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Substituted Quinolinones. Part 27. Synthesis of Some New [1,2]Diazolo and or [1,2,4]triazepino[*b*]or [*c*]quinoline Derivatives

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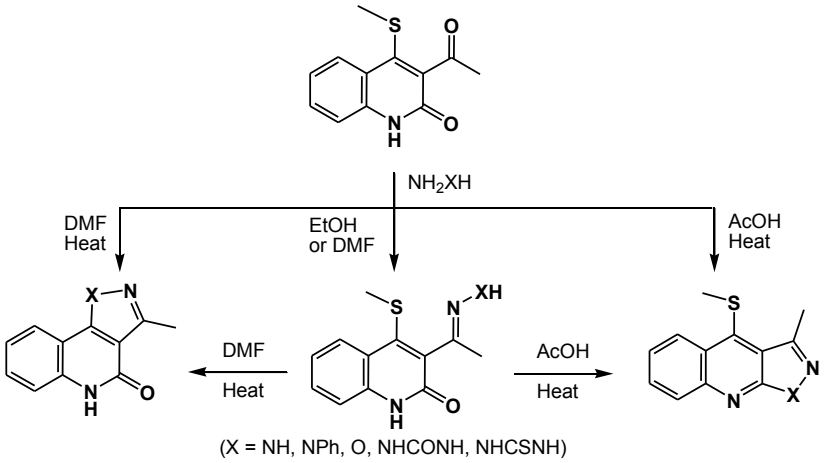


Reactivity of 3-acetyl-4-methylthioquinolin-2(1*H*)-one (**1**) towards 1,2- and/or 1,4-diazanucleophiles has been studied under different reaction conditions. Condensation of key compound **1** with hydrazine, phenylhydrazine, hydroxylamine hydrochloride, semicarbazide and thiosemicarbazide was carried out in different media. It was found that the nature of products is extremely dependent on both reactivity of the reagent and the ambient conditions. Accordingly, the reaction regioselectivety led to different [1,2]diazolo and or [1,2,4]triazepino[*b* or *c*]quinoline derivatives in addition to open chain condensates which were transformed to either annellated heterocyclo[*b* or *c*] quinolines, in good yields. The structure of new products was established on basis of their analytical and spectral data.

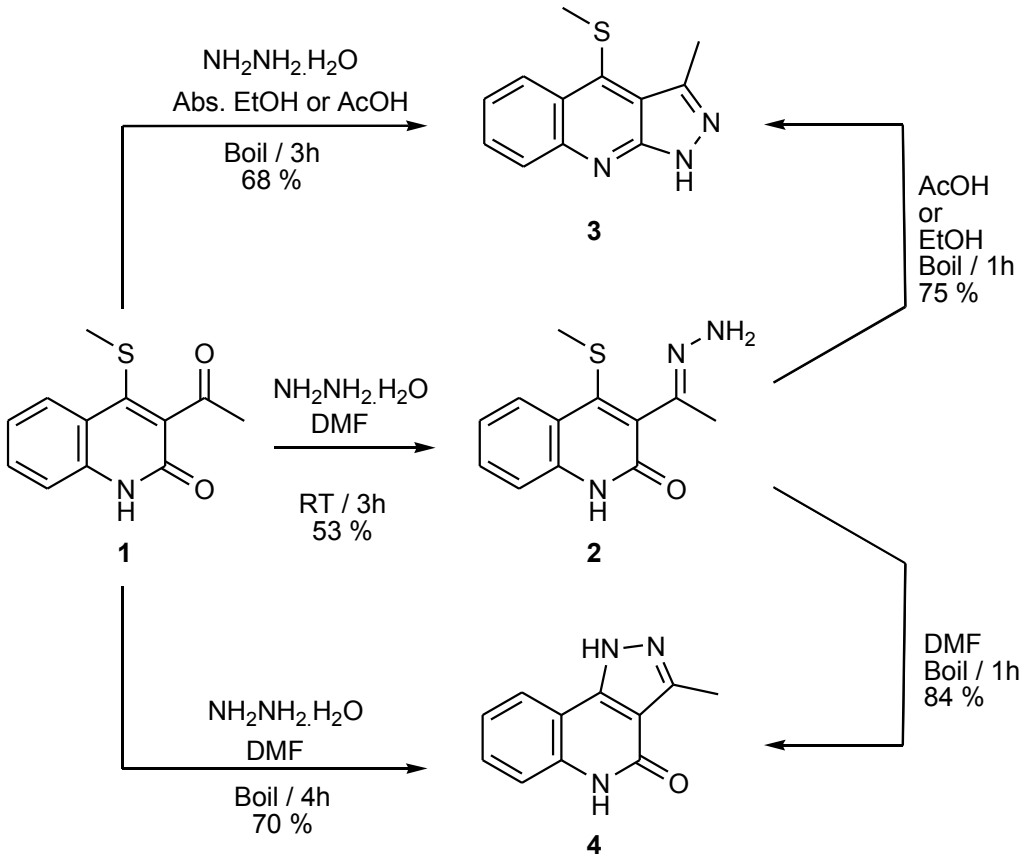
Keywords: Quinolinone, Heterocyclic synthesis, Nucleophilic condensation, Regioselective cyclization, Beckman rearrangement.

Nitrogen containing heterocycles are indispensable structural units in enormous important medicinal formulae. Among the various heterocyclic compounds, quinolinone derivatives including 2- and 4-quinolinones occur in many natural products such as coal tar, oil, herbs, and dyes.[1-2]

2-Quinolinones have long been targeted in synthetic research due to their sound biological activities and pharmacological properties, which include antiparasitic activity, [3,4] antimicrobial potency,[5,6] antioxidant effect, anti-inflammatory activity,[7] anti-convulsion,[8] anti-hepatitis C and B viruses activity,[9,10] anticancer and antitumor activity,[11,12] androgen receptor modulation,[13] CB2 receptor inverse antagonist, potent CDK-5 inhibition,[14] steroid-5a reductase-types inhibition,[15] and potential Rho-kinase inhibition.[16] The great importance of this category of heterocycles oriented our attention to the synthesis of a series of new heterocyclic derivatives combining both known biologically active heterocycles and quinoline in one molecular-frame. Thus, the present research work deals with chemical reactivity of 3-acetyl-4-methylthioquinolin-2(1*H*)-one and its use in synthesis of novel fused heterocyclo[*b* or *c*]quinoline derivatives, such as; pyrazolo, isoxazolo, oxazolo, and triazepino[*b* or *c*]quinolines. The starting material, used in this study, 3-acetyl-4-methylthioquinolin-2(1*H*)-one (**1**) [17] was prepared *via* thermal cyclization of 2-(bis(methylthio)methylene)3-oxo-*N*-phenylbutanamide. The chemical behavior of compound **1** towards different nucleophiles was studied at various reaction conditions. This compound possesses three active centers susceptible for nucleophilic attack, *viz*.; replacement of SCH_3 group at position-4, acetyl group at position-3, and C═O at position-2. Heterocyclization at either face [*b*] or [*c*] of

quinoline moiety can take place when compound **1** was treated with certain dinucleophiles, such as; hydrazines, hydroxylamine hydrochloride, and semicarbazide derivatives. Hence, compound **1** was reacted with high excess of hydrazine hydrate, molar ratio (1: 20), in DMF at room temperature, to give hydrazone **2**, in a good yield (Scheme 1). IR spectrum showed that the product comprises quinolinone C=O which appeared at ν_{max} 1620 cm^{-1}. In addition, an amino group was observed, revealing its characteristic *sym* and *asym* vibrational bands at ν_{max} 3355 and 3243 cm^{-1}, besides the vibration due to N–H of quinolinone, at ν_{max} 3198 cm^{-1}. ^{1}H NMR spectrum showed signals due to both NH_2 and N–H protons, as deuterium exchangeable protons, at δ 4.50 and 10.80. Also, the spectrum revealed the presence of two singlet signals at δ 2.49 and 2.63 due to N=C–CH_3 and SCH_3 protons, respectively.

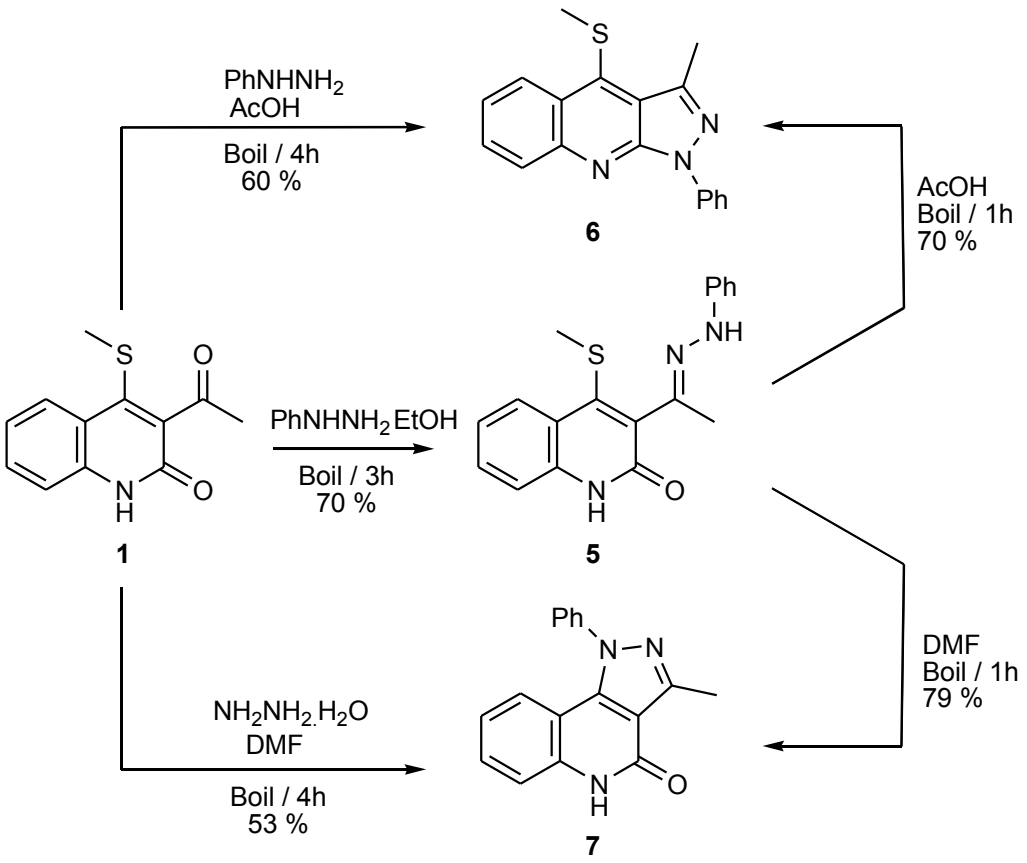
Hydrazone **2** was subjected to different treatment conditions in order to get the possible cyclized heterocyclic compounds. Thus, cyclo-condensation of hydrazone **2**, in boiling acetic acid or absolute ethanol, yielded 3-methyl-4-methylthiopyrazolo[3,4-b]quinolone (**3**) which was obtained directly through the reaction of compound **1** with hydrazine hydrate, under the same conditions (Scheme 1). At the same time, IR spectrum of compound **3** showed absence of both carbonyl functions at position-2 and this of acetyl group. ^{1}H NMR spectrum displayed evidences for existence of singlet signal refer to new N–H proton at δ 13.93 on the expense of N–H quinolinone which normally appears at δ ~ 10.80. In addition, the spectrum revealed presence of two singlet signals, at δ 2.43 and 2.70, stand for 3-CH_3 and SCH_3 protons, respectively. ^{13}C NMR spectrum indicated absence of carbonyls due to acetyl group and carbonyls of 2-quinolinone. The spectrum demonstrated presence of two sp^3-carbons due to SCH_3 and 3-CH_3, at δ 15 and 12, respectively. Interestingly, when hydrazone **2** was heated in boiling DMF, pyrazolo[4,3-*c*]quinolinone **4** was obtained, in 84% yield. The same compound **4** was directly produced, in 70% yield, when compound **1** was treated with hydrazine hydrate, in boiling DMF (Scheme 1). Elemental analysis revealed that compound **4** lacked sulfur, by means the cyclization involved removal of methanethiol. The structure of compound **4** was supported by an authentic sample prepared according to literature procedure.[17]



Scheme1.

In respect to the reactivity of acetyl compound towards phenylhydrazine, treatment of compound **1** with

phenylhydrazine in boiling ethanol afforded a pale brown product that was identified as *Z,E*-phenylhydrazone **5** (65:35)(Scheme 2). IR spectrum of compound **5** exhibited absorption bands at ν_{max} 3620 and 3188 cm^{-1}, corresponding to both H-bonded O–H, N–H functions of 2-quinolinol and hydrazone. ^{1}H NMR spectrum of compound **5** presented four singlet signals at δ 8.50 (hydrazone N–$H_{E\text{-form}}$), 9.00 (hydrazone N–$H_{Z\text{-form}}$), 11.04 (quinolinone N–$H_{Z\text{-form}}$) and 11.20 (quinolinol O–$H_{E\text{-form}}$), besides two signals at δ 2.13, 2.60, due to corresponding chemical shifts of N=C–CH_3, SCH_3, protons. Moreover, ^{13}C NMR spectrum proved that the product contain a carbonyl group which was appeared at δ 174, in addition to chemical shifts of two sp^3-carbons existed at δ 16 and 17, due to two methyl groups. When phenylhydrazone **5** was subjected to boiling in glacial acetic acid, 1-phenylpyrazolo[3,4-*b*]quinolinone **6** afforded in 70% yield. The same compound was directly obtained *via* the reaction of compound **1** with phenylhydrazine, in boiling glacial acetic acid (Scheme 2). The structure of product **6** was inferred from elemental analysis which confirmed presence of sulfur, indicating that SCH_3 group was not involved in the cyclization reaction. ^{1}H NMR spectrum of product **6** exhibited signals at δ 2.84 and 2.88, referred to characteristic chemical shifts of 3-CH_3 and SCH_3 protons. ^{13}C NMR spectrum fortified this conclusion about the structure of product **6** since it points out to absence of any characteristic carbonyl peak. Interestingly, heating of phenylhydrazone **5** in boiling DMF for only one hour led to 1-phenylpyrazolo[4,3-*c*]quinolinone **7**, in 79% yield. The same product **7** was also obtained when compound **1** was treated with phenylhydrazine, in boiling DMF (Scheme 2). Structure of compound **7** was established on basis of its elemental analysis, revealing removal of methanethiol which was noticed during the course of reaction, additionally an authentic sample was obtained according to literature method. [18]



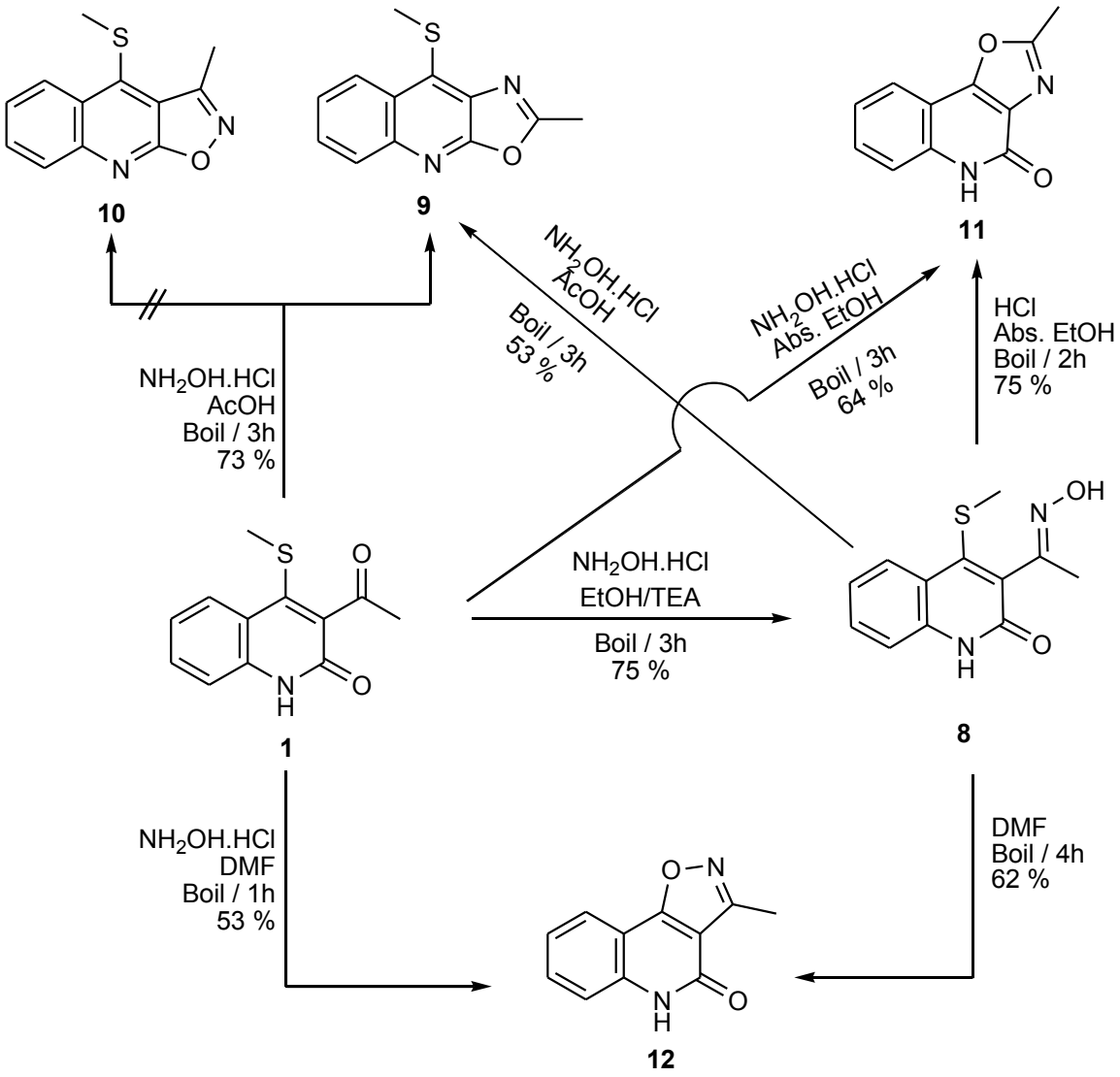
Scheme 2.

It is thought that extension of the above study to investigate the reaction of compound **1** with hydroxylamine hydrochloride under different reaction conditions may furnish new interesting fused heterocyclic compounds. Thus, treatment of compound **1** with hydroxylamine hydrochloride, in boiling ethanol containing drops of triethylamine, led to oxime **8** (Scheme 3)**.** The structure of oxime **8** was verified by elemental analysis and spectroscopic methods. ^{1}H NMR spectrum displayed, in addition to aromatic protons, four singlet signals at δ 2.08, 2.50, 10.87, and 11.20, characteristic for N=C–CH_3, SCH_3, N–$H_{quinolinone}$ and O–H_{oxime} protons, respectively. Also, ^{13}C NMR revealed a distinctive signal at δ 174

refers to the presence of carbonyl group at position-2 of quinolinone moiety. Oxime **8** was subjected to cyclization processes under different conditions in order to obtain a variety of triheterocylcic fused compounds. Surprisingly, when oxime **8** was heated, in boiling glacial acetic acid, led to oxazolo[5,4-*b*]quinoline **9** , in 53% yield. Compound **9** was also obtained directly from compound **1** itself when we carried out its reaction with hydroxylamine hydrochloride, in boiling glacial acetic acid.

Presence of sulfur in the cyclized product **9**, as indicated in its elemental analysis and also evidenced via existence of S–CH_3 protons in ^{1}H NMR spectrum, let us concluded that cyclization, in boiling acetic acid regioselectively takes place at face [*b*] not [*c*].The chemical shift value, at δ 2.48, characteristic for 2-methyloxzaole protons, confirmed that 2-methyloxazolo[5,4-*b*]quinoline **9** was formed on cost of the usually expected 3-methylisoxazolo[5,4-*b*]quinoline **10**, which may reveal chemical shift of methyl protons at a more upfield shifted region, ~ δ 2.3 [20,21] (Scheme 3).

Boiling a solution of oxime **8**, in absolute ethanol in presence of drops of hydrochloric acid, gave oxazolo[4,5-*c*]quinolin-4-one **11**.[22] The same compound was directly obtained *via* treatment of compound **1** with hydroxylamine hydrochloride, in boiling ethanol, without any additives (Scheme 3).

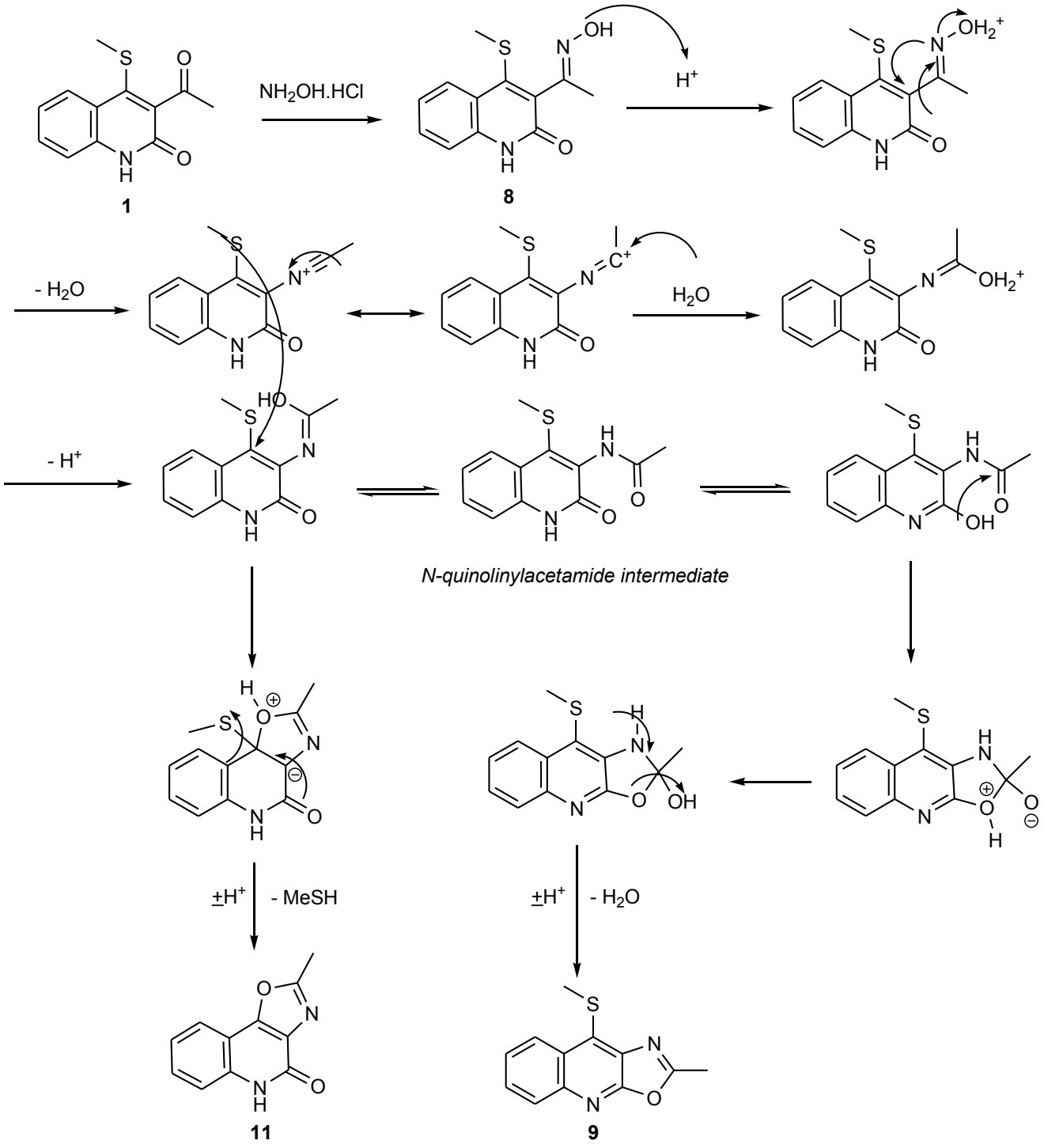


Scheme 3.

Furthermore, oxime compound **8** was refluxed in DMF, gave another product isoxazolo[4,5-*c*]quinolinone **12**. Also, the same compound was obtained *via* refluxing of acetyl **1** with hydroxylamine hydrochloride in DMF (Scheme 3). It is

interesting to compare the analytical and spectral data of both isomers **11** and **12**. Both of them revealed the same elemental analysis results indicating to loss of methanethiol during cyclization process. Moreover both of them are clearly different in their physical and spectral properties. The structures of isomers **11** and **12** found good support through preparation of authentic samples of both compounds according to literature procedures.[20,21] *Beckmann* rearrangement[19] may be a conceivable explanation for formation of products **9** and **11** in acidic media. Thus, protonation of oxime group at the oxygen atom first takes place to give an oxonium cation and the rearrangement proceeds as depicted in figure 4. The path-way leads to the 3-acetamidoquinoline intermediate which regioselectively be cyclized to give either product **9** or **11** (Scheme 4).

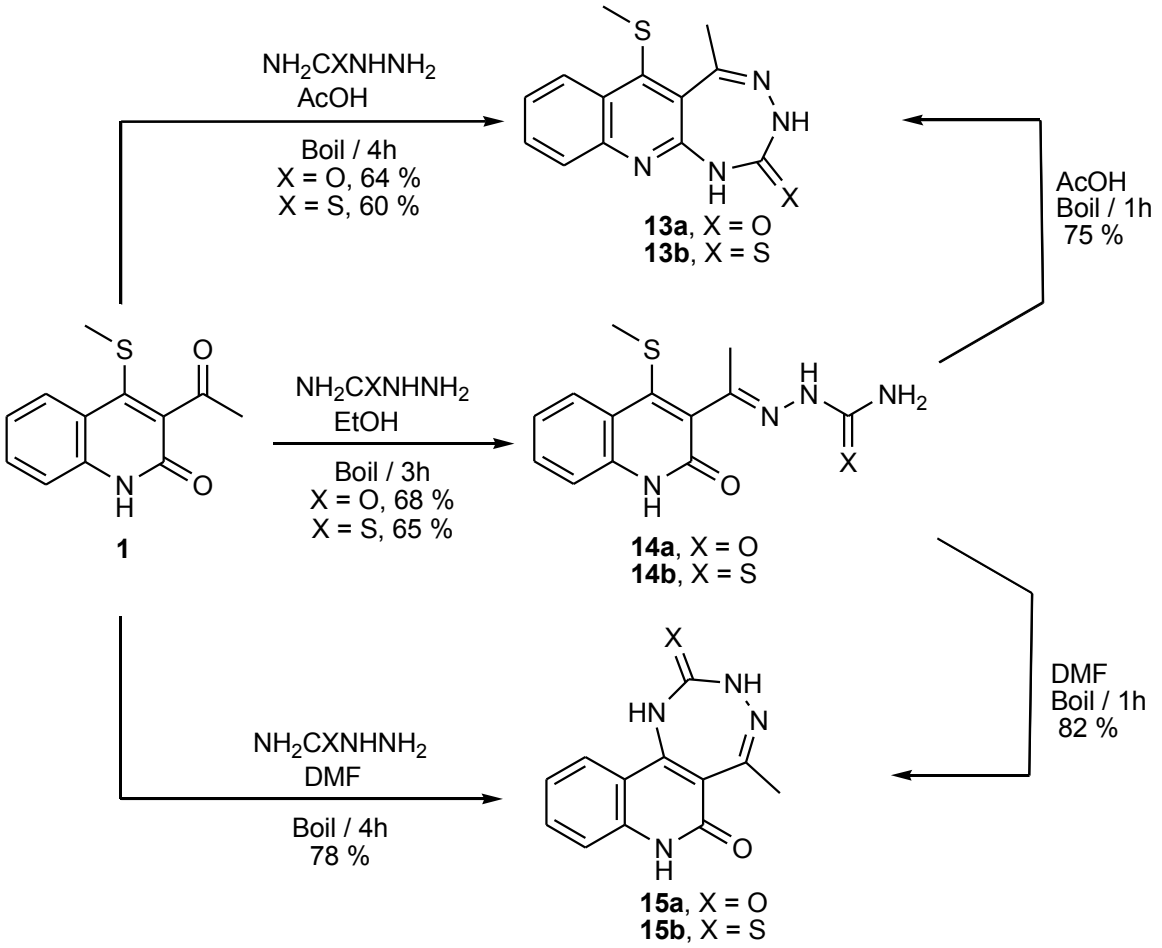
1,4-Dinucleophiles such as semicarbazide and its analogue thiosemicarbazide are known useful reagents in synthesis of 1,2,4-triaza-heterocycles. Treatment of compound **1** with semicarbazide hydrochloride and/or thiosemicarbazide, in boiling ethanol, afforded semicarbazone derivatives **13a,b** (X = O, S) (Scheme 5).



Scheme4.

The analytical and spectral data supported that reaction under these conditions leads to the open semicarbazones. Hence, IR spectrum of semicarbazones **13a**,**b** showed absorption bands at ν_{max} 3277, 3217 and 1655 cm^{-1} corresponding to amino and carbonyl groups, respectively. ^1H NMR spectrum of these products represented two singlet signals at δ 2.5 and 2.7 due to N=C–CH_3 and SCH_3 protons, in addition to a broad signal at δ 4.50 for chemical shift of amino protons. Interestingly herein again it was found that when this reaction was carried out in boiling glacial acetic acid instead of ethanol, the cyclized 1,2,4-triazepino[5,6-*b*]quinolines **14a**,**b** (X = O, S), afforded in 60-64% yields. The same products **14a,b** was also obtained when semicarbazones **13a**,**b** were subjected to heating, in boiling in glacial acetic acid for only 1 hour (Scheme 5).

Analytical data of products **14a,b** showed that in the course of conversion of open chain semicarbazones **13a,b**, dehydration took place to affect annulation at face [*b*]. Moreover, spectral results confirmed that SCH_3 function still present in the structure of both products **14a,b**. ^{1}H NMR spectrum indicated existence of a chemical shift at δ 2.67, characteristic for SCH_3 protons. On the other hand, carrying out the reaction of compound **1** with semicarbazide hydrochloride and/or thiosemicarbazide was, in boiling DMF, furnished 1,2,4-triazepino[6,5-*c*]quinolinones **15a,b** (X = O, S), in 78% yield. Once more, it was found that heating of the corresponding open chain semicarbazones **13a,b**, in boiling DMF, led to the same cyclized products **15a,b** (Scheme 5). Spectral analysis outcomes proved that the cyclization process in DMF, a relatively high boiling neutral solvent effected annellation away from dehydration but involving liberation of methanethiol. Furthermore, authentic samples of both products **15a,b** were prepared according to literature. [17] In conclusion, the condensation reaction of 3-acetyl-4-methylthioquinolin-2(1*H*)-one with certain dinucleophilic reagents, under different reaction conditions, regioselectively leads to different open or cyclized quinoline derivatives.



Scheme 5.

This variability of products is attributed to the presence of three active centers on quinolinone moiety. The key compound may be considered as a good synthone for a wide scale of heterocyclized quinoline derivatives, depending on the nature of reagent and reaction conditions.

Experimental

Melting points are uncorrected and were determined in open capillary tubes one digital Stuart-SMP3 melting point apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 1650 spectrophotometer, using samples in KBr disks. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on Mercury–300BB or Gemini–300BB spectrometers (δ), using DMSO-d_6 or CD_3Cl-$d_6$as solvent and TMS as an internal

reference. Mass spectra (70 eV) were obtained using a Shimadzu GC-2010 Gas–Chromatography instrument mass spectrometer. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer. Compound **1**[17] was prepared according to the reported literature method.

3-(1-Hydrazonoethyl)-4-methylthioquinolin-2(1*H*)-one (2). To a stirred solution of compound **1** (10 mmol, 2.33 g), in DMF (70 mL), hydrazine hydrate (200 mmol, 10 mL, 99%) was added drop wise. The reaction mixture was stirred at room temperature for 3 h and the excess solvent was evaporated at room temperature. The solid, that formed, was collected by filtration, washed by ethanol and dried to give compound **2**, yield 1.30 g (53%), mp 198–199°C (decomp.). IR (KBr, cm^{-1}), ν_{max}: 3355 (NH_2), 3243, 3198, 3129 (N–H), 3064, 2963, 1620, 1603, 1555, 1513, 1480, 1362, 1349, 759. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.49 (3H, s, N=C–CH_3), 2.63 (3H, s, S–CH_3), 4.50 (2H, s, NH_2 disappeared on addition of D_2O), 7.32 (1H, t, *J* = 6.6, 6-CH), 7.67 (2H, m, 7,8-CH), 8.07 (1H, d, *J* = 8.1, 5-CH), 10.80 (1H, s, N–H disappeared on addition of D_2O). MS, m/z (I_r %): 247 (1.12) ($M^{+\cdot}$), 233 (1.80), 232 (2.76), 216 (6.24), 140 (7.18), 130 (11.90), 127 (31. 82), 117 (9.00), 115 (20.93), 104 (14.16), 103 (15.79), 102 (29.38), 97 (16.18), 92 (8.69), 91 (15.51), 89 (38.44), 88 (21.78), 83 (15.90), 77 (70.63), 76 (95.03), 70 (24.18), 63 (83.99), 57 (100). Analysis calculated for $C_{12}H_{13}N_3OS$ (247.32): C, 58.28; H, 5.30; N, 16.99%. Found: C, 58.10; H, 5.20; N, 16.80%.

3-Methyl-4-methylthio-1*H*-pyrazolo[3,4-*b*]quin-oline (3). Procedure a. A mixture of compound **1** (10 mmol, 2.33 g) and hydrazine hydrate (200 mmol, 1 mL) was heated under reflux, in absolute ethanol (100 mL), for 3 h. The reaction mixture was left to cool at room temperature. The precipitate crystalline was filtered, dried and recrystallized from ethanol to give compound **3**, yield 1.56 g (68%), mp 260–262°C. IR (KBr, cm^{-1}), ν_{max}: 3213, 3132 (N–H), 3027, 2919, 1629 (C=N), 1586, 1567, 1518, 1376, 1349, 1294, 763, 756. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.43 (3H, s, (N=C–CH_3), 2.70 (3H, s, S–CH_3), 7.55 (1H, t, *J* = 6.6, 6-CH), 7.67 (1H, d, *J* = 8.4, 8-CH), 7.94 (1H, t, *J* = 8.1, 7-CH), 8.28 (1H, d, *J* = 7.8, 5-CH), 13.93 (1H, s, N–H disappeared on addition of D_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 155.06, 144.94, 143.16, 141.17, 129.44, 128.27, 125.72, 122.35, 114.92, 114.26, 15.09, 11.90. MS, m/z (I_r %): 230 (16.24) (M+1), 229 (97.41) ($M^{+\cdot}$), 228 (31.39), 214 (13.03), 196 (22.77), 183 (77.59), 169 (22.86), 167 (19.08), 154 (61.89), 140 (24.07), 129 (54.23), 128 (35.56), 127 (50.75), 115 (45.43), 114 (100), 102 (94.55), 77 (51.60). Analysis calculated for $C_{12}H_{11}N_3S$ (229.31): C, 62.86; H, 4.84; N, 18.32%. Found: C, 62.80; H, 4.80; N, 18.30%.

Procedure b. A solution of compound **2** (10 mmol, 2.50 g), in glacial acetic acid (25 mL) or absolute ethanol (50 mL), was heated under reflux, for 1 h. The reaction mixture was left to cool at room temperature. The crystallized material, so formed, was filtered, dried, and recrystallized from absolute ethanol to give compound **3**. For the reaction in ethanol yield 1.04 g (45%) and for the reaction in acetic acid yield 1.72 g (75%).

3-Methyl-1*H*-pyrazolo[4,3-*c*]quinolin-4(5*H*)-one (4).

A solution of compound **2** (10 mmol, 2.50 g), in DMF (25 mL), was heated under reflux for 1 h. The reaction mixture was left to cool at room temperature. The precipitate crystalline was filtered, dried to give compound **4** in yield 1.67 g (84%).

(*Z*,*E*)-4-Methylthio-3-[1-(phenylhydrazono)eth-yl]quinolin-2(1*H*)-one (5). A mixture of compound **1** (10 mmol, 2.33 g) and phenyl hydrazine (10 mmol, 1.1 mL), in absolute ethanol (100 mL), was heated under reflux for 3 h. Then, the reaction mixture was left to cool and the solid so precipitated was collected by filtration, washed with diethyl ether and recrystallized from ethanol to give compound **5**, yield 2.30 g (70%), mp. 216–218°C (decomp.). IR (KBr, cm^{-1}), ν_{max}: 3620 (O–H), 3188 (N–H), 3069, 2965, 1620 (C=N), 1559, 1528, 756, 752. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.13 (3H, s, (N=C–CH_3), 2.60 (3H, s, S–CH_3), 6.63–8.08 (9H, m, H_{arom}), 8.50 (1H, s, hydrazone N–$H_{E\text{-form}}$), 9.00 (1H, s, hydrazone N–$H_{Z\text{-form}}$), 11.04 (1H, s, quinolinone N–$H_{Z\text{-form}}$), 11.20 (1H, s, quinolinol O–$H_{E\text{-form}}$). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 174.49, 149.49, 146.74, 140.00, 132.09, 129.09, 128.80, 125.42, 124.00, 123.75, 122.62, 118.99, 118.28, 113.05,112.80, 112.43, 23.65, 17.23. MS, m/z (I_r %): 324 (10.58) (M+1), 323 (39.24) ($M^{+\cdot}$), 308 (13.43), 276 (36.63), 231 (15.40), 217 (12.89), 202 (8.64), 146 (7.02), 132 (15.10), 130 (13.48), 115 (21.33), 114 (13.55), 108 (8.68), 102 (14.15), 93 (100), 91 (61.44), 89 (18.88), 77 (56.08), 65 (57.21). Analysis calculated for $C_{18}H_{17}N_3OS$ (323.42): C, 66.85; H,

5.30; N, 12.99%. Found: C, 66.70; H, 5.10; N, 12.890%.

3-Methyl-4-methylthio-1-phenylpyrazolo[3,4-*b*]-quinoline (6). Procedure a. A mixture of compound **1** (10 mmol, 2.33 g) and phenylhydrazine (10 mmol, 1.1 mL), in glacial acetic acid (100 mL), was heated under reflux for 4 h, then the reaction mixture was left to cool at room temperature. The yellow crystalline material so obtained was filtered, washed with ethanol (30 mL), and recrystallized from glacial acetic acid to give compound **6**, yield 1.60 g (60%), mp 158–160°C. IR (KBr, cm^{-1}), ν_{max}: 3069, 2974, 1617 (C=N), 1597, 1562, 776, 749. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.84 (3H, s, N=C–CH_3), 2.88 (3H, s, S–CH_3), 7.18 (1H, t, *J* = 8, 6-CH), 7.43 (1H, d, *J* = 8, 8-CH), 7.45–7.61 (6H, m, H_{arom} + 7-CH), 8.04 (1H, d, *J* = 8, 5-CH), ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 155.20, 145.86, 143.85, 140.61, 139.75, 130.27, 129.60, 128.84, 127.65, 125.36, 121.67, 115.65, 114.84, 15.02, 12.07. MS, m/z (I_r %): 307 (6.65) (M+2), 306 (21.86) (M+1), 305 (100) ($M^{+\cdot}$), 304 (27.99), 290 (6.70), 272 (7.62), 259 (14.95), 258 (22.36), 228 (6.89), 216 (5.56), 201 (7.17), 190 (17.05), 169 (24.26), 154 (13.14), 128 (11.89), 114 (13.25), 108 (22.42), 102 (13.01), 93 (9.59), 89 (11.71), 77 (88.97). Analysis calculated for $C_{18}H_{15}N_3S$ (305.40): C, 70.79; H, 4.95; N, 5.67%. Found: C, 70.60; H, 4.70; N, 5.60%.

Procedure b. A solution of compound **5** (10 mmol, 3.23 g) in glacial acetic acid (50 mL) was heated under reflux for 1 h. The reaction mixture was left to cool to give a yellow crystalline precipitate which was filtered and washed with ethanol and diethyl ether to give the same compound **6**, yield 2.24 g (70%).

3-Methyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinolin-4(5*H*)-one (7). A solution of compound **5** (10 mmol, 3.23 g), in DMF (50 mL), was heated under reflux for 1 h. The reaction mixture was left to cool and the crystalline precipitate so obtained was filtered, dried and recrystallized from glacial acetic acid to give compound **7**, yield 2.21 g (79%).

3-(1-(Hydroxyimino)ethyl)-4-(methylthio)quin-olin-2(1*H*)-one (8). A mixture of compound **1** (10 mmol, 2.33 g), hydroxylamine hydrochloride (10 mmol, 0.7 g) and triethylamine (0.5 mL), in absolute ethanol (100 mL), was heated under reflux for 3 h. The solid that obtained, after cooling to room temperature, was filtered, dried and recrystallized from ethanol to give compound **8**, yield 1.9 g (75%), mp 198–199°C. IR (KBr, cm^{-1}), ν_{max}: 3446 (O–H), 3243 (N–H), 3061, 2957, 1625 (C=O, C=N), 1606, 1560, 1496, 1473, 758. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.08 (3H, s, N=C–CH_3), 2.50 (3H, s, S–CH_3), 7.32 (1H, t, *J* = 7.2, 6-CH), 7.65 (2H, m, 7,8-CH), 8.03(1H, d, *J* = 7.8 Hz, 5-CH), 10.87 (1H, s, N–H disappeared on addition of D_2O), 11.20 (1H, s, O–H disappeared on addition of D_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 174.00, 152.77, 149.32, 140.74, 132.27, 125.53, 124.57, 123.90, 120.03, 118.31, 16.12, 15.20. MS, m/z (I_r %): 249 (8.95) (M+1), 248 (33.04) ($M^{+\cdot}$), 233 (15.43), 217 (46.97), 216 (100), 215 (15.57), 202 (41.29), 188 (13.37), 185 (14.27), 172 (10.74), 170 (12.61), 158 (18.39), 155 (14.98), 142 (29.48), 132 (16.38), 130 (30.87), 128 (21.98), 120 (16.01), 115 (36.01), 89 (39.70), 76 (43.35). Analysis calculated for $C_{12}H_{12}N_2O_2S$ (248.31): C, 58.05; H, 4.87; N, 11.28%. Found: C, 57.80; H, 4.70; N, 11.10%.

2-Methyl-9-(methylthio)oxazolo[5,4-*b*]quinoline (9).

Procedure a. To a solution of compound **1** (10 mmol, 2.33 g), in glacial acetic acid (100 mL), hydroxylamine hydrochloride (10 mmol, 0.7 g) was added and the reaction mixture was heated under reflux for 3 h. The crystalline precipitate, which formed on cooling, was filtered, dried and recrystallized from acetic acid to give compound **9**, yield 1.70 g (73%), mp 110–112°C. IR (KBr, cm^{-1}), ν_{max}: 3069, 2927, 1632 (C=N), 1590, 1557, 1525, 1297, 761. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.48 (3H, s, N=C–CH_3), 2.50 (3H, s, S–CH_3), 7.61 (1H, t, *J* = 6.9, 6-CH), 7.83 (1H, t, *J* = 7.2, 7-CH), 7.97 (1H, d, *J* = 6 Hz, 8-CH), 8.21 (1H, d, *J* = 8.4, 5-CH), ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 174.00, 153.00, 149.00, 141.00, 132.00, 125.00, 124.00, 123.00, 120.00, 118.00, 16.00, 15.00. MS, m/z (I_r %): 231 (19.33), 230 (100) ($M^{+\cdot}$), 229 (27.79), 215 (1.98), 202 (52.60), 197 (38.63), 184 (23.51), 173 (9.45), 169 (16.15), 155 (14.12), 141 (13.00), 130 (37.62), 129 (27.75), 120 (11.43), 115 (46.43), 114 (85.35), 102 (73.87), 88 (43.70), 76 (64.81). Analysis calculated for $C_{12}H_{10}N_2OS$ (230.29): C, 62.59; H, 4.38; N, 12.16%. Found C, 62.40; H, 4.20; N, 12.00%.

Procedure b. A solution of compound **8** (10 mmol, 2.48 g), in glacial acetic acid (50 mL), was heated under

reflux for 3 h. The reaction mixture was left to cool and the crystalline precipitate so obtained was filtered, and dried to give compound **9** in yield 1.30 g (53%).

2-Methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (11).

Procedure a. To equimolar amount of compound **1** (0.01 mol, 2.33 g) and hydroxylamine hydrochloride (0.01 mol, 0.7 g) was heated under refluxing in absolute ethanol (70 mL) for 3 h. The reaction mixture was left to cool. The solid precipitate was collected by filteration, dried and to give compound **11** in yield 1.4 g (64 %).

Procedure b. A mixture of compound **8** (10 mmol, 2.48 g), conc. hydrochloric acid (1 mL), in absolute ethanol (50 mL), was heated under reflux for 2 h. The reaction mixture was left to cool and the crystalline precipitate so obtained was filtered, dried and crystallized from glacial acetic acid to give the same compound **11**, yield 1.50 g (75%).

3-Methylisoxazolo[4,5-c]quinolin-4(5*H*)-one (12).

A solution of compound **8** (10 mmol, 2.48 g), in DMF (50 mL), was heated under reflux for 4 h. The reaction mixture was left to cool and the crystalline precipitate so obtained was filtered, dried and crystallized from glacial acetic acid to give compound **12** in yield 1.24 g (62%).

General Procedure for Preparation of Semicarbazone 13a and Thiosemicarbazone 13b. To a solution of compound **1** (10 mmol, 2.33 g), in ethanol (50 mL), 10 mmol of either semicarbazide hydrochloride (1.11 g) or thiosemicarbazide (0.92 g), was added and the reaction mixture was heated under reflux for 3 h. The solid deposit that obtained, on cooling to room temperature, was filtered and crystallized from absolute ethanol to give compounds **13a** and **13b**, respectively.

1-(1-(4-(Methylthio)-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene)semicarbazide (13a). This compound was obtained from semicarbazide, yield 1.98 g (68%), mp 221–223 °C. IR (KBr, cm^{-1}), ν_{max}: 3277 (NH_2), 3217, 3143 (N–H), 3058, 2927, 1650 (C=O), 1620 (C=N), 1609, 1567, 1532, 1489, 1380, 1297, 758. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.50 (3H, s, N=C–CH_3), 2.70 (3H, s, S–CH_3), 4.48 (2H, s, NH_2 disappeared on addition of D_2O), 7.39 (1H, t, *J* = 8.1, 6-CH), 7.70 (1H, t, *J* = 7.2, 7-CH), 7.78 (1H, d, *J* = 8.4, 8-CH), 8.13 (1H, d, *J* = 7.8, 5-CH), 8.62 (1H, s, N–H disappeared on addition of D_2O), 10.86 (s, 1H, N–$H_{quinolinone}$ disappeared on addition of D_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 198.00, 178.00, 156.00, 139.00, 132.00, 131.00, 125.00, 124.00, 123.00, 119.00, 118.00, 31.00, 14.00. MS, m/z (I_r %): 290 (undetected) ($M^{+\cdot}$), 235 (2.29), 234 (12.46), 233 (15.60), 220 (7.05), 219 (15.70), 218 (100), 215 (12.45), 200 (14.42), 190 (5.77), 182 (4.52), 173 (3.01), 172 (25.55), 145 (5.34), 132 (2.98), 117 (7.30), 116 (5.42), 90 (3.03), 89 (8.42), 77 (4.94). Analysis calculated for $C_{13}H_{14}N_4O_2S$ (290.35): C, 53.78; H, 4.86; N, 19.30%. Found: C, 53.60; H, 4.60; N, 19.10%.

1-(1-(4-(Methylthio)-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene)thiosemicarbazide (13b). This compound was obtained from thiosemicarbazide, yield 2.00 g (65%), mp 202–204°C. IR (KBr, cm^{-1}), ν_{max}: 3277 (NH_2), 3217, 3143 (N–H), 3070, 2930, 1654 (C=O), 1619 (C=N), 1566, 1540, 1489, 1340, 758. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.20 (3H, s, N=C–CH_3), 2.67 (3H, s, S–CH_3), 4.50 (2H, s, NH_2 disappeared on addition of D_2O), 7.40 (1H, t, *J* = 8.1, 6-CH), 7.71 (1H, t, *J* = 7.2, 7-CH), 7.80 (1H, d, *J* = 8.4, 8-CH), 8.13 (1H, d, *J* = 7.8, 5-CH), 10.30 (1H, s, N–H disappeared on addition of D_2O), 10.86 (1H, s, N–$H_{quinolinone}$ disappeared on addition of D_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 199.17, 179.00, 175.00, 156.70, 150.00, 139.97, 132.86, 125.62, 124.88, 120.08, 118.76, 32.04, 16.23. MS, m/z (I_r %): 306 (2.62) ($M^{+\cdot}$), 305 (10.43), 258 (2.58), 234 (4.59), 233 (9.41), 220 (6.01), 219 (13.36), 218 (100.00), 216 (10.75), 215 (13.14), 199 (33.38), 198 (5.91), 190 (12.52), 182 (8.83), 172 (47.85), 145 (16.79), 142 (7.56), 130 (16.94), 128 (10.58), 117 (25.36), 116 (22.18), 115 (20.01), 102 (21.91), 91 (36.94), 89 (41.59), 77 (46.45),. Analysis calculated for $C_{13}H_{14}N_4OS_2$ (306.41): C, 50.96; H, 4.61; N, 18.28%. Found: C, 50.70; H, 4.50; N, 18.20%.

General Procedures for Preparation of [1,2,4]Triazepino[5,6-*b*]quinolines 14a,b. Procedure a. To a solution of compound **1** (10 mmol, 2.33 g), in glacial acetic acid (50 mL), 10 mmol of either semicarbazide hydrochloride (1.11 g) or thiosemicarbazide (0.92 g), was added and the reaction mixture was heated under reflux for 4 h. Afterwards, the reaction mixture was left to cool and the solid deposit that obtained was filtered

and crystallized to give compound **14a,b.**

5-Methyl-6-(methylthio)-1*H*-[1,2,4]triazepino [5,6-*b*]quinolin-2(3*H*)-one (14a). This compound was obtained from semicarbazide hydrochloride, and recrystallized from absolute ethanol, yield (64%), mp 299–301°C. IR (KBr, cm^{-1}), ν_{max}: 3248, 3135 (N–H), 3061, 2985, 1647 (C=O), 1620 ($C=N_{triazepine}$), 1603, 1560, 1510, 1474, 1344, 758. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.48 (3H, s, N=C–CH_3), 2.67 (3H, s, S–CH_3), 7.37 (1H, t, *J* = 7.8, 9-CH), 7.65 (1H, t, *J* = 8.1, 8-CH), 7.79 (1H, d, *J* = 8.4, 7-CH), 8.11 (1H, d, *J* = 8.1, 10-CH), 9.79 (1H, s, N–H disappeared on addition of D_2O), 13.00 (1H, s, $N–H_{quinolinone}$ disappeared on addition of D_2O). Analysis calculated for $C_{13}H_{12}N_4OS$ (272.33): C, 57.34; H, 4.44; N, 20.57%. Found: C, 57.20; H, 4.40; N, 20.50%.

5-Methyl-6-(methylthio)-1*H*-[1,2,4]triazep-ino[5,6-*b*]quinolin-2(3*H*)-thione (14b). This compound was obtained from thiosemicarbazide and recrystallized from Acetic acid, yield 1.88 g (60%), mp. 130–133°C. IR (KBr, cm^{-1}), ν_{max}: 3316, 3200 (N–H), 3026, 2961, 1622 ($C=N_{triazepine}$), 1592, 1498, 1472, 723. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.14 (3H, s, N=C–*CH*$_3$), 2.69 (3H, s, S–*CH*$_3$), 7.63 (1H, t, *J* = 8.1, 9-CH), 7.70 (2H, m, 7,8-CH), 8.07 (1H, d, *J* = 7.8, 10-CH), 9.66 (1H, s, N–H disappeared on addition of D_2O), 11.97 (1H, s, $N–H_{quinolinone}$ disappeared on addition of D_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 178.55, 172.48, 149.53, 147.85, 146.58, 141.26, 132.35, 125.39, 124.87, 118.39, 116.82, 21.51, 16.16. MS, m/z (I_r %): 288 (0.53) ($M^{+\cdot}$), 272 (1.06), 242 (11.75), 233 (3.86), 229 (7.10), 218 (29.85), 199 (30.53), 190 (5.39), 183 (6.61), 170 (9.91), 145 (11.45), 132 (5.15), 128 (8.44), 120 (11.45), 115 (29.88), 114 (25.99), 94 (24.55), 91 (38.68), 89 (20.07), 77 (44.29), 69 (15.19), 63 (17.05), 60 (47.85), 59 (100). Analysis calculated for $C_{13}H_{12}N_4S_2$ (288.40): C, 54.14; H, 4.19; N, 19.43%. Found: C, 54.00; H, 4.10; N, 19.20%.

Procedure b. A solution of 5 mmol of either compound **13a** (1.45 g) or **13b** (1.53 g), in glacial acetic acid (30 mL), was boiled under reflux for 1 h. The reaction mixture was left to cool and the crystalline product so obtained was filtered, and dried to give compound **14a**, yield 1.01 g (75%) and **14b**, yield 1.09 g (75%), respectively.

General Procedures for Preparation of [1,2,4]Triazepino[6,5-*c*]quinolines 15a,b.

A solution of 5 mmol of either compound **13a** (1.45 g) or **13b** (1.53 g), in DMF (30 mL), was boiled under reflux for 1 h. The reaction mixture was left to cool and the crystalline product so obtained was filtered, and dried to give compound **15a,** yield 0.99 g (82. %) and **15b** in yield 1.06 g (82%), respectively.

5-Methyl-1*H*-[1,2,4]triazepino[6,5-*c*]quinoline-2,6(3*H*,7*H*)-dione (15a). This compound was obtained from semicarbazide hydrochloride, mp > 300°C (Lit. mp > 300°C).[17]

5-Methyl-2-thioxo-2,3-dihydro-1*H*-[1,2,4]triazepino-[6,5-*c*]quinolin-6(7*H*)-one (15b). This compound was obtained from thiosemicarbazide, recrystallized from absolute ethanol, mp > 300°C (Lit. mp > 300°C).[17]

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