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Synthesis of novel 1,2,3-triazolic compounds derived from natural product, by the copper(I)-catalyzed alkyne-azide (CuAAC) cycloaddition

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Abstract

A series of novel 1,2,3-triazolic compounds derived from natural products (thymol, carvacrol and eugenol) was synthesized by the copper(I)-catalyzed alkyne-azide (CuAAC) cycloaddition between the corresponding propargyl ethers of each natural product and a variety of azides. The reaction conducted with catalytic amount of copper (II) sulfate and sodium ascorbate affording desired products in good yields and their structures were confirmed by spectral techniques such as 1H NMR, 13C NMR and high resolution mass spectrometry (HRMS).

Keywords: *thymol; carvacrol; eugenol; 1,2,3-triazoles; click chemistry*

1. Introduction

Nature has been and continues to be an abundant source of novel bioactive compounds. More than 60% of approved drugs are natural product, derivatives of natural product or synthetic drugs but with natural product pharmacophore [1]. Thymol, carvacrol and eugenol (Figure 1) are three phenolic monoterpenoid compounds that are known as traditional therapeutic agents and many researches showed that they have a lot of biological and pharmacological properties including antibacterial, antifungal, anti-inflammatory, anticancer and anti tubercular effects. However, the pharmacokinetic properties of these natural compounds, especially elimination rate and solubility are the major barricades in their drug design [2-22].

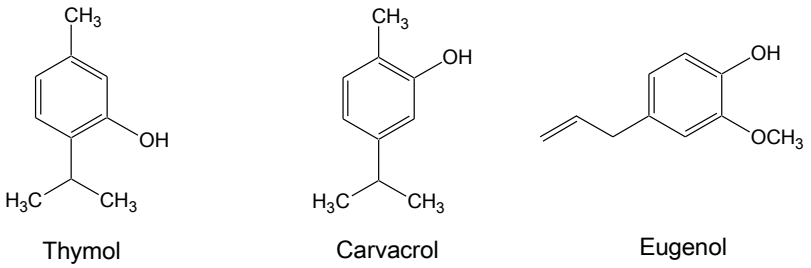
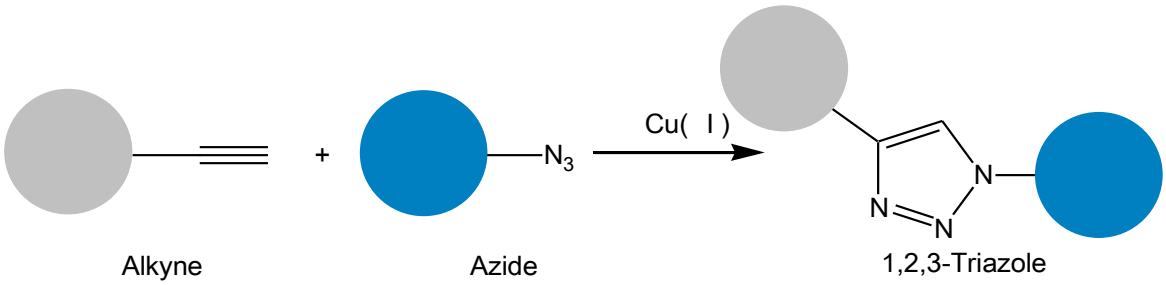


Figure 1: Chemical structures of the monoterpenoids: thymol, carvacrol and eugenol

Hemisynthesis can serve to increase these properties, and this is the aim of this work, by converting this monoterpenoids into triazolic compounds. Triazoles are important molecules that provide a great water solubility and have a lot of effects such as antiviral, anti-inflammatory, anti-HIV, antitumoral, antibacterial, and antifungal [23-28]. So, the idea is to link the natural products into triazolic entities using copper-catalyzed azide alkyne cycloaddition (CuAAC) process [29], as schematized on scheme 1, to increase the biological effects of both of them or maybe reveal new activities.



Scheme 1: The CuAAC reaction.

2. Materials and methods

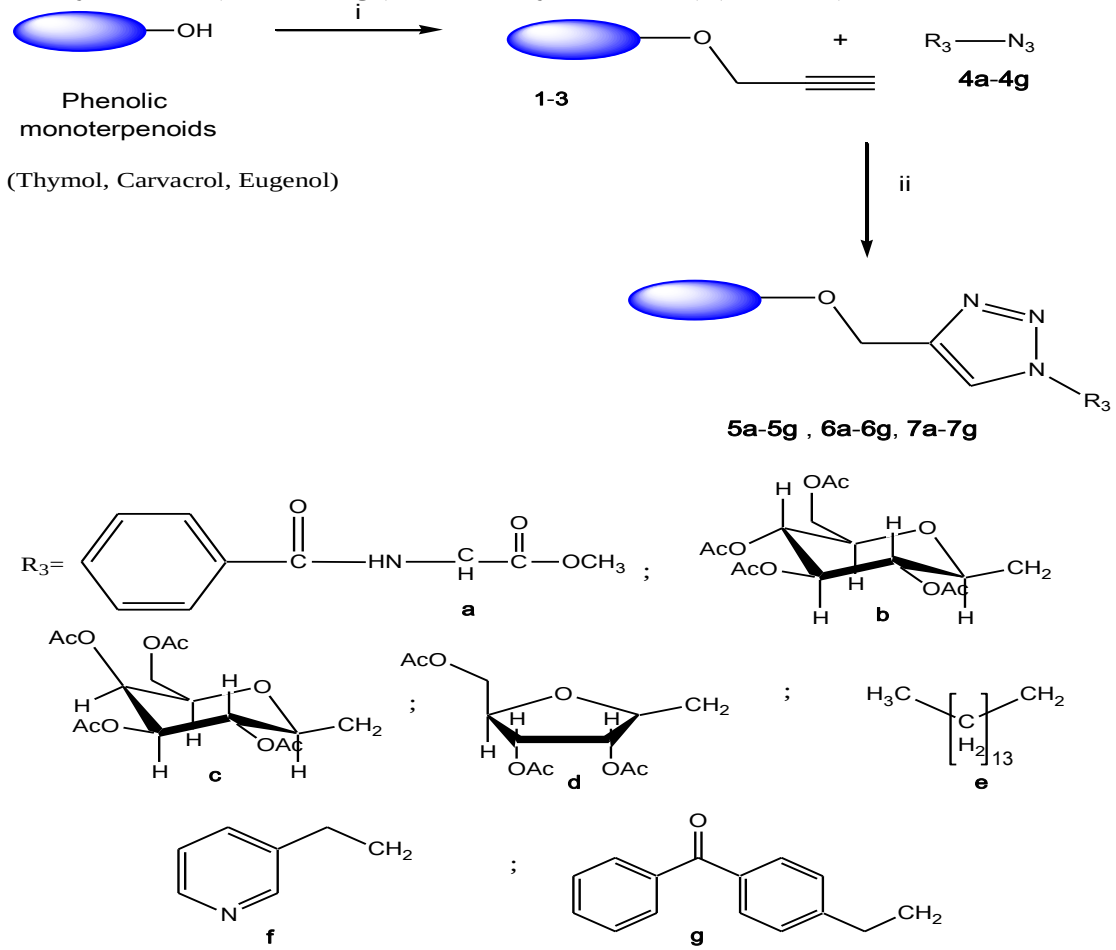
The reaction progress was monitored by TLC using Silica gel 60-F254 plat and visualized under UV light and iodine. Column chromatography was carried out using silica gel 60 (Merck 230-400 mesch) and a hexanes-ethyl acetate eluent mixture. Melting points were determined using open-ended capillary tubes on Electrothermal IA 9000 Series digital fusiometer instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers (300MHz for ^{1}H and 75MHz for ^{13}C) with chemical shift values (δ) given in part per million (ppm) relative to TMS (δ 0.00) as internal standard. Coupling constants (J) are given in Hz and multiplicities are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), and m (multiplet). The mass spectra (MS) were recorded in the ESI mode at the mass spectrometry service of the Universidad de Valencia and the data was reported in m/e (intensity to 100%)

General procedure for synthesis of the 1,2,3-triazoles:

The alkylated natural product (1mmole) was introduced on a round bottom flask with azide (1mmole), $CuSO_4.5H_2O$ (0.063mmole), sodium ascorbate (0.126mmole) and mixture of EtOH / H_2O (1:1) as solvent. The reaction mixture was stirred at room temperature for 24 hours. The solvents were evaporated under reduced pressure and the mixture was extracted with dichloromethane. The obtained crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as eluent.

3. Result and discussion

The copper(I)-catalyzed cycloaddition reaction has found interesting application in drug discovery to generate novel pharmacophores and has proven to be the most used method for the synthesis of bioactive molecules, specially 1,2,3-triazoles which are fundamental building blocks in lots of pharmacophores. These entities are remarkably stable under hydrolytic, oxidative and reductive conditions and they are obtained in good yields and excellent regiospecificity by CuAAC process. The present work describes the synthesis of novel triazolic compounds derived from natural products that are thymol, carvacrol and eugenol (Scheme 2). The alkynes **1-3**, that are known compounds [30-32], were obtained by converting these phenolic monoterpenoids to their corresponding propargyl ethers by Williamson synthesis method [33,34] and they react by CuAAC with a variety of azides **4a-4g** (Scheme 2), that have been prepared according to the literature procedure [35-39], to give desired compounds: **5a-5g** (Table 1: entry N° 1 to 7), **6a-6g** (Table 1: entry N° 8 to 14), and **7a-7g** (Table 1: entry N° 15 to 21) (Scheme 4).



Scheme 2: Synthesis of 1,2,3-triazoles derived from natural products by CuAAC; Reagents: (i) NaH, 18-crown-6, THF, r.t., 24h; (ii) $CuSO_4.5H_2O$, sodium ascorbate, EtOH/H_2O (1:1), r.t., 24h.

The CuAAC between azides **4a-4g** and alkynes **1-3** give a variety of 1,4 disubstituted 1,2,3-triazoles, table 1 shows yields and characteristics of each one. The products were purified by column chromatography using silica gel as a stationary phase and a mixture of hexane/ethyl acetate (3:1) as eluent to give the pure desired product in good yields (70% - 90%) except **5f** and **6d** (respectively 63% and 65%). The chemical structures of all triazolic synthesized compounds were confirmed by spectral techniques such as ^{1}H NMR, ^{13}C NMR and HRMS. The spectrum ^{1}H NMR of triazoles glycoconjugates compounds (**5b**, **5c**, **5d**, **6b**, **6c**, **6d**, **7b**, **7c**, **7d**) shows three or four intense singlet signals between δ=1.8-2.23 ppm, it depends if it's a hexose or pentose, corresponding to the methoxy ester groups that protect the hydroxyls. The non equivalent CH_2OAc protons of glycosyls are manifested by the presence of doublet of doublets at δ=4.24 ppm, while the anomeric carbon proton shows a doublet signal around δ=5.91 ppm with coupling constant J=9.00 Hz. As we can see on 2D NMR spectrum (COSY ^{1}H-^{1}H) of compound **6b** for example (Figure 2), the anomeric proton (δ=5.91 ppm) present a coupling constant (J=9.00 Hz) confirmed by the presence of spot related to neighboring H_2 proton (δ=5.49 ppm) of the glycosyl group and the non equivalent CH_2OAc protons (δ=4.24 ppm) present three coupling constant (12.50, 5.00 and 2.00 Hz) confirmed by the presence of spots related to H_5, H_6 and $H_{6'}$ protons of the glycosyl group

Table 1: Yields and characteristics of synthesized triazoles.

Entry N°	Product N°	Yield %	R_f^*	Melting point (°C)	Aspect
1	**5a**	83	0.42	108	white powder
2	**5b**	84	0.3	112	white powder
3	**5c**	87	0.27	109	white powder
4	**5d**	70	0.42	-	yellow oil
5	**5e**	90	0.9	87	white powder
6	**5f**	63	0.3	-	yellow oil
7	**5g**	84	0.5	105	yellow powder
8	**6a**	75	0.36	119	white powder
9	**6b**	71	0.35	106	white powder
10	**6c**	80	0.31	134	white powder
11	**6d**	65	0.36	-	yellow oil
12	**6e**	70	0.88	110	yellow powder
13	**6f**	72	0.26	112	yellow powder
14	**6g**	78	0.54	86	white powder
15	**7a**	74	0.32	88	white powder
16	**7b**	71	0.2	71	white powder
17	**7c**	80	0.18	80	white powder
18	**7d**	77	0.2	-	yellow oil
19	**7e**	87	0.54	87	white powder
20	**7f**	70	0.28	-	yellow oil
21	**7g**	80	0.41	97	white powder

(-):oily product *: eluent: hexane /ethyl acetate (2/1).

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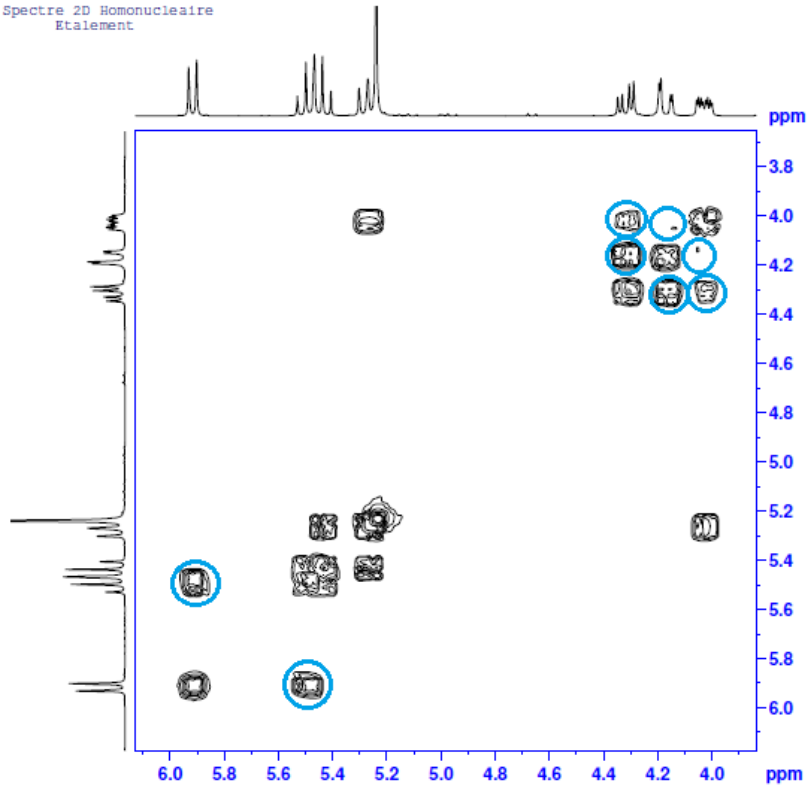

Figure 2: COSY ^{1}H-^{1}H NMR spectrum of compound **6b** in $CDCl_3$.

The compounds that contain protected glycine (**5a**, **6a**, **7a**) show in their ^{13}C NMR spectrums a signal at δ=165.4 ppm assigned to the carbon of amide group and a signal at δ=166.9 ppm assigned to the carbon of ester group. The compounds (**1g**, **2g**, **3g**) that contain benzophenone present spectral region between δ=6.76-7.82 ppm assigned to triazolic and eighteen aromatic protons of the molecule. The ^{13}C NMR spectrum shows a signal between δ=191.62-195.89 ppm corresponding to the carbonyl group (CO) of benzophenone. The ^{1}H NMR spectrums of all synthesized compounds show the characteristic signal of triazolic proton between δ=7.56-8.06 ppm, and a singlet around δ=5.20 ppm correlated to CH_2O which links the phenoxy group to the triazolic ring.

Spectral Data

Benzoylamino-[4-(2-isopropyl-5-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-acetic acid methyl ester (5a):

Yld: 83%, White solid, mp=108°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.19 (d, 6H, CH_3-CH_{thymol} ; J=6.90) ; 2.34 (s, 3H, $CH_{3Ar.thymol}$) ; 3.26 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 3.92 (s, 3H, CH_3O) ; 5.23 (s, 2H, CH_2O) ; 6.79-7.02 (m, 3H, $CH_{Ar.thymol}$) ; 7.11 (d, 1H, $CH_{glycine}$, J=7.94) ; 7.46-7.87 (m, 5H, CH_{Ar}); 7.85 (d, 1H, NH , J=9,00) ; 8.05 (s, 1H, $CH_{triazolique}$). ^{13}C RMN ($CDCl_3$, 75MHz): 21.27 (CH_3) ; 22.81 ($2CH_3$) ; 26.52 (CH) ; 54.11 (CH_2N) ; 62.56 (CH_2O) ; 63.74 (CH_3O) ; 113.12 ($CH_{triazolic}$) ; 122.04 – 128.85 ($7CH_{Ar}$) ; 132.00 (C_{Ar}) ; 132.84 (CH_{Ar}) ; 134.55-144.85 ($3C_{Ar}$) ; 155.34 ($C_{triazolic}$) ; 165.37 (CO_{Amide}) ; 166.92 (CO_{Ester}). MS, m/z: 423.20 $[M+H]^+$.

Acetic acid 4,5-diacetoxy-2-acetoxymethyl-6-[4-(2-isopropyl-5-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (5b):

Yld: 84%, White solid, mp=112°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.21 (d, 6H, CH_3-CH_{thymol} ; J=6.90) ; 1.86-2.1 (4s, 12H, CH_3CO) ; 2.34 (s, 3H, $CH_{3Ar.thymol}$) ; 3.25-3.34 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 4.18 (ddd, H_5, CHO, J=10.00, 3.00,

2.10); 4.32 (2dd, 2H_6, CH_2OAc, J=12.50, 5.00 / 12,50, 2.00) ; 5.22 (s, 2H, CH_2O) ; 5.27 (dd, H_2, CHO, J=9.90, 6.00) ; 5.43 (t, H_4, CHO, J=9.60) ; 5.49 (t, H_3, CHO, J=8.10) ; 5.91 (d, H_1, CHO, J=9.00) ; 6.78-7.14 (m, 3H, CH_{Ar}) ; 7.82 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 20.46 (CH_3) ; 20.90 (CH_3) ; 20.93 (CH_3) ; 21.06 (CH_3) ; 21.71 ($CH_{3thymol}$) ; 23.17 ($2CH_{3thymol}$) ; 27.03 (CH_{thymol}) ; 61.92 (CH_2O) ; 62.66 (CH_2OAc) ; 68.11 (CHO) ; 70.50 (CHO) ; 73.10 (CHO) ; 75.57 (CHO) ; 86.15 (CHO) ; 113.15 ($CH_{triazolic}$);122.34-126.48 ($3CH_{Ar}$) ; 134.74-145.62 ($3C_{Ar}$) ; 155.62 ($C_{triazolic}$); 169.19-170.87 (4C=O). MS, m/z: 562.23 $[M+H]^+$.

Acetic acid 4,5-diacetoxy-6-acetoxymethyl-2-[4-(2-isopropyl-5-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (5c):

Yld: 87%, White solid, mp=109°C, ^1H NMR ($CDCl_3$, 300MHz): 1.21 (d, 6H, CH_3-CH_{thymol} ; J=6.90) ; 1.88 – 2.07 (4s, 12H, CH_3CO) ; 2.34 (s, 3H, $CH_{3Ar.thymol}$) ; 3.29-3.33 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 4.20-4.24 (m, H_5 + 2H_6 + CH_2OAc) ; 5.23 (s, 2H, CH_2O) ; 5.26 (dd, H_2, CHO, J=10.20, 3.60) ; 5.57-5.62 (2t, H_4+H_3, CHO) ; 5.86 (d, H_1, CHO, J=9.30) ; 6.79-7.14 (m, 3H, CH_{Ar}) ; 7.87 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 20.56 (CH_3) ; 20.89 (CH_3) ; 21.05 (CH_3) ; 21.70 (CH_3) ; 21.71 (CH_3) ; 23.19 ($2CH_{3thymol}$) ; 27.01 (CH_{thymol}) ; 61.57 (CH_2O) ; 62.75 (CH_2OAc) ; 67.28 (CHO) ; 68.08 (CHO) ; 71.25 (CHO) ; 74.5 (CHO) ; 86.69 (CHO) ; 113.32 ($CH_{triazolic}$); 121.32-126.47 ($3CH_{Ar}$) ; 134.78-145.94 ($3C_{Ar}$); 155.73 ($C_{triazolic}$); 169.35-170.73 (4C=O). MS, m/z: 562.24 $[M+H]^+$.

Acetic acid 4-acetoxy-2-acetoxymethyl-5-[4-(2-isopropyl-5-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-furan-3-yl ester (5d):

Yld: 70%, Yellow oil, ^1H NMR ($CDCl_3$, 300MHz): 1.18 (d, 6H, CH_3-CH_{thymol}; J=6.90) ; 1.83 – 2.24 (3s, 9H, CH_3CO) ; 2.33 (s, 3H, $CH_{3Ar.thymol}$) ; 3.26 – 3.31 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 3.97- 4.41 (m, 3H, CHO + CH_2OAc) ; 5.22 (s, 2H, CH_2O) ; 5.24-6.18 (m, 3H, CHO) ; 6.77-7.12 (m, 3H, CH_{Ar}) ; 7.78 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 19.83 (CH_3) ; 20.24 (CH_3) ; 20.60 (CH_3) ; 20.78 (CH_3) ; 22.34 ($2CH_{3thymol}$) ; 26.56 (CH_{thymol}) ; 62.26 (CH_2O) ; 63.74 (CH_2OAc) ; 65.60 (CHO) ; 67.44 (CHO) ; 70.51 (CHO) ; 86.76 (CHO) ; 112.58 ($CH_{triazolic}$) ; 121.57-126.00 ($3CH_{Ar}$) ; 133.97- 145.55 ($3C_{Ar}$) ; 155.21 ($C_{triazolic}$); 168.74-170.36 (3C=O). MS, m/z: 490.21 $[M+H]^+$.

4-(2-Isopropyl-5-methyl-phenoxymethyl)-1-tetradecyl-1H-[1,2,3]triazole (5e):

Yld: 90%, White solid, mp=87°C, ^1H NMR ($CDCl_3$, 300MHz): 0.88 (t, 3H, $CH_{3aliphatic}$, J=6.60) ; 1.2 (d, 6H, CH_3-CH_{thymol} ; J=6.90) ; 1.27 – 1.34 (m, 22H, CH_2) ; 1.91-1.96 (m, 2H, CH_2CH_3) ; 2.34 (s, 3H, $CH_{3thymol}$) ;3.28-3.32 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 4.37 (t, 2H, CH_2N, J=7.49) ; 5.24 (s, 2H, CH_2O) ; 6.78-7.14 (m, 3H, CH_{Ar}) ; 7.56 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 14.52 ($CH_{3aliphatic}$); 21.73 ($CH_{3thymol}$) ; 23.09 ($2CH_{3thymol}$) ; 23.18 (CH_2) ; 26.90 (CH_2) ; 27.02 (CH_{thymol}) ; 29.40-32.32 ($10CH_2$) ; 50.84 (CH_2N); 63.04 (CH_2O) ; 113.32 ($CH_{triazolic}$); 122.20-126.41 ($3CH_{Ar}$) ; 134.66-145.27 ($3C_{Ar}$); 155.75 ($C_{triazolic}$). MS, m/z: 428.36 $[M+H]^+$.

2-[4-(2-Isopropyl-5-methyl-phenoxymethyl)-[1,2,3]triazol-1-ylmethyl]-pyridine (5f) :

Yld: 63%, Yellow oil, ^1H NMR ($CDCl_3$, 300MHz): 1.17 (d, 6H, CH_3-CH_{thymol}, J=6.90) ; 2.33 (s, 3H, $CH_{3\text{-}Ar.\ thymol}$) ; 3.17-3.25 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 5.24 (s, 2H, CH_2N) ; 5.69 (s, 2H, CH_2O) ; 6.78-7.12 (m, 3H, $CH_{Ar.\ thymol}$) ; 7.20-7.74 (m , 3H, $CH_{Ar.\ picoline}$) ; 7.77 (s, 1H, $CH_{triazolic}$) ; 8.61 (d, 1H , CH-Nar, J=4.20). ^{13}C RMN ($CDCl_3$, 75MHz): 21.33 (CH_3) ; 22.79 ($2CH_3$) ; 26.57 (CH); 55.69 (CH_2N) ; 62.58 (CH_2O) ; 112.93 $CH_{triazolic}$) ; 121.87-126.03 ($5CH_{Ar}$) ; 134.35 ($2C_{Ar}$) ; 137.39 (CH_{Ar}) ; 145.36 (C_{Ar}) ; 149.78 (CH-N_{Ar}) ; 154.45 (C-N_{Ar}) ; 155.31 ($C_{triazolic}$). MS, m/z: 323.18 $[M+H]^+$.

{3-[4-(2-Isopropyl-5-methyl-phenoxymethyl)-[1,2,3]triazol-1-ylmethyl]-phenyl}-phenyl-methanone (5g):

Yld: 84%, Yellow solid, mp=105°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.17 (d, 6H, CH_3-CH_{thymol}, J=6.90) ; 2.33 (s, 3H, $CH_{3\text{-Ar. thymol}}$) ; 3.18-3.22 (m, 1H, CH-$(CH_3)_{2thymol}$) ; 5.24 (s, 2H, CH_2N) ; 5.65 (s, 2H, CH_2O) ; 6.78-7.13 (m, 3H, $CH_{Ar. thymol}$) ; 7.78 – 7.83 (m, 9H, $CH_{Ar. benzophénone}$ + s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 21.29 (CH_3) ; 22.79 ($2CH_3$) ; 26.60 (CH); 53.72 (CH_2N) ; 62.59 (CH_2O) ; 113.02 ($CH_{triazolic}$); 121.97 – 132.71 (CH_{Ar}) ; 134.35-145.63 (C_{Ar}) ; 155.28 ($C_{triazolic}$); 195.86 (CO). MS, m/z: 426.21 $[M+H]^+$.

Benzoylamino-[4-(5-isopropyl-2-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-acetic acid methyl ester (6a):

Yld: 75%, White solid, mp=119°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.20 (d, 6H, CH_3-$CH_{carvacrol}$; J=6.90) ; 2.22 (s, 3H, $CH_{3Ar.carvacrol}$) ; 2.81-2.94 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 3.91 (s, 3H, CH_3O) ; 5.24 (s, 2H, CH_2O) ; 6.77-7.02 (m, 3H, $CH_{Ar.carvacrol}$) ; 7.06 (d, 1H, $CH_{glycine}$, J=7.80) ; 7.45-7.87 (m, 5H, CH_{Ar}); 7.91 (d, 1H, NH , J=7.80) ; 8.06 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 15.86 (CH_3) ; 24.04 ($2CH_3$) ; 34.04 (CH) ; 54.12 (CHN) ; 62.39 (CH_2O) ; 63.77 (CH_3O) ; 110.30 ($CH_{triazolic}$) ; 118.9-123.99 ($2CH_{Ar}$) ; 124.42 (C_{Ar}) ; 127.44-130.61 ($5CH_{Ar}$) ; 131.96 (C_{Ar}); 132.84 (CH_{Ar}) ; 144.87-148.00 ($2C_{Ar}$) ; 156.34 ($C_{triazolic}$) ; 165.41 (CO_{Amide}) ; 166.96 (CO_{Ester}).

Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-[4-(5-isopropyl-2-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-4-yl ester (6b):

Yld: 71%, White solid, mp=106°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.23 (d, 6H, CH_3-$CH_{carvacrol}$; J=6.90) ; 1.85-2.09 (4s, 12H, CH_3CO) ; 2.22 (s, 3H, $CH_{3Ar.carvacrol}$) ; 2.81-2.94 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 4.00 (ddd, H_5, CHO, J=7.10, 3.00, 2.10); 4.24 (2dd, $2H_6$, CH_2OAc, J=12.50, 5.00 / 12,50, 2.00) ; 5.23 (s, 2H, CH_2O) ; 5.26 (t, H_4, CHO, J=9.30) ; 5.43 (t, H_3, CHO, J=9.30) ; 5.49 (dd, H_2, CHO, J=9.30, 6.00) ; 5.91 (d, H_1, CHO, J=9.00) ; 6.76-7.09 (m, 3H, CH_{Ar}) ; 7.85 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 15.83 (CH_3) ; 20.07 (CH_3) ; 20.49 (CH_3) ; 20.52 (CH_3) ; 20.66 ($CH_{3carvacrol}$) ; 24.08 ($2CH_{3carvacrol}$) ; 34.05 ($CH_{carvacrol}$) ; 61.55 (CH2O) ; 62.19 (CH_2OAc) ; 67.72 (CHO) ; 70.19 (CHO) ; 72.70 (CHO) ; 75.14 (CHO) ; 85.71 (CHO) ; 110.05 ($CH_{triazolic}$);118.85-120.8 ($2CH_{Ar}$) ; 124.31 (C_{Ar}) ; 130.61 (CH_{Ar}) ; 145.72-148.02 ($2C_{Ar}$) ; 156.24 ($C_{triazolic}$); 168.85-170.47 (4C=O).

Acetic acid 4,5-diacetoxy-6-acetoxymethyl-2-[4-(5-isopropyl-2-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (6c):

Yld: 80%, White solid, mp=134°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.23 (d, 6H, CH_3-$CH_{carvacrol}$; J=6.90) ; 1.87-2.23 (4s, 12H, CH_3CO) ; 2.23 (s, 3H, $CH_{3Ar.carvacrol}$) ; 2.81-2.95 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 4.12-4.28 (m, H_{5sugar} + $2H_{6sugar}$ + CH_2OAc); 5.24 (s, 2H, CH_2O) ; 5.26 (dd, H_2, CHO, J=10.20, 3.30) ; 5.56-5.64 (2t, H_4+H_3, CHO) ; 5.86 (d, H_1, CHO, J=9.30) ; 6.77-7.09 (m, 3H, CH_{Ar}) ; 7.89 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 15.83 (CH_3) ; 20.17 (CH_3) ; 20.47 (CH_3) ; 20.62 (CH_3) ; 20.64 (CH_3) ; 24.07 ($2CH_{3carvacrol}$) ; 34.05 ($CH_{carvacrol}$) ; 61.19 (CH_2O) ; 62.27 (CH_2O_{Ac}) ; 66.90 (CHO) ; 67.79 (CHO) ; 70.83 (CHO) ; 74.09 (CHO) ; 86.27 (CHO) ; 110.2 ($CH_{triazolic}$); 118.85-120.96 ($2CH_{Ar}$); 124.35 (C_{Ar}) ; 130.60 (CH_{Ar}) ;145.57-148.02 ($2C_{Ar}$); 156.31 ($C_{triazolic}$); 168.99-170.3 (4C=O).

Acetic acid 4-acetoxy-2-acetoxymethyl-5-[4-(5-isopropyl-2-methyl-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-furan-3-yl ester (6d):

Yld: 65%, Yellow oil, ^{1}H NMR ($CDCl_3$, 300MHz): 1.23 (d, 6H, CH_3-$CH_{carvacrol}$; J=6.90) ; 1.84 -2.21 (3s, 9H, CH_3CO) ; 2.24 (s, 3H, $CH_{3Ar.carvacrol}$) ; 2.86-2.95 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 4.01-4.27 (m, 3H, CHO + CH_2OAc) ; 5.24 (s, 2H, CH_2O) ; 5.25-6.19 (m, 3H, CHO) ; 6.77-7.09 (m, 3H, CH_{Ar}) ; 7.81 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 19.87 (CH_3) ; 20.27 (CH_3) ; 20.60 (CH_3) ; 20.89 (CH_3) ; 22.71 ($2CH_{3carvacrol}$) ; 31.94 ($CH_{carvacrol}$) ; 62.25 (CH_2O) ; 63.75 (CH_2OAc) ; 65.60 (CHO) ; 67.44 (CHO) ; 70.51 (CHO) ; 86.76 (CHO) ; 109.94 ($CH_{triazolic}$); 118.78-

120.80 ($2CH_{Ar}$); 124.22 (C_{Ar}) ; 130.1 (CH_{Ar}) ;145.44-148.11 ($2C_{Ar}$); 156.24 ($C_{triazolic}$); 168.79-170.35 (3C=O). MS, m/z: 490.21 $[M+H]^+$.

4-(5-Isopropyl-2-methyl-phenoxymethyl)-1-tetradecyl-1H-[1,2,3]triazole (6e):

Yld: 70%, Yellow solid, mp=110°C, ^{1}H NMR ($CDCl_3$, 300MHz): 0.88 (t, 3H, $CH_{3aliphatique}$, J=6.30) ; 1.24 (d, 6H, CH_3-$CH_{carvacrol}$; J=6.90) ; 1.26-1.34 (m, 22H, CH_2) ; 1.87-2.01 (m, 2H, CH_2CH_3) ; 2.22 (s, 3H, $CH_{3carvacrol}$) ;2.82-2.96 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 4.37 (t, 2H, CH_2N, J=7.48) ; 5.26 (s, 2H, CH_2O) ; 6.77-7.1 (m, 3H, CH_{Ar}) ; 7.57 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 14.12 ($CH_{3aliphatic}$); 15.89 ($CH_{3carvacrol}$) ; 22.7 (CH_2) ; 24.10 ($2CH_{3carvacrol}$) ; 26.90 (CH_2) ; 26.5-31.93 (CH_2) ; 34.08 ($CH_{carvacrol}$) ; 50.44 (CH_2N); 62.58 (CH_2O) ; 110.18 ($CH_{triazolic}$); 118.71-122.06 ($2CH_{Ar}$) ; 124.25 (C_{Ar}) ; 130.56 (CH_{Ar}) ; 144.88-148.00 ($2C_{Ar}$) ; 156.38 ($C_{triazolic}$). MS, m/z: 428.36 $[M+H]^+$.

2-[4-(5-Isopropyl-2-methyl-phenoxymethyl)-[1,2,3]triazol-1-ylmethyl]-pyridine (6f) :

Yld: 72%, Yellow solid, mp=112°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.23 (d, 6H, CH_3-$CH_{carvacrol}$, J=6.90) ; 2.19 (s, 3H, $CH_{3\text{-}Ar.carvacrol}$) ; 2.60-3.00 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 5.26 (s, 2H, CH_2N) ; 5.68 (s, 2H, CH_2O) ; 6.76-7.08 (m, 3H, $CH_{Ar.carvacrol}$) ; 7.19-7.73 (m , 3H, $CH_{Ar.picoline}$) ; 7.77 (s, 1H, $CH_{triazolic}$) ; 8.61 (d, 1H , CH-N_{Ar}, J= 4.20). ^{13}C RMN ($CDCl_3$, 75MHz): 15.88 (CH_3) ; 24.10 ($2CH_3$) ; 34.06 (CH); 55.70 (CH_2N) ; 62.50 (CH_2O) ; 110.20 ($CH_{triazolic}$) ; 118.76-123.44 ($4CH_{Ar}$) ; 124.31 (C_{Ar}) ; 130.57-137.38 ($2CH_{Ar}$) ; 145.38-148.01 ($2C_{Ar}$) ; 149.79 (CH-N_{Ar}) ; 154.45 (C-N_{Ar}) ; 156.32 ($C_{triazolic}$). MS, m/z: 323.18 $[M+H]^+$.

{3-[4-(5-Isopropyl-2-methyl-phenoxymethyl)-[1,2,3]triazol-1-ylmethyl]-phenyl}-phenyl-methanone (6g):

Yld: 78%, White solid, mp=86°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.22 (d, 6H, CH_3-$CH_{carvacrol}$, J=6.90) ; 2.19 (s, 3H, $CH_{3\text{-}Ar.carvacrol}$) ; 2.82-2.92 (m, 1H, CH-$(CH_3)_{2carvacrol}$) ; 5.26 (s, 2H, CH_2N) ; 5.63 (s, 2H, CH_2O) ; 6.76-7.08 (m , 3H, $CH_{Ar.carvacrol}$) ; 7.35-7.82 (m, 9H, $CH_{Ar.\ benzophénone}$ + s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 15.89 (CH_3) ; 24.11 ($2CH_3$) ; 34.06 (CH); 53.69 (CH_2N) ; 62.48 (CH_2O) ; 110.27 ($CH_{triazolic}$); 118.86-132.73 (CH_{Ar}) ; 137.20-148.05 (C_{Ar}) ; 156.29 ($C_{triazolic}$); 195.89 (CO).

[4-(4-Allyl-2-methoxy-phenoxymethyl)-[1,2,3]triazol-1-yl]-benzoylamino-acetic acid methyl ester (7a):

Yld: 74%, White solid, mp=88°C, ^{1}H NMR ($CDCl_3$, 300MHz): 3.50 (d ,2H ,CH_2-Ar, J=6.90) ; 3.74 (s, 3H, CH_3O) ; 3.91 (s, 3H, CH_3O) ; 5.02-5.04 (m, 2H, $CH_{2acetylenic}$) ; 5.24 (s, 2H, CH_2O) ; 5.88-6.01 (ddt, 1H, $CH_{aceltylenic}$, J=16.80,10.20,6.90) ; 6.77-7.02 (m, 3H, $CH_{Ar.eugenol}$) ; 7.06 (d, 1H, $CH_{glycine}$, J=7.80) ; 7.45-7.87 (m, 5H, CH_{Ar}) ; 7.91 (d, 1H, NH , J=7.80) ; 8.49 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 39.98 (CH_2-Ar) ; 54.12 (CHN) ; 55.81 (OCH_3) ; 62.39 (CH_2O) ; 63.77 (CH_3O) ; 112.93 ($CH_{acetylenic}$) ; 114.05 (CH_{Ar}) ; 116.03 ($CH_{2acetylenic}$) ; 120.6 (CH_{Ar}) ; 124.03 ($CH_{triazolic}$); 133.29 (C_{Ar}) ; 133.84 (CH_{Ar}) ; 143.32-146.32 ($3C_{Ar}$) ; 127.44-130.61 ($5CH_{Ar}$) ; 156.34 ($C_{triazolic}$) ; 165.41 (CO_{Amide}) ; 166.96 (CO_{Ester}). MS, m/z: 437.18 $[M+H]^+$.

Acetic acid 4,5-diacetoxy-2-acetoxymethyl-6-[4-(4-allyl-2-methoxy-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (7b):

Yld: 71%, White solid, mp=71°C, ^{1}H NMR ($CDCl_3$, 300MHz): 1.85-2.1 (4s, 12H, CH_3CO) ; 3.33 (d ,2H , CH_2-Ar, J=6.90) ; 3.88 (s, 3H, CH_3O) ; 3.98-4.03 (ddd, H_5, CHO, J=10.00, 3.00, 2.10); 4.16 (2dd, $2H_6$, CH_2OAc, J=12.50, 5.00/ 12.50 , 2.00) ; 4.27-4.33 (m, 2H, $CH_{2acetylenic}$) ; 5.21-5.28 (dd, H_2, CHO, J=9.90, 6.00) ; 5.28 (s, 2H, CH_2O) ; 5.38-5.46 (2t, H_4+H_3, CHO, J=9.30 , 9.40) ; 5.86 (d, H_1, CHO, J=8.80) ; 5.89-5.97 (ddt, 1H, $CH_{acetylenic}$, J=16.80, 10.10, 6.70) ; 6.69-6.95 (m, 3H, CH_{Ar}) ; 7.88 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 20.15 (CH_3) ; 20.53

(CH_3) ; 20.55 (CH_3) ; 20.70 (CH_3) ; 39.84 (CH_2-Ar) ; 55.87 (OCH_3) ; 61.54 (CH_2O) ; 63.28 (CH_2OAc) ; 67.66 (CHO) ; 70.22 (CHO) ; 72.71 (CHO) ; 75.10 (CHO) ; 85.71 (CHO) ; 112.40 ($CH_{acetylenic}$) ; 114.74 (CH_{Ar}) ; 115.76 ($CH_{2acetytenic}$) ; 120.51 (CH_{Ar}) ; 121.36 ($CH_{triazolic}$); 134.05 (C_{Ar}) ; 137.50 (CH_{Ar}) ; 145.29 (C_{Ar}) ; 146.57 (C_{Ar}); 149.17 ($C_{triazolic}$) ; 168.86-171.41 (4C=O). MS, m/z: 576.21 $[M+H]^+$.

Acetic acid 4,5-diacetoxy-6-acetoxymethyl-2-[4-(4-allyl-2-methoxy-phenoxymethyl)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (7c):

Yld: 80%, White solid, mp=80°C, ^1H NMR ($CDCl_3$, 300MHz): 1.87-2.23 (4s, 12H, CH_3CO) ; 3.33 (d ,2H , CH_2-Ar, J=6.60) ; 3.88 (s, 3H, CH_3O) ; 4.12-4.23 (m, 3H, CHO + CH_2OAc) ; 5.06-5.12 (m, 2H, $CH_{2acetylenic}$) ; 5.245 (dd, H_2, CHO, J=10.20, 3.30) ; 5.27 (s, 2H, CH_2O) ; 5.55-5.61 (2t, H_4+H3, CHO) ; 5.83 (d, H_1, CHO, J=9.30) ; 5.86-6.01 (ddt, 1H, $CH_{acetylenic}$, J=17.00,10.00,6.70) ; 6.7-6.96 (m, 3H, CH_{Ar}) ; 7.96 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 20.27 (CH_3) ; 20.53 (CH_3) ; 20.69 (CH_3) ; 20.70 (CH_3) ; 39.85 (CH_2-Ar) ; 55.88 (OCH_3) ; 61.25 (CH_2O) ; 63.36 (CH_2OAc) ; 66.86 (CHO) ; 67.76 (CHO) ; 70.85 (CHO) ; 73.99 (CHO) ; 86.24 (CHO) ; 112.32 ($CH_{acetylenic}$) ; 114.71 (CH_{Ar}) ; 115.79 ($CH_{2acetylenic}$) ; 120.51 (CH_{Ar}) ; 121.49 ($CH_{triazolic}$); 134 (C_{Ar}) ; 137.49 (CH_{Ar}) ; 145.18 (C_{Ar}) ; 145.88 ($C_{triazolic}$); 149.6 (C_{Ar}) ; 169-170.39 (4C=O). MS, m/z: 576.21 $[M+H]^+$.

Acetic acid 4-acetoxy-2-acetoxymethyl-5-{4-[2-(4-allyl-2-methoxy-phenyl)-ethyl]-[1,2,3]triazol-1-yl}-tetrahydro-furan-3-yl ester (7d) :

Yld: 77%, Yellow oil, ^1H NMR ($CDCl_3$, 300MHz): 1.87-2.23 (3s, 9H, CH_3CO) ; 3.33 (d ,2H ,CH_2-Ar, J=6.60) ; 3.86 (s, 3H, CH_3O) ; 3.88-4.1 (m, 3H, CHO) ; 5.06-5.11 (m, 2H, $CH_{2\ acetylenic}$) ; 5.28 (s, 2H, CH_2O) ; 5.35-6.07 (m, 3H, CHO + CH_2OAc) ; 5.83-5.97 (ddt, 1H, $CH_{\ acetylenic}$, J=16.80, 10.10 ,6.70) ; 6.68-6.93 (m, 3H, CH_{Ar}) ; 7.8 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 21.33 (CH_3) ; 20.24-20.74 ($3CH_3$) ; 39.84 (CH_2-Ar) ; 55.87 (CH_3O) ; 63.30 (CH_2O) ; 63.73 (CH_2OAc) ; 65.74-68.38 (3CHO) ; 83.52 (CHO) ; 112.42 ($CH_{\ acetylenic}$) ; 114.42 (CH_{Ar}) ; 115.76 ($CH_{2\ acetylenic}$) ; 120.5 (CH_{Ar}) ; 121.28 ($CH_{triazolic}$) ; 134.02 (C_{Ar}) ; 137.51 (CH_{Ar}) ; 144.99-145.88 ($2C_{Ar}$) ; 149.55 ($C_{triazolic}$) ; 168.78-169.69 (3CO). MS, m/z: 504.19 $[M+H]^+$.

4-(4-Allyl-2-methoxy-phenoxymethyl)-1-tetradecyl-1H-[1,2,3]triazole (7e):

Yld: 87%, White solid, mp=87°C, ^1H NMR ($CDCl_3$, 300MHz): 0.87 (t, 3H, $CH3_{aliphatic}$, J=6.90) ; 1.27-1.32 (m, 22H, CH_2) ; 1.88-1.93 (m, 2H, CH_2CH_3) ; 3.33 (d , 2H, CH_2-Ar, J=6.60) ; 3.88 (s , 3H, OCH_3) ; 4.31-4.36 (t, 2H, CH_2N, J=7.50) ; 5.06 (m , 2H, $CH_{2\ acetylenic}$) ; 5.29 (s, 2H, CH_2O) ; 5.9 – 6.03 (ddt , 1H, $CH_{\ acetylenic}$, J=16.80, 10.50, 6.60) ; 6.7-6.99 (m, 3H, CH_{Ar}) ; 7.62 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 14.12 ($CH_{3aliphatique}$); 22.69-31.92 ($12CH_2$) ; 39.83 (CH_2-Ar) ; 50.42 (CH_2N) ; 55.87 (OCH_3) ; 63.55 (CH_2O) ; 112.31 ($CH_{\ acetylenic}$) ; 114.47 (CH_{Ar}) ; 115.73 ($CH_{2\ acetylenic}$) ; 120.55 (CH_{Ar}) ; 122.53 (($CH_{triazolic}$) ; 133.77 (C_{Ar}) ; 137.54 CH_{Ar}) ; 144.49-145.99 ($2C_{Ar}$) ; 149.53 ($C_{triazolic}$). MS, m/z: 442.34 $[M+H]^+$.

2-[4-(4-Allyl-2-methoxy-phenoxymethyl)-[1,2,3]triazol-1-ylmethyl]-pyridine (7f):

Yld: 70%, Yellow oil, ^1H NMR ($CDCl_3$, 300MHz): 3.31 (d ,2H ,CH_2-Ar, J=6.90) ; 3.82 (s, 3H, CH_3O) ; 5.03-5.1 (m, 2H, $CH_{2\ acetylenic}$) ; 5.25 (s, 2H, CH_2N) ; 5.63 (s, 2H, CH_2O) ; 5.87-6.01 (ddt, 1H, $CH_{acetylenic}$, J=16.80,10.20,6.90) ; 6.67-6.96 (m, 3H, $CH_{Ar.eugenol}$) ; 7.15-7.70 (m , 3H, $CH_{Ar.\ picoline}$) ; 7.8 (s, 1H, $CH_{triazolic}$) ; 8.57 (d, 1H , CH-N_{Ar}, J= 4.20). ^{13}C RMN ($CDCl_3$, 75MHz): 39.81 (CH_2-Ar) ; 55.62 (CH_2N) ; 55.82 (OCH_3) ; 63.43 (CH_2O) ; 112.34 ($CH_{acetylenic}$) ; 114.65 (CH_{Ar}) ; 115.72 ($CH_{2acetylenic}$) ; 120.51-123.58 ($4CH_{Ar}$) ; 133.87 (C_{Ar}) ; 137.39 (CH_{Ar}) ; 137.52 ($CH_{triazolic}$) ; 144.86-145.91 ($2C_{Ar}$) ; 149.58 (CH-N_{Ar}) ; 149.72 (C-N_{Ar}) ; 154.33 ($C_{triazolic}$). MS, m/z: 337.16 $[M+H]^+$.

{3-[4-(4-Allyl-2-methoxy-phenoxymethyl)-[1,2,3]triazol-1-ylmethyl]-phenyl}-phenyl-methanone (7g):

Yld: 80%, White solid, mp=97°C, ^{1}H NMR ($CDCl_3$, 300MHz): 3.33 (d ,2H , CH_2-Ar, J=6.60) ; 3.88 (s, 3H, CH_3O) ; 5.06-5.12 (m, 2H, $CH_{2a\ acetylenic}$) ; 5.24 (s, 2H, CH_2N) ; 5.65 (s, 2H, CH_2O) ; 5.86-6.01 (ddt, 1H, $CH_{acetylenic}$, J=17.00,10.00,6.70) ; 6.7-6.96 (m, 3H, CH_{Ar}) ; 7.78-7.83 (m, 9H, $CH_{Ar.\ benzophenone}$) ; 7.96 (s, 1H, $CH_{triazolic}$). ^{13}C RMN ($CDCl_3$, 75MHz): 39.94 (CH_2-Ar) ; 55.88 (OCH_3) ; 56.72 (CH_2N) ; 62.59 (CH_2O) ; 113.16 ($CH_{triazolique}$) ; 113.32 ($CH_{acetylenic}$) ; 116.23 ($CH_{2acetylenic}$) ; 122.97-131.51 ($12CH_{Ar}$) ; 133.45-146.38 ($6C_{Ar}$) ; 156.8 ($C_{triazolic}$); 191.62 (CO).

4. Conclusion

A series of novel 1,4 disubstituted 1,2,3 triazoles were successfully prepared by CuAAC process, all desired products are obtained in good yields and their structures were confirmed by spectral techniques ^{1}H NMR, ^{13}C NMR and HRMS. The use of click chemistry helps to quickly assemble different interesting blocks to generate novel molecules that can have important biological effects. The biological analysis of these compounds is proceeding to determine their therapeutic potentials.

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