Carbohydrate Research 345 (2010) 1641–1648

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Regioselective [3+2] cycloaddition of chalcones with a sugar azide: easy access to 1-(5-deoxy-D-xylofuranos-5-yl)-4,5-disubstituted-1*H*-1,2,3-triazoles

Nimisha Singh, S. K. Pandey, Rama P. Tripathi *

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, CSIR, India

ARTICLE INFO

Article history:
Received 6 March 2010
Received in revised form 15 April 2010
Accepted 21 April 2010
Available online 24 April 2010

Keywords:
[3+2] Cycloaddition
Propenones
Chalcones
Sugar azide
1-(5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-4,5-disubstituted-1*H*-1,2,3-triazoles

ABSTRACT

[3+2] Cycloaddition of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose with 1,3-diphenyl-prop-3-enones, followed by oxidation of the intermediate triazolines in a tandem manner, led to the regioselective formation of 4-benzoyl-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-phenyl-1*H*-1,2,3-triazoles in moderate to good yields.

1. Introduction

Owing to their broad spectrum applications in biochemical, pharmaceutical, and material sciences, the 1*H*-1,2,3-triazoles are of key importance in synthetic organic chemistry.[1] They are commercially used as anticorrosive agents,[2] agrochemicals,[3] photostabilizers, and dyes.[4] Several of these triazoles are drugs[5] and have a wide range of biological activities such as the inhibition of prostaglandin synthesis,[6] antimuscarimic activity, which reverses the neurochemical deficiency in Alzheimer's disease,[7,8] inhibitory activity against transforming growth factor β1 type1 receptor,[9] anti-HIV-type I protease,[10] HER2 kinase inhibitory activity in breast cancer,[11] CB1 cannabinoid receptor antagonist activity,[12] antimicrobial activity,[13] antihyperglycemic activity,[14] activity against lung cancer cells,[15] galectin-1 and -3 inhibition,[16] β-galactosidase inhibitory activity,[17] probes of biological processes,[18] glycogen phosphorylase inhibition,[19,20] and antitubercular and antiparasitic activities.[21] The 1,2,3-triazoles are commonly prepared by the Huisgen 1,3-dipolar cycloaddition of azides with alkynes generally with electron-withdrawing substituent(s) on both substrates. The click chemistry developed by Sharpless and co-workers[22] involving 1,3-dipolar cycloaddition of azides with alkynes is one of the best methods to develop 1,2,3-triazoles, in either aqueous or organic medium, and the reaction has a variety of synthetic and biological applications. Among various 1,2,3-triazoles, the preparation of 4- and/or 5-substituted 1*H*-1,2,3-triazoles has gained impetus in organic chemistry where electron-deficient alkenes and different azides undergo [3+2] cycloaddition followed by a subsequent elimination reaction (Chart 1, A and B). However, in these methods the electron-deficient alkene moieties always have an atom or group other than hydrogen to be eliminated during the reaction. There are few reports where azides undergo [3+2] cycloaddition to electron-deficient alkenes followed by SET oxidation to give 1*H*-1,2,3-triazoles.[23] The reaction of alkenes or nitroalkenes with azides has been reported to give the usual Michael addition product or nucleophilic substitution product or other rearranged products.[24,25] The propenone equivalents, the polarized ketene *S*,*S*- and *S*,*N*-acetals, are reported to undergo cycloaddition with azides to give 1,2,3-triazoles by JunJappa's group.[26]

[3+2] Cycloaddition of alkyl azides with enol ethers under solvent-free conditions,[27] and the thermal reaction of an aryl azide with 1,2-dibenzoyl and 1,2-diacetyl ethylene[28] have been reported for the synthesis of substituted 1,2,3-triazoles. A similar reaction of arylacrylyloxiranes with phenyl azide also resulted in epoxypropinyl- and β-hydroxypropinyl triazoles.[29] The cycloaddition product formed during the reaction of chalcones with azides, followed by oxidation to give 1,2,3-triazoles, has not been reported so far to the best of our knowledge. In a continuation of our effort toward the development of new antitubercular molecules, we have recently reported the synthesis of 1,4-disubstituted 1,2,3-triazoles as antitubercular agents.[30,31] We were further interested to synthesize 1,4,5-trisubstituted 1,2,3-triazoles. Very recently Zhang and Chang reported cycloaddition of azides to naphthoquinone

* Corresponding author. Tel.: +91 522 2612411 418x4462; fax: +91 522 2623405/2623938/2629504.
E-mail addresses: rpt.cdri@gmail.com, rp_tripathi@cdri.res.in (R.P. Tripathi).

0008-6215/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2010.04.019

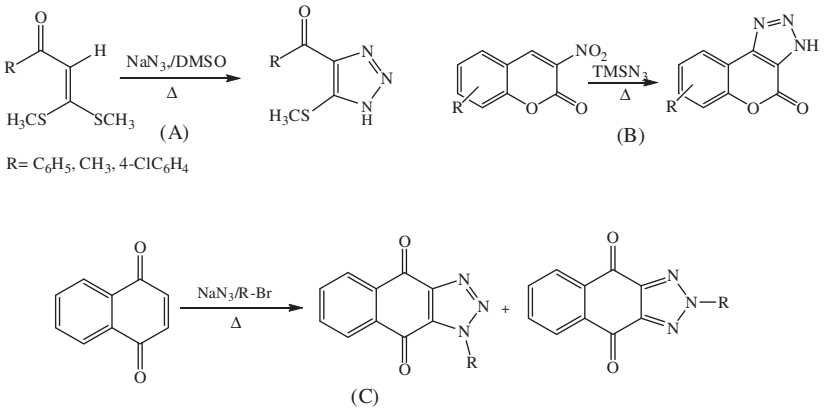


Chart 1. Reaction of labile group bearing alkenes and electron deficient alkenes with azides.

(Chart 1), which upon oxidation results in 1*H*-1,2,3-triazoles.[32] Keeping in mind the above-mentioned points, we were prompted to realize that such cycloadditions of sugar azides with chalcones would generate a library of 1*H*-1,2,3-triazoles suitable for antitubercular evaluations.

2. Results and discussion

The cycloaddition of a chalcone with a sugar azide was optimized by the reaction of one of the prototype chalcones, *E*-3-(4-bromophenyl)-1-(4-fluorophenyl)propenone (**1**) with 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**)[31] (Scheme 1) under different experimental conditions (Table 1) to get the 5-(4-bromophenyl)-1-(5-deoxy-1,2-*O*-isolpropylidene-α-D-xylofuranos-5-yl)-4-(4-fluorobenzoyl)-1*H*-1,2,3-triazole (**5**, entry 3). DMF as the solvent and tetrabutylammonium hydrogen sulfate (TBAHS) (20 mol %) as a catalyst at 100 °C proved to be the optimum reaction conditions.

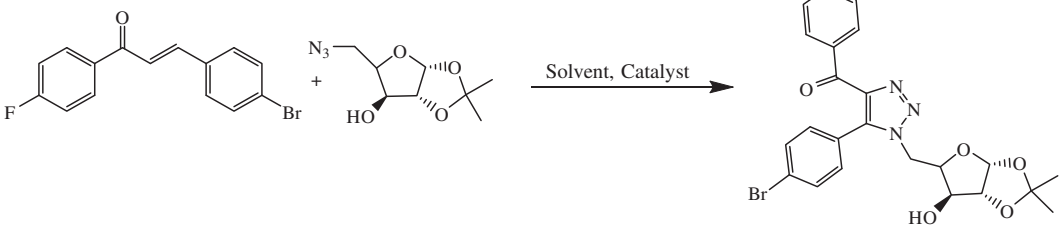
In order to determine the scope of the reaction of different chalcones as substrates in the above-mentioned regioselective [3+2] cycloaddition reaction followed by in situ oxidation, several chalcones were reacted with the above-mentioned 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**) (Scheme 2) to get the respective 4-benzoyl-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-phenyl-1*H*-1,2,3-triazoles (**3–15**) in varying yields (Table 2).

The versatility of this reaction was further explored by reacting *E*-3-(4-benzoyl)-1-(5-chlorophenyl)propenone (**16**) with an arylalkylazide (benzyl azide), generated in situ by the reaction of benzyl bromide and sodium azide (Scheme 3) under the above-mentioned experimental conditions. Interestingly, the reaction led to the formation of the expected product 4-benzoyl-1-benzyl-5-(4-chlorophenyl)-1*H*-1,2,3-triazole (**17**) in good yield. Moreover, the reaction did not succeed when propenone lacked an α-H on the olefinic carbon (Scheme 4). In the reaction, the conjugation of olefinic and carbonyl π-electrons apparently facilitates the attack of the nitrogen atom of the azide (A) directly linked to the carbon (C-5′) of sugar ring on the β-carbon of the propenone (B), then the enol form (C) generated in this process again resumes to its keto form which leads to an attack by the π-electrons of the C–C double bond on the terminal nitrogen of the azide, followed by the oxidation (D) to give the products (E). In the proposed reaction mechanism, TBAHS assists the reaction by acting as a phase-transfer catalyst and possibly by activating the C–C double bond by forming a complex with the lone-pair electrons of the carbonyl oxygen (Fig. 1).

The 1,4,5-substitution pattern in the above-mentioned triazoles is in agreement with the 2D-NOESY and HMBC spectra (Figs. 2a and b) of a prototype compound (**4**) where interactions of the methylene protons of the sugar moiety (H-5′) were observed (δ 4.55–4.50) with the *ortho* aromatic protons (δ 7.38–7.35) of the 4-bromophenyl ring a substitution on the fifth position of the triazole (Fig. 3). Peaks were assigned with the help of 2D-NOESY and HMBC spectra of the compound (**4**), wherein an interaction was observed among the aromatic protons of the same ring. To gain further insight on the 3D aspects of the structure as elucidated by NMR spectral data, a 3D model of compound **4** was subjected to energy minimization using SYBYL 6.3. In consensus with the NMR spectrum, the distance between the aromatic hydrogen of the 4-bromophenyl group and the sugar methylene hydrogen (H-5′) was found to be around 2.8 Å. All the above-mentioned observations conclusively confirm that the 4-bromophenyl group is adjacent to the sugar moiety.

3. Conclusions

In conclusion, we have successfully carried out the regioselective [3+2] cycloaddition reaction of propenones with 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose in the presence of tetrabutylammonium hydrogen sulfate as a catalyst to give the 4-benzoyl-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-

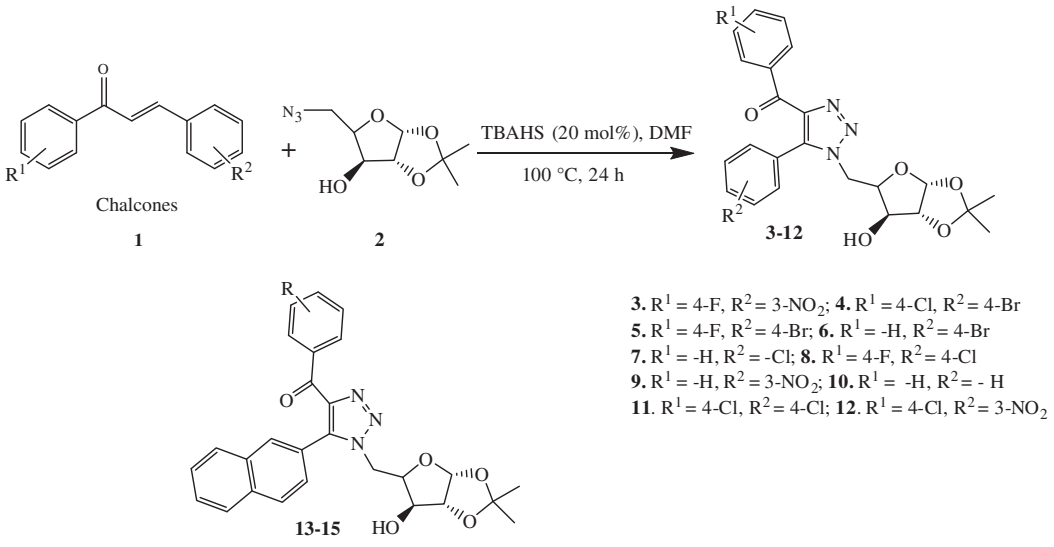


Scheme 1. Scheme for the optimization of reaction conditions.

Table 1
Standardization of the reaction condition for [3+2] cycloaddition of chalcone with sugar azide

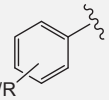
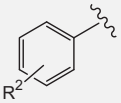
Entry	Solvent	Catalyst (20 mol %)	Temperature (°C)	Time (h)	Yield (%)
1	DMF	TBAHS	25	24	0
2	DMF	TBAHS	50	24	0
3	DMF	TBAHS	80	24	50
4	DMF	TBAHS	100	24	90
5	DMSO	TBAHS	100	36	80
6	CH_3CN	TBAHS	100	36	30
7	H_2O	TBAHS	100	36	0
8	EtOH	TBAHS	100	36	0
9[a]	Toluene	TBAHS	100	36	50
8	1,4 Dioxane	TBAHS	100	36	50
10	CCl_4	TBAHS	100	36	0
11[a]	DMF	L-Proline	100	24	50
12	DMF	TBAB	100	36	50
13	DMF	—	100	36	20
14	DMF	TBAHS	50	24	0

[a] A number of other un-isolable products along with the required product were observed (TLC).



Scheme 2. Synthesis of compounds **3–15**.

Table 2
Regioselective preparation of 4-benzoyl-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-phenyl-1*H*-1,2,3-triazoles by the reaction of different chalcones with a sugar azide

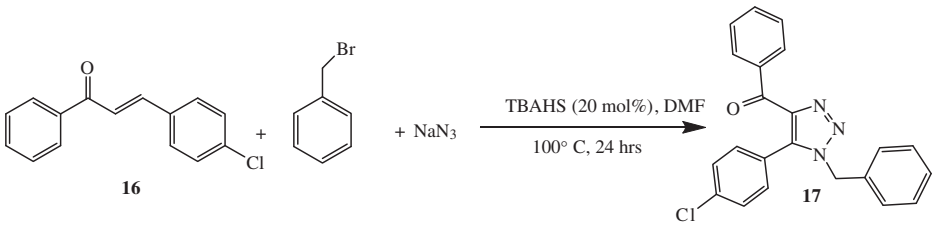
Entry	Chalcones		Product	Yield (%)
	R^1/R  R/R^1 =	 R^2 =		
1	4-F	3-NO_2	3	69
2	4-Cl	4-Br	4	89
3	4-F	4-Br	5	90
4	-H	4-Br	6	83
5	-H	4-Cl	7	65
6	4-F	4-Cl	8	63
7	-H	3-NO_2	9	83
8	-H	-H	10	80
9	4-Cl	4-Cl	11	81
10	4-Cl	3-NO_2	12	74
11	-H	—	13	87
12	4-F	—	14	87
13	4-Cl	—	15	83

yl)-5-phenyl-1*H*-1,2,3-triazoles in moderate to good yields. The reaction is simple as it involves readily available propenones and azides and also does not involve any special reagents or conditions. Application of this reaction and the products obtained are underway to get a library of biologically active compounds.

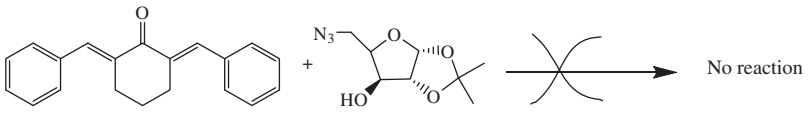
4. Experimental

4.1. General methods

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light and/or spraying with 5% H_2SO_4 in EtOH, followed by heating. Column chromatography was performed on silica gel (60–120 mesh, E. Merck). IR spectra were recorded as thin films or in chloroform solution with a Perkin–Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 in $CDCl_3$. Chemical shift values are reported in parts per million (ppm) relative to $SiMe_4$ as the internal reference, unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet); *J* in hertz. ESI mass spectra were determined with Quattro II (Micromass) instrument.



Scheme 3. Scheme for the synthesis of 1-benzyl-4-benzoyl-5-(4-chlorophenyl)-1*H*-1,2,3-triazole.



Scheme 4. Reaction of xylosyl azide with bis-chalcone having no hydrogen atom on the α-carbon.

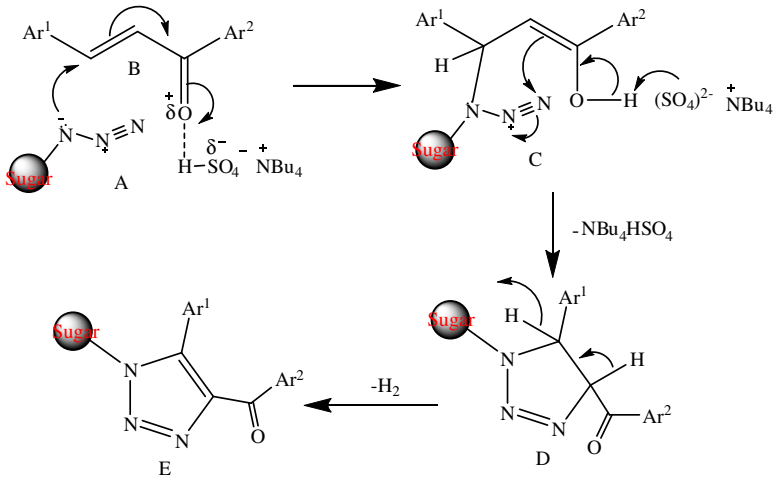


Figure 1. Most plausible reaction mechanism.

Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

4.2. 4-(Benzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-(phenyl)-1*H*-1,2,3-triazol: typical procedure

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**, 1 mmol) and 1,3-diphenyl propenones (1 mmol) were dissolved in 1 mL of DMF by stirring at 100 °C. TBAHS (20 mol %) was added into the reaction mixture, which was further stirred at 100 °C for 24 h. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with EtOAc (50 mL). The organic layer was washed with water (3 × 30 mL) to remove DMF and TBAHS from the reaction mixture then dried (anhyd Na_2SO_4) and evaporated under reduced pressure to get a crude mass. The latter was chromatographed over silica gel (60–120 mesh) using a gradient of 3.5:10 EtOAc–hexane as eluent to afford the desired product. All the products were light-yellow solids.

4.2.1. 1-(5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-4-(4-fluorobenzoyl)-5-(3-nitrophenyl)-1*H*-1,2,3-triazole (3)

Mp 147–149 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{23}$ −0.016 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3457 (OH), 1597 (C=N), 1224, 737 (arom); ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ 8.52 (d, 1H, H-arom), 8.39 (m, 3H, H-arom), 7.89 (d, 1H, H-arom), 7.75 (m, 1H, H-arom), 7.20 (m, 2H, H-arom), 5.95 (d, $J_{1,2}$ 3.51 Hz, 1H, H-1), 4.70 (m, 2H, CH_2), 4.59 (m, 1H, H-2), 4.41 (m, 2H, H-4, H-3), 3.17 (br s, 1H, OH), 1.46 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ 184.0 (C=O), 167.6, 164.2, 148.1, 143.5, 140.4, 136.5, 133.5, 133.4, 132.89, 132.85, 129.6, 127.6, 125.5, 124.9, 115.6, 115.3, 112.2, 104.9 (C-1), 85.2 (C-2), 79.0 (C-4), 74.6 (C-3). 46.7 (C-5), 26.8 (1C, CH_3, isopropyl), 26.2 (1C, CH_3, isopropyl); ESIMS (positive ion): *m*/*z*: 485 $[M+H]^+$. Anal. Calcd for $C_{23}H_{21}FN_4O_7$: C, 57.02; H, 4.37; N, 11.57. Found: C, 56.91; H, 4.55; N, 11.42.

4.2.2. 5-(4-Bromophenyl)-4-(4-chlorobenzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-1*H*-1,2,3-triazole (4)

Mp 164–166 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{20.2}$ −112.6 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3429 (OH), 1637 (C=N), 1217, 770 (arom); ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ 8.31 (d, 1H, H-arom), 7.72 (d, 1H, H-arom), 7.51 (d, 1H, H-arom), 7.38 (d, 1H, H-arom), 5.94 (d, $J_{1,2}$ 3.42 Hz, 1H, H-1), 4.65 (m, 2H, CH_2), 4.55 (m, 1H, H-2), 4.46 (m, 1H, H-4), 4.29 (s, 1H, H-3), 3.15 (br s, 1H, OH), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ 184.1 (C=O), 143.2, 141.6, 139.8, 135.0, 132.2, 132.1, 131.4, 128.6, 125.2, 124.5, 112.0, 105.0 (C-1), 85.1 (C-2), 78.9 (C-4), 74.6 (C-3), 45.8 (C-5), 26.9 (1C, CH_3, isopropyl), 26.2 (1C, CH_3, isopropyl); ESIMS (positive ion): *m*/*z*: 534 $[M+H]^+$. Anal. Calcd for $C_{23}H_{21}BrClN_3O_5$: C, 51.66; H, 3.96; N, 7.86. Found: C, 51.45; H, 4.19; N, 7.68.

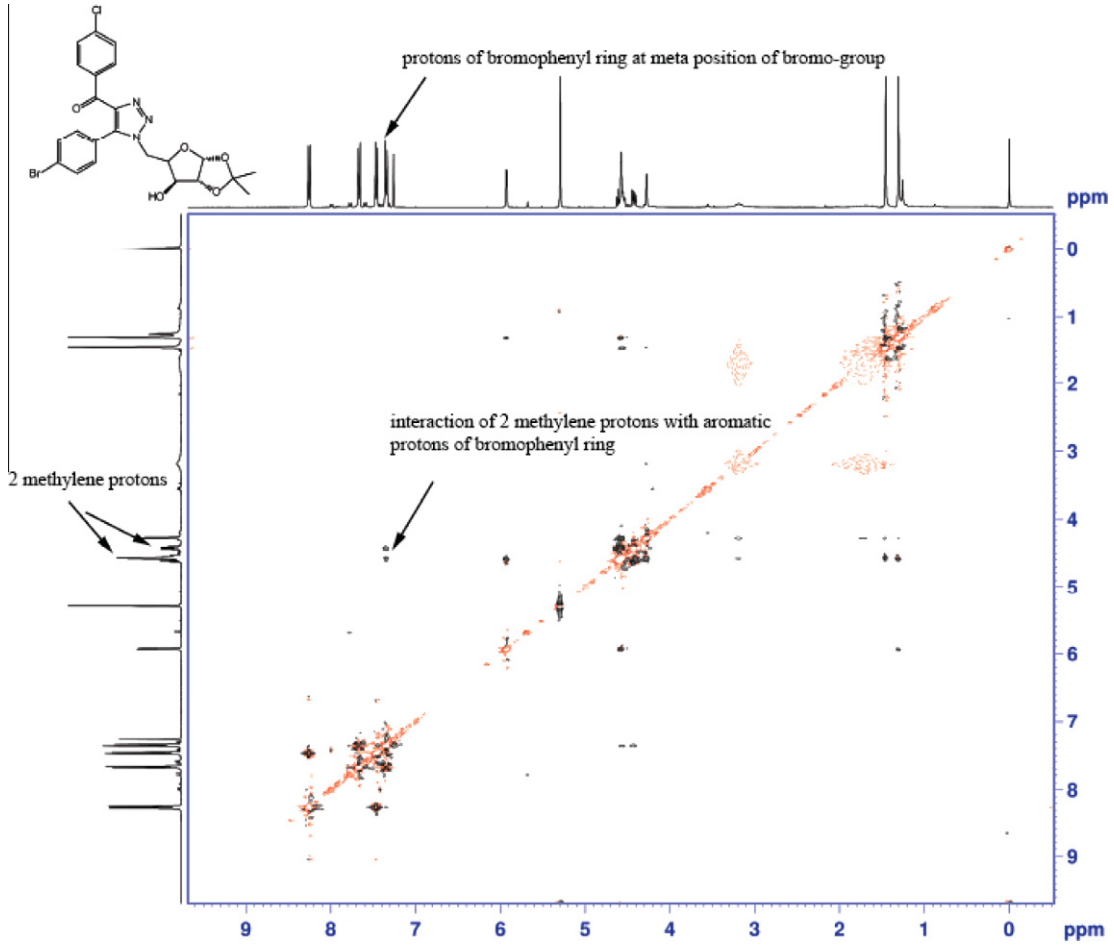


Figure 2a. NOESY spectrum of compound (**4**).

4.2.3. 5-(4-Bromophenyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-4-(4-fluorobenzoyl)-1*H*-1,2,3-triazole (5)

Mp 167–169 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{21.3}$ −170.18 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3422 (OH), 1638 (C=N), 1216, 770 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.42 (m, 2H, H-arom), 7.72 (d, 2H, H-arom), 7.39 (d, 2H, H-arom), 7.22 (t, 2H, H-arom), 5.94 (d, $J_{1,2}$ 3.51 Hz, 1H, H-1), 4.60 (m, 2H, CH_2 and H-2), 4.53 (m, 1H, CH_2), 4.46 (m, 1H, H-4), 4.29 (s, 1H, H-3), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 184.2 (C=O), 143.7, 141.9, 133.9, 133.7, 132.2, 132.5, 131.9, 125.6, 124.2, 116.0, 115.6, 112.4, 105.4 (C-1), 85.5 (C-2), 79.3 (C-4), 75.0 (C-3), 46.2 (C-5), 27.3 (1C, CH_3, isopropyl), 26.6 (1C, CH_3, isopropyl); ESIMS (positive ion): *m*/*z*: 518[M+H]$^+$. Anal. Calcd for $C_{23}H_{21}BrFN_3O_5$: C, 53.30; H, 4.08; N, 8.11. Found: C, 53.89; H, 4.79; N, 8.76.

4.2.4. 4-(Benzoyl)-5-(4-bromophenyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-1*H*-1,2,3-triazole (6)

Mp 143–145 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{23}$ −38.9 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3428 (OH), 1639 (C=N), 1217, 771 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.27 (d, 2H, H-arom), 7.69 (d, 2H, H-arom), 7.63 (m, 1H, H-arom), 7.52 (t, 2H, H-arom), 7.37 (d, 2H, H-arom), 5.92 (d, $J_{1,2}$ 3.39 Hz, 1H, H-1), 4.65 (m, 2H, CH_2), 4.53 (m, 1H, H-2), 4.45 (m, 1H, H-4), 4.28 (m, 1H, H-3), 2.80 (br s, 1H, OH), 1.46 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 185.7 (C=O), 143.4, 141.3, 136.8, 133.1, 132.1, 131.5, 130.6, 128.2, 125.1, 124.6, 112.0, 105.0 (C-1), 85.1 (C-2), 79.0 (C-4), 74.5 (C-3), 45.7 (C-5), 26.9 (1C, CH_3, isopropyl), 26.1 (1C, CH_3, isopropyl); ESIMS (positive ion): *m*/*z*: 502 [M+H]$^+$. Anal. Calcd for $C_{23}H_{22}BrN_3O_5$: C, 55.21; H, 4.43; N, 8.40. Found: C, 55.38; H, 4.32; N, 8.69.

4.2.5. 4-(Benzoyl)-5-(4-chlorophenyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-1*H*-1,2,3-triazole (7)

Mp 131–133 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{26}$ −43.3 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3421 (OH), 1650 (C=N), 1217, 768 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.26 (d, 2H, H-arom), 7.61 (m, 7H, H-arom), 5.90(s, 1H, H-1), 4.61 (m, 2H, CH_2), 4.43 (m, 1H, H-2), 4.31 (m, 1H, H-4), 4.16 (m, 1H, H-3), 3.5 (br s, 1H, OH), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 186.0 (C=O), 143.9, 141.7, 137.2, 137.1, 133.5, 131.7, 131.0, 129.5, 129.4, 128.6, 127.5, 124.5, 112.4, 105.4 (C-1), 85.5 (C-2), 79.4 (C-4), 74.9 (C-3), 46.2 (C-5), 27.3 (1C, CH_3, isopropyl), 26.6 (1C, CH_3, isopropyl); ESIMS (positive ion): *m*/*z*: 456 [M+H]$^+$. Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C, 60.59; H, 4.86; N, 9.22. Found C, 60.42; H, 5.02; N, 9.11.

4.2.6. 5-(4-Chlorophenyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-4-(4-fluorobenzoyl)-1*H*-1,2,3-triazole (8)

Mp 139–141 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{24.4}$ −0.31 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3407 (C=O), 1639 (C=N), 1228, 784 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.40 (m, 2H, H-arom), 7.54 (d, 2H, H-arom), 7.44 (d, 2H, H-arom), 7.20 (t, 3H, H-arom), 5.92 (d, $J_{1,2}$ 3.42 Hz, 1H, H-1), 4.61 (m, 2H, CH_2), 4.52 (m, 1H, H-2), 4.44 (m, 1H, H-4), 4.27 (m, 1H, H-3), 1.46 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 183.8 (C=O), 143.3,

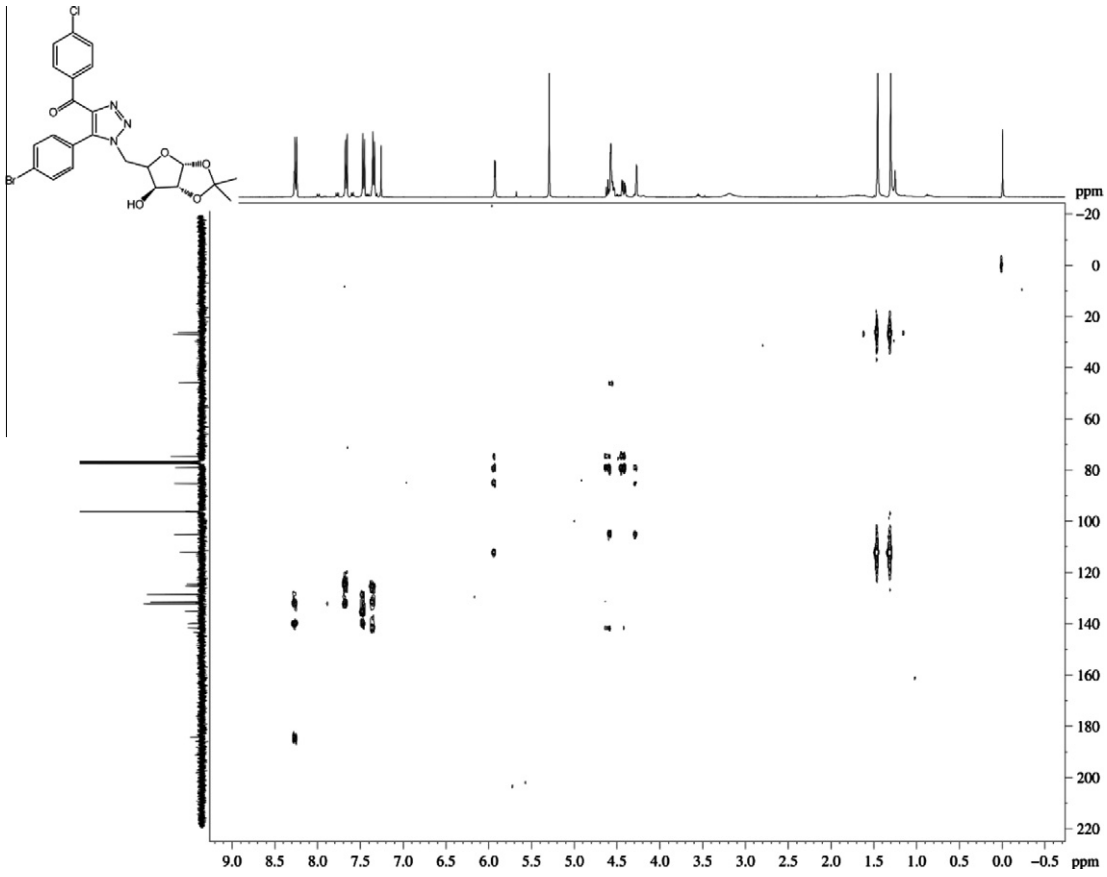


Figure 2b. HMBC spectrum of compound (**4**).

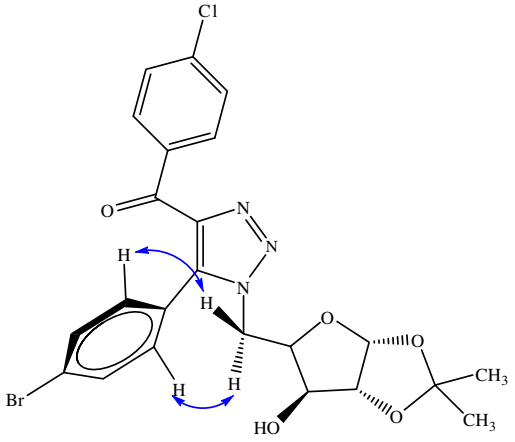


Figure 3. NOE interactions of methylene protons of the sugar moiety with phenyl ring protons.

141.5, 136.8, 133.5, 133.3, 133.1, 131.3, 129.2, 124.1, 115.5, 115.2, 112.0, 105.0 (C-1), 85.1 (C-2), 78.9 (C-4), 74.6 (C-3), 45.8 (C-5), 26.8 (1C, CH_3, isopropyl), 26.1 (1C, CH_3, isopropyl); ESIMS (positive ion): m/z: 474[M+H]$^+$. Anal. Calcd for $C_{23}H_{21}ClFN_3O_5$: C, 58.29; H, 4.47; N, 8.87. Found: C, 58.47; H, 4.33; N, 8.53.

4.2.7. 4-(Benzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-(3-nitrophenyl)-1*H*-1,2,3-triazole (9)

Mp 128–130 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{25.6}$ −9.17 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3409 (OH), 1662 (C=N), 1216, 768 (arom); ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ 8.51 (s, 1H, H-arom), 8.41 (d, 1H, H-arom), 8.30 (d, 2H, H-arom), 7.89 (d, 1H, H-arom), 7.75 (t, 1H, H-arom), 7.61 (m, 1H, H-arom), 7.53 (m, 2H, H-arom), 5.96 (d, $J_{1,2}$ 3.27 Hz, 1H, H-1), 4.65 (m, 2H, CH_2), 4.55 (m, 1H, H-2), 4.41 (m, 1H, H-4), 4.31 (m, 1H, H-3), 3.10 (br s, 1H, OH), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ 185.6 (C=O), 148.2, 143.7, 140.2, 136.6, 136.4, 133.3, 130.7, 129.6, 128.2, 127.7, 125.4, 124.9, 112.2, 105.0 (C-1), 85.2 (C-2), 79.0 (C-4), 74.6 (C-3), 46.5 (C-5), 26.8(1C, CH_3, isopropyl), 26.2(1C, CH_3, isopropyl); ESIMS (positive ion): m/z: 467[M+H]$^+$; Anal. Calcd for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.48; H, 4.54; N, 11.97.

4.2.8. 4-(Benzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-(phenyl)-1*H*-1,2,3-triazole (10)

R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{23}$ −9.83 (*c* 0.1, MeOH); IR (KBr): ν_{max} 3452 (C=O), 1653 (C=N), 1217, 765 (arom); ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ 7.84 (m, 10H, H-arom), 5.93 (d, $J_{1,2}$ 3.39 Hz, 1H, H-1), 4.64 (m, 2H, CH_2), 4.50 (m, 1H, H-2), 4.26 (m, 2H, H-4, H-3), 1.46 (s, 3H, CH_3), 1.37(s, 3H, CH_3); ESIMS (positive ion): m/z: 422[M+2H]$^+$. Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.24; H, 5.37; N, 10.11.

4.2.9. 4-(4-Chlorobenzoyl)-5-(4-chlorophenyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-1*H*-1,2,3-triazole (11)

Mp 155–156 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{26}$ −53.39 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3409 (OH), 1655 (C=N), 1220, 772 (arom); ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ 8.29 (dd, 2H, H-arom), 7.54 (m, 6H, H-arom), 5.93 (d, $J_{1,2}$ 3.54 Hz, 1H, H-1), 4.62 (m, 2H, CH_2), 4.53 (m, 1H, H-2), 4.45 (m, 1H, H-4), 4.28 (m, 1H, H-3), 1.46 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ 184 (C=O), 143.2, 141.5, 139.8, 136.9, 135.1, 132.1, 131.2, 129.2, 128.9, 124.0, 112.0, 105.0 (C-1), 85.1 (C-2), 78.9 (C-4), 74.6 (C-3), 45.8

(C-5), 26.9 (1C, CH_3, isopropyl), 26.1 (1C, CH_3, isopropyl); ESIMS (positive ion): *m/z*: 492[M+2H]$^+$. Anal. Calcd for $C_{23}H_{21}Cl_2N_3O_5$: C, 56.34; H, 4.32; N, 8.57. Found: C, 56.21; H, 4.48; N, 8.43.

4.2.10. 4-(4-Chlorobenzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-(3-nitrophenyl)-1*H*-1,2,3-triazole (12)

Mp 159–160 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{25.4}$ +8.29 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3408 (OH), 1657 (C=N), 1217, 767 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.52 (d, 1H, H-arom), 8.51 (m, 1H, H-arom), 8.33 (m, 2H, H-arom), 7.90 (m, 1H, H-arom), 7.78 (m, 1H, H-arom), 7.75 (m, 2H, H-arom), 5.97 (d, $J_{1,2}$ 3.54 Hz, 1H, H-1), 4.67 (m, 2H, CH_2), 4.57 (m, 1H, H-2), 4.40 (m, 1H, H-4), 4.32 (m, 1H, H-3), 1.48(s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 184 (C=O), 148.2, 143.5, 140.4, 140.0, 136.4, 134.8, 132.1, 129.6, 128.6, 127.5, 125.4, 125.0, 112.3, 104.9 (C-1), 85.2 (C-2), 78.9 (C-4), 74.6 (C-3), 46.5 (C-5), 26.8 (1C, CH_3, isopropyl), 26.2(1C, CH_3, isopropyl); ESIMS (positive ion): *m/z*: 501[M+H]$^+$. Anal. Calcd for $C_{23}H_{21}ClN_4O_7$: C, 55.15; H, 4.23; N, 11.19. Found: C, 55.37; H, 4.01; N, 11.38.

4.2.11. 4-(Benzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-(2-naphthyl)-1*H*-1,2,3-triazole (13)

Mp 170–171 °C. R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{25}$ −47.94 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3402 (OH), 1627 (C=N), 1216, 765 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.31 (d, 2H, H-arom), 8.02 (m, 4H, H-arom), 7.62 (m, 6H, H-arom), 5.92 (d, $J_{1,2}$ 3.48 Hz, 1H, H-1), 4.67 (m, 1H, H-2), 4.59 (m, 3H, CH_2 and H-4), 4.28 (s, 1H, H-3), 3.15 (br s, 1H, OH), 1.46 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 186.1 (C=O), 144.0, 142.9, 137.3, 134.2, 133.4, 133.2, 131.0, 130.6, 129.1, 128.8, 128.6, 128.3, 128.0, 127.3, 126.8, 123.3, 112.3, 105.4 (C-1), 85.4 (C-2), 79.5 (C-4), 74.9 (C-3), 46.0 (C-5), 27.3 (1C, CH_3, isopropyl), 26.6 (1C, CH_3, isopropyl); ESIMS (positive ion): *m/z*: 472[M+H]$^+$. Anal. Calcd for $C_{27}H_{25}N_3O_5$: C, 68.78; H, 5.34; N, 8.91. Found: C, 68.75; H, 5.61; N, 9.13.

4.2.12. 1-(5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-4-(4-fluorobenzoyl)-5-(2-naphthyl)-1*H*-1,2,3-triazole (14)

Mp 177–178 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{23}$ −21.9 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3396 (OH), 1651 (C=N), 1219, 770 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.40 (q, 2H, H-arom), 8.02 (m, 4H, H-arom), 7.62 (m, 3H, H-arom), 7.19 (t, 2H, H-arom), 5.939 (d, $J_{1,2}$ 2.28 Hz, 1H, H-1), 4.68 (d, 1H, $J_{1,2}$ 3.72 Hz, H-2), 4.63 (m, 3H, CH_2, H-4), 4.28 (s, 1H, H-3), 3.20 (br s, 1H, OH), 1.45 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 184.3 (C=O), 143.5, 142.7, 133.8, 133.4, 133.3, 132.8, 129.9, 128.8, 128.4, 127.9, 127.7, 127.0, 26.3, 122.9, 115.6, 115.3, 112.1, 105.0 (C-1), 85.0 (C-2), 79.0 (C-4), 74.6 (C-3), 45.8 (C-5), 26.8 (1C, CH_3, isopropyl), 26.1 (1C, CH_3, isopropyl); ESIMS (positive ion): *m/z*: 490 [M+H]$^+$; Anal. Calcd for $C_{27}H_{24}FN_3O_5$: C, 66.25; H, 4.94; N, 8.58. Found: C, 66.02; H, 4.59; N, 8.31.

4.2.13. 4-(4-Chlorobenzoyl)-1-(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-5-(2-naphthyl)-1*H*-1,2,3-triazole (15)

Mp 179–181 °C; R_f 0.5 (7:4 hexane–EtOAc); $[\alpha]_{546}^{23}$ −37.1 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3408 (OH), 1646 (C=N), 1224, 777 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.29 (m, 2H, H-arom), 8.01 (m, 4H, H-arom), 7.63 (m, 5H, H-arom), 5.92 (d, 1H, $J_{1,2}$ 3.51 Hz, H-1), 4.66 (m, 3H, CH_2, H-2, H-4), 3.45 (br s, 1H, OH), 1.45 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 183.4 (C=O), 158.4, 137.9, 135.2, 133.8, 132.8, 132.1, 129.9, 128.7, 128.5, 128.4, 127.9, 127.6, 127.0, 126.3, 122.8, 112.0, 105.0 (C-1), 85.0 (C-2), 79.0 (C-4), 74.5 (C-3), 45.6 (C-5), 26.9 (1C, CH_3, isopropyl), 26.2 (1C, CH_3, isopropyl); ESIMS (positive ion): *m/z*: 506[M+H]$^+$. Anal. Calcd for $C_{27}H_{24}ClN_3O_5$: C, 64.10; H, 4.78; N, 8.31. Found: C, 63.89; H, 5.00; N, 8.10.

4.2.14. 4-(Benzoyl)-1-benzyl-5-(4-chlorophenyl)-1*H*-1,2,3-triazole (17)

R_f 0.4 (7:2 hexane–EtOAc); mp 129–131 °C; IR (KBr): ν_{max} 3425, 1645 (C=N), 1450, 690 (arom); ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 8.35 (m, 2H, H-arom), 7.62 (m, 12H, H-arom), 5.47(s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 185.7 (C=O), 143.9, 140.6, 136.9, 136.4, 134.5, 133.0, 131.2, 130.8, 128.9, 128.6, 128.2, 127.5, 124.9, 52.0 (1C, CH_2); ESIMS (positive ion): *m/z*: 374[M+H]$^+$. Anal. Calcd for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.4; H, 4.75; N, 11.09.

Acknowledgments

This is CDRI Communication No. 7929. The authors thank DRDO New Delhi, CSIR New Delhi and DBT New Delhi, for financial assistance. Nimisha Singh and S.K. Pandey are thankful to CSIR New Delhi for SRF and RA, respectively. The authors sincerely thank Dr. Ravishankar and Mr. Guniyal SAIF Div., CDRI Lucknow, for providing and analyzing the NOESY and HMBC spectral data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.04.019.

References

1. (a) Wamhoff, H.. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1996; Vol. 5, pp 1–126; (b) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225–1239; (c) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Ali, A. A. S. *J. Heterocycl. Chem.* **1989**, *26*, 1461–1468; (d) Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339–379.
2. Morgan, N. H. *Eur. Pat. Appl.* **1991**, 0724. EP 437979 A2.
3. Fan, W.. In *Comprehensive Heterocyclic Chem. II*; Katritzky, A. R., Rees, C. W., Scrven, E. E. V., Eds.; Pergamon: Oxford, UK, 1996; Vol. 4, pp 1–126.
4. Willis, R. J.; Marlow, I. D. Eur. Pat. Appl. 400842, 1990; *Chem. Abstr.* **1991**, *114*, 164247b.
5. Cai, D.; Journet, M.; Larsen, R. D. US Patent US 6,051,707, 2000.; (b) Chandrasekar, P. H.; Manavathu, E. *Drugs Today (Barc.)* **2001**, *37*, 135; (c) Herbrecht, R. *Int. J. Clin. Pract.* **2004**, *58*, 612–624; (d) Arikan, S.; Rex, J. H. *Curr. Opin. Invest. Drugs* **2002**, *3*, 555–561.
6. (a) Biagi, G.; Livi, O.; Scartoni, V.; Verugi, E. *Farmaco Sci.* **1988**, *43*, 597–611; (b) Biagi, G.; Livi, O.; Ramacciotti, G. L.; Scartoni, V.; Bazzichi, L.; Mazzoni, M. R.; Lucacchini, A. *Farmaco* **1990**, *45*, 49–57.
7. (a) Wadsworth, H. J.; Jenkins, S. M.; Orlek, B. S.; Cassidy, F.; Clark, M. S.; Brown, F.; Riley, G. J.; Graves, D.; Hawkins, J.; Naylor, C. B. *J. Med. Chem.* **1992**, *35*, 1280–1290; (b) Savini, L.; Massarelli, P.; Corti, P.; Chiasserini, L.; Pellerano, C.; Bruni, G. I. *Farmaco* **1994**, *49*, 363–369.
8. Moltzen, E. K.; Pedersen, H.; Bogeso, K. P.; Meier, E.; Frederiksen, K.; Sanchez, C.; Love Lembol, H. J. *Med. Chem.* **1994**, *37*, 4085–4099.
9. Kim, D. K.; Kim, J.; Park, H. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401–2405.
10. (a) Whiting, M.; Tripp, J. C.; Lin, Y. C.; Lindstrom, W.; Olson, A. J.; Elder, J. H.; Sharpless, K. B.; Fokin, V. V. *J. Med. Chem.* **2006**, *49*, 7697–7710; (b) da Silva Fde, C.; de Souza, M. C.; Frugulhetti, I. I.; Castro, H. C.; Souza, S. L.; de Souza, T. M.; Rodrigues, D. Q.; Souza, A. M.; Abreu, P. A.; Passamani, F.; Rodrigues, C. R.; Ferreira, V. F. *Eur. J. Med. Chem.* **2009**, *44*, 373–383.
11. Cheng, Z. Y.; Li, W. J.; He, F.; Zhou, J. M.; Zhu, X. F. *Bioorg. Med. Chem.* **2007**, *15*, 1533–1538.
12. (a) Hou, D. R.; Alam, S.; Kuan, T. C.; Ramanathan, M.; Lin, T. P.; Hung, M. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1022–1025; (b) Shu, H.; Izenwasser, S.; Wade, D.; Stevens, E. D.; Trudell, M. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 891–893.
13. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970.
14. Alexacou, K. M.; Hayes, M. J.; Tiraidis, C.; Zographos, S. E.; Leonidas, D. D.; Chrysina, E. D.; Archontis, G.; Oikonomakos, N. G.; Paul, V. J.; Varghese, B.; Loganathan, D. *Proteins Struct. Funct. Bioinf.* **2008**, *71*, 1307–1323.
15. Zhang, J.; Garrosian, M.; Gardener, D.; Garrosian, A.; Chang, Y. T.; Kim, Y. K.; Chang, C. W. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1359–1363.
16. Giguère, D.; Patnem, R.; Bellefleur, M. A.; St-Pierre, C.; Sato, S.; Roy, R. *Chem. Commun. (Cambridge)* **2006**, 2379–2381.
17. Rossi, L. L.; Basu, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3596–3599.
18. Gouin, G. S.; Vanquelef, E.; Fernandez, J. M. G.; Mellet, C. O.; Dupradeau, F. Y.; Kovensky, J. *J. Org. Chem.* **2007**, *24*, 9032–9045.
19. Bokor, E.; Docsa, T.; Gergely, P.; Somsak, L. *Bioorg. Med. Chem.* **2010**, *18*, 1171–1180.

20. Chrysina, E. D.; Bokor, E.; Alexacou, K. M.; Charavgi, M. D.; Oikonomasok, G. N.; Zographos, S. E.; Leonidas, D. D.; Oikonomasok, N. G.; Somsak, L. *Tetrahedron: Asymmetry* **2009**, *20*, 733–740.
21. (a) Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111–2114; (b) Bakunov, S. A.; Bakunova, S. M.; Wenzler, T.; Ghebru, M.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. *J. Med. Chem.* **2010**, *53*, 254–272.
22. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (c) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364–367; (d) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015; (e) Best, M. D. *Biochemistry* **2009**, *48*, 6571–6584.
23. Kabada, P. K.; Edelstein, S. B. *J. Org. Chem.* **1990**, *55*, 5891–5894.
24. Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777–3780.
25. Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2005**, 3319–3326.
26. Chakarasali, R. T.; Ila, H.; JunJappa, H. *Synthesis* **1988**, 453–455.
27. Roque, D. R.; Neill, J. L.; Antoon, J. W.; Stevens, E. P. *Synthesis* **2005**, 2497–2502.
28. Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2235–2242.
29. Zvonok, A. M.; Kuz'menok, N. M.; Stanishevskii, L. S. *Khim. Geterotsiklicheskikh Soedineii* **1988**, 1022–1027.
30. Tripathi, R. P.; Yadav, A. K.; Bisht, S. S.; Chaturvedi, V.; Sinha, S. K. *Eur. J. Med. Chem.* **2010**, *45*, 142–148.
31. Singh, B. K.; Yadav, A. K.; Kumar, B.; Gaikwad, A.; Sinha, S. K.; Chaturvedi, V.; Tripathi, R. P. *Carbohydr. Res.* **2008**, *343*, 1153–1162.
32. Zhang, J.; Chang, C. W. T. *J. Org. Chem.* **2009**, *74*, 685–695.