Efficient Synthesis of Pyrrolo [2,3-d] Pyrimidines Containing 1,4-Disubstituted-1,2,3-Triazole Derivatives

Radhakrishnamraju Ruddarraju,[a] Adharvana Chari Murugulla,[a]* Shobha Donthabakthuni,[a] Ravindar Kotla,[a] Sandeep Deshmukh,[a] Ravichandar Maroju,[b] and Sadhanandam Palle[c]

[a]Dr. MACS Bio-Pharma Pvt. Ltd, Factory: Plot-79/B&C, Pashamylaram, Patancheru, Medak (Dist) 502307, India
[b]Department of Physics and Chemistry, Mahatma Gandhi Institute of Technology, Gandipet, Hyderabad, Telangana, India
[c]Centre for Chemical Sciences and Technology, IST, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500 085, Telangana, India
*E-mail: drmacs36@gmail.com; drmac_s@yahoo.com

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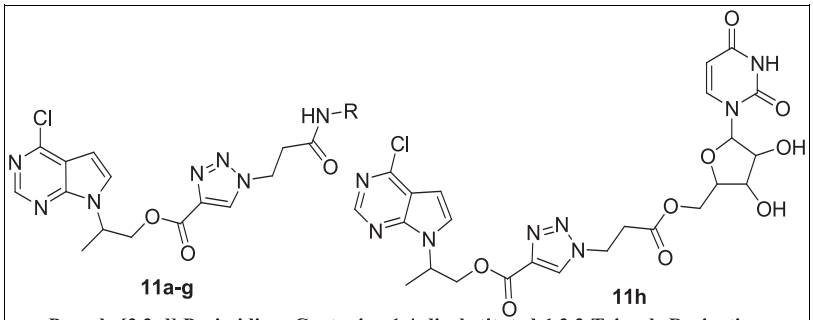


Pyrrolo [2,3-d] Pyrimidines Contaning 1,4-disubstituted-1,2,3-Triazole Derivatives

Here, we demonstrate a simple but highly efficient method for the synthesis of multifunctionalized pyrrolo[2,3-d]pyrimidines containing 1,4-disubstituted 1,2,3-triazole derivative coupled with various amines (**10a–g**) and alcohol (**10h**) to obtain final compounds (**11a–h**) with reasonable to excellent yields (25% to 94%). The newly synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR, and mass spectroscopy analysis.

INTRODUCTION

Among various heterocyclic compounds, *N*-heterocyclic compounds are very important in drug design [1–3]. Compounds containing pyrrolopyrimidine functional groups, collectively referred to as 7-deazapurines, are a structurally diverse class of nucleoside analogs with demonstrated antibiotic [4]. Pyrrolo[2,3-d]pyrimidine derivatives have been attractive in both organic and medicinal chemistry because of their presence in numerous naturally occurring products [5], and designed bioactive compounds [6]. Pyrrolo[2,3-d] pyrimidine derivatives are known to exhibit various biological activities such as antibacterial [7], anti-inflammatory [8], antiallergic [9], antitumor [10], antiviral [11], antiocular hypertension [12], cytotoxic [13], and also exhibit as antifungal [7] and enzyme inhibitors [14].

Pyrrolo[2,3-d]pyrimidines are also interesting intermediates in organic synthesis often serving as scaffolds to provide access to other highly desirable structures [15]. Toyocamycin was a pyrrolo-pyrimidine-based drug, isolated from *Streptomyces* species [5] and showed ability to inhibit RNA self-cleavage in mammalian cells [16], as well as none-peptide drug, antalarmin, which acts as a CRF-1 antagonist and reduces the release of adrenocorticotrophic hormone (ACTH) in response to chronic stress [17]. Triazoles, another important class of N-heterocycles, are employed in many pharmaceutical products. In recent years, 1,2,3-triazoles have gained special attention in the drug discovery field because of the growing use of copper-catalyzed azide-alkyne cycloaddition "click" reaction [18].

1,2,3-Triazole-based derivatives possess a wide variety of biological properties such as cytotoxic [19], antiviral [20], antibacterial [21], and anticancer [22]. Therefore, our aim was to discover novel, stable, cost-effective, and biologically active molecules for synthesis of pyrrolo[2,3-d]pyrimidine containing 1,2,3-triazole derivatives. This aspect continues to attract the attention of researchers. In recent times, the synthesis of novel molecules has received considerable importance in organic synthesis because of their biological activity under mild and convenient conditions resulting in the corresponding products that are excellent yields of high selectivity. However, the reports on the synthesis of these compounds are quite limited. So far, there has been no report available on the synthesis of pyrrolo [2,3-d]pyrimidine containing 1,2,3-triazole derivatives in the open literature. In continuation with our interest on

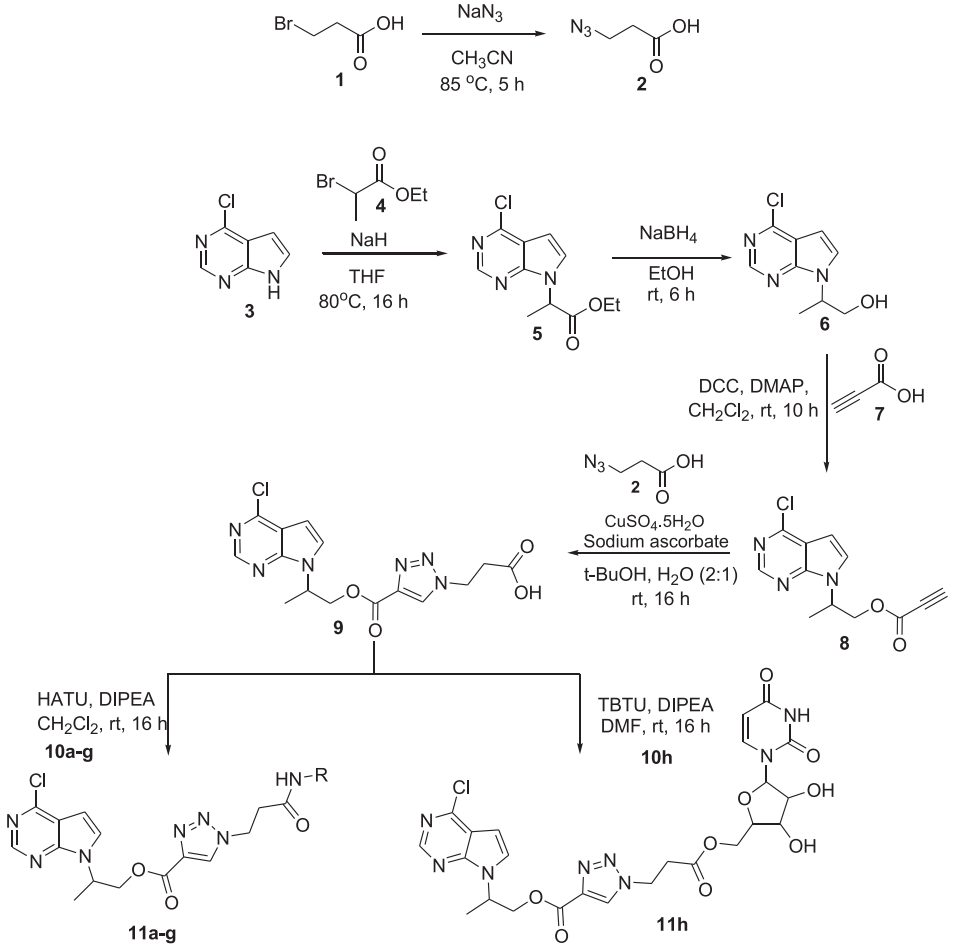
synthesis of various novel molecules, we report a simple, convenient, and efficient method for the synthesis of biologically active pyrrolo[2,3-d]pyrimidine containing 1,2,3-triazole derivatives using various reagents herein.

RESULTS AND DISCUSSION

In the present work, we have attempted to provide convenient and efficient synthetic routes using various reactions such as alkylation, reduction, coupling, and cyclization reactions ranging from 0 to 85°C. Initially, we focused on the optimization of the reaction conditions to synthesize the target compounds such as pyrrolo[2,3-d]pyrimidines containing 1,2,3-triazoles with amide-coupled derivatives **11a–h** as described in Scheme 1.

Commercially available 3-bromopropionic acid **(1)** was treated with NaN_3 in acetonitrile at 85°C for 5 h to afford **(2)** in 90% yield, and it showed IR in azide absorption band at 2105 cm^{-1}, >C=O stretching vibration at 1716 cm^{-1}. 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine **(3)** was alkylating with ethyl 2-bromopropanoate **(4)** by using sodium hydride (NaH) in tetrahydrofuran at 80°C for 16 h gave ethyl 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl) propanoate **(5)** in 85% yield. Structure **5** was confirmed by ^{1}H NMR peaks that showed δ 5.67 (q, J = 7.6 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 1.81 (d, J = 7.6 Hz, 3H), and 1.25 (t, J = 7.2 Hz, 3H). The alkylated compound **5** had undergone reduction with sodium borohydride ($NaBH_4$) in methanol at room temperature to afford **(6)** in yield 90%, and it was confirmed by IR spectral data of **6** that showed absorption bands in the region 3288 cm^{-1} for OH vibration, the strong absorption bands at 1077 cm^{-1} and 1052 cm^{-1} due to C–O stretching vibrations. Compound **6** was coupled with propiolic acid **7** by using *N*,*N*-dicyclohexylcarbodiimide and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane to give 2-(4-chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)propyl propiolate compound **8** in 92% yield. The structure of compound **8** was confirmed by IR and ^{1}H NMR spectral data, which displayed characteristic bands in the region 3388 cm^{-1} for ≡CH stretching vibration and 2107 cm^{-1} for C≡C, and the absorption band region from OH disappeared. In the ^{1}H NMR of **8**, the characteristic protons of acetylene group appeared at 2.86 (s, 1H,

Scheme 1. Synthesis of pyrrolo [2,3-d] pyrimidines containing 1,2,3-triazoles with amide-coupled derivatives **11a–g** and ester compound **11h**.



≡CH). The 1,2,3-triazole ring that was synthesized is based on a Cu(I)-catalyzed 1,3-dipolar cycloaddition as the key step between the alkyne and an appropriate azide. The synthesis of compound **9** was prepared by alkyne **8** and 3-azidopropanoic acid **2** in the presence of a catalytic amount of $CuSO_4.5H_2O$, and sodium ascorbate in *t*-BuOH and H_2O (2:1) gave selectively the desired 1,4-disubstituted 1,2,3-triazole compound **9** in yield 90% of 3-(4-((2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propoxy)carbonyl)-1H-1,2,3-triazol-1-yl)propanoic acid. In the ^{1}HNMR of compound **9**, characteristic proton of the newly formed 1,2,3-triazole resonated at 8.58 (s, 1H, triazole), and IR spectrum showed a free OH stretching frequency 3420 cm^{-1}, and C=O stretching vibration occurs at 1720 cm^{-1} and disappearance of absorption band at 2107 cm^{-1} for C≡C. In the final derivatives, (1-[Bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium3-oxid hexafluorophosphate) (HATU) was used as a suitable amide coupling for these analogs because it proved to be efficient in sterically hindered couplings. The amide coupling derivatives (**11a–g)** were prepared by using compound **9** with different amines (**10a–g**), to obtain (**11a–g)** by using HATU and *N*,*N*′-diisopropylethylamine (DIPEA) in dichloromethane at room temperature for 16 h as presented in Scheme 1, and interestingly, compound **11h** that was synthesized by **9** was coupled with selectively primary alcohol as uridine (**10h**) with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and DIPEA in *N*,*N*-dimethylformamide (DMF) at room temperature for 16 h to give (**11h)** in Scheme 1. All the final analogs (**11a–h)** that were confirmed by ^{1}H NMR showed pyrimidine rings at δ 8.59–8.57 (s, 1H), triazole rings at 8.11–8.01 (s, 1H), and pyrrole rings at 7.46–7.44 (d, J = 3.6 Hz, 1H), 6.62–6.61 (d, J = 3.6 Hz, 1H), 5.40–5.30 (m, 1H, $-CHCH_3$), 4.75–4.57 (m, 4H, O–CH_2, and N–CH_2), 2.94–2.75 (t, J = 6.0 Hz, 2H, CH_2–C=O–), 1.70–1.48 (d, J = 7.2 Hz, 3H, CH_3–CH), and IR spectrum showed absorption bands with broad intensity 3450–3287 cm^{-1} for NH stretching, 3086–3056 cm^{-1} for aromatic C–H stretching vibration, 1739–1729 cm^{-1} (C=O ester), amide at 1690–1632 cm^{-1} (C=O amide), aromatic bands in C=C, C=N at 1591–1452 cm^{-1}, C–N band at 1417–1353 cm^{-1}, and chloro band at 749–730 cm^{-1}.

Analysis of Table 1 shows that, in general, all the reactions proceeded under mild conditions, with a simple methodology, easy isolation, and acceptable yields. Based on the results listed in Table 1, seven compounds can be classified into two groups: the first group consists of **11a**, **11b**, **11c**, and **11d** that were obtained in 94%, 92%, 88%, and 82% yields, respectively, because all amines behave more like nucleophiles. The second group consists of **11e**, **11f**, and **11g** that were produced in 60%, 55%, and 36% yields, respectively. This is due to the ring strain, and the ring strain could explain the low yield formation of products. The ring strain of cyclopropane (bond angle 60°C) and cyclobutane (bond angle 90°C) was 27 and 26 kcal/mol, respectively. They are unhappiest rings, which constrained into uncomfortable angles, with hydrogens forced by geometry to grumpily line up side by side with their repulsive neighbors. Whereas cyclopentane and cyclohexane were 6 and 0 kcal/mol are much happier because these molecules have bond angles between ring atoms that are cyclopentane 108°C (very close to the ideal tetrahedral angle of 109°) and cyclohexane 120°C. The angle strain affects cyclic molecules, which destabilizes the reactivity. Based on these observations, we find that, in the production of the pyrazolo[3,4-d]pyrimidine library, it is not only important to select the more nucleophilic amines as the building blocks but also ensure that the cycloalkyl amines were kept in anhydrous conditions and stored in a refrigerator.

CONCLUSIONS

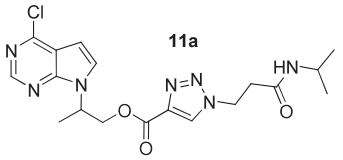
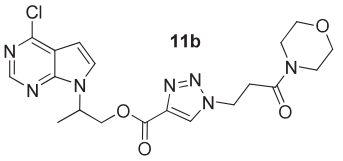
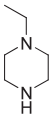
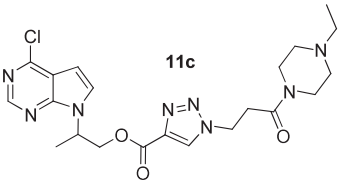
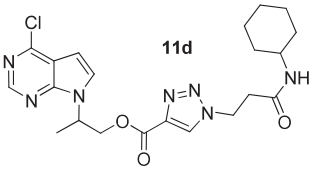
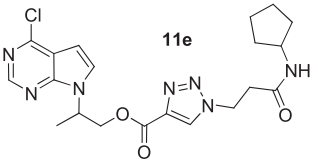
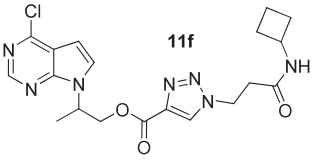
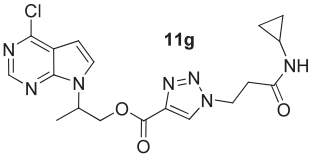
In summary, we have developed an efficient route to synthesize various novel pyrrolo[2,3-d] pyrimidine containing 1,2,3-triazole (**11a–h**) derivatives using the click chemistry concept. Here, detailed optimized conditions for the amide coupling and ester formation reactions were achieved using HATU and TBTU in dichloromethane (DCM) at room temperature for 16 h, and the yields were summarized in Table 1. The synthesis of amide coupling derivatives was prepared by using 1,4-disubstituted 1,2,3-triazole compound **9** that was coupled with various amine compounds **(10a–g)** and alcohol **(10h)** to get the final amide coupling and ester formation derivatives as target compounds by using HATU, TBTU, and DIPEA in dichloromethane and *N*,*N*-dimethylformamide at room temperature for 16 h in Scheme 1. Here, we described **11a**, **11b**, **11c**, and **11d** that obtained excellent yields, and **11e**, **11f**, and **11g** produced reasonable yields because of ring strain effects. These methods proved excellent for synthesis of these molecules making the process simple and clean, thereby creating a platform for the development of various pharmaceutical products.

EXPERIMENTAL

Originally, materials were obtained from commercial suppliers and used without further purification. Melting points were determined in open glass capillaries on a Fisher–Johns melting point apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker 400 MHz spectrometer (CA, USA) using the solvent ($CDCl_3$ 7.26 and 77.0 ppm, DMSO-d_6 2.49 and 39.7 ppm) and tetramethylsilane used as an internal standard. Chemical shifts are given in δ ppm, and coupling constant (J) is given in Hz. IR spectra were recorded on a Perkin Elmer Fourier transform infrared spectroscopy

Table 1

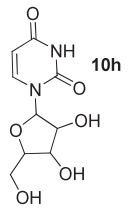
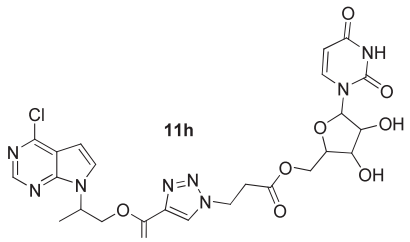
Synthesis of pyrrolo [2,3-d] pyrimidines containing 1,2,3-triazoles with amide-coupled derivatives **11a–g** and ester compound **11h**

Entry	Amines and alcohol	Product (**11a–h**)	Condition/time	% of yield
1	 **10a**	 **11a**	rt, 16 h	94%
2	 **10b**	 **11b**	rt, 16 h	92%
3	 **10c**	 **11c**	rt, 16 h	88%
4	 **10d**	 **11d**	rt, 16 h	82%
5	 **10e**	 **11e**	rt, 16 h	60%
6	 **10f**	 **11f**	rt, 16 h	55%
7	 **10g**	 **11g**	rt, 16 h	36%

(*Continued*)

Table 1

(*Continued*)

Entry	Amines and alcohol	Product (**11a–h**)	Condition/time	% of yield
8	 **10h**	 **11h**	rt, 16 h	25%

1600 spectrometer (CA, USA) for samples in KBr disks. Low-resolution mass spectrometry (MS) data were obtained using electrospray ionization (ESI), and high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, Foster City, CA) under ESI. All compounds were purified by flash chromatography using silica gel (100–200 mesh). All the reactions were monitored by thin layer chromatography on silica gel 60 F254 plates (VWR, Darmstadt, Germany), visualization by UV detection at 254 nm.

3-Azidopropanoic acid (2). 3-Bromopropionic acid **1** (1 g, 6.58 mmol) was dissolved in acetonitrile (20 mL), and NaN_3 (0.85 g, 13.16 mmol) was added at room temperature, stirring the mixture at 85°C for 5 h. The reaction mixture was concentrated under reduced pressure, to which water (20 mL) was added and acidified with 1N HCl up to pH-5 and extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated to afford as a colorless liquid 0.68 g (90%) of **2**. IR (KBr): $\upsilon_{max}/cm^{-1} = 2941$ (OH), 2105 (N_3), 1716 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 3.59 (t, $J = 6.4$ Hz, 2H), 2.64 (t, $J = 6.4$ Hz, 2H); *m/z* $(ES)^+$: 116.08 $[M+1]^+$.

Ethyl 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propanoate (5). NaH (560 mg, 23.52 mmol) was added to a solution of compound **3** (1.2 g, 7.84 mmol) in tetrahydrofuran (18 mL) at 0°C. After 30 min, ethyl 2-bromopropanoate **4** (2.28 mL, 15.68 mmol) was added at 0°C, and the resulting mixture was heated to 80°C for 16 h. The reaction mixture was cooled to 0°C and quenched with crushed ice water and extracted with EtOAc (2 × 30 mL), dried with Na_2SO_4, and then filtered and concentrated. The crude product was purified by column chromatography using a gradient of 2% MeOH in CH_2Cl_2 to obtain as a colorless liquid 1.7 g (85%) of **5**. ^1H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.43 (d, $J = 3.6$ Hz, 1H), 6.68 (d, $J = 3.2$ Hz, 1H), 5.67 (q, $J = 7.6$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 1.81 (d, $J = 7.6$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); *m/z* $(ES + APCI)^+$: 254.1 $[M+1]^+$, 256.1 $[M+3]^+$.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propan-1-ol (6). $NaBH_4$ (470 mg, 12.64 mmol) was added to a 0°C solution of compound **5** (1.6 g, 6.32 mmol) in EtOH (24 mL). The mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with crushed ice water and extracted with EtOAc (2 × 30 mL), dried with Na_2SO_4 and filtered and concentrated to obtain white solid 1.2 g (90%) of **6**. IR (KBr): $\upsilon_{max}/cm^{-1} = 3288$ (OH), 3080 (Ar CH), 2986, 2950, 2929, 2875 (CH_2, CH_3), 1588, 1543, 1505, 1459, 1429 (C=C, C=N), 1360 (C–N), 1077, 1052 (C–O), 747 (C–Cl); ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.36 (d, $J = 3.6$ Hz, 1H), 6.64 (d, $J = 3.6$ Hz, 1H), 4.92–4.90 (m, 1H), 3.99 (qd, $J = 3.2$ Hz, 11.6 Hz, 2H), 1.59 (d, $J = 7.2$ Hz, 3H); *m/z* $(ES + APCI)^+$: 212.0 $[M+1]^+$, 214.0 $[M+3]^+$.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl propiolate (8). *N,N*-dicyclohexylcarbodiimide (700 mg, 3.41 mmol) was added to a 0°C solution of compound **6** (800 mg, 3.79 mmol) and propiolic acid **7** (0.58 mL, 9.47 mmol) in 12 mL of CH_2Cl_2. After 2 min, 4-(*N,N*-dimethylamino) pyridine (46 mg, 0.37 mmol) was added, and the solution was allowed to be stirred at room temperature for 10 h. The reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the crude product was triturated with diethyl ether to obtain an off-white solid 920 mg (92%) of **8**. IR (KBr): $\upsilon_{max}/cm^{-1} = 3388$ (≡CH), 3094 (Ar CH), 2989, 2929, 2890, 2854 (CH_2, CH_3), 2107 (C≡C), 1711 (C=O), 1591, 1547, 1511, 1457, 1426 (C=C, C=N), 1362 (C–N), 1246, 1203 (C–O), 730 (C–Cl); ^1H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.33 (d, $J = 3.6$ Hz, 1H), 6.55 (d, $J = 4.0$ Hz, 1H), 5.27 − 5.25 (m, 1H), 4.51 (qd, $J = 6.8$ Hz, 11.6 Hz, 2H), 2.86 (s, 1H), 1.65 (d, $J = 6.8$ Hz, 3H); *m/z* $(ES)^+$: 263.99 $[M+1]^+$, 265.98 $[M+3]^+$.

3-(4-((2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propoxy) carbonyl)-1H-1,2,3-triazol-1-yl)propanoic acid (9). Sodium ascorbate (105 mg, 0.53 mmol) and $CuSO_4.5H_2O$ (132 mg, 0.53 mmol) were added subsequently to a solution of compound **8** (700 mg, 2.65 mmol) and 3-azido propionic

acid **2** (450 mg, 3.98 mmol) in (2:1) mixture of ter-butyl alcohol and water (21 mL) at room temperature and stirred for 16 h. From the reaction mixture, ter-butyl alcohol was concentrated, added water and the mixture were extracted with 10% MeOH and CH_2Cl_2 (2 × 40 mL). The combined organic layers was dried with Na_2SO_4 and filtered and concentrated to give as an off-white solid 900 mg (90%) of **9**. IR (KBr): $\upsilon_{max}/cm^{-1} = 3420$ (OH), 3087 (Ar CH), 2960, 2932, 2893, 2853 (CH_2, CH_3), 1720 (C=O), 1589, 1543, 1508, 1462, 1422 (C=C, C=N), 1358 (C–N), 1251, 1226, 1211 (C–O), 747 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 8.57 (d, $J = 1.6$ Hz, 2H), 7.95 (d, $J = 4.0$ Hz, 1H), 6.68 (q, $J = 3.6$ Hz, 1H), 5.32 – 5.27 (m, 1H), 4.69 – 4.61 (m, 2H), 4.56 (t, $J = 6.8$ Hz, 2H), 2.90 (t, $J = 6.4$ Hz, 2H), 1.61 (d, $J = 7.2$ Hz, 3H); *m/z* (ES + APCI)$^+$: 379.0 [M + 1]$^+$, 381.0 [M + 3]$^+$.

General procedure for the synthesis of compounds (11a–g). To a solution of compound **9** (1.0 equiv.) and their corresponding amines (**10a–g**) (1.2 equiv.), in CH_2Cl_2 was added HATU (1.5 equiv.) and DIPEA (3.0 equiv.) at room temperature. The reaction mixture is stirred for 16 h. Then the reaction mixture is poured into water and extracted with dichloromethane (20 mL). This is washed with brine solution, dried with Na_2SO_4, and filtered and concentrated. The crude products are purified by silica-gel short-column chromatography using a gradient of 2–5% MeOH in CH_2Cl_2.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl 1-(2-(isopropylcarbamoyl)ethyl)-1H-1,2,3-triazole-4-carboxylate (11a). White solid; yield 94%; mp: 140–143°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3287$ (NH), 3085 (Ar CH), 2975, 2934, 2875 (CH_2, CH_3), 1732 (C=O ester), 1634 (C=O amide), 1588, 1556, 1542, 1508, 1454 (C=C, C=N), 1383, 1360 (C–N), 1223, 1199 (C–O), 731 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.02 (s, 1H), 7.45 (d, $J = 3.6$ Hz, 1H), 6.61 (d, $J = 3.6$ Hz, 1H), 5.37–5.36 (m, 1H), 5.26 (brs, 1H), 4.69–4.59 (m, 4H), 4.04–4.00 (m, 1H), 2.75 (t, $J = 6.0$ Hz, 2H), 1.68 (d, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.70, 159.99, 152.10, 151.00, 150.47, 138.84, 128.96, 126.93, 117.72, 100.09, 66.75, 49.81, 46.46, 41.77, 36.21, 22.52, 16.93; high-resolution mass spectrometry (HRMS) (ESI): calcd for $C_{18}H_{22}ClN_7O_3Na$ [M + Na]$^+$: 442.1365, found: 442.1375.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl 1-(3-morpholino-3-oxopropyl)-1H-1,2,3-triazole-4-carboxylate (11b). Colorless semi-solid; yield 92%; mp: 134–137°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3068$ (Ar CH), 2985, 2926, 2817 (CH_2, CH_3), 1739 (C=O ester), 1632 (C=O amide), 1587, 1532, 1512, 1466 (C=C, C=N), 1389, 1358 (C–N), 1258, 1216 (C–O), 743 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.09 (s, 1H), 7.45 (d, $J = 3.6$ Hz, 1H), 6.62 (d, $J = 3.2$ Hz, 1H), 5.39–5.36 (m, 1H), 4.74–4.61 (m, 4H), 3.65–3.58 (m, 6H), 3.39 (t, $J = 4.8$ Hz, 2H); 2.94 (t, $J = 5.6$ Hz, 2H), 1.69 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.52, 160.04, 152.02, 151.04, 150.42, 138.83, 129.39, 126.95, 117.70, 100.10, 66.79, 66.64, 66.30, 49.78, 46.05, 45.55, 42.06, 33.02, 16.90; *m/z* (MM–ES + APCI)$^+$: 448.0 [M + 1]$^+$, 450.0 [M + 3]$^+$.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl-1-(3-(4-ethylpiperazin-1-yl)-3-oxopropyl)-1H-1,2,3-triazole-4-carboxy late (11c). Off-white solid; yield 88%; mp: 132–135°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3078$ (Ar CH), 2975, 2916, 2820 (CH_2, CH_3), 1732 (C=O ester), 1636 (C=O amide), 1589, 1542, 1506, 1454 (C=C, C=N), 1399, 1356 (C–N), 1238, 1203 (C–O), 749 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.11 (s, 1H), 7.46 (d, $J = 2.4$ Hz, 1H), 6.62 (d, $J = 2.4$ Hz, 1H), 5.38 – 5.36 (m, 1H), 4.72 – 4.58 (m, 4H), 3.60 (brs, 2H), 3.41 (brs, 2H), 2.94 (brs, 2H), 2.49 – 2.39 (m, 6H), 1.69 (d, $J = 6.4$ Hz, 3H), 1.08 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.18, 160.07, 152.08, 151.06, 150.48, 138.83, 129.39, 126.93, 117.71, 100.07, 66.78, 52.43, 52.15, 52.05, 49.77, 46.15, 44.87, 41.47, 33.11, 16.91, 11.58; HRMS (ESI): calcd for $C_{21}H_{28}ClN_8O_3$ [M + H]$^+$: 475.1967, found: 475.1972.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl 1-(2-(cyclohexylcarbamoyl)ethyl)-1H-1,2,3-triazole-4-carboxylate (11d). Off-white solid; yield 82%; mp: 138–140°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3310$ (NH), 3084 (Ar CH), 2929, 2854 (CH_2, CH_3), 1730 (C=O ester), 1637 (C=O amide), 1587, 1545, 1542, 1508, 1452 (C=C, C=N), 1383, 1357 (C–N), 1232, 1220, 1206 (C–O), 731 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.03 (s, 1H), 7.45 (d, $J = 4.8$ Hz, 1H), 6.62 (d, $J = 5.2$ Hz, 1H), 5.37–5.30 (m, 2H), 4.72–4.57 (m, 4H), 3.71–3.68 (m, 1H), 2.76 (t, $J = 7.6$ Hz, 2H), 1.80 (d, $J = 16.4$ Hz, 2H), 1.70–1.63 (m, 6H), 1.34–1.26 (m, 2H), 1.14–1.02 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.62, 160.0, 152.10, 151.0, 150.45, 138.86, 128.98, 126.96, 117.72, 100.09, 66.76, 49.78, 48.60, 46.49, 36.22, 32.89, 25.34, 24.74, 16.92; HRMS (ESI): calcd for $C_{21}H_{26}ClN_7O_3Na$ [M + Na]$^+$: 482.1677, found: 482.1673.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl 1-(2-(cyclopentylcarbamoyl)ethyl)-1H-1,2,3-triazole-4-carboxylate (11e). Colorless semi-solid; yield 60%; mp: 120–123°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3309$ (NH), 3086 (Ar CH), 2958, 2870 (CH_2, CH_3), 1730 (C=O ester), 1635 (C=O amide), 1589, 1546, 1508, 1454 (C=C, C=N), 1385, 1358 (C–N), 1234, 1224, 1206 (C–O), 730 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.01 (s, 1H), 7.44 (d, $J = 4.0$ Hz, 1H), 6.61 (d, $J = 4.0$ Hz, 1H), 5.40–5.33 (m, 2H), 4.70–4.58 (m, 4H), 4.14–4.08 (m, 1H), 2.74 (t, $J = 5.6$ Hz, 2H), 1.90 (brs, 2H), 1.68 (d, $J = 7.2$ Hz, 3H), 1.60–1.57 (m, 4H), 1.27–1.24 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.22, 159.98, 151.95, 151.03, 150.31, 138.85, 128.94, 127.10, 117.74, 100.15, 66.76, 51.45, 49.89, 46.51, 38.63, 36.14, 32.89, 23.60, 16.88; HRMS (ESI): calcd for $C_{20}H_{24}ClN_7O_3$ [M + H]$^+$: 446.1677, found: 446.1680.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl 1-(2-(cyclobutylcarbamoyl)ethyl)-1H-1,2,3-triazole-4-carboxylate (11f). Colorless semi-solid; yield 55%; mp: 126–129°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3400$ (NH), 3078 (Ar CH), 2981, 2946, 2866 (CH_2, CH_3), 1731 (C=O ester),1658 (C=O amide), 1586, 1549, 1542, 1454 (C=C, C=N), 1384, 1353 (C–N), 1215, 1114 (C–O), 741 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.01 (s, 1H), 7.45 (d, $J = 3.6$ Hz, 1H), 6.62 (d, $J = 3.6$ Hz, 1H), 5.58 (d, $J = 6.8$ Hz, 1H), 5.39–5.34 (m, 1H), 4.70–4.58 (m, 4H), 4.34–4.28 (m, 1H), 2.75 (t, $J = 5.6$ Hz, 2H), 2.30–2.25 (m, 2H), 1.79–1.76 (m, 2H), 1.70 (d, $J = 3.6$ Hz, 5H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.82, 160.01, 151.98, 151.02, 150.33, 138.77, 128.92, 127.05, 117.73, 100.12, 66.78, 49.89, 46.45, 44.81, 35.89, 30.81, 16.84, 15.07; *m/z* (ES)$^+$: 432.14 $[M+1]^+$, 434.13 $[M+3]^+$.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl 1-(2-(cyclopropylcarbamoyl)ethyl)-1H-1,2,3-triazole-4-carboxylate (11g). Colorless semi-solid; yield 36%; mp: 130–1320°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3408$ (NH), 3084 (Ar CH), 2948, 2922, 2865 (CH_2, CH_3), 1729 (C=O ester), 1660 (C=O amide), 1590, 1556, 1538, 1455 (C=C, C=N), 1386, 1364 (C–N), 1216, 1112 (C–O), 749 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.04 (s, 1H), 7.45 (d, $J = 4.8$ Hz, 1H), 6.62 (d, $J = 4.8$ Hz, 1H), 5.62 (brs, 1H), 5.40–5.34 (m, 1H), 4.75–4.58 (m, 4H), 2.75 (t, $J = 7.6$ Hz, 2H), 2.65–2.61 (m, 1H), 1.69 (d, $J = 9.6$ Hz, 3H), 0.75 (q, $J = 8.4$ Hz, 2H), 0.42 (q, $J = 8.4$ Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.17, 159.96, 151.83, 151.05, 150.22, 138.84, 128.97, 127.15, 117.74, 100.23, 66.73, 49.94, 46.34, 35.75, 22.70, 16.88, 6.44, 6.43; *m/z* (ES)$^+$: 418.19 $[M+1]^+$, 420.21 $[M+3]^+$.

2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propyl-1-(3-((5-(2,4-dioxo-3,4-dihydro pyrimidin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)-3-oxopropyl)-1H-1,2,3-triazole-4-carboxylate (11h). To a solution of compound 9 (180 mg, 0.47 mmol) in DMF (5 ml), add uridine (110 mg, 0.47 mmol), TBTU (183 mg, 0.57 mmol), and DIPEA (0.24 mL, 1.42 mmol) at room temperature. The reaction mixture was stirred for 16 h. Then the reaction mixture was poured into water and extracted with 10% MeOH in dichloromethane (2 × 10 mL), dried with Na_2SO_4, and filtered and concentrated. The crude product was purified by preparative thin layer chromatography running a gradient of 5% MeOH in CH_2Cl_2 to afford 72 mg (25%) as an off-white solid **11h**. mp: 150–152°C; IR (KBr): $\upsilon_{max}/cm^{-1} = 3450$, 3399, 3298 (NH, OH), 3056 (Ar CH), 2947, 2932, 2834 (CH_2, CH_3), 1758, 1736 (C=O ester), 1690 (C=O amide), 1591, 1558, 1552, 1463 (C=C, C=N), 1417, 1359 (C–N), 1216, 1109, 1052,1031, 1031 (C–O), 749 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.79 (brs, 1H), 8.61–8.52 (m, 1H), 7.84–7.78 (m, 2H), 7.26 (d, $J = 3.2$ Hz, 1H), 6.43 (d, $J = 3.2$ Hz, 1H), 5.77–5.58 (m, 3H), 5.08–5.03 (m, 2H), 4.63–4.51 (m, 4H), 4.02–3.84 (m, 3H), 3.08–3.00 (m, 2H), 2.88 (t, $J = 6.8$ Hz, 2H), 1.48 (d, $J = 7.2$ Hz, 3H); HRMS (ESI): calcd for $C_{24}H_{25}ClN_8O_9Na$ $[M+Na]^+$: 627.1350, found: 627.1345.

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