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Article

Synthesis and Biological Evaluation of New Eugenol-Derived 1,2,3-Triazoles as Antimycobacterial Agents

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Eugenol has diverse biological properties including antimycobacterial activity, and the triazole ring is an important heterocycle in antimycobacterial compounds. Therefore, this research aimed to synthesize novel eugenol-derived 1,2,3-triazole as antimycobacterial agents with interesting cytotoxic profile and pharmacological assets. Sixteen compounds were obtained and characterized by nuclear magnetic resonance (NMR), infrared (IR), and high-resolution mass spectrometry (HRMS). Among them, the best growth inhibition properties from a microdilution assay were observed for three derivatives: a benzylic ether (minimum inhibitory concentration (MIC) = 48.89 μM) against *Mycobacterium abscessus* (ATCC 19977), an *O*-galactosyde (MIC = 31.76 μM) against *Mycobacterium massiliense* (ATCC 48898) and a sulfonate (MIC = 88.64 μM) against *Mycobacterium fortuitum* (ATCC 6841). They can form biofilms, and the infection progression is challenging to control due to multi-drug resistance profiles against diverse antibiotics. In conclusion, the above-mentioned compounds represent starting points in the search of bioactive molecules against mycobacteria with low cytotoxicity and better pharmacological profiles.

Keywords: eugenol, rapid growing mycobacteria, 1,2,3-triazoles, mycobacterium

Introduction

Increasing bacterial resistance has been an emerging problem that can be correlated with the decline of investment in antibiotic research by the pharmaceutical industry. New antibiotics are usually reserved for the treatment of difficulty-manageable infections and are prescribed for a few days. Therefore, they are considered unprofitable in comparison with the drugs to treat chronic diseases.[1]

Additionally to this scenario, the antimicrobial consumption in animal breeding has been unequivocally linked to cases of multi-drug resistance.[2] Although bedaquiline was considered promising against *Mycobacterium tuberculosis* at its approval,[3] efflux-mediated bedaquiline resistance has already been identified in clinical management.[4]

Rapid growing mycobacteria (RGM) can form biofilms drastically affecting immunocompromised hosts, and the infection progression are challenging to control due to multi-drug resistance profiles against different antibiotics,[5] such as clarithromycin, imipenem,[6] rifampicin, isoniazid, ethambutol, pyrazinamide,[7] cefoxitin, and doxycycline.[8] *Mycobacterium fortuitum* is mainly present in skin, soft tissue and catheter associated infections,[9] while *Mycobacterium abscessus* noticeably accounts for pulmonary infections[10] and *Mycobacterium massiliense* for post-surgical ones.[11] Considering the reduced introduction of novel antibiotics in the market and the increasing resistance to the commonly used in mycobacterial infections, the urge

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for new antimycobacterial agents is a reality. Eugenol, a natural phenylpropanoid, is known to display a diverse group of biological activities including antifungal,[12] antiviral,[13] anticancer,[14] leishmanicidal[15] and antimycobacterial activity.[16] Concerning the interest in mycobacteria growth inhibition, the 1,2,3-triazole ring is an important heterocycle in medicinal chemistry and is present in compounds with prominent activity against *M. tuberculosis* strains, such as MDR-TB (multi-drug-resistant tuberculosis) and DR-TB (drug-resistant tuberculosis).[17-20] Despite the lower affinity of the 1,2,3-triazole ring when compared with its congeners, imidazole and 1,2,4-triazole, upon cytochromes P450 (CYPs), this moiety is still capable of a water-bridged connection upon the Fe^{III} of heme associated with a type II optical spectrum.[21] The water participation in such coordination style is also verified for the binding of azole antifungals onto mycobacterial enzymes CYP121 and CYP51.[22,23] Even though CYP121 is restricted to *M. tuberculosis* and essential for its viability,[24] other important CYPs including CYP144 and CYP125 are present in rapid growing mycobacteria showing affinity for the azoles as well. CYP125 is required in the invasion process of macrophages by a mycobacterium.[25] With these facts in mind, this work aimed to synthesize novel eugenol-derived 1,2,3-triazoles and evaluate their cytotoxic profiles and antimycobacterial activity (Figure 1).

Results and Discussion

Chemistry

Different functional groups were attached to the hydroxyl group of the eugenol phenol group to verify the influence of steric, electronic and solubility effects on activity and toxicity. Sixteen compounds were obtained in moderate to good yields (34-92%) and characterized by nuclear magnetic resonance (NMR) spectrometry, infrared (IR) spectroscopy, and high-resolution mass spectrometry (HRMS). The key intermediate **TS6** was furnished by adopting a six-step linear synthetic route starting with a silylation reaction to protect the phenolic hydroxyl group followed by hydroboration-oxidation of the alkene, mesylation and azidation reactions (Scheme 1). **TS1** was successfully obtained in 87% as a yellow oil by employing the silylating agent triisopropylsilyl chloride under microwave irradiation.[26,27] In the ^{1}H NMR spectrum, the hydrogens from the protecting group are represented by a multiplet and duplet at δ 1.31-1.19 and 1.11 ppm, respectively. Borane addition to **TS1** followed by alkaline oxidation led to the primary alcohol **TS2** in 80%.[28] The hydroxyl group is confirmed in the IR spectrum by the –OH stretch band noticed at 3350 cm^{-1} and the singlet at δ 1.65 ppm in ^{1}H NMR spectrum. By a reaction of **TS2** with mesyl chloride,[29,30] the nucleophilic attack of sodium azide was further favored furnishing the desired alkyl azide **TS4**.[31] The substantial withdrawing effect of the sulfonate ester in **TS3** is illustrated by the triplet at δ 4.20 ppm in ^{1}H spectrum that corresponds to –C$\underline{H_2}$SO$_2$Me from the alkyl chain.

Intermediate **TS4** was readily applied for the cycloaddition reaction promoted by copper with phenylacetylene.[32] A singlet at δ 7.70 ppm in the ^{1}H spectrum of **TS5** is attributed to the hydrogen from the triazole ring. To perform the deprotection of the phenolic group from eugenol, a practical protocol with tetrabutylammonium fluoride (TBAF) was considered.[33] A stretch band at 3521 cm^{-1} in the IR spectrum, the absence

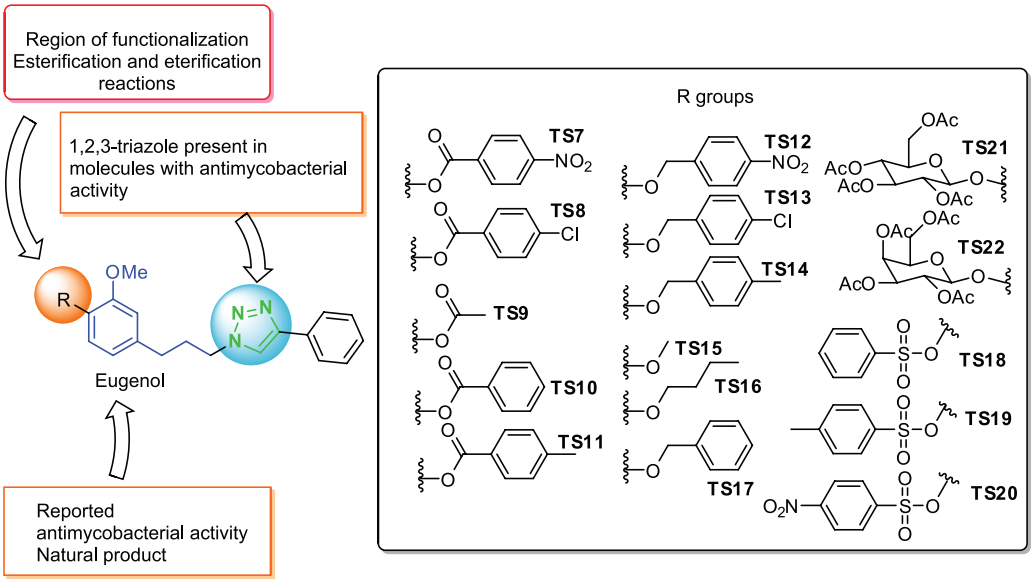
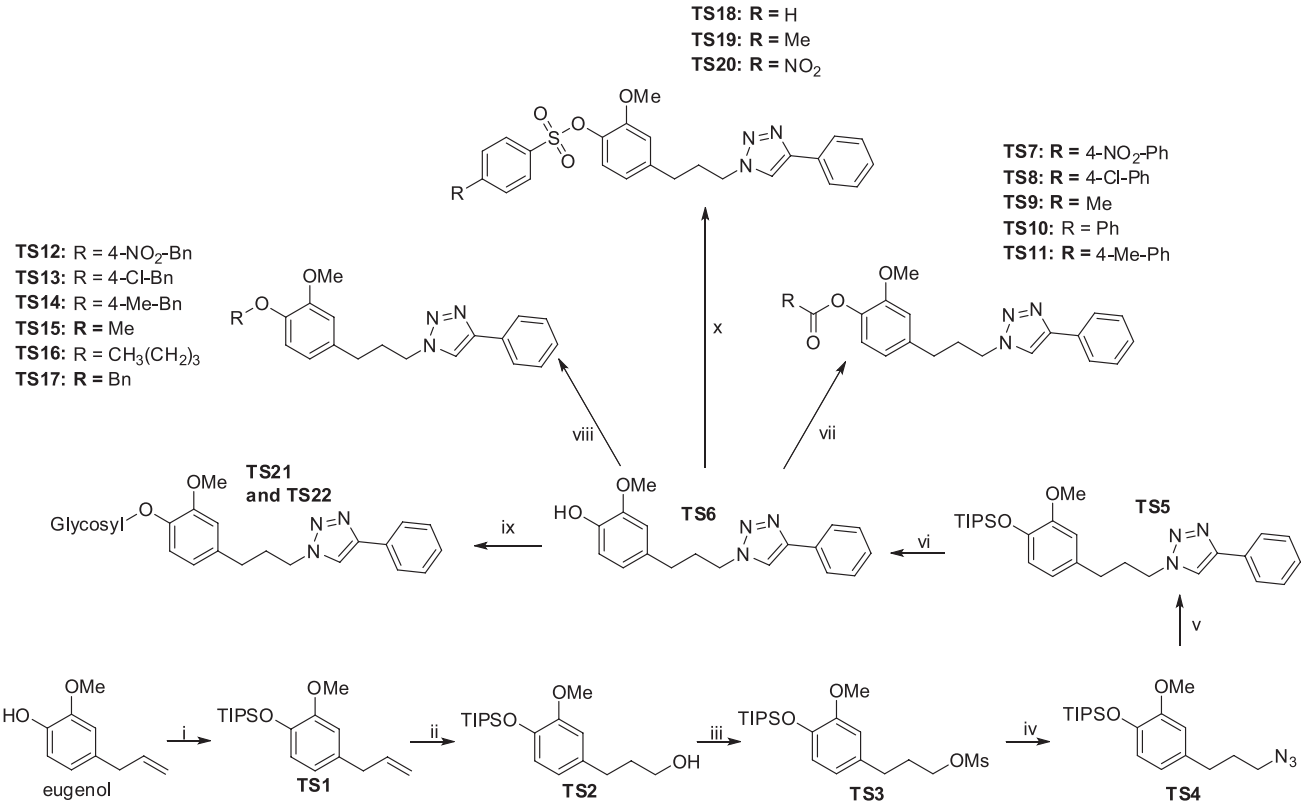


Figure 1. Eugenol-derived 1,2,3-triazoles.



Scheme 1. The employed synthetic route. Reagents and conditions: (*i*) TIPSCl, imidazole, MW, 8 min, 87%; (*ii*) $BH_3.SMe_2$, THF, 0 °C-r.t., followed by NaOH, H_2O_2, 0 °C-r.t., 80%; (*iii*) MsCl, Et_3N, DCM, 0 °C-r.t., 90%; (*iv*) NaN_3, DMF, 80 °C; (*v*) phenylacetylene, sodium ascorbate, copper acetate, DCM:H_2O 1:1, r.t., 96%; (*vi*) TBAF, THF, 0 °C, 20 min, 85%; (*vii*) acetyl chloride or benzoyl chloride, pyridine, DCM, 0 °C-r.t., except for **TS10** (Bz_2O, Et_3N, DCM, 4-DMAP, r.t.) and **TS11** (EDAC, 4-DMAP, DCM, *p*-toluic acid, r.t.), 40-92%; (*viii*) respective alkyl halide or benzyl halide, K_2CO_3, TBAB, H_2O, r.t., 37-61%; (*ix*) peracetylated glycosyl bromide or peracetylated galactosyl bromide, TBAB, $CHCl_3$, K_2CO_3 10% m/v, r.t., 34-35%; (*x*) respective benzenesulfonyl chloride, THF: H_2O, K_2CO_3 10% m/m, 0 °C-r.t., 52-90%.

of signals below δ 1.50 ppm for the protecting group hydrogens and the singlet at δ 5.57 ppm related to the phenolic hydrogen confirm the identity of **TS6**.

For the synthesis of esters **TS7**-**TS11**, the yield ranged from 40 to 92%. Acyl chlorides, benzoic anhydride, and *p*-toluic acid were employed according to the general procedures described by Kieć-Kononowicz *et al.*,[34] Keraani *et al.*,[35] and Pu *et al.*[36] In their IR spectra, the ester function is confirmed by the band stretch of C=O at 1760 (**TS11**), 1730 (**TS10**), 1760 (**TS9**), 1736 (**TS8**) and 1736 cm^{-1} (**TS7**).

The ethers **TS12**-**TS17** were synthesized in polar solvents with tetrabutylammonium bromide (TBAB, yields 37-61%).[37] In their IR spectra, C–O stretch from methoxyl/ether group is related to bands at 1263-1223 cm^{-1}. Singlets at δ 5.18, 5.07, 5.08 and 5.12 ppm are associated with the benzylic hydrogens as expected.

Concluding the library of synthesized compounds, sulfonate esters **TS18**-**TS20** (yields 52-90%) and glycosides **TS21** (yield 34%) and **TS22** (yield 35%) were accomplished by adopting the protocols of Lei *et al.*,[38] Conchie *et al.*,[39] and Zhu *et al.*,[40] respectively. Two bands at 1364-1348 and 1179-1171 cm^{-1} for each sulfonate ester refer to S=O stretch of the functional group. In the IR spectra of the glycosides, two strong bands at 1738 and 1743 cm^{-1} are associated with the C=O stretch of the acetyls. Complementary, their ^{13}C NMR spectra present signals at δ 170.6, 170.3, 169.4 and 169.4 for **TS21** and δ 170.6, 170.3, 169.4 and 169.42 ppm for **TS22** that are attributed to the carbonylic carbons. For the anomeric configuration in **TS22**, the coupling constant *J* 8.0 Hz in its ^1H NMR spectrum is conclusive of the diaxial coupling associated with a β configuration.[41]

Antimycobacterial activity

To assess the compounds' potential antimycobacterial properties, a microdilution assay was employed as the standard method, including *M. abscessus* (ATCC 19977), *M. massiliense* (ATCC 48898), and *M. fortuitum* (ATCC 6841).

Considering the minimum inhibitory concentration (MIC) breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) for RGM,[42]

MICs of sulfamethoxazole (SMZ) ≤ 150 and ≥ 300 μM refer to susceptible and resistant strains, respectively. For clarithromycin (CLR), susceptible, intermediate and resistant strains relate to MICs ≤ 2.7, 5.4, and ≥ 10.7 μM, respectively.[42] Therefore, among the tested strains, *M. fortuitum* is resistant to SMZ and CLR, and *M. abscessus* to CLR.

As shown in Table 1, the best growth inhibition properties from the microdilution assay against *M. abscessus* (ATCC 19977) were observed for **TS22** (MIC = 254.07 μM), **TS16** (MIC = 222.30 μM), **TS7** (170.39 μM), and **TS17** (MIC = 48.89 μM) regarding MIC = 21.39 and 31.59 μM of clarithromycin and sulfamethoxazole, respectively.

Table 1. Antimycobacterial activity of the synthesized compounds

Compound	MIC / μM		
	M. abscessus	*M. massiliense*	*M. fortuitum*
TS5	671.03	671.03	1342.07
TS6	N.A.	N.A.	N.A.
TS7	17039	681.57	681.57
TS8	N.A.	N.A.	N.A.
TS9	N.A.	N.A.	N.A.
TS10	1571.95	1571.95	196.49
TS11	N.A.	N.A.	N.A.
TS12	N.A.	N.A.	N.A.
TS13	N.A.	N.A.	N.A.
TS14	N.A.	N.A.	N.A.
TS15	N.A.	N.A.	N.A.
TS16	222.30	222.30	222.30
TS17	48.89	782.23	391.11
TS18	709.12	354.56	88.64
TS19	N.A.	N.A.	N.A.
TS20	N.A.	N.A.	N.A.
TS21	N.A.	N.A.	N.A.
TS22	254.07	31.76	127.03
CLR	21.39	1.34	42.78
SMZ	31.59	126.34	505.37

MIC: minimum inhibitory concentration; N.A.: no activity at the tested concentrations; CLR: clarithromycin; SMZ: sulfamethoxazole.

In general, absence of activity or its decreasing was associated with the compounds bearing a fourth *para* substituted aromatic ring with electron-withdrawing groups (–NO_2 and –Cl) or an electron-donating group (–CH_3). While the key-intermediate **TS6** bearing no substituent at the hydroxyl group was not active at the tested range, its silylated precursor, **TS5**, showed some inhibition. For the *M. massiliense* inhibition, **TS16** (MIC = 222.30 μM) and **TS22** (MIC = 31.76 μM) showed relevant activities even better than sulfamethoxazole for the glycoside. The presence of a glycosyl unity in **TS22** apparently is an interesting region to be maintained for further modifications. Although **TS22** and **TS21** are both glycosides, the galacto-configuration of **TS22** seemed to consistently imply in activity for all the tested strains despite the absence on inhibition by **TS21**. Against *M. fortuitum*, **TS16** (MIC = 222.30 μM), **TS10** (MIC = 196.49 μM), **TS22** (MIC = 127.03 μM) and **TS18** (MIC = 88.64 μM) displayed the best results mainly when confronted with the SMZ MIC resistant-type of 505.37 μM.

Considering the susceptibility of the same mycobacteria strains comprised in our study to available drugs assayed by the same method (CLSI M07-A10, 2015),[42] an interesting discussion can be made. Referring to the literature, the MIC of **TS17** (48.89 μM) against *M. abscessus* is noticeably inferior to what is observed for trimethoprim (55.11 μM), isoniazid (> 1866.68 μM), dapsone (257.75 μM), tigecycline (218.56 μM), meropenem (166.90 μM), doxycycline (72 μM), cefoxitin (74.86 μM), cefepime (133.18 μM) and ethambutol (156.62 μM).[43,44] Against *M. massiliense*, the MIC of **TS22** (31.76 μM) is only favorable if considered with sulfamethoxazole (252.68 μM) and clarithromycin (42.78 μM, resistant strain).[43,45] For *M. fortuitum*, **TS18** (MIC = 88.64 μM) can be highlighted over sulfamethoxazole (126.34 μM) and trimethoprim (881.79 μM), separately.[43]

The parameters listed on Table 2 were obtained via the SwissADME web tool.[46] Among the eugenol-derived 1,2,3-triazoles, five (**TS5**, **TS8**, **TS13**, **TS21**, and **TS22**) display a certain degree of violation (Table 2) for the Lipinski's rule (MlogP ≤ 4.15, molecular mass < 500 Da, hydrogen bond donor and acceptor groups ≤ 5 and ≤ 10, respectively).[47] Only **TS21** and **TS22** violate more than one rule (molecular masses and hydrogen bond acceptor number). The commercial drug clarithromycin is not in accordance with the same rules as well, a fact that does not exclude **TS22** for a potential candidate.

Cytotoxicity assay

The cytotoxicity of each compound to Vero cells (kidney cells of African green monkey) was evaluated. Comparing the compounds in terms of cytotoxicity (Table 3), **TS20** was the most toxic to Vero cells. Keeping the hydroxyl group without modifications in **TS6** lessened the cytotoxicity to the same cells apart getting no activity against the considered mycobacteria strains. The ether **TS17** exhibited high toxicity to *M. abscessus* with a selectivity index equal to 2.40 despite the other compounds. On the other hand, for *M. massiliense* and *M. fortuitum*, **TS22** was highlighted to be the most toxic compound among all to mycobacteria, with a selectivity index of 7.16 and 1.79, respectively.

Table 2. Drug-likeness and important parameters

Compound	Descriptor				
	MM / (g moL^{-1})	log $P_{o/w}$ [a] (MlogP)	H donor	H acceptor	Lipinski's violation
TS5	465.70	4.35	0	4	1
TS6	309.36	2.41	1	4	0
TS7	458.47	3.04	0	7	0
TS8	447.91	4.40	0	5	1
TS9	351.40	2.80	0	5	0
TS10	413.47	3.92	0	5	0
TS11	427.50	4.13	0	5	0
TS12	444.48	2.81	0	6	0
TS13	433.93	4.20	0	4	1
TS14	413.51	3.93	0	4	0
TS15	323.39	2.64	0	4	0
TS16	365.47	3.31	0	4	0
TS17	399.48	3.73	0	4	0
TS18	449.52	3.66	0	6	0
TS19	463.55	3.87	0	6	0
TS20	494.52	2.81	0	8	0
TS21	639.65	1.72	0	13	2
TS22	639.65	1.72	0	13	2
CLR	747.95	–0.54	4	14	2
SMZ	253.28	–0.15	2	4	0

[a]Lipophilicity descriptor. MM: molecular mass; log $P_{o/w}$: octanol water partition coefficient; CLR: clarithromycin; SMZ: sulfamethoxazole.

Conclusions

All in all, sixteen novel eugenol-derived 1,2,3-triazoles were obtained in moderate to good yields. The best antimycobacterial activity against RGM were observed for **TS17** (MIC = 48.89 μM) against *M. abscessus* (ATCC 19977), **TS22** (MIC = 31.76 μM) against *M. massiliense* (ATCC 48898), and **TS18** (MIC = 88.64 μM) against *M. fortuitum* (ATCC 6841). Therefore, our research group considers these compounds good prototypes in the search of bioactive molecules against rapid-growing mycobacteria of better cytotoxicity and pharmacological profiles.

Experimental

General information

Reagents and solvents employed for the reactions were reagent grade and used as purchased. All the reactions were monitored via thin layer chromatography (TLC) with a uniform layer of silica gel (Macherey-Nagel, DC-Fertigfolien ALUGRAM® Xtra Sil G/UV254). Column chromatography was performed using silica gel 60, 70-230 mesh Sorbline. ^{1}H and ^{13}C spectra were recorded on a Bruker AC-300 spectrometer at 300 and 75 MHz, respectively, using $CDCl_3$ (deuterated chloroform)

Table 3. Cytotoxicity to Vero cells and selectivity index

Compound	CC_{50} / μM	Selectivity index		
		M. abscessus	*M. massiliense*	*M. fortuitum*
TS5	62.16 ± 4.47	0.09	0.09	0.05
TS6	275.95 ± 23.11	–	–	–
TS7	114.22 ± 4.65	0.67	0.17	0.17
TS8	114.13 ± 11.14	–	–	–
TS9	105.55 ± 23.97	–	–	–
TS10	78.63 ± 2.06	0.05	0.05	0.40
TS11	68.91 ± 1.22	–	–	–
TS12	59.48 ± 0.38	–	–	–
TS13	67.13 ± 0.62	–	–	–
TS14	50.69 ± 5.80	–	–	–
TS15	86.05 ± 12.09	–	–	–
TS16	74.34 ± 5.86	0.33	0.33	0.33
TS17	117.42 ± 40.90	2.40	0.15	0.30
TS18	52.86 ± 1.00	0.07	0.15	0.60
TS19	42.13 ± 2.69	–	–	–
TS20	37.84 ± 2.34	–	–	–
TS21	61.36 ± 15.44	–	–	–
TS22	227.46 ± 21.62	0.90	7.16	1.79

CC_{50}: cytotoxic concentration for 50%; –: selectivity index was not calculated (no activity against the tested RGM strains). The best results are highlighted.

as solvent and TMS (tetramethylsilane) as the internal standard. IR data were recorded with a Thermo Scientific Nicolet-iS50 spectrometer with attenuated total reflectance (ATR) and the values are described in wave numbers ($\tilde{\upsilon}_{max}$, in cm^{-1}).

High-resolution mass spectra were obtained with a Bruker Daltonics micrOTOF QII/ESI-TOF (electrospray ionization time-of-flight). For the reactions carried out under microwave (MW) irradiation, a conventional microwave was used (LG MS3048G, output power 800 W, IEC60705). Melting point data was obtained with a Bücher 535 (0-300 °C) instrument, calibrated with vanillin P.A. Merck®.

Synthetic procedures

[2-Methoxy-4-(prop-2-en-1-yl)phenoxy]tris(propan-2-yl) silane (**TS1**)

A mixture of eugenol (1 equiv., 3.2 mmol), TIPSCl (1.5 equiv., 4.8 mmol) and imidazole (3 equiv., 9.6 mmol) in a round-bottom flask was subjected to microwave irradiation in turns of 20 s each until the total of 8 min. The mixture was washed with EtOAc (4 mL). The combined organic layers were quenched with $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 9.8:0.2) to give **TS1** as a light yellow oil, yield 87%, IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3078, 3056, 3037, 2943, 2892, 2865, 1638, 1605, 1584, 1510, 1463, 1282, 1230, 912, 881; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, 1H, *J* 8.0 Hz, Ar-H), 6.68 (d, 1H, *J* 2.1 Hz, Ar-H), 6.63 (dd, 1H, *J* 8.0, 2.1 Hz, Ar-H), 6.05-5.89 (m, 1H, CH_2–C<u>H</u>=CH_2), 5.11-5.06 (m, 1H, CH_2–CH=C<u>H</u>$_2$), 5.04 (t, 1H, *J* 1.4 Hz, CH_2–CH=C<u>H</u>$_2$), 3.80 (s, 3H, OCH_3), 3.33 (d, 2H, *J* 6.6 Hz, CH_2), 1.31-1.19 (m, 3H, CH–Si), 1.11 (d, 18H, *J* 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 143.8, 137.9, 133.0, 120.6, 120.2, 115.4, 112.7, 55.5, 39.9, 17.9, 12.9.

3-(3-Methoxy-4-{[tris(propan-2-yl)silyl]oxy}phenyl)propan-1-ol (**TS2**)

To the round-bottom flask containing **TS1** (1 equiv., 1.88 mmol) and tetrahydrofuran (THF, 11 mL), borane dimethyl sulfide (2 equiv., 3.76 mmol) was added dropwise under argon atmosphere. The mixture was stirred for 1 h at 0 °C and 1 h 30 min at room temperature. Then, 1 M NaOH (2.5 equiv., 4.7 mL) was cautiously added to this flask at 0 °C followed by 30% H_2O_2 (4.7 mL). The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. After, Et_2O was added and the combined organic layers were washed with a NaCl saturated solution, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 6:4) to give **TS2** as a yellow oil, yield 80%, IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3350, 3035, 2941, 2892, 2865, 1606, 1583, 1513, 1463, 1283, 1231; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, 1H, *J* 8.0 Hz, Ar-H), 6.70 (d, 1H, *J* 2.1 Hz, Ar-H), 6.64 (dd, 1H, *J* 8.0, 2.1 Hz, Ar-H), 3.81 (s, 3H, OCH_3), 3.67 (t, 2H, *J* 6.4 Hz, C<u>H</u>$_2$–OH), 2.70-2.61 (t, 2H, CH_2), 1.94-1.83 (m, 2H, CH_2), 1.65 (s, 1H, OH) 1.31-1.20 (m, 3H, C<u>H</u>–Si), 1.11 (d, 18H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 143.6, 134.9, 120.3, 120.2, 112.5, 62.3, 55.5, 34.3, 31.8, 17.9, 12.9.

[4-(3-Azidopropyl)-2-methoxyphenoxy]tris(propan-2-yl) silane (**TS3**)

To the round-bottom flask containing **TS2** (1 equiv., 1.5 mmol) and dry dichloromethane (DCM, 10 mL) at 0 °C under argon atmosphere, it was added triethylamine (3 equiv., 4.5 mmol) and methanesulfonyl chloride (2.5 equiv., 3.75 mmol) dropwise. The mixture was stirred at room temperature for 4 h and then washed with 1 M HCl, $NaHCO_3$, and a NaCl saturated solution. After multiple extractions with minimal quantities of DCM, the organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (DCM) to give **TS3** as a yellow oil, yield 90%, IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3031, 2942, 2892, 2865, 1605, 1583, 1514, 1464, 1351, 1273, 1232, 1172; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, 1H, *J* 8.0 Hz, Ar-H), 6.66 (d, 1H, *J* 2.1 Hz, Ar-H), 6.60 (dd, 1H, *J* 8.0, 2.1 Hz, Ar-H), 4.20 (t, 2H, *J* 6.3 Hz, C<u>H</u>$_2$OSO$_2$CH$_3$), 3.78 (s, 3H, OCH_3), 2.98 (s, 3H, CH_2OSO_2C<u>H</u>$_3$), 2.67 (t, 2H, *J* 7.4 Hz, CH_2), 2.10-1.98 (m, 2H, CH_2), 1.29-1.16 (m, 3H, C<u>H</u>–Si), 1.08 (d, 18H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 143.9, 133.3, 120.4, 112.5, 69.2, 55.5, 37.3, 31.1, 30.8, 17.9, 12.9.

3-(3-Methoxy-4-{[tris(propan-2-yl)silyl]oxy}phenyl)propyl methanesulfonate (**TS4**)

A mixture of sodium azide (2 equiv., 5.08 mmol) and **TS3** (1 equiv., 2.54 mmol) in dimethylformamide (DMF, 10 mL) was stirred for 2 h at 80 °C. After, EtOAc (10 mL) was added, and the mixture was washed with distilled water (4 × 5 mL) to remove DMF and traces of NaN_3. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give pure **TS4** without further purification. **TS4** was readily used in the next synthetic step.

1-[3-(3-Methoxy-4-{[tris(propan-2-yl)silyl]oxy}phenyl) propyl]-4-phenyl-1*H*-1,2,3-triazole (**TS5**)

To the round-bottom flask containing 5 mL of a sodium ascorbate solution (5 mL of distilled water, 0.16 mmol of

ascorbic acid, 0.16 mmol of sodium bicarbonate), **TS4** (1 equiv., 1.13 mmol) in DCM (5 mL), phenylacetylene (1.1 equiv., 1.13 mmol) and copper acetate (5% mmol phenylacetylene, 0.06 mmol) were added in this order. The mixture was stirred overnight at room temperature. Then, DCM (10 mL) was added, and the mixture was washed with distilled water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 6:4) to give **TS5** as a white solid, yield 96%, m.p. 74-80 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3130, 3056, 3034, 3002, 2944, 2892, 2864, 1582, 1512, 1468; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2H, *J* 8.3, 1.3 Hz, Ar-H), 7.70 (s, 1H, triazole-H), 7.46-7.39 (m, 2H, Ar-H), 7.37-7.29 (m, 1H, Ar-H), 6.80 (d, 1H, *J* 8.0 Hz, Ar-H), 6.66 (d, 1H, *J* 2.1 Hz, Ar-H), 6.61 (dd, 1H, *J* 8.0, 2.1 Hz, Ar-H), 4.38 (t, 2H, *J* 7.1 Hz, CH_2–N), 3.78 (s, 3H, OCH_3), 2.61 (t, 2H, *J* 7.4 Hz, CH_2), 2.26 (m, 2H, *J* 7.1 Hz, CH_2), 1.24 (m, 3H, CHSi), 1.09 (d, 18H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 147.7, 144.0, 133.1, 130.6, 128.9, 128.1, 125.7, 120.4 (2C), 119.6, 112.6, 55.5, 49.5, 32.1, 31.8, 17.9, 12.9.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenol (**TS6**)

TBAF (1.5 equiv., 0.69 mmol) was added to a round-bottom flask containing **TS5** (1 equiv., 0.46 mmol) in THF (14 mL) at 0 °C. The mixture was stirred at this temperature for 20 min, and after quenched with NH_4Cl (10 mL). Multiple extractions with minimal quantities of EtOAc were performed, and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 6:4) to give **TS6** as a light yellow solid, yield 85%, m.p. 76-80 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3521, 3141, 3102, 3065, 3030, 2964, 2928, 2850, 1605, 1517, 1461; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2H, Ar-H), 7.70 (s, 1H, triazole-H), 7.49-7.25 (m, 3H, Ar-H), 6.89-6.65 (m, 3H, Ar-H), 5.57 (s, 1H, OH), 4.39 (t, 2H, *J* 7.0 Hz, CH_2N), 3.86 (s, 3H, OCH_3), 2.62 (t, 2H, *J* 7.4 Hz, CH_2), 2.32-2.20 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 146.6, 144.1, 132.0, 130.6, 128.9, 128.2, 125.7, 121.0, 119.6, 114.4, 111.1, 55.9, 49.5, 32.2, 31.9.

General synthetic procedures to obtain **TS7**, **TS8** and **TS9**

The corresponding benzoyl chloride (1.5 equiv., 0.34 mmol, **TS7** (4-nitrobenzoyl chloride), **TS8** (4-chlorobenzoyl chloride)) or acetyl chloride (1.5 equiv., 0.34 mmol, **TS9**) were added to a round-bottom flask containing **TS6** (1 equiv., 0.23 mmol) in pyridine (2 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. After, DCM was added. The mixture was washed with cold 2% HCl and then with $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/EtOAc 6:4) to give **TS7**, **TS8**, and **TS9**.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl 4-nitrobenzoate (**TS7**)

Yellow solid, yield 41%, m.p. 100-110 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3106, 3079, 3052, 3019, 2952, 2924, 2852, 1736, 1526, 1510, 1346; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40-8.29 (m, 4H, Ar-H), 7.88-7.80 (m, 2H, Ar-H), 7.75 (s, 1H, triazole-H), 7.48-7.24 (m, 3H, Ar-H), 7.13-6.79 (m, 3H, Ar-H), 4.44 (t, 2H, *J* 6.9 Hz, CH_2N), 3.80 (s, 3H, OCH_3), 2.71 (t, 2H, *J* 7.5 Hz, CH_2), 2.39-2.26 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 151.0, 150.8, 147.9, 139.8, 138.0, 134.9, 131.4, 130.6, 128.9, 128.2, 125.7, 123.7, 122.6, 120.6, 119.6, 112.9, 55.9, 49.5, 32.5, 31.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 459.1590, found: 459.1639.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl 4-chlorobenzoate (**TS8**)

White solid, yield 50%, m.p. 100-116 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3132, 3077, 3052, 2995, 2949, 2852, 1736, 1509, 1459; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17-8.11 (m, 2H, Ar-H), 7.87-7.82 (m, 2H, Ar-H), 7.75 (s, 1H, triazole-H), 7.51-7.40 (m, 4H, Ar-H), 7.34 (m, 1H, *J* 7.3, 1.3 Hz, Ar-H), 7.07 (d, 1H, *J* 7.9 Hz, Ar-H), 6.83 (s, 1H, Ar-H), 6.80 (d, 1H, *J* 1.9 Hz, Ar-H), 4.44 (t, 2H, *J* 6.9 Hz, CH_2N), 3.80 (s, 3H, OCH_3), 2.70 (t, 2H, *J* 7.5 Hz, CH_2), 2.43-2.19 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 151.2, 147.9, 140.0, 139.3, 138.2, 131.7, 131.5, 130.6, 128.9, 128.2, 127.9, 125.7, 122.8, 120.6, 119.6, 112.9, 56.0, 49.5, 32.5, 31.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 448.1350, found: 448.1424.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl acetate (**TS9**)

Yellow solid, yield 40%, m.p. 110-115 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3130, 3037, 2978, 2921, 2850, 1760, 1508; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2H, *J* 8.2, 1.7 Hz, Ar-H), 7.74 (s, 1H, triazole-H), 7.49-7.20 (m, 3H, Ar-H), 6.96 (d, 1H, *J* 7.9 Hz, Ar-H), 6.80-6.73 (m, 2H, Ar-H), 4.41 (t, 2H, *J* 7.0 Hz, CH_2N), 3.81 (s, 3H, OCH_3), 2.66 (t, 2H, *J* 7.5 Hz, CH_2), 2.34-2.23 (m, 5H, CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 151.1, 147.8, 139.1, 138.2, 130.6, 128.9, 128.2, 125.7, 122.8, 120.5, 119.6, 112.7, 55.9, 49.5, 32.4, 31.7, 20.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 352.1583, found: 352.1656.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl benzoate (**TS10**)

To a round-bottom flask containing **TS6** (1 equiv., 0.26 mmol) in DCM (2 mL) was added Et_3N (2.3 equiv., 0.59 mmol) followed by benzoic anhydride (2.1 equiv., 0.54 mmol) and 4-dimethylaminopyridine (4-DMAP, 0.1 equiv., 0.026 mmol). The mixture was stirred at room temperature for 5 h. After, DCM (4 mL) was added and the mixture was washed with a saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 7:3) to give **TS10** as a light yellow solid, yield 92%, m.p. 75-82 °C; IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3075, 3057, 2980, 2966, 2946, 2913, 2867, 1730, 1600, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25-8.18 (m, 2H, Ar-H), 7.84 (m, 2H, *J* 8.2, 1.8 Hz, Ar-H), 7.75 (s, 1H, triazole-H), 7.66-7.59 (m, 1H, Ar-H), 7.54-7.39 (m, 4H, Ar-H), 7.37-7.30 (m, 1H, Ar-H), 7.08 (d, 1H, *J* 7.9 Hz, Ar-H), 6.83 (s, 1H, Ar-H), 6.79 (d, *J* 1.9 Hz, 1H, Ar-H), 4.42 (t, 2H, *J* 7.0 Hz, CH_2N), 3.79 (s, 3H, OCH_3), 2.69 (t, 2H, *J* 7.5 Hz, 2H, CH_2), 2.37-2.25 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 151.3, 147.8, 139.2, 138.4, 133.5, 130.6, 130.3, 129.4, 128.9, 128.5, 128.2, 125.9, 125.7, 122.9, 120.6, 119.7, 112.9, 56.0, 49.5, 32.5, 31.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 414.1739, found: 414.1815.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl 4-methylbenzoate (**TS11**)

To a round-bottom flask containing *p*-toluic acid (1 equiv., 0.23 mmol) in DCM (3 mL), **TS6** (1 equiv., 0.23 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC, 1.3 equiv., 0.25 mmol), and 4-DMAP (0.25 equiv., 0.06 mmol) were added. The mixture was stirred at room temperature for 24 h. After, $NaHCO_3$ (saturated solution, 4 mL) was added, and extractions (3×) with minimal quantities of DCM were performed. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 7:3) to give **TS11** as a white solid, yield 60%, m.p. 80-95 °C; IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3090, 3050, 3031, 2959, 2923, 2852, 1736, 1610, 1508; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 2H, *J* 8.2 Hz, Ar-H), 7.87-7.81 (m, 2H, Ar-H), 7.75 (s, 1H, triazole-H), 7.43 (t, 2H, *J* 7.4 Hz, Ar-H), 7.37-7.25 (m, 3H, Ar-H), 7.10-6.78 (m, 3H, Ar-H), 4.44 (t, 2H, *J* 7.0 Hz, CH_2N), 3.79 (s, 3H, OCH_3), 2.70 (t, 2H, *J* 7.5 Hz, CH_2), 2.44 (s, 3H, CH_3), 2.38-2.26 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 151.4, 147.8, 144.3, 139.1, 138.5, 130.6, 130.3, 129.2, 128.9, 128.2, 126.7, 125.7, 123.0, 120.5, 119.6, 112.9, 56.0, 49.5, 32.5, 31.7, 21.8; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 428.1896, found: 428.1973.

General synthetic procedures to obtain **TS12**, **TS13**, **TS14**, **TS15**, **TS16** and **TS17**

To a round-bottom flask containing **TS6** (1 equiv., 0.23 mmol) and the respective alkyl halide or benzyl halide (1.2 equiv., 0.27 mmol, **TS12** (4-nitrobenzyl bromide), **TS13** (4-clorobenzyl chloride), **TS14** (4-methylbenzyl chloride), **TS15** (methyl iodide), **TS16** (*n*-butyl bromide), and **TS17** (benzyl bromide)) in water (3 mL), TBAB (1 equiv., 0.23 mmol) and K_2CO_3 (2 equiv., 0.45 mmol) were added. The reaction mixtures were stirred at room temperature for 36 h. After, extractions with DCM (3×) were performed for each reaction, and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/EtOAc 7:3) to furnish **TS12**, **TS13**, **TS14**, **TS15**, **TS16** and **TS17**.

1-(3-{3-Methoxy-4-[(4-nitrophenyl)methoxy]phenyl}propyl)-4-phenyl-1*H*-1,2,3-triazole (**TS12**)

Yellow solid, yield 45%, m.p. 125-130 °C; IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3122, 3062, 2915, 2848, 1604, 1589, 1512, 1345, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25-8.19 (m, 2H, Ar-H), 7.85-7.79 (m, 2H, Ar-H), 7.71 (s, 1H, triazole-H), 7.63-7.57 (m, 2H, Ar-H), 7.46-7.38 (m, 2H, Ar-H), 7.36-7.24 (m, 1H, Ar-H), 6.79-6.64 (m, 3H, Ar-H), 5.18 (s, 2H, OCH_2), 4.40 (t, 2H, *J* 7.1 Hz, CH_2N), 3.89 (s, 3H, OCH_3), 2.63 (t, 2H, *J* 7.4 Hz, CH_2), 2.27 (m, 2H, *J* 7.1 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.8, 147.5, 146.0, 144.9, 134.3, 130.6, 128.9, 128.2, 127.5, 125.7, 123.8, 120.6, 119.5, 114.7, 112.5, 70.1, 56.0, 49.5, 32.2, 31.8; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 444.1797, found: 445.1872.

1-(3-{4-[(4-Chlorophenyl)methoxy]-3-methoxyphenyl} propyl)-4-phenyl-1*H*-1,2,3-triazole (**TS13**)

White solid, yield 61%, m.p. 90-95 °C; IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3120, 3092, 3054, 2933, 2894, 2850, 1589, 1513, 1463, 1263, 1232; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 2H, *J* 7.8 Hz, Ar-H), 7.71 (s, 1H, triazole-H), 7.47-7.29 (m, 7H, Ar-H), 6.82-6.63 (m, 3H, Ar-H), 5.07 (s, 2H, OCH_2), 4.39 (t, 2H, *J* 7.0 Hz, CH_2N), 3.87 (s, 3H, OCH_3), 2.63 (t, 2H, *J* 7.4 Hz, CH_2), 2.34-2.19 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 147.8, 146.4, 135.8, 133.7, 133.6, 130.6, 128.9, 128.7 (2C), 128.2, 125.7, 120.3, 119.5, 114.5, 112.4, 70.5, 56.0, 49.5, 32.1, 31.8; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 434.1557, found: 434.1628.

1-(3-{3-Methoxy-4-[(4-methylphenyl)methoxy]phenyl} propyl)-4-phenyl-1*H*-1,2,3-triazole (**TS14**)

Light yellow solid, yield 57%, m.p. 88-92 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3131, 3052, 2920, 2871, 2853, 1606, 1589, 1514, 1465, 1381, 1261, 1224; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.79 (m, 2H, Ar-H), 7.70 (s, 1H, triazole-H), 7.47-7.39 (m, 2H, Ar-H), 7.35-7.26 (m, 2H, Ar-H), 7.16 (d, 2H, *J* 7.8 Hz, Ar-H), 6.85-6.78 (m, 1H, Ar-H), 6.72 (d, 1H, *J* 2.0 Hz, Ar-H), 6.65 (dd, 1H, *J* 8.1, 2.0 Hz, Ar-H), 5.08 (s, 2H, OCH_2), 4.38 (t, 2H, *J* 7.0 Hz, CH_2N), 3.87 (s, 3H, OCH_3), 2.61 (t, 2H, *J* 7.4 Hz, CH_2), 2.34 (s, 3H, CH_3), 2.24 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 147.8, 146.8, 137.5, 134.2, 133.2, 130.7, 129.2, 128.9, 128.2, 127.4, 125.7, 120.3, 119.6, 114.4, 112.4, 71.1, 56.0, 49.5, 32.1, 31.8, 21.2; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 414.2103, found: 414.2175.

1-[3-(3,4-Dimethoxyphenyl)propyl]-4-phenyl-1*H*-1,2,3-triazole (**TS15**)

White solid, yield 37%, m.p. 98-105 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3130, 3095, 3070, 3001, 2927, 2850, 2829, 1606, 1588, 1514, 1463, 1231, 1258; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.78 (m, 2H, Ar-H), 7.71 (s, 1H, triazole-H), 7.46-7.40 (m, 2H, Ar-H), 7.35 (m, 1H, Ar-H), 6.83-6.69 (m, 3H, Ar-H), 4.40 (t, 2H, *J* 7.0 Hz, CH_2N), 3.86 (d, 6H, OCH_3), 2.64 (t, 2H, *J* 7.4 Hz, CH_2), 2.35-2.21 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 147.8, 147.6, 132.7, 130.6, 128.9, 128.2, 125.7, 120.3, 119.5, 111.8, 111.4, 55.9 (2C), 49.5, 32.1, 31.9; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 324.1634, found: 324.1705.

1-[3-(4-Butoxy-3-methoxyphenyl)propyl]-4-phenyl-1*H*-1,2,3-triazole (**TS16**)

White solid, yield 53%, m.p. 67-74 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3114, 3084, 3063, 2931, 2867, 1606, 1588, 1514, 1463, 1257, 1231; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2H, Ar-H), 7.71 (s, 1H, triazole-H), 7.42 (t, 2H, *J* 7.4 Hz, Ar-H), 7.33 (m, 1H, Ar-H), 6.84-6.67 (m, 3H, Ar-H), 4.40 (t, 2H, *J* 7.0 Hz, CH_2N), 3.98 (t, 2H, CH_2O), 3.85 (s, 3H, OCH_3), 2.63 (t, 2H, *J* 7.3 Hz, CH_2), 2.27 (m, 2H, *J* 7.1 Hz, CH_2), 1.86-1.75 (m, 2H, CH_2O), 1.56-1.41 (m, 2H, CH_2), 0.97 (t, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 147.8, 147.2, 132.7, 130.6, 128.9, 128.2, 125.7, 120.4, 119.6, 113.2, 112.3, 68.9, 56.1, 49.6, 32.1, 31.8, 31.3, 19.2, 13.9; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 366.2103, found: 366.2179.

1-{3-[4-(Benzyloxy)-3-methoxyphenyl]propyl}-4-phenyl-1*H*-1,2,3-triazole (**TS17**)

White solid, yield 50%, m.p. 100-107 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3113, 3083, 3030, 2922, 2869, 2851, 1589, 1511, 1461, 1261, 1223; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, 2H, *J* 8.3, 1.3 Hz, Ar-H), 7.71 (s, 1H, triazole-H), 7.46-7.30 (m, 8H, Ar-H), 6.82 (d, 1H, *J* 8.1 Hz, Ar-H), 6.73 (d, 1H, *J* 2.0 Hz, Ar-H), 6.66 (dd, 1H, *J* 8.1, 2.0 Hz, Ar-H), 5.12 (s, 2H, CH_2O), 4.39 (t, 2H, CH_2N), 3.88 (s, 3H, OCH_3), 2.63 (t, 2H, CH_2), 2.27 (q, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 147.7, 146.8, 137.3, 133.4, 130.5, 128.9, 128.5, 128.2, 127.8, 127.3, 125.7, 120.3, 119.6, 114.4, 112.4, 71.2, 56.1, 49.6, 32.1, 31.8; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 400.1946, found: 400.2019.

General synthetic procedures to obtain **TS18**, **TS19** and **TS20**

The respective benzenesulfonyl chloride (1.01 equiv., 0.23 mmol, **TS18** (benzenesulfonyl chloride), **TS19** (4-toluenesulfonyl chloride) and **TS20** (4-nitrobenzenesulfonyl chloride)) in THF (0.33 mL) was added dropwise to the round-bottom flask containing **TS6** (1 equiv., 0.23 mmol) in THF (0.2 mL) and K_2CO_3 10% m/m (1.88 equiv., 0.42 mmol) at 0 °C. The reactions were stirred at room temperature for 2 h. After, EtOAc (4 mL) was added, and the mixtures were washed with distilled water (3 × 2 mL). The organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/EtOAc 7:3) to furnish **TS18**, **TS19** and **TS20**.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl benzenesulfonate (**TS18**)

Light brown oil, yield 90%, IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3140, 3061, 3004, 2931, 2879, 2854, 1603, 1506, 1464, 1364, 1289, 1278, 1175; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.79 (m, 4H, Ar-H), 7.74 (s, 1H, triazole-H), 7.68-7.59 (m, 1H, Ar-H), 7.54-7.38 (m, 4H, Ar-H), 7.37-7.29 (m, 1H, Ar-H), 7.06 (d, 1H, *J* 8.2 Hz, Ar-H), 6.71 (dd, 1H, *J* 8.2, 1.9 Hz, Ar-H), 6.65 (d, 1H, *J* 1.9 Hz, Ar-H), 4.39 (t, 2H, *J* 6.9 Hz, CH_2N), 3.50 (s, 3H, OCH_3), 2.63 (t, 2H, *J* 7.6 Hz, CH_2), 2.33-2.18 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 147.9, 140.6, 136.8, 136.3, 133.9, 130.5, 128.9, 128.7, 128.6, 128.2, 125.7, 124.1, 120.4, 119.6, 112.9, 55.5, 49.4, 32.4, 31.6; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 450.1409, found: 450.1486.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl 4-methylbenzene-1-sulfonate (**TS19**)

Light yellow solid, yield 53%, m.p. 115-120 °C; IR (ATR) $\bar{\upsilon}_{max}$ / cm^{-1} 3141, 3067, 3008, 2941, 2922, 2859, 1604, 1594, 1506, 1465, 1360, 1291, 1269, 1171; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H, Ar-H), 7.75 (s, 1H, triazole-H), 7.75-7.70 (m, 2H, Ar-H), 7.46-7.35 (m, 2H,

Ar-H), 7.35-7.25 (m, 3H, Ar-H), 7.03 (d, 1H, *J* 8.2 Hz, Ar-H), 6.69 (dd, 1H, *J* 8.2, 1.9 Hz, Ar-H), 6.65 (d, 1H, *J* 1.9 Hz, Ar-H), 4.37 (t, 2H, *J* 6.9 Hz, CH_2N), 3.52 (s, 3H, OCH_3), 2.61 (t, 2H, *J* 7.5 Hz, CH_2), 2.42 (s, 3H, CH_3), 2.30-2.17 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 147.8, 145.0, 140.5, 136.8, 133.3, 130.6, 129.4, 128.9, 128.6, 128.2, 125.7, 123.9, 120.3, 119.7, 113.0, 55.6, 49.4, 32.4, 31.5, 21.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 464.1566, found: 464.1733.

2-Methoxy-4-[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl] phenyl 4-nitrobenzene-1-sulfonate (**TS20**)

Yellow solid, yield 59%, m.p. 110-115 °C; IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3133, 3102, 3065, 3033, 3005, 2927, 2856, 1603, 1532, 1506, 1464, 1381, 1348, 1288, 1260, 1179; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37-8.30 (m, 2H, Ar-H), 8.10-8.03 (m, 2H, Ar-H), 7.84-7.78 (m, 2H, Ar-H), 7.74 (s, 1H, triazole-H), 7.45-7.37 (m, 2H, Ar-H), 7.35-7.30 (m, 1H, Ar-H), 7.12 (d, 1H, *J* 8.2 Hz, Ar-H), 6.77-6.72 (m, 1H, Ar-H), 6.67 (d, 1H, *J* 1.8 Hz, Ar-H), 4.39 (t, 2H, *J* 6.9 Hz, CH_2N), 3.50 (s, 3H, OCH_3), 2.67-2.60 (t, 2H, CH_2), 2.31-2.19 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 150.8, 147.9, 142.0, 141.3, 136.4, 130.5, 129.9, 128.9, 128.3, 125.7, 124.0, 123.9, 120.7, 119.6, 113.1, 55.5, 49.4, 32.4, 31.5; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 495.1260, found: 495.1333.

General synthetic procedures to obtain **TS21** and **TS22**

A mixture of **TS6** (1 equiv., 0.26 mmol) in $CHCl_3$ (4 mL), K_2CO_3 10% m/v (8.8 equiv., 2.29 mmol) and TBAB (0.3 equiv., 0.08 mmol) was added dropwise from an addition funnel to a round-bottom flask containing 2,3,4,6-tetra-*O*-acethyl-alpha-D-glucopyranosyl bromide or 2,3,4,6-tetra-*O*-acetyl-alpha-D-galactopyranosyl bromide (1.1 equiv., 0.29 mmol) at room temperature. Additional 0.5 equiv. of peracetylated glycosyl or galactosyl bromide was added after 20 and 32 h of stirring at room temperature. Then, the mixtures were poured into ice water, and concentrated HCl was added until pH = 4-5. The organic layers were washed with distilled water (3 × 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane/EtOAc 6:4) to furnish **TS21** and **TS22**.

4-[3-(4-Phenyl-1*H*-1,2,3-triazol-1-il)propyl]-2-methoxy-phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glicopyranoside (**TS21**)

White solid, yield 34%, m.p. 115-119 °C; IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3089, 2990, 2952, 2924, 2852, 1747, 1738, 1595, 1515, 1467, 1252, 1217; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.79 (m, 2H, Ar-H), 7.72 (s, 1H, triazole-H), 7.46-7.38 (m, 2H, Ar-H), 7.36-7.29 (m, 1H, Ar-H), 7.04 (d, 1H, *J* 8.0 Hz, Ar-H), 6.71 (d, 1H, *J* 1.9 Hz, Ar-H), 6.68 (dd, 1H, *J* 8.1, 2.0 Hz, Ar-H), 5.27-5.24 (m, 2H, CH), 5.19-5.11 (m, 1H, CH), 4.92-4.86 (m, 1H, CH), 4.39 (t, 2H, *J* 7.0 Hz, CH_2N), 4.21 (dd, 2H, *J* 12.0, 6.0 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.73 (m, 1H, CH), 2.63 (t, 2H, *J* 7.4 Hz, CH_2), 2.26 (m, 2H, *J* 7.0 Hz, CH_2), 2.07-2.02 (m, 12H, $OCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.3, 169.4 (2C), 150.7, 147.8, 144.5, 136.9, 130.6, 128.9, 128.2, 125.7, 120.5, 119.6, 113.1, 101.0, 72.6, 71.9, 71.2, 68.4, 61.9, 56.1, 49.5, 32.3, 31.7, 20.7, 20.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 640.2428, found: 640.2505.

4-[3-(4-Phenyl-1*H*-1,2,3-triazol-1-il)propyl]-2-methoxy-phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**TS22**)

Light yellow oil, yield 35%, IR (ATR) $\tilde{\upsilon}_{max}$ / cm^{-1} 3137, 2958, 2937, 2873, 1743, 1593, 1512, 1465, 1212; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.80 (m, 2H, Ar-H), 7.72 (s, 1H, triazole-H), 7.46-7.39 (m, 2H, Ar-H), 7.37-7.30 (m, 1H, Ar-H), 7.05 (d, 1H, *J* 8.1 Hz, Ar-H), 6.72 (d, 1H, *J* 2 Hz, Ar-H), 6.68 (dd, 1H, *J* 8.1, 2.0 Hz, Ar-H), 5.51-5.40 (m, 2H, CH), 5.07 (dd, 1H, *J* 10.5, 3.4 Hz, CH), 4.84 (d, 1H, *J* 8 Hz, CH), 4.40 (t, 1H, *J* 7.0 Hz, CH_2N), 4.22-4.09 (m, 2H, CH_2), 3.93 (td, 1H, CH), 3.80 (s, 3H, CH_3), 2.64 (t, 2H, *J* 7.4 Hz, CH_2), 2.28 (m, 1H, CH_2), 2.17-2.00 (m, 12H, $OCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 170.2, 169.6, 150.7, 147.8, 144.7, 136.8, 130.6, 128.9, 128.2, 125.7, 120.5, 119.5, 113.1, 101.6, 70.9, 70.8, 68.7, 66.9, 61.2, 56.1, 49.5, 32.3, 31.7, 20.8, 20.7; HRMS (ESI-TOF) *m/z* calculated for $[M + H]^+$: 640.2428, found: 640.2501.

Microdilution assay

To assess the antimycobacterial potential of synthesized compounds, the broth microdilution assay (CLSI M07-A10, 2015)[42] with the strains *Mycobacterium abscessus* (ATCC 19977), *Mycobacterium fortuitum* (ATCC 6841) and *Mycobacterium massiliense* (ATCC 48898) was adopted. Dilutions (dilution factor = 2) in medium Mueller Hinton (MH) from dimethyl sulfoxide (DMSO) solutions of the test compounds were applied to obtain different concentrations. Therefore, eight concentrations at the range 2755-19.53 μg mL^{-1} were tested for each compound. Mycobacterial suspensions at 0.5 McFarland scale were prepared from cultivated strains in medium Lowenstein-Jensen. To obtain the final inoculum solution at 5×10^5 CFU mL^{-1}, 50 mL of mycobacterial suspension was transferred to a test tube containing 9.95 mL of Mueller Hinton broth. 100 μL of the final inoculum and 100 μL of

compound solution were distributed in each well of the microplate. It was incubated at 37 °C for 72 h. For the reading step, the lowest concentration associated with complete visible inhibition of mycobacterial growth was defined as the MIC.

Cytotoxicity assay

The test compounds cytotoxicity were evaluated to Vero cells (kidney cells extracted from African green monkeys) employing the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay. The cell suspension of Vero cells at a concentration of 2.4 × 106 cells mL^{-1} was distributed in a microtiter plate, 90 mL in each well with 10 mL of test compounds at different concentrations: 50, 25, 12.5, 6.25, and 3.125 μg mL^{-1}. The microtiter plate was incubated at 37 °C in an incubator at 5% CO_2 for 48 h. After, 10 μL of MTT at 5 mg mL^{-1} was added and the cells incubated for 4 h. To solubilize the formazan crystals, DMSO (100 μL) was used. The plates were shaken for 5 min, and absorbance for each sample was measured in a spectrophotometric microplate reader at 560 nm. The percentage of cytotoxicity was calculated as [(A – B) / A × 100], where A and B are the absorbances of control and treated cells, respectively. Data were analyzed using linear regression to obtain values for CC_{50} (cytotoxic concentration for 50%). Selectivity indexes were expressed as the ratio CC_{50} / MIC.

Supplementary Information

Supplementary data associated with this article (^1H, ^{13}C, IR and HRMS spectra of the compounds) can be found in the supplementary material available free of charge at http://jbcs.sbq.org.br as PDF file.

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