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ORIGINAL ARTICLE

Functionalization of protected tyrosine via Sonogashira reaction: synthesis of 3-(1,2,3-triazolyl)-tyrosine

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Abstract 1,2,3-Triazol tyrosines were synthesized from tyrosine alkynes that were in turn prepared via Sonogashira cross-coupling reaction. The tyrosine alkynes were subjected to click-chemistry reaction conditions leading to the corresponding 3-(1,2,3-triazolyl)-tyrosines in yields ranging from moderate to good.

Keywords Tyrosine · Alkyne · Click chemistry · Triazole · Peptide bond

Introduction

The amino acid tyrosine, a nonessential amino acid with a polar side chain, is one of the most useful amino acids due to the chemical reactivity of its side-chain phenolic moiety [1]. Reactions such as alkylation and acylation of tyrosine under basic conditions can be carried out in the presence of oxygen. In acidic conditions, an ene-like reaction occurs at a carbon atom on the aromatic ring. Many examples of tyrosine-mediated protein modifications using oxidative reactions [2–4], Mannich-type reactions [5–7], diazonium coupling reactions [8–11], and tyrosine click reactions have been described in previously published reports [12–14].

Just to name a few examples to highlight the importance of this amino acid, tyrosine is a building block for several interesting molecules with biological activity, such as monocyclic peptides, including K-13, a noncompetitive inhibitor of angiotensin I-converting enzyme (ACE) [15] and a weak inhibitor of aminopeptidase B, tumor necrosis factor-α antagonist [16] (Fig. 1), cross-linked tyrosine oligomers [17], glycosylated portions of mannopeptimycin-E [18], and isopeptides [19].

In this sense, there is a great demand for methods that allow the synthesis of a variety of functionalized tyrosine derivatives. However, to the best of our knowledge, methods for the synthesis of the 3-(1,2,3-triazolyl)-tyrosine derivatives have not yet been reported.

Herein, we report an efficient and general access method for the synthesis of 3-(1,2,3-triazolyl)-tyrosine derivatives with a wide range of substituents through click chemistry.

Results and discussion

For our preliminary studies, we used commercially available 3-iodotyrosine without prior protection (**1** or **2**) directly for cross-coupling with terminal alkynes, but the desired product was not observed. Suspecting this was caused due to an incompatibility with the presence of the carboxylic acid, *N*-tert-butyloxycarbonyl-3-iodotyrosine **2** was methylated with dimethyl sulfate in the presence of potassium carbonate in acetone to afford the iodotyrosine **3** ester in 82 % yield (Scheme 1) [20].

With **3** at hand, we sought the best conditions for the Sonogashira-type cross-coupling reaction. For a standard

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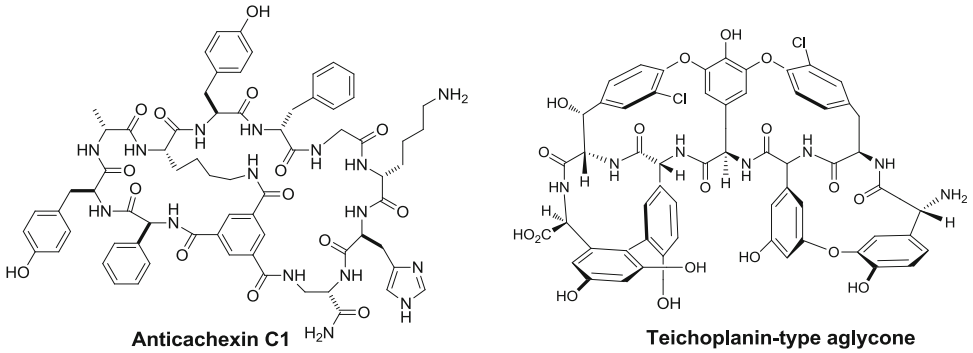
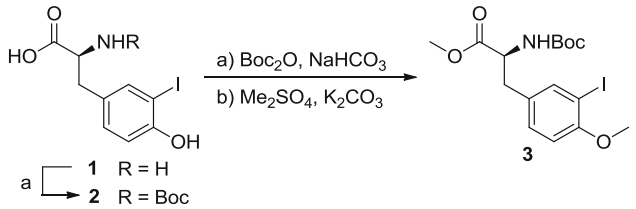


Fig. 1 Structures of Anticachexin C1 and Teicoplanin-type aglycone



Scheme 1 Protection of 3-iodotyrosine

reaction, we used phenylacetylene in a 3:1 ratio for the 3-iodotyrosine. The results are summarized in Table 1.

Different sources of palladium were tested. When we used $Pd(PPh_3)_4$ (Table 1, entry 1), which is commonly employed in the Sonogashira reaction, the desired product was obtained in 75 % yield. When using $Pd(PPh_3)_2Cl_2$ (Table 1, entry 2), which has previously been described for similar compounds [21], the reaction afforded desired product in 58 % yield. Based on the results from entries 3 and 7, we observed that a possible exchange was occurring between the Pd ligands and the amino group on tyrosine as evidenced by mass spectrometry. However, it was not possible to isolate these species to confirm this observation. When we used $Pd_2(dba)_3$ and Pd(PEPPSI)-*i*Pr (Table 1, entries 5 and 6), the desired product was not observed. When inorganic bases were employed, product formation occurred in high yields, with fewer impurities compared to using organic bases. The use of TMEDA as a base (Table 1, entry 12) produced the product in only 8 % yield.

After evaluating different solvents (Table 1, entries 13–17), it became clear that the best solvent for the reaction is THF. We established 24 h as the maximum time for all reactions, after which time the reactions were adequately worked-up and purified to isolate the desired product.

When the amount of copper co-catalyst was changed to 10 mol% (Table 1, entry 18), the product was obtained in 76 % yield with total consumption of the starting material, whereas in the absence of copper salt (Table 1, entry 19), the desired product was obtained only in 35 % yield.

The reaction was found to be dependent on the presence of both palladium catalyst and base (Table 1, entries 20 and 21), as starting material **3** was always recovered; however, without the addition of base, only the homo-coupling product between alkynes **4a** was observed. As an alternative source of heat energy, microwave irradiation was used (Table 1, entry 22). The reaction consisted of the addition of all reagents to a vial and irradiation at 100 °C for 1 h affording product in 32 % yield. The optimized conditions showed that the combination of 3-iodotyrosine (0.1 mmol) **3a** with an excess of phenylacetylene (0.3 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10 mmol%), CuI (0.1 mmol), and THF (2.0 mL) at 60 °C under a nitrogen atmosphere, provided the tyrosine acetylene product **5a** in 91 % yield (Table 1, entry 8) after 6 h of reaction. With the best reaction conditions established, we varied the alkynes, which are listed in Table 2.

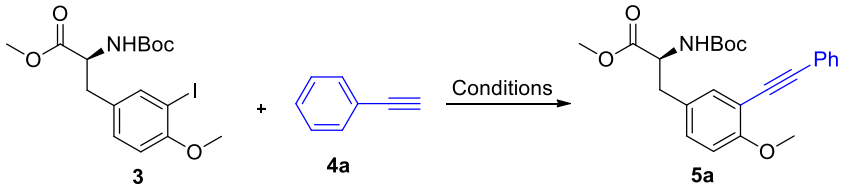
Aromatic rings linked directly to the alkyne *sp* carbon led to their products with yields ranging from moderate to good, 58–91 % (Table 2, entries 1–4). Product **5e**, containing a biphenyl group, was obtained in lower yield, 46 % (Table 2, entry 5), whereas the heterocyclic product **5f** was obtained in 75 % yield (Table 2, entry 6). For both cyclic compounds (Table 2, entries 7 and 12), 80 % yields were achieved. An aliphatic chain binding at the triple bond led to products in similar yields (Table 2, entries 8 and 9) and product **5j** was achieved in 75 % yield (Table 2, entry 10). When used a secondary alcohol attached at the acetylene, the product was obtained in 68 % yield (Table 2, entry 11).

Starting from example **5j** (Table 2, entry 10), and stimulated with the possibility of obtaining triazole rings, we therefore investigated the best conditions for the cycloaddition reaction between 3-(ethynyltrimethylsilyl)-tyrosine **5j** and phenyl azide **6a**.

To obtain 1,4-disubstituted-1,2,3-triazole, it was necessary to add a source of fluoride in situ to deprotect the alkyne and allow the subsequent cycloaddition reaction. TBAF (tetra-*n*-butylammonium fluoride) [22] was used for this purpose; however, before its addition, all reactions were analyzed by TLC and GC-MS, which showed no evidence of the formation of a trisubstituted triazole product confirming the presence of the trimethylsilyl group [23].

As can be seen in Table 3, after screening the reaction with different copper sources, it was determined that a stoichiometric amount of CuI (I) (Table 3, entry 1) was the best

Table 1 Coupling conditions between phenylacetylene and 3-iodotyrosine



Entry	Catalyst	Base	Solvent	Yield (%)[a]
1	$Pd(PPh_3)_4$	TEA	THF	75
2	$Pd(PPh_3)_2Cl_2$	TEA	THF	58
3	$Pd(OAc)_2$	TEA	THF	–
4	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	TEA	THF	87
5	$Pd_2(dba)_3$	TEA	THF	–
6	Pd(PEPPSI)-*i*Pr	TEA	THF	–
7	$PdCl_2$	TEA	THF	–
8	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	THF	91
9	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	K_2CO_3	THF	89
10	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Cs_2CO_3	THF	88
11	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	DIPEA	THF	54
12	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	TMEDA	THF	8
13	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	DMSO	12
14	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	DCM	27
15	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	DMF	7
16	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	Toluene	9
17	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	MeOH	24
18[b]	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	THF	76
19[c]	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	THF	35
20	–	Na_2CO_3	THF	–
21	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	–	THF	–
22[d]	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Na_2CO_3	THF	32

Conditions: **3** (0.1 mmol), **4a** (0.3 mmol), catalyst (10 mol%), base (0.1 mmol), CuI (0.1 mmol), solvent (2 mL), 60 °C
[a] Isolated yields
[b] CuI (10 mol%)
[c] Without copper addition
[d] Reaction under microwave irradiation, 100 °C, 1 h

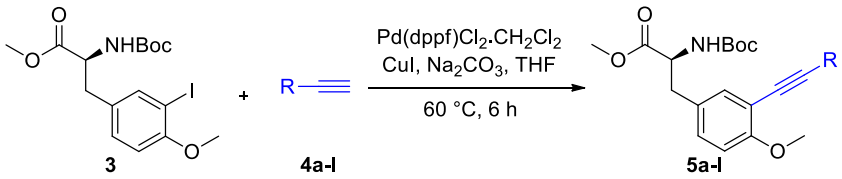
option. When we changed the additive to sodium ascorbate (NaAsc) in organic bases, the best performance was achieved with TEA at 50 °C.

Solvents such as water, toluene, DCM, and ACN led to yields lower than 72 %, which was the yield obtained with THF. In an attempt to form the product through a thermal reaction without the use of additives or copper salts, the reaction was irradiated with microwaves at 120 °C for 1 h (Table 3, entries 22 and 23), but the starting material was fully recovered and, in the case of entry 23, only the desilylated product was obtained as a result of the reaction with the TBAF.

Different examples of triazole rings were obtained, as described in Table 4. Aromatic azides, such as phenyl azide, led to the triazole product in 72 % isolated yield (Table 4, entry 1), azides containing chlorine atoms (Table 4, entries 2 and 3) provided the desired products with moderate yields (55 and 51 %, respectively), indicating that the chlorine atom in the aromatic ring of the azide, bound at the *meta* or *para* position, did not lead to a significant difference in performance between species. In addition, as shown in entry 6, the iodine atom attached at the *para* position of the aromatic ring gave the product with a similar efficiency to their chlorine-containing analogs.

The reaction was sensitive to the presence of electron-withdrawing groups in the case of aromatic azides. The desired product was obtained in 38 % yield when the nitro group was in the *meta* position, and 20 % yield with the nitro group in the *para* position to the triazole ring (Table 4, entries 4 and 5).

Table 2 Examples of Sonogashira cross-coupling reactions



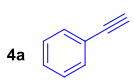
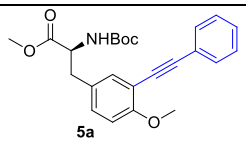
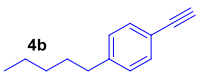
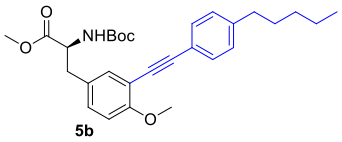
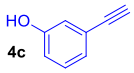
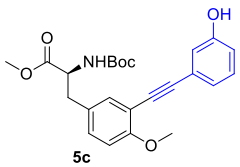
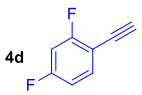
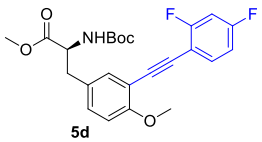
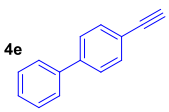
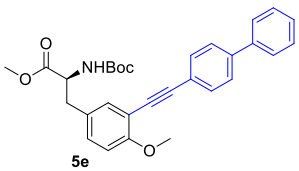
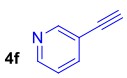
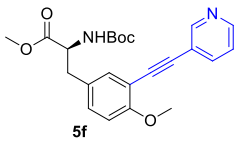
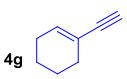
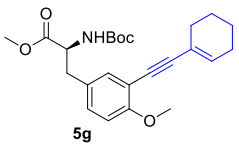
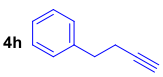
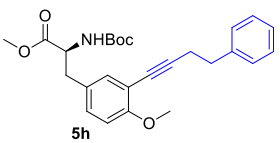
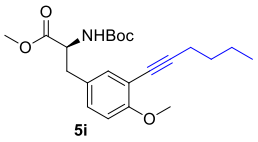
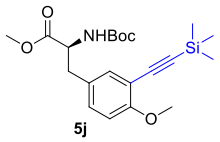
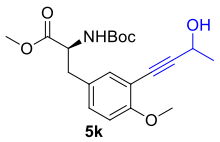
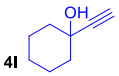
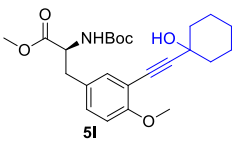
Entry	Alkyne	Product	Yield (%) [a]
1			91
2			58
3			82
4			67
5			46
6			75
7			80
8			77

Table 2 continued

Entry	Alkyne	Product	Yield (%) [a]
9	 4i	 5i	78
10	 4j	 5j	75
11	 4k	 5k	68
12	 4l	 5l	80

[a] Yields refer to isolated products

When alkyl azides were employed, such as benzyl azide, and a fluorine-containing analog bound at the *para* position, respective yields of 65 and 68 % were observed (Table 4, entries 7 and 8). When azides with electron-donating groups were used (Table 4, entries 9, 10, and 11), we did not obtain good yields (36, 38, and 56 %, respectively). When two equivalents of 3-(ethynyltrimethylsilyl)-tyrosine **5j** and octane diazide **6m** were used, we obtained the bis-triazole **7m** in 42 % isolated yield (Table 4, entry 12).

Encouraged by the results of the synthesis of the dipeptide **10** [24], removal of the Boc group in compound **3** with TFA in DCM gave **8** in 68 % yield. At the same time, selective deprotection of the carboxylic acid was achieved through saponification with LiOH, leading to compound **9** in 63 % yield, allowing the coupling of compounds **8** and **9** using DIC and HOBt in DCM over 15 h. After purification, dipeptide **10** was isolated in 57 % yield. When iodine was bound to the dipeptide fragment, the cross-coupling reaction proceeded with the alkynyltrimethylsilyl species **4j** in a single step to give dipeptide **11** in 89 % yield (Scheme 2).

Dipeptide **11** was reacted with octane diazide **6m** in an attempt to form cyclic *bis*-triazolic compound **12** (Scheme 3); however, even though we used the optimized reaction conditions (Table 3), no desired product was observed. Other conditions were tested, such as $Cu(OAc)_2$ 10 mol%, sodium ascorbate 50 mol% in THF or DCM at 0.02 M under reflux; however, the desired product was not observed as assessed by NMR spectroscopy.

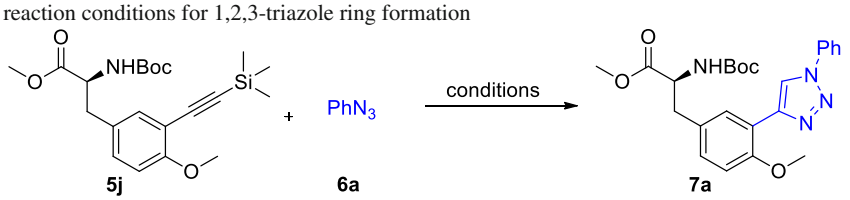
Summary

In summary, we have demonstrated that the Sonogashira cross-coupling of 3-iodotyrosine with different alkynes can be carried out using appropriate conditions. Subsequently, the obtained 3-(ethynyltrimethylsilyl)-tyrosine was submitted to click-chemistry reaction conditions, leading to the desired 3-(1,2,3-triazolyl)-tyrosines in moderate-to-good yields. The dipeptide obtained through a peptide linkage between two tyrosine fragments was submitted to the cross-coupling reaction with two equivalents of ethynyltrimethylsilane leading to the product in good yield. Attempts to prepare a triazole cyclic peptide were not successful.

Experimental section

All of the starting materials were commercial grade and were used without further purification. ^{1}H NMR ^{13}C NMR and spectra were recorded on a Bruker DPX 300 at 300 MHz and 75 MHz, respectively, using $CDCl_3$. Chemical shifts are

Table 3 Survey for the reaction conditions for 1,2,3-triazole ring formation



Entry	[Cu] (equiv)	Base or additive	Solvent	Yield (%)[a]
1	CuI (1)	Na asc	THF	67
2	$CuSO_4$(1)	Na asc	THF	5
3	$Cu(OTf)_2$(1)	Na asc	THF	17
4	$Cu(OAc)_2$(1)	Na asc	THF	42
5	CuCl (1)	Na asc	THF	65
6	$CuSO_4 \cdot 5H_2O$ (1)	Na asc	THF	Trace
7	Cu/Zn (1)	Na asc	THF	Trace
8	CuI (0,1)	Na asc	THF	34
9	$CuSO_4$(0,1)	Na asc	THF	–
10	$Cu(OTf)_2$(0,1)	Na asc	THF	29
11	$Cu(OAc)_2$(0,1)	Na asc	THF	25
12	CuCl (0,1)	Na asc	THF	30
13	$CuSO_4 \cdot 5H_2O$ (0,1)	Na asc	THF	–
14	CuI (1)	–	THF	37
15	CuI (1)	TEA	THF	72
16	CuI (1)	PMDETA	THF	23
17	CuI (1)	TMEDA	THF	5
18	CuI (1)	TEA	H_2O	24
19	CuI (1)	TEA	Toluene	28
20	CuI (1)	TEA	ACN	17
21	CuI (1)	TEA	DCM	26
22[b]	–	–	Toluene	–
23[c]	–	–	Toluene	–

Conditions: **5j** (0.1 mmol), **6a** (0.12 mmol), [Cu] (0.1 mmol), base (0.1 mmol), solvent (3 mL), TBAF (1.2 equiv), 50 °C

[a] Isolated yields

[b] Reaction under microwave irradiation, 120 °C, 1 h, without addition of TBAF

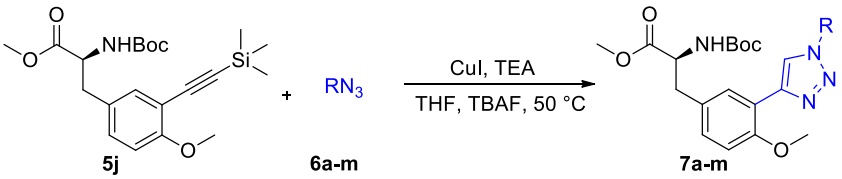
[c] Reaction under microwave irradiation, 120 °C, 1 h, 1.2 equiv of TBAF

reported in*ppm*, referenced to the solvent signal of $CDCl_3$ or tetramethylsilane (TMS) as the internal reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz, and integrated intensity. Abbreviations to denote the multiplicity of a particular signal are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), and m (multiplet). Column chromatography was performed using silica gel (230–400 mesh). Thin-Layer Chromatography (TLC) was performed using silica gel UV254, 0.20 mm thickness. Specific rotations were recorded using chloroform as solvent in different concentrations how is showed in each compound on a polarimeter Anton Paar MCP 200. IR spectra were recorded using an Agilent Cary 630 FTIR Spectrometer. High-Resolution Mass Spectra were obtained using a high-resolution ESI-TOF mass spectrometer Shimadzu LCMS-IT-TOF.

General procedure for tyrosine Sonogashira cross-coupling reaction (5a–l)

N-Boc-3-iodo-$_L$-tyrosine methyl ester **3** (43.5 mg, 0.1 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.1 mg, 0.01 mmol), and CuI (19 mg, 0.1 mmol) were added to a dried flask under nitrogen atmosphere. Freshly distilled THF (2 mL) was added via a syringe, then Na_2CO_3 (10.5 mg, 0.1 mmol) was added and the resulting solution was stirred for 10 min. Alkyne **4a-l** (0.3 mmol) was added slowly. The resulting solution was stirred at 60 °C. The reaction time was determined monitoring by TLC (6 h). The mixture was poured into 10 mL saturated NH_4Cl, and then extracted with ethyl acetate (3 × 15 mL). The organic layer was combined, dried with $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The

Table 4 Synthesis of tyrosine triazole rings



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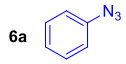
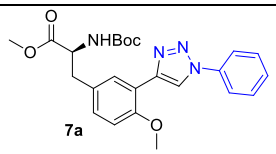
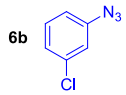
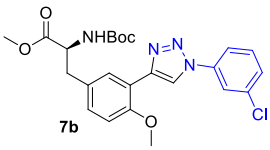
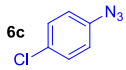
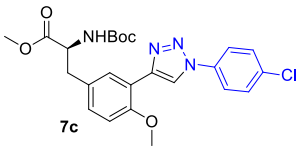
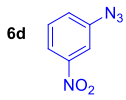
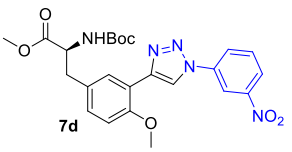
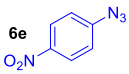
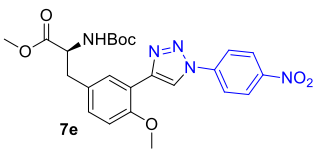
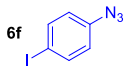
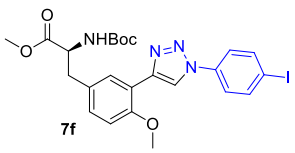
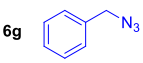
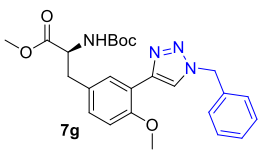
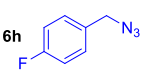
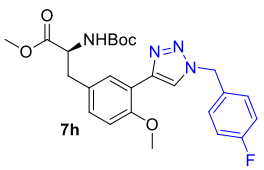
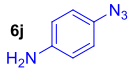
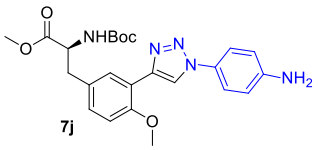
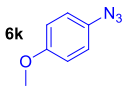
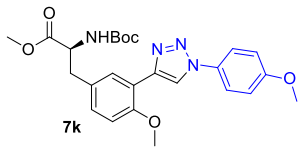
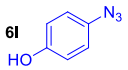
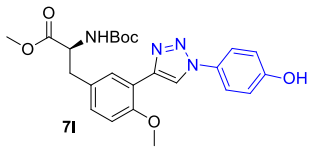
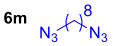
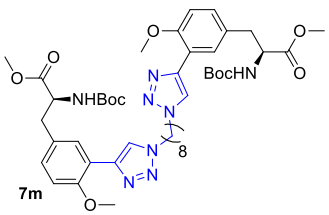
1			72
2			55
3			51
4			38
5			20
6			52
7			65
8			68

Table 4 continued

Entry	Azide	Product	Yield (%)[a]
9			36
10			38
11			56
12			42

[a] Yields refer to isolated products

resulting residue was purified by silica gel chromatography eluting with ethyl acetate/hexane.

*N-Boc-3-((phenyl)ethynyl)-tyrosine methyl ester (**5a**)*

The product was obtained as a brown oil. Yield 37.2 mg (91 %). $[\alpha]_D^{20}$ (c = 0.52, $CHCl_3$): +59.1°. IR (film) cm^{-1}: 3372, 2977, 1707, 1596, 1495, 1369, 1253, 1164, 1030, 780, 739, 683. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.0, 2.2 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.28 (s, 1H), 7.11 – 7.05 (m, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 6.9 Hz, 1H), 4.63 – 4.48 (m, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.04 (ddt, J = 19.5, 13.9, 5.9 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.27, 159.08, 155.06, 134.33, 131.62, 130.48, 128.24, 123.52, 112.60, 110.95, 93.51, 85.58, 79.97, 55.92, 54.55, 52.21, 37.30, 28.30. HRMS calcd. for $[C_{24}H_{27}NO_5 + Na]^+$: 432.1640. Found: 432.1643.

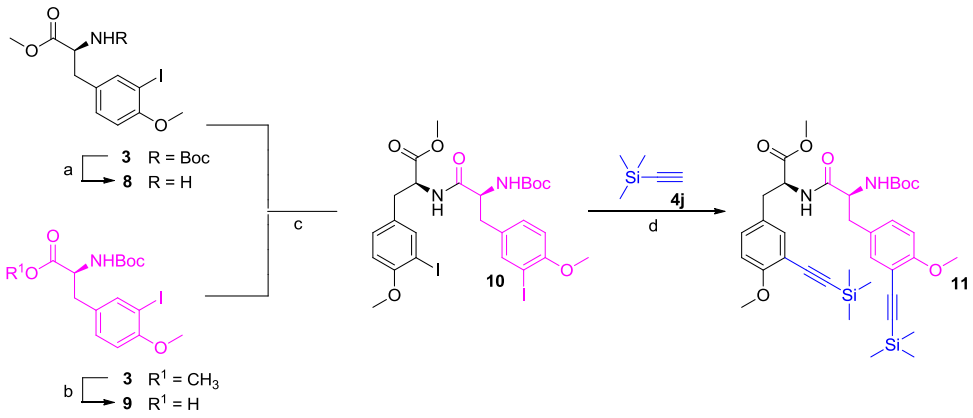
*N-Boc-3-((4-pentylphenyl)ethynyl)-tyrosine methyl ester (**5b**)*

The product was obtained as a brown oil. Yield 27.7 mg (58 %). $[\alpha]_D^{20}$ (c = 0.39, $CHCl_3$) : +56.3°. IR (film) cm-1: 3372, 2933, 1715, 1495, 1369, 1253, 1160, 1022, 817, 739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.33 (m, 2H), 7.12 – 6.92 (m, 3H), 6.70 (dd, J = 24.4, 8.4 Hz, 2H), 4.93 (d, J = 6.8 Hz, 1H), 4.50 – 4.41 (m, 1H), 3.79 (d, J = 10.9 Hz, 3H), 3.64 (s, 3H), 3.03 – 2.84 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.61 – 1.46 (m, 2H), 1.35 (s, 9H), 1.25 (m, 4H), 0.81 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.27, 159.01, 157.25, 143.27, 140.22, 134.27, 131.52, 130.24, 128.35, 128.01, 120.62, 112.84, 110.93, 110.86, 93.76, 84.84, 79.99, 56.33, 55.93, 52.23, 52.20, 35.85, 31.41, 30.88, 28.29, 22.49, 13.98. HRMS calcd. for $[C_{29}H_{37}NO_5 + Na]^+$: 502.2462. Found: 502.2466.

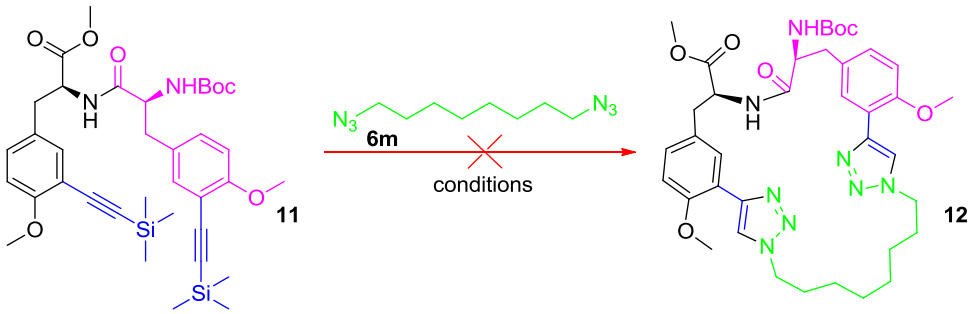
*N-Boc-3-((3-phenol)ethynyl)-tyrosine methyl ester (**5c**)*

The product was obtained as a brown oil. Yield 34.8 mg (82 %). $[\alpha]_D^{20}$ (c = 0.33, $CHCl_3$: +47.6°. IR (film) cm-1: 3346, 2981, 1689, 1581, 1503, 1443, 1369, 1261, 1156, 1026, 873, 788, 739, 691. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.12 – 7.04 (m, 3H), 6.89 – 6.77 (m, 3H), 5.10 (d, J = 8.2 Hz, 1H), 4.60 – 4.51 (m, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.02 (qd, J = 13.8, 6.0 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.38, 159.08, 156.02, 155.31, 134.28, 130.47, 129.43, 127.96, 124.47, 123.80, 118.40, 115.86, 112.59, 111.02, 93.48, 85.28, 80.34, 55.92, 54.56, 52.32, 37.29, 28.29. HRMS calcd. for $[C_{24}H_{27}NO_6 + Na]^+$: 448.1629. Found: 448.1631.

Scheme 2 Synthesis of the peptide **10**, followed by the C-C coupling reaction. Reagents and conditions: *a* TFA, DCM, rt, 12 h, 68 %; *b* LiOH, 1,4-dioxane, 0 °C, 5 h, 63 %; *c* HOBt, DIC, TEA, DCM, rt, 15 h, 57 %; *d* $Pd(PPh_3)Cl_2$, CuI, TEA, THF, 10 h, 89 %



Scheme 3 Unsuccessful macrocyclization with 1,8-diazidooctane



*N-Boc-3-((2,4-difluorophenyl)ethynyl)-tyrosine methyl ester (**5d**)*

The product was obtained as a yellow oil. Yield 29.8 mg (67 %). $[\alpha]_D^{20}$ (*c*= 0.12, $CHCl_3$): + 49.6°. IR (film) cm-1: 3372, 2981, 1711, 1607, 1510, 1443, 1369, 1257, 1164, 1026, 974, 855, 821, 784. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (td, J = 8.6, 8.2, 6.5 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.10 (dd, J = 8.5, 2.4 Hz, 1H), 6.93 – 6.82 (m, 3H), 5.03 (d, J = 7.7 Hz, 1H), 4.56 (s, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.03 (qd, J = 13.4, 5.6 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.21, 159.13, 155.01, 134.35, 134.16, 130.93, 128.13, 112.07, 111.61, 111.27, 110.99, 108.66, 104.51, 104.18, 103.85, 90.43, 85.63, 80.00, 55.96, 54.51, 52.21, 37.30, 28.26. HRMS calcd. for $[C_{24}H_{25}F_2NO_5 + Na]^+$: 468.1090. Found: 468.1092.

*N-Boc-3-(4-ethynyl-1,1' biphenyl)-tyrosine methyl ester (**5e**)*

The product was obtained as a brown oil. Yield 22.3 mg (46 %). $[\alpha]_D^{20}$ (c = 0.11, $CHCl_3$) : +48.4°. IR (film) cm-1: 3361, 2977, 1715, 1503, 1443, 1369, 1283, 1253, 1167, 1026, 847, 769, 702. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.2, 2.7 Hz, 6H), 7.40 – 7.32 (m, 2H), 7.30 – 7.24 (m, 1H), 7.20 (d, J = 2.3 Hz, 1H), 6.99 (dd, J = 8.5, 2.3 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 4.93 (d, J = 8.1 Hz, 1H), 4.47 (d, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.95 (qd, J = 13.9, 6.0 Hz, 2H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.28, 159.09, 140.84, 140.40, 134.34, 132.05, 130.50, 128.83, 128.09, 127.58, 126.99, 126.92, 122.45, 112.65, 110.96, 93.46, 86.28, 80.01, 55.96, 54.55, 52.24, 37.36, 28.31. HRMS calcd. for $[C_{30}H_{31}NO_5 + Na]^+$: 508.2001. Found: 508.2003.

*N-Boc-3-(3-ethynylpyridine)-tyrosine methyl ester (**5f**)*

The product was obtained as a brown oil. Yield 30.7 mg (75 %). $[\alpha]_D^{20}$ (*c*= 0.27, $CHCl_3$) : +49.3°. IR (film) cm-1: 3372, 2951, 1711, 1499, 1369, 1272, 1246, 1164, 1026, 739, 702. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.54 (d, J = 4.8 Hz, 1H), 7.83 (dt, J = 7.9, 1.9 Hz, 1H), 7.34 –7.25 (m, 2H), 7.11 (dd, J = 8.5, 2.3 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 5.06 (d, J = 7.9 Hz, 1H), 4.55 (d, J = 7.4 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.16 – 2.92 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.21, 159.18, 152.24, 148.39, 138.38, 134.36, 131.09, 128.19, 122.94, 120.72, 111.81, 110.93, 89.95, 88.94, 80.00, 55.91, 54.51, 52.23, 37.32, 28.28. HRMS calcd. for $[C_{23}H_{26}N_2O_5 + H]^+$: 411.1800. Found: 411.1804.

*N-Boc-3-(1-ethynylcyclohex-1-ene)-tyrosine methyl ester (**5g**)*

The product was obtained as a brown oil. Yield 33 mg (80 %). $[\alpha]_D^{20}$ (*c*= 0.34, $CHCl_3$) : +37.8°. IR (film) cm-1: 3342, 2977,

1711, 1506, 1521, 1369, 1257, 1167, 1030, 840, 739, 706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.09 – 6.96 (m, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.22 (tt, J = 4.0, 1.8 Hz, 1H), 4.99 (d, J = 8.2 Hz, 1H), 4.56 – 4.47 (m, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 2.98 (dq, J = 20.0, 8.7, 4.7 Hz, 2H), 2.29 – 2.21 (m, 2H), 2.18 – 2.10 (m, 2H), 1.71 – 1.56 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.27, 158.80, 155.04, 135.02, 134.16, 129.85, 127.89, 120.84, 113.07, 110.81, 95.47, 82.73, 79.92, 55.87, 54.50, 52.16, 37.28, 29.25, 28.27, 25.75, 22.35, 21.53. HRMS calcd. for $[C_{24}H_{31}NO_5 + Na]^+$: 436.1640. Found: 436.1646.

*N-Boc-3-(but-3-yn-1-ylbenzene)-tyrosine methyl ester (***5h***)*

The product was obtained as a brown oil. Yield 33.6 mg (77 %). $[\alpha]_D^{20}$ (c = 0.28, $CHCl_3$) : +73.6°. IR (film) cm-1: 2977, 1707, 1503, 1369, 1283, 1253, 1160, 1026, 810, 739, 709. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 5H), 7.16 – 6.94 (m, 2H), 6.80 (d, J = 8.5 Hz, 1H), 5.00 (d, J = 8.5 Hz, 1H), 4.58 – 4.49 (m, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.00 (dt, J = 19.9, 7.8 Hz, 4H), 2.77 (t, J = 7.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.28, 158.99, 155.06, 140.76, 134.46, 129.73, 128.53, 128.45, 128.34, 127.90, 126.25, 113.07, 110.77, 93.81, 79.94, 55.85, 54.51, 52.17, 37.30, 35.25, 28.29, 21.99. HRMS calcd. for $[C_{26}H_{31}NO_5 + Na]^+$: 460.1621. Found: 460.1625.

*N-Boc-3-(hex-1-yne)-tyrosine methyl ester (***5i***)*

The product was obtained as a brown oil. Yield 33.3 mg (78 %). $[\alpha]_D^{20}$ (c = 0.40, $CHCl_3$) : +47.5°. IR (film) cm-1: 3372, 2974, 1704, 1503, 1447, 1369, 1272, 1246, 1160, 1026, 821, 762. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.99 (dd, J = 8.5, 2.2 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 4.98 (d, J = 8.0 Hz, 1H), 4.52 (d, J = 7.3 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 2.98 (qd, J = 13.7, 6.0 Hz, 2H), 2.52 – 2.41 (m, 2H), 1.62 (dd, J = 14.6, 7.1 Hz, 2H), 1.59 – 1.44 (m, 4H), 1.43 (s, 9H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.26, 158.92, 155.01, 134.46, 130.24, 129.51, 127.84, 113.31, 110.84, 110.74, 94.71, 79.88, 55.85, 54.49, 52.22, 52.13, 37.25, 30.89, 28.26, 21.97, 19.41, 13.61. HRMS calcd. for $[C_{22}H_{31}NO_5 + Na]^+$: 412.1960. Found: 412.1963.

*N-Boc-3-(ethynyltrimethylsilyl)-tyrosine methyl ester (***5j***)*

The product was obtained as a yellow oil. Yield 30.3 mg (75 %). $[\alpha]_D^{20}$ (c = 0.07, $CHCl_3$) : +51.4°. IR (film) cm-1: 3394, 2974, 2151, 1711, 1506, 1249, 1160, 1026, 847, 825, 762. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.04 (dd, J = 8.4, 2.5 Hz, 1H), 6.82 (dd, J = 15.8, 8.5 Hz, 1H), 4.98 (d, J = 8.0 Hz, 1H), 4.52 (d, J = 7.4 Hz, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.00 (qd, J = 13.3, 5.6 Hz, 2H), 1.44 (s, 10H), 0.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.16, 159.38, 154.96, 134.97, 130.59, 127.84, 126.26, 110.85, 101.01, 55.87, 54.42, 52.13, 29.05, 28.24, 0.00.

HRMS calcd. for $[C_{21}H_{31}NO_5Si + Na]^+$: 428.1734. Found: 428.1735.

*N-Boc-3-(but-3-yn-2-ol)-tyrosine methyl ester (***5k***)*

The product was obtained as a brown oil. Yield 25.6 mg (68 %). $[\alpha]_D^{20}$ (c = 0.38, $CHCl_3$) : +62.3°. IR (film) cm-1: 3376, 2936, 1715, 1499, 1443, 1369, 1272, 1246, 1167, 1026, 739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.05 (dd, J = 8.5, 2.3 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.84 – 4.73 (m, 1H), 4.52 (d, J = 8.3 Hz, 1H), 3.85 (d, J = 1.7 Hz, 3H), 3.72 (d, J = 1.6 Hz, 3H), 2.98 (qd, J = 14.6, 14.1, 5.6 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.24, 159.03, 155.03, 134.47, 130.53, 128.04, 111.88, 110.83, 95.36, 79.98, 58.86, 55.84, 54.48, 52.20, 37.26, 28.27, 24.33. HRMS calcd. for $[C_{20}H_{27}NO_6 + Na]^+$: 400.1599. Found: 400.1601.

*N-Boc-3-(1-ethynylcyclohexanol)-tyrosine methyl ester (***5l***)*

The product was obtained as a yellow oil. Yield 34.5 mg (80 %). $[\alpha]_D^{20}$ (c = 0.17, $CHCl_3$) : +57.3°. IR (film) cm-1: 3439, 2936, 1704, 1503, 1443, 1369, 1257, 1164, 1063, 1026, 966, 739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.03 (dd, J = 8.5, 2.3 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 5.02 (d, J = 8.3 Hz, 1H), 4.52 (d, J = 7.0 Hz, 1H), 3.84 (d, J = 1.6 Hz, 3H), 3.72 (d, J = 1.6 Hz, 3H), 3.00 (tt, J = 17.1, 8.3 Hz, 2H), 2.54 (s, 1H), 2.06 – 2.00 (m, 2H), 1.75 – 1.54 (m, 8H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.24, 159.11, 155.02, 134.23, 130.25, 127.94, 112.32, 110.92, 97.20, 80.46, 79.94, 69.17, 60.36, 55.86, 54.50, 52.17, 40.11, 37.23, 29.02, 28.27, 25.29, 23.41. HRMS calcd. for $[C_{24}H_{33}NO_6 + Na]^+$: 454.1865. Found: 454.1869.

*Dipeptide (***11***)*

The product was obtained as a yellow oil. Yield 60.3 mg (89 %). $[\alpha]_D^{20}$ (c = 0.10, $CHCl_3$) : +22.2°. IR (film) cm-1: 3301, 2959, 2154, 1748, 1719, 1666, 1503, 1443, 1268, 1253, 1175, 11,38, 1030, 847, 765. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (qd, J = 7.6, 4.9, 3.2 Hz, 2H), 7.30 – 7.23 (m, 3H), 7.13 – 7.09 (m, 1H), 6.92 (dd, J = 8.5, 2.3 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 4.93 (s, 1H), 4.75 (q, J = 6.4 Hz, 1H), 4.26 (d, J = 7.4 Hz, 1H), 3.86 (s, 6H), 3.70 (s, 3H), 3.06 – 2.86 (m, 4H), 1.43 (s, 9H), 0.26 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.24, 170.64, 159.42, 159.36, 135.16, 134.78, 134.66, 130.77, 130.62, 128.25, 127.42, 112.38, 111.00,

110.80, 100.97, 98.64, 60.30, 55.85, 55.79, 53.26, 52.23, 36.87, 28.19, 0.00. HRMS calcd. for $[C_{36}H_{50}N_2O_7Si_2+H]^+$: 679.3350. Found: 679.3355.

General procedure for the azide-alkyne cycloaddition reactions (7a-l)

To a two-necked 25 mL round-bottomed flask under a nitrogen atmosphere containing CuI (19 mg, 0.1 mmol), THF (3 mL), organic azide (**6a-m**) (0.12 mmol), *N*-Boc-3-(trimethylsilylethynyl)-tyrosine methyl ester (40.5 mg, 0.1 mmol), TEA (14 μL, 0.1 mmol) was added TBAF (12 μL, 0.12 mmol, 1.0 M in THF), and the reaction mixture was stirred at 50 °C. The reaction time was determined monitoring by TLC. Then the reaction mixture was diluted with ethyl acetate and washed with aqueous NH_4Cl, the organic phase was collected, dried with $MgSO_4$, filtered, and the solvent was removed under vacuum. The product was purified by flash chromatography and eluted with ethyl acetate/hexane.

*N-Boc-3-(1-phenyl-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (***7a***)*

The product was obtained as a yellow oil. Yield 81.3 mg (72 %). $[\alpha]_D^{20}$ ($c = 0.19, CHCl_3$) : +64.7°. IR (film) cm-1: 3372, 2977, 1745, 1707, 1603, 1506, 1443, 1369, 1253, 1164, 1026, 814, 762, 739, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.11 (s, 1H), 7.71 (d, J = 7.9 Hz, 2H), 7.40 (dt, J = 30.2, 7.5 Hz, 3H), 7.03 (dd, J = 8.4, 2.3 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 5.00 (d, J = 8.2 Hz, 1H), 4.52 (d, J = 7.3 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.06 (q, J = 10.5, 7.4 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.36, 155.15, 154.90, 143.53, 137.26, 129.83, 129.65, 128.56, 128.49, 121.01, 120.55, 119.09, 111.08, 79.84, 55.53, 54.67, 52.29, 37.54, 28.27. HRMS calcd. for $[C_{24}H_{29}N_4O_5 + H]^+$: 453.2005. Found: 453.2009.

*N-Boc-3-(1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (***7b***)*

The product was obtained as a yellow oil. Yield 66.4 mg (55 %). $[\alpha]_D^{20}$ ($c = 0.37, CHCl_3$) : +60.3°. IR (film) cm-1: 3372, 2977, 1745, 1711, 1503, 1443, 1369, 1283, 1249, 1160, 1026, 762, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.09 (s, 1H), 7.67 – 7.58 (m, 1H), 7.44 – 7.27 (m, 2H), 7.04 (dd, J = 8.4, 2.3 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.52 (d, J = 7.7 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.06 (dt, J = 14.8, 7.0 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.35, 155.13, 154.93, 143.79, 138.09, 135.45, 130.76, 130.04, 128.58, 128.49, 120.77, 120.63, 118.76, 118.47, 111.09, 79.87, 55.56, 54.68, 52.30, 37.54, 28.28. HRMS calcd. for $[C_{24}H_{27}ClN_4O_5 + H]^+$: 487.1625. Found: 487.1629.

*N-Boc-3-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (***7c***)*

The product was obtained as a yellow oil. Yield 61.5 mg (51 %). $[\alpha]_D^{20}$ ($c = 0.11, CHCl_3$) : +60.9°. IR (film) cm-1: 3353, 2977, 1741, 1693, 1503, 1451, 1361, 1249, 1175, 1026, 836, 806 732. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.09 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.04 (dd, J = 8.4, 2.3 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.99 (d, J = 8.3 Hz, 1H), 4.51 (d, J = 7.9 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.07 (dt, J = 14.5, 7.0 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.34, 155.12, 154.90, 143.76, 135.73, 134.17, 129.99, 129.81, 128.58, 121.63, 120.78, 118.84, 111.08, 79.86, 55.54, 54.67, 52.29, 37.54, 28.27. HRMS calcd. for $[C_{24}H_{27}ClN_4O_5 + H]^+$: 487.1625. Found: 487.1630.

*N-Boc-3-(1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (***7d***)*

The product was obtained as a yellow oil. Yield 46.9 mg (38 %). $[\alpha]_D^{20}$ ($c = 0.02, CHCl_3$) : +14.1°. IR (film) cm-1: 3372, 2977, 1745, 1711, 1540, 1506, 1443, 1354, 1257, 1167, 1033, 806, 743. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.46 (s, 1H), 8.25 – 8.06 (m, 3H), 7.67 (t, J = 8.2 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 4.99 (d, J = 8.2 Hz, 1H), 4.53 (d, J = 7.4 Hz, 1H), 3.91 (s, 3H), 3.70 (s, 3H), 3.07 (td, J = 12.0, 10.2, 5.7 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.32, 154.99, 148.94, 144.26, 137.94, 130.86, 130.32, 128.65, 125.90, 122.85, 120.57, 118.41, 115.06, 111.11, 79.90, 55.62, 54.66, 52.32, 37.54, 28.28. HRMS calcd. for $[C_{24}H_{27}N_5O_7 + H]^+$: 498.1875. Found: 498.1878.

*N-Boc-3-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (***7e***)*

The product was obtained as a yellow oil. Yield 24.7 mg (20 %). $[\alpha]_D^{20}$ ($c = 0.08, CHCl_3$) : +37.0°. IR (film) cm-1: 3346, 2974, 1741, 1689, 1521, 1506, 1346, 1253, 1175, 1026, 858, 754. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.34 (d, J = 9.1 Hz, 2H), 8.10 (s, 1H), 7.97 (d, J = 9.1 Hz, 2H), 7.08 (dd, J = 8.5, 2.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.98 (d, J = 8.1 Hz, 1H), 4.52 (s, 1H), 3.91 (s, 3H), 3.70 (s, 3H), 3.09 (dt, J = 15.8, 7.3 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.30, 155.01, 147.02, 144.41, 141.40, 130.41, 128.71, 125.46, 120.44, 120.32, 118.32, 111.13, 79.92, 55.62, 54.65, 52.32, 37.58, 28.28. HRMS calcd. for $[C_{24}H_{27}N_5O_7 + H]^+$: 498.1875. Found: 498.1877.

*N-Boc-3-(1-(4-iodophenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (**7f**)*

The product was obtained as a yellow oil. Yield 74.5 mg (52 %). $[\alpha]_D^{20}$ ($c = 0.10, CHCl_3$) : +58.0°. IR (film) cm-1: 3346, 2974, 1741, 1689, 1495, 1443, 1361, 1249, 1171, 1026, 806. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.19 (s, 1H), 7.88 (d, $J = 8.7$ Hz, 2H), 7.59 (d, $J = 8.7$ Hz, 2H), 7.14 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 5.06 (d, $J = 8.3$ Hz, 1H), 4.62 (d, $J = 7.4$ Hz, 1H), 3.97 (s, 3H), 3.79 (s, 3H), 3.15 (s, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.34, 154.92, 143.83, 138.77, 136.91, 130.03, 128.63, 122.04, 120.60, 111.09, 93.19, 55.57, 52.32, 37.57, 28.97, 28.94, 28.29. HRMS calcd. for $[C_{24}H_{27}IN_4O_5+H]^+$: 579.1050. Found: 579.1053.

*N-Boc-3-(1-benzyl-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (**7g**)*

The product was obtained as a yellow oil. Yield 75.8 mg (65 %). $[\alpha]_D^{20}$ ($c = 0.06, CHCl_3$) : +51.5°. IR (film) cm-1: 3353, 2929, 1745, 1711, 1506, 1458, 1369, 1253, 1167, 1030, 817, 728. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.89 (s, 1H), 7.33 – 7.16 (m, 5H), 7.00 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 1H), 5.50 (s, 2H), 4.95 (d, $J = 8.2$ Hz, 1H), 4.50 (d, $J = 7.8$ Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.02 (t, $J = 7.4$ Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.39, 154.75, 143.31, 135.08, 129.66, 129.01, 128.53, 127.75, 123.12, 111.00, 55.42, 54.02, 52.30, 29.67, 28.95, 28.27. HRMS calcd. for $[C_{25}H_{30}N_4O_5+H]^+$: 467.2160. Found: 467.2165.

*N-Boc-3-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (**7h**)*

The product was obtained as a yellow oil. Yield 83 mg (68 %). $[\alpha]_D^{20}$ ($c = 0.06, CHCl_3$) : +60.0°. IR (film) cm-1: 3372, 2977, 1748, 1715, 1510, 1443, 1369, 1253, 1227, 1167, 1074, 1052, 1030, 821, 776. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.87 (s, 1H), 7.21 (dd, $J = 8.6, 5.4$ Hz, 2H), 6.99 (t, $J = 8.5$ Hz, 3H), 6.81 (d, $J = 8.4$ Hz, 1H), 5.48 (s, 2H), 4.94 (d, $J = 8.2$ Hz, 1H), 4.50 (s, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.05 (dt, $J = 14.9$, 7.3 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.37, 154.74, 143.47, 130.99, 129.68, 129.57, 128.49, 122.91, 116.14, 115.85, 110.99, 55.43, 53.23, 52.29, 37.54, 28.98, 28.27. HRMS calcd. for $[C_{25}H_{29}FN_4O_5+H]^+$: 485.2076. Found: 485.2079.

*N-Boc-3-(1-(4-aminophenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (**7i**)*

The product was obtained as a yellow oil. Yield 43 mg (36 %). $[\alpha]_D^{20}$ ($c = 0.13, CHCl_3$) : +46.9°. IR (film) cm-1: 3372, 2936, 1745, 1711, 1506, 1443, 1369, 1253, 1164, 1074, 1052, 1026, 817, 739, 706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.10 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.03 (dd, $J = 8.5$, 2.3 Hz, 1H), 6.85 (d, $J = 8.5$ Hz, 1H), 6.70 (d, $J = 8.8$ Hz, 2H), 4.98 (d, $J = 8.2$ Hz, 1H), 4.52 (s, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.06 (d, $J = 5.7$ Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.40, 154.84, 146.95, 143.11, 129.62, 128.93, 128.52, 122.35, 121.28, 115.26, 111.07, 55.52, 54.57, 52.31, 37.55, 28.28. HRMS calcd. for $[C_{24}H_{29}N_5O_5+H]^+$: 468.2110. Found: 468.2112.

*N-Boc-3-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (**7j**)*

The product was obtained as a yellow oil. Yield 45 mg (38 %). $[\alpha]_D^{20}$ ($c = 0.12, CHCl_3$) : +27.8°. IR (film) cm-1: 3372, 2977, 1748, 1715, 1521, 1443, 1369, 1257, 1171, 1041, 840. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.66 – 7.56 (m, 2H), 7.07 – 6.89 (m, 3H), 6.85 (d, $J = 8.3$ Hz, 1H), 4.98 (d, $J = 8.1$ Hz, 1H), 4.52 (s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.69 (s, 3H), 3.07 (p, $J = 6.6, 5.9$ Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.37, 159.69, 154.86, 143.34, 130.77, 129.73, 128.55, 122.23, 121.26, 119.24, 114.72, 111.07, 60.34, 55.62, 55.52, 54.67, 52.30, 37.56, 28.28, 23.54. HRMS calcd. for $[C_{25}H_{30}N_4O_6+H]^+$: 483.2120. Found: 483.2120.

*N-Boc-3-(1-(4-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)-tyrosine methyl ester (**7k**)*

The product was obtained as a brown oil. Yield 67 mg (56 %). $[\alpha]_D^{20}$ ($c = 0.22, CHCl_3$) : +52.4°. IR (film) cm-1: 3372, 2936, 2195, 1745, 1711, 1503, 1443, 1369, 1249, 1160, 1060, 1026, 739, 706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.08 (d, $J = 2.3$ Hz, 1H), 7.47 (d, $J = 8.9$ Hz, 2H), 7.03 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.87 (dd, $J = 14.3$, 8.5 Hz, 3H), 5.09 (d, $J = 8.5$ Hz, 1H), 4.53 (d, $J = 7.8$ Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.06 (td, $J = 15.2$, 14.5, 6.2 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.59, 157.22, 154.93, 143.20, 129.91, 129.82, 128.45, 122.30, 121.50, 116.35, 111.14, 60.45, 55.51, 52.44, 37.70, 28.28. HRMS calcd. for $[C_{24}H_{28}N_4O_6+H]^+$: 469.1960. Found: 469.1963.

*N-Boc-3-(1,1′-(octane-1,8-diyl)bis(1H-1,2,3-triazol-4, 1-diyl)bis-tyrosine methyl ester (**7l**)*

The product was obtained as a yellow oil. Yield 36.2 mg (42 %). $[\alpha]_D^{20}$ ($c = 0.19, CHCl_3$) : +1.1°. IR (film) cm-1: 3361, 2977, 1741, 1704, 1614, 1525, 1506, 1443, 1369, 1253, 1167, 1030, 832, 739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.00 (dd, $J = 8.4$, 2.3 Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 4.95 (d, $J = 8.0$ Hz, 2H), 4.50 (s, 2H), 4.30 (t, $J = 7.2$

Hz, 4H), 3.84 (s, 6H), 3.68 (s, 6H), 3.09 – 2.91 (m, 4H), 1.86 (t, J = 6.9 Hz, 4H), 1.30 (m, 17H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.39, 154.72, 142.82, 129.46, 128.47, 122.93, 119.55, 111.01, 55.46, 54.66, 52.27, 50.11, 37.53, 30.27, 28.74, 28.26, 26.34. HRMS calcd. for $[C_{44}H_{62}N_8O_{10}+H]^+$: 863.4564. Found: 863.4566.

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