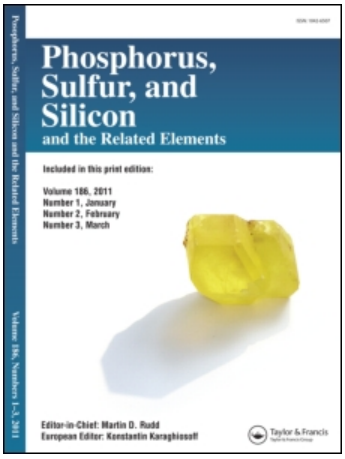

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Chemistry of Substituted Quinolinones. Part 8. Synthesis and Cyclization Reactions of Ethyl 5-Amino-1-(1-methyl-2-oxoquinolin-4-YL)-3-methylsulfanylpyrazole-4-carboxylate

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CHEMISTRY OF SUBSTITUTED QUINOLINONES. PART 8. SYNTHESIS AND CYCLIZATION REACTIONS OF ETHYL 5-AMINO-1-(1-METHYL-2-OXOQUINOLIN-4-YL)-3-METHYLSULFANYLPYRAZOLE-4-CARBOXYLATE

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*The synthesis of the titled amino-ester **3** is described and its hydrolysis and chloroacetylation led to the acid **5** and acetamide **7**, which were cyclized to the pyrazolopyridones **6** and **8**, respectively. Condensation of **3** with 2,5-dimethoxytetrahydrofuran afforded the pyrrolylpyrazole **9**, which underwent cyclization by action of PPA to give pyrazolopyrrolizine **10**. Treating **3** with thiophosgene gave the pyrazolyl isothiocyanate **11**, which added aniline to yield the thiourea derivative **12**, and cyclized to give pyrazolopyrimidinethiones **13–15**. Condensation of **3** with formamide furnished pyrazolopyrimidine **16**, while with triethyl orthoformate produced the ethoxymethyleneaminopyrazole **18**, which condensed with hydrazine to give the aminopyrazoloprimidine **19**. Reaction of **3** with Lawesson's reagent resulted in the pyrazolothiazaphosphinine **21**. Also the cyclization reaction of the compound **3** with malononitrile and its mixtures with carbon disulfide, phenyl isothiocyanate, or benzaldehyde led to the formation of a variety of polyfunctional substituted pyrazolopyrimidines **23** and **26**, pyrazolothiazine **24** and pyrazolopyridine **28**.*

Keywords: Pyrazolopyridine; pyrazolopyrimidine; pyrazolopyrrolizine; pyrazolothiazaphosphinine; pyrazolothiazine; pyrazolylquinolinone

Studies on the biochemical properties of the structures bearing the pyrazole nucleus revealed their ability to uncouple oxidative phosphorylation, stabilize lysosomal membranes, inhibit biosynthesis of various mucopolysaccharides, and perhaps most importantly, inhibit

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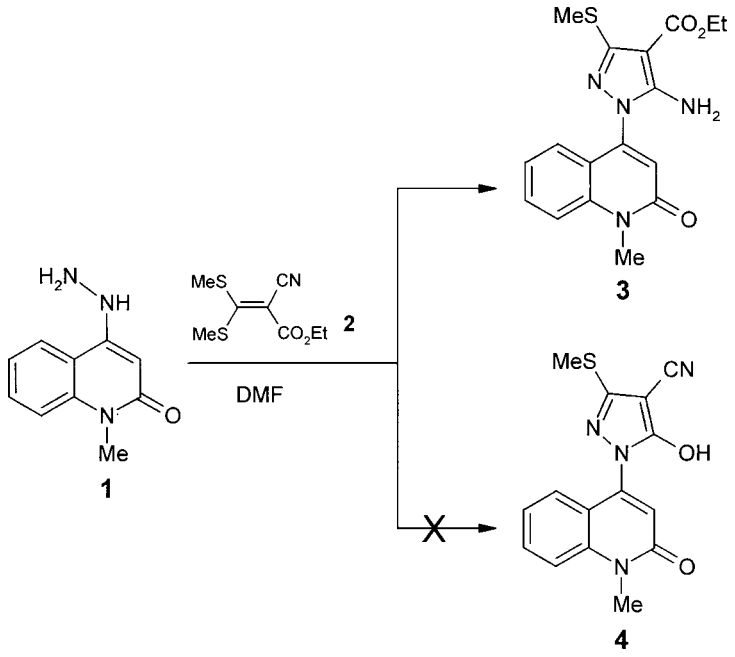
prostaglandin biosynthesis, which accounts for their antiinflammatory activities and analgesic effects.[1] Also several substituted pyrazolo[3,4-*d*]pyrimidines have shown diverse pharmacological activities, for example Allopurinol acts as a potent Xanthine-Oxidase (XO) inhibitor,[2] and has been used as an effective therapy of both the primary hyperuricemia of gout and that secondary to haematological disorders or as antineoplastic therapy.[3] Unfortunately, Allopurinol has some deleterious side effects so that efforts to find novel potent and safe XO-inhibitors need to be continued.[4–6] On the other hand, it is well known that 2(1*H*)quinolinone derivatives are associated with diverse pharmaceutical activities. Many quinolinones showed antihyperplastic activity,[7] anti-cancer effects,[8] Alzheimer's disease healing action,[9] and also antiulcer activity.[10] Due to the above-mentioned medicinal importance, it was planned to carry out a series of synthetic studies on novel heterocyclic derivatives those combined both pyrazole and quinolinone in one molecular frame.[11]

RESULTS AND DISCUSSION

Reactions of ketene dithioacetals with hydrazines are known to give the corresponding multifunctional pyrazole derivatives.[12] It is worthwhile to mention that the heterocyclic products of these reactions not only are interesting from the viewpoint of biological applications, but also they have an important synthetic utility in the field of condensed heteropolycyclic compounds. Thence, 4-hydarzino-1-methyl-2(1*H*)quinolinone (**1**) was reacted with ethyl 2-cyano-3,3-bis(methylsulfanyl)acrylate (**2**),[13] in boiling DMF to afford ethyl 5-amino-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (**3**). ^{1}H NMR spectrum of the amino-ester **3** showed the presence of a set of protons corresponding to an ethyl group as quartet and triplet peaks ($J = 7$ Hz) at δ: 4.19 and 1.27 ppm respectively. No indication was found for the formation of the other possible carbonitrile product **4**. However, this result is coincident with the reported results of the reaction of compound **2** with hydrazines[12,14] (Scheme 1).

Hydrolysis of the amino-ester **3** in an acid medium led to the formation of the corresponding amino-acid **5**. De-esterification of compound **3** under either acidic or basic media was found to be not accompanied by replacement of either methylsulfanyl or amino groups. Eventually, acidic medium was selected for the higher yield. The preparation of the pyrazolopyridone **6** was accomplished from cyclization of the amino-acid **5** by means of acetic anhydride and glacial acetic acid.[15] Chloroacetylation of amino-ester **3** using chloroacetyl chloride furnished the



SCHEME 1

corresponding chloroacetamide **7**, in a good yield (86%). Compound **7** was subjected to a cyclization reaction using triethylamine, in boiling DMSO, to give 5-chloro-4-hydroxy-3-methylsulfanylpyrazolo[3,4-*b*]pyridine **8**, which is the chloro derivative of compound **6**. Obviously, both compounds **6** and **8** sustain acidic character, as they are soluble in dilute alkalis and precipitated upon the addition of acids. Also, both compounds **6** and **8** gave deep violet coloration with ferric chloride neutral solution due to the presence of phenolic hydroxyl group. Condensation reaction of the amino-ester **3** with 2,5-dimethoxytetrahydrofuran, in glacial acetic acid, led to the formation of the expected structure,[16] ethyl 5-pyrrolylpyrazole-4-carboxylate **9**. The structure of the heterotricyclic derivative **9** was inferred from its correct elemental analysis as well as ^{1}H NMR and IR spectra, which showed the disappearance of the amino group at the same time as a pyrrolyl moiety specific protons come into sight (Table I). An interesting linear hetero-polycyclic system bearing quinolinone was obtained, on carrying out catalyzed intramolecular cyclization, by action of polyphosphoric acid (PPA) on compound **9**. The structure of the product was established on the basis of its spectral data. ^{1}H NMR spectrum clearly showed that ethyl ester group disappeared and only seven aromatic protons were integrated in the spectrum chart, δ: 7.83–7.25 ppm, beside the singlet peak at

TABLE I IR and ^{1}H NMR Spectral Data for the New Compounds

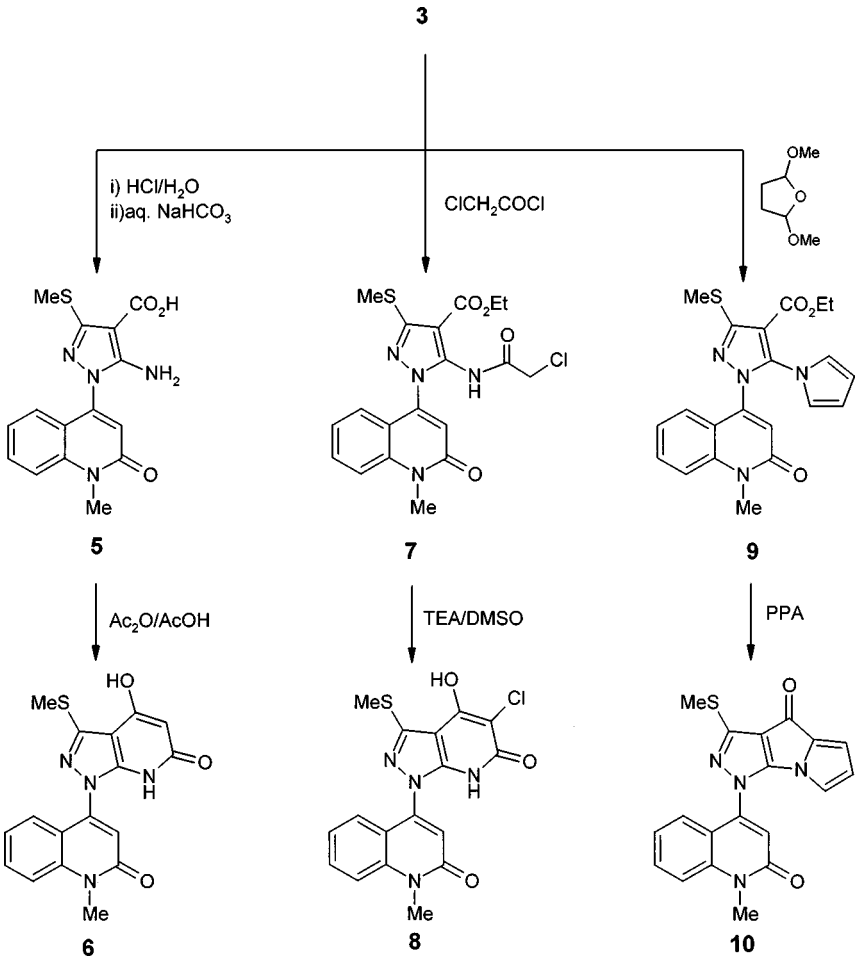
Compd. no.	IR (KBr)/cm^{-1}	^{1}H NMR (DMSO-d$_6$)/δ
3	3385, 3256 (NH), 1731 (C=O$_{ester}$), 1677 (C=O$_{quinolone}$), 1601 (C=N), 1105 (C–O–C)	7.67–7.28 (m, 4H, H$_{arom}$), 6.73 (s, 1H, C3-H), 6.58 (s, 2H, NH$_2$), 4.19 (q, 2H, O$\underline{CH_2}$CH$_3$), 3.68 (s, 3H, NCH$_3$), 2.32 (s, 3H, SCH$_3$), 1.27 (t, 3H, OCH$_2\underline{CH_3}$)
5	3387–2340 (H-bonded NH$_2$, CO$_2$H), 1717 (C=O$_{acid}$), 1657 (C=O$_{quinolone}$), 1608 (C=N)	14.95 (b, 1H, OH), 7.75–7.20 (m, 4H, H$_{arom}$), 6.74 (s, 1H, C3-H), 6.60 (s, 2H, NH$_2$), 3.62 (s, 3H, NCH$_3$), 2.30 (s, 3H, SCH$_3$)
6	3180–2720 (NH, OH), 1662 (C=O$_{pyridone}$), 1647 (C=O$_{quinolone}$), 1605 (C=N)	12.85 (b, 1H, OH), 11.03 (b, 1H, NH), 7.62–7.26 (m, 4H, H$_{arom}$), 6.90 (s, 1H, C5-H$_{pyrazolopyrimidine}$), 6.65 (s, 1H, C3-H$_{quinolone}$), 3.58 (s, 3H, NCH$_3$), 2.25 (s, 3H, SCH$_3$)
7	3270 (NH), 1730 (C=O$_{ester}$), 1695 (C=O$_{acetamide}$), 1671 (C=O$_{quinolone}$), 1602 (C=N), 1110 (C–O–C)	9.40 (b, 1H, NH$_{acetamide}$), 7.75–7.25 (m, 4H, H$_{arom}$), 6.86 (s, 1H, C3-H), 5.24 (s, 2H, COCH$_2$Cl), 4.15 (q, 2H, O$\underline{CH_2}$CH$_3$), 3.55 (s, 3H, NCH$_3$), 2.27 (s, 3H, SCH$_3$), 1.22 (t, 3H, OCH$_2\underline{CH_3}$)
8	3255–2800 (NH, OH), 1661 (C=O$_{pyridone}$), 1650 (C=O$_{quinolone}$), 1612 (C=N)	13.58 (b, 1H, OH), 11.33 (b, 1H, NH), 7.75–7.30 (m, 4H, H$_{arom}$), 6.74 (s, 1H, C3-H), 3.61 (s, 3H, NCH$_3$), 2.27 (s, 3H, SCH$_3$)
9	1708 (C=O$_{ester}$), 1663 (C=O$_{quinolone}$), 1586 (C=N), 1491, 1456, 1115 (C–O–C)	7.75–6.80 (m, 8H, H$_{arom}$), 6.05 (s, 1H, C3-H), 4.10 (q, 2H, O$\underline{CH_2}$CH$_3$), 3.60 (s, 3H, NCH$_3$), 2.43 (s, 3H, SCH$_3$), 1.08 (t, 3H, OCH$_2\underline{CH_3}$)
10	1682 (C=O$_{pyrrolone}$), 1648 (C=O$_{quinolone}$), 1610 (C=N), 1580, 1495, 1480, 1385	7.83–7.25 (m, 7H, H$_{arom}$), 6.96 (s, 1H, C3-H), 3.66 (s, 3H, NCH$_3$), 2.35 (s, 3H, SCH$_3$)
11	2129 (N=C=S), 1719 (C=O$_{ester}$), 1634 (C=O$_{quinolone}$), 1602 (C=N), 1565, 1110 (C–O–C)	7.76–7.23 (m, 4H, H$_{arom}$), 6.70 (s, 1H, C3-H), 4.15 (q, 2H, O$\underline{CH_2}$CH$_3$), 3.60 (s, 3H, NCH$_3$), 2.30 (s, 3H, SCH$_3$), 1.25 (t, 3H, OCH$_2\underline{CH_3}$)
12	3290–3160 (NH), 1712 (C=O$_{ester}$), 1651 (C=O$_{quinolone}$), 1605 (C=N), 1539, 1318, 1245 (NHC=S)	8.48 (b, 1H, NHCS), 8.08–7.52 (m, 10H, H$_{arom}$ + PhNH), 6.56 (s, 1H, C3-H), 4.25 (q, 2H, O$\underline{CH_2}$CH$_3$), 3.80 (s, 3H, NCH$_3$), 2.64 (s, 3H, SCH$_3$), 1.32 (t, 3H, OCH$_2\underline{CH_3}$)
13	3172 (NH), 1673 (C=O$_{pyrimidone}$), 1648 (C=O$_{quinolone}$), 1585 (C=N), 1542, 1328, 1225 (NHC=S)	11.24 (b, 1H, NH), 8.04–7.17 (m, 9H, H$_{arom}$), 6.56 (s, 1H, C3-H), 3.68 (s, 3H, NCH$_3$), 2.28 (s, 3H, SCH$_3$)
14	3200, 3132 (NH), 1680 (C=O$_{pyrimidone}$), 1643 (C=O$_{quinolone}$), 1583 (C=N), 1534, 1321, 1214 (NHC=S)	12.45, 10.83 (b, 2H, 2 × NH$_{pyrimidone}$), 7.73–7.35 (m, 4H, H$_{arom}$), 6.76 (s, 1H, C3-H), 3.67 (s, 3H, NCH$_3$), 2.30 (s, 3H, SCH$_3$)
15	3431, 3357 (NH$_2$), 3146 (NH), 1657 (C=O$_{pyrimidone}$), 1641 (C=O$_{quinolone}$), 1604 (C=N), 1556, 1345, 1287 (NHC=S)	9.90 (b, 1H, NH), 7.72–7.21 (m, 4H, H$_{arom}$), 6.74 (s, 1H, C3-H), 6.05 (s, 2H, NH$_2$), 3.60 (s, 3H, NCH$_3$), 2.40 (s, 3H, SCH$_3$)

(Continued on next page)

TABLE I IR and ^{1}H NMR Spectral Data for the New Compounds *(Continued)*

Compd. no.	IR (KBr)/cm^{-1}	^{1}H NMR (DMSO-d$_6$)/δ
16	3170 (NH), 1673 (C═O$_{pyrimidone}$), 1644 (C═O$_{quinolone}$), 1611 (C═N), 1592, 1546, 1448	11.25 (b, 1H, NH$_{pyrimidone}$), 8.58 (s, 1H, C6-H$_{pyrazolopyrimidine}$), 7.66–7.29 (m, 4H, H$_{arom}$), 6.38 (s, 1H, C3-H$_{quinolone}$), 3.65 (s, 3H, NCH$_3$), 2.31 (s, 3H, SCH$_3$)
18	1742 (C═O$_{ester}$), 1676 (C═O$_{quinolone}$), 1600 (C═N), 1576, 1445, 1120 (C—O—C)	8.55 (s, 1H, H$_{azomethine}$), 7.70–7.29 (m, 4H, H$_{arom}$), 6.73 (s, 1H, C3-H), 4.25–4.08 (m, 4H, 2 × O$\underline{CH_2}$CH$_3$), 3.68 (s, 3H, NCH$_3$), 2.32 (s, 3H, SCH$_3$), 1.30–1.15 (m, 6H, 2 × OCH$_2\underline{CH_3}$)
19	3417, 3350 (NH$_2$), 1665 (C═O$_{pyrimidone}$), 1635 (C═O$_{quinolone}$), 1585 (C═N), 1448, 1395	8.64 (s, 1H, C6-H$_{pyrazolopyrimidine}$), 7.85–6.89 (m, 6H, H$_{arom}$ + NH$_2$), 6.40 (s, 1H, C3-H$_{quinolone}$), 3.68 (s, 3H, NCH$_3$), 2.72 (s, 3H, SCH$_3$)
21	3240 (NH), 1676 (C═O$_{phosphathiazinone}$), 1635 (C═O$_{quinolone}$), 1600 (C═N), 1506, 1252, 1163, 1044 (P═S)	9.15 (b, 1H, NH), 7.88–7.10 (m, 8H, H$_{arom}$), 6.64 (s, 1H, C3-H), 4.05 (s, 3H, OCH$_3$), 3.52 (s, 3H, NCH$_3$), 2.27 (s, 3H, SCH$_3$)
23	3227 (NH), 2203 (C≡N), 1667 (C═O$_{pyrimidone}$), 1631 (C═O$_{quinolone}$), 1617 (C═N), 1590, 1543, 1452	11.45 (b, 1H, NH), 7.60–7.12 (m, 4H, H$_{arom}$), 6.16 (s, 1H, C3-H), 3.70 (s, 3H, NCH$_3$), 3.23 (s, 2H, CH$_2$CN), 2.24 (s, 3H, SCH$_3$)
24	3200 (NH), 2206 (C≡N), 1680 (C═O$_{thiazinone}$), 1640 (C═O$_{quinolone}$), 1589 (C═N), 1571, 1421, 1347, 1051	10.50 (b, 1H, NH), 7.76–7.23 (m, 4H, H$_{arom}$), 6.72 (s, 1H, C3-H), 3.65 (s, 3H, NCH$_3$), 2.30 (s, 3H, SCH$_3$)
25	3242, 3174 (NH), 2210 (C≡N), 1720 (C═O$_{ester}$), 1661 (C═O$_{quinolone}$), 1600 (C═N), 1562, 1483, 1100 (C—O—C)	9.42 (b, 1H, NH$_{amidine}$), 8.93 (b, 1H, PhNH$_{amidine}$), 7.96–7.05 (m, 9H, H$_{arom}$), 6.06 (s, 1H, C3-H), 4.28 (q, 2H, O$\underline{CH_2}$CH$_3$), 3.68 (s, 3H, NCH$_3$), 2.40 (s, 3H, SCH$_3$), 1.18 (t, 3H, OCH$_2\underline{CH_3}$)
26	3185 (NH), 2218 (C≡N), 1668 (C═O$_{pyrimidone}$), 1649 (C═O$_{quinolone}$), 1575 (C═N), 1508, 1482	11.27 (b, 1H, NH), 7.98–7.20 (m, 9H, H$_{arom}$), 6.62 (s, 1H, C3-H), 3.74 (s, 3H, NCH$_3$), 2.25 (s, 3H, SCH$_3$)
28	32580 (NH), 2200 (C≡N), 1660 (C═O$_{pyridone}$), 1642 (C═O$_{quinolone}$), 1590 (C═N), 1541, 1483, 1445	9.92 (b, 1H, NH), 7.72–7.03 (m, 9H, H$_{arom}$), 6.05 (s, 1H, C3-H), 3.60 (s, 3H, NCH$_3$), 2.40 (s, 3H, SCH$_3$)

δ: 6.96 ppm due to the proton at position-3 of quinolinone and also two singlets at δ: 3.66 and 2.35 ppm due to both *N*-methyl and *S*-methyl protons respectively. Building on the above cited data and other analyses, the structure of this product was deduced as 1-quinolinyl-3-methylsulfanylpyrazolo[4,3-*b*]pyrrolizin-4-one **10** (Scheme 2).

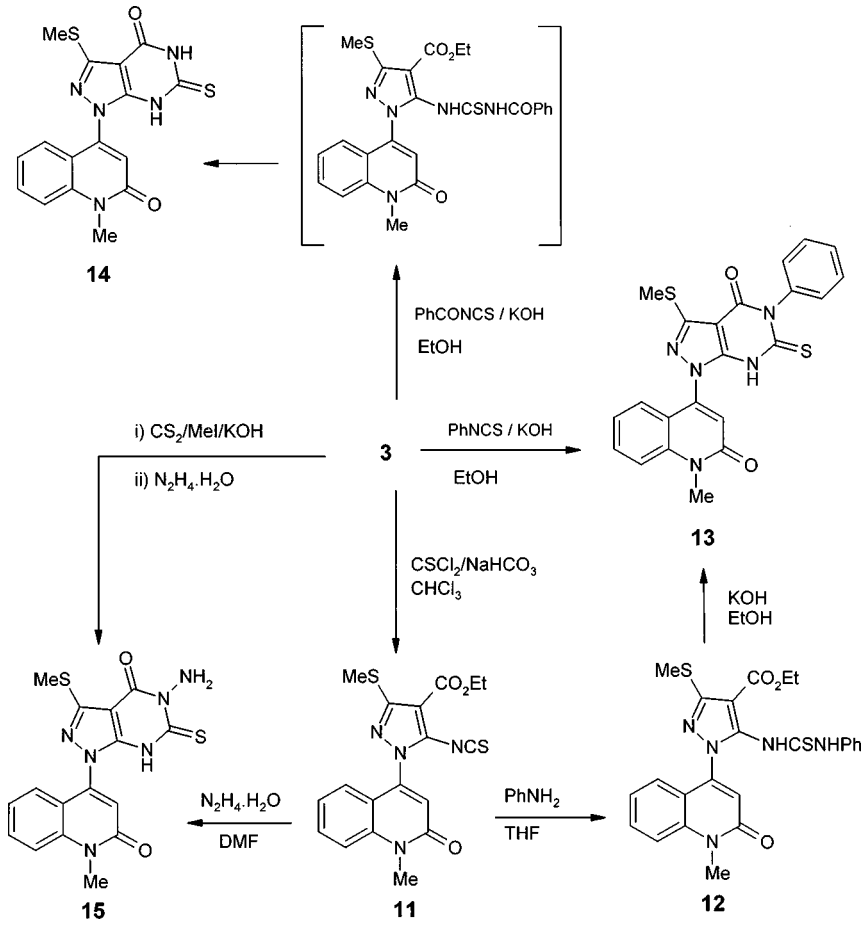


SCHEME 2

Isothiocyanates are distinguished as very useful intermediates for the preparation of thioureas, thiosemicarbazides, thioxopyrimidines, etc. Hence our attention was attracted to transform the amino group in the compound **3** to an isothiocyanato one. To reach this purpose, thiophosgene[17] was used to obtain the targeted isothiocyanate **11** in a moderate yield. IR spectrum of compound **11** reflected the existence of the isothiocyanato group (ν: 2129 cm^{-1}). Addition of aniline to compound **11**, in the molar ratio (1:1), furnished the 1,3-disubstituted thiourea **12** which underwent smooth base-catalyzed intramolecular cyclo-condensation to give 5-phenyl-6-thioxopyrazolo[3,4-*d*]pyrimidine **13**. As another route to obtain compound **13**, the amino-ester **3**

itself was cyclized via an addition-condensation reaction with phenyl isothiocyanate, in the presence of ethanolic potassium hydroxide. It is thought that the formation of the pyrimidine **13** intermediately passes by the formation of the thiourea **12**. Similar behavior was observed again when compound **3** was treated with benzoyl isothiocyanate under the same conditions, giving the thioxopyrazolo[3,4-*d*]pyrimidinone **14**. The spectral data of the product showed that debenzoylation took place during the course of the cyclization reaction. However some reports in the literature recorded similar deacylation during the cyclization of acyl isothiocyanate and/or isoselenocyanate.[18,19] 5-Amino-3-methylsulfanyl-6-thioxopyrazolo[3,4-*d*]pyrimidinone **15** was obtained, in a relatively moderate yield (48%), via a facile one-pot preparation starting with amino-ester **3**. Thus, compound **3** was reacted with carbon disulfide and potassium hydroxide, then the anion that formed was *S*-methylated by means of methyl iodide and subsequently the process was completed by in situ treatment with hydrazine hydrate. On the other hand, compound **15** was obtained through an easier method but in a lesser overall yield. This was achieved by cyclization reaction of the isothiocyanate **11** with hydrazine hydrate in boiling DMF (Scheme 3).

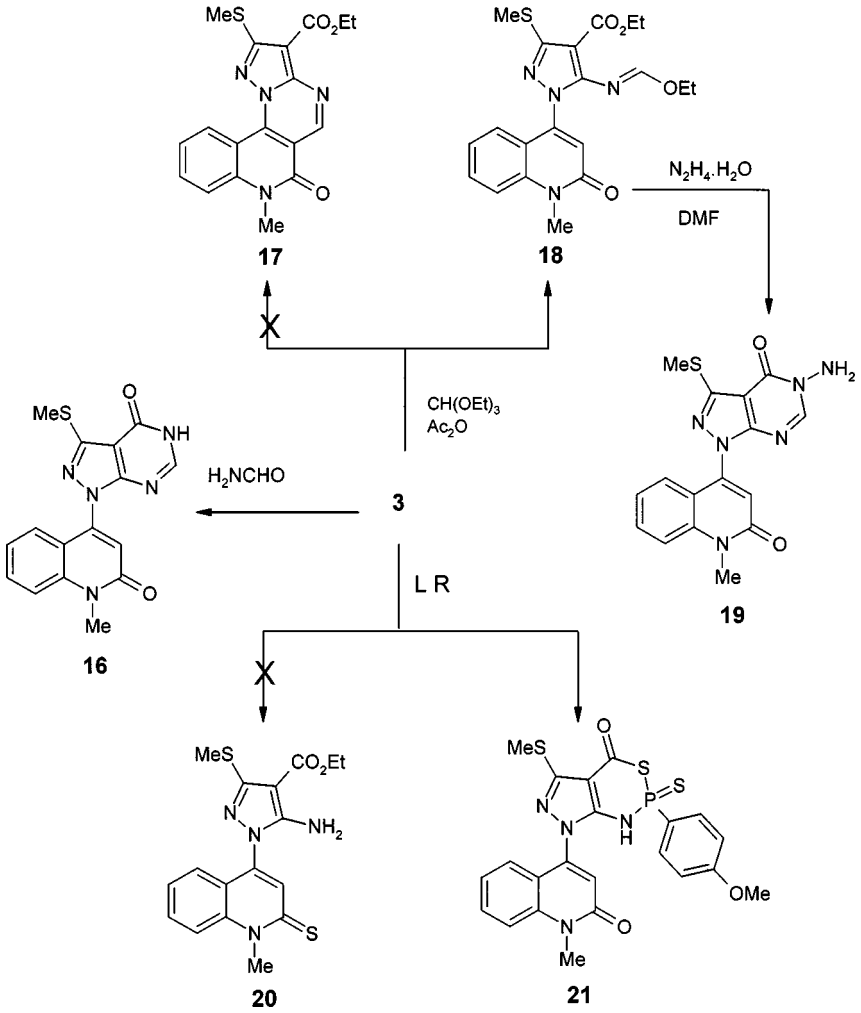
Thermal condensation of the amino-ester **3** with formamide led to smooth formation of pyrazolo[3,4-*d*]pyrimidinone **16**. Compound **16** is another derivative of the pyrazolopyrimidine series, which is structurally related to Allopurinol.[2] Condensation of compound **3** with triethyl orthoformate was carried out, in boiling acetic anhydride, to afford the ethoxymethyleneamino-ester **18**. Although, the position-3 of 2-quinolinone has good susceptibility to be attacked by electrophiles[20] and it was expected in the latter reaction to undergo condensation with ethoxymethyleneamino group, affording pyrazolopyrimidoquinoline **17**, under different reaction conditions, the obtained product was only the compound **18**. This may back to the geometry of the compound that is mainly expected to possess *trans*-form. Herein, no more than one product was isolated, which has a sharp melting point, checked with TLC and its spectral data pointed to a single and pure product. This was strongly supported by the cyclo-condensation of compound **18** with hydrazine hydrate in boiling dimethylformamide,[21] the reaction that led to the formation of 5-amino-3-methylsulfanylpyrazolo[3,4-*d*]pyrimidin-4-one **19**. The structural formula of compound **19** was established upon spectral and analytical data. The reaction of the amino-ester **3** with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, Lawesson's reagent, was carried out, in dry *p*-xylene, giving the novel pyrazolo[3,4-*d*][1,3,2]thiazaphosphinine **21**. The spectral study of the product showed the disappearance of both the amino and carboxylate functions. It is worthwhile to note that Lawesson's



SCHEME 3

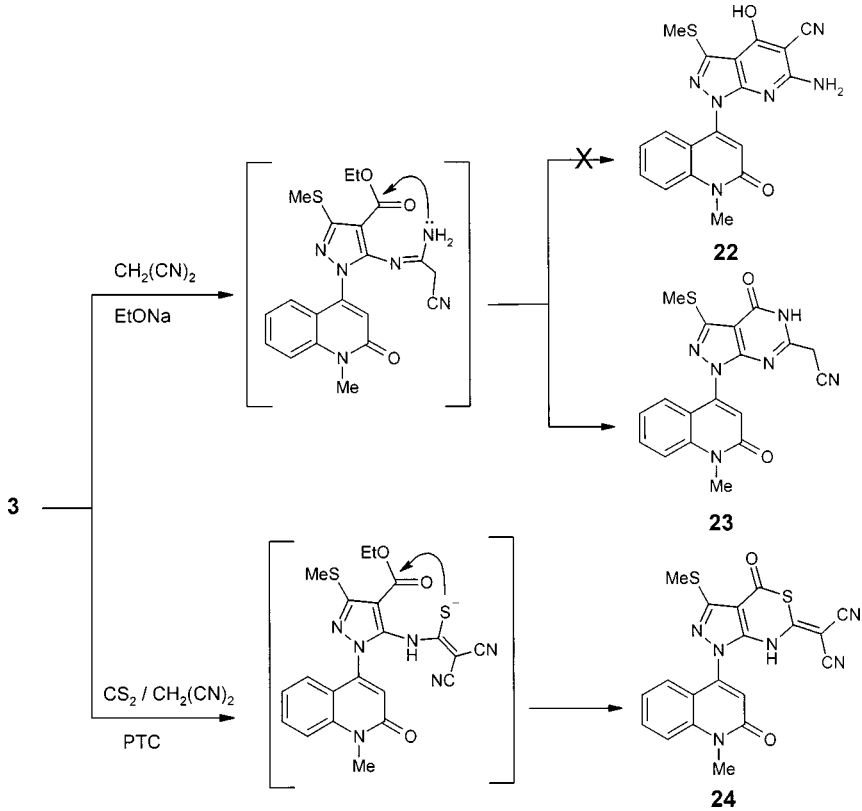
reagent did not lead to the quinolinethione **20** as all features of the product did not point to such replacement. In addition, such cyclization reactions involving Lawesson's reagent were reported, leading to various phospha-heterocycles[22,23] (Scheme 4).

The chemical behavior of the amino-ester **3** toward malononitrile was investigated. Thus, treating compound **3** with malononitrile, in the presence of sodium ethoxide, was carried out at the purpose of production of the pyrazolopyridine **22**. The expected product **22**, which should include amino and cyano groups, was not afforded, while a different compound was obtained and characterized as (pyrazolo[3,4-*d*]pyrimidinyl)acetonitrile **23**. Clearly, the inseparable intermediate; *N*-pyrazolylcyanoacetamidine was formed at first and hence the amino



SCHEME 4

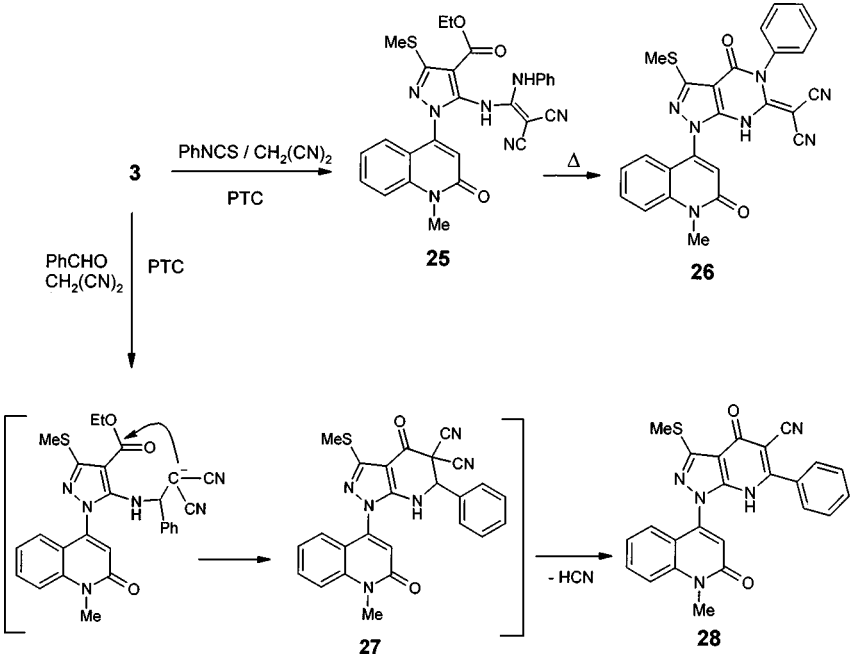
group underwent an intramolecular cyclo-condensation reaction with its neighboring carboxylate group. When the amino-ester **3** was reacted with malononitrile and carbon disulfide under solid-liquid phase transfer catalysis (PTC) conditions,[24] (K_2CO_3/[Bu_4N]Br/dioxane), we have obtained the (pyrazolothiazinylidene)-malononitrile **24**. The production of the latter thiazine derivative might pass through the formation of a dicyanoketene-*N*,*S*-acetal intermediate (not separated), which in a following step underwent catalyzed cyclo-condensation between sulfanyl and carboxylate groups (Scheme 5).



SCHEME 5

Utilizing the same PTC conditions for the reaction of malononitrile and carbon disulfide with the starting compound, malononitrile and phenyl isothiocyanate was reacted with compound **3**. As a very good support for the above hypothesis about formation of an intermediate ketene-acetal in such reactions, the dicyanoketene-*N*,*N*-acetal **25** was separated as the product of the latter reaction. The ketene-acetal **25** was well characterized through its analytical and spectral data, which confirmed the existence of both (NH) and ethyl carboxylate groups. Moreover, the compound **25** underwent smooth thermal cyclization to give the (pyrazolo[3,4-*d*]pyrimidinylidene)malononitrile **26**. ^{1}H NMR of the compound **26** gave us useful information about the nature of protons in this molecule, thus only one proton has the acidic character and appeared at δ: 11.27 ppm due to (NH) of pyrimidinone, besides the other *S*-methyl, *N*-methyl, and aromatic protons chemical shifts. The reaction of compound **3** with malononitrile in the presence of a third partner

reagent was once more performed with benzaldehyde under the same PTC conditions previously described. The reaction is expected to proceed via addition of the amino group in the amino-ester compound, to the so-formed in situ; benzylidenemalononitrile, and subsequently an intramolecular nucleophilic cyclo-condensation, took place between the dicyano-carbanion and the carboxylate group. The compound **27** is thought to be an intermediate in this transformation, even though it was not isolated. The spectral data along with analytical results are well matched with the anticipated structure of the product pyrazolo[3,4-*b*]pyridine-5-carbonitrile **28**. This indicated that during the course of cyclization reaction one molecule of hydrogen cyanide should be expelled. As an evidence for the proposed structure for compound **28**, we carried out an independent synthesis of this compound by action of benzoylacetonitrile on the same starting material **3**, in the presence of sodium ethoxide as the catalyst (Scheme 6). All of the newly obtained compounds were characterized using analytical data (Table II) as well as IR and ^{1}H NMR spectroscopy (Table I).



SCHEME 6

TABLE II Physical and Analytical Data for the New Compounds

Compd. no.	m.p. (°C)	Yield (%)	Mol. formula (mol. wt.)	Analysis calcd./found (%)		
				C	H	N
3	216–217	85	$C_{17}H_{18}N_4O_3S$	56.97	5.06	15.63
			(358.42)	56.80	4.80	15.30
5	280–281	63	$C_{15}H_{14}N_4O_3S$	54.54	4.27	16.96
			(330.37)	54.40	4.40	16.90
6	>300	56	$C_{17}H_{14}N_4O_3S$	57.62	3.98	15.81
			(354.39)	57.40	4.10	15.70
7	181–182	86	$C_{19}H_{19}ClN_4O_4S$	52.47	4.40	12.88
			(434.90)	52.30	4.60	12.70
8	287–288	74	$C_{17}H_{13}ClN_4O_3S$	52.51	3.37	14.41
			(388.84)	52.40	3.20	14.20
9	198–199	79	$C_{21}H_{20}N_4O_3S$	61.75	4.94	13.72
			(408.48)	61.50	5.10	13.60
10	172–174	47	$C_{19}H_{14}N_4O_2S$	62.97	3.89	15.46
			(362.41)	62.70	3.80	15.30
11	112–114(*d*)	52	$C_{18}H_{16}N_4O_3S_2$	53.99	4.03	13.99
			(400.48)	54.20	4.10	13.70
12	160–162	84	$C_{24}H_{23}N_5O_3S_2$	58.40	4.70	14.19
			(493.61)	58.30	4.60	14.00
13	265–266	75[a], 81[b]	$C_{22}H_{17}N_5O_2S_2$	59.04	3.83	15.65
			(447.54)	59.10	3.90	15.40
14	198–200	65	$C_{16}H_{13}N_5O_2S_2$	51.74	3.53	18.85
			(371.44)	51.60	3.30	18.70
15	180–182	48[a], 66[b]	$C_{16}H_{14}N_6O_2S_2$	49.73	3.65	21.75
			(386.46)	49.80	3.50	21.70
16	167–169	56	$C_{16}H_{13}N_5O_2S$	56.63	3.86	20.64
			(339.38)	56.60	3.70	20.50
18	161–162	67	$C_{20}H_{22}N_4O_4S$	57.96	5.35	13.52
			(414.49)	57.80	5.30	13.30
19	210–212	78	$C_{16}H_{14}N_6O_2S$	54.23	3.98	23.71
			(354.39)	54.10	3.80	23.60
21	203–205	56	$C_{22}H_{19}N_4O_3PS_3$	51.35	3.72	10.89
			(514.59)	51.10	3.60	10.80
23	>300	77	$C_{18}H_{14}N_6O_2S$	57.13	3.73	22.21
			(378.42)	57.00	3.50	22.00
24	163–165	58	$C_{19}H_{12}N_6O_2S_2$	54.27	2.88	19.99
			(420.47)	54.30	2.80	19.90
25	178–180	55	$C_{27}H_{23}N_7O_3S$	61.70	4.41	18.65
			(525.59)	61.50	4.40	18.50
26	164–166	75	$C_{25}H_{17}N_7O_2S$	62.62	3.57	20.45
			(479.52)	62.60	3.50	20.30
28	184–186	63[a], 68[b]	$C_{24}H_{17}N_5O_2S$	65.59	3.90	15.93
			(439.50)	65.40	3.80	15.80

[a,b]Yield of methods A and B respectively.

EXPERIMENTAL

Melting points are uncorrected and were determined on a digital Gallen-kamp MFB-595. IR spectra were taken on Perkin-Elmer FT-IR 1650 or Nicolet FT-IR 710 spectrophtometers (ν, cm^{-1}), using samples in KBr disks. ^1H NMR spectra were recorded on Varian Gemini 200 (200 MHz) or Varian EM-360L (60 MHz) spectrometers (δ, ppm), using DMSO-d_6 as the solvent and TMS as an internal reference. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer, at the Cairo University Microanalytical Centre. The compounds **1**[11] and **2**[13] were prepared by the reported methods.

Ethyl 5-Amino-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (3)

A mixture of equimolar amounts (0.1 mmol) of both hydrazinoquinolone **1** (18.92 g) and compound **2** (21.73 g) in DMF (250 ml) was heated under reflux for 1 h. The reaction mixture was left to cool and poured onto crushed ice; the precipitate so formed was filtered off and crystallized from ethanol to give the amino-ester **3** (30.5 g).

5-Amino-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylic acid (5)

Compound **3** (1 g, 2.8 mmol) was dissolved in hydrochloric acid (50 ml, 0.5 M) and then heated under reflux on a boiling water bath for 4 h. The reaction mixture was cooled to room temperature and neutralized using aqueous sodium bicarbonate solution (10%). The white precipitate so obtained was filtered off and crystallized from ethanol to yield the amino-acid **5** (0.58 g).

4-(4-Hydroxy-3-methylsulfanyl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)-1-methylquinolin-2(1*H*)-one (6)

A solution of the amino-acid **5** (0.5 g, 1.5 mmol) in glacial acetic acid (5 ml) and acetic anhydride (5 ml) was heated under reflux for 4 h. Afterward, the excess solvent was evaporated in vacuum, then the residue was treated with sodium hydroxide solution (25 ml, 15%), and left to stand over night. The alkaline solution was filtered off and the clear filtrate was acidified using hydrochloric acid. The so-obtained precipitate was filtered off, washed several times with water, and crystallized from acetic acid to give the pyarzolopyridone **6** (0.3 g).

Ethyl 5-(Acetylamino)-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (7)

To a solution of compound **3** (0.9 g, 2.5 mmol) in dry dioxane (20 ml) and few drops of pyridine, chloroacetyl chloride (0.2 ml, 2.5 mmol) in dioxane (5 ml) were dropwise added with continuous stirring at room temperature for 20 min. After that, the reaction mixture was heated on a boiling water bath for additional 20 min, then left to stand for 1 h and poured onto crushed ice. The precipitate that formed was collected by filtration, washed with cold water, and crystallized from acetone to give the acetamide **7** (0.94 g).

4-(5-Chloro-4-hydroxy-3-methylsulfanyl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)-1-methylquinolin-2(1*H*)-one (8)

A solution of the acetamide **7** (0.65 g, 1.5 mmol) in DMSO (10 ml), containing triethylamine (0.2 ml) was heated under reflux for 3 h. The reaction mixture was left to cool and poured onto crushed ice-cold water (20 ml). The precipitate so obtained was filtered off and crystallized from DMF to give the pyrazolopyridone **8** (0.43 g).

Ethyl 1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carboxylate (9)

A mixture of the amino-ester **3** (1.79 g, 5 mmol) and 2,5-dimethoxytetrahydrofuran (0.7 ml, 5.3 mmol), in glacial acetic acid (20 ml) was heated under reflux for 1 h. Then the excess solvent was evaporated to one-half of its initial volume and left to cool in an ice-bath. The crystalline material so obtained was filtered off and recrystallized from acetic acid to give the pyrrolyl-pyrazole **9** (1.62 g).

1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazolo[3,4-*b*]pyrrolizin-4-one (10)

To a freshly prepared polyphosphoric acid (1.5 g), in a conical flask fitted with a short air condenser, the compound **9** (1 g, 2.5 mmol) was portion-wise added with continuous stirring for 20 min, at a temperature that did not exceed 160°C. After the addition was completed, the temperature was raised gradually to 190–200°C for 1 h. Then the reaction mixture was left to cool and triturated with saturated sodium acetate aqueous solution. The solid deposits were collected by suction,

washed several times with water, and crystallized from DMF to give the pyrrolizinone **10** (0.42 g).

Ethyl 5-Isothiocyanato-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (11)

A solution of the amino-ester **3** (1.79 g, 5 mmol) in chloroform (50 ml) was added to a mixture of thiophosgene (0.4 ml, 5.3 mmol), sodium bicarbonate (0.6 g, 7.14 mmol), water (5 ml), and chloroform (50 ml) with continuous stirring at 20°C over a period of 30 min. The mixture then was stirred for additional 2 h at 30–35°C. The organic layer was separated, washed twice with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The solid residue collected and crystallized from petroleum ether (60–80°C) to give the isothiocyanate **11** (1.04 g).

Ethyl 1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-5-(3-phenylthioureido)-1*H*-pyrazole-4-carboxylate (12)

A solution of the isothiocyanate **11** (0.5 g, 1.25 mmol) in THF (10 ml) was added dropwise with continuous stirring to a solution of aniline (0.12 ml, 1.3 mmol) in THF (10 ml). The suspension so obtained was stirred at room temperature for 1 h, and then the solid deposit so formed was filtered off, washed with diethyl ether (25 ml), and crystallized from ethanol to give the thiourea **12** (0.52 g).

1-Methyl-4-(3-methylsulfanyl-4-oxo-5-phenyl-6-thioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)quinolin-2(1*H*)-one (13)

A: To a solution of potassium hydroxide (0.1 g, 1.8 mmol) in ethanol (10 ml, 95%), the thiourea derivative **12** (0.5 g, 1 mmol) was added and the mixture was heated under reflux for 1 h. The suspension that formed was filtered while hot and the solid residue was dissolved in hot water (5 ml) and filtered off. The clear filtrate was acidified using hydrochloric acid to give a precipitate, which was collected by filtration and crystallized from DMF to furnish the pyrazolopyrimidine **13** (0.34 g).

B: A mixture of the amino-ester **3** (1.07 g, 3 mmol), phenyl isothiocyanate (0.4 ml, 3.3 mmol), and potassium hydroxide (0.18 g, 3.2 mmol) in ethanol (25 ml) was heated under reflux for 2 h. Then the reaction mixture was filtered while hot and the solid residue was dissolved in

hot water (5 ml) and filtered off. The clear filtrate was acidified using hydrochloric acid to give a precipitate, which was collected by filtration and crystallized from DMF to furnish the pyrazolopyrimidine **13** (1.08 g) (m.p., m.m.p. and spectra).

1-Methyl-4-(3-methylsulfanyl-4-oxo-6-thioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)quinolin-2(1*H*)-one (14)

Using the same method (B) for compound **13**, a mixture of the amino-ester **3** (1.07 g, 3 mmol), benzoyl isothiocyanate (0.5 ml, 3.6 mmol), and potassium hydroxide (0.18 g, 3.2 mmol) in ethanol (25 ml) was reacted to give a precipitate, which was crystallized from DMF leading to the pyrazolopyrimidine **14** (0.72 g).

4-(5-Amino-3-methylsulfanyl-4-oxo-6-thioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-methylquinolin-2(1*H*)-one (15)

A: To a cooled (0°C) stirred solution of the amino-ester **3** (1.79 g, 5 mmol) in DMSO (20 ml) and potassium hydroxide aqueous solution (3 ml, 3 M), carbon disulfide (0.3 g, 5 mmol) was dropwise added during a period of 20 min. Then the mixture was stirred at room temperature for an additional 1 h. Methyl iodide (0.32 ml, 5.1 mmol) in dioxane (10 ml) was dropwise added to the above mixture with continuous stirring during a period of 30 min. Afterward, the mixture was dropwise treated with hydrazine hydrate (0.25 ml, 5 mmol) and heated under reflux on a boiling water-bath for 2 h. The reaction mixture was left to cool and diluted with cold water to give a precipitate, which was collected by filtration and crystallized from dioxane to furnish the pyrazolopyrimidine **15** (0.93 g).

B: To a solution of the isothiocyanate **11** (0.8 g, 2 mmol), in DMF (5 ml), hydrazine hydrate (0.1 ml, 2 mmol) was added and the mixture was heated under reflux 3 h. On cooling and addition of cold water (10 ml) a precipitate was obtained, which was filtered off and crystallized from dioxane to afford the pyrazolopyrimidine **15** (0.51 g) (m.p., m.m.p. and spectra).

1-Methyl-4-(3-methylsulfanyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)quinolin-2(1*H*)-one (16)

A mixture of the amino-ester **3** (0.72 g, 2 mmol) and formamide (5 ml) was heated in an oil bath at 180°C for 2 h. After that the mixture was

diluted with water (5 ml) and left to stand in an ice-bath for 2 h to give crystalline material, which was recrystallized from ethanol affording the pyrazolopyrimidine **16** (0.38 g).

Ethyl 5-(Ethoxymethyleneamino)-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (18)

A mixture of the amino-ester **3** (1.79 g, 5 mmol), triethyl orthoformate (0.85 ml, 5 mmol), and acetic anhydride (15 ml) was heated under reflux for 5 h. Then the excess solvent was removed under reduced pressure and the oily material so obtained was triturated with cold water (15 ml) to give solid deposits, which were filtered and crystallized from ethanol to give compound **18** (1.39 g).

4-(5-Amino-3-methylsulfanyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-methylquinolin-2(1*H*)-one (19)

To a solution of the compound **18** (1 g, 2.4 mmol), in DMF (10 ml), hydrazine hydrate (0.15 ml, 3 mmol) in DMF (5 ml) was dropwise added and the mixture was heated under reflux for 2 h. On cooling and addition of cold water (10 ml) a solid precipitate was afforded. The precipitate was filtered and crystallized from ethanol to give the aminopyrimidone **19** (0.67 g).

1–Methyl-4-[2-(4-methoxyphenyl)-5-methylsulfanyl-4-oxo-2-thioxo-2*H*,7*H*-1,4-dihydropyrazolo[3,4-*d*][1,3,2]thiazaphosphinin-7-yl]quinolin-2(1*H*)-one (21)

A mixture of the amino-ester **3** (1.79 g, 5 mmol) and Lawesson's reagent (2.1 g, 5 mmol), in dry p-xylene (20 ml) was heated under reflux for 6 h. Afterward, the solvent was removed under reduced pressure and the obtained residue was triturated with cold methanol (20 ml). The precipitate was collected by suction and crystallized from dioxane to afford the compound **21** (1.44 g).

[1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]acetonitrile (23)

To a mixture of the amino-ester **3** (1.07 g, 3 mmol) and malononitrile (0.2 g, 3 mmol) in absolute ethanol (10 ml), sodium ethoxide (0.3 g,

4.3 mmol) in absolute ethanol (10 ml) was dropwise added with continuous stirring over a period of 30 min. Then the reaction mixture was heated under reflux for 2 h and then poured onto crushed ice and filtered off. The clear filtrate was neutralized using dilute acetic acid to give a yellow precipitate, which was collected by filtration and crystallized from ethanol to afford the acetonitrile **23** (0.87 g).

[1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-4-oxo-4,7-dihydro-1*H*-pyrazolo[3,4-*d*][1,3]thiazin-6-ylidene]malononitrile (24)

To a mixture of malononitrile (0.2 g, 3 mmol), carbon disulfide (0.2 ml, 3.3 mmol) and anhydrous potassium carbonate (0.42 g, 3 mmol) in dioxane (20 ml), tetrabutylammonium bromide (0.1 g, 0.3 mmol) was added and the mixture was stirred at 60°C for 30 min. The amino-ester **3** (1.07 g, 3 mmol), in dioxane (25 ml), was dropwise added to the above mixture with continuous stirring over a period of 30 min. After that, the stirring was continued for additional 3 h and the reaction mixture filtered off. The organic solvent was removed in reduced pressure to give a solid residue, which was washed with water and crystallized from dioxane to afford the pyrazolothiazine **24** (0.73 g).

Ethyl 5-[1-Anilino-2,2-dicyano(vinylamino)]-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-1*H*-pyrazole-4-carboxylate (25)

Following the above method described for compound **24**, a mixture of malononitrile (0.2 g, 3 mmol), phenyl isothiocyanate (0.4 ml, 3.3 mmol), anhydrous potassium carbonate (0.42 g, 3 mmol), tetrabutylammonium bromide (0.1 g, 0.3 mmol), and the amino-ester **3** (1.07 g, 3 mmol) in dioxane (45 ml) was reacted to yield a yellow precipitate that was crystallized from dioxane to give the compound **25** (0.86 g).

[1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-4-oxo-5-phenyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylidene]malononitrile (26)

The compound **25** (0.53 g, 1 mmol) was dissolved in ethylene glycol (10 ml) and heated under short air condenser at 110–120°C for 30 min. After that the temperature was raised gradually to 170–190°C for an additional 30 min. The mixture was left to cool and the white precipitate so formed on addition of cold water (20 ml) was filtered off and crystallized from dioxane to furnish the pyrazolopyrimidine **26** (0.36 g).

1-(1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)-3-methylsulfanyl-4-oxo-6-phenyl-4,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (28)

A: Equimolar amounts (3 mmol) of malononitrile (0.2 g), benzaldehyde (0.3 ml), and potassium carbonate (0.42 g) in dioxane (20 ml) were treated with tetrabutylammonium bromide (0.1 g, 0.3 mmol). The mixture was stirred at 60°C for 1 h, and then the aminoester **3** (1.07 g, 3 mmol) in dioxane (25 ml) was added. The reaction mixture was heated under reflux on boiling water-bath for 2 h and then filtered while hot. The filtrate was concentrated to half of its initial volume and left over night to give a precipitate, which was collected by filtration and crystallized from DMF to furnish the pyrazolopyridine **28** (0.83 g).

B: To a mixture of the amino-ester **3** (0.72 g, 2 mmol) and benzoylacetonitrile (0.3 g, 2 mmol) in ethanol (15 ml), sodium ethoxide (0.27 g, 4 mmol) in ethanol (10 ml) was added and the reaction mixture was heated under reflux on a boiling water bath for 6 h. Then the reaction mixture was left to cool, diluted with water (50 ml), and filtered off. The clear filtrate was acidified using hydrochloric acid to give a precipitate, which was collected by filtration and crystallized from DMF to furnish the pyrazolopyridine **28** (0.6 g) (m.p., m.m.p. and spectra).

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