Electronic Supplementary Material (ESI) for MedChemComm.

Supplementary Information

Identification of a novel NAMPT inhibitor by combinatorial click chemistry and chemical refinement

S. Theeramunkong, U. Galli, A. A. Grolla, A. Caldarelli, C. Travelli, A. Massarotti, M. P. Troiani, M. A. Alisi, G. Orsomando, A. A. Genazzani and G. C. Tron

Table of Contents

Fig. S1 Structure of seventeen compounds able to reduce of > 60% the cell viability. Best compound are marked in red.

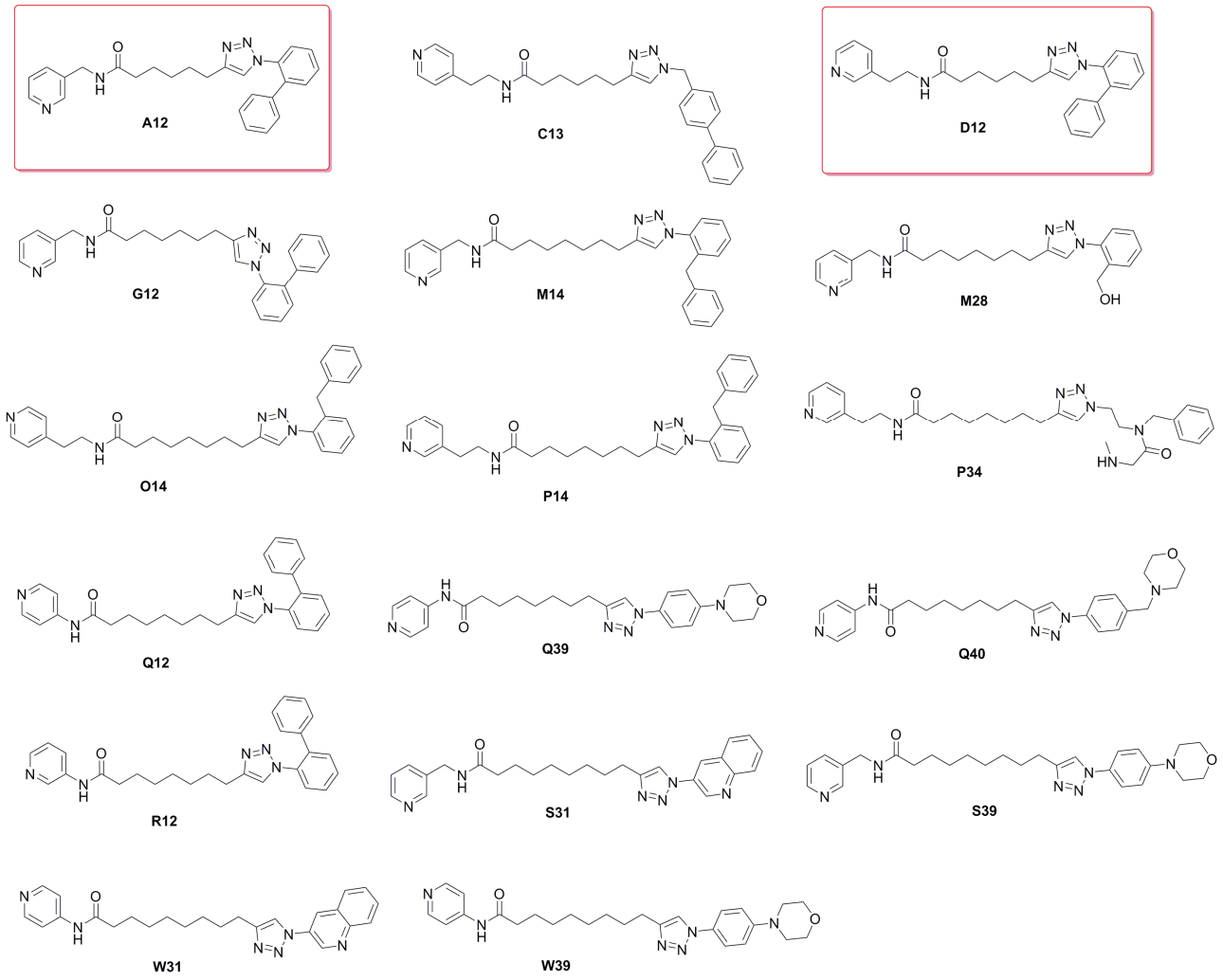

Table S1 Screening viability of SH-SY5Y cell treated with unpurified 720 triazole products at 10 μM for 48 hours. Data represent % cell viability, if the compound displayed significant activity at 10 μM, it will be chosen to be tested further at 1 μM for 48 hours.

	A	B	C	D	E	F	G	H	I	J	K	L
11	87.4	96.4	94.3	100.8	88.3	92.3	90.2	90.1	105.0	90.8	111.1	114.8
12	23.9	103.7	67.3	24.9	83.3	88.3	24.4	77.0	100.4	65.3	104.6	127.6
13	96.5	68.3	29.3	47.3	62.0	71.3	66.1	52.8	70.2	72.7	64.8	76.0
14	93.9	87.8	96.8	92.5	111.8	91.7	93.7	76.3	105.2	101.3	109.4	141.7
15	93.8	96.3	94.7	86.7	103.2	90.7	85.3	79.9	112.3	102.0	115.8	125.1
16	80.0	101.4	98.3	84.2	88.2	105.2	102.6	73.9	117.6	91.9	99.5	117.8
17	105.3	104.3	101.8	90.4	103.9	95.3	99.9	79.2	100.0	90.6	96.4	124.5
18	100.8	78.4	100.4	89.9	92.2	93.6	101.4	75.1	99.6	104.1	92.1	130.9
19	99.2	90.1	92.4	81.6	99.5	86.0	96.8	73.8	101.4	108.8	90.7	126.8
20	98.3	101.3	83.5	87.5	94.1	97.2	95.5	81.5	97.9	105.3	101.4	134.1
21	76.5	88.3	87.3	97.6	88.3	87.6	92.6	96.8	118.9	104.3	92.9	111.0
22	94.5	102.6	98.3	99.5	76.6	85.5	95.2	94.7	108.0	101.5	99.4	130.6
23	112.7	89.4	84.6	80.7	56.5	108.7	70.7	98.3	100.9	98.4	90.6	100.9
24	107.9	73.8	99.4	71.3	80.7	87.8	85.6	81.6	104.3	104.6	96.7	102.1
25	99.9	99.2	104.7	77.1	106.5	71.6	103.5	84.2	107.9	104.3	93.1	108.0
26	100.0	89.3	96.8	83.6	101.9	84.6	95.4	84.6	115.3	102.9	100.1	105.5
27	61.5	76.1	102.4	83.1	103.0	99.4	97.6	78.0	111.7	86.8	100.0	99.9
28	77.7	91.7	104.2	93.4	98.0	104.8	102.9	82.0	109.2	67.8	95.8	102.4
29	60.9	103.2	99.8	102.4	104.2	96.8	89.1	79.6	104.8	78.3	93.1	94.1
30	57.3	116.2	100.3	89.2	99.8	98.8	93.3	76.8	95.2	72.6	112.6	105.7
31	106.0	103.6	71.6	81.8	100.3	92.0	82.1	74.8	99.3	67.0	93.1	118.1
32	94.9	102.4	84.6	80.5	100.2	99.8	94.8	74.9	121.2	75.6	91.5	109.2
33	94.8	79.3	99.4	87.9	94.1	95.1	91.3	98.9	112.2	78.4	101.7	114.3
34	102.9	81.4	102.4	86.9	103.5	93.4	96.8	97.3	108.7	87.1	101.2	112.7
35	103.1	119.8	67.3	100.7	104.7	107.0	98.1	89.3	107.7	97.3	92.3	100.7
36	94.9	82.1	78.4	87.3	117.0	85.0	108.5	99.9	112.9	87.8	92.0	105.7
37	86.9	90.3	91.8	94.3	108.9	86.3	102.2	108.5	105.3	102.0	102.1	118.1
38	67.3	94.8	100.3	82.9	118.8	95.7	99.4	100.9	96.4	103.2	94.7	109.2
39	98.4	78.4	93.5	91.6	94.5	96.8	77.8	95.6	107.2	96.4	90.7	114.3
40	101.9	100.3	92.3	90.9	97.2	99.7	100.5	89.3	106.9	105.9	85.5	112.7

Table S1 (continue)

	M	N	O	P	Q	R	S	T	U	V	W	X
11	93.31	96.29	96.9	93.8	74.8	100.6	114.3	110.1	94.8	83.5	75.7	99.1
12	90.04	95.29	100.1	94.2	34.5	31.8	123.8	113.1	104.0	93.8	78.3	99.5
13	66.14	60.68	57.8	56.4	50.5	52.3	80.0	78.8	57.7	70.8	55.1	64.8
14	18.7	85.99	35.3	29.6	80.3	65.8	112.0	107.3	95.0	84.7	75.2	104.6
15	85.38	93.64	90.5	101.5	62.3	100.2	92.3	114.9	85.9	78.6	43.9	79.6
16	97.54	103.2	98.3	100.9	99.1	103.8	120.3	124.0	107.7	88.8	79.9	100.8
17	95.47	100	97.6	100.8	79.0	98.9	97.8	105.2	99.4	95.9	85.4	103.6
18	86.96	82.39	103.7	101.4	98.2	102.7	100.7	111.6	84.7	89.1	95.5	104.0
19	94.85	80.12	108.4	104.2	88.5	103.0	75.1	91.2	73.7	81.8	41.0	96.7
20	87.37	87.06	98.9	109.3	81.4	97.4	127.2	113.4	95.9	90.3	74.9	93.5
21	103	97.56	98.0	90.9	81.4	98.5	106.4	109.0	100.2	83.6	79.6	95.9
22	81.46	92.78	94.5	87.3	63.4	97.6	116.8	110.0	99.4	91.5	75.8	110.5
23	101.3	96.87	101.5	96.3	79.3	84.0	110.0	97.3	71.6	82.3	50.3	63.8
24	110.5	89.55	105.3	103.1	90.9	90.0	109.8	94.1	98.8	85.2	73.6	90.0
25	105.1	96	86.7	103.0	89.2	100.3	116.2	95.3	104.1	91.0	73.5	116.5
26	103.4	98.92	91.7	99.4	73.6	104.6	103.6	124.6	92.1	73.9	71.9	102.0
27	94.89	97.75	104.5	99.4	88.3	101.4	119.8	102.8	107.8	90.4	69.4	116.3
28	33.57	97.25	100.6	87.7	88.9	102.0	111.4	118.2	112.4	98.5	73.9	110.5
29	99.37	85.55	100.4	103.9	74.4	104.8	100.8	104.8	104.5	94.8	69.9	97.2
30	96.25	87.92	98.0	100.6	97.3	105.2	111.2	95.6	96.4	85.2	66.6	111.2
31	95.26	98.46	100.0	99.8	52.4	92.9	36.7	84.6	73.9	86.6	31.5	89.5
32	108.1	113.7	100.0	89.1	76.9	101.0	125.5	107.9	100.8	90.0	85.3	110.3
33	100.3	100.6	96.1	89.4	70.3	72.5	101.3	122.8	100.0	77.6	69.0	113.7
34	112.7	78.69	99.4	23.4	95.1	95.5	113.8	100.3	95.4	58.5	68.2	127.2
35	104.0	93.3	96.3	95.7	96.2	91.8	115.3	95.8	99.9	85.6	65.9	95.5
36	94.0	94.49	86.8	97.9	94.2	109.0	117.5	111.4	96.0	90.7	65.0	121.6
37	114.9	91.58	91.1	102.2	95.9	106.8	80.0	97.7	97.5	81.6	78.1	121.5
38	112.0	98.11	105.4	98.3	87.0	104.1	97.9	119.4	95.6	88.1	75.0	111.0
39	109.8	89.56	103.1	61.0	37.1	52.5	35.5	113.7	101.7	93.7	26.6	110.6
40	111.8	97.52	102.9	102.5	24.2	46.8	73.9	127.2	104.4	98.9	63.6	81.2

Material and Methods

Chemistry. Commercially available reagents and solvents were purchased from Aldrich or Alfa Aesar and were used without further purification. Tetrahydrofuran (THF) was distilled immediately before use from Na/benzophenone under a slight positive atmosphere of dry nitrogen. Ethylenediamine was distilled immediately before use from CaH_2 under a slight positive atmosphere of dry nitrogen. Dichloromethane 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 nitrogen. Melting points were determined in open glass capillary with a Stuart scientific SMP3 apparatus and are uncorrected. All compounds were checked by IR (FT-IR THERMO-NICOLET AVATAR), ^{1}H and ^{13}C APT (JEOL ECP 300 MHz spectrometer), and mass spectrometry (Thermo Finningan LCQ-deca XP-plus) equipped with an ESI source and an ion trap detector. Chemical shifts are reported in parts per million (ppm). Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230–400 mesh ASTM). Thin layer chromatography (TLC) was carried out on 5x20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$ reagent. Purity of tested compounds was established by elemental analysis. Elemental analysis (C, H, N) of the target compounds are within ±0.4% of the calculated values.

7-octyn-1-ol (**4**), 8-nonyn-1-ol (**5**) and 9-decyn-1-ol (**6**) were synthesized as described by Denmark et al,[1] while 7-octynoic acid (**8**), 8-nonynoic acid (**9**) and 9-decynoic acid (**10**) were synthesized as described previously.[2]

***General procedure A for the synthesis of amides* A-X**

To a solution of the desired carboxylic acid (1 eq) in dry CH_2Cl_2 (6.0 mL), the corresponding amine (1 eq), EDCl (1.1 eq), DMAP (0.1 eq) and TEA (1.1 eq) were added. The resulting mixture was stirred at room temperature until the reaction was finished. The reaction was worked-up by dilution with water and extraction with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over sodium sulfate and concentrated *in vacuo.* Finally the crude material was purified by column chromatography using EtOAc and EtOAc/MeOH 95:5 as eluents to afford the desired product.

***N*-(Pyridin-3-ylmethyl)oct-7-ynamide (A)** Yellow solid; yield 80%; Rf = 0.30 (EtOAc); m.p. 60–62 °C; IR (KBr) 3284, 2937, 2258, 1640, 1425, 1245, 712 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.41 (s, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.63 (br s, 1H), 4.36 (d, *J* = 6.1 Hz, 2H), 2.22–2.09 (m, 4H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.61 (quint, *J* = 7.5 Hz, 2H), 1.52–1.31 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.2, 149.0, 148.7, 135.7, 134.4, 123.7, 84.4, 68.5, 40.9, 36.4, 28.3, 28.1, 25.2, 18.3; MS (ESI) *m/z* 231 $(M+H)^+$.

***N*-(Pyridin-4-ylmethyl)oct-7-ynamide (B)** Yellow solid; yield 85%; Rf = 0.24 (EtOAc); m.p. 61-63 °C; IR (KBr) 3293, 3075, 2936, 2108, 1641, 1562, 1416, 1248 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.42 (dd, *J* = 6.0, 1.4 Hz, 2H), 7.10 (dd, *J* = 6.0, 1.6 Hz, 2H), 6.87 (br s, 1H), 4.35 (d, *J* = 6.1 Hz, 2H), 2.21 (t, *J* =7.6 Hz, 2H), 2.13 (td, *J* = 6.9, 2.6 Hz, 2H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.62 (quint, *J* = 7.5 Hz, 2H), 1.53–1.33 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.8, 148.0, 122.3, 84.3, 68.5, 42.2, 36.3, 28.3, 28.1, 25.2, 18.3; MS (ESI) *m/z* 231 $(M+H)^+$.

***N*-(2-Pyridin-4-ylethyl)oct-7-ynamide (C)** Yellow oil; yield 99%; Rf = 0.20 (EtOAc); IR (KBr) 3306, 3074, 2935, 2114, 1638, 1546, 1417, 1243, 811, 695 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.49 (d, *J* = 5.8 Hz, 2H), 7.11 (d, *J* = 5.8 Hz, 2H), 5.59 (br s, 1H), 3.53 (q, *J* = 6.6 Hz, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.20–2.11 (m, 4H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.66–1.48 (m, 4H), 1.44–1.34 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.2, 149.4, 148.3, 124.1, 84.2, 68.4, 39.5, 36.2, 35.0, 28.2, 28.0, 25.1, 18.1; MS (ESI) *m/z* 245 $(M+H)^+$.

***N*-(2-Pyridin-3-ylethyl)oct-7-ynamide (D)** Yellow oil; yield 93%; Rf = 0.23 (EtOAc); IR (KBr) 3294, 3065, 2934, 2115, 1647, 1551, 1425, 1275, 1028, 714 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.23 (m, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.7, 5.0 Hz,, 1H), 6.83 (br s, 1H), 3.34 (q, *J* = 6.6 Hz, 2H), 2.69 (t, d, *J* = 7.0 Hz, 2H), 2.01 (m, 4H), 1.82 (m, 1H), 1.47 (quint, *J* = 7.4 Hz, 2H), 1.36 (m, 2H), 1.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.2, 149.6, 147.3, 136.2, 134.6, 123.3, 84.1, 68.3, 40.0, 36.1, 32.7, 28.0, 27.9, 25.0, 18.0; MS (ESI) *m/z* 245 $(M+H)^+$.

***N*-Pyridin-4-yloct-7-ynamide (E)** Yellow oil; yield 75%; Rf = 0.29 (EtOAc); IR (KBr) 3260, 2941, 2115, 1686, 1591, 1501, 1295, 1295, 829 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.49 (br s, 1H), 8.45 (dd, *J* = 4.9, 1.5 Hz, 2H), 7.53 (m, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.18 (td, *J* = 6.8, 2.8 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.73 (quint, *J* = 7.4 Hz, 2H), 1.59–1.40 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.1, 149.5, 146.4, 113.8, 83.9, 68.4, 36.9, 27.9, 27.7, 24.6, 17.9; MS (ESI) *m/z* 217 $(M+H)^+$.

***N*-Pyridin-3-yloct-7-ynamide (F)** Yellow solid; yield 83%; Rf = 0.49 (EtOAc); m.p. 59-60 °C; IR (KBr) 3257, 3170, 2941, 2114, 1681, 1552, 1478, 1276, 1129, 804 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, referred to main rotamer) δ 9.24 (br s, 1H), 8.58 (d, *J* = 6.6 Hz, 1H), 8.27 (m, 1H), 8.15 (m, 1H), 7.24 (dd, *J* = 8.3, 4.7 Hz, 1H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.14 (m, 2H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.69 (m, 2H), 1.56–1.35 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, referred to main rotamer) δ 172.7, 144.8, 141.1, 135.8, 127.7, 124.1, 84.5, 68.7, 37.3, 28.4, 28.2, 25.1, 18.4; MS (ESI) *m/z* 217 $(M+H)^+$.

***N*-(Pyridin-3-ylmethyl)non-8-ynamide (G)** Yellow oil; yield 71%; Rf = 0.76 (EtOAc:MeOH 9:1); IR (KBr) 3294, 3065, 2934, 2109, 1678, 1546, 1030, 713 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.41 (s, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.60 (br s, 1H), 4.36 (d, *J* = 5.8 Hz, 2H), 2.22–2.08 (m, 4H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.59 (quint, *J* = 7.4 Hz, 2H), 1.50–1.21 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.3, 149.0, 148.6, 135.7, 134.4, 123.7, 84.5, 68.4, 40.9, 36.5, 28.7, 28.4, 28.2, 25.6, 18.3; MS (ESI) *m/z* 245 $(M+H)^+$.

***N*-(Pyridin-4-ylmethyl)non-8-ynamide (H)** Yellow solid; yield 69%; Rf = 0.43 (EtOAc:MeOH 9:1); m.p. 75-77 °C; IR (KBr) 3275, 3070, 2981, 2107, 1646, 1547, 1416, 1215, 797 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.48 (d, *J* = 3.8 Hz, 2H), 7.14 (d, *J* = 5.0 Hz, 2H), 6.38 (br s, 1H), 4.40 (d, *J* = 6.1 Hz, 2H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.15 (td, *J* = 6.9, 2.7 Hz, 2H), 1.91 (t, *J* = 2.8 Hz, 1H), 1.65 (quint, *J* = 7.4 Hz,

2H), 1.54–1.44 (m, 2H), 1.42–1.31(m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.5, 149.9, 148.0, 122.4, 84.5, 68.4, 42.3, 36.4, 28.8, 28.4, 28.2, 25.6, 18.3; MS (ESI) *m/z* 245 $(M+H)^+$.

***N*-(2-Pyridin-4-ylethyl)non-8-ynamide (I)** Yellow solid; yield 81%; Rf = 0.53 (EtOAc:MeOH 9:1); m.p. 73-75 °C; IR (KBr) 3303, 3076, 2931, 2107, 1631, 1542, 1417, 1281, 995, 810 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.44 (br s, 2H), 7.09 (d, *J* = 5.8 Hz, 2H), 5.95 (br s, 1H), 3.50 (q, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.12 (m, 4H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.57 (q, *J* = 7.5 Hz, 2H), 1.48 (m, 2H), 1.41-1.23 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.3, 149.8, 148.4, 124.3, 84.6, 68.4, 39.7, 36.6, 35.3, 28.8, 28.4, 28.3, 25.6, 18.4; MS (ESI) *m/z* 259 $(M+H)^+$.

***N*-(2-Pyridin-3-ylethyl)non-8-ynamide (J)** Colorless oil; yield 72%; Rf = 0.50 (EtOAc:MeOH 9:1); IR (KBr) 3294, 3066, 2932, 2115, 1648, 1545, 1425, 1263, 714 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.30 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 7.7, 5.0 Hz, 1H), 6.52 (br s, 1H), 3.39 (q, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.05 (m, 4H), 1.85 (t, *J* = 2.6 Hz, 1H), 1.50 (quint, *J* = 7.6 Hz, 2H), 1.42–1.13 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.8, 147.6, 136.5, 134.7, 123.6, 84.5, 68.4, 40.2, 36.5, 32.9, 28.7, 28.3, 28.2, 25.6, 18.3; MS (ESI) *m/z* 259 $(M+H)^+$.

***N*-Pyridin-4-ylnon-8-ynamide (K)** White solid; yield 63%; Rf = 0.41 (EtOAc:MeOH 9:1); m.p. 118-119 °C; IR (KBr) 3261, 3103, 2941, 2111, 1682, 1592, 1463, 1183, 830, 725 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.45 (m, 1H), 8.40 (d, *J* = 6.3 Hz, 2H), 7.57 (d, *J* = 6.3 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.12 (td, *J* = 6.7, 2.7 Hz, 2H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.68 (quint, *J* = 7.4 Hz, 2H), 1.49–1.42 (m, 2H), 1.39-1.30 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.0, 150.1, 146.3, 114.0, 84.5, 84.4, 37.5, 28.7, 28.4, 28.2, 25.2, 18.1; MS (ESI) *m/z* 231$(M+H)^+$.

***N*-Pyridin-3-ylnon-8-ynamide (L)** White solid; yield 68%; Rf = 0.39 (PE:EtOAc 2:8); m.p. 101-102 °C; IR (KBr) 3246, 2935, 2114, 1686, 1584, 1424, 1284, 806, 704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.54 (m, 2H), 8.28 (d, *J* = 4.4 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.24 (m, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 2.15 (td, *J* = 6.9, 2.8 Hz, 2H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.70 (quint, *J* = 7.4 Hz, 2H), 1.54–1.26 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.4, 144.8, 141.0, 135.5, 127.5, 123.9, 84.6, 68.4, 37.4, 28.7, 28.4, 28.2, 25.4, 18.5; MS (ESI) *m/z* 231$(M+H)^+$.

***N*-(Pyridin-3-ylmethyl)dec-9-ynamide (M)** Yellow solid; yield 61%; Rf = 0.51 (EtOAc:MeOH 9:1); m.p. 72-74 °C; IR (KBr) 3293, 3196, 2933, 2107, 1641, 1552, 1425, 1263, 1029, 991 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.49 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 7.8, 4.9 Hz, 1H), 6.02 (br s, 1H), 4.44 (d, *J* = 5.8 Hz, 2H), 2.23–2.13 (m, 4H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.64 (q, *J* = 7.4 Hz, 2H), 1.48 (m, 2H), 1.39–1.23 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.1, 148.7, 135.7, 134.4, 123.6, 84.3, 68.3, 40.9, 36.6, 29.2, 28.8, 28.5, 28.4, 25.7, 18.4; MS (ESI) *m/z* 259 $(M+H)^+$.

***N*-(Pyridin-4-ylmethyl)dec-9-ynamide (N)** Yellow solid; yield 63%; Rf = 0.49 (EtOAc:MeOH 9:1); m.p. 82-83 °C; IR (KBr) 3295, 3199, 3075, 2930, 2108, 1641,1554, 1416, 1265, 803 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.50 (d, *J* = 4.6 Hz, 2H), 7.16 (d, *J* = 4.6 Hz, 2H), 6.18 (br s, 1H), 4.42 (d, *J* = 6.1 Hz, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.16 (m, 2H), 1.92 (t, *J* = 2.5 Hz, 1H), 1.65 (m, 2H), 1.50 (m, 2H), 1.37–1.23 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.6, 150.0, 148.0, 122.4, 84.8, 68.4, 42.3, 36.6, 29.3, 28.9, 28.7, 28.5, 25.8, 18.5; MS (ESI) *m/z* 259 $(M+H)^+$.

***N*-(Pyridin-4-ylmethyl)dec-9-ynamide (O)** White solid; yield 73%; Rf = 0.46 (EtOAc:MeOH 9:1); m.p. 67-69 °C; IR (KBr) 3224, 3076, 2930, 2109, 1637, 1555, 1417, 1228, 811 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.41 (d, *J* = 5.5 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 6.07 (br s, 1H), 3.48 (q, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.15–2.06 (m, 4H), 1.89 (t, *J* = 2.5 Hz, 1H), 1.55 (m, 2H), 1.46 (m, 2H),1.34 (m, 2H), 1.23 (m 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.5, 148.4, 124.3, 84.7, 68.3, 39.7, 36.7, 35.2, 29.2, 28.8, 28.6, 28.4, 25.7, 18.4; MS (ESI) *m/z* 273 $(M+H)^+$.

***N*-(2-Pyridin-3-ylethyl)dec-9-ynamide (P)** Amorphous yellow solid; yield 80%; Rf = 0.47 (EtOAc:MeOH 9:1); IR (KBr) 3209, 3083, 2929, 2117, 1548, 1424, 1307, 1026, 802cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.34 (m, 2H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.18 (dd, , *J* = 7.4, 2.7 Hz, 1H), 6.16 (br s, 1H), 3.44 (q, *J* = 6.6 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.07 (m, 4H), 1.88 (t, *J* = 2.6 Hz, 1H), 1.51 (m, 2H), 1.41 (m, 2H), 1.34–1.18 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.9, 147.7, 136.5, 134.7, 123.6, 84.7, 68.3, 40.3, 36.6, 33.0, 29.1, 28.8, 28.5, 28.4, 25.7, 18.4; MS (ESI) *m/z* 273 $(M+H)^+$.

***N*-Pyridin-4-yldec-9-ynamide (Q)** Yellow solid; yield 48%; Rf = 0.26 (EtOAc); m.p. 108–110 °C; IR (KBr) 3311, 3272, 3097, 2938, 2107, 1679, 1591, 1408, 1288, 1177, 829 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.57 (s, 1H), 8.40 (d, *J* = 5.2 Hz, 2H), 7.57 (d, *J* = 5.2 Hz, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.11 (m, 2H), 1.90 (t, *J* = 2.5 Hz, 1H), 1.67 (m, 2H), 1.45 (m, 2H), 1.38–1.23 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.2, 150.0, 146.4, 114.0, 84.7, 68.4, 37.6, 29.1, 28.8, 28.5, 28.4, 25.3, 18.4; MS (ESI) *m/z* 245 $(M+H)^+$.

***N*-Pyridin-3-yldec-9-ynamide (R)** Yellow solid; yield 62%; Rf = 0.40 (EtOAc); m.p. 73-75 °C; IR (KBr) 3310, 3254, 3046, 2931, 2111, 1663, 1543, 1485, 1284, 1188, 961, 800 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.15 (br s, 1H), 8.59 (d, *J* = 2.5 Hz, 1H), 8.24 (d, *J* = 4.4 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.22 (dd, *J* = 8.3, 4.7 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.10 (td, *J* = 6.6, 2.3 Hz, 2H), 1.89 (m, 1H), 1.65 (q, *J* = 7.1 Hz, 2H), 1.43 (m, 2H), 1.34–1.20 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.8, 144.4, 141.0, 135.8, 127.5, 123.9, 84.6, 68.3, 37.3, 29.1, 28.8, 28.5, 28.4, 25.5, 18.3; MS (ESI) *m/z* 245 $(M+H)^+$.

***N*-(Pyridin-3-ylmethyl)undec-10-ynamide (S)** Yellow solid; yield 83%; Rf = 0.39 (EtOAc:MeOH 9:1); m.p. 62-64 °C; IR (KBr) 3265, 3089, 2930, 2851, 2116, 1631, 1561, 1426, 1260, 1041, 712 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.43 (m, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.22 (dd, *J* = 8.0, 3.0 Hz, 1H), 6.45 (br s, 1H), 4.38 (d, *J* = 5.8 Hz, 2H), 2.17 (t, *J* = 7.7 Hz, 2H), 2.11 (dd, *J* = 7.1, 2.6 Hz, 2H), 1.90 (t, *J* = 2.8 Hz, 1H), 1.59 (q, *J* = 7.1 Hz, 2H), 1.46 (m, 2H), 1.33 (m, 2H), 1.26–1.19 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.3, 149.0, 148.7, 135.7, 134.4, 123.6, 84.7, 68.2, 40.9, 36.6, 29.2 (2-C), 28.9, 28.7, 28.4, 25.7, 18.4; MS (ESI) *m/z* 273 $(M+H)^+$.

***N*-(Pyridin-4-ylmethyl)undec-10-ynamide (T)** White solid; yield 75%; Rf = 0.35 (EtOAc:MeOH 9:1); m.p. 85-87 °C; IR (KBr) 3307, 3202, 3039, 2927, 2851, 2108, 1636, 1537, 1416, 1225, 997, 811 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.54 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.17 (d, *J* = 5.8 Hz, 2H), 5.91 (br s, 1H), 4.45 (d, *J* = 6.1 Hz, 2H), 2.25 (t, *J* = 7.7 Hz, 2H), 2.17 (td, *J* = 6.9, 2.7 Hz, 2H), 1.93 (t, *J* = 2.5 Hz, 1H),

1.67 (m, 2H), 1.51 (quint, *J* = 7.0 Hz, 2H), 1.43–1.24 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.5, 149.9, 148.0, 122.4, 84.8, 68.2, 42.3, 36.6, 29.3, 29.2, 29.0, 28.7, 28.5, 25.7, 18.4; MS (ESI) *m/z* 273 $(M+H)^+$.

***N*-(2-Pyridin-4-ylethyl)undec-10-ynamide (U)** White solid; yield 71%; Rf = 0.48 (EtOAc:MeOH 9:1); m.p. 84-85 °C; IR (KBr) 3307, 3208, 3075, 2927, 2109, 1632, 1560, 1417, 1281, 810, 704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.48 (d, *J* = 4.7 Hz, 2H), 7.11 (d, *J* = 5.5 Hz, 2H), 5.70 (br s, 1H), 3.51 (q, *J* = 6.6 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.18–2.08 (m, 4H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.62–1.44 (m, 4H), 1.35 (m, 2H), 1.31–1.21 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.9, 148.3, 124.3, 84.8, 68.3, 39.7, 36.8, 35.3, 29.3 (2-C), 29.0, 28.8, 28.5, 25.8, 18.5; MS (ESI) *m/z* 287 $(M+H)^+$.

***N*-(2-Pyridin-3-ylethyl)undec-10-ynamide (V)** White solid; yield 89%; Rf = 0.56 (EtOAc:MeOH 9:1); m.p. 57-59 °C; IR (KBr) 3312, 3201, 2927, 2120, 1636, 1545, 1426, 1286, 1025, 710 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.40 (d, *J* = 4.7 Hz, 1H), 8.37 (s, 1H), 7.29 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.19 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.94 (br s, 1H), 3.46 (q, *J* = 6.9 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.15–2.06 (m, 4H), 1.89 (m, 1H), 1.54 (m, 2H), 1.46 (m, 2H), 1.32 (m, 2H), 1.23 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 150.1, 147.9, 136.4, 134.6, 123.6, 84.8, 68.2, 40.3, 36.7, 33.0, 29.3, 29.2, 29.0, 28.7, 28.5, 25.8, 18.4; MS (ESI) *m/z* 287 $(M+H)^+$.

***N*-Pyridin-4-ylundec-10-ynamide (W)** White solid; yield 71%; Rf = 0.55 (EtOAc:MeOH 9:1); m.p. 94-96 °C; IR (KBr) 3246, 3182, 2928, 2112, 1686, 1408, 1297, 830 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.46 (d, *J* = 4.6 Hz, 2H), 8.04 (br s, 1H), 7.51 (d, *J* = 4.3 Hz, 2H), 2.38 (td, *J* = 7.7, 2.1 Hz, 2H), 2.16 (m, 2H), 1.93 (t, *J* = 2.8 Hz, 1H), 1.71 (m, 2H), 1.50 (m, 2H), 1.31 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.0, 150.2, 146.2, 113.9, 84.8, 68.3, 37.7, 29.3 (2-C), 29.0, 28.7, 28.5, 25.4, 18.4; MS (ESI) *m/z* 259 $(M+H)^+$.

***N*-Pyridin-3-ylundec-10-ynamide (X)** White solid; yield 69%; Rf = 0.32 (EtOAc:MeOH 9:1); m.p. 97-99 °C; IR (KBr) 3254, 3117, 2921, 2110, 1683, 1586, 1476, 1292, 1173, 806 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.98 (s, 1H), 8.59 (s, 1H), 8.25 (d, *J* = 4.7 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 8.2, 4.7 Hz, 1H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.10 (m, 2H), 1.90 (m, 1H), 1.66 (m, 2H), 1.46 (m, 2H), 1.26 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.8, 144.5, 141.0, 135.7, 127.6, 124.0, 84.8, 68.3, 37.4, 29.2 (2-C), 28.9, 28.7, 28.4, 25.6, 18.4; MS (ESI) *m/z* 259 $(M+H)^+$.

General procedure B for the synthesis of the 1,4-disubstituted triazoles

Alkyne (1 eq) and azide (1 eq) were dissolved in the minimum amount of dichloromethane. A mixture of water/*tert*-butanol (1:1, 0.5 mL), sodium ascorbate (0.1 eq) and copper (II) sulfate pentahydrate (0.01 eq) were added. The resulting mixture was stirred at room temperature overnight and then was concentrated *in vacuo*. The crude was submitted to biological evaluation as such.

After a preliminary screening, the selected target compounds were re-synthesized, purified by column chromatography and re-submitted to biological evaluation.

6-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)-*N*-(pyridin-3-ylmethyl)hexanamide (A12). Yellow oil; yield 38%; Rf = 0.24 (EtOAc/MeOH 9:1); IR (KBr) 3292, 2930, 1646, 1550, 1044, 764 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.35 (br s, 1H), 7.75 (br s, 1H), 7.59 (m, 1H), 7.55–7.44 (m, 4H), 7.29–7.25 (m, 4H), 7.05 (m, 2H), 6.90 (s, 1H), 6.33 (br s, 1H), 4.52 (s, 2H), 2.58 (t, *J* = 6.5 Hz, 2H), 2.20 (t, *J* = 6.7 Hz, 2H), 1.62–1.50 (m, 4H), 1.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.2, 148.0, 147.4, 137.6, 137.1, 135.3, 131.1, 129.8, 129.6, 128.7, 128.6 (2-C), 128.5, 128.0, 127.8, 126.6, 123.4, 123.3, 36.6, 28.9, 28.3, 25.2, 25.0; MS (ESI) *m/z* 426 $(M+H)^+$. Anal. Calcd for $C_{26}H_{27}N_5O$: C 73.39, H 6.40, N 16.46, found C, 73.56; H, 6.72; N, 16.30.

6-[1-(Biphenyl-4-ylmethyl)-1*H*-1,2,3-triazol-4-yl]-*N*-(2-pyridin-4-ylethyl)hexanamide (C13). White solid; yield 45%; Rf = 0.19 (EtOAc/MeOH 9:1); m.p. 175-176 °C; IR (KBr) 3313, 3068, 1644, 1542, 1211, 1051, 761 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD, 25 °C) δ 8.39 (br s, 2H), 7.75 (s, 1H), 7.60 (m, 4H), 7.45-7.33 (m, 5H), 7.27 (d, *J* = 5.0 Hz, 2H), 5.59 (s, 2H), 3.43 (t, *J* = 7.0 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.66–1.52 (m, 4H), 1.28 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.1, 150.0, 148.6, 148.1, 141.7, 140.3, 133.9, 129.0, 128.5, 127.9, 127.8, 127.2 124.3, 120.7, 53.8, 39.6, 36.5, 35.2, 29.0, 28.6, 25.4, 25.3; MS (ESI) *m/z* 454 $(M+H)^+$. Anal. Calcd for $C_{28}H_{31}N_5O$: C 74.14, H 6.89, N 15.44, found C,74.43; H,7.10; N, 15.64.

6-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl]-*N*-(2-pyridin-3-ylethyl)hexanamide (D12). Colorless oil; yield 66%; Rf = 0.23 (EtOAc/MeOH 9:1); IR (KBr) 3282, 2930, 1648, 1541, 1486, 1042, 763, 701 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.38 (br s, 2H), 7.59–7.38 (m, 5H), 7.25–7.19 (m, 4H), 7.03 (m, 2H), 6.88 (s, 1H), 3.47 (m, 2H), 2.79 (t, *J* = 7.1 Hz, 2H), 2.54 (t, *J* = 7.4 Hz, 2H), 2.08 (t, *J* = 7.5 Hz, 2H), 1.49 (m, 4H), 1.19 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.3, 150.1, 147.9, 147.7, 137.5, 137.0, 136.4, 135.3, 134.7, 131.1, 129.8, 128.7, 128.6, 128.5, 126.6, 123.6, 123.2, 40.3, 36.5, 33.0, 29.0, 28.4, 25.3, 25.1; MS (ESI) *m/z* 440 $(M+H)^+$. Anal. Calcd for $C_{27}H_{29}N_5O$: C 73.78, H 6.65, N 15.93, found C, 73.75; H, 6.54; N, 16.20.

7-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)-*N*-(pyridin-3-ylmethyl)heptanamide (G12). Yellow oil; yield 56%; Rf = 0.21 (EtOAc/MeOH 9:1); IR (KBr) 3283, 2930, 1654, 1541, 1226, 1043, 764 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.54 (br s, 1H), 7.66 (br s, 1H), 7.56–7.46 (m, 4H), 7.22 (m, 4H), 7.00 (m, 3H), 6.87 (s, 1H), 4.44 (s, 2H), 2.66 (br s, 1H), 2.51 (t, *J* = 6.4 Hz, 2H), 2.17 (t, *J* = 6.3 Hz, 2H), 1.57 (m, 2H), 1.44 (m, 2H), 1.21–1.14 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.5, 147.9 (2-C), 137.5, 137.1, 135.3, 131.1, 129.8, 128.9, 128.7 (2-C), 128.6, 128.5 (2-C), 128.5, 128.0, 126.5, 123.2, 41.2, 36.4, 29.1, 28.7, 28.3, 25.6, 25.1; MS (ESI) *m/z* 440 $(M+H)^+$. Anal. Calcd for $C_{27}H_{29}N_5O$: C 73.78, H 6.65, N 15.93, found C,73.90; H, 6.86; N, 15.71.

8-[1-(2-Benzylphenyl)-1*H*-1,2,3-triazol-4-yl]-*N*-(pyridin-3-ylmethyl)octanamide (M14). White solid; yield 60%; Rf = 0.24 (EtOAc/MeOH 9:1); m.p. 103-105 °C; IR (KBr) 3307, 3050, 1645, 1544, 1261, 1039, 766 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.52 (m, 2H), 7.62 (d, *J* = 7.4, Hz, 1H), 7.46–7.14 (m, 10H), 6.94 (d, *J* = 7.4 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.90 (s, 2H), 2.71 (t = 7.8 Hz, 2H), 2.22 (t, *J* = 7.7 Hz, 2H), 1.66 (m, 4H), 1.35 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.5, 149.2, 148.7, 148.0, 139.5, 137.0, 136.6, 135.7, 134.6, 131.5, 130.1, 128.7, 128.5, 127.5, 126.6, 126.4, 123.6, 122.8, 40.9, 37.3, 36.5, 29.3, 29.1, 28.9 (2-C), 25.7, 25.4; MS (ESI) *m/z* 468 $(M+H)^+$. Anal. Calcd for $C_{29}H_{33}N_5O$: C 74.49, H 7.11, N 14.98, found C, 74.50; H, 7.32; N, 15.21.

8-{1-[2-(Hydroxymethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}-*N*-(pyridin-3-ylmethyl) octanamide (M28). Yellow oil; yield 83%; Rf = 0.14 (EtOAc/MeOH 9:1); IR (KBr) 3284, 2928, 1739, 1647, 1542, 1217, 1043, 765 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.35 (br s, 2H), 7.68 (s, 1H), 7.57 (m, 2H), 7.44–7.30 (m, 3H), 7.17 (m, 2H), 4.4 (s, 2H), 4.32 (d, *J* = 5.5 Hz, 2H), 4.03 (br s, 1H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.15 (d, *J* = 7.4 Hz, 2H), 1.62–1.53 (m, 4H), 1.25 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.8, 148.7, 148.4, 148.2, 136.0, 135.9, 134.8, 130.8, 129.8, 128.8, 124.8, 123.7, 122.8 (2-C), 61.1, 40.8, 36.4, 29.1, 29.0, 28.8 (2-C), 25.6, 25.4; MS (ESI) *m/z* 408 $(M+H)^+$. Anal. Calcd for $C_23H_{29}N_5O_2$: C 67.79, H 7.17, N 17.19, found C,70.12; H, 7.42; N, 16.95.

8-[1-(2-Benzylphenyl)-1*H*-1,2,3-triazol-4-yl]-*N*-(2-pyridin-4-ylethyl)octanamide (O14). White solid; yield 28%; Rf = 0.25 (EtOAc/MeOH 9:1); m.p. 109–111 °C; IR (KBr) 3316, 3074, 2917, 1646, 1540, 1418, 1263, 766 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.44 (dd, *J* = 4.4, 1.4 Hz, 2H), 7.42 (m, 1H), 7.33–7.26 (m, 2H), 7.18-7.07 (m, 7H), 6.91 (d, *J* = 6.6 Hz, 2H), 6.08 (br t, 1H), 3.87 (s, 2H), 3.49 (q, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.11 (t, *J* = 7.4 Hz, 2H), 1.57 (m, 4H), 1.25 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 149.9, 148.3, 148.0, 139.5, 137.1, 136.6, 131.5, 130.0, 128.7, 128.5, 127.4, 126.6, 126.4, 124.2, 122.8, 39.7, 37.3, 36.6, 35.2, 29.4, 29.1, 28.9 (2-C), 25.7, 25.5; MS (ESI) *m/z* 482 $(M+H)^+$. Anal. Calcd for $C_{30}H_{35}N_5O$: C, 74.81; H, 7.32; N, 14.54, found C, 74.98; H, 7.70; N, 14.68.

8-[1-(2-Benzylphenyl)-1*H*-1,2,3-triazol-4-yl]-*N*-(2-pyridin-3-ylethyl)octanamide (P14). Colorless oil; yield 33%; Rf = 0.14 (EtOAc/MeOH 9:1); IR (KBr) 3286, 3028, 2856, 1654, 1547, 1453, 1044, 764 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.43 (m, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.45–7.26 (m, 4H), 7.23–7.10 (m, 5H), 6.92 (d, *J* = 7.4 Hz, 2H), 5.87 (s, 1H), 3.89 (s, 2H), 3.49 (q, *J* = 6.7 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.12 (t, *J* = 7.6 Hz, 2H), 1.66–1.49 (m, 4H), 1.31 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.3, 150.2, 148.1, 139.5, 137.1, 136.7, 136.3, 134.6, 131.5, 130.0, 128.7, 128.5, 127.4, 126.6, 126.4, 123.6, 123.2, 122.8, 40.3, 37.3, 36.7, 33.1, 29.4, 29.1, 29.0 (2-C), 25.7, 25.5; MS (ESI) *m/z* 482 $(M+H)^+$. Anal. Calcd for $C_{30}H_{35}N_5O$: C 74.81, H 7.32, N 14.54, found C,75.00; H, 7.56; N, 14.80.

8-(1-{2-[benzyl(*N*-methylglycyl)amino]ethyl}-1*H*-1,2,3-triazol-4-yl)-*N*-(2-pyridin-3-ylethyl)octanamide (P34). Colorless oil; yield 29%; Rf = 0.05 (EtOAc/MeOH 8:2); IR (KBr) 3265, 2929, 1643, 1550, 1363, 1217, 1051, 802, 716 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, refered to the main rotamer) δ 8.46 (br s, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.31–7.25 (m, 5H), 7.04 (d, *J* = 6.4 Hz, 2H), 5.87 (br s, 2H), 4.51 (br s, 2H), 4.16 (br s, 2H), 3.80 (br s, 2H), 3.47 (d, *J* = 6.1 Hz, 2H), 3.44 (s, 3H), 2.80 (t, *J* = 6.6 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.10 (t, *J* = 7.4 Hz, 2H), 1.58 (m, 4H), 1.28 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, refered to the main rotamer) δ 173.4, 170.4, 150.1, 148.6, 148.0, 136.4 (2-C), 135.7, 129.2, 129.0, 128.3, 128.1, 126.5, 121.7, 51.3, 47.7, 47.0, 40.3, 36.7, 33.1, 29.4, 29.3, 29.1, 28.9 (2-C), 25.6, 25.5; MS (ESI) *m/z* 520 $(M+H)^+$. Anal. Calcd for $C_{29}H_{41}N_7O_2$: C 67.02, H 7.95, N 18.87, found C, 67.32; H, 8.21; N, 18.64.

8-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)-*N*-pyridin-4-yloctanamide (Q12). Colorless oil; yield 61%; Rf = 0.30 (EtOAc/MeOH 9:1); IR (KBr) 3238, 2931, 1703, 1510, 1294, 1050, 828, 701 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.82 (s, 1H), 7.63–7.48 (m, 6 H), 7.26–7.22 (m, 4H), 7.06 (d, *J* = 1.7 Hz, 1H), 7.04 (d, *J* = 4.1 Hz, 1H), 6.96 (s, 1H), 2.59 (t, *J* = 7.3 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.67 (m, 2H), 1.49 (q, *J* = 7.6 Hz, 2H), 1.28–1.17 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.8, 150.6, 149.3, 147.9, 140.5, 137.5, 137.2, 135.3, 131.2, 129.9, 128.7, 128.5, 128.0, 126.5, 123.4, 115.9, 37.5, 29.2, 28.8, 28.5, 28.2, 25.1, 25.0; MS (ESI) *m/z* 440 $(M+H)^+$. Anal. Calcd for C 73.78, H 6.65, N 15.93, found C, 74.12; H, 6.80; N, 16.24.

8-[1-(4-Morpholin-4-ylphenyl)-1*H*-1,2,3-triazol-4-yl]-*N*-pyridin-4-yloctanamide (Q39). Brown-red solid; yield 45%; Rf = 0.28 (EtOAc/MeOH 9:1); m.p. 182-184 °C; IR (KBr) 3219, 3068, 1697, 1592, 1511, 1416, 1122, 927 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.70 (s, 1H), 8.48 (s, 1H), 7.66–7.56 (m, 5H), 6.98 (d, *J* = 9.1 Hz, 2H), 3.88 (d, *J* = 4.7 Hz, 4H), 3.21 (d, *J* = 4.7 Hz, 4H), 2.76 (d, *J* = 6.9 Hz, 2H), 2.38 (d, *J* = 6.9 Hz, 2H), 1.69 (br s, 4H), 1.34 (br s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.0, 151.4, 151.2, 145.8, 131.1, 129.6, 121.7, 119.0, 115.9, 112.4, 66.8, 48.9, 37.6, 29.3, 28.8, 28.6 (2-C), 25.4, 25.1; MS (ESI) *m/z* 449 $(M+H)^+$. Anal. Calcd for $C_{25}H_{32}N_6O$: C 66.94 H 7.19, N 18.74, found C, 67.11; H, 7.36; N, 18.43.

8-{1-[4-(Morpholin-4-ylmethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}-*N*-pyridin-4-yloctanamide (Q40). Off-white solid; yield 62 %; Rf = 0.16 (EtOAc/MeOH 9:1); m.p. 115-116 °C IR (KBr) 3244, 2927, 1708, 1593, 1518, 1300, 1116, 833 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.45 (m, 2H), 7.72 (s, 1H), 7.66 (d, *J* = 8.2 Hz 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.26 (s, 1H), 3.71 (t, *J* = 4.67 Hz, 4H), 3.54 (s, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.46 (t, *J* = 4.4 Hz, 4H), 2.38 (d, *J* = 7.4 Hz, 2H), 1.71 (m, 4H), 1.36 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 150.8, 149.0, 138.8, 136.1, 135.8, 132.8, 130.4, 120.3, 119.3, 67.0, 62.6, 53.6, 37.4, 29.4, 29.0, 28.9 (2-C), 25.6, 25.3; MS (ESI) *m/z* 463 $(M+H)^+$. Anal. Calcd for $C_{26}H_{34}N_6O_2$: C 67.51, H 7.41, N 18.17, found C, 67.18; H, 7.77; N, 18.36.

8-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)-*N*-(2-pyridin-3-ylethyl)octanamide (R12). Colorless oil; yield 68 %; Rf = 0.41 (EtOAc/MeOH 9:1); IR (KBr) 3270, 2930, 1689, 1541, 1483, 1420, 1287, 1043, 803, 763 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.62 (br s, 1H), 8.30 (br s, 1H), 8.20 (d, *J* = 8.3, Hz, 1H), 7.62–7.48 (m, 4H), 7.26 (m, 4H), 7.06 (, 2H), 6.92 (s, 1H), 5.29 (s, 1H), 2.59 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.69 (q, *J* = 7.1 Hz, 2H), 1.50 (q, *J* = 7.2 Hz, 2H), 1.29–1.18 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.6, 147.9, 144.8, 141.2, 137.5, 137.1, 135.6, 135.3, 131.1, 129.9, 128.7, 128.5, 128.0, 127.2, 126.6, 123.7 (2-C), 123.3, 37.3, 29.2, 28.9, 28.7 28.4, 25.4, 25.1; MS (ESI) *m/z* 440 $(M+H)^+$. Anal. Calcd for C 73.78, H 6.65, N 15.93, found C, 73.98; H, 6.90; N, 16.11.

***N*-(Pyridin-3-ylmethyl)-9-(1-quinolin-3-yl-1*H*-1,2,3-triazol-4-yl)nonanamide (S31).** Orange solid; yield 58%; Rf = 0.21 (EtOAc/MeOH 9:1); m.p. 143–144 °C; IR (KBr) 3309, 2922, 1649, 1541, 1217, 908, 752 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.30 (dd, *J* = 2.5 Hz, 1H), 8.46 (dd, *J* = 1.9 Hz, 2H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.90 (m, 2H), 7.77 (m, 1H), 7.66–7.59 (m, 2H), 7.23 (br s, 1H), 6.30 (s, 1H), 4.42 (dd, *J* = 5.8 Hz, 2H), 2.80 (t, *J* = 7.7 Hz, 2H), 2.21(t, *J* = 7.6 Hz, 2H), 1.75–1.61 (m, 4H), 1.30 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 150.0, 149.8, 149.1, 148.7, 147.6, 143.1, 135.6, 130.6, 130.4, 129.6, 128.3, 128.2, 127.5, 125.9, 119.3, 119.2, 41.0, 36.6, 29.3, 29.2 (2-C), 29.1(2-C), 25.7, 25.6; MS (ESI) *m/z* 443 $(M+H)^+$. Anal. Calcd for $C_{26}H_{30}N_6O$: C 70.56, H 6.83, N 18.99, found C, 70.77; H, 6.68; N,19.00.

9-[1-(4-Morpholin-4-ylphenyl)-1*H*-1,2,3-triazol-4-yl]-*N*-(pyridin-3-ylmethyl) nonanamide (S39). Brown solid; yield 86%; Rf = 0.23 (EtOAc/MeOH 9:1); m.p. 141-143 °C; IR (KBr) 3276, 2927, 1651, 1522, 1228, 1118, 928 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.75 (br s, 2H), 7.62 (br s, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.38 (br s, 1H), 4.46 (br s, 2H), 3.86 (t, *J* = 4.7 Hz, 4H), 3.19 (t, *J* = 4.7 Hz, 4H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.70–1.61 (m, 4H), 1.29 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.5, 151.3, 149.2, 149.1, 138.3, 134.9, 129.7, 122.1, 119.1 (2-C), 115.9, 66.8, 48.9, 41.5, 36.6, 29.4, 29.2 (2-C), 29.1 (2-C), 25.7, 25.6; MS (ESI) *m/z* 477 $(M+H)^+$. Anal. Calcd for $C_{27}H_{36}N_6O_2$: C 68.04, H 7.61, N 17.63, found C, 68.38; H, 7.60; N, 17.42.

***N*-Pyridin-4-yl-9-(1-quinolin-3-yl-1*H*-1,2,3-triazol-4-yl)nonanamide (W31).** Yellow solid; yield 92%; Rf = 0.29 (EtOAc/MeOH 9:1); m.p. 138–139 °C; IR (KBr) 3291, 3131, 1706, 1680, 1522, 1419, 1161, 902, 784 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.31 (d, *J* = 2.4 Hz, 1H), 8.50 (d, *J* = 2.2 Hz, 1H), 8.47 (br s, 2H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.07 (br s, 1H), 7.93 (m, 2H), 7.80 (t, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.53 (br s, 2H), 2.83 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 1.73 (m, 6H), 1.34 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.4, 150.7, 149.8, 147.7, 145.3 143.1, 130.7, 130.5, 129.7 128.4, 128.2, 127.5, 126.1, 119.2, 115.8, 37.8, 29.3, 29.0 (3-C), 28.9, 25.6, 25.3; MS (ESI) *m/z* 429 $(M+H)^+$. Anal. Calcd for $C_{25}H_{28}N_6O$: C 70.07, H 6.59, N 19.61 found C, 70.17; H, 6.63; N, 19.60.

9-[1-(4-Morpholin-4-ylphenyl)-1*H*-1,2,3-triazol-4-yl]-*N*-pyridin-4-ylnonanamide (W39). Colorless oil; yield 75%; Rf = 0.23 (EtOAc/MeOH 9:1); IR (KBr) 3308, 3139, 2850, 1688, 1593, 1522, 1241, 1119, 928, 823 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.49 (br s, 2H), 7.70 (s, 1H), 7.65 (br s, 2H), 7.58 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 3.87 (t, *J* = 4.7 Hz, 4H), 3.21 (t, *J* = 4.6 Hz, 4H), 2.76 (m, 2H), 2.38 (m, 2H), 1.71 (m, 4H), 1.32 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.8, 151.4, 148.6, 144.0, 133.6, 129.6, 121.7, 119.5, 115.8, 111.8, 66.8, 48.9, 37.7, 29.4, 29.0 (2-C), 28.9 (2-C), 25.5, 25.1; MS (ESI) *m/z* 463 $(M+H)^+$. Anal. Calcd for $C_{26}H_{34}N_6O_2$: C 67.51, H 7.41, N 18.17, found C, 67.67; H, 7.45; N, 17.86.

Preparation of amides 41-43

5-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)pentanenitrile (45). The title compound was prepared starting from heptynenitrile (**44**) and 2-azidobiphenyle (**12**) according to the general procedure **B**. White solid; yield 73%; Rf = 0.29 (PE/EtOAc 6:4); m.p. 74-75 °C; IR (KBr) 3145, 2938, 1554, 1483, 1219, 1047, 765 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.62 (m, 1H), 7.55–7.47 (m, 3H), 7.29 (m, 3H), 7.07 (m, 2H), 6.91 (s, 1H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.27 (d, *J* = 7.1 Hz, 2H), 1.66 (m, 2H), 1.55–1.48 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 146.6, 137.6, 137.1, 135.3, 131.1, 129.9, 128.7 (2-C), 128.6, 128.0, 126.6, 123.3, 119.6; MS (ESI) *m/z* 303 $(M+H)^+$.

5-(1-Biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)pentan-1-amine (46). Compound **45** (2.0 g, 6.62 mmol) was dissolved in 20.0 mL of dry THF and $LiAlH_4$ (0.30 g, 7.95 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 12h. The suspension was quenched by addition dropwise of saturated aqueous Na_2SO_4 at 0 °C. The resulting suspension was filtered and the filtrate was extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over sodium sulfate and concentrated *in vacuo* to give the product as a yellow oil (yield 57%); Rf = 0.45 ($MeOH/NH_4OH_{conc}$ 95:5); IR (KBr) 3299, 2931, 1486, 1317, 1042, 764 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.57-7.53 (m, 1H), 7.50–7.43 (m, 3H), 7.24-7.20 (m, 3H), 7.03-7.00 (m, 2H), 6.87 (s, 1H), 4.31 (br s, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 1.56-1.44 (m, 4H), 1.20 (quint, *J* = 7.0 Hz 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 147.5, 137.3, 136.8, 135.1, 130.8, 129.5, 128.4, 128.3, 128.2, 127.7, 126.3, 122.9, 41.4, 32.1, 28.8, 25.8, 25.0; MS (ESI) *m/z* 307 $(M+H)^+$.

***N*-[5-(1-biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)pentyl]-2-pyridin-3-ylacetamide (41).** The title compound was prepared starting from amine **46** and carboxylic acid **47** according to the general procedure **A**.Yellow oil; yield 32%; Rf = 0.27 (EtOAc/MeOH 9:1); IR (KBr) 3290, 3061, 2935, 1654, 1560, 1487, 1043, 765 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.48 (m, 2H), 7.51 (m, 1H), 7.48 (m, 3H), 7.24–7.19 (m, 5H), 7.02 (m, 2H), 6.90 (s, 1H), 6.48 (br s, 1H), 3.49 (s, 2H), 3.16 (m, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 1.51–1.40 (m, 4H), 1.20 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 169.3, 150.0, 147.5, 144.5, 143.7, 137.5, 137.1, 136.5, 135.2, 131.1, 129.9, 128.7, 128.5, 128.0, 126.5, 124.6, 123.3, 119.2, 42.9, 39.7, 28.8, 28.7, 25.8, 24.9; MS (ESI) *m/z* 426 $(M+H)^+$. Anal. Calcd for $C_{26}H_{27}N_5O$: C 73.39, H 6.40, N 16.46, found C, 73.30; H, 6.11; N, 16.32.

***N*-[5-(1-biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)pentyl]-3-pyridin-3-ylpropanamide (42).** The title compound was prepared starting from amine **46** and carboxylic acid **48** according to the general procedure **A**.Yellow oil; yield 29%; Rf = 0.31 (EtOAc/MeOH 9:1); IR (KBr) 3292, 3062, 1652, 1550, 1486, 1226, 1043, 765 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.40 (m, 2H), 7.60–7.49 (m, 5H), 7.24 (m, 3H), 7.16 (dd, *J* = 8.7, 4.8 Hz, 1H), 7.04 (m, 2H), 6.89 (s, 1H), 6.03 (br s, 1H), 3.16 (q, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.54–1.35 (m, 4H), 1.15 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 171.5, 149.8, 147.7, 147.6, 137.6, 137.1, 136.6, 136.2, 135.3, 131.1, 129.8, 128.7 (2-C), 128.5, 128.0, 126.6, 123.4, 123.2, 39.4, 37.9, 29.0, 28.9, 28.7, 25.9, 25.0; MS (ESI) *m/z* 440 $(M+H)^+$. Anal. Calcd for $C_{27}H_{29}N_5O$: C 73.78, H 6.65, N 15.93, found C, 73.91; H, 6.87; N, 16.15.

(2*E*)-*N*-[5-(1-biphenyl-2-yl-1*H*-1,2,3-triazol-4-yl)pentyl]-3-pyridin-3-ylacrylamide (43). The title compound was prepared starting from amine **46** and carboxylic acid **49** according to the general procedure **A**. Yellow solid; yield 43%; Rf = 0.35 (EtOAc/MeOH 9:1); m.p. 122–123 °C; IR (KBr) 3280, 3115, 1670, 1558, 1231, 981, 767 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.71 (s, 1H), 8.53 (d, *J* = 4.6 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.61–7.50 (m, 5H), 7.27-7.21 (m, 4H), 7.06 (m, 2H), 6.92 (s, 1H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.34 (br s, 1H), 3.36 (q, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.60–1.53 (m, 4H), 1.28 (quint, *J* = 7.0 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ 165.4, 150.1, 149.2, 147.6, 137.4, 137.1, 136.4, 135.2, 134.3, 131.1, 131.0, 129.9, 128.7 (2-C), 128.4, 128.0, 126.5, 123.8, 123.7, 123.4, 39.6, 28.8, 28.7, 25.9, 25.1; MS (ESI) *m/z* 438 $(M+H)^+$. Anal. Calcd for $C_{27}H_{27}N_5O$: C 74.12, H 6.22, N 16.01, found C, 74.21; H, 6.15; N, 16.23.

Biology. Wild type *Mus musculus* NAMPT and NMNAT isoform 3 (mNMNAT-3) were recombinantly expressed in bacteria and purified to homogeneity following established procedures.[3]

Coupled enzymatic assay for NAMPT activity. Assay was conducted as described previously,[4] with some modifications. The reactions were run at 37 °C, 104 nM of murine NAMPT (1.2 μg) reacted in a 200 μL sample containing 30 mM HEPES pH 7.5, 1 mM NAM, 0.2 mM PRPP, 1 mM ATP, 25 mM $MgCl_2$, 1 mM DTT, 75 mM ethanol, 30 mM semicarbazide, 5 mU mNMNAT-3 (2 μg), 2.5 U ADH (11 μg), and 110 μg BSA. For IC_{50} evaluation, each compound was tested in the above assay mixture after serial dilution from a stock solution prepared in DMSO. NADH formation was monitored over a period of 1 hour by emission of fluorescence at 455 nm upon excitation at 340 nm.

Cell culture. Neuroblastoma SH-SY5Y cells were cultured in Minimum Essential Medium leagle (MEM)/F12 (Sigma) supplemented with 10% fetal bovine serum (FBS), 2 mM glutamine, 10 units/mL penicillin, and 100 μg/m streptomycin. Cells were maintained in a humidified incubator supplied with 5% CO_2/95% air at 37 °C and were subcultured as needed by detaching the cells with 0.25% trypsin and 5 mM EDTA.

Cell viability assay. The colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-dipehenyltetrazolium bromide (MTT) method was used to analyze cell viability.[5] Briefly, 1 x 10^5 SH-SY5Y cells were plated in 24-well plates and maintained in incubator for 24h. Cells were treated as indicated for the appropriate time. Compounds were dissolved in DMSO and were added to the cells to give a final DMSO concentration no greater than 0.5%. At the end f the treatment, cells were washed once in 500 μL of Locke buffer (134 mM NaCl, 5 mM KCl, 4 mM NaHCO3, 10 mM Hepes, 2.3 mM $CaCl_2$, 1 mM $MgCl_2$ and 5 mM D-glucose; pH 7.4) and 300 μL of MTT (250 μg/mL in Locke buffer) were added before returning the cells to the incubator for 1 h to allow the formation of the purple formazan crystals. After 1 hour, 600 μL of isopropanol/0.1 M HCl were added to each well, and the absorbance was read at 570 nm in a plate reader (Victor3V, PerkinElmer Life Sciences).

Molecular modeling. All molecular modeling studies were performed on a Tesla workstation. Different crystal structures of human NAMPT homodimer have been reported; in our study, the X-ray structure of the FK866-hNAMPT complex was used (PDB ID: 2GVJ).[6] The FK866 and water molecules were removed; the binding site was detected using the original ligand coordinates. In the crystal structure a water molecules is involved in a hydrogen bond network located between FK866 and protein aminoacids, this water molecule was considered as possible structural water. Ligand structures were built from a SMILES string and were minimized using Omega2.[7-9] The docking simulations were performed using FRED, and default settings were used.[10, 11] To validate the use of the FRED program, the docking studies were performed on the reference compound FK866. FRED successfully reproduced the binding conformations reported in the X-ray structure with acceptable root-mean-square deviation (rmsd < 1 Å) of atom coordinates with or without the water molecule in the active site, for this reason in the other simulation was not considered in the simulations. All structural images were prepared using PyMOL.[12]

References

1. S. E. Denmark and S.-M. Yang, *Tetrahedron*, 2004, **60**, 9695-9708.
2. T. Pirali, F. Pagliai, C. Mercurio, R. Boggio, P. L. Canonico, G. Sorba, G. C. Tron and A. A. Genazzani, *J Comb Chem*, 2008, **10**, 624-627.
3. G. Orsomando, L. Cialabrini, A. Amici, F. Mazzola, S. Ruggieri, L. Conforti, L. Janeckova, M. P. Coleman and G. Magni, *PLoS One*, 2012, **7**, e53271.
4. E. S. Burgos and V. L. Schramm, *Biochemistry*, 2008, **47**, 11086-11096.
5. G. Colombano, C. Travelli, U. Galli, A. Caldarelli, M. G. Chini, P. L. Canonico, G. Sorba, G. Bifulco, G. C. Tron and A. A. Genazzani, *J Med Chem*, 2010, **53**, 616-623.
6. J. A. Khan, X. Tao and L. Tong, *Nat Struct Mol Biol*, 2006, **13**, 582-588.
7. OMEGA, version 2.4.6; OpenEye Scientific Software, Santa Fe, NM. http://www.eyesopen.com
8. P. C. D. Hawkins, A. G. Skillman, G. L. Warren, B. A. Ellingson and M. T. Stahl, *J Chem Inf Model*, 2010, **50**, 572-584.
9. P. C. D. Hawkins and A. Nicholls, *Journal of Chemical Information and Modeling*, 2012, **52**, 2919-2936.
10. FRED, version 3.0.0; OpenEye Scientific Software, Santa Fe, NM. http://www.eyesopen.com
11. M. McGann, *J Chem Inf Model*, 2011, **51**, 578-596.
12. The PyMOL Molecular Graphics System, version 1.3; Schrödinger LLC,