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Article

Microwave-Assisted Synthesis of β-1,2,3-Triazolyl-α-amino Esters

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The reaction of ethyl (*p*-methoxyphenylimino)acetate with propargyl bromide mediated by activated zinc powder afforded alkynyl amine, which was then reacted with a variety of organic azides using a microwave energy source, leading to β-1,2,3-triazolyl-α-amino esters in good yield.

Keywords: microwave, amino ester, click chemistry, addition reaction, 1,2,3-triazole

Introduction

Since the seminal discovery of Sharpless and co-workers[1,2] and Meldal and co-workers[3] on alkyne cycloaddition using copper salts, under mild conditions, to give 1,4-disubstituted 1,2,3-triazoles in high yields and rate acceleration, an immense number of papers have been published.

In 2001, Sharpless, Kolb and Finn[1] of The Scripps Research Institute gave the name "Click chemistry" to the very best chemical reactions. The Cu^{I} catalyzed azide-alkyne cycloaddition (CuAAC) reaction[4] is in fact a premier example of click chemistry that can easily fulfill the prerequisites for making covalent connections between two molecular building blocks in a facile and selective way, under mild reaction conditions with no or little by-products.[5] The azides, being a rare example of a 1,3-dipolar reagent, are not very reactive but are preferred due to their relative lack of side reactions and stability in typical synthetic conditions.

The versatility and range of the reaction has been demonstrated by its use in different areas of science such as materials, drug discovery,[6] bioconjugation,[7] polymers,[8] supramolecular chemistry,[9] DNA labeling,[10] synthesis of oligonucleotides,[11] and the preparation of stationary phases for high performance liquid chromatography (HPLC) columns,[12] to name just some of the recent applications of this reaction.[13] It is noteworthy that the 1,2,3-triazole ring does not occur in nature.

Due to the relative resilience of 1,2,3-triazole species to metabolic degradation and their ability to form hydrogen bonds that can improve solubility,[14,15] the importance of this heterocyclic ring is growing, especially focusing on drug discovery. Some examples of applications of the 1,2,3-triazole moiety in the field of medicinal chemistry as a pharmacophore have been shown, such as anticancer, HIV protease inhibitors, antituberculosis, antifungal, and antibacterial (Figure 1).[13]

β-1,2,3-Triazolyl-α-amino esters are rarely described in the literature; in the previous syntheses described in the

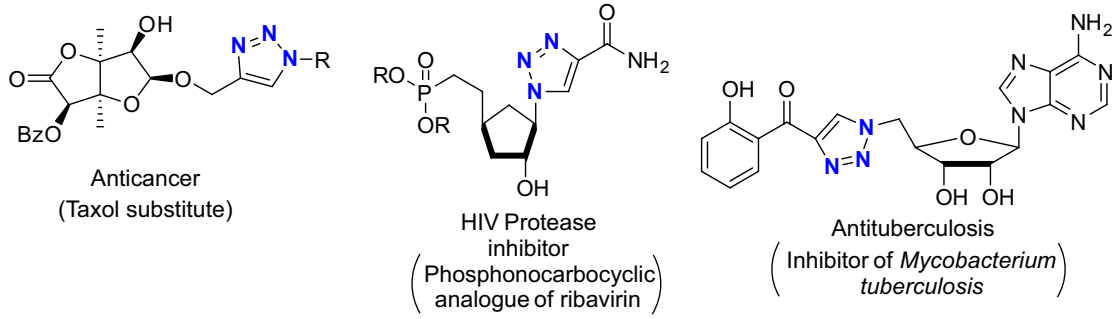

Figure 1. Structures of biologically active 1,2,3-triazoles.

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literature, three approaches were basically used. One of them used propargyl amino acids as building blocks,[16,17] some of which are commercially available, and a second made use of azide amino esters as a precursor for the cycloaddition of the alkynes.[18,19] In both cases, β-1,2,3-triazolyl-α-amino esters were afforded from low to high yields, despite the known complexation of nitrogen ligands with Cu^{I} ligands.[20,21] The third method was based on the reaction between a masked and protected azido-functionalized glycine and an ethynyl glycine, affording disubstituted 1,2,3-triazole *C*-glycosyl amino esters.[22]

Microwave irradiation as a non-conventional heating source has been shown to be of paramount importance as a tool with evident advantages when compared to traditional procedures: reduced reaction times, improved reaction yields, application in solvent-free conditions, and improving the product selectivity and chemical yield.[23]

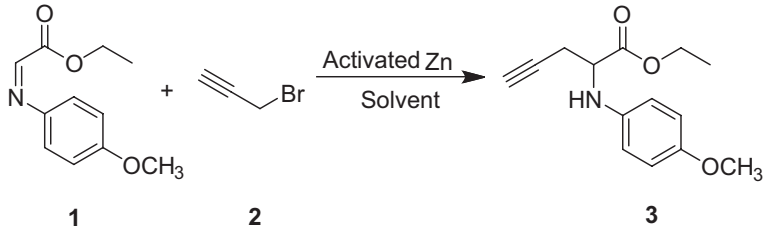
Results and Discussion

To synthesize β-1,2,3-triazolyl-α-amino esters, starting materials were assembled by reaction of propargyl bromide with imino ester in the presence of Zn metal (Scheme 1). Although the reaction conditions are known, we performed a short screen to try to improve the reaction conditions.

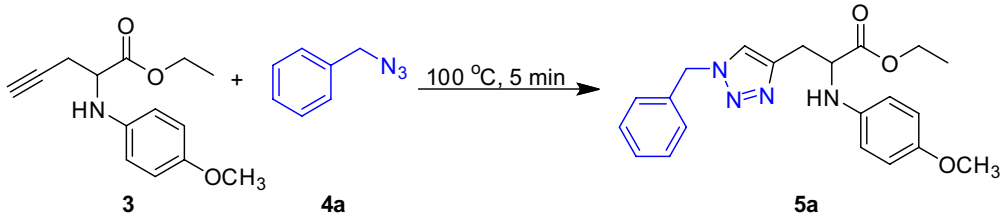
We initially examined the reaction of propargyl bromide (4 mmol) and ethyl(*p*-methoxyphenylimino) acetate (5 mmol) mediated by Zn powder (6 mmol) under solvent free conditions[24] and found a trace amount of the product in our case. The same reaction was carried out in tetrahydrofuran (THF) at different temperatures and it was found that the reaction carried out at room temperature furnished 20% product, while at low temperatures, i.e., 0 °C, this resulted in 36% of the targeted product. When the temperature was decreased to –20 °C, we observed an increase in yield to 52%; however, a further decrease in temperature did not affect the reaction yield. The reaction failed to produce any isolable product when THF-H_2O (1:1) was used as the solvent. After screening the reaction conditions, the optimal solvent for this propargylation was found to be dimethylformamide (DMF), which furnished compound **3** in 62% yield at –20 °C within 20 min.

With the starting material in hand, we began the screen to search for the optimal reaction conditions to produce the 1,2,3-triazole ring via Cu^{I}-catalyzed Huisgen 1,3-dipolar cycloaddition reaction. For this purpose, we used benzyl azide and ethyl 2-(4-methoxyphenylamino)pent-4-ynoate as model reagents in the presence of various copper catalysts using microwaves (MW) as an energy source (Scheme 2).

Only poor yield (5%) and traces (Table 1, entries 3 and 4) of the product were observed when using CuCN and $Cu(OTf)_2$ as catalysts in the absence of a base, while $CuSO_4.5H_2O$ led to product in 51% yield and CuI furnished product in 53 % yield. Further attempts were made to optimize the solvent, we tried this reaction in aprotic solvent (MW-nonabsorbent), e.g., THF; protic solvent (MW-absorbing), e.g., MeOH; and neat conditions (Table 1, entries 2, 5 and 6, respectively). We found that reaction works with and without solvent though yield was poor. In order to increase yield of reaction pentamethyldiethylenetriamine (PMDTA) was used which showed 100% conversion of starting material to product. PMDTA is known to form a complex with copper iodide,[25] but the isolated yield was not 100%. Following the addition of PMDTA, and employing CuI and THF as solvents, the yields increased within the range of 60 to



Scheme 1. Preparation of ethyl 2-(4-methoxyphenylamino)pent-4-ynoate (**3**).



Scheme 2. Synthesis of β-1,2,3-triazolyl-α-amino esters.

75% (Table 1, entries 9 and 7, 8, respectively). We have done a reaction in neat condition using PMDTA which furnished product in 64% yield but solid azides, e.g., sugar azides, didn't work in solvent free conditions so THF was found well suited for this reaction (Table 1, entry 7). This reaction was also carried out in oil bath at 100 °C and after 3 h we obtained product in comparable yield (Table 1, entry 11).

Table 1. Optimized reaction conditions for the synthesis of β-1,2,3-triazolyl-α-amino esters

entry	Cu cat (10 mol%)	Solvent	Base (eq)	Yield / %
1	$CuSO_4.5H_2O$	THF	–	51
2	CuI	THF	–	53
3	CuCN	THF	–	5
4	$Cu(OTf)_2$	THF	–	Trace
5	CuI	MeOH	–	51
6	CuI	–	–	5[a]
7	CuI	THF	PMDTA (1)	75
8	CuI	THF	PMDTA (2)	75
9	CuI	THF	PMDTA (0.5)	60
10	CuI	–	PMDTA (1)	64[a]
11	CuI	THF	PMDTA (1)	72[b]

[a]20 min; [b]100 °C (oil bath), 3h.

With the optimal conditions in hand, ethyl 2-(4-methoxyphenylamino)pent-4-ynoate (0.3 mmol), organic azide (0.4 mmol), PMDTA (1 eq), Cu^I (10 mol%), and THF (3.0 mL) were added to a microwave vial equipped with a magnetic stirring bar (Scheme 3). The sealed mixture was heated under microwave irradiation at 100 °C for 5 min; the scope was then established and the Cu^I-catalyzed cycloaddition of terminal alkyne was subjected to a variety of organic azides. The results are summarized in Table 2.

As is evident from the data in Table 2, the electron-donating and electron-withdrawing substituents in the aryl ring were well tolerated and gave good yields (Table 2, entries 2). A variety of functional groups, including methoxy, chloride, nitro and bromide, along with sugar-containing azides,[26,27] were compatible with the reaction conditions; all gave triazolic products in good yields (Table 2, see entries 2-4 and 6-8).

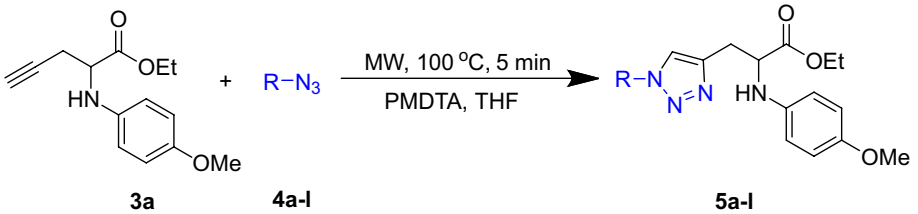
Conclusions

We have demonstrated that non-natural β-1,2,3-triazolyl-α-amino esters can be successfully obtained through a simple reaction from ethyl glyoxyl imines and preformed propargylzinc reagent, followed by the formation of 1,2,3-triazoles through click chemistry, in moderate to good yields. It was found that the microwave irradiation dramatically reduces the reaction times from hours to several minutes, which is an important factor on the viability of this synthetic method. In addition, the products are obtained in comparable yields with those obtained under conventional thermal conditions.

Thus, we found a reliable reaction system, which was able to provide an important variety of 1,2,3-triazolyl-α-amino ester backbones in very useful reaction conditions. The extension of the process to cleavable amines, as well as the development of a chiral version are currently underway and will be reported in due course. The identities and purities of the products were confirmed by ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry.

Experimental

Melting points were determined on a Büchi melting point apparatus and are provided uncorrected. MW assisted reactions were carried out in MW synthesis reactor monowave 300 Anton Paar. All compounds were characterized using ^1H and ^{13}C NMR spectroscopy as well as Fourier transform mass spectrometry (FTMS) with probe electrospray ionization (pESI). Copies of the ^1H and ^{13}C NMR spectra can be found in the Supplementary Information. The ^1H and ^{13}C NMR spectroscopic data were recorded with a 300 MHz instrument. The chemical shifts (δ) for the ^1H NMR experiments are reported in parts *per* million (ppm) and measured relative to the signals for tetramethylsilane (TMS) (δ 0.00 ppm). The chemical shifts for the ^{13}C NMR spectra are reported in ppm relative to deuterated chloroform (δ 77.23 ppm), unless otherwise stated, and all data were recorded using ^1H decoupling. Column chromatography was performed using silica gel (230-400 mesh). Thin-layer



3a **4a-l** **5a-l**

Scheme 3. Synthesis of β-1,2,3-triazolyl-α-amino esters.

Table 2. Reactions of **3** with various aryl and alkyl azides

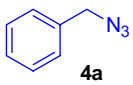
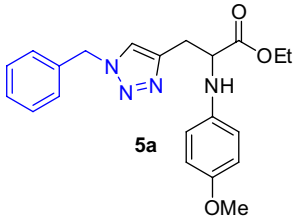
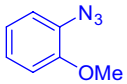
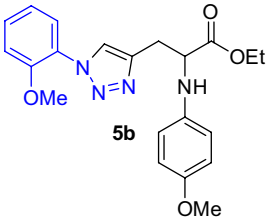
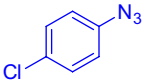
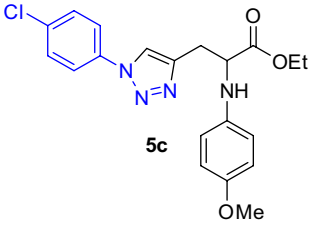
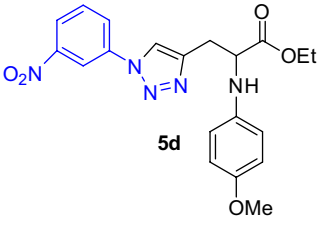
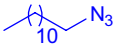
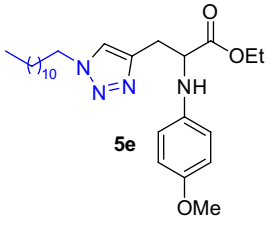
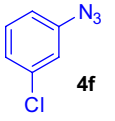
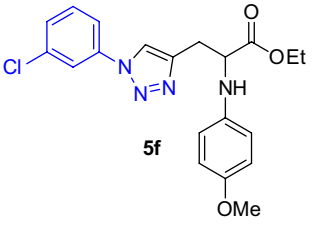
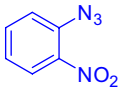
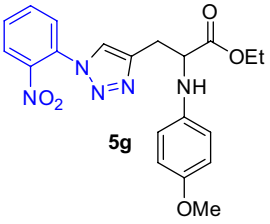
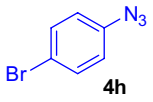
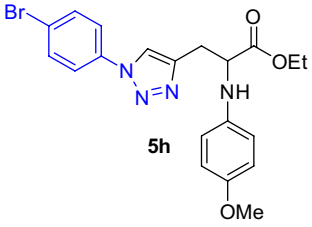
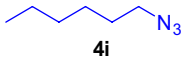
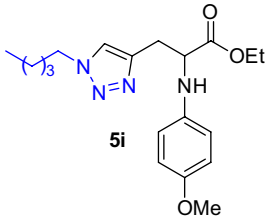
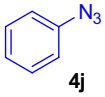
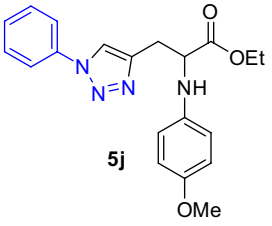
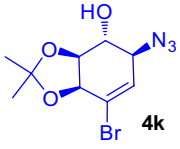
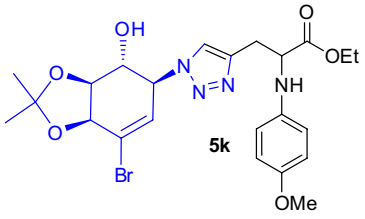
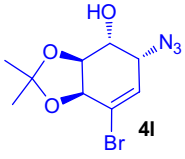
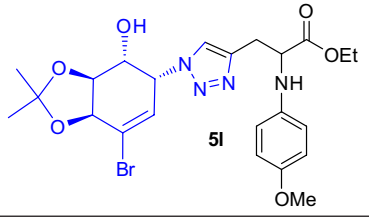
entry	Azide	Product	Yield / %
1	 **4a**	 **5a**	75
2	 **4b**	 **5b**	73
3	 **4c**	 **5c**	72
4	 **4d**	 **5d**	63[a]
5	 **4e**	 **5e**	70
6	 **4f**	 **5f**	71
7	 **4g**	 **5g**	61[a]

Table 2. Reactions of **3** with various aryl and alkyl azides (cont.)

entry	Azide	Product	Yield / %
8	 **4h**	 **5h**	78
9	 **4i**	 **5i**	74
10	 **4j**	 **5j**	75
11	 **4k**	 **5k**	73[a]
12	 **4l**	 **5l**	72[a]

[a]10 min.

chromatography (TLC) was performed using silica gel UV 254, 0.20 mm thickness. For visualization, TLC plates were either placed under UV light, or stained with iodine or acidic vanillin solution. Solvents and reagents were of analytical grade or the highest grade commercially available and were used without further purification.

Synthesis of ethyl (*p*-methoxyphenylimino)acetate (**1**)

A mixture of ethyl (*p*-methoxyphenylimino)acetate (0.62 g, 5 mmol) and ethyl glyoxalate (0.51 g, 5 mmol) in 5 mL of THF was stirred at room temperature for 1 h. Then the corresponding mixture was concentrated under vacuum and used in the next step without any further purification. The product was obtained as a brown oil; infrared (IR) (film) ν_{max} / cm^{-1} 2985, 2941, 2845, 1737, 1643, 1596, 1246, 1032, 840; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.37 (d, 2H, *J* 9 Hz), 6.94 (d, 2H, *J* 9 Hz), 4.42 (q, 2H, *J* 7.2 Hz), 3.84 (s, 3H), 1.42 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 154.2. 151.9, 143.7, 115.8, 114.9, 54.1, 29.2, 14.0.

Procedure to activate zinc dust

Zinc powder (0.39 g, 6 mmol) was added into a flame-dried round-bottom flask fitted with a magnetic bar and

dropping funnel; the flask was flashed with dry nitrogen. The zinc powder was heated to 60-70 °C. 1,2-Dibromomethane (0.1 mL in 0.5 mL THF) was added dropwise, the temperature was maintained for 10 min and then the flask was cooled to room temperature. Trimethylchlorosilane (0.1 mL in 0.5 mL THF) was added, and the mixture was stirred at room temperature for 15 min. Solvent was evaporated from the activated zinc under reduced pressure.

Procedure for the preparation of ethyl 2-((4-methoxy) phenylamino)pent-4-ynoate (**3**)

In a dried round-bottom flask fitted with magnetic bar and dropping funnel, activated zinc powder (0.39 g, 6 mmol) and ethyl (*p*-methoxyphenylimino) acetate (0.83 g, 4 mmol) were added at 0 °C. Propargyl bromide (0.60 g, 5 mmol) in 0.5 ml DMF was added dropwise over 5 min at 0 °C and then stirred for 15 min at room temperature. After complete reaction, saturated aqueous ammonium chloride was poured into the mixture and stirred for 5 min. The reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$; after filtration and solvent removal, the residue was purified by flash chromatography on silica gel (eluent consisting of hexane:EtOAc 9.5:0.5) to obtain oil product.

Ethyl 2-((4-methoxyphenyl)amino)pent-4-ynoate (**3**)

IR (film) ν_{max} / cm^{-1} 3368, 3286, 2985, 2940, 2836, 2121, 1734, 1542, 1514, 1033, 825; ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, 2H, *J* 8.9 Hz), 6.56 (d, 2H, *J* 8.9 Hz), 4.15-4.11 (m, 2H), 4.09-4.05(m, 1H), 3.64 (s, 3H), 2.66-2.64 (m, 2H), 2.01(s, 1H), 1.20 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 154.2, 141.7, 115.7, 114.9, 80.7, 72.3, 61.4, 55.6, 55.5, 22.9, 14.2; HRMS (FTMS + pESI) calcd. for $C_{14}H_{17}NO_3$ $[M]^+$: 247.1247; found: 247.1241.

General procedure for the synthesis of 1,2,3-triazole derivatives **5a-l**

Ethyl 2-(4-methoxyphenylamino)pent-4-ynoate (0.3 mmol), organic azide (0.4 mmol), PMDTA (1 eq), CuI (10 mol%), and THF (3.0 mL) were added to a microwave vial equipped with a magnetic stirring bar. The sealed mixture was heated under microwave irradiation at 100 °C for 5 min. The reaction mixture was cooled to ambient temperature. The reaction mixture was then poured into aq. NH_4Cl and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and solvent was removed under reduced pressure and then the residue was purified by a flash column (hexane:ethyl acetate 4:6) to give the products as light-yellow oil. The identities and purities of the products were confirmed by TLC, ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.

Ethyl 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5a**)

Yield: 0.088 g (74%); brown solid; m.p. 84-85 °C; IR (film) ν_{max} / cm^{-1} 3368, 3131, 2978, 2839, 1723, 1618, 1511, 1468, 1337, 1246, 1175, 1099, 1035, 709, 681; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.24 (m, 3H), 7.20 (s, 1H), 7.14-7.12 (m, 2H), 6.67 (d, 2H, *J* 8.9 Hz), 6.50 (d, 2H, *J* 8.9 Hz), 5.39 (s, 2H), 4.20 (t, 1H, *J* 5.7 Hz), 4.04 (q, 2H, *J* 7.2 Hz), 3.64 (s, 3H), 3.20-3.04 (m, 2H), 1.09 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 152.9, 143.7, 140.6, 134.7, 129.0, 128.6, 127.9, 122.1, 115.4, 114.8, 61.2, 57.8, 55.7, 54.0, 29.2, 14.1; HRMS (FTMS + pESI) calcd. for $C_{21}H_{24}N_4O_3$ $[M]^+$: 381.1899; found: 381.1891.

Ethyl 3-(1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5b**)

Yield: 0.087 g (73%); white solid; m.p. 87-98 °C; IR (film) ν_{max} / cm^{-1} 3363, 2982, 2836, 1732, 1603, 1510, 1467, 1441, 1372, 1236, 1179, 1125, 1099, 1035, 823, 756, 698, 672; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.78 (d, 1H, *J* 7.8 Hz), 7.44-7.39 (m, 1H), 7.13-7.06 (m, 2H), 6.79 (d, 2H, *J* 8.7 Hz), 6.70 (d, 2H, *J* 8.9 Hz), 4.40 (t, 1H, *J* 5.8 Hz), 4.22 (q, 2H, *J* 7.2 Hz), 3.86 (s, 3H), 3.74 (s, 3H), 3.43-3.32 (m, 2H), 1.24 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 153.0, 150.0, 142.5, 140.4, 129.9, 126.3, 125.3, 124.3, 121.2, 115.6, 114.8, 112.3, 61.2, 57.97, 55.91, 55.69, 29.13, 14.12; HRMS (FTMS + pESI) calcd. for $C_{21}H_{24}N_4O_4$ $[M]^+$: 397.1877; found: 397.1850.

Ethyl 3-(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5c**)

Yield: 0.086 g (72%); grey solid; m.p. 108-109 °C; IR (film) ν_{max} / cm^{-1} 3311, 3140, 2987, 2834, 1727, 1618, 1512, 1502, 1469, 1338, 1246, 1236, 1179, 1032, 1039, 817, 830, 707, 683; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.64 (d, 2H, *J* 8.9 Hz), 7.50 (d, 2H, *J* 8.8 Hz), 6.79 (d, 2H, *J* 8.9 Hz), 6.66 (d, 2H, *J* 8.5 Hz), 4.37 (bs, 1H), 4.23 (q, 2H, *J* 7.2 Hz), 3.74 (s, 3H), 3.43-3.32 (m, 2H), 1.26 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 153.0, 144.3, 140.5, 135.5, 134.3, 129.8, 121.5, 120.3, 115.3, 114.9, 115.6, 114.8; 61.3, 57.6, 55.6, 29.1, 14.1; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}{}^{35}ClN_4O_3$ $[M]^+$: 401.1380; found: 401.1347; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}{}^{37}ClN_4O_3$ $[M]^+$: 403.1350; found: 403.1335.

Ethyl 2-(4-methoxyphenylamino)-3-(1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)propanoate (**5d**)

Yield: 0.077 g (63%); orange solid; m.p. 154-155 °C; IR (film) ν_{max} / cm^{-1} 3361, 3140, 2989, 2938, 2832, 1731, 1621, 1534, 1466, 1443, 1356, 1237, 1178, 1029, 826, 753; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.22 (d, 1H, *J* 8.1 Hz), 8.07 (d, 1H, *J* 8.1 Hz), 7.8 (s, 1H), 7.67 (t, 1H, *J* 8.1 Hz), 6.71 (d, 2H, *J* 9 Hz), 6.58 (d, 2H, *J* 9 Hz), 4.30 (t, 1H, *J* 5.6 Hz), 4.16 (q, 2H, *J* 7.2 Hz), 3.65 (s, 3H), 3.37-3.18 (m, 2H), 1.19 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 153.2, 144.8, 140.2, 137.7, 130.9, 125.8, 123.0, 120.4, 115.6, 100.0, 61.5, 57.6, 55.7, 29.1, 14.1; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}N_5O_5$ $[M]^+$: 412.1621; found: 412.1591.

Ethyl 3-(1-decyl-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5e**)

Yield: 0.096 g (70%); brown solid; m.p. 58-59 °C; IR (film) ν_{max} / cm^{-1} 3321, 3141, 2958, 2939, 2831, 1732, 1609, 1511, 1463, 1373, 1214, 1056, 839, 701, 683; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.68 (d, 1H, *J* 8.8 Hz), 6.52 (d, 2H, *J* 8.9 Hz), 4.40 (m, 3H), 4.10 (q, 2H, *J* 7.2 Hz), 3.64 (s, 3H), 3.23-3.05 (m, 2H), 1.79 (t, 3H, *J* 6.7 Hz), 1.20-1.09 (m, 2H), 0.82 (t, 3H, *J* 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 152.8, 140.6, 121.9, 115.3, 114.8, 61.1, 57.8, 55.6, 50.2, 31.85, 30.2, 29.5, 29.4, 29.3, 28.9, 22.6, 14.1, 14.0; HRMS (FTMS + pESI) calcd. for $C_{26}H_{42}N_4O_3$ $[M]^+$: 459.3336; found: 459.3313.

Ethyl 3-(1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5f**)

Yield: 0.085 g (71%); brown solid; m.p. 134-135 °C. IR (film) ν_{max} / cm^{-1} 3317, 3140, 3012, 2834, 1726, 1620, 1512, 1503, 1469, 1338, 1247, 1238, 1171, 1032, 1032, 815, 708, 681; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.63-7.62 (m, 1H), 7.49-7.46 (m, 1H), 7.34-7.28 (m, 2H), 6.67 (d, 2H, *J* 9 Hz), 6.54 (d, 2H, *J* 9 Hz), 4.29 (t, 1H, *J* 5.5 Hz), 4.12 (q, 2H, *J* 7.2 Hz), 3.62 (s, 3H), 3.31-3.13 (m, 2H), 1.14 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 152.0, 144.3, 140.5, 137.8, 135.4, 130.7, 128.6, 120.5, 120.4, 118.3, 115.4, 114.9, 61.3, 57.6, 55.6, 29.1, 14.1; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}{}^{35}ClN_4O_3$ $[M]^+$: 401.1380; found: 401.1350; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}{}^{37}ClN_4O_3$ $[M]^+$: 403.1350; found: 403.1336.

Ethyl 2-(4-methoxyphenylamino)-3-(1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)propanoate (**5g**)

Yield: 0.075 g (61%); brown oil; IR (film) ν_{max} / cm^{-1} 3361, 3139, 2976, 2935, 2825, 1732, 1617, 1532, 1461, 1353, 1231, 1162, 1020, 826, 753, 702, 689; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, 1H, *J* 8.1 Hz), 6.71-7.75 (m, 3H), 7.50 (d, 1H, *J* 7.5 Hz), 6.67 (d, 2H, *J* 8.7 Hz), 6.57 (d, 2H, *J* 8.7 Hz), 4.31 (t, 1H, *J* 5.7 Hz), 4.15 (q, 2H, *J* 7.2 Hz), 3.05 (s, 3H), 3.35-3.17 (m, 2H), 1.18 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 153.0, 143.9, 140.5, 133.7, 130.6, 130.3, 127.9, 125.5, 123.8, 115.5, 114.9, 61.4, 57.6, 55.7, 29.1, 14.1; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}N_5O_5$ $[M]^+$: 412.1621; found: 412.1576.

Ethyl 3-(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5h**)

Yield: 0.104 g (78%); white solid; m.p. 128-129 °C; IR (film) ν_{max} / cm^{-1} 3319, 3142, 2958, 2823, 1726, 1620, 1512, 1498, 1466, 1246, 1238, 1199, 1173, 1052, 817, 707, 678; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.64-7.55 (m, 4H), 6.78 (d, 1H, *J* 8.7 Hz), 6.79 (d, 2H, *J* 8.7 Hz), 6.68 (d, 2H, *J* 8.9 Hz), 4.38 (t, 1H, *J* 5.7 Hz), 4.22 (s, NH), 4.17 (q, 2H, *J* 7.2 Hz), 3.73 (s, 3H), 3.41-3.23 (m, 2H), 1.29 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 152.9, 144.3, 140.5, 135.9, 132.8, 122.1, 120.3, 115.4, 114.9, 61.3, 57.5, 55.6, 29.1, 14.1; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}{}^{79}BrN_4O_3$ $[M]^+$: 445.0875; found: 445.0864; HRMS (FTMS + pESI) calcd. for $C_{20}H_{21}{}^{81}BrN_4O_3$ $[M]^+$: 447.0854; found: 447.0831.

Ethyl 3-(1-hexyl-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenolamino)propanoate (**5i**)

Yield: 0.083 g (74%); brown oil; IR (film) ν_{max} / cm^{-1} 3319, 3128, 2953, 2821, 1722, 1602, 1509, 1461, 1371, 1209, 1238, 1172, 1032, 815, 708, 681; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.69 (d, 1H, *J* 9 Hz), 6.52 (d, 2H, *J* 9 Hz), 4.23 (m, 3H), 4.11 (q, 2H, *J* 7.2 Hz), 3.65 (s, 3H), 3.24-3.06 (m, 2H), 1.80-1.75 (m, 2H), 1.22 (bs, 6H), 1.15 (t, 3H, *J* 7.2 Hz), 0.82 (t, 3H, *J* 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 152.8, 143.1, 140.7, 121.9, 115.3, 114.8, 61.1, 57.7, 55.6, 50.2, 31.0, 30.2, 29.2, 26.0, 22.3, 14.1, 13.8; HRMS (FTMS + pESI) calcd. for $C_{20}H_{30}N_4O_3$ $[M]^+$: 375.2397; found: 375.2359.

Ethyl 2-(4-methoxyphenylamino)-3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)propanoate (**5j**)

Yield: 0.082 g (75%); white solid; m.p. 146-147 °C; IR (film) ν_{max} / cm^{-1} 3317, 3146, 3089, 2989, 2840, 1721, 1614, 1511, 1461, 1380, 1241, 1210, 1090, 752, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60-7.57 (m, 2H), 7.42-7.28 (m, 3H), 6.68 (d, 2H, *J* 8.9 Hz), 6.55 (d, 2H, *J* 9 Hz), 4.29 (t, 1H, *J* 5.7 Hz), 4.12 (q, 2H, *J* 7.2 Hz), 3.62 (s, 3H), 3.31-3.14 (m, 2H), 1.44 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 152.9, 144.0, 140.6, 137.0, 129.7, 128.6, 120.4, 115.4, 114.9, 61.3, 57.6, 55.6, 29.2, 14.1; HRMS (FTMS + PESI) calcd. for $C_{20}H_{22}N_4O_3$ $[M]^+$: 367.1771; found: 367.1731.

Ethyl 3-(1-((3a*R*,4*S*,7a*R*)-7-bromo-4-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro[1,3]benzodioxol-5-yl)-1*H*-1,2,3-triazol-4-yl)-2-(4-methoxyphenylamino)propanoate (**5k**)

Yield: 0.117 g (73%); brown gummy solid; IR (film) ν_{max} / cm^{-1} 3400-3000, 3317, 3297, 2983, 2931, 2821, 1722, 1602, 1623, 1467, 1316, 1234, 1084, 1057, 823; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 6.63 (d, 2H, *J* 9 Hz), 6.52 (d, 2H, *J* 9 Hz), 6.15-6.12 (m, 1H), 4.95-4.91 (m, 1H), 4.72-4.69 (m, 1H), 4.22-4.15 (m, 2H), 4.04 (q, 2H, *J* 7.2 Hz), 3.87-3.81 (m, 1H), 3.57 (s, 3H), 3.15-2.99 (m, 2H), 1.37 (s, 3H), 1.28 (s, 3H), 1.08 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 154.2, 144.5, 142.4, 131.2, 125.0, 122.8, 116.5, 115.8, 111.9, 79.3, 78.4, 72.5, 64.3, 62.2, 59.1, 56.2, 29.8, 28.4, 26.1, 14.5; HRMS (FTMS + pESI) calcd. for $C_{23}H_{29}{}^{79}BrN_4O_6$ $[M]^+$: 537.1349; found: 537.1347; HRMS (FTMS + pESI) calcd. for $C_{23}H_{29}{}^{81}BrN_4O_6$ $[M]^+$: 539.1328; found: 539.1315.

Ethyl 3-(1-((3aR,4S,7aR)-7-bromo-4-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro[1,3]benzodioxol-5-yl)-1*H*-1,2,3-triazol-4-yl)-2-(4methoxyphenylamino)propanoate (**5l**)

Yield: 0.116 g (72%); brown gummy solid; IR (film) ν_{max} / cm^{-1} 3400-3000, 3319, 3296, 2982, 2931, 2823, 1723, 1604, 1621, 1467, 1318, 1235, 1083, 1056, 821; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.76-6.61 (m, 4H) 6.20 -6.15 (m, 1H), 5.47-5.45 (m, 1H), 4.73-4.71 (m, 1H), 4.47-4.43 (m, 2H), 4.37-4.30 (m, 2H), 4.17 (q, 2H, *J* 7.2 Hz), 3.71 (s, 3H), 3.28-3.17 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.22 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 154.3, 144.5, 142.4, 127.3, 126.9, 125.2, 116.7, 116.5, 115.8, 111.6, 78.0, 77.4, 69.7, 62.3, 60.9, 59.2, 56.2, 29.9, 28.0, 26.6, 14.5; HRMS (FTMS + pESI) calcd. for $C_{23}H_{29}{}^{79}BrN_4O_6$ $[M]^+$: 537.1349; found: 537.1338; HRMS (FTMS + pESI) calcd. for $C_{23}H_{29}{}^{81}BrN_4O_6$ $[M]^+$: 539.1328; found: 539.1323.

Supplementary Information

Supplementary information (experimental details and analytical data for all new compounds, as well as the copies of ^{1}H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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