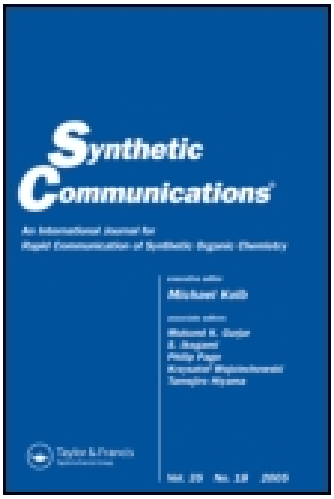

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Novel Approach for the Synthesis of N-Substituted-4-(2-methyl-4-oxo-4H-quinazolin-3-yl)-butyramides

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NOVEL APPROACH FOR THE SYNTHESIS OF *N*-SUBSTITUTED-4-(2-METHYL-4-OXO-4*H*-QUINAZOLIN-3-YL)-BUTYRAMIDES

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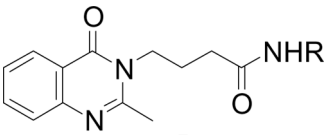
GRAPHICAL ABSTRACT



5a-m

Abstract *A simple and convenient method for the synthesis of* N*-substituted-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramides has been reported. Several aromatic and aliphatic amide derivatives of 4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyric acid were prepared in 60–81% yields by refluxing it with different phosphazo compounds in toluene for approximately 1 h.*

Keywords γ-Amino butyric acid; butyramides; phosphazo compounds; quinazolin-4-one

Quinazolin-4(*3H*)-one is one of the most versatile nuclei in medicinal chemistry, with a wide range of biological properties including antihypertensive,[1] anti-inflammatory,[2] anticonvulsant,[3] antimicrobial,[4] antitumor,[5] antidiabetic,[6] and antihistaminic[7] activities. A literature survey also revealed that the presence of a substituted aromatic ring at position 3 and a methyl group at position 2 are necessary requirements for central nervous system (CNS) depression and anticonvulsant activities (methaqualone, Fig. 1).[8] It has been reported in literature that γ-amino butyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain.[9] Further research has resulted in the discovery of GABA analogs such as vigabatrin and gabapentin (Fig. 1) as useful anticonvulsant drugs.[10]

Because of the importance of a quinazolin-4(*3H*)-one moiety and GABA analogs, our goal was to develop a convenient synthetic protocol for the design and synthesis of amides of GABA-quinazolin-4(*3H*)-one analogs **5**.

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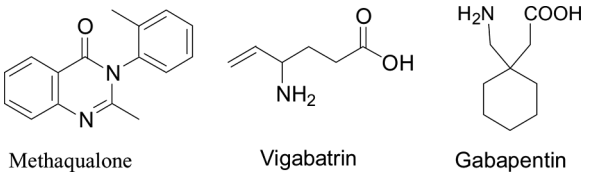


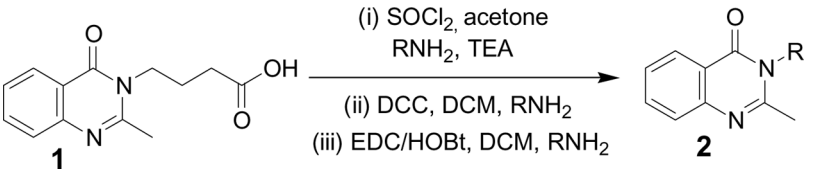
Figure 1. Anticonvulsant drugs.

Although there are a number of synthetic methods available for the preparation of quinazolin-4(*3H*)-one derivatives,[11] synthesis of its amide derivatives having an alkanoic acid side chain has not been reported in literature. Therefore, our objective in the present work is to develop a simple and efficient method for the synthesis of amide derivatives of quinazolin-4(3*H*)-one having a butyric acid side chain **5**.

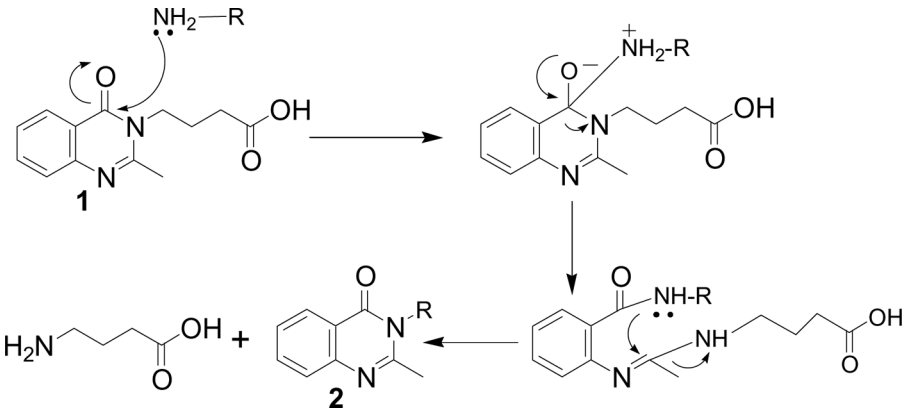
Whereas various methods have been described in literature for amide coupling reactions, our initial approach was to obtain amide derivatives by converting acid **1** into an acid chloride with $SOCl_2$ and then treatment with an amine in the presence of triethylamine and dry acetone (**i**).[12] However, NMR and mass spectral analysis of the resulting product showed the absence of an aliphatic side chain and molecular ion peak, respectively, thus confirming that formation of the amide did not take place. Instead, the spectra confirmed the formation of compound **2** (Scheme 1).

Amide formation is also reported between a carboxylic acid and a free amino group on treatment with *N,N*-dicyclohexylecarbodiimide (DCC) at room temperature (**ii**),[13] so we tried this method for preparation of amide **5** of 4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyric acid **1**. The reaction was carried out at room temperature, 0 °C, −10 °C, and even refluxing temperature for 6 to 10 h in dichloromethane (DCM). The products thus obtained in the reaction conditions were purified by column chromatography using hexane–ethyl acetate mobile phase, and they were found to be the same. When the pure compounds thus obtained were analyzed by NMR and mass spectroscopy, we were surprised to observe that expected peaks of an aliphatic side chain as well as amide linkage and molecular ion peak were missing in the NMR and mass spectra respectively, and the product was identified as compound **2** (Scheme 1).

Amide formation is also reported between a carboxylic acid and a free amino group in the presence of another advance coupling agent, 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloric acid (EDC) and 1-hydroxybenzotriazole (HOBt) in equivalent ratio at 0 °C.[14] Therefore, this coupling reagent (EDC/HOBt) was employed for the synthesis of the desired amide (**1**) in the presence of 20%



Scheme 1. Reagents and conditions.



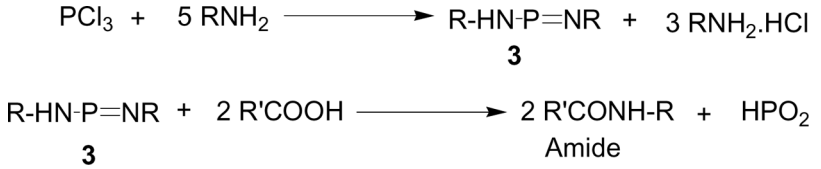
Scheme 2. Plausible mechanism.

dimethylformamide (DMF)–CH_2Cl_2 at 0 °C (**iii**), but NMR and mass spectral data of the resulting product were not in agreement with desired product **5**, and the product was the same as compound **2** (Scheme 1).

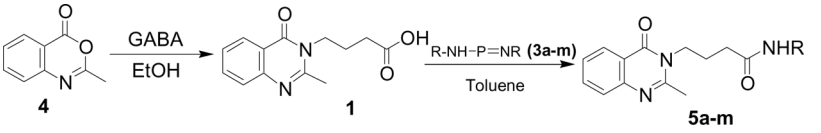
On the basis of all these results, it was observed that instead of amide formation, the substituted amines are replacing the N-$(CH_2)_3$COOH group from the third position of the quinazolin-4(*3H*)-one ring,[15] and formation of 3-alkyl/aryl-2-methyl-3*H*-quinazolin-4-one **2** is taking place (Scheme 2). Thus, we concluded that even in the presence of these advance coupling reagents, the free amino group is not able to form the amide linkage of 4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyric acid (**1**).

Thus, with a free amino (-NH_2) group, the formation of amide **5** was not possible. Therefore, we searched for an alternative method in which the amino (-NH_2) group must not be in the free form, and we found that interaction of carboxylic acids and amines in the presence of phosphorous trichloride to form *N*-substituted amides is reported in literature.[16] In the initial reaction, amines react with phosphorous trichloride to form the phosphazo compound **3**. On heating, the phosphazo compound **3** reacts with carboxylic acid to give an amide (Scheme 3).

Thus, we used the application of phosphazo compounds in the preparation of amide analogs of 4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyric acid **1**. The formation of amide derivatives **5a–m** takes place when compound **1** is refluxed with phosphazo compounds **3a–m** in toluene. We also used different solvents such as



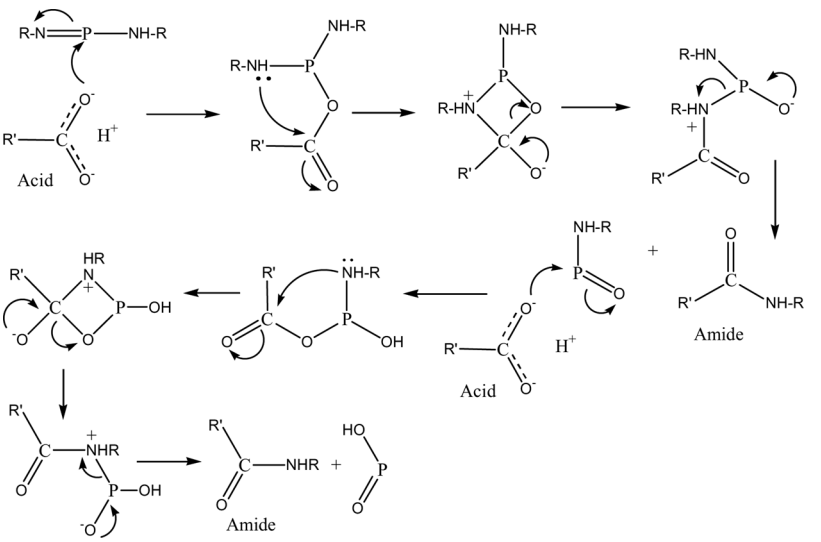
Scheme 3. Formation of phosphazo compounds and their amide derivatives.



Scheme 4. Formation of amide analogs using phosphazo compounds.

dichloromethane, chloroform, and xylene in different reaction conditions to optimize the reaction time and yield, but the best result was obtained (60–81% yield) when toluene was used as a solvent at refluxing temperature for 1 h (Scheme 4). The amides thus obtained were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectral data of compounds **5a–m** showed a triplet of α CH_2 protons from δ 2.12 to 2.48 ppm. The β CH_2 protons were observed as a multiplet from δ 1.50 to 2.16 ppm. The γ CH_2 protons appeared as a triplet from δ 3.18 to 4.22 ppm. Furthermore, the NH proton of amide linkage was observed as a broad singlet from δ 5.26 to 10.00 ppm. ^{13}C NMR spectra of the compounds **5a–m** also showed the signals of α, β, and γ carbons in the spectra. Furthermore, the carbonyl carbon of amide linkage appeared downfield from δ 170.0 to 171.6, confirming formation of the amide derivatives.

In conclusion, we have reported an efficient and convenient one-step synthesis of biologically important *N*-substituted-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramides under mild reaction conditions. The reaction is applicable to a wide range of aliphatic and aromatic amines. The purposed reaction mechanism for this process involves utilization of 2 mol of acid for every 1 mol of phosphazo compound (Scheme 5). Work is under way in our laboratory to further explore the scope of this reaction.



Scheme 5. Plausible mechanism for the amide formation.

EXPERIMENTAL

Melting points were determined in one-end open capillary tubes on a Buchi 530 melting-point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on Bruker Avance-400 instrument (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were measured on Bruker Avance-400 instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Elemental analyses (C, H, and N) were undertaken with a CHNS Elementar (Analysen Systime, GmbH, Germany) Vario EL III. The reactions were monitored by silica gel–GF coated aluminum plates and visualized by iodine vapors and ultraviolet light as visualizing agents. Mass (MS) spectral data were recorded in electron-impact (EI) mode. Removal of solvents was carried out at reduced pressure using a rotary evaporator. Solid products were purified by recrystallization.

Synthesis of 4-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-butyric Acid 1

Freshly prepared 2-methyl-benzo[*d*][1,3]oxazin-4-one[17] **4** (3.75 g, 23.29 mmol, 1.0 equiv) was dissolved in absolute ethanol in a dry and clean round-bottomed flask with condenser and guard tube. 4-Amino-butyric acid (2.02 g, 23.29 mmol, 1.0 equiv) was added to it, and the resulting solution was refluxed for about 2 h. The progress of reaction was monitored by aluminum-coated Merck thin-layer chromatography (TLC) plates using 60% ethyl acetate–hexane solvent system. The solvent was removed by rotary evaporator up to half of its volume, poured into ice-cooled water, and kept aside overnight. The crystals thus obtained were filtered, dried, and recrystallized by methanol (yield 70%). R_f value 0.30. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.50 (br s, 1H, COOH), 8.45 (d, 1H, $J = 8.0$ Hz, 5th ArH), 7.97 (d, 1H, $J = 7.6$ Hz, 8th ArH), 7.30 (t, 1H, $J = 8.4$ Hz, 6th ArH), 6.96 (t, 1H, $J = 7.6$ Hz, 7th ArH), 2.84 (t, 2H, $J = 7.2$ Hz, NCH_2), 2.36 (t, 2H, $J = 7.2$ Hz, $COCH_2$), 1.79 (m, 2H, CH_2); MS (EI) m/z (%): 247.5 (100) [M + 1]. Anal. calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.25; H, 5.78; N, 11.40.

Typical Procedure for Preparation of Phosphazo Compounds 3a–m

A solution of PCl_3 (1 equiv) in toluene (10 mL) was added to a solution of primary amines (5 equiv) in toluene (20–30 mL) slowly at low temperature (0–5 °C). Separation of solid was observed on addition of PCl_3 solution due to formation of hydrochloric salt of amines. The reaction mixture was further stirred at room temperature for approximately 1 h for completion of the reaction. The hydrochloric salts of amines were filtered under dry condition, and the filtrate containing phosphazo compounds (**3a–m**) was used in the next step.

Typical Procedure for Preparation of Amides 5a–m

4-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-butyric acid **1** (2 equiv) was added to the filtrate containing phosphazo compounds **3a–m**, and the solution was refluxed for approximately 1 h. Separation of orange gummy precipitate of metaphosphorous

acid (HPO_2) at the bottom of the flask indicated the formation of product. The progress of the reaction was monitored by aluminum-coated Merck TLC plates using 100% ethyl acetate solvent system, R_f value 0.4–0.6. The hot toluene solution was decanted slowly in a 100-mL conical flask. The flask was rinsed with hot toluene (10 mL). The solution was again decanted in the previous solution of toluene and was kept at room temperature overnight. The amides, which separated out as a white crystalline solid, were filtered and dried in air. The compounds **5a–m** thus obtained were further purified by crystallizing with ethyl acetate. Yield 64–81%.

Characterization Data for Products

4-(2-Methyl-oxo-4*H*-quinazolin-3-yl)-*N*-propyl-butyramide (5a). White solid, yield 81%. R_f value 0.5, mp: 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, $J = 8.0$ Hz, 5th ArH), 7.69 (t, 1H, $J = 8.0$ Hz, 6th ArH), 7.59 (d, 1H, $J = 8.0$ Hz, 8th ArH), 7.40 (t, 1H, $J = 7.6$ Hz, 7th ArH), 6.12 (bs, 1H, CONH), 4.13 (t, 2H, $J = 7.6$ Hz, $ArNCH_2$), 3.16 (q, 2H, $J = 6.8$ Hz, NCH_2), 2.68 (s, 3H, CH_3), 2.30 (t, 2H, $J = 6.4$ Hz, CH_2CO), 2.06 (m, 2H, $ArNCH_2CH_2$), 1.50 (m, 2H, CH_2), 0.89 (t, 3H, $J = 5.2$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 162.4, 154.3, 149.6, 134.6, 126.7, 126.6, 126.4, 120.3, 43.7, 41.3, 33.1, 25.6, 23.1, 22.8, 11.4; MS (EI) m/z (%): 288.3 (100) [M + 1]. Anal. calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.66; H, 7.33; N, 14.54%.

4-(2-Methyl-oxo-4*H*-quinazolin-3-yl)-*N*-iso-propyl-butyramide (5b). White solid, yield 68%. R_f value 0.5, mp: 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J = 8.0$ Hz, 5th ArH), 7.65 (t, 1H, $J = 8.4$ Hz, 6th ArH), 7.55 (d, 1H, $J = 8.0$ Hz, 8th ArH), 7.36 (t, 1H, $J = 7.6$ Hz, 7th ArH), 6.07 (bs, 1H, CONH), 4.09 (t, 2H, $J = 7.6$ Hz, $ArNCH_2$), 4.03 (m, 1H, CH), 2.65 (s, 3H, CH_3), 2.25 (t, 2H, $J = 6.8$ Hz, CH_2CO), 2.00 (m, 2H, CH_2), 1.10 (d, 6H, $J = 6.8$ Hz, $(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 162.3, 154.3, 147.2, 134.2, 126.64, 126.60, 126.3, 120.2, 43.8, 41.4, 33.1, 24.5, 23.0, 22.6. Anal. calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.65; H, 7.34; N, 14.53%.

***N*-Butyl-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5c).** White solid, yield 70%. R_f value 0.45, mp: 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J = 7.6$ Hz, 5th ArH), 7.66 (t, 1H, $J = 8.0$ Hz, 6th ArH), 7.56 (d, 1H, $J = 8.0$ Hz, 8th ArH), 7.37 (t, 1H, $J = 7.6$ Hz, 7th ArH), 6.17 (bs, 1H, CONH), 4.10 (t, 2H, $J = 6.8$ Hz, $ArNCH_2$), 3.18 (q, 2H, $J = 6.4$ Hz, NCH_2), 2.65 (s, 3H, CH_3), 2.28 (t, 2H, $J = 6.4$ Hz, CH_2CO), 2.03 (m, 2H, $ArNCH_2CH_2$), 1.44 (m, 2H, NCH_2CH_2), 1.33 (m, 2H, $NCH_2CH_2CH_2$), 0.85 (t, 3H, $J = 7.2$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 163.4, 154.3, 147.3, 134.3, 126.69, 126.60, 126.3, 120.2, 49.3 43.8, 40.5, 39.3, 33.0, 24.3, 23.1, 20.0. Anal. calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.74; H, 7.66; N, 13.95%.

***N*-*t*-Butyl-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5d).** White solid, yield 65%. R_f value 0.40, mp: 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, 1H, $J = 8.0$ Hz, 5th ArH), 7.68 (t, 1H, $J = 6.8$ Hz, 6th ArH), 7.58 (d, 1H, $J = 8.0$ Hz, 8th ArH), 7.39 (t, 1H, $J = 7.6$ Hz, 7th ArH), 5.73 (bs, 1H, CONH), 4.11 (t, 2H, $J = 7.2$ Hz, NCH_2), 2.66 (s, 3H, CH_3), 2.22 (t, 2H, $J = 6.8$ Hz, CH_2CO),

2.03 (m, 2H, CH_2), 1.29 (m, 9H, $(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 162.3, 154.4, 148.6, 134.3, 126.6, 126.3, 121.0, 54.9, 51.2, 34.0, 28.7, 24.3, 23.0; MS (EI) m/z (%): 302.3 (100) [M + 1]. Anal. calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.73; H, 7.64; N, 13.96%.

***N*-Cyclohexyl-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5e).** White solid, yield 68%. R_f value 0.45, mp: 177–179 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, 1H, $J = 7.6$ Hz, 5th ArH), 7.75–7.70 (q, 2H, 6th ArH & CONH), 7.54 (d, 1H, $J = 8.4$ Hz, 8th ArH), 7.43 (t, 1H, $J = 7.2$ Hz, 7th ArH), 3.98 (t, 2H, $J = 6.8$ Hz, NCH_2), 3.22 (m, 1H, CH of cyc-hex), 2.57 (s, 3H, CH_3), 2.12 (t, 2H, $J = 6.4$ Hz, CH_2CO), 1.84–0.81 (m, 12H, CH_2 & cyc-hex.); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 161.5, 155.4, 147.5, 134.6, 126.9, 126.6, 120.4, 47.8, 43.9, 32.9, 25.7, 25.0, 24.4, 23.1; MS (EI) m/z (%): 328.7 (100) [M + 1]. Anal. calcd. for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.75, H, 7.67; N, 12.86%.

4-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-*N*-phenyl-butyramide (5f). White solid, yield 64%. R_f value 0.6, mp: 139–141 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 10.0 (s, 1H, CONH), 8.07 (d, 1H, $J = 8.0$ Hz, 5th ArH), 7.97–6.74 (m, 8H, ArH), 4.06 (t, 2H, $J = 7.6$ Hz, NCH_2), 2.61 (s, 3H, CH_3), 2.42 (t, 2H, $J = 6.4$ Hz, CH_2CO), 1.94 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 161.6, 155.4, 147.5, 139.6, 134.6, 129.1, 126.9, 126.6, 123.4, 120.9, 119.5, 117.8 43.9, 33.8, 24.1, 23.1. Anal. calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.15; H, 5.94; N, 13.10%.

***N*-(4-Chlorophenyl)-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5g).** White solid, yield 75%. R_f value 0.5, mp: 207–209 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 1H, $J = 8.0$ Hz, 5th ArH), 8.11 (bs, 1H, CONH), 7.71 (t, 1H, $J = 8.0$ Hz, 6th ArH), 7.62 (d, 1H, $J = 8.4$ Hz, 8th ArH), 7.41 (m, 3H, ArH), 7.10 (d, 2H, $J = 8.4$ Hz, ArH), 4.01 (t, 2H, $J = 7.2$ Hz, NCH_2), 2.71 (s, 3H, CH_3), 2.45 (t, 2H, $J = 6.0$ Hz, CH_2CO), 2.12 (m, 2H, CH_2); MS (EI) m/z (%): 356.5 (100) [M + 1], 358.5 (32.5) [M + 2]. Anal. calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.13; H, 5.10; N, 11.81. Found: C, 64.21; H, 5.13; N, 11.84%.

***N*-(4-Fluorophenyl)-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5h).** White solid, yield 80%. R_f value 0.6, mp: 167–169 °C. ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.99 (bs, 1H, CONH), 8.07 (d, 1H, $J = 7.6$ Hz, 5th ArH), 7.75–6.63 (m, 7H, ArH), 4.08 (t, 2H, $J = 6.8$ Hz, NCH_2), 2.62 (s, 3H, CH_3), 2.42 (t, 2H, $J = 6.8$ Hz, CH_2CO), 1.96 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 161.6, 155.4, 147.5, 134.6, 126.8, 126.6, 126.5, 121.8, 121.2, 120.4, 115.7, 115.4, 43.8, 33.7, 24.1, 23.0; MS (CI) m/z (%): 340.5 (100) [M + 1]. Anal. calcd. for $C_{19}H_{18}FN_3O_2$: C, 67.24; H, 5.35; N, 12.38. Found: C, 67.28; H, 5.37; N, 12.35%.

***N*-(3-Chloro-4-fluorophenyl)-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5i).** White solid, yield 64%. R_f value 0.5, mp: 202–204 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.90 (bs, 1H, CONH), 8.08–6.2 (m, 7H, ArH), 4.10 (t, 2H, $J = 7.2$ Hz, NCH_2), 2.62 (s, 3H, CH_3), 2.40 (t, 2H, $J = 6.8$ Hz, CH_2CO), 2.00 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 161.8, 154.6, 147.4, 134.1, 126.7, 126.5, 126.2, 121.2, 120.3, 119.9, 119.8, 116.7, 116.5, 116.3, 43.7, 33.6, 24.0, 23.1. Anal. calcd. for $C_{19}H_{17}ClFN_3O_2$: C, 61.05; H, 4.58; N, 11.24. Found: C, 61.11; H, 4.60; N, 11.22%.

4-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-*N*-o-tolyl-butyramide (5j). White solid, yield 66%. R_f value 0.5, mp: 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 1H, $J = 7.2$ Hz, 5th ArH), 7.73–6.90 (m, 7H, ArH), 5.26 (bs, 1H, CONH), 4.23 (t, 2H, NCH_2), 2.71 (s, 3H, CH_3), 2.54 (t, 2H, CH_2CO), 2.29 (s, 3H, CH_3), 2.16 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 162.5, 154.4, 147.1, 137.9, 134.4, 130.8, 130.5, 127.1, 126.7, 126.5, 125.4, 123.6, 122.8, 118.8, 43.7, 33.8, 24.6, 23.0, 17.6; MS (EI) m/z (%): 336.2 (100) [M + 1]. Anal. calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.65; H, 6.33; N, 12.56%.

4-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-*N*-p-tolyl-butyramide (5k). White solid, yield 72%. R_f value 0.55, mp: 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H, $J = 8.0$ Hz, 5th ArH), 8.11 (bs, 1H, CONH), 7.72 (t, 1H, $J = 8.0$ Hz, 6th ArH), 7.61 (d, 1H, $J = 8.4$ Hz, 8th ArH), 7.44 (m, 3H, ArH), 7.11 (d, 2H, $J = 8.4$ Hz, ArH), 4.22 (t, 2H, $J = 7.2$ Hz, NCH_2), 2.71 (s, 3H, CH_3), 2.48 (t, 2H, $J = 6.0$ Hz, CH_2CO), 2.30 (s, 3H, CH_3), 2.16 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 162.7, 158.6, 154.2, 135.4, 134.4, 133.8, 129.4, 126.74, 126.71, 126.5, 120.2, 120.0, 43.7, 35.9, 24.4, 23.1, 20.6. Anal. calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.67; H, 6.35; N, 12.55%.

***N*-(4-Methoxyphenyl)-4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)-butyramide (5l).** White solid, yield 79%. R_f value 0.5, mp: 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (bs, 1H, CONH), 8.23 (d, 1H, $J = 7.6$ Hz, 5th ArH), 7.71 (t, 1H, $J = 7.6$ Hz, 6th ArH), 7.61 (d, 1H, $J = 8.0$ Hz, 8th ArH), 7.44 (d, 2H, $J = 8.8$ Hz, ArH), 7.42 (d, 1H, $J = 7.6$ Hz, 7th ArH), 6.84 (d, 2H, ArH), 4.21 (t, 2H, $J = 7.2$ Hz, NCH_2), 3.77 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.48 (t, 2H, $J = 6.0$ Hz, CH_2CO), 2.14 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 162.7, 156.3, 154.2, 147.3, 134.4, 131.1, 126.7, 126.6, 126.5, 121.7, 120.2, 114.1, 55.4, 43.7, 33.9, 24.4, 23.1; MS (CI) m/z (%): 352.3 (100) [M + 1]. Anal. calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.40; H, 6.10; N, 11.95%.

4-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-*N*-naphthalen-1-yl-butyramide (5m). White solid, yield 60%. R_f value 0.55, mp: 219–221 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (bs, 1H, CONH), 8.10–7.3 (m, 11H, ArH), 4.02 (t, 2H, $J = 7.2$ Hz, NCH_2), 2.62 (s, 3H, CH_3), 2.25 (t, 2H, $J = 6.4$ Hz, CH_2CO), 2.04 (m, 2H, CH_2); MS (EI) m/z (%): 373.6 (100) [M + 1]. Anal. calcd. for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.21; H, 5.76; N, 11.33%.

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