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Efficient synthesis and antioxidant activity of novel *N*-propargyl tetrahydroquinoline derivatives through the cationic Povarov reaction

Yeray A. Rodriguez Núñez [a], Maximiliano Norambuena [a], Arnold R. Romero Bohorquez [b], Alejandro Morales-Bayuelo [c], Margarita Gutíerrez [a,*]

[a] *Laboratorio Síntesis Orgánica, Instituto de Química de Recursos Naturales, Universidad de Talca, Casilla 747, Talca, 3460000, Chile*
[b] *Grupo de Investigación de Compuestos Orgánicos de Interés Medicinal (CODEIM), Parque Tecnológico Guatiguará, Universidad Industrial de Santander, A.A. 678, Piedecuesta, Colombia*
[c] *Centro de Investigación de Procesos del Tecnologico Comfenalco (CIPTEC), programa de Ingeniería Industrial, Fundacion Universitaria Tecnologico Comfenalco – Cartagena, Cr 44 D N 30A, 91, Cartagena-Bolívar, Colombia*

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ABSTRACT

New N-propargyl tetrahydroquinolines **6a-g** have been synthesized efficiently through the cationic Povarov reaction (a domino Mannich/Friedel-Crafts reaction), catalyzed by Indium (III) chloride ($InCl_3$), from the corresponding *N*-propargylanilines preformed, formaldehyde and *N*-vinylformamide, with good to moderate yields. All tetrahydroquinoline derivatives obtained were evaluated *in vitro* as free radical scavengers. Results showed that compound **6c** presents a potent antioxidant effect compared with ascorbic acid, used as a reference compound. ADME predictions also revealed favorable pharmacokinetic parameters for the synthesized compounds, which warrant their suitability as potentials antioxidant. Additionally, a theoretical study using Molecular Quantum Similarity and reactivity indices were developed to discriminate different reactive sites in the new molecules in which the oxidative process occurs.

1. Introduction

In the research of biologically active molecules, free radicals have been linked to several degenerative diseases including neurodegenerative and cardiovascular disorder, atherosclerosis and cancer (Aruoma, 1998). Although the discovery of antioxidant compounds has been an area widely studied (Kouznetsov et al., 2011; Bulut et al., 2018; Martelli and Giacomini, 2018) it is necessary to continue in the search of new natural or synthetic compounds that can act as free radical scavengers and help in the treatment or control of diseases related to oxidative stress.

Heterocyclic compounds, especially nitrogen heterocycles, are a very important class of compounds with application in the pharmaceutical industries, which comprise about 60% of all pharmacological substances. The tetrahydroquinoline (THQ) ring system, in particular, is a common structural motif found in numerous biologically active natural products showing broad biological activities (Nammalwar and Bunce, 2014). Because of the significance of these scaffolds in drug discovery and medicinal chemistry, the development of new methodologies for the synthesis of THQs derivatives continues to be an active field of investigation, as is evidenced by the appearance of over 400 research articles in this area during the last years (Sridharan et al., 2011; Katritzky et al., 1996).

In the last decades, a great number of synthetic methods for access to THQs derivatives have been reported (Sridharan et al., 2011). In many cases, these methodologies involve an intramolecular Friedel-Crafts reaction of *N*-substituted anilines with a suitable functional group bound to the nitrogen atom (Abonia et al., 2013). In this sense, the use of multicomponent Povarov reaction, catalyzed by Lewis or Brønsted acids between *N*-arylimines (obtained from anilines and aryl (alkyl)aldehydes) and electron-rich alkenes, is maybe the most powerful tool that provides quick and efficiently THQ scaffold with great structural diversity. Recently, we have been successfully exploring the cationic version of the Povarov reaction (a domino Mannich/Friedel-Crafts reaction). This method resulted highly efficient to access different N-derivatives of THQs (Romero Bohórquez et al., 2016; Acelas et al., 2017), including the synthesis of new *N*-allyl/propargyl 1,2,3,4-THQs, promissory dual inhibitors against AChE and BChE enzymes (Rodriguez et al., 2016).

Diverse amine derivatives with the propargyl fragment in its structure are versatile compounds with demonstrated pharmacological and pharmaceutical applications such as antioxidant agents (Dragoni et al., 2006) and as inhibitors of some monoamine oxidases MAO-B. Selegiline,

* Corresponding author.
E-mail address: mgutierrez@utalca.cl (M. Gutíerrez).

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Rasagiline, Pargyline, and Ladostigil drugs are widely used as enzymatic inhibitors in treatments of neurodegenerative diseases (Fig. 1) (Baranyi et al., 2016; Bolea et al., 2013; Mao et al., 2015). Taking into account all the above, in the present study, we report the synthesis, spectroscopic characterization and antioxidant activity of a new series of *N*-propargyl-THQs obtained via mild and expeditious $InCl_3$ catalyzed-cationic Povarov reaction. Results indicated that some THQs derivatives evaluated showed good activity as potential free radical scavengers. In addition, theoretical studies of Molecular Quantum Similarity Measure allowed explaining the biological activity reported. Local reactivity descriptors like the local softness and electrophilicity indices were obtained with the help of Fukui function calculation.

2. Results and discussion

The preparation of new *N*-propargyl THQs **6a-g** via domino Mannich addition/Friedel-Crafts intramolecular alkylation reactions catalyzed by $InCl_3$, was effective under mild condition reactions using N-propargylamines with formaline (37% in methanol) and *N*-vinylformamide as an electron-rich alkene. Acetonitrile (CH_3CN) was used as solvent based on previous reports (Romero Bohórquez et al., 2016; Abonia et al., 2013). Synthetic route and structures of final compounds are shown in Scheme 1. According to the results, although fluctuations in the reaction yield were shown, in general, the reaction showed to be powerful synthetic strategy to obtain the corresponding 1,2,3,4-THQ compounds with high structural diversification (Table 1).

All new *N*-propargyl THQ derivatives **6a-g** were obtained as stable solids and were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and MS. In the IR spectra, C=O vibration bands (1643-1658 cm^{-1}) and propargyl fragment vibration bands (3231-3279 cm^{-1}) were observed. ^{1}H NMR spectral analysis of the synthesized *N*-propargyl tetrahydroquinolines showed four groups of characterized signals. First, signals between 6.88-7.31 ppm indicated the presence of aromatic protons corresponding to the tetrahydroquinoline ring. Also was possible to observe the aliphatic proton signals, around 5.10–1.99 ppm, corresponding to THQ nucleus and the signal for the alkyne proton between 2.13–2.28 ppm. Finally, around 8.11–8.21 ppm, proton signal for formamide group was observed. This set of signals constitutes evidence that the formation of the tetrahydroquinoline compounds took place favorably. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra of compound **6a-6g** are included in supplementary material (Fig S1-FigS7).

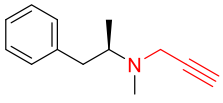
The presence of a fragment *N*-propargyl in the new compounds is interesting owing to propargylamines are useful synthetic precursors in the obtaining of different organic substrates, natural products, and drugs as evidenced by the large number of articles published in the literature (Hua and Nizami, 2018; Lauder et al., 2017: Yang et al., 2018). The versatility of propargylamines is due to its unique structure composed of an amine group in β-position to an alkyne moiety. Compounds with a carbon−carbon triple bond have characteristic reactivity and can behave as electrophilic substrates and as an electron source in nucleophilic reactions (Mao et al., 2015). It is worth noting that, as mentioned above, some *N*-propargyl derivatives have been applied mainly as monoamine oxidase inhibitors (IMAO) and, according to the literature, could promote antioxidant effects by acting as radical scavengers (Dragoni et al., 2006).

All compounds obtained were evaluated as antioxidant agents in presence of the stable radical DPPH (1,1-diphenyl-2-picrylhydrazyl) at a concentration ranging from 10 to 100 μL and compared with ascorbic acid as shown in Table 2. The DPPH scavenging activity varied greatly. There were no clear differences in IC_{50} values between the compounds synthesized despite the presence of substituents with different chemical properties and was not possible to observe an antioxidant effect compared with standard.

On the other hand, Table 3 showed that compounds **6b**, **6c**, **6d**, and **6g** have good activity in scavenging ABTS radical, presenting better IC_{50} values than those found for ascorbic acid, used as reference. This is consistent with the results reported previously where described compounds having an electron withdrawing group like fluorine, and electron donating groups, like methoxy on the phenyl rings, exhibit good antioxidant activity (Mubeen et al., 2015; Polo et al., 2016).

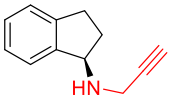
Computational methods are important tools to predict some compound properties with interesting experimental biological activities, e.g, QikProp is a quick, accurate, and easy to use absorption, distribution, metabolism, and excretion (ADME) prediction program (Schrödinger, 2017). The main parameters are shown in Table 4. Taking into account the Lipinski's rule of five (molecular weight below 500 Da, hydrogen bond donor less than 5, acceptor less than 10, and Log P (octanol/water partition coefficient) for the ligand less than five), the synthesized compounds did not present violations to this rule, being within of permissible range of each descriptor (Lipinski et al., 1997). Likewise, the synthesized THQ series satisfies other parameters involved in the absorption, distribution and membrane penetration as water solubility (Log S) and polar surface area (PSA). Finally, the predicted qualitative oral absorption was calculated. This prediction is made through the analysis of the appropriate values of different descriptors. The analysis showed that the compounds could present good oral absorption. In general, the new *N*-propargyl tetrahydroquinolines presented permissible values in the different descriptors calculated (Singh et al., 2012).

To understand the biological activity reported, an analysis of chemical reactivity were developed and Quantum Similarity field and



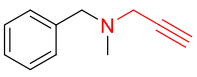
Selegiline (Deprenyl)

Selective irreversible MAO-B inhibitor



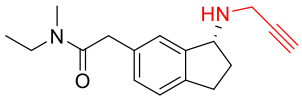
Rasagiline (Azilect)

Irreversible MAO-B Inhibitor



Pargyline

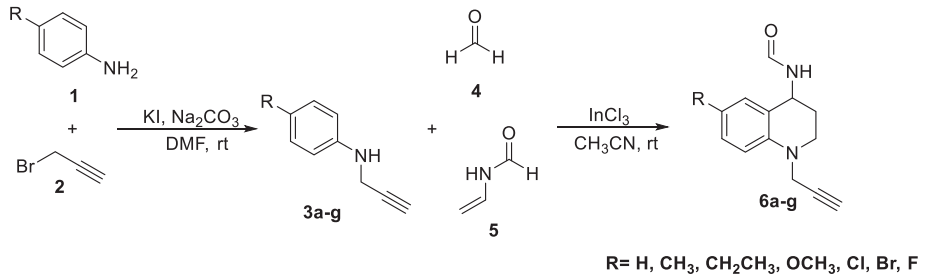
Irreversible MAO-A (IC_{50} = 11.52 nmol/L) and MAO-B (IC_{50} = 8.20 nmol/L) inhibitor



Ladostigil (TV-3,326)

Reversible AChE and BChE inhibitor and Irreversible MAO-B inhibitor

Fig. 1. Propargylamines inhibitors of monoamine oxidases MAO-A and MAO-B.



Scheme 1. Synthesis of *N*-propargyl THQs 6a-g from *N*-propargylamines via domino Mannich/Friedel-Crafts alkylation reactions.

Table 1
Physicochemical parameters obtained for the new THQ compounds.

Compound	R	MW (g/mol)	Time (h)	Yield (%)	m.p. (°C)[a]
3a	H	131.17	3	51%	Oil
3b	CH_3	145.20	3	49%	Oil
3c	OCH_3	161.20	3	48%	Oil
3d	CH_2CH_3	159.23	3	45%	Oil
3e	Br	210.07	3	51%	Oil
3f	Cl	165.62	3	44%	Oil
3g	F	149.16	3	58%	Oil
6a	H	214.26	4	51%	118–120
6b	CH_3	228.29	4	95%	134–136
6c	OCH_3	244.29	4	66%	110–112
6d	CH_2CH_3	242.32	4	31%	116–118
6e	Br	293.16	4	52%	164–166
6f	Cl	248.71	4	23%	158–160
6g	F	232.25	4	71%	144–146

[a] Uncorrected.

Table 2
% Decoloration of DPPH solution for synthesized compounds in comparation with ascorbic acid. Values are the average of triplicate experiments.

	Concentration (μg/mL)			
Compound	100	50	10	IC_{50}
6a	12.63 ± 1.2	5.26 ± 1.5	1.04 ± 0.2	>100
6b	19.74 ± 3.2	10.52 ± 1.5	0.00 ± 0.0	>100
6c	45.53 ± 5.6	29.47 ± 4.1	21.05 ± 5.1	>100
6d	22.37 ± 2.4	16.58 ± 3.3	7.11 ± 2.0	>100
6e	22.63 ± 3.7	18.42 ± 2.5	6.58 ± 2.1	>100
6f	18.16 ± 5.5	7.89 ± 1.3	5.26 ± 1.2	>100
6g	20.00 ± 7.0	9.73 ± 0.8	2.8 ± 1.3	>100
Ascorbic acid	-	-	-	1 ± 0.3

Table 3
ABTS radical scavenging activity (%) of the synthesized compounds, measured at 745 nm, compared to standard ascorbic acid. Values are the average of triplicate experiments.

	Concentration (μg/mL)			
Compound	100	50	10	IC_{50}
6a	90.41 ± 8.7	75.27 ± 6.4	46.27 ± 2.1	12.30 ± 4.2
6b	98.08 ± 5.8	88.49 ± 6.6	79.32 ± 9.3	3.72 ± 0.7
6c	93.54 ± 7.5	91.68 ± 5.9	82.30 ± 5.4	2.12 ± 0.8
6d	94.03 ± 9.2	53.73 ± 5.0	78.46 ± 9.5	3.35 ± 0.5
6e	81.45 ± 6.2	68.88 ± 4.8	36.93 ± 8.6	41.15 ± 6.3
6f	86.31 ± 5.6	70.95 ± 6.6	6.85 ± 2.0	32.09 ± 2.5
6g	92.53 ± 8.7	82.99 ± 8.5	72.82 ± 6.5	2.98 ± 0.7
Ascorbic acid	-	-	-	35 ± 2.7

Chemical reactivity framework were used. Taking into account the structural features of these molecular sets, which have only a substitute, the molecular quantum similarity indices allowed us to quantify the structural and electronic effects from a local point of view. The highest overlap similarity was observed between **6e** and **6b** and for **6d** and **6f** with a value of 0.9998 in both cases (Table 5), with a Euclidean distance of 1.3725 and 0.7756 respectively (Table 6).

The most active compound **6c** has a high overlap similarity value with the compounds **6b** (0.9985), **6e** and **6f** (0.9985), with euclidean distances of 4.5485, 4.8028 and 4.2535 respectively. Compound **6c** also has a high electronic similarity with the compounds **6d** (0.9709), **6e** (0.9417), **6f** (0.9512), **6g** (0.9589) (See Table S1, supporting information) with euclidean distances of 0.9481, 1.3324, 1.2288, 1.1379, respectively (See Table S2, supporting information). These compounds **6e**, **6f**, and **6g** have strong electron withdrawing groups such as –Br, -Cl and –F compared with compound **6c** which has a methoxy group. In general, the electronic similarity values are higher than the Overlap similarity values. For this reason, chemical reactivity descriptors are reported in Table 7.

The higher chemical potential is shown for the compound **6f** (μ = -3.6551 eV), hardness (η = 7.3985 eV), softness (S = 0.2735 eV^{-1}) and electrophilicity (ω = 0.9028 eV). The most reactive compound **6c** has chemical potential (μ = -3.2856), hardness (η = 7.2253 eV), softness (S = 0.3043 eV^{-1}) and electrophilicity (ω = 0.7470 eV). These reactivity parameters of new compounds can be related to the properties as free radical scavengers.

Fig. 2 shows the Fukui Function $\langle f_k^- \rangle \approx |HOMO|^2$ and $\langle f_k^+ \rangle \approx |LUMO|^2$ figures for the selected compound **6c** (most active compound, **3a** and **6a** (reference compound to series **3** and **6** respectively).

Compounds **3a** and **6a** have the same reactivity maps in both figures. These reactivity maps can be related to the retrodonor process on the non-covalent interaction for these compounds (Wenqin et al., 2015; Jørgensen, 2000). Unlike the reference compounds, the most active compound **6c** has different maps for the Fukui Functions $\langle f_k^- \rangle \approx |HOMO|^2$ and $\langle f_k^+ \rangle \approx |LUMO|^2$ respectively. Therefore, the compound **6c** has zones good defined for electrophilic and nucleophilic attacks that can influence their activity. Finally, the local electrophilicity and nucleophilicity dissimilarity using DFT Based Reactivity Descriptors, to relate the chemical reactivity with the quantum similarity, are shown in Table 8. The compound **6c** has the higher local reactivity similarity (electrophilicity dissimilarity: 0.041), and the compound **6d** has the higher nucleophilicity dissimilarity: 5.52 × 10^{-3} with respect to the reference compound **6a**. Theses dissimilarities can be related to the zone of reactivity (the Fukui function maps, see Fig. 2) in this series of compounds.

3. Experimental

3.1. Chemistry

All reagents were purchased from either Merck (Darmstadt, Germany) or Sigma and Aldrich Chemical Co (St. Louis, MO, USA) and used without further purification. All products were characterized by spectral data (IR, MS, ^{1}H-NMR, ^{13}C-NMR). NMR spectra (^{1}H and ^{13}C) were measured on a Bruker Ultrashield-400 spectrometer (Rheinstetten, Germany), using $CDCl_3$ as solvent and reference. *J* values are reported in Hz;

Table 4
Computer aided ADME screening of the synthesized compounds *N*-propargyl tetrahydroquinolines.

Compound	M.W. (g/mol)	Log P (o/w)[a]	donors HB[b]	acceptors HB[c]	Log S[d]	PSA[e]	Human Oral Absorption[f]
6a	214.266	1.628	1.500	3.500	−1.827	51.657	3
6b	228.293	1.882	1.500	3.500	−2.030	51.857	3
6c	244.293	1.697	1.500	4.250	−1.750	60.103	3
6d	242.320	2.230	1.500	3.500	−2.398	51.878	3
6e	293.162	2.068	1.500	3.500	−2.225	50.692	3
6f	248.711	2.068	1.500	3.500	−2.205	51.858	3
6g	232.257	1.725	1.500	3.500	−1.710	50.726	3

[a] log *P* for octanol/water (−2.0 – −6.5).
[b] Estimated number of H-bonds that would be donated by the solute to water molecules in an aqueous solution.
[c] Estimated number of H-bonds that would be accepted by solute from water molecules in an aqueous solution.
[d] Predicted aqueous solubility, log *S*, *S* in mol dm^{-3} (−6.5 – 0.5).
[e] Van der Waals surface areas of polar nitrogen and oxygen atoms.
[f] Qualitative human oral absorption predicted: 1, 2 or 3 for low, medium or high.

Table 5
Molecular quantum Similarity values using the overlap operator.

	6a	6b	6c	6d	6e	6f	6g
6a	1.0000						
6b	0.9954	1.0000					
6c	0.9897	0.9985	1.0000				
6d	0.9895	0.9958	0.9935	1.0000			
6e	0.9957	0.9998	0.9958	0.9964	1.0000		
6f	0.9913	0.9995	0.9958	0.9998	0.9993	1.0000	
6g	0.9915	0.9978	0.9932	0.9952	0.9959	0.9964	1.0000

Table 6
Molecular Quantum Similarity values using the Euclidean distance for the overlap operator.

	6a	6b	6c	6d	6e	6f	6g
6a	0.0000						
6b	4.1721	0.0000					
6c	7.9565	4.5485	0.0000				
6d	7.4087	4.1515	2.2423	0.0000			
6e	3.9958	1.3725	4.8028	4.2161	0.0000		
6f	4.2546	1.5458	4.2535	0.7756	3.5410	0.0000	
6g	5.3227	2.8750	4.6077	5.1883	3.5665	3.0600	0.0000

Table 7
Global reactivity descriptors for the compounds.

Compound	C. Potential (μ, eV)	C. Hardness (η,eV)	Softness (S, $eV)^{-1}$	Electrophilicity (ω, eV)
6a	-3.5233	7.8842	0.1268	0.7873
6b	-3.3652	7.5548	0.2838	0.7494
6c	-3.2856	7.2253	0.3043	0.7470
6d	-3.3456	7.6528	0.2989	0.7313
6e	-3.6483	7.3599	0.2741	0.9042
6f	-3.6551	7.3985	0.2735	0.9028
6g	-3.6085	7.3956	0.2771	0.8803

chemical shifts are reported in ppm (δ) relative to the solvent peak (residual $CHCl_3$ in $CDCl_3$ at 7.26 ppm for protons and 77 ppm for carbon atoms). Signals were designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet, and br., broad. IR spectra (KBr pellets, 500–4000 cm^{-1}) were recorded on a NEXUS 670 FT-IR spectrophotometer (Thermo Nicolet, Madison, WI, USA). GC-MS analyses were performed on a model Trace 1300 GC-MS instrument (Thermo Fisher Scientific, Waltham, MA, USA) equipped with a Rtx-5MS on-column auto-injector and a fused silica capillary column (DB-5, 30 m ˆ 0.25 mm ID, 0.25 μm film thickness). MS were recorded in electron ionization (EI) mode, with the energy of 70 eV. The ion source temperature was 200 °C; 4.00 min solvent cut time. Melting points (uncorrected) were measured on an Electrothermal IA9100 melting point apparatus (Stone, Staffs, UK). The reaction progress was monitored using thin layer chromatography on PF254 TLC aluminum sheets from Merck. Column chromatography was performed using Silica gel (60–120 mesh) and Solvents employed were of analytical grade.

3.2. General procedure for the synthesis of N-propargyl-1,2,3,4-THQs

THQ derivatives were efficiently synthesized according to methodology reported previously (Rodriguez et al., 2016), the protocol outlined in Fig. 1. This protocol can be divided into two steps:

3.2.1. Step 1: preparation of N-propargylamine

In a round-bottomed flask, a 5-mL solution in anhydrous DMF of the corresponding anilines **1** (1.8 mmol), potassium iodide (0.1 mmol) and anhydrous sodium carbonate (2 mmol) was prepared and stirred constantly at 0 °C. A solution of propargyl bromide **2** (1.0 mmol) in anhydrous DMF was added dropwise and the mixture was kept at 0 °C for 20 minutes. The reaction was allowed to stir at room temperature for 3–4 h, indicated on TLC. The reaction mixture was diluted with water and extracted with ethyl acetate (3 × 20 mL), the organic phase was separated and dried (Na_2SO_4), the solvent removed under vacuum and the resulting product was purified by column chromatography on silica gel, (petroleum ether: ethyl acetate) to obtain the pure *N*-propargyl anilines **3a-g**.

3.2.2. Step 2: preparation of N-propargyl THQs

All the reactions were performed at room temperature. In a round bottom flask, a 5 mL solution in CH_3CN of preformed *N*-propargylaniline **3a-g** (1.0 mmol) and formaldehyde (37% in methanol) **4** (1.1 mmol) was prepared and stirred for 10 minutes. 5 mL solution of $InCl_3$ (20% mol) in CH_3CN was then added. After 20 minutes a solution of *N*-vinylformamide **5** (1.1 mmol) in CH_3CN was incorporated to the reaction mixture and was vigorously stirred. The resulting mixture was stirred for 3–4 h. After the workup, the final product was purified by column chromatography, eluted with the appropriate mixture of petroleum ether and ethyl acetate to afford pure THQs **6a-g**.

3.2.3. N-(1-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl)formamide *(6a)*

Coffee solid; m.p. 118–120 °C; Yield 51%; **IR**: 3279, 3038, 2958, 2922, 2847, 1658, 1492, 751; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.20 (1H, s), 7.22–7.31 (2H, m), 6.82–6.88 (2H, m), 5.21–5.28 (1H, m), 4.19–4.26 (1H, dd, J = 18.2, 1.7 Hz), 4.00–4.07 (1H, dd, J = 18.2, 1.1 Hz), 3.32–3.39 (2H, m), 2.25–2.28 (1H, s), 2.15–2.24 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm):160.09, 144.57, 129.60, 129.17, 122.23, 118.11, 112.81, 79.01, 72.09, 45.24, 44.76, 40.72, 28.48; **GC-MS m/z (rel. int. %):** 213.80 (24), 174.88 (10), 167.78 (100), 129.88 (20). *Anal.*

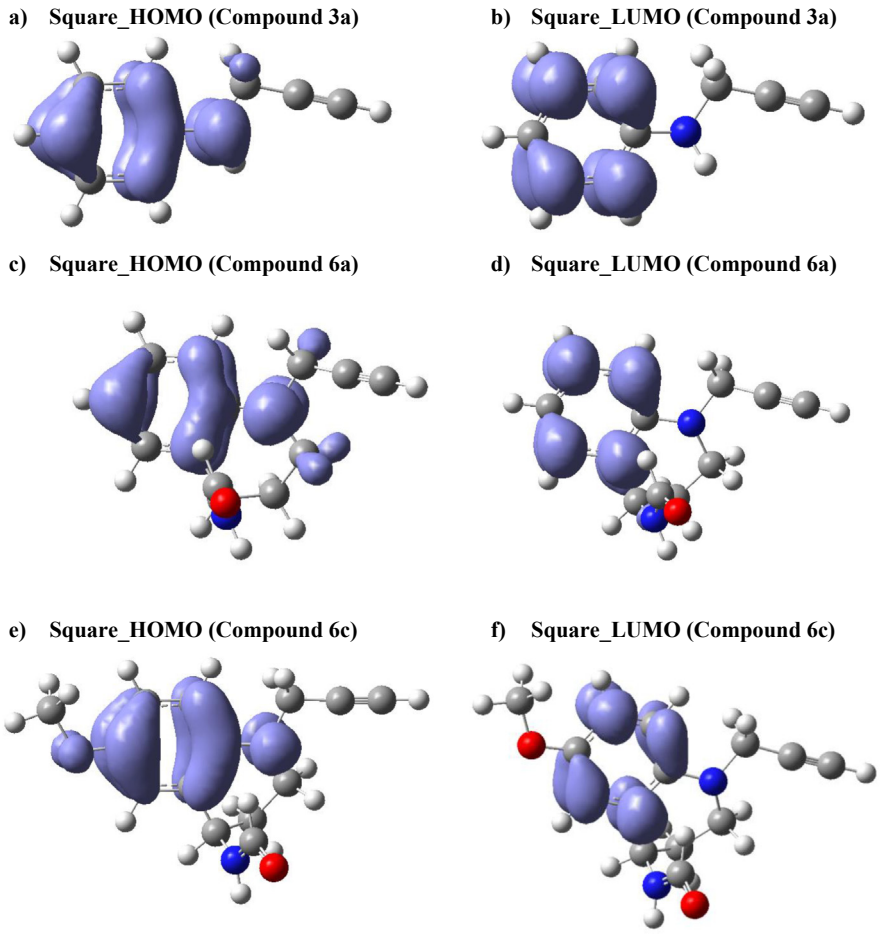


Fig. 2. Fukui Funtions$\langle f_k^- \rangle \approx |HOMO|^2and\langle f_k^+ \rangle \approx |LUMO|^2$, for the compound selected **6c** (most active compound), **6a** and **3a** (reference compounds to series **6** and precursors **3** respectively).

Table 8
Local electrophilicity and nucleophilicity dissimilarity.

Reference Compound (6a) vs	Electrophilicity dissimilarity	Nucleophilicity dissimilarity
6b	7.51×10^{-3}	4.09×10^{-3}
6c	0.041	4.91×10^{-3}
6d	9.89×10^{-3}	5.52×10^{-3}
6e	3.35×10^{-3}	1.19×10^{-3}
6f	5.22×10^{-3}	4.28×10^{-4}
6g	4.29×10^{-3}	2.79×10^{-3}

Calc. for $C_{13}H_{14}N_2O$: 214.11 uma.

3.2.4. N-(6-methyl-1-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl) formamide ***(6b)***

Orange solid; m.p. 134–136 °C; Yield 95%; **IR**: 3278, 2951, 2923, 2854, 1655, 1506, 1380, 1328, 1230, 803; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.18 (1H, s), 6.97–7.05 (2H, m), 6.70 (1H, d, J = 8.3 Hz), 5.16 (1H, d, J = 6.1 Hz), 4.09–4.16 (1H, d, J = 18.1 Hz), 3.88–3.95 (1H, d, J = 18.1 Hz), 3.21–3.26 (2H, m), 2.22–2.24 (3H, s), 2.15 (1H, br), 1.99–2.14 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.04, 142.37, 130.11, 129.74, 127.53, 122.40, 113.11, 79.08, 72.08, 45.34, 44.66, 40.86, 28.75, 20.23; **GC-MS m/z (rel. int. %):** 227.71 (38), 188.92 (10), 181.88 (100), 166.87 (12), 143.97 (24). *Anal. Calc. for* $C_{14}H_{16}N_2O$: 228.13 uma.

3.2.5. N-(6-methoxy-1-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl) formamide ***(6c)***

Coffee solid; m.p. 110–112 °C; Yield 66%; **IR**: 3262, 3231, 2953, 2917, 2845, 1653, 1501, 1460, 1374, 1048, 737; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.18 (1H, s), 6.80 (1H, dd, J = 8.9, 3.0 Hz), 6.71–6.76 (2H, m), 5.17 (1H, dd, J = 12.9, 5.1 Hz), 4.10 (1H, dd, J = 18.1, 2.2 Hz), 3.90 (1H, dd, J = 18.1, 2.3 Hz), 3.73 (3H, s), 3.18–3.22 (2H, m), 2.13–2.15 (1H, br), 2.04–2.23 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.05, 152.33, 138.91, 123.74, 115.25, 114.57, 114.51, 79.11, 72.20, 55.71, 45.55, 44.85, 41.22, 28.94; **GC-MS m/z (rel. int. %):** 243.76 (80), 204.89 (12), 197.97 (100), 159.64 (28), 144.80 (16). *Anal. Calc. for* $C_{14}H_{16}N_2O_2$: 244.12 uma.

3.2.6. N-(6-ethyl-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl)formamide ***(6d)***

Beige solid; m.p. 116–118 °C; Yield 31%; **IR**: 3273, 3231, 2951, 2923, 2849, 1648, 1506, 1376, 1331, 804; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.11 (1H, s), 7.03 (1H, d, J = 8.1 Hz), 6.97 (1H, d, J = 14.5 Hz), 6.71 (1H, d, J = 8.4 Hz), 5.10–5.17 (1H, m), 4.11 (1H, d, J = 18.1 Hz), 3.91 (1H, d, J = 18.1 Hz), 3,18–33.26 (2H, m), 2.52 (2H, q, J = 7.5 Hz), 2.15 (1H, t, J = 6.6 Hz), 2.03–2.13 (2H, m), 1.18 (3H, t, J = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.15, 142.56, 133.99, 128.94, 128.50, 122.32, 113.02, 79.19, 72.11, 45.32, 44.70, 40.83, 28.74, 27.74, 15.74; **GC-MS m/z (rel. int. %):** 242.03 (34), 195.93 (100), 181.81 (12), 157.78 (22). *Anal. Calc. for* $C_{15}H_{18}N_2O$: 242.14 uma.

3.2.7. N-(6-bromo-1-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl) formamide ***(6e)***

White solid; m.p. 164–166 °C; Yield 52%; **IR**: 3239, 3044, 2956, 2920, 2851, 1645, 1490, 1241, 891; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.19 (1H, s), 7.21–7.25 (2H, m), 6.62 (1H, d, J = 9.1 Hz), 5.15 (1H, dd, J

= 11.4, 5.1 Hz), 4.07 (1H, d, *J* = 18.3 Hz), 3.91 (1H, d, *J*= 18.2 Hz), 3.26 (2H, t, *J*= 5.6 Hz), 2.13–2.17 (1H, br), 1.99–2.13 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.85, 143.81, 131.33, 131.03, 125.38, 114.35, 109.09, 78.92, 72.90, 45.90, 43.78, 40.71, 28.59; **GC-MS m/z (rel. int. %):** 291.52 (40), 247.98 (100), 209.76 (28), 166.82 (62). *Anal. Calc. for* $C_{13}H_{13}BrN_2O$: 292.02 uma.

3.2.8. *N-(6-chloro-1-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl) formamide* ***(6f)***

Beige solid; m.p. 158–160 °C; Yield 23%; **IR**: 3231, 2949, 2914, 2842, 1643, 1494, 1387, 1331, 1238; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.21 (1H, s); 7.11–7.16 (2H, m), 6.69 (1H, d, *J* = 9.0 Hz), 5.14–5.20 (1H, m), 4.10 (1H, d, *J* = 18.2 Hz), 3.94 (1H, d, *J* = 18.3 Hz), 3.20–3.25 (2H, m), 2.15–2.18 (1H, br), 2.02–2.15 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.09, 143.15, 129.19, 128.95, 123.86, 122.84, 114.16, 78.50, 72.37, 45.43, 44.48, 40.86, 28.43; **GC-MS m/z (rel. int. %):** 247.78 (44), 208.85 (15), 201.64 (100), 166.90 (40). *Anal. Calc. for* $C_{13}H_{13}ClN_2O$: 248.07 uma.

3.2.9. *N-(6-fluoro-1-prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl) formamide* ***(6g)***

Beige solid; m.p. 144–146 °C; Yield 71%; **IR**: 3273, 3257, 2954, 2915, 1650, 1503, 801; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.19 (1H, s), 6.88–6.93 (2H, m), 6.67–6.73 (1H, m), 5.17 (1H, dd, *J* = 13.2, 5.4 Hz), 4.08 (1H, dd, *J* = 18.2, 2.2 Hz), 3.93 (1H, dd, *J* = 18.2, 2.2 Hz), 3.21–3.26 (2H, m), 2.15–2.17 (1H, br), 1.99–2.20 (2H. m). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.14, 141.04, 123.94, 115.78, 115.56, 114.13, 114.06, 78.74, 72.34, 45.67, 44.60, 41.16, 28.72; **GC-MS m/z (rel. int. %):** 231.80 (28), 192.85 (10), 185.78 (100), 147.74 (30). *Anal. Calc. for* $C_{13}H_{13}FN_2O$: 232.10 uma.

3.3. *Measurement of DPPH radical scavenging activity*

DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable molecule. The antioxidant activity can be observed by a change of coloration deep violet to yellow in the mixture of compounds with a methanolic solution of DPPH. The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of DPPH (Kedare and Singh, 2011).

The free radical scavenging effect of the compounds was assessed by the discoloration of a methanolic solution of DPPH as previously reported (Polo et al., 2016). Tetrahydroquinolines **6a-g** was assayed at 100, 50 and 10 μg/mL. The scavenging of free radicals by THQs was evaluated spectrophotometrically at 517 nm against the absorbance of the DPPH radical. The percentage of discoloration was calculated as follows:

$$\% \text{ scavenging DPPH free radical} = 100 \times (1\text{-AE/AD})$$

Where AE, is the absorbance of the solution after adding the extract and AD is the absorbance of the blank DPPH solution. Ascorbic acid was used as reference compounds, with IC_{50} value of 1 μg/mL.

3.4. *Measurement of ABTS radical scavenging activity*

The ABTS (2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical scavenging assay is a rapid and efficient method, based on the ability of the hydrogen donating antioxidants to scavenge the long-life radical cation $ABTS^{\bullet+}$. In this method, the preformed radical monocation of ABTS is generated by the oxidation of ABTS with potassium persulfate and is reduced in the presence of such hydrogen donating antioxidants (Karadag et al., 2009).

ABTS assay was performed according to the protocol (Polo et al., 2016; Re et al., 1999). The ABTS radical cation ($ABTS^{\bullet+}$) was produced by reaction of 7 mM stock solution of ABTS with 2.45 mM potassium persulfate and allowing the mixture to stand in dark at room temperature for 12 h before use. The $ABTS^{\bullet+}$ solution was diluted with methanol to give an absorbance of 0.7 ± 0.01 at 745 nm. Compounds (1 mL) were allowed to react with 2 ml of the $ABTS^{\bullet+}$ solution and the absorbance was measured at 745 nm after 1 min. Data for each assay was recorded in triplicate. Ascorbic acid was used as positive controls with IC_{50} value of 35 μg/mL. The scavenging activity was estimated based on the percentage of ABTS radicals scavenged by the following formula:

$$\% \text{ scavenging} = [(A0 - As)/A0] \times 100$$

Where A0 is the absorption of control, AS is the absorption of a tested compound solution.

3.5. *In silico prediction of pharmacokinetic properties*

Pharmacokinetic properties of THQ compounds were calculated an *in silico* way through ADME descriptors using QikProp (Caporuscio et al., 2011). Based on the Lipinski's rule of 5, some of the descriptors predicted were molecular weight, Van der Waals, surface areas of polar nitrogen and oxygen atoms, H bond acceptors, H bond donors, Log P (octanol/-water) and aqueous solubility (Lipinski et al., 1997), proposing a first analysis of the newly synthesized compounds as drug-likeness.

3.6. *Computational methods*

The theoretical study was realized based on Molecular Quantum Similarity Measure (MQSM), density functions, analyzing a series of reactive descriptors as chemical hardness (η), chemical potential (μ), electrophilicity index (ω), softness(s), and Fukui functions. All the structures included in this study were optimized at B3LYP/6-31G(d) level of theory by using the Gaussian 09 package (Frisch et al., 2016). Detail and basis of the methods used are included in the supplementary material.

4. Conclusion

In summary, the synthesis of a new series of substituted *N*-propargylTHQs derivatives has been developed in mild conditions and simple procedure through the Domino Mannich/Friedel - Crafts reactions using $InCl_3$ as catalyst. The antioxidant activity is dependent on the concentration of the compounds, likewise, the compound **6c** and **6g** (with methoxy and fluorine group on the aromatic ring respectively) presented the most favorable antioxidant activity values. Physicochemical descriptors, calculated theoretically, indicated that the new compounds have a low toxicity risk. Structurally the *N*-propargyl THQs are attractive for the production of a second generation of compounds due to the reactivity of the propargyl fragment. In this study, we obtained compounds with higher antioxidant capacity than the reference compound. From the theoretical calculations (MQSM, Global reactivity descriptors, and Fukui Functions), we can establish similarity and discriminate different reactive sites in the new molecules where the oxidative process occurs. These sites can be used for the design of new compounds with interesting biological activity.

Declarations

Author contribution statement

Y Rodríguez: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

A Romero: Conceived and designed the experiments; Wrote the paper.

M Gutiérrez: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M Norambuena: Performed the experiments.

A Morales: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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