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Arkivoc **2017**, part iv, 104-120

Synthesis of methyl [3-alkyl-2-(2,4-dioxo-3,4-dihydro-2*H*-quinazolin-1-yl)-acetamido] alkanoate

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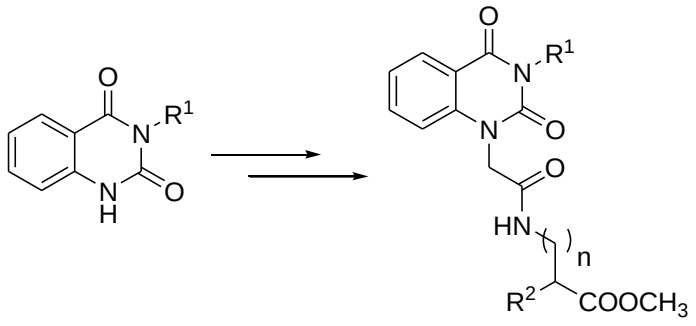
Received 11-20-2016 **Accepted** 02-25-2017 **Published on line** 05-11-2017

Abstract

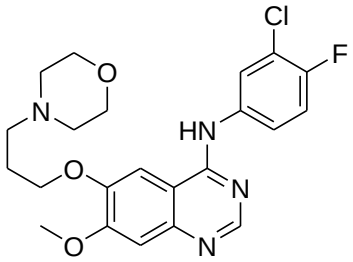
A series of methyl [3-alkyl-2-(2,4-dioxo-3,4-dihydro-2*H*-quinazolin-1-yl)-acetamido] alkanoate **10-13a-f** has been developed on the basis of the N-chemoselective reaction of 3-substituted quinazoline-2,4-diones **3**a-d with ethyl chloroacetate and azide coupling method with amino acid ester hydrochloride. The precursor quinazoline diones **3a-d** chemoselective reactions were studied using DFT(B3LYP)/6-311G level of theory and were prepared by a new rearrangement method from the corresponding 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-ylthio) acetohydrazide **6**.



Keywords: Chemoselective reactions, heterocyclic amides, amino acid coupling, thiamide-amide transformation, DFT

Introduction

Receptor tyrosine kinases have a critical role in the development and progression of many types of cancer (e.g., breast, ovarian, colon, and prostate).[1] The quinazoline nucleus is the scaffold of many antitumor drugs mainly acting as inhibitors of tyrosine kinase receptors (RTK). Anticancer agent Iressa (ZD1839) **A** is a clinically approved example of quinazoline-based inhibitors which is in phase III clinical trials for cancer used to inhibit the receptor tyrosine kinase of epidermal growth factor.[2,3]



A

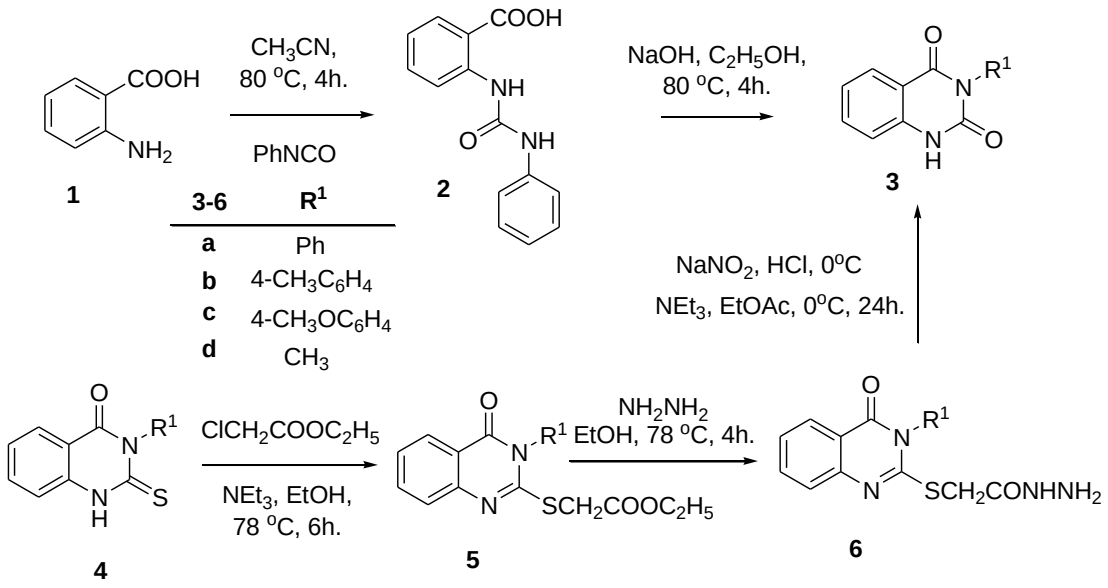
Moreover fused tricyclic quinazolines such as pyrrolo- and pyrazoloquinazolines showed IC50 values in the nanomolar range in the inhibition of the receptor tyrosine kinase of the epidermal growth factor.[4] Pyrrolo[3,2-*f*]quinazolines as inhibitors of non-classical dihydrofolate reductase (DHFR) are effective for neoplastic diseases.[5] Quinazolines[6] also exhibit pronounced biological activities as antimicrobial,[7,8] anti-HIV (NNRTI),[9,10] anti-tumour,[11-16] potential analgesic and anti-inflammatory activity.[17] Non-proteinogenic amino acids are major component in a number of drugs including β-lactam antibiotics[18] and glutamate antagonists.[19] The attachment of new heterocyclic compounds to amino acid esters might provide structures with interesting conformation, stability and biological activity. Recently we reported the molecular modeling studies and syntheses of methyl 2-(2-(4-oxo-3-aryl-3,4-dihydroquinazolin-2-ylthio)acetamido) alkanoates with potential anticancer activity as inhibitors for methionine synthase.[20]

However a strong query still remains that is the development of simple, mild and efficient methods for preparation of quinazoline derivatives linked to amino acid residues by a spacer and the evaluation of their biological activities. In view of these facts and in continuation of our efforts in studing the chemoselective reactions of heterocyclic amides[21-23] and thioamides,[20,24-37] we found interesting to synthesize a series of quinazoline derivatives linked to amino acids by a spacer. Here in we wish to report a novel synthesis of 3-arylquinazoline-2,4-dione and use this precursor in the synthesis of methyl [3-alkyl-2-(2,4-dioxo-3,4-dihydro-2*H*-quinazolin-1-yl)-acetamido] alkanoate.

Results and Discussion

The hydrazide **6a-d** reacted with a mixture of $NaNO_2$ and HCl at 0 ^oC to presumably produce the azide. Then the *in situ* generated azide derivative was treated with triethyl amine in ethyl acetate to afford an interesting rearrangement and gave the dione **3a-d** (Scheme 1). This procedure was discovered by our group on applying the amino acid azide coupling method to hydrazide **6a** in the attempted preparation of methyl 2-(2-(4-oxo-3-aryl-3,4-dihydroquinazolin-2-ylthio)acetamido) alkanoates.[20] The precursor 3-phenylquinazoline-2,4-dione **3a**

was alternatively, prepared by refluxing anthranilic acid with phenyl isocyanate in acetonitrile for 4h. The produced urea derivative **2** was cyclized using NaOH in ethanol under reflux for 4h, Scheme 1.

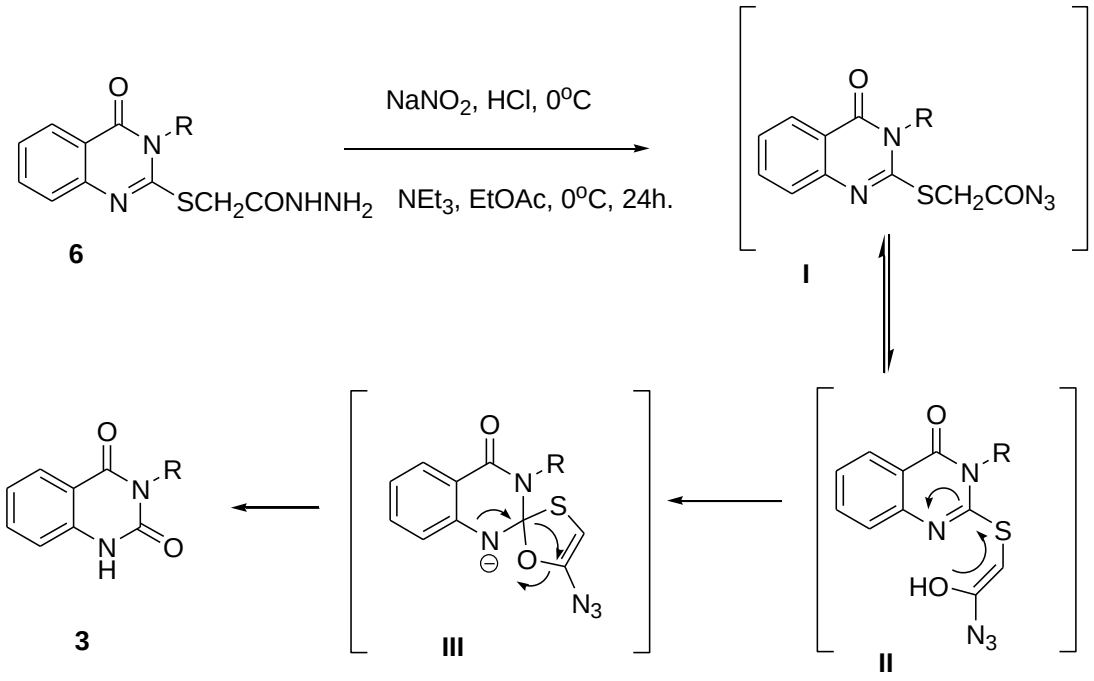


Scheme 1

We further explored a suggested rationalized mechanism for formation of dione **3a-d**. *via* azide **I** through tautomeric irreversible rearrangement which showed to start by Smiles rearrangement[38] as shown in Scheme 2.

A first step: acid catalyzed tautomerization of the azide derivative **I** giving rise to the enol **II**. Second step: oxygen nucleophilic attack on electrophilic carbon located at position 2 of the quinazoline system to give a five membered spiro-intermediate **III** leaving a negative charge on the nitrogen atom. This negative charge will localize again forcing the C-S bond cleavage which in return will attack the O-C-N_3 carbon and the subsequent cleavage of $SCHCN_3$ group to finally afford the dione **3a-d,** Scheme 2.

Several examples were reported in literature showing similar results.[39-40] The results obtained earlier show the formation of amides from resembling examples with the elimination of thiirane ring residue. A similar result was obtained by our group applying the azide coupling method to 2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl) acetohydrazide giving an interesting rearrangement with the formation of 4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxaline-1(2*H*) thione. This latter reaction appears to confirm the formation of intermediates **I** and **II**, but differs in the cleavage of the spiro system probably due to the differences in the properties of quinazoline and triazoloquinoxaline ring systems.[36]



Scheme 2

The structure assignment of quinazoline dione derivative **3c** (R^1 = $C_6H_4OCH_3$) is based on ^{1}H NMR spectroscopy, as well as physicochemical analysis. The ^{1}H NMR spectrum of the dione **3c** gave an interesting pattern and it gave the clear evidence for the presence of dione derivatives in the form of tautomeric mixture in a ratio of 1:1. Thus the ^{1}H NMR of **3c** shows broad singlet signal at 11.48 ppm corresponding to NH group. The ^{1}H NMR spectrum gave multiplet signals ranging from 8.35-7.01 ppm corresponding to eight aromatic protons, two singlet signals at 3.87 ppm and 3.82 ppm of OCH_3 for each tautomer. ^{13}C NMR spectrum confirmed the structure of compound **3c**. It showed signals at 162.8 and 160.2 ppm for (CO) group, signals at 159.6, 150.9, 140.2, 136.3, 133.1, 130.5, 129.9, 129.0, 127.8, 122.9, 117.8 and 115.6 ppm for C-Ar group and a signal at 55.8 ppm for OCH_3 group.

Structure modification of the model compound **3a-d** could be simply achieved by chemoselective alkylation reactions with electrophiles. Thus, the reaction of quinazoline **3a-d** with ethyl chloroacetate in the presence of NaH gave chemoselective N-substituted quinazoline derivatives **7a-d** in good yield, Scheme 3.

The O/N reaction competitions in heterocyclic amides with electrophiles were considered as a major element for the synthesis of great variety of heterocyclic compounds of promising biological activities. Despite these types of reactions show great selectivity; the reason for the O- and N-atoms contributions were not yet described. Calculation of a number of parameters such as molecular orbital coefficients, charge distribution, and fukui functions of the model compound beside the experimental results might give us clear picture. The calculations were performed using MOLPRO program package. The optimized geometric structures were calculated using DFT(B3LYP)/6-311G level of theory.

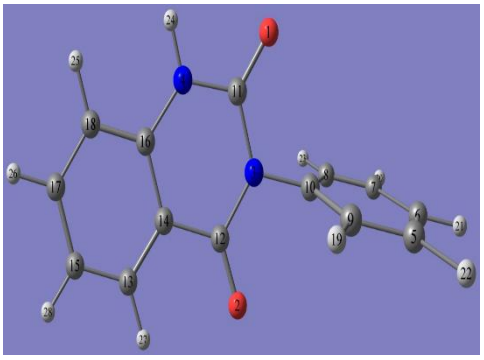


Figure 1. Optimized geometric structure and numbering for **3a** calculated using DFT(B3LYP)/6-311G level of theory.

Taking into consideration the Fukui function reactivity indices; they give us information about which atoms in a molecule have a larger tendency to either loose or accept an electron. This function is used by a number of researchers to distinguish between soft and hard sites of different nucleophiles.[41] For simplicity we will focus only on the values of Fukui function related only to the competing ambident nucleophilic sites. The following table shows with no doubts that *N*-atom is the most susceptible site for nucleophilic attacks, soft site of the ambident nucleophile with larger value of Fukui function, Table 1.

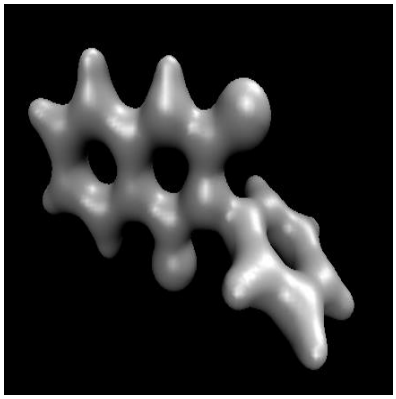
Table1. The Fukui indices of the atoms in molecule **3a** calculated at DFT (B3LYP)/6311G level of theory using Mulliken population analysis

atom	$q_k(N)$	$q_k(N+1)$	$q_k(N-1)$	f_k^+	f_k^-
O1	-0.388	-0.476	-0.347	-0.088	**-0.041**
O2	-0.371	-0.497	-0.307	-0.126	-0.064
N3	-0.839	-0.821	-0.811	0.018	-0.028
N4	-0.844	-0.846	-0.826	-0.002	**-0.018**
C5	-0.184	-0.188	-0.155	-0.004	-0.029
C6	-0.113	-0.145	-0.070	-0.032	-0.043
C7	-0.185	-0.188	-0.155	-0.003	-0.03
C8	-0.032	-0.071	-0.020	-0.039	-0.012

The charge distribution on atoms in the model compound **3a** as shown by Mulliken population analysis in the following table and the electron density represented by the following graphical presentation suggests that the oxygen atom is the hard site of the ambident nucleophile **3a,** Table 2, figure 2.

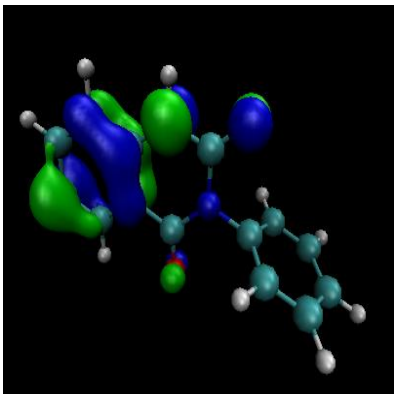
Table 2. Mulliken population analysis **3a**

Atom	Mulliken atomic charges
O1	**-0.388**
O2	-0.371
N3	-0.839
N4	**-0.844**
C5	-0.184
C6	-0.113
C7	-0.185



Total electron density of **3a**

Figure 2

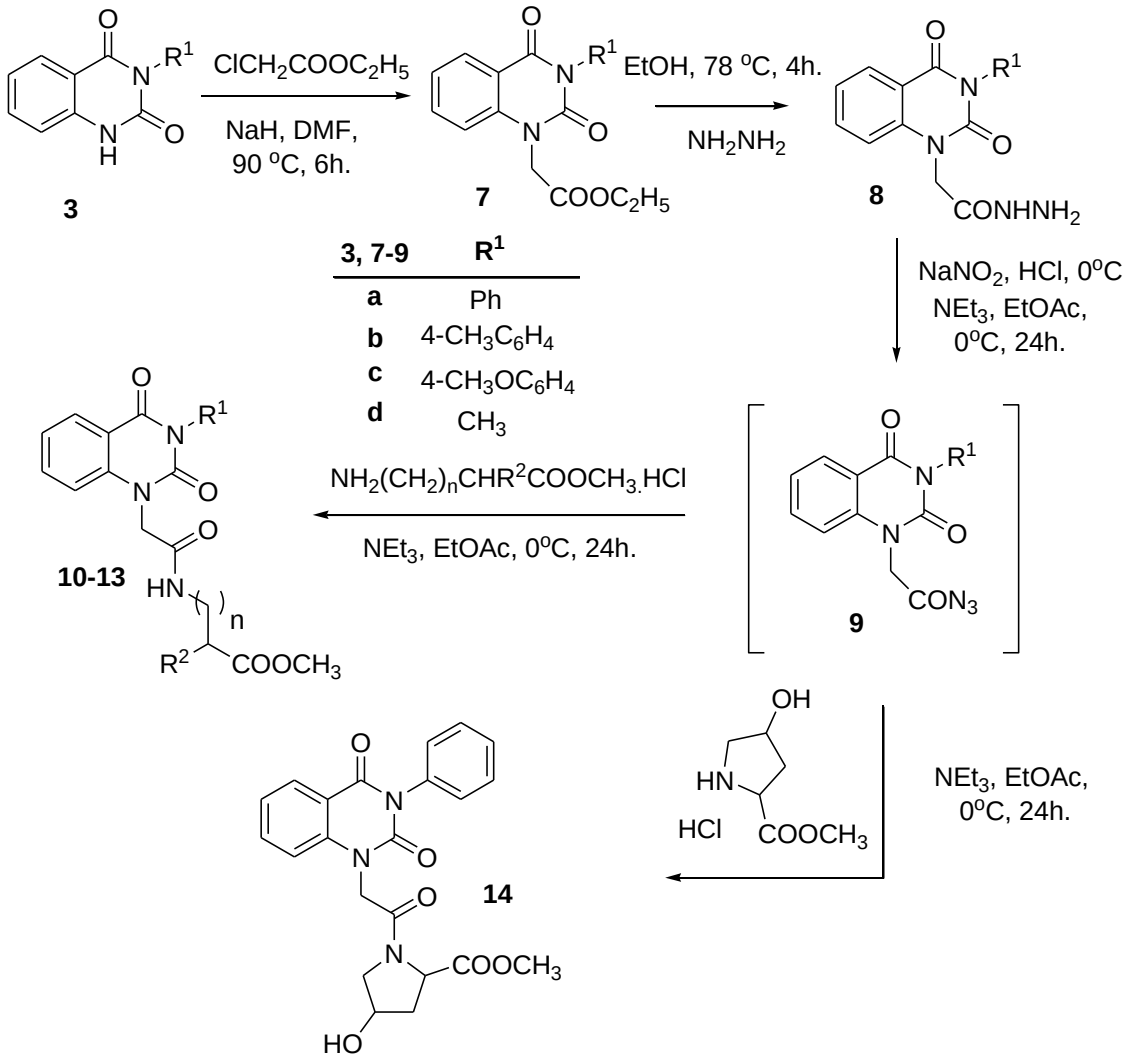


HOMO orbital of **3a**

Figure 3

Finally, the graphical presentation of the HOMO orbitals shown, describes that the nitrogen atom has the highest-occupied molecular orbitals (HOMO) of high energy compared to that of oxygen atom, Figure 3.

To summarize the results obtained from computational studies we found out that the nitrogen atom of the ambident nucleophile **3a** has larger Fukui function, lower electron density, polarizable, high chemical reactivity and is termed as the soft part of the ambident nucleophile. The obtained chemoselective N-alkylation reaction of **3a** with ethyl chloroacetate was favoured due to interaction between HOMO at the nitrogen atom of the ambident nucleophile with high energy and the LUMO of the electrophile with low energy, resulting in a narrow energy gap and high reactivity to finally give N-alkylation. This result was deduced on the basis of Pearson`s hard soft- acid base (HSAB) principle.



10-13	R^1	n	R^2	10-13	R^1	n	R^2
10a	Ph	0	H	**12b**	4-$CH_3OC_6H_4$	0	CH_3
10b	Ph	0	CH_3	**12c**	4-$CH_3OC_6H_4$	1	H
10d	Ph	0	$CH_2CH(CH_3)_2$	**12d**	4-$CH_3OC_6H_4$	0	$CH_2CH(CH_3)_2$
10e	Ph	0	CH_2OH	**12f**	4-$CH_3OC_6H_4$	0	$CH(CH_3)OH$
10f	Ph	0	$CH(CH_3)OH$	**13a**	CH_3	0	H
11c	4-$CH_3C_6H_4$	1	H	**13b**	CH_3	0	CH_3
12a	4-$CH_3OC_6H_4$	0	H	**13c**	CH_3	1	H

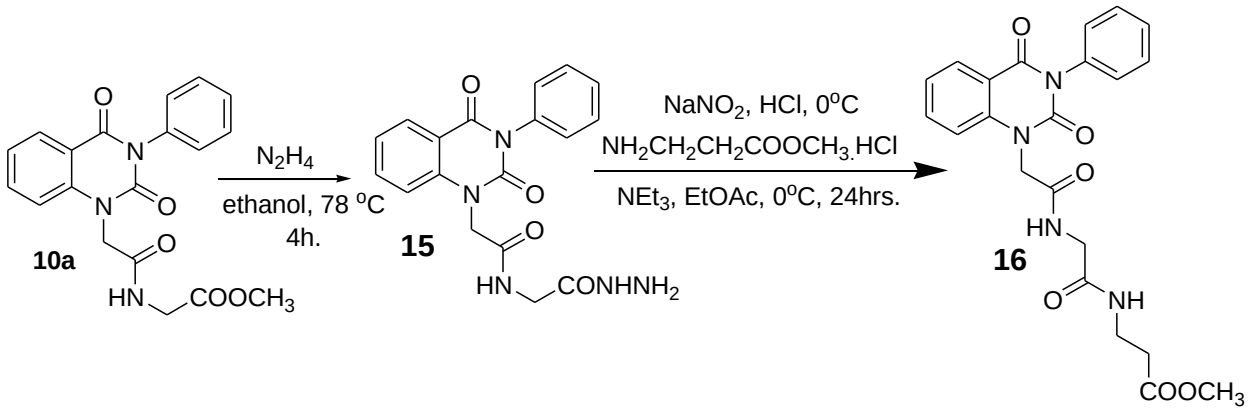
Scheme 3

The esters **7a-d** were reacted with hydrazine hydrate in ethyl alcohol for 4 h and gave hydrazide **8a-d**, Scheme 3. Hydrazides **8a-d** are excellent precursors for the quinazoline structure modification *via* azide coupling method. Azide coupling method is well recognized in the field of amino acid and protein chemistry *via* peptide bond formation leading to decrease in degree of racemization with easily removable by products. Thus, the reaction of hydrazides **8a-d** with $NaNO_2$ and HCl mixture at 0 °C principally gave the azide **9a-d**. The in situ generated azide **9a-d** solution in ethyl acetate subsequently reacted with amino acid methyl ester

hydrochloride in the presence of triethyl amine to afford methyl 2-(2-(2,4-dioxo-3-substitutedquinazolin-1-yl)acetamido) alkanoate **10**-**13** in moderate to good yields. The in situ generated azide **9a** also reacted with hydroxy proline hydrochloride in the presence of NEt_3 and gave the N-substituted hydroxy proline derivative **14** in 62 % yield, Scheme 3.

The structure assignment of 2-(2-(2,4-dioxo-3-substitutedquinazolin-1-yl)acetamido) alkanoate **10-13** was based on ^1H, ^{13}C NMR as well as physicochemical analysis. The ^1H NMR clearly confirm the alkylation site for all the isolated *N*-substituted derivatives **10-13**. Thus the ^1H NMR spectrum of **10a** exhibits a singlet signal at δ 4.82 ppm typically associated with NCH_2 group. The ^1H NMR also gave triplet, doublet and singlet signals at 8.73, 3.89 and 3.61 ppm associated with NH, $NHC\underline{H}_2$ and OCH_3 respectively. The ^{13}C NMR spectra of **10-13** gave clear evidence for the site of alkylation. Thus, the ^{13}C NMR spectrum of **10a** showed signals at *δ* 170.0, 167.4, 161.4, 51.8, 46.0 and 39.6 ppm associated with three amide carbonyl quaternary carbons, OCH_3, NCH_2, $NHCH_2$, respectively.

The amino acid ester derivative **10a** was our key substrate to produce the quinazoline ring system linked to a dipeptide by a spacer as a representative example. Thus the reaction of hydrazine hydrate with **10a** in ethanol under reflux condition for 4 h afforded the hydrazide **15**. Reaction of hydrazide **15** with β-alanine methyl ester in the presence of acetic acid, hydrochloric acid and sodium nitrite to produce the corresponding dipeptide **16** *via* azide coupling method discussed earlier.



Scheme 4

The structure of dipeptide **16** was confirmed by ^1H NMR and ^{13}C NMR. The ^1H NMR spectrum of **16** exhibits a multiplet signal at δ 3.52-3.46 ppm associated with four protons of two $NHCH_2$ groups. The ^1H NMR also gave signals at 7.00, 6.52, 3.98, 3.64 and 3.52-3.46 ppm associated with NH, NH, $NC\underline{H}_2$, OCH_3 and CH_2 groups, respectively. The ^{13}C NMR spectrrum showed signals at 172.8, 168.0, 167.4 and 135.7 ppm for (CO) groups, signals at 128.9, 128.3, 123.8, and 114.2 ppm for C-Ar group, signal at 51.8 ppm for NCH_2 group, signal at 47.6 ppm for OCH_3 group, signal at 35.0 ppm for $NH\underline{CH}_2$ group and signal at 33.5 ppm for CH_2 group.

Experimental Section

General. The boiling point range of the petroleum ether used was 40-60 ^{0}C. Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm), The spots on thin layer plates were detected by UV lamp. Melting points were determined on a Buchi 510 melting-point apparatus

and the values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively (Bruker AC 300) in $CDCl_3$ and DMSO solution with tetramethylsilane as an internal standard. The NMR analysis were performed at the Organic Chemistry Department Masaryk University, Brno, Czech Republic. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Quinazoline derivatives, their ester and hydrazide **3-5** were prepared according to the method described.[42-47]

General procedures for preparation compounds 2-(3-aryl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (6a-d). To a solution of ester **5a-d** (1.0 mmol) in ethyl alcohol (30 mL), hydrazine hydrate (2.4 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 hours, cooled and the resultant precipitate was filtered off, washed with ethanol and ether then crystallized from ethanol to yield the hydrazide as a white crystals **6a-d**.

2-(3-Phenyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (6a).[20] White crystals (0.14 g, 59%). Mp 187-188 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 9.31 (1H, bs, NH), 8.10-8.08 (1H, m, Ar-H), 7.94-7.83 (2H, m, Ar-H), 7.65-7.31 (6H, m, Ar-H), 4.25(2H, s, NH_2), 3.86 (2H, s, SCH_2). ^{13}C NMR (75.0 MHz, $CDCl_3$): 166.6 (CO), 161.2 (CO), 157.2, 147.6, 136.2, 135.4, 130.4, 130.0, 129.9, 127.0, 126.6, 126.5, 120.0 (C-Ar), 35.0 (SCH_2). Found, %: C: 58.73; H: 4.11; N: 17.32. For $C_{16}H_{14}N_4O_2S$ (326.1). Calculated, %: C: 58.88; H: 4.32; N: 17.17.

2-(3,4-Dihydro-4-oxo-3-*p*-tolylquinazolin-2-ylthio)acetohydrazide (6b). White crystals (0.20 g, 61%), mp 195-196 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 9.38 (1H, bs, NH), 8.04 (1H, d, *J* 8.1 Hz, ArH), 7.84 (1H, t, *J* 8.1 Hz, ArH), 7.63 (2H, d, *J* 8.0 Hz, ArH), 7.50 (1H, t, *J* 8.1 Hz, ArH), 7.47–7.30 (3H, m, ArH), 4.48 (3H, bs, NH_2), 3.93 (2H, s, SCH_2), 2.42 (3H, s, CH_3). Found, %: C, 59.63; H, 4.61; N, 16.37. For $C_{17}H_{16}N_4O_2S$ (340.1). Calculated, %: C, 59.98; H, 4.74; N, 16.46.

2-(3-(4-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio)aceto hydrazide (6c).[20] White crystals (0.27 g, 77 %), mp 211-212 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 11.48 (1H, bs, NH), 7.95-7.92 (1H, m, Ar-H), 7.71-7.66 (1H, m, Ar-H), 7.66-7.19 (4H, m, Ar-H), 7.03-6.99 (2H, m, Ar-H), 3.77 (2H, s, SCH_2), 3.33 (2H, bs, NH_2). Found, %: C: 57.52; H: 4.62; N: 15.90. For $C_{17}H_{16}N_4O_3S$ (356.1). Calculated, %: C: 57.29; H: 4.52; N: 15.72.

2-(3-Methyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (6d).[20] White crystals (0.23 g, 89 %); mp 195-196 °C. ^{1}H NMR (300 MHz, DMSO): 8.30 (1H, bs, NH), 7.70-7.30 (4H, m, Ar-H), 3.80 (2H, s, SCH_2), 3.71 (3H, s, NCH_3), 1.70 (2H, bs, NH_2). Found, %: C: 50.09; H: 4.58; N: 21.08. For $C_{11}H_{12}N_4O_2S$ (264.1). Calculated, %: C: 49.99; H: 4.58; N: 21.20.

General procedures for preparation of compounds 3-alkylquinazoline-2,4-(1*H*,3*H*)-dione (3a-d). To a cold solution (-5 ^{o}C) of hydrazide **6a-d** (1.0 mmol) in AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of $NaNO_2$ (0.34 g, 5.0 mmol) in cold water (3 mL). After stirring at -5 ^{o}C for 1 hour, a thick precipitate was formed. The reaction mixture was extracted in cold ethyl acetate (30 mL), washed with cold 3% $NaHCO_3$, H_2O and finally dried by (Na_2SO_4). The reaction mixture mixture was kept at -5 $^{\circ}$C for 24 hour, then at 25 $^{\circ}$C for another 24 hour. The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether/ ethyl acetate to give the corresponding quinazoline dione **3a-d**.

3-Phenylquinazoline-2,4-(1*H*,3*H*)-dione (3a).[20,48] White crystals (0.16 g, 67 %), mp 235-236 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$):11.50 (1H, bs, NH), 7.97-7.21 (9H, m Ar-H). ^{13}C NMR (75.0 MHz, $CDCl_3$): 162.6 (CO), 150.6 (CO), 140.3, 136.2, 135.6, 129.5, 129.2, 128.5, 128.0, 122.9, 115.7, 114.7 (C-Ar). Found, %: C: 70.63; H: 4.70; N: 11.97. For $C_{14}H_{10}N_2O_2$ (238.1). Calculated, %: C: 70.58; H: 4.23; N: 11.76.

3-(4-Methylphenyl)quinazoline-2,4(1*H*,3*H*)-dione (3b).[49] White crystals (0.07 g, 28 %), mp 263-264 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 9.91 (1H, bs, NH), 8.17 (1 H, d, *J* 8.0 Hz, Ar-H), 7.69 (2H, d, *J* 8.0 Hz, ArH), 7.60-7.53 (1 H, m,

Ar-H), 7.50 (1H, t, *J* 8.1 Hz, ArH), 7.41–7.30 (3H, m, ArH), 2.42 (3H, s, CH_3). Found, %: C: 71.28; H: 4.63; N: 10.67. For $C_{15}H_{12}N_2O_2$ (252.1). Calculated, %: C: 71.42; H: 4.79; N: 11.10.

3-(4-Methoxyphenylquinazoline-2,4-(1*H*,3*H*)-dione (3c).[50-51] White crystals (0.18 g, 66%), mp 301-302 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 11.48 (1H, bs, NH), 8.35 (1H, d, *J* 9.0 Hz, Ar-H), 8.31-8.09 (1H, t, *J* 9.0 Hz, Ar-H), 8.07 (1H, m, Ar-H), 7.92-7.04 (5H, m, Ar-H), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 162.8 (CO), 160.1 (CO), 159.6, 150.9, 140.2, 136.3, 133.1, 130.5, 129.9, 129.0, 127.8, 122.9, 117.8, 115.6, (C-Ar), 55.8 (OCH_3). Found, %: C: 67.02; H: 4.75; N: 10.10. For $C_{15}H_{12}N_2O_3$ (268.1). Calculated, %: C: 67.16; H: 4.51; N: 10.44.

3-Methylquinazoline-2,4-(1*H*,3*H*)-dione (3d).[48] White crystals (0.11 g, 62%), m.p 240-241 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 10.35 (1H, s, NH), 7.89-7.7.70 (4H, m, Ar-H), 3.23 (3H, s, CH_3). Found, %: C: 61.88; H: 4.78; N: 16.14. For $C_9H_8N_2O_2$ (176.1). Calculated, %: C: 61.36; H: 4.58; N: 15.90.

General procedures for preparation of alkyl 2-(3-substituted-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (7a-d). To a mixture of quinazoline dione **3a-d** (1.0 mmol) and Sodium hydride 60 % (0.38 g, 2 mmol) dispersion in mineral oil in dry DMF (10 mL) was added ethyl chloroacetate (0.1 mL, 1.1 mmol). The reaction mixture was heated at 90 ^{o}C for 6 h. The reaction mixture was avaporated under reduced pressure and the solid obtained was recrystallized from ethyl alcohol.

Ethyl-2-(3-phenyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (7a). White crystals (0.21 g, 64%), mp 239-240 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.33 (1H, d, *J* 12.0 Hz, Ar-H), 7.74 (1H, t, *J* 9.0 Hz, Ar-H), 7.56-7.35 (3H, m, Ar-H), 7.33-7.28 (3H, m, Ar-H), 7.07-7.04 (1H, d, *J* 9.0 Hz, Ar-H), 4.95 (2H, s, NCH_2), 4.33 (2H, q, *J* 9.0 Hz, CH_2), 1.34 (3H, t, *J* 9.0 Hz, CH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 167.7 (CO), 161.7 (CO), 151.1 (CO), 140.0, 135.5, 135.3, 129.7, 129.4, 128.8, 128.4, 123.5, 116.1, 113.2 (C-Ar), 62.01 (CH_2), 44.9 (NCH_2), 14.41 (CH_3). Found, %: C: 66.53; H: 4.76; N: 8.41. For $C_{18}H_{16}N_2O_4$ (324.1). Calculated, %: C: 66.66; H: 4.97; N: 8.64.

Ethyl 2-(3,4-dihydro-2,4-dioxo-3-p-tolylquinazolin-1(2*H*)-yl)acetate (7b). White crystals (0.12 g, 35%), mp 218-219 ^{0}C. ^{1}HNMR (300 MHz, $CDCl_3$): 7.96 (1H, d, *J* 8.1 Hz, ArH), 7.91 (1H, t, *J* 8.1 Hz, ArH), 7.59 (2H, d, *J* 8.1 Hz, ArH), 7.47 (1H, t, *J* 8.1 Hz, ArH), 7.37 -7.31 (3H, m, ArH), 4.81 (2H, d, *J* 9.0 Hz, NCH_2), 4.33 (2 H, q, *J* 8.0 Hz, OCH_2), 2.31 (3H, s, CH_3), 1.32 (3 H, t, *J* 8.0 Hz, CH_3). Found, %: C, 67.35; H, 5.21; N, 8.14. For $C_{19}H_{18}N_2O_4$ (338.1). Calculated, %: C, 67.44; H, 5.36; N, 8.28.

Methyl-2-(3-(4-methoxyphenyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (7c). White crystals (0.25 g, 76%), mp 248-249 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 8.35-7.12 (8H, m, Ar-H), 8.12-8.06 (1H, m, Ar-H), 7.81-7.75 (1H, m, Ar-H), 7.48-7.44 (2H, m, Ar-H), 7.19-7.12 (2H, m, Ar-H), 4.83 (2H, s, NCH_2), 3.31(6H, s, $2OCH_3$). Found, %: C, 63.49; H, 4.65; N, 8.11. For $C_{18}H_{16}N_2O_5$ (340.1). Calculated, %: C, 63.52; H, 4.74; N, 8.23.

Ethyl 2-(3,4-dihydro-3-methyl-2,4-dioxoquinazolin-1(2*H*)-yl)acetate (7d). White crystals (0.20 g, 78 %), mp 227-228 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.15 (1H, d, *J* 9.0 Hz, Ar-H), 7.75 (1H, t, *J* 9.0Hz, Ar-H), 7.36-7.25 (2H, m, Ar-H), 4.91 (2H, s, NCH_2), 4.33 (2 H, q, *J* 7.06 Hz, OCH_2), 3.50 (3H, s, NCH_3), 1.32 (3 H, t, *J* 7.02 Hz, CH_3). Found, %: C C, 59.35; H, 5.28; N, 10.51. For $C_{13}H_{14}N_2O_4$ (262.1). Calculated, %: C, 59.54; H, 5.38; N, 10.68.

General procedures for preparation of 2-(3-alkyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetohydrazide (8a-d). To a solution of ester **7a-d** (1.0 mmol) in ethyl alcohol (30 mL), hydrazine hydrate (2.4 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 hours, cooled and the resultant precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazide as a white crystals **8a-d**.

2-(2,4-Dioxo-3-phenyl-3,4-dihydroquinazolin-1(2*H*)-yl) acetohydrazide (8a). White crystals (0.23 g, 74%), mp 196-197 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 9.40 (1H, bs, NH), 8.10-7.53 (3H, m, Ar-H), 7.51-7.29 (6H, m, Ar-H), 4.76 (2H, s, NCH_2), 3.38 (2H, bs, NH_2). Found, %: C: 61.70; H: 4.32; N: 17.8. For $C_{16}H_{14}N_4O_3$ (310.1). Calculated, %: C: 61.93; H: 4.55; N: 18.06.

2-(3,4-Dihydro-2,4-dioxo-3-p-tolylquinazolin-1(2*H*)-yl)acetohydrazide (8b). White crystals (0.16 g, 51 %), mp 221-222 ^{0}C. ^{1}HNMR (300 MHz, DMSO): 9.41 (1H, bs, NH), 8.07 (1H, d, *J* 7.8 Hz, ArH), 7.83 (1H, t, *J* 7.8 Hz, ArH), 7.55 (2H, d, *J* 8.0 Hz, ArH), 7.49 (1H, t, *J* 7.8 Hz, ArH), 7.46 -7.30 (3H, m, ArH), 5.25 (3H, bs, NH_2), 4.84 (2H, s, NCH_2), 2.31 (3H, s, CH_3). Found, %: C, 62.81; H, 4.84; N, 17.15. For $C_{17}H_{16}N_4O_3$ (324.1). Calculated, %: C, 62.95; H, 4.97; N, 17.27.

2-(3-(4-Methoxyphenyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl) aceto hydrazide (8c). White crystals (0.25 g, 72%), mp 232-233 ^{0}C. ^{1}HNMR (300 MHz, DMSO): 8.34-8.29 (2H, m, Ar-H), 8.11-8.06 (1H, m, NH), 7.80-7.75 (1H, m, Ar-H), 7.48-7.44 (3H, m, Ar-H), 7.15-7.12 (3H, m, Ar-H), 4.48 (2H, s, NCH_2), 3.31 (3H, s, OCH_3). Found, %: C: 60.27; H: 4.23; N: 16.51. For $C_{17}H_{16}N_4O_4$ (340.1). Calculated, %: C: 59.99; H: 4.74; N: 16.46.

2-(3,4-dihydro-3-methyl-2,4-dioxoquinazolin-1(2H)-yl)acetohydrazide (8d). White crystals (0.12 g, 49 %), mp 194-195 ^{0}C. ^{1}HNMR (300 MHz, DMSO): 8.84 (1H, bs, NH), 8.16 (1H, d, *J* 8.0 Hz, Ar-H), 7.57 (1H, t, *J* 8.0 Hz, Ar-H), 7.39-7.26 (2H, m, Ar-H), 4.75 (2H, s, NCH_2), 3.50 (3H, s, CH_3)**,** 3.37 (2H, bs, NH_2). Found, %: C, 53.01; H, 4.65; N, 22.48. For $C_{11}H_{12}N_4O_3$ (248.1). Calculated, %: C, 53.22; H, 4.87; N, 22.57.

General procedures for preparation of methyl 2-(2-(2,4-dioxo-3-substitutedquinazolin-1-yl)acetamido) alkanoates (10-13). To a cold solution (-5 ^{o}C) of hydrazide **8a-d** (1.0 mmol) in AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of $NaNO_2$ (0.07 g, 1.0 mmol) in cold water (3 mL). After stirring at -5 ^{o}C for 1 hour, a thick precipitate was formed. The reaction mixture was extracted in cold ethyl acetate (30 mL), washed with cold 3% $NaHCO_3$, H_2O and finally dried by (Na_2SO_4). A solution of amino acid esters hydrochloride (1.2 mmol) in ethyl acetate (20 mL) containing 0.2 mL of triethyl amine was added to the azide solution **9**. The mixture was kept at -5 ^{o}C for 24 h., then at 25 ^{o}C for another 24 h., followed by washing with 0.5 N HCl, water, 3% solution of $NaHCO_3$ and finally dried by (Na_2SO_4). The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether/ ethyl acetate 3:1 to give the corresponding quinazoline amino acid ester derivatives **10-13.**.

Methyl 2-(2-(2,4-dioxo-3-phenylquinazolin-1-yl)acetamido) acetate (10a). White crystals (0.24 g, 65%), mp 247-248 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.73 (1H, s, NH), 8.09-7.33 (9H, m, Ar-H), 4.82 (2H, s, NCH_2), 3.89 (2H, d, *J* 9.0 Hz, NCH_2), 3.61 (3H, s, OCH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 170.0 (CO), 167.4 (CO), 161.4 (CO), 150.6 (CO), 140.3, 136.1, 135.5, 129.0, 128.8, 123.1, 115.6, 115.0 (C-Ar), 51.8 (NCH_2), 46.0 (OCH_3), 39.6 ($NHCH_2$). Found, %: C: 61.80; H: 5.01; N: 11.83. For $C_{19}H_{17}N_3O_5$ (367.1). Calculated, %: C: 62.12; H: 4.66; N: 11.44.

Methyl 2-(2-(2,4-dioxo-3-phenylquinazolin-1-yl)acetamido) propanoate (10b). White crystals (0.27 g, 70 %), mp 210-211 ^{0}C.^{1}H NMR (300 MHz, $CDCl_3$): 9.85 (1H, bs, NH), 8.30 (1H, d, *J* 9.0 Hz, Ar-H), 8.17 (1H, d, *J* 9.0 Hz, Ar-H), 7.57-7.46 (4H, m, Ar-H), 7.35-7.20 (3H, m, Ar-H), 4.90-4.79 (2H, m, NCH_2), 4.66-4.55 (1H, m, NHCH), 3.73 (3H, s, OCH_3) , 1.42-1.39 (3H, d, *J* 9.0Hz, CH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 173.0 (CO), 167.0 (CO), 162.0 (CO), 152.0 (CO), 138.8, 135.7, 135.3, 134.8, 129.4, 129.3, 128.8, 128.4, 123.5, 115.2 (C-Ar), 52.5 (OCH_3), 48.3 (NCH_2), 47.8 (NCH), 18.0 ($CHCH_3$). Found, %: C: 62.50; H: 5.39; N: 11.15. For $C_{20}H_{19}N_3O_5$ (381.1). Calculated, %: C: 62.99; H: 5.02; N: 11.02.

Methyl 4-methyl-2-(2-(2,4-dioxo-3-phenylquinazolin-1-yl)acetamido) pentanoate (10d). White crystals (0.34 g, 81 %), mp 202-203 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 8.10 (1H, d, *J* 9.0 Hz, NH), 8.09-8.08 (1H, m, Ar-H), 7.93-7.91 (1H, m, Ar-H), 7.79-7.79 (1H, m, Ar-H), 7.52-7.39 (1H, m, Ar-H), 7.34-7.17 (5H, m, Ar-H), 4.84-4.81 (2H, m, NCH_2), 4.35-4.33 (1H, m, NCH), 3.61 (3H, s, OCH_3), 1.71-1.58 (3H, m, CH_2, CH), 0.89 (6H, 2d, *J* 6.0 Hz, $2CH_3$). ^{13}C NMR (75.0 MHz, DMSO): 172.7 (CO), 167.0 (CO), 161.4, 151.0 (CO), 140.4, 136.0, 135.4, 135.0, 129.1, 129.0, 128.8, 128.7, 128.3, 128.1, 128.0, 127.5, 123.0, 122.1, 115.5, 114.5, 114.4 (C-Ar), 52.0 (NCH_2), 50.3 (OCH_3), 45.8 (NHCH), 24.2 (CH_2), 22.8 (CH), 21.2 ($2CH_3$). Found, %: C: 64.80; H: 6.07; N: 10.14. For $C_{23}H_{25}N_3O_5$ (423.2). Calculated, %: C: 65.24; H: 5.95; N: 9.92.

Methyl 3-hydroxy-2-(2-(2,4-dioxo-3-phenylquinazolin-1-yl)acetamido) propanoate (10e). White crystals (0.18 g, 45 %), mp 231-232 ^{0}C.^{1}H NMR (300 MHz, $CDCl_3$): 8.92 (1H, d, *J* 9.0Hz , Ar-H), 8.10 (1H, d, *J* 9.0Hz, Ar-H), 7.81-7.75 (1H, m, Ar-H), 7.53-7.21 (6H, m, Ar-H), 7.20 (1H, d, *J* 6.0Hz, NH), 4.85 (2H, s, NCH_2), 4.68-4.59 (1H, m, NHCH), 3.65 (3H, s, OCH_3), 3.33-3.05 (3H, m, CH_2, OH). ^{13}C NMR (75.0MHz, $CDCl_3$): 171.0 (CO), 167.5 (CO), 161.8 (CO), 151.0 (CO), 140.7, 136.4, 136.0, 129.3, 129.2, 128.7, 128.5, 115.9, 115.0 (C-Ar), 52.7 (OCH_3), 51.8 (NCH_2), 46.2 (NHCH), 46.0 (CH_2OH). Found, %: C: 60.86; H: 4.45; N: 10.29. For $C_{20}H_{19}N_3O_6$ (397.1). Calculated, %: C: 60.45; H: 4.82; N: 10.57.

Methyl 3-hydroxy-2-(2-(2,4-dioxo-3-phenyl-quinazolin-1-yl)acetamido) butanoate (10f). White crystals (0.29 g, 71%), mp 286-287 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.95 (1H , d , *J* 6.0 H_Z , Ar-H) , 7.72 (1H, d, *J* 9.0 H_Z, Ar-H), 7.25-7.22 (4H, m, Ar-H), 7.04-7.01 (2H, m, *J* 9.0 H_Z, Ar-H), 5.10-5.08 (1H, m, CH), 4.85 (2H, s, NCH_2), 4.13–4.25 (1H, m, CH), 3.82 (3H, s, OCH_3), 2.50 (1H, s, OH), 1.21 (3H, d, *J* 7.2, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 163 (CO), 159 (CO), 151 (CO), 140 (CO), 136, 130, 129, 123, 116, 115, 114 (C-Ar), 63.2 (CH), 52.7 (OCH_3), 47.9 (NCH_2), 46.1 (CH), 24.92 (CH_3). Found, %: C: 61.50; H: 4.93; N: 9.88. For $C_{21}H_{21}N_3O_6$ (411.1). Calculated, %: C: 61.31; H: 5.14; N: 10.21.

Methyl 3-(2-(2,4-dioxo-3-(4-methylphenyl)quinazolin-1-yl)acetamido) propanoate (11c). White crystals (0.21 g, 54 %), mp 239-240 ^{0}C.^{1}H NMR (300 MHz, $CDCL_3$): 8.30 (1H, d, *J* 9.0 Hz, Ar-H), 7.74 (1H, t, *J* 9.0 Hz, Ar-H), 7.39-7.20 (7H, m, Ar-H), 6.79 (1H, bs, NH), 4.78 (2H, s, NCH_2), 3.68-3.42 (5H, m, OCH_3, CH_2), 2.52 (2H, t, *J* 6.0 Hz, CH_2), 2.44 (3H, s, CH_3). ^{13}C NMR (75.0 MHz, $CDCL_3$): 172.0 (CO), 167.1 (CO), 163.1 (CO), 152.0 (CO), 135.5, 130.1, 129.4, 127.9, 123.8, 114.3, 102.9 (C-Ar), 51.7 (OCH_3), 48.0 (CH_2), 35.0 (NCH_2), 33.5 (CH_2), 21.2 (CH_3). Found, %: C: 63.45; H: 5.06; N: 10.32. For $C_{21}H_{21}N_3O_5$ (395.2). Calculated, %: C: 63.79; H: 5.35; N: 10.63.

Methyl 2-(2-(2,4-dioxo-3-(4-methoxyphenyl)quinazolin-1-yl)acetamido) acetate (12a). White crystals (0.24 g, 61 %), mp 248-249 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.30 (1H, d, *J* 9.0Hz, Ar-H), 7.75 (1H, t, *J* 9.0Hz, Ar-H), 7.43-7.22 (4H, m, Ar-H), 7.03 (2H, d, *J* 6.0Hz, NH), 4.85 (2H, s, NCH_2), 4.06 (2H, d, *J* 3.0Hz, NCH_2), 3.87 (3H, s, OCH_3), 3.74 (3H, s, OCH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 169.7 (CO), 167.3 (CO), 159.7 (CO), 152.1 (CO), 140.0, 135.7, 129.4, 129.3, 127.7, 123.9, 116.0, 114.8, 114.4 (C-Ar) 55.5 (OCH_3), 52.4 (OCH_3), 47.8 (NCH_2), 41.2 (NCH_2). Found, %: C: 60.14; H: 4.40; N: 10.93. For $C_{20}H_{19}N_3O_6$ (397.1). Calculated, %: C: 60.45; H: 4.82; N: 10.57.

Methyl 2-(2-(2,4-dioxo-3-(4-methoxyphenyl)quinazolin-1-yl)acetamido) propanoate (12b). White crystals (0.28 g, 69 %), mp 216-217 ^{0}C.^{1}H NMR (300 MHz, $CDCl_3$): 8.29 (1H , d, *J* 9.0 Hz, Ar-H), 7.73-7.71(1H, t, *J* 9.0 Hz, Ar-H), 7.38-7.22 (4H, m, Ar-H), 7.03 (2H, d, *J* 9.0 Hz, Ar-H), 6.78 (1H, d, *J* 9.0 Hz, NH), 4.88-4.76 (2H, m, NCH_2), 4.65-4.55 (1H, m, NCH), 3.87 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 1.42 (3H, d, *J* 9.0 Hz, CH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 172.8 (CO), 166.6 (CO), 161.8 (CO), 159.7 (CO), 151.9, 140.1, 135.7, 123.8, 116.1, 114.8, 114.3 (C-Ar), 55.5 (OCH_3), 52.5 (OCH_3), 48.3 (NCH_2), 47.7 (NHCH), 18.2 (CH_3). Found, %: C: 61.03; H: 5.45; N: 10.70. For $C_{21}H_{21}N_3O_6$ (411.1). Calculated, %: C: 61.31; H: 5.14; N: 10.21.

Methyl 3-(2-(2,4-dioxo-3-(4-methoxyphenyl)quinazolin-1-yl)acetamido) propanoate (12c). White crystals (0.32 g, 79 %), mp 224-225 ^{0}C.^{1}H NMR (300 MHz, $CDCl_3$): 8.29 (1H, d, *J* 6.0 Hz, Ar-H), 7.75 (1H, t, *J* 6.0 Hz, Ar-H), 7.37-7.21 (4H, m, Ar-H), 7.06-7.03 (2H, m, Ar-H), 6.87 (1H, bs, NH), 4.78 (2H, s, NCH_2), 3.60 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.53 (2H, q, *J* 9.0Hz, NCH_2), 2.54 (2H, t, *J* 6.0 Hz, NCH_2). ^{13}C NMR (75.0 MHz, $CDCl_3$): 172.6 (CO), 167.1 (CO), 159.7 (CO), 151.9 (CO), 140.0, 135.7, 129.4, 129.3, 123.8, 114.7, 114.2, (C-Ar), 55.5 (OCH_3), 51.8 (OCH_3), 45.1 (NCH_2), 35.1 (CH_2), 33.5 (CH_2). Found, %: C: 60.98; H: 4.86; N: 10.51. For $C_{21}H_{21}N_3O_6$ (411.1). Calculated, %: C: 61.31; H: 5.14; N: 10.21.

Methyl 4-methyl-2-(2-(2,4-dioxo-3-(4-methoxyphenyl)quinazolin-1-yl)acetamido) pentanoate (12d). Faint yellow crystals (0.32 g, 71%), mp 227-228 ^{0}C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.29 (1H, d, *J* 6.0 Hz, Ar-H), 7.40-7.28 (1H, m, Ar-H), 7.24-7.21 (5H, m, Ar-H), 7.06-7.03 (2H, d, *J* 9.0Hz, Ar-H), 6.67 (1H, d, *J* 6.0 Hz, NH), 4.82 (2H, s, NCH_2), 4.65-4.55 (1H, m, NCH), 3.86 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 1.69-1.42 (3H, m, CH_2CH), 0.92 (6H, d, *J*

6.0 Hz, CH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 172.8 (CO), 167.0 (CO), 161.8 (CO), 159.7 (CO), 140.0, 135.7, 129.4, 129.3, 127.8, 123.8, 116.0, 114.8, 114.4 (C-Ar), 55.5 (OCH_3), 52.1 (OCH_3), 50.9 (NCH), 47.7 (NCH_2), 24.9 (CH_2), 22.7 (CH), 21.8 (CH_3). Found, %: C: 63.15; H: 5.87; N: 9.70. For $C_{24}H_{27}N_3O_6$ (453.2). Calculated, %: C: 63.56; H: 6.00; N: 9.27.

Methyl 3-hydroxy-2-(2-(2,4-dioxo-3-(4-methoxyphenyl)quinazolin-1-yl)acet-amido) butanoate (12f). White crystals (0.32 g, 72 %), mp 220-221 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 8.56 (1H, d, *J* 6.0 Hz, NH), 8.08-8.05 (1H, d, Ar-H), 7.75 (1H, m, Ar-H), 7.34-7.18 (4H, m, Ar-H), 7.04 (2H, d, *J* 9.0 Hz, Ar-H), 5.10-5.08 (1H, m, CH), 4.94-4.92 (2H, m, NCH_2), 4.36-4.32 (1H, m, CH), 4.11 (1H, bs, OH), 3.81 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 1.10 (3H, d, *J* 6.0 Hz, CH_3). m/z 442. Found, %: C: 60.19; H: 5.32; N: 9.11. For $C_{22}H_{23}N_3O_7$ (441.2). Calculated, %: C: 59.86; H: 5.25; N: 9.52.

Methyl 2-(2-(2,4-dioxo-3-methylquinazolin-1-yl)acetamido) acetate (13a). White crystals (0.23 g, 74%), mp 285-284 ^{0}C.^{1}H NMR (300 MHz, $CDCl_3$): 8.25 (1H, d, *J* 9.0 Hz, Ar-H), 7.70 (1H, t, *J* 9.0 Hz, Ar-H), 7.33-7.28 (2H, m, Ar-H), 6.78 (1H, bro, NH), 4.85 (2H, s, NCH_2), 4.08 (2H, d, *J* 6.0Hz, NCH_2), 3.74 (3H, s, OCH_3), 3.50 (3H, s, NCH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 169.7 (CO), 167.4 (CO), 161.7(CO), 151.7(CO), 139.6, 135.4, 129.0, 123.7, 115.5, 114.0 (C-Ar), 52.4 (OCH_3), 47.6 (NCH_2), 41.2 ($NHCH_2$), 28.6 (NCH_3). Found, %: C: 55.01; H: 4.87; N: 13.69.. For $C_{14}H_{15}N_3O_5$ (305.1). Calculated, %: C: 55.08; H: 4.95; N: 13.76.

Methyl 2-(2-(2,4-dioxo-3-methylquinazolin-1-yl)acetamido) propanoate (13b). White crystals (0.21 g, 65 %), mp 183-184 ^{0}C.^{1}H NMR (300 MHz, $CDCL_3$): 8.22 (1H, d, *J* 9.0 Hz, Ar-H), 7.68 (1H, t, *J* 9.0Hz, Ar-H), 7.31-7.24 (2H, m, Ar-H), 6.80 (1H, d, *J* 6.0 Hz, NH), 4.82 (2H, s, NCH_2), 4.65-4.55 (1H, m, NCH), 3.72 (3H, s, OCH_3), 3.50 (3H, s, CH_3), 1.43 (3H, d, *J* 6.0Hz, CH_3). ^{13}C NMR (75.0 MHz, $CDCl_3$): 172.9 (CO), 166.7 (CO), 161.7 (CO), 151.7 (CO) 139.7, 135.3, 129.0, 123.6, 115.5, 114.0 (C-Ar), 52.5 (OCH_3), 48.3 (NCH_2), 47.5 (NHCH), 28.6 (NCH_3), 18.1 ($CHCH_3$). Found, %: C: 56.07; H: 4.94; N: 13.51. For $C_{15}H_{17}N_3O_5$ (319.1). Calculated, %: C: 56.42; H: 5.37; N: 13.16.

Methyl 3-(2-(2,4-dioxo-3-methylquinazolin-1-yl)acetamido) propanoate (13c). White crystals (0.25 g, 78%), mp 254-255 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 8.33 (1H, bs, Ar-H), 8.08 (1H, d, *J* 6 Hz, NH), 7.80-7.75 (1H, m, Ar-H), 7.35-7.16 (2H, m, Ar-H), 4.72 (2H, s, NCH_2), 3.58 (3H, s, OCH_3), 3.35-3.31 (2H, m, NCH_2), 2.51-2.37(5H, m, CH_2, NCH_3). Found, %: C: 56.50; H: 5.39; N: 13.15. For $C_{15}H_{17}N_3O_5$ (319.3). Calculated, %: C: 56.42; H: 5.37; N: 13.16.

Methyl 4-hydroxy-1-(2(2,4-dioxo-3-phenylquinazolin-1-yl)acetyl) pyrrolidine-2-carboxylate (14). Follows the azide coupling method of the hydrazide **8a** with hydroxyl proline methyl ester hydrochloride. White crystals (0.26 g, 62%), mp 194-195 ^{0}C. ^{1}HNMR (300 MHz, DMSO): 11.62 (1H, bs, OH), 8.04 (1H, d, *J* 9.0 Hz, Ar-H), 7.74-7.69 (2H, m, Ar-H), 7.30-7.25 (2H, m, Ar-H), 7.14-7.11 (4H, m, Ar-H), 5.33 (3H, d, *J* 6.0 Hz, NCH_2), 4.46 (2H, d, *J* 15 Hz, NCH_2), 3.89-3.57 (7H, m, *J* 12 Hz, OCH_3). ^{13}CNMR (75.0 MHz, $CDCl_3$): 172(CO), 166(CO), 162(CO), 151(CO), 141.6, 135.4, 127.8 (C-Ar), 69.4(CH), 58.19(NCH_2), 54.3 (NCH), 52.2 (OCH_3), 9.0 (CH_2). Found, %: C: 62.66; H: 4.82; N: 10.02. For $C_{22}H_{21}N_3O_6$ (423.4). Calculated, %: C: 62.41; H: 5.00; N: 9.92.

2-(2-(3,4-Dihydro-2,4-dioxo-3-phenylquinazolin-1(2*H*)-yl)acetamido) acetohydrazide (15).

To a solution of ester **10a** (0.37 g, 1.0 mmol) in ethyl alcohol (30 mL), hydrazine hydrate (2.4 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 hours, cooled and the resultant precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazide **(15)**. White crystals (0.23 g, 74%), mp 196-197 ^{0}C. ^{1}H NMR (300 MHz, DMSO): 9.26 (1H, bs, NH), 8.27-7.73 (3H, m, Ar-H), 7.63-7.31 (6 H, m, Ar-H), 4.76 (2H, s, NCH_2), 4.06 (2 H, d, *J* 3.0 Hz, NCH_2), 3.59 (2H, bs, NH_2). 4.85 (2H, s, NCH_2), Found, %: C, 58.43; H, 4.45; N, 18.87. For $C_{18}H_{17}N_5O_4$ (367.1). Calculated, %: C, 58.85; H, 4.66; N, 19.06.

General procedures for preparation of methyl 3-(2-2-((2,4-dioxo-3-(4-methylphenyl)quinazolin-1-yl)acetamido)acetamido) propanoate (16). To a cold solution (-5 ^{o}C) of hydrazide **15** (0.37 g, 1.0 mmol) in

AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of $NaNO_2$ (0.34 g, 5.0 mmol) in cold water (3 mL). After stirring at -5 ^oC for 1 h. a thick precipitate was formed. The reaction mixture was extracted in cold ethyl acetate (30 mL), washed with cold 3% $NaHCO_3$, H_2O and finally dried (Na_2SO_4). A solution of □-alanine hydrochloride (0.16 g, 1.1 mmol) in ethyl acetate (20 mL) containing 0.2 mL of triethyl amine was added to the ethyl acetate azide solution. The mixture was kept at -5 ^oC for 24 hrs., then at 25 ^oC for another 24 hrs., followed by washing with 0.5 N HCl, water, 3% solution of $NaHCO_3$ and finally dried (Na_2SO_4). The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether/ ethyl acetate to give the corresponding quinazoline dipeptide of dione derivative (**16)**. White crystals (0.27 g, 62%), mp 173-174 ^0C. ^1H NMR (300 MHz, $CDCl_3$): 8.30 (1H, d, *J* 9.0 Hz, Ar-H), 7.54-6.98 (8H, m, Ar-H), 7.0 (1H, bs, NH), 6.52 (1H, t, *J* 6.0 Hz, NH), 3.92 (2H, d, *J* 6.0 Hz , NCH_2), 3.64 (3H, s, OCH_3), 3.52-3.46 (2H, m, $NHCH_2$), 2.50-2.46 (2H, t, *J* 6.0 Hz, CH_2). ^{13}C NMR (75.0 MHz, $CDCl_3$): 172.8 (CO), 168.0 (CO), 167.4, 135.7 (CO), 129.4 (CO), 128.9, 128.3, 123.8, 114.2, (C-Ar), 51.8 (NCH_2), 47.6 (OCH_3), 35.0 ($NHCH_2$), 33.5 (CH_2). Found, %: C: 59.89; H: 4.94; N: 13.09. For $C_{22}H_{22}N_4O_6$ (438.2). Calculated, %: C: 60.27; H: 5.06; N: 12.78.

Quantum chemistry computations (neutral fragments). The computations in this work were performed with a MOLPRO program package[52] The initial structures of **3a** was edited by an Avogadro package[53] The structure was optimized using the DFT calculations at the B3LYP level of theory employing 6-311G basis set. The optimized geometric structures of **3a** calculated using DFT(B3LYP)/6-311G level of theory are presented in (Figure 1).

Fukui functions. They were calculated for all atoms within structure **3a** at the DFT(B3LYP)/6-311G level of theory using Mulliken population analysis. Applying finite difference approximation, it can be written as:[54] $f_k^+ = q_k(N+1) - q_k(N)$ (nucleophilic attack) and $f_k^- = q_k(N) - q_k(N-1)$(electrophilic attack). Herein, $q_k(N)$, $q_k(N+1)$, and $q_k(N-1)$ are defined as the atomic charges of the neutral, anionic, and cationic species, respectively. The nucleophilic and electrophilic Fukui functions are reported in (Table 1).

The calculated Fukui functions for the charged species (N, N+1, and N-1) within the molecule **3a** are reported in Table 1. It can be seen from Table 1 that the nitrogen atoms (N-4) is the most susceptible site for electrophilic attacks due to the largest values of f_k^- which is -0.018.

Frontier molecular orbitals (FMO). The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are the most important orbitals in a molecule. These orbitals are named as the frontier molecular orbitals (FMOs). The HOMO orbital acts as an electron donor and the LUMO orbital acts as the electron acceptor. FMOs play key roles in interactions between the molecules. The frontier orbital gap (E_{LUMO}-E_{HOMO}) gives information about the chemical reactivity, kinetic stability and chemical hardness-softness of a molecule. A molecule with a small frontier orbital gap is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule. On the contrary, the large LUMO-HOMO energy gap implies that the molecule has low chemical reactivity, high kinetic stability and is also termed as hard molecule. The soft molecules are more polarizable than the hard ones because they need small energy to excitation.[55]

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