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ANTIMICROBIAL AND DEGRADATIVE BACTERIAL DNA EFFECTS OF NEW 2-ALKYL (TETRAHYDROQUINOLINE-4-YL) FORMAMIDE

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Abstract

Carried out the synthesis of new N-(n-ethyl-1,2,3,4-tetrahydroquinolin-4-il) acetamide and N-[2-(n-butyl)tetrahydroquinolin-4-il] acetamide using multicomponent imine-Diels-Alder methodology with high yields, besides of synthesis of 2-methyl-1,2,3,4-tetrahydroquinolin-4-yl) formamide using the imine Diels-Alders (iDA) reactions. The antimicrobial activity of the tetrahidroquinoline was evaluated against strain clinical isolated of P. aeruginosa, E. coli, S. aureus, K. pneumoniae and C. Albicans. Show important activity values of the (6-fluor-2-pentyl-1,2,3,4-(tetrahidro)quinolin-4-il) formamide (MIC = 0.003 µg/mL), N-(6-nitro-2-penthyl-1,2,3,4-(tetrahidro)quinolin-4-il) formamide (MIC= 0.025 µg/mL) and N-(6-Chloro-2-etil-1,2,3,4-(tetrahidro)quinolin-4-il) formamide (MIC = 0.025 µg/mL), against P. aeruginosa (PA2).

Keywords: Tetrahydroquinoline, imino Diels-Alders, Multicomponent Reactions, tandem reactions, Antimicrobial Pseudomonas aeruginosa, DNA Degradation

Introduction

Tetrahydroquinoline (THQ) ring, is a common core in many natural products and pharmaceutical agents with promising biological activities [1,2]. These derivatives are privileged links in the development of medicinal chemistry as well as being associated with biologically active natural products [3,4].

2-alkyl-THQ derivatives are few common natural compounds [5]; however, its derivatives show important pharmacological activities, Benzastatins C and D isolated of *Streptomyces* sp showed significant activity as inhibitors of glutamate toxicity and lipidic peroxidation [6], martinelline and martinellic acid isolated of Martinella iquitosensis, showed pharmacologic properties as inhibitors of bradykinin receptors and antibiotic potential (Figure 1) [7]. Well as, the potent antifungal agent Virantmycin, isolated of *Streptomyces nitrosporeus*, besides the antimalaric agents Cuspareine, Galipinine, Galipeine and Angustureine (*Galipea officinalis*) [8]. The pharmacological potential of the THQ systems has allowed the interest in the synthesis of the 2-alkyl-THQ core, based in cicloadditions reactions [9]. The total synthesis of martinelline alkaloids was based in the access to the hexahydropirrole [3,2-c] quinoline core way an imine Diels-Alder (DA) methodology [10], using a tandem aza-Michael-iDA reaction with dihydropirrole compounds. This is a ABB DA reaction, another applications using 3,4-dihydro-2H-pyran (2,3-dihydrofuran) as dual agents in the synthesis of the [3,4-c] pyran(furan) THQ rings [11].

Some strategies use β-unsaturated compounds as "dual" systems in tandem-iDA reactions, obtaining c-fused THQ core [12]. However very few efficient methods based in iDA multicomponent methodology for the synthesis of C-2 alkyl-THQ compounds have been reported, due to aliphatic aldehydes employed as azadiene component precursors in iDA multicomponent reaction and N-alkyl aldimines, are hydroscopic, unstable, and difficult to purify and are easily polymerized under acidic conditions [13]. Keeping in view the above facts and continuing our programme on the development of efficient methods to generate drug-like nitrogen-containing molecules [14], using $BiCl_3$ as effective catalyzer in DA reactions, we were interested in new heterocyclic molecules needed for our biological interest.

The purpose of our work was to develop a general protocol for the simple and efficient synthesis of 2-alkyl- 1,2,3,4-tetrahydroquinolin-4-yl)formamide and 2-methyl-1,2,3,4-tetrahydroquinolin-4-yl) formamide exploring the versatility of the DA reaction in one-pot and AdNu/E/iDA tandem process, using the same reagents anilines and N-vinylformamide (NVF) in the iDA process where the third component aliphatic aldehydes (valeraldehyde and propynaldehyde), is presenting or not, studying the biological properties as antimicrobial agents and analyzing his DNA degradative effects.

Methods

The melting points (uncorrected) were determined on a Fisher– Johns melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 or Bruker AC-400 spectrometers. Chemical shifts are reported in ppm (d) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for protons). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet; br.s, broad singlet. Elemental analyses were performed on a Perkin–Elmer 2400 Series II analyzer, and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminum sheet.

General procedure for synthesis of N-(2-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (5a-d) and N-(2-butyl-1,2,3,4-tetrahydroquinolin-4-yl) formamide (6a-d).

To a solution of the appropriate aniline (1) (1.0 mmol) and propionaldehyde (2) (pentanal (3)) (1.0 mmol) in CH3CN (15 ml), 10 mol% Bicl3 was added, the resulting mixture was added NVF (4) (1.2 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with a solution of Na2CO3. The organic layer was separated, and dried with Na2SO4. The organic solvent was removed in vacuo to afford the respective tetrahydroquinoline compound.

6-chloro-2-ethyl-1,2,3,4-tetrahydroquinolin-4-yl formamide (5b)

Yellow solid; Yield 85%; mp 189-190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (1H, s, 2´´-H-(C=O)), 7.06 (1H, s, 5-H), 6.96 (1H, dd, *J* = 8.5, 2.4 Hz, 7-H), 6.42 (1H, d, *J* = 8.6 Hz, 8-H), 5.70 (1H, d, *J* = 8.7 Hz, N-H(C=O), 5.41- 5.35 (1H, m, 4-H_{ax}), 3.80 (1H, s, N-H), 3.36- 3.30 (1H, m, 2-H_{ax}), 2.31 (1H, ddd, *J* = 2.2, 5.9, 12.4 Hz, 3-H_{ax}), 1.55- 1.49 (2H, m, 1'-H), 1.50- 1.40 (1H, m, 3-H_{eq}), 0.98 (3H, t, *J* = 7.4 Hz, 2'-CH_3); ^{13}C NMR (CDC_{l3}, 100 MHz): (ppm δ) 161.0 (+), 143.7 (+), 128.3 (+), 126.5 (+), 122.4 (+), 122.1 (+), 115.5 (+), 52.3 (+), 44.7 (+), 35.2 (-), 29.0 (-), 9.7 (+);

COSY [δH/ δH]: 8.35/5.68 [2´´-H (C=O) / N-H(C=O)], 6.96/6.42 [7-H/8-H], 6.42/6.96 [8-H/7-H], 5.70/ 8.35 [N-H(C=O)/ 2´´-H (C=O)], 5.70 / 5.41- 5.35 [N-HC(O)/4-H_{ax}], 5.41- 5.35/ 5.70 [4-H_{ax}/ N-H(C=O)], 5.41- 5.35/ 2.31 [4-H_{ax}/3-H_{ax}], 5.41- 5.35/ 1.50-1.40 [4-H_{ax}/3-H_{ec}], 3.36- 3.30/ 2.31 [2-H_{ax}/3-H_{ax}], 3.36- 3.30/ 1.50-1.40 [2-H_{ax}/3-H_{eq}], 3.36- 3.30/ 1.55-1.49 [2-H_{ax}/1'-H], 2.31/5.41- 5.35 [3-H_{ax}/4-H_{ax}], 2.31/3.36- 3.30 [3-H_{ax}/2-H_{ax}], 2.31/1.50-1.40 [3-H_{ax}/3-H_{eq}], 1.55-1.49/3.36- 3.30 [1'-H/2-H_{ax}], 1.55-1.49/0.98 [1'-H/2'-CH_3], 1.50-1.40/5.41-5.35 [3-H_{eq}/4-H_{ax}], 1.50-1.40/3.36- 3.30 [3-H_{eq}/2-H_{ax}], 1.50-1.40/2.31 [3-H_{eq}/3-H_{ax}], 0.98/1.55-1.49 [2'-CH_3/1'-H]; Anal. Calcd for $C_{12}H_{15}ClN_2O$; C, 60.38; H, 6.33; Cl, 14.85; N, 11.74; O, 6.70, Found C, 60.37; H, 6.34; Cl, 14.87; N, 11.72; O, 6.71.

2-ethyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl formamide (5c)

Yellow solid, Yield 88%; mp 195-196 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.34 (1H, d, *J* = 1.4, 1.0 Hz, 2´´-H-(C=O)), 6.85-6.84 (1H, m, 5-H), 6.78 – 6.74 (1H,m ,7-H), 6.47 – 6.42 (1H, m,8-H), 5.88 (1H, d, *J*= 7.8 Hz, N-H(C=O)), 5.45- 5.37 (1H, m, 4-H_{ax}), 3.73 (1H, b.s, N-H), 3.57- 3.48 (1H, m, 2-H_{ax}), 2.28 (1H, ddd, *J* = 12.4, 6.2, 2.1 Hz, 3-H_{ax}), 2.20-2.12 (1H, m, 3-H_{ec}), 1.48 (2H, s, 1'-H), 1.27 – 1.18 (3H, m, 2'-2'-CH_3); Anal. Calcd for $C_{12}H_{15}FN_2O$; C, 64.85; H, 6.80; F, 8.55; N, 12.60; O, 7.20, Found C, 64.83; H, 6.81; F, 8.53; N, 12.61; O, 7.23.

2-ethyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (5d)

Yellow solid; Yield 88 %; mp 195-196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (1H, s, 2´´-H-(C=O)), 8.03 (1H, b.s, 5-H), 7.95 (1H, dd, *J*= 2.5, 9.2 Hz, 7-H), 6.43 (1H, d, *J* = 9.0 Hz, 8-H), 5.73 (1H, d, *J* = 8.8 Hz, N-H(C=O), 5.44- 5.37 (1H, m, 4-H), 4.58 (1H, b.s, N-H), 3.57-3.50 (1H, m, 2-H_{ax}), 2.40- 2.34 (1H, m, 3-H_{ax}), 2.26 (1H, ddd, *J* = 2.1, 6.1, 12.4 Hz, 3-H_{ax}), 1.49-1.40 (2H, m, 1'-H), 1.24-1.19 (3H, m, 2'-2'-CH_3); Anal. Calcd for $C_{12}H_{15}N_3O_3$; C, 57.82; H, 6.07; N, 16.86; O, 19.26; Found C, 57.83; H, 6.05; N, 16.87; O, 19.26.

2-butyl-6-methyl-3-propylquinoline (7)

Yellow solid; Yield 87 %; mp 138-140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (1H, d, *J* = 9.1 Hz, 8-H), 7.74 (1H, b.s, 4-H), 7.25 (1H, dd, *J* = 9.1, 2.7 Hz, 7-H), 6.99 (1H, b.s, 5-H), 3,89 (3H, s, 6-CH_3), 2.92 (2H, t, *J* = 8.0 Hz, 1'-H), 2.75 (2H, t, *J* = 7.7 Hz, 1''-H), 1.81-1.73 (2H, m, 2'-H), 1.70-1.62 (2H, m, 2''-H), 1.48-1.35 (2H, m, 3'-H), 0.98 (3H, t, *J* = 7.3 Hz, 3''-CH_3), 0.92 (3H, t, *J* = 7.0 Hz, 4'- CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): (ppm δ) 159.6, 157.1, 142.5, 134.3, 133.8, 129.8, 128.0, 120.7, 104.6, 55.4, 35.6, 32.7, 32.1, 32.0, 29.5, 22.6, 14.0 ppm; COSY [δH/ δH]: 7.90/7.25 [8-H/7-H], 7.25/7.90 [7-H /8-H], 2.92/ 1.81-1.73 [1'-H /2'-H], 2.75/1.70-1.62 [1''-H /2''-H], 1.81-1.73/2.92 [2'-H/1'-H], 1.70-1.62/2.75 [2''-H/1''-H], 1.70-1.62/0.98 [2''-H/3''-CH_3], 1.48-1.35/1.81-1.73 [3'-H /2'-H], 1.48-1.35/0.92 [3'-H /4'-CH_3], 0.98/1.70-1.62 [2''-H/3''-CH_3], 0.92/1.48-1.35 [4'-CH_3/3'-H]. Anal. Calcd for $C_{17}H_{23}N$; C, 84.59; H, 9.60; N, 5.80; Found C, 84.61; H, 9.60; N, 5.82.

2-butyl-6-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (6a)

Yellow solid; Yield 64; mp 221-220 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.33 (1H, s, 2´´-(C=O)), 6.92 (1H, s, 5-H), 6.84 (1H, d, *J* = 8.4 Hz, 7-H), 6.44 (1H, d, *J* = 8.1 Hz, 8-H), 5.78 (1H, d, *J* = 8.9 Hz, N-H(C=O), 5.38 (1H, dd, *J* = 16.3, 10.4 Hz, 4-H_{ax}), 3.71 (1H, b.s, NH), 3.34 (1H, m, 2-H_{ax}), 2.33 (1H, ddd, *J* = 1.6, 5.9, 12.1 Hz, 3-H_{ax}), 2.19 (3H, s, 6-CH_3), 1.55- 1.51 (1H, m, 3-H_{ec}), 1.42- 1.34 (2H, m, 1'-H), 1.42- 1.34 (2H, m, 2'-H), 1.42- 1.34 (2H, m, 3'-H), 1.42- 1.34 (2H, m, 4'-H), 0.92 (3H, t, *J* = 5.1 Hz, 4'-CH_3); ppm; Anal. Calcd for $C_{15}H_{22}N_2O$; C, 73.13; H, 9.00; N, 11.37; O, 6.49; Found C, 73.14; H, 9.02; N, 11.38; O, 6.49.

2-butyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (6b)

Yellow solid; Yield 84%; mp 217-218 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (1H, s, H-(C=O)), 7.10 (1H, d, *J* = 2.3 Hz, 5-H), 6.96 (1H, dd, *J* = 2.3, 8.5 Hz, 7-H), 6.42 (1H, d, *J* = 8.5 Hz, 8-H), 5.69 (1H, d, *J* = 8.9 Hz, N-H(C=O), 5.43-5.40 (1H, m, 4-H_{ax}), 3.80 (1H, s, N-H), 3.42- 3.35 (1H, m, 2-H_{ax}), 2.30 (1H, ddd, *J* = 12.4, 5.9, 2.2 Hz, 3-H_{ax}), 1.72-1.59 (1H, m, 3-H_{eq}), 1.50 – 1.32 (2H, m, 1'-H), 1.50–1.32 (2H, m, 2'-H), 1.50–1.32 (2H, m, 3'-H), 1.50–1.32 (2H, m, 4'-H), 0.90 (3H, t, *J* = 6.5 Hz, 5'-CH_3); ^{13}C RMN (CDC_{l3}, 100 MHz): δ 161.44 (+), 141.80 (+), 128.24 (+), 126.05 (+), 122.35 (+), 115.78 (+),113.79 (+), 56.66 (+), 45.33(+), 36.70(-), 36.05(-), 32.21(-), 25.45(-), 22.96(-), 14.40(+). COSY [δH/ δH]: 8.38/5.69 [2´´-C(O)H)/ N-HC(O)], 6.96/ 6.44 [7-H/8-H], 6.44/6.96 [8-H/7-H], 5.69/5.43-5.40 [N-HC(O)/4-H_{ax}], 5.43-5.40/5.69 [4-H_{ax}/N-HC(O)], 5.43-5.40/2.30 [4-H_{ax}/3-H_{ax}], 5.43-5.40/1.72-1.59 [4-H_{ax}/3-H_{eq}], 3.42- 3.35/2.30 [2-H_{ax}/ 3-H_{ax}], 3.42-3.35/1.72-159 [2-H_{ax}/ 3-H_{eq}], 3.42- 3.35/1.50-1.32 [2-H_{ax}/ 2´-H], 2.30/ 1.72-1.59 [3-H_{ax}/ 3-H_{eq}], 2.30/ 3.42- 3.35 [3-H_{ax}/ 2-H_{ax}], 2.30/ 5.43-5.40 [3-H_{ax}/ 4-H_{ax}], 1.50–1.32/3.42-3.35 [2'-H / 2-H_{ax}], 1.51 – 1.25/0.91[4´-H/5´-H]; HMQC [δ_H/ δ_C]: 8.38 /161.44 [2´´-C(O)H), /C-2''], 7.10 / 126.05 [5-H /C-7], 6.99/126.05 [7-H/C-7], 6.45/113.79 [8-H/C-8], 5.40 / 45.33 [4-H_{ax}/ C-3],

3.42- 3.36 /56.66 [2-H/ C-1], 2.32 /1.72-1.59 /36.70 [3-H_{ac} / 3-H_{ax} /C-2], 1.51 – 1.25/32.21 [3´-H/ C-3´], 1.51 – 1.25/ 22.96 [4´-H/ C-4´],0.91/14.40[5´-H/ C-5´]; HMBC [δ_H/ δ_C]: 8.38 /45.33 [2´´-C(O)H/ C-3], 7.10 /126.05/122.35 [5-H/ C-5 /C-6], 6.99 /126.05/122.35 /141.80 [7-H/C-5/C-6/C-9], 6.45 / 126.05 [8-H/ C-5], 2.32 / 45.33/126.05 [3-H_{ec}/ C-3/C-5], 2.32 / 36.05 [3-H_{ax} /C-1´], 1.51 – 1.25 / 56.66/ 32.21 [1'-H/C-1/C-3´],0.91/32.21/22.96 [5´-H/C-3´/C-4´]; Anal. Calcd for $C_{14}H_{19}ClN_2O$; C, 63.03; H, 7.18; Cl, 13.29; N, 10.50; O, 6.00; Found C, 63.03; H, 7.19; Cl, 13.30; N, 10.50; O, 6.02.

2-butyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)formamide

Yellow solid; mp 219-220 °C; Yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (1H, s, 2´´-H-(C=O)), 6.84 (1H, dd, *J* = 2.9, 9.6 Hz, 5-H), 6.76 (1H, td, *J* = 2.7, 8.2 Hz, 7-H), 6.44 (1H, dd, *J* = 4.7, 8.7 Hz, 8-H), 5.70 (1H, d, *J* = 8.9 Hz, N-H(C=O), 5.44-5.36 (1H, m, 4-H_{ax}), 3.69 (1H, b.s, N-H), 3.39- 3.33 (1H, m, 2-H_{ax}), 2.30 (1H, ddd, *J* = 2.1, 6.1, 12.4, Hz, 3-H_{ax}), 1.49-1.43 (1H, m, 3-H_{ec}), 1.43- 1.30 (2H, m, 1'-H), 1.43-1.30 (2H, m, 2'-H), 1.43- 1.30 (2H, m, 3'-H), 1.43-1.30 (2H, m, 4'-H), 0.90 (3H, t, *J* = 6.7 Hz, 5'-H); **^{13}C** NMR ($CDCl_3$, 100 MHz): δ 161.44 (+), 141.80 (+), 128.24 (+), 126.05 (+), 122.35 (+), 115.78 (+),113.79 (+), 56.66 (+), 45.33(+), 36.70(-), 36.05(-), 32.21(-), 25.45(-), 22.96(-), 14.40(+); Anal. Calcd for $C_{14}H_{19}FN_2O$; C, 67.18; H, 7.65; F, 7.59; N, 11.19; O, 6.39; Found C, 67.16; H, 7.65; F, 7.59; N, 11.21; O, 6.40.

2-butyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (6d)

Yellow solid; Yield 89%; mp 222-223 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (1H, s, 2´´-H-(C=O), 8.00 (1H, b.s, 5-H), 7.88 (1H, d, *J* = 7.1 Hz, 7-H), 6.40 (1H, d, *J* = 8.9 Hz, 8-H), 5.95 (1H, d, *J* = 9.2 Hz, N-H(C=O)), 5.39-5.32 (1H, m, , 4-H_{ax}), 4.65 (1H, b.s, NH), 3.60-3.54 (1H, m, 2-H_{ax}), 2.32 (1H, b.d, *J* = 11.2 Hz, 3-H_{ax}), 1.67- 1.58 (1H, m, 3-H_{ec}), 1.54- 1.29 (2H, m, 1'-H), 1.54- 1.29 (2H, m, 2'-H), 1.54- 1.29 (2H, m, 3'-H), 1.54-1.29 (2H, m, 4'-H), 0.91 (3H, t, *J* = 6.7 Hz, 5'-CH_3); **^{13}C RMN** (CDC_{l3}, 100 MHz): δ. 161.37 (+), 138.59 (+), 125.77 (+), 123.52(+), 119.75 (+), 115.66 (+), 113.21 (+) , 51.46 (+), 44.75 (+), 36.34(-), 34.98 (-), 32.06 (-), 25.33(-), 22.89 (-), 14.32(+);Anal. Calcd for $C_{14}H_{19}N_3O_3$; C, 60.63; H, 6.91; N, 15.15; O, 17.31; Found C, 60.64; H, 6.90; N, 15.15; O, 17.31.

2-butyl-6-methoxy-3-propylquinoline (7)

Yellow solid; Yield 87 %; mp 138-140 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.90 (1H, d, *J* = 9.1 Hz, 8-H), 7.74 (1H, b.s, 4-H), 7.46 (1H, s.a, 5-H), 7.26 (1H, dd, *J* = 2.7, 9.1 Hz, 7-H), 6.99 (1H, d, *J* = 2.6 Hz, 5-H), 3.89 (3H, s, 6-OCH_3), 2.92 (2H, t, *J* = 8.0 Hz, 1'-H), 2.75 (2H, t, *J* = 7.7 Hz, 1''-H), 1.81-1.73 (2H, m, 2'-H), 1.70-1.62 (2H, m, 2''-H), 1.48-1.35 (2H, m, 3'-H), 1.48-1.35 (2H, m, 4'-H), 1.48-1.35 (2H, m, 3''-H), 1.03 (3H, t, *J* = 7.3 Hz, 3''-H), 0.90 (3H, t, *J* = 7.3 Hz, 4'-H); **^{13}C RMN** ($CDCl_3$, 100 MHz): δ 159.6, 157.07, 142.50, 134.29, 133.81, 129.85, 127.99, 120.72, 104.57, 55.39, 35.60, 32.68, 32.12, 32.05, 29.48, 22.63, 22.59, 14.03, 13.93 ppm; Anal. Calcd for $C_{19}H_{27}NO$; C, 79.95; H, 9.54; N, 4.91; O, 5.61; Found C, 79.96; H, 9.53; N, 4.91; O, 5.61.

General procedure for synthesis of 2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide using Tandem AdNu/E/iDA reaction.

To a solution of the appropriate aniline (**1**) (1.0 mmol) and n-vinylformamide (**4**) (2.2 mmol) in CH_3CN (15 ml), 20 mol % $BiCl_3$ was added, the reaction mixture was stirred at room temperature for 6 h and then quenched with a solution of Na_2CO_3. the organic layer was separated, and dried with Na_2SO_4. the organic solvent was removed in vacuo to afford the respective tetrahydroquinoline compound.

2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (8a)

Yellow solid, Yield 78%; mp 189-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (1H, s, H-(C=O)), 7.12-7.09 (1H, m, 6-H), 7.05-7.01 (1H, m, 7-H), 6.69-6.65 (1H, m, 5-H), 6.49 (1H, dd, *J* = 1.0, 8.0, 8-H), 5.76 (1H, d, *J* = 7.4 Hz, N-H(C=O)), 5.44-5.37 (1H, m, 4-H_{ax}), 3.79 (1H, b.s, NH), 3.58- 3.50 (1H, m, 2-H_{ax}), 2.29 (1H, ddd, *J* = 2.3, 6.0, 12.3 Hz, 3-H_{ax}), 1.51- 1.42 (1H, m, 3-H_{ec}), 1.21 (3H, d, *J* = 6.3 Hz, 2-CH_3) ppm. **^{13}C RMN** (101 MHz, $CDCl_3$) δ 161.31, 128.57, 127.00, 117.90, 114.55, 46.73, 45.05, 38.08, 37.85, 22.32, 22.31 ppm; Anal. Calcd for $C_{12}H_{16}N_2O$; C, 69.45; H, 7.42; N, 14.73; O, 8.41; Found C, 69.43; H, 7.41; N, 14.73; O, 8.38.

2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl formamide (8b)

Yellow solid; Yield 76%; mp 210-212 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (1H, s, H-(C=O)); 6.91 (1H, br.S, 5-H); 6.84 (1H,d, *J* = 8.3 Hz, 7-H); 6.41 (1H, d, *J* = 8.1 Hz, 8-H); 5.81 (1H, d, *J* = 8.1 Hz, N-H(C=O)), 5.37 (1H, dd, *J* = 6.7, 10.3 Hz, 4-H_{ax}), 3.66 (1H, s, NH), 3.50 (1H, ddd, *J* = 2.4, 6.4, 11.6 Hz, 2-H_{ax}); 2.26 (1H, ddd, *J* = 2.0, 6.2, 12.4 Hz, 3-H_{ax}); 2.20 (1H, s, 6-CH_3); 1.46-1.39 (1H,m, 3-H_{eq}); 1.19 (1H, d, *J* = 6.3 Hz, 2-CH_3) ppm; **^{13}C RMN** (101 MHz, $CDCl_3$) δ 161.10, 142.90, 129.03,

127.33, 127.29, 127.10, 120.84, 114.9, 46.73, 44.84, 36.11, 22.13, 20.42 ppm.; **COSY** [δH/ δH]: 8.30/5.81 [2´H-(C=O)/ N-H(C=O)], 6.84/ 6.41 [7-H/8-H], 6.416.84 [8-H/7-H], 5.81/5.37 [N-HC(O)/4-H_{ax}], 5.37/5.81 [4-H_{ax}/N-HC(O)], 5.37/2.26 [4-H_{ax}/3-H_{ax}], 5.37/1.46-1.39 [4-H_{ax}/3-H_{eq}], 3.50/2.26 [2-H_{ax}/ 3-H_{ax}], 3.50/1.46-1.39 [2-H_{ax}/ 3-H_{eq}], 3.50/1.19 [2-H_{ax}/ 2-CH_3], 2.26/ 5.37 [3-H_{ax}/ 4-H_{ax}], 2.26/ 3.50 [3-H_{ax}/ 2-H_{ax}], 2.26/ 1.46-1.39 [3-H_{ax}/ 3-H_{eq}], 1.46-1.39/5.37 [3-H_{eq}/4-H_{ax}], 1.46-1.39/3.50 [3-H_{eq}/2-H_{ax}], 1.46-1.39/2.26 [3-H_{eq}/3-H_{ax}], 1.19/3.50 [2-CH_3/2-H_{ax}]; Anal. Calcd for $C_{12}H_{16}N_2O$; C, 70.56; H, 7.90; N, 13.71; O, 7.83; Found C, 70.55; H, 7.91; N, 13.71; O, 7.81.

6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl formamide (8c)

Yellow Solid; Yield 81 %; mp. 205-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$)**:** δ δ 8.34 (1H, s, H-(C=O)), 7.06 (1H, dd, *J* = 1.1, 2.4 Hz, 5-H), 6.96 (1H, dd, *J* = 2.4, 8.5 Hz, 7-H), 6.40 (1H, d, *J*= 8.5 Hz, 8-H), 5.74 (1H, d, *J* = 8.1 Hz, N-H(C=O)), 5.41-5.34 (1H, m, 4-H_{ax}), 3.78 (1H, b.s, HN); 3.54 (1H, ddd, *J* = 2.4, 6.3, 11.3, 2-H_{ax}); 2.26 (1H, ddd, *J* = 2.3, 6.0, 12.4 Hz, 3-H_{ax}); 1.50-1.41 (1H, m,3-H_{eq}); 1.21 (1H, d, *J* = 6.3 Hz, 2-**$\underline{CH_3}$**) ppm**;** Anal. Calcd for $C_{11}H_{13}ClN_2O$; C, 58.80; H, 5.83; Cl, 15.78; N, 12.47; O, 7.12; Found C, 58.80; H, 5.85; Cl, 15.74; N, 12.46; O, 7.11.

6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (8d)

Yellow solid; Yield 83 %; mp 167-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (1H, s, H-(C=O)), 6.82 (1H, dd, *J* = 2.9, 9.5 Hz, 5-H), 8.76-8.71 (1H, m, 7-H), 6.42 (1H, dd, *J* = 4.6, 8.7 Hz, 8-H), 5.84 (1H, d, *J* = 7.8 Hz, N-H(C=O), 5.42-5.35 (1H, m, 4-H_{ax}), 3.68 (1H, b.s, HN); 5.50 (1H, ddd, *J* = 2.2, 6.3, 11.3, 2-H_{ax}), 2.26 (1H, ddd, *J* = 2.1, 6.1, 12.4 Hz, 3-H_{ax}), 1.49-1.40 (1H,m, 3-H_{eq}), 1.20 (1H, d, *J* = 6.3 Hz, 2-CH_3) ppm**;** Anal. Calcd for $C_{11}H_{13}FN_2O$; C, 63.45; H, 6.29; F, 9.12; N, 13.45; O, 7.68; Found C, 63.43; H, 6.28; F, 9.12; N, 13.44; O, 7.69.

Antimicrobial assay

The antimicrobial activity of five THQ selected (**5b, 5d, 6b, 6c y 6d** with deactivating groups) was evaluated on the strains: *P.aeruginosa* (PA1 mixed strain resistance), *P.aeruginosa* (PA2, PA3 sensitive strains), *P.aeruginosa* (PA4, PA5 multiresistant strains), *E. coli*, *K. pneumoniae*, *S. aureus* and *C. albicans*. All strains come from hospital clinical isolates from patients with infections at different levels (surgical wounds, invasive devices, urinary tract infections and lung), which were identified phenotypically and tested for antimicrobial susceptibility by automated method (auto SCAN®-4 SIEMENS). Minimal Inhibitory Concentration (MIC) was calculated following the recommendations of the CLSI-2012 for microdilution (IC50) by using the Graphpad Prism 5.0 statistical package. A serial dilution set of each THQ was prepared using DMSO as solvent. The final volume was 100µL and the final concentration of DMSO in the assay did not exceed 1%. Each treatment consisted of suitable culture medium (nutrient broth for bacteria strain and Sabouraud dextrose broth for yeast strait), containing adequate THQ concentration and microbial strains. Each treatment was carried out by triplicate. Afterwards, the cultures were incubating at 37°C and the growth was monitoring at OD600 until reaching the stationary phase, negative and positive controls were used; the negative control contained all except THQ and the positive control contained all except THQ, which was substituted by Gentamicin or Levofloxacine or Fluconazole or Ketoconazole as reference antibiotic.

Results and Discussion

The N-[2-(n-butyl)-1,2,3,4-tetrahydro-4-yl] acetamide (6a-d) and N-[2-(n-ethyl)-1,2,3,4-tetrahydro-4-yl] acetamide (5a-d) was synthetized by applying a iDA multicomponent reaction, using as catalyst bismuth trichloride (III), acetonitrile under nitrogen atmosphere and diverse reactants as substituted anilines, propionaldehyde (valeraldehyde), and N-vinylacetamide (NVF) (Scheme 1). All the 2-alkyl-THQ compounds (5a-d) and (6a-d), was obtained with good yields and mild reactions conditions (Table 1). Keeping in mind the effect of temperature in the yield of the iDA methodology, the reaction was carried out between p-methoxianiline, NVF and hexanal at heating under the conditions established ($BiCl_3$, CH_3CN, N_2 atmosphere), obtaining the 2-butyl-6-methoxy-3-propylquinoline (7) in an 87 % yield (Scheme 2). This novel fact shows competition process between N-vinyl formamide and valeraldehyde enolate formed by *in situ* dienophile (N-alkyl aldimines), which is favored by the second due to temperature increase. Considering the above results we proceeded to evaluate the reactivity of the NVF in the tandem method, in the synthesis of new N-[2-methyl tetrahydroquinolyl-4-yl)] acetamide (**8a-d**) using substituted anilines (Scheme 3).

All the N- [2-methyl tetrahydroquinolyl-4-yl)] acetamide (**8a-d**), was obtained as solid compounds and good yields (Table 2). The role of bacteria, fungi and viruses as etiologic agents of infectious diseases that afflict alarmingly patients admitted to intensive

care units (ICU) where multiresistant strains are more frequent and dangerous, besides the increase of the mechanisms of microbial resistance to existing drug therapies reveals the need for new therapeutic agents [15]. Selected 2-alquil THQ (5b, 5d, 6b, 6c y 6d) with deactivating groups was evaluated as potential antimicrobial agents against clinical isolated strains of bacteria and fungi, microorganisms were chosen for the purpose of analyzing strains with variable sensitivity to antibiotics, including sensitive, resistant and mixed-resistance strains, especially *P. aeruginosa* responsible for many deaths by multidrug resistant infectious diseases worldwide [16].

All strains come from hospital clinical isolates from patients with infections at different levels (surgical wounds, invasive devices, urinary tract infections, lung, etc.), which were identified phenotypically and tested for antimicrobial susceptibility by automated method (auto SCAN®- 4 SIEMENS). Five strains of *P.aeruginosa* were selected: sensitive strains (PA2, PA3) multiresistant strains (PA4, PA5) and a mixed strain resistance (PA1) (Table 3), in order to evaluate if the molecules showed a wide spectrum antimicrobial, other gram-negative, gram-positive and fungi sensitive strains [*E. coli* (E.c), *K. pneumoniae* (K.p), *S. aureus* (S.a) and *C. albicans* (C.a)] was facing the candidate molecules.

The new 1,2,3,4-tetrahydroquinolin-4-yl)formamide compounds showed a high range of antimicrobial activity, relative to the antibacterial activity is demonstrate that the best response was achieved with the gram negative bacteria, since the lower MIC values were obtained by the N-(2-butyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (6c) against PA2 (0.003 µg/mL), besides 0.0025 µg/mL N-(-2-butyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-yl) formamide (6d) and N-(2-ethyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (5d), which showed the best MICs values than those obtained by the reference drug against *E. coli* (0.19 µg/mL) (Table 3).

However against multiresistant strain PA4 no activity was found by any of the test compounds (5,6a-d), although the -N-(2-butyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (6b), N-(2-butyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (6c) and N-(2-ethyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (5d) show 0.8 µg/mL PA1 (multiresistant strain), in addition to the values of activity of the (6b) (0.4 µg/mL), and the 2-ethyltetrahydroquinoline compounds (5b) (0.4 µg/mL) and (5d) (0.8 µg/mL) against the PA5 (multiresistant strain) (Table 1).

P. aeruginosa strain was used as model for to evaluate the effect of THQ tested on bacterial DNA. Results suggest that DNA of PA1 strain was partially degraded by 5b and 6d molecules, PA2 strain showed smear DNA when was exposed to 6b molecule, PA3 and PA4 DNA straits not showed degradative effect and finally DNA of PA5 strain was degraded when exposed to 5b and 6c molecules (Figure 2).

Results of the degradative possible effect suggest that not all strain are inhibiting by the same mechanism, and as showed in the table 3, the differential susceptibility to antibiotics for each tested bacteria can be associated to deferential results obtain.

However more detailed studies are necessary to enable associate the results obtained in this research with potential target molecules to provide more accurate information on the mechanisms of action of these new molecules information.

Conclusion

The Lewis acid catalized iDA reaction was effective in the synthesis of 2-(n-butyl)-1,2,3,4-tetrahydro-4-yl acetamide (6a-d) and 2-(n-ethyl)-1,2,3,4-tetrahydro-4-yl acetamide (5a-d) using a multicomponent strategy. However, using the same conditions (BiCl3, CH3CN) and iDA reactions modifications allowed the synthesis new 2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (8a-d) and 2-butyl-6-methyl-3-propylquinoline (7), applying a tandem iDA/AdNu/E methodology show the versatility and efficiency of the DA reaction and Lewis acid conditions. The tetrahidroquinoline compounds showed interesting antimicrobial properties against clinical isolated strains of *P. aeruginosa*, *E. coli*, *S. aureus*, *K. pneumoniae* and *C. albicans*. For *P. aeruginosa* (PA2) strain showing higher values than the reference drug, for compounds N-(2-butyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (MIC = 0.003 µg/ml), N-(2-butyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-yl)formamide (MIC = 0.025 µg/ml) and N-(6-chloro-2-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (MIC = 0.025 µg/ml).

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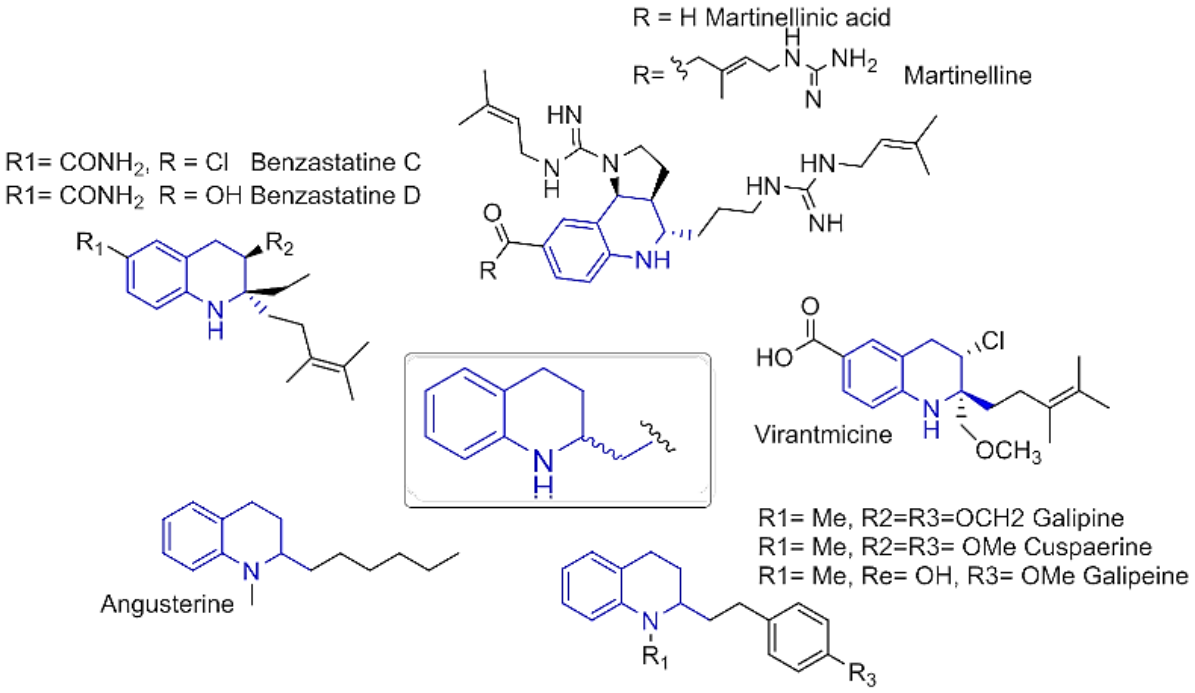


Figure 1. Natural tetrahydroquinole compounds.

Table 1. Features of the substituents of derivatives (5a-d, 6a-d) and reaction yields.

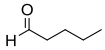
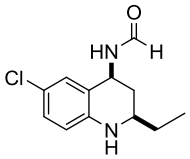
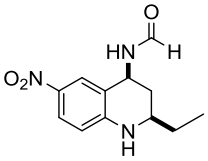
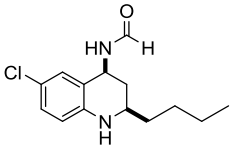
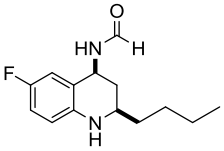
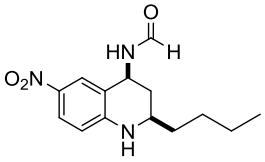
Entry	R1	Aldehyde	Mol. Form	Comp.	Yield
1	CH_3		$C_{13}H_{18}N_2O$	(**5a**)	69
2	Cl		$C_{12}H_{15}ClN_2O$	(**5b**)	85
3	F		$C_{12}H_{15}FN_2O$	(**5c**)	88
4	NO_2		$C_{12}H_{15}N_3O_3$	(**5d**)	88
5	CH_3		$C_{15}H_{22}N_2O$	(**6a**)	64
6	Cl		$C_{14}H_{19}ClN_2O_2$	(**6b**)	84
7	F		$C_{12}H_{15}FN_2O$	(**6c**)	82
8	NO_2		$C_{14}H_{19}N_3O_3$	(**6d**)	89

Table 2. Features of the substituents of derivatives (8a-d) and reaction

Entry	R	Mol. Form	Comp.	Yield
1	H	$C_{11}H_{14}N_2O$	(**8a**)	78
2	CH_3	$C_{12}H_{16}N_2O$	(**8b**)	76
3	Cl	$C_{11}H_{13}ClN_2O$	(**8c**)	81
4	F	$C_{11}H_{13}FN_2O$	(**8d**)	83

Table 3. Minimal inhibitory concentration for each molecule tested and the reference molecule on the microbial evaluated.

		Minimum inhibitory concentration (µg/mL)								
		Gram negative							Gram Positive	Fungi
Compound	Structure	*PA1*	*PA2*	*PA3*	*PA4*	*PA5*	*E.c*	*K.p*	*S.A*	*C.a*
(**5b**)		N.A	00025	0.4	N.A	0.4	0.19	1.56	0.19	6.25
(**5d**)		0.8	0.4	0.4	N.A	0.8	12.5	12.5	>3.15	50
(**6b**)		0.8	0.4	0.8	N.A	0.4	0.78	3.15	>100	3.15
(**6c**)		0.8	0.003	0.8	N.A	N.A	1.56	6.25	>50	1.56
(**6d**)		N.A	0.025	0.4	N.A	N.A	6.25	3.15	>100	6.25
	Levofloxacine	0.4	0.8	0.4	N.A	N.A	0.39	3.15	1.56	--
	Gentamicine	--	--	--	--	--	1.56	50	1.56	--
	Fluconazole	--	--	--	--	--	--	--	--	0.19
	Ketoconazole	--	--	--	--	--	--	--	--	0.19

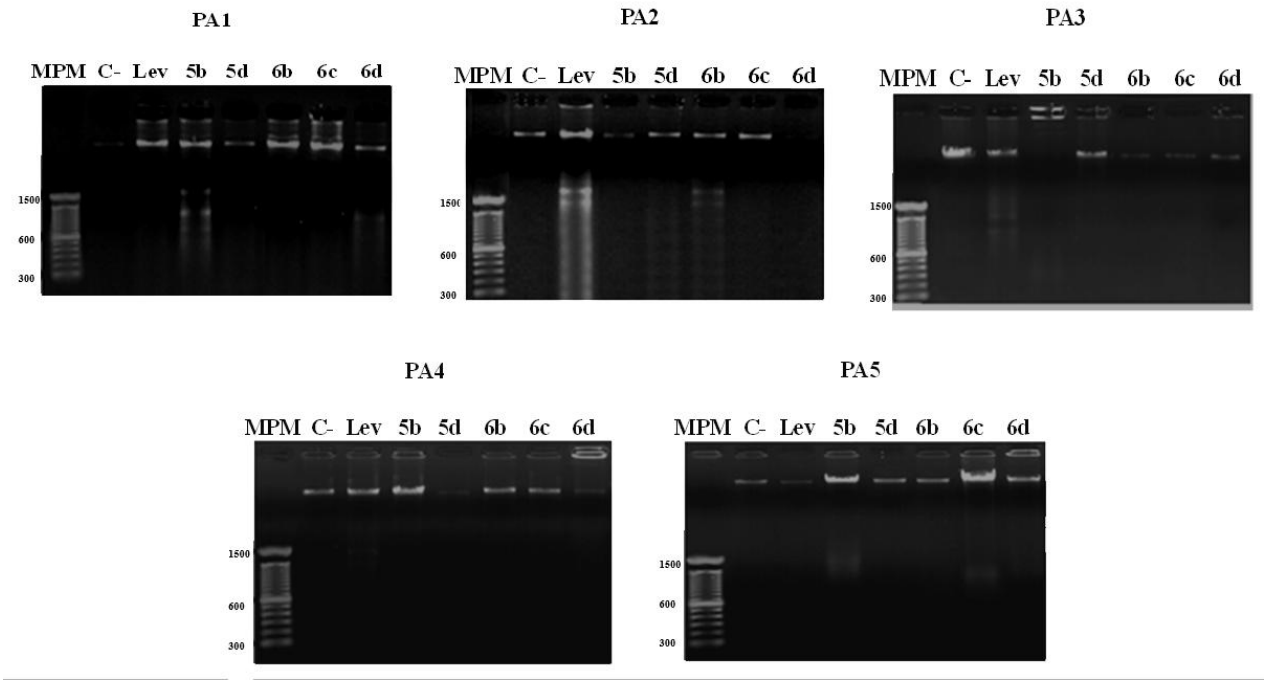
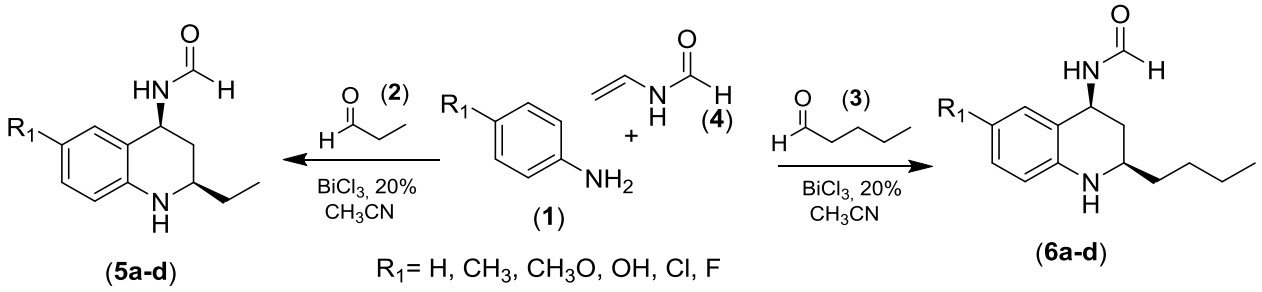
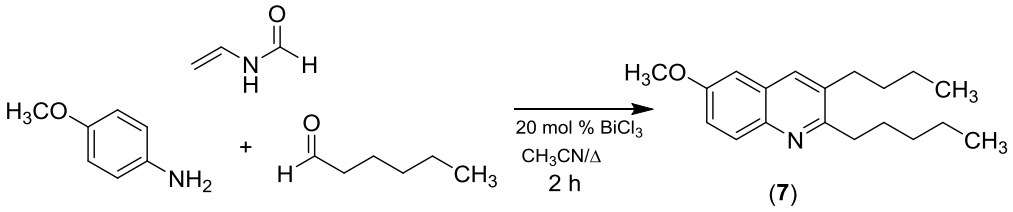


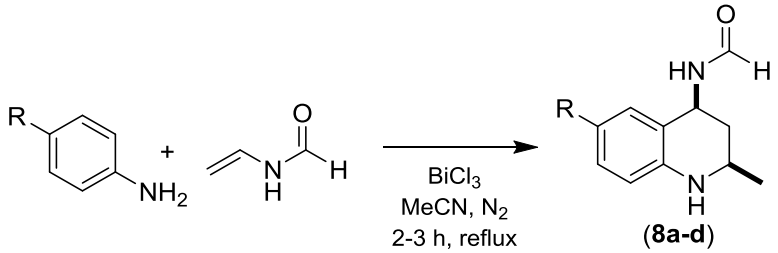
Figure 2. Degradative effect of THQ molecules on *P. aeruginosa* strain, DNA viewed in agarose gel electrophoresis.



Scheme 1. Synthesis of new derivates 2-butyl (Ethyl)-1,2,3,4-tetrahydroquinolin-4-yl)formamide substituted (5a-d).



Scheme 2. Synthesis of 2-butyl-6-methyl-3-propylquinoline.



Scheme 3. Synthesis of2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (8a-d).