Stereoselective synthesis of tetrahydrofuranyl 1,2,3-triazolyl *C*-nucleoside analogues by 'click' chemistry and investigation of their biological activity

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Abstract

The construction of a novel series of enantiopure tetrahydrofuranyl 1,2,3-triazolyl *C*-nucleoside analogues utilizing click reaction of sugar derived tetrahydrofuranyl alkynes with various 'in house' synthesized sugar derived tetrahydrofuranyl azides and an adamantyl azide is described. The biological significance of the synthesized *C*-nucleosides was highlighted by evaluating them *in vitro* for anti-bacterial and anti-fungal activity, wherein a number of compounds were found to show excellent anti-bacterial activity and moderate anti-fungal activity.

Keywords: THF alkynes, THF azides, *C*-nucleosides, 'click' chemistry, 1,2,3-triazoles

Introduction

C-Nucleosides have been recognized as important compounds in the field of medicinal chemistry and chemical biology.[1,2] These are unique class of nucleosides in which the heterocycle is connected to the sugar moiety with a stable C-C bond instead of labile nucleosidic C-N bond. The strong C-C bond increases the stability of the glycosidic bond. The naturally occurring as well as synthetic *C*-nucleosides are known for their interesting biological properties like antibiotic, antiviral and antineoplastic (Figure1).[3-12] Owing to their structural relationship to the naturally occurring nucleosides the *C*-nucleosides can be incorporated into DNA/RNA instead of the naturally occurring nucleosides.[12]

1,2,3-Triazoles have emerged as an important pharmacophore[13-14] showing diverse type of bioactivities.[15-20] In this context the importance of 1,2,3-triazole nucleosides exhibiting anti-viral,

immunosuppressant and anti-tumor cell proliferation activities have been well documented in literature.[21-25] Recently a number of 1,2,3-triazolyl carba-nucleosides have also been reported as anti-viral agents.[26-28] A literature survey revealed that 1,2,3- triazole *C*-nucleosides have been less intensively studied than the other classes of 1,2,3-triazole nucleosides. Only few reports are available on synthesis of 1,2,3- triazole C-nucleosides. In 1980s M. A. E. Sallam and co-workers[29-34] and later on some other research groups have reported the synthesis of 1,2,3-triazole *C*-nucleosides[35] including biologically relevant molecules like 1,2,3- triazolyl analogues of ribavirin,[36] an anti-viral drug and other *C*-nucleosides like ethynyl-bridged *C*-nucleoside.[37]

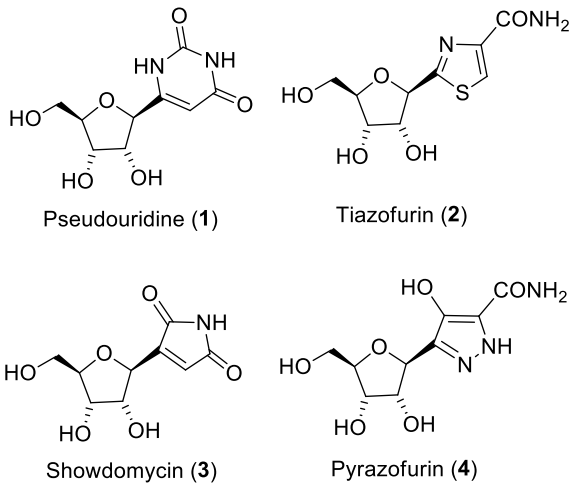


Figure 1. Some biologically important *C*-nucleosides.

The interesting biological activities exhibited by 1,2,3-triazole containing compounds, specifically 1,2,3- triazole *C*-nucleosides coupled with the biological importance of *C*-nucleosides prompted us to design and synthesize stereochemically pure tetrahydrofuran (THF)-alkynes and polyynes derived novel tetrahydrofuranyl 1,2,3-triazolyl *C*-nucleoside analogues and screen them for biological activity.

Huisgen 1,3-dipolar cycloaddition between an alkyne and azide is an important reaction for the preparation of 1,2,3-triazole derivatives.[38-43] The development of its very efficient copper catalyzed click reaction has made this reaction the most widely used method for the synthesis of 1,2,3-triazole.[39,40] Consequently in our present study we chose the copper catalyzed click reaction for the synthesis of the targeted 1,2,3- triazolyl *C*-nucleoside analogues of prototype-I and prototype-II (Figure 2).

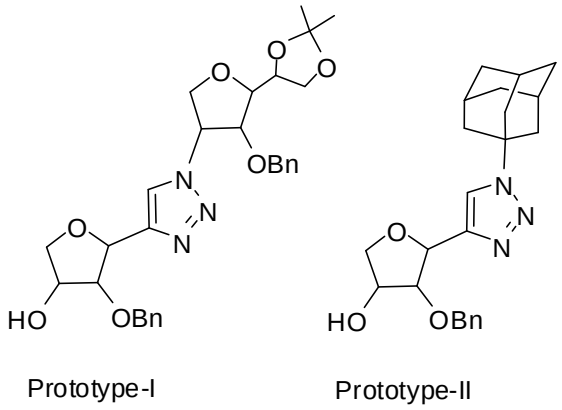


Figure 2. Prototype tetrahydrofuranyl 1,2,3-triazolyl C-nucleoside analogue molecules.

Results and Discussion

Retrosynthetic strategy for the construction of 1,2,3-triazolyl C-nucleoside analogues is summarized in figure 3. The synthetic route depicted in figure 3 allowed us to prepare several 1,2,3-triazolyl *C*-nucleoside analogues differing in the relative stereochemical configuration at C-2, C-3, and C-4 positions of the THF ring. The THF domain **6** was easily obtained in three steps from 3,4,6-tri-*O*-benzyl-D-glucal or 3,4,6-tri-*O*-benzyl-D-galactal following our previously published procedure which were in turn synthesized from D-glucose and D-galactose respectively.[44,45]

The domain **6** was then subjected to oxidative cleavage with H_5IO_6 followed by treatment with Bestmann-Ohira reagent (dimethyl-1-diazo-2-oxopropylphosphonate) to yield the THF alkynes of the general formula **7**.[46] These alkynes were reacted with different THF azides, **9-11**[47] and an adamanty azide (Figure 4) to obtain the target tetrahydrofuranyl 1,2,3-triazolyl C-nucleoside analogues of general formula **8**.

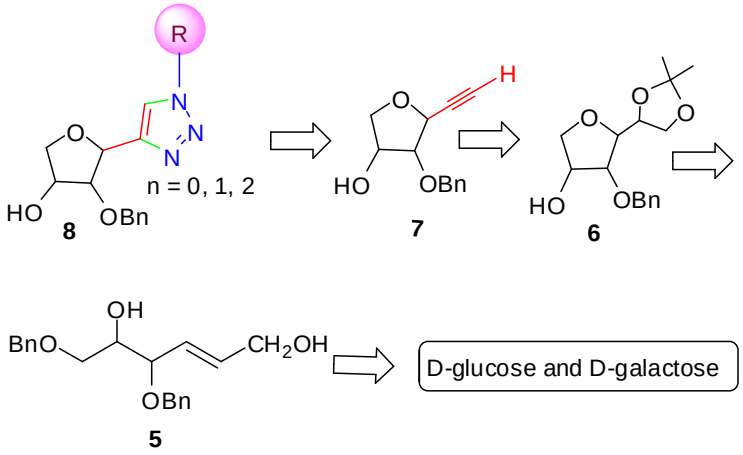


Figure 3. Retrosynthetic strategy for the construction of 1,2,3- triazolyl *C*-nucleoside analogues.

The treatment of alkyne **13** with THF azide **9** in the presence of $CuSO_4.5H_2O$, (+)-sodium L-ascorbate and t-BuOH-H_2O (1:1), at ambient temperature furnished the desired triazolyl *C*-nucleoside analogue **14** in 62% yield (Scheme 1).

The structure of triazolyl *C*-nucleoside analogue **14** was established by its NMR and mass spectroscopic data. Its ^{1}H NMR spectrum showed a singlet at δ 7.44 corresponding to the triazolyl proton while the ^{13}C NMR spectrum showed peaks at δ 121.5 and 147.8 corresponding to CH and qC characteristic to the triazole core unit. Finally the ESI-MS spectrum displayed the $[M+H]^+$ peak at *m/z* 538 and its HRMS spectrum showed the $[M]^+$ peak at 537.2490, which confirmed its structure.

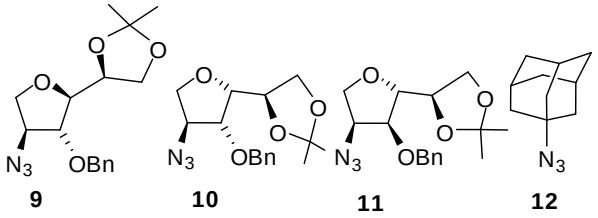
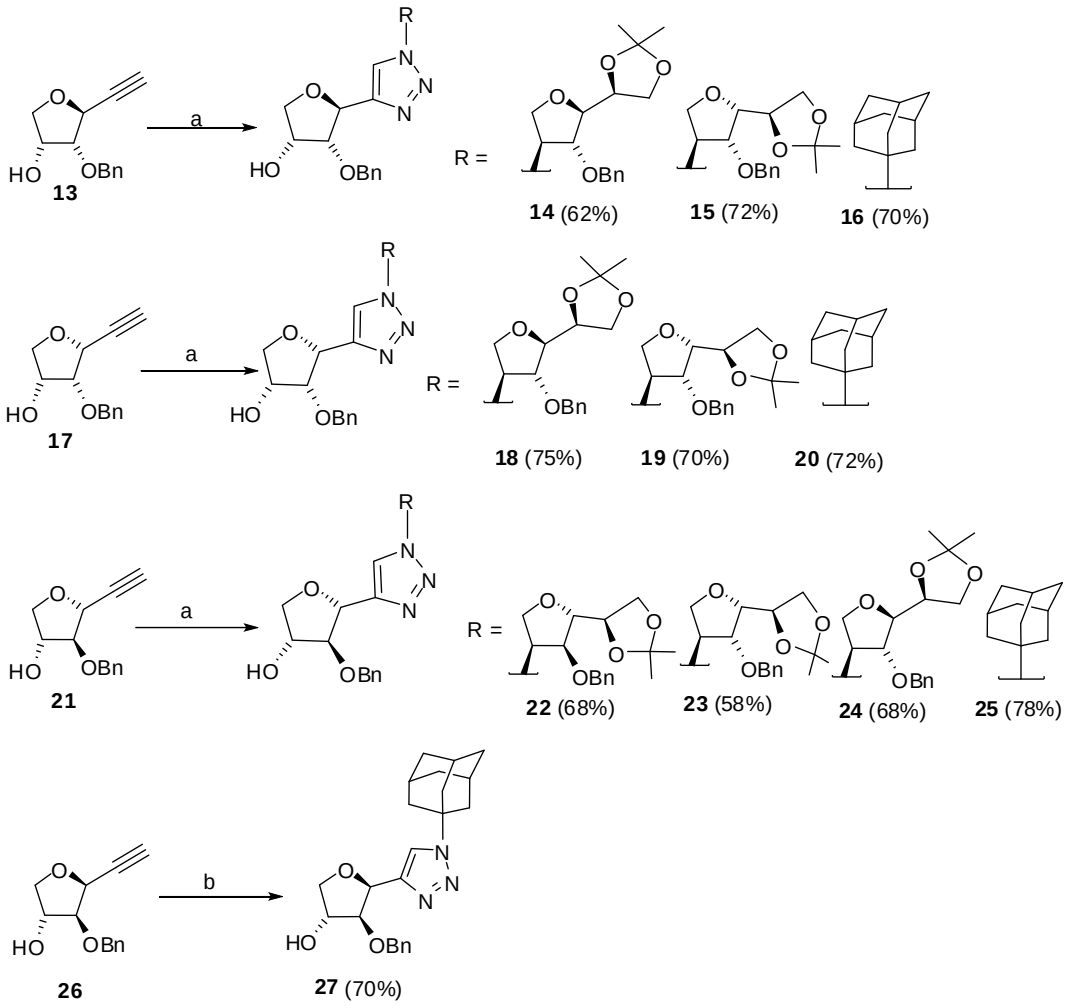


Figure 4. Azides used in the present study.

Once the synthesis of triazolyl C-nucleoside **14** has been successfully achieved we extended the synthetic strategy to access more compounds of this series. Different stereoisomers of THF alkynes and azides were prepared and coupled with each other to obtain a series of isomeric 1,2,3-triazolyl *C*-nucleoside analogues. Consequently when the stereoisomeric alkynes **13**, **17** and **21** were treated with THF azides **9-11** under Huisgen 1,3-dipolar cycloaddition reaction condition, the corresponding tetrahydrofuranyl 1,2,3-triazolyl *C*-nucleosides analogues **15**, **18**, **19**, **22**, **23** and **24** were obtained in 58% - 75% yields (Scheme 1).

In recent years adamantane containing molecules have received much attention in medicinal chemistry.[48-51] Adamantyl compounds are currently in clinical use for the treatment of neurogenerative diseases, influenza, type II diabetes and acne vulgaris.[49] Many adamantane derivatives have been reported to show anti-bacterial and anti-fungal activities.[50,51] The above reports encouraged us to carry out the synthesis of adamantane containing 1,2,3-triazolyl *C*-nucleosides analogues. Consequently on treating alkynes **13**, **17**, **21**, **26** with adamantyl azide **12**, adamantyl substituted triazolyl C-nucleoside analogues **16**, **20**, **25** and **27** respectively were obtained in 70-78% yields (Scheme 1).

Interestingly in the case of alkyne **17** derived triazoles **18**, **19** and **20** the peak characteristic of CH and q*C* of the triazole was inexplicably recorded as a very weak signal in ^{13}C NMR spectrum, but their ^{1}H NMR, ESI mass and HRMS spectroscopic studies clearly showed that the desired triazoles were formed. The structures of the triazoles **18**, **19** and **20** were finally confirmed by recording their HSQC spectra which showed a correlation between carbon signals at 120.4 ppm in case of compounds **18**, **19**, and 122.4 ppm in compound **20** with their respective triazole *C*H protons.



Scheme 1. Reagents and condition: (a) R-N_3, $CuSO_4.5H_2O$, (+)-Sodium L-ascorbate, t-BuOH-H_2O (1:1), rt, 6-8 h. (b) Adamantyl azide **12**, $CuSO_4.5H_2O$, (+)-Sodium L-ascorbate, t-BuOH-H_2O (1:1), rt, 8 h

All the above described tetrahydrofuranyl 1,2,3-triazoly C-nucleoside analogues were evaluated for their *in vitro* anti-bacterial and anti-fungal activities (See Table 1 and 2 in SI). It was found that the adamantane containing 1,2,3-triazolyl *C*-nucleoside analogue **25** was active at a MIC of 1.56 μg/ml against *S. aureus* which is two fold better activity than standard drug gentamycin and three fold better activity than ampicillin while in case of *K. pneumoniae* it exhibited a MIC of 0.78 μg/ml which is equivalent to the activity of gentamycin. Another adamantane containing analogue **27** was found active at a MIC of 0.78 μg/ml against *S. aureus* which is three fold better activity than gentamycin, four fold better activity than ampicillin and equal to ciprofloxacin. In case of *K. pneumoniae* it again exhibited a MIC of 0.78 μg/ml which is equivalent to the activity of gentamycin. However, none of the other 1,2,3-triazolyl C-nucleoside analogues were found to show any anti-bacterial activity.

The 1,2,3-triazoly *C*-nucleoside analogues were also screened against a panel of six fungal strains. Only molecules **16**, **18**, **19** and **20** were found active against *T. mentagrophytes* at MIC of 25 μg/ml, 12.5 μg/ml, 25 μg/ml and 25 μg/ml respectively. None of the other molecules showed any activity against the fungal strains.

Conclusions

In summary we have disclosed the stereoselective construction of a novel class of 1,2,3-triazolyl *C*-nucleoside analogues (**14-16**, **18-20**, **22-25** and **27**), with multiple points for skeletal diversification, from 'THF alkynes and THF azides, using 'click' chemistry as the key step. The alkynes and azides used in this study were easily accessed from commercially available sugars. In order to demonstrate the potential biological utility of the synthesized 1,2,3-triazolyl *C*-nucleoside analogues, they were evaluated for *in vitro* anti-bacterial and anti-fungal activity. It was found that the adamantane containing 1,2,3-triazolyl *C*-nucleoside analogues **25** and **27** exhibited excellent activity against *S. aureus* and *K. pneumoniae* in a MIC range of 0.78 μg/ml to 1.56 μg/ml which was comparable or better than the activity of many standard drugs while compounds **16**, **18**, **19** and **20** exhibited moderate anti-fungal activity in a MIC range of 12.5 μg/ml to 25 μg/ml. A detailed study on further elaboration of these 1,2,3-triazolyl *C*-nucleoside analogues and investigation of their prospective bioactivities is currently underway and would be disclosed in due course.

Supporting Information

Copies of ^{1}H, ^{13}C and 2D NMR spectral data of all the synthesized 1,2,3-triazolyl *C*-nucleoside analogues, general procedure for *in vitro* anti-bacterial and anti-fungal activity evaluation and tabulated results of *in vitro* anti-bacterial and anti-fungal activity evaluation of the 1,2,3-triazolyl *C*-nucleoside analogues.

Experimental Section

General. Organic solvents were dried by standard methods. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60 F-254), visualization was accomplished with $CeSO_4$ or 10% H_2SO_4/EtOH and subsequent charring over hot plate. Column chromatography was performed using silica gel (60-120), (100-200) and (230-400). All the products were characterized by ^{1}H, ^{13}C, DEPT pulse sequence, Heteronuclear Single Quantum Correlation (HSQC), IR, MS (ESI), HRMS (EI) and HRMS (DART). All NMR spectra were recorded with spectrometers at 200, 300, (^{1}H) and 50, 75, MHz (^{13}C). Experiments were

recorded in $CDCl_3$ at 25 °C. Chemical shifts are given on the δ scale. Optical rotations were determined using a 1 dm cell in chloroform as solvent; concentrations mentioned are in g/100 mL.

General procedure for the synthesis of tetrahydrofuranyl 1,2,3-triazolyl *C*-nucleoside analogues. To a vigorously stirred solution of azide (0.5 mmol) in *tert*-butyl alcohol (5 mL) was added acetylene (0.6 mmol) and the reaction was initiated by the addition of a solution of $CuSO_4.5H_2O$ (0.1 mmol) and sodium ascorbate (0.2 mmol) in distilled water. The colored suspension formed was stirred at the room temperature till the formation of triazole (6 - 8h). After completion of the reaction, ice-cold water was added and the aqueous layer was extracted with $CHCl_3$ (3 x15 mL). The combined organic extracts were dried evaporated and purified by column chromatography to afford the pure 1,2,3-triazolyl *C*-nucleoside analogues.

Compound 14. Oil, 62% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v) $[\alpha]_D^{30}$ +33.3° (*c* 0.30, $CHCl_3$), R_f 0.32 (3/2 EtOAc/hexane). IR (neat): 3428, 3021, 2929, 2364, 1593, 1478,1216. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.84 (brs, 1H), 3.90 (dd, *J* 3.6, 9.7 Hz, 1H), 4.01 (dd, *J* 6.1, 8.4 Hz, 1H), 4.12-4.21 (m, 4H), 4.35-4.46 (m, 5H), 4.66-4.77 (m, 4H), 5.04 (d, *J* 5.6 Hz, 1H), 5.11-5.14 (m, 1H), 7.32-7.36 (m, 10H, ArH), 7.44 (s, 1H, triazolyl H).^{13}C NMR (50MHz, $CDCl_3$): δ 25.8 (CH_3), 27.1(CH_3), 66.0 (CH), 67.3 (CH_2), 70.7 (CH), 71.2 (CH_2), 73.4 (CH_2), 73.6 (CH_2), 73.6 (CH), 73.8 (CH_2), 75.9 (CH), 82.3 (CH), 83.3 (CH), 83.9 (CH), 109.4 (qC) 121.5 (CH of triazole), 128.4 (ArC), 128.5 (ArC), 128.6 (ArC), 129.0 (ArC), 137.5 (ArqC), 137.6 (ArqC), 147.8 (qC of triazole). Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$.EI-HRMS *m/z*: Calc. for $C_{29}H_{35}N_3O_7$ $[M]^+$ 537.2475, measured 537.2490.

Compound 15. Oil, 72% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v) $[\alpha]_D^{30}$ + 25.2° (*c* 0.30, $CHCl_3$), R_f 0.32 (3/2 EtOAc/hexane). IR (neat): 3430, 3020, 2925, 2360, 1600, 1376, 1216, 1067, 761.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.84 (S, 1H), 3.76 (dd, *J* 5.9, 8.5 Hz, 1H), 3.87-3.93 (m, 2H), 4.08 (dd, *J* 6.1, 8.5 Hz 1H), 4.15- 4.20 (m, 2H), 4.23-4.35 (m, 4H), 4.44 (t, *J* 5.3 Hz, 1H), 4.61-4.79 (m, 4H), 5.06 (d, *J* 5.4 Hz, 1H), 5.27-5.28 (m, 1H), 7.31-7.34 (m, 10H, ArH), 7.70 (S, 1H, triazolyl H). ^{13}C NMR (75MHz, $CDCl_3$): δ 25.3 (CH_3), 26.5 (CH_3), 66.5 (CH), 66.6 (CH_2), 70.7 (CH), 71.9 (CH_2),72.9 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 74.9 (CH), 76.1 (CH), 83.3 (CH), 85.5 (CH), 85.9 (CH), 110.3 (qC) 121.4 (CH of triazole), 128.4 (ArC), 128.6 (ArC), 128.6 (ArC), 128.6 (ArC), 129.0(ArC), 136.9 (ArqC), 137.6 (ArqC), 147.7 (qC of triazole). Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$. ESI-HRMS *m/z*: Calc. for $C_{29}H_{36}N_3O_7$ $[M + H]^+$ 538.2553, measured 538.2525.

Compound 16. Oil, 70% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v), $[\alpha]_D^{29}$ -66.6° (*c* 0.36, $CHCl_3$), R_f 0.36 (1/1 EtOAc/hexane). IR (KBr, cm^{-1}): 3403, 2988, 2925, 2364, 1725, 1457, 1218, 1068, 769.^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 6H, 3 x CH_2), 2.23 (s, 9H, 3 x CH_2, 3 x CH), 2.82 (d, *J* 4.4 Hz, 1H, OH), 3.87 (dd, *J* 3.9, 9.6 Hz, 1H), 4.17 (dd, *J* 4.9, 9.6 Hz, 1H), 4.32-4.36 (m, 1H), 4.46 (t, *J* 5.4 Hz, 1H), 4.66 (d, *J* 11.7 Hz, 1H), 4.77 (d, *J*

11.7 Hz, 1H), 5.06 (d, *J* 5.6 Hz, 1H), 7.32 (brs, 5H, ArH), 7.52 (s, 1H, triazolyl H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.9 (3 x CH), 36.3 (3 x CH_2), 43.4 (3 x CH_2), 60.1 (1C, qC adametane), 70.8, (CH), 73.3 (CH_2), 73.5 (CH_2), 76.4 (CH), 83.1 (CH), 118.9 (CH of triazole), 128.5 (ArC), 128.5 (ArC), 129.0 (ArC), 137.8 (ArqC), 146.5 (qC of triazole). Mass (ESI-MS) *m/z* 395, found 396 $[M + H]^+$.ESI-HRMS: Calculated for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2287, measured 396.2268.

Compound 18. Oil, 75% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v) $[\alpha]_D^{29}$ + 184.3 (*c* 0.70, $CHCl_3$), R_f 0.32 (3/2 EtOAc/hexane). IR (neat): 3483, 3021, 2931, 2367, 1217, 1070, 765. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 3H, CH_3), 1.31 (S, 3H, CH_3), 3.75 (dd, *J* 5.9, 8.5 Hz, 1H), 3.89 (t, *J* 4.8 Hz, 1H), 3.96- 4.01 (m, 5H), 4.17-4.34 (m, 3H), 4.40-4.50 (m, 3H), 4.55-4.74 (m, 2H), 5.21-5.24 (m, 2H), 7.13-7.17 (m, 2H, ArH), 7.26-7.33 (m, 8H, ArH), 7.79 (s, 1H, triazolyl H). ^{13}C NMR (75MHz, $CDCl_3$): δ 25.3 (CH_3), 26.5 (CH_3), 66.6 (CH), 66.7 (CH_2), 71.3 (CH), 71.8 (CH_2),72.9 (CH_2), 73.3 (CH_2), 74.2 (CH_2), 74.9 (CH), 75.2 (CH), 79.5 (CH), 85.7 (CH), 85.9 (CH), 110.3 (qC), 128.0 (ArC), 128.3 (ArC), 128.6 (ArC), 128.6 (ArC), 128.8 (ArC), 128.9 (ArC), 137.0 (ArqC), 137.6 (ArqC). Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$. ESI-HRMS *m/z*: Calc. for $C_{29}H_{36}N_3O_7$ $[M+H]^+$ 538.2553, measured 538.2549.

Compound 19. Solid, mp 109-110 °C, 70% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v) $[\alpha]_D^{29}$ +116.5° (*c* 0.30, $CHCl_3$), R_f 0.35 (3/2 EtOAc/hexane). IR (neat): 3420, 3155, 3025, 2882, 2365, 1719, 1455, 1220, 1044, 742. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.83 (d, *J* 7.8 Hz, 1H), 3.97-4.02 (m, 3H), 4.10-4.16 (m, 3H), 4.26-4.43 (m, 5H), 4.56 (d, *J* 11.5, 1H), 4.69 (S, 2H), 5.08-5.12 (m, 1H), 5.21 (d, *J* 6.2 Hz, 1H), 7.10-7.14 (m, 2H, ArH), 7.26-7.33 (m, 8H, ArH), 7.53 (s, 1H, triazolyl H).^{13}C NMR (50MHz, $CDCl_3$): δ 25.4 (*C*H_3), 26.7 (*C*H_3), 65.6 (*C*H), 66.9 (*C*H_2), 70.8 (*C*H), 71.0 (*C*H_2), 73.0 (*C*H_2), 73.1 (*C*H_2), 73.2 (*C*H), 73.8 (*C*H_2), 74.8 (*C*H), 79.2(CH), 81.8 (*C*H), 83.6 (*C*H), 109.0 (qC) 122.4 (*C*H of triazole), 127.6 (ArC), 127.9 (ArC), 128.0 (ArC), 128.2 (ArC), 128.5 (ArC), 128.6 (ArC), 137.1 (ArqC), 137.2 (ArqC), Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$, 560 $[M+Na]^+$.EI-HRMS *m/z*: Calc. for $C_{29}H_{36}N_3O_7$ $[M+H]^+$ 538.2553, measured 538.2530.

Compound 20. Oil, 72% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v), $[\alpha]_D^{29}$ +29.9 (*c* 0.30, $CHCl_3$), R_f 0.29 (1/1 EtOAc/hexane). IR (KBr, cm^{-1}): 3410, 2921, 2366, 1813, 1728, 1653, 1457, 1375, 1215, 1067, 752.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (s, 6H, 3 x CH_2), 2.21 (s, 6H, 3 x CH_2,), 2.26(s, 3H, 3 x CH), 3.97-4.07 (m, 2H), 4.17 (brs, 1H, OH), 4.27-4.37 (m, 2H), 4.50-4.57 (m, 2H), 5.24 (d, *J* 5.6 Hz, 1H), 7.13 (brs, 2H, ArH), 7.28 (brs, 3H, ArH), 7.65 (s, 1H, triazolyl H).^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8 (3 x CH), 36.3 (3 x CH_2), 43.3 (3 x CH_2), 60.0 (1C, qC adametane), 71.4 (CH), 73.3 (CH_2), 74.3 (CH_2), 75.5 (CH), 79.5 (CH), 128.1 (ArC), 128.3 (ArC), 128.7 (ArC), 137.7 (ArqC). Mass (ESI-MS) *m/z* 395, found 396 $[M + H]^+$ and 418 $[M+Na]^+$. ESI-HRMS : Calculated for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2287, measured 396.2272.

Compound 22. Oil, 68% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v)), $[\alpha]_D^{30}$ +37° (*c* 0.6, $CHCl_3$), R_f 0.30 (3/2 EtOAc/hexane). IR (neat): 3422, 3033, 2919,

2363, 2103, 1599, 1456, 1376, 1217, 1066, 732.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.83 (dd, *J* 5.4, 8.6 Hz, 1H), 4.03-4.22 (m, 5H), 4.23-4.26 (m, 2H), 4.29- 4.35 (m, 2H), 4.38-4.44 (m, 3H), 4.59 (d, *J* 11.7 Hz, 1H), 4.66 (d, *J* 11.7 Hz, 1H), 4.92 (brs, 1H), 5.05 (brs, 1H), 5.44 (q, *J* 6.0 Hz, 1H), 7.09-7.11 (m, 2H), 7.28-7.32 (m, 8H, ArH), 7.72 (s, 1H, triazolyl H).^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2 (CH_3), 26.5 (CH_3), 66.5 (CH), 66.6 (CH_2), 71.87 (CH_2), 72.3 (CH_2), 72.9 (CH_2), 74.9 (CH), 76.1 (CH), 76.2 (CH_2), 77.9 (CH), 85.5 (CH), 85.9 (CH), 89.4 (CH), 110.3 (qC), 121.3 (CH of triazole), 128.1 (ArC), 128.3 (ArC), 128.6 (ArC), 128.9 (ArC), 129.9 (ArC), 136.9 (ArqC), 137.9 (ArqC), 147.8 (qC of triazole). Mass (ESI-MS): *m/z* 537, found 538 $[M + H]^+$ and 560 $[M+Na]^+$

Compound 23. Oil, 58% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v)), $[\alpha]_D^{30}$ +51.4° (*c* 0.6, $CHCl_3$), R_f 0.30 (3/2 EtOAc/hexane). IR (neat): 3422, 3033, 2919, 2363, 2103, 1599, 1456, 1376, 1217, 1066, 732. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.78 (dd, *J* 5.7, 8.6Hz, 1H), 3.92 (t, *J* 4.7Hz, 1H), 4.07-4.12 (m, 2H), 4.19- 4.26 (m, 4H), 4.31-4.36 (m, 1H), 4.45 (brs, 1H), 4.62-4.78 (m, 5H), 5.05 (brs, 1H), 5.26 (brs, 1H), 7.31-7.35 (m, 10H, ArH), 7.74 (s, 1H, triazolyl H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3 (CH_3), 26.5 (CH_3), 66.6 (CH), 66.6 (CH_2), 71.8 (CH_2), 72.3 (CH_2), 73.0 (CH_2), 74.9 (CH), 76.1 (CH), 76.3 (CH_2), 77.9 (CH), 85.6 (CH), 86.0 (CH), 89.5 (CH), 110.3 (qC), 121.3 (CH of triazole), 128.1 (ArC), 128.3 (ArC), 128.7 (ArC), 128.9 (ArC), 129.0 (ArC), 137.0 (ArqC), 137.9 (ArqC), 147.8 (qC of triazole). Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$. ESI-HRMS *m/z*: Calc. for $C_{29}H_{36}N_3O_7$ $[M + H]^+$ 538.2553, measured 538.2521.

Compound 24. Solid, mp 112-114 °C, 68% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v), $[\alpha]_D^{28}$ +71.8° (*c* 0.30, $CHCl_3$), R_f 0.36 (3/2 EtOAc/hexane). IR (neat): 3422, 3033, 2916, 2363, 2103, 1599, 1456, 1376, 1217,1066, 738. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.78-3.85 (m,1H), 3.99- 4.24 (m, 8H), 4.35 (s, 1H), 4.38- 4.43 (m, 2H), 4.62-4.74 (m, 4H), 5.03 (brs, 1H), 5.10 (brs, 1H), 7.34-7.36 (m, 10H, ArH), 7.47 (s, 1H, triazolyl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4 (CH_3), 26.7 (CH_3), 65.6 (CH), 66.9 (CH_2), 70.7 (CH_2), 72.1 (CH_2), 73.2 (CH), 73.2 (CH_2), 75.8 (CH),77.6 (CH), 81.8 (CH), 83.4 (CH), 89.0 (CH), 109.0 (qC), 120.9 (CH of triazole), 127.8 (ArC), 127.9 (ArC), 128.0 (ArC), 128.2 (ArC), 128.5, (ArC), 128.6 (ArC), 137.1 (ArqC), 137.6 (ArqC), 147.5 (qC of triazole). Mass (ESI-MS) *m/z* 537, found 538 $[M + H]^+$. ESI-HRMS *m/z*: Calc. for $C_{29}H_{36}N_3O_7$ $[M + H]^+$ 538.2553, measured 538.2533.

Compound 25. Oil, 78% yield, eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v), $[\alpha]_D^{30}$ + 44.0° (*c* 1.20, $CHCl_3$), R_f 0.30 (1/1 EtOAc/hexane). IR (Neat, cm^{-1}): 3327, 3008, 2919, 2857, 2361, 1726, 1598, 1454, 1218, 1099, 759. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 6H, 3 x CH_2), 2.23 (brs, 9H, 3 x CH_2, 3 x CH), 4.07 (d, *J* 9.5 Hz, 1H), 4.19-4.28 (m, 2H), 4.43 (brs, 1H), 4.65 (d, *J* 11.9 Hz, 1H, C*H*$_2$Ph), 4.69 (d, *J* 11.9Hz, 1H, C*H*$_2$Ph), 5.06 (s, 1H), 5.38 (brs, 1H) 7.33 (brs, 5H, ArH), 7.57 (S, 1H, triazolyl H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8 (3 x CH), 36.2 (3 x CH_2), 43.3 (3 x CH_2), 60.4 (1C, qC adametane) 72.3 (CH_2), 76.1 (CH), 76.4 (CH_2), 77.9 (CH), 89.4 (CH), 118.9 (CH of triazole), 128.2 (ArC), 128.3 (ArC), 128.9 (ArC), 138.1 (ArqC), 146.3

(qC of triazole). Mass (ESI-MS) *m/z* 395, found 396 $[M + H]^+$ and 418 $[M + Na]^+$. ESI-HRMS *m/z*: Calc. for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2287, measured 396.2262.

Compound 27. Solid, mp: 162-164 °C, 70% yield, Eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v), $[\alpha]_D^{29}$ -8.8° (*c* 0.30, $CHCl_3$), R_f 0.33 (1/1 EtOAc/hexane). IR (KBr, cm^{-1}): 3205, 2915, 2363, 1813, 1725, 1662, 1592, 1446, 1296, 1225, 1130, 727. ^1H NMR (200 MHz, $CDCl_3$): δ 1.76 (s, 6H, 3 x CH_2), 2.16 (s, 6H, 3 x CH_2), 2.22 (s, 3H, 3 x CH), 3.49 (brs, 1H, OH), 3.85 (d, *J* 9.8 Hz, 1H), 4.06 (s, 1H), 4.18-4.33 (m, 2H), 4.47-4.57 (m, 2H), 5.48 (s, 1H), 7.07 (brs, 2H, ArH), 7.23 (brs, 3H, ArH), 7.68 (s, 1H, triazolyl H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8 (3 x CH), 36.3 (3 x CH_2), 43.3 (3 x CH_2), 59.9 (1C, qC adametane) 72.6 (CH_2), 74.3 (CH_2), 75.9 (CH), 76.8 (CH), 85.7 (CH), 120.6 (CH of triazole), 127.7 (ArC), 128.0 (ArC), 128.6 (ArC), 138.3 (ArqC), 144.0 (qC of triazole). Mass (ESI-MS) *m/z* 395, found 396 $[M + H]^+$ and 418 $[M + Na]^+$. ESI-HRMS : Calculated for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2287, measured 396.2265.

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