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Chemoselective reactions of electrophiles with quinazoline amides; 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones, and 2-arylquinazoline-4(3*H*)ones and their thioamide regioisomers

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ABSTRACT

The study draws a solid theoretical basis governing the reaction of amides and thioamides with electrophiles to give either *N*, *O* or *S*- substitutions. This study was carried out on the model compounds quinazoline amides; 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones and 2-arylquinazoline-4(3*H*)ones and their thioamide regioisomers. The normal behavior of amides represented by 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones; amides react with soft electrophiles and gave N-substitution, while expected to give *O*-substitution with hard electrophiles. For a special case structure feature represented by 2-arylquinazoline-4(3*H*)ones, the amide group specially *O*-atom of the lactim form contributes in a continuous conjugated system, extended by an almost planar aryl group at position 2. Amides react with both soft electrophiles and hard electrophiles to give *O*-substitution. Similarly, for thioamides the normal behavior represented by 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones; thioamides react with soft electrophiles and gave *S*-substitution while expected to give *N*-subsitution with hard electrophiles. For a special case structure feature represented by 2-phenylquinazoline-4(3*H*)thione, the thioamide group specially *S*-atom of the thiol form contributes in a continuous conjugated system, extended by an almost planar aryl group at position 2. Thioamides react with both soft electrophiles and hard electrophiles to give S-substitution. This behavior was ruled by Hard-Soft Acid-Base Principle (HSAB Principle) and supported computational analysis and reported literature.

Keywords: soft electrophile, hard electrophile, ambident nucleophile, HSAB Principle, computational analysis.

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1. INTRODUCTION

Quinazoline derivatives have gained significant interest among medicinal chemists because of their recognized anticancer properties. Numerous research teams have studied the anticancer effects of benzamides on human breast cancer cell lines (MCF-7) and human lung cancer cell lines (A549).[1] Quinazoline-thione and quinazoline-dione are considered some of the most crucial classes of heterocyclic compounds in pharmacology, due to their broad range of biological activities,[2] including anticancer,[3],[4] antitubercular,[5] antibacterial,[6,7] antifungal,[8] anti-HIV,[9] anthelmintic,[10] anti-inflammatory ,[11,12] and antihypertensive properties.[13] The chemoselective reactions of amides and thioamides attracted our research group towards the structure modification of biologically active heterocyclic compounds. The heterocyclic amides and thioamides reaction with electrophiles has broad applications in medicinal chemistry. Although these types of reactions exhibit high selectivity, the specific contributions of the *O*-, *S*- and *N*-atoms have been rarely discussed in literature. [14-24] Due to the previously mentioned data we were prompted to synthesize a series of quinazoline amides; 3-alkylquinazoline-2,4-(1*H*,3*H*)-dione and 2-arylquinazoline-4(3*H*)one and their corresponding thioamide regioisomers; 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one and 2-arylquinazoline-4(3*H*)thiones and to study the selective behavior against different electrophiles. The importance of this study is the construction of a theoretical basis for the formation of quinazoline building blocks as an interesting biologically active ring system.

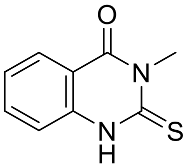
2. MATERIALS AND METHODS

- **General procedures**

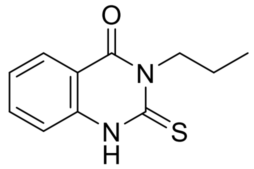
Petroleum ether with a boiling point range of 40–60 °C was employed in the experiments. Thin layer chromatography (TLC) was performed using silica gel 60 F254 plastic plates (E. Merck, 0.2 mm layer thickness), and the spots were visualized under a UV lamp. Melting points were measured using a Buchi 510 melting point apparatus, and the recorded values are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were measured on Bruker (400 MHz) in $CDCl_3$ or DMSO as solvent and TMS was used as internal standard. 2-phenylquinazolin-4(3*H*)one (**6a**) [16] and *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt were prepared according to the reported literature.[25]

2.1. General procedures for preparation of compounds 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one 1a-c.

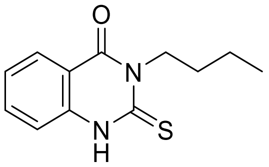
Anthranilic acid (1.37 g, 0.01 mol) was dissolved in acetic acid 15 mL and the appropriate; methyl, propyl and butyl isothiocynates were added during stirring. The reaction mixture was heated at 150°C for 24 hr. The reaction mixture was cooled and the obtained crystals were used without further purification to produce the pure quinazoline **1a-c**.



3-Methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (1a). yellow crystals (1.8g, 92%), m.p 280^{0}C. ^{1}H-NMR spectrum, (400iMHz, DMSO-d6), δ, ppm (*J*, Hz): 12.93 (1H, bs, NH), 7.94-7.29 (4H, m, Ar-H), 3.64 (3H, s, NCH_3). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 177.1 (CS), 161.4 (CO), 157.3, 147.2, 134.7, 125.8, 118.9 (C-Ar), 31.3 (NCH_3). Found, %: C, 56.11; H, 4.16; N, 14.46; For $C_9H_8N_2OS$ (192.24). Calculated, %: C, 56.23; H, 4.19; N,14.57.



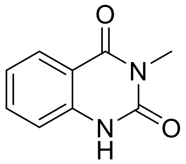
3-Propyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (1b). yellow crystals (1.90g, 89%), m.p 195^{0}C. ^{1}H-NMRispectrum,i(400iMHz, DMSO-d6), δ, ppm (*J*, Hz): 12.89 (1H, bs, NH), 7.94-7.28 (4H, m, Ar-H), 4.33 (2H, t, *J* = 8.0 Hz, NCH$_2$), 1.7`4-1.64 (2H, m, CH$_2$), 0.90 (2H, t, *J* = 8.0 Hz, CH$_3$). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 176.8 (CS), 161.7 (CO), 157.5, 147.6, 134.3, 126.7, 125.9, 119.1 (C-Ar), 42.2 (NCH$_2$), 21.2 (CH$_2$), 14.1 (CH$_3$). Found, %: C, 59.85; H, 5.44; N, 12.64 For $C_{11}H_{12}N_2OS$ (220.29). Calculated, %: C, 59.98; H, 5.49; N, 12.72



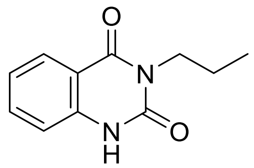
3-Butyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (1c). yellow crystals (1.75g, 86%), m.p 158^{0}C. ^{1}H-NMRispectrum,i(400iMHz, DMSO-d6), δ, ppm (*J*, Hz): 12.90 (1H, bs, NH), 7.94-7.29 (4H, m, Ar-H), 4.38 (2H, t, *J* = 8.0 Hz, NCH$_2$), 1.69-1.61 (2H, m, CH$_2$), 1.38-1.29 (2H, m, CH$_2$), 0.92 (2H, t, *J* = 8.0 Hz, CH$_3$). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 176.6 (CS), 161.4 (CO), 157.8, 147.9, 134.6, 126.9, 125.6, 118.8 (C-Ar), 42.5 (NCH$_2$), 29.4 (CH$_2$), 20.4 (CH$_2$), 13.8 (CH$_3$). Found, %: C, 61.47; H, 6.00; N, 11.87 For $C_{12}H_{14}N_2OS$ (234.32). Calculated, %: C, 61.51; H, 6.02; N, 11.96

2.2. Generaliproceduresiforipreparationioficompoundsi3-alkylquinazoline-2,4-(1*H*,3*H*)-dione 2a-c

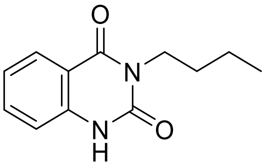
A solution of 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one derivatives (**1a–c**, 10 mmol) in 10% aqueous potassium hydroxide (30 mL) was heated to 50 °C. Hydrogen peroxide (15 mL) was then added dropwise over the course of 1 hour. The reaction mixture was subsequently heated at 60–70 °C for an additional hour. After cooling, the resulting solution was filtered and acidified with acetic acid, leading to the formation of a white precipitate. This solid was collected by filtration, washed with water, dried, and recrystallized from ethanol to yield compounds **2a–c.**



3-Methylquinazoline-2,4-(1*H*,3*H*)-dione (2a). White crystals (0.94g, 86%), m.p 260 ^{0}C. ^{1}H-NMR spectrum, (400iMHz, DMSO), δ, ppm (*J*, Hz): 11.44 (1H, s, NH), 7.94-7.17 (4H, m, Ar-H), 3.25(3H, s, NCH$_3$). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 161.2 (CO), 151.4 (CO), 140.8, 134.7, 128.6, 122.9, 115.3, 113.4 (C-Ar), 31.4 (NCH$_3$). Found, %: C, 61.23; H, 4.42; N, 15.76 For $C_9H_8N_2O_2$ (176.18). Calculated, %: C, 61.36; H, 4.58; N, 15.90.



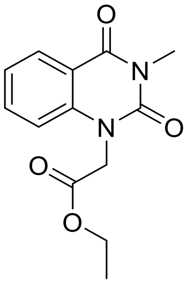
3-Propylquinazoline-2,4(1*H*,3*H*)-dione (2b). White crystals (0.87g, 80%), m.p 165 ^{0}C. ^{1}H-NMR ispectrum,i(400iMHz, DMSO-d6), δ, ppm (*J*, Hz): 11.41 (1H, bs, NH), 7.93-7.16 (4H, m, Ar-H), 3.84 (2H, t, *J* = 8.0 Hz, NCH$_2$), 1.63-1.54 (2H, m, CH$_2$), 0.86 (2H, t, *J* = 4.0 Hz, CH$_3$). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 161.5 (CO), 151.7 (CO), 140.9, 134.8, 128.9, 122.5, 115.7, 113.8 (C-Ar), 41.5 (NCH_2), 21.9 (CH_2), 13.6 (CH_3). Found, %: C, 64.53; H, 5.81; N, 13.63 For $C_{11}H_{12}N_2O_2$ (204.23). Calculated, %: C, 64.69; H, 5.92; N, 13.72.



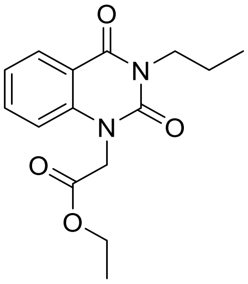
3-Butylquinazoline-2,4-(1*H*,3*H*)-dione (2c). White crystals (0.92g, 89%), m.p 140-145 ^{0}C. ^{1}H-NMRispectrum,i(400iMHz, DMSO-d6), δ, ppm (*J*, Hz): 11.40 (1H, bs, NH), 7.92-7.15 (4H, m, Ar-H), 3.86(2H, t, *J* = 4.0 Hz, NCH_2), 1.58-1.50(2H, m, CH_2), 1.32-1.27(2H, m, CH_2), 0.89 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 161.6 (CO), 151.2 (CO), 140.6, 134.2, 128.7, 122.8, 115.6, 113.5 (C-Ar), 41.7 (NCH_3), 29.6 (CH_2), 20.4 (CH_2), 13.9 (CH_3). Found, %: C, 65.83; H, 6.38; N, 12.66. For $C_{12}H_{14}N_2O_2$ (218.26). Calculated, %: C, 66.04; H, 6.47; N, 12.84.

2.3. Generaliproceduresiforipreparationioficompoundsi1-alkyl-3-alkylquinazoline-2,4(1*H*,3*H*)-diones 3-5(a-c).

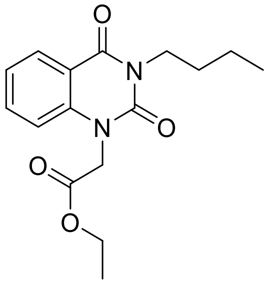
A solution of quinazoline dione derivatives 2a–c (22.5 mmol) in DMF (30 mL) was treated sequentially with potassium carbonate (3.1 g, 22.5 mmol) and electrophilic reagents: (ethyl chloroacetate, dimethyl sulfate (DMS), and benzyl chloride) (30 mmol). The reaction mixture was then refluxed for 24 hrs. The reaction mixture was filtered to remove K_2CO_3, then poured the filtrate on H_2O and let it form ppt. filter the ppt and wash by dist. water. The resultant solid was crystalized to give the pure esters **3-5(a-c)**.



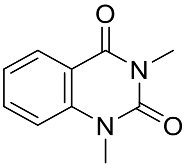
Ethyl 2-(3-methyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (3a). White crystals (0.69g, 75%), m.p 90^{0}C. ^{1}H-NMR spectrum, (400iMHz, $CDCl_3$): 8.38-7.98 (4H, m, Ar-H), 4.95 (2H, s, NCH_2), 4.11 (2H, q, *J* = 8.0 Hz, OCH_2), 3.58 (2H, s, NCH_3), 0.98 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 167.2 (CO), 161.7 (CO), 151.2 (CO), 140.8, 134.4, 128.9, 123.1, 113.7 (C-Ar), 62.1 (OCH_2), 47.3 (NCH_2), 31.1 (NCH_3), 11.8 (CH_3). Found, %: C, 59.48; H, 5.23; N, 10.57 For $C_{13}H_{14}N_2O_4$ (262.27). Calculated, %: C, 59.54; H, 5.38; N, 10.68.



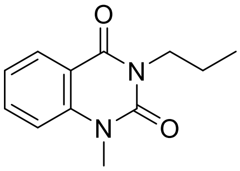
Ethyl 2-(2,4-dioxo-3-propyl-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (3b). yellowish crystals (0.71g, 70%), m.p 95^{0}C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.27-7.96 (4H, m, Ar-H), 4.91 (2H, s, NCH_2), 4.25 (2H, q, *J* = 8.0 Hz, OCH_2), 4.07 (2H, t, *J* = 8.0 Hz, NCH_2), 1.79-1.69 (2H, m, CH_2) , 1.29 (2H, t, *J* = 8.0 Hz, CH_3), 0.99 (2H, t, *J* = 4.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 167.1 (CO), 161.5 (CO), 151.3 (CO), 140.8, 134.1, 128.5, 122.6, 115.5, 113.3 (C-Ar), 62.3 (OCH_2), 47.2 (NCH_2), 41.5 (NCH_2), 21.1 (CH_2), 13.9 (CH_3), 11.5 (CH_3). Found, %: C, 61.94; H, 6.18; N, 9.48; $C_{15}H_{18}N_2O_4$ (290.32). Calculated, %: C, 62.06; H, 6.25; N, 9.65.



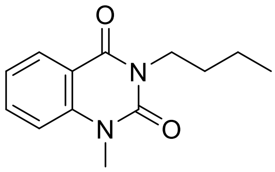
Ethyl 2-(3-butyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (3c). White crystals (0.76g, 72%), m.p 80^{0}C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.28-6.97 (4H, m, Ar-H), 4.92 (2H, s, NCH_2), 4.28 (2H, q, *J* = 8.0 Hz, OCH_2), 4.10 (2H, t, *J* = 4.0 Hz, NCH_2), 1.74-1.67 (2H, m, CH_2), 1.49-1.42 (2H, m, CH_2) , 1.30 (2H, t, *J* = 8.0 Hz, CH_3), 0.98 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 167.0 (CO), 161.5 (CO), 151.7 (CO), 140.4, 134.0, 128.4, 122.5, 115.4, 113.2 (C-Ar), 62.4 (OCH_2), 47.6 (NCH_2), 41.3 (NCH_2), 29.8 (CH_2), 21.4 (CH_2), 14.1 (CH_3), 11.7 (CH_3). Found, %: C, 63.07; H, 6.59; N, 9.09. For $C_{16}H_{20}N_2O_4$ (304.35). Calculated, %: C, 63.14; H, 6.62; N, 9.20.



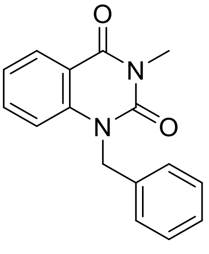
1,3-Dimethylquinazoline-2,4(1*H*,3*H*)-dione (4a). White crystals (0.82g, 65%), m.p 160 ^{0}C. ^{1}H-NMR spectrum, (400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.10-7.10 (4H, m, Ar-H), 3.51(2H, s, NCH_3), 3.38(2H, s, NCH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 161.5 (CO), 151.2 (CO), 141.2, 135.3, 129.1, 123.5, 115.1, 114.0 (C-Ar), 31.4 (NCH_3), 30.3 (NCH_3). Found, %: C, 63.13; H, 5.28; N, 14.68 For $C_{10}H_{10}N_2O_2$ (190.20). Calculated, %: C, 63.15; H, 5.30; N, 14.73.



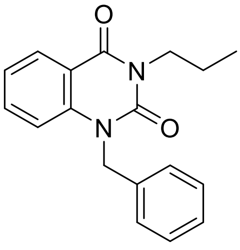
1-Methyl-3-propylquinazoline-2,4(1*H*,3*H*)-dione (4b). White crystals (0.84g, 68%), m.p 90 ^{0}C. ^{1}H-NMR spectrum, (400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.16-7.14 (4H, m, Ar-H), 4.00 (2H, t, *J* = 8.0 Hz, NCH_2), 3.55(2H, s, NCH_3), 1.73-1.64(2H, m, CH_2), 0.94 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 161.1 (CO), 151.4 (CO), 141.3, 135.4, 129.2, 123.1, 115.1, 113.9 (C-Ar), 41.5 (NCH_2), 30.9 (NCH_3), 20.9 (CH_2), 14.0 (CH_3). Found, %: C, 65.97; H, 6.35; N, 12.72 $C_{12}H_{14}N_2O_2$ (218.26). Calculated, %: C, 66.04; H, 6.47; N, 12.84.



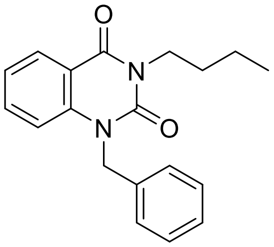
3-Butyl-1-methylquinazoline-2,4(1*H*,3*H*)-dione (4c). White crystals (0.98g, 72%), m.p 100^{0}C. ^{1}H-NMR spectrum, (400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.25-7.20 (4H, m, Ar-H), 4.11 (2H, t, *J* = 8.0 Hz, NCH_2), 3.62 (2H, s, NCH_3), 1.73-1.65(2H, m, CH_2), 1.48-1.38 (2H, m, CH_2), 0.98 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 161.7 (CO), 151.0 (CO), 140.5, 134.9, 128.9, 122.8, 115.6, 113.4 (C-Ar), 41.8 (NCH_2), 30.6 (NCH_3), 29.9 (CH_2), 20.2 (CH_2), 13.8 (CH_3). Found, %: C, 67.18; H, 6.85; N, 12.01 for $C_{13}H_{16}N_2O_2$ (232.28). Calculated, %: C, 67.22; H, 6.94; N, 12.06.



1-Benzyl-3-methylquinazoline-2,4(1*H*,3*H*)-dione (5a). White crystals (1.10g, 75%), m.p 155 ^{0}C. ^{1}H-NMR spectrum, (400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.27-7.13 (9H, m, Ar-H), 5.41(2H, s, NCH_2), 3.57(2H, s, NCH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 161.5 (CO), 151.3 (CO), 139.7, 135.6, 135.1, 134.7, 129.1, 127.5, 126.3, 123.2, 122.8, 115.6, 114.2 (C-Ar), 47.1 (NCH_2), 31.9 (NCH_3). Found, %: C, 72.05; H, 5.27; N, 10.42 For $C_{16}H_{14}N_2O_2$ (266.30). Calculated, %: C, 72.17; H, 5.30; N, 10.52**.**



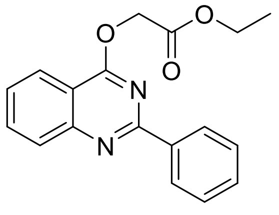
1-Benzyl-3-propylquinazoline-2,4(1*H*,3*H*)-dione (5b). White crystals (0.85g, 78%), m.p 115^{0}C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.25-7.12 (9H, m, Ar-H), 5.39(2H, s, NCH_2), 4.14 (2H, t, *J* = 8.0 Hz, NCH_2), 1.81-1.77(2H, m, CH_2), 1.02 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 161.7 (CO), 151.1 (CO), 140.1, 136.0, 135.2, 135.0, 129.2, 127.8, 126.7, 123.5, 123.2, 115.9, 114.6 (C-Ar), 47.8 (NCH_2), 42.2 (NCH_2), 20.5 (CH_2), 14.1 (CH_3). Found, %: C, 73.29; H, 6.09; N, 9.41 For $C_{18}H_{18}N_2O_2$ (294.35). Calculated, %: C, 73.45; H, 6.16; N, 9.52



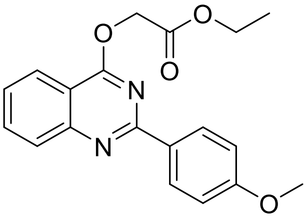
1-Benzyl-3-butylquinazoline-2,4(1*H*,3*H*)-dione (5c). White crystals (1.05g, 70%), m.p 110^{0}C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.22-7.09 (9H, m, Ar-H), 5.36(2H, s, NCH_2), 4.04 (2H, t, *J* = 8.0 Hz, NCH_2), 1.81-1.70(2H, m, CH_2), 1.48-1.42(2H, m, CH_2), 0.98 (2H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 161.8 (CO), 151.4 (CO), 139.9, 135.8, 135.0, 134.9, 129.0, 127.7, 126.5, 123.3, 123.0, 115.8, 114.4 (C-Ar), 47.3 (NCH_2), 42.0 (NCH_2), 30.0 (CH_2), 20.3 (CH_2), 13.9 (CH_3). Found, %: C, 73.84; H, 6.37; N, 8.92. For $C_{19}H_{20}N_2O_2$ (308.38). Calculated, %: C, 74.00; H, 6.54; N, 9.08.

2.4. Generaliproceduresiforipreparationioifiethyli2-(2-arylquinazolin-4-yloxy)iacetate 7a–b.

A solution**i**of**i**quinazoline-4-one**i**derivatives**i6a–b** (22.5 mmol) in DMF (30 mL) was sequentially treated with potassium carbonate (3.1 g, 22.5 mmol) and ethyl chloroacetate (3.7 mL, 30 mmol). The mixture was stirred at room**i**temperature**i**for**i**24 hrs. Upon completion, the reaction mixture was filtered and poured into 50 mL of ice-cold water, resulting in the formation of a white precipitate. The solid was collected by filtration, dried, and recrystallized from 95% ethanol to yield the pure ester compounds**7a–b**.



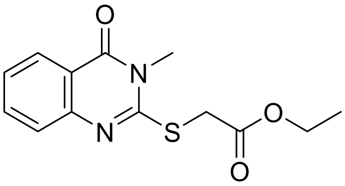
Ethyl 2-(2-phenylquinazolin-4-yloxy) acetate (**7a**). White crystals 0.84 g (75%), m.p. 110–111°C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.75–8.54 (2H, m, Ar–H), 8.26 (1H, d, *J* = 6.0 Hz, Ar–H), 8.04 (1H, d, *J* = 9.0 Hz, Ar–H), 7.85 (1H, t, *J* = 8.0 Hz, Ar–H), 7.58–7.50 (4H, m, Ar–H), 5.20 (2H, s, OCH_2), 4.28 (2H, q, *J* = 6.0 Hz, CH_2CH_3), 1.31–1.27 (3H, t, J = 6.0 Hz, CH3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 168.3**i** (C═O),**i**165.7,i159.4,i152.2,i137.7,i133.9, 130.6,i128.4,i128.4, 128.0, 126.7, 123.5, 114.8 (C–Ar), 63.3 (OCH_2), 61.4 (OCH_2CH_3), 14.2 (CH_3).iFound %:iC, 69.48; H, 5.64; N, 8.88. For $C_{18}H_{18}N_2O_3$ (310.13). Calculated %: C, 69.66; H, 5.85; N, 9.03.



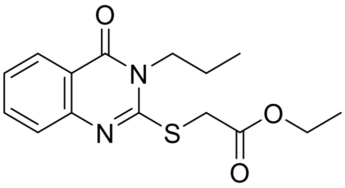
Ethyli**2-[2-(4-methoxy-phenyl)quinazolin-4-yloxy]**i**acetate**i(**7b**). White crystals 0.74 g (69%), m.p. 120–121°C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.49i(2H, d, *J* = 9.0 Hz, Ar–H), 8.22i(1H, d, *J* = 9.0 Hz, Ar–H), 7.98i(1H, d, *J* = 6.0 Hz, Ar–H), 7.80i(1H, t, *J* = 9.0 Hz, Ar–H), 7.54–7.49 (1H, t, *J* = 9.0 Hz, Ar–H), 7.02i(2H, d, *J* = 9.0 Hz, Ar–H), 5.18i(2H, s, OCH_2), 4.29i(2H, q, *J* = 6.0 Hz, CH_2CH_3), 3.89i(3H, s, OCH_3), 1.30–1.25i(3H, t, *J* = 6.0 Hz, CH_3). ^{13}C-NMRi(100.0 MHz, $CDCl_3$), δ, ppm: 168.4 (C═O),i165.5, 161.9,i159.2, 152.3, 133.8, 130.4,i130.1, 127.7,i126.2, 123.5,i114.5, 113.8 (C–Ar), 63.3i(OCH_2), 61.3 (OCH_2CH_3), 55.4i(OCH_3), 14.2 (CH_3).iFound %:iC,i66.67; H, 5.63;iN, 8.08. For $C_{19}H_{20}N_2O_4$ (340.14).Calculated %:iC, 67.05; H, 5.92; N, 8.23.

2.5. General**i**procedures**i**for**i**preparation**i**of**i**alkyl**i**2-(3-alkyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl) i acetate 9a-c.

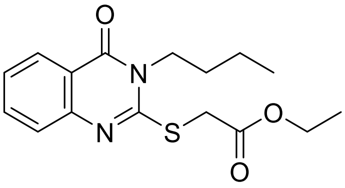
To a solution of 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **1a-c** (1.52 g, 0.02 mole) in 15 mL ethanol, was added ethyl chloroacetate (1.2 ml, 0.01 mole) and triethylamine (1 mL) subsequently The reaction mixture was heated under reflux for 24 hours. The reaction mixture was cooled and the resultant crystals was filtered and crystalized from methanol to get pure ester **9a-c**.



Ethyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetate (**9a**). White crystals (0.65g, 68%), m.p 118 ^{0}C. ^{1}H-NMR spectrum, (400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.24-7.40 (4H, m, Ar-H), 4.29-4.23 (4H, m, OCH_2, SCH_2), 3.69 (3H, s, NCH_3), 1.32 (3H, t, *J* = 8.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 168.4 (CO), 161.9 (CO), 157.6, 147.7, 134.6, 126.3, 126.0, 125.4, 118.5 (C-Ar), 61.2 (OCH_2), 34.5 (SCH_2), 30.9 (NCH_3), 13.9 (CH_3). Found, %: C, 55.93; H, 5.02; N, 10.04 For $C_{13}H_{14}N_2O_3S$ (278.33). Calculated, %: C, 56.10; H, 5.07; N, 10.07.



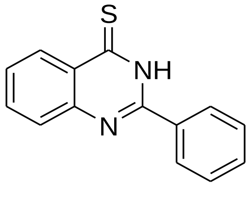
Ethyl 2-(4-oxo-3-propyl-3,4-dihydroquinazolin-2-ylsulfanyl)acetate (9b). White crystals (0.69g, 64%), m.p 95^{0}C. ^{1}H-NMRispectrum,i(400iMHz, CDCl$_3$), δ, ppm (*J*, Hz): 8.17-7.33 (4H, m, Ar-H), 4.21 (2H, t, *J* = 8.0 Hz, NCH$_2$), 4.12-4.05 (2H, m, OCH$_2$), 4.01 (2H, s, SCH$_2$), 1.86-1.73 (2H, m, CH$_2$), 1.28 (2H, t, *J* = 8.0 Hz, CH$_3$), 0.98 (2H, t, *J* = 8.0 Hz, CH$_3$). ^{13}C-NMR (100.0 MHz, CDCl$_3$), δ, ppm: 169.1 (CO), 161.4 (CO), 157.9, 147.8, 134.7, 126.8, 126.3, 125.8, 118.7 (C-Ar), 60.9 (OCH$_2$), 41.2 (NCH$_2$), 34.3 (SCH$_2$), 20.1 (CH$_2$), 14.1 (CH$_2$), 11.9 (CH$_3$). Found, %: C, 58.64; H, 5.83; N, 9.01; $C_{15}H_{18}N_2O_3S$ (306.38). Calculated, %: C, 58.80; H, 5.92; N, 9.14.



Ethyl 2-(3-butyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetate (9c). White crystals (0.72g, 68%), m.p 80^{0}C. ^{1}H-NMRispectrum,i(400iMHz, CDCl$_3$), δ, ppm (*J*, Hz): 8.19-7.31 (4H, m, Ar-H), 4.19 (2H, q, *J* = 8.0 Hz, OCH$_2$), 4.07 (2H, t, *J* = 8.0 Hz, NCH$_2$), 4.02 (2H, s, SCH$_2$), 1.78-1.70 (2H, m, CH$_2$), 1.44-1.40 (2H, m, CH$_2$) , 1.26 (2H, t, *J* = 8.0 Hz, CH$_3$), 0.96 (2H, t, *J* = 8.0 Hz, CH$_3$). ^{13}C-NMR (100.0 MHz, CDCl$_3$), δ, ppm: 168.7 (CO), 162.1 (CO), 157.5, 147.6, 134.3, 126.6, 126.1, 125.4, 118.5 (C-Ar), 61.4 (OCH$_2$), 41.5 (NCH$_2$), 34.1 (SCH$_2$), 29.8 (CH$_2$), 20.4 (CH$_2$), 14.0 (CH$_3$), 12.1 (CH$_3$). Found, %: C, 59.88; H, 6.14; N, 8.64. For $C_{16}H_{20}N_2O_3S$ (320.41). Calculated, %: C, 59.98; H, 6.29; N, 8.74

2.6. General procedure for preparation of 2-phenylquinazolin-4(3*H*)thione (11) and its derivatives

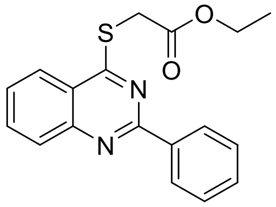
2.6.1. preparation of 2-phenylquinazolin-4(3*H*)thione (11)



2-Phenylquinazolin-4(3*H*)one (**6a**) (0.69g, 2.5 mmol) was dissolve in methylene chloride and thionyl chloride was added at -5 ^{o}C with stirring. DMF (2 mL) was added to this reaction mixture dropwise and the reaction mixture was heated at 50 ^{o}C for 5 h. The reaction mixture was evaporated under reduced pressure till dryness and dissolved in methylene chloride, washed with sodium carbonate solution and finally dried over sodium sulfate overnight. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The resultant white precipitate is pure enough for further reactions and was identified as 4-chloro-2-phenylquinazoline (**10**). (0.5g, 2.1 mmol) was dissolved in ethanol (10 mL) and *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (0.7g, 2.6 mmol) was added. The reacted mixture was heated under reflux for 12 hr. The reaction mixture was concentrated under reduced pressure and colled. The resultant yellow crystals were crystalized from ethanol and was identified as 2-phenylquinazolin-4(3*H*)thione (**11**).

yellowish –orange crystals (1.32 g, 92%),[i] m.p 195 ^{0}C. ^{1}H-NMRispectrum,i(400iMHz, DMSO-d6), δ, ppm (*J*, Hz): 13.85 (1H, bs, NH), 8.63 (1H, d, *J* = 8.0 Hz, Ar-H), 8.17 (2H, d, *J* = 8.0 Hz, Ar-H), 7.93-7.77 (2H, m, Ar-H), 7.62-7.57 (4H, m, Ar-H). ^{13}C-NMR (100.0 MHz, DMSO-d6), δ, ppm: 188.4 (C=S), 152.0, 144.8, 135.9, 132.7, 131.9, 129.8, 129.0, 128.9, 128.6, 128.4, 128.2, 128.1(C-Ar). Found, %: C, 70.48; H, 4.17; N, 11.63 For $C_{14}H_{10}N_2S$ (324.40). Calculated, %: C, 70.56; H, 4.23; N, 11.76.

2.6.2. Reaction with ethyl chloroacetate

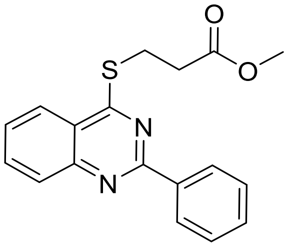


Ethyl 2-(2-phenylquinazolin-4-ylsulfanyl) acetate (**12**). A solution of 2-phenylquinazolin-4(3*H*)-thione (**11**, 1.0 mmol) in ethanol (30 mL) was treated with ethyl chloroacetate (1.2 mL, 1.0 mmol) and triethylamine (1.2 mL, 1.2 mmol). The reaction mixture was refluxed with stirring for 12 hrs. Upon completion, it was filtered and poured into 50 mL of ice-cold water, resulting in the formation of a white precipitate. The solid was collected by filtration, dried, and recrystallized from 95% ethanol–water to afford the pure ester **12.**

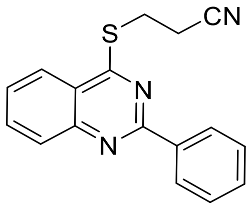
White crystals 0.54 g (80%), mp: 180–181°C; ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.64–8.62 (2H, m, Ar–H), 8.12–8.03 (2H, m, Ar–H), 7.86 (1H, t, *J* = 9.0 Hz, Ar–H), 7.60–7.53 (4H, m, Ar–H), 4.30–4.22 (4H, m, OCH_2, SCH_2), 1.31 (3H, t, *J* = 6.0 Hz, CH_3). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 172.7 (C═O), 168.9, 158.9, 149.0, 137.8, 133.9, 130.6, 129.1, 128.6, 128.4, 126.9, 123.7 (C–Ar), 61.9 (OCH_2), 32.2 (SCH_2), 14.2 (CH_3). Found %: C: 66.35; H: 4.82; N: 8.47. For $C_{18}H_{16}N_2O_2S$ (324.1), calculated %: C: 66.64; H: 4.97; N: 8.64.

2.6.3 Reaction with Acrylic acid derivatives

A solution of 2-phenylquinazolin-4(3*H*)-thione (**11**) (0.69 g, 1.0 mmol) in ethanol (30 mL) was treated with acrylate derivatives (1.2 mL, 2.0 mmol) and potassium carbonate (1.2 mmol). The reaction mixture was stirred under reflux for 24 hrs. After completion, the mixture was filtered and allowed to cool, leading to the formation of a precipitate. The solid was collected by filtration, dried, and recrystallized from 95% ethanol–water to yield the acrylic acid derivatives **13a,b**.



Methyl 3-[2-phenyl-quinazolin-4-ylsulfanyl]propanoate (13a) White crystals (0.23 g, 84%), mp 70 ^{0}C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.56-7.55 (9H, m, Ar-H), 3.69 (2H, t, *J*=8.0Hz, SCH_2), 3.66 (3H, s, OCH_3), 2.95 (2H, t, *J*=8.0Hz, CH_2). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 171.1 (C=O), 149.3, 149.0, 137.8, 133.9, 130.6, 129.1, 128.4, 126.9, 123.7 (C-Ar), 55.2 (OCH_3), 32.1 (SCH_2), 25.1 ($\underline{C}H_2CO$). Found, %: C, 66.42; H, 4.86; N, 8.49 For $C_{18}H_{16}N_2O_2S$ (324.40). Calculated, %: C, 66.65; H, 4.97; N, 8.64.



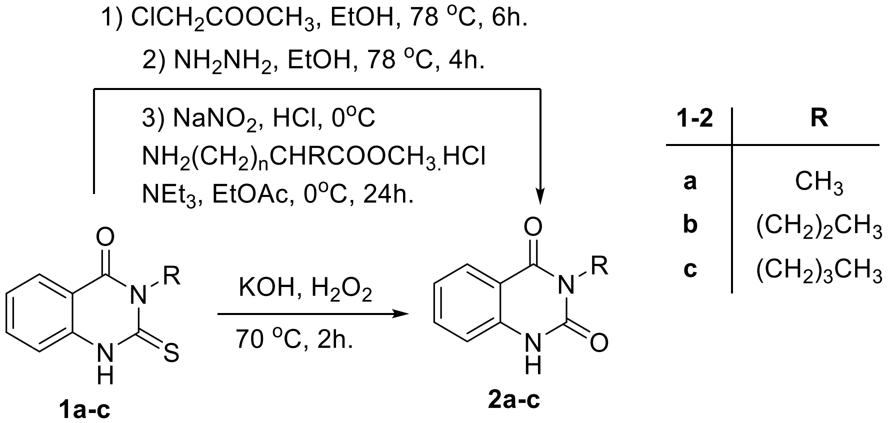
3-(2-Phenylquinazolin-4-ylsulfanyl)propanenitrile (13b) yellow crystals (0.23 g, 74%), m.p. 70 ^{0}C. ^{1}H-NMRispectrum,i(400iMHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.63-7.29 (9H, m, Ar-H), 3.77 (2H, t, *J*=8.0Hz, SCH_2), 3.07 (2H, t, *J*=8.0Hz, CH_2). ^{13}C-NMR (100.0 MHz, $CDCl_3$), δ, ppm: 149.3, 149.0, 137.8, 133.9, 130.6, 128.4, 126.9, 123.7 (C-Ar), 119.3 (CN), 30.2 (SCH_2), 22.4 ($S\underline{C}H_2CN$). Found, %: C, 69.93; H, 4.38; N, 14.31 For $C_{17}H_{13}N_3S$ (291.37). Calculated, %: C, 70.08; H, 4.50; N, 14.42.

3. RESULTS AND DISCUSSION

3.1. Amides

The model compound 3-methylquinazoline-2,4-(1*H*,3*H*)-dione **2a** was earlier synthesized through an interesting thioamide-amide transformation *via* a unique rearrangement method from 3-methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**1**). A multi-sequential reactions starting from the 3-methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**1**) selective reaction with ethyl chloroacetate, hydrazinolysis and finally the reaction with sodium nitrite to afford the model compound **2a**,[15] Scheme 1. This method gave rather pure product with an overall 55 % yield.

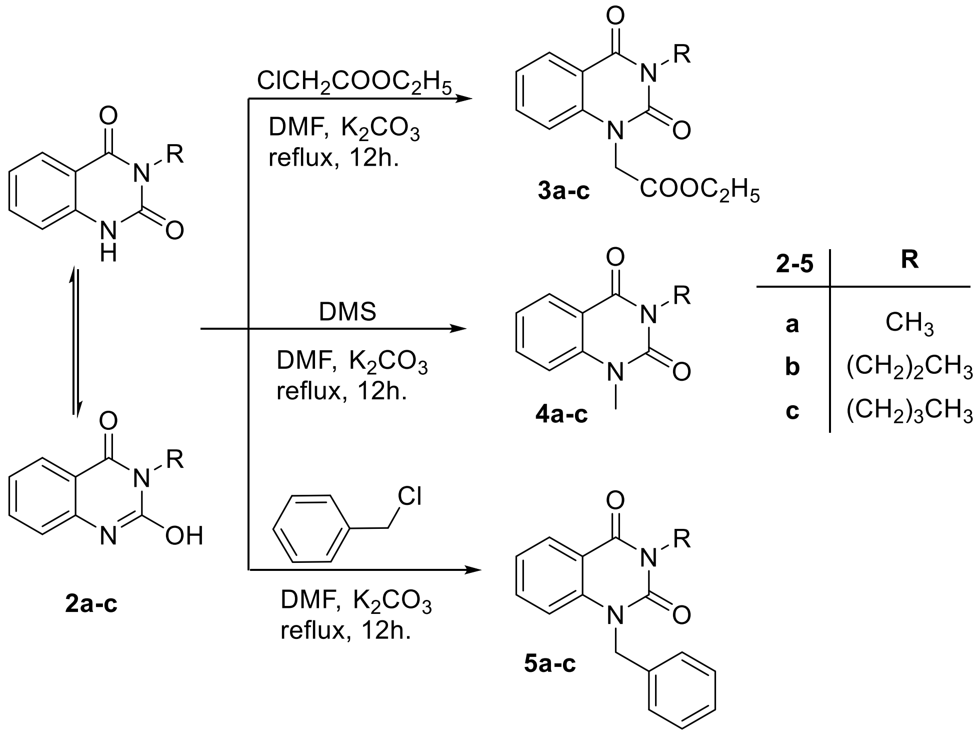
Although, this method was reliable to prepare methyl 2-(2-(2,4-dioxo-3-substitutedquinazolin-1-yl)acetamido) alkanoates[15] for biological evaluation but suffers from, the multiple reactions and moderate overall yields. Our alternative method used to overcome this obstacle was the direct thioamide-amide transformation in a single step. Thus, the reaction of 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **1a-c** with potassium hydroxide and hydrogen peroxide for 2hr. at 60-70^{0}C to get the desired product; 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones **2a-c** in high yield, **Scheme 1**.



1-2	R
a	CH_3
b	$(CH_2)_2CH_3$
c	$(CH_2)_3CH_3$

Scheme 1. Preparation of 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones **2a-c**.

3-Alkylquinazoline-2,4-(1*H*,3*H*)-diones **2a-c** are excellent precursors to study the selective reactions of amides with electrophiles. The reaction of quinazoline **2a-c** with electrophiles; ethyl chloroacetate, dimethylsulfate (DMS) and benzyl chloride in the presence of potassium carbonate always gave chemoselective *N*-substituted quinazoline derivatives **3-5**(**a-c**) in good yield, **Scheme 2**. The reaction of quinazoline **2a-c** with a number of activated acrylic acid derivatives; acrylonitrile, ethyl acrylate and acrylamide failed to give products under a variety of conditions.



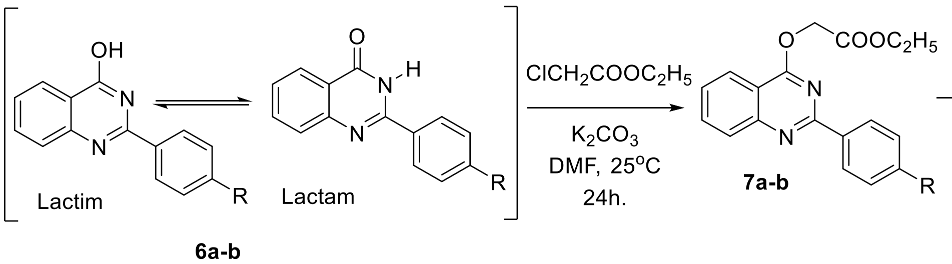
2-5	R
a	CH_3
b	$(CH_2)_2CH_3$
c	$(CH_2)_3CH_3$

Scheme 2. Alkylation of 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones **2a-c**.

The structure assignment of 1-alkyl-3-alkylquinazoline-2,4(1*H*,3*H*)-dione**s** **3-5(a-c).** were based on ^{1}H-NMR and ^{13}C-NMR as well as physicochemical analysis. The ^{1}H-NMR spectrum of 3-butyl-1-methylquinazoline-2,4(1*H*,3*H*)-dione **4c** exhibit signals between δ 4.11, 3.62, 1.73-1.65, 1.48-1.38 and 0.98 ppm corresponding to NCH_2, NCH_3,CH_2, CH_2 and CH_3 groups, respectively . The ^{13}C-NMR spectrum of **4c** reveal signals at δ 41.8, 30.6, 29.9, 20.2 and 13.8 ppm corresponding to NCH_2, CH_2, CH_2, CH_3 groups of the butyl residue, respectively. The ^{13}C-NMR spectrum of **5c** also shows signals at δ 161.7, 151.0 and 30.6 ppm corresponding to two C=O and NCH_3 groups, respectively, these definite signals are typically associated with *N*-substitution.

3-Alkylquinazoline-2,4-(1*H*,3*H*)-diones **2a-c** is found in the form of two tautomeric mixtures, **Scheme 2**. The ambident behavior and the *O*/*N* competitions of **2a-c** with electrophiles is ruled by Hard-Soft Acid-Base Principle (HSAB Principle), other factors is related to solvent and bases. This behavior directed the reaction of amides with electrophiles to produce one of the following three categories; *N*-substituted, *O*-substituted and a mixture of both *N* and *O*-. The obtained chemoselective *N*-alkylation; 1-alkyl-3-alkylquinazoline-2,4(1*H*,3*H*)-diones **3-5**(**a-c**) reported herein was favored due to strong interactions between *N*-atom higher energy HOMO molecular orbital and the lower energy LUMO molecular orbital of the soft electrophiles according to Pearson`s hard soft- acid base (HSAB) principle. This result was supported by computational studies of similar compound; 3-phenylquinazoline-2,4-(1*H*,3*H*)-dione showed that *N*-atom of the ambident nucleophile has larger Fukui function, lower electron density, polarizable, high chemical reactivity and is termed as the soft part of the ambident nucleophile. [15] We might conclude that reaction of amides with soft electrophiles in normal cases will prefer *N*-substitution.

Our second model was 2-arylquinazoline-4(3*H*)ones **6a-b** was prepared through a multiple sequential reactions from anthranilic acid according to reported literature. [16] 2-Arylquinazoline **6a-b** structure is almost planar and is found in the form of two tautomric mixture, **Scheme 3**. 2-Arylquinazoline **6a-b** reacted with soft electrophile**;** ethyl chloroacetate in the presence of potassium carbonate always gave chemoselective *O*-substituted quinazoline derivatives **7a-b** in good yield, Scheme 2. *O*-Substituted esters was used as the building block to prepare a series of methyl 2-(2-(2-arylquinazolin-4-yl)oxy) acetylamino alkanoates for biological evaluation**.** The reaction of quinazoline **6a-b** with a number of activated acrylic acid derivatives; acrylonitrile, ethyl acrylate and acrylamide failed to give products under a variety of conditions.



6-7	R
a	H
b	OCH_3

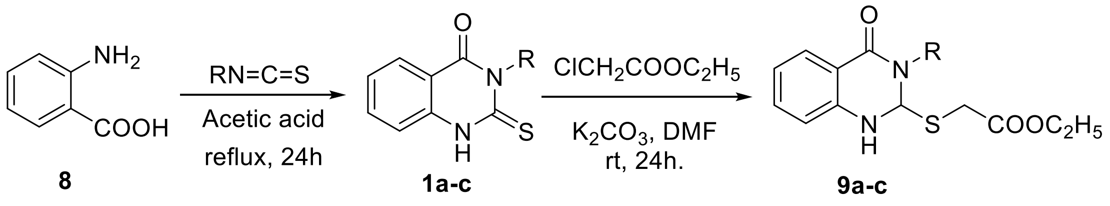
Scheme 3. Preparation of *O*-substituted quinazoline derivatives **7a-b**

The structure assignment of the *O*-substituted quinazoline derivatives **7a-b** were based on ^1H-NMR, ^{13}C-NMR as well as physicochemical analysis. Thus the ^1H-NMR spectrum of ethyl (2-phenylquinazolin-4-yloxy) acetate (**7a**) gave signals at δ 5.20, 4.28 and 1.31–1.27 ppm corresponding to OCH_2, OCH_2 and CH_3 groups, respectively. The ^{13}C-NMR spectrum of **7a** reveal signals at δ 168.3, 61.4 and 14.2 ppm corresponding to C=O group, $O\underline{C}H_2CH_3$ and CH_3 groups, respectively. The ^{13}C-NMR spectrum of **7a** also shows signals at δ 63.3 ppm corresponding to OCH_3 group, these definite signals are typically associated with *O*-substitution.

The oxygen atom of the lactim form of the ambident nucleophile; 2-arylquinazoline-4(3*H*)ones **6a-b** contributes in a continuous conjugated system, extended by an almost planar aryl group at position 2 is reflected in a unique structure feature. This will cause an energy rise of HOMO molecular orbital on the *O*-atom of the ambident nucleophile and the consequent softer *O*-atom. The softer *O*-atom of the ambident nucleophile will interact strongly with soft electrophiles. Nevertheless, *O*-atom hard character still remains according to computational studies in our previously reported literature. [16] Similar were observed when 2-phenylquinazolin-4(3H)-one (**6a**) was reacted with alkyl halides in the presence of potassium carbonate (K_2CO_3) in dimethylformamide (DMF), resulting in the chemoselective formation of *O*-alkylated quinazoline derivatives.[26]

3.2. Thioamides

Our next model thiomide; 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **1a-c** is prepared by the reaction of anthranilic acid (**8**) with alkyl isothiocynates in acetic acid under reflux condition for 24h. and gave quinazoline **1a-c** in excellent yield. The reaction of 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **1a-c** with ethyl chloroacetate in the presence of potassium carbonate in DMF at room temperature for 24h, **Scheme 4**. always afforded the *S*-substituted quinazolines; methyl 2-(3-alkyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate **9a-c**. The esters **9a-c** are used as building blocks for the preparation of *N*-alkyl-2-(3-alkyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetamide and methyl 2-(2-(4-oxo-3-alkylquinazolin-2-sulfanyl)acetamido)alkanoate for biological evaluation. The reaction of 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **1a-c** with acrylic acid derivatives under a variety of conditions failed to give products.



9	R
a	CH_3
b	$(CH_2)_2CH_3$
c	$(CH_2)_3CH_3$

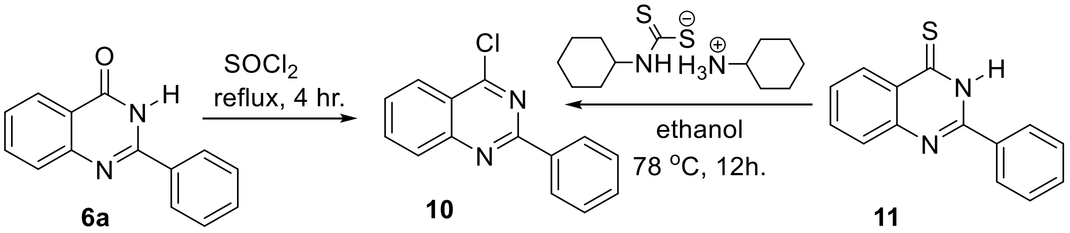
Scheme 4. Preparation of methyl 2-(3-alkyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetates **9a-c**.

The structure assignment of the *S*-substituted quinazoline derivatives **9a-c** were based on ^{1}H-NMR, ^{13}C-NMR as well as physicochemical analysis. Thus the ^{1}H NMR spectrum of ethyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetate (**9a**) gave signals at δ 4.29-4.23, 4.29-4.23, 3.69 and 1.32 ppm corresponding to OCH_2, SCH_2, NCH_3 and CH_3 groups, respectively. The ^{13}C-NMR spectrum of **9a** reveal signals at δ 169.1, 162.4 60.9, 30.5 and 14.1 ppm corresponding to C=O group, C=O group of ester, $O\underline{C}H_2CH_3$, NCH_3 and CH_3 groups, respectively. The ^{13}C-NMR spectrum of **9a** also shows signals at δ 34.4 ppm corresponding to SCH_2 group, these definite signals are typically associated with *S*-substitution.

The ambident behavior and the *S*/*N* competitions of **1a-c** with electrophiles is ruled by Hard-Soft Acid-Base Principle (HSAB Principle), other factors is related to solvent and bases. The obtained chemoselective *S*-alkylation; ethyl 2-(3-alkyl-2,4-dioxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetates **9a-c** reported herein was favored due to strong interactions between nitrogen atom higher energy HOMO molecular orbital and the lower energy LUMO molecular orbital of the soft electrophiles according to Pearson`s hard soft- acid base (HSAB) principle.

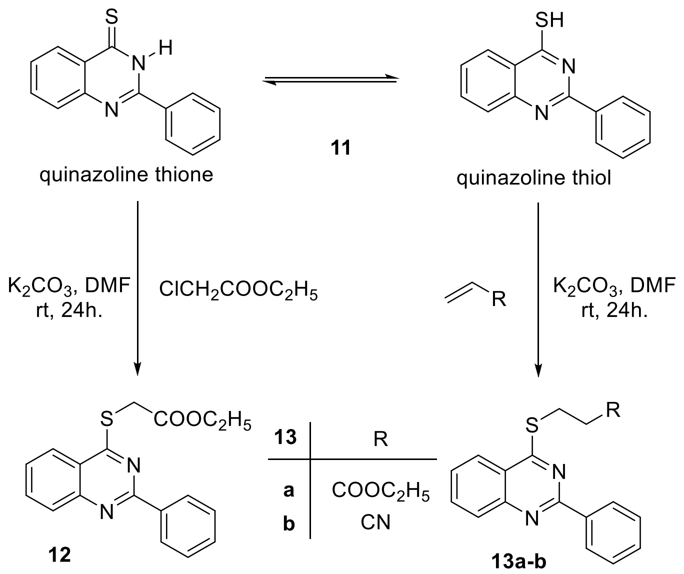
This result was supported by computational studies of analogues compounds; 4-methyl-1-thioxo-1,2,4,5-tetrahydro [1,2,4] triazolo [4,3-a]quinazolin-5-one that showed similar structural feature and gave *S*-alkylation on reaction with soft electrophiles. The *S*-substitution is the major product expected for the reaction of thioamides with soft electrophiles, this conclusion was supported by a large number of reported articles. The *N*-substitution as reported in literature is formed by the reaction of thioamides with hard electrophiles such as acrylic acid derivatives.[27,28]

2-Phenylquinazoline-4(3*H*)thione **11** is an excellent precursor used in structure modification of quinazoline ring system and gave a number of biologically valuable products. 2-Phenylquinazoline-4(3*H*)thione **11** was prepared by an interesting thionation process in a two-step reaction from the corresponding 2-phenylquinazolin-4(3*H*)ones **6a**; first chlorination with thionyl chloride in the presence of DMF in methylene chloride to afford the corresponding chloroquinazoline **10**. The second step involves heating **10** with *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt in ethanol for 12 hr. at 78°C in excellent yields, **Scheme 5**. This catalyst free thionation method was innovated by our research group, which gave great applications in organic synthesis.



Scheme 5. Preparation of 2-arylquinazoline-4(3*H*)thione **11a.**

2-Phenylquinazoline-4(3*H*)thione (**11**) has almost planar structure[29,30] and is found in the form of two tautomeric mixture, **Scheme 6**. Quinazoline **11** chemoselectively reacted with soft electrophile; ethyl chloroacetate in the presence of potassium carbonate under reflux condition to afford the *S*-substituted derivatives; ethyl (2-phenylquinazolin-4-ylsulfanyl) acetate (**12**).[22] This ester was used as a building block for the preparation of methyl [2-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetamido] alkanoates for biological evaluation. 2-Phenylquinazoline-4(3*H*)thiones (**11**) reacted with hard electrophiles, acrylic acid derivatives; methyl acrylate and acrylonitrile and acrylamide in the presence of potassium carbonate under reflux condition to afford the *S*-substituted derivatives; 3-[2-phenyl-quinazolin-4-ylsulfanyl]-propanoic acid derivatives **13a-b**, **Scheme 6.**



Scheme 6. Preparation of ethyl (2-phenylquinazolin-4-ylsulfanyl) acetate (**12**) and [2-phenyl-quinazolin-4-ylsulfanyl]-propanoic acid derivatives **13a-b**.

The structure assignment of ethyl (2-phenylquinazolin-4-ylsulfanyl) acetate (**12**) and [2-phenyl-quinazolin-4-ylsulfanyl]-propanoic acid derivatives **13a-b** were based on ^{1}H NMR, ^{13}C-NMR as well as physicochemical analysis. Thus the ^{1}H-NMR spectrum of methyl 3-[2-phenyl-quinazolin-4-ylsulfanyl] propanoate **13a** gave signals at δ3.69, 3.66 and 2.95 ppm due to SCH_2, OCH_3 and $C\underline{H}_2CO$ groups, respectively. The ^{13}C-NMR spectrum of **13a** reveals signals at δ 171.1, 55.2, 32.1 and 25.1 ppm corresponding to C=O group, OCH_3, SCH_2 and CH_2CO groups, respectively.

The *S*-substitution obtained by the reaction of 2-phenylquinazoline-4(3*H*)thione (**11**) with soft electrophile, ethyl chloroacetate is normally due the strong interaction between the soft part of the ambident nucleophile, *S* atom and the LUMO of the soft electrophile. However, the reaction of 2-phenylquinazoline-4(3*H*)thione with hard electrophiles; activated acrylic acid derivatives also gave *S*-substitution; [2-phenyl-quinazolin-4-ylsulfanyl]-propanoic acid derivatives **13a-b**. The *S*-substitution product in case of hard electrophiles could be explained as follows; The presence of the thiol group contributing to an extended conjugated system, a phenyl ring at position 2 with almost planar configuration making the extended conjugated system even more larger. This unique structure affects the soft and hard character to be collected on the sulfur atom. Hard electrophiles: acrylic acid derivative will be attracted to the harder part of the ambident nucleophile; *S*-atom according to Pearson`s hard soft- acid base (HSAB) principle. Similar results were obtained for the reaction of 3-phenylquinoxalin-2(1*H*)-thione having the same structure feature as our model compound with both soft and hard electrophiles gave *S*-substitution products.[31,32].

4. CONCLUSION

Amides and thiomides reactions with electrophiles might seem very simple but actually it produces ambiguous *N*, *O* or *S*-substituted products. Herein we wish to draw a solid theoretical basis governing the orientation of the reaction towards either *N*, *O* or *S*- substitutions. This study was carried out on the model compounds quinazoline amides; 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones and 2-arylquinazoline-4(3*H*)ones and their thioamide regioisomers. The normal behavior represented by 3-alkylquinazoline-2,4-(1*H*,3*H*)-diones; amides react with soft electrophiles and gave *N*-substitution, while expected to give *O*-substitution with hard electrophiles.

For a special case structure feature represented by 2-arylquinazoline-4(3*H*)ones, The amide group specially *O*-atom of the lactim form contributes in a continuous conjugated system, extended by an almost planar aryl group at position 2.

Amides react with both soft electrophiles and hard electrophiles to give *O*-substitution. Similarly, for thioamides the normal behavior represented by 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones; thioamides react with soft electrophiles and gave *S*-substitution while expected to give *N*-substitution with hard electrophiles.

For a special case structure feature represented by 3-alkyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one, The thioamide group specially *S*-atom of the thiol form contributes in a continuous conjugated system, extended by an almost planar aryl group at position 2. Thioamides react with both soft electrophiles and hard electrophiles to give *S*-substitution. This behavior was ruled by Hard-Soft Acid-Base Principle (HSAB Principle) and supported computational analysis and reported literature.

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