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Fused ring aziridines as a facile entry into triazole fused tricyclic and bicyclic heterocycles†

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The intramolecular dipolar cycloaddition of an azide with an alkyne has provided a useful entry into triazole fused tricyclic heterocycles containing both the triazole ring and the oxazolidin-2-one ring system. The requisite azido-alkynes have been prepared *via* a two-step sequence from fused ring aziridines. A series of 6–12 membered rings containing both the oxazolidinone and triazole rings have been prepared. These ring systems have been designed as conformationally restrained analogs of RNA-binding oxazolidinones.

Introduction

Fused ring aziridines such as **1** have been shown to be useful precursors for the synthesis of oxazolidinones **2**[1–3] and vicinal amino alcohols **3** (Scheme 1).[3] Conversion of aziridines such as **1** to the oxazolidinone can be effected through the ring opening reaction of **1** with a variety of nucleophiles including organocuprates, alcohols and azides.[3–11]

The oxazolidinones in particular (**ANB-22**) have been shown to be high affinity ligands for the T box RNA antiterminator transcription system.[12,13–15] Enantiomers of **ANB-22** bind the antiterminator RNA element of the bacterial T box riboswitch with equal affinity, due in large part to conformational flexibility around the C4-C1′ bond.[15] This flexibility enables the enantiomers to form comparable binding interactions with different functional group partners along the surface of the RNA. As part of a comprehensive drug discovery project, we were interested in preparing conformationally restricted analogs of **ANB-22** in order to achieve greater RNA-binding specificity.

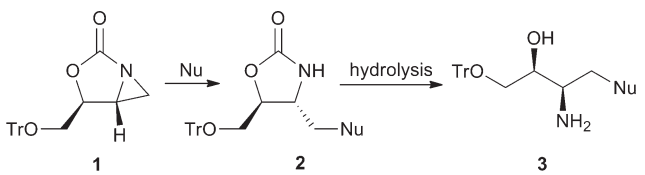
The synthesis of fused ring derivatives of the oxazolidinone ring system (*e.g.* **4**) where a heterocyclic ring is fused to the oxazolidinone was thus examined. Such work would both allow for the synthesis of conformationally restricted analogs of oxazolidinones such as **ANB-22** as well as further define the synthetic utility of fused ring aziridines **1**.

The intramolecular dipolar cycloaddition of an azide with an alkyne could provide a useful entry into triazole fused tricyclic heterocycles containing both the triazole ring and the oxazolidinone ring system. In addition the hydrolysis of the oxazolidinone ring would provide access to hydroxymethyl substituted bicyclic triazoles. Such molecules would be of value in the synthesis of analogs of **ANB-22** as well as for the synthesis of triazole-fused heterocycles in general (Fig. 1).

The replacement of a piperazine ring with a triazole is not a common isosteric replacement. While chemically the piperazine and triazole rings differ substantially, a model (Fig. 2) of the *N*-phenylpiperazine and 4-phenyltriazole shows a reasonable overlap in terms of general positioning of the phenyl ring and the piperazine ring with the phenyl and triazole ring respectively.

These compounds would also provide a unique scaffold for parallel synthesis containing three points of diversity. First the hydroxymethyl group on the oxazolidinone ring can be readily functionalized using a variety of acylating agents. The ring size of the ring fused to the triazole can be readily changed to provide different molecular shapes and finally, substitution on the triazole can be changed through use of different alkynes or subsequent modification of existing substitution on the triazole ring.

The proposed synthesis of the triazolo-oxazolidinones is outlined in Scheme 2. The fused ring aziridine **1** would be opened with azide to provide azido oxazolidinone **2**. Alkylation the oxazolidinone with an alkynyl halide (or tosylate **5**) would provide the cyclization precursor **6**. Given the intramolecular nature of the cyclization a thermal dipolar cycloaddition was planned.[17–28] The corresponding Cu-catalyzed reaction would be expected to



Scheme 1

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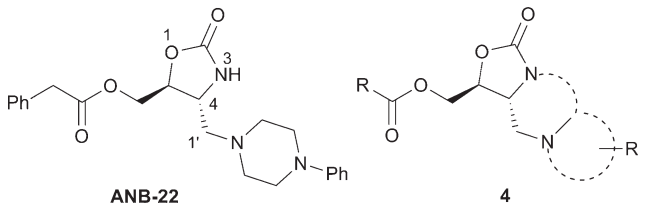


Fig. 1 General plan for conformationally restrained analogs of **ANB-22**.

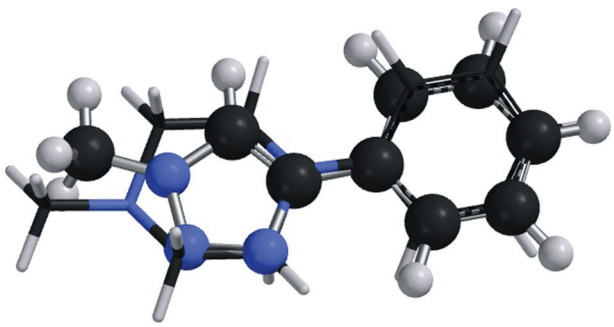
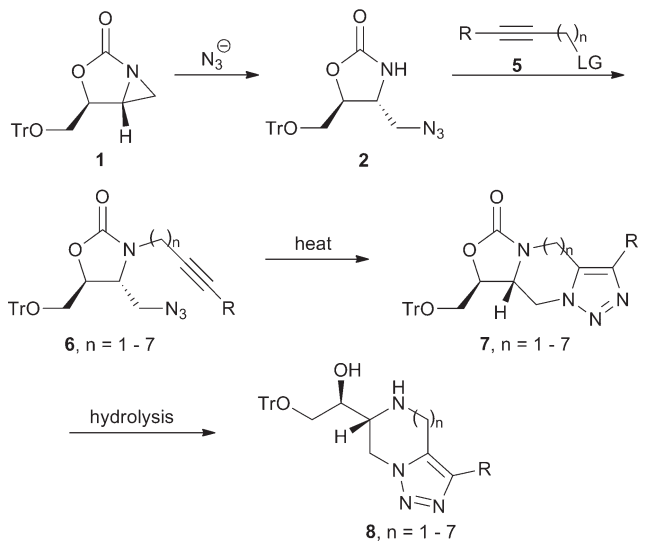


Fig. 2 Overlay of *N*-methyl, *N*-phenylpiperazine (tube model) with 1-methyl-4-phenyltriazole (ball and stick model).[16]

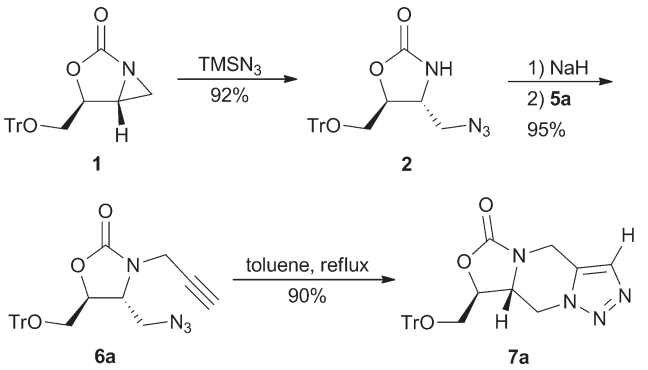


Scheme 2

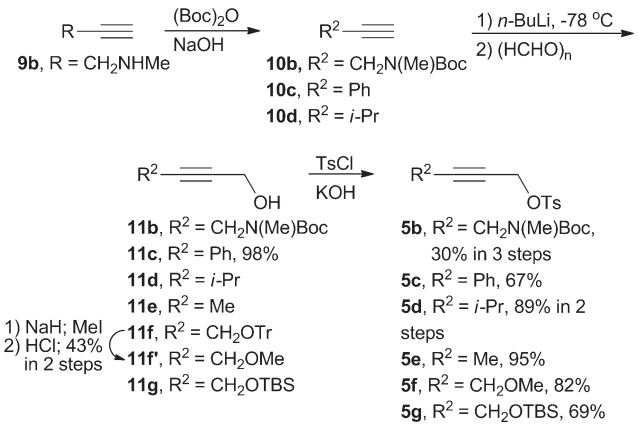
provide the 1,4-triazole which could not be readily accommodated in such a tricyclic ring system.[5,17,26,29] Hydrolysis of the oxazolidinone **7** would lead directly to the triazolo-piperazine ring system.

Results and discussion

The initial synthesis of a simple tricyclic triazole is outlined in Scheme 3. Reaction of aziridine **1** with $TMSN_3$ provided the expected azido oxazolidinone **2** in 92% yield. Alkylation of **2** with propargyl bromide (**5a**) yielded cyclization precursor **6a** in 95% yield. Heating **6a** in refluxing toluene provided the expected triazole **7a** in 90% yield.



Scheme 3



Scheme 4

With a general methodology worked out a series of substituted propargyl derivatives were needed for the synthesis of a series of derivatives. A group of longer chain alkynyl halides were also needed in order to prepare larger ring sizes and determine how large of a ring size can be readily prepared.

The requisite alkynes were generally prepared as described in Schemes 4–6. Aminomethyl substituted alkyne **10b** was prepared from *N*-methyl propargyl amine **9b** *via* an initial protection of the amine with $(Boc)_2O$. Terminal alkynes such as **10b**, **1c** or **10d** were deprotonated and treated with formaldehyde to provide **11b**, **11c** or **11d** respectively.[30,31] The known monoprotected alkyne **11f** was alkylated with MeI and detritylated to provide methoxymethyl substituted alkyne **11f′**. Alcohols **11b**, **11c**, **11d**, **11f′**, **11g** or the commercially available **11e** were then converted to the corresponding tosylates **5b–g** for alkylation of the oxazolidinone.[32]

In addition to the substituted alkynes already proposed, we wished to use an alkyne substituted with an ester or other electron stabilizing group which was also described. Propargyl alcohol **12** was first converted to the trityl ether and then deprotonated and acylated with methyl chloroformate to provide the alkynyl ester,[33–35] removal of the trityl group and tosylation provided ester substituted alkyne **5h**.

A series of longer chain alkynols were also made in order to prepare larger ring sizes. These longer chain alkynols were substituted on the alkyne with H, methyl or phenyl. Several such alkynols **11i**, **11j**, **11k**, **11l**, **11m**, or **11n** were obtained

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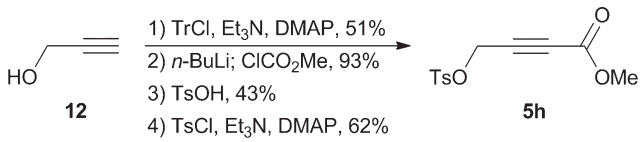
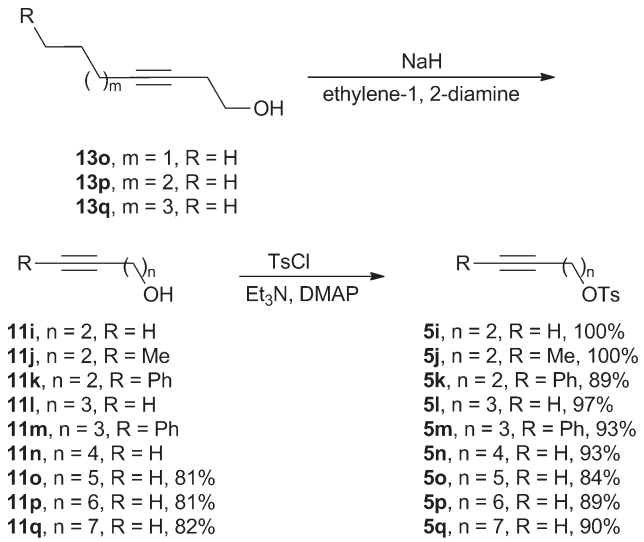
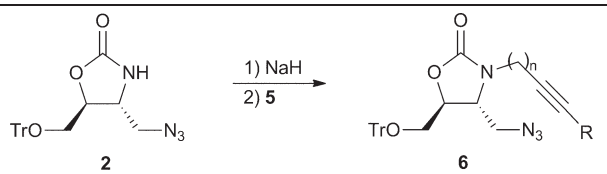


Scheme 5



Scheme 6

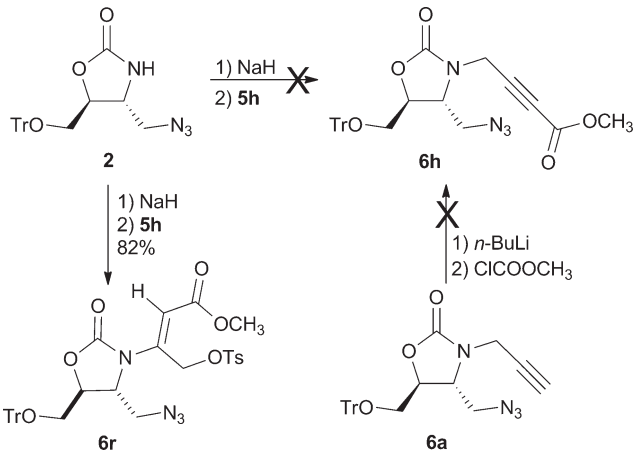
Table 1 Alkylation of oxazolidinone **2**



Entry	Compound	*n*	R	Yield (%)
1	**6a**	1	H	95
2	**6b**	1	$CH_2N(Me)Boc$	97
3	**6c**	1	Ph	77
4	**6d**	1	i-Pr	94
5	**6e**	1	Me	85
6	**6f**	1	CH_2OCH_3	95
7	**6g**	1	CH_2OTBS	75
8	**6h**	1	COOMe	0
9	**6i**	2	H	82
10	**6j**	2	Me	79
11	**6k**	2	Ph	82
12	**6l**	3	H	78
13	**6m**	3	Ph	88
14	**6n**	4	H	93
15	**6o**	5	H	94
16	**6p**	6	H	93
17	**6q**	7	H	98

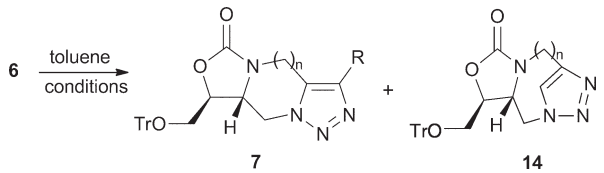
commercially. Longer chain alkynols were prepared by the method of Macaulay.[36,37] Treatment of alkynols **13o**, **13p** or **13q** with sodium hydride in ethylene diamine provided the respective terminal alkynes in excellent yields.

With a series of alkynyl tosylates in hand oxazolidinone **2** was alkylated using the general conditions developed for propargyl



Scheme 7

Table 2 Intramolecular azide-alkyne cycloaddition reactions



Entry	Compound	*n*, R	Conditions	Yield (%)
1	**7a**	1, H	Reflux, 2 h	90
2	**7b**	1,$CH_2N(Me)Boc$	Reflux, 2 h	94
3	**7c**	1, Ph	Reflux, 2 h	96
4	**7d**	1, i-Pr	Reflux, 3 h	90
5	**7e**	1, Me	Reflux, 3 h	84
6	**7f**	1, CH_2OCH_3	Reflux, 3 h	95
7	**7g**	1, CH_2OTBS	Reflux, 2 h	91
8	**7i**	2, H	Reflux, 3 h	95
9	**7j**	2, Me	Reflux, 4 h	99
10	**7k**	2, Ph	Reflux, 19 h	93
11	**7l**	3, H	Reflux, 18 h	98
12	**7m**	3, Ph	Reflux, 22 h	46
13	**7m**	3, Ph	MW, 160 °C, 5 h	89
14	**7n**	4, H	Reflux, 3 d	62
15	**7n**	4, H	MW, 160 °C, 10 h	80
16	**7o**	5, H	MW, 160 °C, 28 h	76
17	**7p**	6, H	MW, 160 °C, 36 h	52
18	**7p**	6, H	80 °C, 20 min $Cp^*RuCl(PPh_3)_2$	37
19	**7q**	7, H	MW, 170 °C, 36 h	32,20 (**14q**)
20	**7q**	7, H	80 °C, 20 min $Cp^*RuCl(PPh_3)_2$	71
21	**14q**	7, H	MW, 100 °C, 30 min, $CuSO_4{\cdot}5H_2O$, sodium ascorbate	12

bromide. As shown in Table 1, the yields for this alkylation were generally excellent.

Only one tosylate did not provide the expected product. As outlined in Scheme 7 alkylation of **2** with alkynyl tosylate **5h** was expected to provide oxazolidinone **6h**. The only product obtained (in 82% yield) was **6r**, resulting from conjugate addition of the oxazolidinone to the alkynyl ester. In an effort to circumvent this problem, **6a** was deprotonated and treated with

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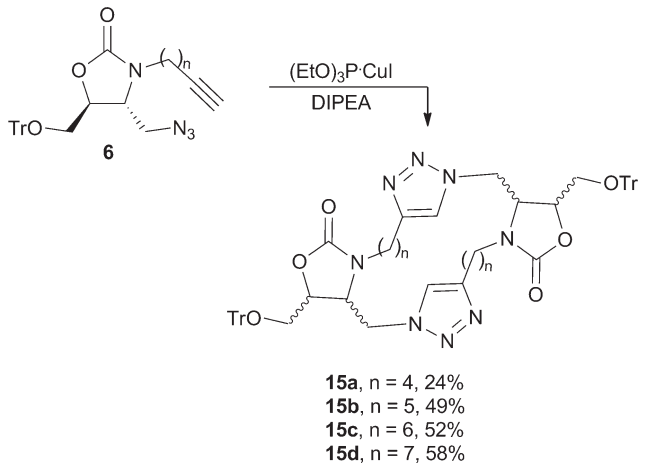


Scheme 8

methyl chloroformate. None of the expected product was obtained.

The dipolar cycloaddition reactions of the oxazolidinone azide-alkynes are summarized Table 2. When n = 1, the cycloaddition to form the 6-membered ring fused to the triazole **7a–g** proceeded in uniformly excellent yield, regardless of the substitution on the alkyne. The cycloaddition was complete after refluxing for only 2–3 hours. Increasing the length of the tether between the oxazolidinone and alkyne to 2 carbons led to a 7-membered ring fused between the oxazolidinone ring and the triazole. Refluxing in toluene for a relatively short amount of time again provided excellent yields of the triazole when R = H or Me. When R = Ph, the reaction time was increased to 19 hours in order for the reaction to proceed to completion. Increasing the length of the tether to 3 carbons provided the 8-membered ring. When R = H, the reaction time was increased to 18 hours in order for the reaction to go to completion (entry 11). However when R = Ph, the reaction had not gone completion after 22 hours and a 46% yield of **7m** was obtained (entry 12). The relatively poor yield was improved to 89% by heating to 160 °C in a microwave for 5 hours (entry 13). Increasing the tether length to provide a 9-membered ring was next evaluated. As might be expected, refluxing toluene provided a lower yield and required a significantly longer reaction time (3 days). The yield and reaction time was dramatically improved with microwave heating. Heating to 160 °C for 10 hours provided the triazole **7n** in 80% yield (entry 15). With a tether of 5 carbons the cyclization was affected by heating to 160 °C in the microwave to yield the product **7o** containing a fused 10-membered ring in a reasonable yield (entry 16).

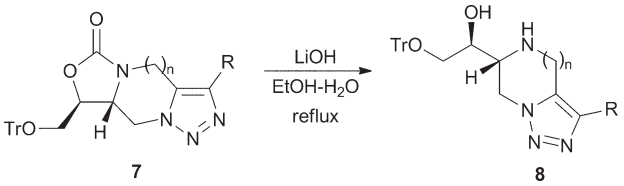
Increasing the tether length to 6 carbons (**6p**) would generate an 11-membered ring. Microwave heating conditions provided **7p** in only 52% yield. Ruthenium catalysis has been reported as an effective manner to carry out 1,5-regioselective triazole formation.[5,38,39] The application of this method was applied to **6p** in an effort to improve the yield of **7p**. While this method did provide the expected product, the yield decreased relative to the thermal conditions.

Increasing the tether length to 7 carbons to provide a fused 12 membered ring, the thermal cyclization of **6q** provided a mixture of the expected 1,5-triazole (**7q**) and the 1,4-triazole (**14q**) in 32% and 20% yields respectively. The use of Cp*RuCl-$(PPh_3)_2$ catalysis with azide **6q** did provide a much better yield of **7q** (entry 20). An attempt to generate the 1,4-triazole (**14q**) as the sole product using Cu-catalysis, provided a low yield of 1,4-triazole (entry 21).

Given the poor yield of the 1,4-triazole using Cu-catalysis the possibility of preparing dimers of **6** using this chemistry was appealing (Scheme 8). The initial Cu-catalyzed conditions with **6q** provided no dimeric products. Switching to a DBU-CuI catalyst system[40] provided only a trace of the desired dimer. The use of $(EtO)_3$P.CuI/DIPEA catalyst system[41] proved much more successful. When n equals 5, 6 or 7 yields of dimer **15b**, **15c** and **15d** were approximately 50%. The yield of **15a** (n = 4) was less successful with a yield of only 24%. We should note that since **6** is racemic, **15a–d** were formed as a 1 : 1 mixture of diastereomers.

Given the utility of the oxazolidinone ring as a precursor to a vicinal amino alcohol[3,42–45] the triazole derivatives **7a–q** were hydrolyzed using LiOH in refluxing EtOH–H_2O (Table 3). The isolated yields of the hydrolyzed products were in general quite good. As with the cyclization reactions, as the ring size increased, the time required for the reaction to go to completion increased, likely due to decreased strain of the fused ring system. For example when n = 1, the reaction time varied from 6 to 9 hours while when n = 7 the reaction time was 48 hours.

Table 3 Hydrolysis of tricyclic oxazolidinones



Entry	Compound	n, R	Time (h)	Yield (%)
1	**8a**	1, H	6	96
2	**8c**	1, Ph	9	92
3	**8i**	2, H	18	88
4	**8k**	2, Ph	18	98
5	**8l**	3, H	37	65
6	**8m**	3, Ph	32	70
7	**8n**	4, H	21	77
8	**8o**	5, H	65	90
9	**8p**	6, H	48	75
10	**8q**	7, H	48	95

Conclusions

We have developed a facile and high yielding method for the synthesis of triazoles fused to an oxazolidinone ring from fused ring aziridine **1**. A range of substitution on the triazole was tolerated and quite large rings could be made using this method. Hydrolysis of the oxazolidinones provided the interesting triazole piperazines (as well as larger ring system) in very good yields. Conversion of the triazoles to analogs of RNA binding agents **ANB-22** as well as their RNA affinity will be reported in due course.

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Experimental section

^{1}H NMR (300 MHz) and ^{13}C NMR spectra were measured on Bruker Avance 300 MHz NMR spectrometer and referenced to TMS as an internal standard. High Resolution Mass Spectrometry measurements were performed at the Old Dominion University COSMIC Lab through positive electrospray ionization on a Bruker 12 Tesla APEX–Qe FTICR-MS with and Apollo II ion source. High Performance Liquid Chromatography was conducted on Shimadzu LC-10AT liquid chromatograph coupled with a SIL-HT autosampler equipped with a SPD-10A UV-vis detector with Supelco discovery C8 column (15 cm × 4.6 cm, 5 μm). Method 1: eluting at 1.0 mL min^{-1} with a gradient elution starting at 60% of CH_3CN–H_2O for 5 min going to 80% over 20 min. Method 2: eluting at 1.0 mL min^{-1} with a gradient elution starting at 50% of CH_3CN–H_2O going to 70% over 15 min. Method 3: eluting at 1.0 mL min^{-1} with a gradient elution starting at 60% of MeOH–H_2O going to 80% over 15 min. IR data were recorded on a Shimadzu FTIR-8400. All reagents were purchased from commercial suppliers and used without further purification unless noted. CH_2Cl_2 and THF were dried with a SOLVTEK column purification system. Toluene was distilled from and stored over molecular sieves. All reactions were conducted under an atmosphere of argon. The products were purified with flash chromatography on silica gel (230–400 mesh).[46]

4-Azidomethyl-5-(trityloxymethyl)oxazolidin-2-one (2)

$TMSN_3$ (0.41 mL, 2.97 mmol) was added dropwise to a solution of aziridine **1**[1,15] (1 g, 2.70 mmol) in dry DMF (30 mL) at 0 °C. The reaction mixture was warmed up to room temperature slowly and stirred for 20 h. The solution was diluted with EtOAc (150 mL) and washed with water (3 × 50 mL) and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated and chromatographed (CH_2Cl_2–EtOAc, 50 : 1, 20 : 1) to give 1.03 g of azide **2** (92%) as a white solid; mp 162.0–163.1 °C; R_f = 0.37 (CH_2Cl_2–EtOAc, 15 : 1); IR (KBr): 3244, 2116, 1747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.41 (m, 6H), 7.33–7.21 (m, 9H), 6.33 (br s, 1H), 4.33 (q, J = 4.5 Hz, 1H), 3.79 (q, J = 5.1 Hz, 1H), 3.43–3.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 143.3, 128.5, 128.0, 127.3, 87.1, 78.0, 63.8, 54.1, 53.9; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{24}H_{22}N_4O_3Na^+$: 437.1584; Found: 437.1584; HPLC (214 nm, Method 2): 16.625 min, 100%.

4-(*tert*-Butoxycarbonyl(methyl)amino)but-2-ynyl 4-methylbenzenesulfonate (5b). $(Boc)_2O$ (1.9 g, 8.69 mmol) was added to a solution of *N*-Methylpropargyl-amine (546 mg, 7.90 mmol) in THF–H_2O (20 mL, 1 : 1) followed by NaOH (727 mg, 18.17 mmol). The reaction mixture was stirred for 20 hours at room temperature. THF was removed *in vacuo*. The aqueous layer was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$ and concentrated to give crude **10b** (1.27 g).

BuLi (3.5 mL, 2.5 M in hexane, 8.53 mmol) was added dropwise to a solution of **10b** (crude, 1.20 g, 7.11 mmol) in THF (20 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. Paraformaldehyde (267 mg, 8.53 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was then cooled to 0 °C, TsCl (1.63 g, 8.53 mmol) was added, followed by KOH (4 g, 71.1 mmol, freshly powdered). The resulting reaction mixture was stirred at room temperature for 15 h and quenched with crushed ice. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, concentrated and chromatographed (hexanes–EtOAc, 20 : 1, 10 : 1, 7 : 1) to provide 790 mg of **5b** (30% from *N*-methyl propargyl amine) as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, 9H), 2.45 (s, 3H), 2.78 (s, 3H), 3.96 (s, 2H), 4.72 (t, J = 1.8 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.0, 145.1, 133.1, 130.0, 128.0, 85.0, 80.1, 75.2, 58.0, 37.7, 33.4, 28.2, 21.5.

Methyl 4-(tosyloxy)but-2-ynoate (5h). Methyl 4-hydroxybut-2-ynoate (380 mg, 3.33 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, and then DMAP (41 mg, 0.33 mmol), tosyl chloride (762 mg, 4.0 mmol) and Et_3N (0.56 mL, 4.0 mmol) were added. The reaction mixture was stirred for 30 min and then quenched with an aqueous NH_4Cl solution, extracted with EtOAc, dried over anhydrous $MgSO_4$, concentrated and chromatographed (hexanes–EtOAc, 10 : 1 to 2 : 1) to afford 551 mg of **5h** (62%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 4.86 (s, 2H), 3.72 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.5, 145.8, 132.2, 130.1, 128.0, 79.3, 78.7, 56.6, 52.8, 21.4.

General procedure for alkylation of oxazolidinone 6

NaH (1.2 equiv, 60% in mineral oil) was added to a solution of azide **2** (1.0 equiv.) in THF (15 mL) at 0 °C. After stirring at 0 °C for an additional hour, propargyl bromide (1.2 equiv.) (for compound **6a**) or a solution of tosylate **5** (1.2 equiv.) in THF (2 mL) was added. The reaction mixture was stirred at 0 °C (for compound **6a**, **6c**, **6d**, **6e** and **6r**), rt (for compound **6b** and **6g**), 60 °C (for compound **6i–6n**) or 70 °C (**6o–6q**) until there was no change in the reaction as indicated by TLC. The reaction was quenched with an aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated and chromatographed to provide **6**.

4-(Azidomethyl)-3-(prop-2-ynyl)-5-(trityloxymethyl)oxazoli-din-2-one (6a). Prepared by the general procedure using 62 mg (0.15 mmol) of **2** which provided 63 mg (95%) of **6a**. R_f = 0.50 (hexanes–EtOAc, 3 : 2); IR (KBr): 3306, 2111, 1749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.34–7.22 (m, 9H), 4.40–4.30 (m, 2H), 3.99–3.89 (m, 2H), 3.63 (dd, J = 13.0, 4.6 Hz, 1H), 3.48–3.38 (m, 2H), 3.20 (dd, J = 10.5, 3.7 Hz, 1H), 2.28 (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 143.2, 128.6, 128.0, 127.3, 87.1, 76.8, 75.4, 73.8, 63.3, 56.2, 51.4, 32.8; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{27}H_{24}N_4O_3Na^+$: 475.1741; Found: 475.1744; HPLC (254 nm, Method 2): 13.142 min, 97.8%.

***tert*-Butyl 4-(4-(azidomethyl)-2-oxo-5-(trityloxymethyl)oxazolidin-3-yl)but-2-ynyl-(methyl)carbamate (6b).** Prepared by the general procedure using 200 mg (0.48 mmol) of **2** which provided 278 mg (97%) of **6b** as a pale yellow oil; R_f = 0.51

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(hexanes–EtOAc, 3 : 2); IR (KBr): 2111, 1760, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.40 (m, 6H), 7.33–7.24 (m, 9H), 4.35–4.29 (m, 2H), 4.06–3.99 (m, 3H), 3.82 (dd, J = 9.1, 4.4 Hz, 1H), 3.63 (dd, J = 13.0, 4.7 Hz, 1H), 3.46–3.36 (m, 2H), 3.21 (dd, J = 10.5, 3.9 Hz, 1H), 2.81 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 155.2, 143.2, 128.5, 128.0, 127.3, 87.2, 81.1, 80.2, 76.5, 75.4, 63.7, 56.6, 51.4, 38.0, 33.6, 33.1, 28.4; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{34}H_{37}N_5O_5Na^+$: 618.2687; Found: 618.2685; HPLC (254 nm, Method 1): 16.458 min 98.8%.

4-(Azidomethyl)-3-(3-phenylprop-2-ynyl)-5-(trityloxymeth-yl)-oxazolidin-2-one (6c). Prepared by the general procedure using 82 mg (0.20 mmol) of **2** which provided 81 mg (77%) of **6c** as a colorless oil; R_f = 0.67 (hexanes–EtOAc, 3 : 2); IR (KBr): 2108, 1757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (dd, J = 8.1, 1.3 Hz, 6H), 7.35–7.15 (m, 14H), 4.59 (d, J = 17.9 Hz, 1H), 4.33 (dd, J = 8.9, 4.4 Hz, 1H), 4.18 (d, J = 17.9 Hz, 1H), 3.94 (dd, J = 9.2, 4.6 Hz, 1H), 3.65 (dd, J = 13.0, 4.7 Hz, 1H), 3.43 (ddd, J = 16.9, 11.7, 4.2 Hz, 2H), 3.20 (dd, J = 10.5, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 143.3, 131.9, 128.8, 128.6, 128.4, 128.3, 128.1, 127.4, 122.1, 87.2, 85.7, 81.9, 75.5, 63.6, 56.5, 51.6, 33.7; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{33}H_{28}N_4O_3Na^+$: 551.2054; Found: 551.2056; HPLC (214 nm, Method 2): 16.825 min, 93.3%.

4-(Azidomethyl)-3-(4-methylpent-2-ynyl)-5-(trityloxymethyl) oxazolidin-2-one (6d). Prepared by the general procedure using 350 mg (0.85 mmol) of **2** which provided 393 mg (94%) of **6d** as a colorless oil; R_f = 0.63 (hexanes–EtOAc, 3 : 2); IR (KBr): 2108, 1758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.31–7.21 (m, 9H), 4.34–4.28 (m, 2H), 3.94 (dd, J = 17.6, 2.1 Hz, 1H), 3.88 (dd, J = 8.9, 4.8 Hz, 1H), 3.59 (dd, J = 13.0, 4.8 Hz, 1H), 3.42 (dd, J = 10.4, 4.4 Hz, 1H), 3.34 (dd, J = 13.0, 3.6 Hz, 1H), 3.18 (dd, J = 10.4, 3.8 Hz, 1H), 2.53–2.39 (m, 1H), 1.07 (dd, J = 6.9, 1.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 143.3, 128.5, 128.0, 127.3, 91.7, 87.0, 75.3, 71.9, 63.6, 56.3, 51.3, 33.2, 22.7, 20.4; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{30}H_{30}N_4O_3Na^+$: 517.2210; Found: 517.2210; HPLC (254 nm, Method 2): 16.175 min, 98.8%.

4-(Azidomethyl)-3-(but-2-ynyl)-5-(trityloxymethyl)oxazoli-din-2-one (6e). Prepared by the general procedure using 251 mg (0.61 mmol) of **2** which provided 240 mg (85%) of **6e** as a colorless oil; R_f = 0.62 (hexanes–EtOAc, 3 : 2); IR (KBr): 2110, 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.31–7.19 (m, 9H), 4.33–4.26 (m, 2H), 3.91–3.84 (m, 2H), 3.56 (dd, J = 13.0, 4.6 Hz, 1H), 3.44 (dd, J = 10.5, 4.2 Hz, 1H), 3.29 (dd, J = 13.1, 3.7 Hz, 1H), 3.16 (dd, J = 10.5, 3.7 Hz, 1H), 1.68 (t, J = 2.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 143.3, 128.5, 128.0, 127.2, 87.0, 81.6, 75.3, 72.0, 63.5, 56.1, 51.2, 33.0, 3.4; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{28}H_{26}N_4O_3Na^+$: 489.1897; Found: 489.1899; HPLC (214 nm, Method 1): 13.983 min, 97.3%.

4-(Azidomethyl)-3-(4-methoxybut-2-ynyl)-5-(trityloxymeth-yl) oxazolidin-2-one (6f). Prepared by the general procedure using 168 mg (0.41 mmol) of **2** which provided 190 mg (95%) of **6f** as a colorless oil; R_f = 0.72 (hexanes–EtOAc, 3 : 2); IR (KBr): 2109, 1765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.33–7.23 (m, 9H), 4.41 (dt, J = 17.8, 1.8 Hz, 1H), 4.30 (dd, J = 9.2, 4.0 Hz, 1H), 4.04–3.93 (m, 3H), 3.89–3.84 (m, 1H), 3.60 (dd, J = 13.1, 4.6 Hz, 1H), 3.46 (dd, J = 10.5, 4.3 Hz, 1H), 3.35 (dd, J = 13.1, 3.8 Hz, 1H), 3.27 (s, 3H), 3.17 (dd, J = 10.5, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 143.3, 128.6, 128.1, 127.4, 87.1, 81.5, 79.3, 75.4, 63.5, 59.7, 57.7, 56.3, 51.3, 33.0; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{29}H_{28}N_4O_4Na^+$: 519.2003; Found: 519.2008; HPLC (254 nm, Method 2): 13.483 min, 99.3%.

4-(Azidomethyl)-3-(4-(*tert*-butyldimethylsilyloxy)but-2-yn-yl)-5-(trityloxymethyl)oxazolidin-2-one (6g). Prepared by the general procedure using 246 mg (0.59 mmol) of **2** which provided 265 mg (75%) of **6g**; R_f = 0.63 (hexanes–EtOAc, 3 : 2); IR (KBr): 2110, 1760, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.33 (m, 6H), 7.26–7.14 (m, 9H), 4.30 (dt, J = 17.8, 1.8 Hz, 1H), 4.22 (dd, J = 9.4, 4.3 Hz, 1H), 4.18–4.06 (m, 2H), 3.92 (dt, J = 17.8, 1.6 Hz, 1H), 3.78 (dd, J = 9.0, 4.8 Hz, 1H), 3.53 (dd, J = 13.0, 4.8 Hz, 1H), 3.39–3.28 (m, 2H), 3.13 (dd, J = 10.5, 4.0 Hz, 1H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 143.3, 128.6, 128.0, 127.3, 87.1, 84.3, 77.6, 75.4, 63.7, 56.4, 51.6, 51.3, 33.0, 25.8, 18.3, −5.2; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{34}H_{40}N_4O_4SiNa^+$: 619.2711; Found: 619.2708; HPLC (214 nm, Method 2): 24.192 min, 91.6%.

4-(Azidomethyl)-3-(but-3-ynyl)-5-(trityloxymethyl)oxazoli-din-2-one (6i). Prepared by the general procedure using 100 mg (0.24 mmol) of **2** which provided 92 mg (82%) of **6i** as a colorless oil; R_f = 0.49 (hexanes–EtOAc, 3 : 2); IR (KBr): 3290, 2109, 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.40 (m, 6H), 7.34–7.25 (m, 9H), 4.29 (q, J = 4.7 Hz, 1H), 3.89 (q, J = 4.5 Hz, 1H), 3.70–3.55 (m, 2H), 3.44–3.37 (m, 2H), 3.30–3.20 (m, 2H), 2.46 (tt, J = 6.5, 2.3 Hz, 2H), 1.87 (t, J = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 143.2, 128.6, 128.0, 127.4, 87.2, 81.0, 75.3, 70.6, 63.6, 56.9, 51.8, 41.1, 17.9; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{28}H_{26}N_4O_3Na^+$: 489.1897; Found: 489.1898; HPLC (214 nm, Method 1): 14.142 min, 90.2%.

4-(Azidomethyl)-3-(pent-3-ynyl)-5-(trityloxymethyl) oxazo-lidin-2-one (6j). Prepared by the general procedure using 100 mg (0.24 mmol) of **2** which provided 92 mg (79%) of **6j** as a colorless oil; R_f = 0.80 (hexanes–EtOAc, 3 : 2); IR (KBr): 2108, 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.33–7.21 (m, 9H), 4.27 (dd, J = 9.3, 4.7 Hz, 1H), 3.90 (dd, J = 9.1, 4.7 Hz, 1H), 3.67–3.51 (m, 2H), 3.42–3.36 (m, 2H), 3.27–3.14 (m, 2H), 2.41–2.36 (m, 2H), 1.64 (t, J = 2.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 143.4, 128.6, 128.1, 127.4, 87.2, 78.0, 75.9, 75.3, 63.7, 56.7, 51.7, 41.7, 18.3, 3.4; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{29}H_{28}N_4O_3Na^+$: 503.2054; Found: 503.2049; HPLC (214 nm, Method 1): 15.092 min, 95.3%.

4-(Azidomethyl)-3-(4-phenylbut-3-ynyl)-5-(trityloxymethyl) oxazolidin-2-one (6k). Prepared by the general procedure using 100 mg (0.24 mmol) of **2** which provided 108 mg (82%) of **6k** as a colorless oil; R_f = 0.54 (hexanes–EtOAc, 3 : 2); IR (KBr): 3357, 3058, 3028, 2924, 2854, 2107, 1756, 1597, 1490, 1447, 1283, 1229, 1081, 1029, 758, 704 cm^{-1}; ^1H NMR (300 MHz,

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$CDCl_3$): δ 7.40–7.37 (m, 6H), 7.30–7.23 (m, 14H), 4.25 (dd, J = 9.2, 4.8 Hz, 1H), 4.00 (dd, J = 9.1, 4.6 Hz, 1H), 3.82–3.73 (m, 1H), 3.66–3.60 (m, 1H), 3.46–3.21 (m, 4H), 2.69 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 143.3, 131.5, 128.5, 128.3, 128.1, 128.0, 127.3, 123.0, 87.2, 86.6, 82.6, 75.3, 63.6, 56.8, 51.7, 41.4, 19.1; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{34}H_{30}N_4O_3Na^+$: 565.2210; Found: 565.2209; HPLC (214 nm, Method 2): 16.833 min, 96.0%.

4-(Azidomethyl)-3-(pent-4-ynyl)-5-(trityloxymethyl)oxazolidi-*n*-2-one (6l). Prepared by the general procedure using 100 mg (0.24 mmol) of **2** which provided 90 mg (78%) of **6l** as a colorless oil; R_f = 0.62 (hexanes–EtOAc, 3 : 2); IR (KBr): 3292, 2109, 1761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.37 (m, 6H), 7.34–7.19 (m, 9H), 4.28 (dd, J = 8.6, 4.6 Hz, 1H), 3.66 (dd, J = 8.6, 4.4 Hz, 1H), 3.52 (ddd, J = 17.8, 10.6, 5.7 Hz, 2H), 3.35 (ddd, J = 16.7, 11.6, 4.3 Hz, 2H), 3.24–3.09 (m, 2H), 2.16 (td, J = 6.8, 2.4 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.89–1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 143.2, 128.5, 128.0, 127.3, 87.1, 82.9, 75.0, 69.5, 63.4, 56.7, 51.5, 41.2, 26.2, 15.9; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{29}H_{28}N_4O_3Na^+$: 503.2054; Found: 503.2050; HPLC (254 nm, Method 2): 14.167 min, 97.2%.

4-(Azidomethyl)-3-(5-phenylpent-4-ynyl)-5-(trityloxymethyl) oxazolidin-2-one (6m). Prepared by the general procedure using 100 mg (0.24 mmol) of **2** which provided 118 mg (88%) of **6m** as a colorless oil; R_f = 0.60 (hexanes–EtOAc, 3 : 2); IR (KBr): 2108, 1754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.34 (m, 8H), 7.34–7.17 (m, 12H), 4.28 (dd, J = 8.5, 4.8 Hz, 1H), 3.72 (dd, J = 8.7, 4.5 Hz, 1H), 3.66–3.47 (m, 2H), 3.37 (ddd, J = 16.7, 11.6, 4.4 Hz, 2H), 3.22 (ddd, J = 22.5, 9.2, 5.0 Hz, 2H), 2.39 (t, J = 7.0 Hz, 2H), 1.98–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 143.2, 131.5, 128.5, 128.3, 128.0, 127.8, 127.3, 123.5, 88.4, 87.1, 81.7, 75.1, 63.4, 56.8, 51.6, 41.3, 26.5, 16.8; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{35}H_{32}N_4O_3Na^+$: 579.2367; Found: 579.2361; HPLC (254 nm, Method 2): 18.858 min, 95.0%.

4-(Azidomethyl)-3-(hex-5-ynyl)-5-(trityloxymethyl)oxazoli-din-2-one (6n). Prepared by the general procedure using 300 mg (0.73 mmol) of **2** which provided 334 mg (93%) of **6n** as a white solid; mp 102.3–103.4 °C; R_f = 0.59 (hexanes–EtOAc, 3 : 2); IR (KBr): 3294, 2109, 1757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.36–7.21 (m, 9H), 4.29 (dd, J = 8.8, 4.9 Hz, 1H), 3.67 (dd, J = 8.9, 4.7 Hz, 1H), 3.57–3.44 (m, 2H), 3.44–3.32 (m, 2H), 3.21 (dd, J = 10.3, 3.8 Hz, 1H), 3.09 (ddd, J = 14.1, 8.2, 5.4 Hz, 1H), 2.23–2.14 (m, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.70–1.58 (m, 2H), 1.54–1.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 143.2, 128.5, 128.0, 127.3, 87.2, 83.7, 75.0, 69.0, 63.4, 56.4, 51.7, 41.8, 26.3, 25.3, 17.9; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{30}H_{30}N_4O_3Na^+$: 517.2210; Found: 517.2206; HPLC (254 nm, Method 2): 14.742 min, 98.6%.

4-(Azidomethyl)-3-(hept-6-ynyl)-5-(trityloxymethyl) oxazolid-in-2-one (6o). Prepared by the general procedure using 200 mg (0.48 mmol) of **2** which provided 232 mg (94%) of **6o** as a white solid; mp 111.0–111.9 °C; R_f = 0.63 (hexanes–EtOAc, 3 : 2); IR (KBr): 3297, 2105, 1754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.41 (m, 6H), 7.32–7.20 (m, 9H), 4.26 (dd, J = 8.8, 4.6 Hz, 1H), 3.64 (dd, J = 8.7, 4.5 Hz, 1H), 3.52–3.36 (m, 3H), 3.27 (dd, J = 12.9, 3.8 Hz, 1H), 3.19 (dd, J = 10.3, 3.8 Hz, 1H), 3.06–2.97 (m, 1H), 2.12 (td, J = 6.8, 2.5 Hz, 2H), 1.90 (t, J = 2.6 Hz, 1H), 1.56–1.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 143.2, 128.5, 128.0, 127.3, 87.0, 84.1, 74.9, 68.6, 63.5, 56.2, 51.5, 42.1, 27.9, 26.9, 25.6, 18.2; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{31}H_{32}N_4O_3Na^+$: 531.2367; Found: 531.2372; HPLC (214 nm, Method 1): 15.575 min, 99.3%.

4-(Azidomethyl)-3-(oct-7-ynyl)-5-(trityloxymethyl)oxazolid-in-2-one (6p). Prepared by the general procedure using 300 mg (0.73 mmol) of **2** which provided 354 mg (93%) of **6p** as a white solid; mp 78.5–79.2 °C; R_f = 0.64 (hexanes–EtOAc, 3 : 2); IR (KBr): 3295, 2108, 1753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.41 (m, 6H), 7.31–7.19 (m, 9H), 4.25 (dd, J = 8.2, 4.0 Hz, 1H), 3.71–3.54 (m, 1H), 3.54–3.29 (m, 3H), 3.20 (m, 2H), 3.08–2.89 (m, 1H), 2.19–2.03 (m, 2H), 1.93 (m, 1H), 1.62–1.34 (m, 6H), 1.31– 1.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 143.1, 128.4, 127.9, 127.2, 86.9, 84.3, 74.8, 68.4, 63.4, 56.1, 51.4, 42.1, 28.1, 28.1, 27.2, 26.0, 18.2; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{32}H_{34}N_4O_3Na^+$: 545.2523; Found: 545.2518; HPLC (254 nm, Method 2): 16.608 min, 98.4%.

4-(Azidomethyl)-3-(non-8-ynyl)-5-(trityloxymethyl)oxazoli-din-2-one (6q). Prepared by the general procedure using 200 mg (0.48 mmol) of **2** which provided 254 mg (98%) of **6q** as a colorless oil; R_f = 0.73 (hexanes–EtOAc, 3 : 2); IR (KBr): 3295, 2108, 1764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (dd, J = 8.2, 1.2 Hz, 6H), 7.35–7.19 (m, 9H), 4.27 (dd, J = 8.7, 4.7 Hz, 1H), 3.65 (dd, J = 8.8, 4.6 Hz, 1H), 3.55–3.24 (m, 4H), 3.19 (dd, J = 10.3, 3.8 Hz, 1H), 3.01 (ddd, J = 14.2, 8.7, 5.6 Hz, 1H), 2.16 (td, J = 7.0, 2.6 Hz, 2H), 1.92 (t, J = 2.6 Hz, 1H), 1.61–1.42 (m, 4H), 1.42–1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 143.2, 128.5, 128.0, 127.3, 87.1, 84.5, 74.9, 68.3, 63.5, 56.3, 51.6, 42.3, 28.6, 28.5, 28.3, 27.3, 26.5, 18.3; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{33}H_{36}N_4O_3Na^+$: 559.2680; Found: 559.2681; HPLC (214 nm, Method 2): 17.892 min, 98.6%.

Methyl 3-(4-(azidomethyl)-2-oxo-5-(trityloxymethyl) oxazoli-din-3-yl)-4-(tosyloxy)but-2-enoate (6r). Prepared by the general procedure using 50 mg (0.12 mmol) of **2** which provided 51 mg (82%) of **6r** as a colorless oil; R_f = 0.42 (hexanes–EtOAc, 3 : 2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 8.3 Hz, 2H), 7.40–7.21 (m, 17H), 6.72 (s, 1H), 4.35 (AB dd, J = 8.3, 4.2 Hz, 1H), 3.88–3.84 (m, 1H), 3.61–3.45 (m, 6H), 3.37 (AB dd, J = 13.0, 2.9 Hz, 1H), 3.20–3.13 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 146.1, 143.1, 136.0, 131.8, 130.2, 128.5, 128.2, 128.1, 127.4, 123.0, 87.2, 75.5, 63.5, 57.4, 52.2, 50.7, 31.9, 21.8.

General procedure of the preparation of 1, 3-dipolarcyclo-addition products 7

Method A: thermal cyclization. A solution of compound **6** in toluene (0.02 mM) was heated at reflux until completion of the reaction as indicated by TLC. The reaction mixture was concentrated and chromatographed to provide the triazole **7**.

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Method B: microwave heating. A solution of **6** in toluene (6.0 mM) was heated at 170 °C with a microwave reactor (Initiator-Biotage: power max 400 W, internal pressure max 290 psi, ramp time 2 min) until completion of the reaction as indicated by TLC. The reaction mixture was concentrated and chromatographed to provide the triazole **7**.

Method C: utilizing Ru catalyst. A solution of **6** in toluene (2.0 mM) was degassed for 30 min. Cp*RuCl(PPh_3)$_2$ (20% wt %) was added and the reaction was heated to 80 °C. After 20 min the reaction mixture was cooled and filtered. The reaction mixture was concentrated and chromatographed to provide the triazole **7**.

8-(Trityloxymethyl)-8a,9-dihydro-4*H*-oxazolo[3,4-*α*][1,2,3] triazolo[1,5-*d*]pyrazin-6(8*H*)-one (7a). Prepared by Method A using 200 mg (0.44 mmol) of **6a** which provided 180 mg (90%) of **7a** as a white solid; mp 159.5 °C (dec.); R_f = 0.19 (hexanes–EtOAc 1 : 2); IR (KBr): 1761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.44–7.41 (m, 6H), 7.33–7.26 (m, 9H), 5.07 (d, J = 16.9 Hz, 1H), 4.76 (dd, J = 11.7, 3.5 Hz, 1H), 4.44 (d, J = 16.9 Hz, 1H), 4.34 (dd, J = 9.7, 4.2 Hz, 1H), 4.13–3.97 (m, 2H), 3.50 (AB dd, J_{AB} = 23.1 Hz, δ_A = 3.54, J = 10.5, 5.7 Hz, δ_B = 3.46, J = 10.5, 4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 143.0, 129.7, 128.5, 128.4, 128.2, 127.6, 87.5, 76.0, 63.4, 53.2, 49.1, 37.2; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{27}H_{24}N_4O_3Na^+$: 475.1741; Found: 475.1732; HPLC (214 nm, Method 2): 8.508 min, 99.8%.

***tert*-Butyl methyl((6-oxo-8-(trityloxymethyl)-6,8,8a,9-tetra hydro-4*H*-oxazolo[3,4-*α*]-[1,2,3]triazolo[1,5-*d*]pyrazin-3-yl) methyl)carbamate (7b).** Prepared by Method A using 205 mg (0.34 mmol) of **6b** which provided 192 mg (94%) of **7b** as a white solid; mp 97.7–99.0 °C; R_f = 0.49 (hexanes–EtOAc, 2 : 3); IR (KBr): 1768, 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.41 (m, 6H), 7.34–7.25 (m, 9H), 5.04 (d, J = 17.3 Hz, 1H), 4.71–4.67 (m, 1H), 4.52–4.29 (m, 4H), 4.08–3.95 (m, 2H), 3.48 (AB dd, J_{AB} = 20.6 Hz, δ_A = 3.52, J = 10.4, 3.5 Hz, δ_B = 3.45, J = 10.4, 3.4 Hz, 2H), 2.89 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 155.5, 143.1, 140.6, 128.4, 128.2, 127.5, 87.5, 80.2, 75.9, 63.4, 53.0, 49.3, 43.2, 37.4, 34.4, 28.5; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{34}H_{37}N_5O_5Na^+$: 618.2687; Found: 618.2684; HPLC (254 nm, Method 1): 14.742 min 96.5%.

3-Phenyl-8-(trityloxymethyl)-8a,9-dihydro-4*H*-oxazolo[3,4-*α*]-[1,2,3]triazolo[1,5-*d*]-pyrazin-6(8*H*)-one (7c). Prepared by Method A using 33 mg (0.06 mmol) of **6c** which provided 32 mg of **7c** (96%) as a white solid; mp 238.8–239.7 °C; R_f = 0.37 (hexanes–EtOAc, 3 : 2); IR (KBr): 1763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74–7.67 (m, 2H), 7.51–7.21 (m, 18H), 5.27 (d, J = 16.9 Hz, 1H), 4.78 (dd, J = 11.8, 3.5 Hz, 1H), 4.59 (d, J = 16.9 Hz, 1H), 4.35 (dd, J = 9.8, 4.3 Hz, 1H), 4.19–3.98 (m, 2H), 3.52 (ddd, J = 14.7, 10.5, 5.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 143.1, 142.3, 130.2, 129.1, 128.4, 128.3, 128.2, 127.6, 126.1, 124.7, 87.6, 76.1, 63.4, 53.0, 49.5, 38.6; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{33}H_{28}N_4O_3Na^+$: 551.2054; Found: 551.2045; HPLC (214 nm, Method 2): 13.283 min, 100.0%.

3-Isopropyl-8-(trityloxymethyl)-8a,9-dihydro-4*H*-oxazolo-[3,4-*α*][1,2,3]triazolo[1,5-*d*]pyrazin-6(8*H*)-one (7d). Prepared by Method A using 390 mg (0.79 mmol) of **6d** which provided 351 mg (90%) of **7d** as a white solid; mp 215.2–215.6 °C; R_f = 0.09 (hexanes–EtOAc, 3 : 2); IR (KBr): 1771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 6H), 7.34–7.25 (m, 9H), 5.00 (d, J = 16.6 Hz, 1H), 4.67 (dd, J = 18.3, 10.0 Hz, 1H), 4.37 (d, J = 16.6 Hz, 1H), 4.30 (dd, J = 9.2, 4.3 Hz, 1H), 4.05–3.95 (m, 2H), 3.47 (AB dd, J_{AB} = 22.7 Hz, δ_A = 3.51, J = 10.5, 5.6 Hz, δ_B = 3.43, J = 10.5, 4.3 Hz, 2H), 3.05 (sep, J = 7.0 Hz, 1H), 1.3132 (dd, J = 7.0, 2.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 148.2, 143.1, 128.4, 128.2, 127.5, 123.7, 87.5, 76.0, 63.4, 53.1, 49.3, 37.5, 25.8, 21.9, 21.8; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{30}H_{30}N_4O_3Na^+$: 517.2210; Found: 517.2202; HPLC (254 nm, Method 2): 11.958 min, 97.36%.

3-Methyl-8-(trityloxymethyl)-8a,9-dihydro-4*H*-oxazolo[3,4-*α*]-[1,2,3]triazolo[1,5-*d*]-pyrazin-6(8*H*)-one (7e). Prepared by Method A using 204 mg (0.44 mmol) of **6e** which provided 172 mg (84%) of **7e** as a white solid; mp 142.6–143.7 °C; R_f = 0.18 (hexanes–EtOAc, 1 : 2); IR (KBr): 1762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.40 (m, 6H), 7.33–7.21 (m, 9H), 4.92 (d, J = 16.6 Hz, 1H), 4.63 (dd, J = 18.5, 20.0 Hz, 1H), 4.34–4.26 (m, 2H), 4.03–3.93 (m, 2H), 3.46 (AB dd, J_{AB} = 28.3 Hz, δ_A = 3.51, J = 10.5, 5.5 Hz, δ_B = 3.42, J = 10.5, 4.2 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 143.1, 138.6, 128.5, 128.2, 127.6, 125.1, 87.5, 76.1, 63.5, 53.2, 49.2, 37.1, 10.0; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{28}H_{26}N_4O_3Na^+$: 489.1897; Found: 489.1888; HPLC (214 nm, Method 1): 9.408 min, 99.5%.

3-(Methoxymethyl)-8-(trityloxymethyl)-8a,9-dihydro-4*H*-oxazolo-[3,4-*α*][1,2,3]triazo-lo[1,5-*d*]pyrazin-6(8*H*)-one (7f). Prepared by Method A using 196 mg (0.39 mmol) of **6f** which provided 186 mg (95%) of **7f** as a white solid; mp 174.3–175.2 °C; R_f = 0.14 (hexanes–EtOAc, 3 : 2); IR (KBr): 1771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.41 (m, 6H), 7.33–7.21 (m, 9H), 5.04 (d, J = 17.2 Hz, 1H), 4.64 (d, J = 8.3 Hz, 1H), 4.56 (s, 2H), 4.41 (d, J = 17.2 Hz, 1H), 4.31 (dd, J = 8.6, 4.2 Hz, 1H), 4.05–3.94 (m, 2H), 3.51 (dd, J = 10.5, 5.4 Hz, 1H), 3.43–3.38 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 143.1, 140.1, 128.5, 128.2, 127.5, 127.2, 87.4, 76.0, 66.1, 63.4, 58.7, 53.0, 49.2, 37.4; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{29}H_{28}N_4O_4Na^+$: 519.2003; Found: 519.1994; HPLC (214 nm, Method 2): 9.567 min, 98.6%.

3-((*tert*-Butyldimethylsilyloxy)methyl)-8-(trityloxymethyl)-8a,9-dihydro-4*H*-oxazolo-[3,4-*α*][1,2,3]triazolo[1,5-*d*]pyrazin-6(8*H*)-one (7g). Prepared by Method A using 163 mg (0.27 mmol) of **6g** which provided 148 mg (91%) of **7g** as a white solid; mp 88.6–89.7 °C; R_f = 0.24 (hexanes–EtOAc, 3 : 2); IR (KBr): 1769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.21 (m, 6H), 7.17–7.13 (m, 9H), 4.97 (d, J = 17.2 Hz, 1H), 4.76 (s, 2H), 4.55 (d, J = 8.7 Hz, 1H), 4.32 (d, J = 17.3 Hz, 1H), 4.18 (dd, J = 9.0, 4.2 Hz, 1H), 3.95–3.83 (m, 2H), 3.35 (AB dd, J_{AB} = 26.6 Hz, δ_A = 3.40, J = 10.4, 5.6 Hz, δ_B = 3.31, J = 10.4, 4.2 Hz, 2H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 143.1, 142.7, 128.4, 128.2, 127.5, 126.5, 87.5, 75.9, 63.5, 58.4, 53.1, 49.2, 37.7, 25.9, 18.4, −5.4, −5.5; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{34}H_{40}N_4O_4SiNa^+$: 619.2711; Found: 619.2701; HPLC (Method 1. 214 nm): 19.500, 98.9%.

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9-(Trityloxymethyl)-4,5,9a,10-tetrahydrooxazolo[3,4-*α*]-[1,2,3]triazolo[1,5-*d*][1,4]-diazepin-7(9*H*)-one (7i). Prepared by Method A using 87 mg (0.19 mmol) of **6i** which provided 82 mg (95%) of **7i** as a white solid; mp 219.3–220.7 °C; R_f = 0.20 (hexanes–EtOAc, 1 : 3); IR (KBr): 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (br s, 1H), 7.42–7.39 (m, 6H), 7.34–7.22 (m, 9H), 4.86 (dd, J = 14.1, 1.6 Hz, 1H), 4.34–4.18 (m, 3H), 3.61 (AB dd, J_{AB} = 10.7 Hz, δ_A = 3.63, J = 5.4, 1.8 Hz, δ_B = 3.59, J = 5.4, 1.8 Hz, 1H), 3.40 (AB dd, J_{AB} = 32.6 Hz, δ_A = 3.46, J = 10.6, 4.7 Hz, δ_B = 3.35, J = 10.6, 4.1 Hz, 2H), 3.21–3.14 (m, 1H), 2.95–2.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 143.1, 136.4, 133.6, 128.5, 128.2, 127.5, 87.4, 74.7, 63.6, 58.0, 54.6, 42.5, 24.4; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{28}H_{26}N_4O_3Na^+$: 489.1897; Found: 489.1897; HPLC (214 nm, Method 1): 12.567 min, 92.3%.

3-Methyl-9-(trityloxymethyl)-4,5,9a,10-tetrahydrooxazolo [3,4-*α*][1,2,3]triazolo[1,5-*d*][1,4]diazepin-7(9*H*)-one (7j). Prepared by Method A using 145 mg (0.30 mmol) of **6j** which provided 143 mg (99%) of **7j** as a white solid; mp 101.8–102.7 °C; R_f = 0.16 (hexanes–EtOAc, 1 : 4); IR (KBr): 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.24 (m, 15H), 4.78 (dd, J = 14.2, 1.8 Hz, 1H), 4.34–4.29 (m, 1H), 4.24–4.15 (m, 2H), 3.65 (AB dd, J_{AB} = 10.7 Hz, δ_A = 3.67, J = 5.4, 1.8 Hz, δ_B = 3.63, J = 5.4, 1.8 Hz, 1H), 3.40 (AB dd, J_{AB} = 54.2 Hz, δ_A = 3.49, J = 10.6, 4.5 Hz, δ_B = 3.31, J = 10.6, 4.1 Hz, 2H), 3.08–3.02 (m, 1H), 2.93–2.74 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 143.1, 141.6, 132.8, 128.5, 128.1, 127.5, 87.4, 74.8, 63.6, 58.0, 54.7, 42.5, 23.8, 10.1; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{29}H_{28}N_4O_3Na^+$: 503.2054; Found: 503.2056; HPLC (214 nm, Method 1): 12.925 min, 92.5%.

3-Phenyl-9-(trityloxymethyl)-4,5,9a,10-tetrahydrooxazolo-[3,4-*α*][1,2,3]triazolo[1,5-*d*][1,4]diazepin-7(9*H*)-one (7k). Prepared by Method A using 91 mg (0.17 mmol) of **6k** which provided 85 mg (93%) of **7k** as a white solid; mp 103.9–105.2 °C; R_f = 0.10 (hexanes–EtOAc, 3 : 2); IR (KBr): 1759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57–7.54 (m, 2H), 7.47–7.37 (m, 9H), 7.31–7.22 (m, 9H), 4.84 (dd, J = 14.2, 1.5 Hz, 1H), 4.31–4.21 (m, 3H), 3.69 (ddd, J = 10.5, 5.4, 1.5 Hz, 1H), 3.48 (dd, J = 10.5, 4.6 Hz, 1H), 3.39–3.32 (m, 2H), 2.93–2.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 145.9, 143.1, 133, 130.7, 128.9, 128.5, 128.3, 128.1, 127.9, 127.4, 87.3, 74.6, 63.6, 57.8, 54.8, 42.3, 24.2; HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{34}H_{30}N_4O_3Na^+$: 565.2210; Found: 565.2212; HPLC (214 nm, Method 2): 14.417 min, 100.0%.

10-(Trityloxymethyl)-5,6,10a,11-tetrahydro-4*H*-oxazolo[3,4-*α*]-[1,2,3]triazolo[1,5-*d*]-[1,4]diazocin-8(10*H*)-one (7l). Prepared by Method A using 32 mg (0.067 mmol) of **6l** which provided 31 mg (98%) of **7l** as a white solid; mp 95.9–97.4 °C; R_f = 0.15 (hexanes–EtOAc, 1 : 2); IR (KBr): 1756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.37 (m, 7H), 7.37–7.17 (m, 9H), 4.54–4.34 (m, 3H), 3.91 (ddd, J = 14.7, 3.6, 2.4 Hz, 1H), 3.80 (dd, J = 9.9, 4.3 Hz, 1H), 3.38 (ddd, J = 14.2, 10.4, 4.3 Hz, 2H), 3.09–2.91 (m, 1H), 2.78–2.47 (m, 2H), 2.27–2.09 (m, 1H), 1.89–1.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 143.1, 137.3, 132.9, 128.5, 128.1, 127.4, 87.2, 74.5, 63.4, 60.8, 49.3, 43.6, 28.7, 20.7; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{29}H_{28}N_4O_3Na^+$: 503.2054; Found: 503.2049; HPLC (254 nm, Method 2): 8.533 min, 96.7%.

3-Phenyl-10-(trityloxymethyl)-5,6,10a,11-tetrahydro-4*H*-oxazolo-[3,4-*a*][1,2,3]triazo-lo[1,5-*d*][1,4]diazocin-8(10*H*)-one (7m). Prepared by Method B using 64 mg (0.12 mmol) of **6m** which provided 57 mg of **7m** (89%) as a pale yellow solid; mp 92.9–94.4 °C; R_f = 0.51 (hexanes–EtOAc, 2 : 3); IR (KBr): 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.64 (m, 2H), 7.51–7.38 (m, 8H), 7.38–7.19 (m, 10H), 4.64–4.33 (m, 3H), 3.98 (dd, J = 12.9, 1.8 Hz, 1H), 3.84 (dd, J = 9.0, 5.6 Hz, 1H), 3.41 (ddd, J = 14.2, 10.4, 4.3 Hz, 2H), 3.13–3.05 (m, 1H), 2.87–2.83 (m, 1H), 2.65 (t, J = 13.2 Hz, 1H), 2.43–2.21 (m, 1H), 1.99–1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 145.0, 143.1, 133.2, 131, 128.9, 128.5, 128.1, 127.4, 127.1, 87.3, 74.5, 63.4, 60.9, 50.3, 43.7, 28.2, 20.9; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{35}H_{32}N_4O_3Na^+$: 579.2367; Found: 579.2362; HPLC (254 nm, Method 2): 12.933 min, 94.7%.

11-(Trityloxymethyl)-4,5,6,7,11a,12-hexahydrooxazolo[3,4-*a*]-[1,2,3]triazolo[1,5-*d*]-[1,4]diazonin-9(11*H*)-one (7n). Prepared by Method B using 61 mg (0.12 mmol) of **6n** which provided 49 mg (80%) of **7n** as a white solid; mp 73.1–74.5 °C; R_f = 0.18 (hexanes–EtOAc, 1 : 2); IR (KBr): 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47–7.39 (m, 6H), 7.37–7.21 (m, 9H), 4.59 (dd, J = 14.5, 2.4 Hz, 1H), 4.45 (dd, J = 9.2, 4.4 Hz, 1H), 4.37 (dd, J = 14.5, 8.0 Hz, 1H), 3.86 (ddd, J = 8.0, 5.6, 2.4 Hz, 1H), 3.67–3.57 (m, 1H), 3.50 (dd, J = 10.4, 4.6 Hz, 1H), 3.30 (dd, J = 10.4, 3.9 Hz, 1H), 3.00–2.71 (m, 2H), 2.22–2.04 (m, 2H), 1.94 (dd, J = 11.2, 5.6 Hz, 2H), 1.47–1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 143.1, 138.0, 133.6, 128.6, 128.1, 127.4, 87.3, 75.2, 63.9, 60.7, 51.5, 43.6, 25.6, 23.4, 22.0; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{30}H_{30}N_4O_3Na^+$: 517.2210; Found: 517.2205; HPLC (254 nm, Method 3): 12.842 min, 97.2%.

12-(Trityloxymethyl)-5,6,7,8,12a,13-hexahydro-4*H*-oxazolo [3,4-*a*][1,2,3]triazolo[1,5-*d*][1,4]diazecin-10(12*H*)-one (7o). Prepared by Method B using 61 mg (0.12 mmol) of **6o** which provided 46 mg (76%) of **7o** as a white solid; mp 92.5–93.8 °C; R_f = 0.38 (hexanes–EtOAc, 1 : 8); IR (KBr): 1756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.42 (m, 7H), 7.34–7.22 (m, 9H), 5.19 (br s, 1H), 4.41 (dd, J = 15.1, 3.1 Hz, 1H), 4.28 (dd, J = 15.1, 3.5 Hz, 1H), 3.91 (d, J = 3.5 Hz, 1H), 3.76–3.66 (m, 1H), 3.56 (dd, J = 10.4, 4.1 Hz, 1H), 3.21 (dd, J = 10.4, 3.0 Hz, 1H), 2.90–2.63 (m, 3H), 1.84–1.52 (m, 4H), 1.26–1.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 143.2, 138.5, 132.4, 128.6, 128.1, 127.3, 87.1, 75.3, 63.8, 60.6, 49.1, 45.8, 27.4, 24.7, 20.8; HRMS-ESI: m/z [M + Na$^+$] calcd for $C_{31}H_{32}N_4O_3Na^+$: 531.2367; Found: 531.2369; HPLC (254 nm, Method 2): 11.417 min, 99.7%.

13-(Trityloxymethyl)-4,5,6,7,8,9,13a,14-octahydrooxazolo-[3,4-*a*][1,2,3]triazolo[1,5-*d*][1,4]diazacycloundecin-11(13*H*)-one (7p). Prepared by Method B using 92 mg (0.18 mmol) of **6p** which provided 48 mg (52%) of **7p** as a white solid; mp 77.5–79.4 °C; R_f = 0.52 (hexanes–EtOAc, 1 : 4); IR (KBr): 1756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.41 (m, 7H), 7.38–7.21 (m, 9H), 4.60 (t, J = 6.7 Hz, 1H), 4.40–4.23 (m, 3H), 3.55 (dd, J = 10.4, 4.6 Hz, 1H), 3.44–3.31 (m, 2H), 2.84–2.77 (m, 2H),

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2.26–2.12 (m, 2H), 1.82–1.79 (m, 2H), 1.44–1.37 (m, 1H), 1.30–1.26 (m, 2H), 1.13–1.02 (m, 1H), 0.92–0.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 143.2, 137.7, 132.4, 128.7, 128.1, 127.4, 87.4, 75.8, 64.0, 60.8, 51.8, 44.8, 27.0, 26.0, 23.1, 21.1, 20.0; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{32}H_{34}N_4O_3Na^+$: 545.2523; Found: 545.2527; HPLC (254 nm, Method 1): 12.483 min, 97.1%.

14-(Trityloxymethyl)-5,6,7,8,9,10,14a,15-octahydro-4*H*-oxazolo-[3,4-*a*][1,2,3]triazolo-[1,5-*d*][1,4]diazacyclododecin-12(14*H*)-one (7q). Prepared by Method C using 97 mg (0.18 mmol) of **6q** which provided 68 mg (71%) of **7q** as a white solid; mp 215.0–216.9 °C; R_f = 0.41 (hexanes–EtOAc, 1 : 8); IR (KBr): 1755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.32–7.17 (m, 15H), 4.87 (dd, *J* = 6.6, 3.8 Hz, 1H), 4.45 (dd, *J* = 14.2, 3.5 Hz, 1H), 4.34 (dd, *J* = 14.1, 8.2 Hz, 1H), 4.17–4.12 (m, 1H), 3.66 (dt, *J* = 15.0, 4.8 Hz, 1H), 3.47 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.27–3.18 (m, 1H), 2.88 (dd, *J* = 10.4, 2.6 Hz, 1H), 2.81–2.71 (m, 1H), 2.65–2.56 (m, 1H), 1.78–1.67 (m, 1H), 1.55–1.16 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 143.0, 137.3, 132.9, 128.4, 127.9, 127.2, 86.9, 77.3, 63.0, 58.5, 48.2, 39.2, 27.0, 26.2, 24.8, 23.5, 22.1, 20.2; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{33}H_{36}N_4O_3Na^+$: 559.2680; Found: 559.2676; HPLC (214 nm, meth.3): 13.783 min, 97.7%.

1(4,3)[(5-Trityloxymethyl)oxazolidin-2-one]3(4,1)triazola-cyclo-nonaphane (14q). Prepared by Method B using 74 mg (0.14 mmol) of **6q** which provided 15 mg (20%) of **14q** as a white solid; mp 85.5–87.0 °C; R_f = 0.68 (hexanes–EtOAc, 1 : 8); IR (KBr): 1755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.44 (m, 6H), 7.37–7.25 (m, 10H), 4.58–4.49 (m, 1H), 4.37 (d, *J* = 14.1 Hz, 1H), 4.17 (d, *J* = 4.3 Hz, 2H), 3.52 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.38–3.35 (m, 1H), 2.88–2.67 (m, 3H), 2.50–2.41 (m, 1H), 1.77–1.60 (m, 2H), 1.26–1.14 (m, 4H), 0.99–0.93 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 147.8, 143.1, 128.6, 128.1, 127.5, 122.8, 87.4, 74.9, 63.6, 58.5, 54.7, 44.1, 25.9, 25.6, 25.2, 24.1, 23.9, 23.5; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{33}H_{36}N_4O_3Na^+$: 559.2680; Found: 559.2681; HPLC (214 nm, meth.2): 13.017 min, 100.0%.

General procedure of preparation of dimers

iPr_2NEt (300 mol%) and $(EtO)_3P{\cdot}CuI$ (20 mol%) were added to a solution of azide **6** in toluene (0.03 M). The mixture was heated at 80 °C with microwave reactor (Initiator-Biotage: power max 400 W, internal pressure max 290 psi, ramp time 1 min) for 1 hour, cooled, concentrated and chromatographed to provide dimer **17**.

1(4,3)[(5-Trityloxymethyl)oxazolidin-2-one]3(4,1)triazolo-8-(4,3)-[(5-trityloxymethyl)oxazolidin-2-one]10(4,1)triazolacyclo-tetra-decaphane (15a). Prepared by general procedure using 143 mg (0.29 mmol) of **6n** which provided 35 mg (24%) of **17a** as a pale yellow solid; mp 130.4–132.1 °C; IR (KBr): 1758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.46 (s, 1H), 7.38–7.20 (m, 30H), 4.59 –4.31 (m, 6H), 4.10–4.05 (m, 2H), 3.42–3.34 (m, 4H), 3.23–3.12 (m, 3H), 3.06–2.98 (m, 1H), 2.73–2.68 (m, 4H), 1.71–1.54 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 157.3, 147.8, 147.6, 143.1, 143.1, 128.5, 128.5, 128.0, 127.4, 122.5, 122.2, 87.3, 87.2, 75.9, 75.5, 63.5, 63.5, 58.1, 58.0, 52.0, 51.8, 43.1, 42.8, 26.1, 25.9, 25.6, 25.5, 24.0, 23.9; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{60}H_{60}N_8O_6Na^+$: 1011.4528; Found: 1011.4517; HPLC (254 nm, meth.2): 15.850 min, 97.6%.

1(4,3)[(5-Trityloxymethyl)oxazolidin-2-one]3(4,1)triazolo-9-(4,3)-[(5-trityloxymethyl)oxazolidin-2-one]11(4,1)triazolacyclo-hexadeca-phane (15b). Prepared by general procedure using 71 mg (0.14 mmol) of **6o** which provided 35 mg (49%) of **17b** as a white solid; mp 134.4–136.2 °C; IR (KBr): 1754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.43–7.35 (m, 12H), 7.33–7.22 (19H), 4.56–4.53 (m, 1H), 4.48–4.32 (m, 5H), 4.07–4.04 (m, 2H), 3.55–3.35 (m, 3H), 3.30–3.25 (m, 1H), 3.18–3.13 (m, 1H), 3.09–3.05 (m, 1H), 2.93–2.54 (m, 6H), 1.74–0.96 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 156.8, 148.0, 147.5, 142.9, 142.8, 128.3, 128.2, 127.8, 127.1, 127.1, 122.5, 121.6, 87.0, 86.9, 75.2, 74.3, 62.9, 57.0, 56.6, 51.2, 50.3, 42.1, 41.7, 27.6, 27.1, 26.1, 25.1, 24.4, 23.8, 23.4; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{62}H_{64}N_8O_6Na^+$: 1039.4841; Found: 1039.4826; HPLC (254 nm, Method 2): 16.592 min, 97.8%.

1(4,3)[(5-Trityloxymethyl)oxazolidin-2-one]3(4,1)triazolo-10-(4,3)[(5-trityloxymethyl)oxazolidin-2-one]12(4,1)triazolacyclo-octadecaphane (15c). Prepared by general procedure using 107 mg (0.21 mmol) of **6p** which provided 56 mg (52%) of **17c** as a white solid; mp 217.5 (dec.); IR (KBr): 1751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 2H), 7.38–7.35 (m, 11H), 7.29–7.19 (m, 19H), 4.52–4.39 (m, 6H), 3.95–3.94 (m, 2H), 3.66–3.55 (m, 2H), 3.28–3.22 (m, 2H), 3.11–3.02 (m, 4H), 2.84–2.75 (m, 2H), 2.70–2.60 (m, 2H), 1.71–1.52 (m, 8 H), 1.26–1.21 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 148.5, 143.2, 128.6, 128.1, 127.4, 122.0, 87.2, 74.1, 63.1, 55.9, 49.3, 40.8, 28.0, 26.3, 26.0, 25.4, 24.9; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{64}H_{68}N_8O_6Na^+$: 1067.5154; Found: 1067.5140; HPLC (254 nm, Method 2): 13.258 min, 97.0%.

1(4,3)[(5-Trityloxymethyl)oxazolidin-2-one]3(4,1)triazolo-11-(4,3)[(5-trityloxymethyl)oxazolidin-2-one]13(4,1)triazolacyclo-icosanaphane (15d). Prepared by general procedure using 106 mg (0.20 mmol) of **6q** which provided 62 mg (58%) of **17d** as a white solid; mp 111.1–112.8 °C; IR (KBr): 1755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.34 (m, 12H), 7.31–7.19 (m, 20H), 4.55–4.30 (m, 6H), 4.03–3.99 (m, 2H), 3.61–3.41 (m, 2H), 3.40–3.31 (m, 2H), 3.18–3.13 (m, 1H), 2.97–2.85 (m, 3H), 2.78–2.60 (m, 4H), 1.65–1.61 (m, 4H), 1.40–1.33 (m, 4H), 1.26–1.16 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 148.6, 148.4, 143.1, 128.5, 128.5, 128.0, 128.0, 127.4, 127.3, 121.8, 121.6, 87.2, 87.1, 74.6, 74.3, 63.2, 56.7, 56.2, 50.5, 50.3, 42.3, 42.0, 28.4, 28.2, 27.7, 27.6, 27.5, 26.9, 26.2, 25.9, 25.9, 25.8, 24.9, 24.5; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{66}H_{72}N_8O_6Na^+$: 1095.5467; Found: 1095.5448; HPLC (254 nm, Method 2): 20.550 min, 98.7%.

General procedure of hydrolysis of 7. Lithium hydroxide (3000 mol%) was added to a solution of compound **7** (5.0 mM) in EtOH–H_2O (5 : 2). The reaction mixture was refluxed until completion of the reaction as indicated by TLC. The reaction was cooled, concentrated (to remove EtOH) and extracted with iPrOH–CH_2Cl_2 (3 : 1). The combined organic phase was dried

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over anhydrous $MgSO_4$, concentrated and chromatographed to provide **8**.

1-(4,5,6,7-Tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazin-6-yl)-2-(trityloxy)ethanol (8a). Prepared by the general procedure using 50 mg (0.11 mmol) of **7a** which provided 45 mg (96%) of **8a** as a colorless oil; R_f = 0.26 (EtOAc–MeOH, 98 : 2); IR (KBr): 3323 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.36 (m, 7H), 7.35–7.20 (m, 9H), 4.27–4.17 (m, 2H), 3.98–3.90 (m, 2H), 3.72 (dd, J = 9.9, 5.5 Hz, 1H), 3.45 (dd, J = 10.0, 4.1 Hz, 1H), 3.31 (dd, J = 10.0, 5.7 Hz, 1H), 3.23–3.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 131.7, 128.6, 128.5, 128.0, 127.8, 127.3, 87.1, 71.0, 64.7, 54.7, 47.6, 40.2; HRMS-ESI: m/z [M + Na^+] calcd for $C_{26}H_{26}N_4O_2Na^+$: 449.1948; Found: 449.1941; HPLC (214 nm, Method 2): 6.117 min, 95.5%.

1-(3-Phenyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazin-6-yl)-2-(trityloxy)-ethanol (8c). Prepared by the general procedure using 25 mg (0.05 mmol) of **7c** which provided 22 mg (92%) of **8c** as a white solid; mp 196.3–198.3 °C; R_f = 0.39 (hexanes–EtOAc, 2 : 3); IR (KBr): 3336, 3228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.61 (m, 2H), 7.49–7.38 (m, 8H), 7.38–7.18 (m, 12H), 4.41 (d, J = 16.3 Hz, 1H), 4.31 (dd, J = 12.7, 4.0 Hz, 1H), 4.18 (d, J = 16.3 Hz, 1H), 4.08–3.95 (m, 1H), 3.73 (s, 1H), 3.49 (dd, J = 10.0, 3.8 Hz, 1H), 3.35 (dd, J = 10.0, 5.9 Hz, 1H), 3.26–3.10 (m, 1H), 2.86 (s, 1H), 2.12 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 141.2, 131.3, 128.8, 128.6, 128.3, 128.1, 127.6, 127.4, 126.1, 87.3, 71.1, 64.7, 54.4, 48.0, 41.7; HRMS-ESI: m/z [M + Na^+] calcd for $C_{32}H_{30}N_4O_2Na^+$: 525.2261; Found: 525.2252; HPLC (254 nm, Method 2): 12.325 min, 99.7%.

1-(5,6,7,8-Tetrahydro-4*H*-[1,2,3]triazolo[1,5-*d*][1,4]diazepin-7-yl)-2-(trityloxy)-ethanol (8i). Prepared by the general procedure using 43 mg (0.09 mmol) of **7i** which provided 35 mg (88%) of **8i** as a white solid; mp 71.7–73.6 °C; R_f = 0.21 (EtOAc–MeOH, 98 : 2); IR (KBr): 3334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.39 (m, 7H), 7.39–7.19 (m, 9H), 4.78 (d, J = 14.3 Hz, 1H), 4.16 (dd, J = 14.3, 9.4 Hz, 1H), 3.67 (dd, J = 9.9, 5.6 Hz, 1H), 3.47–3.30 (m, 2H), 3.26 (dd, J = 12.1, 3.9 Hz, 1H), 3.00 (dd, J = 14.4, 5.2 Hz, 1H), 2.87 (dd, J = 8.7, 6.1 Hz, 1H), 2.81–2.61 (m, 2H), 2.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 137.6, 132.9, 128.6, 128.0, 127.3, 87.2, 71.2, 65.1, 59.1, 55.9, 46.2, 26.9; HRMS-ESI: m/z [M + Na^+] calcd for $C_{27}H_{28}N_4O_2Na^+$: 463.2104; Found: 463.2099; HPLC (254 nm, Method 3): 12.625 min, 94.0%.

1-(3-Phenyl-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*d*][1,4] diazepin-7-yl)-2-(trityloxy)ethanol (8k). Prepared by the general procedure using 42 mg (0.08 mmol) of **7k** which provided 39 mg (98%) of **8k** as a white solid; mp 199.3–201.1 °C; R_f = 0.21 (hexanes–EtOAc, 1 : 8); IR (KBr): 3333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63–7.53 (m, 2H), 7.45–7.40 (m, 8H), 7.38–7.14 (m, 10H), 4.81 (d, J = 14.2 Hz, 1H), 4.23 (dd, J = 14.3, 9.4 Hz, 1H), 3.70 (dd, J = 9.9, 5.6 Hz, 1H), 3.38 (ddd, J = 15.9, 10.0, 5.0 Hz, 2H), 3.29–3.17 (m, 2H), 3.00–2.78 (m, 2H), 2.78–2.62 (m, 1H), 2.55 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 143.5, 134.2, 131.3, 128.7, 128.6, 128.0, 127.8, 127.8, 127.3, 87.2, 71.2, 65.1, 59.0, 56.2, 46.1, 26.8; HRMS-ESI: m/z [M + Na^+] calcd for $C_{33}H_{32}N_4O_2Na^+$: 539.2417; Found: 539.2412; HPLC (214 nm, Method 3): 14.467 min, 95.3%.

1-(4,5,6,7,8,9-Hexahydro-[1,2,3]triazolo[1,5-*d*][1,4]diazocin-8-yl)-2-(trityloxy)-ethanol (8l). Prepared by the general procedure using 49 g (0.10 mmol) of **7l** which provided 32 mg (65%) of **8l** as a white solid; mp 176.4–176.9 °C; R_f = 0.20 (EtOAc); IR (KBr): 3383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.29 (m, 7H), 7.27–7.22 (m, 9H), 4.50 (dd, J = 14.4, 3.5 Hz, 1H), 4.08 (dd, J = 14.4, 7.8 Hz, 1H), 3.71–3.66 (m, 1H), 3.45 (dd, J = 10.0, 4.1 Hz, 1H), 3.33 (dd, J = 10.0, 5.2 Hz, 1H), 3.11–3.00 (m, 2H), 2.83–2.79 (m, 2H), 2.39–2.30 (m, 1H), 1.88–1.77 (m, 1H), 1.67–1.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 137.8, 132.0, 128.6, 128.0, 127.2, 87.0, 70.9, 65.0, 61.4, 49.8, 44.4, 33.2, 20.8; HRMS-ESI: m/z [M + Na^+] calcd for $C_{28}H_{30}N_4O_2Na^+$: 477.2261; Found: 477.2269; HPLC (254 nm, Method 3): 12.717 min, 93.0%.

1-(3-Phenyl-4,5,6,7,8,9-hexahydro-[1,2,3]triazolo[1,5-*d*][1,4]-diazocin-8-yl)-2-(trityloxy)ethanol (8m). Prepared by the general procedure using 57 mg (0.10 mmol) of **7m** which provided 40 mg (70%) of **8m** as a white solid; mp 193.2–193.9 °C; R_f = 0.19 (hexanes–EtOAc, 2 : 3); IR (KBr): 3374 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H), 7.49–7.40 (m, 8H), 7.35–7.22 (m, 10H), 4.54 (dd, J = 14.4, 3.3 Hz, 1H), 4.12 (dd, J = 14.4, 7.9 Hz, 1H), 3.75–3.69 (m, 1H), 3.47 (dd, J = 10.0, 4.1 Hz, 1H), 3.35 (dd, J = 10.0, 5.2 Hz, 1H), 3.14–3.06 (m, 2H), 3.01–2.88 (m, 2H), 2.44–2.35 (m, 1H), 1.96–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 143.6, 134.0, 131.7, 128.7, 128.6, 128.0, 127.7, 127.2, 127.0, 87.1, 71.0, 65.0, 61.5, 50.5, 44.6, 32.6, 20.9; HRMS-ESI: m/z [M + Na^+] calcd for $C_{34}H_{34}N_4O_2Na^+$: 553.2574; Found: 553.2580; HPLC (254 nm, Method 3): 14.575 min, 91.2%.

1-(5,6,7,8,9,10-Hexahydro-4*H*-[1,2,3]triazolo[1,5-*d*][1,4]-diazonin-9-yl)-2-(trityloxy)-ethanol (8n). Prepared by the general procedure using 46 mg (0.09 mmol) of **7n** which provided 33 mg (77%) of **8n** as a colorless oil; R_f = 0.24 (CH_2Cl_2–MeOH, 95 : 5); IR (KBr): 3377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.42 (m, 7H), 7.33–7.22 (m, 9H), 4.66 (d, J = 14.1 Hz, 1H), 4.15 (dd, J = 14.1, 8.2 Hz, 1H), 4.03–3.98 (m, 1H), 3.60–3.50 (m, 1H), 3.28 (dd, J = 9.6, 4.7 Hz, 1H), 3.20 (dd, J = 9.5, 7.3 Hz, 1H), 2.82–2.62 (m, 3H), 2.44–2.39 (m, 1H), 2.18 (br s, 1H), 1.78–1.71 (m, 2H), 1.25–1.19 (m, 1H), 0.88–0.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 138.3, 133.0, 128.6, 128.0, 127.3, 87.2, 72.8, 64.8, 58.6, 55.5, 49.0, 29.1, 25.1, 22.9; HRMS-ESI: m/z [M + Na^+] calcd for $C_{29}H_{32}N_4O_2Na^+$: 491.2417; Found: 491.2421; HPLC (254 nm, Method 3): 14.217 min, 96.1%.

1-(4,5,6,7,8,9,10,11-Octahydro-[1,2,3]triazolo[1,5-*d*][1,4]- diazecin-10-yl)-2-(trityloxy)-ethanol (8o). Prepared by the general procedure using 46 mg (0.09 mmol) of **7o** which provided 41 mg (90%) of **8o** as a white solid; mp 81.3–83.2 °C; R_f = 0.31 (CH_2Cl_2–MeOH, 95 : 5); IR (KBr): 3333, 3206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (m, 7H), 7.34–7.21 (m, 9H), 4.37 (dd, J = 14.5, 4.3 Hz, 1H), 4.20 (dd, J = 14.5, 5.7 Hz, 1H), 3.94 (dd, J = 10.5, 5.2Hz, 1H), 3.38 (AB dd, J_{AB} = 28.3 Hz, δ_A = 3.43, J = 9.8, 4.5 Hz, δ_B = 3.33, J = 9.8, 5.3 Hz, 2H), 3.16 (dd, J = 10.3, 5.6 Hz, 1H), 2.98–2.89 (m, 1H), 2.80–2.71 (m,

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2H), 2.44–2.38 (m, 1H), 1.88–1.78 (m, 2H), 1.43–1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 138.8, 132.1, 128.7, 127.9, 127.2, 86.9, 71.5, 64.6, 59.1, 48.2, 45.5, 28.7, 28.7, 21.8, 20.9; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{30}H_{34}N_4O_2Na^+$: 505.2574; Found: 505.2572; HPLC (254 nm, Method 3): 14.242 min, 94.7%.

1-(5,6,7,8,9,10,11,12-Octahydro-4*H*-[1,2,3]triazolo[1,5-*d*]-[1,4]-diazacycloundecin-11-yl)-2-(trityloxy)ethanol (8p). Prepared by the general procedure using 67 mg (0.13 mmol) of **7p** which provided 48 mg (75%) of **8p** as a white solid; mp 81.5–82.8 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 95 : 5); IR (KBr): 3347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.41 (m, 7H), 7.34–7.22 (m, 9H), 4.41 (dd, *J* = 13.7, 2.2 Hz, 1H), 4.15 (dd, *J* = 13.6, 9.1 Hz, 1H), 4.03–3.98 (m, 1H), 3.33–3.20 (m, 3H), 2.97–2.92 (m, 1H), 2.62–2.54 (m, 1H), 2.40–2.36 (m, 1H), 2.02 (br s, 1H), 1.90–1.81 (m, 1H), 1.70–1.62 (m, 2H), 1.42–1.30 (m, 3H), 1.26–1.09 (m, 2H), 0.98–0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 138.7, 131.7, 128.6, 128.0, 127.3, 87.2, 72.0, 65.1, 60.9, 53.2, 46.3, 27.8, 27.2, 21.4, 21.3, 20.0; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{31}H_{36}N_4O_2Na^+$: 519.2730; Found: 519.2732; HPLC (254 nm, Method 3): 15.667 min, 99.7%.

1-(4,5,6,7,8,9,10,11,12,13-Decahydro-[1,2,3]triazolo[1,5-*d*]-[1,4]-diazacyclododecin-12-yl)-2-(trityloxy)ethanol (8q). Prepared by the general procedure using 61 mg (0.11 mmol) of **7q** which provided 55 mg (95%) of **8q** as a white solid; mp 142.2–143.4 °C. R_f = 0.21 (CH_2Cl_2–MeOH, 95 : 5); IR (KBr): 3335 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.43 (m, 7H), 7.34–7.22 (m, 9H), 4.33 (dd, *J* = 14.1, 3.3 Hz, 1H), 4.13 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.96 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.34 (d, *J* = 5.5 Hz, 2H), 3.25–3.20 (m, 1H), 2.77–2.60 (m, 2H), 2.50–2.46 (m, 1H), 1.90–1.74 (m, 2H), 1.39–1.23 (8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 139.0, 132.2, 128.6, 127.9, 127.2, 87.0, 71.6, 64.9, 60.1, 50.3, 47.0, 27.4, 26.0, 25.0, 24.1, 23.4, 21.0; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{32}H_{38}N_4O_2Na^+$: 533.2887; Found: 533.2888; HPLC (254 nm, Method 3): 16.233 min, 97.4%.

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References

1 S. C. Bergmeier and S. J. Katz, *J. Comb. Chem.*, 2002, **4**, 162–166.
2 S. C. Bergmeier and D. M. Stanchina, *J. Org. Chem.*, 1997, **62**, 4449–4456.
3 S. C. Bergmeier and D. M. Stanchina, *J. Org. Chem.*, 1999, **64**, 2852–2859.
4 M. C. McMills and S. C. Bergmeier, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, pp. 105–172.
5 A. R. Kelly, J. Q. Wei, S. Kesavan, J. C. Marie, N. Windmon, D. W. Young and L. A. Marcaurelle, *Org. Lett.*, 2009, **11**, 2257–2260.
6 R. Hili, V. Rai and A. K. Yudin, *J. Am. Chem. Soc.*, 2010, **132**, 2889–2891.
7 T. Yoshimitsu, T. Ino and T. Tanaka, *Org. Lett.*, 2008, **10**, 5457–5460.
8 G. Malik, A. Esteoule, P. Retailleau and P. Dauban, *J. Org. Chem.*, 2011, **76**, 7438–7448.
9 R. Liu, S. R. Herron and S. A. Fleming, *J. Org. Chem.*, 2007, **72**, 5587–5591.
10 Q.-H. Deng, J.-C. Wang, Z.-J. Xu, C.-Y. Zhou and C.-M. Che, *Synthesis*, 2011, 2959–2967.
11 A. Esteoule, F. Duran, P. Retailleau, R. H. Dodd and P. Dauban, *Synthesis*, 2007, 1251–1260.
12 R. Anupam, A. Nayek, N. J. Green, F. J. Grundy, T. M. Henkin, J. A. Means, S. C. Bergmeier and J. V. Hines, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3541–3544.
13 J. A. Means, S. Katz, A. Nayek, R. Anupam, J. V. Hines and S. C. Bergmeier, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3600–3604.
14 I. Maciagiewicz, S. Zhou, S. C. Bergmeier and J. V. Hines, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4524–4527.
15 C. M. Orac, S. Zhou, J. A. Means, D. Boehm, S. C. Bergmeier and J. V. Hines, *J. Med. Chem.*, 2011, **43**, 6786–6795.
16 Molecular modeling was performed with Spartan '08 for Macintosh, Wavefunction Inc., Irvine, CA. The lowest energy conformer for each compound was obtained using molecular mechanics MMFF base set.
17 I. Akritopoulou-Zanze, V. Gracias and S. W. Djuric, *Tetrahedron Lett.*, 2004, **45**, 8439–8441.
18 R. A. Brawn, M. Welzel, J. T. Lowe and J. S. Panek, *Org. Lett.*, 2010, **12**, 336–339.
19 K. C. Majumdar, K. Ray, S. Ganai and T. Ghosh, *Synthesis*, 2010, 858–862.
20 F. Dolhem, F. Al Tahli, C. Lievre and G. Demailly, *Eur. J. Org. Chem.*, 2005, 5019–5023.
21 F. Couty, F. Durrat and D. Prim, *Tetrahedron Lett.*, 2004, **45**, 3725–3728.
22 D. K. Mohapatra, P. K. Maity, R. G. Gonnade, M. S. Chorghade and M. K. Gurjar, *Synlett*, 2007, 1893–1896.
23 V. S. Sudhir, R. B. N. Baig and S. Chandrasekaran, *Eur. J. Org. Chem.*, 2008, 2423–2429.
24 H. Yanai and T. Taguchi, *Tetrahedron Lett.*, 2005, **46**, 8639–8643.
25 V. S. Sudhir, N. Y. P. Kumar, R. B. N. Baig and S. Chandrasekaran, *J. Org. Chem.*, 2009, **74**, 7588–7591.
26 K. C. Majumdar and K. Ray, *Synthesis*, 2011, 3767–3783.
27 M. S. Kim, H. J. Yoon, B. K. Lee, J. H. Kwon, W. K. Lee, Y. Kim and H. J. Ha, *Synlett*, 2005, 2187–2190.
28 W. H. Pearson, S. C. Bergmeier and J. A. Chytra, *Synthesis*, 1990, 156–159.
29 C. Chowdhury, S. Mukherjee, B. Das and B. Achari, *J. Org. Chem.*, 2009, **74**, 3612–3615.
30 J. J. Lian, P. C. Chen, Y. P. Lin, H. C. Ting and R. S. Liu, *J. Am. Chem. Soc.*, 2006, **128**, 11372–11373.
31 O. V. Larionov and E. J. Corey, *J. Am. Chem. Soc.*, 2008, **130**, 2954–2955.
32 H. M. Sheldrake and T. W. Wallace, *Tetrahedron Lett.*, 2007, **48**, 4407–4411.
33 A. I. Hernandez, J. Balzarini, A. Karlsson, M. J. Camarasa and M. J. Perez-Perez, *J. Med. Chem.*, 2002, **45**, 4254–4263.
34 H. M. Zhang and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7048–7056.
35 T. Yasukouchi and K. Kanematsu, *Tetrahedron Lett.*, 1989, **30**, 6559–6562.
36 S. E. Denmark and S. M. Yang, *J. Am. Chem. Soc.*, 2002, **124**, 2102–2103.
37 S. R. Macaulay, *J. Org. Chem.*, 1980, **45**, 734–735.
38 B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. T. Zhao, Z. Y. Lin, G. C. Jia and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923–8930.
39 L. Zhang, X. G. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. C. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998–15999.
40 K. D. Bodine, D. Y. Gin and M. S. Gin, *Org. Lett.*, 2005, **7**, 4479–4482.
41 N. Pietrzik, D. Schmollinger and T. Ziegler, *Beilstein J. Org. Chem.*, 2008, **4**, 30.
42 T. Hakogi, T. Yamamoto, S. Fujii, K. Ikeda and S. Katsumura, *Tetrahedron Lett.*, 2006, **47**, 2627–2630.
43 P. Wei and R. J. Kerns, *Tetrahedron Lett.*, 2005, **46**, 6901–6905.
44 S. J. Katz and S. C. Bergmeier, *Tetrahedron Lett.*, 2002, **43**, 557–559.
45 G. S. Lemen and J. P. Wolfe, *Org. Lett.*, 2010, **12**, 2322–2325.
46 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923–2925.