

Article

Synthesis of 6-Amino-5-cyano-1,4-disubstituted-2(1*H*)-Pyrimidinones via Copper-(I)-catalyzed Alkyne-azide ‘Click Chemistry’ and Their Reactivity

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Received: 15 October 2010; in revised form: 25 November 2010 / Accepted: 30 November 2010 / Published: 3 December 2010

Abstract: In this paper we present the room temperature synthesis of a novel serie of 1,4-disubstituted-1,2,3-triazoles **4a-l** by employing the (3 + 2) cycloaddition reaction of pyrimidinones containing alkyne functions with different model azides in the presence of copper sulphate and sodium ascorbate. To obtain the final triazoles, we also synthesized the major precursors 6-amino-5-cyano-1,4-disubstituted-2(1*H*)-pyrimidinones **3a-r** from ethyl 2,2-dicyanovinylcarbamate derivatives **2a-c** and various primary aromatic amines containing an alkyne group. The triazoles were prepared in good to very good yields.

Keywords: 2(1*H*)-pyrimidinones; 1,2,3-triazoles; (3 + 2) cycloaddition; alkynes; azides

Introduction

The copper(I)-catalyzed Huisgen–Sharpless–Meldal 1,3-dipolar cycloaddition between alkynes and azides (‘click’ chemistry) resulting in the formation of 1,4-disubstituted-1,2,3-triazoles has gained significant importance because of its wide range of applications in various fields of drug discovery [1], bioconjugation [2] and material or surface science [3,4]. Amongst the various classes of nitrogen heterocycles, 1,2,3-triazoles and their derivatives deserve special recognition due to their wide usage in industrial applications as dyes, photographic materials, corrosion inhibitors and as herbicidal, fungicidal and antibacterial agrochemicals [5,6]. Several members of the 1,2,3-triazole family exhibit a broad spectrum of anti-infectious properties such as antimicrobial [7], anti-HIV [8], anti-allergic [9] and antimalarial activities [10]. On the other hand, 2(1*H*)-pyrimidinones also show significant biological activities [11]. For instance, 2(1*H*)-pyrimidinones derivatives have been screened for antihypertension [12], insulin-mimetic [13], anti-inflammatory [14] and anti-proliferative [15] activities or as selective α_{1a} -adrenergic receptor antagonists [16]. Interested by the wide variety of pharmacological properties and potential applications of both 2(1*H*)-pyrimidinones and 1,2,3-triazoles we have designed the synthesis of hybrid molecules consisting of both moieties. Our method is based on the (3 + 2) cycloaddition reaction of 6-amino-5-cyano-1-(*meta*- or *para*-ethynylphenyl)-4-substituted-2(1*H*)-pyrimidinones with different azides in the presence of copper sulphate and sodium ascorbate at room temperatures that affords 1,4-disubstituted-1,2,3-triazoles.

Results and Discussion

Ethyl 2,2-dicyanovinylcarbamate derivatives **2a–c** were prepared in good yields by action of malononitrile with ethyl *N*-(ethoxycarbonyl)imidates **1a–c** following a previously reported method [17] (Scheme 1). The reaction of these compounds **2a–c** with primary aromatic amines in chlorobenzene under reflux yielded the 6-amino-5-cyano-1,4-disubstituted-2(1*H*)-pyrimidinones **3a–r** in yields ranging from 55 to 76% (Table 1). This synthetic method is more general and easier to implement than the methods already described in the literature [18,19].

Scheme 1. Synthesis of 6-amino-5-cyano-1,4-disubstituted-2(1*H*)-pyrimidinones (**3a–r**).

Reagents and conditions: (i) primary aromatic amines, chlorobenzene, 110 °C, (2~4) h.

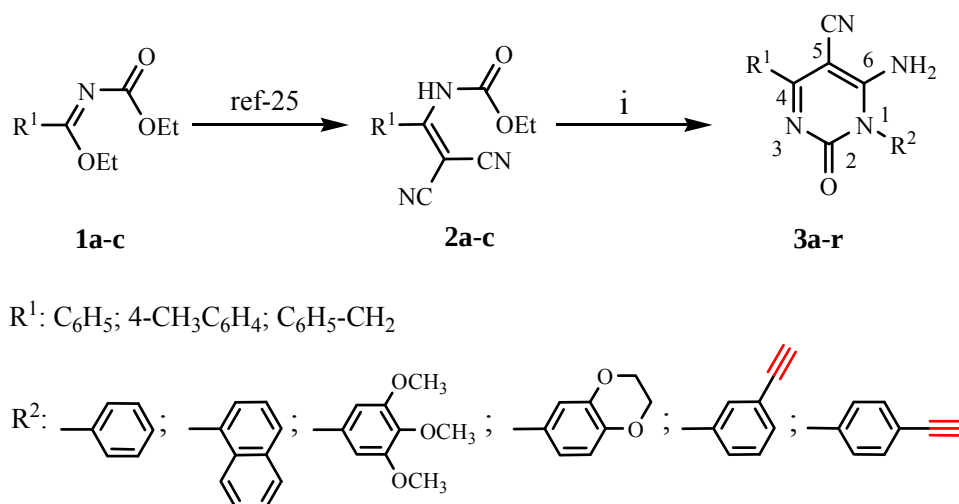


Table 1. Synthesis of 6-amino-5-cyano-1,4-disubstituted-2(1*H*)-pyrimidinones **3a-r**.

Entry	Compound	R ¹	R ²	Yields ^a
1	3a ²⁶	Ph	Phenyl	75%
2	3b	Ph	Naphthalen-1-yl	68%
3	3c	Ph	3,4,5-Trimethoxyphenyl	71%
4	3d	Ph	2,3-Dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl	74%
5	3e	Ph	3-Ethynylphenyl	62%
6	3f	Ph	4-Ethynylphenyl	60%
7	3g ²⁶	4-CH ₃ Ph	Phenyl	73%
8	3h	4-CH ₃ Ph	Naphthalen-1-yl	67%
9	3i	4-CH ₃ Ph	3,4,5-Trimethoxyphenyl	75%
10	3j	4-CH ₃ Ph	2,3-Dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl	72%
11	3k	4-CH ₃ Ph	3-Ethynylphenyl	70%
12	3l	4-CH ₃ Ph	4-Ethynylphenyl	61%
13	3m	Ph-CH ₂	Phenyl	76%
14	3n	Ph-CH ₂	Naphthalen-1-yl	59%
15	3o	Ph-CH ₂	3,4,5-Trimethoxyphenyl	65%
16	3p	Ph-CH ₂	2,3-Dihydrobenzo[<i>b</i>][1,4]dioxin-6-yl	55%
17	3q	Ph-CH ₂	3-Ethynylphenyl	62%
18	3r	Ph-CH ₂	4-Ethynylphenyl	58%

^a Isolated yield.

The (3 + 2) cycloaddition of 6-amino-5-cyano-1-(*meta*- or *para*-ethynylphenyl)-4-substituted-2(1*H*)-pyrimidinones **3k**, **3l**, **3q** and **3r** with different azides **A₁**, **A₂** and **A₃** (Figure 1) in the presence of Na-ascorbate, THF/*t*-BuOH/H₂O and CuSO₄·5H₂O, at room temperature resulted in the corresponding 1,4-disubstituted-1,2,3-triazole compounds **4a-l** (Scheme 2) in good yields (Table 2). The structures of compounds **3a-r** were in accordance with their spectroscopic data. The IR spectra of the compounds in general exhibited an absorption band at 2,210 cm^{−1} indicating the presence of one cyano group. The absorption band at around 3,265–3,275 cm^{−1} for the compounds **3e**, **3f**, **3k**, **3l**, **3q** and **3r** indicated that the terminal alkyne C≡C-H was present in these compounds.

Scheme 2. Synthesis of 1,4-disubstituted-1,2,3-triazoles **4a-l**. Reagents and conditions: (a) Na-ascorbate (0.45 equiv), CuSO₄·5H₂O (0.1 equiv), THF/H₂O/*t*-BuOH (3:1:1, v/v/v), rt, 2d.

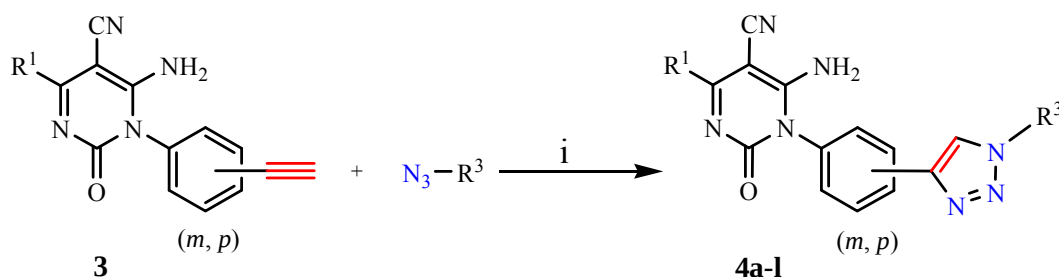
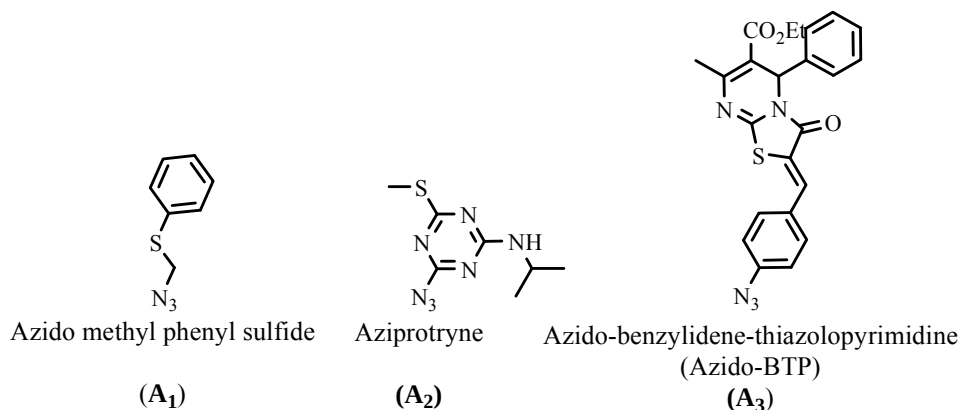
R¹: 4-CH₃C₆H₄; C₆H₅-CH₂R³: See **A₁**, **A₂** and **A₃** in Figure 1.

Figure 1. Structures of the three different azides used in this work.**Table 2.** Synthesis of 1,4-disubstituted-1,2,3-triazoles **4a-l**.

Entry	Compound	Alkynes	Azides	Yields ^a
1	4a	3k	A ₁	82%
2	4b	3l	A ₁	72%
3	4c	3q	A ₁	80%
4	4d	3r	A ₁	75%
5	4e	3k	A ₂	73%
6	4f	3l	A ₂	94%
7	4g	3q	A ₂	76%
8	4h	3r	A ₂	71%
9	4i	3k	A ₃	84%
10	4j	3l	A ₃	72%
11	4k	3q	A ₃	81%
12	4l	3r	A ₃	88%

^a Isolated yield.

The mass spectra showed the respective $[\text{M} + \text{H}]^+$ peaks. In the $^1\text{H-NMR}$ spectra the most significant information was the disappearance of triplet and quadruplet of ethoxy groups present in the starting reagent **2a-c** and the appearance of signals for the protons of the group R^2 introduced by the primary aromatic amines.

Structures of compounds **4a-l** were established on the basis of their spectroscopic data. The IR absorption band corresponding to a terminal $\text{C}\equiv\text{C-H}$ group was not observed around $3,271\text{ cm}^{-1}$. The mass spectra showed the respective $[\text{M} + \text{H}]^+$ peaks. According to $^1\text{H-NMR}$ spectra of the ‘click’ products the terminal triple bonded proton signal ($\delta\text{H} = 4.3\text{ ppm}$) of the alkynes **3** disappeared and the newly formed triazole signal was observed at 8.5–9.5 ppm. The triazole ring formation was also identified from the $^{13}\text{C-NMR}$ spectra with the new signals of the ethylenic C atoms of the 1,2,3-triazole moiety at $\delta = 120\text{--}122\text{ ppm}$ ($\text{CH}_{\text{ar-triazole}}$) and $\delta = 146\text{--}148\text{ ppm}$ ($\text{C}_{\text{q-triazole}}$).

X-ray crystal analysis of compounds **3b** and **3g**

To further confirm the structure of compounds **3**, an X-ray crystallographic study of compounds **3b** and **3g** was carried out (Figures 2 and 3). Crystals were obtained by slow evaporation from methanol

solution. Crystallographic data were collected at 180K with an Oxford-Diffraction XCALIBUR CCD Diffractometer equipped with a Cryojet cooler device from Oxford Instruments. Structures were solved by direct methods using SIR92 [20] and refined by full-matrix least-squares procedures on F using the programs of the PC version of CRYSTALS [21]. Atomic scattering factors were taken from the International Tables for X-ray Crystallography [22].

Figure 2. X-ray crystal analysis of compound **3b**.

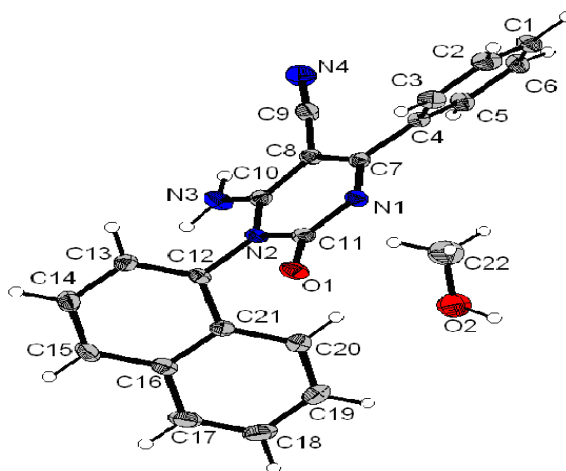
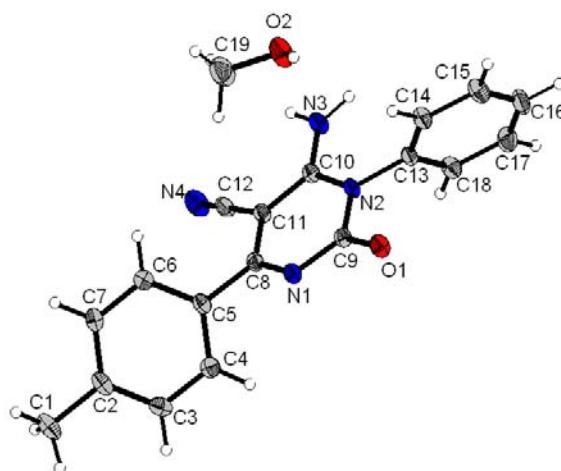


Figure 3. X-ray crystal analysis of compound **3g**.



Data for 3b: $C_{21}H_{14}N_4O$, CH_4O , $M = 370.41$, colorless block crystal, $0.15 \times 0.20 \times 0.25 \text{ mm}^3$, monoclinic, space group $P 2_1/c$, $a = 11.1402(4)$, $b = 19.9585(6)$, $c = 8.4770(3) \text{ \AA}$, $\beta = 105.839(4)^\circ$, $V = 1813.23(11) \text{ \AA}^3$, $Z = 4$, $d = 1.36$, $\mu(\text{MoK}\alpha) = 0.090$, 253 parameters, 17,459 reflexions measured, 4,850 unique ($R \text{ int} = 0.030$), 3,133 reflexions used in the calculations ($I > 3\sigma[I]$), $R = 0.0345$, $wR = 0.0403$, residual electronic density = $-0.17/0.32 \text{ (e.\AA}^{-3})$.

Data for 3g: $C_{18}H_{14}N_4O$, CH_4O , $M = 334.38$, colorless block crystal, $0.20 \times 0.20 \times 0.20 \text{ mm}^3$, monoclinic, space group $P 2_1/c$, $a = 10.5511(3)$, $b = 14.2950(5)$, $c = 10.9120(4) \text{ \AA}$, $\beta = 93.184(3)^\circ$, $V = 1643.29(10) \text{ \AA}^3$, $Z = 4$, $d = 1.35$, $\mu(\text{MoK}\alpha) = 0.091$, 226 parameters, 14,902 reflexions measured, 4,408 unique ($R \text{ int} = 0.030$), 2,930 reflexions used in the calculations ($I > 3\sigma[I]$), $R = 0.0428$, $wR = 0.0462$, residual electronic density = $-0.22/0.39 \text{ (e.\AA}^{-3})$.

CCDC contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conclusions

In summary, various 6-amino-5-cyano-1-(*meta*- or *para*-ethynylphenyl)-4-substituted-2(1*H*)-pyrimidinones were synthesized and utilized as starting materials in the ‘click’ reaction to attach azido residues. Consequently, we have employed these, in house synthesized precursors, to prepare a new class of hybrid molecules 1,4-disubstituted-1,2,3-triazoles employing already known chemistry of (3 + 2) cycloaddition of azides and acetylenes in good to very good yields. All products that we have obtained were hitherto unknown. A number of them are presently under pharmacological screening.

Experimental

Commercially available reagent grade chemicals were used as received without additional purification. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with detection by UV light at 254 nm. Column chromatography was performed on silica gel (60–200 mesh E. Merck). IR spectra were recorded on a Perkin-Elmer PARAGON 1000 FT-IR spectrometer. ¹H- and ¹³C-NMR spectra were recorded on an AC Bruker spectrometer at 300 MHz (¹H) and 75 MHz (¹³C) using (CD₃)₂SO as solvent with (CD₃)₂SO (δ_H 2.5) or (CD₃)₂SO (δ_C 39.5). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0 ppm) as internal reference and the following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; *J* in hertz. The mass spectra were recorded on an ion trap mass spectrometer (Finnigan LCQ Deca XP Max) using electrospray as an ionization source. Melting points were determined on an Electrothermal 9300 capillary melting point apparatus and are uncorrected. UV-visible spectra were recorded on a Specord 205 Analytikjena spectrophotometer. The purity of all compounds was determined by LC-PDA-MS methods and was found to be in the range between 96–99%.

General experimental procedure for preparation of 6-amino-5-cyano-1,4-disubstituted-2(1H)-pyrimidinones 3a-r

To a magnetically stirred solution of the ethyl 2,2-dicyanovinylcarbamate derivatives **2a-c** (1 equiv) in chlorobenzene (25 mL), a primary aromatic amine (1.2 equiv) added and reaction mixture was stirred for 2–4 h at 110 °C. Reaction progress was monitored by TLC using the indicated eluents. The resulting mixture was allowed to cool at room temperature. The formed precipitate was isolated by filtration and washed with ethanol or with diethyl ether for **3e**, **3f**, **3k**, **3l**, **3q** and **3r** to give pure products.

6-Amino-5-cyano-1,4-diphenyl-2(1H)-pyrimidinone (3a). White crystals, yield (75%), C₁₇H₁₂N₄O, M = 288 g·mol^{−1}, mp 252–254 °C, R_f = 0.21 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm (ε L·mol^{−1}·cm^{−1}): 248 (32,400), 318 (11,232); IR (KBr) cm^{−1}: 3,450–3,310 (NH₂), 2,212 (CN), 1,665 (C=O), 1,616 (C=N); ¹H-NMR: (DMSO-d₆): δ = 7.34–7.82 (m, 12H, Ar-H + NH₂); ¹³C-NMR

(DMSO- d_6): δ = 72.9 (C-5), 117.1 (CN), 128.8, 128.9, 130, 130.7, 131.5, 135.1, 137.5, 154.1 (C-2), 160.5 (C-4), 172 (C-6); MS-(+)ESI: m/z (%): 599 ($[2M+Na]^+$, 35), 311 ($[M+Na]^+$, 4), 289 ($[M+H]^+$, 100).

6-Amino-5-cyano-1-(naphthalen-1-yl)-4-phenyl-2(1H)-pyrimidinone (3b). Greyish white solid, yield (68%), $C_{21}H_{14}N_4O$, $M = 338 \text{ g}\cdot\text{mol}^{-1}$, mp 198–200 °C, $R_f = 0.54$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 248 (37,518), 318 (14,196); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,211 (CN), 1,672 (C=O), 1,620 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): δ = 7.42–8.15 (m, 14H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ = 73.1 (C-5), 117.2 (CN), 122, 127.1, 127.2, 127.8, 128, 128.8, 129, 129.2, 129.7, 130.7, 131.5, 131.6, 135.1, 137.6, 154.2 (C-2), 160.9 (C-4), 172.6 (C-6); MS-(+)ESI: m/z (%): 699 ($[2M+Na]^+$, 16), 339 ($[M+H]^+$, 100).

6-Amino-5-cyano-1-(3,4,5-trimethoxyphenyl)-4-phenyl-2(1H)-pyrimidinone (3c). Yellowish white solid, yield (71%), $C_{20}H_{18}N_4O_4$, $M = 378 \text{ g}\cdot\text{mol}^{-1}$, mp 255–257 °C, $R_f = 0.21$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 249 (51,030), 320 (14,742); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,209 (CN), 1,687 (C=O), 1,620 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): δ = 3.74 (s, 6H, 2OCH₃), 3.76 (s, 3H, OCH₃), 7.39–7.60 (m, 9H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ = 56.5 (2C, 2OCH₃), 60.4 (OCH₃), 72.6 (C-5), 106.4, 117.1 (CN), 125.9, 128.6, 130.5, 136.9, 138, 138.4, 153.9, 154 (C-2), 160.7 (C-4), 172 (C-6); MS-(+)ESI: m/z (%): 779 ($[2M+Na]^+$, 3), 379 ($[M+H]^+$, 100).

6-Amino-5-cyano-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-phenyl-2(1H)-pyrimidinone (3d). Pale brown solid, yield (74%), $C_{19}H_{14}N_4O_3$, $M = 346 \text{ g}\cdot\text{mol}^{-1}$, mp 283–285 °C, $R_f = 0.49$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 248 (37887), 318 (12456); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,210 (CN), 1,696 (C=O), 1,662 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): δ = 4.30 (s, 4H, 2CH₂), 6.80–7.59 (m, 10H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ = 64.5 (CH₂), 64.6 (CH₂), 72.6 (C-5), 117.2 (CN), 118.5, 121.7, 125.7, 127.6, 129.2, 131.9, 137.7, 138.1, 144.5, 144.6, 154.1 (C-2), 160.7 (C-4), 171.8 (C-6); MS-(+)ESI: m/z (%): 715 ($[2M+Na]^+$, 8), 347 ($[M+H]^+$, 100).

6-Amino-5-cyano-1-(3-ethynylphenyl)-4-phenyl-2(1H)-pyrimidinone (3e). Pale yellow solid, yield (62%), $C_{19}H_{12}N_4O$, $M = 312 \text{ g}\cdot\text{mol}^{-1}$, mp 237–239 °C, $R_f = 0.52$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 254 (36,972), 307 (14,508); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 3,270 ($\equiv\text{C-H}$), 2,209 (CN), 1,665 (C=O), 1,636 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): δ = 4.32 (s, 1H, $\text{C}\equiv\text{CH}$), 7.27–7.86 (m, 11H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ = 73.7 (C-5), 82.4 ($\text{C}\equiv\text{CH}$), 83.2 ($\text{C}\equiv\text{CH}$), 117.2 (CN), 124.1, 128.6, 129.2, 129.9, 131.1, 132.4, 133.4, 134.5, 135.4, 141.5, 154 (C-2), 160.5 (C-4), 171.7 (C-6); MS-(+)ESI: m/z (%): 647 ($[2M+Na]^+$, 21), 313 ($[M+H]^+$, 100).

6-Amino-5-cyano-1-(4-ethynylphenyl)-4-phenyl-2(1H)-pyrimidinone (3f). White solid, yield (60%), $C_{19}H_{12}N_4O$, $M = 312 \text{ g}\cdot\text{mol}^{-1}$, mp 206–208 °C, $R_f = 0.57$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 247 (38,844), 309 (13,572); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 3,268 ($\equiv\text{C-H}$), 2,210 (CN), 1,676 (C=O), 1,635 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): δ = 4.31 (s, 1H, $\text{C}\equiv\text{CH}$), 7.34–7.91 (m, 11H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ = 73.7 (C-5), 82.3 ($\text{C}\equiv\text{CH}$), 83.2

(C≡CH), 117.2 (CN), 125, 128.5, 130.1, 131.2, 132.4, 133.4, 135.4, 141.3, 154 (C-2), 160 (C-4), 172.1 (C-6); MS-(+)ESI: m/z (%): 647 ([2M+Na]⁺, 10), 313 ([M+H]⁺, 100).

6-Amino-5-cyano-4-(4-methylphenyl)-1-phenyl-2(1H)-pyrimidinone (3g). White solid, yield (73%), C₁₈H₁₄N₄O, M = 302 g·mol⁻¹, mp 257–259 °C, R_f = 0.47 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm (ε L·mol⁻¹·cm⁻¹): 250 (26,727), 319 (11,325); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,211 (CN), 1,674 (C=O), 1,619 (C=N); ¹H-NMR: (DMSO-d₆): δ = 2.52 (s, 3H, CH₃), 7.45–7.9 (m, 11H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 21.5 (CH₃), 72.6 (C-5), 118.3 (CN), 128.8, 129, 130.1, 130.8, 131.5, 132.4, 135.1, 137.5, 154.3 (C-2), 160.8 (C-4), 172.5 (C-6); MS-(+)ESI: m/z (%): 627 ([2M+Na]⁺, 31), 325 ([M+Na]⁺, 3), 303 ([M+H]⁺, 100).

6-Amino-5-cyano-4-(4-methylphenyl)-1-(naphthalen-1-yl)-2(1H)-pyrimidinone (3h). Greyish green solid, yield (67%), C₂₂H₁₆N₄O, M = 352 g·mol⁻¹, mp 261–263 °C, R_f = 0.57 (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm (ε L·mol⁻¹·cm⁻¹): 251 (26,928), 318 (12,672); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,209 (CN), 1,686 (C=O), 1,617 (C=N); ¹H-NMR: (DMSO-d₆): δ = 2.43 (s, 3H, CH₃), 7.38–8.15 (m, 13H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 21.5 (CH₃), 72.4 (C-5), 118.3 (CN), 122.5, 127, 127.2, 127.9, 128.1, 128.9, 129.1, 129.3, 129.8, 130.7, 131.4, 132.1, 135.6, 137.7, 154.6 (C-2), 161 (C-4), 172.8 (C-6); MS-(+)ESI: m/z (%): 727 ([2M+Na]⁺, 15), 353 ([M+H]⁺, 100).

6-Amino-5-cyano-4-(4-methylphenyl)-1-(3,4,5-trimethoxyphenyl)-2(1H)-pyrimidinone (3i). Pale yellow solid, yield (75%), C₂₁H₂₀N₄O₄, M = 392 g·mol⁻¹, mp 292–294 °C, R_f = 0.53 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm (ε L·mol⁻¹·cm⁻¹): 250 (52,920); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,212 (CN), 1,671 (C=O), 1,625 (C=N); ¹H-NMR: (DMSO-d₆): δ = 2.41 (s, 3H, CH₃), 3.74 (s, 6H, 2OCH₃), 3.77 (s, 3H, OCH₃), 7.4–7.59 (m, 8H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 21.4 (CH₃), 56.6 (2C, 2OCH₃), 60.4 (OCH₃), 72.6 (C-5), 106.4, 117.1 (CN), 125.8, 128.6, 130.5, 137.5, 138.1, 138.5, 154, 154.5 (C-2), 160.6 (C-4), 171.9 (C-6); MS-(+)ESI: m/z (%): 393 ([M+H]⁺, 100).

6-Amino-5-cyano-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-(4-methylphenyl)-2(1H)-pyrimidinone (3j). Yellow solid, yield (72%), C₂₀H₁₆N₄O₃, M = 360 g·mol⁻¹, mp 284–286 °C, R_f = 0.54 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm (ε L·mol⁻¹·cm⁻¹): 251 (32,940), 280 (19,980), 318 (13,500); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,211 (CN), 1,658 (C=O), 1,634 (C=N); ¹H-NMR: (DMSO-d₆): δ = 2.40 (s, 3H, CH₃), 4.30 (s, 4H, 2CH₂), 6.79–7.60 (m, 9H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 21.4 (CH₃), 64.5 (CH₂), 64.6 (CH₂), 72.6 (C-5), 117.1 (CN), 117.9, 121.5, 125.8, 127.7, 128.5, 132, 137.4, 138, 144.8, 144.8, 154.1 (C-2), 160.7 (C-4), 171.8 (C-6); MS-(+)ESI: m/z (%): 743 ([2M+Na]⁺, 9), 361 ([M+H]⁺, 100).

6-Amino-5-cyano-1-(3-ethynylphenyl)-4-(4-methylphenyl)-2(1H)-pyrimidinone (3k). Pale yellow solid, yield (70%), C₂₀H₁₄N₄O, M = 326 g·mol⁻¹, mp 247–249 °C, R_f = 0.61 (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm (ε L·mol⁻¹·cm⁻¹): 252 (24,339), 307 (16,137); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 3,271 (≡C-H), 2,211 (CN), 1,671 (C=O), 1,640 (C=N); ¹H-NMR: (DMSO-d₆): δ = 2.41 (s, 3H, CH₃), 4.32 (s, 1H, C≡CH), 7.25–7.75 (m, 10H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆):

δ = 21.5 (CH₃), 73.81 (C-5), 82.4 (C $\equiv$ CH), 83.2 (C $\equiv$ CH), 117.2 (CN), 124, 128.8, 129.3, 129.8, 131, 132.5, 133.3, 134.6, 135.6, 141.5, 153.9 (C-2), 160.5 (C-4), 171.8 (C-6); MS-(+)-ESI: m/z (%): 675 ([2M+Na]⁺, 19), 327 ([M+H]⁺, 100).

6-Amino-5-cyano-1-(4-ethynylphenyl)-4-(4-methylphenyl)-2(1H)-pyrimidinone (3l). Brownish yellow solid, yield (61%), C₂₀H₁₄N₄O, M = 326 g·mol⁻¹, mp 192–194 °C, R_f = 0.49 (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 250 (28,851), 308 (15,159); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 3,270 ($\equiv$ C-H), 2,209 (CN), 1,662 (C=O), 1,638 (C=N); ¹H-NMR: (DMSO-d₆): δ = 2.41 (s, 3H, CH₃), 4.30 (s, 1H, C $\equiv$ CH), 7.27–7.94 (m, 10H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 21.5 (CH₃), 72.9 (C-5), 82.3 (C $\equiv$ CH), 83.3 (C $\equiv$ CH), 117.2 (CN), 124.1, 128.9, 129.3, 131.1, 132.5, 134.4, 135.8, 141.3, 153.9 (C-2), 160.1 (C-4), 171.6 (C-6); MS-(+)-ESI: m/z (%): 675 ([2M+Na]⁺, 9), 327 ([M+H]⁺, 100).

6-Amino-4-benzyl-5-cyano-1-phenyl-2(1H)-pyrimidinone (3m). White solid, yield (76%), C₁₈H₁₄N₄O, M = 302 g·mol⁻¹, mp 276–278 °C, R_f = 0.31 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 248 (22,197), 308 (14,043); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,211 (CN), 1,680 (C=O), 1,614 (C=N); ¹H-NMR: (DMSO-d₆): δ = 3.9 (s, 2H, CH₂), 7.3–7.53 (m, 12H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 43.4 (CH₂), 73.7 (C-5), 116.7 (CN), 127.3, 128.9, 129, 129.4, 129.7, 130.7, 135, 137.1, 154.1 (C-2), 159.7 (C-4), 175.4 (C-6); MS-(+)-ESI: m/z (%): 627 ([2M+Na]⁺, 20), 325 ([M+Na]⁺, 3), 303 ([M+H]⁺, 100).

6-Amino-4-benzyl-5-cyano-1-(naphthalen-1-yl)-2(1H)-pyrimidinone (3n). Pale violet solid, yield (59%), C₂₂H₁₆N₄O, M = 352 g·mol⁻¹, mp 252–254 °C, R_f = 0.47 (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 248 (24,288), 296 (17,952); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,212 (CN), 1,678 (C=O), 1,618 (C=N); ¹H-NMR: (DMSO-d₆): δ = 3.97 (s, 2H, CH₂), 7.27–8.27 (m, 14H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 43.6 (CH₂), 73.7 (C-5), 116.6 (CN), 117.9, 121.7, 126.5, 126.9, 127.4, 127.8, 127.9, 129.1, 129.6, 129.7, 131.3, 134.3, 135, 137.1, 154.1 (C-2), 160 (C-4), 175.9 (C-6); MS-(+)-ESI: m/z (%): 727 ([2M+Na]⁺, 10), 353 ([M+H]⁺, 100).

6-Amino-4-benzyl-5-cyano-1-(3,4,5-trimethoxyphenyl)-2(1H)-pyrimidinone (3o). Yellow solid, yield (65%), C₂₁H₂₀N₄O₄, M = 392 g·mol⁻¹, mp 224–226 °C, R_f = 0.26 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 247 (39,396), 307 (19,404); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,208 (CN), 1,687 (C=O), 1,627 (C=N); ¹H-NMR: (DMSO-d₆): δ = 3.91 (s, 2H, CH₂), 3.75 (s, 6H, 2OCH₃), 3.77 (s, 3H, OCH₃), 7.47–8.62 (m, 9H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 43.4 (CH₂), 56.6 (2C, 2OCH₃), 60.4 (OCH₃), 72.7 (C-5), 107.1, 116.9 (CN), 126, 128.6, 129.9, 137.1, 138.3, 138.5, 153.6, 154.4 (C-2), 160.7 (C-4), 175 (C-6); MS-(+)-ESI: m/z (%): 393 ([M+H]⁺, 100).

6-Amino-4-benzyl-5-cyano-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2(1H)-pyrimidinone (3p). Dark brown solid, yield (55%), C₂₀H₁₆N₄O₃, M = 360 g·mol⁻¹, mp 287–289 °C, R_f = 0.41 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 251 (31,320), 318 (15,120); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,210 (CN), 1,661 (C=O), 1,609 (C=N); ¹H-NMR: (DMSO-d₆): δ = 3.9 (s, 2H, CH₂), 4.32 (s, 4H, 2CH₂), 6.79–8.05 (m, 10H, Ar-H + NH₂); ¹³C-NMR (DMSO-d₆): δ = 43.4 (CH₂), 64.5 (CH₂), 64.8 (CH₂), 72.6 (C-5), 116.9 (CN), 117.4, 121.7, 126, 127.5, 128.1,

131.5, 136.9, 138.1, 143.9, 144.2, 153.9 (C-2), 160.5 (C-4), 175.4 (C-6); MS-(+)ESI: m/z (%): 743 ($[2M+Na]^+$, 11), 361 ($[M+H]^+$, 100).

6-Amino-4-benzyl-5-cyano-1-(3-ethynylphenyl)-2(1H)-pyrimidinone (3q). White solid, yield (62%), $C_{20}H_{14}N_4O$, $M = 326 \text{ g}\cdot\text{mol}^{-1}$, mp 224–226 °C, $R_f = 0.47$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 248 (40,587), 308 (15,160); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 3,271 ($\equiv\text{C-H}$), 2,209 (CN), 1,662 (C=O), 1,625 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): $\delta = 3.9$ (s, 2H, CH_2), 4.3 (s, 1H, $\text{C}\equiv\text{CH}$), 7.32–7.83 (m, 11H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): $\delta = 43.4$ (CH_2), 73.8 (C-5), 82.3 ($\text{C}\equiv\text{CH}$), 83.2 ($\text{C}\equiv\text{CH}$), 116.5 (CN), 123.9, 128.5, 129.2, 130.2, 131.4, 132.7, 132.9, 134.3, 136.4, 142.1, 154.1 (C-2), 160.8 (C-4), 174.9 (C-6); MS-(+)ESI: m/z (%): 675 ($[2M+Na]^+$, 17), 327 ($[M+H]^+$, 100).

6-Amino-4-benzyl-5-cyano-1-(4-ethynylphenyl)-2(1H)-pyrimidinone (3r). White solid, yield (58%), $C_{20}H_{14}N_4O$, $M = 326 \text{ g}\cdot\text{mol}^{-1}$, mp 252–254 °C, $R_f = 0.56$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 250 (44,010), 318 (12,714); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 3,269 ($\equiv\text{C-H}$), 2,211 (CN), 1,668 (C=O), 1,639 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): $\delta = 3.89$ (s, 2H, CH_2), 4.31 (s, 1H, $\text{C}\equiv\text{CH}$), 7.27–7.63 (m, 11H, Ar-H + NH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): $\delta = 43.4$ (CH_2), 73.8 (C-5), 82.3 ($\text{C}\equiv\text{CH}$), 83.4 ($\text{C}\equiv\text{CH}$), 116.5 (CN), 123.4, 127.2, 128.9, 129.5, 129.6, 133.9, 135.5, 137, 153.9 (C-2), 159.6 (C-4), 175.5 (C-6); MS-(+)ESI: m/z (%): 675 ($[2M+Na]^+$, 8), 327 ($[M+H]^+$, 100).

General experimental procedure for preparation of 1,4-disubstituted-1,2,3-triazoles 4a-l

The mixture of alkyne **3** (1 mmol) and azides (1 mmol) was suspended in a mixture of THF/ t -BuOH/ H_2O (3:1:1, v/v/v, 6/2/2 mL). Sodium ascorbate (89 mg, 0.45 equiv) was added followed by addition of $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (16 mg, 0.1 equiv). The heterogeneous mixture was stirred vigorously for 2 days, at which time TLC showed complete conversion. The reaction mixture was concentrated under vacuum and the residue was treated with H_2O (50 mL) and extracted with dichloromethane ($3 \times 15 \text{ mL}$). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and evaporated under reduced pressure to give a crude mass. Column chromatography purification using ethyl acetate/dichloromethane as eluent gave the clicked product **4**.

6-Amino-5-cyano-4-(4-methylphenyl)-1-(3-(1-(phenylthiomethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2(1H)-pyrimidinone (4a). White solid, yield (82%), $C_{27}H_{21}N_7OS$, $M = 491 \text{ g}\cdot\text{mol}^{-1}$, mp 220–222 °C, $R_f = 0.34$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 253 (57,447), 319 (13,993); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,225 (CN), 1,677 (C=O), 1,643 (C=N); $^1\text{H-NMR}$: (DMSO- d_6): $\delta = 2.41$ (s, 3H, CH_3), 6.02 (s, 2H, CH_2), 7.30–7.98 (m, 15H, Ar-H + NH_2), 8.65 (s, 1H, $\text{CH}_{\text{ar-triazole}}$); $^{13}\text{C-NMR}$ (DMSO- d_6): $\delta = 21$ (CH_3), 52.1 (CH_2), 72.1 (C-5), 116.7 (CN), 121.3 ($\text{CH}_{\text{ar-triazole}}$), 125.3, 125.9, 127.8, 127.9, 128.3, 128.8, 129.3, 130.6, 130.7, 132.2, 132.4, 134.1, 135.3, 141, 146 ($\text{C}_{\text{q-triazole}}$), 153.5 (C-2), 160 (C-4), 171.3 (C-6); MS-(+)ESI: m/z (%): 983 ($[2M+H]^+$, 19), 514 ($[M+Na]^+$, 7), 492 ($[M+H]^+$, 100), MS-(-)ESI: m/z (%): 464 (26), 354 (8).

6-Amino-5-cyano-4-(4-methylphenyl)-1-(4-(1-(phenylthiomethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2(1H)-pyrimidinone (4b). White solid, yield (72%), $C_{27}H_{21}N_7OS$, $M = 491 \text{ g}\cdot\text{mol}^{-1}$, mp 259–261 °C,

$R_f = 0.27$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 251 (46,399), 318 (15,466); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,226 (CN), 1,681 (C=O), 1,648 (C=N); ¹H-NMR: (DMSO-d₆): $\delta = 2.4$ (s, 3H, CH₃), 6.08 (s, 2H, CH₂), 7.29–8.11 (m, 15H, Ar-H + NH₂), 8.72 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): $\delta = 21$ (CH₃), 52.3 (CH₂), 72.7 (C-5), 116.5 (CN), 121.7 (CH_{ar-triazole}), 125.6, 127.4, 127.7, 128.6, 129.7, 130.5, 130.9, 132.1, 132.5, 133.9, 135.4, 140.9, 146.1 (C_{q-triazole}), 154 (C-2), 160.1 (C-4), 171.4 (C-6); MS-(+)ESI: m/z (%): 983 ([2M + H]⁺, 20), 514 ([M + Na]⁺, 8), 492 ([M+H]⁺, 100), MS-(-)ESI: m/z (%): 464 (22), 354 (9).

6-Amino-4-benzyl-5-cyano-1-(3-(1-(phenylthiomethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2(1H)-pyrimidinone (4c). White solid, yield (80%), C₂₇H₂₁N₇OS, M = 491 g·mol⁻¹, mp 235–237 °C, $R_f = 0.36$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 250 (62,602), 318 (19,939); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,208 (CN), 1,668 (C=O), 1,616 (C=N); ¹H-NMR: (DMSO-d₆): $\delta = 3.90$ (s, 2H, CH₂), 6.13 (s, 2H, CH₂), 7.27–7.65 (m, 16H, Ar-H + NH₂), 8.85 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): $\delta = 43.4$ (CH₂), 52.2 (CH₂), 73.4 (C-5), 117 (CN), 122.3 (CH_{ar-triazole}), 124.9, 125.6, 126.9, 127.7, 128.3, 129.2, 129.6, 131.2, 131.8, 133.1, 133.4, 134.7, 136.5, 140.9, 147.3 (C_{q-triazole}), 154 (C-2), 159.6 (C-4), 175.7 (C-6); MS-(+)ESI: m/z (%): 983 ([2M + H]⁺, 19), 514 ([M + Na]⁺, 7), 492 ([M+H]⁺, 100), MS-(-)ESI: m/z (%): 464 (2), 354 (8).

6-Amino-4-benzyl-5-cyano-1-(4-(1-(phenylthiomethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2(1H)-pyrimidinone (4d). White solid, yield (75%), C₂₇H₂₁N₇OS, M = 491 g·mol⁻¹, mp 262–264 °C, $R_f = 0.30$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 248 (61,129), 319 (18,412); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,226 (CN), 1,685 (C=O), 1,647 (C=N); ¹H-NMR: (DMSO-d₆): $\delta = 3.9$ (s, 2H, CH₂), 6.23 (s, 2H, CH₂), 7.2–7.91 (m, 16H, Ar-H + NH₂), 8.64 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): $\delta = 43.5$ (CH₂), 51.9 (CH₂), 73.7 (C-5), 116.5 (CN), 120.5 (CH_{ar-triazole}), 126, 126.9, 127.2, 129.1, 129.9, 129.9, 129.9, 131.9, 132.2, 134.2, 136.4, 141.2, 146.7 (C_{q-triazole}), 153.5 (C-2), 159.3 (C-4), 175.6 (C-6); MS-(+)ESI: m/z (%): 983 ([2M + H]⁺, 22), 514 ([M + Na]⁺, 7), 492 ([M+H]⁺, 100), MS-(-)ESI: m/z (%): 464 (25), 354 (9).

6-Amino-5-cyano-1-(3-(1-(4-(isopropylamino)-6-(methylthio)-1,3,5-triazin-2-yl)-1H-1,2,3-triazol-4-yl)-phenyl)-4-(4-methylphenyl)-2(1H)-pyrimidinone (4e). Pale yellow solid, yield (73%), C₂₇H₂₅N₁₁OS, M = 551 g·mol⁻¹, mp 230–232 °C, $R_f = 0.39$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 248 (71,905), 318 (19,009); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂ + NH), 2,208 (CN), 1,671 (C=O), 1,627 (C=N); ¹H-NMR: (DMSO-d₆): $\delta = 1.21$ (d, 3H, $J = 9$ Hz, CH₃), 1.23 (d, 3H, $J = 9$ Hz, CH₃), 2.41 (s, 3H, CH₃), 2.59 (s, 3H, -SCH₃), 4.3 (m, 1H, CH), 7.25–7.77 (m, 11H, Ar-H + NH₂ + NH), 8.1 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): $\delta = 21.2$ (SCH₃), 21.5 (CH₃), 22.3 (CH₃), 22.6 (CH₃), 42.8 (CH), 73.8 (C-5), 117.2 (CN), 120.7 (CH_{ar-triazole}), 126.3, 128.8, 129.3, 129.4, 131.3, 132.1, 132.1, 134.6, 135.9, 141.5, 146.4 (C_{q-triazole}), 154 (C-2), 160.5 (C-4), 164, 171.8 (C-6), 182.1, 183.1; MS-(+)ESI: m/z (%): 574 ([M + Na]⁺, 7), 552 ([M+H]⁺, 100), MS-(-)ESI: m/z (%): 524 (64), 482 (7).

6-Amino-5-cyano-1-(4-(1-(4-(isopropylamino)-6-(methylthio)-1,3,5-triazin-2-yl)-1H-1,2,3-triazol-4-yl)-phenyl)-4-(4-methylphenyl)-2(1H)-pyrimidinone (4f). white solid, yield (94%), C₂₇H₂₅N₁₁OS, M = 551 g·mol⁻¹, mp 253–255 °C, $R_f = 0.31$ (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH)

$\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 251 (64,467), 319 (15,703); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂ + NH), 2,225 (CN), 1,663 (C=O), 1,638 (C=N); ¹H-NMR: (DMSO-d₆): δ = 1.21 (d, 3H, J = 9 Hz, CH₃), 1.23 (d, 3H, J = 9 Hz, CH₃), 2.4 (s, 3H, CH₃), 2.61 (s, 3H, -SCH₃), 4.31 (m, 1H, CH), 7.21–7.75 (m, 11H, Ar-H + NH₂ + NH), 8.21 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): δ = 21.1 (SCH₃), 21.5 (CH₃), 22.3 (CH₃), 22.5 (CH₃), 42.9 (CH), 73.8 (C-5), 116.9 (CN), 120.6 (CH_{ar-triazole}), 124.2, 128.8, 129.6, 131.4, 133.3, 134.6, 136, 141.3, 146.7 (C_{q-triazole}), 153.9 (C-2), 160.3 (C-4), 163.9, 171.7 (C-6), 182.1, 183.2; MS-(+)-ESI: m/z (%): 574 ([M + Na]⁺, 7), 552 ([M+H]⁺, 100), MS-(-)-ESI: m/z (%): 524 (54), 482 (9).

6-Amino-4-benzyl-5-cyano-1-(3-(1-(4-(isopropylamino)-6-(methylthio)-1,3,5-triazin-2-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2(1H)-pyrimidinone (4g). Yellowish solid, yield (88%), C₂₇H₂₅N₁₁OS, M = 551 g·mol⁻¹, mp 241–243 °C, R_f = 0.37 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 249 (50,416), 307 (27,274); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,206 (CN), 1,670 (C=O), 1,629 (C=N); ¹H-NMR: (DMSO-d₆): δ = 1.21 (d, 3H, J = 9 Hz, CH₃), 1.23 (d, 3H, J = 9 Hz, CH₃), 2.59 (s, 3H, -SCH₃), 3.9 (s, 2H, CH₂), 4.3 (m, 1H, CH), 7.27–7.43 (m, 12H, Ar-H + NH₂ + NH), 8.29 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): δ = 22.2 (SCH₃), 22.3 (CH₃), 22.5 (CH₃), 42.8 (CH), 43.4 (CH₂), 73.8 (C-5), 116.6 (CN), 120.8 (CH_{ar-triazole}), 127.4, 128, 128.3, 129, 129.8, 130, 131.3, 135.2, 137.3, 146.5 (C_{q-triazole}), 153.9 (C-2), 160.2 (C-4), 163.8, 164.2, 175.4 (C-6), 182.1, 183; MS-(+)-ESI: m/z (%): 574 ([M + Na]⁺, 9), 552 ([M+H]⁺, 100), MS-(-)-ESI: m/z (%): 524 (61), 482 (7).

6-Amino-4-benzyl-5-cyano-1-(4-(1-(4-(isopropylamino)-6-(methylthio)-1,3,5-triazin-2-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2(1H)-pyrimidinone (4h). White solid, yield (71%), C₂₇H₂₅N₁₁OS, M = 551 g·mol⁻¹, mp 274–276 °C, R_f = 0.32 (ethyl acetate/dichloromethane, 70:30, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 250 (52,069), 308 (25,621); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,226 (CN), 1,685 (C=O), 1,642 (C=N); ¹H-NMR: (DMSO-d₆): δ = 1.21 (d, 3H, J = 9 Hz, CH₃), 1.23 (d, 3H, J = 9 Hz, CH₃), 2.60 (s, 3H, -SCH₃), 3.9 (s, 2H, CH₂), 4.3 (m, 1H, CH), 7.36–7.47 (m, 12H, Ar-H + NH₂ + NH), 8.3 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): δ = 21.5 (SCH₃), 22.3 (CH₃), 22.5 (CH₃), 42.8 (CH), 43.4 (CH₂), 73.8 (C-5), 116.5 (CN), 120.7 (CH_{ar-triazole}), 127.2, 127.8, 128.9, 129.6, 131.1, 135, 137.1, 146.5 (C_{q-triazole}), 154.1 (C-2), 159.7 (C-4), 163.6, 164, 175.4 (C-6), 182.1, 183.1; MS-(+)-ESI: m/z (%): 574 ([M + Na]⁺, 7), 552 ([M+H]⁺, 100), MS-(-)-ESI: m/z (%): 524 (56), 482 (7).

(Z)-Ethyl-2-(4-(4-(3-(6-amino-5-cyano-4-(4-methylphenyl)-2-oxopyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (4i). Golden yellow solid, yield (84%), C₄₃H₃₃N₉O₄S, M = 771 g·mol⁻¹, mp 285–287 °C, R_f = 0.28 (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) $\lambda_{\max}$ nm (ϵ L·mol⁻¹·cm⁻¹): 248 (95,989), 308 (35,851); IR (KBr) cm⁻¹: 3,450–3,310 (NH₂), 2,211 (CN), 1,715 (C=O, ester), 1,677 (C=O); ¹H-NMR: (DMSO-d₆): δ = 1.13 (t, 3H, J = 6 Hz, CH₃), 2.40 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 4.04 (q, 2H, J = 6 Hz, CH₂), 6.06 (s, 1H, C-CH-N), 7.31–8.14 (m, 20H, Ar-H + NH₂), 9.47 (s, 1H, CH_{ar-triazole}); ¹³C-NMR (DMSO-d₆): δ = 14.3 (CH₃-CH₂), 21.5 (CH₃), 22.9 (CH₃), 55.5 (C-CH-N), 60.7 (CH₃-CH₂), 72.6 (C-5), 109.4, 117.1 (CN), 120.4, 120.8 (CH_{ar-triazole}), 121.3, 125.9, 126.7, 127.9, 128.8, 129.1, 129.2, 129.3, 131.5, 131.9, 132.1, 132.5, 133.4, 134.6, 135.9, 137.7, 140.7, 141.5, 147.3 (C_{q-triazole}), 151.5, 154 (C-2), 155.7, 160.5 (C-4), 164.6 (C=O), 165.3, 171.9 (C-6); MS-(+)-ESI: m/z (%): 794 ([M + Na]⁺, 3), 772 ([M+H]⁺, 100), MS-(-)-ESI: m/z (%): 744 (10).

(*Z*)-Ethyl-2-(4-(4-(4-(6-amino-5-cyano-4-(4-methylphenyl)-2-oxypyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**4j**). Golden yellow solid, yield (72%), $C_{43}H_{33}N_9O_4S$, $M = 771 \text{ g}\cdot\text{mol}^{-1}$, mp 292–294 °C, $R_f = 0.25$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 249 (84,424), 307 (38,164); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,225 (CN), 1,727 (C=O, ester), 1,685 (C=O); $^1\text{H-NMR}$: (DMSO- d_6): $\delta = 1.15$ (t, 3H, $J = 6 \text{ Hz}$, CH_3), 2.41 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.11 (q, 2H, $J = 6 \text{ Hz}$, CH_2), 6.02 (s, 1H, C-CH-N), 7.29–8.20 (m, 20H, Ar-H + NH_2), 9.32 (s, 1H, $\text{CH}_{\text{ar-triazole}}$); $^{13}\text{C-NMR}$ (DMSO- d_6): $\delta = 14.3$ ($\underline{\text{CH}_3\text{-CH}_2}$), 21.5 (CH_3), 22.9 (CH_3), 55.5 (C- $\underline{\text{CH-N}}$), 60.6 ($\text{CH}_3\text{-}\underline{\text{CH}_2}$), 72.6 (C-5), 109.4, 117.4 (CN), 120.7, 120.8 ($\text{CH}_{\text{ar-triazole}}$), 122, 126.2, 126.7, 128.1, 129, 129.3, 131.6, 132, 132.2, 132.6, 133.6, 134.5, 136.1, 137.7, 140.6, 141.4, 147.5 ($\text{C}_{\text{q-triazole}}$), 151.7, 152.2 (C-2), 156.2, 161.2 (C-4), 165.1 (C=O), 165.6, 172.5 (C-6); MS-(+)ESI: m/z (%): 794 ($[\text{M} + \text{Na}]^+$, 3), 772 ($[\text{M} + \text{H}]^+$, 100), MS-(-)ESI: m/z (%): 744 (7).

(*Z*)-Ethyl-2-(4-(4-(3-(6-amino-4-benzyl-5-cyano-2-oxypyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**4k**). Golden yellow solid, yield (81%), $C_{43}H_{33}N_9O_4S$, $M = 771 \text{ g}\cdot\text{mol}^{-1}$, mp 277–279 °C, $R_f = 0.32$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 250 (72,859), 318 (27,756); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,212 (CN), 1,721 (C=O, ester), 1,671 (C=O); $^1\text{H-NMR}$: (DMSO- d_6): $\delta = 1.12$ (t, 3H, $J = 6 \text{ Hz}$, CH_3), 2.40 (s, 3H, CH_3), 3.9 (s, 2H, CH_2), 4.09 (q, 2H, $J = 6 \text{ Hz}$, CH_2), 5.98 (s, 1H, C-CH-N), 7.33–8.02 (m, 21H, Ar-H + NH_2), 9.33 (s, 1H, $\text{CH}_{\text{ar-triazole}}$); $^{13}\text{C-NMR}$ (DMSO- d_6): $\delta = 14.3$ ($\underline{\text{CH}_3\text{-CH}_2}$), 22.9 (CH_3), 43.5 (CH_2), 55.4 (C- $\underline{\text{CH-N}}$), 60.7 ($\text{CH}_3\text{-}\underline{\text{CH}_2}$), 73.4 (C-5), 110.2, 116.5 (CN), 119.9, 121.2 ($\text{CH}_{\text{ar-triazole}}$), 122, 126, 126.6, 128.3, 128.9, 129, 129.8, 130.1, 131.5, 132, 132.4, 132.9, 134.2, 134.7, 136.1, 137.5, 139.9, 142, 146.7 ($\text{C}_{\text{q-triazole}}$), 150.9, 153.6 (C-2), 156.2, 159.6 (C-4), 164.5 (C=O), 166.2, 175.8 (C-6); MS-(+)ESI: m/z (%): 794 ($[\text{M} + \text{Na}]^+$, 3), 772 ($[\text{M} + \text{H}]^+$, 100), MS-(-)ESI: m/z (%): 744 (9).

(*Z*)-ethyl-2-(4-(4-(4-(6-amino-4-benzyl-5-cyano-2-oxypyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**4l**). Golden yellow solid, yield (68%), $C_{43}H_{33}N_9O_4S$, $M = 771 \text{ g}\cdot\text{mol}^{-1}$, mp 281–283 °C, $R_f = 0.61$ (ethyl acetate/dichloromethane, 50:50, v/v); UV (MeOH) λ_{max} nm ($\epsilon \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$): 253 (90,207), 319 (15,381); IR (KBr) cm^{-1} : 3,450–3,310 (NH_2), 2,226 (CN), 1,728 (C=O, ester), 1,676 (C=O); $^1\text{H-NMR}$: (DMSO- d_6): $\delta = 1.15$ (t, 3H, $J = 6 \text{ Hz}$, CH_3), 2.41 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 4.12 (q, 2H, $J = 6 \text{ Hz}$, CH_2), 6.00 (s, 1H, C-CH-N), 7.28–8.46 (m, 21H, Ar-H + NH_2), 9.40 (s, 1H, $\text{CH}_{\text{ar-triazole}}$); $^{13}\text{C-NMR}$ (DMSO- d_6): $\delta = 14.3$ ($\underline{\text{CH}_3\text{-CH}_2}$), 22.9 (CH_3), 43.5 (CH_2), 56.2 (C- $\underline{\text{CH-N}}$), 60.7 ($\text{CH}_3\text{-}\underline{\text{CH}_2}$), 73.8 (C-5), 112.5, 117.2 (CN), 120.3, 120.9 ($\text{CH}_{\text{ar-triazole}}$), 121.9, 126.3, 128.6, 129.4, 129.5, 129.9, 131.6, 131.8, 133.5, 133, 135.2, 135.4, 135.9, 137.6, 140.1, 142.2, 147.7 ($\text{C}_{\text{q-triazole}}$), 149.5, 153.9 (C-2), 157, 159.9 (C-4), 164.6 (C=O), 167.2, 174.9 (C-6); MS-(+)ESI: m/z (%): 794 ($[\text{M} + \text{Na}]^+$, 3), 772 ($[\text{M} + \text{H}]^+$, 100), MS-(-)ESI: m/z (%): 744 (6).

Acknowledgements

Thanks are due to the Ministry of Higher Education and Scientific Research of Tunisia for awarding a fellowship to Ennaji Najahi. The Authors wish to thank R Duval for gift of the azide

derivative A₃. We thank Dr. Carine Duhayon for providing the X-ray crystal analysis. Hany Ibrahim and Pierre Perio for their help in the physico-chemical characterization of our compounds.

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Sample Availability: Samples of the compounds are available from the authors.

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