Arylhydrazononitriles as precursors to 2-substituted 1,2,3-triazoles and 4-amino-5-cyano-pyrazole derivatives utilizing microwave and ultrasound irradiation

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**RESEARCH LETTER**

**Arylhydrazononitriles as precursors to 2-substituted 1,2,3-triazoles and 4-amino-5-cyano-pyrazole derivatives utilizing microwave and ultrasound irradiation**

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Cyanoacetamides 3a–d were prepared by reacting ethyl cyanoacetate with primary aliphatic amines 2a–d. The formed cyanoacetamides 3a–d were coupled with aromatic diazonium salts to give the corresponding arylhydrazones 4a–i which were used as precursors to title triazoles and pyrazoles by reacting with hydroxylamine and chloroacetonitrile. Yields of products formed by conventional heating are compared with those of microwave and ultrasound irradiation.

**Keywords:** green synthetic approaches; 2-arylhydrazononitriles; X-ray crystal structure determination; 4-amino-5-cyano-pyrazoles; 1,2,3-triazoles

**Introduction**

Recently, many papers have been published dealing with 2-arylhydrazononitriles as precursors to heteroaromatics (1–6). Elnagdi et al. (7–10) have reported efficient synthetic approaches to functionally substituted pyrazoles and 1,2,3-triazoles utilizing arylhydrazonitrile precursors. In the light of our recent interest in adopting green synthetic methodologies for the synthesis of functionally substituted heteroaromatics utilizing microwave (Mw) heating and ultrasound (Us) irradiation (11–25), we aim in this work to report on the synthesis and utility of arylhydrazonitrile as precursors to 1,2,3-triazoles 7, 10, and pyrazole derivatives 13.

**Results and discussion**

Ethyl cyanoacetate (1) was reacted with a variety of aliphatic amines 2a–d under Mw heating or Us activation to yield cyanoacetamides 3a–d (Scheme 1).

Compounds 3a–d were coupled readily with aromatic diazonium salts to yield the corresponding arylhydrazononitriles 4a–i, in 67–95% yields (Scheme 2). The structures of compounds 4a–i were established on the basis of their elemental analyses and spectral data. \(^1\)H NMR spectra of compounds 4a–i showed a singlet signal in region 11.10–14.97 ppm corresponding to the hydrazone (NH) proton. The structure assigned to compounds 4a–i could be unequivocally established by single crystal X-ray diffraction of compound 4c (26), as shown in Figure 1.

Parallel to the recent literature data (7,8,27–29), compounds 4a–i reacted with hydroxylamine hydrochloride in the presence of sodium acetate to yield the amidoximes 5a–h. It has been found that the reaction completion time was 1 h in refluxing ethanol and 2–5 min under Mw heating. The structures of the new amidoximes 5a–h have been elucidated by elemental analyses and spectroscopic measurements. For example, the \(^1\)H NMR spectra of compound 5a revealed the presence of (NH\(_2\)) protons at 86.52 ppm and a broad singlet signal at 814.21 ppm corresponding to (OH) proton. The IR spectra of compound 5a showed absorption bands at \(\nu = 3587, 3456,\) and 3420 cm\(^{-1}\) due to OH and NH\(_2\) groups, respectively.

Upon heating 5 in dimethylformamide (DMF) at reflux temperature for 1 h or under Mw irradiation for 2–5 min or by utilizing Us irradiation for 1 h at 40°C, this compound gave solid products whose structures were assumed to be 6, 7, or 8 (Scheme 3).

The structure of isoxazoles 6 was readily ruled out for the reaction products on the basis of spectral data. Thus, the presence of an amide carbonyl absorption in region \(\nu = 1642–1658\) cm\(^{-1}\) in the IR spectra of the reaction products allowed us to discard the possible structure 6. Moreover, \(^13\)C NMR spectra of the reaction products confirmed the presence of a CO carbon at \(\delta \approx 164\) ppm. If the reaction product was

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the isomer 6, it would be difficult to assign this signal. Elemental analysis and spectral data could not unequivocally differentiate the two isomers 7 and 8. Therefore, the 1,2,3-triazolo[4,5-d]pyrimidines 10 was prepared to chemically verify the structure of 7. Reaction of aminotriazoles 7 with dimethylformamide dimethyacetal (DMF DMA), under different reaction conditions, gave the ring-closed 1,2,3-triazolo[4,5-d]pyrimidines 10, via the intermediate 9 (Scheme 3). It is difficult to obtain these reaction products 10 with the isomer 8.

Recently, Elnagdi et al. (2,7,30) have reported that refluxing 2-arylhydrazononitriles with functionally substituted alkyl halides afforded 4-aminopyrazole derivatives. Now, compound 4 was next reacted with chloroacetanitorile, under conventional heating, Mw irradiation, and sonication, to afford the 4-aminopyrazoles 13, via the acyclic non-isolable intermediate 12 (Scheme 4). The identity of compounds 13 was supported by correct elemental analyses and mass spectra as well as the IR and NMR spectra which were compatible with assigned structures (see Section “Experimental”). The reaction times and yields of the products formed via traditional methods were compared with those of Mw and Us irradiation (see Table 1).

In conclusion, we have shown that the synthesis of 2-aryl-1,2,3-triazoles and 4-aminopyrazoles from arylhydrazononitriles is better conducted by green methodologies through the avoidance of heating and excessive use of solvents. On the other hand, it should be noted that reactions occur at different temperatures with these techniques and therefore strict comparisons will require a balance between effectiveness and energy costs.

**Experimental**

**General**

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. The IR absorption spectra were measured on a Nicolet Magna 520 FT IR spectrophotometer. \(^1\)H and \(^13\)C NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO) or deuterated chloroform (CDCl₃) at Bruker DPX 400 MHz.
spectrometer using tetramethylsilane (TMS) as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Mw irradiation was carried out using the commercial Mw oven (SGO 1000 W). A thermometer used to monitor the temperature inside the Mw vessel during the reactions found that the temperature was approximately 105–110°C. Us irradiation was carried out with a microprocessor controlled-2004, high intensity ultrasonic processor with temperature controller (750 W). The ultrasonic frequency of the cleaning bath used was equal to 25

![Scheme 3. Synthesis of 5-amino-1,2,3-triazole and 1,2,3-triazolo[4,5-d]pyrimidin-7-one derivatives.](image)

Scheme 3. Synthesis of 5-amino-1,2,3-triazole and 1,2,3-triazolo[4,5-d]pyrimidin-7-one derivatives.

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![Scheme 4. Synthesis of pyrazole derivatives.](image)

Scheme 4. Synthesis of pyrazole derivatives.
Table 1. Yield as well as reaction times by the three methodologies are compared.

| No. | Δ | Mw | Us | Δ | Mw | Us |
|-----|---|----|----|---|----|----|
| 3a  | 3 h 4 min 7 min | 67 | 89 | 74 |
| 3b  | 4 h 3 min 10 min | 90 | 91 | 88 |
| 3c  | 2 h 2 min 5 min | 83 | 90 | 80 |
| 3d  | 1 h 1 min 2 min | 89 | 93 | 90 |
| 5a  | 1 h 2 min 30 min | 40 | 80 | 72 |
| 5b  | 1 h 5 min 30 min | 37 | 74 | 70 |
| 5c  | 1 h 4 min 30 min | 48 | 80 | 76 |
| 5d  | 1 h 3 min 30 min | 35 | 35 | 66 |
| 5e  | 1 h 2 min 30 min | 40 | 75 | 78 |
| 5f  | 1 h 3 min 30 min | 44 | 89 | 81 |
| 5g  | 1 h 5 min 30 min | 48 | 80 | 77 |
| 5h  | 1 h 3 min 30 min | 39 | 79 | 78 |
| 7a  | 1 h 2 min 1 h | 40 | 60 | 58 |
| 7b  | 1 h 2 min 1 h | 44 | 73 | 70 |
| 7c  | 1 h 3 min 1 h | 45 | 77 | 68 |
| 7d  | 1 h 2 min 1 h | 43 | 79 | 71 |
| 7e  | 1 h 4 min 1 h | 40 | 66 | 56 |
| 10a | 7 h 2 min – | 47 | 90 | – |
| 10b | 7 h 2 min – | 46 | 88 | – |
| 13a | 1 h 2 min 1 h | 60 | 77 | 73 |
| 13b | 1 h 2 min 1 h | 55 | 84 | 78 |
| 13c | 1 h 2 min 1 h | 59 | 79 | 70 |
| 13d | 1 h 2 min 1 h | 58 | 89 | 84 |
| 13e | 1 h 2 min 1 h | 54 | 80 | 78 |

General procedure for the preparation of N-substituted-2-cyanoacetamide 3a–d

**Method I (Δ).** Equimolar amounts (0.1 mol) of both ethyl cyanoacetate and the aliphatic amines 2a–d were stirred at room temperature for 1–4 h and the resulting solid product was re-crystallized from ethanol.

**Method II (μ).** A mixture of ethyl cyanoacetate (0.1 mol) and the appropriate amount of aliphatic amines 2a–d (0.1 mol) was placed in the Mw oven and irradiated at 460 W for 1–4 min. Then, the reaction mixture was left to cool to room temperature. The solid product so-formed was filtered and re-crystallized from ethanol.

**Method III (Us).** Equimolar amounts (0.1 mol) of both ethyl cyanoacetate and the aliphatic amines 2a–d were mixed and heated under Us irradiation at 40 °C for 2–10 min, and then left to cool to room temperature. The solid product so-formed was filtered and re-crystallized from ethanol.

**N-Butyl-2-cyanoacetamide (3a).** Orange crystals from ethanol; mp 72 °C; IR ν max cm⁻¹: 3299 (NH), 2954 (CH aliphatic), 2258 (CN), and 1653 (C = O); ¹H NMR; (DMSO-d₆); δ = 0.85 (t, 3H, CH₃, J = 7 Hz), 1.27 (m, 2H, CH₂, J = 7 Hz), 1.38 (m, 2H, CH₂, J = 7 Hz), 3.06 (q, 2H, CH₂, J = 7 Hz), 3.56 (s, 2H, CH₂CN), and 8.18 (br s, 1H, NH) ppm; ¹³C NMR; (DMSO-d₆); δ = 14.02, 20.00, 25.76, 31.40 (butyl carbons), 39.27 (CH₂CN), 116.71 (CN), and 162.39 (C = O) ppm; MS: 141 [M⁺ + 1]. Analysis calculated for C₇H₁₂N₂O (140.19): C, 59.98; H, 8.63; and N, 19.98. Found: C, 59.90; H, 8.70; and N, 19.92.

**2-Cyano-N-hexylacetamide (3b).** Yellow crystals from ethanol; mp 67°C; IR ν max cm⁻¹: 3299 (NH), 2932 (CH aliphatic), 2260 (CN), and 1645 (C = O); ¹H NMR; (CDCl₃); δ = 0.81 (t, 3H, CH₃, J = 6 Hz), 1.24 (m, 6H, 3CH₂), 1.45 (m, 2H, CH₂, J = 7 Hz), 3.17 (q, 2H, CH₂, J = 7 Hz), 3.42 (s, 2H, CH₂CN), and 7.17 (s, 1H, NH) ppm; ¹³C NMR; (CDCl₃); δ = 13.99, 22.54, 26.04, 26.55, 29.11, 31.43 (hexyl carbons), 40.45 (CH₂CN), 115.22 (CN), and 162.03 (C = O) ppm; MS: 169 [M⁺ + 1]. Analysis calculated for C₁₂H₁₅N₂O (168.24); C, 64.25; H, 9.59; and N, 16.65. Found: C, 64.20; H, 9.61; and N, 16.69.

**2-Cyano-N-cyclohexyl-acetamide (3c).** Colorless crystals from ethanol; mp 136°C; IR ν max cm⁻¹: 3272 (NH), 2933 (CH aliphatic), 2261 (CN), and 1628 (C = O); ¹H NMR; (DMSO-d₆); δ = 1.12 – 1.68 (m, 6H, 3CH₂), 1.70–2.03 (m, 4H, 2CH₂), 3.46–3.54 (m, 1H, CH), 3.22 (s, 2H, CH₂CN), and 8.14 (d, 1H, NH, J = 7 Hz) ppm; ¹³C NMR; (DMSO-d₆); δ = 24.35, 24.87, 25.62, 25.84, 30.91, 32.60 (cyclohexyl carbons), 48.73 (CH₂CN), 116.73 (CN), and 161.51 (C = O) ppm; MS: 166 [M⁺]. Analysis calculated for C₉H₁₄N₂O (166.22): C, 65.05; H, 8.49; and N, 16.85. Found: C, 65.10; H, 8.36; and N, 16.89.

**N-Benzyl-2-cyanoacetamide (3d).** Brown crystals from ethanol; mp 124°C; IR ν max cm⁻¹: 3295 (NH), 3091 (CH aromatic), 2923 (CH aliphatic), 2220 (CN), and 1640 (C = O); ¹H NMR; (DMSO-d₆); δ = 3.71 (s, 2H, CH₂CN), 4.30 (d, 2H, PhCH₂, J = 5 Hz), 7.29–7.34 (m, 5H, ph–H), and 8.74 (t, 1H, NH, J = 7 Hz) ppm; MS: 174 [M⁺]. Analysis calculated for
C_{10}H_{10}N_{2}O (174.20): C, 68.95; H, 5.79; and N, 16.08. Found: C, 68.90; H, 5.67; and N, 16.20.

Preparation of arylhydrazine derivatives 4a–i
A cold solution of arylidiamonium salt (10 mmol) was prepared by adding a solution of sodium nitrite (1 g into 10 mL H_{2}O) to a cold solution of arylamine hydrochloride or arylamine nitrate (10 mmol) with stirring. The resulting solution of the arylidiamonium was then added to a cold solution of N-substituted-2-cyanoacetamides 3a–d (0.1 mmol) in ethanol (50 mL) containing sodium acetate (1 g into 10 mL H_{2}O). The mixture was stirred at room temperature for 1 h and the solid product so-formed was collected by filtration and recrystallized from ethanol.

2-[N-((Butylcarbamoyl-cyano-methylene)-hydrazino]-benzoic acid methyl ester (4a). Yellow crystals from ethanol; yield 70%, mp 166°C; IR ν_{max} cm^{-1}: 3388 (NH), 3026 (CH aromatic), 2953 (CH aliphatic), 2214 (CN), 1696 (C = O ester), and 1668 (C = O amide); 1H NMR; (DMSO-d_{6}); δ = 1.09–1.62 (m, 6H, 3CH_{2}), 1.78–2.11 (m, 4H, 2CH_{2}), 3.62–3.88 (m, 1H, cyclohexyl CH), 3.91 (s, 3H, COCH_{3}), 7.01 (d, 1H, NH, J = 7 Hz), 7.20 (t, 1H, Ar H, J = 7 Hz), 7.70 (t, 1H, Ar H, J = 7 Hz), 7.79 (d, 1H, Ar H, J = 8 Hz), 8.13 (d, 1H, Ar H, J = 8 Hz), and 12.28 (s, 1H, NH) ppm; 13C NMR; (DMSO-d_{6}); δ = 25.58, 25.73, 32.76, 49.01 (cylohexyl carbons), 53.33 (ester CH_{2}), 111.24, 113.23, 113.54, 123.61, 131.22, 134.48 (C_{6}H_{4}COCH_{3}-α), 116.66 (CN), 143.62 (C = N–NH), and 159.17, 168.15 (2C = O) ppm; MS: 327[M^{+}–1]. Analysis calculated for C_{17}H_{22}N_{4}O_{3} (328.37): C, 62.18; H, 6.14; and N, 17.06. Found: C, 62.26; H, 6.32; and N, 17.00.

N'-Butyl-2-[((4-chlorophenyl)-hydrazono]-2-cyano-acetamide (4d). Brown crystals from ethanol; yield 90%, mp 185°C; IR ν_{max} cm^{-1}: 3380 (2NH), 3086 (CH aromatic), 2927 (CH aliphatic), 2211 (CN), and 1646 (C = O); 1H NMR; (DMSO-d_{6}); δ = 0.86 (t, 3H, CH_{3}, J = 7 Hz), 1.28 (m, 2H, CH_{2}, J = 7 Hz), 1.45 (m, 2H, CH_{2}, J = 7 Hz), 3.19 (q, 2H, CH_{2}, J = 7 Hz), 7.35 (d, 2H, Ar H, J = 7 Hz), 7.63 (d, 2H, Ar H, J = 8 Hz), 8.26 (t, 1H, NH, J = 5 Hz), and 13.90 (s, 1H, NH) ppm; MS: 277 [M^{+}–1]. Analysis calculated for C_{15}H_{13}ClN_{4}O (278.74): C, 56.02; H, 5.42; and N, 20.10. Found: C, 56.15; H, 5.58; and N, 20.22.

2-[4-Chlorophenyl]-hydrazono]-2-cyano-N-hexyl-acetamide (4e). Orange crystals from ethanol; yield 85%, mp 176°C; IR ν_{max} cm^{-1}: 3391 (NH), 3089 (CH aromatic), 2939 (CH aliphatic), 2212 (CN), and 1654 (C = O); 1H NMR; (CDCl_{3}); δ = 0.60 (d, 3H, CH_{3}, J = 6 Hz), 1.30 (m, 6H, 3CH_{2}), 2.29 (m, 2H, CH_{2}, J = 7 Hz), 3.05 (q, 2H, CH_{2}, J = 7 Hz), 6.90 (t, 1H, NH, J = 5 Hz), 6.98 (dd, 2H, Ar H, J = 8 Hz), 7.18 (d, 2H, Ar H, J = 8 Hz), and 11.10 (s, 1H, NH) ppm; 13C NMR; (CDCl_{3}); δ = 13.93, 22.36, 26.42, 29.53, 31.30 (hexyl carbons), 108.74, 128.83, 129.02, 140.75 (C_{6}H_{4}=Cl–p), 117.06 (CN), 157.30 (C = N–NH), and 160.56 (C = O) ppm; MS: 306 [M^{+}]. Analysis calculated for C_{15}H_{15}ClN_{4}O (306.80): C, 58.73; H, 6.24; and N, 18.26. Found: C, 58.51; H, 6.15; and N, 18.40.

N'-Benzy1-2-[4-chlorophenyl]-hydrazono]-2-cyano-acetamide (4f). Yellow crystals from ethanol; yield 85%, mp 129°C; IR ν_{max} cm^{-1}: 3336 (NH), 3032 (CH aromatic), 2928 (CH aliphatic), 2218 (CN), and 1643 (C = O); 1H NMR; (DMSO-d_{6}); δ = 4.29 (d, 2H, CH_{2}ph, J = 5 Hz), 7.23–7.36 (m, 5H, Ph–H), 7.41 (d, 2H, Ar–H, J = 8 Hz), 7.70 (d, 2H, Ar–H, J = 8 Hz), 9.12 (t, 1H, NH, J = 5 Hz), and 13.83 (s, 1H,
Preparation of 5a-h

Method I (A). To a solution of hydroxylamine hydrochloride (0.1 mol) and hydrazono-2-cyanoacetamide derivatives 4a-i (0.1 mol) in ethanol (50 mL), anhydrous sodium acetate (0.1 mol) was added and the reaction mixture was refluxed for 1 h. After concentration and cooling to room temperature, the solid product so-formed was filtered and re-crystallized from ethanol.

Method II (μι). A mixture of hydroxylamine hydrochloride (0.1 mol), hydrazono-2-cyanoacetamide derivatives 4a-i (0.1 mol), anhydrous sodium acetate, and drops of ethanol was irradiated under Mw irradiation at 460 W for 1–5 min, until no starting materials were present (monitored by TLC) in 1-min intervals. The reaction mixture was left to cool to room temperature. The solid product so-formed was filtered and re-crystallized from ethanol.

Method III (Us). To a solution of hydroxylamine hydrochloride (0.1 mol) and hydrazono-2-cyanoacetamide derivatives 4a-i (0.1 mol) in ethanol (50 mL), anhydrous sodium acetate (0.1 mol) was added and the reaction mixture was irradiated under Us irradiation at 40°C for 30 min, until no starting materials were present (monitored by TLC). The solid product so-formed was filtered and re-crystallized from ethanol.

2-{N-[Hexylcarbamoyl-(N-hydroxycarbamimidoyl)-methylene]-hydrazino}-benzoic acid methyl ester (5a). Yellow crystals from ethanol; mp 130°C; IR \nu_{max} cm^{-1}: 3587 (br OH), 3456, 3420 (NH\_2), 3379 (br \text{N-H}), 3097 (CH aromatic), 2955 (CH aliphatic), 1701 (C=O ester), and 1651 (C=O amide); \text{^1}H NMR; (CDCl\textsubscript{3}); \delta = 0.87 (t, 3H, CH\textsubscript{3}, J = 6 Hz), 1.35 (m, 6H, 3CH\textsubscript{2}), 1.59 (m, 2H, CH\textsubscript{2}, J = 7 Hz), 3.34 (q, 2H, CH\textsubscript{2}, J = 7 Hz), 3.87 (s, 3H, ester CH\textsubscript{3}), 6.52 (s, 2H, NH\textsubscript{2}), 6.98 (t, 1H, NH, J = 5 Hz), 7.16 (t, 1H, Ar H, J = 7 Hz), 7.50 (t, 1H, Ar H, J = 7 Hz), 7.70 (d, 1H, Ar H, J = 8 Hz), 7.96 (d, 1H, Ar H, J = 8 Hz), 13.88 (s, 1H, NH), and 14.21 (s, 1H, OH) ppm; \text{^{13}}C NMR; (CDCl\textsubscript{3}); \delta = 14.10, 22.68, 26.76, 29.68, 31.56, 39.48 (hexyl carbons), 52.33 (ester CH\textsubscript{3}), 113.98, 114.65, 121.31, 122.23, 131.34, 134.29 (CH\textsubscript{2}COOCH\textsubscript{3}), 145.30 (C = N–NH), 151.35 (C = N–OH), 165.70 (HN–C = O), and 167.29 (COOCH\textsubscript{3}) ppm; MS: 363 [M\textsuperscript{+}]. Analysis calculated for C\textsubscript{17}H\textsubscript{25}N\textsubscript{5}O\textsubscript{4} (536.42): C, 56.19; H, 6.93; and N, 19.27. Found: C, 56.31; H, 6.45; and N, 19.55.

2-{N-[Cyclohexylcarbamoyl-(N-hydroxycarbamimidoyl)-methylene]-hydrazino}-benzoic acid methyl ester (5b). Brown crystals from ethanol; mp 134°C; IR
\( \nu_{\text{max}} \, \text{cm}^{-1} \): 3520 (br OH), 3423, 3401 (NH\(_2\)), 3279 (NH), 3088 (CH aromatic), 2933 (CH aliphatic), and 1650 (2C = O); MS: 361 [M\(^+\)]. Analysis calculated for C\(_7\)H\(_{11}\)N\(_3\)O\(_4\) (361.40): C, 56.50; H, 6.41; and N, 20.56. Found: C, 56.36; H, 6.70; and N, 20.56.

\( N\)-Butyl-2-[(4-chlorophenyl)-hydrazono]-2-(N-hydroxycarbamimidoyl)-acetamide (5c). Orange crystals from ethanol; mp 86\(^\circ\)C; IR \( \nu_{\text{max}} \, \text{cm}^{-1} \): 3568 (OH), 3498, 3471 (NH\(_2\)), 3379, 3356 (NH), 3047 (CH aromatic), 2958 (CH aliphatic), and 1643 (C = O); \(^1\)H NMR; (DMSO-\(d_6\)); \( \delta \) = 0.89 (t, 3H, CH\(_3\), \( J = 7 \) Hz), 1.30 (m, 2H, CH\(_2\), \( J = 7 \) Hz), 1.46 (m, 2H, CH\(_2\), \( J = 7 \) Hz), 3.21 (q, 2H, CH\(_2\), \( J = 7 \) Hz), 6.72 (s, 2H, NH\(_2\)). 7.29 (d, 2H, Ar H, \( J = 8 \) Hz), 7.44 (d, 2H, Ar H, \( J = 8 \) Hz), 8.32 (t, 1H, NH, \( J = 8 \) Hz), 10.11 (s, 1H, NH), and 13.48 (s, 1H, OH) ppm; MS: 358 [M\(^+\)]. Analysis calculated for C\(_{13}\)H\(_{18}\)N\(_6\)O\(_4\) (322.33): C, 48.44; H, 6.41; and N, 23.81. Found: C, 48.42; H, 6.43; and N, 23.71.

\( N\)-Hexyl-2-[(4-chlorophenyl)-hydrazono]-2-(N-hydroxycarbamimidoyl)-acetamide (5f). Orange crystals from ethanol; mp 282\(^\circ\)C; IR \( \nu_{\text{max}} \, \text{cm}^{-1} \): 3501 (br OH), 3454, 3398 (NH\(_2\)), 3242 (NH), 3103 (CH aromatic), 2925 (CH aliphatic), and 1644 (C = O); \(^1\)H NMR; (DMSO-\(d_6\)); \( \delta \) = 1.11–1.65 (m, 6H, CH\(_3\)), 1.78–2.12 (m, 4H, 2CH\(_2\)), 3.61–3.89 (m, 1H, cyclohexyl CH), 6.62 (s, 2H, NH\(_2\)), 7.59 (d, 2H, Ar H, \( J = 8 \) Hz), 8.05 (d, 2H, Ar H, \( J = 8 \) Hz), 8.16 (d, 2H, Ar H, \( J = 8 \) Hz), 8.22 (t, 1H, NH, \( J = 5 \) Hz), 10.12 (s, 1H, NH), and 13.52 (s, 1H, OH) ppm; MS: 338 [M\(^+\)]. Analysis calculated for C\(_{15}\)H\(_{20}\)N\(_6\)O\(_4\) (348.36): C, 51.56; H, 6.29; and N, 23.81. Found: C, 51.61; H, 6.50; and N, 24.38.

**Preparation of triazole compounds 7a-e**

**Method I (\( \Delta \)).** To a solution of compounds 5c and 5e-h (0.1 mol) in DMF (10 mL), triethylamine (0.1 mol) was added. The reaction mixture was heated under reflux for 1 h. Then, it was left to cool to room temperature. The solid product so-formed was filtered and re-crystallized from ethanol.

**Method II (\( \mu \)).** A mixture of compounds 5e and 5e-h (0.1 mol) and triethylamine (0.1 mol) was placed in a tightly closed tube and subjected to a Mw irradiation for 1–5 min until completion of the reaction (monitored by TLC). The reaction mixture was left to cool to room temperature. The solid product so-formed was filtered and re-crystallized from ethanol.

**Method III (\( \lambda \)).** Triethylamine (0.1 mol) was added to a solution of compounds 5e and 5e-h (0.1 mol) in
DMF (10 mL). The reaction mixture was irradiated under Uv irradiation at 40°C for 1 h. Then, it was left to cool to room temperature. The solid product so-formed was filtered and re-crystallized from ethanol.

5-Amino-2-(4-chlorophenyl)-2H-[1,2,3]triazole-4-carboxylic acid butyl amide (7a). Yellow crystals from ethanol; mp 120°C; IR νmax cm⁻¹: 3474, 3431 (NH₂), 3335 (NH), 3080 (CH aromatic), 2930 (CH aliphatic), and 1648 (C = O); ¹H NMR; (CDCl₃); δ = 0.93 (t, 3H, CH₃, J = 7 Hz), 1.39 (m, 2H, CH₂, J = 7 Hz), 1.57 (m, 2H, CH₂, J = 7 Hz), 3.34 (q, 2H, CH₂, J = 7 Hz), 6.69 (s, 2H, NH₂), 7.08 (d, 2H, Ar H, J = 8 Hz), 7.26 (d, 2H, Ar H, J = 8 Hz), and 9.28 (t, 1H, NH, J = 5 Hz) ppm; ¹³C NMR; (CDCl₃); δ = 13.87, 20.26, 31.34, 38.81 (butyl carbons), 115.44, 119.34, 128.06, 129.48 (C₈H₄-Cl-p), 141.46, 153.50 (triazole carbons), and 165.7 (C = O) ppm; MS: 293 [M⁺]. Analysis calculated for C₁₅H₁₆N₆O₃ (304.31): C, 51.31; H, 5.30; and N, 23.80.

5-Amino-2-(4-chlorophenyl)-2H-[1,2,3]triazole-4-carboxylic acid benzyl amide (7b). Brown crystals from ethanol; mp 137°C; IR νmax cm⁻¹: 3461, 3430 (NH₂), 3221 (NH), 3021 (CH aromatic), 2920 (CH aliphatic), and 1642 (C = O); ¹H NMR; (CDCl₃); δ = 5.21 (d, 2H, CH₂ph, J = 5 Hz), 6.67 (s, 2H, NH₂), 7.31–7.83 (m, 9H, Ar–H), and 7.97 (t, 1H, NH, J = 5 Hz) ppm; MS: 327 [M⁺]. Analysis calculated for C₁₆H₁₅ClN₆O (327.78): C, 58.63; H, 4.31; and N, 21.37. Found: C, 58.60; H, 4.47; and N, 21.41.

5-Amino-2-(4-nitrophenyl)-2H-[1,2,3]triazole-4-carboxylic acid butyl amide (7c). Brown crystals from ethanol; mp 103°C; IR νmax cm⁻¹: 3484, 3452 (NH₂), 3325 (NH), 3099 (CH aromatic), 2990 (CH aliphatic), and 1658 (C = O); ¹H NMR; (CDCl₃); δ = 5.21 (d, 2H, CH₂ph, J = 5 Hz), 1.35 (m, 2H, CH₂, J = 7 Hz), 1.56 (m, 2H, CH₂, J = 7 Hz), 3.41 (q, 2H, CH₂, J = 7 Hz), 6.68 (s, 2H, NH₂), 7.19 (d, 2H, Ar H, J = 8 Hz), 7.51 (d, 2H, Ar H, J = 8 Hz), and 9.31 (t, 1H, NH, J = 5 Hz) ppm; MS: 304 [M⁺]. Analysis calculated for C₁₅H₁₅NO₃ (304.31): C, 51.31; H, 5.30; and N, 27.62. Found: C, 51.24; H, 5.42; and N, 27.51.

5-Amino-2-(4-nitrophenyl)-2H-[1,2,3]triazole-4-carboxylic acid hexyl amide (7d). Brown crystals from ethanol; mp 176°C; IR νmax cm⁻¹: 3492, 3386 (NH₂), 3344 (NH), 3053 (CH aromatic), 2920 (CH aliphatic), and 1653 (C = O); ¹H NMR; (DMSO-d₆); δ = 0.84 (t, 3H, CH₃, J = 6 Hz), 1.27 (m, 6H, 3CH₂), 1.48 (m, 2H, CH₂, J = 7 Hz), 3.19 (t, 2H, CH₂, J = 7 Hz), 6.18 (s, 2H, NH₂), 7.58 (d, 2H, Ar H, J = 8 Hz), 8.12 (d, 2H, Ar H, J = 8 Hz), and 9.40 (t, 1H, NH, J = 5 Hz) ppm; MS: 332 [M⁺]. Analysis calculated for C₁₅H₁₅N₆O₃ (332.37): C, 54.21; H, 6.07; and N, 25.29. Found: C, 54.29; H, 6.16; and N, 25.32.

General method to reaction of triazole compounds 7a–e with dimethylformamide dimethylethylacetic (DMF DMA)

Method I (Δ). To a solution of compounds 7a–e (0.1 mol) in dry xylene (20 mL), DMF DMA (0.1 mol) was added. The reaction mixture was refluxed for 30 min. Then it was left to cool to room temperature, and poured into ice-cold water. The solid product so-formed was filtered and re-crystallized from ethanol.

Method II (μ). A mixture of compounds 7a–e (0.1 mol) and of DMF DMA (0.1 mol) was placed in a tightly closed tube, and subjected to a Mw irradiation for 2–5 min until completion of the reaction (monitored by TLC). The reaction mixture was left to cool to room temperature, and then poured into ice-cold water. The solid product so-formed was filtered and re-crystallized from ethanol.

2-(4-Chlorophenyl)-6-hexyl-2,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (10a). Yellow crystals from ethanol; mp 78°C; IR νmax cm⁻¹: 3089 (CH aromatic), 2925 (CH aliphatic), and 1645 (C = O); ¹H NMR; (CDCl₃); δ = 0.91 (t, 3H, CH₃, J = 6 Hz), 1.29 (m, 6H, 3CH₂), 1.47 (m, 2H, CH₂, J = 7 Hz), 3.29 (t, 2H, CH₂, J = 7 Hz), 7.05 (s, 1H, pyrimidine CH), 7.32 (d, 2H, Ar, J = 8 Hz), and 7.61 (d, 2H, Ar, J = 8 Hz) ppm; MS: 331 [M⁺]. Analysis calculated for C₁₅H₁₅NO₃ (331.81): C, 57.92; H, 5.47; and N, 21.11. Found: C, 57.75; H, 5.25; and N, 21.47.

6-Butyl-2-(4-nitrophenyl)-2,6-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (10b). Brown crystals from ethanol; mp 190°C; IR νmax cm⁻¹: 3092 (CH aromatic), 2939 (CH aliphatic), and 1670 (C = O);
1H NMR; (CDCl3); δ = 0.89 (t, 3H, CH3, J = 6 Hz), 1.40 (m, 2H, CH2, J = 7 Hz), 1.66 (m, 2H, CH2, J = 7 Hz), 3.49 (q, 2H, CH2, J = 7 Hz), 7.15 (s, 1H, pyrimidine CH), 7.31 (d, 2H, Ar H, J = 8 Hz), and 7.65 (d, 2H, Ar H, J = 8 Hz) ppm; MS: 314 [M⁺]. Analysis calculated for C14H14N6O3 (314.31): C, 62.11; H, 5.76; and N, 19.06. Found: C, 62.26; H, 4.64; and N, 26.59.

Preparation of pyrazole compounds 13a-e

Method I (Δ). To a solution of compounds 4a-i (0.1 mol) in triethylamine (20 mL) and chloroacetonitrile (0.1 mol) were refluxed for 30 min. The reaction mixture was cooled to room temperature, and then poured into ice-cold water. The solid product so-formed was filtered and re-crystallized from ethanol.

Method II (μo). To a mixture of compounds 4a-i (0.1 mol) and chloroacetonitrile (0.1 mol), a few drops of triethylamine were added, then the mixture was placed in a tightly closed tube and subjected to a MW irradiation for 2 min until completion of the reaction (monitored by TLC). The reaction mixture was cooled to room temperature, and then poured into ice-cold water. The solid product so-formed was filtered and re-crystallized from ethanol.

Method III (Us). Chloroacetonitrile (0.1 mol) was added to a solution of compounds 4a-i (0.1 mol) in triethylamine (20 mL), under Us irradiation at 40°C for 30 min. The reaction mixture was left to cool to room temperature, and then poured into ice-cold water. The solid product so-formed was filtered and re-crystallized from ethanol.

4-Amino-1-(4-chlorophenyl)-5-cyano-1H-pyrazole-3-cyclohexylic acid hexyl amide (13c). Brown crystals from ethanol; mp 125°C; IR ν_max cm⁻¹: 3450, 3428, 3388 (NH, NH₂), 3109 (CH aromatic), 2926 (CH aliphatic), 2211 (CN), and 1645 (C=O); 1H NMR; (CDCl₃); δ = 0.88 (t, 3H, CH2, J = 6 Hz), 1.30 (m, 6H, 3CH2), 1.57 (m, 2H, CH2, J = 7 Hz), 6.49 (s, 2H, NH2), 7.15 (d, 2H, Ar H, J = 8 Hz), 7.36 (d, 2H, Ar H, J = 8 Hz), and 8.96 (t, 1H, NH, J = 5 Hz) ppm; MS: 345 [M⁺]. Analysis calculated for C₁₉H₁₆ClN₅O (345.83): C, 59.04; H, 5.83; and N, 20.25. Found: C, 59.17; H, 5.42; and N, 20.54.

4-Amino-1-(4-chlorophenyl)-5-cyano-1H-pyrazole-3-cyclohexylic acid benzyl amide (13d). Brown crystals from ethanol; mp 130°C; IR ν_max cm⁻¹: 3371, 3326, 3299 (NH, NH₂), 3064 (CH aromatic), 2923 (CH aliphatic), 2225 (CN), and 1644 (C=O); 1H NMR; (CDCl₃); δ = 4.28 (d, 2H, phCH₂, J = 5 Hz), 6.21 (s, 2H, NH2), 7.25--8.10 (m, 9H, Ar--H), and 8.89 (t, 1H, NH, J = 5 Hz) ppm; MS: 351 [M⁺]. Analysis calculated for C₁₉H₁₄ClN₅O (351.80): C, 61.46; H, 4.01; and N, 19.91. Found: C, 61.54; H, 4.20; and N, 19.83.

4-Amino-1-(4-chlorophenyl)-5-cyano-1H-pyrazole-3-cyclohexylic acid butyl amide (13e). Brown crystals from ethanol; mp 153°C; IR ν_max cm⁻¹: 3401, 3358, 3226 (NH, NH₂), 3090 (CH aromatic), 2927 (CH aliphatic), 2218 (CN), and 1660 (C=O); 1H NMR; (CDCl₃); δ = 0.88 (t, 3H, CH3, J = 6 Hz), 1.32 (m, 6H, 3CH₂), 1.58 (m, 2H, CH₂, J = 7 Hz), 3.40 (t, 2H, CH₂, J = 7 Hz), 6.59 (s, 2H, NH₂), 7.40 (d, 2H, Ar H, J = 8 Hz), 7.95 (d, 2H, Ar H, J = 8 Hz), and 9.62 (t, 1H, NH, J = 5 Hz) ppm; MS: 356 [M⁺]. Analysis calculated for C₁₉H₂₀N₆O₃ (356.39): C, 57.29; H, 5.66; and N, 23.58. Found: C, 57.20; H, 5.72; and N, 23.68.
Table 2. Crystal data of compound 4c.

| Chemical formula | C_{17}H_{20}N_{4}O_{3} |
|------------------|------------------------|
| M                | 328.372                |
| System           | Monoclinic             |
| space group      | P2_1/c                 |
| a                | 9.9877 (6) Å           |
| b                | 18.0058 (8) Å          |
| c                | 9.8843 (4) Å           |
| α                | 90.00°                 |
| β                | 96.078 (2)°            |
| V                | 1767.6 (2) Å^3        |
| Z                | 4                     |
| Dc               | 1.234 mg m^-3         |
| μ(Mo–Kα)         | 2.910–24.713^a        |
| T                | 298 K                  |
| Measured reflections | 4990               |
| Independent reflections | 3497             |
| Observed reflections | 1335              |
| R_{int}          | 0.031                  |
| R(all)           | 0.140                  |
| wR(ref)          | 0.184                  |
| wR(all)          | 0.238                  |
| S(ref)           | 1.429                  |
| S(all)           | 1.364                  |
| D/s_{max}        | 0.027                  |
| D_r_{max}        | 0.380 Å                |
| D_r_{min}        | −0.41e Å              |

X-ray crystallography

A single crystal of compound 4c was obtained by slow evaporation from a mixture of ethanol:DMF (2:1). The crystal structure was solved and refined using maxus (nonius, Delft and MacScience, Japan) (27) Mo–Kα radiation (λ = 0.71073 Å) and a graphite monochromator were used for data collection. The chemical formula and ring labeling system is shown in Figure 1. Crystallographic data (Table 2, excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 686225. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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(26) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).
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