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By modifying previously described methods for the synthesis of 9-substituted-guanines from imidazoles, we have developed a new procedure for the regioselective synthesis of 9-substituted-8-azaguanines (5-amino-3-substituted-3,6-dihydro-7H-1,2,3-triazolo[4,5-d]pyrimidin-7-one) from triazoles in high yields. The method seems suitable for the introduction of a variety of substituents including sugars, carbocyclic, acyclic and carboacyclic chains.

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Introduction.

Since the discovery of acyclovir (ACV) [1] as a potent antiherpetic agent, a large variety of analogues with various side chains and/or heterocyclic bases have been synthesized and their biological activity extensively studied [2]. One particular class of compounds, 9-substituted-8-azaguanines, in which the C-8 of the guanine base has been replaced by a nitrogen, has been shown to possess antiviral, immunosuppressive and anticancer activity [3-8]. So far, these compounds have been synthesized by one of these two major routes: direct alkylation of an activated form of 8-azaguanine (Route A, Scheme 1) [3-7] or

by multistep synthesis starting with a properly substituted pyrimidine ring (Route B, Scheme 1) [8-15]. So far, no examples of the synthesis of 9-substituted-8-azaguanines from a triazole ring (Route C, Scheme 1) have been described.

In connection with our systematic search for new antiviral and anticancer agents [1,7,16,17], we were interested in studying the biological activity of 9-substituted-8-azaguanines. In order to have easy access to these products we needed an efficient way of synthesizing them, so we could introduce a variety of side chains in a regiospecific manner. We now report the results of the comparative studies we have conducted towards the synthesis of 9-substituted-8-azaguanines, following the aforementioned routes. In most cases 9-benzyl-8-azaguanine (**9**) was used as a model compound.

Results and Discussion.

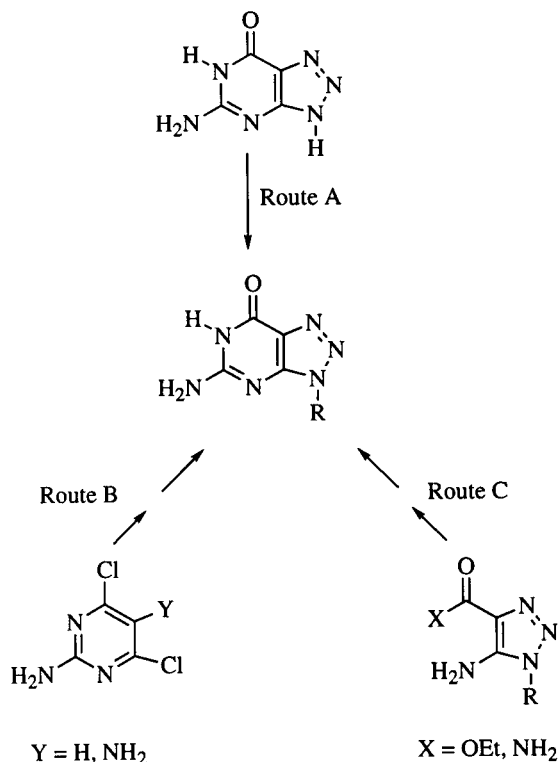
Direct Alkylation of 8-Azaguanine (Route A, Scheme 1).

Direct alkylation is usually performed by reacting the persilylated or peracetylated form of 8-azaguanine with the appropriate side chain (halomethoxyalkyl or acetoxy-methoxyalkyl, respectively), but in most cases mixtures of isomers are obtained [3-7]. This route is a well known method for the introduction of sugars or acyclic chains that possess a glycosidic type of bond. In our hands, preliminary results of these type of reactions produced mixtures that in most cases were very difficult to separate and hence lacked any synthetic value. Direct alkylation of the free base using either Mitsunobu [18] type of conditions or catalytic amounts of tetrabutylammonium fluoride as described elsewhere [19] either failed to give the desired product or it was isolated as a minor compound of a complex mixture. For these reasons this approach was abandoned.

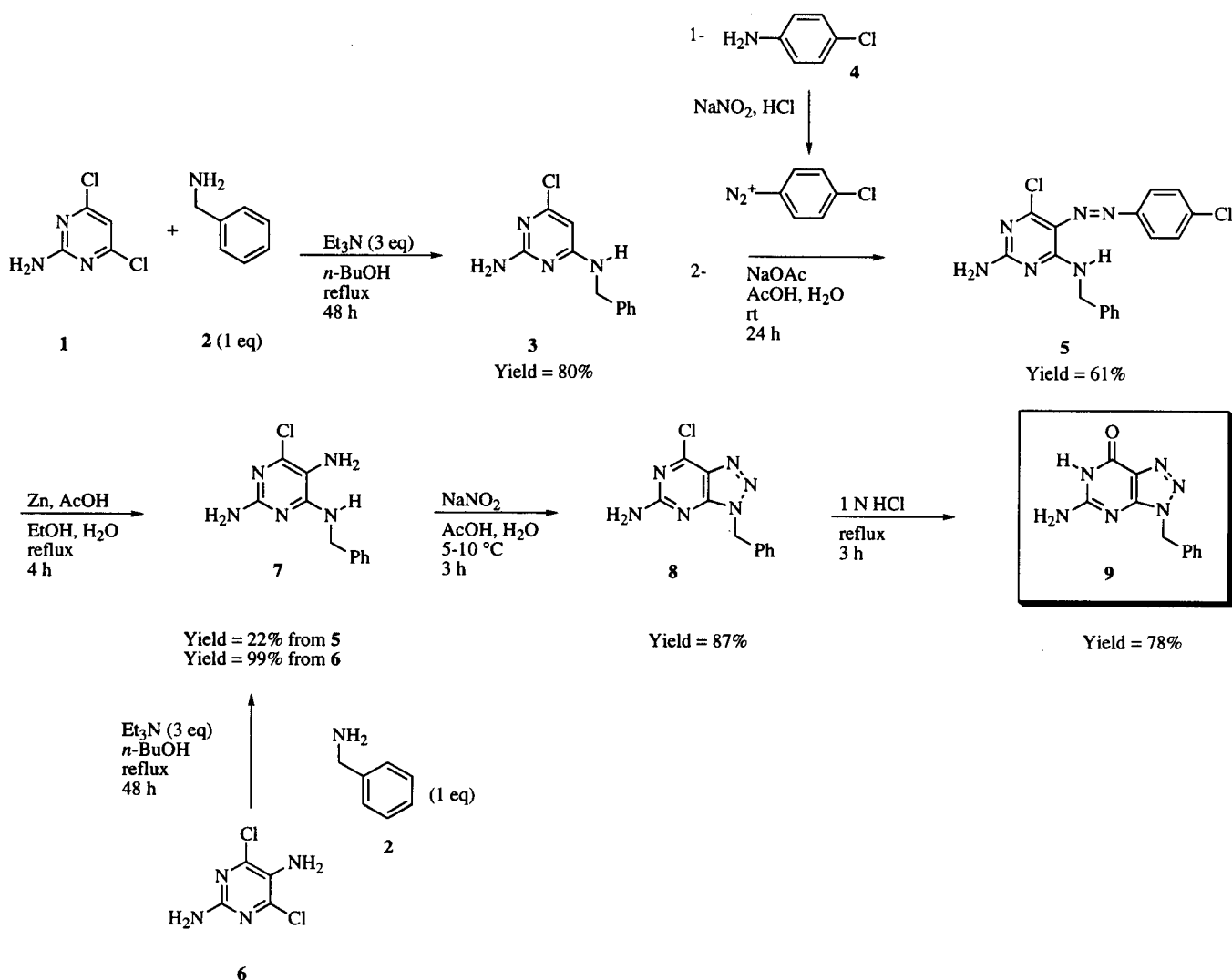
Synthesis from the Pyrimidine Ring (Route B, Scheme 1 and Scheme 2).

Synthesis of 9-substituted-8-azaguanines from pyrim-

Scheme 1



Scheme 2



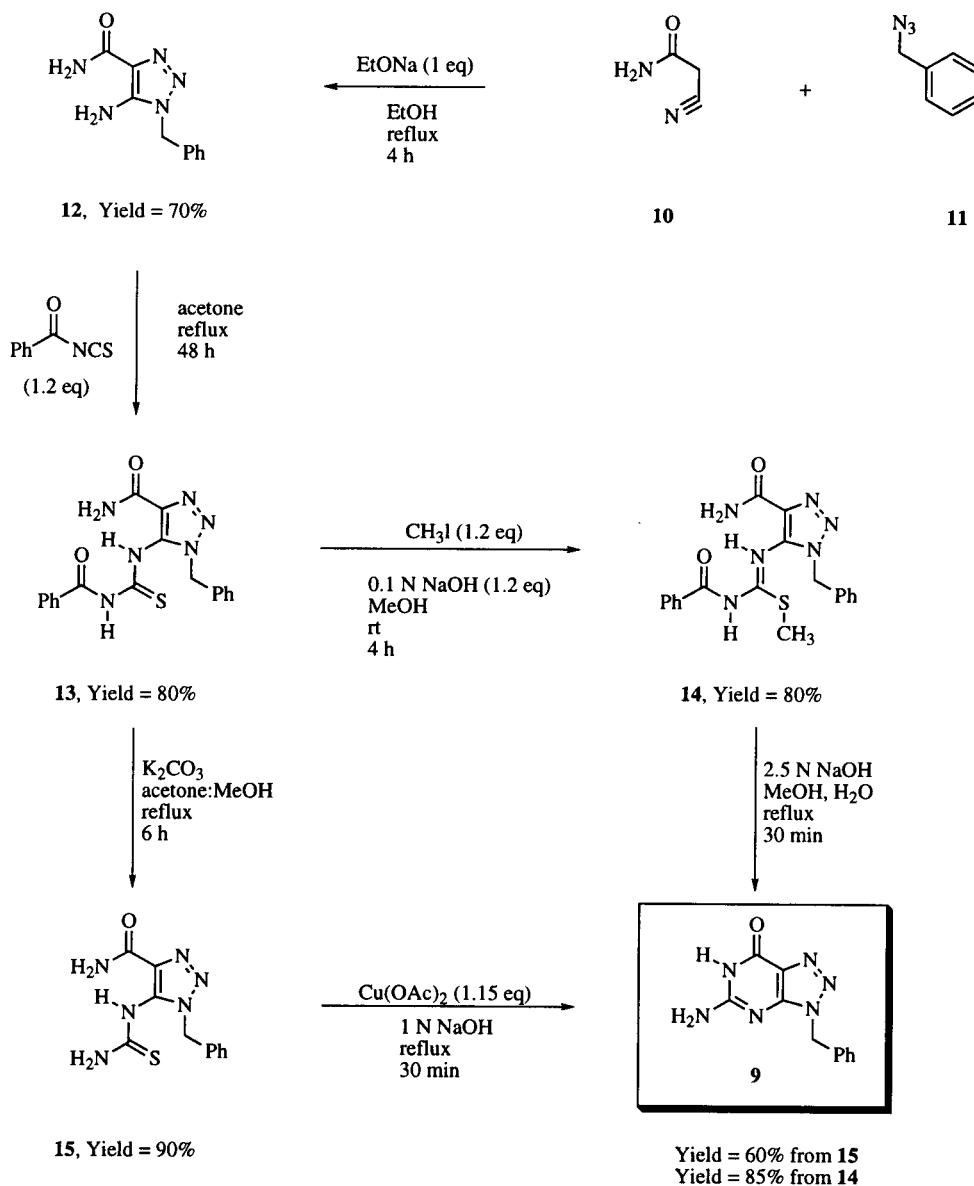
idines is well documented in the literature [8-15]. The most common starting material is the commercially available 2-amino-4,6-dichloropyrimidine (**1**). A typical case is depicted in Scheme 2, which is based on the method originally developed by Shealy [20] and co-workers. Pyrimidine **1** was condensed with benzylamine (**2**) in refluxing 1-butanol in the presence of triethylamine to afford **3** in 80% yield. Treatment of this material with the diazonium salt of *p*-chloroaniline (**4**) gave the azo compound **5** in 61% yield. Subsequent reduction of **5** with zinc in acetic acid afforded the 2,4-diamino compound **7** in low yield. This compound was obtained in better yield (99%) by condensing 2,5-diamino-4,6-dichloropyrimidine [21,22] (**6**) with benzylamine as described before. Ring closure was achieved *via* diazotization of **7** with sodium nitrite in aqueous acetic acid to afford **8** in 87% yield. Refluxing **8** with acid afforded the desired 9-benzyl-8-azaguanine (**9**) in 78% yield.

Synthesis of **9** from **1** could be a useful one, if it were possible to improve the yields in the reduction step. Synthesis from **6** seems to be more efficient, but preparation of this material is still problematic [21,22]. Since an amino functional group is required for the coupling with either pyrimidine, this method is useful for the introduction of non glycosidic type of chains (*i.e.* carboacyclic or carbocyclic chains) but not for the glycosidic ones (*i.e.* sugars or acyclic chains). Other pyrimidines are used in the literature as starting materials, but the yields are only low to moderate [8,10].

Synthesis from Triazoles (Route C, Scheme 1 and Schemes 3 and 4).

As previously mentioned, since there is no reported synthesis of 9-substituted-8-azaguanines from triazole rings, we decided to adapt the synthesis of 9-substituted-guanines from imidazoles following the methodologies

Scheme 3



developed by Yamazaki and co-workers [23,24] and the modification made by Clausen and co-workers [25]. These two procedures are depicted in Scheme 3. Coupling of cyanoacetamide (**10**) and benzyl azide (**11**) as described in the literature [26] afforded the triazole ring **12** in 70% yield. Treatment of **12** with one equivalent of benzoyl isothiocyanate in refluxing acetone gave the *N*-benzoylthiocarbamoyl amino derivative **13** in 80% yield. Two alternative routes are subsequently possible. The Yamazaki procedure involves treatment of **13** with methyl iodide under basic conditions to afford the *S*-methyl derivative **14** in 80% yield. Under basic conditions, both the *S*-methyl group and the benzoyl group are removed to

afford the final 9-substituted-8-azaguanine **9** in 85% yield. Under the Clausen approach compound **13** is hydrolyzed to the thiocarbamoyl amino derivative **15** which is further cyclized with copper(II) acetate to the final product **9** in 60% yield.

These two approaches proceeded with high yields (~40% yield from **10** and **11**) and are suitable for the synthesis of both glycosidic and non glycosidic side chains. This is the first reported synthesis of 9-substituted-8-azaguanines by this method. In comparison, compound **9** was previously synthesized [9] from 2-amino-4-chloro-6-hydroxypyrimidine in 20% yield overall.

Direct ring closure from the triazole ring failed to give

the desired product (Scheme 4). All the attempts using either amide **12** or ester **16** with guanidine or thio-pseudourea gave complex mixtures. There are many examples of this type of ring closures with different heterocycles: reaction of properly substituted pyrazines with guanidine afforded the corresponding pteridines [27-29], in a similar way pyrimidino[4,5-*d*]pyridazines were obtained from pyridazines [30], pyrrolo[3,4-*d*]pyrimidines from 2,3-dioxopyrrolidines [31], pyrido[2,3-*d*]pyrim-

regioselective synthesis of this type of compounds in high yields and it was successfully implemented in the general synthesis of acyclic and carbocyclic derivatives of 8-azaguanines of chemotherapeutic value [37].

EXPERIMENTAL

General Methods.

Melting points were determined in open glass capillaries by use of a Thomas-Hoover apparatus, and are uncorrected. The ^1H nmr spectra were recorded at 300 MHz with a Varian XL-300 spectrometer. Mass spectra (CI) were recorded with a platform mass spectrometer (Fisons Instrument) operated in a APcI (Atmospheric pressure chemical ionization) mode. Evaporations were performed under diminished pressure in a Buchi rotatory evaporator at 40° unless otherwise indicated. Solutions were dried over anhydrous sodium sulfate. Tlc was performed on pre-coated glass plates (0.25 mm) with Silica Gel 60F₂₅₄ (E. Merck, Darmstadt). Flash column chromatography was performed with Silica Gel 60 (230-400 mesh, E. Merck, Darmstadt). Elemental analyses were performed by Atlantic Microlab (Atlanta, GA).

Synthesis from Pyrimidines (Scheme 2).

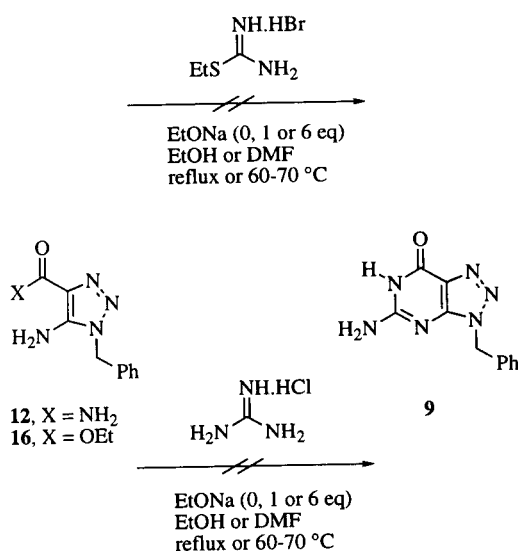
2-Amino-4-benzylamino-6-chloropyrimidine (**3**).

A well stirred mixture of **1** (4.75 g, 29 mmoles), **2** (3.21 g, 3.34 ml, 30 mmoles) and triethylamine (9.81 g, 13.51 ml, 97 mmoles) in 1-butanol (80 ml) was refluxed under nitrogen for 48 hours. After chilling, the resulting white precipitate was redissolved by adding dichloromethane (500 ml). The organic solution was washed with water (2 x 250 ml), dried, filtered and evaporated to a yellow solid. Purification by flash column chromatography (1:1 hexane-acetone) afforded pure **3** (5.5 g, 23.4 mmoles, Yield = 80%) as a white solid, mp 136-138° (lit [38] mp 129°); ^1H nmr (DMSO-*d*₆): δ 4.54 (br s, 2H, NCH₂Ph), 5.77 (s, 1H, H-5), 6.42 (s, 2H, NH₂), 7.20-7.30 (m, 5H, ArH), 7.59 (t, *J* = 6.0, 1H, BnNH); ms: (CI) *m/z* 235 (M + 1)⁺.

2-Amino-4-benzylamino-5-(*p*-chlorophenylazo)-6-chloropyrimidine (**5**).

To a well stirred solution of *p*-chloroaniline (**4**, 2.93 g, 23 mmoles) in concentrated hydrochloric acid (15 ml) and water (25 ml) cooled in an ice bath was slowly added a solution of sodium nitrite (1.84 g, 26.7 mmoles) in water (30 ml). A light yellow solution resulted. After stirring at 0° for 15 minutes, this cooled solution of *p*-chlorobenzenediazonium chloride was added dropwise to a mixture containing **3** (4.7 g, 20 mmoles) buffered with sodium acetate (28 g) and acetic acid (100 ml) in water (100 ml). A yellow precipitate appeared almost immediately. The mixture was allowed to stir at room temperature for 24 hours. The precipitated brown solid was filtered, washed thoroughly with water, and dried at 60° under vacuum to yield **5** (4.54 g, 12.2 mmoles, Yield = 61%). This material was used in the next step without any further purification. An analytical sample was prepared by flash column chromatography (2:1 hexane-acetone) followed by recrystallization from hexane-acetone to afford pure **5** as a yellow solid, mp 205-207°; ^1H nmr (DMSO-*d*₆): δ 4.54 (d, *J* = 6.0, 2H, NCH₂Ph), 7.20-7.30 (m, 5H, ArH), 7.55 (d, *J* = 9.0, 2H) and 7.75 (d, *J* = 9.0, 2H)

Scheme 4



idines from pyridines [32], and 2-amino-6-methyl-4-(3*H*)-quinazolinone has been made from ethyl 2-amino-5-methylbenzoate with either guanidine [33] or chloroformamide [34]. In all of these examples the heterocycle ring has no more than two nitrogens suggesting that the higher basicity of the triazole ring may impede the reaction of guanidine with the carbonyl group of either amide **12** or ester **16**. The only reported attempt of ring closure from a triazole ring was reported by Albert and co-workers [35] in which they failed to induce reaction of 4-amino-1-methyl-1,2,3-triazole-5-carboxamide with guanidine under various conditions. This, and the absence of examples in the literature for successful ring closures are in accordance with our results. Although some 4-amino-2-alkyl-1,2,3-triazole-5-carbonitriles have been successfully coupled with guanidine [36] to afford 2,6-diamino-9-alkyl-8-azapurines, the results were inconsistent and depended on the substituents.

Conclusions.

We have developed a new synthetic route (Scheme 3) as an alternative for the synthesis of glycosidic derivatives of 8-azaguanines other than direct alkylation of the heterocyclic base (Route A, Scheme 1) which produces mixtures of regioisomers. This new methodology provides the first

(N₂C₆H₄Cl), 7.63 (br s, 2H, NH₂), 10.53 (t, J = 6.0, 1H, BnNH); ms: (CI) m/z 374 (M + 1)⁺.

Anal. Calcd. for C₁₇H₁₄N₆Cl₂: C, 54.71; H, 3.78; N, 22.52; Cl, 19.00. Found: C, 54.79; H, 3.83; N, 22.43; Cl, 18.92.

2,5-Diamino-4-benzylamino-6-chloropyrimidine (**7**) from 2-Amino-4-benzylamino-5-(*p*-chlorophenylazo)-6-chloropyrimidine (**5**).

A suspension of **5** (2.80 g, 7.5 mmoles) and zinc dust (4.90 g, 75 mg-atoms) in acetic acid (3 ml), water (75 ml) and ethanol (75 ml) was refluxed under nitrogen for 4 hours. The excess zinc was filtered from the still-warm solution and washed with ethanol, and then the dark filtrate and washings were evaporated *in vacuo*. Traces of water were azeotropically removed with benzene. The brown residue was purified by flash column chromatography (2:1 hexane-acetone) to give **7** (0.42 g, 1.68 mmoles, Yield = 22%) as a brown solid. Since the material decomposed rapidly at room temperature, it was immediately used in the next step without any further purification; ¹H nmr (DMSO-*d*₆): δ 3.93 (br s, 2H, NH₂), 4.54 (d, J = 6.0, 2H, NCH₂Ph), 5.63 (s, 2H, NH₂), 7.00 (t, J = 6.0, 1H, BnNH), 7.20-7.30 (m, 5H, ArH); ms: (CI) m/z 250 (M + 1)⁺.

2,5-Diamino-4-benzylamino-6-chloropyrimidine (**7**) from **6**.

A mixture of **6** [21,22] (0.52 g, 2.9 mmoles), **2** (0.32 g, 0.33 ml, 3 mmoles) and triethylamine (0.98 g, 1.35 ml, 9.7 mmoles) in 1-butanol (8 ml) was refluxed with stirring under nitrogen for 48 hours. The solvent was evaporated *in vacuo* and the dark residue was partitioned between dichloromethane (100 ml) and water (100 ml). The organic solution was washed with water (50 ml), dried, filtered and evaporated to afford **7** (0.72 g, 2.9 mmoles, Yield = 99%). This material was used in the next step without any further purification.

2-Amino-6-chloro-9-benzylamino-8-azapurine (**8**).

To a cold (0-5°) stirred solution of **7** (0.60 g, 2.4 mmoles) in acetic acid (4.1 ml) and water (15 ml), a solution of sodium nitrite (0.20 g, 2.89 mmoles) in water (5 ml) was added dropwise. The mixture was stirred at 0-5° for 3 hours. The precipitate was filtered, washed with water and dried under reduced pressure at 55°. The solid was purified by flash column chromatography (2:1 hexane-acetone) to afford **8** (0.54 g, 2.1 mmoles, Yield = 87%) as a white solid. This material was used in the next step without any further purification. An analytical sample was prepared by crystallization from hexane-acetone to afford pure **8** as a white solid, mp 150-151°; ¹H nmr (DMSO-*d*₆): δ 5.63 (s, 2H, NCH₂Ph), 7.20-7.30 (m, 5H, ArH), 7.70 (br s, 2H, NH₂); ms: (CI) m/z 261 (M + 1)⁺.

Anal. Calcd. for C₁₁H₉N₆Cl: C, 50.68; H, 3.48; N, 32.24; Cl, 13.60. Found: C, 50.74; H, 3.53; N, 32.24; Cl, 13.51.

5-Amino-3-benzyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (9-Benzyl-8-azaguanine) (**9**).

A suspension of **8** (0.22 g, 0.84 mmole) in 1 *N* hydrochloric acid (10 ml) was refluxed for 3 hours. After cooling to room temperature the solution was neutralized with 1 *N* sodium hydroxide (10 ml). The precipitate was filtered off, washed with water, dried at 60° under vacuum to give **9** (0.16 g, 0.66 mmole, Yield = 78%) as a brown solid. An analytical sample was prepared by crystallization from acetone to afford pure **9** as a white solid, mp 310-313° (lit [9] mp 313-315°); ¹H nmr (DMSO-*d*₆): δ

5.53 (s, 2H, NCH₂Ph), 6.97 (br s, 2H, NH₂), 7.20-7.30 (m, 5H, ArH), 10.99 (br s, 1H, NH); ms: (CI) m/z 243 (M + 1)⁺.

Synthesis from Triazoles (Scheme 3).

5-Amino-1-phenylmethyl-1*H*-1,2,3-triazole-4-carboxamide (**12**).

Sodium (2.3 g, 100 mmoles) was added to absolute ethanol (100 ml). After reaction was completed, cyanoacetamide (**10**, 8.4 g, 100 mmoles), and benzyl azide (**11**, 13.3 g, 12.48 ml, 100 mmoles) were sequentially added. The solution was refluxed for 4 hours. On cooling, a precipitate separated and was filtered, washed with water and dried at 60° under vacuum to afford **12** (14.8 g, 70 mmoles, Yield = 70%) as a white solid, mp 234-236° (lit [26] mp 233-235°); ¹H nmr (DMSO-*d*₆): δ 5.40 (s, 2H, NCH₂Ph); 6.38 (s, 2H, NH₂), 7.05 and 7.34 (br s, 2H, CONH₂), 7.18-7.30 (m, 5H, ArH); ms: (CI) m/z 218 (M + 1)⁺.

5-(*N*-Benzoylthiocarbamoyl)amino-1-phenylmethyl-1*H*-1,2,3-triazole-4-carboxamide (**13**).

To a stirred suspension of **12** (2.17 g, 10 mmoles) in dry acetone (20 ml), benzoyl isothiocyanate (1.96 g, 1.60 ml, 12 mmoles) was slowly added, and the reaction mixture was refluxed for 48 hours. The bright orange solution was evaporated under vacuum to afford a yellow solid that was purified by flash column chromatography (1:1 hexane-acetone). Compound **13** (3.0 g, 8.0 mmoles, Yield = 80%) was obtained as a yellow solid. This material was used in the next step without any further purification. An analytical sample was prepared by crystallization from hexane-acetone to afford pure **13** as a white solid, mp 171-173°; ¹H nmr (DMSO-*d*₆): δ 5.49 (s, 2H, NCH₂Ph), 7.20-8.00 (m, 7H, ArH and CONH₂), 12.09 (br s, 2H, PhCONHCSNH); ms: (CI) m/z 381 (M + 1)⁺.

Anal. Calcd. for C₁₈H₁₆N₆O₂S: C, 56.83; H, 4.24; N, 22.09; S, 8.43. Found: C, 56.94; H, 4.33; N, 21.97; S, 8.32.

5-(*N*-Benzoyl-*S*-methylisothiocarbamoyl)amino-1-phenylmethyl-1*H*-1,2,3-triazole-4-carboxamide (**14**).

To a well stirred solution of **13** (0.76 g, 2 mmoles) in methanol (10 ml) containing 0.1 *N* sodium hydroxide (28 ml, 2.8 mmoles), was added methyl iodide (0.35 g, 0.15 ml, 2.5 mmoles). The reaction mixture was stirred at room temperature for 4 hours and then neutralized with acetic acid (0.15 ml) and diluted with water. The white precipitate was filtered, washed with water and dried at 60° under vacuum to afford **14** (0.62 g, 1.57 mmoles, Yield = 80%) as a white solid. This material was used in the next step without any further purification. An analytical sample was prepared by crystallization from hexane-acetone to afford pure **14** as a white solid: mp 218-220°; ¹H nmr (DMSO-*d*₆): δ 2.38 (SCH₃), 5.43 (s, 2H, NCH₂Ph), 7.20-8.00 (m, 7H, ArH and CONH₂), 11.34 (br s, 1H, PhCON=C(SMe)NH); ms: (CI) m/z 395 (M + 1)⁺.

Anal. Calcd. for C₁₉H₁₈N₆O₂S: C, 57.85; H, 4.60; N, 21.31; S, 8.13. Found: C, 57.88; H, 4.58; N, 21.22; S, 8.16.

5-(Thiocarbamoyl)amino-1-phenylmethyl-1*H*-1,2,3-triazole-4-carboxamide (**15**).

To a well stirred solution of **13** (0.76 g, 2 mmoles) in acetone-methanol (1:1, 10 ml) was added a solution of potassium carbonate (0.14 g, 1 mmole) in water (0.6 ml). The solution was refluxed for 6 hours. After cooling to room temperature it was neutralized with acetic acid (0.14 ml) and the solution evapo-

rated to dryness. The remaining syrup was treated with dichloromethane. The resulting precipitate was filtered to give **15** (0.50 g, 1.8 mmoles, Yield = 90%) as a yellow solid. This material was used in the next step without any further purification. An analytical sample was prepared by crystallization from hexane-acetone to afford pure **15** as a white solid, mp 243-245°; ¹H nmr (DMSO-d₆): δ 5.49 (s, 2H, NCH₂Ph), 7.20-8.00 (m, 7H, ArH and CONH₂), 8.20 (br s, 2H, CSNH₂), 9.60 (br s, 1H, CSNH); ms: (CI) m/z 243 (M + 1)⁺.

Anal. Calcd. for C₁₁H₁₂N₆OS: C, 47.82; H, 4.38; N, 30.41; S, 11.60. Found: C, 47.58; H, 4.44; N, 30.18; S, 11.49.

5-Amino-3-benzyl-3,6-dihydro-7H-1,2,3-triazolo[4,5-d]pyrimidin-7-one (9-Benzyl-8-azaguanine) (**9**) from 5-(*N*-Benzoyl-5-methylisothiocarbamoyl)amino-1-phenylmethyl-1H-1,2,3-triazole-4-carboxamide (**14**).

To a well stirred suspension of **14** (0.20 g, 0.50 mmole) in methanol (1 ml) was added 2.5 *N* sodium hydroxide (5 ml). The reaction mixture was refluxed for 30 minutes. After cooling to room temperature the clear solution was neutralized with acetic acid. The resulting precipitate was filtered, washed with water and dried at 60° under vacuum to afford **9** (0.11 g, 0.43 mmole, Yield = 85%) as a white solid.

5-Amino-3-benzyl-3,6-dihydro-7H-1,2,3-triazolo[4,5-d]pyrimidin-7-one (9-Benzyl-8-azaguanine) (**9**) from 5-(Thiocarbamoyl)-amino-1-phenylmethyl-1H-1,2,3-triazole-4-carboxamide (**15**).

To a solution of **15** (0.27 g, 1 mmole) in 1 *N* sodium hydroxide (8 ml) was added copper(II) acetate (0.23 g, 1.15 mmoles). The reaction mixture was refluxed for 30 minutes. After cooling to room temperature the solids were filtered off through celite and washed with 1 *N* sodium hydroxide. The clear filtrate was adjusted to pH 5 with acetic acid. The white precipitate was filtered, washed with water and dried at 60° under vacuum to afford **9** (0.15 g, 0.6 mmole, Yield = 60%).

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REFERENCES AND NOTES

- [1] G. B. Elion, P. A. Furman, J. A. Fyfe, P. De Miranda, L. Beauchamp, and H. Schaeffer, *J. Proc. Natl. Acad. Sci. U.S.A.*, **74**, 5716 (1977).
- [2] C. K. Chu and S. J. Cutler, *J. Heterocyclic Chem.*, **23**, 289 (1986) and references cited therein.
- [3] J. M. Stein, J. D. Stoeckler, S. Y. Li, R. L. Tolman, M. MacCoss, A. Chen, J. D. Karkas, W. T. Ashton, and R. E. Parks, *Biochem. Pharmacol.*, **36**, 1237 (1987).
- [4] J. A. Montgomery, R. D. Elliot, and H. J. Thomas, *Ann. N. Y. Acad. Sci.*, **255**, 292 (1975).
- [5] J. A. Montgomery, A. T. Shortnacy, and J. A. Secrist III, *J. Med. Chem.*, **26**, 1483 (1983).
- [6] W. Hutzenlaub, R. L. Tolman, and R. K. Robins, *J. Med. Chem.*, **15**, 879 (1972).
- [7] L. M. Beauchamp, B. L. Dolmatch, H. J. Schaeffer, P. Collins, D. J. Bauer, and P. M. Keller, *J. Med. Chem.*, **28**, 982 (1985).
- [8] W. T. Ashton, L. C. Meurer, C. L. Cantone, A. K. Field, J. Hannah, J. D. Kamas, R. Liou, G. F. Patel, H. C. Perry, A. F. Wagner, E. Walton, and R. L. Tolman, *J. Med. Chem.*, **31**, 2304 (1988).
- [9] H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 3046 (1959).
- [10] R. D. Elliott and J. A. Montgomery, *J. Med. Chem.*, **19**, 1186 (1976).
- [11] C. Parkanyi and H. L. Yuan, *J. Heterocyclic Chem.*, **27**, 1409 (1990).
- [12] M. L. Peterson and R. Vince, *J. Med. Chem.*, **33**, 1214 (1990).
- [13] R. Vince and M. Hua, *J. Med. Chem.*, **33**, 17 (1990).
- [14] Y. F. Shealy, C. A. O'Dell and G. Arnett, *J. Med. Chem.*, **30**, 1090 (1987).
- [15] Y. F. Shealy, C. A. O'Dell, W. M. Shannon, and G. Arnett, *J. Med. Chem.*, **27**, 1416 (1984).
- [16] H. J. Schaeffer, L. Beauchamp, P. de Miranda, G. B. Elion, D. J. Bauer, and P. Collins, *Nature (London)*, **272**, 583 (1978).
- [17] J. L. Kelley, M. P. Krochmal, and H. J. Schaeffer, *J. Med. Chem.*, **24**, 1528 (1981).
- [18] O. Mitsunobu, *Synthesis*, 1 (1981).
- [19] G. H. Hakimelahi and A. Khalafi-Nezhad, *Helv. Chim. Acta*, **72**, 1495 (1989).
- [20] Y. F. Shealy, R. F. Struck, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **26**, 4433 (1961).
- [21] M. Legraverend, H. Boumchita, and E. Bisagni, *Synthesis*, 587 (1990).
- [22] C. Temple, Jr., B. H. Smith, and J. A. Montgomery, *J. Org. Chem.*, **21**, 3141 (1975).
- [23] A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **32**, 1825 (1967).
- [24] A. Yamazaki, M. Okutsu, and Y. Yamada, *Nucl. Acids Res.*, **3**, 251 (1976).
- [25] B. Alhede, F. P. Clausen, J. Juhl-Christensen, K. K. McCluskey, and H. F. Preikschat, *J. Org. Chem.*, **56**, 2139 (1991).
- [26] J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **78**, 5832 (1958).
- [27] J. H. Jones and E. J. Cragoe, Jr., *J. Med. Chem.*, **11**, 322 (1968).
- [28] E. C. Taylor and P. A. Jacobi, *J. Am. Chem. Soc.*, **98**, 2301 (1976).
- [29] J. B. Neilsen, H. S. Broadbent, and W. J. Hennen, *J. Heterocyclic Chem.*, **24**, 1621 (1987).
- [30] T. Kinoshita and R. N. Castle, *J. Heterocyclic Chem.*, **5**, 845 (1968).
- [31] P. L. Southwick and G. H. Hofmann, *J. Org. Chem.*, **28**, 1332 (1963).
- [32] R. Bernetti, F. Mancini, and C. C. Price, *J. Org. Chem.*, **27**, 2863 (1962).
- [33] S. P. Archara and J. B. Hynes, *J. Heterocyclic Chem.*, **12**, 1283 (1975).
- [34] D. J. McNamara, E. M. Berman, D. W. Fry, and L. M. Werbe, *J. Med. Chem.*, **33**, 2045 (1990).
- [35] A. Albert and H. Taguchi, *J. Chem. Soc. Perkin Trans. 1*, 449 (1972).
- [36] A. Albert, *J. Chem. Soc. Perkin Trans. 1*, 345 (1975).
- [37] L. M. Beauchamp, J. V. Tuttle, M. E. Rodriguez, and M. L. Sznajdman, *J. Med. Chem.*, **39**, 949 (1996).
- [38] C. W. Noell and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 558 (1962).