SUPPORTING INFORMATION

Rapid synthesis of triazole-modified resveratrol analogues *via* click chemistry

Francesca Pagliai[$], Tracey Pirali[$], Erika Del Grosso, Riccardo Di Brisco, Gian Cesare Tron*, Giovanni Sorba and Armando A. Genazzani*

Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche and Drug and Food Biotechnology Center

Università degli Studi del Piemonte Orientale "A. Avogadro"

Via Bovio 6, 28100 Novara, Italy.

Contents:

Experimental section

Commercially available reagents and solvents were used without further purification and were purchased from Fluka-Aldrich or Lancaster. Tetrahydrofuran (THF) was distilled immediately before use from Na/benzophenone under a slight positive atmosphere of N_2 and dicholoromethane was dried by distillation from P_2O_5 and stored on activated molecular sieves (4 Å). When needed the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2 . NMR spectra were recorded with a JEOL ECP 300 Mhz spectrometer and the δ values are in part per million. Mass spectra were recorded using a Thermo Finningan LCQ Deca XP-*plus* equipped with an ESI source and an ion trap detector; HPLC data were acquired with a Thermo Finnigan Surveyor equipped with a quaternary pump, a Surveyor AS autosampler and a PDA detector. Column chromatography was performed on silica gel (Merck Kieselgel 70-230 mesh ASTM). Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}).

Compounds **1**, **a**, **c**, **g**, **B** were purchased from Sigma-Aldrich. Compounds **h** was synthesized as described previously.[1] Compounds **4**, **5**, **6** were synthesized using the classical click chemistry protocol.[2]

General procedure for the synthesis of azide derivatives (A, C, D, E, F, G, H, I, L, M):

The amine derivative (1 eq) was dissolved in HCl aq. at room temperature. Upon cooling to 0 °C and addition of a solution of $NaNO_2$ (1 eq), the reaction mixture was stirred for 10 minutes at 0-5 °C. Sodium azide (1,2 eq) was added and the mixture was stirred at room temperature for 2 h. The reaction was worked up by dilution with EtOAc. The organic layer was washed with brine and dried over sodium sulphate. After evaporation of the solvent, the crude was pure enough for further reactions. All the azide synthesized were stored at -20 °C.

General procedure for the synthesis of alkynes derivatives (b, d, e, f):[3]

1) To a solution of the corresponding aldehyde (1 eq) in CH_2Cl_2 dry, triphenylphosphine (2 eq) was added. The resulting solution was cooled at 0 °C and a solution of carbon tetrabromide (1,1 eq) in dry CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 2 h and quenched adding water. The organic layer was separated and washed with brine (x1). After drying over sodium sulphate and evaporation of the solvent, the crude was purified by column chromatography to give the corresponding dibromoethene derivative.

2) BuLi (2,5 eq, sol. 1,6 M solution in hexane) was added slowly (over 1 h) to a solution containing the dibromoethene derivative (1 eq) in dry THF cooled at -78 °C. The resulting solution was stirred at -78 °C for 1h then warmed slowly to room temperature. The reaction was quenched by addition of sat. aq. NH_4Cl and the mixture extracted with EtOAc. The organic layer was washed with water (x1) and brine (x1). After drying over sodium sulphate and evaporation of the solvent, the crude was purified by column chromatography to give the corresponding alkyne.

Click reaction procedure

The parallel synthesis was carried out with the following conditions: the overall volume in each test tube was 2 mL (H_2O:*t*-ButOH 1:1), containing a solution of azide (1 eq) and alkyne (1 eq). Sodium ascorbate (0,1 eq) of freshly prepared 1 M solution in water was added, followed by the addition of copper (II) sulfate pentahydrate (0,01 eq). The resulting reaction was vigorously stirred for 24 h at room temperarure.

The reaction mixture was then diluted with water, cooled in ice, and the precipitate was collected by filtration. After washing the precipitate with diethyl ether, it was dried under vacuum to afford a solid which was submitted to MS analysis to confirm the molecular weight.

All positive hits were used for biological assays and the more potent compounds were analyzed by HPLC to investigate purity. The compounds with a purity lower than 95% were resynthesized and re-evalutated.

Procedure for the synthesis of compounds (2) and (3) :

To a cooled (-78 °C) and stirred solution of 4-(3,5-dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole or 1-(3,5-dimethoxyphenyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (1 eq) in dry CH_2Cl_2, BBr_3 (1 M solution in CH_2Cl_2, 15 eq) was added dropwise. The resulting solution was warmed slowly to room temperature and stirred overnight. The reaction mixture was then worked up by dilution with EtOAc and washed with saturated aqueous sodium bicarbonate. The organic layer was re-extracted with EtOAc (x 3) and the combined organic layers were washed with Brine (x1). After drying over sodium sulphate and evaporation of the solvent, **2** (93%) or **3** (70%) were obtained as a off-white solid and NMR analysis reveals they were pure enough (> 95%) for the preliminary biological assays.

Cell culture and morphological observation :

MDA-MB-231, SH-SY5Y, RBL-2H3 and FG2 cells were obtained from ATCC (LGC Promochem Teddington, UK).MDA-MB-231 cells were cultured in DMEM supplemented with 10% foetal bovine serum, 2mM L-glutamine, penicillin (100µg/mL) and streptomycin (100µg/mL). The RBL-2H3 were cultured in DMEM supplemented with 16% foetal bovine serum, 2mM L-glutamine, penicillin (100µg/mL) and streptomycin (100µg/mL). SH-SY5Y cells were cultured in 50% DMEM

and 50% Nutrient F-12 supplemented with 10% foetal bovine serum, 2mM L-glutamine, penicillin (100µg/mL) and streptomycin. FG2 cells were cultured in RPMI 1640 and supplemented with 10% foetal bovine serum, 2mM L-glutamine, penicillin (100µg/mL) and streptomycin.

To observe morphological changes, MDA-MB-231 cells were plated on 6-well plates and grown to subconfluency for 48 h in the presence or absence of resveratrol and of triazole-modified resveratrol analogues, and on the experimental day cells observed by phase-contrast microscopy (40X); we used an adaptation of the method described by Azios and Dharmawardhane.[4]

Cytotoxicity assay:

Cells were plated on 96-well plates and grown for 48 h in the presence or absence of resveratrol or its triazole analogues**.** Cell viability was determined with the conventional MTT assay.[5] The assay is based on the conversion of tetrazolium salt into an insoluble formazan product by various dehydrogenase in mitochondria The MTT solution was added to the cells (final concentration 0,5 mg/ml) and cultures were allow to incubate at 37^{o}C for 3-4 h. The cells were dissolved in 100 µl isopropanol containing 0.1 M HCl, and then the absorbance was measured at 570 nm by using a BIO-RAD Ultramark Microplate Imaging System. Cell viability is expressed as absorbance and compared with control value.

Flow- cytometric analysis of cell-cycle status:

MDA-MB-231 grown in the presence or absence of compounds for 48 h were washed once in PBS, and re-suspended in 1 ml 30:70 ice cold PBS/EtOH and stored at –20°. Cells were then washed twice in PBS, re-suspended in PBS containing RNAse (100 µg/mL) for 1 hour at 37°. DNA was then stained with a PBS solution containing 5mM EDTA and 100 µg/mL propidium iodide for 30 min at 4° in the dark. Cell cycle was determined with a FACSVantage SE DiVa (Becton

Dickinson).Resusts were further analyzed with flow cytometry modelling software (ModFit LT, ,Verity Software House).

MS data of all compounds synthesized

The ESI-MS spectra were acquired in positive and/or negative ion mode using a Thermo Finnigan LCQ Deca XP-*plus* Ion Trap Mass Spectrometer instrument from Thermo Finnigan (San Josè, CA, USA) equipped with an electrospray ion source (ESI) and an Xcalibur® system manager data acquisition software. Sample solutions (3 μg ml^{-1}) were infused in the ESI source using a syringe pump at a flow rate of 2 μl $ml^{-1}$and the mass scan range was m/z 100-500. Operating conditions on the ion trap mass spectrometer were as follows: source voltage, 5.30 kV; source current, 0 μA; capillary temperature, 350 °C; capillary voltage, -10 V (negative mode) 12 V (positive mode); tube lens offset, 0 V (negative mode) 10 V (positive mode); sheath gas flow (N_2), 60 A.U. Data were acquired in full MS mode and are reported in the table.

	a		b		c		d		e		f		g		h	
A	MW 281	m/z 282 $[M+H]^+$ (100%) m/z 304 $[M+Na]^+$ (7%)	MW 341	m/z 342 $[M+H]^+$ (100%) m/z 364 $[M+Na]^+$ (18%)	MW 266	m/z 267 $[M+H]^+$ (100%)	MW 311	m/z 312 $[M+H]^+$ (100%)	MW 297	m/z 298 $[M+H]^+$ (100%)	MW 297	m/z 298 $[M+H]^+$ (100%)	MW 311	m/z 312 $[M+H]^+$ (100%) m/z 334$[M+Na]^+$ (15%) m/z $[M-H]^-$ (100%)	MW 283	m/z 284 $[M+H]^+$ (100%) m/z 306 $[M+Na]^+$ (10%) m/z 282 $[M-H]^-$ (100%)
B	MW 266	m/z 267 $[M+H]^+$ (100%) m/z 289 $[M+Na]^+$ (7%)	MW 326	X	MW 251	X	MW 296	X	MW 282	X	MW 282	m/z 283 $[M+H]^+$ (100%) m/z 305 $[M+Na]^+$ (10%) m/z 281 $[M-H]^-$ (100%)	MW 296	X	MW 268	X
C	MW 311	m/z 312 $[M+H]^+$ (100%) m/z 334 $[M+Na]^+$ (12%)	MW 371	m/z 372 $[M+H]^+$ (100%) m/z 394 $[M+Na]^+$ (7%)	MW 296	m/z 297 $[M+H]^+$ (100%)	MW 341	m/z 342 $[M+H]^+$ (100%)	MW 327	m/z 328 $[M+H]^+$ (100%) m/z 350 $[M+Na]^+$ (15%) m/z 326 $[M-H]^-$ (100%)	MW 327	m/z 328 $[M+H]^+$ (100%) m/z 250 $[M+Na]^+$ (15%) m/z 326 $[M-H]^-$ (100%)	MW 341	m/z 342 $[M+H]^+$ (100%)	MW 313	m/z 314 $[M+H]^+$ (100%) m/z 312 $[M-H]^-$ (100%)
D	MW 297	m/z 298 $[M+H]^+$ (100%) m/z 320 $[M+Na]^+$ (15%) m/z 296 $[M-H]^-$ (100%)	MW 357	m/z 358 $[M+H]^+$ (100%) m/z 380 $[M+Na]^+$ (24%) m/z 356 $[M-H]^-$ (100%)	MW 282	m/z 283 $[M+H]^+$ (100%) m/z 281 $[M-H]^-$ (100%)	MW 327	m/z 328 $[M+H]^+$ (100%) m/z 326 $[M-H]^-$ (100%)	MW 313	m/z 315 $[M+H]^+$ (100%) m/z 337 $[M+Na]^+$ (18%) m/z 312 $[M-H]^-$ (100%)	MW 313	m/z 314 $[M+H]^+$ (100%) m/z 336 $[M+Na]^+$ (25%) m/z 312 $[M-H]^-$ (100%)	MW 327	m/z 328 $[M+H]^+$ (100%) m/z 350 $[M+Na]^+$ (20%) m/z 326 $[M-H]^-$ (100%)	MW 299	m/z 300 $[M+H]^+$ (100%) m/z 322 $[M+Na]^+$ (18%) m/z 298 $[M-H]^-$ (100%)
E	MW 343	m/z 344 $[M+H]^+$ (100%) m/z 366 $[M+Na]^+$ (8%)	MW 403	m/z 404 $[M+H]^+$ (100%) m/z 426 $[M+Na]^+$ (30%)	MW 328	m/z 329 $[M+H]^+$ (100%)	MW 373	m/z 374 $[M+H]^+$ (100%)	MW 359	X	MW 359	m/z 360 $[M+H]^+$ (100%) m/z 358 $[M-H]^-$ (100%)	MW 373	m/z 374 $[M+H]^+$ (100%) m/z 396 $[M+Na]^+$ (20%)	MW 345	m/z 346 $[M+H]^+$ (100%) m/z 344 $[M-H]^-$ (100%)
F	MW 335	m/z 336 $[M+H]^+$ (100%)	MW 395	m/z 396 $[M+H]^+$ (100%) m/z 418 $[M+Na]^+$ (17%)	MW 320	m/z 321 $[M+H]^+$ (100%)	MW 365	m/z 366 $[M+H]^+$ (100%)	MW 351	m/z 352 $[M+H]^+$ (100%) m/z 350 $[M-H]^-$ (100%)	MW 351	m/z 352 $[M+H]^+$ (100%) m/z 350 $[M-H]^-$ (100%)	MW 365	m/z 366 $[M+H]^+$ (100%) m/z 388 $[M+Na]^+$ (10%)	MW 337	m/z 338 $[M+H]^+$ (100%) m/z 360 $[M+Na]^+$ (30%) m/z 336 $[M-H]^-$ (100%)
G	MW 311	m/z 312 $[M+H]^+$ (100%) m/z 334 $[M+Na]^+$ (15%)	MW 371	X	MW 296	m/z 297 $[M+H]^+$ (100%)	MW 341	X	MW 327	X	MW 327	m/z 328 $[M+H]^+$ (100%) m/z 350 $[M+Na]^+$ (20%)	MW 341	m/z 341 $[M+H]^+$ (100%) m/z 364 $[M+Na]^+$ (20%)	MW 313	m/z 314 $[M+H]^+$ (100%) m/z 336 $[M+Na]^+$ (20%) m/z 312 $[M-H]^-$ (100%)
H	MW 341	m/z 342 $[M+H]^+$ (100%) m/z 364 $[M+Na]^+$ (15%)	MW 401	m/z 402 $[M+H]^+$ (100%) m/z 424 $[M+Na]^+$ (40%)	MW 326	m/z 327 $[M+H]^+$ (100%)	MW 371	X	MW 357	m/z 358 $[M+H]^+$ (100%) m/z 356 $[M-H]^-$ (100%)	MW 357	m/z 358 $[M+H]^+$ (100%) m/z 380 $[M+Na]^+$ (25%) m/z 356 $[M-H]^-$ (100%)	MW 371	m/z 372 $[M+H]^+$ (100%) m/z 394 $[M+Na]^+$ (15%)	MW 343	m/z 344 $[M+H]^+$ (100%) m/z 360 $[M+Na]^+$ (20%) m/z 342 $[M-H]^-$ (100%)
I	MW 323[a]	m/z 322 $[M-H]^+$ (100%) m/z 320 $[M-3H]^-$ (100%)	MW 383	X	MW 308[a]	m/z 307 $[M-H]^+$ (100%) m/z 305 $[M-3H]^-$ (100%)	MW 353[a]	m/z 352 $[M-H]^+$ (100%) m/z 350 $[M-3H]^-$ (100%)	MW 339	X	MW 339[a]	m/z 336 $[M-3H]^-$ (100%)	MW 353[a]	m/z 352 $[M-H]^+$ (100%) m/z 350 $[M-3H]^-$ (100%)	MW 325	X
L	MW 295	m/z 296 $[M+H]^+$ (100%) m/z 318 $[M+Na]^+$ (15%)	MW 355	m/z 356 $[M+H]^+$ (100%) m/z 378 $[M+Na]^+$ (25%)	MW 280	m/z 281 $[M+H]^+$ (100%)	MW 325	m/z 326 $[M+H]^+$ (100%)	MW 311	m/z 312 $[M+H]^+$ (100%) m/z 310 $[M-H]^-$ (100%)	MW 311	m/z 312 $[M+H]^+$ (100%) m/z 334 $[M+Na]^+$ (10%)	MW 325	m/z 326 $[M+H]^+$ (100%) m/z 348 $[M+Na]^+$ (20%)	MW 297	m/z 298 $[M+H]^+$ (100%) m/z 296 $[M-H]^-$ (100%)
M	MW 311	m/z 312 $[M+H]^+$ (100%) m/z 334 $[M+Na]^+$ (12%)	MW 371	m/z 372 $[M+H]^+$ (100%) m/z 394 $[M+Na]^+$ (12%)	MW 296	m/z 297 $[M+H]^+$ (100%)	MW 341	X	MW 327	X	MW 327	m/z 328 $[M+H]^+$ (100%) m/z 350 $[M+Na]^+$ (15%) m/z 326 $[M-H]^-$ (100%)	MW 341	m/z 342 $[M+H]^+$ (100%) m/z 364 $[M+Na]^+$ (15%)	MW 313	m/z 314 $[M+H]^+$ (100%) m/z 336 $[M+Na]^+$ (20%) m/z 312 $[M-H]^-$ (100%)

[a] These MW are refered to the feasible products, that did not corresponding to the real one found

Spectroscopic data of the selected compounds (^{1}H, ^{13}C, MS)

2-azido-3,4,6-trifluorophenol (I). ^{1}H-NMR (300 MHz, $CDCl_3$, 273 K) δ 6.75 (m, 1-H) ; ^{13}C-NMR (75 MHz, CDCl3, 273 K) δ 146.1 (dd, J= 241.6 / 10.8 Hz), 143.5 (dt, J= 241.6 / 12.6 Hz), 141.4 (dd, J= 248,0 / 12,0 Hz), 133.9 (d, J= 16.6 Hz), 118.5 (br s), 101.01 (t, J= 22,3 Hz); MS (ESI) *m/z* 189 (100%) $(M-H)^-$

5-[4-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-1-yl]-1,3-benzenediol (2). ^{1}H-NMR (300 MHz, CD_3OD, 273 K) δ 8.60 (s, 1-H), 7.71 (d, J=8.8 Hz, 2-H), 6.88 (d, J=8.8 Hz, 2-H), 6.78 (d, J=1.9 Hz, 2-H), 6.35 (t, J=1.9 Hz, 1-H); ^{13}C-NMR (75 MHz, CD_3OD, 373 K) δ 159.8, 158.1, 148.0, 138.7, 127.4, 121.8, 118.5, 116.2, 102.9, 98.8; MS (ESI) *m/z* 268 (100%) $(M-H)^-$

5-[1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl]-1,3-benzenediol (3). ^{1}H-NMR (300 MHz, DMSO-d_6, 273 K) δ 9.96 (s, OH), 9.42 (s, OH), 8.96 (s, 1-H), 7.71 (d, J=8.8 Hz, 2-H), 6.96 (d, J=8.8 Hz, 2-H), 6.83 (br s, 2-H), 6,25 (br s, 1-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 159.4, 158.1, 147.9, 132.6, 129.4, 122.4, 119.8, 116.6, 104.2, 103.0; MS (ESI) *m/z* 268 (100%) $(M-H)^-$

1-(3,5-dimethoxyphenyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (4 or Ca bis). ^{1}H-NMR (300 MHz, $CDCl_3$, 273 K) δ 9.00 (s, 1-H), 7.85 (d, J=8.5 Hz, 2-H), 7.11 (d, J=2.2 Hz, 2-H), 7.06 (d, J=8.5 Hz, 2-H), 6.62 (t, J=2.2, 1-H), 3.87 (s, 6-H), 3.83 (s, 3-H); ^{13}C-NMR (75 MHz, $CDCl_3$, 273 K) δ 162.1, 159.0, 148.7, 139.0, 127.4, 123.7, 115.1, 101.2, 99.3, 56.4, 55.9; MS (ESI) *m/z* 312 (100%) $(M+H)^+$

4-(3,5-dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (5). ^{1}H-NMR (300 MHz, $CDCl_3$, 273 K) δ 8.07 (s, 1-H), 7.64 (d, J=8.8 Hz, 2-H), 7.04 (br s, 2-H), 7.00 (d, J=8.8 Hz, 2-H), 6.46 (br s, 1-H), 3.85 (br s, 9-H); ^{13}C-NMR (75 MHz, $CDCl_3$, 273 K) δ 161.3, 160.0, 148.2, 132.2, 130.5, 122.3, 118.3, 115.0, 104.0, 100.6, 55.7, 55.6; MS (ESI) *m/z* 312 (100%) $(M+H)^+$

5-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-1,3-benzenediol (6). ^{1}H-NMR (300 MHz, $CDCl_3$, 273 K) δ 8.03 (s, 1-H), 7.70 (d, J=8.5 Hz, 2-H), 6.86 (d, J=8.5 Hz, 2-H), 6.70 (d, 1.9 Hz, 2-H), 6.36 (br s, 1-H), 3.74 (s, 3-H); ^{13}C-NMR (75 MHz, $CDCl_3$, 373 K) δ 159.9, 159.6, 147.5, 138.7, 127.4, 123.4, 120.0, 114.9, 102.9, 98.8, 55,7 MS (ESI) *m/z* 282 (100%) $(M-H)^-$

1,4-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (Aa bis). ^{1}H-NMR (300 MHz, DMSO-d_6, 373 K) δ 8.88 (s, 1-H), 7.83 (br t, 4-H), 7.14 (d, J=8.8 Hz, 2-H,), 7.04 (d, J=8.3 Hz, 2-H), 3.86 (s, 3-H), 3.83 (s, 3-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 159.8, 147.6, 130.7, 127.2, 123.5, 122.1, 119.2, 115.5, 115.0, 56.1, 55.7

4-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]aniline (Ac). ^{1}H-NMR (300 MHz, DMSO-d_6, 373 K) δ 8.69 (s, 1-H), 7.80 (d, J=8.7 Hz, 2-H), 7.58 (d, J=8.5 Hz, 2-H,), 7.13 (d, J=8.7 Hz, 2-H), 6.68 (d, J=8.5 Hz, 2H), 4,98 (br s, 2H), 3.86 (s, 3-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 159.6, 148.9, 148.6, 130.8, 126.9, 122.0, 118.4, 117.8, 115.4, 114.5, 56.1

4-(3,4-dimethoxyphenyl)-1-(4-phenoxyphenyl)-1*H*-1,2,3-triazole (Ed). ^{1}H-NMR (300 MHz, DMSO-d_6, 373 K) δ 8.98 (s, 1-H), 7.91 (d, J=8.8 Hz, 2-H), 7.52-7.40 (m, 5-H), 7.20 (br d, J=8.8 Hz, 2-H), 7.09 (m, 3-H), 3.88 (s, 3-H), 3.83 (s, 3-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 157.4, 156.6, 149.6, 149.4, 148.0, 132.7, 130.8, 124.6, 123.5, 122.5, 119.9, 119.7, 119.5, 118.3, 112.7, 109.5, 56.1

1-(1,3-benzodioxol-5-yl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (La bis). ^{1}H-NMR (300 MHz, DMSO-d_6, 373 K) δ 8.87 (s, 1-H), 7.83 (d, J=8.5 Hz, 2-H), 7.47 (d, J=2.2 Hz, 1-H), 7.39 (dd, J=8.5/2.2 Hz), 7.08 (d, J=8.5 Hz, 2-H), 7.04 (d, J=8.5 Hz, 2-H), 6.14 (s, 2-H), 3.83 (s, 3-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 160.1, 148.8, 148.5, 148.4, 131.6, 127.4, 123.8, 119.3, 115.1, 114.5, 109.1, 102.6, 56.0

2-methoxy-5-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenol (Da bis). ^{1}H-NMR (300 MHz, DMSO-d_6, 373 K) δ 9.20 (br s, OH), 8.82 (s, 1-H), 7.84 (d, J=8.8 Hz, 2-H), 7.35 (d, J=2.7 Hz, 1-H), 7.28 (dd, J=8.5/2.7 Hz, 1-H), 7.10 (d, J=8.5 Hz, 1-H), 7.04 (d, J=8.8 Hz, 2-H), 3.87 (s, 3-H), 3.82 (s, 3-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 160.0, 148.8, 148.2, 148.0, 131.3, 127.4, 123.9, 119.0, 115.0, 114.0, 111.6, 109.0, 57.0, 56.0

4-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (Ad). ^{1}H-NMR (300 MHz, $CDCl_3$, 273 K) δ 8.06 (br s, 1-H), 7.67 (d, J=7.9 Hz, 2-H), 7.56 (br s, 1-H), 7.35 (br d, J=7.9, 1-H), 7.02 (d, J=7.9 Hz, 2-H), 6.92 (br d, 6.9 Hz, 1-H), 3.98 (s, 3-H), 3.91 (s, 3-H), 3.87 (s, 3-H); ^{13}C-NMR (75 MHz, $CDCl_3$, 273 K) δ 160.0, 149.4, 148.0, 130.5, 123.0, 122.3, 118.4, 117.5, 114.9, 111.4, 109.2, 56.2, 56.0, 55.7

4-(3,4-dimethoxyphenyl)-1-[4-(trifluoromethoxy)phenyl]-1*H*-1,2,3-triazole (Fc). ^{1}H-NMR (300 MHz, DMSO-d_6, 273 K) δ 9.01 (s, 1-H), 8.06 (d, J=8.8 Hz, 2-H), 7.63 (d, J=8.2 Hz, 2-H), 7.58 (d, J=8.2 Hz, 2-H), 6.64 (d, J=8.2 Hz, 2-H), 5,33 (br s, 2-H); ^{13}C-NMR (75 MHz, DMSO-d_6, 373 K) δ 149.6, 149.1, 148.2, 136.2, 127.0, 123.2, 122.2, 118.0, 117.9, 114.5

HPLC purities data of the selected compounds

The purity of the selected compounds was determined by two different HPLC systems:

Method A:

Column: Waters X terra Phenyl 3.5 μm 3.0x150mm

Solvent A: water

Solvent B: acetonitrile

Elution: 40% A in 10 min

Flow rate: 300ul/min. Detection: UV absorbance at 220, 254 nm. Column temperature: 35 °C

Method B:

Column: Phenomenex Prodigy 5μ ODS(2) 150x4.6 mm

Solvent A: water

Solvent B: acetonitrile

Elution: 40% A in 10 min

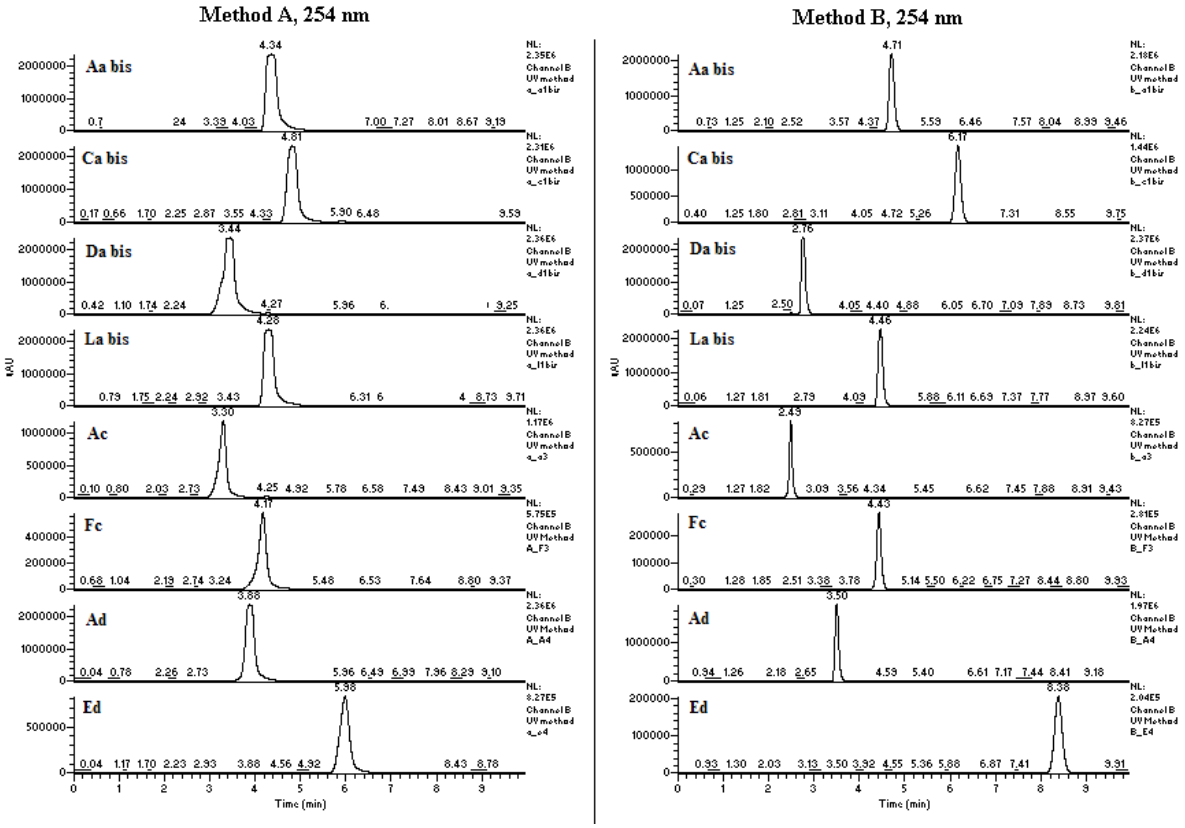
Flow rate: 1ml/min. Detection: UV absorbance at 220, 254 nm. Column temperature: 25 °C

The results were reported in the Table and in the Figure below.

- **Table**

Compound	Formula	HPLC Analysis Data
Aa bis	$C_{16}H_{15}N_3O_2$	Method A: t_R = min 4.34 (220 nm = 98.97%; 254 nm = 99.58%)
		Method B: t_R = min 4.71 (220 nm = 97.43%; 254 nm = 99.14%)
Ca bis	$C_{17}H_{17}N_3O_3$	Method A: t_R = 4.81 min (220 nm = 97.40%; 254 nm = 97.61%)
		Method B: t_R = 6.17 min (220 nm = 95.70 %; 254 nm = 97.40%)
Da bis	$C_{16}H_{15}N_3O_3$	Method A: t_R = 3.43 min (220 nm = 97.54%; 254 nm = 97.93%)
		Method B: t_R = 2.76 min (220 nm = 95.71%; 254 nm = 97.55%)
La bis	$C_{16}H_{13}N_3O_3$	Method A: t_R = 4.29 min (220 nm = 95.26%; 254 nm = 99.35 %)
		Method B: t_R = 4.46 min (220 nm = 95.35%; 254 nm = 98.47%)
Ac	$C_{15}H_{14}N_4O$	Method A: t_R = 3.30 min (220 nm = 95.02%; 254 nm = 97.85 %)
		Method B: t_R = 2.49 min (220 nm = 95.07%; 254 nm = 96.09%)
Fc	$C_{15}H_{11}F_3N_4O$	Method A: t_R = 4.17 min (220 nm = 95.02%; 254 nm = 98.07%)
		Method B: t_R = 4.43 min (220 nm = 95.03%; 254 nm = 97.84%)
Ad	$C_{17}H_{17}N_3O_3$	Method A: t_R = 3.88 min (220 nm = 99.02%; 254 nm = 99.89%)
		Method B: t_R = 3.50 min (220 nm = 97.01%; 254 nm = 98.98 %)
Ed	$C_{22}H_{19}N_3O_3$	Method A: t_R = 5.98 min (220 nm = 96.32%; 254 nm = 99.30%)
		Method B: t_R = 8.38 min (220 nm = 96.70 %; 254 nm = 99.32%)

- **Figure:** HPLC Method A at 254 nm for all the analyzed compounds

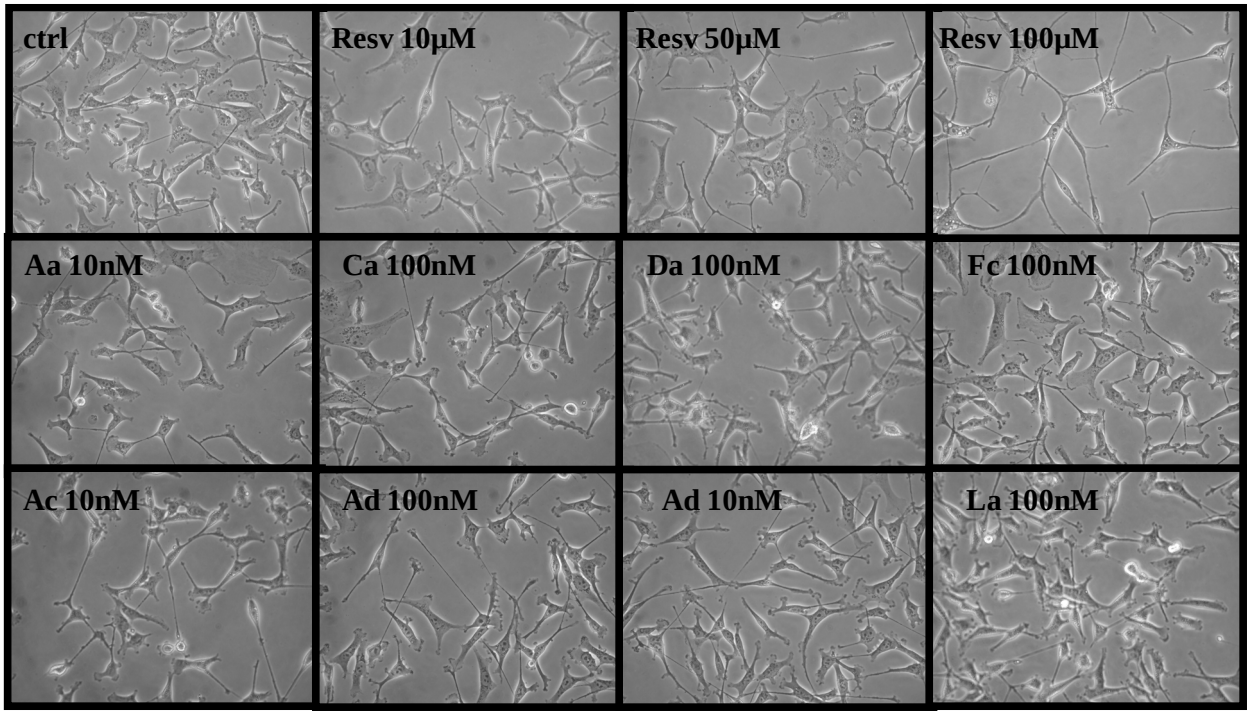


Raw data of the cytotoxicity of the click chemistry generated compounds

	A	b	c	D	e	f	g	h
A	**I** 44,6±6,3 **II** 38,2±6,2 **III** 56,3±4,6	**I** 87,9±8,3	**I** 64,6±4,0 **II** 44,8±8,0 **III** 56,4±8,8	**I** 52,3±8,9 **II** 40,0±2,7 **III** 61,2±2,6	**I** 80,6±0,0	**I** 131,1±12,9	**I** 151,3±10,5	**I** 111,2±8,6
B	**I** 22,7±2,6 **II** 23,8±3,4 **III** 84,5±6,1	n.p.	n.p.	n.p.	m.f.	**I** 99,9±17,0	m.f.	n.p.
C	**I** 47,0±3,3 **II** 18,1±2,9 **III** 89,0±3,3	**I** 42,0±5,0 **II** 126,9±4,6	**I** 123,9±17,0	**I** 35,7±7,1 **II** 71,0±4,0	**I** 58,1±0,0	**I** 123,9±14,0	**I** 104,3±28,2	**I** 110,9±12,5
D	**I** 31,4±4,1 **II** 38,9±3,7 **III** 74,5±11,6	**I** 68,0±8,1	**I** 144,9±12,1	**I** 55,4±4,8 **II** 65,6±4,6	**I** 77,5±0,0	**I** 75,8±11,6	**I** 147,8±6,9	**I** 90,8±6,8
E	**I** 26,7±2,7 **II** 38,8±4,5 **III** 88,1±5,4	**I** 65,6±10,4	**I** 84,9±1,3	**I** 55,6±4,8	n.p.	**I** 89,1±11,7	**I** 112,8±35,3	**I** 98,4±16,8
F	**I** 24,2±3,6 **II** 59,4±4,4	**I** 95,5±11,2	**I** 63,1±1,3 **II** 30,2±6 **III** 44,7±8,7 **IV** 81,2±2,9	**I** 40,8±4,5 **II** 78,4±9,3	**I** 65,8±0,0	**I** 101,3±6,9	**I** 35,3±4,2 **II** 109,4±4,8	**I** 82,0±5,4
G	**I** 82,8±13,2	n.p.	**I** 101,2±3,7	n.p.	n.p.	**I** 30,9±0,9 **II** 20,5±3,3 **III** 63,8±3,2	**I** 55,8±5,7	**I** 98,2±8,7
H	**I** 71,7±11,8	**I** 98,9±4,0	**I** 122,8±4,7	n.p.	**I** 74,2±0,0	**I** 103,6±12,7	**I** 122,1±37,7	**I** 94,0±5,6
I	**I** 22,0±2,8 **II** 121±4,5 m.f.*	n.p.	**I** 154,5±12,8 m.f.*	**I** 53,0 ± 4,8	n.p.	**I** 99,1±9,0 m.f.*	**I** 138,0±43,1 m.f.*	n.p.
L	**I** 21,2±3,7 **II** 63,6±4,7	**I** 58,2±4,2	**I** 117,1±11,5	**I** 55,5±5,5	**I** 78,7±0,0	**I** 139,8±8,5	**I** 212,7±9,2	**I** 39,5±6,4 **II** 106,3±5,9
M	**I** 93,8±12,4	**I** 103,8±9,4	**I** 174,2±11,2	n.p.	n.p.	**I** 111,9±4,9	**I** 156,3±61,8	**I** 69,9±9,8

Values are % of control and are mean± S.E.M. of 4 - 6 determinations.
I= 10 µM; II=1 µM; III=100 nM; IV=10 nM

Morphological changes in induced by resveratrol or triazole-modified resveratrol analogues



References

1) Gibtner, T.; Hampel, F.; Gisselbrecht, J. P.; Hirsch, A. End-cap stabilized oligoynes: model compounds for the linear sp carbon allotrope carbyne. *Chem. Eur. J.* **2002,** *8*, 408-432
2) Rostovtsev, V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A stepwise Huisgen cycloaddition process: copper (I) catalyzed regioselective "ligation" of azide and terminal alkynes. *Angew. Chem. Int. Ed.* **2002,** *41*, 2596-2599.
3) Lawrence, N. J.; Ghani, F. A.; Hepworth, L.A.; Hadfield, J.A.; McGown, A.T.; Pritchard, R.G. The synthesis of (*E*) and (*Z*)-combretastatins A-4 and a phenanthrene from *Combretum Caffrum*. *Synthesis*. **1999,** 1656-1660.
4) Azios, N. G., Dharmawardhane, S. F. Resveratrol and estradiol exert disparate effects on cell migration, cell surface actin structures, and focal adhesion assembly in MDA-MB-231 human breast cancer cells. *Neoplasia*. **2005**, *7*, 128-140.
5) Mosmann, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol*. *Methods*. **1983,** *65*, 55-63.