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 pharmacophore13-14 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. Recently a number of 1,2,3-triazolyl carba-nucleosides have also been reported as anti-viral agents. 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 and later on some other research groups have reported the synthesis of 1,2,3-triazole C-nucleosides including biologically relevant molecules like 1,2,3-triazolyl analogues of ribavirin, an anti-viral drug and other C-nucleosides like ethynyl-bridged C-nucleoside.

![Figure 1. Some biologically important C-nucleosides.](image)

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. 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. 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).
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 \(\text{H}_2\text{IO}_6\) 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 adamantyl azide (Figure 4) to obtain the target tetrahydrofuranyl 1,2,3-triazolyl C-nucleoside analogues of general formula 8.

![Figure 2. Prototype tetrahydrofuranyl 1,2,3-triazolyl C-nucleoside analogue molecules.](image)

![Figure 3. Retrosynthetic strategy for the construction of 1,2,3-triazolyl C-nucleoside analogues.](image)
The treatment of alkyne 13 with THF azide 9 in the presence of CuSO$_4$·5H$_2$O, (+)-sodium L-ascorbate and t-BuOH·H$_2$O (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 $\delta$ 7.44 corresponding to the triazolyl proton while the $^{13}$C NMR spectrum showed peaks at $\delta$ 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.

![Azides used in the present study.](image)

**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. Adamantyl compounds are currently in clinical use for the treatment of neurogenerative diseases, influenza, type II diabetes and acne vulgaris. Many adamantane derivatives have been reported to show anti-bacterial and anti-fungal activities. 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 qC 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 CH protons.
Scheme 1. Reagents and condition: (a) R-N₃, CuSO₄.5H₂O, (+)-Sodium L-ascorbate, t-BuOH-H₂O (1:1), rt, 6-8 h. (b) Adamantyl azide 12, CuSO₄.5H₂O, (+)-Sodium L-ascorbate, t-BuOH-H₂O (1:1), rt, 8 h

All the above described tetrahydrofuranyl 1,2,3-triazolyl 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 ¹H, ¹³C 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 CeSO₄ or 10% H₂SO₄/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 ¹H, ¹³C, 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, (¹H) and 50, 75, MHz (¹³C). Experiments were
recorded in CDCl₃ 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 CuSO₄.5H₂O (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 (6-8 h). After completion of the reaction, ice-cold water was added and the aqueous layer was extracted with CHCl₃ (3 x 15 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/CHCl₃ (1/49, v/v) [α]D30 +33.3° (c 0.30, CHCl₃), Rf 0.32 (3/2 EtOAc/hexane). IR (neat): 3428, 3021, 2929, 2364, 1593, 1478,1216. ¹H NMR (300 MHz, CDCl₃): δ 1.39 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 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). ¹³C NMR (50MHz, CDCl₃): δ 25.8 (CH₃), 27.1(CH₃), 66.0 (CH), 67.3 (CH₂), 70.7 (CH), 71.2 (CH₂), 73.4 (CH₂), 73.6 (CH₂), 73.6 (CH), 73.8 (CH₂), 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 (ArC), 137.6 (ArC), 147.8 (qC of triazole). Mass (ESI-MS) m/z 537, found 538 [M + H]⁺.EI-HRMS m/z: Calc. for C₂₉H₃₅N₅O₇ [M⁺] 537.2475, measured 537.2490.

**Compound 15.** Oil, 72% yield, Eluent for column chromatography: MeOH/CHCl₃ (1/49, v/v) [α]D30 +25.2° (c 0.30, CHCl₃), Rf 0.32 (3/2 EtOAc/hexane). IR (neat): 3403, 3020, 2925, 2360, 1600, 1376, 1216, 1067, 761. ¹H NMR (300 MHz, CDCl₃): δ 1.26 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 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). ¹³C NMR (75MHz, CDCl₃): δ 25.3 (CH₃), 26.5 (CH₃), 66.5 (CH), 66.6 (CH₂), 70.7 (CH), 71.9 (CH₂), 72.9 (CH₂), 73.3 (CH₂), 73.6 (CH₂), 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 (ArC), 137.6 (ArC), 147.7 (qC of triazole). Mass (ESI-MS) m/z 537, found 538 [M + H]⁺. EI-HRMS m/z: Calc. for C₂₉H₃₅N₅O₇ [M⁺] 537.2475, measured 537.2490.

**Compound 16.** Oil, 70% yield, Eluent for column chromatography: MeOH/CHCl₃ (1/49, v/v), [α]D30 -66.6° (c 0.36, CHCl₃), Rf 0.36 (1/1 EtOAc/hexane). IR (KBr, cm⁻¹): 3403, 2988, 2925, 2364, 1725, 1457, 1218, 1068, 769. ¹H NMR (200 MHz, CDCl₃): δ 1.79 (s, 6H, 3 x CH₂), 2.23 (s, 9H, 3 x CH₂, 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). 13C NMR (50 MHz, CDCl3): δ 29.9 (3 x CH), 36.3 (3 x CH2), 43.4 (3 x CH2), 60.1 (1C, qC adametane), 70.8, (CH), 73.3 (CH2), 73.5 (CH2), 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 C23H30N3O3 [M + H]+ 396.2287, measured 396.2268.

**Compound 18.** Oil, 75% yield, Eluent for column chromatography: MeOH/CHCl3 (1/49, v/v) [α]D29 +184.3 (c 0.70, CHCl3), Rf 0.32 (3/2 EtOAc/hexane). IR (neat): 3483, 3021, 2931, 2367, 1217, 1070, 765. 1H NMR (300 MHz, CDCl3): δ 1.23 (s, 3H, CH3), 1.31 (s, 3H, CH3), 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). 13C NMR (75MHz, CDCl3): δ 25.3 (CH3), 26.5 (CH3), 66.6 (CH), 66.7 (CH2), 71.3 (CH), 71.8 (CH2), 72.9 (CH2), 73.3 (CH2), 74.2 (CH2), 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), 128.8 (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 C20H36N3O7 [M+H]+ 538.2553, measured 538.2549.

**Compound 19.** Solid, mp 109-110 °C, 70% yield, Eluent for column chromatography: MeOH/CHCl3 (1/49, v/v) [α]D29 +116.5° (c 0.30, CHCl3), Rf 0.35 (3/2 EtOAc/hexane). IR (neat): 3420, 3155, 3025, 2882, 2365, 1719, 1455, 1220, 1044, 742. 1H NMR (300 MHz, CDCl3): δ 1.37 (s, 3H, CH3), 1.40 (s, 3H, CH3), 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). 13C NMR (50MHz, CDCl3): δ 25.4 (CH3), 26.7 (CH3), 65.6 (CH), 66.9 (CH2), 70.8 (CH), 71.0 (CH2), 73.0 (CH2), 73.1 (CH2), 73.2 (CH), 73.8 (CH2), 74.8 (CH), 79.2 (CH), 81.8 (CH), 83.6 (CH), 109.0 (qC) 122.4 (CH 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]+. ESI-HRMS m/z: Calc. for C20H36N3O7 [M+H]+ 538.2553, measured 538.2530.

**Compound 20.** Oil, 72% yield, Eluent for column chromatography: MeOH/CHCl3 (1/49, v/v), [α]D29 +29.9 (c 0.30, CHCl3), Rf 0.29 (1/1 EtOAc/hexane). IR (KBr, cm⁻¹): 3410, 2921, 2366, 1813, 1728, 1653, 1457, 1375, 1215, 1067, 752. 1H NMR (300 MHz, CDCl3): δ 1.79 (s, 6H, 3 x CH2), 2.21 (s, 6H, 3 x CH2), 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). 13C NMR (50 MHz, CDCl3): δ 29.8 (3 x CH), 36.3 (3 x CH2), 43.3 (3 x CH2), 60.0 (1C, qC adametane), 71.4 (CH), 73.3 (CH2), 74.3 (CH2), 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 C23H30N3O3 [M + H]+ 396.2287, measured 396.2272.

**Compound 22.** Oil, 68% yield, Eluent for column chromatography: MeOH/CHCl3 (1/49, v/v), [α]D30 +37° (c 0.6, CHCl3), Rf 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\(_3\)): \(\delta\) 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). \(^1^3\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 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), 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), \([\alpha]_D^{20} +51.4\)° (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\(_3\)): \(\delta\) 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). \(^1^3\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 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), 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\(_3\)O\(_7\) [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\(_3\)): \(\delta\) 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). \(^1^3\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 25.4 (CH\(_3\)), 26.7 (CH\(_3\)), 65.6 (CH), 66.9 (CH), 70.7 (CH\(_2\)), 72.1 (CH\(_2\)), 73.2 (CH), 73.2 (CH\(_2\)), 75.8 (CH\(_2\)), 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\(_3\)O\(_7\)[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\(_3\)): \(\delta\) 1.79 (s, 6H, 3 x CH\(_2\)), 2.23 (brs, 9H, 3 x CH\(_2\)), 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, CH\(_2\)Ph), 4.69 (d, J 11.9Hz, 1H, CH\(_2\)Ph), 5.06 (s, 1H), 5.38 (brs, 1H), 7.33 (brs, 5H, ArH), 7.57 (S, 1H, triazolyl H). \(^1^3\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 29.8 (3 x CH), 36.2 (3 x CH\(_2\)), 43.3 (3 x CH\(_2\)), 60.4 (1C, qC admetane) 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_{3}O_{3} [M + H]+ 396.2287, measured 396.2262.

**Compound 27.** Solid, mp: 162-164 °C, 70% yield. Eluent for column chromatography: MeOH/CHCl₃ (1/49, v/v), [α]D²⁹ -8.8° (c 0.30, CHCl₃), Rf 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, CDCl₃): δ 1.76 (s, 6H, 3 x CH₂), 2.16 (s, 6H, 3 x CH₂), 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). 

13C NMR (50 MHz, CDCl₃): δ 29.8 (3 x CH), 36.3 (3 x CH₂), 43.3 (3 x CH₂), 59.9 (1C, qC adamantane) 72.6 (CH₂), 74.3 (CH₂), 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_{3}O_{3} [M + H]+ 396.2287, measured 396.2262.

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