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CLICK CHEMISTRY AS AN EFFICIENT TOOL TO ACCESS 6-AMINO-5-CYANO-2(1*H*)-PYRIMIDINONE DIMERS

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Abstract
We describe here the synthesis of triazole-linked 6-amino-5-cyano-2(1H)-pyrimidinone dimers using 1,3-dipolar cycloaddition. The azido-precursor was prepared through the reaction of ethyl 2,2-dicyanovinylcarbamate derivatives with p-azidoaniline. The second precursor, a 6-amino-5-cyano-1-(3 or 4-ethynylphenyl)-4-substituted-2(1H)-pyrimidinone, was obtained from ethyl 2,2-dicyanovinylcarbamate derivatives reacting with 3-ethynylaniline or 4-ethynylaniline. Consequently, the two 'click systems' were mixed together in order to obtain the desired dimer.

Keywords: triazole, pyrimidine, 1,3-dipolar cycloaddition.

Introduction

Pyrimidines, being an integral part of DNA and RNA, exhibit biodynamic properties and a variety of biological activities, such as antimicrobial, fungicides and insecticides.[1–3] Other pyrimidine derivatives also display anticancer [4] and antiparasitic properties.[5, 6] The triazoles have been shown to possess a number of desirable features in the context of medicinal chemistry. Some heterocyclic systems containing 1,2,3-triazoles possess various pharmacological properties such as antitubercular,[7] antibacterial [8] and antiviral activity.[9] The biodynamic properties of these molecules prompted us to design a system, combining two pyrimidines and triazole components in a ring together using one of the most reliable reactions in click chemistry, namely the copper(I)-catalyzed azide-alkyne one.[10] This reaction appeared to be a great alternative to the traditional thermal Huisgen 1,3-dipolar cycloaddition. Its development by Sharpless et al. a few years ago enabled the synthesis of numerous 1,2,3-triazole derivatives and constitutes one of the current main topic of interest in organic chemistry.[11] The click chemistry has also been used in the synthesis of pyrimidine dimmers.[12-14] We report in this paper on the synthesis of original 6-amino-5-cyano-2(1*H*)-pyrimidinone dimers compounds though 1,3-dipolar cycloaddition reaction of 6-amino-5-cyano-1-(4-azidophenyl)-2(1*H*)-pyrimidinone derivatives with 6-amino-5-cyano-1-(*meta*- or *para*-ethynylphenyl)-2(1*H*)-pyrimidinone derivatives. These new dimers were fully characterized by IR, NMR and mass spectrometry.

Results and discussion

(Scheme 1)

First, the 6-amino-5-cyano-1-(*meta*- or *para*-ethynylphenyl)-4-substituted-2(1*H*)-pyrimidinones **2a-d** were prepared in yields ranging from 58% to 70% by reaction of (3 or 4-ethynyl)aniline with ethyl 2,2-dicyanovinylcarbamate derivatives **1a-b**.[15] Second, the reaction of compounds **1a-b** with *p*-azidoaniline hydrochloride in chlorobenzene in the presence of triethylamine under reflux provided the 6-amino-5-cyano-1-(4-azidophenyl)-4-substituted-2(1*H*)-pyrimidinones **3a-b** in good yields.

(Scheme 2)

Finally, the (3 + 2) cycloaddition **2a-d** with **3a-b** in the presence of Na-ascorbate, DMF/H_2O and $CuSO_4.5H_2O$, at room temperature resulted in the corresponding 1,4-disubstituted-1,2,3-triazole compounds **4a-h** (Scheme 2) in good yields (Table 1).

(Table 1)

The structures of compounds **2a-d** and **3a-b** were in accordance with their spectroscopic data. The IR spectra of the compounds exhibited the absorption band at 2210 cm^{-1} indicating the presence of one cyano group, at around 2096-2094 cm^{-1} showing that the terminal azido $-N_3$ was present in the compounds **3a-b** and, at around 3265-3275 cm^{-1} for the compounds **2a-d** demonstrating the presence of the terminal alkyne ≡C-H. The mass spectra showed the respective $[M + H]^+$ peaks. In ^1H NMR spectra the most significant information was the disappearance of the triplet and the quadruplet of ethoxy groups of the starting reagent **1a-b**.

Structures of compounds **4a-h** were established on the basis of their spectroscopic data. In IR spectra, the absorption band at around 2096 cm^{-1}, corresponding to azido group of the azides **3**, was not observed. The mass spectra showed the respective $[M + H]^+$ peaks. According to ^1H NMR spectra of the 'click' products the terminal triple bonded proton signal (δH = 4.3 ppm) of the alkynes **2** 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}C spectra with the new signals of the ethylenic C atoms of the 1,2,3-triazole moiety at δ = 120 – 122 ppm ($CH_{ar\text{-}triazole}$) and δ = 146 – 148 ppm ($C_{q\text{-}triazole}$).

Conclusion

In summary, we utilized ethyl 2,2-dicyanovinylcarbamate derivatives and *p*-azidoaniline and *meta*- or *para*-ethynylaniline, respectively, for the synthesis of azides and alkynes. We have synthesized a new molecules of triazole-linked 6-amino-5-cyano-2(1*H*)-pyrimidinone dimers using the copper(I)-catalyzed azide-alkyne in good to very good yields. All products 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. ^{1}H and ^{13}C NMR spectra were recorded on an AC Bruker spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C) using $(CD_3)_2SO$ as solvent with $(CD_3)_2SO$ (δ_H 2.5) or $(CD_3)_2SO$ (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 electrospary as an ionization source. Melting points were determined on an Electrothermal 9300 capillary melting point apparatus and are uncorrected. 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 (2a-d)

To a magnetically stirred solution of the ethyl 2,2-dicyanovinylcarbamate derivatives **1a-c** (0.255 g: 1 mmol:1 equiv) in chlorobenzene (10 mL), *meta*- or *para*-ethynylaniline (0.140 g: 1.2 mmol: 1.2 equiv) added and reaction mixture was stirred for 2~4 h at 110 °C. Reaction progress was monitored by TLC. The resulting mixture was allowed to cool at room temperature. The formed precipitate was isolated by filtration and washed with diethyl ether for to get pure product.

6-amino-5-cyano-1-(3-ethynylphenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (2a). Pale yellow solid, yield (70%), $C_{20}H_{14}N_4O$, m = 326 g.mol^{-1}, mp 247-249 °C, R_f = 0.61 (ethyl acetate/dichloromethane, 50:50, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 3271 (≡C-H), 2211 (CN), 1671 (C=O), 1640 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 2.41 (3H, s, CH_3), 4.32 (1H, s, C≡CH), 7.25-7.75 (10H, m, Ar-H + NH_2); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 21.5 (CH_3), 73.81 (C5), 82.36 (C≡<u>C</u>H), 83.19 (<u>C</u>≡CH), 117.20 (CN), 124.01, 128.79, 129.29, 129.84, 131.03, 132.48, 133.32, 134.58, 135.57, 141.52, 153.92 (C2), 160.53 (C4), 171.77 (C6); MS-(+)ESI: m/z(%): 675 ([2M+Na]$^+$, 19), 327 ([M+H]$^+$, 100).

6-amino-5-cyano-1-(4-ethynylphenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (2b). Brownish yellow solid, yield (61%), $C_{20}H_{14}N_4O$, m = 326 g.mol^{-1}, mp 192-194 °C, R_f = 0.49 (ethyl acetate/dichloromethane, 50:50, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 3270(≡C-H), 2209 (CN), 1662 (C=O), 1638 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 2.41 (3H, s, CH_3), 4.30 (1H, s, C≡CH), 7.27-7.94 (10H, m, Ar-H + NH_2); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 21.50 (CH_3), 72.94 (C5), 82.32 (C≡<u>C</u>H), 83.35 (<u>C</u>≡CH), 117.23 (CN), 124.12, 128.91, 129.36, 131.12, 132.52, 134.38, 135.78, 141.34, 153.92 (C2), 160.1 (C4), 171.58 (C6); MS-(+)ESI: m/z(%): 675 ([2M+Na]$^+$, 9), 327 ([M+H]$^+$, 100).

6-amino-4-benzyl-5-cyano-1-(3-ethynylphenyl)-2(1*H*)-pyrimidinone (2c). White solid, yield (62%), $C_{20}H_{14}N_4O$, m = 326 g.mol^{-1}, mp 224-226 °C, R_f = 0.47 (ethyl acetate/dichloromethane, 50:50, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 3271 (≡C-H), 2209 (CN), 1662 (C=O), 1625 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 3.9 (2H, s, CH_2), 4.3 (1H, s, C≡CH),

7.32-7.83 (11H, m, Ar-H + NH_2); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 43.45 (CH_2), 73.79 (C5), 82.35 (C≡CH), 83.26 (C≡CH), 116.54 (CN), 123.97, 128.52, 129.23, 130.21, 131.43, 132.68, 132.91, 134.31, 136.41, 142.12, 154.07 (C2), 160.76 (C4), 174.9 (C6); MS-(+)ESI: m/z(%): 675 ($[2M+Na]^+$, 17), 327 ($[M+H]^+$, 100).

6-amino-4-benzyl-5-cyano-1-(4-ethynylphenyl)-2(1*H*)-pyrimidinone (2d). White solid, yield (58%), $C_{20}H_{14}N_4O$, m = 326 g.mol^{-1}, mp 252-254 °C, R_f = 0.56 (ethyl acetate/dichloromethane, 50:50, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 3269 (≡C-H), 2211 (CN), 1668 (C=O), 1639 (C=N); ^1H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 3.89 (2H, s, CH_2), 4.31 (1H, s, C≡CH), 7.27-7.63 (11H, m, Ar-H + NH_2); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 43.4 (CH_2), 73.82 (C5), 82.32 (C≡CH), 83.38 (C≡CH), 116.51 (CN), 123.37, 127.25, 128.92, 129.47, 129.60, 133.98, 135.49, 137.03, 153.91 (C2), 159.59 (C4), 175.46 (C6); MS-(+)ESI: m/z(%): 675 ($[2M+Na]^+$, 8), 327 ($[M+H]^+$, 100).

***General experimental procedure for preparation of 6-amino-5-cyano-1-(4-azidophenyl)-4-substituted-2(1H)-pyrimidinones* (3a-b)**

To a magnetically stirred solution of the ethyl 2,2-dicyanovinylcarbamate derivatives **1a-b** (1mmol: 1 equiv) in chlorobenzene (10 mL), *p*-azidoaniline hydrochloride (1.2 mmol: 1.2 equiv) was added followed by addition of triethylamine (1,2 equiv). The reaction mixture was stirred for 2~4 h at 110 °C. Reaction progress was monitored by TLC. The resulting mixture was allowed to cool at room temperature. The formed precipitate was isolated by filtration and washed with water. Column chromatography purification using ethyl acetate/dichloromethane (70:30, v:v) as eluent gave pure product.

6-amino-5-cyano-1-(4-azidophenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (3a). white solid, yield (76%), $C_{18}H_{13}N_7O$, m = 343 g.mol^{-1}, mp 236-238 °C, R_f = 0.42 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2096 (N_3), 1674 (C=O), 1619 (C=N); ^1H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 2.52 (3H, s, CH_3), 7,45-7,9 (10H, m, Ar-H + NH_2); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 21.44 (CH_3), 72.61 (C5'), 118.3 (CN), 128.85, 128.97, 130.14, 130.82, 131.5, 132.42, 135.15, 140.64, 154.31 (C2'), 160.76 (C4'), 172.46 (C6'); MS-(+)ESI: m/z(%): 709 ($[2M+Na]^+$, 34), 366 ($[M+Na]^+$, 6), 344 ($[M+H]^+$, 100).

6-amino-5-cyano-1-(4-azidophenyl)-4-benzyl-2(1*H*)-pyrimidinone (3b). white solid, yield (81%), $C_{18}H_{13}N_7O$, m = 343 g.mol^{-1}, mp 256-258 °C, R_f = 0.38 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2094 (N_3), 1680 (C=O), 1614 (C=N); ^1H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 3.9 (2H, s, CH_2), 7,3-7,53 (11H, m, Ar-H + NH_2); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 43.45 (CH_2), 73.86 (C5'), 116.66 (CN), 127.35, 128.94, 129.01, 129.45, 129.66, 130.68, 134.99, 140.12, 154.15 (C2'), 159.67 (C4'), 175.42 (C6'); MS-(+)ESI: m/z(%): 709 ($[2M+Na]^+$, 20), 366 ($[M+Na]^+$, 3), 344 ($[M+H]^+$, 100).

***General experimental procedure for preparation of 1,4-disubstituted-1,2,3-triazoles* (4a-h)**

The mixture of alkynes **2** (1 mmol) and azides **3** (1 mmol) were suspended in a mixture of DMF/H_2O (2:1, 4/2 mL). Sodium ascorbate (89 mg, 0.45 equiv) was added followed by addition of $CuSO_4.5H_2O$ (16 mg, 0.1 equiv). The heterogeneous mixture was stirred vigorously for 2

days. TLC after that time 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 ×15 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 (70:30, v/v) as eluent gave the clicked product **4**.

6-amino-5-cyano-1-(4-(4-(4-(6-amino-5-cyano-4-(4-methylphenyl)-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (4a). White solid, yield (85%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 250-252 °C, R_f = 0.28 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2226 (CN), 2211 (CN), 1681 (C=O), 1676 (C=O), 1648 (C=N), 1631 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 2.4 (3H, s, CH_3), 2.39 (3H, s, CH_3), 7.25-8.2 (20H, m, Ar-H + 2 NH_2), 9.32 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 21.44 (CH_3), 21.45 (CH_3), 72.61 (C5), 72.67 (C5'), 116.47 (CN), 118.29 (CN), 120.87 ($CH_{ar\text{-}triazole}$), 122.1, 124.01, 127.43, 128.56, 129.85, 129.97, 130.14, 130.53, 130.82, 130.87, 131.5, 132.11, 132.49, 133.97, 137.53, 140.87, 147.06 ($C_{q\text{-}triazole}$), 154.03 (C2), 154.31 (C2'), 160.07 (C4), 160.76 (C4'), 171.37 (C6), 172.46 (C6'); MS-(+)ESI: m/z(%): 692 ([M + Na]$^+$, 3), 670 ([M+H]$^+$, 100).

6-amino-5-cyano-1-(4-(4-(4-(6-amino-4-benzyl-5-cyano-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (4b). White solid, yield (72%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 220-222 °C, R_f = 0.33 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2206 (CN), 1674 (C=O), 1662 (C=O), 1638 (C=N), 1614 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 2.4 (3H, s, CH_3), 3.97 (2H, s, CH_2), 7.28-8.11 (21H, m, Ar-H + 2 NH_2), 8.87 (s, 1H, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 21.44 (CH_3), 43.56 (CH_2), 72.59 (C5), 73.86 (C5'), 116.66 (CN), 117.07 (CN), 121.17 ($CH_{ar\text{-}triazole}$), 121.75, 125.21, 126.49, 127.38, 129.78, 129.84, 130.3, 130.64, 130.96, 131.2, 131.73, 132.41, 132.52, 134.01, 136.92, 141.14, 146.48 ($C_{q\text{-}triazole}$), 154.15 (C2), 154.48 (C2'), 159.67 (C4), 160.60 (C4'), 171.89 (C6), 175.68 (C6'); MS-(+)ESI: m/z(%): 692 ([M + Na]$^+$, 6), 670 ([M+H]$^+$, 100).

6-amino-5-cyano-1-(4-(4-(4-(6-amino-4-benzyl-5-cyano-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4-benzyl-2(1*H*)-pyrimidinone (4c). White solid, yield (68%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 236-238 °C, R_f = 0.25 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2210 (CN), 1678 (C=O), 1661 (C=O), 1618 (C=N), 1609 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 3.9 (2H, s, CH_2), 3.93 (2H, s, CH_2), 7.30-8.15 (22H, m, Ar-H + 2 NH_2), 8.54 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 43.4 (CH_2), 43.4 (CH_2), 72.74 (C5), 73.82 (C5'), 116.51 (CN), 116.97 (CN), 120.54 ($CH_{ar\text{-}triazole}$), 123.37, 124.91, 127.13, 129.02, 129.53, 129.92, 130.47, 130.81, 130.87, 131.46, 132.31, 132.45, 132.52, 133.98, 136.76, 140.71, 146.45 ($C_{q\text{-}triazole}$), 153.91 (C2), 154.38 (C2'), 159.59 (C4), 160.71 (C4'), 175.04 (C6), 175.46 (C6'); MS-(+)ESI: m/z(%): 692 ([M + Na]$^+$, 3), 670 ([M+H]$^+$, 100).

6-amino-5-cyano-1-(4-(4-(4-(6-amino-5-cyano-4-(4-methylphenyl)-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-4-benzyl-2(1*H*)-pyrimidinone (4d). Dark brown solid, yield (86%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 269-271 °C, R_f = 0.38 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2217 (CN), 1674 (C=O), 1668 (C=O), 1622 (C=N), 1617 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300

MHz) δ_H, ppm: 2.4 (3H, s, CH_3), 3.9 (2H, s, CH_2), 7.17-8.22 (21H, m, Ar-H + 2 NH_2), 8.5 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-*d*$_6$, 75 MHz) δ_C, ppm: 21.5 (CH_3), 43.4 (CH_2), 73.8 (C5), 73.91 (C5'), 116.14 (CN), 116.97 (CN), 121.2 ($CH_{ar\text{-}triazole}$), 124.54, 124.83, 128.21, 128.34, 128.51, 128.74, 129.64, 130.42, 130.63, 131.67, 132.3, 131.97, 132.21, 134.38, 136.32, 140.57, 147.51 ($C_{q\text{-}triazole}$), 153.62 (C2), 154.42 (C2'), 159.61 (C4), 159.67 (C4'), 171.2 (C6), 175.42 (C6'); MS-(+)ESI: m/z(%): 692 ($[M + Na]^+$, 3), 670 ($[M+H]^+$, 100).

6-amino-5-cyano-1-(3-(1-(4-(6-amino-5-cyano-4-(4-methylphenyl)-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)phenyl)-4-benzyl-2(1*H*)-pyrimidinone (4e). White solid, yield (63%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 257-259 °C, R_f = 0.24 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2210 (CN), 1671 (C=O), 1668 (C=O), 1637 (C=N), 1620 (C=N); ^1H NMR spectrum (DMSO-*d*$_6$, 300 MHz) δ_H, ppm: 2.4 (3H, s, CH_3), 3.9 (2H, s, CH_2), 7.30-8.17 (21H, m, Ar-H + 2 NH_2), 8.72 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-*d*$_6$, 75 MHz) δ_C, ppm: 21.5 (CH_3), 43.4 (CH_2), 72.54 (C5), 73.83 (C5'), 117 (CN), 117.07 (CN), 120.5 ($CH_{ar\text{-}triazole}$), 122.86, 124.03, 125.29, 126.12, 126.5, 128.34, 129.43, 129.69, 129.82, 129.97, 130.77, 131.76, 131.78, 132.83, 132.92, 133.94, 137.05, 140.71, 146.34 ($C_{q\text{-}triazole}$), 154.27 (C2), 154.32 (C2'), 159.87 (C4), 160.74 (C4'), 172.09 (C6), 175.68 (C6'); MS-(+)ESI: m/z(%): 692 ($[M + Na]^+$, 6), 670 ($[M+H]^+$, 100).

6-amino-5-cyano-1-(3-(1-(4-(6-amino-5-cyano-4-(4-methylphenyl)-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)phenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (4f). white solid, yield (76%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 228-230 °C, R_f = 0.27 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2226 (CN), 2211 (CN), 1676 (C=O), 1672 (C=O), 1650 (C=N), 1648 (C=N); ^1H NMR spectrum (DMSO-*d*$_6$, 300 MHz) δ_H, ppm: 2.4 (3H, s, CH_3), 2.4 (3H, s, CH_3), 7.32-8.47 (20H, m, Ar-H + 2 NH_2), 9.3 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-*d*$_6$, 75 MHz) δ_C, ppm: 21.41 (CH_3), 21.4 (CH_3), 72.6 (C5), 72.64 (C5'), 117.22 (CN), 118 (CN), 121.47 ($CH_{ar\text{-}triazole}$), 121.91, 124.01, 125.74, 126.93, 128.43, 128.77, 128.94, 129.86, 129.94, 129.83, 130.65, 131.37, 131.5, 132.54, 132.62, 134.11, 138.28, 141.38, 146.5 ($C_{q\text{-}triazole}$), 154.21 (C2), 154.34 (C2'), 160.53 (C4), 160.82 (C4'), 171.47 (C6), 171.83 (C6'); MS-(+)ESI: m/z(%): 692 ($[M + Na]^+$, 3), 670 ($[M+H]^+$, 100).

6-amino-5-cyano-1-(3-(1-(4-(6-amino-4-benzyl-5-cyano-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)phenyl)-4-(4-methylphenyl)-2(1*H*)-pyrimidinone (4g). White solid, yield (66%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 242-244 °C, R_f = 0.32 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2209 (CN), 1674 (C=O), 1671 (C=O), 1627 (C=N), 1624 (C=N); ^1H NMR spectrum (DMSO-*d*$_6$, 300 MHz) δ_H, ppm: 2.4 (3H, s, CH_3), 3.9 (2H, s, CH_2), 7.30-8.27 (21H, m, Ar-H + 2 NH_2), 8.52 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-*d*$_6$, 75 MHz) δ_C, ppm: 21.5 (CH_3), 43.4 (CH_2), 72.83 (C5), 73.62 (C5'), 116.14 (CN), 117.32 (CN), 120.28 ($CH_{ar\text{-}triazole}$), 124.04, 124.21, 125.46, 126.74, 127.85, 128.44, 128.67, 128.97, 129.62, 130.56, 130.71, 130.78, 131.78, 132.83, 132.96, 134.34, 136.96, 141.27, 145.82 ($C_{q\text{-}triazole}$), 154.32 (C2), 154.32 (C2'), 159.97 (C4), 161.31 (C4'), 172.18 (C6), 175.73 (C6'); MS-(+)ESI: m/z(%): 692 ($[M + Na]^+$, 6), 670 ($[M+H]^+$, 100).

6-amino-5-cyano-1-(3-(1-(4-(6-amino-4-benzyl-5-cyano-2-oxopyrimidin-1(2*H*)-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)phenyl)-4-benzyl-2(1*H*)-pyrimidinone (4h). Grey solid, yield (70%), $C_{38}H_{27}N_{11}O_2$, m = 669 g.mol^{-1}, mp 247-249 °C, R_f = 0.26 (ethyl acetate/dichloromethane, 70:30, v/v); IR (KBr), ν_{max}, cm^{-1}: 3450-3310 (NH_2), 2211 (CN), 2209 (CN), 1678 (C=O), 1668 (C=O),

1620 (C=N), 1610 (C=N); ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) δ_H, ppm: 3.9 (2H, s, CH_2), 3.9 (2H, s, CH_2), 7.30-8.09 (22H, m, Ar-H + 2 NH_2), 8.5 (1H, s, $CH_{ar\text{-}triazole}$); ^{13}C NMR spectrum (DMSO-d_6, 75 MHz) δ_C, ppm: 43.4 (CH_2), 43.4 (CH_2), 72.74 (C5), 72.82 (C5'), 116.31 (CN), 117 (CN), 120.56 ($CH_{ar\text{-}triazole}$), 122.41, 124.47, 125.02, 126.93, 128.27, 129.37, 129.74, 129.97, 129.98, 130.76, 130.91, 131.5, 132.77, 132.43, 132.52, 134.11, 136.39, 141.21, 146.54 ($C_{q\text{-}triazole}$), 154.1 (C2), 154.42 (C2'), 160.13 (C4), 160.83 (C4'), 175.34 (C6), 175.45 (C6'); MS-(+)ESI: m/z(%): 692 ($[M + Na]^+$, 4), 670 ($[M+H]^+$, 100).

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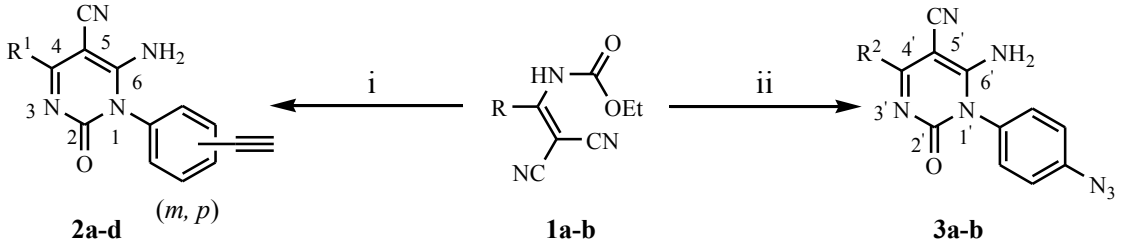
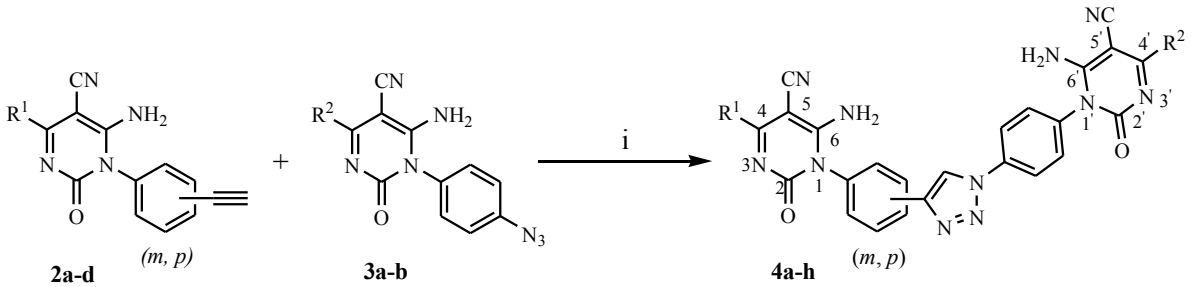


2a-d **1a-b** **3a-b**

2a: R^1 = 4-$CH_3C_6H_4$; meta, 70%
2b: R^1 = 4-$CH_3C_6H_4$; para, 61%
2c: R^1 = C_6H_5-CH_2; meta, 62%
2d: R^1 = C_6H_5-CH_2; meta, 58%

3a: R^2 = 4-$CH_3C_6H_4$, 76%
3b: R^2 = C_6H_5-CH_2, 81%

Scheme 1. Synthesis of alkynes **2** and azides **3**. Reagents and conditions: (i) *meta*- or *para*-ethynylaniline (1.2 equiv), chlorobenzene, 110 °C, 2~4 h; (ii) *p*-azidoaniline hydrochloride (1.2 equiv), $N(Et)_3$ (1.2 equiv), chlorobenzene, 110 °C, 2~4 h.



2a-d **3a-b** **4a-h**

Scheme 2. Click chemistry. Reagents and conditions: (i) Na-ascorbate (0.45 equiv), $CuSO_4.5H_2O$ (0.1 equiv), DMF/H_2O/ (2:1, v/v), rt, 2d.

Table 1. Synthesis of triazole-linked 6-amino-5-cyano-2(1H)-pyrimidinone dimers **4a-h**

Entry	Compound	Azides	Alkynes	Yields[a]
1	**4a**	3a	2b	85%
2	**4b**	3a	2d	72%
3	**4c**	3b	2d	68%
4	**4d**	3b	2b	86%
5	**4e**	3a	2c	63%
6	**4f**	3a	2a	76%
7	**4g**	3b	2a	66%
8	**4h**	3b	2c	70%

[a] Isolated yield