

Multicomponent Synthesis of C(8)-Substituted Purine Building Blocks of Peptide Nucleic Acids from Prebiotic Compounds

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We have explored the reaction of a three-components mixture of aminomalononitrile, urea and α -amino acid methyl esters for the multicomponent synthesis substituted purines resembling PNA's building blocks. 2,6-diamino-purines, 6-amino-3,9-dihydro-2H-purin-2-one (iso-guanines), and 3,9-dihydro-6H-purin-6-one derivatives, selectively decorated at C(8)-position of the purine ring with different amino acid residues, were obtained from acceptable to good yields. The regio-selectivity of the transformation was controlled by the use of urea in the ternary mixture and by the annulation agent involved in the ring-

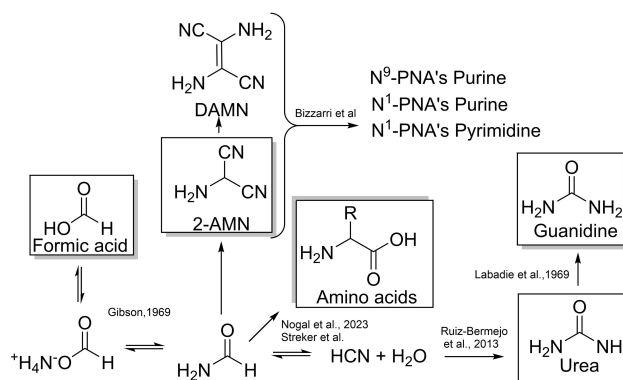
closure of amino-imidazole carbonitrile intermediates. Solvent free conditions, microwave irradiation and simple one-carbon containing reagents further satisfied the major requirement of atom economy and sustainable chemistry. Due to the prebiotic nature of the three-components mixture and of annulation agents, it also embodies the possibility for the synthesis of novel PNAs bearing purine nucleobases decorated at C(8)-position of the imidazole ring as alternative RNA analogues in molecular evolution.

Introduction

The pioneering Miller-Urey experiment highlighted possible pathways to set molecular evolution, which involve electric discharge and plasma and primitive atmosphere combined together to improve chemical complexity.^[1] In the modifications of the original experimental set, amino acids and hydroxy acids were synthesized and identified as chemical precursors for the pre-metabolic machinery. Successively, RNA's nucleobases were obtained from a variety of gas mixtures and energy sources, and the unprecedented catalytic role of minerals and metal oxides in these transformations was analyzed in detail.^[2–6] Building blocks of peptide nucleic acids (PNAs)^[7] were also isolated besides to canonical nucleobases, suggesting that PNAs, and PNAs like molecules, may have co-evolved with RNA.^[8,9] In this latter case, the structural integrity of PNAs is favored by the 2-aminoethylglycine motif instead of labile sugar–phosphate backbone, the nucleobase being linked to pseudopeptide by carboxy-methylene spacer.^[10] The exploration of the chemical space of nucleobases by decoration with amino acid opens new possibility of alternative PNA's structures.^[11,12] We recently reported that aminomalononitrile (AMN) and diaminomaleonitrile (DAMN) are effective precursors for the synthesis of PNA's building blocks decorated at N(9), and N(1)-

positions of the purine ring, as well as at N(1)-position of the pyrimidine ring.^[13–15] The reaction proceeds by formation of imidazole intermediates, followed by heterocyclic annulation with simple compounds of prebiotic relevance, such as formic acid, urea and guanidine. In these experimental conditions, the scaffold morphing of the reaction (that is the formation of purine versus pyrimidine derivatives) was controlled by the appropriate energy source (thermal and photothermal conditions), favoring different reaction pathways. Prebiotic relationships between AMN, DAMN and annulation agents, and the reaction pathways to different PNA's building blocks, are reported in Scheme 1.^[13,15–21] Interestingly, novel PNA's derivatives showed high biological activity and good selectivity against a broad spectrum of RNA, DNA and retro-viruses.^[13,15,22]

Purine derivatives decorated at C(8)-position of the heterocyclic ring may be of particular interest for the synthesis of biologically active PNAs. C(8)-oxo-purines are involved in non-enzymatic primer extension,^[23] and they are template in the assembly of complex networks of nucleotides.^[24] In addition, 8-



Scheme 1. Chemistry of PNA's derivatives and related condensing agents.

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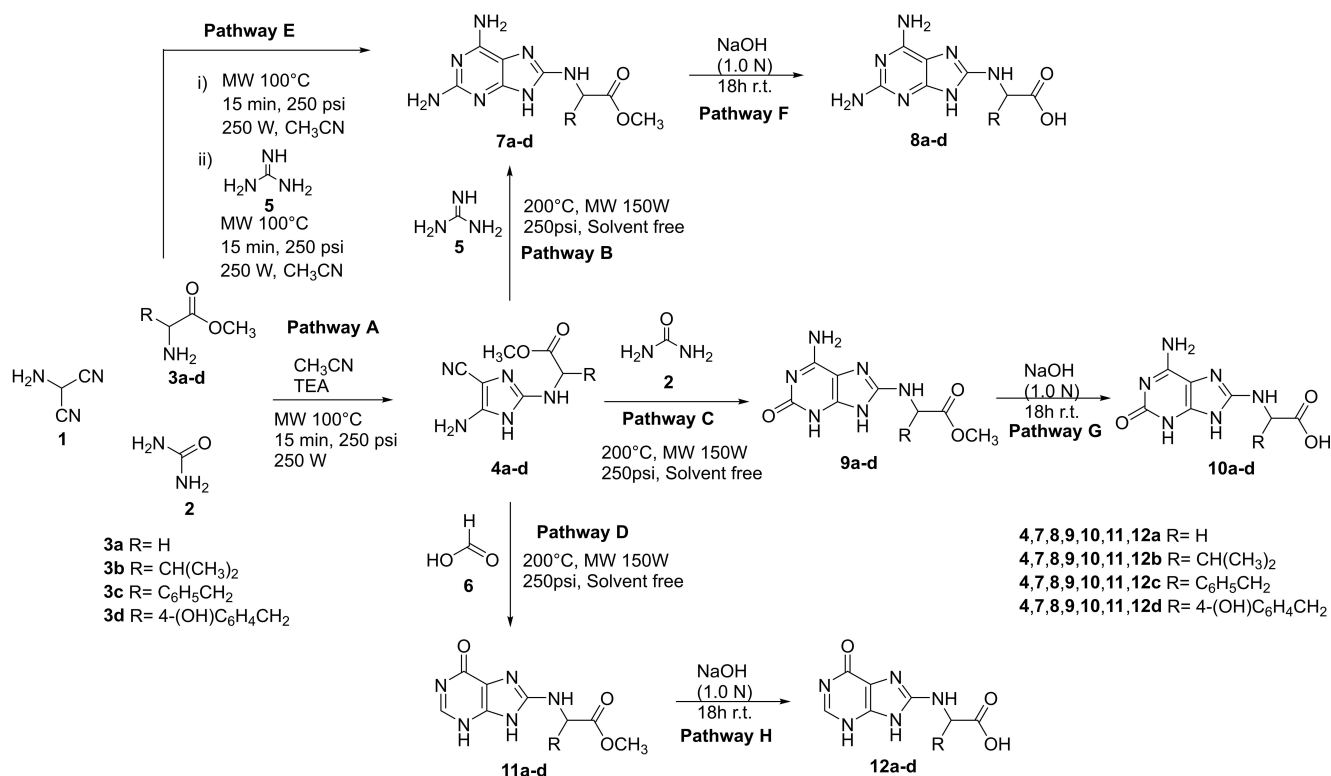
thio-adenine is a key intermediate in the prebiotic synthesis of 2'-deoxyriboadenosine,^[25–27] and C(8)-substituted purines are inhibitors of respiratory syncytial virus^[28] and herpes simplex virus (type 1),^[29] showing high affinity towards human adenosine A1 receptor.^[30] The synthesis of C(8)-substituted purines usually requires transition-metal catalysis and cross-coupling reactions encompassing toxic reagents, such as organotin,^[31–34] organozinc,^[35] alkylaluminum,^[36–37] alkylboronic acids,^[38] and Grignard reagents.^[39–41] These procedures are not sustainable, and require expensive ligands, pre-activation of the reagents, and anhydrous and/or anaerobic conditions.^[42] In order to overcome these drawbacks, and with the aim to design a sustainable synthesis of alternative PNA's purine nucleobases, we describe here the synthesis of C(8)-substituted purine derivatives decorated with α -amino-acid residues, taking inspiration from previous prebiotic chemistry studies. The reaction involves the multicomponent synthesis of C(2)-substituted amino imidazole carbonitriles from the ternary mixture of AMN, urea and α -amino-acid esters in the presence of triethylamine (TEA), followed by domino ring annulation with formic acid, urea and guanidine. The use of eco-friendly solvents and microwave irradiation conditions improved the sustainability of the overall transformation. Finally, we moved toward original prebiotic multicomponent chemistry, overcoming the use of TEA and of organic solvents, and using α -amino-acids instead of the corresponding methyl ester derivatives.

Results and Discussion

Synthesis of C(2)-Substituted Amino-Imidazole Carbonitrile Derivatives 4a–d

C(2)-substituted amino imidazole carbonitriles **4a–d** were synthesized by a multicomponent procedure involving the condensation of AMN **1**, urea **2**, and α -amino acid methyl esters **3a–d** (glycine **3a**, valine **3b**, phenylalanine **3c**, and tyrosine **3d**), in the presence of TEA (Scheme 2, Pathway A).

Reaction conditions were investigated for the synthesis of **4a** from glycine **3a** as a selected case. Different molar ratio of compounds **1**, **2**, and **3a** (from 1:1.2:1.4 to 1:1.4:1.6), reaction solvents (solvent free condition, THF, 2-MeTHF and CH₃CN), temperature (from 25 °C to 250 °C), and energy sources (microwave and thermal heating) were studied. Results are reported in Table 1 (entries 1–9). The optimal experimental conditions were consistent with 1:1.4:1.2 molar ratio of the ternary mixture, TEA (1.2 eq), and MW irradiation (250 W, 250 psi) in CH₃CN (3.0 mL) at 200 °C for 15 min (Table 1; entry 9). CH₃CN is a well-recognized prebiotic compound,^[43] with high solvent capacity.^[44] MW irradiation were generally more effective than heat (Table 1; entries 6,7,9 vs entries 1–5,8), minimizing the formation of polar AMN oligomers as side-products, the increasing of temperature above 200 °C (220 °C or 250 °C) determined a significative decreasing of the yields (45 % vs 35 %



Scheme 2. Multicomponent synthesis of C(8)-substituted purines from the ternary mixture of AMN **1**, urea **2**, and α -amino acid methyl esters **3a–d**. Pathway A: preparation of amino imidazole carbonitriles **4a–d**. Pathway B: preparation of C(8)-substituted 2,6-diamino-purine methyl esters **7a–d**. Pathway C: preparation of C(8)-substituted iso-guanine methyl esters **9a–d**. Pathway D: preparation of C(8)-substituted 3,9-dihydro-6H-purin-6-one methyl esters **11a–d**. Pathway E: one-pot preparation of C(8)-substituted 2,6-diamino-purine methyl ester **7a**. Pathways F–H: preparation of C(8)-substituted purine carboxylic acids **8a–d**, **10a–d** and **12a–d**.

Table 1. Amino imidazole carbonitrile methyl esters **4 a–d** from three component condensation of AMN, urea and α -amino acids.

Entry	α -Amino acid residues	Conditions	Product	R	Yield (%) ^[d]
1	Glycine	r.t. 6 day, THF ^[a]	4 a	H	6
2		100 °C 24 h, THF ^[a]			–
3		100 °C 24 h, THF ^[b]			3
4		100 °C 24 h, THF ^[c]			5
5		100 °C 24 h, 2-Me-THF ^[a]			6
6		M.W. 250 psi, 250 W, 150 °C 15 min, THF ^[a]			6
7		M.W. 250 psi, 250 W, 200 °C 15 min, solvent free ^[a]			7
8		100 °C 24 h, CH ₃ CN ^[a]			17
9		M.W. 250 psi, 250 W, 200 °C 15 min, CH ₃ CN ^[a]			45, 35 ^[e] , 20 ^[f]
10	Valine		4 b	CH(CH ₃) ₂	39
11	Phenylalanine		4 c		65
12	Tyrosine		4 d		53

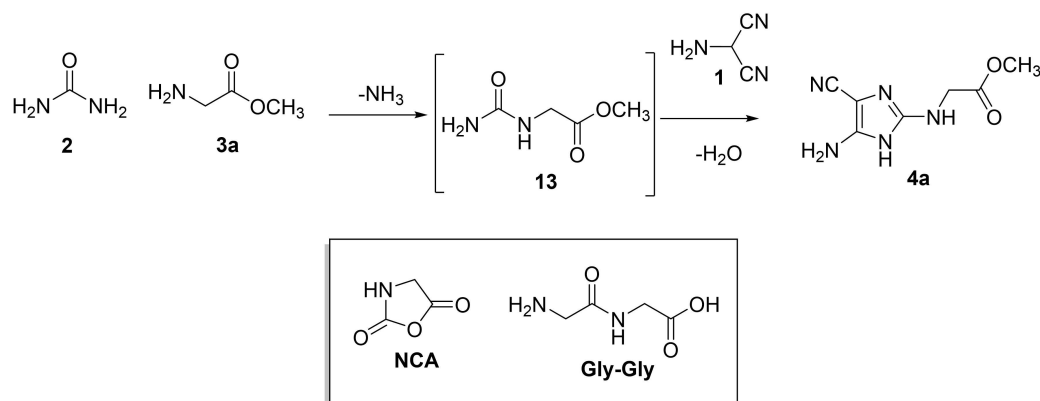
[a] **1** (0,20 mmol), **2** (0,28 mmol), triethylamine (0,24 mmol) and **3 a–d** (0,24 mmol). [b] **1** (0,20 mmol), **2** (0,28 mmol), triethylamine (0,24 mmol) and **3 a–d** (0,28 mmol). [c] **1** (0,20 mmol), **2** (0,32 mmol), triethylamine (0,24 mmol) and **3 a–d** (0,24 mmol). [d] Yield is referred to the conversion of **1**. [e] **1** (0,20 mmol), **2** (0,28 mmol), triethylamine (0,24 mmol) and **3 a** (0,24 mmol), M.W. 250 psi, 250 W, 220 °C 15 min, CH₃CN. [f] **1** (0,20 mmol), **2** (0,28 mmol), triethylamine (0,24 mmol) and **3 a** (0,24 mmol), M.W. 250 psi, 250 W, 220 °C 15 min, CH₃CN.

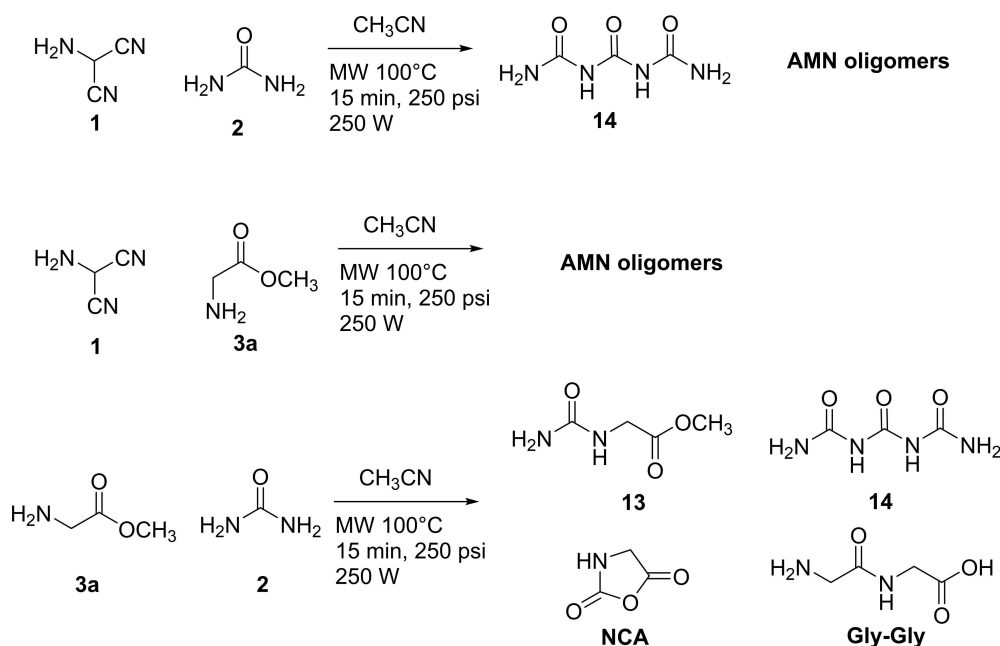
vs 20%): Compound **4 a** was probably obtained by initial condensation of **2** with **3 a** to yield *N*-carbamoyl glycine methyl ester **13**, followed by reaction of **13** with **1** (Scheme 3).^[4,45] In accordance with this hypothesis, *N*-carbamoyl glycine methyl ester **13** was isolated in the reaction mixture. Traces amount of Gly–Gly and *N*-carboxy anhydride (NCA) were also detected, the latter compound being a well-recognized condensing agent in prebiotic processes involving amino acids.^[46]

A set of different combination of the three reagents was performed to further confirm the suggested reaction pathway (Scheme 4). The condensation of **1** with **2** afforded triuret **14** as the main reaction product besides AMN oligomers (SI#2).^[14,47–50] and AMN oligomers were the only products obtained from the reaction of **1** with **3 a**.^[6] As expected, the reaction of **2** with **3 a**

afforded **13** in appreciable yield (30%), besides to **14** (12%), NCA (14%) and Gly–Gly (5%), confirming the pivotal role of urea in the control of regioselectivity of the first step of the transformation (reaction pathways for the formation of **14**, NCA and Gly–Gly are in SI#2, Scheme S3).

The synthetic scope of the reaction was generalized to α -amino-acid methyl esters **3 b–d** bearing aliphatic and aromatic side-chains. Amino imidazole carbonitriles **4 b–d** were obtained from acceptable to good yields (Scheme 2; Table 1, entries 10–11). Structural data of compounds **4 b–d** are in SI#1. The presence of aromatic substituents improved the overall yield of the reaction (Table 1, entries 11–12). Examples of the reactivity of α -amino acids in multicomponent chemistry are reported, and the role played by the isoelectric point, as well as by

**Scheme 3.** Proposed reaction pathway for the synthesis of **4 a**.



Scheme 4. Two component reactions designed on the basis of different combination of compounds 1, 2 and 3a.

hydrogen bonding and $n \rightarrow \pi$ interactions between adjacent amino acids, discussed in detail.^[49] A similar trend of reactivity was observed in the synthesis of 1H-purin-6-one derivatives,^[13] amino-imidazoles,^[14] *N*-9 di-aminopurines and guanine analogues.^[15] In these latter cases, the pKa and nucleophilicity of aromatic amino acids were critical parameters for the efficacy of the reaction.

Synthesis of C(8)-Substituted Purines

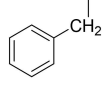
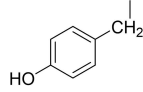
Compounds 4a–d were used as starting material for the synthesis of C(8)-substituted 2,6-diamino-purines 7a–d and 8a–d, 6-amino-3,9-dihydro-2H-purin-2-one derivatives (iso-guanines) 9a–d and 10a–d, and 3,9-dihydro-6H-purin-6-one derivatives 11a–d and 12a–d, by applying annulation protocols with formic acid, urea and guanidine (Scheme 2).^[13,51] As a general procedure, compounds 4a–d (0,28 mmol) were reacted with the selected annulation agent, guanidine carbonate 5 (0,56 mmol) (Scheme 2, Pathway B), urea 2 (0,56 mmol) (Scheme 2, Pathway C), and formic acid 6 (0,56 mmol) (Scheme 2, Pathway D), in solvent free conditions^[52] under MW irradiation (2.0 min 200 °C, 150 W, 250 psi). Methyl ester derivatives 7a–d, 9a–d, and 11a–d were obtained from appreciable to high yield (Table 2) by simple work-up of the reaction mixture with AcOEt and H₂O (SI#1). The annulation process was more effective for aromatic 4c and 4d than other cases (Table 2, entries 7–12 vs entries 1–6). Urea showed a low annulation efficacy, probably due to the formation of the undesired biuret and oligomers (Scheme 4).^[47–48] Next, the one pot synthesis of C(8)-substituted purines was evaluated without isolation of the amino imidazole carbonitrile intermediate, analyzing the case of 3a as a representative example. AMN 1

(1.0 eq), urea 2 (1.4 eq) and glycine methyl ester 3a (1.2 eq) were irradiated with MW (250 W) assistance at 200 °C for 2 min in CH₃CN, and the crude added with 5 (2.0 eq) without any preliminary work-up, followed by irradiation with MW (250 W) at 200 °C for 2 min. Under this experimental conditions 7a was isolated in a total yield comparable to that previously obtained by the domino (two steps) procedure (Scheme 2, Pathway E). C(8)-substituted purine derivatives 7a–d, 9a–d, and 11a–d were converted into the corresponding carboxylic-acids 8a–d, 10a–d and 12a–d in quantitative yields by standard hydrolysis conditions (NaOH 1.0 N) at 25 °C (Scheme 2, Pathways F–H) (SI#1). These latter compounds are suitably to be directly coupled with pseudopeptide backbone 2-aminoethyl glycine in order to obtain novel PNAs.^[53]

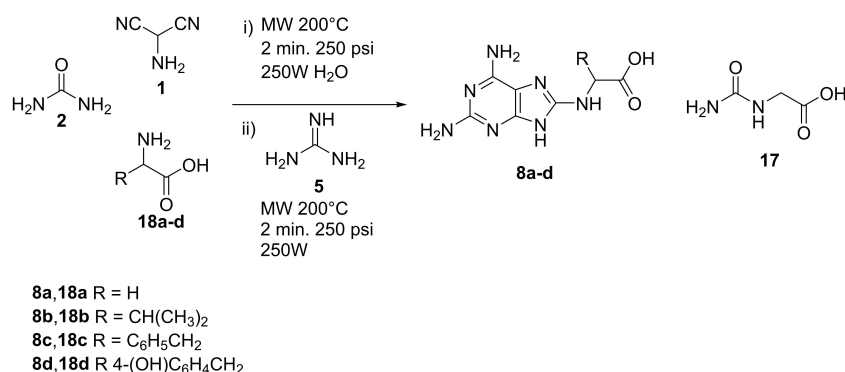
Finally, the efficacy of the multicomponent reaction was studied under more reasonable prebiotic conditions in H₂O, overcoming TEA and using α -amino-acids instead of the corresponding methyl esters. Briefly, AMN 1 (1.0 eq), urea 2 (1.4 eq), and α -amino acids 13a–d (1.2 eq) were irradiated with MW (250 W) in H₂O at 200 °C for 2 min (Scheme 5). Guanidine (2.0 eq) was added to the reaction mixture and the crude was irradiated with MW (250 W) at 200 °C for 2 min.

The yields of 8a–d were evaluated by HPLC by comparison with original samples after simple extraction of the reaction mixture with AcOEt and H₂O mixture (1:1 v/v) (Table 3, entries 1–4). Compounds 8a–d were obtained in appreciable yield, besides hydantoic acid 17, unreacted AMN and different unidentified products. These latter were expected as a result of the chemical complexity for unselective prebiotic processes (Table 3, entries 1–4). Again, aromatic amino acids afforded C(8)-substituted purines in yield higher than aliphatic counterpart, confirming previous reactivity data (chromatographic profiles are in SI#3).

Table 2. Synthesis of diaminopurine analogues **7a–d**, aminopurine analogues **9a–d**, and isoguanine analogues **11a–d**.

	α -Amino acid	Condition ^[a]	Product	R	Yield (%) ^[b]
1	Glycine	Solvent free MW 2.0 min 200 °C, 150 W, 250 psi	7a	H	51, 42 ^c
2			9a		26
3			11a		39
4	Valine		7b	CH(CH ₃) ₂	30
5			9b		22
6			11b		73
7	Phenylalanine		7c		88
8			9c		84
9			11c		86
10	Tyrosine		7d		58
11			9d		35
12			11d		47

[a] compound **4a–d** (0.28 mmol) and carbon donor source **2** or **5** or **6** (0.56 mmol) for 2 min at 200 °C in MW assistance. [b] Yield have been calculated with respect to converted C-2 imidazole derivatives **4a–d**. The conversion of the reaction was evaluated on the basis of unreacted **4a–d**. [c] Yield is referred to the one pot two steps procedure.

**Scheme 5.** Preparation of C(8)-substituted 2,6-diamino-purine acetic acids **8a–d** in H₂O, overcoming TEA and using α -amino-acids instead of the corresponding methyl esters.**Table 3.** Synthesis of C(8)-substituted 2,6-diamino-purine acetic acids **8a–d** under prebiotic conditions.

Entry	α -Amino acid	Condition ^[a]	Products	Yield (%) ^[b]
1	Glycine	H ₂ O, MW 200 °C, 250 W 250 psi 2 min.	8a	8
2	Valine		8b	5
3	Phenylalanine		8c	15
4	Tyrosine		8d	10

[a] AMN **1** (0.20 mmol), urea **2** (0.28 mmol), α -amino acid **13a–d** (0.24 mmol) were dissolved in CH₃CN and under MW assistance at 200 °C for 2 min. Guanidine (0.40 mmol) was added and the reaction mixture was irradiated at 200 °C for 2 min. [b] Yield have been calculated with respect to converted AMN **1**. The conversion of the reaction was evaluated on the basis of unreacted **1**.

Conclusions

The multicomponent synthesis of C(8)-substituted purine derivatives decorated with different α -amino-acid residues has been developed taking inspiration from the chemistry of the origins. It involves prebiotic compounds, such as AMN, urea, α -amino-acids, guanidine, and formic acid. AMN is prebiotically obtained from universally ubiquitous HCN, amino acids are facile products of HCN chemistry, urea and guanidine are product of HCN condensation, and formic acid is easily produced from prebiotic formamide and ammonium formate.^[54] The use of water, eco-friendly organic solvents, and microwave assisted irradiation, improved the atom economy and sustainability of the process. The reaction proceeds in two steps: i) the

multicomponent synthesis of amino C(2)-substituted imidazole carbonitrile intermediates from the ternary mixture of AMN, urea and α -amino-acids, in the presence of TEA; ii) microwave assisted annulation of C(2)-substituted imidazole carbonitrile intermediates with urea, formic acid and guanidine. In the first step, the regioselectivity of the condensation was controlled by urea. We observed that the overall yield of the process was dependent by the α -amino acid, the presence of aromatic substituents affording the best results. The synthetic procedure was effective when performed without TEA. The use of free amino acids and H₂O activated different reaction pathways and self-condensation processes providing expected high chemical complexity. The comparison between the two multicomponent approaches highlighted the higher selectivity and yield of the reaction with amino acid methyl esters than simple amino acids, CH₃CN favoring the solubility of the reagents. On the other hand, the higher chemical variability observed with no protected amino acids in solvent free conditions provides, in principle, variety and structural complexity typical of Darwinian molecular evolution.^[48–49]

Material and Methods

Materials

All solvents and reagents were purchased from Aldrich Chemical Co. (purity grade >99%). Monitoring and purification of the reactions have been performed with silica gel 60 and silica 60-F254 acquired from Merck. Visualization of plates has been performed using a UV lamp at 254 nm. All products were completely dried under high vacuum (10–3 mbar) prior to the spectroscopic characterization. All of the NMR spectra were acquired on a Bruker Advance DRX400 (400 MHz/100 MHz) spectrometer. Signals and chemical shifts of the reported ¹H and ¹³C-NMR spectra are in parts per million and internally referenced to DMSO-*d*₆; CdCl₂ and MeOD-*d*₄. Coupling constants (*J*) are reported in Hz. Multiplicities are reported as follows: s=singlet, d=doublet, t=triplet, dd=double doublets, m=multiplet. UHPLC were performed on Ultimate 3000 Rapid Resolution system (DIONEX, Sunnyvale, USA) using Hypersil GOLD™ (3 μ m, 150 mm 4.6 mm) or by a Vanquish U-HPLC (Thermo scientific) associated to ISQ-EC MS(Thermo scientific) equipped with C18 Avantor ACE-5 (5 μ m×250 mm×4.6 mm).

General procedure for the synthesis of imidazoles 4a–d

To a solution of Urea **2** (0.28 mmol) in CH₃CN (3 mL) was added triethylamine (0.24 mmol) and a selected alpha amino-acid methyl ester **3a–d** (0.24 mmol). The mixture was stirred at room temperature for 30 min. To this solution was added aminomalononitrile p-toluenesulfonate **1** (0.20 mmol), and the solution was stirred under microwave condition using the following program:

N° of cycles	Temperature	Ramp Time	Hold Time	Pressure (psi)	Power (W)
3	200°C	2min	5min	250	250

At the end of the reaction, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and extracted with H₂O (3×10 mL). The organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude was purified by flash-chromatography eluting with diethyl ether/hexane (6:1) to afford **4a–d** from 25 to 45% of yield.

General Procedure for the Synthesis of Diaminopurine 7a–d, Isoguanine 9a–d and Aminopurine 11a–d

Imidazole **4a–d** (0.20 mmol) and guanidine carbonate **5** (for derivatives **7a–d**) or urea **2** (for derivatives **9a–d**) or formic acid **6** (for derivatives **11a–d**) (0.56 mmol) were irradiated under microwave conditions using the following program:

N° of cycles	Temperature	Ramp Time	Hold Time	Pressure (psi)	Power (W)
1	200°C	1min	2min	250	150

The solution stirred under microwave condition above described. At the end of the reaction, the mixture was dissolved in ethyl acetate (10 mL) and extracted with H₂O (3×10 mL). The organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. Compounds **7a–d**, **9a–d** and **11a–d** were obtained with yield from 12 to 88%.

General Procedure for the Synthesis of Diaminopurine 8a–d by Prebiotic Chemistry Approach

To a solution of Urea **2** (0.28 mmol) in water (3 mL) was added triethylamine (0.24 mmol) and a selected alpha amino-acid methyl ester **3a–d** (0.24 mmol). The mixture was stirred at room temperature for 30 min. To this solution was added aminomalononitrile p-toluenesulfonate **1** (0.20 mmol), and the solution was stirred under microwave condition using the following program:

The solution stirred under microwave condition above described. At the end of the reaction the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and extracted with H₂O (3×10 mL). The organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. Then, guanidine **5** (0.56 mmol) was added to the crude of reaction and the mixture was stirred under microwave condition by the same condition previously describe. Finally, the crude was dissolved in ethyl acetate (10 mL) and extracted with H₂O (3×10 mL). The organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. Compounds **8a–d** were detected in the crude using the Ultimate 3000 Rapid Resolution UHPLC system (DIONEX, Sunnyvale, USA) equipped with C18 Hypersil GOLD™ column (3 μ m×150 mm×4.6 mm). Chromatographic separations were achieved using the following conditions: column temperature 25 °C, flow rate 1.0 ml/min, gradient elution with phase A (H₂O, 0.1% formic acid) and phase B (acetonitrile, CH₃CN). The gradient employed was as follows: 5 min 90% A; 35 min 70% A; 45 min 90% A. Products were detected by their absorbance at 254 nm with yield from 5 to 15%.

General Procedure for the Synthesis of Diaminopurine, Isoguanine and Aminopurine Analogues Bearing Free Carboxylic Acid Moiety (7a–d, 9a–d and 11a–d)

Compounds **7a–d** or **9a–d** or **11a–d** (0.10 mmol) were treated with an aqueous solution of NaOH (1.0 N, 1.0 mL) and stirred for 18 h at room temperature. The solution was acidified with HCl 1.0 N until reaching neutral pH, freeze-dried, and washed with methanol. Compound **8a–d**, **10a–d** and **12a–d** were obtained in quantitative yield after evaporation of the solvent.

Spectroscopic Data

Compound 4a Methyl (5-amino-4-cyano-1H-imidazol-2-yl)glycinate. The crude residue was purified by silica gel chromatography eluting with Diethyl ether/Hexane (6:1). ¹H-NMR (400 MHz, DMSO-*d*₆, ppm): δ 7.97 (s, 1H, NH), 6.80 (s, 1H, NH₂), 6.24 (s, 1H, NH), 3.96–3.88 (m, CH₂), 3.64 (s, 3H, O–CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆, ppm): δ 170.76 (C=O), 157.09 (C), 139.09 (C), 116.75 (C), 89.41 (C), 55.29 (O–CH₃), 31.13 (CH₂). MS (ESI): *m/z* (M+H) + 196.08. Elemental analysis for C₇H₇N₅O₂ calcd C, 43.08; H, 4.65; N, 35.88; O, 16.39. Found: C, 43.10; H, 4.67; N, 35.90; O, 16.35.

Compound 4b Methyl (5-amino-4-cyano-1H-imidazol-2-yl)valinate. The crude residue was purified by silica gel chromatography eluting with Diethyl ether/Hexane (6:1). ¹H-NMR (400 MHz, DMSO-*d*₆, ppm): δ 7.24 (s, 1H, NH), 6.40 (d, J = 2.8 Hz, NH), 4.08–4.04 (m, 1H, CH), 3.63 (s, 3H, O–CH₃), 1.95–1.98 (m, 1H, CH); 0.87–0.84 (m, 6H, CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 174.31 (C=O), 158.84 (C), 140.08 (C), 120.89 (CN), 89.16 (C), 58.04 (CH), 52.16 (O–CH₃), 31.31 (CH), 19.03 (CH₃), 17.71 (CH₃). MS (ESI): *m/z* (M+H) + 238.12. Elemental analysis for C₁₀H₁₅N₅O₂ calcd C, 50.62; H, 6.37; N, 29.52; O, 13.49. Found: C, 50.58; H, 6.34; N, 29.51; O, 13.49.

Compound 4c Methyl (5-amino-4-cyano-1H-imidazol-2-yl)phenylalaninate. The crude residue was purified by silica gel chromatography eluting with Diethyl ether/Hexane (6:1). ¹H-NMR (400 MHz, DMSO-*d*₆, ppm): δ 7.31–7.15 (m, 5H, CH–Ar x5), 6.49 (d, J = 4 Hz, NH), 4.40–4.36 (m, 1H, CH), 3.59 (s, 3H, O–CH₃), 2.99–2.84 (m, 2H, CH₂). ¹³C-NMR (100 MHz, DMSO-*d*₆, ppm): δ 175.68 (C=O), 158.44 (C), 138.29 (C), 137.59 (C), 129.61 (C–Ar x2), 128.66 (C–Ar x2), 126.71 (C–Ar), 120.04 (CN), 89.73 (C–Ar), 56.12 (CH), 51.74 (O–CH₃), 30.79 (CH₂). MS (ESI): *m/z* (M+H) + 286.12. Elemental analysis for C₁₄H₁₅N₅O₂ calcd C, 58.94; H, 5.30; N, 24.55; O, 11.22. Found: C, 58.92; H, 5.28; N, 24.52; O, 11.20.

Compound 4d Methyl (5-amino-4-cyano-1H-imidazol-2-yl)tyrosinate. The crude residue was purified by silica gel chromatography eluting with Diethyl ether/Hexane (6:1). ¹H-NMR (400 MHz, DMSO-*d*₆, ppm): δ 9.18 (s, 1H, NH), 6.95 (d, J = 4 Hz, CH–Ar x2), 6.66 (d, J = 4 Hz, CH–Ar x2), 5.60 (s, 1H, OH), 4.06–3.58 overlapped (m, 1H, CH) 3.58 (s, 3H, O–CH₃), 2.79–2.66 (m, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 175.84 (C=O), 168.23 (C), 156.28 (C–OH), 139.28 (C), 130.54 (C–Ar x2), 128.21 (C–Ar), 120.52 (CN), 115.43 (C–Ar x2), 97.48 (C–Ar), 56.34 (CH), 51.74 (O–CH₃), 36.50 (CH₂). MS (ESI): *m/z* (M+H) + 302.12. Elemental analysis for C₁₄H₁₅N₅O₃ calcd C, 55.81; H, 5.02; N, 23.24; O, 15.93. Found: C, 55.79; H, 4.98; N, 23.20; O, 15.90.

Compound 7a Methyl (2,6-diamino-9H-purin-8-yl)glycinate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 8.12 (s, 1H, NH), 6.80 (s, 2H, NH₂) 5.61 (s, 1H, NH), 4.61 (s, 1H, NH₂), 4.03 (d, J = 2.7 Hz, CH₂), 3.79 (s, 3H, O–CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 161.15 (C=O), 158.06 (C–Ar), 155.78 (C–Ar), 145.83 (C–Ar), 135.20 (C–Ar), 129.50 (C–Ar), 63.92 (CH₂) 52.38 (O–CH₃). MS (ESI): *m/z* (M+H) + 338.10. Elemental analysis for C₈H₁₁N₇O₂ calcd C, 40.51; H, 4.67; N, 41.33; O, 13.49. Found: C, 40.49; H, 4.64; N, 41.30; O, 13.44.

Compound 7b Methyl (2,6-diamino-9H-purin-8-yl)valinate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 7.69 (s, 1H, NH), 5.93 (s, 2H, NH₂), 4.84 (s, 2H, NH₂), 4.02 (d, J = 1.8 Hz, CH), 3.84 (s, 3H, O–CH₃), 3.75 (t, J = 8.8 Hz, NH), 2.27–2.23 (m, 1H, CH), 1.07 (d, J = 3.6 Hz, CH₃), 0.97 (d, J = 3.4 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 174.13 (C=O), 157.87 (C), 153.80 (C), 135.74 (C), 125.53 (C), 116.37 (C), 63.99 (CH), 51.90 (O–CH₃), (C), 30.32 (CH), 18.75 (CH₃), 16.09 (CH₃). MS (ESI): *m/z* (M+H) + 280.30. Elemental Analysis for C₁₁H₁₇N₇O₂ calcd C, 47.30; H, 6.67; N, 35.10; O, 11.46. Found: C, 40.45; H, 4.60; N, 41.28; O, 13.45.

Compound 7c Methyl (2,6-diamino-9H-purin-8-yl)phenylalaninate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 7.23–7.15 (m, 4 Hz, CH–Ar x3), 7.12 (d, J = 3.4 Hz, CH–Ar x2r), 5.80 (s, 2H, NH₂) 5.37 (d, J = 3.7 Hz, NH₂), 4.86–4.76 (m, 1H, CH), 3.74 (s, 3H, O–CH₃), 3.12–3.09 (m, 2H, CH₂). ¹³C-NMR (100 MHz, DMSO-*d*₆, ppm): δ 175.65 (C=O), 173.53 (C), 158.42 (C), 157.58 (C), 137.62 (C), 136.09 (C), 130.19 (C), 129.59 (C–Ar x2), 128.73 (C–Ar), 128.55 (C–Ar), 127.12 (C–Ar), 126.99 (C), 58.84 (CH), 52.12 (O–CH₃), 38.06 (CH₂). MS (ESI): *m/z* (M+H) + 328.14. Elemental analysis for C₁₅H₁₇N₇O₂ calcd C, 55.04; H, 5.23; N, 29.95; O, 9.77. Found: C, 54.50; H, 5.20; N, 29.90; O, 9.71.

Compound 7d Methyl (2,6-diamino-9H-purin-8-yl)tyrosinate. ¹H-NMR (400 MHz, CDCl₃, ppm): 7.00 (d, J = 4 Hz, CH–Ar x2), 6.77 (d, J = 4 Hz, CH–Ar x2), 4.88 (d, J = 4.4 Hz, NH), 4.76–3.55 (m, 1H, CH), 4.34–3.09 (m, 2H, CH₂), 3.76 (s, 3H, O–CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 177.91 (C=O), 162.57 (C), 161.44 (C), 155.11 (C–Ar), 153.78 (C), 144.48 (C), 143.80 (C–Ar), 135.44 (C–Ar x2), 130.92 (C–Ar), 119.39 (C–Ar x2), 67.61 (CH), 52.68 (O–CH₃), 32.11 (CH₂). MS (ESI): *m/z* (M+H) + 344.14. Elemental analysis for C₁₅H₁₇N₇O₃ calcd C, 52.47; H, 4.99; N, 28.56; O, 13.98. Found: C, 52.42; H, 4.90; N, 28.51; O, 13.93.

Compound 8a (2,6-diamino-9H-purin-8-yl)glycine ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.56 (s, 1H, NH), 8.13 (s, 1H, NH), 3.37 (s, 2H, CH₂). MS (ESI): *m/z* (M+H) + 224.08. Elemental analysis for C₇H₉N₇O₂ C, 37.67; H, 4.06; N, 43.93; O, 14.34. Found: C, 37.67; H, 4.06; N, 43.93; O, 14.34.

Compound 8b (2,6-Diamino-9H-purin-8-yl)valine. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 6.99 (s, 1H, NH), 6.46 (s, 1H, NH), 4.02 (s, 1H, OH), 4.78–3.73 (m, 1H, CH), 2.29–2.21 (m, 1H, CH), 1.08–0.96 (m, 6H, CH₃). MS (ESI): *m/z* (M+H) + 266.13. Elemental analysis for C₁₀H₁₅N₇O₂ C, 45.28; H, 5.70; N, 36.96; O, 12.06. Found: C, 44.90; H, 5.55; N, 35.91; O, 12.00.

Compound 8c (2,6-Diamino-9H-purin-8-yl)phenylalanine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): 7.29–7.23 (m, 5H, CH–Ar x5), 4.61 (s, 2H, OH), 4.39 (t, J = 2.5 Hz, NH₂), 3.37 (s, 1H, CH), 3.14–3.00 (m, 2H, CH₂). MS (ESI): *m/z* (M+H) + 314.13. Elemental analysis for C₁₄H₁₅N₇O₂ C, 53.67; H, 4.83; N, 31.29; O, 10.21. Found: C, 53.57; H, 4.43; N, 31.09; O, 10.01.

Compound 8d (2,6-Diamino-9H-purin-8-yl)tyrosine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.56 (s, 1H, OH), 7.05 (d, J = 4.2 Hz, CH–Ar x2), 6.71 (d, J = 4.2 Hz, CH–Ar x2), 4.59 (s, OH), 4.34–4.31 (m, CH), 3.01–2.92 (m, 2H, CH₂). MS (ESI): *m/z* (M+H) + 330.12. Elemental analysis for C₁₄H₁₅N₇O₃ C, 51.06; H, 4.59; N, 29.77; O, 14.57. Found: C, 51.00; H, 4.51; N, 29.71; O, 14.51.

Compound 9a Methyl (6-amino-2-oxo-3,9-dihydro-2H-purin-8-yl)glycinate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 8.12 (s, 1H, NH), 7.00 (s, 1H, NH), 5.29 (d, J = 0.8 Hz, NH₂), 4.03 (d, J = 2.6 Hz, CH₂), 3.79 (s, 3H, O–CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 165.06 (C=O), 160.75 (C=O), 153.98 (C), 148.7 (C), 141.98 (C), 129.56 (C), 67.83 (CH₂), 52.23 (O–CH₃). MS (ESI): *m/z* (M+H) + 239.08. Elemental analysis for C₈H₁₀N₆O₃ C, 40.34; H, 4.23; N, 35.28; O, 20.15. Found: C, 40.31; H, 4.20; N, 35.22; O, 20.12.

Compound 9b Methyl (6-amino-2-oxo-3,9-dihydro-2H-purin-8-yl)valinate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 7.19 (s, 1H, NH), 6.24

(d, $J=4.5$ Hz, NH), 5.25 (s, 1H, NH₂), 4.38–4.35 (m, 1H, CH), 3.73 (s, 3H, O–CH₃), 2.14–2.09 (m, 1H, CH), 0.95 (d, $J=3.4$ Hz, 3H, CH₃), 0.88 (d, $J=3.4$ Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 174.47 (C=O), 161.26 (C), 159.48 (C=O), 156.66 (C), 155.18 (C), 128.94 (C–Ar), 125.81 (C), 58.09 (CH), 52.14 (O–CH₃), 19.02 (CH₃), 17.69 (CH₃). MS (ESI): m/z (M+H) + 281.32. Elemental analysis for C₁₁H₁₆N₆O₃ C, 47.14; H, 5.75; N, 29.98; O, 17.12. Found: C, 47.11; H, 5.72; N, 29.94; O, 17.10.

Compound 9c Methyl (6-amino-2-oxo-3,9-dihydro-2H-purin-8-yl)phenylalaninate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 7.21 overlapped (t, CH–Ar), 7.20 (d, $J=3.6$ Hz, CH–Ar x2), 7.12 (d, $J=3.6$ Hz, CH–Ar x2), 5.79–4.74 (m, CH), 4.99 (s, 2H, NH₂), 3.71 (s, 3H, O–CH₃), 3.12–3.09 (m, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 174.00 (C=O), 173.43 (C), 158.15 (C), 157.16 (C=O), 136.09 (C–Ar) 135.37 (C), 129.37 (C–Ar), 129.23 (C–Ar), 128.94 (C), 128.52 (C–Ar), 127.44 (C–Ar), 127.02 (C), 59.94 (O–CH₃), 54.03 (CH), 38.41 (CH₂). MS (ESI): m/z (M+H) + 329.13. Elemental analysis for C₁₅H₁₆N₆O₃ C, 54.87; H, 4.91; N, 25.60; O, 14.62. Found: C, 54.87; H, 4.91; N, 25.60; O, 14.62.

Compound 9d Methyl (6-amino-2-oxo-3,9-dihydro-2H-purin-8-yl)tyrosinate. ¹H-NMR (400 MHz, DMSO-*d*₆, ppm): δ 8.10 (s, 2H, NH₂), 7.05 (d, $J=4.2$ Hz, CH–Ar x2), 6.71 (d, $J=4.2$ Hz, CH–Ar x2), 5.60 (s, 1H, OH), 4.06–3.99 (m, 1H, CH) 3.58 (s, 3H, O–CH₃), 2.96–2.80 (m, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 171.75 (C=O), 166.89 (C), 164.59 (C), 158.97 (C), 154.88 (C), 148.75 (C=O), 130.60 (C–Ar x2), 128.05 (C–Ar x2), 115.52 (C–Ar), 107.60 (C), 70.03 (CH), 51.33 (O–CH₃), 29.57 (CH₂). MS (ESI): m/z (M+H) + 345.33. Elemental analysis for C₁₅H₁₆N₆O₃ C, 52.32; H, 4.68; N, 24.41; O, 18.59. Found: C, 54.814; H, 4.87; N, 25.40; O, 14.00.

Compound 10a (6-Amino-2-oxo-3,9-dihydro-2H-purin-8-yl)glycine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.56 (s, 1H, NH), 8.13 (s, 1H, OH), 3.69 (s, 1H, NH), 3.37 (s, 1H, CH₂). MS (ESI): m/z (M+H) + 225.07. Elemental analysis for C₇H₈N₆O₃ C, 37.50; H, 3.60; N, 37.49; O, 21.41. Found: C, 36.80; H, 3.40; N, 37.41; O, 21.38.

Compound 10b (6-Amino-2-oxo-3,9-dihydro-2H-purin-8-yl)valine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 3.99 (s, 1H, CH), 3.39 (s, 1H, NH), 2.15 (d, $J=1.5$ Hz, CH), 1.05 (d, $J=3.4$ Hz, CH₃), 0.92 (d, $J=3.4$ Hz, CH₃). MS (ESI): m/z (M+H) + 267.11. Elemental analysis for C₁₀H₁₄N₆O₃ C, 45.11; H, 5.30; N, 31.56; O, 18.03. Found: C, 45.01; H, 5.22; N, 31.50; O, 17.02.

Compound 10c (6-Amino-2-oxo-3,9-dihydro-2H-purin-8-yl)phenylalanine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 7.31–7.23 (m, 5H, CH–Ar x5), 4.39 (t, $J=5$ Hz, CH), 3.14–3.01 (m, 2H, CH₂). MS (ESI): m/z (M+H) + 315.11. Elemental analysis for C₁₄H₁₄N₆O₃ C, 53.50; H, 4.49; N, 26.74; O, 15.25. Found: C, 53.40; H, 4.49; N, 26.72; O, 15.21.

Compound 10d (6-Amino-2-oxo-3,9-dihydro-2H-purin-8-yl)tyrosine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 7.05 (d, $J=4.2$ Hz, CH–Ar x2), 6.71 (d, $J=4.2$ Hz, CH–Ar x2), 4.32 (t, $J=5$ Hz, CH), 3.00–2.92 (m, 2H, CH₂). MS (ESI): m/z (M+H) + 331.11. Elemental analysis for C₁₄H₁₄N₆O₄ C, 50.91; H, 4.27; N, 25.44; O, 19.37. Found: C, 50.89; H, 4.22; N, 25.41; O, 19.32.

Compound 11a Methyl (6-oxo-6,9-dihydro-3H-purin-8-yl)glycinate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 8.57 (s, 1H, NH), 8.36 (s, 1H, CH), 4.11 (d, $J=2.8$ Hz, CH₂), 3.80 (s, 3H, O–CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 169.55 (C=O), 161.55 (C), 161.06 (C=O), 153.31 (C), 147.87 (C), 124.96 (C), 52.48 (O–CH₃), 31.92 (CH₂). MS (ESI): m/z (M+H) + 224.07. Elemental analysis for C₈H₈N₅O₃ C, 43.05; H, 4.06; N, 31.38; O, 21.50. Found: C, 43.00; H, 4.01; N, 31.35; O, 21.54.

Compound 11b Methyl (6-oxo-6,9-dihydro-3H-purin-8-yl)valinate. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 8.60 (s, 1H, NH), 8.38 (s, 1H, CH–Ar), 5.93 (s, 1H, NH), 4.43 (s, 1H, CH), 3.76 (s, 3H, O–CH₃), 2.16–2.11 (m, 1H, CH), 0.97–0.90 (m, 6H, CH₃). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ

173.85 (C=O), 164.61 (C), 161.67 (C), 157.35 (C=O), 146.97 (C), 131.37 (C), 58.11 (C), 52.11 (O–CH₃), 31.40 (C), 18.98 (CH₃), 17.74 (CH₃). MS (ESI): m/z (M+H) + 266.12. Elemental analysis for C₁₁H₁₅N₅O₃ C, 49.81; H, 5.70; N, 26.40; O, 18.09. Found: C, 49.80; H, 5.65; N, 26.42; O, 18.00.

Compound 11c Methyl (6-oxo-6,9-dihydro-3H-purin-8-yl)phenylalaninate. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.04 (s, 1H, CH–Ar), 7.31–7.25 (m, CH–Ar x5), 4.39 (t, $J=5.2$ Hz, CH), 3.36 (s, 1H, O–CH₃), 3.14–3.01 (m, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 180.66 (C=O), 173.88 (C), 163.70 (C), 158.30 (C=O), 153.53 (C) 129.43 (C–Ar x2), 128.78 (C–Ar x2), 127.92 (C–Ar), 112.17 (C–Ar), 100.62 (C), 53.46 (O–CH₃), 33.77 (CH₂). MS (ESI): m/z (M+H) + 314.12. Elemental analysis for C₁₅H₁₅N₅O₃ C, 57.50; H, 4.83; N, 22.35; O, 15.32. Found: C, 49.80 H, 5.66; N, 26.44; O, 18.02.

Compound 11d Methyl (6-oxo-6,9-dihydro-3H-purin-8-yl)tyrosinate. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.37 (s, 1H, CH–Ar), 7.20 (d, $J=4$ Hz, CH–Ar x2), 6.85 (d, $J=4$ Hz, CH–Ar x2), 5.70 (s, 1H, OH), 4.36–4.30 (m, 1H, CH) 3.36 (s, 1H, O–CH₃), 3.06–2.90 (m, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃, ppm): δ 172.26 (C=O), 162.81 (C), 161.27 (C), 156.67 (C), 154.88 (C), 147.98 (C=O), 130.86 (C–Ar x2), 128.81 (C–Ar x2), 115.52 (C–Ar), 70.79 (CH), 57.91 (O–CH₃), 37.11 (CH₂). MS (ESI): m/z (M+H) + 330.11. Elemental analysis for C₁₅H₁₅N₅O₄ C, 54.71; H, 4.59; N, 21.27; O, 19.43. Found: C, 49.80; H, 5.60; N, 26.32; O, 18.07.

Compound 12a (6-oxo-6,9-dihydro-3H-purin-8-yl)glycine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.56 (s, 1H, CH), 3.69 (s, 2H, CH₂). MS (ESI): m/z (M+H) + 210.05. Elemental analysis for C₇H₇N₅O₃ C, 40.20; H, 3.37; N, 33.48; O, 22.95. Found: C, 40.15; H, 3.31; N, 33.42; O, 22.90.

Compound 12b (6-oxo-6,9-dihydro-3H-purin-8-yl)valine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.56 (s, 1H, CH), 4.59 (s, 1H, NH), 4.02 (s, 1H, CH), 2.17–2.09 (m, 1H, CH), 0.97–0.91 (m, 6H, 2xCH₃). MS (ESI): m/z (M+H) + 252.25. Elemental analysis for C₁₀H₁₃N₅O₃ C, 47.81; H, 5.22; N, 27.88; O, 19.10. Found: C, 47.77; H, 5.20; N, 27.81; O, 19.08.

Compound 12c (6-oxo-6,9-dihydro-3H-purin-8-yl)phenylalanine. ¹H-NMR (400 MHz, CDCl₃, ppm): δ 9.09 (s, 1H, CH–Ar), 7.34–7.28 (m, CH–Ar x3), 7.09 (d, $J=1.8$ Hz, 2H, CH–Ar), 4.81 (d, $J=1.3$ Hz, CH), 3.64–3.34 (m, 2H, CH₂). MS (ESI): m/z (M+H) + 300.10. Elemental analysis for C₁₄H₁₃N₅O₃ C, 56.18; H, 4.38; N, 23.40; O, 16.04. Found: C, 56.12; H, 4.34; N, 23.35; O, 16.00.

Compound 12d (6-oxo-6,9-dihydro-3H-purin-8-yl)tyrosine. ¹H-NMR (400 MHz, MeOD-*d*₄, ppm): δ 8.37 (s, 1H, CH–Ar), 7.95 (s, 1H, OH), 7.05 (d, $J=4$ Hz, CH–Ar x2), 6.77 (d, $J=4$ Hz, CH–Ar x2), 4.40–4.39 (m, 1H, CH), 3.06–2.90 (m, 2H, CH₂).

MS (ESI): m/z (M+H) + 316.10. Elemental analysis for C₁₄H₁₃N₅O₄ C, 53.33; H, 4.16; N, 22.21; O, 20.30. Found: C, 53.31; H, 4.18; N, 22.20; O, 20.15.

Supporting Information

Supporting information materials contains: SI#1: Spectroscopic data, ¹H-NMR and ¹³C-NMR of **4a–4d**; **7a–d**; **8a–d**; **9a–d**; **10a–d**; **11a–d**; **12a–d** and SI#2: Experimental details of two component reactions SI#3: Chromatographic profile of reactions under complete prebiotic conditions.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

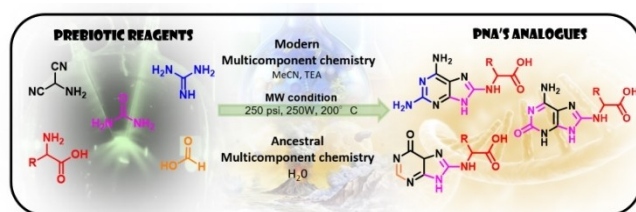
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Multicomponent Synthesis · Peptide Nucleic Acid · C(8)-substituted purines · PNA's building block · Prebiotic synthesis

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RESEARCH ARTICLE



Prebiotic reagents (AMN, Amino-acids, Urea, Guanidine and Formic Acid) react via modern or ancestral multicomponent chemistry to produce

selected C8-PNA's derivatives. The synthesis is effective under MW assistance in MeCN and H₂O as solvents.

Dr. E. Mancin, Dr. E. Capecchi, Prof. L. Botta, Dr. B. M. Bizzarri*

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Multicomponent Synthesis of C(8)-Substituted Purine Building Blocks of Peptide Nucleic Acids from Prebiotic Compounds

