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Substituted quinolinones

27.* Regioselective synthesis of pyrazolo-, oxazolo-, and triazepinoquinoline derivatives

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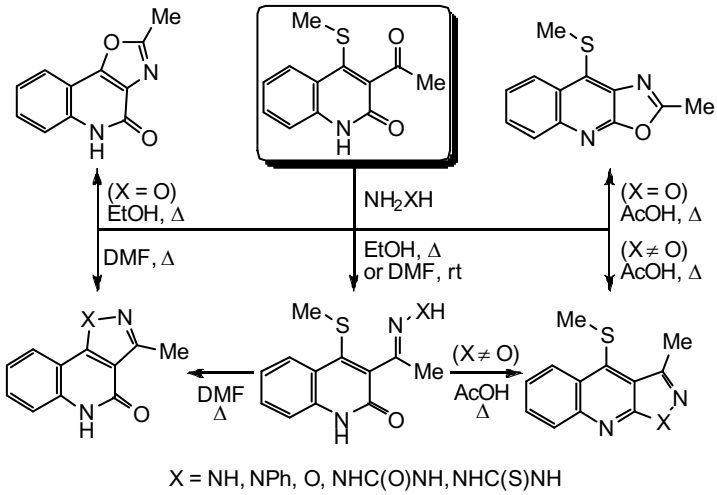


Reactivity of 3-acetyl-4-(methylsulfanyl)quinolin-2(1*H*)-one towards 1,2- and/or 1,4-diazanucleophiles has been studied under different reaction conditions. Condensation of 3-acetyl-4-(methylsulfanyl)quinolin-2(1*H*)-one with hydrazine, phenylhydrazine, hydroxylamine hydrochloride, semicarbazide, and thiosemicarbazide was carried out in different media. The structure of the reaction products was dependent not only on the reagent used, but also on the solvent and reaction temperature. Accordingly, the reaction regioselectively produced in good yields pyrazolo[3,4-*b*]quinoline, pyrazolo[4,3-*c*]quinoline, oxazolo[5,4-*b*]quinoline, oxazolo[4,5-*c*]quinoline, isoxazolo-[4,5-*c*]quinoline, [1,2,4]triazepino[5,6-*b*]quinoline, and [1,2,4]triazepino[6,5-*c*]quinoline derivatives in addition to open-chain condensates which, too, were transformed to the respective cyclic products. The structures of new products were established on basis of their analytical and spectral data.

Keywords: quinolinone, Beckmann rearrangement, heterocyclic synthesis, nucleophilic condensation, regioselective cyclization.

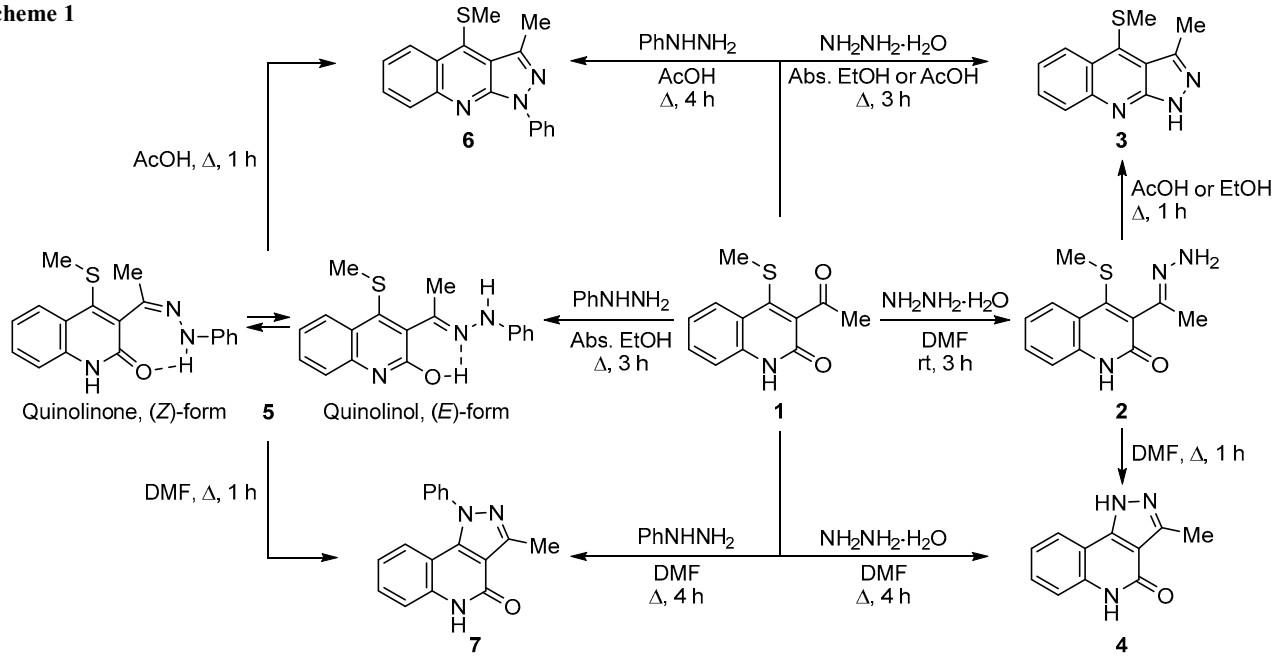
Nitrogen-containing heterocycles are nearly indispensable structural units in the development of medicinal compounds. Among the various heterocyclic compounds, quinolinone derivatives including 2- and 4-quinolinones, occur in many natural products, such as found in coal tar, oils, herbs, as well as in dyes.[2,3]

2-Quinolinones have long been targeted in synthetic research due to their interesting biological and pharmacological properties, which include antiparasitic[4,5] and antimicrobial,[6,7] antioxidant and anti-inflammatory,[8] anticonvulsive,[9] antiviral (against hepatitis C and B),[10,11] antitumor activity.[12] Among 2-quinolinones also androgen receptor modulators,[13] CB2 receptor inverse antagonists, potent CDK-5 inhibitors,[14] steroid-5a reductase-type enzyme inhibitors,[15] and potential Rho-kinase inhibitors[16] have been found.

The great importance of this class of heterocycles turned 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 the chemical reactivity of 3-acetyl-4-(methylsulfanyl)quinolin-2(1*H*)-one and its use in synthesis of novel fused heterocyclo[*b* or *c*]quinoline derivatives where quinoline ring is fused with pyrazole, isoxazole, oxazole, and triazepine rings. The starting material used in this study, 3-acetyl-4-(methylsulfanyl)-quinolin-2(1*H*)-one (**1**),[17] was prepared *via* thermal cycli-

* For Communication 26, see[1].

Scheme 1



zation of 2-[bis(methylsulfanyl)methylidene]-3-oxo-*N*-phenylbutanamide.

Compound **1** possesses three active centers susceptible to nucleophilic attack, *viz*. C-4 (with replacement of SCH_3 group), acetyl group carbon atom, and C-2 (quinolinone carbon atom). Heterocyclization at either [*b*] or [*c*] face of quinoline moiety can take place when compound **1** is treated with certain dinucleophiles, such as hydrazines, hydroxylamine hydrochloride, and semicarbazide derivatives. Hence, compound **1** was reacted with high excess (20 equiv) of hydrazine hydrate in DMF at room temperature to give hydrazone **2** in a good yield (Scheme 1). IR spectrum of compound **2** showed that the product comprises a quinolinone C=O group with the corresponding absorption band at 1620 cm^{-1}. In addition, the presence of an amino group was revealed by its characteristic *sym* and *asym* vibrational bands at 3355 and 3243 cm^{-1} along with the vibration band due to the N–H bond of quinolinone at 3198 cm^{-1}. ^1H NMR spectrum of compound **2** showed signals due to both NH_2 and NH protons at 6.15 and 10.80 ppm, both disappearing upon addition of D_2O. Also, the spectrum revealed the presence of two singlet signals at 2.49 and 2.63 ppm due to N=C–CH_3 and SCH_3 protons, respectively.

Hydrazone **2** was subjected to different treatment conditions in order to obtain cyclization products. Thus, cyclocondensation of hydrazone **2** in refluxing acetic acid or absolute ethanol yielded 3-methyl-4-(methylsulfanyl)-pyrazolo[3,4-*b*]quinoline (**3**) which was also obtained directly by the reaction of compound **1** with hydrazine hydrate under the same conditions (Scheme 1). The IR spectrum of compound **3** showed absence of both carbonyl functions (at C-2 and that of the acetyl group). ^1H NMR spectrum displayed a singlet signal at 13.93 ppm that was attributed to an NH proton different from that of 1-NH of quinolinone system, which normally appears at ~10.80 ppm and was absent from this spectrum. In addition, the spectrum featured two singlet signals at 2.43 and 2.70 ppm standing for N=C–CH_3 and SCH_3 protons, respectively. ^{13}C NMR spectrum of compound **3** indicated the absence of both acetyl group and 2-quinolinone carbonyl group, as well as the presence of two sp^3-carbons SCH_3 and 3-CH_3 represented by signals at 15.1 and 11.9 ppm, respectively.

Interestingly, when hydrazone **2** was refluxed in 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). A positive Lassaigne's test for sulfur revealed that compound **4** did not contain sulfur, which implies that the cyclization involved elimination of methanethiol. The structure of compound **4** was confirmed by comparison with the sample prepared according to literature procedure.[17]

Treatment of compound **1** with phenylhydrazine in boiling ethanol afforded a pale-brown product that was identified as phenylhydrazone **5** with (*Z*/*E*)-isomer ratio 65:35 (Scheme 1). IR spectrum of compound **5** exhibited absorption bands at 3620 and 3188 cm^{-1}, corresponding to both H-bonded O–H, N–H functions of 2-quinolinol and hydrazone, respectively. ^1H NMR spectrum of compound **5** presented four singlet signals at 8.50 (NH hydrazone, (*E*)-form), 9.00 (NH hydrazone, (*Z*)-form), 11.04 (NH quinolinone, (*Z*)-form) and 11.20 ppm (OH quinolinol, (*E*)-form), besides two signals at 2.13 and 2.60 ppm due to the corresponding chemical shifts of N=C–CH_3 and SCH_3 protons. Moreover, ^{13}C NMR spectrum proved that the structure of product **5** contains a carbonyl group with a corresponding resonance at 174.5 ppm in addition to two methyl groups with the resonances of sp^3-carbons at 16.1 and 23.7 ppm.

Refluxing phenylhydrazone **5** in glacial acetic acid afforded 1-phenylpyrazolo[3,4-*b*]quinoline **6** in 70% yield. The same compound was directly obtained by the reaction

of compound **1** with phenylhydrazine in boiling glacial acetic acid (Scheme 1). The structure of product **6** was inferred from the sulfur test which confirmed the presence of sulfur and the presence of the signal of SCH_3 protons in its ^{1}H NMR spectrum, indicating that SCH_3 group was not involved in the cyclization reaction. ^{1}H NMR spectrum of product **6** exhibited signals at 2.84 and 2.88 ppm, assigned to characteristic chemical shifts of N=C–CH_3 and SCH_3 protons. ^{13}C NMR spectrum supported the conclusion about the structure of product **6**, since no signal in the chemical shift range characteristic for carbonyl carbon was observed.

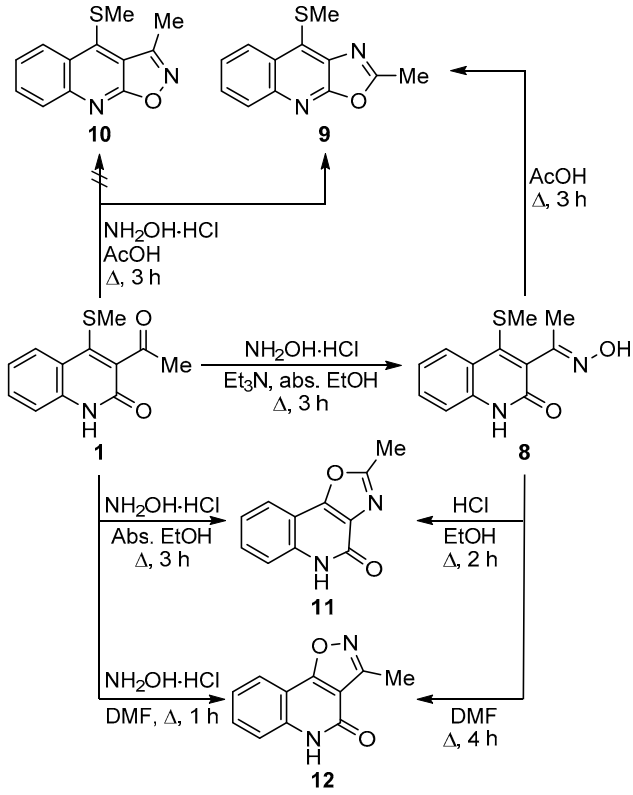
Refluxing phenylhydrazone **5**, in DMF, for only 1 h led to 1-phenylpyrazolo[4,3-*c*]quinolinone **7** in 79% yield. The same product **7** was also obtained when compound **1** was treated with phenylhydrazine in boiling DMF (Scheme 1). Structure of compound **7** was established on the basis of sulfur test, revealing the elimination of methanethiol, which was noticed also during the course of reaction by the characteristic odor, and, additionally, by a comparison with the sample obtained according to literature method.[18]

It was reasonable to assume that extension of the above study to investigate the reactivity 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 few drops of trimethylamine led to oxime **8** (Scheme 2). 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 1.98, 2.62, 10.87, and 11.20 ppm assigned to the protons of N=C–CH_3, SCH_3, quinolinone NH, and oxime OH groups, respectively. Also, ^{13}C NMR revealed a distinctive signal at 174.0 ppm that points 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 tricylcic fused systems. When oxime **8** was refluxed in glacial acetic acid oxazolo-[5,4-*b*]quinoline **9** was obtained in 53% yield. Compound **9** was also obtained directly from compound **1** when reacted with hydroxylamine hydrochloride in boiling glacial acetic acid.

Presence of sulfur in the cyclized product **9**, as indicated by a positive Lassaigne's sulur test and by the signal of SCH_3 protons in its ^{1}H NMR spectrum, led us to the conclusion that cyclization in boiling acetic acid takes place regioselectively at the face [*b*] and not face [*c*] of the quinoline ring. The chemical shift value at 2.68 ppm characteristic for 2-methyloxazole[20,21] methyl group protons confirmed that 2-methyloxazolo[5,4-*b*]quinoline **9** was formed instead of the usually expected 3-methyl-isoxazolo[5,4-*b*]quinoline **10**, for which the chemical shift of methyl protons is expected at a more upfield region, δ ~2.3 ppm [20,21] (Scheme 2).

Boiling a solution of oxime **8** in absolute ethanol in the presence of a few drops of hydrochloric acid gave oxazolo-[4,5-*c*]quinolin-4-one **11** (Scheme 2).[22] The same compound was directly obtained by treatment of compound **1** with hydroxylamine hydrochloride in boiling ethanol without any additives. Furthermore, refluxing oxime **8** in DMF

Scheme 2



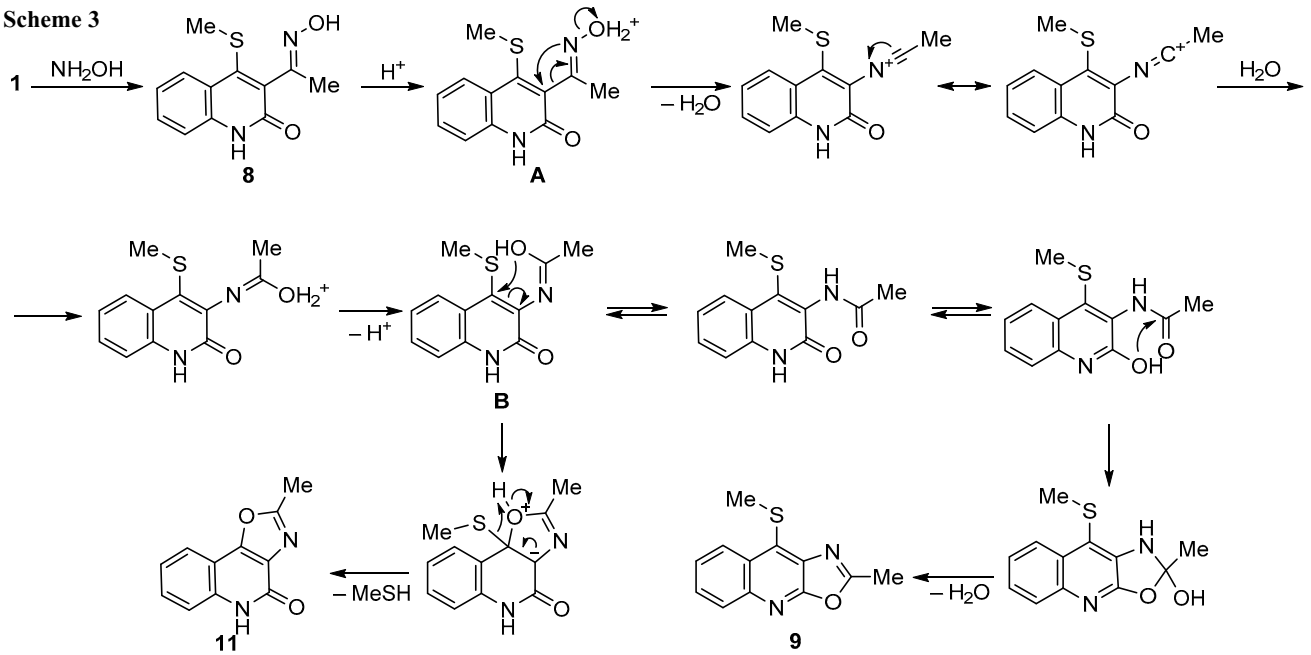
gave a different heterocyclic product isoxazolo[4,5-*c*]-quinolinone **12**. The same compound was obtained *via* refluxing of acetylquinoline **1** with hydroxylamine hydrochloride in DMF (Scheme 2). It is interesting to compare the analytical and spectral data of both isomers **11** and **12**. Both of them have the same empirical formula as revealed by elemental analysis, indicating the loss of methanethiol fragment during cyclization process. Nevertheless, both of them are clearly different in their physical and spectral properties. The structures of isomers **11** and **12** were confirmed also by a comparison with the samples prepared according to literature procedures.[20,21]

The Beckmann rearrangement[19] may be a conceivable explanation for the formation of products **9** and **11** in acidic medium. Thus, protonation of oxime group at the oxygen atom takes place first to give an oxonium cation **A** from which the rearrangement proceeds (Scheme 3). The pathway leads to the 3-acetamidoquinoline intermediate **B** which regioselectively can be cyclized to give either product **9** or **11**.

1,4-Dinucleophiles such as semicarbazide and its analog thiosemicarbazide are known useful reagents in the synthesis of 1,2,4-triazaheterocycles. Treatment of compound **1** with semicarbazide hydrochloride or thiosemicarbazide in boiling ethanol afforded semicarbazone derivatives **13a**,**b**, respectively (Scheme 4).

The analytical and spectral data of the reaction products confirmed that reaction under these conditions leads to the open-chain semicarbazones. Thus, IR spectrum of semicarbazones **13a**,**b** showed absorption bands at 3277 and 3217, 3143, and 1650–1654 cm^{-1} corresponding to NH_2, NH, and carbonyl groups, respectively. ^{1}H NMR spectrum of these products represented two singlet signals at 2.53–

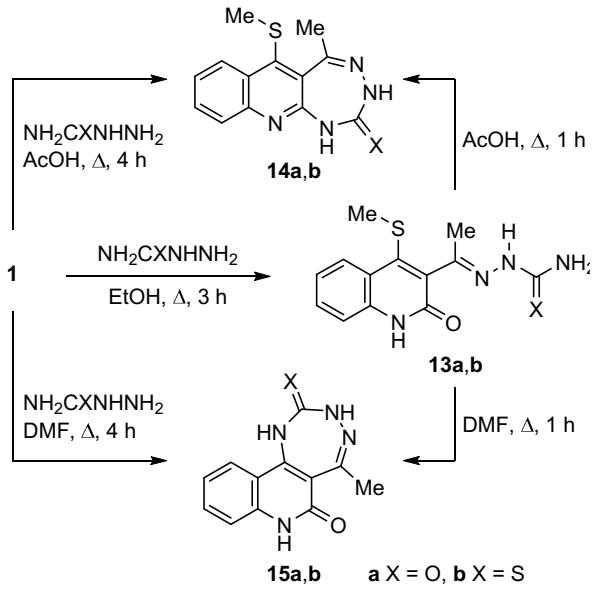
Scheme 3



2.61 and 2.67–2.70 ppm due to N=C–CH_3 and SCH_3 protons, in addition to a broad signal of the amino protons at 4.48 ppm. Interestingly, it was again the case that when this reaction was carried out in boiling glacial acetic acid instead of ethanol the cyclization into [1,2,4]triazepino[5,6-*b*]-quinolines **14a**,**b** took place with the respective yields of 64 and 60%. The same products **14a**,**b** were also obtained when semicarbazones **13a**,**b** were subjected to heating in boiling glacial acetic acid for only 1 h (Scheme 4). Analytical data of products **14a**,**b** showed that in the course of the conversion of open-chain semicarbazones **13a**,**b** dehydration took place to affect annulation at face [*b*] of the quinoline ring. Moreover, a signal with a chemical shift 2.64–2.69 ppm, characteristic of SCH_3 protons in the ^{1}H NMR spectrum confirmed that SCH_3 group is still present in the structure of both products **14a**,**b**. On the other hand, carrying out the reaction of compound **1** with semicarbazide hydrochloride or thiosemicarbazide in boiling DMF furnished known 1,2,4-triazepino[6,5-*c*]quinolinones **15a**,**b** in 78% yield in both cases.[17] Once more, it was found that in refluxing DMF open-chain semicarbazones **13a**,**b** led to the respective cyclized products **15a**,**b** (Scheme 4). The lack of proton signal of SCH_3 group in the ^{1}H NMR spectra proved that the cyclization process in DMF, a relatively high-boiling neutral solvent, proceeded not by dehydration, but involving the liberation of methanethiol. Furthermore, compounds **15a**,**b** with identical characteristics were prepared according to a literature procedure.[17]

In conclusion, the condensation reaction of 3-acetyl-4-(methylsulfanyl)quinolin-2(1*H*)-one with certain dinucleophilic reagents under different reaction conditions regioselectively leads to different open or cyclized quinoline derivatives. This variability of products is attributed to the presence of three active reaction centers in the quinolinone moiety. The key compound may be considered as a good synthon for a wide scale of heterocyclized quinoline derivatives, depending on the nature of reagent and reaction conditions.

Scheme 4



Experimental

IR spectra were recorded on a Perkin Elmer FT-IR 1650 spectrophotometer using samples in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 and 75 MHz, respectively) or Bruker Avance III (400 and 100 MHz, respectively) spectrometers using DMSO-d_6 or $CDCl_3$ as solvent. The internal standard was either TMS or solvent signal (for ^{1}H nuclei, 7.22 ppm in $CDCl_3$ and 2.50 ppm in DMSO-d_6; for ^{13}C nuclei, 40.0 ppm in DMSO-d_6). Mass spectra (electron ionization, 70 eV) were obtained using a Shimadzu GC-2010 gas chromatograph-mass spectrometer. Elemental microanalyses were performed on a Perkin Elmer CHN-2400 analyzer. Melting points are uncorrected and were determined in open capillary tubes by digital Stuart-SMP3 melting point apparatus. Compound **1** was prepared according to the reported literature method.[17]

3-(1-Ethanehydrazonoyl)-4-(methylsulfanyl)quinolin-2(1*H*)-one (2). Hydrazine hydrate (99%, 10 ml, 200 mmol) was added dropwise to a stirred solution of compound **1** (2.33 g, 10 mmol) in DMF (70 ml). The reaction mixture was stirred at room temperature for 3 h, and the excess solvent was evaporated at room temperature. The precipitated solid was collected by filtration, washed with ethanol, and dried to give compound **2**. Yield 1.30 g (53%), mp 198–199°C (decomp.). IR spectrum, ν, cm^{-1}: 3355, 3243 (NH_2), 3198, 3129 (N–H), 3064, 2963, 1620, 1603, 1555, 1513, 1480, 1362, 1349, 759. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.49 (3H, s, N=C–CH_3); 2.63 (3H, s, SCH_3); 6.15 (2H, s, NH_2, exchangeable with D_2O); 7.28–7.38 (1H, m, H-6); 7.55–7.71 (2H, m, H-7,8), 8.07 (1H, d, *J* = 8.1, H-5); 10.80 (1H, s, NH, exchangeable with D_2O). Mass spectrum, *m*/*z* (I_{rel}, %): 247 $[M]^+$ (1), 130 (12), 127 (32), 115 (21), 104 (14), 103 (16), 102 (29), 97 (16), 91 (16), 89 (38), 88 (22), 83 (16), 77 (71), 76 (95), 70 (24), 63 (84), 57 (100). Found, %: C 58.10; H 5.20; N 16.80. $C_{12}H_{13}N_3OS$. Calculated, %: C 58.28; H 5.30; N 16.99.

3-Methyl-4-(methylsulfanyl)-1*H*-pyrazolo[3,4-*b*]quinoline (3). I. A mixture of compound **1** (2.33 g, 10 mmol) and hydrazine hydrate (1 ml, 200 mmol) was heated under reflux in absolute ethanol (100 ml) for 3 h. The reaction mixture was left to cool at room temperature. The crystalline precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.56 g (68%), mp 260–262°C. IR spectrum, ν, cm^{-1}: 3213, 3132 (N–H), 3027, 2919, 1629 (C=N), 1586, 1567, 1518, 1376, 1349, 1294, 763, 756. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.43 (3H, s, (N=C–CH_3); 2.70 (3H, s, SCH_3); 7.55 (1H, t, *J* = 6.6, H-6); 7.67 (1H, t, *J* = 8.4, H-7); 7.94 (1H, d, *J* = 8.1, H-8); 8.28 (1H, d, *J* = 7.8, H-5); 13.93 (1H, s, NH, exchangeable with D_2O). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 155.1; 144.9; 143.2; 141.2; 129.4; 128.3; 125.7; 122.4; 114.9; 114.3; 15.1; 11.9. Mass spectrum, *m*/*z* (I_{rel}, %): 229 $[M]^+$ (97), 228 (31), 214 (13), 196 (23), 183 (78), 169 (23), 167 (19), 154 (62), 140 (24), 129 (54), 128 (36), 127 (51), 115 (45), 114 (100), 102 (95), 77 (52). Found, %: C 62.80; H 4.80; N 18.30. $C_{12}H_{11}N_3S$. Calculated, %: C 62.86; H 4.84; N 18.32.

II. A solution of compound **2** (2.50 g, 10 mmol) 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 crystalline precipitate was filtered off, dried, and recrystallized from absolute ethanol. For the reaction carried out in ethanol, yield 1.04 g (45%), for the reaction carried out in acetic acid, yield 1.72 g (75%).

3-Methyl-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-one (4). A solution of compound **2** (2.50 g, 10 mmol) in DMF (25 ml) was heated under reflux for 1 h. The reaction mixture was left to cool to room temperature. The crystalline precipitate was filtered off and dried. Yield 1.67 g (84%).

(*Z*,*E*)-4-(Methylsulfanyl)-3-[1-(phenylhydrazinylidene)-ethyl]quinolin-2(1*H*)-one (5). A mixture of compound **1** (2.33 g, 10 mmol) and phenylhydrazine (1.1 ml, 10 mmol) in absolute ethanol (100 ml) was heated under reflux for 3 h. Then the reaction mixture was left to cool, and the precipitated solid was collected by filtration, washed with diethyl ether, and recrystallized from ethanol. Yield 2.30 g (70%), mp 216–218°C (decomp.). IR spectrum, ν, cm^{-1}: 3620 (O–H), 3188 (N–H), 3069, 2965, 1620 (C=N), 1559, 1528, 756, 752. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.13 (3H, s, N=C–CH_3); 2.60 (3H, s, SCH_3); 6.63–6.71 (1H, m, H Ar); 7.01–7.14 (4H, m, H Ar); 7.32–7.35 (1H, m, H Ar); 7.62–7.73 (2H, m, H Ar); 8.08–8.10 (1H, m, H Ar); 8.50 (0.35H, s, NH hydrazone, (*E*)-form); 9.00 (0.65H, s, NH hydrazone, (*Z*)-form); 11.04 (br. s, NH quinolinone, (*Z*)-form) and 11.20 (1H in total, br. s, OH quinolinol, (*E*)-form). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 174.5; 149.5; 146.7; 141.9; 132.1; 129.1; 128.8; 125.4; 123.8; 122.6; 119.0; 118.3; 113.1; 112.5; 23.7; 17.2; 16.1 (2C). Mass spectrum, *m*/*z* (I_{rel}, %): 323 $[M]^+$ (39), 308 (13), 276 (37), 231 (15), 217 (13), 132 (15), 130 (13), 115 (21), 114 (14), 108 (9), 102 (14), 93 (100), 91 (61), 89 (19), 77 (56), 65 (57). Found, %: C 66.70; H 5.10; N 12.89. $C_{18}H_{17}N_3OS$. Calculated, %: C 66.85; H 5.30; N 12.99.

3-Methyl-4-(methylsulfanyl)-1-phenylpyrazolo[3,4-*b*]-quinoline (6). I. A mixture of compound **1** (2.33 g, 10 mmol) and phenylhydrazine (1.1 ml, 10 mmol) in glacial acetic acid (100 ml) was heated under reflux for 4 h, then the reaction mixture was left to cool to room temperature. The precipitated yellow crystalline material was filtered off, washed with ethanol (30 ml), and recrystallized from glacial acetic acid. Yield 1.60 g (60%), mp 158–160°C. IR spectrum, ν, cm^{-1}: 3069, 2974, 1617 (C=N), 1597, 1562, 776, 749. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.84 (3H, s, N=C–CH_3); 2.88 (3H, s, SCH_3); 7.15–7.24 (1H, m, H-6); 7.43 (1H, d, *J* = 7.8, H-8); 7.55–7.61 (6H, m, H-7, H Ph); 8.04 (1H, d, *J* = 8.0, H-5). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 155.2; 145.9; 143.6; 140.6; 139.8; 130.3 (3C); 129.6; 128.8; 127.7 (2C), 125.4; 121.7; 115.6; 114.8; 15.0; 12.1. Mass spectrum, *m*/*z* (I_{rel}, %): 305 $[M]^+$ (100), 304 (28), 259 (15), 258 (22), 190 (17), 169 (24), 154 (13), 128 (12), 114 (13), 108 (22), 102 (13), 93 (10), 89 (12), 77 (89). Found, %: C 70.60; H 4.70; N 13.67. $C_{18}H_{15}N_3S$. Calculated, %: C 70.79; H 4.95; N 13.76.

II. A solution of compound **5** (3.23 g, 10 mmol) 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 a product identical with that obtained by method I. Yield 2.24 g (70%).

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

3-(*N*-Hydroxyethanimidoyl)-4-(methylsulfanyl)quinolin-2(1*H*)-one (8). A mixture of compound **1** (2.33 g, 10.0 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol), and triethylamine 0.5 (1.0 mml, 10 mmol) in absolute ethanol (100 ml) was heated under reflux for 3 h. The solid that obtained, after cooling to room temperature, was filtered

off, dried, and recrystallized from ethanol. Yield 1.9 g (75%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 3446 (O–H), 3243 (N–H), 3061, 2957, 1625 (C=O, C=N), 1606, 1560, 1496, 1473, 758. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.98 (3H, s, N=C–CH_3); 2.62 (3H, s, SCH_3); 7.32 (1H, t, *J* = 7.2, H-6); 7.65–7.69 (2H, m, H-7,8); 8.03 (1H, d, *J* = 7.8, H-5); 10.87 (1H, s, NH, exchangeable. with D_2O); 11.20 (1H, s, OH, exchangeable with D_2O). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 174.0; 152.8; 149.3; 140.7; 132.3; 125.5; 124.6; 123.9; 120.0; 118.3; 16.1; 15.2. Mass spectrum, *m*/*z* (I_{rel}, %): 248 $[M]^+$ (33), 233 (15), 217 (47), 216 (100), 215 (16), 202 (41), 188 (13), 185 (14), 172 (11), 170 (13), 158 (18), 155 (15), 142 (29), 132 (16), 130 (31), 128 (22), 120 (16), 115 (36), 89 (40), 76 (43). Found, %: C 57.80; H 4.70; N 11.10. $C_{12}H_{12}N_2O_2S$. Calculated, %: C 58.05; H 4.87; N 11.28.

2-Methyl-4-(methylsulfanyl)[1,3]oxazolo[5,4-*b*]quinoline (9). I. Hydroxylamine hydrochloride (0.7 g, 10 mmol) was added to a solution of compound **1** (2.33 g, 10.0 mmol) in glacial acetic acid (100 ml), and the reaction mixture was heated under reflux for 3 h. The crystalline precipitate, which formed upon cooling, was filtered off, dried, and recrystallized from acetic acid. Yield 1.70 g (73%), mp 110–112°C. IR spectrum, ν, cm^{-1}: 3069, 2927, 1632 (C=N), 1590, 1557, 1525, 1297, 761. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.68 (3H, s, N=C–CH_3); 2.73 (3H, s, SCH_3); 7.61 (1H, t, *J* = 6.9, H-6); 7.83 (1H, t, *J* = 7.2, H-7); 7.97 (1H, d, *J* = 8.4, H-8); 8.21 (1H, d, *J* = 8.4, H-5). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 169.3; 161.7; 130.7; 127.8; 126.5; 123.9; 122.1; 121.4; 120.7; 120.6; 34.0; 23.0. Mass spectrum, *m*/*z* (I_{rel}, %): 230 $[M]^+$ (100), 229 (28), 202 (53), 197 (39), 184 (24), 173 (10), 169 (16), 155 (14), 141 (13), 130 (38), 129 (28), 120 (11), 115 (46), 114 (85), 102 (74), 88 (44), 76 (65). Found, %: C 62.40; H 4.20; N 12.00. $C_{12}H_{10}N_2OS$. Calculated, %: C 62.59; H 4.38; N 12.16.

II. A solution of compound **8** (2.48 g, 10.0 mmol) in glacial acetic acid (50 ml) was heated under reflux for 3 h. The reaction mixture was left to cool and the crystalline precipitate was filtered off and dried. Yield 1.30 g (53%).

2-Methyl[1,3]oxazolo[4,5-*c*]quinolin-4(5*H*)-one (11). I. Compound **1** (2.33 g, 10.0 mmol) and hydroxylamine hydrochloride (0.70 g, 10 mmol) were heated under reflux in absolute ethanol (70 ml) for 3 h. The reaction mixture was left to cool. The solid precipitate was collected by filtration and dried. Yield 1.40 g (64%).

II. A mixture of compound **8** (2.48 g, 10.0 mmol) and concd. hydrochloric acid (1 ml) in ethanol (50 ml) was heated under reflux for 2 h. The reaction mixture was left to cool and the crystalline precipitate was filtered, dried, and recrystallized from glacial acetic acid. Yield 1.50 g (75%).

3-Methyl[1,2]oxazolo[4,5-*c*]quinolin-4(5*H*)-one (12). I. A mixture of compound **1** (2.33 g, 10.0 mmol) and hydroxylamine hydrochloride (0.7 g, 10 mmol) in DMF (100 ml) was heated under reflux for 1 h. The brown solid obtained after cooling was filtered, dried, and recrystallized from ethanol to give compound **12**. Yield 1.06 g (53 %).

II. A solution of compound **8** (2.48 g, 10.0 mmol) in DMF (50 ml) was heated under reflux for 4 h. The reaction mixture was left to cool and the crystalline precipitate was filtered off, dried, and crystallized from glacial acetic acid. Yield 1.24 g (62%).

2-{1-[4-(Methylsulfanyl)-2-oxo-1,2-dihydroquinolin-3-yl]ethylidene}hydrazinecarboxamide (13a). Semicarbazide hydrochloride (1.11 g, 10.0 mmol) was added to a solution of compound **1** (2.33 g, 10.0 mmol) in ethanol (50 ml), and the reaction mixture was heated under reflux for 3 h. Upon cooling to room temperature, a solid precipitate formed was filtered off and recrystallized from absolute ethanol. Yield 1.98 g (68%), mp 221–223°C. IR spectrum, ν, cm^{-1}: 3277, 3217 (NH_2), 3143 (N–H), 3058, 2927, 1650 (C=O), 1620 (C=N), 1609, 1567, 1532, 1489, 1380, 1297, 758. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.61 (3H, s, N=C–CH_3); 2.70 (3H, s, SCH_3); 4.48 (2H, s, NH_2, exchangeable with D_2O); 7.39 (1H, t, *J* = 7.5, H-6); 7.70 (1H, t, *J* = 7.7, H-7); 7.78 (1H, d, *J* = 8.4, H-8), 8.13 (1H, d, *J* = 7.8, H-5), 8.62 (1H, s, NNH, exchangeable with D_2O); 10.86 (1H, s, 1-NH, exchangeable with D_2O). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 198.7; 178.9; 156.0; 139.5; 132.3; 131.8; 125.0; 124.3; 123.4; 119.6; 118.3; 31.5; 14.9. Mass spectrum, *m*/*z* (I_{rel}, %): 234 (12), 233 (16), 218 $[M–N_2CONH_2]^+$ (100), 215 (12), 200 (14), 172 (26). Found, %: C 53.60; H 4.60; N 19.10. $C_{13}H_{14}N_4O_2S$. Calculated, %: C 53.78; H 4.86; N 19.30.

2-{1-[4-(Methylsulfanyl)-2-oxo-1,2-dihydroquinolin-3-yl]ethylidene}hydrazinecarbothioamide (13b) was obtained analogously from compound **1** (2.33 g, 10.0 mmol) and thiosemicarbazide (0.92 g, 10.1 mmol). Yield 2.00 g (65%), mp 202–204°C. IR spectrum, ν, cm^{-1}: 3277, 3217 (NH_2), 3143 (N–H), 3070, 2930, 1654 (C=O), 1619 (C=N), 1566, 1540, 1489, 1340, 758. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.53 (3H, s, N=C–CH_3); 2.67 (3H, s, SCH_3); 4.50 (2H, s, NH_2, exchangeable with D_2O); 7.30–7.45 (1H, m, H-6); 7.65–7.85 (2H, m, H-7,8); 8.02–8.23 (1H, m, H-5); 10.30 (1H, s, NNH, exchangeable with D_2O); 10.86 (1H, s, 1-NH, exchangeable with D_2O). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 199.2; 179.0; 175.0; 156.7; 150.0; 140.0; 132.9; 125.6; 124.9; 120.1; 118.8; 32.0; 16.2. Mass spectrum, *m*/*z* (I_{rel}, %): 306 $[M]^+$ (3), 305 (10), 218 $[M–N_2CSNH_2]^+$ (100), 216 (11), 215 (13), 199 (33), 190 (13), 172 (48), 145 (17), 130 (17), 128 (11), 117 (25), 116 (22), 115 (20), 102 (22), 91 (37), 89 (42), 77 (46). Found, %: C 50.70; H 4.50; N 18.20. $C_{13}H_{14}N_4OS_2$. Calculated, %: C 50.96; H 4.61; N 18.28.

5-Methyl-6-(methylsulfanyl)-1,3-dihydro-2*H*-[1,2,4]-triazepino[5,6-*b*]quinolin-2-one (14a). I. Semicarbazide hydrochloride (1.11 g, 10.0 mmol) was added to a solution of compound **1** (2.33 g, 10.0 mmol) in glacial acetic acid (50 ml), and the reaction mixture was heated under reflux for 4 h. Upon cooling to room temperature, a solid precipitate formed was filtered off and recrystallized from absolute ethanol. Yield (64%), mp 299–301°C. IR spectrum, ν, cm^{-1}: 3248, 3135 (N–H), 3061, 2985, 1647 (C=O), 1620 (C=N triazepine), 1603, 1560, 1510, 1474, 1344, 758. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.48 (3H, s, N=C–CH_3); 2.64 (3H, s,

SCH_3); 7.37 (1H, t, *J* = 7.8, H-9); 7.65 (1H, t, *J* = 8.1, H-8); 7.79 (1H, d, *J* = 8.4, H-7); 8.11 (1H, d, *J* = 8.1, H-10); 8.50 (1H, s, NH, exchangeable with D_2O), 10.86 (1H, s, NH, exchangeable with D_2O). Found, %: C 57.20; H 4.40; N 20.50. $C_{13}H_{12}N_4OS$. Calculated, %: C 57.34; H 4.44; N 20.57.

II. A solution of compound **13a** (1.45 g, 5.00 mmol) in glacial acetic acid (30 ml) was heated under reflux for 1 h. The reaction mixture was left to cool, and the crystalline product was filtered off and dried. Yield 1.01 g (75%).

5-Methyl-6-(methylsulfanyl)-1,3-dihydro-2*H*-[1,2,4]triazepino[5,6-*b*]quinoline-2-thione (14b). I. Thiosemicarbazide (0.92 g, 10.0 mmol) was added to a solution of compound **1** (2.33 g, 10.0 mmol) in glacial acetic acid (50 ml), and the reaction mixture was heated under reflux for 4 h. Upon cooling to room temperature, a solid precipitate formed was filtered off and recrystallized from absolute ethanol. Yield 1.88 g (60%), mp 130–133°C. IR spectrum, ν, cm^{-1}: 3316, 3200 (N–H), 3026, 2961, 1622 (C=N triazepine), 1592, 1498, 1472, 723. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.14 (3H, s, N=C–CH_3); 2.69 (3H, s, SCH_3); 7.40 (1H, t, *J* = 8.1, H-9); 7.65–7.78 (2H, m, H-7,8); 8.07 (1H, d, *J* = 7.8, H-10); 9.66 (1H, s, NH, exchangeable with D_2O); 11.97 (1H, s, NH, exchangeable with D_2O). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 178.6; 172.5; 149.5; 147.9; 146.6; 141.3; 132.4; 125.4; 124.0; 118.4; 116.8; 23.8; 16.2. Mass spectrum, *m*/*z* (I_{rel}, %): 288 $[M]^+$ (1), 242 (12), 218 (30), 199 (31), 170 (10), 145 (12), 120 (11), 115 (30), 114 (26), 94 (25), 91 (39), 89 (20), 77 (44), 69 (15), 63 (17), 60 (48), 59 (100). Found, %: C 54.00; H 4.10; N 19.20%. $C_{13}H_{12}N_4S_2$. Calculated, %: C 54.14; H 4.19; N 19.43.

II. A solution of compound **13b** (1.53 g, 5.00 mmol) in glacial acetic acid (30 ml) was heated under reflux for 1 h. The reaction mixture was left to cool, and the crystalline product was filtered off and dried. Yield 1.09 g (75%).

Preparation of [1,2,4]triazepino[6,5-*c*]quinolines 15a,b (General method). I. A solution of either compound **13a** (1.45 g, 5 mmol) or **13b** (1.53 g, 5 mmol) in DMF (30 ml) was heated under reflux for 1 h. The reaction mixture was left to cool and the crystalline product was filtered off and dried.

II. To a solution of compound **1** (2.33 g, 10 mmol) in DMF (50 ml), semicarbazide hydrochloride (1.11 g, 10.0 mmol) or thiosemicarbazide (0.92 g, 10.1 mmol) was added, and the reaction mixture was heated under reflux for 4 h. After cooling to room temperature, the solid precipitate was filtered and recrystallized from ethanol to give compounds **15a** and **15b**, respectively.

5-Methyl-3,7-dihydro-1*H*-[1,2,4]triazepino[6,5-*c*]quinoline-2,6-dione (15a). This compound was obtained from semicarbazide hydrochloride, mp > 300°C (mp > 300°C[17]). Yield 1.88 g (78%, method I and II).

5-Methyl-2-thioxo-1,2,3,7-tetrahydro-6*H*-[1,2,4]triazepino[6,5-*c*]quinolin-6-one (15b). This compound was obtained from thiosemicarbazide, recrystallized from absolute ethanol, mp > 300°C (mp > 300°C[17]). Yield 2.06 g (80%, method I), 2.00 g (78%, method II).

Supporting material to this article containing ^{1}H, ^{13}C NMR, and mass spectra of the synthesized compounds is available online at http://link.springer.com/journal/10593.

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