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ORIGINAL ARTICLE

Click inspired synthesis of antileishmanial triazolyl *O*-benzylquercetin glycoconjugates

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Abstract The 1,3-dipolar cycloaddition of deoxy-*azido* sugars **1** with *O*-benzylquercetin alkynes (**5**–**7**) to afford regioselective triazole-linked *O*-benzylquercetin glycoconjugates (**8**–**10**) was investigated in the presence of CuI/DIPEA in dichloromethane. All the developed glycoconjugates (**8**–**10**) were evaluated for anti-leishmanial activity against the promastigotes and amastigotes of *Leishmania donovani*.

Keywords Carbohydrates · Antileishmanial Agents · Flavonoids · Quercetin · Click chemistry · Glycoconjugates

Abbreviations

FBS	Fetal bovine serum
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide
IC	inhibitory concentrations
SI	selective Index
SIRC cell line	Statens Seruminstitut Rabbit Corneal (SIRC) cell line
MIA PaCa cell line	MIA PaCa pancreatic epithelial cell lines.

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Introduction

Leishmaniasis, a neglected tropical disease caused by parasites of genus *Leishmania*, is among the major health problems worldwide, especially in developing nations. Pentavalent antimonial compounds like Pentostam or Glucantime are first line antileishmanials that have been used clinically for over 50 years [1, 2]. Antimonial treatments, however, is far from satisfactory due to the need for intramuscular administration and long treatment time, side effects and emergence of antimonials-resistant cases. Notwithstanding the two treatment alternatives, amphotericin B and miltefosine are being effectively used but their high cost and therapeutic complications limit their use in endemic areas [3, 4]. There is an urgent need for more novel, cheaper, potent, and safe antileishmanial compounds for treating leishmaniasis.

The coupling of two or more molecular entities with distinct properties to form novel conjugates with combined properties of parent components, has emerged as a fast growing technology in recent years [5–7]. Several new conjugates arising *via* such bioconjugation have been found to exhibit unusual biological properties and activities as the different molecular segments act cooperatively [8–10]. Alternatively, the growing development of 'click' chemistry [11] has also had an impact on the development of novel sugar based hybrid architectures [12–14].

The flavonoids are the most important dietary polyphenols in human diets, and are of great general interest due to their diverse biological activity [15]. The antioxidant potential and inhibition of digestive enzymes of flavonoid glycosides are most frequently reported [16]. Among the flavonoid glycosides, flavonol and flavone glycosides are more frequently mentioned than other flavonoids. The sugar moiety attached to flavonoid aglycone generally influences the absorption, distribution, and metabolism to some extent, and enhances certain types of bioactivities including anti-HIV [17], anti-rotavirus [18], anti-stress [19], anti-allergic [20], and anti-adipogenic activity [21]. In a relevant context, we envisioned exploring the *in vitro* anti-leishmanial potential of triazole-linked *O*-benzylquercetin glycoconjugates readily prepared from quercetin, one of the most abundant natural flavonoids known to exert leishmanicidal effect on the amastigote stage of *Leishmania donovani* while showing poor or no activity against promastigote forms.

Among the reactions comprising the click universe, the perfect example is the Huisgen 1,3-dipolar cycloaddition of terminal alkynes and organic azides to form 1,4-disubstituted-1,2,3-triazoles [22]. In addition, because of important role of carbohydrate in biological systems [23], and their great chemotherapeutic potential [24, 25], a wide variety of glycoconjugates so far have been reported using azide-alkyne cycloaddition approach [26–29]. However, the synthesis of flavonoid-glycoconjugates using ‘click’ chemistry has not yet realized. Moreover, their preparation through integration and/or linkage of flavonoids with sugar set hurdles due to the presence of several phenolic groups, and pose significant challenges in their synthesis. Thus, in view of numerous medicinal effects of quercetin, and the utility of carbohydrates in numerous chemical, biological, medicinal, and pharmacological investigations, we herein report the high-yielding synthesis of triazole-linked *O*-benzylquercetin glycoconjugates (**8**–**10**) *via* Cu(I) catalyzed click reaction of *azido*-sugars (**1a-g**) with *O*-benzylquercetin alkynes (**5**–**7**).

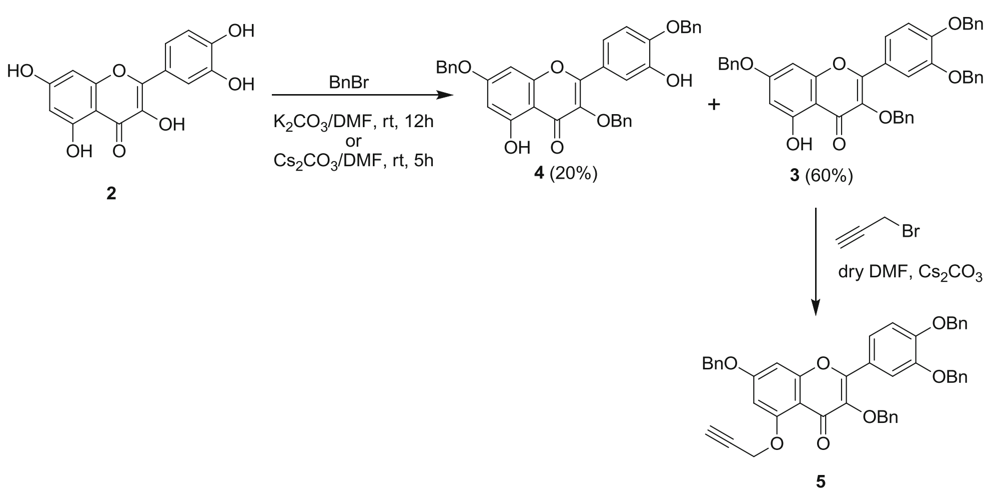
Result and discussion

The synthetic strategy begins with the cheap and readily available monosaccharides *i.e.,* D-glucose, D-galactose and D-xylose *etc.*, which after processing to a number of high-yielding steps for protection and modification, afforded deoxy-*azido* sugars **1a-g** in good yields [30–35].

After the synthesis of *azido*-sugars **1a-g**, we next attempted the synthesis of *O*-benzylquercetin alkynes **5**–**7**. Earlier, Bouktaib *et al.* reported the partial benzylation of quercetin **2** using benzyl bromide in presence of K_2CO_3 in dry DMF after 12 h afforded 3,7,3’,4’-*O*-tetrabenzylquercetin **3** (60 % isolated yield) and 3,7,4’-*O*-tribenzylquercetin **4** (20 % isolated yield) along with pentabenzylquercetin (detected in traces, 3 % isolated yield) [36]. However, we accomplished such a partial benzylation of compound **2** (Scheme 1) using Cs_2CO_3 as a base, and obtained **3** and **4** with almost same stereoslectivity in a significantly reduced reaction time (5 h). The compound **3** was further propargyled using Cs_2CO_3 in dry DMF under inert condition to afford 3,7,3’,4’-*O*-tetrabenzyl-5-*O*-propagylquercetin **5** in 92 % yield (Scheme 1).

Once the synthesis of alkyne **5** was achieved, we next turned our attention towards its CuAAC click reaction with developed *azido*-sugars **1a-g**. The click reaction of **5** (1.0 equiv.) with deoxy-*azido* sugar **1a** (1.2 equiv.) in presence of CuI (0.5 equiv.) and DIPEA (1.0 equiv.) was carried out in anhydrous dichloromethane at rt to afford 1-(methyl-5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosid-5-yl)-4-(1-*O*-methylene-3,7,3’,4’-*O*-tetrabenzylquercetin)-1,2,3-triazole **8a** regioselectively in 95 % yield. The regioisomeric nature of the compound **8a** was established on basis of its spectroscopic data. In mass spectrum, the compound **8a** displayed a molecular ion peak $[M+H]^+$ at *m/z* 931. In 300 MHz ^1H NMR spectrum, the signals corresponding to 25 aromatic protons resonated between δ 7.70 and 6.55 along with a triazolyl

Scheme 1 Synthesis of *O*-benzylquercetin alkyne **5**



proton singlet observed at δ 8.19. A total of five singlets, two proton each appeared between δ 5.35 and 4.94, were collectively assigned to a trizolyl methylene and four oxymethylene resonances. The anomeric proton resonated as doublet at δ 4.79 (J=5.7 Hz) while rest of the five sugar protons appeared between δ 4.68 and 4.47. A three proton singlet appeared at δ 3.40 was established for methoxy resonance while six protons of isopropylidene moiety were observed as singlets, three proton each at δ 1.29 and δ 1.25.

Once having established the reaction conditions for the regioselective cycloaddition of the *O*-benzylquercetin alkyne **5** and the ribofuranosyl azide **1a**, we explored the scope of other sugar azides in such a cycloaddition, and prepared a library of *O*-benzylquercetin triazolyl glycoconjugates **8a-g** in efficient yields (Table 1). Also, we investigated the reaction under microwave *(MW)* condition, where a significant reduction of reaction time to 10 min was observed. The structures of all the developed glycoconjugates **8a-g** were elucidated using spectral studies (IR, ^{1}H NMR, ^{13}C NMR, and MS).

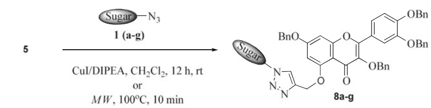
Further, we extended the work, and successfully prepared two different *O*-benzylated quercetin-alkynes **6 & 7** readily by taking the advantage of difference in the reactivity of hydrogen bonded OH-group compared to free phenolic group towards propargylation in presence of Cs_2CO_3 as a base. Thus, the treatment of **4** with 1.2 equivalent propargyl bromide and in excess (4.0 equiv.) using Cs_2CO_3 in dry DMF under inert condition at rt after 12 h furnished 3,7,4'-*O*-tribenzyl-1-hydroxy-3'-*O*-propagylquercetin **6** and 3,7,4'-*O*-tribenzyl-1,3'-di-*O*-propagylquercetin **7**, respectively in good yields (Scheme 2).

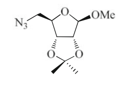
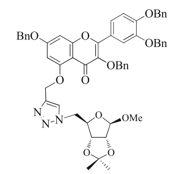
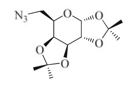
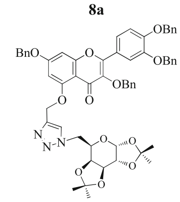
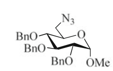
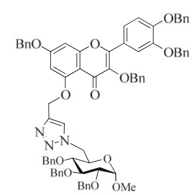
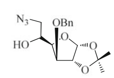
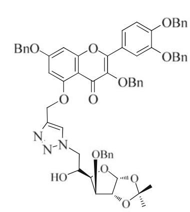
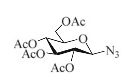
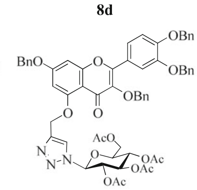
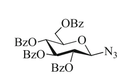
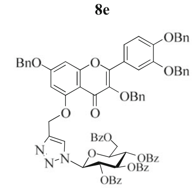
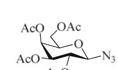
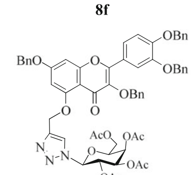
Both of the terminal alkynes **6** and **7** were further successfully utilized for the synthesis of *O*-benzylquercetin triazolyl glycoconjugates **9** and **10**, respectively, *via* click reaction with *azido*-sugars **1** under optimized reaction condition (Table 2). The structure of compounds **9** and **10** were deduced from their extensive spectral studies (IR, NMR, and MS).

In view of poor or no *in vitro* antileishmanial activity but considerable *in vivo* activity of quercetin metabolite **2** in earlier reports [37–39], the methodology described herein was effectively utilized to achieve bioactivation of **2** *via* 'click' inspired synthesis of numerous quercetin-carbohydrate conjugates differing in triazolylated monosaccharide substituent of the A-ring (at C-5), lateral B-ring (at C-3'), and both (at C-5 & C-3'). The *in vitro* antileishmanial activity in terms of IC_{50} against promastigotes and amastigotes of *L. donovani*, and CC_{50} for RAW 264.7 macrophages, determined after 24 h exposure to different concentrations of compounds **8**–**10** and miltefosine, are presented in Table 3.

The compounds **8**–**10** (Table 3) were evaluated against the promastigotes and amastigotes of *Leishmania donovani* using miltefosine, the latest and only approved oral drug for clinical

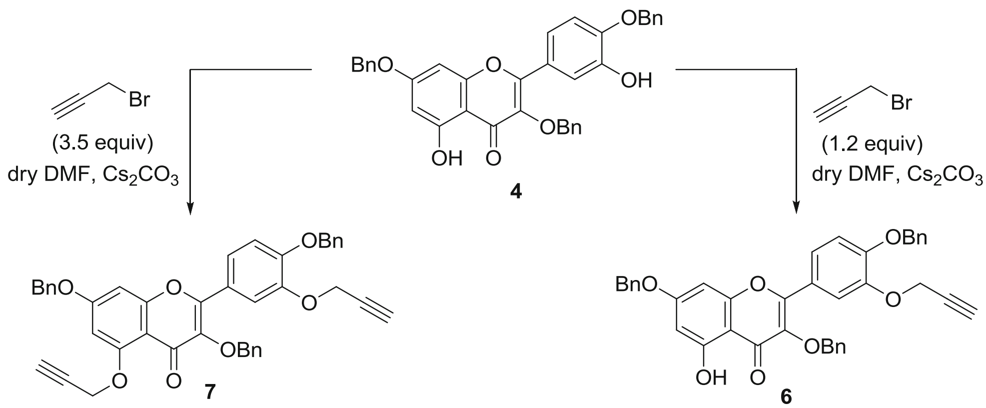
Table 1 Synthesis of *O*-benzylquercetin glycoconjugates **8a-g** *via* Cu-catalyzed click chemistry



Entry[a]	Sugar azides	Click product[b]	Yield (%)[c]	Yield (%)[d]
1	 **1a**	 **8a**	95	94
2	 **1b**	 **8b**	92	92
3	 **1c**	 **8c**	90	92
4	 **1d**	 **8d**	92	92
5	 **1e**	 **8e**	94	94
6	 **1f**	 **8f**	90	90
7	 **1g**	 **8g**	92	90

[a] Molar ratios: deoxy-azido sugar (1.2 equiv.), *O*-benzylquercetin alkyne **5** (1.0 equiv.), CuI (0.5 equiv.) and DIPEA (1.0 equiv.). [b] *O*-benzylquercetin triazolyl glycoconjugates. [c] Isolated yield at rt (time 10 h). [d] Isolated yield through reaction under microwave at 100 °C with a stirring rate 200 rpm in 10 min

Scheme 2 Synthesis of *O*-benzylquercetin alkynes **6** and **7**



use against visceral leishmaniasis in India [40]. The data are presented in mean±standard deviation. The triazolylated monosaccharides linked to 3,7,3',4'-*O*-tetrabenzylquercetin skeleton at position C-5 exhibited efficient activity in compared to C-3' linked triazolyl glycoconjugates **9** and *bis*--triazolyl glycocojugates **10**. The IC_{50} values of glycoconjugates **8** ranged between 7.76 to 41.47 μg/mL and 6.08 to 32.43 μg/mL against promastigote and amastigote forms of *L. donovani*, respectively. The compound **8d** displayed highest activity among all the compounds tested in this study, with an IC_{50} values of 7.76 and 6.08 μg/mL against extra- and intra-cellular forms, respectively. The glycoconjugates **9c** and **9d** exhibited low activity while compound **9g** with IC_{50} value of 18.51 and 14.5 μg/mL displayed significant activity against *L. donovnai* promastigotes and amastigotes, respectively. The compounds **8c**, **8e-g**, and **10b-d** demonstrated good to moderate activity in their respective series while the glycoconjugates **9b**, **9e**, **9f**, **10e**, and **10f** were inactive (IC_{50}>100 μg/mL) against both the forms.

It is imperative to point out that the antileishmainal activities of these compounds may be primarily due to the triazolyl substituent present at C-5/C-3' or both. Hence, the debenzylation of developed glycoconjugates to generate free phenolic groups do not appear promising for *in vitro* antileishmanial activity. Further, despite the presence of five hydroxyl groups, the quercetin molecule has a lipophilic character. Glycosylation at just one hydroxyl group of quercetin will result in an increase of its hydrophilicity. Thus, deprotection may be argued to have a better solubility of resulting glycoconjugates in water for future *in vivo* applications.

On the basis of results evident from Table 3, the potential compounds **8a** and **8d** were further screened for non specific cytotoxicity on SIRC, Statens Seruminstitut Rabbit Corneal cell line and MIA PaCa pancreatic epithelial cell line. Both the compounds displayed cytotoxicity at lower concentration against these cell lines as compared to RAW 264.7 macrophage but significantly higher than IC_{50} of *L. donovani* intra-macrophage amastigotes (Table 4).

Conclusion

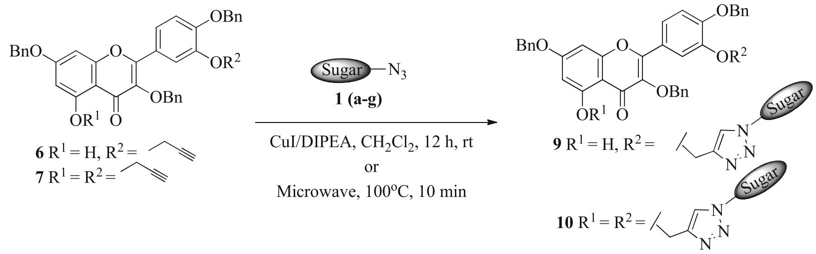
A number of deoxy-*azido* sugars were prepared by nucleophilic substitution from *O*-*p*-toluenesulfonyl glycofurano/pyranoses using sodium azide in anhydrous DMF under inert condition. The deoxy-*azido* sugars were further subjected to CuAAC reaction with *O*-benzylquercetin alkynes, to afford numerous triazolyl *O*-benzylquercetin glycoconjugates in excellent yields. The reaction time has been significantly reduced (10 min) under microwave heating. Moreover, anti-leishmanial assay pointed towards some interesting compounds exhibiting significant *in vitro* activity against promastigotes and intra-macrophage amastigote forms of *L. donovani.* Despite the toxicity of these developed triazolyl *O*-benzylquercetin glycoconjugates, an *in vivo* evaluation on the *L. donovani*/Balb/c mice model could be performed on compounds **8a** and **8d** before designing new pharmacomodulations.

Experimental

General methods

All of the reactions were executed using anhydrous solvents under an argon atmosphere in 1-hour oven-dried glassware at 100 °C. All reagents and solvents were of pure analytical grade. Thin-layer chromatography (TLC) was performed on 60 F254 silica gel, pre-coated on aluminum plates and revealed with either a UV lamp (λ_{max}=254 nm) or a specific color reagent (iodine vapors) or by spraying with methanolic H_2SO_4 solution and subsequent heating at 60 °C. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts given in ppm downfield from internal TMS; *J* values in Hz. Mass spectra recorded using electrospray ionization mass spectrometry (ESI-MS) in $CH_3OH/HCOOH$:100/0.05 % for better ionization, electrospray temperature chamber 350 °C for desolvation, and applied capillary voltage 3.5 kV. Infrared spectra

Table 2 Synthesis of *O*-benzylquercetin glycoconjugates **9** and **10** *via* Cu-catalyzed click chemistry



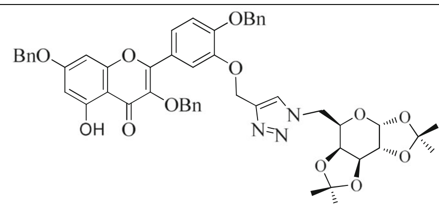
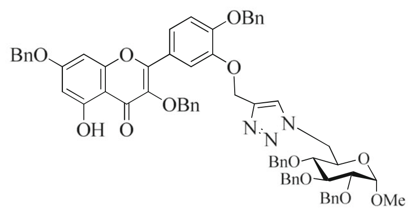
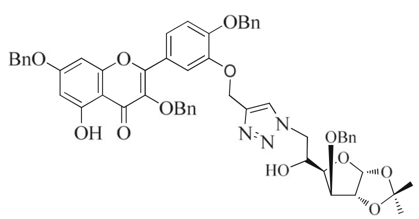
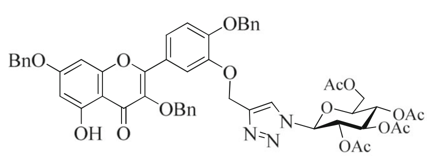
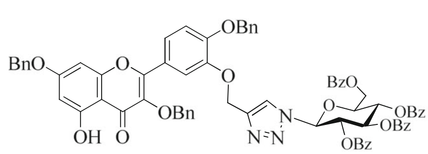
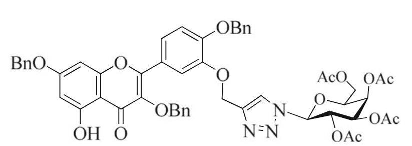
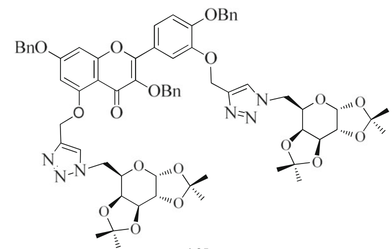
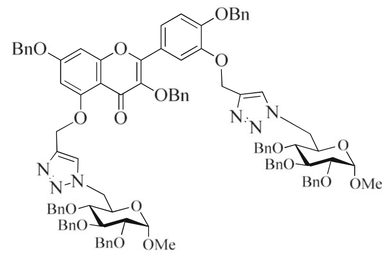
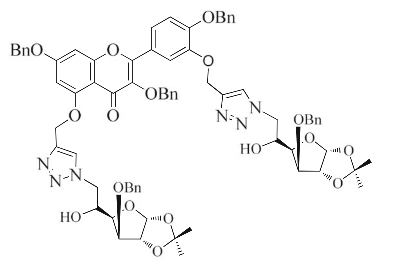
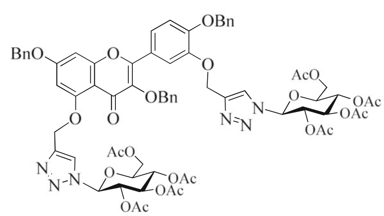
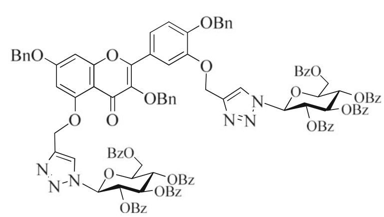
Entry[a]	Sugar azides	Click product[b]	Yield (%)[c]	Yield (%)[d]
1	**1b**	 **9b**	94	92
2	**1c**	 **9c**	92	92
3	**1d**	 **9d**	92	90
4	**1e**	 **9e**	90	90
5	**1f**	 **9f**	92	92
6	**1g**	 **9g**	94	92

Table 2 (continued)

Entry[a]	Sugar azides	Click product[b]	Yield (%)[c]	Yield (%)[d]
7	**1b**	 **10b**	92	92
8	**1c**	 **10c**	90	92
9	**1d**	 **10d**	94	92
10	**1e**	 **10e**	92	92
11	**1f**	 **10f**	90	90

[a] Molar ratios: deoxy-azido sugar (1.2–2.4 equiv.), *O*-benzylquercetin alkyne **6 & 7** (1.0 equiv.), CuI (0.5 equiv.) and DIPEA (1.0 equiv.). [b] *O*-benzylquercetin triazolyl glycoconjugates. [c] Isolated yield at rt (time 10 h). [d] Isolated yield through reaction under microwave at 100 °C with a stirring rate 200 rpm in 10 min

recorded as Nujol mulls in KBr plates. Elemental analysis was performed using a C, H, N analyzer, and results were found to be within ±0.4 % of the calculated values. Reaction under microwave condition was carried out on Microwave CEM Discover R Lab Mate.

General procedure for synthesis of sugar azides (1a-g)

The compounds **1a-g** were prepared from readily available carbohydrates (D-glucose, D-galactose, and D-ribose) using standard protection and modification methodologies [30–35].

Table 3 *In vitro* antileishmanial activity of *O*-benzylquercetin glycoconjugates **8**–**10** against *Leishmania donovani* promastigotes and intramacrophage amastigotes

Sr. No.	Compounds[a]	IC_{50}±SD on promastigotes	IC_{50}±SD on *L. donovani* intra-macrophage amastigotes	CC_{50}±SD on RAW 264.7 macrophage	SI (CC_{50}/IC_{50} of intra-macrophage amastigotes)
1	**8a**	9.92±2.16	7.65±0.93	107.38±3.89	13.99
2	**8b**	8.12±2.44	9.08±0.03	53.95±0.55	5.94
3	**8c**	21.67±1.06	16.03±0.40	49.06±0.60	3.06
4	**8d**	7.76±2.44	6.08±0.03	53.95±0.55	8.87
5	**8e**	34.82±2.55	29.65±1.49	203.39±4.89	6.86
6	**8f**	41.47±2.35	32.43±0.93	166.46±1.63	5.13
7	**8 g**	32.61±0.61	21.42±0.81	225.01±5.54	10.5
8	**9b**	>100	ND	ND	/
9	**9c**	92.4±2.14	80.37±1.16	205.78±2.80	2.56
10	**9d**	74.08±3.01	66.5±2.13	178.57±2.13	2.68
11	**9e**	>100	ND	ND	/
12	**9f**	>100	ND	ND	/
13	**9g**	18.51±1.59	14.5±0.43	39.79±0.21	2.74
14	**10b**	25.75±1.29	22.25±0.62	50.16±0.34	2.25
15	**10c**	18.78±0.82	28.07±2.37	66.13±0.34	2.36
16	**10d**	47.48±0.24	36.17±1.13	130.12±1.21	3.59
17	**10e**	>100	ND	ND	/
18	**10f**	>100	ND	ND	/
19	**HePC**[b]	5.95+0.95	4.16+0.20	23.80±0.15	5.71

[a] Triazolyl *O*-benzylquercetin glycoconjugates

[b] HePC=hexadecylphosphocholine=miltefosine (reference drug)

IC_{50} and CC_{50} shown in μg/mL

ND=not determined

General procedure for synthesis of tetra- and tri-benzylatedquercetin (3 & 4)

To a solution of quercetin **2** (5.0 g, 16.5 mmol) in DMF (100 mL), cesium carbonate (3.5 equiv., 18 g, 57.9 mmol) and benzyl bromide (3.5 equiv., 6.89 mL, 57.9 mmol) were added under inert condition. The reaction mixture was stirred for 5 h from 0 °C to rt. After completion of reaction (monitored by TLC), the reaction mixture was *in vacuo* concentrated, extracted with CH_2Cl_2, and washed twice with 10 % Na_2CO_3, water, and saturated brine solution. The organic layer was dried over anhydrous Na_2SO_4. The residue obtained after removal of the solvent was purified by flash column chromatography using gradient mixtures of *n*-hexane-ethyl acetate as eluent to afford three products: the tribenzylether **4**, the tetrabenzylether **3** and traces of pentabenzylether.

3,7,3’,4’-O-tetrabenzylquercetin (3) Yellowish solid (5.88 g, 60 % yield); mp=140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.68 (s, 1H), 7.70 (s, 1H), 7.53 (m, 1H), 7.45–7.25 (m, 20H), 6.97 (d, *J*=8.4, 1H), 6.45 (s, 1H), 6.43 (s, 1H), 5.24 (s, 2H), 5.13 (s, 2H), 5.03 (s, 2H), 4.99 (s, 2H); MS: *m/z* 663 $[M+H]^+$.

3,7,4’-O-tribenzylquercetin (4) Yellowish solid (1.69 g, 20 % yield); mp=148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.68 (s, 1H), 7.60 (m, 2H), 7.42–7.25 (m, 15H), 6.96 (d, *J*= 9.0, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 5.71 (s, 1H), 5.18 (s, 2H), 5.12 (s, 2H), 5.06 (s, 2H); MS: *m/z* 573 $[M+H]^+$.

Table 4 *In vitro* cytotoxic activity of compound **8a** and **8d** against SIRC and MIA PaCa cell line

Compounds[a]	CC_{50}±SD on SIRC and MIA PaCa cell line[b]	
	SIRC cell line[c]	MIA PaCa cell line[d]
8a	50.77±3.04	43.60±2.32
8d	20.97±1.81	29.58±1.56

[a] Triazolyl *O*-benzylquercetin glycoconjugates

[b] CC_{50} shown in μg/mL

[c] SIRC=Statens Seruminstitut Rabbit Corneal cell line

[d] MIA PaCa=MIA PaCa pancreatic epithelial cell line

General procedure for synthesis of O-benzylquercetin alkynes (5–7)

3,7,3',4'-O-tetrabenzyl-5-O-propagylquercetin (5) A stirring solution of compound **3** (1.0 g, 1.5 mmol) in dry DMF was treated with propargyl bromide (0.173 mL, 1.95 mmol) in presence Cs_2CO_3 (589 mg, 1.8 mmol) under inert condition. The reaction mixture was further stirred overnight at rt. After completion of reaction (monitored by TLC), the reaction mixture was *in vacuo* concentrated, extracted with CH_2Cl_2, and washed twice with 10 % Na_2CO_3, water, and saturated brine solution. The organic layer was dried over anhydrous Na_2SO_4. Further, concentration under reduced pressure followed by purification with flash column chromatography using gradient mixtures of *n*-hexane and ethyl acetate afforded compound **5** (966 mg, yield 92 %). Yellowish solid, mp=114–116 °C; IR (KBr) ν_{max}: 3244, 2949, 2854, 1743, 1624, 1512, 1455, 1431, 1372, 1223, 1033, 969, 862, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.57–7.54 (m, 1H), 7.44–7.25 (m, 20H), 6.96 (d, *J*=8.7, 1H), 6.64 (s, 1H), 6.59 (s, 1H), 5.23 (s, 2H), 5.14 (s, 2H), 5.05 (s, 2H), 4.96 (s, 2H), 4.89 (s, 2H), 2.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 162.5, 158.5, 153.0, 150.5, 148.1, 139.6, 136.9, 136.6, 135.5, 128.8, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 127.2, 127.1, 123.7, 122.0, 115.1, 113.6, 98.8, 94.6, 77.7, 73.8, 71.0, 70.7, 70.4, 57.0; MS: *m/z* 701 $[M+H]^+$; Anal. Calcd for $C_{46}H_{36}O_7$: C, 78.83; H, 5.18. Found: C, 78.48; H, 5.57.

3,7,4'-O-tribenzyl-1-hydroxy-3'-O-propagylquercetin (6) A stirring solution of compound **4** (1.0 g, 1.7 mmol) in dry DMF was treated with propargyl bromide (0.181 mL, 1.2 equiv., 2.0 mmol) in presence Cs_2CO_3 (1.1 g, 3.4 mmol) under inert condition. Yellow solid (881 mg, yield 85 %), IR (KBr) ν_{max}: 3241, 2937, 2842, 1746, 1622, 1518, 1460, 1429, 1365, 1230, 1034, 952, 848, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.60 (s, 1H), 7.70 (m, 1H), 7.52 (m, 1H), 7.36–7.17 (m, 15H), 6.85 (m, 1H), 6.39 (s, 1H), 6.25 (s, 1H), 5.13–5.01 (m, 6H), 4.53 (s, 2H), 2.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 164.4, 162.5, 162.0, 156.6, 151.1, 146.8, 137.5, 136.4, 136.3, 135.7, 128.7, 128.6, 128.4, 128.2, 128.0, 127.5, 127.4, 127.2, 123.4, 123.3, 123.0, 115.7, 113.4, 106.1, 98.5, 93.0, 78.3, 74.3, 70.8, 70.4, 57.0; MS: *m/z* 611 $[M+H]^+$; Anal. Calcd for $C_{39}H_{30}O_7$: C, 76.71; H, 4.95. Found: C, 76.40; H, 5.22.

3,7,4'-O-tribenzyl-1,3'-di-O-propagylquercetin (7) A stirring solution of compound **4** (1.0 g, 1.7 mmol) in dry DMF was treated with propargyl bromide (0.623 mL, 4.0 equiv., 6.9 mmol) in presence Cs_2CO_3 (1.6 g, 5.2 mmol) under anhydrous condition. White solid (1.01 g, yield 90 %); mp=118–120 °C; IR (KBr) ν_{max}: 3284, 3242, 3063, 2957, 2893, 1633, 1454, 1323, 1241, 1014, 823, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.60 (m, 1H), 7.42–7.37 (m, 15H), 6.93 (d, *J*=8.4, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 5.18 (s, 2H), 5.12 (s, 2H), 5.09 (s, 2H), 4.85 (s, 2H), 4.57 (s, 2H), 2.52 (s, 1H), 2.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 162.5, 158.5, 152.9, 150.5, 146.7, 139.7, 137.0, 136.4, 135.6, 128.7 (2C), 128.5, 128.3, 128.1, 127.9, 127.5, 127.3, 127.1, 123.6, 122.9, 115.5, 113.4, 110.0, 98.8, 94.7, 78.4, 77.8, 76.0, 75.8, 73.9, 70.7, 70.4, 57.0; MS: *m/z* 649 $[M+H]^+$; Anal. Calcd for $C_{42}H_{32}O_7$: C, 77.75; H, 4.98. Found: C, 78.01; H, 5.17.

General procedure for synthesis of triazolyl O-benzylquercetin glycoconjugates (8–10)

1-(Methyl-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranosid-5-yl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (**8a**):A solution of **5** (80 mg, 0.11 mmol) and *azido*-sugar **1a** (31 mg, 0.13 mmol) in presence of DIPEA (0.02 ml, 0.11 mmol) and CuI (9 mg, 0.05 mmol) in dry CH_2Cl_2 was stirred at room temparature under inert atmosphenre for 10 h. After completion of reaction (monitored by TLC), the reaction mixture was *in vacuo* concentrated to obtain a crude residue which was further purified by silica gel (100–200 mesh) column chromatography to afford compound **8a**. Yellowish solid (97 mg, yield 95 %); mp=126–128 °C; IR (KBr) ν_{max}: 3061, 2925, 2830, 1627, 1511, 1431, 1273, 1197, 1025, 870, 736, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.70 (s, 1H), 7.53–7.22 (m, 21H), 6.95 (d, *J*=8.7, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 5.35 (s, 2H), 5.22 (s, 2H), 5.12 (s, 2H), 5.03–5.00 (m, 3H), 4.94 (s, 2H), 4.79–4.77 (m, 1H), 4.68–4.47 (m, 4H), 3.40 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 162.8, 159.3, 158.5, 153.4, 150.5, 148.1, 144.5, 139.6, 136.9, 136.8, 136.7, 135.5, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9 (2C), 127.7, 127.5, 127.3, 127.1, 123.8, 123.7, 122.1, 115.1, 113.7, 112.8, 110.0, 109.9, 109.7, 97.9, 94.4, 85.1, 85.0, 81.8, 74.0, 73.9, 71.0, 70.8, 70.4, 64.1, 55.6, 55.5, 53.1, 26.3, 24.9; MS: *m/z* 931 $[M+H]^+$; Anal. Calcd for $C_{55}H_{51}N_3O_{11}$: C, 71.02; H, 5.53; N, 4.52. Found: C, 70.65; H, 5.77; N, 4.19.

Additionally, an equimoler mixture of *azido*-sugar **1a** (31 mg, 0.13 mmol) and compound **5** (80 mg, 0.11 mmol) in anhydrous toluene (10 ml) in presence of DIPEA (0.02 ml, 0.11 mmol) and CuI (9 mg, 0.05 mmol) was heated at 100 °C for 10 min in a microwave reactor (Microwave CEM Discover R Lab Mate). After completion of reaction (monitored by TLC), the reaction mixture was *in vacuo* concentrated, extracted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous Na_2SO_4 followed by *in vacuo* concentration. Purification using flash column chromatography afforded triazolyl *O*-benzylquercetin glycoconjugate **8a**. The physical data was closely matched with the developed molecule **8a**, when the reaction was carried out at room temperature.

1-(6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-5-yl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (8b) A solution of **5** (100 mg, 0.14 mmol) and *azido*-sugar **1b** (48 mg, 0.17 mmol) in presence of DIPEA (0.023 ml, 0.14 mmol) and CuI (13 mg, 0.07 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (127 mg, yield 92 %); mp=118–120 °C; IR (KBr) ν_{max}: 3063, 2923, 2854, 1626, 1453, 1511, 1213, 1070, 819, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.70 (s, 1H), 7.53–7.20 (m, 21H), 6.94 (d, *J*=8.4, 1H), 6.62 (s, 1H), 6.53 (s, 1H), 5.48 (d, *J*=4.5, 1H), 5.36 (s, 2H), 5.21 (s, 2H), 5.10 (s, 2H), 5.04 (s, 2H), 4.94 (s, 2H), 4.62–4.47 (m, 3H), 4.29–4.15 (m, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 162.7, 159.4, 158.4, 153.2, 150.4, 148.1, 143.6, 139.6, 136.9, 136.8, 136.6, 135.6, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 127.2, 127.0, 124.6, 123.7, 122.0, 115.0, 113.6, 109.7, 108.8, 97.9, 96.1, 96.0, 94.4, 74.0, 73.9, 70.9, 70.8, 70.7, 70.6, 70.4, 70.2, 66.9, 63.9, 50.3, 25.9, 25.8, 24.7, 24.3; MS: *m/z* 987 $[M+H]^+$; Anal. Calcd for $C_{58}H_{55}N_3O_{12}$: C, 70.65; H, 5.62; N, 4.26. Found: C, 70.86; H, 5.98; N, 4.07.

1-(Methyl-2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranos-5-yl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (8c) A solution of **5** (100 mg, 0.14 mmol) and *azido*-sugar **1c** (83 mg, 0.17 mmol) in presence of DIPEA (0.023 ml, 0.14 mmol) and CuI (13 mg, 0.07 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. White solid (150 mg, yield 90 %); mp=156–158 °C; IR (KBr) ν_{max}: 3031, 2922, 2851, 1646, 1514, 1453, 1195, 1102, 1051, 733, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.70 (s, 1H), 7.54–7.29 (m, 36H), 6.95 (d, *J*=8.4, 1H), 6.62 (s, 1H), 6.52 (s, 1H), 5.38–4.55 (m, 18H), 3.98–3.95 (m, 2H), 3.42–3.39 (m, 1H), 3.19–3.11 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 162.7, 159.3, 158.5, 153.3, 150.6, 148.2, 144.0, 139.6, 138.4, 137.9, 137.8, 136.9, 136.7, 135.5, 128.7. 128.3, 128.1, 127.9, 127.5, 127.3, 127.1, 124.8, 123.7, 122.1, 115.2, 113.8, 98.0, 97.8, 97.7, 94.4, 81.7, 79.9, 78.0, 75.6, 74.9, 74.0, 73.2, 70.8, 70.4, 69.0, 63.9, 55.1, 50.7; MS: *m/z* 1191 $[M+H]^+$; Anal. Calcd for $C_{74}H_{67}N_3O_{12}$: C, 74.67; H, 5.67; N, 3.53. Found: C, 75.04; H, 6.02; N, 3.91.

1-(3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranos-5-yl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (8d) A solution of **5** (100 mg, 0.14 mmol) and *azido*-sugar **1d** (56 mg, 0.17 mmol) in presence of DIPEA (0.023 ml, 0.14 mmol) and CuI (13 mg, 0.07 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (133 mg, yield 92 %); mp=148–150 °C; IR (KBr) ν_{max}: 3061, 2928, 2848, 1632, 1456, 1521, 1224, 1062, 828, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.69 (s, 1H), 7.52–7.23 (m, 25H), 6.90 (d, *J*=8.7, 1H), 6.47 (s, 1H), 6.31 (s, 1H), 5.97 (s, 1H), 5.19–4.63 (m, 16H), 4.37–4.29 (m, 1H), 4.18–4.15 (m, 2H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 162.6, 159.0, 158.0, 152.7, 150.5, 148.2, 143.4, 139.7, 137.3, 136.9 (2C), 136.6, 135.6, 128.6. 128.4, 128.3 (2C), 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.0, 127.4, 124.9, 123.7, 127.0, 124.9, 123.7, 121.9, 114.8, 113.6, 111.8, 109.1, 105.3, 105.2, 96.9, 94.1, 82.5, 82.3, 81.2, 73.9, 72.7, 72.6, 70.9, 70.7, 70.6, 70.2, 67.3, 63.7, 54.9, 26.8, 26.2; MS: *m/z* 1037 $[M+H]^+$; Anal. Calcd for $C_{62}H_{57}N_3O_{12}$: C, 71.87; H, 5.54; N, 4.06. Found: C, 72.24; H, 5.22; N, 3.77.

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucoopyranosyl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (8e) A solution of **5** (100 mg, 0.14 mmol) and *azido*-sugar **1e** (63 mg, 0.17 mmol) in presence of DIPEA (0.023 ml, 0.14 mmol) and CuI (13 mg, 0.07 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (141 mg, yield 94 %); mp=132–134 °C; IR (KBr) ν_{max}: 3058, 2921, 2859, 1630, 1456, 1518, 1217, 1068, 823, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.70 (s, 1H), 7.54–7.22 (m, 21H), 6.95 (d, *J*=8.7, 1H), 6.56 (s, 2H), 5.89 (d, *J*=9.3, 1H), 5.66–5.59 (m, 1H), 5.45–5.22 (m, 5H), 5.12–4.95 (s, 5H), 4.26–4.01 (m, 5H), 2.06–2.02 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 170.5, 169.9, 169.1, 168.5, 162.7, 159.1, 158.5, 153.4, 150.5, 148.1, 144.8, 139.6, 136.9, 136.8, 136.6, 135.5, 129.6, 128.7, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.5, 127.2, 127.1, 123.6, 122.5, 122.1, 115.1, 113.6, 109.7, 98.0, 94.5, 58.6, 75.0, 74.0, 72.8, 70.9, 70.7, 70.4, 70.1, 67.5, 63.7, 61.4, 20.6, 20.4, 20.0; MS: *m/z* 1075 $[M+H]^+$; Anal. Calcd for $C_{60}H_{55}N_3O_{16}$: C, 67.09; H, 5.16; N, 3.91. Found: C, 66.84; H, 4.87; N, 3.59.

1-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (8f) A solution of **5** (100 mg, 0.14 mmol) and *azido*-sugar **1f** (105 mg, 0.17 mmol) in presence of DIPEA (0.023 ml, 0.14 mmol) and CuI (13 mg, 0.07 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (166 mg, yield 90 %); mp=160–162 °C; IR (KBr) ν_{max}: 3063, 2924, 2853, 1731, 1510, 1452, 1267, 1092, 820, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.99–7.90 (m, 4H), 7.82–7.80 (m, 2H), 7.73–7.71 (m, 3H), 7.53–7.21 (m, 29H), 6.95 (d, *J*=8.4, 1H), 6.54 (s, 1H), 6.50 (s, 1H), 6.27 (d, *J*=8.4, 1H), 6.17–6.10 (m, 2H), 5.91–5.85 (m, 1H), 5.33 (s, 2H), 5.22 (s, 2H), 5.05 (m, 4H), 4.96 (s, 2H), 4.67–4.63 (m, 1H), 4.52–4.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 166.0, 165.5, 164.9, 164.3, 162.7, 159.1, 158.4, 153.3, 150.5, 148.1, 144.8, 139.6, 136.9, 136.8, 136.7, 135.5, 133.5, 133.3, 133.1, 129.8, 129.7, 129.2, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.5, 127.3, 127.1, 123.7, 122.5, 122.1, 115.1, 113.7, 109.7, 97.9, 94.7, 86.0, 75.4, 74.1, 73.1, 70.8, 70.4, 68.8, 63.6; MS: *m/z* 1323 $[M+H]^+$; Anal. Calcd for $C_{80}H_{63}N_3O_{16}$: C, 72.66; H, 4.80; N, 3.18. Found: C, 73.04; H, 4.53; N, 3.57.

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-4-(5-O-methylene-3,7,3',4'-O-tetrabenzylquercetin)-1,2,3-triazole (8 g) A solution of **5** (100 mg, 0.14 mmol) and *azido*-sugar **1 g** (63 mg, 0.17 mmol) in presence of DIPEA (0.023 ml, 0.14 mmol) and CuI (13 mg, 0.07 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon, atmosphenre for 12 h. White solid (138 mg, yield 92 %); mp=152–154 °C; IR (KBr) ν_{max}: 3445, 3033, 2925, 2855, 1751, 1628, 1513, 1196, 1104, 1053, 807, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.63 (s, 1H), 7.36–7.18 (m, 21H), 6.89 (d, *J*=7.8, 1H), 6.51 (m, 2H), 5.77 (d, *J*=9.0, 1H), 5.62 (m, 1H), 5.46 (m, 1H), 5.30–4.88 (m, 10H), 4.14 (m, 4H), 2.10 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5 (2C), 170.4, 170.3, 151.8, 148.9, 139.7, 130.4, 128.7, 128.5, 128.4, 128.1, 128.0, 127.5, 127.3, 127.1, 123.7, 122.4, 120.5, 118.5, 113.7, 113.3, 89.0, 86.2, 74.0, 71.0, 70.9, 63.4, 55.2, 48.4, 40.7, 38.3, 37.0, 35.8, 20.7, 20.6, 20.5, 20.4; MS: *m/z* 1075 $[M+H]^+$; Anal. Calcd for $C_{60}H_{55}N_3O_{16}$: C, 67.09; H, 5.16; N, 3.91. Found: C, 67.40; H, 5.50; N, 4.24.

1-(6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-5-yl)-4-(3'-O-methylene-3,7,4'-O-tribenzylquercetin)-1,2,3-triazole (9b) A solution of **6** (100 mg, 0.16 mmol) and *azido*-sugar **1b** (54 mg, 0.19 mmol) in presence of DIPEA (0.027 ml, 0.16 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (134 mg, yield 94 %); mp=142–144 °C; IR (KBr) ν_{max}: 3439, 3036, 2925, 2837, 1657, 1587, 1453, 1320, 1150, 806, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.65 (s, 1H), 7.75–7.62 (m, 3H), 7.42–7.24 (m, 15H), 6.94 (d, *J*=8.7, 1H), 6.55 (s, 1H), 6.42 (s, 1H), 5.48 (d, *J*=5.1, 1H), 5.20–5.09 (m, 8H), 4.62–4.57 (m, 2H), 4.45–4.38 (m, 1H), 4.4.31–4.29 (m, 1H), 4.18–4.15 (m, 2H), 1.33–1.24 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 164.4, 161.9, 156.6, 156.0, 151.0, 147.9, 143.5, 137.6, 136.5, 136.4, 135.8, 128.7, 128.6, 128.5, 128.2, 127.9, 127.4, 127.2, 124.3, 123.4, 123.2, 115.3, 113.7, 109.8, 108.9, 106.1, 98.6, 96.0, 93.0, 74.3, 71.0, 70.8, 70.7, 70.3, 67.1, 63.4, 50.5, 25.9, 25.8, 24.7, 24.3; MS: *m/z* 896 $[M+H]^+$; Anal. Calcd for $C_{51}H_{49}N_3O_{12}$: C, 68.37; H, 5.51; N, 4.69. Found: C, 67.98; H, 5.84; N, 5.05.

1-(Methyl-2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranos-5-yl)-4-(3'-O-methylene-3,7,4'-O-tribenzylquercetin)-1,2,3-triazole (9c) A solution of **6** (100 mg, 0.16 mmol) and *azido*-sugar **1c** (92 mg, 0.19 mmol) in presence of DIPEA (0.027 ml, 0.16 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (161 mg, yield 92 %); mp=121–123 °C; IR (KBr) ν_{max}: 3439, 3031, 2922, 2852, 1659, 1592, 1497, 1197, 1096, 806, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.6 (s, 1H), 7.74 (s, 1H), 7.64–7.59 (m, 2H), 7.40–7.22 (m, 30H), 6.92 (d, *J*=8.7, 1H), 6.54 (s, 1H), 6.41 (s, 1H), 5.17–5.03 (m, 9H), 4.97–4.66 (m, 4H), 4.58–4.41 (m, 4H), 4.00–3.90 (m, 2H), 3.39–3.35 (m, 1H), 3.16–3.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 164.4, 161.9, 156.6, 155.9, 150.9, 147.7, 143.7, 138.3, 137.8 (2C), 137.5, 136.4, 135.7, 128.7, 128.6, 128.5, 128.4 (3C), 128.2 (2C), 128.1, 128.0, 127.9, 127.6, 127.4, 127.3, 127.1, 124.3, 123.4, 123.2, 115.1, 113.5, 106.1, 98.6, 97.8, 92.9, 81.7, 79.9, 77.9, 75.7, 74.9, 74.3, 73.3, 70.8, 70.3, 69.0, 63.4, 63.3, 55.1, 50.6; MS: *m/z* 1101 $[M+H]^+$; Anal. Calcd for $C_{67}H_{61}N_3O_{12}$: C, 73.14; H, 5.59; N, 3.82. Found: C, 73.39; H, 5.36; N, 4.16.

1-(3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranos-5-yl)-4-(3'-O-methylene-3,7,4'-O-tribenzylquercetin)-1,2,3-triazole (9d) A solution of **6** (100 mg, 0.16 mmol) and *azido*-sugar **1d** (63 mg, 0.19 mmol) in presence of DIPEA (0.027 ml, 0.16 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (139 mg, yield 92 %); mp=136–138 °C; IR (KBr) ν_{max}: 3438, 3048, 2930, 2836, 1652, 1470, 1525, 1221, 1069, 837, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.65 (s, 1H), 7.74 (s, 1H), 7.63 (m, 2H), 7.41–7.24 (m, 20H), 6.92 (d, *J*=8.7, 1H), 6.52 (s, 1H), 6.41 (s, 1H), 5.93 (s, 1H), 5.16–5.02 (m, 8H), 4.68–4.51 (m, 4H), 4.33–4.28 (m, 2H), 4.08 (m, 1H), 3.93 (m, 1H), 3.21 (s, 1H), 1.29–1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 164.4, 161.8, 156.6, 155.9, 151.0, 147.7, 143.5, 137.4, 137.0, 136.3, 135.7, 128.6, 128.2, 127.8, 127.4, 127.2, 124.7, 123.3, 115.4, 113.3, 112.0, 106.0, 105.2, 105.1, 98.6, 92.8, 82.1, 81.1, 80.1, 74.3, 72.2, 70.3, 67.6, 63.3, 53.8, 26.7, 26.2; MS: *m/z* 947 $[M+H]^+$; Anal. Calcd for $C_{55}H_{51}N_3O_{12}$: C, 69.83; H, 5.43; N, 4.44. Found: C, 70.11; H, 5.80; N, 4.71.

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucoopyranosyl)-4-(3'-O-methylene-3,7,4'-O-tribenzylquercetin)-1,2,3-triazole (9e) A solution of **6** (100 mg, 0.16 mmol) and *azido*-sugar **1e** (70 mg, 0.19 mmol) in presence of DIPEA (0.027 ml, 0.16 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (141 mg, yield 90 %); mp=140–142 °C; IR (KBr) ν_{max}: 3440, 3033, 2930, 2848, 1651, 1476, 1538, 1233, 1078, 853, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.65 (s, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 7.66 (d, *J*=8.7, 1H), 7.47–7.23 (m, 15H), 6.96 (d, *J*=8.7, 1H), 6.54 (s, 1H), 6.43–6.42 (m, 1H), 5.84 (d, *J*=9.0, 1H), 5.60–5.53 (m, 2H), 5.42–5.41 (m, 1H), 5.27–5.01 (m, 8H), 4.61 (d, *J*=8.4, 1H), 4.21–4.10 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.9 (2C), 169.7, 164.4, 161.9, 156.6, 155.9, 137.5, 136.4, 136.3, 135.7, 128.2, 127.4, 127.1, 123.4, 123.3, 113.6, 106.5, 106.0, 98.6, 88.1, 86.2, 73.9, 72.7, 70.7, 67.7, 66.8 (2C), 66.7, 63.1, 61.0, 39.5, 34.4, 26.1, 20.6, 20.5 (2C), 20.3; MS: *m/z* 984 $[M+H]^+$; Anal. Calcd for $C_{53}H_{49}N_3O_{16}$: C, 64.69; H, 5.02; N, 4.27. Found: C, 64.33; H, 4.71; N, 4.60.

1-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)-4-(3'-O-methylene-3,7,4'-O-tribenzylquercetin)-1,2,3-triazole (9f) A solution of **6** (100 mg, 0.16 mmol) and *azido*-sugar **1f** (117 mg, 0.19 mmol) in presence of DIPEA (0.027 ml, 0.16 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellow solid (181 mg, yield 92 %); mp=136–138 °C; IR (KBr) ν_{max}: 3443, 3032, 2924, 2853, 1658, 1496, 1452, 1269, 1092, 812, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.6 (s, 1H), 7.98–7.91 (m, 5H), 7.80 (d, *J*=7.5 Hz, 1H), 7.69–7.63 (m, 3H), 7.49–7.13 (m, 29H), 6.92 (d, *J*=8.7, 1H), 6.48–6.40 (m, 2H), 6.23 (d, *J*=9.3, 1H), 6.09 (m, 1H), 5.93–5.80 (m, 2H), 5.13–5.02 (m, 8H), 4.66–4.62 (m, 1H), 4.49–4.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 165.9, 165.4, 165.0, 164.4, 164.3, 161.9, 161.8, 156.5, 155.7, 150.9, 147.6, 144.9, 137.5, 136.4 (2C), 135.8, 133.6, 133.4, 133.1, 129.6, 129.1, 128.6, 128.4, 128.3, 128.2 (2C), 128.0, 127.6, 127.4, 127.3, 127.2, 123.9, 123.4, 121.4, 121.3, 115.1, 113.6, 106.0, 98.6, 92.7, 86.0, 75.4, 74.4, 74.3, 72.8, 70.8, 70.4, 70.3, 68.7, 63.2, 62.6; MS: *m/z* 1232 $[M+H]^+$; Anal. Calcd for $C_{73}H_{57}N_3O_{16}$: C, 64.69; H, 5.02; N, 4.27. Found: C, 64.47; H, 4.75; N, 3.98.

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-4-(3'-O-methylene-3,7,4'-O-tribenzylquercetin)-1,2,3-triazole (9 g) A solution of **6** (100 mg, 0.16 mmol) and *azido*-sugar **1 g** (70 mg, 0.19 mmol) in presence of DIPEA (0.027 ml, 0.16 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. Yellowish solid (147 mg, yield 94 %); mp=152–154 °C; IR (KBr) ν_{max}: 3473, 3032, 2924, 2853, 1754, 1653, 1511, 1454, 1226, 1062, 807, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.67 (s, 1H), 7.79–7.64 (m, 3H), 7.45–7.26 (m, 15H), 6.97 (d, *J*=8.7, 1H), 6.54 (s, 1H), 6.43 (s, 1H), 5.84 (m, 1H), 5.39–5.34 (m, 2H), 5.21–5.09 (m, 8H), 4.25–3.99 (m, 4H), 2.10–2.03 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 170.4, 169.8, 169.3, 168.7, 164.4, 161.9, 156.6, 155.9, 151.0, 147.6, 144.8, 137.5, 136.4, 136.3, 135.7, 128.6, 128.2, 128.1, 127.4, 127.2, 123.4, 121.4, 115.3, 113.5, 106.1, 98.6, 92.9, 85.6, 75.0, 74.3, 72.5, 70.8, 70.3, 70.1, 67.6, 63.2, 61.4, 20.5 (2C), 20.0 (2C); MS: *m/z* 984 $[M+H]^+$; Anal. Calcd for $C_{53}H_{49}N_3O_{16}$: C, 64.69; H, 5.02; N, 4.27. Found: C, 64.31; H, 5.34; N, 4.06.

5,3'-Bis-(1-(6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-5-yl)-4-(O-methylene)-1H-1,2,3-triazole)-3,7,4'-O-tribenzylquercetin (10b) A solution of **7** (100 mg, 0.15 mmol) and *azido*-sugar **1b** (102 mg, 0.36 mmol) in presence of DIPEA (0.025 ml, 0.15 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. White solid (179 mg, yield 92 %); mp=160–162 °C; IR (KBr) ν_{max}: 3029, 2924, 2833, 1660, 1581, 1467, 1334, 1162, 818, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.67 (d, *J*=6.0 Hz, 1H), 7.57 (d, *J*=8.4 Hz, 1H), 7.37–7.14 (m, 15H), 6.84 (d, *J*=9.0, 1H), 6.59 (s, 1H), 6.56 (s, 1H), 5.40 (d, *J*=4.5 Hz, 2H), 5.30–5.19 (m, 3H), 5.11–4.97 (m, 7H), 4.54–4.30 (m, 6H), 4.22–4.09 (m, 6H), 1.41–1.17 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 162.8, 159.3, 158.5, 150.4, 147.8, 143.6, 139.7, 136.9, 136.6, 135.6, 128.6, 128.1, 127.6, 127.3, 127.1, 124.6, 124.2, 123.8, 122.8, 114.9, 113.6, 109.7, 108.8, 98.1, 96.1, 94.4, 74.0, 70.9, 70.5, 70.2, 70.1, 67.0, 63.9, 50.3, 25.8, 24.7, 24.3; MS: *m/z* 1220 $[M+H]^+$; Anal. Calcd for $C_{66}H_{70}N_6O_{17}$: C, 65.01; H, 5.79; N, 6.89. Found: C, 65.27; H, 5.50; N, 6.55.

5,3'-Bis-(1-(methyl-2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranos-5-yl)-4-(O-methylene)-1H-1,2,3-triazole)-3,7,4'-O-tribenzylquercetin (10c) A solution of **7** (100 mg, 0.15 mmol) and *azido*-sugar **1c** (176 mg, 0.36 mmol) in presence of DIPEA (0.025 ml, 0.15 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. White solid (219 mg, yield 90 %); mp=156–158 °C; IR (KBr) ν_{max}: 3030, 2922, 2854, 1666, 1585, 1468, 1241, 1092, 1012, 846 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.75–7.59 (m, 2H), 7.41–7.24 (m, 46H), 6.91 (d, *J*=8.7, 1H), 6.66 (s, 1H), 6.62 (s, 1H), 5.38–5.34 (m, 2H), 5.17–4.46 (m, 25H), 4.12–3.98 (m, 5H), 3.40 (m, 2H), 3.16–3.04 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 162.8, 159.2, 158.5, 152.9, 150.4, 147.7, 143.9, 139.7, 138.4, 138.3, 137.8 (2C), 136.9, 136.5, 135.5, 128.6 (2C), 128.5, 128.4, 128.3, 128.1, 127.9, 127.6, 127.3, 127.1, 124.2, 123.7, 114.9, 113.6, 109.6, 97.8, 97.6, 94.5, 81.8, 81.6, 79.9, 77.9, 75.6, 74.8, 74.0, 73.2, 70.8, 70.4, 69.0, 63.3, 55.1, 50.7; MS: *m/z* 1628 $[M+H]^+$; Anal. Calcd for $C_{98}H_{94}N_6O_{17}$: C, 72.31; H, 5.82; N, 5.16. Found: C, 72.66; H, 5.43; N, 5.39.

5,3'-Bis-(1-(3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranos-5-yl)-4-(O-methylene)-1H-1,2,3-triazole)-3,7,4'-O-tribenzylquercetin (10d) A solution of **7** (100 mg, 0.15 mmol) and *azido*-sugar **1d** (120 mg, 0.36 mmol) in presence of DIPEA (0.025 ml, 0.15 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. White solid (198 mg, yield 94 %); mp=146–148 °C; IR (KBr) ν_{max}: 3042, 2931, 2830, 1670, 1456, 1528, 1231, 1064, 840, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.91 (s, 1H), 7.74–7.23

(m, 27H), 6.96 (d, J=8.4, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 5.86–5.81 (m, 2H), 5.73–5.54 (m, 4H), 5.38 (s, 2H), 5.27–5.10 (m, 11H), 4.22–4.16 (m, 9H), 1.28–1.25 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 170.2, 170.1, 169.9, 169.7, 168.8, 168.7, 162.8, 159.2, 158.5, 153.1, 150.4, 147.7, 144.7, 139.8, 136.9, 136.5, 135.6, 128.7, 128.5, 128.3, 128.1, 127.9 (2), 127.6, 127.1, 123.8, 123.0, 121.4, 113.7, 86.2, 74.0, 70.8, 70.6, 70.5, 67.7, 66.8, 66.7, 61.1, 20.4(2), 20.1(2); MS: m/z 1320 $[M+H]^+$; Anal. Calcd for $C_{74}H_{74}N_6O_{17}$: C, 67.36; H, 5.65; N, 6.37. Found: C, 67.09; H, 5.44; N, 6.69.

5,3'-Bis-(1-(2,3,4,6-Tetra-O-acetyl-β-D-glucoopyranosyl)-4-(O-methylene)-1H-1,2,3-triazole)-3,7,4'-O-tribenzylquercetin (10e) A solution of **7** (100 mg, 0.15 mmol) and *azido*-sugar **1e** (134 mg, 0.36 mmol) in presence of DIPEA (0.025 ml, 0.15 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. White solid (192 mg, yield 92 %); mp=163–165 °C; IR (KBr) ν_{max}: 3049, 2926, 2859, 1642, 1461, 1524, 1221, 1061, 833, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.91 (s, 1H), 7.74–7.65 (m, 2H), 7.45–7.23 (m, 16H), 6.96 (d, J=8.4, 1H), 6.70 (s, 1H), 6.60 (s, 1H), 5.82–5.67 (m, 3H), 5.60–5.41 (m, 4H), 5.38 (s, 2H), 5.26–5.13 (m, 8H), 4.22–4.13 (m, 8H), 2.16 (s, 6H), 2.02 (s, 6H), 2.00 (s, 6H), 1.84 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 168.6, 162.8, 159.1, 158.5, 150.4, 144.7, 136.5, 135.5, 134.4, 128.6, 128.5, 128.1, 127.6, 127.0, 121.5, 109.7, 98.1, 93.6, 86.1, 73.9, 70.7, 67.7, 66.8, 61.0, 20.5 (3C), 20.0 (3C); MS: m/z 1396 $[M+H]^+$; Anal. Calcd for $C_{70}H_{70}N_6O_{25}$: C, 60.26; H, 5.06; N, 6.02. Found: C, 59.87; H, 5.41; N, 5.79.

5,3'-Bis-(1-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)-4-(O-methylene)-1H-1,2,3-triazole)-3,7,4'-O-tribenzylquercetin (10f) A solution of **7** (100 mg, 0.15 mmol) and *azido*-sugar **1f** (223 mg, 0.36 mmol) in presence of DIPEA (0.025 ml, 0.15 mmol) and CuI (15 mg, 0.08 mmol) in dry CH_2Cl_2 was stirred at room temparature under argon atmosphenre for 12 h. White solid (255 mg, yield 90 %); mp=152–154 °C; IR (KBr) ν_{max}: 3034, 2928, 2846, 1668, 1482, 1462, 1258, 1075, 820, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (s, 1H), 8.09–7.91 (m, 8H), 7.82–7.80 (m, 2H), 7.73–7.63 (m, 4H), 7.45–7.13 (m, 44H), 6.92 (d, J=8.4, 1H), 6.57 (s, 1H), 6.53 (s, 1H), 6.31–5.90 (m, 7H), 5.32–4.91 (m, 10H), 4.67–4.48 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): 173.8, 165.9, 165.5, 164.9, 164.2, 162.7, 158.9, 158.3, 152.9, 150.3, 147.6, 144.8, 139.7, 136.8, 136.5, 135.7, 133.4, 133.0, 129.6, 129.1, 128.7, 128.2, 127.5, 127.2, 123.7, 123.0, 122.6, 121.5, 114.8, 113.5, 109.5, 94.49, 85.90, 75.32, 74.1, 73.1, 70.8, 68.8, 63.0, 62.6; MS: m/z 1892 $[M+H]^+$; Anal. Calcd for $C_{110}H_{86}N_6O_{25}$: C, 69.83; H, 4.58; N, 4.44. Found: C, 70.07; H, 4.95; N, 4.13.

Antileishmanial activity evaluation

Culture and maintenance of the parasites

A cloned line of *Leishmania donovani* (MHOM/IN/80/Dd8) promastigotes was used throughout this study. The promastigote forms of parasites were maintained *in vitro* in complete Dulbecco minimum essential medium (DMEM, Invitrogen, USA) supplemented with 10 % FBS (Invitrogen, USA) and antibiotics (gentamycin 20 μg/mL, streptomycin 100 μg/mL, penicillin 100 U/mL, Sigma Chemicals, USA) pH 7.2 in a BOD incubator at 25 °C.

Anti-promastigote assay

The compounds **8**–**10** were initially dissolved in dimethyl sulphoxide (DMSO; Sigma, USA) and further diluted with the complete DMEM medium. To examine the anti-leishmanial activity of **8**–**10**, logarithmic phase promastigotes of *L. donovani* (1×10^6 cells/100 μL/well were seeded in 96-well microtiter plate in the presence of 100 μL of compounds in each well (which were 2 fold serially diluted over seven points starting from 200 μg/mL to get a final concentration of compounds ranging from 100 to 1.56 μg/mL. The plates were further incubated for 48 h at 26 °C to assay activities of compounds. The viability of parasites was assayed colorimetrically by MTT assay, based on the reduction of the tetrazolium dye to insoluble formazan, as described previously with minor modifications.[28] Briefly, 25 μL of MTT (5 mg/mL) was added to each well and plates were incubated for 2 h at 37 °C. After incubation, plates were centrifuged at 3000 rpm for 5 min and supernatant was removed. The wells were washed with PBS and the precipitated formazan was dissolved in DMSO (150 μL) and plates absorbance was read at 540 nm on an ELISA plate reader. Three separate experiments in duplicate were performed each of compound and the concentration that inhibited viability by 50 % (IC_{50}) was determined by nonlinear regression analysis of Masterplex® QT 2010 using 5 logistic parameters.

Anti-amastigote assay

In order to evaluate the effect of compounds **8**–**10** on intracellular amastigotes, the J774.1 macrophage cell lines were used. Macrophages (5×10^5 cells/ml) in complete DMEM medium were plated onto 13-mm coverslips in 24-well plates for 2 h at 37 °C in a 5 % CO_2 atmosphere. Non adherent cells were removed by washing and cells were further incubated overnight. After incubation the adherent cells were infected with *L. donovani* metacyclic promastigotes (5×10^6/100 μL/well) at a parasite/macrophage ratio of 10:1 and incubated for 4–5 h at 37 °C in 5 % CO_2. Non internalized parasites were removed by extensive washing with PBS. Compounds (200 μL), 2 fold serially diluted with complete DMEM medium over six concentrations (50–1.56 μg/mL), were added to each well and then plates were further incubated for 48 h. After incubations, cells were washed with PBS, fixed in methanol, and stained with Giemsa stain. At least 200 macrophages per experiment were inspected by bright-field microscopy. The IC_{50} was estimated as described earlier. The selective Index (SI) for each compound was calculated as the ratio between cytotoxicity (CC_{50}) and the activity (IC_{50}) against *Leishmania* amastigotes.[18] These tests were performed in duplicate with three independent experiments.

Cytotoxicity assay

Briefly, J774.1 macrophage cell lines were maintained in complete DMEM medium at 37 °C in a humidified mixture of 5 % CO_2. Macrophages (1×10^6 cells/mL) were seeded in 96-well culture plates in the presence of compounds, which were two-fold, diluted serially over six concentrations (500–7.8125 μg/mL) in DMEM medium and further incubated for 48 h at 37 °C in a CO_2 incubator. The cell viability was determined using the MTT assay as described in earlier section. The control wells without any compounds (untreated cells) were used as control and considered as 100 percent viable cells.[29] The CC_{50} values were estimated by Masterplex QT 2010 as described earlier. This cytotoxicity assay was performed for compounds having antipromastigote activity, $IC_{50}<100$. Each assay was performed in duplicate with three independent experiments. Miltefosine was used as reference standard drug everywhere. A similar procedure was followed for cytotoxic assay of compounds against Statens Seruminstitut Rabbit Corneal (SIRC) and MIA PaCa pancreatic epithelial cell lines.

Data represented the mean±SD of duplicate samples from three independent assays. The IC_{50} values were calculated by using nonlinear regression analysis of Masterplex QT 2010 using 5 logistic parameters.

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References

1. Mishra, B.B., Tiwari, V.K.: Natural products: an evolving role in future drug discovery. Eur. J. Med. Chem. **46**, 4769–4807 (2011)
2. Wong, I.L.K., Chan, K.F., Chen, Y.F., Lun, Z.R., Chan, T.H., Chow, L.M.C.: *In vitro* and *in vivo* efficacy of novel flavonoid dimers against cutaneous leishmaniasis. Antimicrob. Agents Chemother. **58**, 3379–3388 (2014)
3. Singh, N., Mishra, B.B., Bajpai, S., Singh, R.K., Tiwari, V.K.: Natural product based leads to fight against leishmaniasis. Bioorg. Med. Chem. **22**, 18–45 (2014)
4. Mishra, B.B., Singh, R.K., Srivastava, A., Tripathi, V., Tiwari, V.K.: Fighting against leishmaniasis: search of alkaloids as future true potential anti-leishmanial agents. Mini-Rev. Med. Chem. **9**, 107–123 (2009)
5. Singh, Y., Spinelli, N., De Francq, E., Dumy, P.: A novel heterobifunctional linker for facile access to bioconjugates. Org. Biomol. Chem. **4**, 1413–1419 (2006)
6. Virta, P., Katajisto, J., Niittymaki, T., Lonnberg, H.: Solid-orted synthesis of oligomeric bioconjugates. Tetrahedron **59**, 5137–5174 (2003)
7. Dedola, S., Nepogodiev, S.A., Field, R.A.: Recent applications of the Cu^I-catalysed huisgen azide-alkyne 1,3-dipolar cycloaddition reaction in carbohydrate chemistry. Org. Biomol. Chem. **5**, 1006–1017 (2007)
8. Bock, V.D., Hiemstra, H., van-Maarseveen, J.H.: Cu^I-catalyzed alkyne-azide "click" cycloadditions from a mechanistic and synthetic perspective. Eur. J. Org. Chem. 51–68 (2006)
9. Binder, W.H., Sachsenhofer, R.: 'Click' chemistry in polymer and materials science. Macromol. Rapid Commun. **28**, 15–54 (2007)
10. Binder, W.H., Sachsenhofer, R.: Click' chemistry in polymer and material science: an update. Rapid. Commun. **29**, 952–981 (2008)
11. Kolb, H.C., Finn, M.G., Sharpless, K.B.: Click chemistry: diverse chemical function from a few good reactions. Angew. Chem. Int. Ed. **40**, 2004–2021 (2001)
12. Gallos, J.K., Koumbis, A.E.: 1,3-dipolar cycloadditions in the synthesis of carbohydrate mimics. Part 1: nitrile oxides and nitronates. Curr. Org. Chem. **7**, 397–426 (2003)
13. Koumbis, A.E., Gallos, J.K.: 1,3-dipolar cycloadditions in the synthesis of carbohydrate mimics. Part 2: nitrones and oximes. Curr. Org. Chem. **7**, 585–628 (2003)
14. Koumbis, A.E., Gallos, J.K.: 1,3-dipolar cycloadditions in the synthesis of carbohydrate mimics. Part 3: azides, diazo compounds and other dipoles. Curr. Org. Chem. **7**, 771–797 (2003)
15. Szeja, W., Swierk, P., Grynkiewicz, G., Rusin, A., Papaj, K.: An approach to *C*-glycosidic conjugates of isoflavones. Heterocycl. Commun. **19**, 133–138 (2013)
16. Xiao, J., Chen, T., Cao, H.: Advances in the biotechnological glycosylation of valuable flavonoids. Biotech. Adv. **32**, 1145–1156 (2014)
17. Olivero-Verbel, J., Pacheco-Londono, L.: Structure–activity relationships for the anti-HIV activity of flavonoids. J. Chem. Inf. Comput. Sci. **42**, 1241–1246 (2002)
18. Bae, E.A., Han, M.J., Lee, M., Kim, D.H.: *In vitro* inhibitory effect of aome flavonoids on rotavirus infectivity. Biol. Pharm. Bull. **23**, 1122–1124 (2000)
19. Gupta, P., Sharma, U., Gupta, P., Siripurapu, K.B., Maurya, R.: Evolvosides C-E, flavonol-4-*O*-triglycosides from *Evolvulus alsinoides* and their anti-stress activity. Bioorg. Med. Chem. **21**, 1116–1122 (2013)
20. Makino, T., Kanemaru, M., Okuyama, S., Shimizu, R., Tanaka, H., Mizukami, H.: Anti-allergic effects of enzymatically modified isoquercitrin (α-oligoglucosyl quercetin 3-*O*-glucoside), quercetin 3-*O*-glucoside, α-oligoglucosyl rutin, and quercetin, when administered orally to mice. J. Nat. Med. **67**, 881–886 (2013)
21. Kong, C.S., Lee, J.I., Kim, Y.A., Kim, J.A., Bak, S.S., Hong, J.W., Park, H.Y., Yea, S.S., Seo, Y.: Evaluation on anti-adipogenic activity of flavonoid glucopyranosides from *Salicornia herbacea*. Process Biochem. **47**, 1073–1078 (2012)
22. Huisgen, R.: 1,3-dipolar cyloadditions past and future. Angew. Chem. Int. Ed. **2**, 565–598 (1963)
23. Varki, A.: Biological roles of oligosaccharides: all of the theories are correct. Glycobiology **3**, 97–130 (1993)

24. Tiwari, V.K., Mishra, R.C., Sharma, A., Tripathi, R.P.: Carbohydrate based potential chemotherapeutic agents: recent developments and their scope in future drug discovery. Mini-Rev. Med. Chem. **12**, 1497–1519 (2012)
25. Cao, H., Hwang, J., Chen, X.: Carbohydrate-containing natural products in medicinal chemistry. In: Tiwari, V.K., Mishra, B.B. (eds.) Opportunity, challenge and scope of natural products in medicinal chemistry, pp. 166–180. Research Signpost Publication, Trivandrum (2011)
26. Kushwaha, D., Dwivedi, P., Kuanar, K.S., Tiwari, V.K.: Click reaction in carbohydrate chemistry: recent developments and future perspective. Curr. Org. Syn. **10**, 90–135 (2013)
27. Tiwari, V.K., Kumar, A., Schmidt, R.R.: Disaccharide-containing macrocycles by click chemistry and intramolecular glycosylation. Eur. J. Org. Chem. 2945–2956 (2012).
28. Kuijpers, B.H.M., Groothuys, S., Keerweer, A.R., Quaedflieg, P.J.L.M., Blaqυw, R.H., Van Delft, F.L., Rutjes, F.P.J.T.: Expedient synthesis of triazole-linked glycosyl amino acids and peptides. Org. Lett. **6**, 3123–3126 (2004)
29. Bouktaib, M., Lebrun, S., Atmani, A., Rolando, C.: Hemisynthesis of all the *O*-monomethylated analogues of quercetin including the major metabolites, through selective protection of phenolic functions. Tetrahedron **58**, 10001–10009 (2002)
30. Singh, A., Mishra, B.B., Kale, R.R., Kushwaha, D., Tiwari, V.K.: A convenient synthesis of novel glycosyl azetidines under mitsunobu reaction conditions. Synth. Commun. **42**, 3598–3613 (2012)
31. Mishra, K.B., Tiwari, V.K.: Click chemistry inspired synthesis of morpholine-fused triazoles. J. Org. Chem. **79**, 5752–5762 (2014)
32. Kumar, D., Mishra, A., Mishra, B.B., Tiwari, V.K.: Synthesis of glycoconjugate benzothiazoles *via* cleavage of benzotriazole ring. J. Org. Chem. **78**, 899–909 (2013)
33. Kushwaha, D., Singh, R.S., Tiwari, V.K.: Fluorogenic dual click derived bis-glycoconjugated triazolocoumarins for selective recognition of Cu(II) ion. Tetrahedron Lett. **55**, 4532–4536 (2014)
34. Kumar, D., Mishra, K.B., Mishra, B.B., Mondal, S., Tiwari, V.K.: Click chemistry inspired highly facile synthesis of triazolyl ethisterone glycoconjugates. Steroids **80**, 71–79 (2014)
35. Mishra, K.B., Mishra, B.B., Tiwari, V.K.: Efficient synthesis of ethisterone glycoconjugate *via* bis-triazole. Carbohydrate Res. **399**, 2–7 (2014)
36. Sousa, M.C., Varandas, R., Santos, R.C., Santos-Rosa, M., Alves, V., Salvador, J.A.R.: Antileishmanial activity of semisynthetic lupane triterpenoids betulin and betulinic acid derivatives: synergistic effects with miltefosine. PLoS ONE **9**, e89939 (2014)
37. Mishra, B.B., Gour, J.K., Kishore, N., Singh, R.K., Tripathi, V., Tiwari, V.K.: An antileishmanial prenyloxy-naphthoquinone from roots of plumbago zeylanica. Nat. Prod. Res. **27**, 480–485 (2013)
38. Mittra, B., Saha, A., Chowdhury, A.R., Pal, C., Mandal, S., Mukhopadhyay, S., Bandyopadhyay, S., Majumder, H.K.: Luteolin, an abundant dietary component is a potent anti-leishmanial agent that acts by inducing topoisomerase II-mediated kinetoplast DNA cleavage leading to apoptosis. Mol. Med. **6**, 527–541 (2000)
39. Lewin, G., Cojean, S., Guptac, S., Verma, A., Puri, S.K., Loiseau, P.M.: *In vitro* antileishmanial properties of new flavonoids against *Leishmania donovani*. Biomed. Prevent. Nutrit. **1**, 168–171 (2011)
40. Sundar, S., Olliaro, P.L.: Miltefosine in the treatment of leishmaniasis: clinical evidence for informed clinical risk management. Ther. Clin. Risk Manag. **3**, 733–740 (2007)