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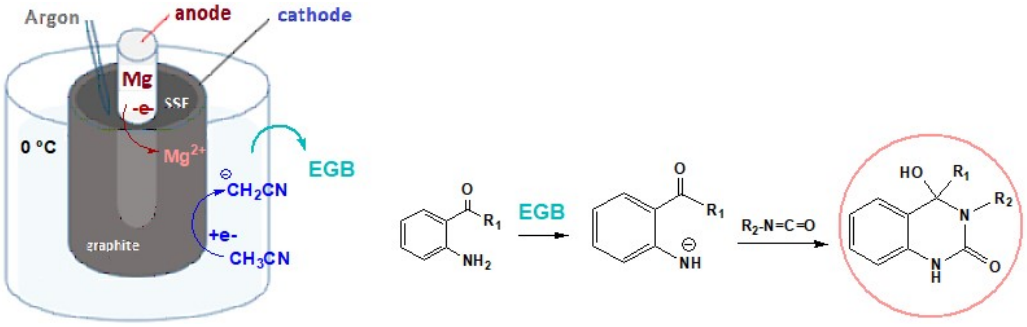

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Facile Preparation of 3-Substituted 2-Quinazolinones via Electrogenerated Base

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:

Quinazolin-2-ones,
N-heterocyclic olefins
magnesium sacrificial anode,
electrogenerated cyanomethyl anion,
organic isocyanates.

ABSTRACT

A new series of 3,4-disubstituted quinazolin-2-ones, with potential T-type calcium channel antagonist activity, and new 4-methylene-quinazolin-2-ones, promising catalysts as *N*-heterocyclic olefins, have been prepared in good yield by a simple reaction between 2-aminobenzophenone, or 2-aminoacetophenone, and cyanomethyl anion electrogenerated by acetonitrile reduction at a graphite electrode, followed by the addition of different organic isocyanates and subsequent heterocyclization.

1. Introduction

Quinazolinone and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from plants, microorganisms and animals.[1] Some compounds incorporating quinazolinone motif possess antitumor activities[2,3] and exhibit a variety of biological functions like DNA binding agents[4] non-steroidal anti-inflammatory potential or sedative analgesic effects.

A vast number of 4-quinazolinones have been synthesized[5] to provide synthetic drugs and to design more effective medicines. However there have been few reports about the synthesis of 2-quinazolinones. The general protocol involves the cyclization of *o*-disubstituted benzene derivatives such as 2-acyl or 2-cyanoanilines in combination with appropiate electrophiles or nucleophiles. Conley et al.[6] utilized a direct metalation approach starting with 3,4-dimethoxyanilin with n-butyllithium, then treating with potassium cyanate and followed by cyclization in polyphosphoric acid. Vicente et al.[7] reported the first ortho-palladated arylurea complexes, obtained by oxidative addition reactions, and studied their reactivity toward different reagents to prepare 2-quinazoline-2,4-dione derivatives. Ivanov[8] synthesized 6,7-dimethoxy-3,4-diphenyl-2(1*H*)-quinazolinone from 1-(3,4-dimethoxyphenyl)-3-phenyl-urea and benzoic acid. Zhu et al.[9] described an efficient synthesis of 4-alkyl-2(1*H*)-quinazolinones by cyclization of 1-(2-alkynyl-phenyl)ureas catalyzed by TfOH. More recently Odell et al.[10] published a rapid access to polyfunctionalized 3,4-dihydroquinazolinones through a sequential *N*-acyliminium ion Mannich reaction cascade.

Merck[11] was interested in the synthesis of a series of 4-(arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2 (1*H*)-ones as novel non-nucleoside HIV-1 reverse-transcriptase inhibitors. Modification at the 3- and 4-positions of the quinazolinone ring by different substituents afforded potent and selective T-type calcium channel antagonist[12,13] that displayed in vivo central nervous system efficacy in epilepsy and tremor models.[14] Furthermore these antagonists are attracting a lot of interest for the treatment of peripheral and central nervous system (CNS) disorders[15] or as effective agents for pain therapies.[16]

The first 4-alkenylquinazolinone synthesis was described by Brack[17] as an acidic rearrangement reaction starting from quinoline-1-carboxamides. This procedure was applied by Zolotykh.[18] Similarly, Molina et al.[19] described the 4-methylene derivatives formation when refluxing 2-[(aminocarbonyl) amino]- 3,1-benzoxazines. However in the last 30 years only a

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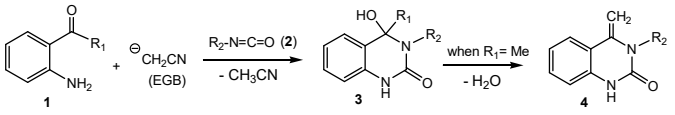
few new approaches to prepare them have been achieved. In the synthesis of 4-methylene-3,4-dihydroquinazolin-2-ones it has been found that 1-(*o*-alkynylaryl)ureas are privileged substrates that provide an adequate framework to explore alternative reaction pathways in the metal-catalysed hydroamidation of alkynes.[20,21] This effective gold(I)complex-catalysed approach to 4-methylenequinazolin-2-ones, similarly to their formation via the palladium oxidative alkoxycarbonylation of 2-ethynylaniline derivatives,[22] suffer however the drawbacks that these transition metal reagents entail.

4-Methylene quinazolin-2-one core structures represent, as recently discovered,[23] new potential inhibitors of FGFR kinases with substantial therapeutic value in different cancers, including breast, pancreatic or prostate cancers. On the other hand, 4-methylene *N*-substituted quinazolin-2-one frameworks, due to their structural exocyclic double bond, could be promising compounds to be applied as organocatalyst in polymer chemistry, similarly to *N*-heterocyclic olefins (NHO), with demonstrated ability to promote or catalyse such reactions.[24]

Electrogenerated radical anions and anions are basic reagents, called EGBs which can be used to deprotonate and to initiate many base catalyzed reactions. The use of EGB in organic synthesis is well documented.[25] Carbanions, as strong bases, may be used to generate nucleophiles from other acidic components of the reaction mixture. Moreover radical anions as EGBs have a great potential in organic synthesis, as demonstrated in the stereoselective cyclopropanation to homoquinones from phenacyl carbenes, that we have recently highlighted.[26]

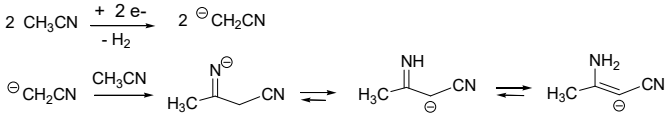
Intrigued now by promising further expectation of acetonitrile anion, as strong EGB, in the preparation of many heterocyclic molecules, we focused our attention on using the electrochemistry as a tool to prepare quinazolin-2-one moieties. Herein we report, as outlined in Scheme 1, a novel strategy for the conversion of readily available substrates into 3,4-disubstituted quinazolin-2-ones (**3**) and 4-methylene-3-substituted quinazolin-2-ones (**4**). Electrogenerated cyanomethyl anion (EGB) and 2-aminophenones evolve to **3** (or **4**) when reacted with aryl (or alkyl) isocyanates by heterocyclization.



Scheme 1. Outline of the synthetic procedure described in this paper

2. Results and Discussion

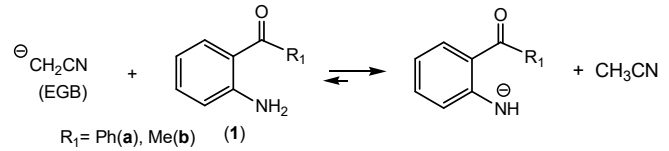
It is well established that the electrochemical reduction of acetonitrile in the presence of a quaternary ammonium salt as supporting electrolyte yields the corresponding cyanomethyl anion, a strong basic entity, with a pKa value of c.a. 32[27] capable of removing a weak acidic proton. When this reduction is carried out at a platinum, graphite or stainless steel cathode, under an argon atmosphere, the anion of 3-aminocrotonitrile[28,29] is also formed after the nucleophilic attack of the cyanomethyl anion to a new solvent molecule, as indicated in Scheme 2. However, the use of low temperatures and a sacrificial magnesium anode, in an undivided cell, avoids to a large extent this undesired reaction. It occurs because the subsequently formed magnesium cations, present in solution, stabilize the cyanomethyl anions by ion-pair association.[30]



Scheme 2. Cathodic formation of 3-amino-crotonitrile anion.

The quantity of the electrogenerated cyanomethyl anion (EGB) depends on the total circulated charge through the electrochemical cell (solution). In absence of a proton donor the carbanion is produced in a 1 F/mol process, however at the present work, to synthesize 2-quinazolinones, a significant excess of the EGB was necessary. It was because a complete proton abstraction from anilines (as acidic substrates) requires a higher base concentration, but also due to the inherent dimerization of cyanomethyl anion that, even minimized, takes place in some extend.

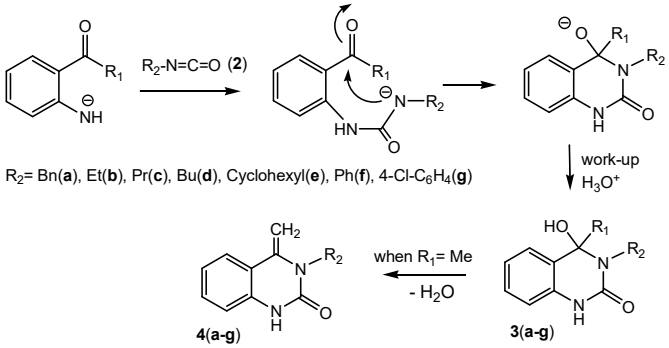
Once the optimal quantity of electrogenerated base was formed, the current supplier was switched off and then the corresponding 2-aminophenone (**1**) was added to the reaction medium. Subsequent deprotonation of the amine to a nitride occurs by the effect of the EGB, as indicated in Scheme 3.



Scheme 3. Deprotonation of 2-aminophenones (**1a**) and (**1b**) by EGB.

Aromatic ketones are well known electro-reducible carbonyl substrates, both under protic and aprotic solvents. For this reason compounds **1** are avoided to be present in the electrolytic solution at the applied galvanostatic conditions, needed to produce the EGB.

The freshly generated nitride attacks further an organic isocyanate molecule (**2**), subsequently introduced into the reaction medium, providing a new anionic intermediate. The latter finally cyclises through an addition reaction to the carbonyl group of the ketone, leading, as detailed in Scheme 4, to the 2-quinazolinone scaffolds after protonation during the work-up.



Scheme 4. Formation of 3,4-disubstituted-2-quinazolinones **3**(**a-g**) and 4-methylene-3-substituted-2-quinazolinones **4**(**a-g**).

Moreover, the electrolytic conditions were optimized in terms of reaction times (once selected a constant current value of 120 mA, see experimental section) in order to get the best obtained yield on **3** or **4**, regarding the cyanomethyl anion dimerization product, 2-aminocrotonitrile, finally formed by the excess of EGB.

The afforded yields of a variety of substituted products **3** (**a-g**) and **4** (**a-g**), when alkyl: benzyl (**a**), ethyl (**b**), propyl (**c**), butyl (**d**) and cyclohexyl (**e**) or aryl: phenyl (**f**) and 4-chlorophenyl (**g**)

isocyanates were used, are summarized in the experimental section of the manuscript. The complete characterization of these quinazolin-2-ones was performed according to their spectroscopic and spectrometric properties, becoming curious, at time that relevant, the final spontaneous dehydration of 4-hydroxy derivatives from starting acetophenone to the corresponding isolated compounds **4**, while 2-amino benzophenone derivatives were isolated as 4-hydroxy-4-phenyl-2-quinazolinones (**3**).

The heterocyclization reaction that evolves to the quinazolinone ring was further supported by the heteronuclear multiple bond correlation (gradient HMBC) two-dimensional spectrum (^{13}C and ^{1}H-NMR data) of 4-hydroxy-4-phenyl-3-butyl-2-quinazolinone (**3d**), that is shown in Figure 1. The two un-equivalent methylene hydrogen atoms, directly joined to the nitrogen at 3-position of the ring (that appear at δ= 3.20 ppm and 3.40 ppm) correlate, according to a three-bond distance, with quaternary sp^3 carbon at the C4 position of the diazine ring (δ= 66.9 ppm) and with the carbonyl group (δ= 153.1 ppm). Such reciprocity is essential to characterize the cyclization product.

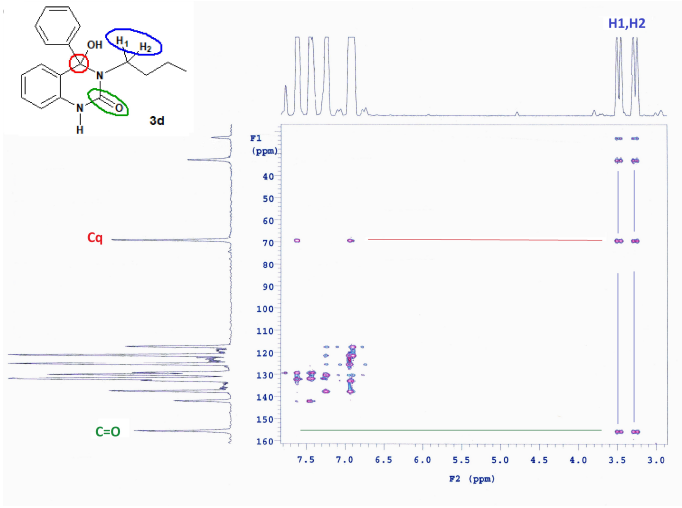
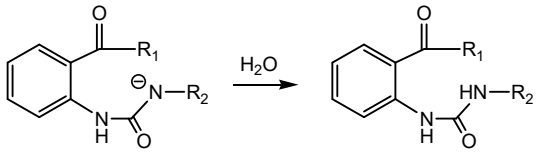


Figure 1. Two-dimensional HMBC correlation spectrum of **3d** in $CDCl_3$.

When the reaction is performed in absence of argon, the water molecules from air protonate the anionic intermediate evolving to the corresponding urea (not cyclized product, Scheme 5), whose HMBC spectrum does not present the above-mentioned ^{13}C- ^{1}H-NMR correlations, because the diazine ring has not been formed.



Scheme 5. Obtained side product: 1-(2-acyl(aroyl)phenyl)-3-alkyl(aryl) urea.

In summary, a new alternative reaction pathway, involving cyanomethyl anion as electrogenerated base, allows the good yield formation of 3,4-disubstituted 4-hydroxy-quinazolin-2-ones (**3**) and the obtaining of 4-methylene *N*-substituted quinazolin-2-one core **4**. The later is synthetically valuable when compared with previously reported multistep reactions or the harsh protocols described to get this interesting type of heterocycles.

3. Conclusion

Although numerous organic reactions using bases as catalysts have already been studied, the number and types of these bases are rather limited. Hence the generation of active bases "*in situ*" with adequate control of the amount of the base is often highly desirable in the development of new synthetic reactions, as the preparation of quinazolin-2-one moieties now described. Cathodic reduction is evidently one of the most efficient methods to generate such bases in the reaction systems.

4. Experimental Section

Electrolyses were carried out using a DC-Power Promax Model FA-672 as constant current supply. The temperature was maintained constant at 0 ºC by a cryostat Grant Model LTD 6G. Mass spectra (EI, ionizing voltage 70 eV) were determined using a THERMOFISHER ITQ-900 DIP/GC-MS_n mass-selective detector. IR spectra of the compounds were recorded as dispersions in KBr or NaCl films on a Perkin-Elmer FT-IR spectrometer Spectrum 2000. ^{1}H NMR and ^{13}C NMR spectra were recorded in a Varian Mercury 300 (^{1}H 300 MHz and ^{13}C 75.4 MHz) spectrometer and a Bruker 500 spectrometer (^{1}H 500 MHz and ^{13}C 125 MHz) at 25 ºC, as $CDCl_3$ solutions with tetramethylsilane (TMS) as the internal standard. Two-dimensional HMBC correlation NMR experiments were performed in the Bruker 500 MHz spectrometer. The chemical shifts are given in ppm. Melting points were measured on a Reichert Thermovar microhot stage apparatus and are uncorrected. Elemental analyses were performed on a Leco CHNS Model 932 analyser.

4.1. Electrochemical formation of cyanomethyl anion:

A solution of dry acetonitrile (60 mL) and tetrabutyl ammonium tetrafluoroborate ($TBABF_4$) (2.6 g, 8 mmol) was electrolyzed under galvanostatic conditions (I= 120, 140 or 200 mA) in an undivided cell, equipped with a magnetic stirrer, using a graphite cylinder (40 cm^2, empty) as the cathode and a sacrificial magnesium rod (9 cm^2) as the anode (Figure 2).

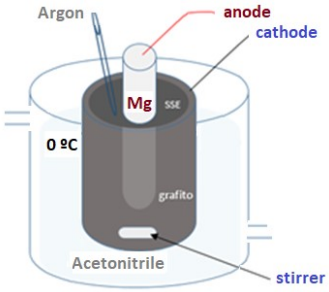


Figure 2. Electrolytic cell for acetonitrile reduction.

The electrochemical reactions were performed at 0 °C under an argon atmosphere, and different reaction times. The last parameter was modified in order to optimize the results. The best obtained yield on **3** (or **4**) regarding the cyanomethyl anion dimerization product was obtained when the charge consumption corresponded to the formation of 10 mmol of the desired base (EGB) (approximately 1000 coulombs). When shorter reaction times were applied, with subsequent lower charges circulated through the cell, the yields on quinazolin-2-ones were definitively decreased.

4.2. Synthesis of 2-Quinazolinones (3) and (4):

Once the galvanostatic acetonitrile reduction was finished, the imposed current was switched off and immediately 2-aminophenone (**1a, 1b**) (1.0 mmol) was added to the reaction medium. The resulting solution was stirred under argon at low temperature for 1 hour. At the end of this period 1.1 mmol of an

alkyl (or aryl) isocyanate (**2**) was introduced in the reaction cell, and kept overnight under stirring at room temperature.

General Procedure:

The solvent in the reaction crude was then removed under reduced pressure and the residue was stirred for 2h in diethyl ether in order to extract the organic products from the insoluble magnesium salts and the supporting electrolyte. The final solution was filtered, the ether was then washed with water, dried over anhydrous $MgSO_4$ and finally the ether was removed by evaporation in vacuo. The resulting residue was purified by chromatography on a silica gel 60 (35-70 mesh) column (22 x 3 cm) using different mixtures (depending on the product) of EtOAc/petroleum ether (or hexane) as eluent.

Spectroscopic and physical properties of the new obtained compounds (**3**) and (**4**) are given below.

3-Benzyl-3,4-dihydro-4-hydroxy-4-phenylquinazolin-2(1*H*)-one (3a)

(247 mg, 75% yield). Solid. m.p: 160-163 °C; Rf (25% EtOAc/Hex) 0.45; IR (KBr) ν= 3197 (NH), 3119, 3064, 2922, 2852, 1674 (C=O), 1606 1502, 1447, 1405, 1266, 1028, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.59 (d, 1H, J= 15.7 Hz), 4.65 (d, 1H, J= 15.7 Hz), 6.80 (dd, 1H, J_1= 8.3 Hz, J_2= 1.0 Hz), 6.84 (dd, 1H, J_1= 7.9 Hz, J_2= 1.5 Hz), 6.92 (td, 1H, J_1= 7.9 Hz, J_2= 1.0 Hz), 7.12-7.16 (m, 2H), 7.18-7.21 (m, 3H), 7.24 (td, 1H, J_1= 7.8 Hz, J_2= 1.5 Hz), 7.32-7.40 (m, 3H), 7.51 (dd, 2H, J_1= 7.8 Hz, J_2= 1.5 Hz), 8.6 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 49.5 (-CH_2-Ph), 66.8 (Cq), 114.5, 117.4, 119.3, 123.0, 127.2, 127.8, 127.9, 128.1, 129.0, 129.6, 130.4, 134.7, 136.9, 137.9, 153.0. EI-MS: m/z (relative intensity): 312 (M^+-18, 29), 311(M^+-18-1, 81), 296(77), 234(64), 207(100), 206 (37), 180(11), 106(30), 91(40), 77(5). Anal. Calc. for C_{21} H_{18} N_2 O_2: C, 76.40; H, 5.50; N, 8.50. Found: C, 76.09; H, 5.72; N, 8.48.

3-Ethyl-3,4-dihydro-4-hydroxy-4-phenylquinazolin-2(1*H*)-one (3b)

(198 mg, 74% yield). Oil. Rf (25% EtOAc/Hex) 0.63; IR (NaCl) ν= 3197 (NH), 3130, 3070, 2984, 2919, 1666 (C=O), 1602 1501, 1451, 1348, 1269, 975, 748, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.17 (s, 3H), 3.37 (bs, 1H) 3.50 (bs, 1H), 6.89 (s, 3H), 7.23 (bs, 1H), 7.43 (bs, 3H), 7.60 (s, 2H), 9.33 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 13.6, 41.7, 66.4, 114.6, 118.1, 118.7, 122.8, 126.6, 127.7, 129.2, 129.5, 130.3, 134.8, 139.4, 152.4. EI-MS: m/z (relative intensity): 250 (M^+-18, 44), 249(M^+-18-1, 100), 236(11), 221(36), 207(17), 194(15), 180(4), 151(5), 145(18), 117(10), 104(17), 91(13), 77(12). Anal. Calc. for C_{16} H_{16} N_2 O_2: C, 71.60; H, 6.00; N, 10.40. Found: C, 71.44; H, 5.73; N, 10.17.

3,4-Dihydro-4-hydroxy-4-phenyl-3-propylquinazolin-2(1*H*)-one (3c)

(197 mg, 70% yield). Solid. m.p: 141-143 °C; Rf (25% EtOAc/Hex) 0.65; IR (KBr) ν= 3202 (NH), 3133, 3068, 2972, 2921, 1669 (C=O), 1605, 1502, 1450, 1409, 1364, 1265, 1066, 982, 752, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.83 (t, 3H, J= 7.4 Hz), 1.40-1.60 (m, 1H), 1.70-1.90 (m, 1H), 3.14-3.25 (m, 1H) 3.35-3.48 (m, 1H), 6.85-6.95 (m, 3H), 7.22-7.27 (m, 1H), 7.38-7.46 (m, 3H), 7.58 (d, 2H, J= 7.9 Hz), 9.71 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 11.8, 21.9, 48.8, 66.8, 114.9, 118.3, 118.9, 123.0, 126.7, 127.8, 129.4, 129.7, 130.4, 135.0, 139.6, 153.0. EI-MS: m/z (relative intensity): 264 (M^+-18, 65), 263(M^+-18-1, 100), 247(7), 235(68), 222(70), 221(93), 207(49), 194(11), 187(19), 180(6), 145(9), 132(5), 117(5), 104(10), 91(24), 77(8). IQ-MS: m/z (relative intensity): 305 (M^+-18+41, 3), 293 (M^+-18+29, 21), 265 (M^+-18+1, 100). Anal. Calc. for C_{17} H_{18} N_2 O_2: C, 72.30; H, 6.40; N, 9.90. Found: C, 72.03; H, 6.22; N, 10.10.

3-Butyl-3,4-dihydro-4-hydroxy-4-phenyl-quinazolin-2(1*H*)-one (3d)

(210 mg, 71% yield). Solid. m.p: 138-140 °C; Rf (25% EtOAc/Hex) 0.63; IR (KBr) ν= 3201 (NH), 3134, 3072, 2974, 2919, 1671 (C=O), 1604, 1501, 1460, 1406, 1367, 1334, 1264, 1073, 980, 940, 748, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (t, 3H, J= 7.4 Hz), 1.20-1.35 (m, 2H), 1.36-1.56 (m, 1H), 3.20-3.32 (m, 1H) 3.40-3.54 (m, 1H), 6.82-6.97 (m, 3H), 7.23 (td, 1H, J_1= 7.0 Hz, J_2= 2.2 Hz), 7.36-7.48 (m, 3H), 7.60 (d, 2H, J= 7.9 Hz), 10.09 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 14.0, 20.6, 30.6, 46.9, 66.9, 115.0, 118.3, 118.9, 122.9, 126.8, 127.7, 129.3, 129.7, 130.4, 135.1, 139.6, 153.1. EI-MS: m/z (relative intensity): 279 (M^+-18+1, 23), 278 (M^+-18, 29), 277(M^+-18-1, 29), 261(23), 249(28), 235(100), 222(34), 221(56), 208(36), 207(95), 201(88), 194(11), 180(7), 165(5), 151(8), 145(10), 132(7), 117(8), 104(14), 91(27), 77(14). Anal. Calc. for C_{18} H_{20} N_2 O_2: C, 73.00; H, 6.80; N, 9.50. Found: C, 73.21; H, 6.82; N, 9.75.

3-Cyclohexyl-3,4-dihydro-4-hydroxy-4-phenyl-quinazolin-2(1*H*)-one (3e)

(203 mg, 63% yield). Solid. m.p: 124-126 °C; Rf (25% EtOAc/Hex) 0.52; IR (KBr) ν= 3203 (NH), 3127, 3073, 2920, 1670 (C=O), 1606, 1501, 1432, 1367, 1272, 1002, 896, 751, 702, 669 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (d, 1H, J= 11.7 Hz), 1.15 (q, 1H, J= 12.7 Hz), 1.20-1.30 (m, 2H), 1.55 (t, 2H, J= 11.7 Hz), 1.84 (d, 1H, J= 12.2 Hz), 2.11 (d, 1H, J= 12.2 Hz), 2.35 (qd, 1H, J_1= 12.3 Hz, J_2= 3.0 Hz), 2.50 (qd, 1H, J_1= 12.3 Hz, J_2= 3.0 Hz), 3.01(t, 1H, J= 10.7 Hz), 6.82-6.9 (m, 3H), 7.21 (ddd, J_1= 8.8 Hz, J_2= 5.9 Hz, J_3= 2.9 Hz, 1H), 7.37-7.45 (m, 3H), 7.62 (dd, J_1= 8.3 Hz, J_2= 1.0 Hz, 1H), 9.26 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 24.6, 25.5, 26.6, 29.8, 32.7, 49.3, 67.5, 114.2, 118.1, 118.3, 122.5, 126.6, 128.0, 129.0, 129.4, 130.1, 134.5, 140.6, 151.3. EI-MS: m/z (relative intensity): 304 (M^+-18, 25), 303 (M^+-18-1, 35), 275(7), 261(12), 249(11), 247(16), 233(12), 227(14), 223(100), 221(64), 207(17), 194(7), 179(7), 145(5), 117(6), 104(5), 77(6). Anal. Calc. for C_{20} H_{22} N_2 O_2: C, 74.50; H, 6.80; N, 8.70. Found: C, 74.17; H, 6.88; N, 8.68.

3,4-Dihydro-4-hydroxy-3,4-diphenylquinazolin-2(1*H*)-one (3f)

(205 mg, 65% yield). Solid. m.p: 122-124 °C; Rf (25% EtOAc/Hex) 0.38; IR (KBr) ν= 3202 (NH), 3133, 3079, 3064, 2975, 2915, 1675 (C=O), 1604, 1493, 1387, 1267, 860, 746, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.79 (d, 1H, J= 7.4 Hz), 6.90 (d, 1H, J= 6.8 Hz), 6.95 (t, 1H, J= 6.8 Hz), 7.00-7.10 (m, 2H), 7.24-7.28 (m, 4H), 7.30-7.36 (m, 3H), 7.4 (d, 2H, J= 7.8 Hz), 8.65 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 67.9, 115.1, 117.9, 123.0, 127.6, 127.8, 128.4, 128.7, 128.9, 129.4, 130.1, 130.4, 135.0, 137.7, 138.5, 152.0. EI-MS: m/z (relative intensity): 298 (M^+-18, 100), 271(40), 257(22), 222(43), 207(12), 180(35), 151(4), 77(32). Anal. Calc. for C_{20} H_{16} N_2 O_2: C, 75.90; H, 5.10; N, 8.90. Found: C, 76.20; H, 5.31; N, 9.07.

3-(4-Chlorophenyl)-3,4-dihydro-4-hydroxy-4-phenylquinazolin-2(1*H*)-one (3g)

(235 mg, 67% yield). Solid. m.p: 123-125 °C; Rf (25% EtOAc/Hex) 0.35; IR (KBr) ν= 3262 (NH), 3061, 2960, 2922, 1682 (C=O), 1609, 1492, 1388, 1093, 1018, 819, 756, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.79 (d, 1H, J= 8.0 Hz), 6.87 (d, 1H, J= 7.7 Hz), 6.94 (t, 1H, J= 7.7 Hz), 7.18-7.26 (m, 3H), 7.26-7.50 (m, 6H), 9.03 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 68.0, 115.2, 119.2, 123.5, 127.7, 128.2, 128.4, 129.1, 129.4, 129.9, 130.8, 131.7, 135.0, 136.3, 138.3, 151.9. EI-MS: m/z (relative intensity): 334 (M^+-18+2, 24), 332 (M^+-18, 70), 306(9), 304(26), 292(6), 290(16), 268(8), 257(15), 255(38), 220(10), 216(8), 214(23), 206(15), 192(7), 151(7), 113(7), 111(19), 77(8), 75(19). Anal. Calc. for C_{20} H_{15} Cl N_2 O_2: C, 68.50; H, 4.30; N, 8.00. Found: C, 68.77; H, 4.23; N, 8.11.

3-Benzyl-3,4-dihydro-4-methylenequinazolin-2(1*H*)-one (4a)

(175 mg, 70% yield). Solid. m.p: 191-193 °C [Lit.[20] 193-195 ºC]; Rf (20% EtOAc/Petroleum ether) 0.67; IR (KBr) ν= 3203, 3059, 2924, 1679, 1633, 1605, 1494, 1443, 1260, 958, 757, 715 cm^{-1}; EI-MS: m/z (relative intensity): 250 (M^+, 89), 249(M^+-1, 100), 235(22), 221(10), 206(7), 180(2), 145(14), 117(7), 104(6), 91(32), 89(10), 77(7), 65(14), 63(7).

3-Ethyl-3,4-dihydro-4-methylenequinazolin-2(1*H*)-one (4b)

(104 mg, 55% yield). Solid. m.p: 176-178 °C [Lit.[20] 178-180 ºC]; Rf (20% EtOAc/Petroleum ether) 0.74; IR (KBr) ν= 3200, 3061, 2980, 1676, 1600, 1442, 1372, 760 cm^{-1}; EI-MS: m/z (relative intensity): 188 (M^+, 100), 173(3), 160(98), 145(40), 132(94), 116(13), 104(14), 89(26), 77(9), 63(13).

3,4-Dihydro-4-methylene-3-propylquinazolin-2(1*H*)-one (4c)

(123 mg, 61% yield). Solid. m.p: 179-182 °C [Lit.[20] 182-184 ºC]; Rf (20% EtOAc/Petroleum ether) 0.75; IR (KBr) ν= 3234, 2925, 1691, 1633, 1604, 1444, 1368, 1256, 1084, 791, 748 cm^{-1}; EI-MS: m/z (relative intensity): 202 (M^+, 29), 187 (M^+-15, 99), 174(7), 160(83), 145(31), 132(100), 116(27), 104(14), 89(21), 77(8), 63(7).

3-Butyl-3,4-dihydro-4-methylenequinazolin-2(1*H*)-one (4d)

(130 mg, 60% yield). Solid. m.p: 182-185 °C; Rf (20% EtOAc/Petroleum ether) 0.72; IR (KBr) ν= 3202, 2927, 1688, 1633, 1373, 1295, 790, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (t, 3H, J= 7.3 Hz), 1.37-1.46 (m, 2H), 1.7 (c, 2H, J= 6.8 Hz), 3.86 (t, 2H, J= 7.3 Hz), 4.3 (d, 1H, J= 2.4 Hz), 4.83 (d, 1H, J= 2.4 Hz), 6.79 (d, 1H, J= 7.9 Hz), 7.00 (t, 1H, J= 7.3 Hz), 7.20 (d, 1H, J= 8.3 Hz), 7.55 (d, 1H, J= 8.3 Hz), 8.80 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.8, 20.2, 27.6, 43.1, 84.1 (=CH_2), 114.6, 116.9, 122.5, 123.9, 130.0, 135.1, 140.2, 151.2. EI-MS: m/z (relative intensity): 216 (M^+, 5), 201 (M^+-15, 100), 187(10), 174(26), 160(41), 145(25), 132(60), 116(19), 104(9), 89(17), 77(5), 63(6). Anal. Calc. for $C_{13}H_{16}N_2O$: C, 72.20; H, 7.40; N, 13.00. Found: C, 71.99; H, 7.27; N, 13.28.

3-Cyclohexyl-3,4-dihydro-4-methylenequinazolin-2(1*H*)-one (4e)

(128 mg, 53% yield). Oil. Rf (20% EtOAc/Petroleum ether) 0.63; IR (NaCl) ν= 3207, 3072, 2937, 1675, 1618, 1508, 1450, 1374, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15-2.10 (m, 10H), 3.88 (t, 1H, J= 11.7 Hz), 4.56 (d, 1H, J= 2.4 Hz), 4.85 (d, 1H, J= 2.4 Hz), 6.70 (d, 1H, J= 7.8 Hz), 6.95-7.00 (m, 1H), 7.30-7.38 (m, 1H), 7.7 (d, 1H, J= 7.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.9, 25.5, 26.5, 29.0, 33.6, 49.3, 89.1 (=CH_2), 113.6, 117.2, 122.4, 124.0, 129.6, 134.2, 142.2, 151.7. EI-MS: m/z (relative intensity): 242 (M^+, 7), 227(3), 185(2), 171(5), 161(100), 145(3), 132(14), 116(8), 104(5), 89(5), 77(4), 63(2). Anal. Calc. for $C_{15}H_{18}N_2O$: C, 74.40; H, 7.40; N, 11.60. Found: C, 74.69; H, 7.21; N, 11.73.

3,4-Dihydro-4-methylene-3-phenylquinazolin-2(1*H*)-one (4f)

(170 mg, 72% yield). Solid. m.p: 188-190 °C [Lit.[20] 191-192 ºC. Rf (20% EtOAc/Petroleum ether) 0.60; EI-MS: m/z (relative intensity): 236 (M^+, 35), 235(M^+-1, 100), 217(25), 207(4), 190(6), 165(3), 116(2), 89(8), 77(5).

3-(4-Chlorophenyl)-3,4-dihydro-4-methylenequinazolin-2(1*H*)-one (4g)

(189 mg, 70% yield). Solid. m.p: 214-217 °C; Rf (20% EtOAc/Petroleum ether) 0.53; IR (KBr) ν= 3460, 3048, 2934, 1680. 1630. 1409, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (d, 1H, J= 2.5 Hz), 4.77 (d, 1H, J= 2.5 Hz), 6.74 (d, 1H, J= 6.9 Hz), 7.03 (td, 1H, J_1= 7.7 Hz, J_2= 1.1 Hz), 7.20-7.50 (m, 5H), 7.55 (d, 1H, J= 7.9 Hz), 7.70 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 88.2 (=CH_2), 114.3, 114.9, 123.2, 124.3, 129.9, 130.4, 130.6, 130.8, 143.1, 152.8, 161.7. EI-MS: m/z (relative intensity): 272 (M^++2, 11), 271 (M^++2-1, 38), 270 (M^+, 35), 269 (M^+-1, 100), 251(7), 234(72), 206(8), 190(4) 117(3), 89(12), 75(7). Anal. Calc. for $C_{15}H_{11}ClN_2O$: C, 66.50; H, 4.10; N, 10.40. Found: C, 66.37; H, 4.29; N, 10.64.

Acknowledgments

The authors gratefully acknowledge the financial support of the University of Alcala- proyect Nº CCG2017/EXP-009.

Electronic Supplementary Information (ESI) available:

Copy of ^{1}H/^{13}C NMR spectrum, IR and MS (EI or IQ) of new compounds **3** and **4** is provided. This material is available free of charge via Internet.

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