



Synthesis of New 2-(N'-Allylidene-hydrazino)quinazolinones and 2-(4,5-Dihydropyrazolyl)-quinazolinones and Their Antimicrobial and Antifungal Activity Screening

NEZIRE SAYGILI^{1*}, MELIKE EKIZOGLU² and CEREN ERDOGDU²

¹Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Hacettepe University, Sıhhiye, 06100 Ankara, Turkey

²Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Hacettepe University, Sıhhiye, 06100 Ankara, Turkey

*Corresponding author: Fax: +90 312 3114777; Tel: +90 312 3054016-18; E-mail: nezires@hacettepe.edu.tr

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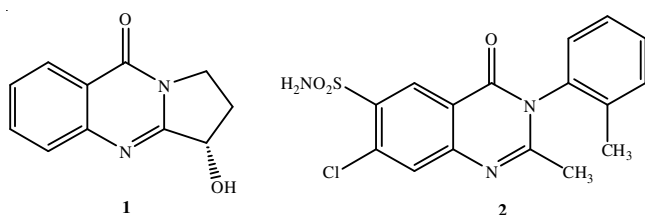
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Novel 2-[N'-(1,3-disubstituted-phenyl)allylidene]hydrazine-3-ethyl-3H-quinazolin-4-one (**8**) and 2-(3,5-disubstituted-phenyl-4,5-dihydropyrazol-1-yl)-3-ethyl-3H-quinazolin-4-one (**9**) compounds have been prepared and tested for antibacterial and antifungal activities. ¹H NMR, ¹³C NMR, elemental analysis and mass spectroscopy methods have been used to identify molecular structures of the newly synthesized compounds. For screening antibacterial and antifungal activities of the new compounds, minimum inhibitory concentration (MIC) values were evaluated against the *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Candida albicans*, *Candida parapsilosis* and *Candida krusei* using microdilution broth method. Compounds **8a-8h** exhibited the best antibacterial activity against *E. faecalis*.

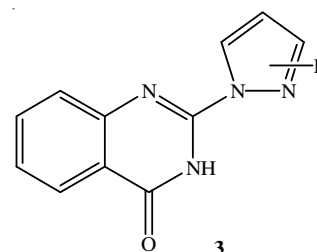
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INTRODUCTION

The 4-(3H)quinazolinone compounds are a class of heterocyclic compounds that have wide variety of biological activities¹⁻⁴. The biological importance of these heterocyclics has lead synthetic organic chemists to explore new synthetic routes and thus their syntheses are available in literature⁵⁻⁷. A brief search on the pharmaceutical activities of quinazolin-4(3H)-ones showed antiinflammatory⁸, antitumor⁹, anti HIV¹⁰, antibacterial¹¹, CNS depressant¹² and anticonvulsant^{12,13} activities. 3H-Quinazolin-4-one framework is commonly found unit in natural product alkaloids, such as L-vasicinone (**1**)¹⁴ and drugs such as diuretic and antihypertensive metolazone (**2**)¹⁵. On the other hand, it was found that not only quinazolinones showed diverse biological activities, but also pyrazole moiety possesses some important activities. Pyrazolines are five-membered heterocyclics having two adjacent nitrogen atoms within the ring and display a wide spectrum of pharmacological activities¹⁶.



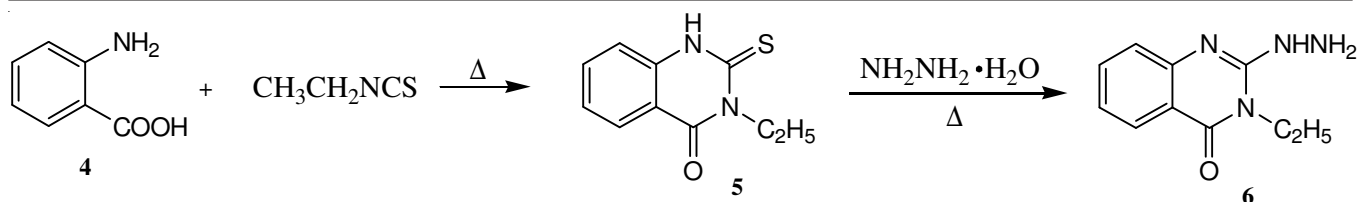
Pyrazolyl-4(3H)quinazolinones were also synthesized and screened for some biological activities^{17,18}. 2-(1H-pyrazol-1-yl)-4-(3H)quinazolinones possess antitubercular, antihistaminic, platelet aggregation inhibitor and microbicidal activities (**3**)¹⁹.



In view of the broad spectrum of pharmacological activity of quinazolinone derivatives, we previously published certain substituted quinazolinone derivatives¹⁸. In this work, we aimed to synthesize some new 2-(N'-allylidene-hydrazino)quinazolinone and 2-(4,5-dihydropyrazolyl)quinazolinone compounds and investigate their antimicrobiological activities.

EXPERIMENTAL

2-Thioxoquinazolinone molecule which was formed from antranilic acid^{18,20}, was used as starting material in this chemistry. 2-Thioxoquinazolinones could also be prepared from 2-amino-benzoic acid methyl ester^{21,22} and isatoic anhydride²³. In our



Scheme-I: Synthesis of 3-ethyl-2-hydrazino-3H-quinazolin-4-one (6)

synthetic procedure 3-ethyl-2-thio-2,3-dihydro-1H-quinazolin-4-one (5) was synthesized by refluxing anthranilic acid (4) and ethyl isothiocyanate and then 5 was transformed to 3-ethyl-2-hydrazino-3H-quinazolin-4-one (6) by refluxing with hydrazine hydrate^{18,24} (**Scheme-I**).

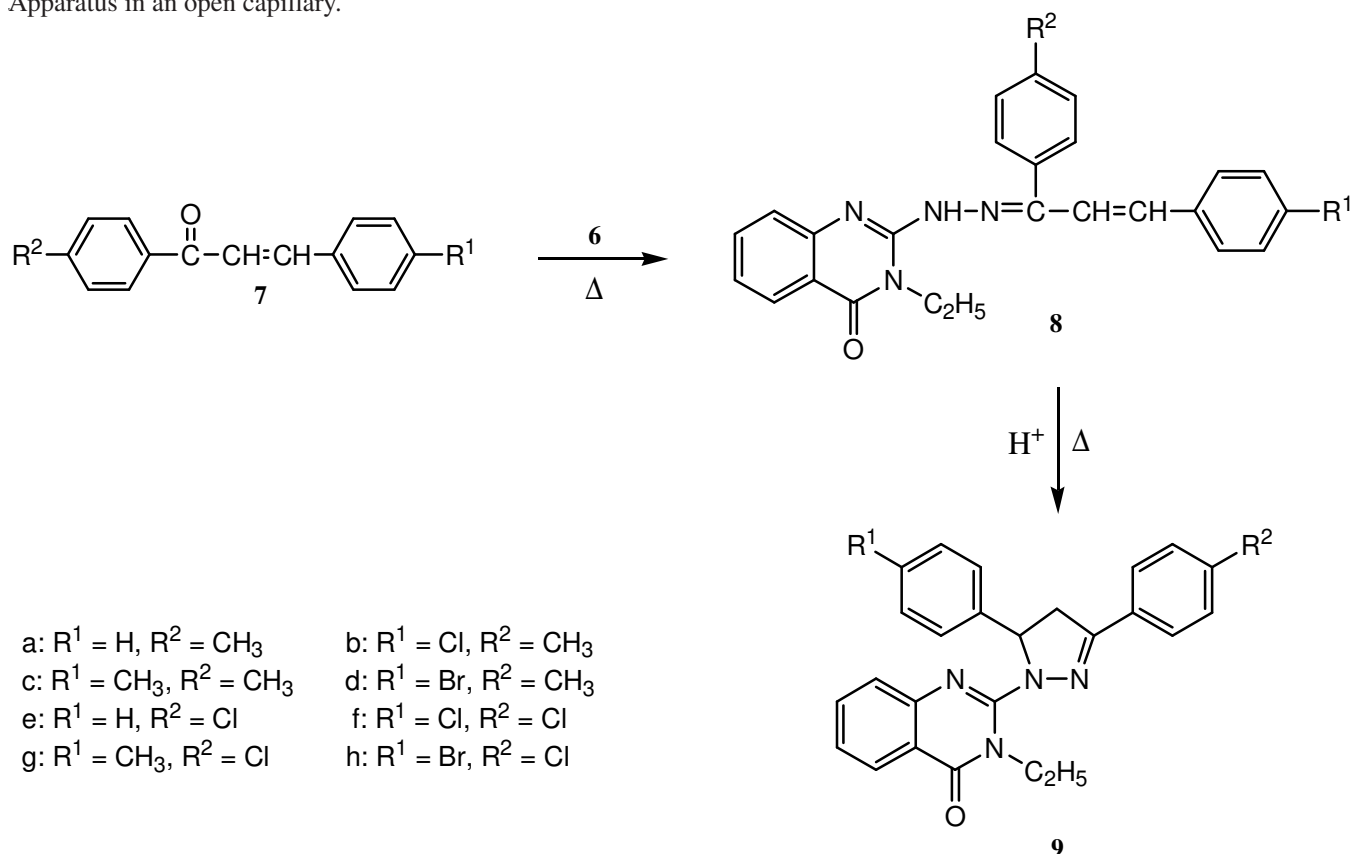
Various α,β -unsaturated ketones (7) was further reacted with 6 to give hydrazino-3-ethyl-4(3H)quinazolinone (8) derivatives. In the last step 2-[3,5-bis-(substituted-phenyl)-4,5-dihydro-pyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9) compounds were produced by refluxing hydrazone derivatives in anhydrous acetic acid (**Scheme-II**).

All reagents were of commercial quality and reagent quality solvents were used without further purification. ¹H and ¹³C NMR spectra were determined on a Bruker DPX 400 MHz FT spectrometer. Mass spectra were obtained on an Agilent 5973 Network Mass Selective Detector via HPP7-M Direct Insertion Probe. IR spectra (KBr) were recorded on a Shimadzu FT-IR DR-8001 FT infrared spectrophotometer. The purity of the compounds was assessed by thin layer chromatography on silica gel 60 F254. Column chromatography was conducted on silica gel 60 (mesh size 0.063-0.200 mm). Melting points were measured on a Thomas Hoover Capillary Melting Point Apparatus in an open capillary.

The starting materials, 3-ethyl-2-thio-2,3-dihydro-1H-quinazolin-4-one 5²⁵, 3-ethyl-2-hydrazino-3H-quinazolin-4-one 6^{26,27} and α,β -unsaturated ketone derivatives (chalcones) 7^{28,29}, were prepared according to the methods given in the literature.

2-[N'-(1,3-diphenyl-allylidene)-hydrazino]-3-ethyl-3H-quinazolin-4-ones (8): A mixture of 7 (1 mmol) and 3-ethyl-2-hydrazino-3H-quinazolin-4-one (6) (204 mg, 1 mmol) and 2 mL of acetic acid in *n*-propanol (100 mL) was stirred under reflux for 4-7 h. After the reaction was cooled to room temperature, the resulting residue was filtered, washed with *n*-propanol and dried. Recrystallization of the crude product from ethanol gave 8 as a yellow solid.

2-(3,5-Diphenyl-4,5-dihydro-pyrazol-1-yl)-3-ethyl-3H-quinazolin-4-ones (9): A solution of 2-[N'-(1,3-diphenyl-allylidene)hydrazino]-3-ethyl-3H-quinazolin-4-one (8) (0.5 mmol) in glacial acetic acid was stirred under reflux for 72 h. The resulting solution was poured into ice-water, neutralized with concentrated NaOH solution and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and evaporated to dryness to yield the oily residue. The crude product was further purified by chromatography



Scheme-II: Synthesis of new 2-(4,5-dihydropyrazolyl)quinazolinones

on a silica gel column (elution with chloroform) followed by crystallization from diethyl ether to give **9** as a white solid.

Antimicrobial activity: Minimum inhibitory concentrations (MICs) were tested by microdilution broth method recommended by Clinical and Laboratory Standards Institute (CLSI)^{30,31}. According to these procedure, antibacterial activity was determined against following microorganisms: *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853). The following yeast-like fungi were used for antifungal activity studies: *Candida albicans* (ATCC 90028), *Candida parapsilosis* (ATCC 90018) and *C. krusei* (ATCC 6258).

The stock solutions of the synthesized compounds were prepared in dimethyl sulfoxide (DMSO). Test was performed in Mueller-Hinton Broth (MHB) (BBL, MD, USA) for bacteria. Fungi were cultivated in Sabouraud Dextrose Agar (SDA) (Merck). RPMI-1640 medium (ICN-Flow, Aurora, OH-USA) with L-glutamin, buffered with 3-(N-morpholino)propane sulphonic acid (MOPS) (Buffer-ICN-Flow, Aurora, OH-USA) at pH = 7.4 was used as the test medium. The final inoculum densities were 5×10^5 cfu/mL for bacteria and $0.5\text{-}2.5 \times 10^3$ cfu/mL for fungi. The dilutions in the test medium were prepared in the wells of the microtiter plates at the required concentration of 1024-1.0 $\mu\text{g/mL}$ and for reference compounds at 64-0.0625 $\mu\text{g/mL}$. Fluconazole and ciprofloxacin were used as the reference compounds for fungi and bacteria, respectively. The microtiter plates were incubated at 35 °C for 18-24 h for bacteria and 48 h for fungi. MICs were defined as the lowest concentration of the compound that inhibited visible growth of the microorganisms. It was established that dilution of DMSO lacked antimicrobial activity against any of the test microorganisms.

RESULTS AND DISCUSSION

New quinazolinone compounds have been synthesized and their structures were proven by ¹H- and ¹³C NMR, mass spectra, elemental analysis and all spectral data are in accordance with

the assigned structures. The first step involves the ring closure reaction to form 2-thioxoquinazoline which in turn converted to 2-hydrazinoquinazoline *via* nucleophilic addition and then elimination reaction. Amino group of **6** gives 1,4-addition reaction with α,β -unsaturated ketones (**7**) to afford hydrazone (**8**) derivatives. Acid catalyzed pyrazole ring formation occurs with subsequent addition of NH group on olefinic bond to give 2-pyrazolylquinazolinones (**9**). In the ¹H NMR spectra of the compounds **5**, olefinic protons (2'-CH and 3'-CH) appeared as doublets at about 6.63-6.93 and 7.82-8.10 ppm, respectively ($J_{trans} = 16.2\text{-}16.8$ Hz). After the ring closure, ring protons (4'-CH_a and 4'-CH_b) of the compounds **9** showed double doublets at around 3.59-3.78 ($J_{dd} = 11.2\text{-}11.4$ and $16.8\text{-}17.0$ Hz) and 3.16-3.32 ppm ($J_{dd} = 12.0$ and $16.8\text{-}17.0$ Hz) and also 5'-CH gave triplet at about 5.79-5.96 ppm ($J_i = 11.2\text{-}12.0$ Hz) due to vicinal coupling with the two magnetically nonequivalent protons of the methylene group. The quinazolinone and phenyl protons were observed at the expected chemical shifts and integral values. In the ¹³C NMR spectra of the compound **8c**, olefinic carbons (2'-C and 3'-C) appeared at 138.69 and 119.84 ppm respectively. After the ring closure, ring carbons (5'-C and 4'-C) of compound **9c** gave signals at 62.88 and 40.85 ppm, respectively. In the ESI-MS spectra, molecular ion [M]⁺ peaks, which were the base peaks, provided the molecular formula of all synthesized compounds **8a-8h** and **9a-9h**. Microanalysis results are within ± 0.4 % of the theoretical values.

Antimicrobial activity studies: Antifungal and antibacterial activities of the 2-thioxoquinazolinone (**5**), 2-hydrazinoquinazolinone (**6**), 2-(N'-allylidene-hydrazino)quinazolinone (**8**) and 2-(4,5-dihydropyrazolyl)quinazolinone (**9**) compounds were tested by microdilution broth method as MIC values. The MIC values of the compounds are presented in the Table-1. These results indicate that compounds **8a** through **8h** showed the best antibacterial activity against gram positive bacteria, especially *E. faecalis*. However compounds **8d** and **8h** had no significant activity against *S. aureus*. All compounds showed similar antifungal activity. Their antifungal activity was not

TABLE-1

ANTIFUNGAL AND ANTIBACTERIAL ACTIVITIES OF 2-THIOXOQUINAZOLINONE (5), 2-HYDRAZINOQUINAZOLINONE (6), 2-(N'-ALLYLIDENE-HYDRAZINO)-QUINAZOLINONES (8) AND 2-(4,5-DIHYDROPIRAZOLYL)-QUINAZOLINONES (9) (MIC in $\mu\text{g/mL}$)

Compound No.	<i>S. aureus</i> ATCC 29213	<i>E. faecalis</i> ATCC 29212	<i>E. coli</i> ATCC 25922	<i>P. aeruginosa</i> ATCC 27853	<i>C. albicans</i> ATCC 90028	<i>C. krusei</i> ATCC 6258	<i>C. parapsilosis</i> ATCC 90018
5	256	256	256	256	32	128	128
6	64	128	256	256	ND	64	128
8a	128	32	256	512	ND	128	128
8b	128	16	256	256	ND	128	128
8c	128	16	256	256	64	128	128
8d	>1024	64	1024	1024	256	256	128
8e	128	256	512	256	128	128	128
8f	64	32	256	256	128	128	256
8g	256	32	256	256	128	128	256
8h	1024	64	256	512	128	128	128
9c	512	512	256	512	128	128	128
9d	512	>1024	512	>1024	1024	128	128
9e	512	>1024	1024	1024	64	128	128
9h	1024	128	512	256	32	256	64
Ciprofloxacin	0.5	2	0.015	1	-	-	-
Fluconazole	-	-	-	-	0.25	16	1

ND: not done

promising, but compound **9h** seem to possess activity with the higher MIC values, except for *C. krusei* strain.

A new series of 2-[N'-(1,3-diphenyl-allylidene)-hydrazino]-3-ethyl-3H-quinazolin-4-one (**8**) and 2-(3,5-diphenyl-4,5-dihydro-pyrazol-1-yl)-3-ethyl-3H-quinazolin-4-one (**9**) compounds have been synthesized and screened for their antibacterial [*Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853)] and antifungal [*Candida albicans* (ATCC 90028), *Candida parapsilosis* (ATCC 90018) and *C. krusei* (ATCC 6258)] activities. **8** compounds were found most effective on bacteria *E. faecalis* with the higher MIC values whereas **9h** was most effective on *C. albicans* and *C. parapsilosis* fungies. With these results in our hand, future work is aimed to be done for the synthesis and activity studies of new quinazolinone compounds.

3-Ethyl-2-[N'-(3-phenyl-1-p-tolyl-allylidene)hydrazino]-3H-quinazolin-4-one (8a): Obtained according to the general procedure, by using **7a** (222 mg, 1.0 mmol), as a white solid (335 mg, 82 %); m.p. 163-164 °C; R_f 0.35 (CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 9.40 (1H, br-s, NH), 8.10 (1H, d, J = 8.4 Hz, 5-CH), 8.00 (1H, d, J = 16.8 Hz, 3'-CH), 7.51 (2H, d, J = 8.0 Hz, 2 × CH(Ar)), 7.48 (1H, t, J = 7.6 Hz, 7-CH), 7.30 (7H, m, 7 × CH(Ar)), 7.09 (1H, t, J = 7.6 Hz, 6-CH), 6.93 (1H, d, J = 8.0 Hz, 8-CH), 6.86 (1H, d, J = 16.4, 2'-CH), 4.37 (2H, q, J = 7.0 Hz, NCH₂CH₃), 2.50 (3H, s, PhCH₃), 1.48 (3H, t, J = 7.0 Hz, NCH₂CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ_C 160.85 (4-C), 160.17 (1'-C), 148.94 (2-C), 138.68 (2'-C), 136.91, 135.26, 134.70, 129.50, 129.34, 128.99, 128.91, 128.82, 128.39, 127.38, 127.16, 122.20 (Ar-C), 120.81 (3'-C), 36.59 (NCH₂CH₃), 21.41 (PhCH₃), 12.59 (NCH₂CH₃); MS (EI) m/z 408.2 (M⁺, 100 %); Anal. calcd. for C₂₆H₂₄N₄O: C, 76.45; H, 5.92; N, 13.72. Found: C, 76.74; H, 6.28; N, 13.97 %.

2-{N'-[3-(4-Chlorophenyl)-1-p-tolyl-allylidene]hydrazino}-3-ethyl-3H-quinazolin-4-one (8b): Obtained according to the general procedure, by using **7b** (256 mg, 1.0 mmol), as a white solid (349 g, 79 %); m.p. 178-179 °C; R_f 0.38 (CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 9.44 (1H, br-s, NH), 8.15 (1H, d, J = 8.0 Hz, 5-CH), 8.05 (1H, d, J = 16.6 Hz, 3'-CH), 7.56 (2H, d, J = 7.6 Hz, 2 × CH(Ar)), 7.55 (1H, t, J = 7.7 Hz, 7-CH), 7.37 (2H, d, J = 7.8 Hz, 2 × CH(Ar)), 7.32 (2H, d, J = 8.1 Hz, 2 × CH(Ar)), 7.23 (2H, d, J = 8.0 Hz, 2 × CH(Ar)), 7.14 (1H, t, J = 7.6 Hz, 6-CH), 7.03 (1H, d, J = 8.1 Hz, 8-CH), 6.90 (1H, d, J = 16.6, 2'-CH), 4.36 (2H, q, J = 6.8 Hz, NCH₂CH₃), 2.42 (3H, s, PhCH₃), 1.45 (3H, t, J = 6.8 Hz, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 160.51 (4-C), 159.85 (1'-C), 148.98 (2-C), 138.57 (2'-C), 135.30, 134.94, 134.77, 132.90, 129.38, 129.23, 129.06, 128.54, 128.49, 126.85, 122.84, 122.37 (Ar-C), 121.14 (3'-C), 36.75 (NCH₂CH₃), 21.42 (PhCH₃), 12.58 (NCH₂CH₃); MS (EI) m/z 442.1 (M⁺, 100 %), 444.1; Anal. Calcd. for C₂₆H₂₃N₄OCl: C, 70.50; H, 5.23; N, 12.65. Found: C, 70.85; H, 5.49; N, 12.93 %.

2-[N'-(1,3-Di-p-tolylallylidene)hydrazino]-3-ethyl-3H-quinazolin-4-one (8c): Obtained according to the general procedure, by using **7c** (236 g, 1.0 mmol), as a white solid (380 mg, 90 %); m.p. 172-173 °C; R_f 0.40 (CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 9.43 (1H, br-s, NH), 8.13 (1H, d, J =

7.9 Hz, 5-CH), 8.06 (1H, d, J = 16.4 Hz, 3'-CH), 7.58 (2H, d, J = 8.0 Hz, 2 × CH(Ar)), 7.53 (1H, t, J = 7.0 Hz, 7-CH), 7.44 (2H, d, J = 8.0 Hz, 2 × CH(Ar)), 7.32 (2H, d, J = 7.8 Hz, 2 × CH(Ar)), 7.22 (2H, d, J = 7.9 Hz, 2 × CH(Ar)), 7.13 (1H, t, J = 7.4 Hz, 6-CH), 7.00 (1H, d, J = 8.1 Hz, 8-CH), 6.93 (1H, d, J = 16.6, 2'-CH), 4.38 (2H, q, J = 7.0 Hz, NCH₂CH₃), 2.49 (3H, s, PhCH₃), 2.41 (3H, s, PhCH₃), 1.47 (3H, t, J = 7.0 Hz, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 160.84 (4-C), 160.44 (1'-C), 148.80 (2-C), 138.69 (2'-C), 135.22, 134.68, 134.12, 129.56, 129.38, 128.96, 128.38, 127.36, 122.17 (Ar-C), 119.84 (3'-C), 36.57 (NCH₂CH₃), 21.40 (PhCH₃), 12.58 (NCH₂CH₃); MS (EI) m/z 422.2 (M⁺, 100 %); Anal. Calcd. for C₂₇H₂₆N₄O: C, 76.75; H, 6.20; N, 13.26. Found: C, 76.98; H, 6.51; N, 13.57 %.

2-[N'-[3-(4-Bromophenyl)-1-p-tolyl-allylidene]hydrazino]-3-ethyl-3H-quinazolin-4-one (8d): Obtained according to the general procedure, by using **7d** (301 mg, 1.0 mmol), as a white solid (418 g, 86 %); m.p. 185-186 °C; R_f 0.36 (CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 9.26 (1H, br-s, NH), 8.07 (1H, d, J = 7.6 Hz, 5-CH), 8.00 (1H, d, J = 16.7 Hz, 3'-CH), 7.50 (1H, t, J = 7.2 Hz, 7-CH), 7.47 (4H, d, J = 8.3 Hz, 4 × CH(Ar)), 7.33 (2H, d, J = 8.4 Hz, 2 × CH(Ar)), 7.24 (2H, d, J = 8.0 Hz, 2 × CH(Ar)), 7.08 (1H, t, J = 7.6 Hz, 6-CH), 6.93 (1H, d, J = 8.1 Hz, 8-CH), 6.78 (1H, d, J = 16.7, 2'-CH), 4.31 (2H, q, J = 7.0 Hz, NCH₂CH₃), 2.44 (3H, s, PhCH₃), 1.41 (3H, t, J = 7.0 Hz, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 160.42 (4-C), 159.37 (1'-C), 149.11 (2-C), 138.69 (2'-C), 136.78, 135.90, 134.48, 132.15, 131.95, 129.67, 129.29, 129.22, 128.93, 128.65, 128.57, 122.77 (Ar-C), 122.14 (3'-C), 36.44 (NCH₂CH₃), 21.42 (PhCH₃), 12.64 (NCH₂CH₃); MS (EI) m/z 486.1 (M⁺, 100 %), 488.1; Anal. Calcd. for C₂₆H₂₃N₄OBr: C, 64.07; H, 4.76; N, 11.50. Found: C, 64.39; H, 5.12; N, 11.83 %.

2-{N'-[1-(4-Chlorophenyl)-3-phenyl-allylidene]hydrazino}-3-ethyl-3H-quinazolin-4-one (8e): Obtained according to the general procedure, by using **7e** (242 mg, 1.0 mmol), as a white solid (325 g, 76 %); m.p. 191-192 °C; R_f 0.38 (CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 9.43 (1H, br-s, NH), 8.14 (1H, d, J = 7.9 Hz, 5-CH), 8.10 (1H, d, J = 16.7 Hz, 3'-CH), 7.62 (2H, d, J = 8.5 Hz, 2 × CH(Ar)), 7.54 (3H, m, 7-CH and 2 × CH(Ar)), 7.48 (2H, d, J = 8.5 Hz, 2 × CH(Ar)), 7.42 (2H, t, J = 6.9 Hz, 2 × CH(Ar)), 7.38 (1H, t, J = 7.0 Hz, 2 × CH(Ar)), 7.16 (1H, t, J = 8.0 Hz, 6-CH), 7.04 (1H, d, J = 8.0 Hz, 8-CH), 6.91 (1H, d, J = 16.8, 2'-CH), 4.37 (2H, q, J = 7.0 Hz, NCH₂CH₃), 1.45 (3H, t, J = 7.0 Hz, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 160.13 (4-C), 159.23 (1'-C), 149.35 (2-C), 138.83 (2'-C), 136.65, 135.27, 134.41, 130.60, 129.56, 129.43, 129.31, 129.01, 128.80, 128.46, 128.38, 128.14, 127.92, 127.33, 122.13 (Ar-C), 120.42 (3'-C), 36.56 (NCH₂CH₃), 12.45 (NCH₂CH₃); MS (EI) m/z 428.1 (M⁺, 100 %), 430.1; Anal. Calcd. for C₂₅H₂₁N₄OCl: C, 70.01; H, 4.93; N, 13.06. Found: C, 70.29; H, 5.27; N, 13.23 %.

2-[N'-[1,3-bis-(4-Chlorophenyl)allylidene]hydrazino]-3-ethyl-3H-quinazolin-4-one (8f): Obtained according to the general procedure, by using **7f** (277 m, 1.0 mmol), as a white solid (374 mg, 81 %); m.p. 206-207 °C; R_f 0.36 (CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 9.13 (1H, br-s, NH), 7.92 (1H, d, J = 7.9 Hz, 5-CH), 7.82 (1H, d, J = 16.7 Hz, 3'-CH), 7.57 (1H, t, J = 7.1 Hz, 7-CH), 7.39 (2H, d, J = 8.5 Hz, 2 × CH(Ar)),

7.27 (2H, d, $J = 8.5$ Hz, $2 \times CH(Ar)$), 7.23 (2H, d, $J = 8.7$ Hz, $2 \times CH(Ar)$), 7.16 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 6.95 (1H, t, $J = 7.2$ Hz, 6-CH), 6.81 (1H, d, $J = 8.2$ Hz, 8-CH), 6.63 (1H, d, $J = 16.7$, 2'-CH), 4.15 (2H, q, $J = 7.0$ Hz, NCH_2CH_3), 1.23 (3H, t, $J = 7.0$ Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.36 (4-C), 158.20 (1'-C), 149.45 (2-C), 138.44 (2'-C), 136.78, 135.18, 134.80, 130.53, 129.84, 129.54, 129.29, 129.08, 128.94, 128.60, 128.48, 128.38, 128.00, 127.93, 122.34 (Ar-C), 120.99 (3'-C), 36.49 (NCH_2CH_3), 12.63 (NCH_2CH_3); MS (EI) m/z 462.1 (M^+ , 100 %), 464.1, 466.1; Anal. Calcd. for $C_{25}H_{20}N_4OCl_2$: C, 64.80; H, 4.35; N, 12.09. Found: C, 65.16; H, 4.72; N, 12.30 %.

2-{N'-[1,3-bis-(4-Chlorophenyl)allylidene]hydrazino}-3-ethyl-3H-quinazolin-4-one (8g): Obtained according to the general procedure, by using **7g** (256 g, 1.0 mmol), as a white solid (324 mg, 74 %); m.p. 182-183 °C; R_f 0.39 ($CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 9.48 (1H, br-s, NH), 8.13 (1H, d, $J = 7.9$ Hz, 5-CH), 7.83 (1H, d, $J = 16.2$ Hz, 3'-CH), 7.55 (1H, t, $J = 8.0$ Hz, 7-CH), 7.57 (2H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 7.43 (2H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 7.26 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.22 (2H, d, $J = 7.9$ Hz, $2 \times CH(Ar)$), 7.15 (1H, t, $J = 8.0$ Hz, 6-CH), 7.05 (1H, d, $J = 8.2$ Hz, 8-CH), 6.89 (1H, d, $J = 16.6$, 2'-CH), 4.37 (2H, q, $J = 7.0$ Hz, NCH_2CH_3), 2.43 (3H, s, $PhCH_3$), 1.45 (3H, t, $J = 7.0$ Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.41 (4-C), 158.86 (1'-C), 149.15 (2-C), 138.96 (2'-C), 138.55, 138.41, 136.81, 134.82, 134.49, 133.95, 130.62, 129.54, 128.58, 128.40, 127.30, 122.19 (Ar-C), 119.59 (3'-C), 36.48 (NCH_2CH_3), 21.63 ($PhCH_3$), 12.68 (NCH_2CH_3); MS (EI) m/z 442.1 (M^+ , 100 %), 444.1; Anal. Calcd. for $C_{26}H_{23}N_4OCl$: C, 70.50; H, 5.23; N, 12.65. Found: C, 70.84; H, 5.57; N, 13.01 %.

2-{N'-[3-(4-Bromophenyl)-1-(4-chlorophenyl)-allylidene]hydrazino}-3-ethyl-3H-quinazolin-4-one (8h): Obtained according to the general procedure, by using **7h** (321 mg, 1.0 mmol), as a white solid (430 mg, 85 %); m.p. 218-219 °C; R_f 0.30 ($CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 9.24 (1H, br-s, NH), 8.07 (1H, d, $J = 7.9$ Hz, 5-CH), 8.00 (1H, d, $J = 16.7$ Hz, 3'-CH), 7.52 (1H, t, $J = 7.0$ Hz, 7-CH), 7.44 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 7.41 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 7.28 (2H, d, $J = 8.3$ Hz, $2 \times CH(Ar)$), 7.26 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 7.10 (1H, t, $J = 7.6$ Hz, 6-CH), 7.02 (1H, d, $J = 8.1$ Hz, 8-CH), 6.75 (1H, d, $J = 16.8$, 2'-CH), 4.32 (2H, q, $J = 7.0$ Hz, NCH_2CH_3), 1.41 (3H, t, $J = 7.0$ Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.21 (4-C), 159.81 (1'-C), 149.03 (2-C), 138.42 (2'-C), 135.50, 135.24, 134.57, 134.11, 132.04, 131.89, 130.75, 130.53, 130.27, 128.68, 128.49, 128.28, 127.94, 122.43 (Ar-C), 122.36 (3'-C), 36.32 (NCH_2CH_3), 12.47 (NCH_2CH_3); MS (EI) m/z 506.0 (M^+ , 100 %), 508.0; Anal. Calcd. for $C_{25}H_{20}N_4OClBr$: C, 59.13; H, 3.97; N, 11.03. Found: C, 59.42; H, 4.35; N, 11.38 %.

3-Ethyl-2-(5-phenyl-3-*p*-tolyl-4,5-dihydropyrazol-1-yl)-3H-quinazolin-4-one (9a): Obtained according to the general procedure, by using **8a** (102 mg, 0.5 mmol), as a white solid (173 g, 85 %); m.p. 125-126 °C; R_f 0.39 ($CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 8.00 (1H, d, $J = 8.0$ Hz, 5-CH), 7.51 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.55 (1H, t, $J = 8.4$ Hz, 7-CH), 7.44 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.39 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.35 (1H, d, $J = 8.0$ Hz, 8-CH), 7.25 (1H, t, $J = 7.6$ Hz, 6-CH), 7.21 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$),

5.94 (1H, t, $J = 11.2$ Hz, 5'-CH), 4.40 (2H, q, $J = 7.0$ Hz, NCH_2CH_3), 3.75 (1H, dd, $J = 11.2$ and 17.0 Hz, 4'-CH_a), 3.21 (1H, dd, $J = 12.0$ and 16.9 Hz, 4'-CH_b), 2.35 (3H, s, $PhCH_3$), 1.48 (3H, t, $J = 7.0$ Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.48 (4-C), 151.85 (2-C), 149.42 (3'-C), 136.91, 135.26, 134.70, 129.50, 129.34, 128.99, 128.91, 128.82, 128.39, 127.38, 127.16, 122.20 (Ar-C), 63.57 (5'-C), 40.43 (4'-C), 36.65 (NCH_2CH_3), 21.51 ($PhCH_3$), 13.73 (NCH_2CH_3); MS (EI) m/z 408.2 (M^+ , 100 %); Anal. Calcd. for $C_{26}H_{24}N_4O$: C, 76.45; H, 5.92; N, 13.72. Found: C, 76.79; H, 6.27; N, 14.05 %.

2-[5-(4-Chlorophenyl)-3-*p*-tolyl-4,5-dihydropyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9b): Obtained according to the general procedure, by using **8b** (221 mg, 0.5 mmol), as a white solid (181 g, 82 %); m.p. 152-153 °C; R_f 0.42 ($CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (1H, d, $J = 8.1$ Hz, 5-CH), 7.64 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.59 (1H, t, $J = 7.6$ Hz, 7-CH), 7.45 (2H, d, $J = 8.3$ Hz, $2 \times CH(Ar)$), 7.39 (2H, d, $J = 7.8$ Hz, $2 \times CH(Ar)$), 7.32 (2H, d, $J = 8.1$ Hz, 8-CH), 7.19 (1H, t, $J = 7.6$ Hz, 6-CH), 7.07 (2H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 5.93 (1H, t, $J = 11.2$ Hz, 5'-CH), 4.36 (2H, q, $J = 6.8$ Hz, NCH_2CH_3), 3.59 (1H, dd, $J = 11.2$ and 17.0 Hz, 4'-CH_a), 3.29 (1H, dd, $J = 12.0$ and 16.8 Hz, 4'-CH_b), 2.48 (3H, s, $PhCH_3$), 1.45 (3H, t, $J = 6.8$ Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.04 (4-C), 152.43 (2-C), 148.56 (3'-C), 136.30, 135.94, 135.77, 131.90, 128.38, 128.23, 128.06, 127.54, 127.49, 125.85, 121.84, 121.37 (Ar-C), 62.63 (5'-C), 40.71 (4'-C), 36.23 (NCH_2CH_3), 20.98 ($PhCH_3$), 13.08 (NCH_2CH_3); MS (EI) m/z 442.1 (M^+ , 100 %), 444.1; Anal. Calcd. for $C_{26}H_{23}N_4OCl$: C, 70.50; H, 5.23; N, 12.65. Found: C, 70.83; H, 5.58; N, 12.93 %.

2-(3,5-Di-*p*-tolyl-4,5-dihydropyrazol-1-yl)-3-ethyl-3H-quinazolin-4-one (9c): Obtained according to the general procedure, by using **8c** (211 mg, 0.5 mmol), as a white solid (205 mg, 97 %); m.p. 136-137 °C; R_f 0.35 ($CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (1H, d, $J = 7.9$ Hz, 5-CH), 7.58 (2H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 7.54 (1H, t, $J = 8.0$ Hz, 7-CH), 7.38 (2H, d, $J = 7.9$ Hz, $2 \times CH(Ar)$), 7.37 (1H, m, 8-CH), 7.21 (1H, m, 6-CH), 7.20 (1H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 7.10 (1H, d, $J = 7.9$ Hz, $2 \times CH(Ar)$), 5.92 (1H, t, $J = 11.6$ Hz, 5'-CH), 4.46 (2H, q, $J = 6.9$ Hz, NCH_2CH_3), 3.68 (1H, dd, $J = 11.2$ and 17.0 Hz, 4'-CH_a), 3.19 (1H, dd, $J = 12.0$ and 17.0 Hz, 4'-CH_b), 2.40 (3H, s, $PhCH_3$), 2.30 (3H, s, $PhCH_3$), 1.54 (3H, t, $J = 6.9$ Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.47 (4-C), 151.81 (2-C), 148.43 (3'-C), 136.20, 132.65, 129.59, 128.53, 128.35, 128.27, 126.52, 126.08, 125.47, 125.05, 123.56, (Ar-C), 62.88 (5'-C), 40.85 (4'-C), 39.87 (NCH_2CH_3), 20.60 ($PhCH_3$), 20.23 ($PhCH_3$), 13.45 (NCH_2CH_3); MS (EI) m/z 422.2 (M^+ , 100 %); Anal. Calcd. for $C_{27}H_{26}N_4O$: C, 76.75; H, 6.20; N, 13.26. Found: C, 77.06; H, 6.51; N, 13.51 %.

2-[5-(4-Bromophenyl)-3-*p*-tolyl-4,5-dihydro-pyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9d): Obtained according to the general procedure, by using **8d** (243 mg, 0.5 mmol), as a white solid (231 g, 95 %); m.p. 174-175 °C; R_f 0.42 ($CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 8.00 (1H, d, $J = 8.0$ Hz, 5-CH), 7.58 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.55 (1H, t, $J = 8.4$ Hz, 7-CH), 7.44 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.39 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.35 (1H, d, $J = 8.0$ Hz, 8-CH), 7.25

(1H, t, $J = 7.6$ Hz, 6-CH), 7.21 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 5.94 (1H, t, $J = 11.2$ Hz, 5'-CH), 4.46 (2H, q, $J = 6.8$ Hz, NCH_2CH_3), 3.70 (1H, dd, $J = 11.2$ and 17.0 Hz, 4'-CH_a), 3.16 (1H, dd, $J = 12.0$ and 16.8 Hz, 4'-CH_b), 2.41 (3H, s, $PhCH_3$), 2.30 (3H, s, $PhCH_3$), 1.55 (3H, t, $J = 7.2$ Hz, NCH_2CH_3); ¹³C NMR (100 MHz, $CDCl_3$) δ_C 162.24 (4-C), 151.73 (2-C), 149.31 (3'-C), 135.46, 133.90, 132.01, 131.80, 129.50, 129.43, 129.30, 129.18, 129.12, 128.96, 128.50, 126.98, 126.41, 125.79, 124.46, 122.36 (Ar-C), 63.38 (5'-C), 40.35 (4'-C), 36.95 (NCH_2CH_3), 21.42 ($PhCH_3$), 13.92 (NCH_2CH_3); MS (EI) m/z 486.1 (M^+ , 100 %), 488.1; Anal. Calcd. for $C_{26}H_{23}N_4OBr$: C, 64.07; H, 4.76; N, 11.50. Found: C, 64.36; H, 4.97; N, 11.83 %.

2-[3-(4-Chlorophenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9e): Obtained according to the general procedure, by using **8e** (214 mg, 0.5 mmol), as a white solid (199 mg, 93 %); m.p. 165-166 °C; R_f 0.43 ($CHCl_3$); ¹H NMR (400 MHz, $CDCl_3$) δ_H 8.14 (1H, d, $J = 8.0$ Hz, 5-CH), 7.63 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.55 (1H, t, $J = 8.0$ Hz, 7-CH), 7.49 (2H, d, $J = 7.2$ Hz, $2 \times CH(Ar)$), 7.40 (1H, m, 8-CH) 7.40 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.32 (2H, t, $J = 7.6$ Hz, $2 \times CH(Ar)$), 7.25 (1H, t, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.25 (1H, t, $J = 8.0$, 6-CH), 6.03 (1H, t, $J = 11.4$ Hz, 5'-CH), 4.46 (2H, q, $J = 6.9$ Hz, NCH_2CH_3), 3.71 (1H, dd, $J = 11.3$ and 16.9 Hz, 4'-CH_a), 3.21 (1H, dd, $J = 12.0$ and 16.9 Hz, 4'-CH_b), 1.54 (3H, t, $J = 6.9$ Hz, NCH_2CH_3); ¹³C NMR (100 MHz, $CDCl_3$) δ_C 162.89 (4-C), 151.95 (2-C), 148.96 (3'-C), 136.12, 133.81, 130.49, 130.06, 129.65, 129.09, 128.83, 128.69, 127.87, 127.56, 127.34, 127.21, 127.02, 125.72, 124.86 (Ar-C), 64.27 (5'-C), 41.67 (4'-C), 40.89 (NCH_2CH_3), 14.37 (NCH_2CH_3); MS (EI) m/z 428.1 (M^+ , 100 %), 430.1; Anal. Calcd. for $C_{25}H_{21}N_4OCl$: C, 70.01; H, 4.93; N, 13.06. Found: C, 70.29; H, 5.34; N, 13.32 %.

2-[3,5-bis-(4-Chlorophenyl)-4,5-dihydro-pyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9f): Obtained according to the general procedure, by using **8f** (231 mg, 0.5 mmol), as a white solid (199 mg, 86 %); m.p. 189-190 °C; R_f 0.41 ($CHCl_3$); ¹H NMR (400 MHz, $CDCl_3$) δ_H 8.25 (1H, d, $J = 8.0$ Hz, 5-CH), 7.54 (1H, t, $J = 8.0$ Hz, 7-CH), 7.44 (1H, m, 8-CH) 7.40 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.35 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.31 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.28 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.20 (1H, t, $J = 8.0$, 6-CH), 6.12 (1H, t, $J = 11.2$ Hz, 5'-CH), 4.36 (2H, q, $J = 7.0$ Hz, NCH_2CH_3), 3.78 (1H, dd, $J = 11.2$ and 17.0 Hz, 4'-CH_a), 3.25 (1H, dd, $J = 12.0$ and 17.0 Hz, 4'-CH_b), 1.63 (3H, t, $J = 7.0$ Hz, NCH_2CH_3); ¹³C NMR (100 MHz, $CDCl_3$) δ_C 161.78 (4-C), 152.43 (2-C), 149.11 (3'-C), 136.78, 135.18, 134.80, 130.53, 129.84, 129.54, 129.29, 129.08, 128.94, 128.60, 128.48, 128.38, 128.00, 127.93, 122.34 (Ar-C), 64.36 (5'-C), 41.73 (4'-C), 40.76 (NCH_2CH_3), 13.89 (NCH_2CH_3); MS (EI) m/z 462.1 (M^+ , 100 %), 464.1, 466.1; Anal. Calcd. for $C_{25}H_{20}N_4OCl_2$: C, 64.80; H, 4.35; N, 12.09. Found: C, 65.16; H, 4.64; N, 12.33 %.

2-[3-(4-Chlorophenyl)-5-p-tolyl-4,5-dihydro-pyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9g): Obtained according to the general procedure, by using **8g** (110 mg, 0.5 mmol), as a white solid (183 mg, 83 %); m.p. 173-174 °C; R_f 0.44 ($CHCl_3$); ¹H NMR (400 MHz, $CDCl_3$) δ_H 8.14 (1H, d, $J = 7.8$ Hz, 5-CH), 7.61 (2H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 7.61 (1H, t, $J = 7.6$ Hz, 7-CH), 7.38 (2H, d, $J = 8.0$ Hz, $2 \times CH(Ar)$), 7.30

(1H, d, $J = 8.0$ Hz, 8-CH), 7.22 (1H, t, $J = 7.4$, 6-CH), 7.17 (1H, d, $J = 8.1$ Hz, $2 \times CH(Ar)$), 7.08 (1H, d, $J = 7.9$ Hz, $2 \times CH(Ar)$), 5.79 (1H, t, $J = 11.6$ Hz, 5'-CH), 4.58 (2H, q, $J = 6.9$ Hz, NCH_2CH_3), 3.74 (1H, dd, $J = 11.4$ and 17.0 Hz, 4'-CH_a), 3.32 (1H, dd, $J = 12.0$ and 17.0 Hz, 4'-CH_b), 2.37 (3H, s, $PhCH_3$), 1.63 (3H, t, $J = 6.9$ Hz, NCH_2CH_3); ¹³C NMR (100 MHz, $CDCl_3$) δ_C 162.37 (4-C), 151.73 (2-C), 148.28 (3'-C), 135.46, 134.89, 134.65, 132.79, 129.56, 129.43, 129.26, 128.66, 128.43, 126.74, 122.65, 122.25 (Ar-C), 62.66 (5'-C), 40.34 (4'-C), 39.54 (NCH_2CH_3), 20.53 ($PhCH_3$), 13.19 (NCH_2CH_3); MS (EI) m/z 442.1 (M^+ , 100 %), 444.1; Anal. Calcd. for $C_{26}H_{23}N_4OCl$: C, 70.50; H, 5.23; N, 12.65. Found: C, 70.82; H, 5.51; N, 12.88 %.

2-[5-(4-Bromophenyl)-3-(4-chloro-phenyl)-4,5-dihydro-pyrazol-1-yl]-3-ethyl-3H-quinazolin-4-one (9h): Obtained according to the general procedure, by using **8h** (253 mg, 0.5 mmol), as a white solid (230 mg, 91 %); m.p. 210-211 °C; R_f 0.36 ($CHCl_3$); ¹H NMR (400 MHz, $CDCl_3$) δ_H 8.15 (1H, d, $J = 7.6$ Hz, 5-CH), 7.63 (2H, d, $J = 8.8$ Hz, $2 \times CH(Ar)$), 7.57 (1H, t, $J = 8.0$ Hz, 7-CH), 7.45 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 7.40 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 7.39 (2H, d, $J = 8.4$ Hz, $2 \times CH(Ar)$), 7.35 (1H, d, $J = 8.0$ Hz, 8-CH), 7.27 (1H, t, $J = 7.2$, 6-CH), 5.95 (1H, t, $J = 12.0$ Hz, 5'-CH), 4.44 (2H, q, $J = 7.2$ Hz, NCH_2CH_3), 3.69 (1H, dd, $J = 11.2$ and 16.8 Hz, 4'-CH_a), 3.17 (1H, dd, $J = 12.0$ and 17.0 Hz, 4'-CH_b), 1.52 (3H, t, $J = 7.1$ Hz, NCH_2CH_3); ¹³C NMR (100 MHz, $CDCl_3$) δ_C 163.10 (4-C), 152.21 (2-C), 149.10 (3'-C), 136.34, 133.91, 131.96, 131.73, 129.19, 129.00, 127.39, 126.95, 124.82, 122.03 (Ar-C), 63.91 (5'-C), 41.51 (4'-C), 40.58 (NCH_2CH_3), 14.23 (NCH_2CH_3); MS (EI) m/z 506.0 (M^+ , 100 %), 508.0; Anal. Calcd. for $C_{25}H_{20}N_4OBrCl$: C, 59.13; H, 3.97; N, 11.03. Found: C, 59.41; H, 4.39; N, 11.37 %.

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