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Graphical Abstract

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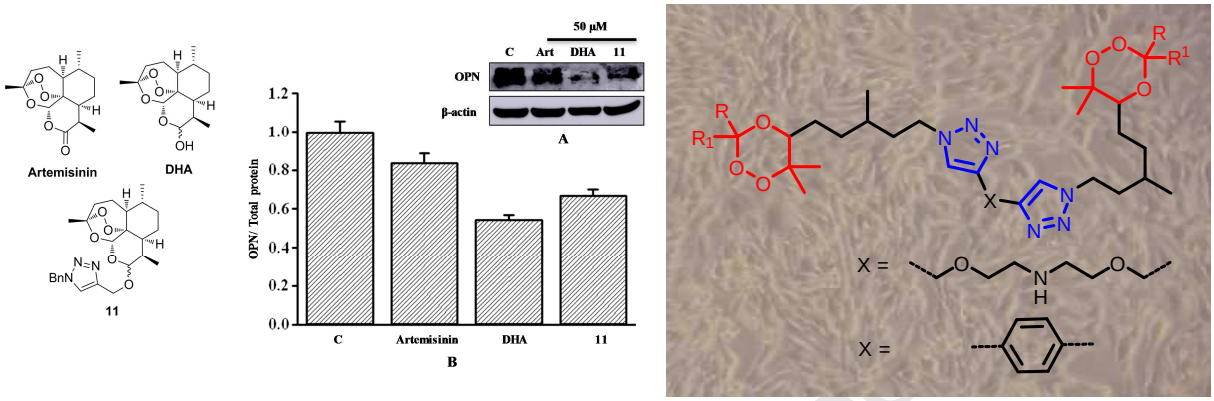

1,2,3-Triazole tethered 1,2,4-trioxanes: Studies on their synthesis and effect on osteopontin expression in MDA-MB-435 breast cancer cells

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Abstract

Artemisinin and its analogs have shown potent anticancer activity in primary cancer cultures and cell lines by inhibiting cancer proliferation, metastasis, and angiogenesis. Despite its apparent compatibility to normal cells and low IC_{50} values in comparison to the commonly used anticancer drugs, the underlying mechanisms behind their cytotoxic effects are not yet fully understood. Surprisingly, the efficacy of synthetic 1,2,4-trioxanes against cancer has not been explored yet. Given the high antitumor activity of artemisinin dimers in comparison to their monomers, we report here the synthesis of simple 1,2,3-triazole conjugated 1,2,4-trioxanes and their potential antitumor activity by studying their inhibitory effect on osteopontin (OPN) expression in MDA-MB-435 breast cancer cells. It may be noted that despite being a strong marker to identify human tumor metastasis, no study on effect of artemisinin and its synthetic and semisynthetic derivatives on OPN expression has ever been studied. Although our initial studies did not notice any straight-line relationship between the number of trioxane units in a molecule to the extent of inhibition of OPN protein expression, we could observe better results in some cases in comparison to artemisinin. Although artemisinin did not show appreciable OPN downregulation in MDA-MB-435 cancer cells, dihydroartemisinin (DHA) and some synthetic 1,2,4-trioxane monomers and dimers showed downregulation of OPN expression. Therefore, these compounds may act as an anti-metastatic agent in controlling breast cancer cells metastasis.

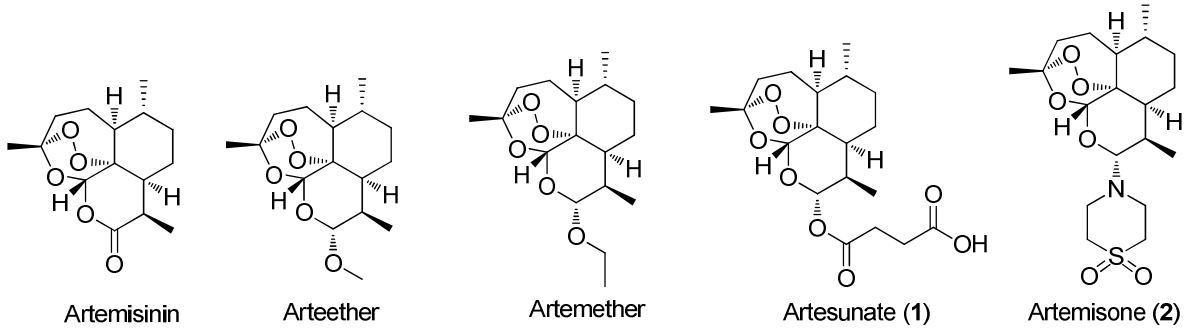
Keywords: 1,2,4-trioxanes, 1,2,3-triazoles, cancer metastasis, OPN, MDA-MB-435 cells

Introduction

Osteopontin (OPN) is a non-collagenous and sialic acid-rich extra cellular glycosylated phosphoprotein that can be used as a biomarker to determine the oncogenic potential of various cancers [1,2]. OPN plays crucial roles in cancer cell metastasis and upregulation of OPN expression can be correlated with enhanced tumor progression and metastasis in a variety of cancers [3-5]. Since OPN regulates various cell signaling pathways leading to tumor progression by interacting with its receptor site, its inhibition can block downstream cell signaling pathways to interrupt tumor cell progression and metastasis.

Since the discovery of anticancer properties of artemisinin by Woerdenberg and coworkers in 1993 [6], various artemisinin derivatives have demonstrated decreased proliferation, increased level of oxidative stress, induction of apoptosis, and angiogenesis in cancer cells. Given the dose-dependent toxicity is one of the major concerns in current anticancer therapy, artemisinin may have benefits as an anticancer agent due to its negligible toxicity even after prolong exposure till one year [7]. Among the semisynthetic artemisinin derived antitumor compounds such as arteether, artemether, artesunate (**1**), and artemisone (**2**), the last one has shown better pharmacokinetic profiles including a longer half-life and lower toxicity [8]. It is believed that replacement of oxygen at C-10 by nitrogen might have removed the possibility of formation of DHA during metabolic process and hence toxicity is reduced further. Artemether and artesunate showed very low side effects in pituitary macroadenoma, malignant skin cancer, laryngeal squamous cell carcinoma, and advanced non-small cell lung [9-11]. They substantially reduced the tumor size and cancer metastasis with combination chemotherapy [9]. A host of semisynthetic artemisinin derivatives, both monomers and dimers, were synthesized to observe that majority of them showed better anticancer activity than the corresponding monomers. Since various theory on anticancer property of artemisinin derivatives suggest that the endoperoxide ring is crucial to its activity [12], it is natural to correlate the enhanced activity of the dimers to the presence of two endoperoxide ring in the same molecule. Although there are many reports on synthesis of synthetic 1,2,4-trioxanes to evaluate their antimalarial activity, to our surprise, their anticancer activities have not been explored yet. Since artemisinin as a drug is not cost-effective due to poor natural abundance and its derivatisation makes it even dearer, we planned to synthesize some synthetic 1,2,4-trioxanes from readily available starting material by following simple synthetic protocols and study their plausible antitumor properties.

1,2,3-triazoles show diverse pharmacological activities such as antiretroviral, antimicrobial, anti-inflammatory, anticonvulsant, antiproliferative, etc. [13,14]. Since 1,2,3-triazole moiety acts as H-bond acceptors of biomolecular targets, they are found in many interesting drugs [15-19]. Due to their stability against metabolic degradation under a wide pH range [20] and redox conditions under physiological conditions, they have found immense importance as a linker in the synthesis of bioconjugates [16,21]. It is already established via various proof of concepts that if two pharmacophores are linked through appropriate spacers to develop a new drug candidate, both pharmacophores may interact synergistically to display higher activity [22]. Such concept was proven in artemisinin and quinine hybrid to achieve enhanced antimalarial effect in comparison to that of the stoichiometric mixture of artemisinin and quinine [23]. Benoit-Vical and coworkers [24] also observed better antimalarial activity in trioxaquine, a trioxane-chloroquine hybrid than the individual precursors. Similar observations were made in the case of artemisinin-primaquine phosphate and stilbene-chalcone hybrids as well [25,26]. The fact that inhibition of tumor metastasis in cancer cells by artemisinin and their derivatives has not been tested for OPN protein expression inspired us to study the synthesis of some 1,2,3-traizole tethered 1,2,4-trioxanes (Scheme 1) and their effect on OPN protein expression. Only in 2018, the first example of effect of 1,2,4-trioxanes on OPN expression was carried out by Bai et al. where they observed decreased OPN level upon treatment of osteoarthritic rat with artesunate (**1**) [27]. Since synthetic 1,2,4-trioxanes have never been studied for their anticancer activity and 1,2,3-triazoles possess antiproliferative properties besides being a biocompatible linker, we assumed that both 1,2,3-triazole and 1,2,4-trioxane cores may act synergistically in a 1,2,3-triazole tethered 1,2,4-trioxanes to show antitumor activity.



Given the fact that osteopontin (OPN) can act as a marker for identification of metastatic cancer cells, we synthesized a series of synthetic 1,2,4-trioxanes monomers and two series of 1,2,4-

dimers (Figure 1) starting from readily available citronellol with 1,2,3-triazoles as linkers to study their effect on down regulation of OPN expression in MDA-MB-435 breast cancer cell lines.

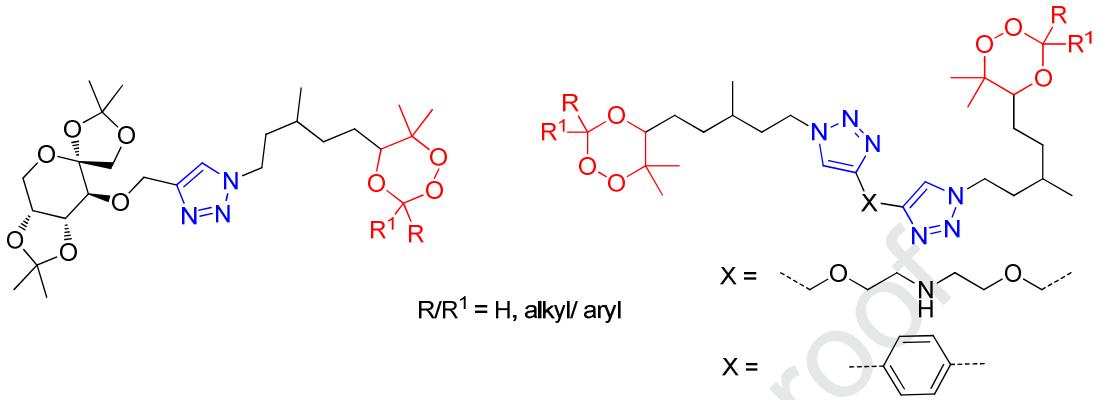


Figure 1.1,2,4-Trioxane for downregulation of OPN expression in breast cancer cell

Results and Discussion

Chemistry

For the synthesis of 1,2,4-trioxanes, we chose citronellol because the diversity points, viz. the double bond and the hydroxy group are separated by five carbon aliphatic chain (Fig. 1). We proposed to introduce the 1,2,3-triazole linker in place of the hydroxy group because of its easy accessibility, physiological stability and the ease of tethering suitable moieties to study their effect on biological activity. For that purpose, we proposed to convert the trisubstituted double bond of citronellol to a 1,2,4-trioxane core having a diversity point and the primary hydroxy group to an azide for the synthesis of 1,2,3-triazole linker (Figure 2).

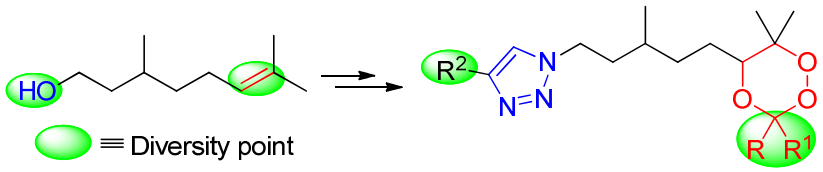


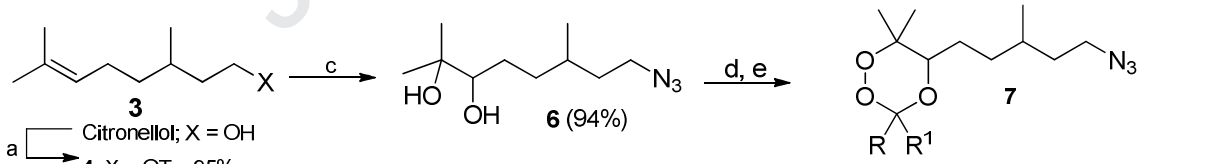
Figure 2. Proposed 1,2,4-trioxane core

To achieve our objective, citronellol (**3**) was converted to its tosylated derivative using *p*-toluenesulfonyl chloride in pyridine at 0-5 ^{o}C to get desired 3,7-dimethyl-6-octenyl tosylate (**4**) [28] in 81% isolated yield (Scheme 1). Then the 3,7-dimethyl-6-octenyl tosylate (**4**) was converted to its azide derivative (**5**) [29] in 78% isolated yield by stirring with two equivalents of

NaN_3 at 40 ^oC overnight in dry DMF. Subsequently, the trisubstituted double bond of 8-azido-2,6-dimethyloct-2-ene (**5**) was dihydroxylated with 1.2 equiv of NMO and 10 mol% OsO_4 in acetone/water (8/2) mixture at room temperature to get a diastereomeric pair of 8-azido-2,6-dimethyloctane-2,3-diol (**6**) [30] in 87% isolated yields. To achieve the azido tethered 1,2,4-trioxane compound (**7a**), we optimized the method (refer to Table S1 in supplementary data) reported by Yadav and Coworkers [31] by treating 8-azido-2,6-dimethyloctane-2,3-diol (**6**) with 50% H_2O_2 (8 equiv.), conc. H_2SO_4 (0.25 equiv.) in dry CH_2Cl_2 to form azido tethered hydroperoxide which upon treatment with *p*-nitrobenzaldehyde in the presence of *p*-TsOH yielded the 1,2,4-trioxane derivative **7a** as an inseparable diastereomeric mixture in 68% overall yield.

The ratio ofdiastereomeric mixture of azido tethered 1,2,4-trioxane (Figure 3) was determined from ^{1}HNMR data where the protons at C3 (δ 6.04 ppm and δ 5.88 ppm) of 1,2,4-trioxane nucleus have shown 1:3 ratio in favor of the nitrophenyl group in the equatorial position. While the *p*-nitrophenyl group at the equatorial position is devoid of 1,3-diaxial interaction to form the major diastereomer, its presence in the axial position experiences 1,3-diaxial interaction with the axial hydrogen at C5 to form the minor diastereomer. The axial orientation of the nitrophenyl group in the minor diastereomer was also confirmed by downfield shift of the proton [δ 3.77-3.73 ppm (minor) and δ 3.61-3.57 ppm (major)] at C5 due to diamagnetic field of the phenyl ring.

Scheme 1. Synthesis of 1,2,4-trioxanes with azide terminal



7a: R= H, R^1= *p*-$NO_2C_6H_4$; 86%
7b: R= H, R^1= *o*-BrC_6H_4; 69%
7c: R= H, R^1= *p*-FC_6H_4; 68%
7d: R= H, R^1= *p*-ClC_6H_4; 65%
7e: R= H, R^1= *m*-BrC_6H_4; 65%
7f: R= H, R^1= *m,p*-$(CH_2O_2)C_6H_3$; 55%
7g: R= H, R^1= *p*-OHC_6H_4; 85%
7h: R= H, R^1= C_6H_5; 61%
7i: R= H, R^1= *p*-$MeOC_6H_4$; 59%
7j: R= H, R^1= *p*-MeC_6H_4; 60%
7k: R= H, R^1= *m*-$NO_2C_6H_4$; 83%
7l: R= H, R^1= $C_{10}H_7$; 77%
7m: R= H, R^1= C_4H_3O; 76%
7n: R, R^1= C_5H_{10}; 53%
7o R= CH_3, R^1= *p*-ClC_6H_4; 44%

Reaction conditions: a) dry pyridine, *p*-TsCl, 0-5 ^{o}C, 12 h; b) dry DMF, NaN_3, 40 ^{o}C, overnight; c) NMO.H_2O, OsO_4 (10 mol%), acetone/water(8/2), RT, 24 h; d) H_2O_2, H_2SO_4, dichloromethane, 0-5 ^{o}C, 4 h; e) *p*-nitrobenzaldehyde, *p*-TsOH, dry dichloromethane, 0-5 ^{o}C-r.t, 12-18 h.

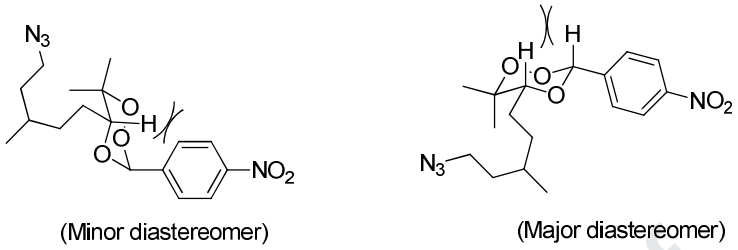
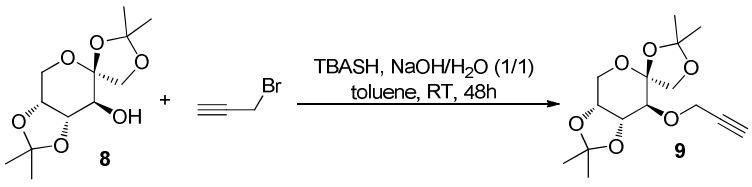


Figure 3. Plausible diastereoselective preference

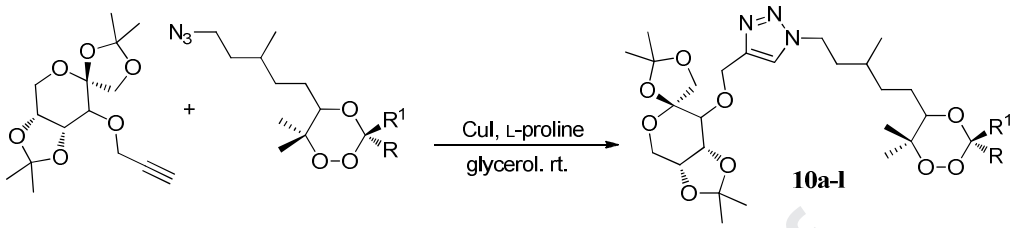
The optimized reaction conditions were applied to synthesize various azido tethered 1,2,4-trioxanes by varying the carbonyl counterpart (Scheme 1). The aromatic benzaldehydes bearing both electron-releasing and electron withdrawing groups on the phenyl ring gave similar yields under the optimized reaction conditions (**7a**-**m**). In contrast, cyclohexanone (**7n**) and *p*-chloro acetophenone (**7o**) required 1.5 equiv. of *p*-TsOH to give the optimum yields.

Having synthesized a library of 1,2,4-trioxane derivatives with azide terminal, we proposed to conjugate the trioxane with acetonide protected D-fructose derived carbohydrate in order to manipulate the solubility of the trioxane by shuttling between protected and unprotected hydroxy groups. For that purpose, D-Fructose derived acetonide derivative (**8**) [32] was subjected to propargylation with propargyl bromide in the presence alkaline solution in the presence of a phase transfer catalyst, tetrabutylammonium hydrogen sulfate (TBAHS) to get the propargylated derivative (**9**), as shown in Scheme 2.

Scheme 2: Propargylation of D-Fructose acetonide



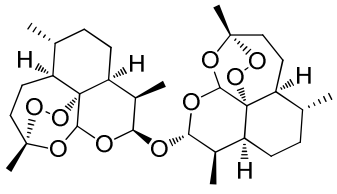
Scheme 3. Synthesis of 1,2,4-trioxanes bearing carbohydrate moiety



10a: R= H, R^1= *p*-$NO_2C_6H_4$; 10 h, 67%
10b: R= H, R^1= *o*-BrC_6H_4; 11 h, 69%
10c: R= H, R^1= *p*-FC_6H_4; 12 h, 68%
10d: R= H, R^1= *p*-ClC_6H_4; 10 h, 65%
10e: R= H, R^1= *m*-BrC_6H_4; 12 h, 65%
10f: R= H, R^1= *m,p*-$(CH_2O_2)C_6H_3$; 12 h, 69%
10g: R= H, R^1= *p*-$MeOC_6H_4$; 10 h, 70%
10h: R= H, R^1= *p*-MeC_6H_4; 12 h, 70%
10i: R= H, R^1= *m*-$NO_2C_6H_4$; 12 h, 68%
10j: R= H, R^1= $C_{10}H_7$; 12 h, 65%
10k: R= H, R^1= C_4H_3O; 11 h, 68%
10l: R, R^1= C_5H_{10}; 12 h, 67%

Then the compound **9** was subjected to CuI catalyzed CuAAC reaction with azido-1,2,4-trioxane derivative, **7n** in the presence of L-proline/glycerol [33] to obviate a carbohydrate bearing 1,2,4-trioxane tethered 1,2,3-triazole, **10l** (Scheme 3)**.** The ^{13}C-NMR spectra showed characteristic signals at 145.30 (–C=CH-$N_{triazole}$) and δ 122.10 ppm (–C=CH-$N_{triazole}$) indicating the formation of 1,4-substituted 1,2,3-triazole. The absence of any peak at ~133 ppm in ^{13}C-NMR spectra confirmed that 1,5-disubstituted 1,2,3-triazole regisoisomer is absent. The reaction was extended to other azido-tethered 1,2,4-trioxanes to synthesize a library **10a-l** in good yields.

It is known that many artemesinin dimers have shown better antimalarial and anticancer properties than the parent artemesinin. For example, the artemisinin ether dimer (Figure 4) was 22 times more cytotoxic than artemesinin and 60 times more than dihydroartemesinin, DHA. It may be due to the presence of two reactive peroxide centers in the dimer that can behave as better radical generator *via*homolytic cleavage of ether bridges linking to two monomeric units [34].

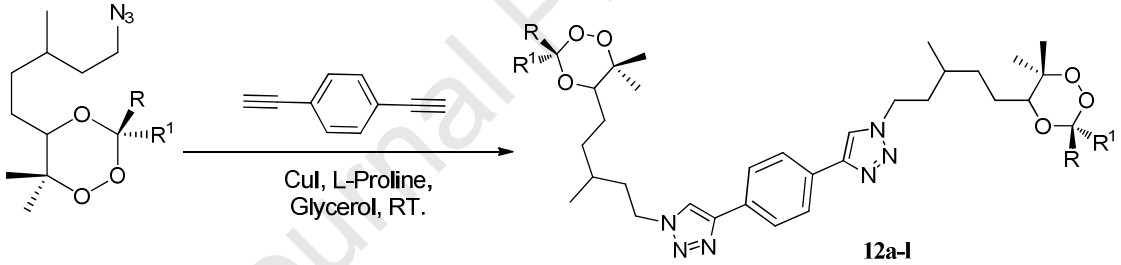


Artemisinin dimer

Figure 4. Artemisinin dimer

With an aim to synthesize 1,2,4-trioxane dimers (**12a-l**), the reaction between azido tethered 1,2,4-trioxanes with diethynylbenzenewas carried out following our method [33] (Scheme 4). For example, the product (**12e**) exhibited a singlet at δ 7.88 ppm integrating four protons representing the symmetrical benzene ring between two 1,2,3-triazole rings in ^{1}HNMR. A doublet at δ 7.79 ppm with *J* value 4.4 Hz integrating two protons represented the protons in the 1,2,3-triazole rings; a muliplet at δ 4.48-4.41 ppm represented the methylene protons attached to triazole ring. The ^{13}C-NMR spectra also showed the characteristic signals at δ147.3 ppm (–C=CH-$N_{triazole}$) and δ119.5 ppm (–C=CH-$N_{triazole}$) to prove the formation of 1,4-substituted 1,2,3-triazole. The absence of any peak at ~133 ppm in ^{13}CNMR spectra confirmed that 1,5-disubstituted 1,2,3-triazole regisoisomer is absent. Nevertheless, the HRMS also showed a peak at m/z 945.23 equivalent to $(M+Na)^{+}$ of the compound **12e**. The structures of other compounds were also confirmed by IR, ^{1}H-NMR, and ^{13}CNMR spectral data shown in experimental section.

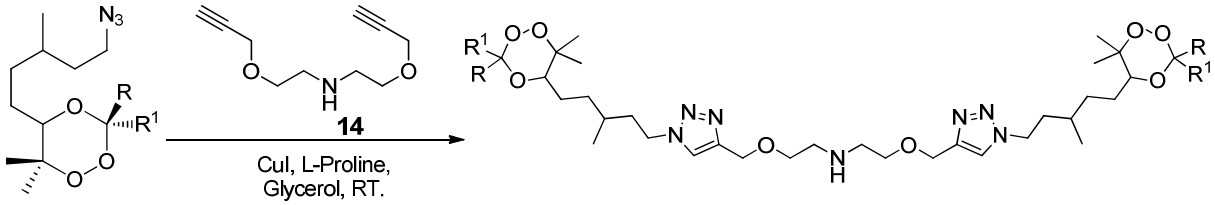
Scheme 4. 1,2,4-Trioxane dimers with 1,4-bis(triazolyl)benzene linker



12a: R= H, R^1= *p*-$NO_2C_6H_4$; 14 h, 67% **12b**: R= H, R^1= *o*-BrC_6H_4; 14 h, 64%
12c: R= H, R^1= *p*-FC_6H_4; 15 h, 66% **12d**: R= H, R^1= *p*-ClC_6H_4; 15 h, 65%
12e: R= H, R^1= *m*-BrC_6H_4; 14 h, 61% **12f**: R= H, R^1= *m,p*-$(CH_2O_2)C_6H_3$; 14 h, 69%
12g: R= H, R^1= *p*-$MeOC_6H_4$; 16 h, 64% **12h**: R= H, R^1= *p*-MeC_6H_4; 16 h, 62%
12i: R= H, R^1= $C_{10}H_7$; 16 h, 65% **12j**: R= H, R^1= C_4H_3O; 14 h, 68%
12k: R, R^1= C_5H_{10}; 14 h, 67% **12l**: R= CH_3, R^1= *p*-ClC_6H_4, 16 h, 61%.

Given the structural rigidity of 1,4-bis(1,2,3-triazolyl)benzene system, we synthesized another series of 1,2,4-trioxane dimers (**13a-i**) starting from bispropargylated diethanolamine (refer to the supplementary materials) by reacting with azido tethered 1,2,4-trioxanes under the same click conditions (Scheme 5).

Scheme 5. 1,2,4-Trioxane dimers with bis(triazolyl)ethylamine linker



13a-h

13a: R= H, R^1= *p*-$NO_2C_6H_4$; 15 h, 60% **13b**: R= H, R^1= *p*-FC_6H_4; 14 h, 57%
13c: R= H, R^1= *p*-ClC_6H_4; 15 h, 61% **13d**: R= H, R^1= *m*-BrC_6H_4; 16 h, 59%
13e: R= H, R^1= *m*,*p*-$(CH_2O_2)C_6H_3$; 14 h, 64% **13f**: R= H, R^1= C_6H_5, 16 h, 61%.
13g: R= H, R^1= *p*-$MeOC_6H_4$; 16 h, 56% **13h**: R= H, R^1= *p*-MeC_6H_4; 16 h, 64%
13i: R, R^1= C_5H_{10}; 15 h, 62%

Biological Studies

OPN plays a functional role in progression and malignancy of breast cancer [35] and high expression of OPN is observed in the highly invasive and metastatic human breast cancer cell lines [36]. To study the effect of 1,2,4-trioxane monomers and dimers on OPN expression, MDA- MB-435 cells (Fig. 5) were maintained using Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1x antibiotic mix (penicillin and streptomycin) at 37 ˚C in a humidified atmosphere of 5% CO_2 (Fig. 1A). $1x10^6$ MDA-MB-435 cells were seeded in a 6 cm plate and incubated for 24 h. The cells were then serum starved for 24 h and treated with 50 µM of the 1,2,4-trioxane derivatives for 24 h except for **13a-i** (10 µM) and OPN protein levels were analyzed by western blot.

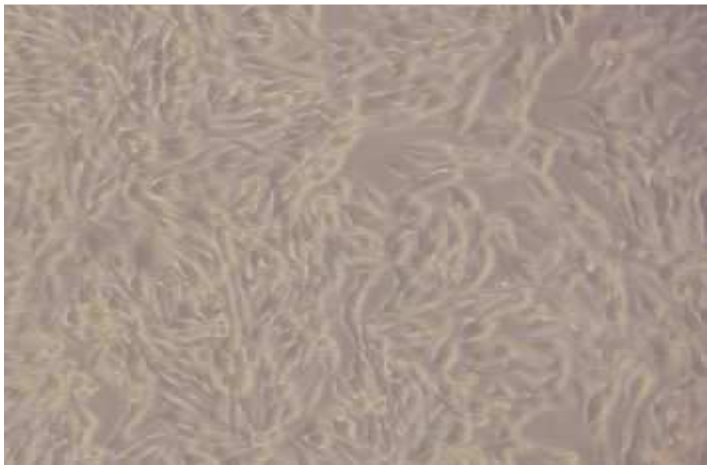


Figure 5. MDA-MB-435 breast cancer cells maintenance under 40x magnification

Upon treatment with 1,2,4-trioxane monomer, a decrease in OPN expression were observed in case compounds **10g** (~ 0.2fold), **10k** (~ 0.12 fold), **10d** (~ 0.15 fold), and **10e** (~ 0.15 fold) while the rest did not show appreciable changes in their respective OPN expressions as compared to the control (Fig. 6A-F). Interestingly, the reference compounds artemisinin showed no effect on OPN expression while DHA and 1,2,3-triazole bearing DHA ether (**11**) decreased OPN expression by ~ 0.45 and ~ 0.3fold respectively (Fig. 7A and 7B).

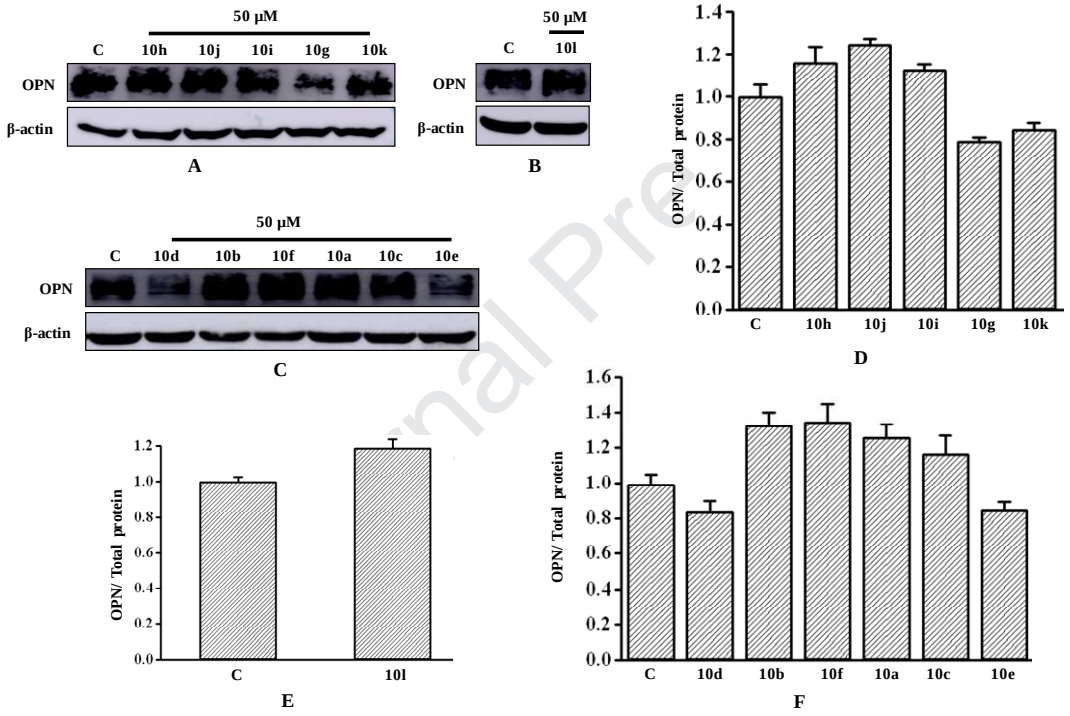


Figure 6. Effect of 1,2,4-trioxane monomers (**10a-l**) on OPN protein level in MDA-MB-435 breast cancer cells (A, B, C). Effect of monomers (50 µM) on OPN protein level treated for 24 h and its corresponding densitometric analyses (D, E, F).

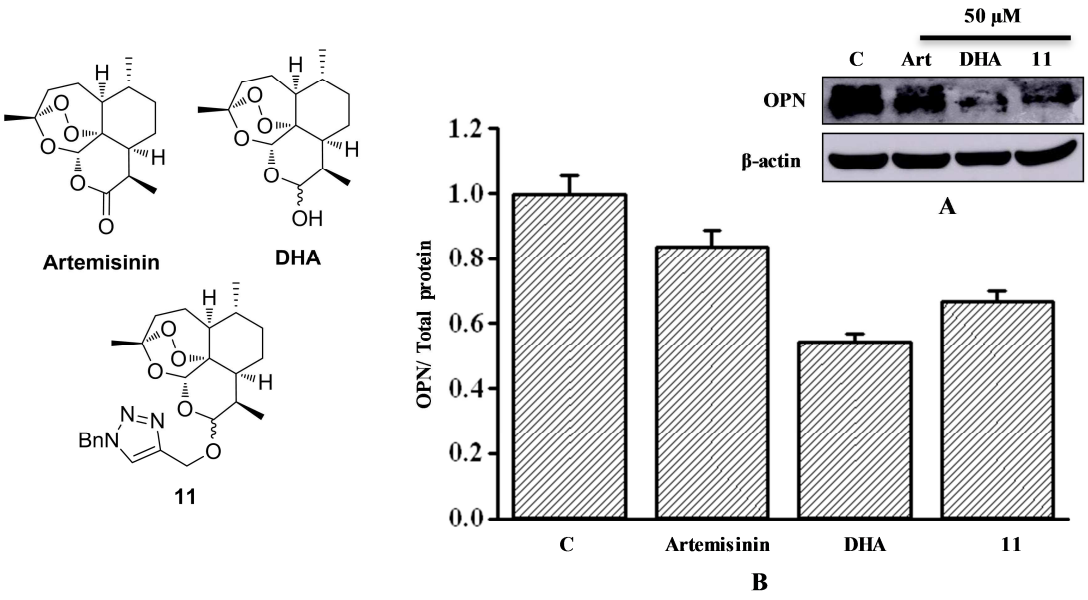


Figure 7. Effect of artemisinin, DHA and **11** (50 μM) on OPN protein level in MDA-MB-435 breast cancer cells after 24 h treatment and its corresponding densitometric analyses (B).

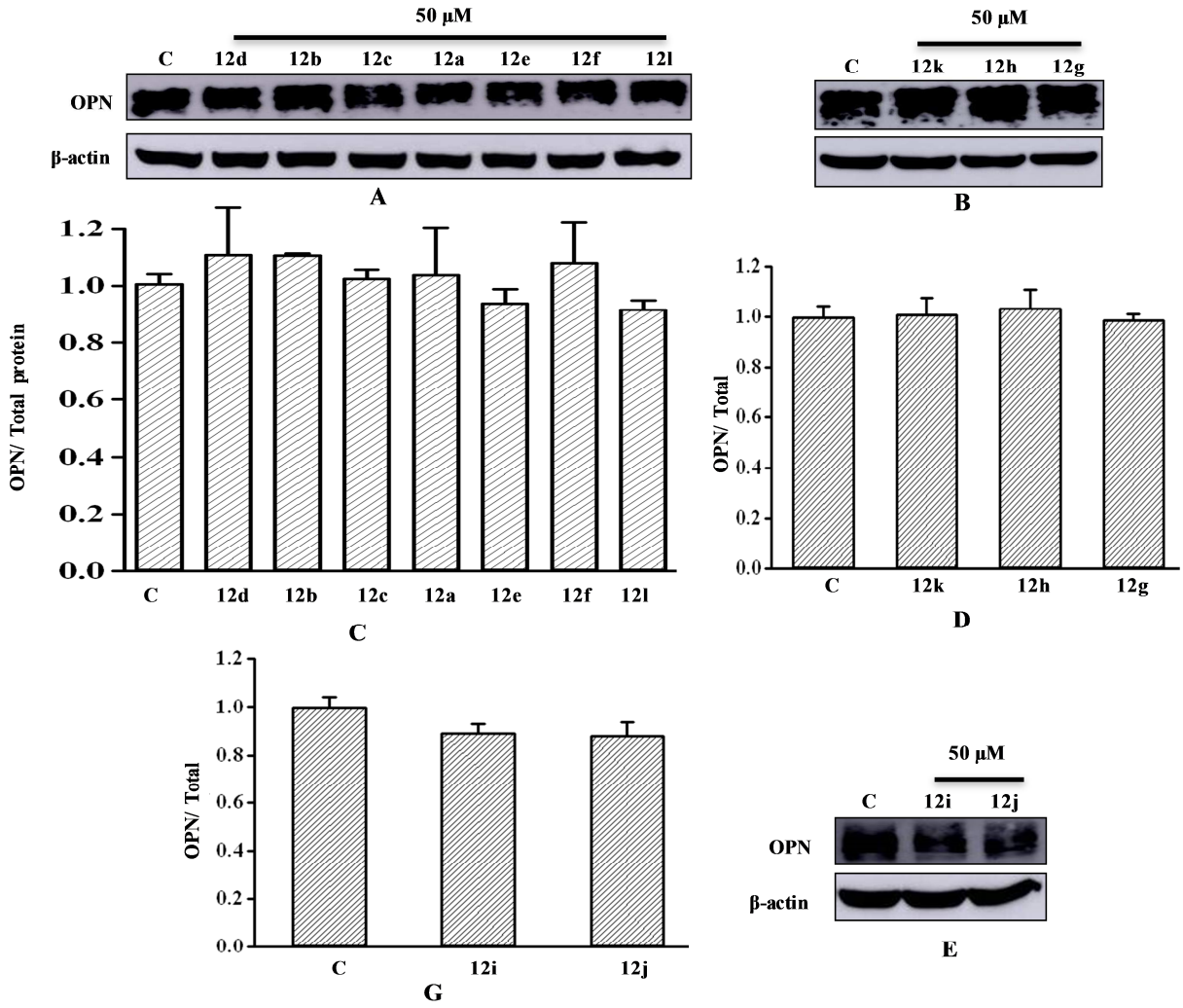


Figure 8. Effect of 1,2,4-trioxane dimers (**12a-l**) on OPN protein level in MDA-MB-435 breast cancer cells (A, B, E). Effect of dimers (50 µM) on OPN protein level treated for 24 h and its corresponding densitometric analyses (C, D, G).

The 1,2,4-trioxane dimers **12a-l** showed no alterations in OPN expression level (**Fig. 8**) at 50 µM level despite having two 1,2,4-trioxane units in those compounds. Surprisingly, treatment of MDA-MB-435 cells with 1,2,4-trioxanes **13a-i** bearing bis(triazolyl)ethylamine linker showed significant decrease in OPN expression at 10 µM level, e.g. **13i** (~ 0.27 fold), **13d** (~ 0.26 fold), **13h** (~ 0.15 fold), **13b** (~ 0.17 fold), **13e** (~ 0.33 fold), **13f** (~ 0.11 fold), **13g** (~ 0.43 fold), **13c** (~ 0.45 fold) and **13a** (~ 0.28 fold) (Figs. 9). The fact that OPN plays a functional role in progression and malignancy of breast cancer [35] and high expression of OPN is observed in the highly invasive and metastatic human breast cancer cell lines [36], the compounds such as **10g**,

11, **13a**, **13c**, **13d**, **13e**, **13g**, **13i**, and DHA may act as an anti-metastatic agent in controlling MDA-MB-435 breast cancer cells metastasis. We are undertaking further studies to understand the mechanism and functional sequel involved in this event.

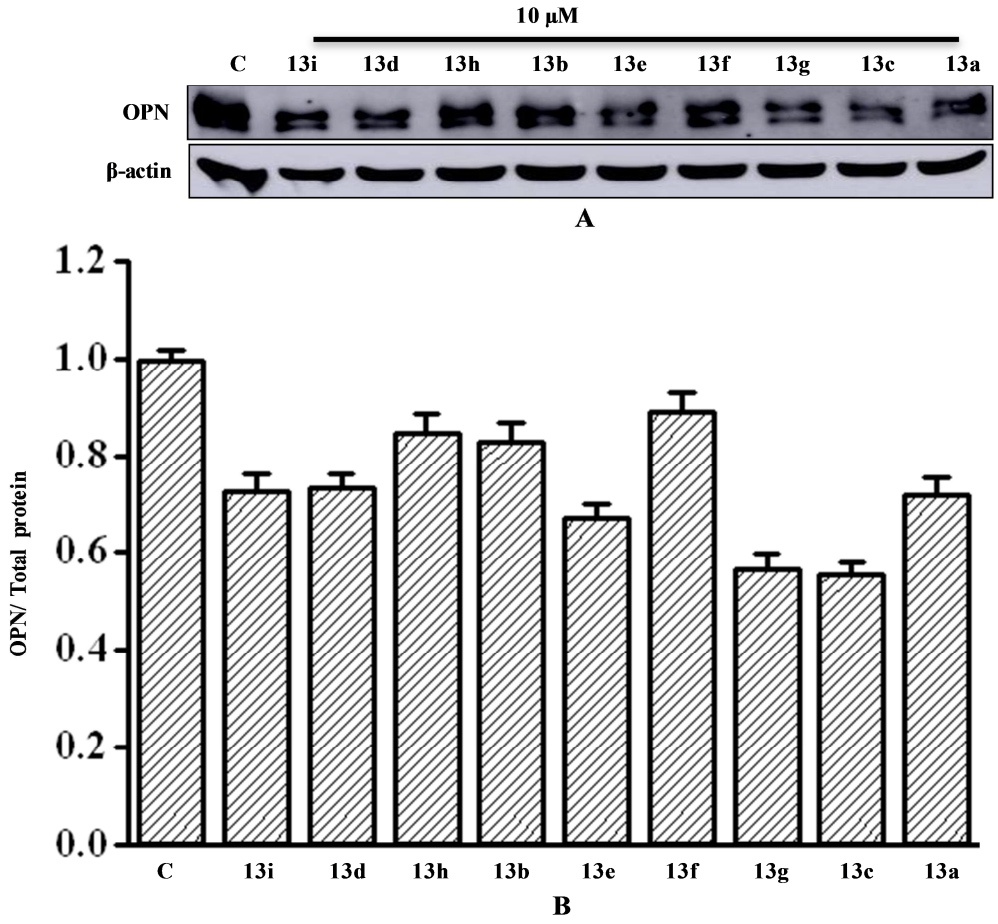


Figure 9. Effect of 1,2,4-trioxane dimers with bis(triazolyl)ethylamine linkers (**13a-i**) on OPN protein level in MDA-MB-435 breast cancer cells (A). Effect of dimers (10 µM) on OPN protein level treated for 24 h and its corresponding densitometric analyses (B).

Conclusion

In summary, we have synthesized three series 1,2,4-trioxanes starting from citranellol. These trioxanes were used for a preliminary study on downregulation of OPN expression in MDA-MB-435 breast cancer cells where most of the synthetic 1,2,4-trioxanes were effective against metastatic cancer. Interestingly, artemisinin hardly showed OPN downregulation in MDA-MB-435 cells, while dihydroartemisinin and its ether derivative **11** showed promising results. We found no direct correlation between 1,2,4-trioxane monomers and dimers in affecting OPN

downregulation, but more flexible 1,2,4-trioxane dimers (**13a-i**) showed better activity. The results suggest that synthetic 1,2,4-trioxanes can be employed against cancer metastasis. Although artemisinin derived 1,2,4-trioxanes are being used for anticancer studies, we report here the first study on anticancer properties of synthetic 1,2,4-trioxanes. More studies are required to understand the mechanism behind downregulation of OPN expression in cancer cell.

Experimental section

Chemistry

Metarials and Methods

Chemicals purchased from the commercial source were used without further purification unless otherwise mentioned. ^{1}H-NMR, and ^{13}C NMR spectra of the compounds were obtained using a Brucker Avance 400 MHz machine at 400 MHz and 100 MHz, respectively. Multiplicity of the peaks is reported as s = singlet, d = doublet, t = triplet, m = multiplet, b = broad. Coupling constants are presented in the hertz (Hz). LRMS data were recorded by using the ESI method.

3,7-Dimethyl-6-octenyltosylate (4):To a solution of citronellol (10 g, 64.1 mmol), dry pyridine (61 mL, 769 mmol) was added and stirred for 30 min. Then the temperature was brought down to 0 ^{o}C and *p*-toluenesulfonyl chloride (18.26 g, 96.15 mmol) was added. Upon completion of the reaction, the solution was poured into a mixture of ice cold water and HCl (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic phase was washed with dilute HCl (50 mL), water (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) and dried in Na_2SO_4, concentrated in vacuo to give an oil which was purified by column chromatography (SiO_2, Hexane: EtOAc , 9.5: 0.5) to give as an oil in 61% Yield (12.2 g). IR (KBr, cm^{-1}): υ1599, 1362, 1177, 815, 664. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 5.02 (t, *J* = 8.4 Hz, 1H), 4.09-4.03 (m, 2H), 2.45 (d, *J* = 2.8 Hz, 3H), 1.98-1.84 (m, 2H), 1.71-1.65 (m, 6H), 1.54-1.40 (m, 2H), 1.26-1.22 (m, 1H), 1.13-1.03 (m, 2H), 0.85-0.79 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ144.6, 133.1, 131.4, 129.8, 127.8, 124.3, 69.1, 36.6, 35.6, 28.8, 25.7, 25.2, 21.6, 19.0, 17.6 ppm. ESI-MS (m/z): 328 (M^{+}+ NH_4^{+}).

8-Azido-2,6-dimethyloct-2-ene (5): To a solution of 3,7-dimethyl-6-octenyl tosylate (12 g, 38.70 mmol) in dry DMF was added NaN_3, and stirred at 40 ^{o}C. After completion of reaction, the reaction solution was kept round-bottom flask in refrigerator overnight. The reaction was

quenched by adding 50 mL of ice cold water and extracted with ethyl acetate (3 x 50 mL) and the combined organic layer was concentrated in vacuo to give the crude product as oil. The crude was purified by column chromatography with hexane as eluent to get the product in 78% yield (5.5 g). IR (KBr, cm^{-1}): υ 2097, 1457, 1379, 1216, 760. ^{1}HNMR (400 MHz, $CDCl_3$): □5.09 (t, *J* = 7.6 Hz, 1H), 3.30-3.24 (m, 2H), 2.03-1.96 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56-1.53 (m, 1H), 1.43-1.30 (m, 2H), 1.23-1.11 (m, 2H), 0.91 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ131.4, 124.4, 49.4, 36.8, 35.6, 29.9, 25.7, 25.3, 19.2, 17.6 ppm. ESI-MS (m/z): 181 (M^+).

8-Azido-2,6-dimethyloctane-2,3-diol(6): To a solution of 8-azido-2,6-dimethyloct-2-ene (5.4 g, 29.83 mmol) in mixture of acetone : water (8:2), NMO.H_2O (4.8 g, 35.80 mmol) was added and stirred at room temperature until NMO.H_2O was dissolved. OsO_4 (10 mol %) mixture was added to the solution and stirred at room temperature until starting material got consumed. After completion of the reaction, a saturated solution of $Na_2S_2O_5$ (50 mL) was added and extracted with ethyl acetate (3 x 75 mL), washed with brine (50 mL) and water (3 x 50 mL), and concentrated in vacuo to get an oily crude which was purified by column chromatography employing 40% ethyl acetate in hexane. Yield: 87%, (5.6 g). IR (KBr, cm^{-1}): υ 3420, 2097, 1463, 1382, 1262, 1072, 917. ^{1}HNMR (400 MHz, $CDCl_3$): □ 3.36-3.24 (m, 3H), 2.46 (d, *J* = 4.4 Hz, 1H), 2.17 (s, 0.8H), 1.92 (s, 0.2H), 1.69-1.33 (m, 7H), 1.22 (s, 3H), 1.16 (s, 3H), 0.94-0.91 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ7 8.8, 78.5, 73.2, 73.2, 49.4, 49.4, 35.8, 35.4, 34.0, 33.6, 30.4, 30.2, 29.0, 28.7, 26.5, 26.5, 23.1, 19.4, 19.1 ppm. ESI-MS (m/z): 215 (M^+).

8-Azido-2-hydroperoxy-2,6-dimethyloctan-3-ol (6a): To an ice-cooled (0-5 ^{o}C) solution of 8-azido-2,6-dimethyloctane-2,3-diol (5.5 g, 25.58 mmol), was added 50% H_2O_2 (5.8 mL, 204.65 mmol) followed by H_2SO_4 (0.34 mL, 6.3 mmol). After 4 h, the reaction was quenched by adding ice cold water and extracted with $CHCl_3$ (3 x 50 mL). The organic layer was washed with saturated solution of $NaHSO_4$ (50 mL) and water (50 mL), and concentrated in vacuo to get an oily crude product which was used directly for the next reaction.

Typical procedure for synthesis of azido tethered 1,2,4-trioxane monomers: A solution of 4-nitro benzaldehyde (0.218 g, 1.449 mmol) in dry dichloromethane was stirred at 0-5 ^{o}C for 15

min. Then *p*-TsOH (0.274 g, 1.449 mmol) and 8-azido-2-hydroperoxy-2,6-dimethyloctan-3-ol crude (0.5 g, 2.17 mmol) were added to the solution sequentially. After completion of reaction, solvent was evaporated at low temperature and purified by column chromatography (SiO_2, hexane: ethyl acetate, 9:1).

5-(5-Azido-3-methylpentyl)-6,6-dimethyl-3-(4-nitrophenyl)-1,2,4-trioxane(7a):Oil, 86% yields. IR (KBr, cm^{-1}): υ 2096, 1637, 1533, 1460, 1351, 1262, 1098, 906, 807. ^{1}HNMR (400 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 8.24-821 (m, 2H), 7.68-761 (m, 2H), 6.04 (s, 0.9H), 5.88 (s, 0.2H), 3.77-3.74 (m, 0.3H), 3.60-3.58 (m, 1.1H), 3.38-3.26 (m, 2H), 1.70-1.38 (m, 6H), 1.36 (s, 3H), 1.25 (s, 3H), 1.21-1.18 (m, 1H), 0.95-0.93 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 148.3, 148.1, 147.1, 145.4, 127.5, 127.1, 123.5, 123.5, 100.0, 99.67, 86.3, 86.1, 84.3, 84.1, 81.9, 80.97, 49.3, 35.5, 35.4, 34.0, 33.8, 30.4, 30.2, 26.9, 26.7, 25.4, 25.0, 23.3, 20.3, 19.1, 19.1 ppm. ESI-MS (m/z): 387.15 $(M+Na)^+$.

5-(5-Azido-3-methylpentyl)-3-(2-bromophenyl)-6,6-dimethyl-1,2,4-trioxane(7b): Oil; IR (KBr, cm^{-1}): υ 2931, 2095, 1699, 1464, 1264, 1210, 1159, 1121, 1089, 1041, 757. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 7.67-7.57 (m, 1H), 7.55-7.52 (m, 1H), 7.35-7.31 (m, 1H), 7.22-7.17 (m, 1H), 6.25(s, 0.4H), 6.10 (s, 1.1H), 3.76-3.66 (m, 1H), 3.36-3.23 (m, 2H), 1.69-1.38 (s, 10H), 1.27-1.23 (m, 3H), 0.94-0.92 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 138.2, 136.9, 132.9, 132.7, 130.4, 130.2, 128.1, 127.8, 127.5, 127.3, 123.2, 122.9, 100.1, 100.0, 86.1, 85.9, 84.1, 84.0, 81.6, 80.4, 49.4, 49.4, 35.6, 35.5, 33.9, 33.7, 30.4, 30.3, 27.1, 26.9, 25.6, 25.1, 23.4, 20.2, 19.2, 19.2 ppm. ESI-MS (m/z): 421.23 $(M+Na)^+$.

5-(5-Azido-3-methylpentyl)-3-(4-fluorophenyl)-6,6-dimethyl-1,2,4-trioxane(7c): Oil; IR (KBr, cm^{-1}): υ 2968, 2096, 1607, 1464, 1226, 1155, 1101, 1085, 835. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 7.48-7.41 (m, 2H), 7.07-7.03 (m, 2H), 5.96 (s, 0.3H), 5.78 (s, 0.9H), 3.72-3.62 (m, 1H), 3.35-3.23 (m, 2H), 1.69-1.22 (s, 13H), 0.94-0.92 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 164.3, 161.9 (d, J = 23 Hz), 135.9, 134.0, 128.7, 128.0, 115.3, 115.1, 101.0, 100.5, 86.2, 86.0, 84.2, 84.0, 81.4,

80.3, 49.3, 35.5, 35.5, 34.0, 33.8, 30.4, 30.3, 27.1, 26.9, 25.6, 25.2, 23.5, 20.2, 19.1, 19.1 ppm. ESI-MS (m/z): 360.22 $(M+Na)^+$.

5-(5-Azido-3-methylpentyl)-3-(4-chlorophenyl)-6,6-dimethyl-1,2,4-trioxane(7d): Oil; IR (KBr, cm^{-1}): υ 2932, 2098, 1600, 1492, 1262, 1217, 1161, 1087, 1015. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 7.41-7.38 (m, 2H), 7.35-7.33 (m, 2H), 5.96 (s, 0.9H), 5.78 (s, 0.5H), 3.72-3.60 (m, 1H), 3.35-3.25 (m, 2H), 1.69-1.18 (m, 13H), 0.94-0.92 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 134.9, 134.5, 130.9, 129.4, 128.5, 128.5, 128.1, 127.6, 100.9, 100.4, 86.2, 86.0, 84.1, 84.0, 81.5, 80.4, 49.3, 35.6, 35.5, 34.0, 33.9, 30.5, 30.3, 27.0, 26.9, 25.5, 25.1, 23.5, 20.3, 19.2, 19.1 ppm. ESI-MS (m/z): 376.23 $(M+Na)^+$

5-(5-Azido-3-methylpentyl)-3-(3-bromophenyl)-6,6-dimethyl-1,2,4-trioxane(7e): Oil; IR (KBr, cm^{-1}): υ2931, 2095, 1703, 1464, 1371, 1257, 1210, 1161, 1099, 1066, 786. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □7.63-7.21 (m, 4H), 5.93 (s, 0.8H), 5.76 (s, 0.3H), 3.71-3.60 (m, 1H), 3.37-3.23 (m, 2H), 1.70-1.23 (m, 13H), 0.95-0.93 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □142.4, 140.5, 132.1, 131.7, 129.9, 129.7, 129.3, 125.4, 124.9, 124.9, 122.4, 122.4, 100.6, 100.1, 86.2, 86.0, 84.2, 84.0, 81.6, 80.5, 49.3, 35.5, 35.5, 34.0, 33.7, 30.5, 30.3, 27.0, 26.8, 25.5, 25.1, 23.4, 20.2, 19.2, 19.1 ppm. ESI-MS (m/z): 420.19 $(M+Na)^+$

5-(5-(5-Azido-3-methylpentyl)-6,6-dimethyl-1,2,4-trioxan-3-yl)benzo[d][1,3]dioxole(7f):Oil; IR (KBr, cm^{-1}): υ 2971, 2870, 2096, 1688, 1489,1449, 1123, 1038, 603. ^{1}HNMR (400 MHz, $CDCl_3$; diastereomeric pairs): □ 6.94-6.91 (m, 2H), 6.78 (d, *J* = 8 Hz, 1H), 5.95 (s, 2H), 5.90 (s, 1.2H), 5.72 (s, 0.1H), 3.68-3.64 (m, 1H), 3.35-3.24 (m, 2H), 1.69-1.37 (m, 10H), 1.22 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs): □ 148.0, 147.7, 134.0, 120.2, 107.9, 106.6, 101.1, 100.9, 84.2, 84.0, 81.3, 49.3, 35.5, 33.9, 30.4, 27.0, 25.2, 20.1, 19.1 ppm. ESI-MS (m/z): 386.56 $(M+Na)^+$

4-(5-(5-Azido-3-methylpentyl)-6,6-dimethyl-1,2,4-trioxan-3-yl)phenol (7g): Oil; IR (KBr, cm^{-1}): υ 3442, 2932, 2098, 1600, 1492, 1262, 1217, 1161, 1087, 1015. ^{1}HNMR (400 MHz, $CDCl_3$;

diasteromeric pairs as major/minor): □ 7.32-7.27 (m, 2H), 6.71 (m, 2H), 6.05 (br s, 1H,), 5.94 (s, 0.7H), 5.75 (s, 0.4H), 3.71-3.24 (m, 3H), 1.67-1.36 (m, 10H), 1.24 (s, 3H), 0.91 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 157.76, 156.4, 131.5, 129.5, 128.4, 127.9, 115.3, 115.2, 101.6, 101.1, 86.1, 85.9, 84.2, 84.1, 81.4, 80.2, 49.3, 35.5, 35.5, 34.0, 33.8, 30.5, 30.3, 27.1, 27.0, 25.6, 25.2, 23.5, 20.1, 19.2, 19.1 ppm. ESI-MS (m/z): 358.45 $(M+Na)^+$

5-(5-Azido-3-methylpentyl)-6,6-dimethyl-3-phenyl-1,2,4-trioxane(7h): Oil; IR (KBr, cm^{-1}): υ 2930, 2097, 1641, 1463, 1382, 1262, 1162, 1072, 961. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 7.49-7.44 (m, 2H), 7.38-7.33 (m, 3H), 5.99 (s, 0.4H), 5.81 (s, 0.6H), 3.73-3.64 (m, 1H), 3.36-3.22 (m, 2H), 1.69-1.23 (m, 13H), 0.94-0.89 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 138.1, 134.4, 129.1, 128.7, 128.3, 128.3, 126.7, 126.2, 101.7, 101.1, 86.1, 86.0, 84.1, 84.0, 81.3, 80.2, 49.3, 35.5, 35.5, 34.1, 33.8, 30.4, 30.3, 27.1, 27.0, 25.6, 25.2, 23.5, 20.3, 19.2, 19.1 ppm. ESI-MS (m/z): 342.34 $(M+Na)^+$

5-(5-Azido-3-methylpentyl)-3-(4-methoxyphenyl)-6,6-dimethyl-1,2,4-trioxane(7i): Oil; IR (KBr, cm^{-1}): υ 2932, 2873, 2096, 1616, 1518, 1458, 1371, 1264, 1220, 1086, 1068, 833. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 7.42-7.36 (m, 2H), 6.90-6.87 (m, 2H), 5.95 (s, 0.8H), 5.76 (s, 0.4H), 3.79 (s, 3H), 3.70-3.66 (m, 1H), 3.58-3.22 (m, 2H), 1.82-1.23 (m, 13H), 0.93-0.91 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 160.3, 160.0, 132.2, 130.2, 128.2, 127.6, 113.7, 113.7, 101.5, 101.0, 86.0, 85.9, 84.1, 83.9, 81.1, 80.0, 55.3, 55.2, 49.3, 35.5, 35.5, 33.9, 33.6, 30.5, 30.4, 27.1, 27.0, 25.6, 25.3, 23.6, 20.1, 19.2, 18.8 ppm. ESI-MS (m/z): 372.65 $(M+Na)^+$

5-(5-Azido-3-methylpentyl)-6,6-dimethyl-3-(p-tolyl)-1,2,4-trioxane(7j): Oil; IR (KBr, cm^{-1}): υ 2969, 2931, 2872, 2095, 1617, 1460, 1370, 1263, 1089, 815. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 7.38-7.33 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.96 (s, 0.3H), 5.78 (s, 0.8H), 3.71-3.63 (m, 1H), 3.36-3.22 (m, 2H), 2.34 (s, 3H), 1.69-1.23 (m, 13H), 0.94-0.88 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 138.9, 138.5, 137.1, 135.1, 129.0, 128.9, 126.7, 126.1, 101.7, 101.1, 86.0, 85.9, 84.0, 83.9, 81.20,

80.1, 49.3, 35.5, 35.5, 34.0, 33.8, 30.4, 30.3, 27.1, 27.0, 25.6, 25.2, 23.5, 21.2, 20.2, 19.1, 18.3 ppm. ESI-MS (m/z): 356.23 $(M+Na)^+$

5-(5-Azido-3-methylpentyl)-6,6-dimethyl-3-(3-nitrophenyl)-1,2,4-trioxane(7k): Oil; IR (KBr, cm^{-1}): υ 2932, 2096, 1637, 1533, 1460, 1351, 1262, 1098, 906, 807. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 8.36-8.31 (m, 1H), 8.23-8.18 (m, 1H), 7.83-7.78 (m, 1H), 7.57-7.55 (m, 1H), 6.04 (s, 0.3H), 5.88 (s, 1H), 3.77-3.73 (m, 1H), 3.65-3.62 (m, 0.4H), 3.37-3.26 (m, 2H), 1.71-1.29 (m, 10H), 1.22 (s, 3H), 0.95-0.93 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 148.2, 142.4, 140.7, 132.8, 132.4, 129.3, 123.9, 123.6, 121.8, 121.3, 100.0, 99.6, 86.3, 86.1, 84.3, 84.2, 82.0, 80.9, 49.3, 35.5, 35.5, 33.9, 33.7, 30.4, 30.2, 27.0, 26.9, 25.4, 25.1, 23.4 and 20.3, 19.1, 19.1 ppm. ESI-MS (m/z): 387.53 $(M+Na)^+$.

5-(5-Azido-3-methyl)-6,6-dimethyl-3-(napthalen-1-yl)-1,2,4-trioxane(7l): Oil; IR (KBr, cm^{-1}): υ 2932, 2098, 1610, 1601, 1492, 1475, 1262, 1217, 1161, 1087, 1015. ^{1}HNMR (400 MHz, $CDCl_3$; diasteromeric pairs as major/minor): □ 8.22-8.18 (m, 1H), 7.85-7.74 (m, 3H), 7.53-7.43 (m, 3H), 6.67 (s, 0.3H), 6.50 (s, 0.6H), 3.85-3.80 (m, 0.5H), 3.69-3.66 (m, 0.4H), 3.55-3.20 (m, 2H), 1.82-1.22 (m, 13H), 0.91-0.89 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 135.1, 133.9, 133.8, 133.7, 131.1, 131.0, 129.3, 129.1, 128.5, 126.2, 126.1, 125.6, 125.2, 125.1, 124.2 123.9, 123.2, 122.8, 99.1, 86.1, 85.9, 83.9, 83.7, 81.4, 80.3, 49.4, 35.6, 35.5, 34.1, 33.8, 30.5, 30.3, 27.1, 27.0, 25.7, 25.2, 23.4, 20.6, 19.2, 18.9 ppm. ESI-MS (m/z): 392.49 $(M+Na)^+$.

5-(5-Azido-3-methylpentyl)-3-(furan-2-yl)-6,6-dimethyl-1,2,4-trioxane(7m): Oil; IR (KBr, cm^{-1}): υ 2971, 2870, 2096, 1688, 1489,1449, 1123, 1038, 603. ^{1}HNMR (400 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 7.42-7.40 (m, 1H), 6.46-6.31 (m, 2H), 5.99 (s, 0.5H), 5.86 (s, 0.9H), 3.75-3.72 (m, 0.5H), 3.66-3.63 (m, 1H), 3.35-3.21 (m, 2H), 1.71-1.33 (m, 10H), 1.25 (s, 3H), 0.93-0.91 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 152.6, 151.1, 143.2, 142.9, 110.1, 110.0, 109.1, 108.2, 95.6, 95.3, 85.8, 85.6, 83.6, 83.5, 81.1, 80.4, 49.3, 35.5, 35.5, 33.9, 33.7, 30.4, 30.3, 26.9, 26.8, 25.0, 24.8, 22.8, 20.4, 19.1, 19.1 ppm. ESI-MS (m/z): 332.15 $(M+Na)^+$.

4-(5-Azido-3-methylpentyl)-3,3-dimethyl-1,2,5-trioxaspiro[5.5]undecane(7n): Oil; IR (KBr, cm^{-1}): υ 2935, 2862, 2096, 1449, 1365, 1259, 1100, 950. ^{1}HNMR (400 MHz, $CDCl_3$): □ 3.63-3.59 (m, 1H), 3.35-3.25 (m, 2H), 1.66-1.24 (m, 20H), 1.08 (s, 3H), 0.94-0.90 (m, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): □ 106.3, 82.5, 82.3, 78.9, 48.8, 37.7, 35.5, 35.11, 34.8, 33.5, 33.3, 29.8, 29.7, 26.3, 26.1, 25.7, 24.6, 23.4, 23.2, 22.6, 18.7, 18.5 ppm. ESI-MS (m/z): 334.47 $(M+Na)^+$.

5-(5-Azido-3-methylpentyl)-3-(4-chlorophenyl)-3,6,6-trimethyl-1,2,4-trioxane(7o): Oil; IR (KBr, cm^{-1}): υ 2974, 2928, 2871, 2096, 1598, 1488, 1462, 1370, 1248, 1091, 830. ^{1}HNMR (400 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 7.45-7.40 (m, 2H), 7.30-7.26 (m, 2H), 3.79-3.75 (m, 0.5H), 3.37-3.23 (m, 2.5H), 1.68-0.87 (m, 19H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$; diastereomeric pairs as major/minor): □ 144.6, 144.3, 133.1, 133.0, 128.1, 127.9, 126.6, 126.2, 106.4, 106.1, 84.5, 84.3, 83.8, 83.5, 81.2, 81.1, 49.3, 35.6, 35.4, 34.0, 33.7, 30.4, 30.2, 26.7, 26.5, 26.3, 25.9, 25.4, 23.4, 22.0, 19.8, 19.1 ppm. ESI-MS (m/z): 390.75 $(M+Na)^+$.

Synthesis of 2,2,2',2'-tetramethyl-7-(prop-2-yn-1-yloxy)tetrahydrospiro[[1,3]-dioxolo[4,5-c] pyran-6,4`-[1,3]dioxolane] (9): A 50% NaOH (aq) solution was made by dissolving NaOH (0.83 g) in H_2O (0.8 mL). The compound **8** (1.5 g, 5.76 mmol) was dissolved in toluene (5 mL) and slowly poured over the aqueous solution. Tetrabutylammonium hydrogen bisulphate (0.002 g, 0.0069 mmol) and propargyl bromide (1.2 mL, 11.23 mmol) were added and the stirred gently for 48 h. After completion of the reaction, the compound was extracted with ethyl acetate and evaporated under reduced pressure to get the crude product as a yellow oil. Purification using column chromatography with silica gel and EtOAc/hexane (1:1) as eluent gave pure **9** (0.98 g, 52%) as a pale yellow viscous oil. IR (KBr, cm^{-1}): υ 3291, 2988, 2936, 2115, 1632, 1456, 1383, 1220, 1116, 1084, 1018, 886. ^{1}HNMR (400MHz, $CDCl_3$): □ 4.54 (dd, *J* = 16.0 Hz, 2.4 Hz, 1H), 4.44 (dd, *J* = 16.0 Hz, 2.4 Hz, 1H), 4.31 (dd, *J* = 7.6 Hz, 5.4 Hz, 1H), 4.25 (d, *J* = 8.6 Hz, 1H), 4.20-4.10 (m, 2H), 4.16 (m, 2H), 3.95 (d, *J* = 8.6 Hz, 1H), 3.76 (d, *J* = 7.6 Hz, 1H), 2.44 (t, *J* = 2.3 Hz, 0.6H), 2.35 (s, 0.3H), 1.58 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 111.5, 108.6, 103.7, 79.0, 77.1, 74.4, 73.5, 73.4, 71.2, 59.5, 57.8, 27.6, 26.2, 25.8, 25.4 ppm. ESI-MS (m/z): 299.17 $(M+H)^+$.

Typical procedure for 1,2,3-triazole linked 1,2,4-trioxane monomers: A mixture of CuI (2 mg, 1 mol%) and L-proline (1.2 mg, 1 mol%) taken in an oven-dried two-neck round bottom flask was mixed with glycerol (4 mL) in a bath sonicator for 30 min. Then azido tethered 1,2,4-trioxane derivative (**7a**) (0.364 g, 1 mmol) and compound **9** (0.3 g,1 mmol) were added to the solution and stirred at room temperature. The progress of the reaction was monitored by TLC and found completed within 5 h. The reaction was quenched by adding water (5 mL) to the suspension and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated the organic layer to afford the crude product. The crude was purified by column chromatography employing 15% ethyl acetate in hexane as eluent.

1-(5-(6,6-Dimethyl-3-(4-nitrophenyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R, 7aS)-2,2,2',2'-tetramethyl tetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy) methyl)-1*H*-1,2,3-triazole(**10a**): Yield 67%, gum. IR (KBr, cm^{-1}): υ 3291, 3123, 2988, 2936, 1383, 1220, 1116, 1084, 1018, 886. ^{1}HNMR (400 MHz, $CDCl_3$): ^{1}HNMR (400 MHz, $CDCl_3$): □ 8.23 (d, *J* = 8.2 Hz, 2H), 7.68-7.62 (m, 2H), 7.55 (s, 1H), 6.05 (s, 0.5H), 5.88 (d, *J* = 12.4 Hz, 0.5H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.42-4.34 (m, 2H), 4.22 (d, *J* = 6.4 Hz, 1H), 4.13 (d, *J* = 13.6 Hz, 1H), 4.05-4.03 (m, 3H), 3.89 (d, *J* = 8.4 Hz, 1H), 3.75-3.65 (m, 1H), 3.59 (d, *J* = 7.6 Hz, 1H), 2.01-1.98 (m, 1H), 1.78-1.71 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 12H), 1.25-1.19 (m, 5H), 1.01-0.98 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 148.26, 148.07, 147.09, 145.30, 145.06, 127.59, 127.13, 123.57, 123.53, 122.18, 112.05, 109.13, 104.28, 100.04, 99.64, 86.30, 86.03, 84.25, 84.13, 81.99, 81.96, 80.96, 80.92, 77.46, 76.52, 73.81, 71.73, 65.19, 60.14, 48.31, 37.24, 37.18, 33.66, 33.25, 30.27, 30.11, 28.20, 26.86, 26.78, 26.51, 26.25, 26.00, 25.81, 25.41, 25.00, 23.99, 23.36, 20.38, 19.03 ppm.Anal. Calcd for ($C_{32}H_{46}N_4O_{11}$): C 57.99, H 7.00, N 8.45. Found: C 57.95, H 6.95, N 8.50.

1-(5-(3-(2-Bromophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R,7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10b**): Gum; IR (KBr, cm^{-1}): υ 3296, 2981, 2932, 2875, 1713, 1642, 1572, 1461, 1246, 1217, 1038, 1022. ^{1}HNMR (400 MHz, $CDCl_3$): □7.66 (d, *J* = 7.8 Hz, 1H), 7.59-7.51 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.24 (s, 0.4H), 6.09 (s, 0.6H), 5.04 (d, *J* = 12.4 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.43-4.30 (m,

2H), 4.20 (d, *J* = 6.4 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 1H), 4.05-3.98 (m, 3H), 3.87 (d, *J* = 8.4 Hz, 1H), 3.74-3.62 (m, 1H), 3.59 (d, *J* = 7.4 Hz, 1H), 2.02-1.92 (m, 1H), 1.74-1.65 (m, 1H), 1.56 (s, 3H), 1.47 (s, 3H), 1.36 (s, 12H), 1.26-1.22 (m, 5H), 0.97 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.10, 144.84, 138.14, 136.84, 132.85, 132.65, 130.46, 130.21, 128.12, 127.48, 123.08, 122.74, 122.25, 111.94, 109.00, 104.24, 100.05, 99.96, 85.95, 85.70, 83.99, 83.80, 81.54, 81.53, 80.37, 80.32, 77.40, 76.35, 73.75, 71.64, 64.99, 60.08, 48.23, 37.17, 37.04, 33.82, 33.53, 30.25, 30.02, 28.15, 26.93, 26.77, 26.56, 26.22, 25.95, 25.55, 25.00, 23.97, 23.41, 20.20, 18.96 ppm. Anal. Calcd for ($C_{32}H_{46}BrN_3O_9$): C 55.17, H 6.66, N 6.03. Found: C 55.10, H 6.60, N 6.10.

1-(5-(3-(4-Fluorophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R, 7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10c**):Gum; IR (KBr, cm^{-1}): υ 3210, 2976, 2912, 2871, 1642, 1421, 1121, 1011. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.52 (d, *J* = 4.8 Hz, 1H), 7.48-7.45 (m, 2H), 7.05 (t, *J* = 8.4 Hz, 2H), 5.96 (s, 0.2H), 5.78 (d, *J* = 3.8 Hz, 0.8H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.83-4.78 (m, 1H), 4.43-4.34 (m, 2H), 4.22 (d, *J* = 6.0 Hz, 1H), 4.13 (d, *J* = 13.6 Hz, 1H), 4.05-3.99 (m, 3H), 3.89 (d, *J* = 8.8 Hz, 1H), 3.75-3.65 (m, 1H), 3.59 (d, *J* = 7.4 Hz, 1H), 1.99-1.90 (m, 1H), 1.77-1.63 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.39-1.33 (m, 12H), 1.26-1.23 (m, 5H), 1.00-0.97 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 164.49, 162.04, 145.31, 145.07, 133.94, 128.74, 128.65, 128.18, 128.09, 122.33, 122.14, 115.36, 115.15, 112.07, 109.15, 101.00, 86.13, 85.88, 84.17, 84.03, 81.44, 81.42, 80.31, 80.28, 77.46, 76.56, 73.83, 71.77, 65.22, 60.17, 48.34, 37.26, 37.22, 33.99, 33.73, 30.38, 30.17, 28.20, 26.79, 26.52, 26.26, 26.01, 25.83, 25.57, 25.30, 24.01, 23.56, 20.19, 19.02 ppm. Anal. Calcd for ($C_{32}H_{46}FN_3O_9$): C 60.46, H 7.29, N 6.61. Found: C 60.40, H 7.20, N 6.56.

1-(5-(3-(4-Chlorophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R, 7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10d**): Gum; IR (KBr, cm^{-1}): υ 3211, 2989, 2851, 1600, 1492, 1262, 1217, 1161, 1087, 1015. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.52 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.95 (s, 0.2H), 5.79 (d, *J* = 4.2 Hz, 0.8H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.83-4.79 (m, 1H), 4.41-4.34 (m, 2H), 4.22 (d, *J* = 6.4 Hz, 1H), 4.13 (d, *J* = 13.6 Hz, 1H),

4.05-3.99 (m, 3H), 3.89 (d, *J* = 8.6 Hz, 1H), 3.75-3.62 (m, 1H), 3.59 (d, *J* = 7.4 Hz, 1H), 1.98-1.91 (m, 1H), 1.77-1.64 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.39-1.33 (m, 12H), 1.26-1.20 (m, 5H), 0.99-0.97 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.29, 138.56, 136.73, 134.90, 128.51, 128.17, 127.68, 122.19, 112.05, 109.13, 104.30, 100.86, 100.36, 86.13, 85.87, 84.11, 83.96, 81.51, 81.49, 80.42, 80.39, 77.11, 76.56, 73.82, 71.75, 65.19, 60.16, 48.33, 37.24, 37.20, 33.96, 33.70, 30.34, 30.13, 28.20, 26.97, 26.80, 26.53, 26.26, 26.01, 25.83, 25.54, 24.01, 23.50, 20.26, 19.02 ppm. Anal. Calcd for ($C_{32}H_{46}ClN_3O_9$): C 58.93, H 7.11, N 6.44. Found: C 58.88, H 7.05, N 6.52.

1-(5-(3-(3-Bromophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R, 7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10e**): Gum; IR (KBr, cm^{-1}): υ 3296, 2981, 2932, 2875, 1713, 1642, 1572, 1461, 1246, 1217, 1038, 1022.^{1}HNMR (400 MHz, $CDCl_3$): □ 7.63-7.40 (m, 4H), 7.21-7.23 (m, 1H), 5.93 (s, 0.2H), 5.76 (d, *J* = 4.0 Hz, 0.8H), 5.06 (d, *J* = 12.6 Hz, 1H), 4.83-4.79 (m, 1H), 4.41-4.34 (m, 2H), 4.22 (d, *J* = 6.4 Hz, 1H), 4.13 (d, *J* = 13.8 Hz, 1H), 4.05-4.00 (m, 3H),3.89 (d, *J* = 8.6 Hz, 1H), 3.76-3.65 (m, 1H), 3.59 (d, *J* = 7.2 Hz, 1H), 1.98-1.89 (m, 1H), 1.76-1.65 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.40-1.33 (m, 12H), 1.25-1.08 (m, 5H), 1.00-0.94 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.23, 140.46, 140.45, 132.20, 131.83, 129.96, 129.76, 129.29, 125.47, 124.98, 122.43, 122.35, 122.17, 112.08, 109.16, 104.29, 100.64, 100.17, 86.14, 85.89, 84.17, 84.01, 81.61, 80.57, 80.54, 77.07, 73.82, 71.74, 65.18, 60.15, 48.29, 37.54, 37.27, 33.97, 33.70, 29.95, 29.83, 28.21, 26.82, 26.53, 26.27, 25.99, 25.83, 25.52, 25.31, 24.01, 23.48, 19.06, 18.31 ppm. Anal. Calcd for ($C_{32}H_{46}BrN_3O_9$): C 55.17, H 6.66, N 6.03. Found: C 55.11, H 6.60, N 6.10.

1-(5-(3-(Benzo[d][1,3]dioxol-5-yl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R,7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10f**): Gum; IR (KBr, cm^{-1}): υ 3289, 2986, 2921, 2861, 1643, 1541, 1453, 1248, 1219, 1081, 1039.^{1}HNMR (400 MHz, $CDCl_3$): □ 7.51 (s, 1H), 6.94-6.87 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 5.85 (s, 0.6H), 5.68 (d, *J* = 4.6 Hz, 0.6H), 5.01 (d, *J* = 12.4 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.37-4.30 (m, 2H), 4.18 (d, *J* = 6.6 Hz, 1H), 4.10-4.05 (m, 1H), 4.01-3.95 (m, 3H), 3.84 (d, *J* = 8.6 Hz, 1H), 3.63-3.60 (m, 1H), 3.55

(d, *J* = 7.4 Hz, 1H), 1.96-1.87 (m, 1H), 1.73-1.60 (m, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.36-1.29 (m, 12H), 1.23-1.21 (m, 5H), 0.95 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 148.29, 148.00, 147.66, 145.16, 133.90, 131.93, 122.22, 120.94, 120.20, 111.99, 109.06, 107.86, 106.91, 106.53, 104.25, 101.40, 101.06, 85.92, 85.66, 84.11, 83.95, 81.22, 81.20, 80.06, 80.03, 77.54, 76.43, 73.76, 71.67, 65.05, 60.10, 48.27, 37.18, 37.15, 33.93, 33.66, 30.29, 30.21, 28.14, 26.83, 26.75, 26.21, 25.94, 25.57, 25.55, 25.14, 23.96, 23.55, 20.98, 20.10, 19.01, 18.98 ppm. Anal. Calcd for ($C_{33}H_{47}N_3O_{11}$): C 59.90, H 7.16, N 6.35. Found: C 59.95, H 7.10, N 6.41.

1-(5-(3-(4-Methoxyphenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R, 7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (10g): Gum; IR (KBr, cm^{-1}): υ 3289, 2976, 2924, 1642, 1572, 1461, 1246, 1217, 1038, 1022.^{1}HNMR (400 MHz, $CDCl_3$): □ 7.55-7.51 (m, 1H), 7.42-7.36 (m, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.95 (s, 0.5H), 5.77 (d, *J* = 3.4 Hz, 0.5H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.41-4.34 (m, 2H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 4.05-3.99 (m, 3H), 3.88 (d, *J* = 8.6 Hz, 1H), 3.80 (s, 3H), 3.69-3.65 (m, 1H), 3.59 (d, *J* = 7.6 Hz, 1H), 1.99-1.87 (m, 1H), 1.76-1.64 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.37-1.35 (m, 12H), 1.16-1.08 (m, 5H), 1.00-0.94 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 160.34, 160.05, 145.33, 132.11, 130.17, 128.17, 127.65, 122.29, 122.12, 113.73, 113.70, 112.06, 109.14, 104.31, 101.57, 101.02, 86.02, 85.76, 84.09, 83.93, 81.16, 81.14, 80.01, 79.98, 77.48, 76.56, 73.83, 71.78, 65.24, 60.18, 55.28, 48.36, 37.53, 37.27, 34.02, 33.76, 30.43, 30.32, 29.98, 29.68, 28.20, 27.05, 26.93, 26.82, 26.26, 26.01, 25.64, 25.28, 23.61, 20.18, 19.06, 18.30 ppm. Anal. Calcd for ($C_{33}H_{49}N_3O_{10}$): C 61.19, H 7.62, N 6.49. Found: C 61.11, H 7.58, N 6.55.

1-(5-(6,6-Dimethyl-3-(*p*-tolyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R,7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy) methyl)-1*H*-1,2,3-triazole (**10h**): Gum; IR (KBr, cm^{-1}): υ 3276, 2954, 2927, 1635, 1577, 1465, 1238, 1210, 1029. ^{1}HNMR (400 MHz, $CDCl_3$): ▪ 7.55-7.51 (m, 1H), 7.38-7.33 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.96 (s, 0.5H), 5.78 (d, *J* = 3.4 Hz, 0.5H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.41-4.34 (m, 2H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 4.05-3.99 (m, 3H), 3.89 (d, *J* = 8.4 Hz, 1H), 3.69-3.64 (m, 1H), 3.59 (d, *J*= 7.2 Hz, 1H), 2.35 (s, 3H), 1.98-1.88 (m, 1H), 1.76-1.65 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.37-1.33 (m, 6H), 1.26-1.07 (m,

12H), 0.99-0.83 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.30, 139.05, 138.62, 137.00, 135.09, 129.01, 126.70, 126.19, 122.15, 112.08, 109.16, 104.30, 101.70, 101.16, 86.05, 85.78, 84.04, 83.87, 81.22, 80.11, 80.08, 77.48, 76.56, 73.83, 71.77, 65.23, 60.17, 48.38, 37.54, 37.24, 34.01, 33.74, 29.85, 29.69, 28.21, 27.04, 26.81, 26.26, 26.00, 25.59, 25.34, 25.18, 23.55, 22.69, 21.29, 19.06, 18.30 ppm. Anal. Calcd for ($C_{33}H_{49}N_3O_9$): C 62.74, H 7.82, N 6.65. Found: C 62.81, H 7.76, N 6.60.

1-(5-(6,6-Dimethyl-3-(3-nitrophenyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-((((3aS,4'R,7aS)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl) oxy)methyl)-1*H*-1,2,3-triazole (**10i**): Gum; IR (KBr, cm^{-1}): υ 3291, 2966, 2920, 1652, 1580, 1525, 1475, 1370, 1233, 1211, 1023. ^{1}HNMR (400 MHz, $CDCl_3$): □ 8.36-8.32 (m, 1H), 8.24-8.20 (m, 1H), 7.83-7.77 (m, 1H), 7.58-7.52 (m, 2H), 6.04 (s, 0.6H), 5.89 (d, *J* = 3.6 Hz, 0.4H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.40-4.34 (m, 2H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 4.05-4.00 (m, 3H), 3.89 (d, *J* = 8.4 Hz, 1H), 3.76-3.61 (m, 1H), 3.59 (d, *J* = 7.6 Hz, 1H), 2.00-1.95 (m, 1H), 1.76-1.67 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.38-1.36 (m, 12H), 1.25-1.08 (m, 5H), 1.01-0.94 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.38, 142.34, 140.61, 132.48, 129.41, 124.00, 123.69, 122.14, 121.88, 121.38, 112.08, 109.17, 104.31, 100.11, 99.68, 86.30, 86.08, 84.37, 84.19, 82.04, 80.98, 77.49, 76.58, 73.84, 71.78, 65.27, 60.18, 48.37, 37.55, 37.29, 33.97, 33.84, 30.48, 30.30, 28.23, 26.96, 26.81, 26.28, 26.03, 25.48, 25.06, 23.45, 20.32, 19.02, 18.31 ppm. Anal. Calcd for ($C_{32}H_{46}N_4O_{11}$): C 57.99, H 7.00, N 8.45. Found: C 57.91, H 6.95, N 8.50.

1-(5-(6,6-dimethyl-3-(napthalen-1-yl)-1,2,4-trioxan-5-yl)3-methylpentyl)-4-(((2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10j**): Gum; IR (KBr, cm^{-1}): υ 3291, 3123, 2988, 2936, 1632, 1614, 1456, 1414, 1383, 1220, 1116, 1084, 1018, 886. ^{1}HNMR (400 MHz, $CDCl_3$): ▪ 8.22-8.17 (m, 1H), 7.86-7.73 (m, 3H), 7.53-7.44 (m, 4H), 6.66 (s, 0.5H), 6.51 (d, *J* = 3.2 Hz, 0.5H), 5.04 (d, *J* = 12.4 Hz, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 4.36-4.31 (m, 2H), 4.20 (d, *J* = 8.2 Hz, 1H), 4.12 (d, *J* = 13.6 Hz, 1H), 4.04-3.98 (m, 3H), 3.88 (d, *J* = 8.4 Hz, 1H), 3.85-3.65 (m, 1H), 3.58 (d, *J* = 7.4 Hz, 1H), 1.98-1.91 (m, 1H), 1.75-1.69 (m, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.44-1.31 (s, 12H), 1.25-1.19 (m, 5H), 1.00-0.96 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.3, 135.0, 133.9, 133.8,

133.6, 131.0, 130.9, 129.2, 129.1, 128.5, 126.2, 126.1, 125.6, 125.2, 125.0, 124.1, 123.8, 123.1, 122.8, 122.1, 112.0, 109.1, 104.3, 99.0, 86.0, 85.8, 83.8, 83.6, 81.4, 81.3, 80.3, 80.2, 77.4, 76.5, 73.8, 71.8, 65.2, 60.2, 48.3, 37.3, 37.1, 34.0, 33.7, 30.4, 30.2, 28.2, 27.0, 27.0, 26.8, 26.2, 26.0, 25.6, 25.1, 23.3, 20.5, 19.1, 19.0 ppm. Anal. Calcd for ($C_{36}H_{49}N_3O_9$): C 64.75, H 7.40, N 6.29. Found: C 64.80, H 7.35, N 6.25.

1-(5-(3-(furan-2-yl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-4-(((2,2,2′,2′-tetra methyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4′-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (10k): Gum; IR (KBr, cm^{-1}): υ 3291, 3123, 2971, 2870, 2096, 1688, 1489,1449, 1123, 1038, 603. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.52 (s, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 6.47-6.18 (m, 2H), 5.99 (d, *J* = 2.0 Hz, 0.5H), 5.86 (d, *J* = 3.6 Hz, 0.5H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.41-4.35 (m, 2H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 4.05-3.99 (m, 3H), 3.89 (d, *J* = 8.4 Hz, 1H), 3.74-3.61 (m, 1H), 3.58 (d, J = 7.4 Hz, 1H), 1.99-1.91 (m, 1H), 1.75-1.69 (m, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.39-1.33 (m, 12H), 1.27-1.18 (m, 5H), 1.00-0.97 (m, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 152.1, 151.4, 144.7, 142.7, 142.5, 121.7, 111.5, 109.6, 109.5, 108.6, 108.6, 107.7, 103.8, 95.1, 94.8, 85.2, 85.0, 83.2, 83.0, 80.7, 79.9, 76.9, 76.2, 73.3, 71.3, 64.6, 59.7, 47.9, 36.7, 36.6, 33.3, 33.2, 30.0, 29.7, 27.6, 26.2, 26.2, 25.9, 25.7, 25.5, 24.5, 24.3, 22.2, 20.0, 18.5, 18.5 ppm. Anal. Calcd for ($C_{30}H_{45}N_3O_{10}$): C 59.29, H 7.46, N 6.91. Found: C 59.25, H 7.40, N 6.99.

1-(5-(3,3-Dimethyl-1,2,5-trioxaspiro[5.5]undecan-4-yl)-3-methyl pentyl)-4-(((2,2,2′,2′-tetra-methyltetrahydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4′-[1,3]dioxolan]-7-yl)oxy)methyl)-1*H*-1,2,3-triazole (**10l**): Gum, IR (KBr, cm^{-1}): υ 3291, 3123, 2988, 2936, 1383, 1220, 1116, 1084, 1018, 886. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.54 (s, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.41-4.34 (m, 2H), 4.22 (d, *J* = 8.4Hz, 1H), 4.13 (d, *J*= 13.4 Hz, 1H), 4.06-4.00 (m, 3H), 3.89 (d, *J* = 8.4 Hz, 1H), 3.65-3.58 (m, 2H), 2.01-1.93 (m, 1H), 1.76-1.71 (m, 1H), 1.64-1.55 (m, 10H), 1.49 (s, 3H), 1.38 (s, 10H), 1.24 (s, 7H), 1.07 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 145.3, 122.1, 112.0, 109.1, 106.9, 104.2, 83.0, 82.8, 79.5, 77.4, 77.4, 73.8, 71.7, 65.2, 60.1, 48.4, 38.3, 37.3, 36.1, 36.0, 34.08, 33.8, 30.4, 30.2, 29.6, 28.1, 26.8, 26.5, 26.2, 25.9, 25.1, 24.0, 23.7, 23.2, 23.1, 19.1, 19.0 ppm. Anal. Calcd for ($C_{31}H_{51}N_3O_9$): C 61.06, H 8.43, N 6.89. Found: C 61.00, H 8.35, N 6.96.

Typical procedure for synthesis of 1,2,3-triazole tethered 1,2,4-trioxane with 1,4-disubstituted benzene core: A mixture of CuI (2 mg, 1 mol%) and L-proline (1.2 mg, 1 mol%) taken in an oven-dried two-neck round bottom flask was mixed with glycerol (4 mL) in a bath sonicator for 30 min. Then azido-1,2,4-trioxane derivative of compound (**6a**) (0.364 g, 1 mmol) and 1,4-diethylene benzene (0.126 g, 1 mmol) were added to the solution and stirred at room temperature. The progress of the reaction was monitored by TLC and found completed within 6 h. The reaction was quenched by adding water (5 mL) to the suspension and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated the organic layer to afford the crude product. The crude was purified by column chromatography employing 15% ethyl acetate in hexane as eluent.

1,4-bis(1-(5-(6,6-dimethyl-3-(4-nitrophenyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12a): Yield 67%, gum. IR (KBr, cm^{-1}): υ 3312, 3134, 2972, 2871, 1619, 1461, 1531, 1384, 1350, 1192, 1107. ^{1}HNMR (400MHz, $CDCl_3$): □ 8.22-8.18 (m, 4H), 7.87 (s, 4H), 7.80 (s, 2H), 7.65-7.58 (m, 4H), 6.02 (s, 0.5H), 5.86 (s, 1.5H), 4.51-4.43 (m, 4H), 3.74-3.55 (m, 2H), 2.06-2.01 (m, 2H), 1.83-1.67 (m, 4H), 1.56-1.50 (m, 4H), 1.36-1.32 (m, 6H), 1.04-1.01 (m, 4H), 0.88-0.80 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 148.3, 148.1, 147.3, 147.1, 145.3, 130.3, 127.5, 127.5, 127.1, 126.0, 123.5, 119.5, 100.0, 99.6, 86.3, 86.0, 84.2, 84.1, 81.9, 80.9, 48.4, 37.2, 37.1, 33.9, 33.6, 30.2, 30.0, 26.9, 26.7, 25.4, 25.0, 23.3, 20.3, 19.1, 19.1 ppm. Anal. Calcd for ($C_{44}H_{54}N_8O_{10}$): C 61.81, H 6.37, N 13.11. Found: C 61.75, H 6.32, N 13.20.

1,4-Bis(1-(5-(3-(2-bromophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl) -1*H*-1,2,3-triazol-5-yl)benzene (12b): White solid; Mp: 119-120 ^{o}C, IR (KBR, cm^{-1}): υ 3051, 3025, 2956, 2926, 2866, 1634, 1492, 1443, 1070, 786. ^{1}HNMR (400 MHz, $CDCl_3$): □7.88 (s, 4H), 7.78-7.64(m, 4H), 7.58-7.16 (m, 6H), 6.24 (s, 1H), 6.10 (d, *J* = 4.4 Hz, 1H), 4.47-4.43 (m, 4H), 3.76-3.63 (m, 2H), 2.04-1.99 (m, 2H), 1.83-1.37 (m, 18H), 1.26-1.20 (m, 6H), 1.03-1.00 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 147.3, 138.1, 136.9, 132.9, 132.7, 130.5, 130.3, 130.2, 128.1, 127.8, 127.5, 127.3, 126.0, 123.2, 122.8, 119.5, 100.1, 100.1, 86.0, 85.7, 84.0, 83.8, 81.6, 80.4, 48.5, 37.3, 37.1, 33.9, 33.6, 30.5, 30.1, 26.9, 26.8, 25.6, 25.1, 23.4, 20.2, 19.2, 19.1 ppm. Anal. Calcd for ($C_{44}H_{54}Br_2N_6O_6$): C 57.27, H 5.90, N 9.11. Found: C 57.21, H 5.95, N 9.06.

1,4-Bis(1-(5-(3-(4-fluorophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12c): White solid; Mp: 110-113 ^{o}C, IR (KBr, cm^{-1}): υ 3315, 3129, 2974, 2935, 2870, 1609, 1460, 1192, 1107. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.81 (s, 4H), 7.71 (d, *J* = 4.4 Hz, 2H), 7.40-7.33 (m, 4H), 7.00-6.94 (m, 4H), 5.88 (s, 1H), 5.70 (s, 1H), 4.41-4.35 (m, 4H), 3.63-3.61 (m, 1H), 3.59-3.54 (m, 1H), 1.98-1.93 (m, 2H), 1.51-1.27 (m, 8H), 1.25-1.14 (m, 13H), 0.98-0.94 (m, 3H), 0.82-0.75 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 163.3 (d, *J* = 22.9 Hz), 160.9 (d, *J* = 21.6 Hz), 146.3, 134.7, 132.9, 129.3, 127.7, 127.1, 125.0, 118.4, 114.3, 114.0, 100.0, 99.5, 85.1, 84.8, 83.1, 83.0, 80.4, 79.2, 47.4, 36.2, 36.2, 33.0, 32.8, 29.1, 28.6, 26.0, 25.8, 24.5, 24.2, 22.5, 21.6, 19.1, 18.0 ppm. Anal. Calcd for ($C_{44}H_{54}F_2N_6O_6$): C 65.98, H 6.80, N 10.49. Found: C 64.92, H 6.75, N 1056.

1,4-Bis(1-(5-(3-(4-chlorophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12d): White solid; Mp: 146-148 ^{o}C, IR (KBr, cm^{-1}): υ 3051, 3025, 2956, 2926, 2866, 1634, 1492, 1443, 1070. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.81 (s, 4H), 7.70 (d, *J* = 4.8 Hz, 2H), 7.34-7.19 (m, 8H), 5.87 (s, 1H), 5.69 (s, 1H), 4.42-4.34 (m, 4H), 3.63-3.51 (m, 2H), 1.98-1.91 (m, 2H), 1.48-1.21 (m, 24H), 0.95 (d, *J* = 6.0 Hz, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 146.3, 137.5, 135.7, 133.9, 133.5, 129.3, 127.5, 127.4, 127.1, 126.6, 125.0, 118.4, 99.8, 99.3, 85.1, 84.8, 83.1, 82.9, 80.5, 79.3, 47.4, 36.2, 36.2, 32.9, 32.6, 29.3, 29.2, 26.0, 25.8, 25.7, 24.5, 24.1, 22.4, 19.2, 18.0 ppm. Anal. Calcd for ($C_{44}H_{54}Cl_2N_6O_6$): C 63.38, H 6.53, N 10.08. Found: C 63.32, H 6.48, N 10.15.

1,4-Bis(1-(5-(3-(3-bromophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12e): White solid; M.p: 103-105 ^{o}C, IR (KBr, cm^{-1}): υ 3315, 3127, 3090, 2970, 2871, 1595, 1441, 1193, 1122. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.88 (s, 4H), 7.79 (d, *J* = 4.4 Hz, 2H), 7.62-7.58 (m, 2H), 7.47-7.35 (m, 4H), 7.25-7.20 (m, 2H), 5.92 (s, 1H), 5.75 (s, 1H), 4.48-4.39 (m, 4H), 3.71-3.59 (m, 2H), 2.05-1.20 (m, 26H), 1.02 (d, *J* = 6.4 Hz, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 147.3, 142.3, 140.5, 132.2, 131.8, 130.2, 129.9, 129.7, 129.3, 126.0, 125.4, 124.9, 122.4, 119.5, 100.6, 100.1, 86.1, 85.8, 84.1, 84.0, 81.6, 80.5, 48.5, 37.3, 37.2, 33.9, 33.6, 30.4, 30.1, 27.0, 26.7, 25.5, 25.1, 23.4, 20.2, 19.1, 19.1 ppm. Anal. Calcd for ($C_{44}H_{54}Br_2N_6O_6$): C 57.27, H 5.90, N 9.11. Found: C 57.22, H 5.85, N 9.19.

1,4-Bis(1-(5-(3-(benzo[d][1,3]dioxol-5-yl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12f): White solid; M.p: 127.5-128.5 ^{o}C; IR (KBr, cm^{-1}): υ 3133, 2969, 2931, 2875, 1633, 1503, 1441, 1193, 1122. ^{1}HNMR (400 MHz, $CDCl_3$): □7.88 (s, 4H), 7.78 (d, *J* = 4.0 Hz, 2H), 6.98-6.92 (m, 4H), 6.78 (d, *J* = 8.0 Hz, 2H), 5.94 (d, *J* = 1.2 Hz, 4H), 5.89 (d, *J* = 1.6 Hz, 1H), 5.71 (d, *J* = 2.0 Hz, 1H), 4.50-4.43 (m, 4H), 3.69-3.64 (m, 2H), 2.06-1.97 (m, 2H), 1.83-1.21 (m, 24H), 1.03-1.01 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 148.3, 148.3, 148.0, 147.7, 147.3, 133.9, 132.0, 130.3, 126.0, 121.0, 120.2, 119.5, 107.9, 106.9, 106.6, 101.4, 101.1, 101.0, 86.0, 85.7, 84.2, 84.0, 81.2, 80.1, 48.5, 37.3, 37.2, 34.0, 33.9, 30.5, 30.3, 27.1, 26.8, 25.6, 25.2, 23.6, 20.1, 19.1, 19.1 ppm. Anal. Calcd for ($C_{46}H_{56}N_6O_{10}$): C 64.77, H 6.62, N 9.85. Found: C 64.71, H 6.56, N 9.95.

1,4-Bis(1-(5-(3-(4-methoxyphenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpent-yl)-1*H*-1, 2,3-triazol-4-yl)benzene (12g): Gum; IR (KBr, cm^{-1}): υ 3133, 2969, 2931, 2875, 1616, 1518, 1458, 1371, 1264, 1220, 1086, 1068, 833. ^{1}HNMR (400 MHz, $CDCl_3$): □ 8.03-7.91 (m, 4H), 7.81-7.78 (m, 2H), 7.42-7.36 (m, 4H), 6.90-6.87 (m, 4H), 5.95 (d, *J* = 2.0 Hz, 1H), 5.77 (d, *J* = 2.6 Hz, 1H), 4.50-4.43 (m, 4H), 3.79 (s, 6H), 3.71-3.65 (m, 2H), 2.07-1.97 (m, 2H), 1.84-1.23 (m, 24H), 1.10-1.00 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 160.3, 160.0, 147.3, 130.7, 130.2, 129.9, 128.1, 127.8, 125.7, 119.6, 113.7, 113.7, 101.5, 101.0, 86.0, 85.9, 84.1, 83.9, 81.1, 80.0, 55.3, 49.2, 48.5, 37.3, 36.6, 34.0, 33.7, 30.4, 30.1, 27.1, 26.8, 25.6, 25.3, 23.6, 20.2, 19.2, 18.3 ppm. Anal. Calcd for ($C_{46}H_{60}N_6O_8$): C 66.97, H 7.33, N 10.19. Found: C 66.90, H 7.21, N 10.25.

1,4-Bis(1-(5-(6,6-dimethyl-3-(p-tolyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12h): Gum; IR (KBr, cm^{-1}): υ 3133, 2969, 2931, 2875, 1633, 1503, 1441, 1193, 1122. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.90 (d, *J* = 2.6 Hz, 4H), 7.78 (d, *J* = 4.4 Hz, 2H), 7.37-7.32 (m, 4H), 7.18-7.15 (m, 4H), 5.96 (d, *J* = 2.0 Hz, 1H), 5.78 (d, *J* = 2.8 Hz, 1H), 4.48-4.42 (m, 4H), 3.70-3.63 (m, 2H), 2.33 (s, 6H), 2.00-1.92 (m, 2H), 1.85-1.41 (m, 12H), 1.26-1.21 (m, 6H), 1.09-1.07 (m, 6H), 1.03-0.95 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 147.3, 139.0, 130.3, 129.0, 126.6, 126.1, 126.0, 119., 119.4, 101.7, 101.1, 86.0, 85.7, 84.0, 83.8, 81.2, 80.1, 48.3, 37.5, 37.3, 34.0, 33.8, 30.2, 29.8, 27.1, 26.8, 25.6, 25.1, 23.5, 21.8, 20.2, 19.1, 18.3 ppm. Anal. Calcd for ($C_{46}H_{60}N_6O_6$): C 69.67, H 7.63, N 10.60. Found: C 66.61, H 7.58, N 10.69.

1,4-Bis(1-(5-(6,6-dimethyl-3-(naphthalen-1-yl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (**12i**): Gum, IR (KBr, cm^{-1}): υ 2932, 2098, 1610, 1601, 1492, 1475, 1192, 1107. ^{1}HNMR (400 MHz, $CDCl_3$): □ 8.23-8.18 (m, 2H), 7.86-7.61 (m, 12H), 7.61-7.45 (m, 6H), 6.67 (s, 1H), 6.51 (d, *J* = 3.6 Hz, 1H), 4.46-4.31 (m, 4H), 3.87-3.65 (m, 2H), 2.04-1.94 (m, 2H), 1.82-0.83 (m, 30H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 147.35, 135.01, 133.96, 133.80, 133.67, 131.03, 130.97, 130.30, 129.30, 129.13, 128.53, 126.24, 126.14, 126.04, 125.66, 125.63, 125.25, 125.22, 125.09, 124.12, 123.88, 123.85, 123.17, 122.83, 119.51, 99.10, 99.07, 86.08, 85.80, 83.89, 83.62, 81.42, 81.41, 80.37, 80.29, 48.53, 37.32, 37.07, 33.99, 33.69, 30.48, 30.23, 27.15, 26.72, 25.66, 25.10, 23.35, 22.71, 20.54, 19.17 ppm. Anal. Calcd for ($C_{52}H_{60}N_6O_6$): C 72.20, H 6.99, N 9.71. Found: C 72.15, H 6.91, N 9.79.

1,4-Bis(1-(5-(3-(furan-2-yl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (**12j**): White Solid, M.p.: 110-112 ^{o}C, IR (KBr, cm^{-1}): υ 3196, 2932, 2098, 1610, 1601, 1492, 1475, 1192, 1107. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.89 (s, 4H), 7.80 (s, 2H), 7.42-7.40 (m, 2H), 6.47-6.33 (m, 4H), 5.99 (s, 1H), 5.86 (s, 1H), 4.48-4.39 (m, 4H), 3.75-3.62 (m, 2H), 2.06-1.97 (m, 2H), 1.83-1.18 (m, 24H), 1.03-0.98 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ1 52.58, 151.07, 147.34, 143.27, 143.02, 130.33, 126.06, 119.56, 110.21, 110.05, 109.18, 108.30, 95.62, 95.33, 85.77, 85.46, 83.70, 83.49, 81.21, 81.19, 80.50, 80.45, 48.50, 37.27, 37.24, 33.88, 33.70, 30.48, 30.21, 26.75, 26.49, 25.05, 24.86, 22.81, 22.69, 20.52, 19.12 ppm. Anal. Calcd for ($C_{40}H_{52}N_6O_8$): C 64.50, H 7.04, N 11.28. Found: C 64.45, H 7.11, N 11.35.

1,4-Bis(1-(5-(3,3-dimethyl-1,2,5-trioxaspiro[5,5]undecan-4-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12k): Gum; IR (KBr, cm^{-1}): υ 3133, 2969, 2931, 2875, 1633, 1503, 1441, 1193, 1122. ^{1}HNMR (400 MHz, $CDCl_3$): □8.02-7.80 (m, 5H), 4.53-4.45 (m, 4H), 3.62-3.58 (m, 2H), 2.11-1.95 (m, 2H), 1.79-1.42 (m, 32H), 1.31-1.23 (m, 6H), 1.07-1.01 (m, 12H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 149.1, 147.4, 130.3, 129.9, 127.8, 127.4, 126.0, 125.7, 119.5, 119.4, 107.0, 83.0, 82.8, 79.5, 49.2, 48.5, 38.3, 37.2, 36.8, 36.1, 34.0, 33.8, 30.5, 30.4, 26.8, 26.6, 26.3, 25.1, 24.0, 23.8, 23.2, 19.2, 18.3 ppm. Anal. Calcd for ($C_{42}H_{64}N_6O_6$): C 67.35, H 8.61, N 11.22. Found: C 67.28, H 8.52, N 11.30.

1,4-Bis(1-(5-(3-(4-chlorophenyl)-3,6,6-trimethyl-1,2,4-trioxan-5-yl)-3-methyl-pentyl)-1*H*-1,2,3-triazol-4-yl)benzene (12l): Gum; IR (KBr, cm^{-1}): υ 3133, 2969, 2931, 2875, 1633, 1503, 1441, 1193, 1122. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.90-7.87 (m, 4H),7.81-7.79 (m, 2H), 7.44-7.25 (m, 8H), 4.48-4.39 (m, 4H), 3.77-3.26 (m, 2H), 2.06-1.99 (m, 2H), 1.82-1.67 (m, 6H), 1.56-1.49 (m, 6H), 1.48-1.30 (m, 6H), 1.23-1.07 (m, 12H), 1.02-0.84 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 147.3, 144.2, 133.1, 130.3, 128.1, 127.9, 126.6, 126.2, 126.0, 119.4, 106.4, 106.1, 84.4, 84.2, 83.7, 83.5, 81.1, 81.1, 48.5, 37.4, 37.2, 33.9, 33.7, 30.3, 30.0, 26.8, 26.2, 25.9, 25.4, 23.4, 22.1, 22.0, 19.1, 19.0 ppm. Anal. Calcd for ($C_{46}H_{58}Cl_2N_6O_6$): C 64.10, H 6.78, N 9.75. Found: C 64.05, H 6.70, N 9.83.

Typical procedure for synthesis of 1,2,3-triazoles tethered 1,2,4-trioxane dimers with diethanolamine core: A mixture of CuI (1 mg, 1 mol%) and L-proline (0.6 mg, 1 mol%) taken in an oven-dried two-neck round bottom flask was mixed with glycerol (4 mL) in a bath sonicator for 30 min. Then 5-(5-Azido-3-methylpentyl)-6,6-dimethyl-3-(4-nitrophenyl)-1,2,4-trioxane derivative of compound (0.154 g, 0.5 mmol) and (0.90 g, 0.5 mmol) were added to the solution and stirred at room temperature. The progress of the reaction was monitored by TLC and found completed within 18 h. The reaction was quenched by adding water (5 mL) to the suspension and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated the organic layer to afford the crude product. The crude was purified by column chromatography employing 5% methanol in chloroform as eluent to achieve bis(2-((1-(5-(6,6-dimethyl-3-(4-nitrophenyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)amine in

Bis(2-((1-(5-(6,6-dimethyl-3-(4-nitrophenyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4yl)methoxy)ethyl)amine (**13a**): Yield 60%, gum. IR (KBr, cm^{-1}): υ 3246, 2957, 2925, 2855, 2388, 1638, 1525, 1461, 1380, 1193, 1107, 762. ^{1}HNMR (400 MHz, $CDCl_3$): □ 8.24 (d, *J* = 8.4 Hz, 4H), 7.68-7.62 (m, 4H), 7.52-7.49 (m, 2H), 6.04 (s, 1H), 5.83 (d, *J* = 2.4 Hz, 1H), 4.59 (s, 4H), 4.44-4.37 (m, 4H), 4.21 (s, 1H), 3.76-3.56 (m, 8H), 3.40 (t, *J* = 5.2 Hz, 2H), 2.02-1.3 (m, 2H), 1.80-1.73 (m, 2H), 1.56-1.49 (m, 5H), 1.43-1.19 (m, 5H), 1.25-1.19 (m, 12H), 1.02-0.99 (m, 5H), 0.88-0.86 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.34, 148.15, 147.15, 145.42, 144.68, 127.57, 127.13, 123.59, 123.54, 122.32, 100.08, 99.71, 86.33, 86.09, 84.29, 84.08, 82.00, 80.99, 68.33, 67.64, 64.74, 64.34, 59.89, 48.47, 47.13, 46.22, 37.23, 37.13, 33.92, 33.68, 30.45,

30.31, 26.98, 26.81, 25.45, 25.05, 23.35, 22.57, 20.42, 19.07 ppm. Anal. Calcd for ($C_{44}H_{63}N_9O_{12}$): C 58.07, H 6.98, N 13.85. Found: C 58.00, H 6.91, N 13.95.

Bis(2-((1-(5-(3-(4-fuorophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4yl)methoxy)ethyl)amine (**13b**): Gum, IR (KBr, cm^{-1}): υ 3239, 2934, 2857, 2363, 1645, 1516, 1382, 1193, 1107, 762. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.51-740 (m 6H), 7.05 (t, *J* = 8.6 Hz, 4H), 5.95 (s, 1H), 5.78 (s, 1H), 4.63-4.57 (m, 4H), 4.41-4.34 (m, 4H), 4.20 (s, 1H), 3.80-3.36 (m, 10H), 2.01-1.92 (m, 2H), 1.76-1.35 (m, 18H), 1.25-1.22 (m, 6H), 1.00-0.82 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.51, 164.28, 162.05, 161.82, 144.52, 136.55, 133.94, 128.74, 128.65, 128.19, 128.10, 122.39, 115.38, 115.17, 101.01, 100.51, 86.16, 85.89, 84.19, 84.00, 81.45, 80.31, 68.35, 67.58, 64.63, 64.28, 59.87, 48.49, 47.11, 46.19, 37.21, 37.11, 33.99, 33.74, 30.48, 29.70, 27.02, 26.82, 25.60, 25.22, 23.56, 22.67, 20.19, 19.07 ppm. Anal. Calcd for ($C_{44}H_{63}F_2N_7O_8$): C 61.74, H 7.42, N 11.45. Found: C 61.65, H 7.49, N 11.40.

Bis(2-((1-(5-(3-(4-chlorophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4yl)methoxy)ethyl)amine (**13c**): Gum, IR (KBr, cm^{-1}): υ 3246, 2926, 2859, 1640, 1462, 1381, 1268, 1107, 1068, 762. ^{1}HNMR (400 MHz, $CDCl_3$): □7.49-7.46 (m, 2H), 7.42-7.39 (m, 4H), 7.37-7.32 (m, 4H), 5.94 (s, 1H), 5.77 (d, *J* = 2.6 Hz, 1H), 4.57 (s, 4H), 4.44-4.34 (m, 4H), 4.20 (s, 1H), 3.70-3.56 (m, 8H), 3.38 (t, *J* = 5.2 Hz, 2H), 2.01-1.92 (m, 2H), 1.78-1.35 (m, 18H), 1.26-1.20 (m, 6H), 1.00-0.85 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.65, 138.66, 136.86, 128.85, 128.52, 128.15, 127.67, 122.23, 100.89, 100.43, 86.18, 85.93, 84.15, 83.94, 81.51, 80.45, 68.36, 67.64, 64.72, 64.36, 59.90, 48.44, 47.14, 46.27, 37.23, 37.13, 34.02, 33.96, 30.58, 30.51, 27.04, 26.87, 25.57, 25.19, 23.48, 22.55, 20.32, 19.09 ppm. Anal. Calcd for ($C_{44}H_{63}Cl_2N_7O_8$): C 59.45, H 7.14, N 11.03. Found: C 59.40, H 7.06, N 11.15.

Bis(2-((1-(5-(3-(3-bromophenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4yl)methoxy)ethyl)amine (**13d**): Gum, IR (KBr, cm^{-1}): υ 3239, 2925, 2857, 1641, 1462, 1380, 1259, 1102, 762. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.62 (m, 8H), 7.24-7.22 (m, 2H), 5.93 (s, 1H), 5.76 (s, 1H), 4.57 (s, 4H), 4.45-4.35 (m, 4H), 4.21 (s, 1H), 3.73-3.37 (m, 10H), 2.01-1.92 (m, 2H), 1.78-1.71 (m, 8H), 1.53-1.49 (m, 4H), 1.36 (s, 6H), 1.25-1.21 (m, 6H), 1.00-0.85 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 144.54, 142.33, 140.55, 132.20, 131.83, 129.98, 129.77, 129.31, 129.20, 125.47, 124.98, 122.45, 122.37, 122.30, 100.65, 100.17, 86.17, 85.89,

84.18, 84.04, 81.62, 80.55, 68.37, 67.59, 64.66, 64.31, 59.88, 48.50, 47.12, 46.21, 37.28, 37.14, 34.01, 33.85, 30.49, 30.26, 29.71, 25.54, 25.11, 23.47, 20.30, 19.08 ppm. Anal. Calcd for ($C_{44}H_{63}Br_2N_7O_8$): C 54.05, H 6.49, N 10.03. Found: C 55.10, H 6.41, N 10.15.

Bis(2-((1-(5-(3-(benzo[d][1,3]dioxol-5-yl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)amine (**13e**): Gum, IR (KBr, cm^{-1}): υ 3236, 2925, 2855, 1643, 1541, 1378, 1248, 1117, 1081, 1031, 669.^{1}HNMR (400 MHz, $CDCl_3$): □7.50-7.48 (m, 2H), 6.98-6.90 (m, 4H), 7.98 (d, *J* = 8.0 Hz, 2H), 5.95 (s, 4H), 5.89 (s, 1H), 5.71 (s, 1H), 4.64-4.57 (m, 4H), 4.41-4.34 (m, 4H), 4.21 (s, 1H), 3.73-3.37 (m, 10H), 1.98-1.94 (m, 2H), 1.74-1.34 (m, 18H), 1.22 (s, 6H), 1.00-0.85 (s, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ148.23, 147.94, 147.74, 147.58, 144.57, 133.83, 133.76, 122.21, 120.87, 120.15, 107.82, 107.80, 106.84, 106.47, 101.35, 100.98, 85.90, 85.65, 84.07, 83.93, 81.15, 79.98, 68.24, 67.43, 64.51, 64.18, 59.73, 48.36, 47.32, 46.97, 37.16, 37.01, 33.85, 33.68, 30.25, 30.11, 26.96, 26.75, 25.50, 25.08, 23.46, 21.47, 19.98, 18.94 ppm. Anal. Calcd for ($C_{46}H_{65}N_7O_{12}$): C 60.84, H 7.22, N 10.80. Found: C 60.75, H 7.29, N 10.75.

Bis(2-((1-(5-(6,6-dimethyl-3-phenyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)amine (13f): Gum, IR (KBr, cm^{-1}): υ 3239, 2926, 2856, 1645, 1541, 1456, 1379, 1266, 1094, 740. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.51-7.45 (m, 8H), 7.40-7.33 (m, 4H), 6.90 (s, 1H), 5.82 (d, *J* = 2.8 Hz, 1H), 4.65-4.59 (m, 4H), 4.42-4.33 (m, 4H), 4.22 (s, 1H), 3.80-3.38 (m, 10H), 2.06-1.98 (m, 2H), 1.78-1.44 (m, 12H), 1.38 (s, 6H), 1.29-1.21 (m, 6H), 1.02-0.95 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 144.52, 140.00, 138.12, 129.69, 129.21, 128.82, 128.34, 126.79, 126.28, 122.34, 101.69, 101.16, 86.15, 85.91, 84.17, 83.86, 81.32, 80.22, 68.39, 67.91, 64.36, 63.86, 59.90, 48.52, 47.13, 46.24, 37.30, 37.14, 33.99, 33.85, 30.54, 29.70, 27.07, 26.78, 25.64, 25.23, 23.54, 22.57, 20.30, 19.10 ppm. Anal. Calcd for ($C_{44}H_{65}N_7O_8$): C 64.45, H 7.99, N 11.96. Found: C 64.39, H 8.05, N 11.91.

Bis(2-((1-(5-(3-(4-methoxyphenyl)-6,6-dimethyl-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)amine (**13g**): Gum, IR (KBr, cm^{-1}): υ 3236, 2925, 2855, 1632, 1515, 1462, 1381, 1249, 1106, 739. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.43-7.38 (m, 6H,), 6.91 (d, *J* = 8.4 Hz, 4H), 5.95 (d, *J* = 2.6 Hz, 1H), 5.77 (d, *J* = 2.6 Hz, 1H), 4.65-4.59 (m, 4H), 4.40-4.38

(m, 4H), 4.23 (s, 1H), 3.82 (s, 6H), 3.70-3.40 (m, 10H), 2.03-1.96 (m, 2H), 1.78-1.38 (m, 12H), 1.27-1.24 (m, 6H), 1.11-1.09 (m, 6H), 1.02-0.87 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 144.56, 133.96, 131.74, 128.19, 127.66, 113.76, 113.74, 101.57, 101.05, 86.06, 85.83, 84.11, 83.90, 81.16, 80.03, 68.41, 67.62, 64.38, 64.16, 59.90, 55.31, 48.56, 47.14, 46.27, 37.30, 37.27, 34.06, 34.01, 30.90, 29.69, 27.91, 27.73, 25.66, 25.35, 24.52, 23.61, 22.67, 20.19, 20.19, 19.15 ppm. Anal. Calcd for ($C_{46}H_{69}N_7O_{10}$): C 62.78, H 7.90, N 11.14. Found: C 62.71, H 7.85, N 11.19.

Bis(2-((1-(5-(6,6-dimethyl-3-(*p*-tolyl)-1,2,4-trioxan-5-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)amine (**13h**): Gum, IR (KBr, cm^{-1}): υ 3233, 2927, 2851, 1641, 1461, 1382, 1189, 1118, 762. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.51-7.47 (m, 2H), 7.37-7.32 (m, 4H), 7.17 (d, *J* = 7.8 Hz, 4H), 5.96 (s, 1H), 5.78 (s, 1H), 4.64-4.57 (m, 4H), 4.40-4.32 (m, 4H), 4.21 (s, 1H), 3.78-3.25 (m, 10H), 2.34 (s, 6H), 1.99-1.95 (m, 2H), 1.93-1.35 (m, 12H), 1.27-1.22 (m, 12H), 1.00-0.85 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 144.39, 138.91, 134.99, 129.58, 128.87, 126.55, 126.05, 101.56, 101.00, 85.96, 85.78, 83.92, 83.70, 81.07, 79.95, 68.24, 67.42, 64.43, 64.16, 49.24, 48.37, 48.00, 37.18, 36.71, 33.92, 33.70, 30.33, 30.21, 26.99, 26.87, 25.48, 25.06, 23.42, 21.16, 20.08, 19.02 ppm. Anal. Calcd for ($C_{46}H_{69}N_7O_8$): C 65.15, H 8.20, N 11.56. Found: C 65.10, H 8.25, N 11.50.

Bis(2-((1-(5-(3,3-dimethyl-1,2,5-trioxaspiro[5.5]undecan-4-yl)-3-methylpentyl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)amine (13i): Gum, IR (KBr, cm^{-1}): υ 3239, 2928, 2856, 1643, 1462, 1365, 1285, 1143, 1098, 796. ^{1}HNMR (400 MHz, $CDCl_3$): □ 7.52 (d, *J* = 9.4 Hz, 2H), 4.59 (s, 4H), 4.46-4.35 (m, 4H), 4.23 (s, 1H), 3.69-3.55 (m, 8H), 3.40 (t, *J* =5.4 Hz, 2H), 2.02-1.94 (m, 2H), 1.77-1.53 (m, 24H), 1.24 (s, 12H), 1.07-0.85 (m, 16H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ 144.59, 122.34, 107.04, 83.07, 82.85, 79.60, 77.34, 77.22, 77.02, 76.70, 68.39, 67.58, 64.68, 64.34, 59.89, 48.57, 47.12, 46.21, 38.33, 36.15, 36.11, 34.09, 33.84, 30.57, 30.37, 26.87, 26.85, 26.32, 25.14, 24.05, 23.82, 23.24, 23.20, 19.20, 19.05 ppm. Anal. Calcd for ($C_{46}H_{69}N_7O_8$): C 62.74, H 9.15, N 12.19. Found: C 62.68, H 9.08, N 12.28.

Biology

Maintenance of MDA-MB-435 cells

MDA-MB-435 breast cancer cells were procured from National Centre for Cell Science (NCCS), Pune, and maintained using Dulbecco's modified Eagle medium (DMEM) supplemented with 10 % fetal bovine serum (FBS), 1x antibiotic mix (penicillin and streptomycin) at 37 ^{o}C in a humidified atmosphere of 5 % CO_2.

Treatment of MDA-MB-435 cancer cells with 1,2,4-trioxane monomers and dimers

Analysis of OPN expression under the influence of the synthesised 1,2,4-trioxanes was studied. In brief, 1 x 10^6 MDA-MB-435 cells were seeded in a 6 cm plate containing 4 mL DMEM supplemented with 10 % FBS and 1x antibiotic mix (penicillin and streptomycin), and cultured at 37 ^{o}C in an incubator with 5 % CO_2 for 24 h. The cells were then serum starved for 24 h and divided into control (DMSO treated) and treated (different compounds) groups. The cells were then treated with 10 or 50 µM concentration of different compounds and incubated for 24 h. After treatment, culture medium and cells were collected and processed for western blot analysis of OPN and β-actin, respectively.

Western blot analyses

For the analysis of secreted OPN, serum-free cell culture supernatants were collected from the control and each treated group. 25 µL of supernatant per sample was electrophoresed on 10 % SDS–polyacrylamide mini-gels with non-reducing sample buffer. For β-actin analysis, the cells were lysed in RIPA buffer containing 1x protease inhibitor cocktail and equal volumes of the total protein extract (~10 µl) were resolved on 10 % SDS-PAGE and electroblotted onto a polyvinylidene difluoride membrane (PVDF) by using a semi dry transfer cell (Bio-Rad). The PVDF membrane was blocked for 1 h at room temperature in 1x Tris-buffered saline with Tween-20 (TBST) containing 5 % (w/v) non-fat dried milk, and then incubated overnight with monoclonal anti-OPN antibody (1:500 dilution) and anti-β-actin (1:1000 dilution) (Cell Signaling Technology) primary antibody at 4 ^{o}C. After washing 3 times in TBST, the PVDF membrane was then incubated with horseradish peroxidase-conjugated secondary antibody in 5 % (w/v) skim milk/TBST for 2 h at room temperature. Protein bands were developed using a chemiluminescence western blotting detection reagent (BioRad) and visualized using ImageQuant LAS 500 imaging system (GE Healthcare). The OPN expression levels were

normalized to their respective total cellular protein and also subsequently checked by loading equal volume of the total protein extract and confirmed by β-actin quantification.

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1,2,3-triazole linked 1,2,4-trioxanes: Studies on their synthesis and effect on osteopontin expression in MDA-MB-435 breast cancer cells

Highlights

- For the first time, synthetic 1,2,4-trioxanes are employed in anticancer studies
- First report on the effect of 1,2,4-trioxanes on OPN expression in cancer cells
- Synthetic 1,2,4-trioxanes have shown OPN downregulation in MDA-MB-435 breast cancer cell lines
- 1,2,4-Trioxane dimers with structurally flexible linker shows better OPN downregulation

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: