Cu-Mediated Selective *N*-Arylation of Aminotriazole Acyclonucleosides

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Novel *N*-aryltriazole nucleosides were synthesized *via* a Cu-mediated C–N cross-coupling reaction, using 3-aminotriazole acyclonucleosides and various boronic acid reagents. Interestingly, *N*-arylation proceeded much more rapidly on the amide group than on the amine group, leading to selective *N*-arylation of the amide functionality on nucleosides containing both groups on the triazole nucleobase.

Introduction. – Nucleoside analogs are of considerable importance in the search of promising candidates endowed with potent antiviral, anticancer, and antibacterial activities [1]. We have been actively engaged in a program to develop structurally novel and diverse triazole nucleosides [2–8]. These nucleosides contain triazole, an unnatural heterocycle, as nucleobase. Because of its broad H-bonding scope and its unique geometrical size between pyrimidine and purine, triazole is considered as a universal base [9] for base pairing in nucleoside chemistry. One important triazole nucleoside is ribavirin (*Fig. 1*), representing the first synthetic nucleoside drug to have antiviral activity against many DNA and RNA viruses [10], and remaining the only small-molecular-weight drug available to date for treating viral infections caused by hepatitis C virus (HCV) [11]. Recently, we have synthesized a series of triazole nucleosides substituted with aromatic moieties on the triazole ring, such as aryltriazolyl [3][4], bitriazolyl [5][6], and arylethynyltriazolyl nucleosides [7][8], with the rationale that these nucleosides may combine the intrinsic properties of the triazole ring with the enlarged aromatic systems to form special nucleobases, leading to advantageous binding properties with the corresponding biological targets *via* base pairing and/or base stacking. Indeed, some of these nucleosides have displayed potent and promising antiviral [5–8] and anticancer activity [8]. In our continuing efforts to further develop novel triazole nucleoside analogs, we are interested in synthesizing *N*-aryltriazole acyclonucleosides of types **A** and **B** (*Fig. 1*). The aryl group is introduced at the amine functionality on nucleosides of type **A** and at the amide moiety on those of type **B**.

The main challenge faced when synthesizing *N*-aryltriazole nucleosides **A** and **B** is the formation of a C–N bond between the aryl moieties and the N-atom on the amine functionality. C–N Bond construction has been a research subject of considerable

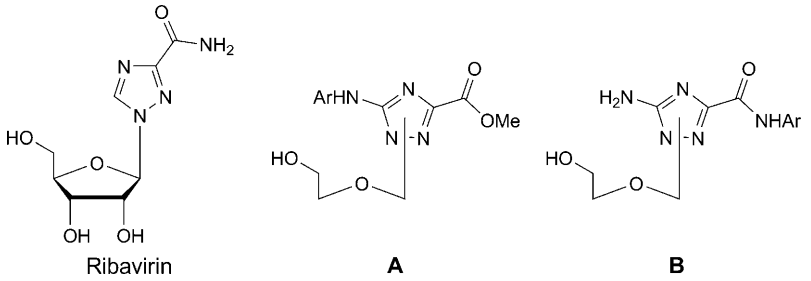

Fig. 1. *Structure of ribavirin and proposed* N*-arylated triazole acyclonucleosides* **A** *and* **B**

interest relating to bioactive nucleoside derivatives [12], and numerous methods exist for C–N cross-coupling [13]. The direct nucleophilic aromatic substitution of amine with aryl halides is one of the most commonly used methods for constructing a C–N bond. However, this approach requires special aryl halides and may result in several *N*-arylation products in an uncontrollable way, thereby severely limiting its scope. The traditional *Ullman*-type coupling is performed at high temperatures in the presence of strong bases, and gives varying yields. Although various methods using arylleads [14], arylstannanes [15], arylsiloxanes [16], *etc.* have been reported for *N*-arylation, the toxicity and/or the availability of the reagents makes these methods less attractive. The recently developed Pd-catalyzed C–N cross-coupling by *Buchwald*, *Hartwig*, and others has provided considerable improvements: the reaction can be carried out conveniently at reasonably elevated temperatures and is efficient enough to give various products [17]. Furthermore, Cu-mediated *N*-arylation, discovered by *Chan* and *Lam* [18], employs various arylboronic acids and is performed at room temperature under very mild conditions, constituting an important progress for *N*-arylation. Based on the mild reaction conditions and the simple reaction protocols, as well as the ready availability of starting materials in our laboratories, we decided to choose the Pd-catalyzed and Cu-mediated C–N cross-coupling reactions to synthesize *N*-aryltriazole nucleoside analogs **A** and **B**.

Results and Discussion. – To perform Pd-catalyzed and Cu-mediated *N*-arylation for the synthesis of the nucleoside analogs **A** and **B**, we used the bromotriazole nucleosides **1** and **1′**, and the aminotriazole nucleosides **2**, **2′**, **3**, and **3′** as starting materials (*Fig. 2*). Both 3- and 5-bromotriazole nucleosides **1** and **1′** were prepared according to our previously reported protocol [4]. 3- and 5-aminotriazole nucleosides **2** and **2′** were obtained with almost quantitative yields *via* catalytic hydrogenation of the corresponding 3- and 5-azidotriazole nucleosides [6]. Subsequent ammonolysis of **2** and **2′** in NH_3/MeOH led to the deprotection of the 'sugar moiety' and transformation of the exocyclic Me ester into the amide functionality, giving 3- and 5-aminotriazole nucleosides **3** and **3′**, respectively.

We first attempted to perform Pd-catalyzed *N*-arylation of bromotriazole nucleosides **1** and **1′** with aniline. We have tried different conditions using various catalysts ($Pd(OAc)_2$, $Pd(OAc)_2$/DPDBP, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, *etc.*), bases (K_2CO_3, Li_2CO_3, ^{t}BuONa, *etc.*), solvents (MeCN, MeCN/H_2O, DME, toluene, *etc.*), reaction temper-

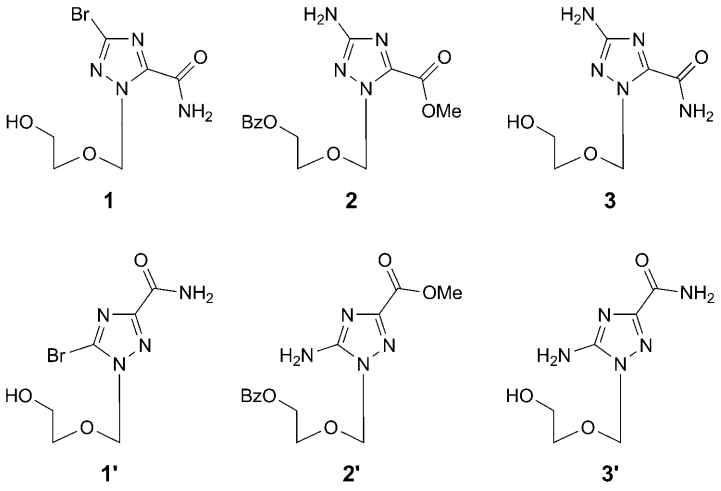

Fig. 2. *Triazole acyclonucleosides as starting materials for C–N coupling reactions.*

atures and times, as well as with or without microwave irradiation *etc.* (data not shown). Neither the 3- nor the 5-bromotriazole nucleoside yielded the expected *N*-arylation products, whereas the starting materials could be recovered with yields up to 80%. In some cases, a cyclization product[1]) was obtained when starting from **1′** due to the intramolecular nucleophilic substitution of the Br-atom at the triazole moiety by the free OH group in the 'sugar moiety' of **1′**. The same cyclization reaction was previously observed by us when **1′** was subjected to *Suzuki* [4] and *Sonogashira* [7] reactions. The particularly favorable electronic and geometric properties of **1′** explain its readiness for intramolecular cyclization *via* nucleophilic substitution [4].

We further tried to perform Pd-catalyzed C–N coupling between aminotriazole nucleosides (**2**, **2′**, **3**, and **3′**) and bromobenzene using similar conditions as mentioned above. No *N*-arylation product could be identified, and only starting materials were recovered (data not shown). We, therefore, concluded that neither bromotriazole nucleosides **1** and **1′** nor aminotriazole nucleosides **2**, **2′**, **3**, and **3′** are reactive enough to undergo Pd-catalyzed C–N coupling under those experimental conditions. It is worthy to note that, due to poor availability and the high price, we did not try the various types of new generation ligands reported for Pd-catalyzed C–N coupling [17].

We then focused our attention to performing *Chan–Lam* modified Cu-mediated *N*-arylation with arylboronic acid using aminotriazole nucleosides (**2**, **2′**, **3**, and **3′**) (*Scheme*). Reaction between **2** and phenylboronic acid ($PhB(OH)_2$) gave the corresponding *N*-arylation product **4a** with a good yield of 70% (*Scheme*, path *a*, *Table 1*). Surprisingly, reaction with 5-aminotriazole nucleoside **2′**, an isomer of **2**, did

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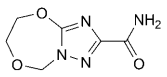
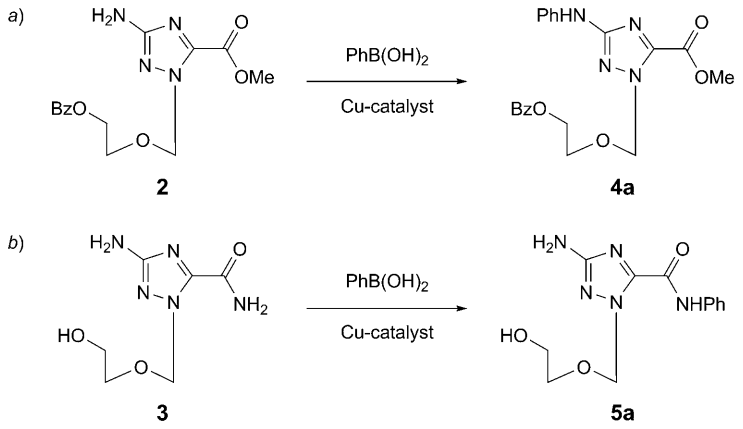
[1]) The cycling product has been previously identified by NMR, MS, and X-ray analysis as follows [4]:



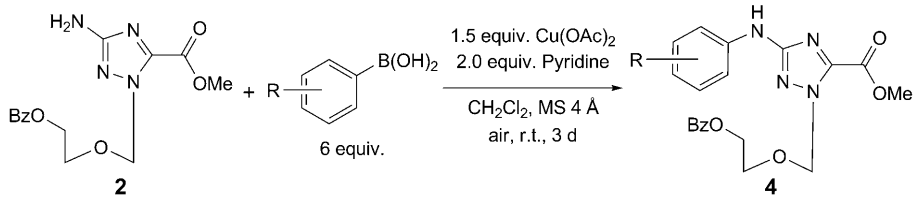
Scheme. N-*Arylation on Aminotriazole Acyclonucleosides* via *Cu-Mediated C–N Cross-Coupling*



not yield the corresponding *N*-arylation product, and more than 80% of the starting material **2′** was recovered after three days of reaction (data not shown). Neither did *N*-arylation with the deprotected 5-aminotriazole nucleoside **3′** deliver any desired product (data not shown), and the starting material **3′** was recovered almost quantitatively. To our delight, the reaction of 3-aminotriazole nucleoside **3** with various arylboronic acids resulted in the C–N coupling products, with *N*-arylation occurring, however, selectively on the amide instead of the amine functionality (*Scheme*, path *b*, *Table 2*). The different reactivity noticed for *N*-arylation of 3- and 5-aminotriazole nucleosides may mainly result from the unfavorable steric congestion created between the amino group at the 5-position and the adjacent acyclic 'sugar moiety' in **2′** and **3′**, since steric hindrance is an important factor affecting *N*-arylation. Another factor may be the different electronic properties of 3- and 5-aminotriazole nucleosides, as we have already reported previously for 3- and 5-bromotriazole ribonucleosides [2], and for 3- and 5-azidotriazole nucleosides [5a][6]. Finally, it is not totally surprising that *N*-arylation was occurred selectively at the amide functionality instead of the amino group in **3** (*Scheme*, path *b*, *Table 2*), because similar cases are also reported in the literature [19]. This may be mainly due to the different reactivity of the amide and the amine functionalities in **3**, since the amino group in **3** is directly conjugated with the triazole ring, and consequently, is less reactive to Cu-mediated C–N coupling under our experimental conditions. Additionally, *N*-arylation at the amide functionality is less sterically hindered than at the amino group in **3**.

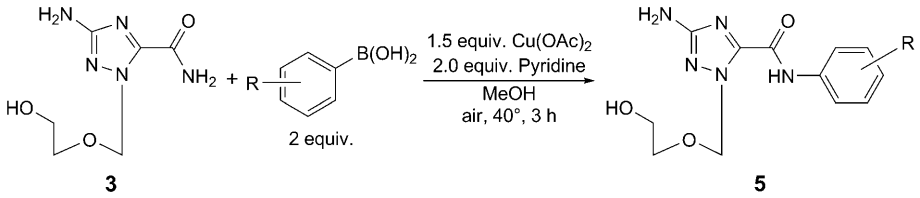
We tried to optimize the *N*-arylation reaction between the aminotriazole nucleoside **2** and $PhB(OH)_2$ by varying the catalysts ($Cu(OAc)_2$, $Cu(OAc)_2 \cdot H_2O$, $CuBr_2$, CuI, CuCl, $Cu(PPh_3)_3Br$, *etc.*), bases (Et_3N, $EtN(i\text{-}Pr)_2$, pyridine, NaH, pyridine/Et_3N, *etc.*), solvents (CH_2Cl_2, DMF, toluene, MeOH/ H_2O, *etc.*), reaction temperature and duration, *etc.* (data not shown). The best results were obtained with $Cu(OAc)_2$ and pyridine in the presence of freshly prepared molecular sieves, in CH_2Cl_2 at room temperature and open air for three days (*Table 1*). Importantly, using excess equivalents of arylboronic acid reagent is necessary to obtain acceptable yields. It is

Table 1. *Cu-Mediated* N-*Arylation of* **2**



Entry	R	Product	Yield [%]
1	H	**4a**	70
2	*p*-Me	**4b**	31
3	*p*-MeO	**4c**	24
4	*m*-MeO	**4d**	35
5	*o*-MeO	**4e**	0
6	*p*-F	**4f**	46
7	*m*-F	**4g**	64
8	*o*-F	**4h**	0
9	*p*-Cl	**4i**	35
10	*m*-Cl	**4j**	77
11	*o*-Cl	**4k**	0

Table 2. *Cu-Mediated* N-*Arylation of* **3**



Entry	R	Product	Yield [%]
1	H	**5a**	75
2	*p*-Me	**5b**	60
3	*p*-MeO	**5c**	51
4	*m*-MeO	**5d**	40
5	*o*-MeO	**5e**	21
6	*p*-F	**5f**	36
7	*m*-F	**5g**	57
8	*o*-F	**5h**	47
9	*p*-Cl	**5i**	48
10	*m*-Cl	**5j**	32
11	*o*-Cl	**5k**	41

noteworthy that the Cu-mediated *N*-arylation reaction of **2** was significantly affected by the electronic properties and the steric hindrance of the substituents in the arylboronic reagents (*Table 1*). The presence of electron-donating groups at the phenyl ring was not favorable for *N*-arylation, yielding the corresponding products with low

yields (*Table 1*, *Entries 2–4*). It seems that electron-withdrawing groups at the *meta*-position of the phenyl ring promoted the reaction, giving the corresponding products with up to 2-fold yields compared to those at the *para*-position. However, any substituent at the *ortho*-position of the phenyl ring, regardless of electron-donating or electron-withdrawing (*Table 1*, *Entries 5*, *8*, and *11*), prevented product formation. This is mainly due to the strong steric hindrance created by the substituent at the *ortho*-position, which strongly impedes the C−N coupling reaction.

We have further carried out an optimization process on the *N*-arylation reaction with **3**. Under optimized conditions, $Cu(OAc)_2$ was used as the catalyst, pyridine as the base, and MeOH as the solvent under open air at 40°. Most importantly, the quantity of boronic acid required could be reduced considerably to two equivalents, and the reaction time shortened significantly to three hours, compared to the *N*-arylation of **2**, which required six equivalents of boronic acid reagent, and three days of reaction time. In contrast to *N*-arylation with **2**, *N*-arylation of **3** showed no considerable correlation between reactivity and electronic properties of the substituents on the phenyl ring of the boronic acid reagents (*Table 2*, *Entries 2*, *3*, *6*, and *9*). Furthermore, no noticeable steric effect was observed, since similar yields were obtained regardless of whether the substituents were in *ortho*-, *meta*- or *para*-position (*Table 2*, *Entries 3–5*, *6–8*, and *9–11*). This may be attributed to the presence of the CO group of the amide function in **3**, which can ease the steric congestion and facilitate C−N coupling.

We next assessed the above synthesized *N*-aryltriazole acyclonucleosides for their antiviral activity against hepatitis C virus and their anticancer activity against human cancer cell lines such as prostate cancer PC-3 cells, pancreatic cancer MiaPaCa-2, and Capan-2 cells. The anti-HCV assay was performed using a HCV subgenomic RNA replicon assay in Huh-5-2 cells [20], and the anticancer evaluation was carried out using a MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay to determine the inhibition effect on cell proliferation. Unfortunately, none of the synthesized compounds elicited any notable antiviral activity or anticancer activity.

Conclusions. – We have attempted both Pd-catalyzed and Cu-mediated C−N cross-coupling reactions to synthesize *N*-arylated triazole nucleoside analogs. No *N*-arylation product could be obtained *via* Pd-catalyzed C−N coupling starting with either bromotriazole nucleosides (**1** and **1′**) or aminotriazole nucleosides (**2**, **2′**, **3**, and **3′**) under our experimental conditions. This may be due to the limited reactivity of these triazole nucleosides when subjected to the Pd-catalyzed reaction conditions used in the present study. Gratifyingly, we succeeded in achieving *N*-arylation *via* Cu-mediated C−N cross-coupling using 3-aminotriazole nucleosides (**2** and **3**) as starting materials. However, 5-aminotriazole nucleosides (**2′** and **3′**), the isomers of 3-aminotriazole nucleosides (**2** and **3**), could not deliver the corresponding *N*-arylation products under similar conditions. This is mainly due to the unfavorable steric congestion and/or electronic properties of 5-aminotriazole nucleosides. Even between the 3-aminotriazole nucleosides **2** and **3**, very different reactivity was observed: *N*-arylation at the amide functionality in **3** proceeded much faster than arylation at the amine group in **2**, and required a much reduced quantity of boronic acid reagent. This may be the direct consequence of the different reactivity of amide and amine functionalities. Accordingly, selective *N*-arylation at the amide group in **3** was achieved easily. Although none

of the *N*-arylated triazole nucleosides disclosed here elicited any significant antiviral and anticancer activity, the syntheses presented in this study may offer alternative methods to prepare structurally diverse triazole nucleoside analogs, for which we are actively working.

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Experimental Part

General. Flash chromatography (FC): silica gel (SiO_2; 200–300 mesh) from *Qingdao Ocean Chemicals*, P. R. China. ^{1}H- and ^{13}C-NMR spectra: at 300 MHz for ^{1}H, and at 75 MHz or 150 MHz for ^{13}C; *Varian Mercury-VX300* and *Varian Inova-600* spectrometers; δ in ppm; J in Hz; chemical shifts recorded in parts per million [ppm], with TMS as internal reference. ESI-MS: *Finnigan LCQ Advantage* mass spectrometer; in *m*/*z*. MALDI-MS and HR-MS: by Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) using an *IonSpec 4.7 Tesla* fourier transform mass spectrometer; in *m*/*z*.

*Methyl 3-Amino-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H*-1,2,4-triazole-5-carboxylate* (**2**). To a soln. of 1.00 g of methyl 3-azido-1-({2-[phenylcarbonyl)oxy]ethoxy}methyl)-1*H*-1,2,4-triazole-5-carboxylate (2.9 mmol) in 50 ml MeOH, 0.10 g Pd/C catalyst (5 wt-% of Pd, 25.6 μmol) was added. The reaction was then carried out with H_2 at a pressure of 1.01 MPa. After the complete consumption of the starting material (detected with TLC), the mixture was filtered over *Celite*, the filtrate was concentrated under reduced pressure, and the residue was purified through a SiO_2 column with CH_2Cl_2/MeOH (30:1), giving 0.86 g of **2** as white powder in the yield of 93%. White solid. R_f (CH_2Cl_2/MeOH, 30:1) 0.47. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.03 (*d*, J = 7.5, 2 arom. H); 7.57 (*t*, J = 7.4, 1 arom. H); 7.44 (*t*, J = 7.8, 2 arom. H); 5.83 (*s*, 2 CH_2); 4.48–4.43 (*m*, CH_2); 4.26 (br. *s*, NH_2); 3.97–3.92 (*m*, CH_2, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.6; 158.8; 129.6; 126.2; 124.8; 74.7; 64.3; 59.9; 49.6. MALDI-MS: 321.1 ($[M+H]^+$), 343.1 ($[M+Na]^+$). HR-MS: 321.1198 ($[M+H]^+$, $C_{14}H_{17}N_4O_5^+$; calc. 321.1199).

*Methyl 5-Amino-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H*-1,2,4-triazole-3-carboxylate* (**2′**). Similar to **2**, **2′** was obtained as white powder (0.88 g, 95%) starting with 1.00 g methyl 5-azido-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H*-1,2,4-triazole-3-carboxylate (2.9 mmol). White solid. R_f (CH_2Cl_2/MeOH, 30:1) 0.23. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (*d*, J = 7.2, 2 arom. H); 7.57 (*t*, J = 7.4, 1 arom. H); 7.44 (*t*, J = 7.7, 2 arom. H); 5.48 (*s*, CH_2); 5.34 (br. *s*, NH_2); 4.49–4.46 (*m*, CH_2); 3.95 (*s*, MeO); 3.92–3.89 (*m*, CH_2). ^{13}C-NMR (150 MHz, $CDCl_3$): 166.6; 160.6; 156.2; 151.4; 133.5; 129.8; 128.7; 77.7; 67.6; 63.2; 52.9. MALDI-MS: 321.1 ($[M+H]^+$), 343.1 ($[M+Na]^+$). HR-MS: 321.1196 ($[M+H]^+$, $C_{14}H_{17}N_4O_5^+$; calc. 321.1199).

*3-Amino-1-[(2-hydroxyethoxy)methyl]-1*H*-1,2,4-triazole-5-carboxamide* (**3**). A soln. of 1.00 g of **2** (3.1 mmol) in 25 ml of NH_3/MeOH soln. (10 wt-%) was stirred at r.t. After complete consumption of starting material (detected with TLC), the soln. was concentrated under reduced pressure, and the residue was purified on a SiO_2 column with CH_2Cl_2/MeOH (10:1), giving 0.53 g of product **3** as white powder in the yield of 85%. White solid. R_f (CH_2Cl_2/MeOH, 10:1) 0.15. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.85 (br. *s*, C(O)NH_2); 5.67 (*s*, CH_2); 5.55 (*s*, NH_2); 4.64 (*t*, J = 5.6, OH); 3.53–3.50 (*m*, CH_2); 3.47–3.42 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 159.5; 146.3; 77.9; 71.6; 60.5. MALDI-MS: 224.1 ($[M+Na]^+$). HR-MS: 224.0756 ($[M+Na]^+$, $C_6H_{11}N_5NaO_3^+$; calc. 224.0760).

*5-Amino-1-[(2-hydroxyethoxy)methyl]-1*H*-1,2,4-triazole-3-carboxamide* (**3′**). Similar to **3**, **3′** was obtained as a white powder (0.56 g, 89%) starting with 1.00 g of **2′** (3.1 mmol). White solid. R_f (CH_2Cl_2/MeOH, 10:1) 0.05. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.40 (br. *s*, C(O)NH_2); 6.62 (br. *s*, NH_2); 5.33 (*s*, CH_2); 4.72 (*t*, J = 4.8, OH); 3.57–3.46 (*m*, 2 CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 161.9; 157.0; 154.4;

75.9; 71.0; 60.6. MALDI-MS: 202.1 ($[M+H]^+$), 224.1 ($[M+Na]^+$). HR-MS: 202.0937 ($[M+H]^+$, $C_6H_{12}N_5O_3^+$; calc. 202.0940).

General Procedure for the Preparation of **4** via *Cu-Mediated* N-*Arylation with Arylboronic Acid*. To a mixture of 32.0 mg **2** (0.10 mmol), 6 equiv. arylboronic acid (0.60 mmol), and 27.2 mg anh. $Cu(OAc)_2$ (0.15 mmol) was added 5 ml CH_2Cl_2 (dist. freshly over CaH_2). Then, 16.1 µl freshly distilled pyridine (0.20 mmol) and *ca.* 20 mg powder of 4 Å molecular sieve (activated at 500° for 5 h) were added rapidly. The mixture was stirred at r.t. for 3 d, and then filtered over *Celite*. The filtrate was concentrated under reduced pressure, and the obtained residue was purified on SiO_2 with petroleum ether (PE)/AcOEt (2:1), giving the corresponding product **4** as powder.

*Methyl 3-(Phenylamino)-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H-*1,2,4-triazole-5-carboxylate* (**4a**). White solid (70%). R_f (PE/AcOEt, 1:1) 0.54. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (*d*, *J* = 7.2, 2 arom. H); 7.54 (*t*, *J* = 7.7, 1 arom. H); 7.46–7.26 (*m*, 6 arom. H); 6.97 (*t*, *J* = 7.4, 1 arom. H); 6.75 (br. *s*, NH); 5.93 (*s*, CH_2); 4.48 (*t*, *J* = 4.7, CH_2); 4.03 (*t*, *J* = 4.8, CH_2); 3.97 (*s*, MeO). ^{13}C-NMR (150 MHz, $CDCl_3$): 166.7; 159.5; 158.0; 142.9; 140.2; 133.3; 130.0; 129.9; 129.4; 128.6; 121.5; 116.7; 78.8; 68.3; 63.7; 53.5. ESI-MS: 397 ($[M+H]^+$). HR-MS: 397.1514 ($[M+H]^+$, $C_{20}H_{21}N_4O_5^+$; calc. 397.1512).

*Methyl 3-[(4-Methylphenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H-*1,2,4-triazole-5-carboxylate* (**4b**). White solid (31%). R_f (PE/AcOEt, 1:1) 0.56. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02 (*d*, *J* = 7.2, 2 arom. H); 7.55 (*t*, *J* = 7.2, 1 arom. H); 7.43–7.33 (*m*, 4 arom. H); 7.11 (*d*, *J* = 8.7, 2 arom. H); 6.76 (br. *s*, NH); 5.92 (*s*, CH_2); 4.48 (*t*, *J* = 4.4, CH_2); 4.03 (*t*, *J* = 4.7, CH_2); 3.98 (*s*, MeO); 2.31 (*s*, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.7; 159.9; 158.0; 142.9; 137.8; 133.3; 130.9; 130.1; 129.9; 129.8; 128.6; 117.0; 78.8; 68.2; 63.8; 53.4; 20.9. ESI-MS: 411.2 ($[M+H]^+$), 433.1 ($[M+Na]^+$). HR-MS: 411.1660 ($[M+H]^+$, $C_{21}H_{23}N_4O_5^+$; calc. 411.1668).

*Methyl 3-[(4-Methoxyphenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H-*1,2,4-triazole-5-carboxylate* (**4c**). White solid (24%). R_f (PE/AcOEt, 1:1) 0.38. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02 (*d*, *J* = 8.1, 2 arom. H); 7.55 (*t*, *J* = 7.4, 1 arom. H); 7.43–7.35 (*m*, 4 arom. H); 6.87 (*d*, *J* = 9.0, 2 arom. H); 6.52 (br. *s*, NH); 5.91 (*s*, CH_2); 4.48 (*t*, *J* = 4.8, CH_2); 4.02 (*t*, *J* = 4.8, CH_2); 3.97 (*s*, MeO); 3.79 (*s*, MeO). ^{13}C-NMR (150 MHz, $CDCl_3$): 166.6; 160.0; 158.0; 154.7; 142.9; 133.7; 133.3; 130.1; 129.9; 128.6; 118.5; 114.7; 78.7; 68.2; 63.7; 55.8; 53.5. ESI-MS: 427.2 ($[M+H]^+$), 449.1 ($[M+Na]^+$). HR-MS: 427.1611 ($[M+H]^+$, $C_{21}H_{23}N_4O_6^+$; calc. 427.1618).

*Methyl 3-[(3-Methoxyphenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H-*1,2,4-triazole-5-carboxylate* (**4d**). White solid (35%). R_f (PE/AcOEt, 1:1) 0.48. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02 (*d*, *J* = 7.2, arom. H); 7.55 (*t*, *J* = 7.4, 1 arom. H); 7.41 (*t*, *J* = 7.7, 2 arom. H); 7.27–7.16 (*m*, 2 arom. H); 6.97 (*d*, *J* = 6.6, 1 arom. H); 6.76 (br. *s*, NH); 6.53 (*d*, *J* = 7.8, 1 arom. H); 5.93 (*s*, CH_2); 4.48 (*t*, *J* = 4.8, CH_2); 4.04 (*t*, *J* = 4.5, CH_2); 3.98 (*s*, MeO); 3.81 (*s*, MeO). ^{13}C-NMR (150 MHz, $CDCl_3$): 166.6; 160.7; 159.4; 158.0; 142.9; 141.4; 133.3; 130.14; 130.07; 129.9; 128.6; 109.4; 106.6; 103.0; 78.9; 68.3; 63.7; 55.5; 53.5. ESI-MS: 427 ($[M+H]^+$), 449 ($[M+Na]^+$). HR-MS: 427.1613 ($[M+H]^+$, $C_{21}H_{23}N_4O_6^+$; calc. 427.1618).

*Methyl 3-[(4-Fluorophenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H-*1,2,4-triazole-5-carboxylate* (**4f**). White solid (46%). R_f (PE/AcOEt, 1:1) 0.53. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (*d*, *J* = 8.1, 2 arom. H); 7.55 (*t*, *J* = 7.7, 1 arom. H); 7.43–7.37 (*m*, 4 arom. H); 7.00 (*t*, *J* = 8.4, 2 arom. H); 6.65 (br. *s*, NH); 5.92 (*s*, CH_2); 4.48 (*t*, *J* = 4.5, CH_2); 4.02 (*t*, *J* = 4.8, CH_2); 3.98 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.6; 159.8; 157.9; 157.8 (*d*, ^1J(F,C) = 238.4); 143.0; 136.6; 133.3; 130.0; 129.8; 128.6; 118.3 (*d*, ^3J(F,C) = 7.9); 115.7 (*d*, ^2J(F,C) = 23.6); 78.8; 68.3; 63.7; 53.3. ESI-MS: 415.1 ($[M+H]^+$), 437.1 ($[M+Na]^+$). HR-MS: 415.1409 ($[M+H]^+$, $C_{20}H_{20}FN_4O_5^+$; calc. 415.1418).

*Methyl 3-[(3-Fluorophenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H-*1,2,4-triazole-5-carboxylate* (**4g**). White solid (64%). R_f (PE/AcOEt, 1:1) 0.58. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (*d*, *J* = 7.2, 2 arom. H); 7.54 (*t*, *J* = 7.8, 1 arom. H); 7.43–7.38 (*m*, 3 arom. H); 7.26–7.19 (*m*, 1 arom. H); 7.05 (*d*, *J* = 8.1, 1 arom. H); 6.80 (br. *s*, NH); 6.66 (*t*, *J* = 8.1, 1 arom. H); 5.94 (*s*, CH_2); 4.48 (*t*, *J* = 4.4, CH_2); 4.04 (*t*, *J* = 4.4, CH_2); 3.98 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.1; 161.0 (*d*, ^1J(F,C) = 240.5); 156.7; 155.3; 140.3; 139.5; 130.7; 127.6; 127.3; 126.0; 109.8; 105.2 (*d*, ^2J(F,C) = 20.0); 101.4 (*d*, ^2J(F,C) = 24.5); 76.4; 65.8; 61.2; 50.8. ESI-MS: 415.1 ($[M+H]^+$), 437.1 ($[M+Na]^+$). HR-MS: 415.1408 ($[M+H]^+$, $C_{20}H_{20}FN_4O_5^+$; calc. 415.1418).

*Methyl 3-[(4-Chlorophenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H*-1,2,4-triazole-5-carboxylate* (**4i**). White solid (35%). R_f (PE/AcOEt, 1:1) 0.46. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02–7.99 (*m*, 2 arom. H); 7.55 (*t*, *J* = 7.7, 1 arom. H); 7.43–7.36 (*m*, 4 arom. H); 7.28–7.24 (*m*, 2 arom. H); 6.66 (br. *s*, NH); 5.93 (*s*, CH_2); 4.48 (*t*, *J* = 4.4, CH_2); 4.03 (*t*, *J* = 4.4, CH_2); 3.99 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.6; 159.4; 157.9; 143.0; 139.0; 133.3; 130.0; 129.9; 129.2; 128.6; 126.0; 118.1; 78.9; 68.3; 63.7; 53.4. ESI-MS: 431.1, 433.1 ($[M+H]^+$), 453.1, 455.1 ($[M+Na]^+$). HR-MS: 431.1110 ($[M+H]^+$, $C_{20}H_{20}ClN_4O_5^+$; calc. 431.1122).

*Methyl 3-[(3-Chlorophenyl)amino]-1-({2-[(phenylcarbonyl)oxy]ethoxy}methyl)-1*H*-1,2,4-triazole-5-carboxylate* (**4j**). White solid (77%). R_f (PE/AcOEt, 1:1) 0.74. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (*d*, *J* = 8.1, 2 arom. H); 7.60–7.51 (*m*, 2 arom. H); 7.40 (*t*, *J* = 7.4, 2 arom. H); 7.30 (*t*, *J* = 9.5, 1 arom. H); 7.21 (*t*, *J* = 8.1, 1 arom. H); 7.10 (br. *s*, NH); 6.93 (*d*, *J* = 7.5, 1 arom. H); 5.94 (*s*, CH_2); 4.49 (*t*, *J* = 4.5, CH_2); 4.05 (*t*, *J* = 4.8, CH_2); 3.96 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.6; 159.3; 157.7; 142.9; 141.8; 134.7; 133.3; 130.2; 130.0; 129.8; 128.6; 121.0; 116.7; 114.9; 78.9; 68.3; 63.8; 53.3. ESI-MS: 431.1, 433.1 ($[M+H]^+$), 453.1, 455.1 ($[M+Na]^+$). HR-MS: 431.1114 ($[M+H]^+$, $C_{20}H_{20}ClN_4O_5^+$; calc. 431.1122).

General Procedure for the Preparation of **5** via *Cu-Mediated* N*-Arylation with Arylboronic Acid*. To a mixture of 20.1 mg **3** (0.10 mmol), 2.0 equiv. of arylboronic acid (0.20 mmol), and 27.2 mg of anh. $Cu(OAc)_2$ (0.15 mmol) was added 5 ml MeOH (freshly dist. over Mg turning and I_2), followed by rapid addition of 16.1 µl freshly dist. pyridine (0.20 mmol). The mixture was stirred at 40° until complete consumption of **3** (detected by TLC). The mixture was filtered over *Celite*, and the filtrate was concentrated under reduced pressure. The obtained residue was purified on SiO_2 with CH_2Cl_2/MeOH (20:1), giving the corresponding product **5** as a powder.

*3-Amino-1-[(2-hydroxyethoxy)methyl]-*N*-phenyl-1*H*-1,2,4-triazole-5-carboxamide* (**5a**). White solid (75%). R_f (CH_2Cl_2/MeOH, 20:1) 0.34. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.50 (br. *s*, C(O)NH); 7.78 (*d*, *J* = 8.1, 2 arom. H); 7.35 (*t*, *J* = 8.0, 2 arom. H); 7.14 (*t*, *J* = 7.4, 1 arom. H); 5.70 (*s*, CH_2); 5.65 (*s*, NH_2); 4.66 (*t*, *J* = 5.1, OH); 3.56 (*t*, *J* = 5.1, CH_2); 3.53–3.41 (*m*, CH_2). ^{13}C-NMR (150 MHz, (D_6)DMSO): 162.7; 155.9; 146.2; 138.0; 129.5; 125.4; 121.1; 78.1; 71.5; 60.4. ESI-MS: 278.1 ($[M+H]^+$), 300.1 ($[M+Na]^+$). HR-MS: 278.1250 ($[M+H]^+$, $C_{12}H_{16}N_5O_3^+$; calc. 278.1253).

*3-Amino-1-[(2-hydroxyethoxy)methyl]-*N*-(4-methylphenyl)-1*H*-1,2,4-triazole-5-carboxamide* (**5b**). White solid (60%). R_f (CH_2Cl_2/MeOH, 20:1) 0.23. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.42 (br. *s*, C(O)NH); 7.66 (*d*, *J* = 8.1, 2 arom. H); 7.15 (*d*, *J* = 8.7, 2 arom. H); 5.69 (*s*, CH_2); 5.64 (*s*, NH_2); 4.66 (*t*, *J* = 5.6, OH); 3.56–3.54 (*m*, CH_2); 3.48–3.45 (*m*, CH_2); 2.27 (*s*, Me). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 156.0; 146.4; 136.0; 134.2; 129.8; 121.2; 78.1; 71.7; 60.6; 21.2. ESI-MS: 292.1 ($[M+H]^+$), 314.1 ($[M+Na]^+$). HR-MS: 292.1414 ($[M+H]^+$, $C_{13}H_{18}N_5O_3^+$; calc. 292.1410).

*3-Amino-1-[(2-hydroxyethoxy)methyl]-*N*-(4-methoxyphenyl)-1*H*-1,2,4-triazole-5-carboxamide* (**5c**). White solid (51%). R_f (CH_2Cl_2/MeOH, 20:1) 0.18. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.40 (*s*, C(O)NH); 7.69 (*d*, *J* = 8.7, 2 arom. H); 6.92 (*d*, *J* = 9.6, 2 arom. H); 5.70 (*s*, CH_2); 5.63 (*s*, NH_2); 4.66 (*t*, *J* = 5.6, OH); 3.74 (*s*, MeO); 3.56 (*t*, *J* = 4.8, CH_2); 3.48–3.45 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 163.7; 157.5; 156.6; 147.2; 132.3; 123.6; 115.3; 78.8; 72.5; 61.4; 56.7. ESI-MS: 308.1 ($[M+H]^+$), 330.1 ($[M+Na]^+$). HR-MS: 308.1346 ($[M+H]^+$, $C_{13}H_{18}N_5O_4^+$; calc. 308.1359).

*3-Amino-1-[(2-hydroxyethoxy)methyl]-*N*-(3-methoxyphenyl)-1*H*-1,2,4-triazole-5-carboxamide* (**5d**). White solid (40%). R_f (CH_2Cl_2/MeOH, 20:1) 0.45. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.46 (*s*, C(O)NH); 7.46 (*s*, 1 arom. H); 7.39 (*d*, *J* = 9.0, 1 arom. H); 7.25 (*t*, *J* = 8.4, 1 arom. H); 6.72 (*d*, *J* = 8.1, 1 arom. H); 5.69 (*s*, CH_2); 5.65 (*s*, NH_2); 4.66 (*t*, *J* = 5.6, OH); 3.74 (*s*, MeO); 3.56 (*t*, *J* = 4.7, CH_2); 3.49–3.45 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 160.1; 156.2; 146.3; 139.7; 130.2; 113.4; 110.6; 107.0; 78.1; 71.7; 60.6; 55.8. ESI-MS: 308.1 ($[M+H]^+$), 330.1 ($[M+Na]^+$). HR-MS: 308.1356 ($[M+H]^+$, $C_{13}H_{18}N_5O_4^+$; calc. 308.1359).

*3-Amino-1-[(2-hydroxyethoxy)methyl]-*N*-(2-methoxyphenyl)-1*H*-1,2,4-triazole-5-carboxamide* (**5e**). White solid (21%). R_f (CH_2Cl_2/MeOH, 20:1) 0.18. ^{1}H-NMR (300 MHz, (D_6)DMSO): 9.56 (*s*, C(O)NH); 8.23 (*d*, *J* = 8.1, 1 arom. H); 7.14 (br. *s*, 2 arom. H); 7.02–6.98 (*m*, 1 arom. H); 5.84 (*s*, NH_2); 5.74 (*s*, CH_2); 4.67 (*t*, *J* = 5.1, OH); 3.90 (*s*, MeO); 3.62–3.56 (*m*, CH_2); 3.49–3.46 (*m*, CH_2). ^{13}C-NMR (150 MHz, (D_6)DMSO): 165.0; 157.1; 151.4; 147.7; 129.0; 127.9; 123.5; 122.4; 114.1; 80.5; 74.0; 62.8; 59.0. ESI-MS: 308.1 ($[M+H]^+$), 330.1 ($[M+Na]^+$). HR-MS: 308.1357 ($[M+H]^+$, $C_{13}H_{18}N_5O_4^+$; calc. 308.1359).

3-Amino-N-*(4-fluorophenyl)-1-[(2-hydroxyethoxy)methyl]-1*H-*1,2,4-triazole-5-carboxamide* (**5f**). White solid (36%). R_f (CH_2Cl_2/MeOH, 20:1) 0.35. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.63 (*s*, C(O)NH); 7.81 (*dd*, ^3J(H,H) = 8.1, ^4J(F,H) = 6.0, 2 arom. H); 7.20 (*t*, ^3J(H,H) = ^3J(F,H) = 8.7, 2 arom. H); 5.69 (*s*, CH_2); 5.65 (*s*, NH_2); 4.66 (*t*, *J* = 5.6, OH); 3.56–3.54 (*m*, CH_2); 3.49–3.45 (*m*, CH_2). ^{13}C-NMR (150 MHz, (D_6)DMSO): 165.1; 161.7 (*d*, ^1J(F,C) = 265.4); 158.3; 148.4; 137.0; 125.4; 118.1 (*d*, ^2J(F,C) = 21.2); 80.3; 73.9; 62.8. ESI-MS: 296.1 ($[M+H]^+$), 318.1 ($[M+Na]^+$). HR-MS: 296.1152 ($[M+H]^+$, $C_{12}H_{15}FN_5O_3^+$; calc. 296.1159).

3-Amino-N-*(3-fluorophenyl)-1-[(2-hydroxyethoxy)methyl]-1*H-*1,2,4-triazole-5-carboxamide* (**5g**). White solid (57%). R_f (CH_2Cl_2/MeOH, 20:1) 0.32. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.77 (*s*, C(O)NH); 7.73 (*d*, ^3J(F,H) = 11.7, 1 arom. H); 7.64 (*d*, ^3J(H,H) = 8.1, 1 arom. H); 7.39 (*dd*, ^3J(F,H) = 15.6, ^3J(H,H) = 8.1, 1 arom. H); 7.01–6.95 (*m*, 1 arom. H); 5.70 (*s*, CH_2); 5.67 (*s*, NH_2); 4.67 (*t*, *J* = 5.6, OH); 3.57 (*t*, *J* = 5.1, CH_2); 3.49–3.44 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 162.6 (*d*, ^1J(F,C) = 239.0); 156.4; 146.0; 140.3 (*d*, ^3J(F,C) = 10.7); 131.0 (*d*, ^3J(F,C) = 8.6); 117.1; 111.6 (*d*, ^2J(F,C) = 21.5); 108.1 (*d*, ^2J(F,C) = 26.8); 78.2; 71.8; 60.6. ESI-MS: 296.1 ($[M+H]^+$), 318.1 ($[M+Na]^+$). HR-MS: 296.1154 ($[M+H]^+$, $C_{12}H_{15}FN_5O_3^+$; calc. 296.1159).

3-Amino-N-*(2-fluorophenyl)-1-[(2-hydroxyethoxy)methyl]-1*H-*1,2,4-triazole-5-carboxamide* (**5h**). White solid (47%). R_f (CH_2Cl_2/MeOH, 20:1) 0.43. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.03 (*s*, C(O)NH); 7.84–7.79 (*m*, 1 arom. H); 7.35–7.21 (*m*, 3 arom. H); 5.76 (*s*, NH_2); 5.71 (*s*, CH_2); 4.67 (*t*, *J* = 5.6, OH); 3.57 (*t*, *J* = 4.8, CH_2); 3.47 (*t*, *J* = 5.1, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 163.0; 155.8; 145.5; 127.5 (*d*, ^3J(F,C) = 6.7); 125.6; 125.4; 125.3; 116.4 (*d*, ^2J(F,C) = 18.9); 78.1; 71.8; 60.6. ESI-MS: 296.1 ($[M+H]^+$), 318.1 ($[M+Na]^+$). HR-MS: 296.1151 ($[M+H]^+$, $C_{12}H_{15}FN_5O_3^+$; calc. 296.1159).

3-Amino-N-*(4-chlorophenyl)-1-[(2-hydroxyethoxy)methyl]-1*H-*1,2,4-triazole-5-carboxamide* (**5i**). White solid (48%). R_f (CH_2Cl_2/MeOH, 20:1) 0.30. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.71 (*s*, C(O)NH); 7.83 (*d*, *J* = 8.1, 2 arom. H); 7.42 (*d*, *J* = 8.7, 2 arom. H); 5.82 (*s*, CH_2); 5.66 (*s*, NH_2); 4.66 (*t*, *J* = 5.7, OH); 3.56–3.54 (*m*, CH_2); 3.47–3.45 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 156.3; 146.1; 137.5; 129.3; 128.8; 122.9; 78.1; 71.7; 60.6. ESI-MS: 312.1, 314.1 ($[M+H]^+$), 334.1, 336.1 ($[M+Na]^+$). HR-MS: 312.0854 ($[M+H]^+$, $C_{12}H_{15}ClN_5O_3^+$; calc. 312.0863).

3-Amino-N-*(3-chlorophenyl)-1-[(2-hydroxyethoxy)methyl]-1*H-*1,2,4-triazole-5-carboxamide* (**5j**). White solid (32%). R_f (CH_2Cl_2/MeOH, 20:1) 0.38. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.76 (*s*, C(O)NH); 7.97 (*s*, 1 arom. H); 7.74 (*d*, *J* = 7.8, 1 arom. H); 7.38 (*t*, *J* = 8.1, 1 arom. H); 7.20 (*d*, *J* = 7.2, 1 arom. H); 5.70 (*s*, CH_2); 5.67 (*s*, NH_2); 4.66 (*t*, *J* = 5.6, OH); 3.56 (*t*, *J* = 4.8, CH_2); 3.49–3.44 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 156.4; 145.9; 140.0; 133.7; 131.1; 124.8; 120.7; 119.8; 78.2; 71.7; 60.6. ESI-MS: 312.1, 314.1 ($[M+H]^+$), 334.1, 336.1 ($[M+Na]^+$). HR-MS: 312.0859 ($[M+H]^+$, $C_{12}H_{15}ClN_5O_3^+$; calc. 312.0863).

3-Amino-N-*(2-chlorophenyl)-1-[(2-hydroxyethoxy)methyl]-1*H-*1,2,4-triazole-5-carboxamide* (**5k**). White solid (41%). R_f (CH_2Cl_2/MeOH, 20:1) 0.40. ^{1}H-NMR (300 MHz, (D_6)DMSO): 9.93 (*s*, C(O)NH); 8.04 (*d*, *J* = 8.1, 1 arom. H); 7.58 (*d*, *J* = 8.1, 1 arom. H); 7.41 (*t*, *J* = 6.6, 1 arom. H); 7.26 (*t*, *J* = 7.2, 1 arom. H); 5.82 (*s*, NH_2); 5.72 (*s*, CH_2); 4.67 (*t*, *J* = 5.6, OH); 3.58 (*t*, *J* = 4.8, CH_2); 3.50–3.44 (*m*, CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): 162.9; 155.5; 145.3; 134.3; 130.2; 128.6; 127.3; 126.0; 124.6; 78.3; 71.8; 60.6. ESI-MS: 312.1, 314.1 ($[M+H]^+$), 334.1, 336.1 ($[M+Na]^+$). HR-MS: 312.0858 ($[M+H]^+$, $C_{12}H_{15}ClN_5O_3^+$; calc. 312.0863).

Anti-Cancer Assay in PC-3, MiaPaCa-2, and Capan-2 Cells. Prostate cancer PC-3 and pancreatic cancer MiaPaCa-2 cells were cultured in DMEM medium (*Gibco*) supplemented with 10% fetal bovine serum (FBS). Cells were seeded at a densitiy of 15,000 cells per well in 96 well *View Plate*™ (*Packard*) in 250 µl of medium containing the same components as described above. For Capan-2 cell lines, the cells were cultured in *RPMI 1640* medium supplemented with 10% FBS and 1% glutamine. Cells were seeded at a densitiy of 20,000 cells per well in 96 well *View Plate*™ (*Packard*) in 250 µl of medium containing the same components as described above. Cells were allowed to attach overnight, and then the culture medium was removed and replaced with fresh media alone as the control or containing different compounds. Plates were further incubated at 37° and 5% CO_2 for 48 h. The number of viable cells remaining after the appropriate treatment was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay.

Anti-HCV Assay in Huh-5-2 Cells. Huh 5-2 cells were seeded at a density of 5000 per well in a tissue culture-treated white 96-well view plate (*Packard*, Canberra, Canada) in complete *Dulbecco*'s modified *Eagle* medium (DMEM) supplemented with 250 μg/ml *G418*. After incubation for 24 h at 37° (5% CO_2), the medium was removed, and 3-fold serial dilutions in complete DMEM (without *G418*) of the test compounds were added in a total volume of 100 μl. After 4 d of incubation at 37°, the cell culture medium was removed and luciferase activity was determined using the *Steady-Glo* luciferase assay system (*Promega*, Leiden, The Netherlands); the luciferase signal was measured using a *Luminoskan* ascent (*Thermo*, Vantaa, Finland).

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