Investigation of an Amidation Reaction for the Preparation of Some 2-(2-Phenyl-4-Oxoquinazolin-3(4*H*)-yl)-*N*-Substituted Acetamides and *N*-Substituted 2-(2-(4-Oxo-2-Phenylquinazolin-3(4*H*)-yl)Acetylhydrazine -1-Carboxamides

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Abstract   A previously reported amide bond formation performed by treating ethyl 2-phenyl-4-oxo-3(4*H*) quinazolineacetate with the appropriate amine in boiling HOAc to synthesize a series of quinazolin-4-one derivatives was investigated. Elucidation of the structure of the synthesized products by IR, ^{1}H NMR and ^{13}C NMR indicated that, unfortunately, no amide bond was formed. The only product produced in all reactions was 4-oxo-2-phenyl-4(3*H*)-quinazolineacetic acid even when using different amines. Repeating the afore-mentioned reaction, amide formation was attempted for the synthesis of a series of 4-oxoquinazolinecarboxamide derivatives by treating 2-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetyl)hydrazine carboxylate with the appropriate 1° or 2° amine in boiling HOAc. Unfortunately, the reaction did not proceed as designed and recovery of the starting ester was the only product detected. Structure elucidation of the product obtained was also made by IR, ^{1}H NMR and ^{13}C NMR spectroscopy which indicated that no amide bond was formed. Therefore, in the present investigation, *N*-substituted acetamide derivatives were synthesized, by using known synthetic approaches, from the corresponding acid *via* treatment with SOCl₂ in different solvent systems followed by amidation with the selected amines.

Keywords   Quinazolin-4-ones, Amide formation, 2-phenyl-4-oxo-3(4*H*)quinazolineacetic acid, *N*-substituted acetamides, Ethyl 2-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetyl)hydrazinecarboxylate, Acetyl-*N*-phenylhydrazinecarboxamide

1. Introduction

Quinazolinone represents one of the most important classes of heterocycles possessing wide spectrum of biological activities [1] that has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents [2].

Coupling reactions between acid chlorides, esters or acids and substituted amines have been extensively studied for the synthesis of a huge number of amides [3-6]. In the present investigation, *N*-substituted acetamide derivatives **4a-f** were synthesized by using known synthetic approaches. As far as acid chlorides are concerned as starting materials for amide formation, they can be easily obtained from the corresponding acids *via* treatment with SOCl₂ in different solvent systems followed by reaction with the selected amines [3, 4]. Other coupling methods were also found using different reaction conditions [6].

Applying one of the reported studies to synthesize series of quinazolin-4-one derivatives by treating synthetically available esters **3** and **6** with the appropriate amine in boiling HOAc was carried out as depicted in scheme 1. All synthesized compounds were characterized by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Aiming at improving the yield of the reaction and purity of the product, it was required to reinvestigate the previously reported amide bond formation reaction using different

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reaction conditions.

2. Results and Discussion

In the present work, attempt was made to prepare a series of 2-(2-phenyl-4-oxoquinazolin-3(4*H*)-yl)-*N*-substituted acetamides. Elucidation of the structure of the synthesized products by IR, ^{1}H NMR and ^{13}C NMR indicated that, unfortunately, no amide bond was formed and, consequently, products **4a-f** were not obtained. The only product produced in all trials was 4-oxo-2-phenyl-4(3*H*)-quinazolineacetic acid **1** [7] even when using differnt amines as aniline, *p*-anisidine, ethanolamine, tris-(hydroxymethyl)methylamine, piperazine and morpholine. Therefore, it was assumed that under the highly acidic conditions used, that is refluxing HOAc, hydrolysis of the ester has occured. IR spectra of the product, obtained from all reactions, showed stretching absorption bands for the carboxylic OH at high frequency. In addition, absorption bands for two C=Os, C=N, C=C Ar functionalities were also observed. Evidence was obtained by the superposition of IR spectra obtained for products obtained from reaction of the ester **3** with *p*-anisidine and ethanolamine. Similarily, ^{1}H NMR and ^{13}C NMR confirmed the proposed structure as 4-oxo-2-phenyl-4(3*H*)-quinazolineacetic acid **1** for all reactions attempted. Comparison of the ^{1}H NMR and ^{13}C NMR spectra of product **1** obtained from both reactions, that is reaction of the ester **3** with ethanolamine and piperazine, showed a sharp D_2O-exchangeable singlet at 12.20 ppm assigned for COO*H*. Quinazoline C^7-, C^6-, C^8- and C^5-protons resonated as 2 triplets and 2 doublets successively at their expected chemical shifts while CH_2 protons resonated as singlet at 7.65 ppm. The 5 aromatic protons of 2-phenylquinazoline resonated as a downfield multiplet at its expected chemical shift. In ^{13}C NMR of **1**, chemical shift assignments were made for all 16 carbons in the molecule. 3^{ary} and 4^{ary} Carbons of the quinazoline nucleus, methylene-C and C2-phenyl ring were assigned downfield and were well resolved. The spectrum indicated the presence of two carbonyl carbons as evidenced by the appearance of 2 highly deshielded signals at 165.16 and 170.50 ppm assigned for C^4=O and *C*OOH respectively. Therefore, another method was adopted and conversion of 2-phenyl-4-oxo-3(4*H*)quinazoline acetic acid **1** with $SOCl_2$ into the corresponding acid chloride derivative **2** was performed as the first step for amide formation. The acid chloride **2** was then used without further purification for amide formation by treatment with the appropriate amine as aniline, *p*-anisidine, ethanolamine, tris-(hydroxymethyl)-methylamine, piperazine, morpholine, in dry dioxane containing NEt_3 [3]. Confirmatory evidence for structures **4a-f** was provided by elemental analyses and spectral data (IR, ^{1}H NMR and ^{13}C NMR). IR spectra of compounds **4a-f** showed stretching absorption bands for NH at high frequency. In addition, absorption bands for 2 x C=O, C=N, C=C Ar functionalities were also observed, υ_{as} and υ_s C-O-C stretching absorption bands were identified for

compound **4b** while OH stretching absorption bands were observed for compounds **4c,d**. ^{1}H NMR spectrum of **4a** showed a downfield D_2O-exchangeable singlet assigned for N*H* of the acetamide moiety. The usual singlet signal assigned for C*H*$_2$ protons was included within multiplet assigned for aromatic protons which were detected at their expected chemical shifts. ^{1}H NMR spectrum of **4b** showed an upfield singlet assigned for OC*H*$_3$ protons and a downfield D_2O-exchangeable singlet assigned for N*H* of the acetamide moiety. Protons characterizing the *p*-methoxyphenyl group were detected as two well defined doublets. In ^{13}C NMR spectrum of **4b** chemical shift assignments were made for all 23 carbons in the molecule. 3^{ary} and 4^{ary} Carbons of the quinazoline nucleus, *p*-anisidine and C^2-phenyl ring were assigned downfield and were well resolved. A shielded signal assigned for OC*H*$_3$ and resonating at 55.68 ppm confirmed the compound structure. The two carbonyl carbons of side chain and the quinazolinone nucleus were assigned successively at 165.59 and 167.63 ppm. ^{1}H NMR spectrum of **4c** showed 2 upfield singlets resonating at 3.39 and 3.55 ppm assigned for NHC*H*$_2$ and OHC*H*$_2$ protons respectively and two downfield D_2O-exchangeable singlets at 8.86 and 12.63 ppm assigned for N*H* of the acetamide moiety and OH respectively. The characteristic singlet signal assigned for C*H*$_2$ protons was well detected at 4.78 ppm. ^{1}H NMR spectrum of **4d** showed an upfield singlet resonating at 4.45 ppm integrated for 6 protons and assigned for 3 x OHC*H*$_2$ protons, well resolved after D_2O, and two downfield D_2O-exchangeable singlets at 8.07 and 14.83 ppm assigned for N*H* of the acetamide moiety and OH respectively. ^{1}H NMR spectrum of **4e** showed an upfield singlet resonating at 3.23 ppm, well resolved into 2 singlets at 2.96 and 3.55 ppm after D_2O, integrated for 8 protons and assigned for 4 x C*H*$_2$ protons of the piperazine moiety and a downfield D_2O-exchangeable singlet at 14.24 ppm assigned for N*H* of the piperazine ring. In ^{13}C NMR spectrum of **4e** chemical shift assignments were made for all 20 carbons in the molecule. 3^{ary} and 4^{ary} Carbons of the quinazoline nucleus and C^2-phenyl ring were assigned downfield and were well resolved. In addition, high field signals for the methylene carbons of the piperazine ring were also detected upfield at 66.72 ppm. A signal at 122.94 ppm was assigned for *C*H$_2$CO while a highly deshielded signal at 165.20 ppm was assigned for the 2 carbonyl carbons of the molecule. ^{1}H NMR spectrum of **4f** showed two upfield singlets resonating at 3.15 and 3.82 ppm, integrated for 8 protons and assigned for 2 x NC*H*$_2$ and 2 x OC*H*$_2$ protons respectively of the morpholine moiety. Obviously, C^7-*H* signal resonated at 7.06 ppm and split into *ddd* (doublet of doublet of doublet) with coupling constants of 1.08, 1.04, 0.60, 7.28, 7.68 Hz. The 2 *J* constants of 7.28 and 7.68 Hz belong to 2 different *o*-protons in the neighboring while *J* constants of 1.08, 1.04 Hz indicated the presence of a*m*-proton. A similar pattern was observed for C^6-*H*. Such pattern disappeared upon deuteration where 2 triplets were detected for C^7-*H* and C^6-*H* at 7.07 and 7.41 ppm respectively with again 2 different coupling constants for
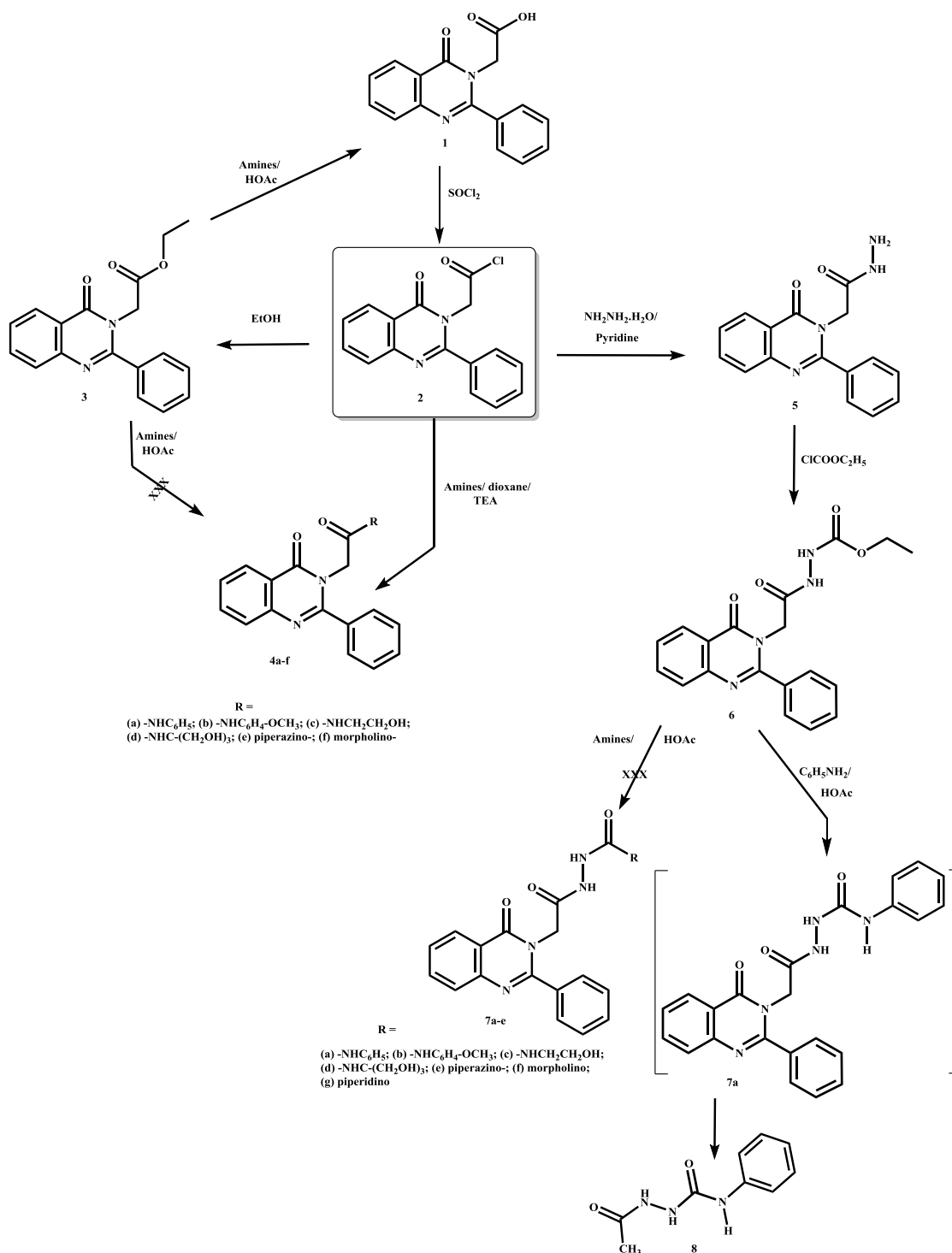
each of them. C^8-*H* and C^5-*H* signals resonated at their expected chemical shifts as 2 *dd* pattern changing into only 2 *d* upon deuteration. It was also noted that $C^{2,6}$-*H*s of the C-2 phenyl ring resonated as a *dd* at 8.04 ppm with 2 different coupling constants of 1.76 Hz for *p*- coupling and 7.92 Hz for *o*- coupling becoming a *d* after D_2O at 7.98 ppm with *J* = 7.24 Hz. Increasing dilution of the sample after addition of D_2O could be an explanantion for such change. Expanding the amidation reaction in HOAc, it was attempted to synthesize a series of quinazolinone derivatives by treating the ester **6** with the appropriate 1° or 2° amine, namely aniline, *p*-anisidine, ethanolamine, tri-(hydroxymethyl)-methylamine, piperidine, morpholine in boiling HOAc. Unfortunately, the reaction did not proceed as designed and recovery of the starting ester **6** was the only product detected. Structure elucidation of the product obtained was made by IR, ^{1}H NMR and ^{13}C NMR spectra which indicated that, unfortunately, no amide bond was formed and that the only product recovered in all trials was ethyl 2-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetyl)-hydrazine carboxylate **6** even when using differnt 1° and 2° amines. IR spectra of the product, obtained from all reactions, showed 2 stretching absorption bands for NHs at high frequency. In addition, stretching absorption bands for 3 x C=O (ester, quinazolinone and acetyl side chain) and υ_{as} and υ_s C-O-C functionalities were detected. Mixed vibrational bands for C=N and C=C Ar, were also observed. This was evidenced by the superposition of IR spectra obtained for products obtained from reaction of the ester **6** with tri-(hydroxymethyl)methyl amine and with piperidine. Similarily, ^{1}H NMR and ^{13}C NMR confirmed the recovery of the starting ester **6** for all reactions attempted. Study of the ^{1}H NMR and ^{13}C NMR spectra of the product obtained from the 2 reactions, that is reaction of the ester **6** with tri-(hydroxymethyl)methyl amine and with piperidine, are given for comparison purpose. ^{1}H NMR spectra showed two D_2O-exchangeable singlets resonating at low field assigned for the deshielded CON*H* and N*H*COOEt protons respectively. The spectrum also showed a triplet and quartet assigned for C*H*$_3$C*H*$_2$ protons of the ester group at high field. In addition, C*H*$_2$ and aromatic protons resonated downfield at their expected chemical shifts. In ^{13}C NMR spectrum of compound **6**, chemical shift assignments were made for all 19 carbons of the molecule. 3^{ary} and 4^{ary} Carbons of the phenyl ring and of the quinazoline nucleus were assigned downfield at their expected chemical shifts in addition to the high field signals due to methyl and methylene carbons of side chain ester. Three highly deshielded signals at 155.92, 156.90 and 160.27 ppm were assigned for the ester carbonyl and 2 carbonyl carbons of the quinazolinone nucleus and side chain, respectively. However, in only one case, attempt formation of *N*-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetylhydrazine-1-carboxamide **7a** by treating ester **6** with aniline in

refluxing HOAc according to the previously reported method produced the required amide **7a** followed by instantaneous splitting of the side chain to afford 1-acetyl-4-phenylsemicarbazide **8** that had a melting point concordant with the one previously prepared [8]. Search in literature indicated that it was previously synthesized by treatment of *N*-acetylhydrazine with phenyl isothiocyanate in hot benzene [8]. IR, ^{1}H NMR and ^{13}C NMR confirmed the proposed structure as 1-acetyl-4-phenylsemicarbazide **8** for the reaction product. ^{1}H NMR spectrum of **8** showed a D_2O-exchangeable singlet at 9.92 ppm assigned for N*H*s. Quinazoline C^7-, C^6-, C^8- and C^5-protons and the 5 aromatic protons of 2-phenyl moiety were not identified at their expected chemical shifts. Instead, a singlet signal resonating at 2.04 ppm and integrated for 3 protons was assigned for the C*H*$_3$ group. Two Downfield triplets at 7.02 and 7.28 ppm integrated for one and 2 protons were identified and assigned for C^4-*H* and $C^{3,5}$-*H*s respectively. $C^{2,6}$-*H*s resonated as a doublet at 7.58 ppm. In ^{13}C NMR spectrum of compound **8**, chemical shift assignments were made for the 9 carbons present in the molecule. Again, downfield 3^{ary} and 4^{ary} carbons of the quinazoline nucleus and C^2-phenyl ring could not be detected and were completely absent. The spectrum indicated that cleavage of the side chain has occurred as evidenced by the appearance of an upfield signal resonating at 24.45 ppm assigned for C*H*$_3$ carbon and other deshielded signals assigned for the 6 carbon atoms of the phenyl ring of acetyl-*N*-phenylhydrazinecarboxamide **8**. *C*=O carbons were highly deshielded and resonated at 168.72 ppm.

3. Experimental Section

Chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals company, Inc., USA, and used without further purification. TLC was performed on aluminum sheets of silica gel 60F254, E-Merk, Germany, using iodine as visualizing agent. Melting points were determined in open-glass capillaries on an electro thermal melting point apparatus (Stuart Scientific, Model SMP1, UK) and were uncorrected. IR Spectra were recorded as KBr pellets on Shimadzu Infrared Spectrophotometer IR 470 at the Faculty of Pharmacy, Cairo University and Bruker Tensor 37 FT-IR Spectrometer, Central Laboratory Unit, Faculty of Science, Cairo University, Egypt and reported in cm^{-1}. All ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III apparatus 400MHz; Central Laboratory Unit, Faculty of Pharmacy, Cairo University, 400 MHz for ^{1}H NMR and 100.63 MHz for ^{13}C NMR and Varian Mercury VX 300 BB spectrophotometer; Faculty of Science, Cairo University, Egypt, 300 MHz for ^{1}H NMR and 75.45 MHz for ^{13}C NMR. Elemental analyses were run on Vario EL III German CHN Elemental analyser model, Regional Centre for Mycology and Biotechnology, Al-Azhar University, Nasr City, Cairo, Egypt.

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Scheme 1.   Synthesis of 2-(2-phenyl-4-oxoquinazolin-3(4*H*)-yl)-*N*-substituted Acetamides and *N*-substituted
2-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetylhydrazine-1-carboxamides

Attempt preparation of 2-(2-phenyl-4-oxoquinazolin-3(4*H*)-yl)-N-substituted acetamides from ester 3: Formation of 4-oxo-2-phenyl-4(3*H*)-quinazolineacetic acid 1:

Glacial acetic acid (5 mL) was added slowly while shaking to a mixture of ethyl (2-phenyl-4-oxoquinazolin-3(4*H*)-yl)acetate **3** (0.306 g, 1 mmol) and the corresponding 1° or 2° amine (1 mmol). The mixture was heated under reflux for 4-6 h, left to cool to R.T. and poured onto crushed ice. The obtained solid was filtered, dried and crystallized from EtOH. All products obtained had superimposable IR, ^{1}H NMR and ^{13}C NMR. The structure was elucidated and found to be 4-oxo-2-phenyl-4(3*H*)-quinazolineacetic acid **1** [7]. M.p.: 133°C (Reported M.p.:130-132°C) [7]. IR (KBr, ט, cm^{-1}): 2924 (OH), 1686, 1643 (C=O), 1609 (C=N), 1590, 1497

(C=C Ar). ^{1}HNMR (DMSO-d$_6$, 400 MHz, δ ppm): 7.22 (*t*, 1H, C^7-*H*, *J* = 7.32 Hz), 7.60 (*t*, 1H,C^6-*H*, *J* = 7.6 Hz), 7.65 (s, 2H, C*H*$_2$), 7.66-7.69 (*m*, 3H, C$^{3',4',5'}$-*H*s), 7.96 (*d*, 2H,C$^{2',6'}$-*H*s, *J* = 8.3 Hz), 8.07 (*dd*, 1H, C^8-*H*, *J* = 8.3 Hz, 1.36 Hz), 8.73 (*d*, 2H, C^5-*H*, *J* = 8.2 Hz), 12.20 (*s*, 1H, COO*H*, D$_2$O-exchangeable). ^{13}C NMR (DMSO-d$_6$, 100 MHz, δ ppm): 117.02 (*C*H$_2$), 120.34 (*C*^{4}), 123.40 (*C*^{6} + *C*^{7}), 127.48, 127.70 (*C*$^{3',5'}$), 129.01, 129.19 (*C*$^{2',6'}$), 131.75 (*C*^{5,8}), 133.31 (*C*$^{1'}$), 134.77 (*C*^{8a}), 135.00 (*C*^{4a}), 141.59 (*C*^{2}), 165.16 (*C*^{4}=O), 170.50 (*C*=OOH).

General Procedure for synthesis of 2-(2-phenyl-4-oxoquinazolin-3(4*H*)-yl)-N-Substituted acetamides 4a-f from 2-phenyl-4-oxo-3(4*H*)quinazolineacetyl chloride 2:

A mixture of 2-phenyl-4-oxo-3(4*H*)quinazolineacetic acid **1** (1.40 g, 5 mmol) and thionyl chloride (3 mL) was heated under reflux for 1 hr. The deposited precipitate **2** was separated by filtration and used without further purification for the next step [1]. A solution of the acid chloride **2** (2.99 g, 10 mmol) in dry dioxane (10 mL) was treated with a solution of the appropriate amine (10 mmol) and triethylamine (1 mL) in dry dioxane (10 mL) and the mixture was heated for 1 h at 100°C, cooled and diluted with H$_2$O. The obtained solid products were dried and crystallized from EtOH. IR (KBr, ύ, cm^{-1}) for **4a-f**: 3471-3329 (NH), 1774-1700, 1660-1643 (2 x C=O), 1636-1610 (C=N), 1604-1590, 1512-1497 (C=C Ar); in addition to: 1250, 1107 and 1090, 1049 (υ$_{as}$ and υ$_s$ C-O-C) for **4b,f**; 3472-31210 (OH mixed with NH) for **4c,d**.

N-Phenyl 2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetamide 4a:

Yield: 52% (1.85 g), M.p.: 230-232°C. IR (KBr, ύ, cm^{-1}): 3341 (NH), 1660, 1654 (C=Os), 1597 (C=N), 1490 (C=C Ar). ^{1}HNMR (DMSO-d$_6$, 400 MHz, δ ppm): 7.11 (*t*, 1H, C^7-*H*, *J* = 7.36 Hz), 7.15 (*t*, 1H, C^6-*H*, *J* = 7.36 Hz), 7.29-7.94 (*m*, 12H, 10 Ar-*H*s overlapping with C*H*$_2$), 7.96 (*d*, 1H, C^8-*H*, *J* = 7.96 Hz), 8.50 (*d*, 1H, C^5-*H*, *J* = 8.20 Hz), 10.24 (*s*, 1H, N*H*, D$_2$O-exchangeable). Anal. Calcd for C$_{22}$H$_{17}$N$_3$O$_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.53; H, 4.85; N, 12.01.

N-(4-Methoxyphenyl)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide 4b:

Yield: 63% (2.43 g), M.p.:159-161°C. IR (KBr, ύ, cm^{-1}): 3329 (NH), 1762, 1643 (C=Os), 1600 (C=N), 1490 (C=C Ar). ^{1}HNMR (DMSO-d$_6$, 400 MHz, δ ppm): 3.75 (*s*, 3H, O-C*H*$_3$), 6.93 (*d*, 2H, *m*- to OCH$_3$, *J* = 9.08 Hz), 7.52 (*t*, 1H, C^7-*H*, *J* = 7.52 Hz), 7. 56-7.75 (*m*, 8H, 5 Ar-*H*s overlapping with C^6-*H* + C*H*$_2$), 7.69 (*d*, 2H, *o*- to OCH$_3$, *J* = 9.0 Hz), 7.95 (*d*, 1H, C^8-*H*, *J* = 7.08 Hz), 8.22 (*d*, 1H, C^5-*H*, *J* = 7.08 Hz), 10.13 (*s*, 1H, N*H*, D$_2$O-exchangeable). ^{13}C NMR (DMSO-d$_6$, 100 MHz, δ ppm): 55.68 (OCH$_3$), 114.19 (*C*H$_2$), 122.47 (*C*$^{4'}$), 127.39, 127.43 (*C*$^{3',5'}$), 128.00 (*C*^{3,5} of *p*-methoxyaniline), 128.29 (*C*^{7}), 128.54 (*C*^{6}), 128.80 (*C*$^{2',6'}$), 129.40, 129.51 (*C*^{2,6} of *p*-methoxyaniline), 131.83 (*C*^{8}), 132.68 (*C*^{5}), 135.50 (*C*^{8a}), 137.34 (*C*$^{1'}$), 146.75 (*C*^{4a}), 156.02 (*C*^{4} of *p*-methoxyaniline), 156.89 (*C*^{1} of *p*-methoxyaniline), 159.38 (*C*^{2}), 165.59 and 167.63 (2 x *C*=O). Anal. Calcd for C$_{23}$H$_{19}$N$_3$O$_3$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.74; H, 5.28; N, 11.19.

N-(2-Hydroxyethyl)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide 4c:

Yield: 50% (1.62 g), M.p.: 185-187°C. IR (KBr, ύ, cm^{-1}): 3352-3194 (NH+OH), 1650, 1635 (C=Os), 1590 (C=N), 1489 (C=C Ar). ^{1}HNMR (DMSO-d$_6$, 400 MHz, δ ppm): 3.39 (*t*, 2H, NH-C*H*$_2$, *J* = 5.76 Hz), 3.55 (*t*, 2H, OH-C*H*$_2$, *J* = 5.64 Hz), 4.78 (*s*, 2H, C*H*$_2$), 7.21 (*t*, 1H, C^7-*H*, *J* = 7.56 Hz), 7.60 (*t*, 1H, C^6-*H*, *J* = 7.52 Hz), 7.52-7.96 (*m*, 6H, 5 Ar-*H*s overlapping with C^6-*H*), 7.88 (*d*, 1H, C^8-*H*, *J* = 7.8 Hz), 8.67 (*d*, 1H, C^5-*H*, *J* = 8.28 Hz), 8.86 (*s*, 1H, N*H*, D$_2$O-exchangeable), 12.63 (*s*, 1H, O*H*, D$_2$O-exchangeable). Anal. Calcd for C$_{18}$H$_{17}$N$_3$O$_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 67.11; H, 5.38; N, 13.23.

N-(1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide 4d:

Yield: 58% (2.22 g), M.p.: 138-140°C. ^{1}HNMR (DMSO-d$_6$, 400 MHz, δ ppm): 4.45 (*s*, *br*, 6H, 3 x (OH-C*H*$_2$) well resolved after D$_2$O), 7.04 (*t*, 1H, C^7-*H*, *J* = 7.32 Hz), 7.32 (*t*, 1H, C^6-*H*, *J* = 7.44 Hz), 7.34-8.46 (*m*, 7H, 5 Ar-*H*s overlapping with C*H*$_2$), 7.88 (*dd*, 1H, C^8-*H*, *J* = 7.8 Hz, 1.36 Hz), 8.07 (*s*, 1H, N*H*, D$_2$O-exchangeable), 8.70 (*d*, 1H, C^5-*H*, *J* = 8.12Hz), 14.83 (*s*, 1H, O*H*, D$_2$O-exchangeable).Anal.Calcd for C$_{20}$H$_{21}$N$_3$O$_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.79; H, 5.58; N, 11.13.

3-(2-Oxo-2-(piperazin-1-yl)ethyl)-2-phenylquinazolin-4(3*H*)-one 4e:

Yield: 50% (1.74 g), M.p.: 278-280°C. ^{1}HNMR (DMSO-d$_6$, 400 MHz, δ ppm): 3.23 (*s*, 8H, 4 x C*H*$_2$ well resolved into 2 singlets at 2.96 and 3.55 after D$_2$O), 7.09 (*t*, 1H, C^7-*H*, *J* = 7.32 Hz), 7.47 (*t*, 1H, C^6-*H*, *J* = 6.96 Hz), 7.57 (*s*, 2H, C*H*$_2$), 7.51-8.05 (*m*, 5H, 5 Ar-*H*s overlapping with C*H*$_2$), 8.18 (*dd*, 1H, C^8-*H*, *J* = 8.8 Hz, 1.12 Hz), 8.73 (*d*, 1H, C^5-*H*, *J* = 8.12 Hz), 14.24 (*s*, 1H, N*H*, D$_2$O-exchangeable). ^{13}C NMR (CDCl$_3$, 100 MHz): 66.72 (4 x *C*H$_2$ of piperazine), 119.25 (*C*$^{4'}$), 122.94 (*C*H$_2$), 123.07 (*C*^{6,7}), 127.46 (*C*$^{3',5'}$), 129.09 (*C*^{8}), 129.36 (*C*$^{2',6'}$), 131.84 (*C*^{5}), 132.03 (*C*^{8a}), 132.39 (*C*$^{1'}$), 135.15 (*C*^{4a}), 140.67 (*C*^{2}), 165.20 (2 x *C*=O). Anal. Calcd for C$_{20}$H$_{20}$N$_4$O$_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.21; H, 5.85; N, 16.32.

3-(2-Morpholino-2-oxoethyl)-2-phenylquinazolin-4(3*H*)-one 4f:

Yield: 65% (2.27 g), M.p.: 176-178°C. ^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 3.15 (*t*, 4H, 2 x C*H*$_2$N, *J* = 4.92 Hz), 3.82 (*t*, 4H, 2 x C*H*$_2$O, *J* = 5.0 Hz), 7.06 (*ddd*, 1H, C^7-*H*, *J* = 7.68, 7.28, 1.08 Hz, becoming *t* after D$_2$O at 7.07 ppm, *J* = 7.52 Hz, 7.48 Hz), 7.42 (*ddd*, 1H, C^6-*H*, *J* = 1.68 and 7.32, 8.24 Hz, becoming *t* after D$_2$O at 7.41 ppm, *J* = 7.84, 7.6 Hz), 7.57 (*s*, 2H, C*H*$_2$ included within Ar multiplet), 7.52-7.62 (*m*, 3H, C^{3,4,5}-*H*s of 2-phenyl overlapping with C*H*$_2$), 8.04 (*dd*, 2H, C^{2,6}-*H*s of 2- phenyl, *J* = 7.92 Hz, 1.76 Hz, becoming *d* after D$_2$O at 7.98 ppm, *J* = 7.24 Hz), 8.11 (*dd*, 1H, C^8-*H*, *J* = 7.76 Hz, 1.60 Hz, becoming *d* after D$_2$O at 8.03 ppm, *J* = 7.72 Hz), 8.73 (*dd*, 1H, C^5-*H*, *J* = 8.20 Hz, 0.72 Hz, becoming *d* after D$_2$O at 8.63 ppm, *J* = 8.2 Hz). Anal. Calcd for C$_{20}$H$_{19}$N$_3$O$_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 69.01; H, 5.35; N, 12.32.

2-(4-Oxo-2-phenylquinazolin-3(4H)-yl)acetohydrazide 5:

Thionyl chloride (5 ml) was added to 2-phenyl-4-oxo-3(4*H*)-quinazolineacetic acid (**1**) (2.8 g, 10 mmol), and the solution was heated under reflux on a water bath for 1 h followed by removal of excess thionyl chloride

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under reduced pressure. Without further purification, the obtained acid chloride **2** was dissolved in dry pyridine (10 ml) and cooled to 0°C. To this solution, hydrazine hydrate (99%) (1.25 g, 1.23 ml, 25 mmol) was added at once with vigorous stirring. The mixture was stirred for 1 h and poured onto crushed ice with continuous stirring. The obtained product was filtered off, washed with H_2O, dried and crystallized from EtOH; m.p. = 240-242°C; (reported m.p. = 242-245°C) [7], Yield 2 g (71%). IR (KBr, ʋ, cm^{-1}): 3317 (br, NH_2, NH), 1652 (2 x C=O), 1603 (mixed vibration C=N + C=C Ar), 1529 (C=C Ar). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ ppm): 3.12 (*s*, *br*, 2H, NH_2, D_2O-exchangeable), 7.08 (*t*, 1H, C^7-*H*, *J* = 7.6 Hz), 7.28 (*s*, 2H, C*H$_2$*), 7.48 (*t*, 1H, C^6-*H*, *J* = 7.7 Hz, included within multiplet for 5 Ar-Hs), 7.52-7.60 (*m*, 5H, Ar-Hs), 8.05 (*d*, 1H, C^8-*H*, *J* = 7.08 Hz), 8.79 (*d*, 1H, C^5-*H*, *J* = 8.4 Hz), 11.86 (*s*, 1H, N*H*, D_2O-exchangeable). EI-MS, m/z (% relative abundance): 294 [M$^+$] (1), 238 (11), 237 (61), 236 (58), 224 (16), 223 (19), 222 (16), 208 (29), 180 (18), 179 (19), 139 (11), 120 (16), 119 (54), 111 (16), 105 (100), 103 (18), 98 (10), 97 (17), 92 (14), 91 (12), 90 (18), 85 (13), 83 (18), 81 (12), 77 (97), 76 (38), 73 (19), 71 (23), 69 (25), 67 (14), 63 (16), 60 (21), 57 (40), 55 (37).

Ethyl 2-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetyl)-hydrazi necarboxylate 6: Ethyl chloroformate (0.163g, 0.143 ml, 1.5 mmol) was added to a solution of acetohydrazide **5** (0.294 g, 1 mmol) and anhydrous K_2CO_3 (0.276 g, 2 mmol) in dry dioxane (5 mL) and the mixture was heated under reflux for 4 h. The reaction mixture was concentrated to half its volume, left to cool to R.T. and the separated product was filtered off and crystallized from dioxane; yield 60% (0.22 g), M.p.: 215-217°C. IR (KBr, ʋ, cm^{-1}): 3271 (NHs), 1715 (ester C=O), 1663 (2 x C=O), 1600 (mixed vibrational band for C=N + C=C Ar), 1444 (C=C Ar), 1251, 1041 (υ_{as} and υ_s C-O-C). ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 1.22 (*t*, *dist*, 3H, CH$_2$-C*H$_3$*), 4.11 (*q*, *dist*, 2H, C*H$_2$*-CH$_3$), 7.24 (*t*, 1H, C^7-*H*, *J* = 7.5 Hz), 7.61 (*t*, 1H, C^6-*H*, *J* = 7.0 Hz, overlapping with C*H$_2$* at 7.62), 7.56-7.82 (*m*, 5H, Ar-*H*s), 7.93 (*d*, 1H, C^8-*H*, *J* = 7.8 Hz), 8.66 (*d*, 1H, C^5-*H*, *J* = 8.0 Hz), 10.66 (*s*, 1H, CON*H*, D_2O-exchangeable), 12.00 (*s*, 1H, N*H*COOEt, D_2O-exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz):14.45 (*C*H$_3$), 60.77 (COO*C*H$_2$), 120.55 (*C*H$_2$), 123.04 (*C*^{4} of 2-phenyl), 123.04 (*C*^{3,5} of 2- phenyl), 126.91 (*C*^{2,6} of 2- phenyl), 128.139 (*C*^{6,7}), 128.94 (*C*^{5,8}), 132.15 (*C*^{8a}), 132.88 (*C*^{4a}),134.36 (*C*$^{1'}$ of 2-phenyl), 139.34 (*C*^{2}), 156.16 (*C*=O ester), 164.44 and 168.55 (2 x *C*=O). EI-MS m/z (relative abundance %):366 [M$^+$] (0.05), 236 (22), 224 (600, 223 (11), 208 (14), 180 (11), 179 (23), 146 (17), 119 (23), 111(18), 105 (100), 104 (13), 90 (17), 85 (19), 83 (17), 77 (92), 76 (29), 71 (29), 69 (21), 64 (18), 57 (47), 55 (22), 50 (18). Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29; Found C, 62.35; H, 4.99; N, 15.41.

2.2.4. Attempt preparation of *N*-substituted 2-(2-(4-oxo-2-phenyquinazolin-3(4*H*)-yl)acetylhydrazine -1-carboxamides 7a-e from ethyl 2-(2-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)acetyl)hydrazi ne carboxylate 6:

Glacial acetic acid (5 mL) was added slowly while shaking to a mixture of ethyl 2-(2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetyl)hydrazine carboxylate **6** (0.366 g, 1 mmol) and the appropriate 1° or 2° amine (1 mmol). The mixture was heated under reflux for 4-6 h, left to cool to R.T. and poured onto crushed ice. The obtained solid was filtered, dried and crystallized from EtOH. All products obtained had superimposable IR, ^{1}H NMR and ^{13}C NMR spectra. The structure was elucidated and found to be concordant with ethyl 2-(2-(4-oxo-2-phenylquinazolin -3(4*H*)-yl)-acetyl)hydrazine carboxylate **6**. IR (KBr, ʋ, cm^{-1}): 3248 (NHs), 1744 (ester C=O), 1678 (2 x C=O), 1608 (C=N), 1596, 1474 (C=C Ar), 1258, 1064 (υ_{as} and υ_s C-O-C). ^{1}H-NMR (DMSO-d$_6$, 400 MHz) for products obtained from all reactions: 1.13-1.14 (*t*,3H, -C*H$_3$*), 4.04-4.06 (*q*,*dist*, 2H, COOC*H$_2$*), 7.51 (*t*, *dist*, 1H, C^7-*H*, *J* = 7.5 Hz), 7.61-7.64 (*t*, 3H, C^6-*H*, *J* = 7.0 Hz, overlapping with C*H$_2$*), 7.49-7.99 (*m*, 5H, Ar-*H*s), 7.79 (*d*, 1H, C^8-*H*, *J* = 7.8 Hz), 8.20 (*d*, 1H, C^5-*H*, *J* = 8.0 Hz), 10.05 (*s*, 1H, CON*H*, D_2O-exchangeable), 10.47-10.48 (*s*, 1H, N*H*COOEt, D_2O-exchangeable).^{13}C NMR (DMSO-d$_6$, 100 MHz, δ ppm) for products obtained from reactions of the ester with tris-(hydroxymethyl)methyl amine and piperidine: 14.73 (*C*H$_3$), 62.11 (COO*C*H$_2$), 121.11 (*C*H$_2$), 126.98 (*C*^{4} of 2- phenyl), 128.01 (*C*^{7}), 128.21 (*C*^{6}), 128.41 (*C*^{3,5}), 129.00 (*C*^{2,6} of 2- phenyl), 129.10 (*C*^{8}), 130.59 (*C*^{5}), 134.03 (*C*^{4a,8a}), 135.81 (*C*^{1} of 2- phenyl), 146.95 (*C*^{2}), 155.92 (*C*=O ester), 156.90 and 160.27 (2 x *C*=O).

Unexpectedly, treating ester **6** with aniline and glacial HOAc as previously mentioned above afforded 1-acetyl-4-phenyl semicarbazide **8** [8] instead of the amide **7a**. Yield: 40% (0.77 g), M.p.: 168-170°C (Reported yield 30%); M.p.: 174.7-175.2°C. [8] IR (KBr, ʋ, cm^{-1}): 3294, 3260 (3 x NH), 1663, 1640 (2 x C=O), 1597, 1489 (C=C Ar). ^{1}H NMR (DMSO-d$_6$, 400 MHz) for compound **8**: 2.04 (*s*, 3H, C*H$_3$*), 7.02 (*t*, 1H, C^4-*H*, *J* = 7.36 Hz), 7.28 (*t*, 2H, C^{3,5}-*H*s, *J* = 7.68 Hz),7.58 (*d*, 2H, C^{2,6}-*H*s, *J* = 7.90 Hz), 9.92 (*s*, 3H, N*H*s, D_2O-exchangeable).^{13}C NMR (DMSO-d$_6$, 100 MHz) of **9**: 24.45 (*C*H$_3$), 119.44 (*C*^{3,5}), 123.41 (*C*^{4}), 129.10 (*C*^{2,6}), 139.79 (*C*^{1}), 168.72 (2 x *C*=O).

4. Conclusions

In this study, the notably popular amidation reaction was explored for the preparation of some amides **4a-f**, derived from quinazolinone starting from the ester **3** or the acid chloride **2**. From this study, it appears that:

- Amidation was first attempted, as previously reported, by reacting a mixture of ethyl (2-phenyl-4-oxoquinazolin-3(4*H*)-yl)acetate **3** and various 1° or 2° amines in hot refluxing glacial HOAc. The only product obtained in all trials was 4-oxo-2-phenyl-4(3*H*)-quinazolineacetic acid **1** instead of the required amides **4a-f** assuming hydrolysis of the ester **3**. This was confirmed by superimposition of all IR, ^{1}H NMR and ^{13}C NMR spectra of products obtained from all reactions (supplementary data).
- To overcome the hydrolysis problem, amidation was

carried out in alkaline medium and all proposed amides **4a-f** were prepared in good yields upon treating acid chloride **2** with various 1° and 2° amines in presence of triethyl amine.

Study also was expanded to determine the efficacy of the acid-catalyzed amidation reactions. Reacting ester **6** with the appropriate 1° or 2° amines in hot refluxing glacial HOAc did not afford the expected amides and recovery of the starting carbamate ester **6** was the only product obtained (supplementary data). In only one case, treating ester **6** with aniline in refluxing HOAc afforded 1-acetyl-4-phenylsemicarbazide **8** that had a melting point concordant with the one previously prepared.

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