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

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Keywords:
Organic chemistry
Theoretical chemistry
Pharmaceutical chemistry
Tetrahydroquinolines
Antioxidant activity
Free radical
Molecular quantum similarity measure

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 (InCl₃), 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 multi-component 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. Selegeline,
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 InCl₃ 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 InCl₃, was effective under mild condition reactions using N-propargylamines with formaline (37% in methanol) and N-vinylformamide as an electron-rich alkene. Acetonitrile (CH₃CN) 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, 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, ¹H-NMR, ¹³C-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. ¹H 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 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)](image)
Selective irreversible MAO-B inhibitor

![Rasagline (Azilect)](image)
Irreversible MAO-B Inhibitor

![Pargyline](image)
Irreversible MAO-A (IC₅₀ = 11.52 nmol/L) and MAO-B (IC₅₀ = 8.20 nmol/L) inhibitor

![Ladostigil (TV-3,326)](image)
Reversible AChE and BChE inhibitor and Irreversible MAO-B inhibitor

Fig. 1. Propargylamines inhibitors of monoamine oxidases MAO-A and MAO-B.
overlap similarity was observed between structural and electronic effects from a local point of view. The highest the molecular quantum similarity indices allowed us to quantify the Chemical reactivity framework were used. Taking into account the experiments.

Table 3

| Concentration (µg/mL) | 100 | 50 | 10 | IC50 |
|-----------------------|-----|----|----|------|
| 6a                    | 90.41 ± 8.7 | 75.27 ± 6.4 | 46.27 ± 2.1 | 13.20 ± 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 - - - 1 ± 0.3

Table 4

| Concentration (µg/mL) | 100 | 50 | 10 | IC50 |
|-----------------------|-----|----|----|------|
| 6a                    | 90.41 ± 8.7 | 75.27 ± 6.4 | 46.27 ± 2.1 | 13.20 ± 4.2 |
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| 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 - - - 1 ± 0.3

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) and 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 = -3.6851 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 f± = |HOMO|² and f± = |LUMO|² figures for the selected compound 6c (most active compound, 6a 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; Jörgensen, 2000). Unlike the reference compounds, the most active compound 6c has different maps for the Fukui Functions f± = |HOMO|² and f± = |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 nucleophiliy 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 nucleophiliy dissimilarity: 5.52 × 10⁻³ with respect to the reference compound 6a. Theses dissimilarities can be related the zone of activity (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, ¹H-NMR, ¹³C-NMR). NMR spectra (¹H and ¹³C) were measured on a Bruker Ultrashield-400 spectrometer (Rheinstetten, Germany), using CDCl₃ as solvent and reference. J values are reported in Hz;
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Table 4
Computer aided ADME screening of the synthesized compounds N-propargyl tetrahydroquinolines.

| Compound | M.W. (g/mol) | Log P (o/w) | Log S | PSA | Human Oral Absorption |
|---------|--------------|-------------|-------|-----|-----------------------|
| 6a      | 214.266      | 1.628       | 1.500 | 3.500 | ~0.827               |
| 6b      | 228.293      | 1.882       | 1.500 | 3.500 | ~0.803               |
| 6c      | 244.293      | 1.697       | 1.500 | 3.500 | ~0.750               |
| 6d      | 242.320      | 2.230       | 1.500 | 3.500 | ~2.398               |
| 6e      | 293.162      | 2.068       | 1.500 | 3.500 | ~2.225               |
| 6f      | 248.711      | 2.068       | 1.500 | 3.500 | ~2.205               |
| 6g      | 232.257      | 1.725       | 1.500 | 3.500 | ~1.710               |

6a: Estimated number of H-bonds that would be donated by the solute to water molecules in an aqueous solution.
6b: Estimated number of H-bonds that would be accepted by solute from water molecules in an aqueous solution.
6c: Predicted aqueous solubility, log S, in mol dm⁻³ (~6.5 – 0.5).
6d: Van der Waals surface areas of polar nitrogen and oxygen atoms.
6e: 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 | 0.9985 | 0.9935 | 0.9964 | 0.9964 |
| 6c | 0.9897 | 6d | 0.9958 | 0.9958 | 0.9964 | 1.0000 | 0.9964 |
| 6e | 0.9957 | 6f | 0.9995 | 0.9998 | 0.9998 | 0.9993 | 1.0000 |
| 6g | 0.9915 | 6a | 0.9997 | 0.9932 | 0.9952 | 0.9959 | 0.9964 |

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 | 0.0000 | 0.0000 |
| 6c | 7.9565 | 6d | 4.1515 | 2.2423 | 0.0000 | 0.0000 |
| 6e | 3.9958 | 6f | 1.3725 | 4.8028 | 4.2161 | 0.0000 |
| 6g | 5.3227 | 6a | 2.8750 | 4.6077 | 5.1883 | 3.5665 |

Table 7
Global reactivity descriptors for the compounds.

| Compound | C. Potential (u, eV) | C. Hardness (n.u, eV) | Softness (S, eV) | Electrophilicity (u, eV) |
|----------|----------------------|----------------------|-----------------|------------------------|
| 6a       | -3.5233              | 7.8842               | 0.1268          | 0.7873                 |
| 6b       | -3.3652              | 7.5548               | 0.2838          | 0.7494                 |
| 6c       | -3.2856              | 7.2523               | 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                 |

Melting points (uncorrected) were measured on an Electrothermal IA9100 melting point apparatus (Stone, Staffs, UK). The reaction progressed was monitored using thin layer chromatography on PF254 TLC aluminum sheets from Merck. 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 (Na2SO4), 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 CH3CN 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 InCl3 (20% mol) in CH3CN 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-(prop-2-ynyl-1,2,3,4-tetrahydro-quinolin-4-yl)methanone (6a)

Coffee solid; m.p. 118–120 °C; Yield 51%; IR: 3279, 3038, 2958, 2922, 2847, 1658, 1492, 751; 1H NMR (400 MHz, CDCl3) 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), 13C NMR (100 MHz, CDCl3) 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.

chemical shifts are reported in ppm (δ) relative to the solvent peak (residual CHCl3 in CDCl3 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 × 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; 4.0 min solvent cut time.
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$_2$O: 228.13 uma.

Table 8

| Reference Compound | Electrophilicity dissimilarity | Nucleophilicity dissimilarity |
|--------------------|-------------------------------|-------------------------------|
| 6b                 | 7.51 x 10$^{-3}$              | 4.09 x 10$^{-3}$              |
| 6c                 | 0.041                         | 4.91 x 10$^{-3}$              |
| 6d                 | 9.89 x 10$^{-3}$              | 5.52 x 10$^{-3}$              |
| 6f                 | 5.22 x 10$^{-3}$              | 4.28 x 10$^{-4}$              |
| 6g                 | 4.29 x 10$^{-3}$              | 2.79 x 10$^{-3}$              |

Fig. 2. Fukui Functions of the compound selected 6c (most active compound), 6a and 3a (reference compounds to series 6 and precursors 3 respectively).

3.2.5. 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), 3.18–3.36 (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. %): 243.76 (38), 195.93 (100), 181.88 (12), 175.78 (22). Anal. Calc. for C$_{15}$H$_{18}$N$_2$O: 242.13 uma.

3.2.6. 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, 1340, 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 = 3.4 Hz).
= 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, CDCl3) 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_{2}O: 292.02 uma.

3.2.8. N-(6-chloro-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; ^1H NMR (400 MHz, CDCl3) 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, CDCl3) δ (ppm): 160.09, 145.15, 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}FN_{2}O: 231.80 uma.

3.2.9. N-(6-fluoro-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; ^1H NMR (400 MHz, CDCl3) 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, CDCl3) 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_{2}O: 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 were 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:

% scavenging DPPH free radical = 100 × (1–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-ethylenothiazoline-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”? 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”) 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”? 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” 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 percent-age of ABTS radicals scavenged by the following formula:

% scavenging = [(A0 – As)/A0] × 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

Theoretical properties of THQ compounds were calculated as an in silico way through ADMET 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 (\(\eta\)), chemical potential (\(\mu\)), electrophilicity index (\(\omega\)), 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-propargylicharsol derivatives has been developed in mild conditions and simple procedure through the Domino Mannich/Friedel - Crafts reactions using InCl₃ 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**

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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; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; 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.

Funding statement

This work was supported by the Institute of Chemistry of Natural Resources, University of Talca, Chile and PIEI QUIMIBIO project, UTalca.

Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2019.e02174.