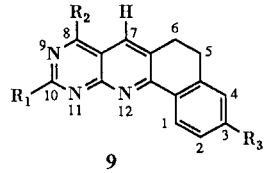

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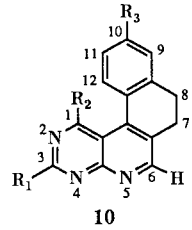

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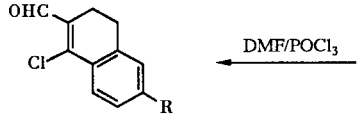
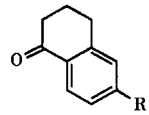


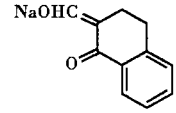
13 R = H
14 R = OMe

DMF/$POCl_3$



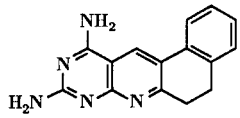
11 R = H
12 R = OMe

Na/EtOH
HCOOEt



15

6 + 15 ⟶ 2
7 + 15 ⟶ 3
1 ⟶ 2



16

ppm, 138.86 ppm, and 140.5 ppm respectively with a one bond coupling constant $^1J_{C\gamma\text{-}H}$ of 161 Hz, 165.2 Hz, 164.2 Hz, and 167 Hz respectively. These values compare favorably with literature reports [17,18] for compounds with an aromatic carbon gamma to the nitrogen atom of the pyridine ring.

Not withstanding the fact that the chemical shift positions and coupling constants established the linear structures of these compounds, we also confirmed our structural assignment by an independent and unequivocal synthesis. Using an independent synthesis, Robins and Hitchings [19] established that ketoaldehydes when condensed with substituted 6-aminopyrimidines regiospecifically afford linear isomers. Gangjee *et al.* [7,12] confirmed this regiospecificity with ^1H nmr, ^{13}C nmr, and X-ray crystal studies of the products. Thus condensation of a ketoaldehyde derived from 1-tetralone (**11**) with the aminopyrimidines should give the target compounds **1-3** exclusively. Condensation of 2,6-diamino-4-hydroxypyrimidine (**6**) with the sodium salt of 2-hydroxymethylene-1-tetralone (**15**) in 85% phosphoric acid gave **2**. Similarly condensation of 6-aminouracil (**7**) with **15** in 85% phosphoric acid

afforded **3**. Compound **15** was synthesized following a modification of literature procedures [20]. Both the ir and ^{1}H nmr spectra of **15** were as expected. Comparison of the spectral data (ir, ^{1}H nmr and ^{13}C nmr) of compounds **2** and **3** obtained from the condensation of chlorovinyl aldehyde **13** with pyrimidines **6** and **7** with the spectra of the compounds synthesized *via* the condensation of ketoaldehyde **15** with the pyrimidines indicated that the compounds were identical and hence confirmed that reaction of chlorovinyl aldehyde **13** with pyrimidines **6** and **7** are regiospecific and give linear regioisomers.

The product obtained from the condensation of ketoaldehyde **15** with pyrimidine **5** in 85% phosphoric acid was difficult to purify possibly due to contamination with compound **2** which could result from partial hydrolysis of the 8-amino group of the product (compound **1**) in the acidic solvent. Hence to further confirm that chlorovinyl aldehyde **13** reacts with pyrimidine **5** to give the linear isomer, the 8-amino group of **1**, obtained *via* the condensation of chlorovinyl aldehyde **13** with pyrimidine **5**, was hydrolysed to an oxo group by heating in 20% hydrochloric acid for five hours to give **2** as established by elemental analysis. Comparison of the spectral data (ir, ^{1}H nmr, and ^{13}C nmr) of **2** so obtained with those of **2** synthesized *via* the condensation of ketoaldehyde **15** with pyrimidine **6** indicated that the two compounds are identical and hence confirmed that the reaction of chlorovinyl aldehyde **13** and pyrimidine **5** was also regiospecific and gave a linear product.

Compounds **2** and **3** could not be evaluated for biological activity due to solubility problems. Compounds **1** and **4** had IC_{50} values of 4.5×10^{-6} *M* and 1.2×10^{-6} *M* for inhibition of the growth of Manca human lymphoma cells [21] respectively. These compounds inhibited human dihydrofolate reductase (DHFR) [22] by 50% at 4.4×10^{-6} *M*, and 1.4×10^{-6} *M* respectively. They also inhibited *L. casei* DHFR [23] by 50% at 1.9×10^{-5} *M* and 1.1×10^{-5} *M* respectively. We have reported the synthesis of compound **16**, a positional isomer of compound **1** in an earlier publication [10]. Compound **16** inhibited the growth of Manca Human lymphoma cells by 50% at 9×10^{-8} *M* and inhibited human DHFR by 50% at about the same concentration, 8×10^{-8} *M*. However, *L. casei* DHFR was about 240 fold less sensitive, 50% inhibition occurring at 1.9×10^{-5} *M*. Compound **16**, was the most potent of the series studied. We are currently synthesizing analogues and homologues of **16** for screening as potential antitumor agents.

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded with a Perkin-Elmer 1320 Infrared Spectrophotometer in nujol mulls. Nuclear magnetic resonance spectra for proton (^{1}H nmr) were run on a Varian EM 390 nmr spectrometer and for carbon-13 (^{13}C) on a Brucker WH-300 at 75.46 MHz, 90° pulse, 14 μsec. The data was accumulated by 16K size with 0.5 sec. delay time and 70° tip angle with internal standard TMS; s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet. Thin layer chromatography (tlc) was performed on cellulose or silica gel plates with fluorescent indicator and were visualized with light at 254 nm. Elemental analysis were performed by Atlantic Microlabs Inc., Atlanta, Georgia.

1-Chloro-3,4-dihydronaphthyl-2-carboxaldehyde (**13**).

Into a three-necked flask fitted with a drying tube, a thermometer and a nitrogen inlet tube, was placed 16.73 g (229 mmoles) dimethylformamide and cooled to 0-5°. To this was added dropwise 22.52 g (146.7 mmoles) phosphorus oxychloride with continuous stirring while maintaining the temperature below 20°. After 30 minutes the reaction mixture became turbid and 60 ml of methylene chloride was added. After the addition of phosphorus oxychloride was complete (about 40 minutes), the reaction was continued at 27° for 2 hours. A solution of 10 g (68.49 mmoles) of 1-tetralone (**11**) in 30 ml of methylene chloride was added dropwise to the mixture while maintaining the temperature of the reaction below 30°. After addition was completed (about 45 minutes), the reaction was continued at 27° for 2 hours. Following this period 200 g of crushed ice was added and the mixture was stirred for 15 minutes and the methylene chloride fraction was separated. The aqueous portion was extracted twice with methylene chloride (80 ml). The combined methylene chloride extracts were poured into 150 ml of saturated sodium bicarbonate solution and the mixture was stirred vigorously for 15 minutes. The organic phase was then separated, washed twice with water (50 ml), dried (magnesium sulfate) and evaporated under reduced pressure (water aspirated). The residue was flash chromatographed on silica gel with methylene chloride-methanol (20:1, v/v) as the eluant to give 11.11 g (88%) of **13**; tlc (silica gel: methylene chloride-methanol, 20:1) R_f 0.88; ir (neat): 1675 cm^{-1} (CHO); ^{1}H nmr (deuteriochloroform): δ 2.85 (m, 4H, CH_2CH_2), 7.15 (m, 2H, aromatic), 7.95 (m, 2H, aromatic), 10.40 (s, 1H, CHO).

1-Chloro-6-methoxy-3,4-dihydronaphthyl-2-carboxaldehyde (**14**).

Chloroformylation of 6-methoxy-1-tetralone (**12**) as described for **11** gave 1-chloro-6-methoxy-3,4-dihydronaphthyl-2-carboxaldehyde (**14**) in 84% yield; tlc (silica gel: methylene chloride-methanol, 20:1, v/v) R_f 0.90; ir (neat): 1670 cm^{-1} (CHO); ^{1}H nmr (deuteriochloroform): δ 2.50 (m, 4H, CH_2CH_2), 3.74 (s, 3H, OCH_3), 6.75 (d, 1H, aromatic), 7.60 (d, 1H, aromatic), 7.85 (dd, 1H, aromatic), 10.25 (s, 1H, CHO).

Sodium Salt of 2-Hydroxymethylene-1-tetralone (**15**).

Into a three-necked flask fitted with a drying tube containing 500 ml anhydrous ether was added 0.8 g (34 mmoles) of sodium metal which had been cut into small pieces (about 1 cm^3). To this mixture was added 3.77 g (51 mmoles) of ethyl formate (dried with potassium carbonate) and 5.0 g (34 mmoles) of **11**. The reaction was initiated by the addition of 0.15 ml of absolute ethanol to the mixture which had been cooled in an ice bath to 5°. The reaction was allowed to proceed for 6 hours with continuous stirring and then stirring was discontinued and the mixture was left to stand for 6 hours. The reaction was completed by the addition of 0.2 ml of absolute ethanol, and stirred for an additional hour.

The solid that formed was filtered, washed with anhydrous ether and dried *in vacuo* with phosphorus pentoxide for 4 hours to give 5.7 g (85%) of **15**. Further purification of the product was not possible due to its nature; tlc (silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:5:2 (v/v), R_f 0.80; ir (nujol): 1645 cm^{-1} (CHO); 1555 (C=C); ^1H nmr (deuteriodimethyl sulfoxide): δ 2.25 (m, 2H, CH_2), 2.52 (m, 2H, CH_2), 7.14 (m, 3H, C_6H_4), 7.75 (m, 1H, C_6H_4), 9.48 (s, 1H, HCONa).

8,10-Diamino-5,6-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline (**1**).

A solution of 7.0 g (36 mmoles) of 1-chloro-3,4-dihydronaphthyl-2-carboxaldehyde (**13**) in 30 ml glacial acetic acid was added dropwise to a refluxing solution of 4.55 g (36 mmoles) of 2,4,6-triaminopyrimidine (**5**) in 150 ml of glacial acetic acid over a period of 40 minutes. The mixture was refluxed for 18 hours, cooled to room temperature and the precipitated solid was filtered and air dried. It was suspended in 100 ml of 10% ammonium hydroxide solution, stirred for 15 minutes, filtered and the solid was washed with water until neutral. The air dried solid was suspended in boiling ethanol and drops of concentrated hydrochloric acid was added to make the mixture acidic. It was allowed to cool to room temperature, filtered and dried over phosphorus pentoxide for 24 hours to give 7.08 g (65%) of **1** as the hydrochloride salt, mp >300°. The compound was homogenous on tlc in three different systems: a) cellulose: butanol-water-acetic acid, 3:3:1 (v/v), R_f 0.83; b) silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:2:1 (v/v), R_f 0.69; c) silica gel: methylene chloride-methanol, 3:1 (v/v), R_f 0.52; ir (nujol): 3140 cm^{-1} (NH_2); ^1H nmr (deuteriotrifluoroacetic acid): δ 3.27 (s, 4H, 5-CH_2 and 6-CH_2), 7.80 (m, 3H, aromatic), 8.40 (d, 1H, aromatic), 9.17 (s, 1H, 7-CH); ^{13}C nmr (deuteriotrifluoroacetic acid): 137.91 ppm (161 Hz) (C_7 aromatic carbon).

Anal. Calcd. for $C_{15}H_{13}N_5 \cdot HCl \cdot 0.82H_2O$: C, 57.28; H, 4.98; N, 22.27; Cl, 11.30. Found: C, 57.66; H, 4.88; N, 21.87; Cl, 10.94.

10-Amino-8-oxo-9*H*-5,6-dihydrobenzo[*h*]pyrimido[5,4-*b*]quinoline (**2**).

Method A.

To a refluxing solution of 3.24 g (25.71 mmoles) of 2,6-diamino-4-hydroxypyrimidine (**6**) in 100 ml of glacial acetic acid was added dropwise a solution of 5.0 g (25.71 mmoles) of 1-chloro-3,4-dihydronaphthyl-2-carboxaldehyde (**13**) in 20 ml glacial acetic acid over a period of 40 minutes. The mixture was refluxed for 18 hours, cooled to room temperature and the precipitated solid was filtered and air dried. It was suspended in 100 ml of 10% ammonium hydroxide solution, stirred for 15 minutes, filtered and the solid was washed with water until neutral. The air dried solid was recrystallized from ethanol acidified with concentrated hydrochloric acid to give 4.9 g (72%) of **2** as the hydrochloride salt, mp >300°. The compound was homogenous on tlc [cellulose: butanol-water-acetic acid, 3:3:1 (v/v), R_f 0.80]; ir (nujol): 3110 cm^{-1} (NH_2), 1650 cm^{-1} (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 3.24 (s, 4H, 5-CH_2 and 6-CH_2), 7.70 (m, 3H, aromatic), 8.30 (d, 1H, aromatic), 8.98 (s, 1H, 7-CH); ^{13}C nmr (deuteriotrifluoroacetic acid) 140.4 ppm (165.24 Hz) (C_7 aromatic carbon).

Anal. Calcd. for $C_{15}H_{12}N_4O \cdot HCl$: C, 59.90; H, 4.33; N, 18.64; Cl, 11.88. Found: C, 59.79; H, 4.31; N, 18.28; Cl, 11.73.

Method B.

To a solution of 1.04 g (8.3 mmoles) of 2,6-diamino-4-hydroxypyrimidine (**6**) in 15 ml of 85% phosphoric acid was added 2.0 g (8.3 mmoles) of ketoaldehyde **15** and the mixture was heated at 100° for 90 minutes. The reaction mixture was cooled to room temperature and 80 ml of ice-water mixture was added and then basified to *p*H 8 with ammonium hydroxide while maintaining the temperature below 15° with an ice bath. The precipitated solid was filtered and washed with water until the washings were neutral. The solid was dried and recrystallized from 2*N* aqueous hydrochloric acid to give 2.35 g (95%) of **2** as the hydrochloride salt. the spectal data (ir, ^1H nmr, and ^{13}C nmr) of this compound were identical to that reported in method A for compound **2**.

Method C.

A suspension of 3.0 g (11.41 mmoles) of **1** in 800 ml of 20% aqueous hydrochloric acid was refluxed for 5 hours and filtered while hot. The filtrate was allowed to cool to room temperature and the precipitated pale yellow solid was filtered and dried *in vacuo* over phosphorus pentoxide for 24 hours to give 2.81 g (82%) of **2** as the hydrochloride salt. The spectral data (ir, ^1H nmr, and ^{13}C nmr) or this compound were identical to that reported in method A for compound **2**.

8,10-Dioxo-9*H*,11*H*-5,6-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline (**3**).

Method A.

A solution of 7.0 g (36 mmoles) of 1-chloro-3,4-dihydronaphthyl-2-carboxaldehyde (**13**) in 30 ml of glacial acetic acid was added dropwise to a refluxing solution of 4.55 g (0.036 moles) of 6-aminouralcil (**7**) in 150 ml of glacial acetic acid over a period of 40 minutes. The mixture was refluxed for 18 hours, cooled to room temperature and the precipitated solid was filtered and air dried. It was suspended in 100 ml of 10% ammonium hydroxide solution, stirred for 15 minutes, filtered and the solid was washed with water until neutal. The air dried solid was suspended in boiling ethanol and drops of concentrated hydrochloric acid was added to make the mixture acidic. It was allowed to cool to room temperature, filtered and dried *in vacuo* over phosphorus pentoxide for 24 hours to give 7.08 g (83%) of **3**, mp >300°. The compound was homogenous on tlc in three different systems: a) cellulose: butanol-water-acetic acid, 3:3:1 (v/v), R_f 0.83; b) silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:2:1 (v/v), R_f 0.69; c) silica gel: methylene chloride-methanol, 3:1 (v/v), R_f 0.52; ir (nujol): 3500 cm^{-1} (NH), 3420 cm^{-1} (NH), 1690 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.24 (s, 4H, 5-CH_2 and 6-CH_2), 7.74 (m, 3H, aromatic), 8.20 (d, 1H, aromatic), 9.04 (s, 1H, 7-CH); ^{13}C nmr (deuteriotrifluoroacetic acid) 138.86 ppm (164.2 Hz) C_7 aromatic carbon).

Anal. Calcd. for $C_{15}H_{11}N_3O_2 \cdot H_2O$: C, 63.60; H, 4.63; N, 14.74. Found: C, 63.57; H, 4.59; N, 14.68.

Method B.

To a solution of 0.52 g (4.1 mmoles) of 6-aminouracil (**7**) in 10 ml of 85% phosphoric acid was added 1.0 g (4.1 mmoles) of ketoaldehyde **15** and the mixture was heated at 100° for 60 minutes. The reaction mixture was cooled to room temperature and 40 ml of ice-water mixture was added and then basified to *p*H 8 with ammonium hydroxide at temperatures not exceeding 15°. The precipitated solid was filtered and washed with water until the washings were neutral. The solid was suspended in ethanol-10% hydrochloric acid mixture and heated to boiling. The mixture was filtered hot and the solid was dried *in vacuo* over phosphorus

pentoxide for 24 hours to give 0.92 g (85%) yield of **3**. The spectral data (ir, ^{1}H nmr, and ^{13}C nmr) of this compound were identical to that reported in method A for compound **3**.

8,10-Diamino-3-methoxy-5,6-dihydrobenzo[*h*]pyrimido[4,5-*b*]-quinoline (**4**).

To a refluxing solution of 3.38 g (27 mmoles) of **5** in 100 ml of glacial acetic acid was added dropwise a solution of 6.0 g (27 mmoles) of **14** in 20 ml glacial acetic acid over a period of 30 minutes and the mixture was refluxed for 20 hours. The reaction mixture was cooled to room temperature and the precipitated yellow solid was filtered. The solid was suspended in 100 ml of 10% ammonium hydroxide solution, stirred for 15 minutes, filtered and the residue was washed with water until neutral. It was air dried and suspended in boiling ethanol and concentrated hydrochloric acid was added dropwise to make the mixture acidic. The mixture was allowed to cool, filtered, and the solid was dried *in vacuo* over phosphorus pentoxide for 24 hours to give 5.6 g (63%) of **4** as the hydrochloride salt, mp >300°. The compound was homogeneous on tlc in three different systems: a) cellulose: 1-butanol-water-acetic acid, 3:3:1 (v/v), R_f 0.75; b) silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:2:1 (v/v), R_f 0.69, c) silica gel: methylene chloride-methanol, 3:1 (v/v), R_f 0.52; ir (nujol): 3140 cm^{-1} (NH_2); ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.28 (s, 4H, 5-CH_2 and 6-CH_2), 4.10 (s, 3H, OCH_3), 7.22 (m, 2H, 1-CH and 2-CH), 8.35 (d, 1H, 4-CH), 8.98 (s, 1H, 7-CH); ^{13}C nmr (deuteriotrifluoroacetic acid) 140.5 ppm (167 Hz) (C_7 aromatic carbon).

Anal. Calcd. for $C_{16}H_{15}N_5O\cdot HCl\cdot 1.2H_2O$: C, 54.69; H, 5.28; N, 19.93; Cl, 10.09. Found: C, 54.29; H, 5.36; N, 19.66; Cl, 10.01.

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